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Characterization of tricuspid regurgitation and its prognostic implications

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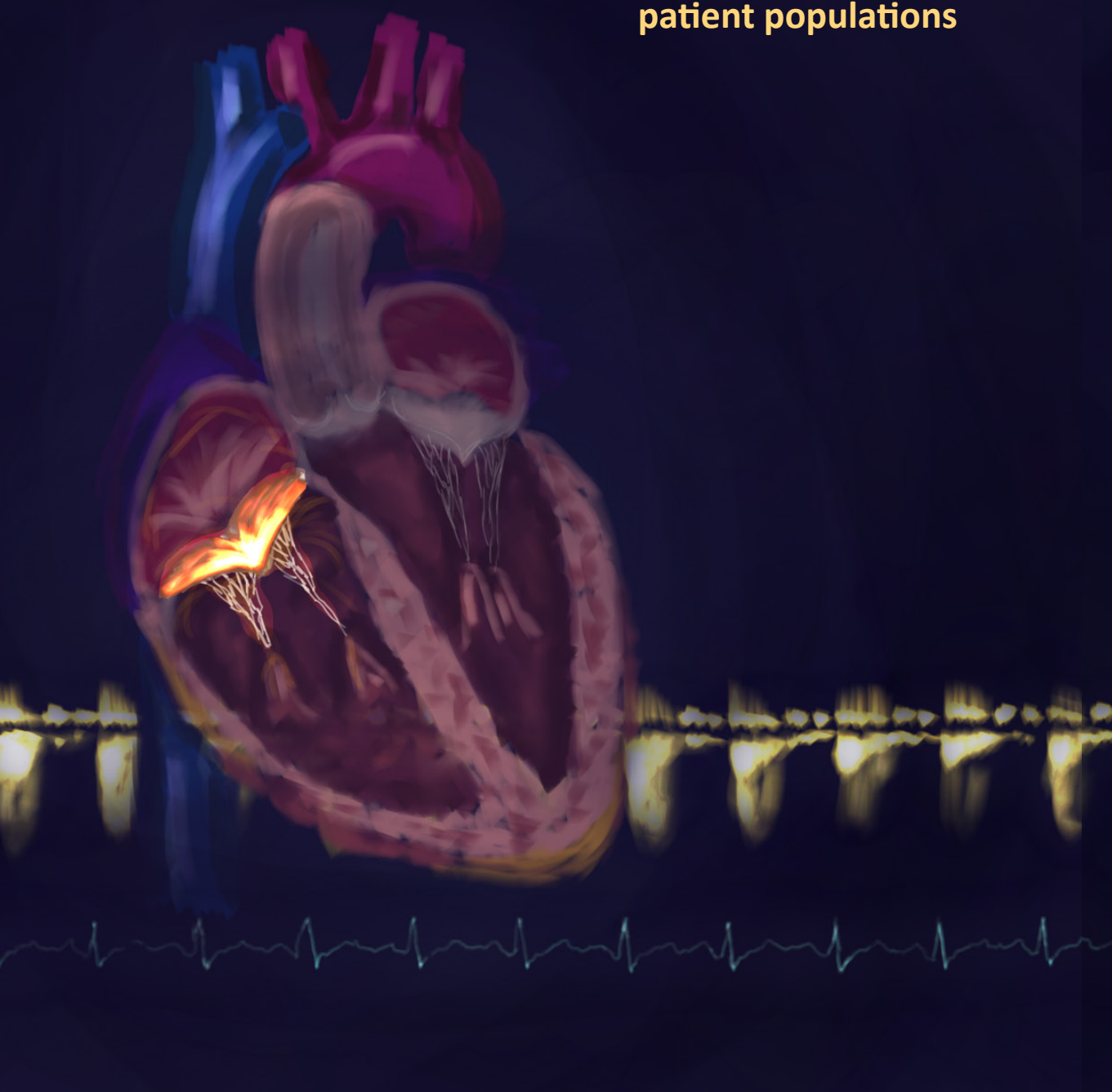
Part II

Tricuspid regurgitation in specific patient populations



Chapter 5

Sex-specific differences in etiology and prognosis in patients with significant tricuspid regurgitation

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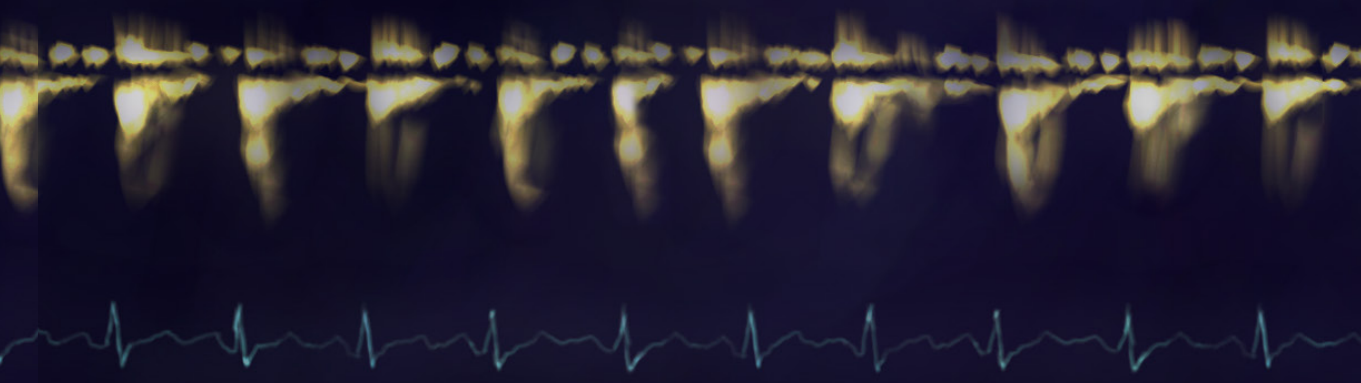

ABSTRACT

Background: The aim of this study was to assess differences in etiology, comorbidities, echocardiographic parameters and prognosis between men and women with significant TR.

Methods: Clinical and echocardiographic characteristics of 1569 patients (age 71 (62-78) years) at first diagnosis of significant TR were compared between men and women. Patients with congenital heart disease or previous tricuspid valve surgery were excluded. TR etiologies were defined as primary, left valvular disease related, left ventricular (LV) dysfunction related, pulmonary hypertension related, or isolated. The primary endpoint was all-cause mortality. Sex differences in outcomes were compared in the total population and after propensity score matching.

