Characterization of tricuspid regurgitation and its prognostic implications

Dietz, M.F.

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Marlieke F. Dietz

Colophon

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Wherever you go, go with all your heart.

Confucius, 551-479 BC

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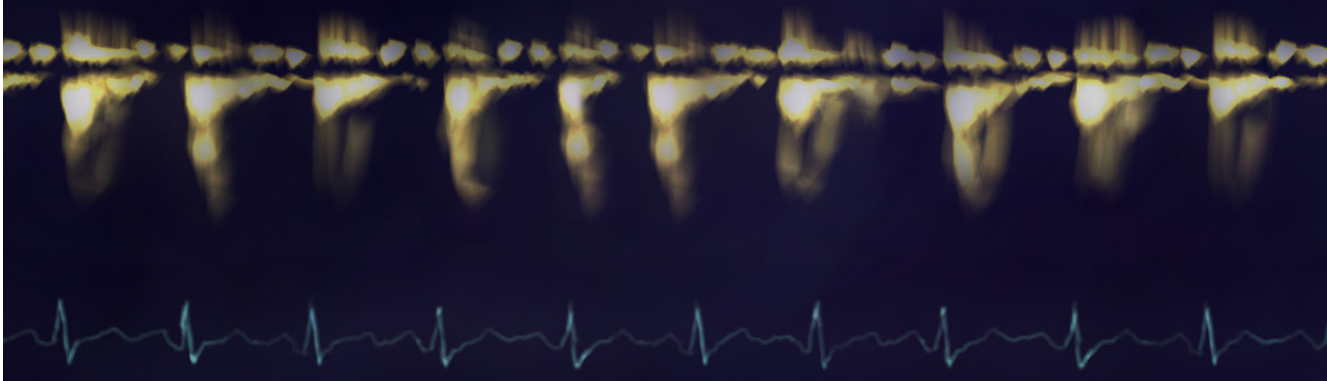
Chapter 1

General introduction and outline of the thesis



1

GENERAL INTRODUCTION

The tricuspid valve is often referred to as 'the forgotten valve', since it was virtually ignored by clinicians until the beginning of the 21st century. Known for much longer, tricuspid regurgitation – a disorder in which the tricuspid valve does not close properly, causing backward flow of blood - was first described by T.W. King in 1837. He found that distention of the right ventricle with water often caused substantial reflux through the tricuspid valve, while a similar procedure in the left ventricle would leave the mitral valve firmly closed (1). The conclusion that the tricuspid valve was physiologically weak to form a safety valve for the right ventricle was generally accepted, and for a long time tricuspid regurgitation was neglected while treatment for left valvular heart disease evolved (2). Unfortunately, tricuspid regurgitation has recently been demonstrated to be less harmless than had been thought. In 2004, Nath et al. (3) demonstrated that increasing tricuspid regurgitation severity was associated with worse survival in a large cohort of 5,507 war veterans. These results initiated extensive research, which has led to improved knowledge on the tricuspid valve and tricuspid regurgitation in the past two decades.

Tricuspid valve anatomy

Situated between the right atrium and right ventricle, the tricuspid valve is the largest of the heart valves with an anatomical area of 4-6cm^2 (4). Its structure consists of the tricuspid annulus, the 3 leaflets, the chordae and the papillary muscles. The function of the valve depends on the cohesion and coordination of all these components.

A normal tricuspid annulus has a highly dynamic shape with changes in area exceeding 20% during the cardiac cycle, thus facilitating passive transfer of blood from the atrium to the ventricle (5, 6). This flexibility is enabled by the little fibrous tissue or collagen along the right ventricular free wall, which also causes it to be sensitive to dilation of the base of the right ventricle or the right atrium. The resulting tricuspid annular dilation may impede leaflet coaptation and therefore cause tricuspid regurgitation (6).

The 3 leaflets of the tricuspid valve (anterior, posterior and septal) are attached to the right ventricular free wall and the interventricular septum through chordae and papillary muscles. The septal and posterior leaflets are directly attached to the interventricular septum or to multiple small septal papillary muscles, as well as to the posterior papillary muscle. The large anterior papillary muscle is attached to the right ventricular free wall and supplies chordae to the anterior and posterior leaflets. In case of dilation of the right

ventricle, stretching of the papillary muscles and chordae may cause leaflet tethering and subsequent tricuspid regurgitation due to reduced leaflet coaptation (6, 7).

Mechanisms of tricuspid regurgitation

Tricuspid regurgitation is a heterogeneous disease which can be classified based on the underlying mechanism. Approximately 8-10% of all tricuspid regurgitation is primary, characterized by the presence of a primary abnormality of the tricuspid valve structure (8). Etiologies of primary tricuspid regurgitation include Ebstein's disease, infective endocarditis, valve prolapse, tumor, trauma and acute rheumatic disease.