Results: There were 798 (51%) women and 771 (49%) men in the study population. Women were diagnosed with significant TR at an older age compared to men (72 [62-79] years vs. 70 [61-77] years; p=0.003). The TR etiology in women was more often left valvular disease related and isolated whereas men more often had LV dysfunction related TR. In the total population women had better 10-year survival compared to men (49% vs. 39%; p=0.001). After propensity score matching, the influence of sex on survival was neutralized (p=0.228) but the TR etiologies remained significantly associated with all-cause mortality. Patients with left valvular disease or LV dysfunction related TR had lower survival compared to patients with primary TR (p=0.004 and p=0.019, respectively).

Conclusion: Long-term survival of patients with significant TR was similar between men and women after propensity score matching, while the etiology of TR remained significantly associated with all-cause mortality.

INTRODUCTION

The prevalence of tricuspid regurgitation (TR) increases with age and is higher in women than in men in the general population (1-3). Multiple studies have demonstrated the impact of significant (moderate and severe) TR on prognosis, but differences between men and women remain unclear (4, 5). TR is a heterogeneous disease with different characteristics, treatment and prognosis depending on the etiology (6). The prevalence of the cardiac diseases that may cause TR, e.g. ischemic heart disease, left valvular disease or atrial fibrillation, vary between men and women (7). Recent studies have demonstrated differences in the distribution of the various TR etiologies between sexes (1, 8, 9). Consequently, differences between men and women in clinical and echocardiographic characteristics may be expected. It is important to clarify these sex-specific differences in presentation of TR and their prognostic implications to improve risk stratification and treatment. However, differences between men and women in characteristics, etiology and prognosis in the natural history of TR have not been extensively studied. Therefore, the aim of our study was [1] to describe sex-specific differences in clinical characteristics, echocardiographic parameters and etiology in patients with significant TR and [2] to assess the association between sex and prognosis in the overall population and a propensity score matched population of patients with significant TR.

METHODS

The data that support the findings of this study are available on reasonable request to the corresponding author. Patients diagnosed with significant (moderate and severe) tricuspid regurgitation (TR) at the Leiden University Medical Center (Leiden, the Netherlands) between June 1995 and September 2016 were identified by performing a query in the departmental echocardiographic database. TR was evaluated in all patients by transthoracic echocardiography using a multiparametric approach as recommended by the current guidelines (10). Patients with previous surgery of the tricuspid valve and patients with congenital heart disease were excluded. Demographics and clinical data were retrospectively obtained and analyzed from the departmental Cardiology Information System (EPD-vision; Leiden University Medical Center). The institutional review board of the Leiden University Medical Center approved this observational design and retrospective analysis of clinically acquired anonymized data and waived the need for patient written informed consent.

Baseline was determined at the moment of first diagnosis of significant TR by transthoracic echocardiography. Clinical and echocardiographic characteristics and TR etiology were

compared between men and women. Clinical data included demographics, cardiovascular risk factors and comorbidities, diuretic use and glomerular filtration rate, which was calculated by the Modification of Diet in Renal Disease formula (11).

Transthoracic 2-dimensional echocardiography was performed with patients at rest. Commercially available ultrasound systems (Vivid 7, E9 and E95 systems; GE-Vingmed) equipped with 3.5 MHz or M5S transducers were used to acquire images that were digitally stored for offline analysis with commercially available software (EchoPAC version 113.0.3 and 202; GE-Vingmed). Mmode, 2-dimensional, color, continuous- and pulsed-wave Doppler data were acquired on parasternal, apical and subcostal views according to the current recommendations (10, 12-14). Left ventricular (LV) ejection fraction was derived by the Simpson method from LV volumes that were measured on the apical 2- and 4-chamber views (15). Left atrial (LA) maximum volume was assessed on the apical 2- and 4-chamber views and corrected for body surface area (15). Significant (moderate or severe) aortic stenosis was defined by an aortic valve area ≤ 1.5 cm2, which was calculated by the continuity equation (16). Mitral regurgitation and TR severity were graded by an integrative approach based on qualitative, semiquantitative and quantitative parameters evaluated on 2-dimensional, color, continuous and pulsed wave Doppler data according to the current recommendations (10). The tricuspid annular diameter, right atrial (RA) and right ventricular (RV) areas were measured on a focused RV apical 4-chamber view and corrected for body surface area. RV systolic function was quantified by tricuspid annular plane systolic excursion (TAPSE) as measured on M-mode recordings of the lateral tricuspid annulus (15). Systolic pulmonary artery pressure (sPAP) was estimated by the simplified Bernoulli equation, derived from the tricuspid regurgitant jet peak velocity with addition of 3, 8 or 15 mmHg based on the size and collapsibility of the inferior vena cava (14). Quantitative parameters of TR were measured as recommended by current guidelines (10).

Etiology of TR was defined by a stepwise classification based on the method introduced by Topilsky and colleagues (1). Firstly, primary TR was defined in case of structural abnormalities of the tricuspid valve. Secondly, patients with moderate or severe (significant) left-sided valvular disease at baseline, e.g. mitral regurgitation, or with previous left-sided valvular surgery were classified as having left valvular disease related TR. The third category was characterized as LV dysfunction related TR, occurring in patients with a LV ejection fraction <50%. The fourth step defined TR associated with pulmonary hypertension in case of sPAP ≥50 mmHg and the remaining patients were categorized as isolated TR.

The primary outcome of interest was all-cause mortality while on optimal medical therapy. Survival data were verified by the departmental Cardiology Information System which is linked to the Social Security Death Index. Secondary endpoints included hospitalization for heart failure, tricuspid valve surgery, any valvular surgery, coronary artery bypass grafting and the occurrence of atrial arrhythmias during follow-up. Outcome was assessed in the total population and in a subpopulation of propensity score matched pairs of men and women to account for the effect of baseline clinical and echocardiographic differences on prognosis.

Continuous variables with normal distribution are expressed as mean ± standard deviation and continuous variables with non-normal distribution as median (interquartile range). A histogram of the sample data was compared to a normal probability curve to determine the adherence to normality. Categorical variables are presented as frequencies and percentages. Baseline differences between men and women were analyzed by the unpaired T-test, the Mann-Whitney U test and the chi-square test as appropriate. To account for potential confounders in the determination of sex-related differences in prognosis, a matched subgroup for comparative outcome analysis was formed using propensity scores. Baseline variables used to calculate propensity score are presented in Supplementary Table S1. All women were entered into a nearest neighbor 1:1 variable ratio, parallel, balanced propensity score matching model using a caliper width of 0.05, and thereby matched 1:1 to men. The 1-, 5- and 10-year survival rates in the total population and in the propensity score matched population were calculated with the Kaplan Meier curves censored for tricuspid valve surgery. Differences between men and women in the primary endpoint were analyzed using the log-rank test. Sex differences in the secondary endpoints were compared using the chi-square test. Cox proportional hazards regression analysis was performed to test the association of TR etiologies with all-cause mortality in the propensity score matched population. Hazard ratios and 95% confidence intervals were calculated. All p-values were 2-sided and values <0.05 were considered significant. Statistical analyses were performed with SPSS for Windows, version 25 (SPSS Inc, IBM Corp).

RESULTS

A total of 1569 patients with significant TR (median age 71 years [62-78]) were included in the analysis. There were 798 (51%) women and 771 (49%) men. Baseline clinical characteristics of the total population and according to sex are presented in Table 1. In per-group analysis, women were older at diagnosis of significant TR compared to men (72 years [62-79] vs. 70 years [61-77]; p=0.003). Men were more likely to have

Table 1. Baseline characteristics of the total unmatched population of patients with moderate and severe tricuspid regurgitation and the differences between men and women

Variable	Overall (n=1569)	Women (n=798)	Men (n=771)	P-value
Age (years)	71 (62-78)	72 (62-79)	70 (61-77)	**0.003**
Body mass index (kg/m^2)	26 ± 4	26 ± 5	26 ± 4	0.188
Hypertension	1143 (80%)	574 (78%)	569 (81%)	0.182
Hypercholesterolemia	668 (47%)	291 (40%)	377 (54%)	**<0.001**
Diabetes mellitus	289 (20%)	132 (18%)	157 (22%)	**0.043**
(Ex-)smoker	450 (31%)	197 (27%)	253 (36%)	**<0.001**
Coronary artery disease	588 (38%)	221 (28%)	367 (48%)	**<0.001**
Atrial fibrillation	739 (50%)	373 (50%)	366 (51%)	0.735
Pacemaker/ICD	516 (33%)	201 (26%)	315 (41%)	**<0.001**
Oral anticoagulants	824 (58%)	391 (54%)	433 (62%)	**0.003**
Aspirin	285 (20%)	147 (20%)	138 (20%)	0.834
Betablockers	844 (59%)	412 (57%)	432 (62%)	0.060
ACE-inhibitors	867 (61%)	412 (57%)	455 (65%)	**<0.001**
Aldosterone antagonists	307 (22%)	130 (18%)	177 (26%)	**0.001**
Calcium antagonists	152 (11%)	81 (11%)	71 (10%)	0.530
Statins	633 (45%)	268 (37%)	365 (52%)	**<0.001**
Diuretic use	876 (58%)	445 (58%)	431 (58%)	0.811
eGFR (ml/min/1.73m^2)	65 (46-84)	63 (47-81)	66 (46-86)	0.278
Echocardiographic characteristics				
LV end diastolic volume (ml/m^2)	63 (47-93)	54 (41-75)	78 (54-115)	**<0.001**
LV ejection fraction (%)	45 ± 16	47 ± 15	42 ± 16	**<0.001**
LA maximum volume (ml/m^2)	50 (34-69)	48 (34-67)	51 (34-70)	0.454
Significant aortic stenosis	314 (23%)	185 (27%)	129 (19%)	**0.001**
Significant mitral regurgitation	457 (29%)	232 (29%)	225 (29%)	0.950
RV end diastolic area (cm^2/m^2)	13 (10-16)	12 (10-14)	14 (11-17)	**<0.001**
TAPSE (mm)	16 ± 5	16 ± 5	15 ± 5	**<0.001**
sPAP (mmHg)	42 ± 17	42 ± 16	43 ± 18	**0.049**
RA maximum area (cm^2/m^2)	15 ± 5	14 ± 5	15 ± 5	**0.004**
Severe tricuspid regurgitation	367 (23%)	196 (25%)	171 (22%)	0.265
Tricuspid annular diameter (mm/m^2)	22 ± 4	22 ± 4	22 ± 4	0.956
Tricuspid leaflet tenting area (mm^2)	1.9 (0.0-3.9)	1.6 (0.0-3.4)	2.3 (0.2-4.4)	**<0.001**
PISA radius (mm)	11.1 ± 4.0	10.8 ± 3.9	11.3 ± 4.2	**0.016**
EROA (mm^2)	62 (39-99)	59 (37-94)	65 (41-104)	**0.020**
RVol (mL/beat)	59 (35-99)	55 (33-94)	62 (36-103)	**0.021**

Values are mean ±SD, median (IQR) or n (%). P-value by unpaired t-test or Mann-Whitney U test for Gaussian and non-Gaussian distributed continuous variables, respectively. P-value by chi-square for categorical variables.

ACE = angiotensin converting enzyme; eGFR = estimated glomerular filtration rate; EROA = effective regurgitant orifice area; ICD = implantable cardioverter-defibrillator; IQR = interquartile range; LA = left atrium; LV = left ventricle; PISA = proximal isovelocity surface area; RA = right atrium; RV = right ventricle; RVol = regurgitant volume; SD = standard deviation; sPAP = systolic pulmonary artery pressure; TAPSE = tricuspid annular plane systolic excursion

hypercholesterolemia, diabetes mellitus and a smoking habit. Men more often had known coronary artery disease compared to women (48% vs. 28%; p<0.001) and more often had a pacemaker or ICD in situ (41% vs. 26%; p<0.001). No significant differences between sexes were found in the presence of atrial fibrillation.

Baseline echocardiographic characteristics of the total population and according to sex are shown in Table 1. LV ejection fraction (45 ± 16%) and RV systolic function (TAPSE 16 ± 5 mm) were reduced in the overall population. In per group analysis, LV and RV systolic function were better in women compared to men (p<0.001 for both). Furthermore, despite correction for body surface area, LV and RV size were larger in men than in women (p<0.001 for both). Women more often had significant aortic stenosis (27% vs. 19%; p=0.001), but no differences were found in the presence of mitral regurgitation (29% vs. 29%; p=0.950).

Figure 1 shows the distribution of the total population according to the 5 etiologies of TR. Left valvular disease related TR was the most common etiology (n=902; 58%) of which 50% had significant mitral regurgitation, 34% had significant aortic stenosis and 42% had previous left-sided heart valve surgery. In this category, 586 patients (65%) had concomitant LV dysfunction (LV ejection fraction <50%). Compared to men, women had more left valvular disease related TR and isolated TR (59% vs. 56% and 16% vs. 11%, respectively) whereas LV dysfunction related TR was more common in men (25% vs. 17%). In patients with pacemaker or ICD leads across the tricuspid valve, the TR etiologies were distributed similarly to the overall population (Supplementary Figure S1).

During a median follow-up of 4.2 years (0.7-7.2) with censoring for tricuspid valve surgery, 728 patients (46%) died. The cumulative 1-, 5- and 10-year survival rates were 81%, 57% and 44%, respectively. In the evaluation of outcome according to sex, the Kaplan-Meier analysis demonstrated a significantly better survival during medical treatment for women compared to men (log-rank chi square 10.38; p=0.001; Figure 2A). One-, 5- and 10-year survival rates according to sex were as follows: 83%, 60% and 49% for women and 78%, 53% and 39% for men, respectively.

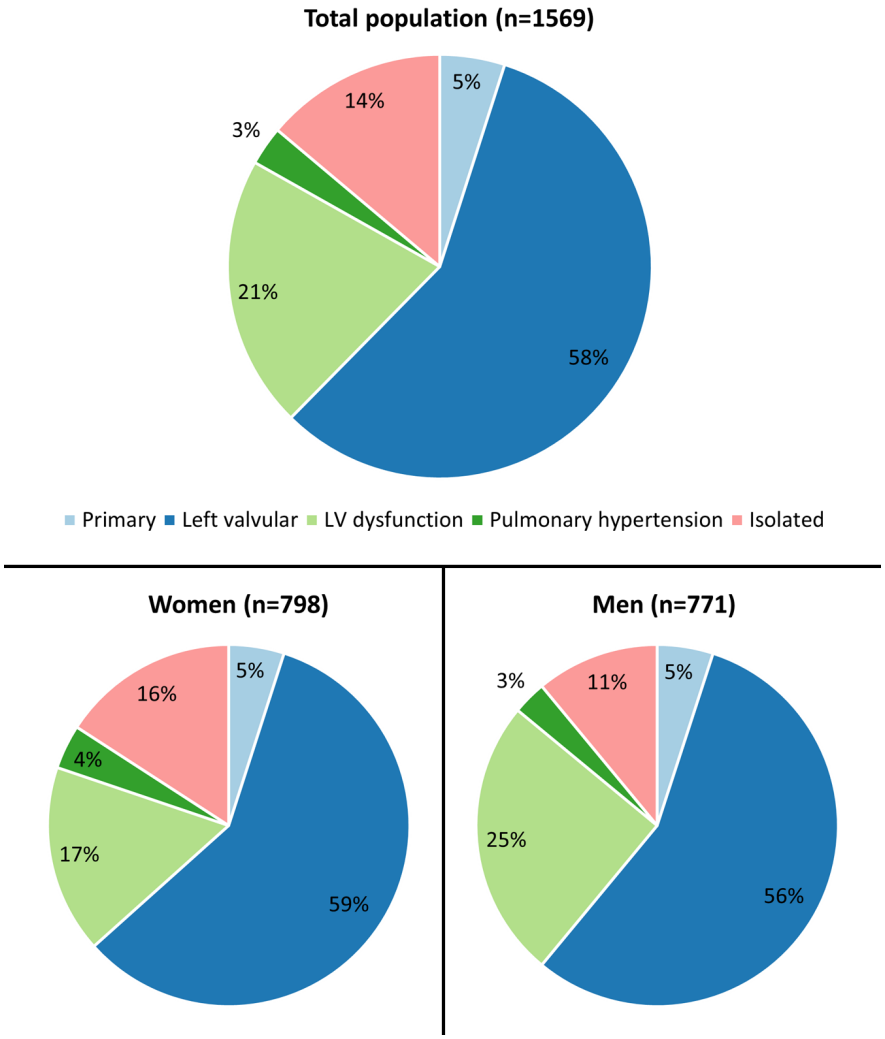

Figure 1. Distribution of tricuspid regurgitation (TR) etiologies in the total unmatched population of patients with moderate and severe TR and the differences between men and women

LV = left ventricular

Differences between men and women for the occurrence of secondary endpoints are shown in Figure 2B. Only 204 patients (13%) underwent tricuspid valve surgery during follow-up, with no significant differences between men and women. In contrast, women received more valvular surgery in general compared to men (38% vs. 32%; p=0.010). Apart from having higher all-cause mortality rates, men were also more often hospitalized for heart failure during follow-up compared to women (23% vs. 16%; p=0.001). No sex-related

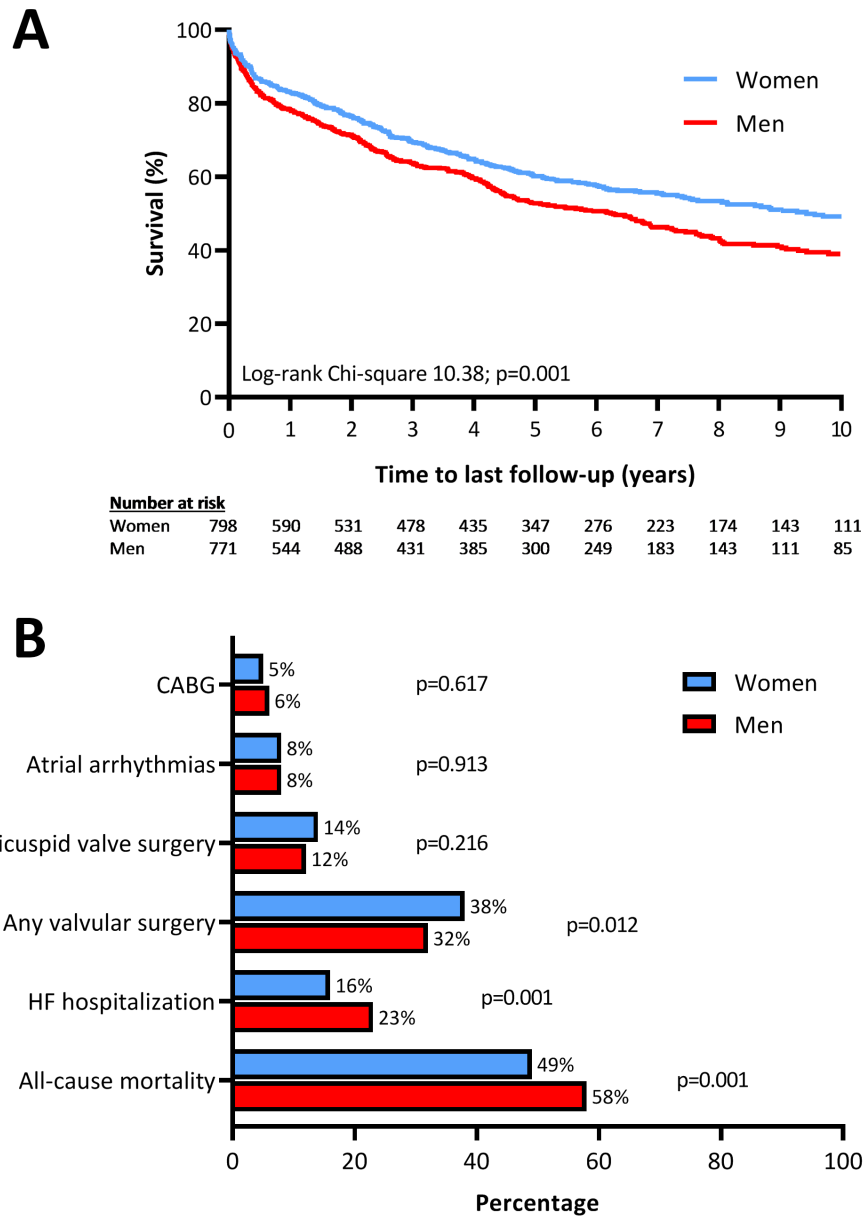

Figure 2. Outcomes according to sex for the total unmatched population of patients with moderate and severe tricuspid regurgitation

Panel A shows the Kaplan-Meier curves for survival censored for tricuspid valve surgery in men and women. Panel B shows the occurrence of secondary endpoints in men and women during follow-up.

CABG = coronary artery bypass grafting; HF = heart failure

differences were demonstrated in the occurrence of atrial arrhythmias and referral for coronary artery bypass grafting.

Propensity score matching yielded 288 pairs of matched men and women with significant TR. Baseline clinical and echocardiographic characteristics of the matched population were adequately balanced between men and women (Supplementary Table S2). The distribution of TR etiologies after matching is shown in Figure 3. Left valvular disease related TR was

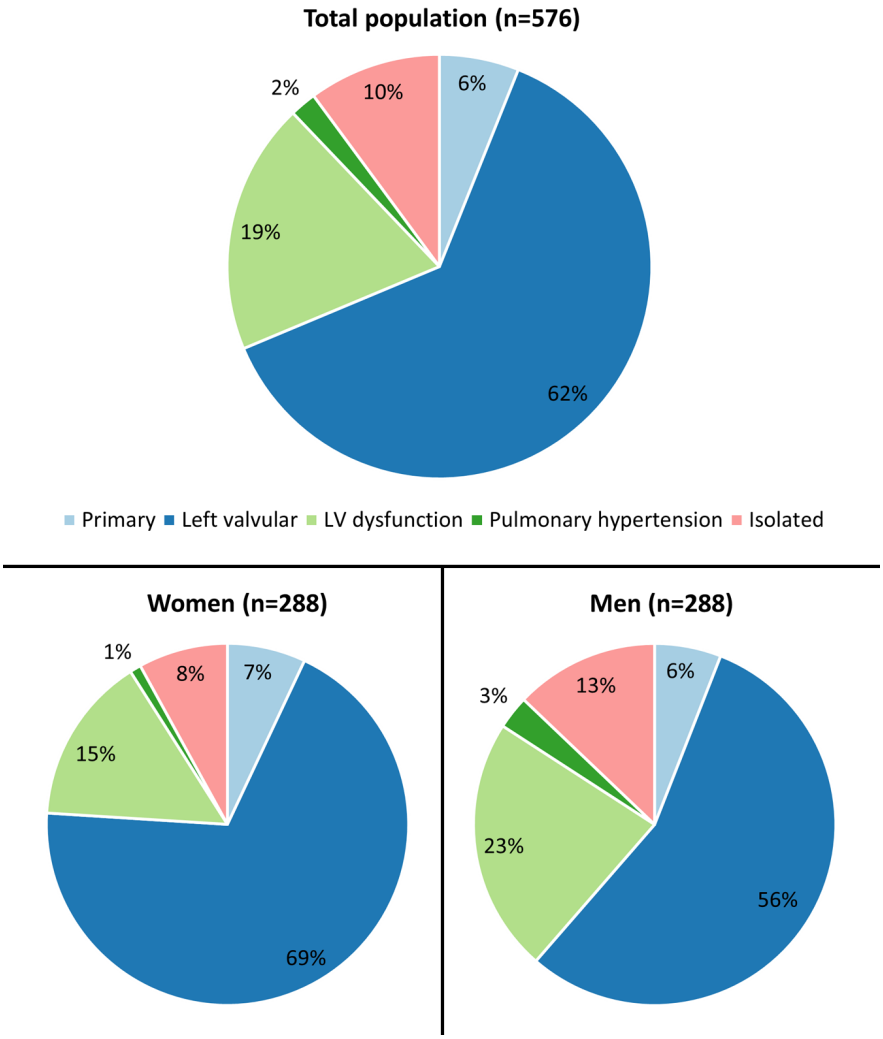

Figure 3. Distribution of tricuspid regurgitation (TR) etiologies in the propensity score matched population of patients with moderate and severe TR and the differences between men and women

LV = left ventricular

most prevalent in women (n=198; 69%) while more men had LV dysfunction related TR (n=66; 23%). Only 22 women (8%) with isolated TR remained in the matched population, compared to 38% men (13%) with isolated TR.

Figure 4 shows the primary and secondary endpoints in the propensity score matched subpopulation of patients with significant TR. The Kaplan-Meier analysis showed a neutralization of the survival benefit for women after matching (log-rank chi-square 1.454; p=0.228; Figure 4A). In addition, there were no differences in heart failure hospitalization rates during follow-up (18% in women vs. 19% in men; p=0.776; Figure 4B). In contrast, the difference between men and women in the occurrence of any valvular surgery during follow-up became more substantial (34% vs. 53%; p=0.001). Of these surgeries, 110 (45%) were isolated aortic valve intervention. The remaining secondary endpoints (tricuspid valve surgery, atrial arrhythmias, coronary artery bypass grafting) remained comparable between men and women after propensity score matching.

Univariable Cox regression analysis of the matched cohort showed that the TR etiologies were significantly associated with all-cause mortality censored for tricuspid valve surgery after matching (p=0.018; Table 2). Left valvular disease related TR and LV dysfunction related TR were associated with an increased risk of all-cause mortality compared to primary TR (hazard ratio, 2.666; 95% confidence interval, 1.362-5.219; p=0.004 and hazard ratio, 2.340; 95% confidence interval, 1.1534.750; p=0.019, respectively). The potential interaction between gender and TR etiology was not statistically significant (p=0.300).

Table 2. Univariable Cox regression analysis for all-cause mortality censored for tricuspid valve surgery in the propensity score matched population of patients with significant tricuspid regurgitation

	Hazard Ratio (95% CI)	P-value
TR etiology		**0.018**
Primary (reference)	----------	----------
Left valvular	2.666 (1.362-5.219)	**0.004**
LV dysfunction	2.340 (1.153-4.750)	**0.019**
Pulmonary hypertension	2.658 (0.945-7.477)	0.064
Isolated	1.662 (0.769-3.593)	0.197

TR etiologies were defined by stepwise classification. Primary TR = structural abnormalities of the tricuspid valve. Left valvular disease related TR = moderate or severe (significant) left-sided valvular disease at baseline, or previous left-sided valvular surgery. LV dysfunction related TR = LV ejection fraction <50%. Pulmonary hypertension related TR = systolic pulmonary artery pressure ≥50 mmHg.
CI = confidence interval; LV = left ventricular; ref = reference; TR = tricuspid regurgitation

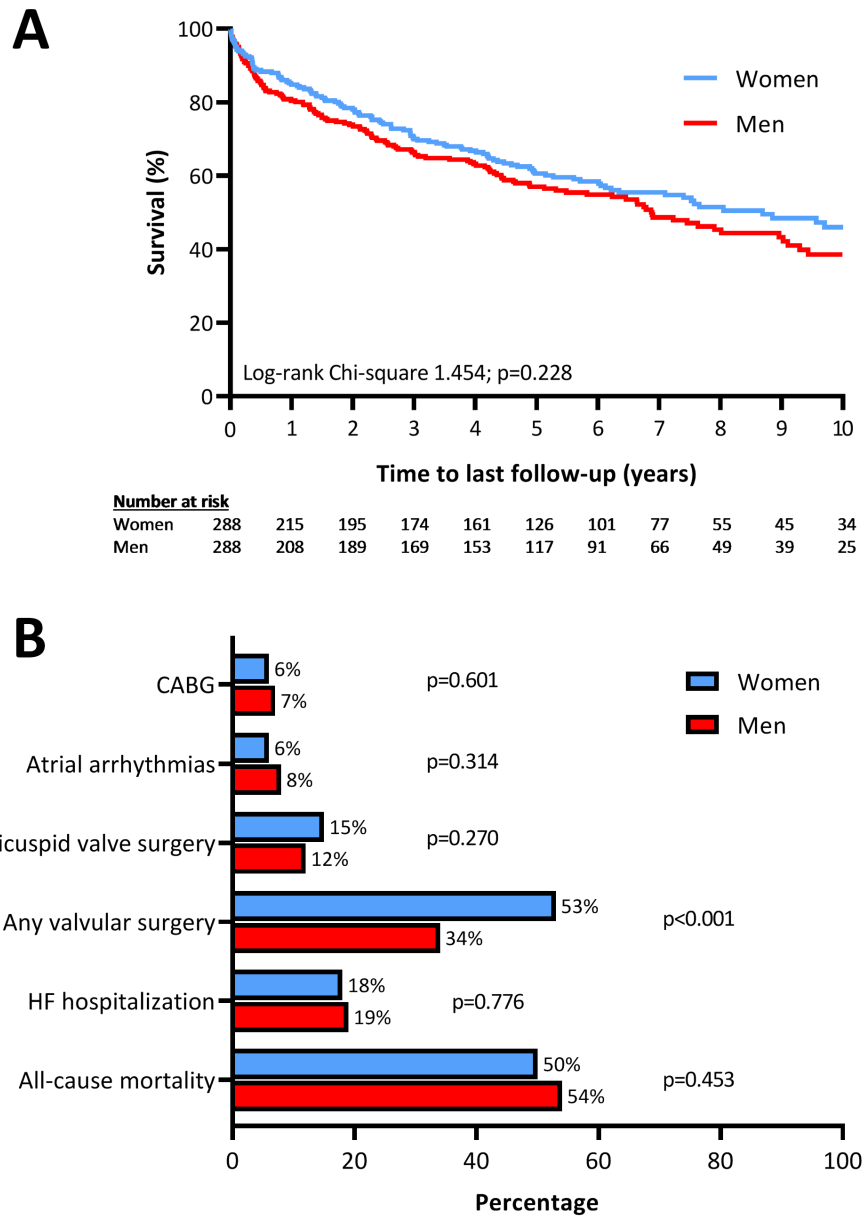

Figure 4. Outcomes according to sex for the propensity score matched population of patients with moderate and severe tricuspid regurgitation

Panel A shows the Kaplan-Meier curves for survival censored for tricuspid valve surgery in men and women. Panel B shows the occurrence of secondary endpoints in men and women during follow-up.

CABG = coronary artery bypass grafting; HF = heart failure

DISCUSSION

In a large cohort of patients with moderate and severe TR, women had more left valvular disease related TR and isolated TR, whereas men had more LV dysfunction related TR. Women had better prognosis in terms of all-cause mortality and hospitalization for heart failure compared to men. However, after matching the patients for clinical and echocardiographic characteristics, sex-specific differences in survival disappeared, while TR etiology remained significantly associated with all-cause mortality.

The distribution of men and women diagnosed with significant TR in the current study was 49% vs. 51%, respectively. These findings are in contrast with the higher prevalence and incidence of TR among women in previous nationwide and community-based studies (1-3). These differences could be explained by the specific patient population referred to a tertiary level hospital in the present study. Similar to the results of a Swedish nationwide hospital-based registry, women presented with significant TR at an older age than men (3). The mechanisms for the sex-specific imbalance in prevalence of TR remain to be investigated.

To date, sex differences in clinical presentation and etiology of TR have not been extensively studied. To the best of our knowledge, the only 2 studies focusing on sex differences in patients with TR were retrospective cohort studies of patients undergoing isolated tricuspid valve surgery (17, 18). As isolated tricuspid valve surgery is only feasible in patients without significant left-sided valve disease and referral is often delayed, the characteristics of these patients will not reflect the overall population of patients with TR and are therefore difficult to compare to our study population (13). However, the sex differences reported in the present study confirmed the results of these studies: men were more likely to have cardiovascular risk factors and coronary artery disease while women more often underwent left valvular surgery (17, 18). No studies to date have compared echocardiographic characteristics between men and women with TR.

In terms of etiology, more women in the current study had TR associated with left valvular disease and isolated TR, while men more often had TR associated with LV dysfunction. A similar sex distribution was demonstrated by Topilsky et al. (1): 63% of patients with left valvular disease related TR and even 72% of patients with isolated TR were women, while only 40% of patients with LV dysfunction related TR were of the female sex. In contrast to the present study, pulmonary hypertension related TR accounted for 23% of the total population with 74% women (1). The studies by Bohbot et al. (8) and Santoro et al. (9) also reported relatively more women in the isolated TR group compared to the other etiologies,

although results from these studies are not comparable to the present study due to different definitions of the etiologies of TR. Interestingly, Santoro et al. (9) found only 17 women in 103 patients with TR in the context of left valvular disease. This may be caused by the inclusion of a different patient population consisting of 249 patients with severe TR of whom only 29.8% were women or due to the method of defining TR etiologies which was based on expert opinion instead of a stepwise categorization.

Previous studies demonstrating the independent prognostic impact of significant TR frequently neglected to report the independent influence of sex on prognosis (4, 5). Nevertheless, Bohbot et al. (8) reported a significant association of the male sex with worse all-cause mortality in 208 patients with moderate and severe TR. Additionally, men with incident TR had a significantly higher risk for mortality compared to women in a large cohort of heart failure patients from the Optum longitudinal database (19). These findings confirm the results of the current study that women had a better prognosis compared to men in the overall population of patients with significant TR.

However, after propensity score matching for known relevant clinical and echocardiographic parameters, sex was no longer associated with prognosis in patients with TR. In contrast, left valvular heart disease related TR and LV dysfunction related TR were still associated with lower survival compared to primary TR. This suggests that the survival benefit in women is confounded by clinical presentation and comorbidities while the categorization in TR etiologies is a relevant prognostic method for risk stratification in both men and women presenting with significant TR in daily clinical practice. These findings confirm and extend the utility of the method to define TR etiologies as proposed by Topilsky et al. (1), who also demonstrated lowest survival in patients with left valvular disease related TR and LV dysfunction related TR in 1.095 patients with significant TR in a community-based setting.

The current study assessed prognosis in patients with significant TR while on medical therapy. Even in our tertiary center, the referral rate for tricuspid valve surgery was as low as 13%. Nevertheless, tricuspid valve surgery may significantly improve prognosis in both men and women (20). Chandrashekar et al. (17) found no differences in in-hospital complications after isolated tricuspid valve surgery between 366 pairs of propensity score matched men and women. Likewise, Pfannmueller et al. (18) demonstrated no sex-specific differences in long-term survival after isolated tricuspid valve surgery in a small population of 92 patients with severe symptomatic TR or active endocarditis. Contrarily, in a subgroup analysis of a case-control study assessing the potential benefit of transcatheter tricuspid valve interventions over medical therapy in 536 propensity matched TR patients,

Taramasso et al. (21) demonstrated a significant reduction of mortality and heart failure hospitalization after transcatheter therapy in men only. Unfortunately, TR etiologies were not examined in this study. It would be interesting to investigate if variation in TR etiology between men and women who underwent transcatheter therapy was the underlying cause of the differences in outcome. As the success of tricuspid valve interventions begins with the appropriate selection of patients, further prospective studies are needed to assess the prognostic benefit of transcatheter and surgical tricuspid valve interventions for men and women and to investigate the importance of etiology-specific approaches in the management of TR.

The limitations of this single tertiary center study are inherent to its retrospective design. Although a careful propensity score analysis was performed, the current study is not a randomized trial and relevant confounders might not be represented in the propensity score model, which could have influenced the results. However, the selected method attempted to provide maximal patient inclusion while keeping sex differences of known confounders statistically and clinically insignificant. Although different methods of defining etiologies of TR have been proposed (8, 9), we chose to follow the stepwise categorization of Topilsky et al. (1) because it was the most well defined approach and its prognostic relevance was determined in a large patient population. However, it is important to acknowledge certain limitations to this method. Firstly, the order of defining TR etiologies strongly influences the distribution. Secondly, the use of cut-off values may over- or underestimate the amount of patients in a certain category. We excluded patients with congenital heart disease as they represent a fundamentally different patient population.

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SUPPLEMENTAL MATERIAL

Supplemental Table S1. Variables used for propensity score matching

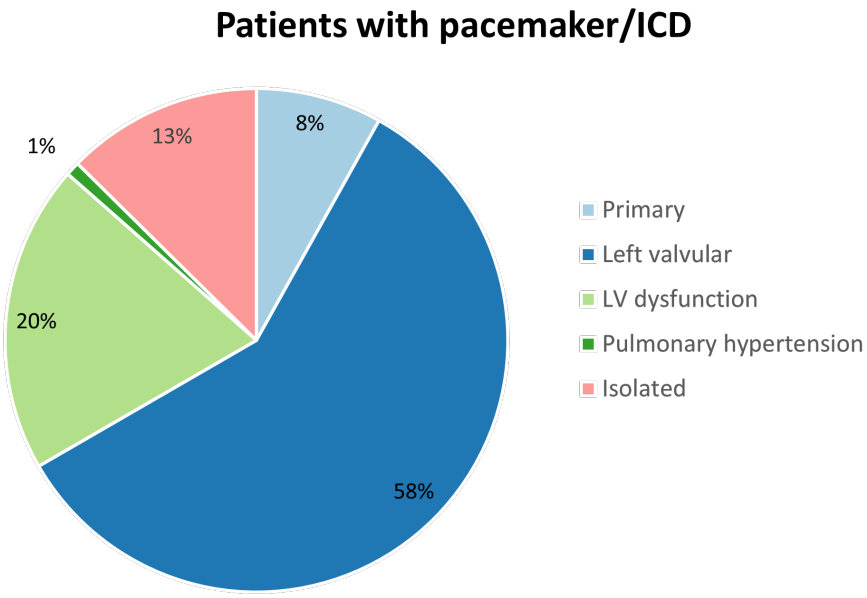
Clinical variables	Echocardiographic variables
Age (years)	LV end diastolic volume (ml/m^2)
Body mass index (kg/m^2)	LV ejection fraction (%)
Hypertension	LA maximum volume (ml/m^2)
Hypercholesterolemia	Significant aortic stenosis
Diabetes mellitus	Significant mitral regurgitation
(Ex-)smoker	RV end diastolic area (mm^2/m^2)
Coronary artery disease	TAPSE (mm)
Atrial fibrillation	sPAP (mmHg)
Pacemaker/ICD	RA maximum area (cm^2/m^2)
Diuretic use	Tricuspid annular diameter (mm/m^2)
eGFR (ml/min/1.73m^2)	

eGFR = estimated glomerular filtration rate; ICD = implantable cardioverter-defibrillator; LA = left atrial; LV = left ventricular; TAPSE = tricuspid annular plane systolic excursion; RA = right atrial; RV = right ventricular; sPAP = systolic pulmonary artery pressure

Supplemental Table S2. Baseline characteristics of the propensity score matched population with moderate and severe tricuspid regurgitation

Variable	Overall (n=576)	Women (n=288)	Men (n=288)	P-value
Age (years)	70 (62-77)	70 (62-78)	70 (62-77)	0.946
Body mass index (kg/m^2)	25 ± 4	25 ± 4	25 ± 4	0.909
Hypertension	465 (81%)	231 (80%)	234 (81%)	0.751
Hypercholesterolemia	294 (51%)	151 (52%)	143 (50%)	0.505
Diabetes mellitus	121 (21%)	61 (21%)	60 (21%)	0.919
(Ex-)smoker	191 (33%)	93 (32%)	98 (34%)	0.658
Coronary artery disease	235 (41%)	119 (41%)	116 (40%)	0.799
Atrial fibrillation	283 (49%)	143 (50%)	140 (49%)	0.803
Pacemaker/ICD	208 (36%)	104 (36%)	104 (36%)	1.000
Oral anticoagulants	338 (59%)	161 (57%)	177 (62%)	0.188
Aspirin	119 (21%)	67 (24%)	52 (18%)	0.127
Betablockers	341 (60%)	169 (59%)	172 (60%)	0.721
ACE-inhibitors	344 (60%)	172 (60%)	172 (60%)	0.959
Aldosterone antagonists	121 (21%)	60 (21%)	61 (21%)	0.918
Calcium antagonists	55 (10%)	30 (11%)	25 (9%)	0.470
Statins	279 (49%)	138 (48%)	141 (49%)	0.802
eGFR (ml/min/1.73m^2)	65 (46-83)	63 (46-83)	66 (47-84)	0.732
Echocardiographic characteristics				
LV end diastolic volume (ml/m^2)	63 (48-89)	60 (47-84)	67 (49-92)	0.163
LV ejection fraction (%)	44 ± 15	44 ± 15	44 ± 15	0.921
LA maximum volume (ml/m^2)	48 (35-67)	48 (36-67)	48 (31-67)	0.518
Significant aortic stenosis	140 (25%)	75 (26%)	65 (23%)	0.331
Significant mitral regurgitation	191 (33%)	102 (35%)	89 (31%)	0.250
RV end diastolic area (cm^2/m^2)	13 (11-16)	13 (11-16)	13 (11-16)	0.166
TAPSE (mm)	15 ± 5	15 ± 5	15 ± 5	0.957
sPAP (mmHg)	41 ± 17	41 ± 17	42 ± 18	0.897
RA maximum area (cm^2/m^2)	15 ± 5	15 ± 6	15 ± 5	0.764
Severe tricuspid regurgitation	149 (26%)	82 (29%)	67 (23%)	0.154
Tricuspid annular diameter (mm/m^2)	23 ± 4	22 ± 4	23 ± 4	0.943
Tricuspid leaflet tenting area (mm^2)	2.0 (0-4.0)	2.0 (0.1-3.7)	2.1 (0-4.7)	0.138
PISA radius (mm)	11 ± 4	11 ± 4	11 ± 4	0.596
EROA (mm^2)	66 (42-101)	63 (40-98)	68 (47-104)	0.249
RVol (mL/beat)	60 (36-99)	60 (34-99)	60 (37-99)	0.928

Values are mean ±SD, median (IQR) or n (%). P-value by unpaired t-test or Mann-Whitney U test for Gaussian and non-Gaussian distributed continuous variables, respectively. P-value by chi-square for categorical variables. ACE = angiotensin converting enzyme; eGFR = estimated glomerular filtration rate; EROA = effective regurgitant orifice area; ICD = implantable cardioverter-defibrillator; IQR = interquartile range; LA = left atrium; LV = left ventricle; PISA = proximal isovelocity surface area; RA = right atrium; RV = right ventricle; RVol = regurgitant volume; SD = standard deviation; sPAP = systolic pulmonary artery pressure; TAPSE = tricuspid annular plane systolic excursion



Supplemental Figure S1. Distribution of tricuspid regurgitation etiologies in a subpopulation of patients with pacemaker or implantable cardioverter defibrillator

ICD = implantable cardioverter defibrillator; LV = left ventricular