The large majority of tricuspid regurgitation is secondary to conditions that cause tricuspid annulus dilation or leaflet tethering due to right ventricular or right atrial dilation, while the tricuspid valve apparatus is not primarily diseased (Figure 1). The conditions that can cause secondary tricuspid regurgitation are various and include left-sided valvular disease, myocardial disease associated with elevated left atrial pressures and pulmonary hypertension. All of these diseases cause right ventricular pressure overload. The right ventricle responds with myocardial hypertrophy and dilation to increase right ventricular preload and therefore maintain right ventricular systolic function (Frank-Starling law). However, as described in the previous paragraph, dilation of the right ventricle may lead to tricuspid annulus dilation and leaflet tethering which causes tricuspid regurgitation. The reflux of blood and volume overload induced by the tricuspid regurgitation leads to further right ventricular and atrial dilation, which worsens the existing tricuspid regurgitation due to further tricuspid annulus dilation and leaflet tethering in a vicious circle. Right ventricular dilation may eventually lead to right ventricular dysfunction (9, 10).

A type of secondary tricuspid regurgitation that is increasingly recognized as a separate entity is isolated tricuspid regurgitation, accounting for 6-10% of all significant (moderate or severe) tricuspid regurgitation (8, 11, 12). This form of tricuspid regurgitation differs from the above mentioned types of secondary tricuspid regurgitation by the absence of concomitant left-sided heart diseases or pulmonary hypertension. While the left-sided heart disease related types of tricuspid regurgitation have more prominent right ventricular dilation and tricuspid leaflet tethering, isolated tricuspid regurgitation mainly results from right atrial and tricuspid annulus dilation, as the right ventricular afterload is normal in these patients. Isolated tricuspid regurgitation is frequently associated with older age, the female sex and atrial fibrillation (13, 14). Because longstanding atrial fibrillation leads to right atrial enlargement and subsequent tricuspid annular dilation, various studies have suggested atrial fibrillation to be a major cause of isolated tricuspid regurgitation (15, 16). Nevertheless, atrial fibrillation and isolated significant tricuspid

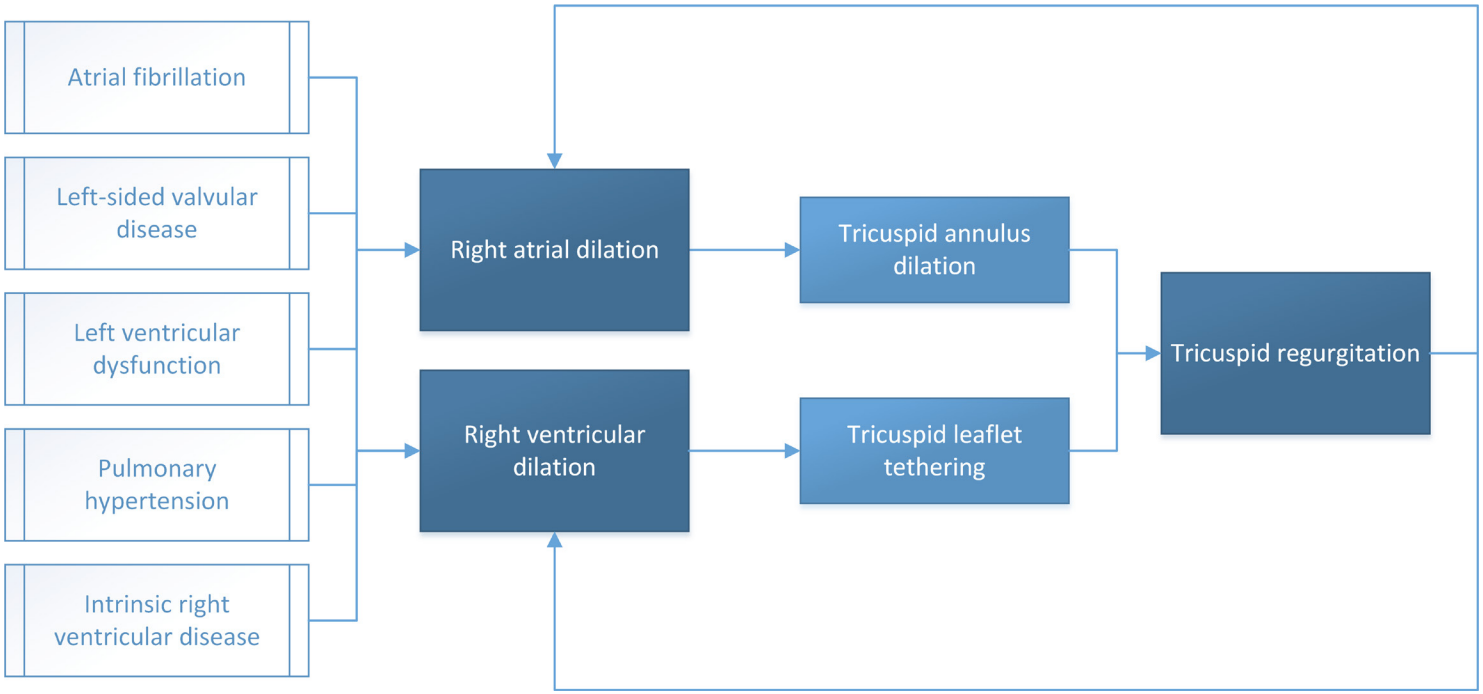


Figure 1. Mechanisms of secondary tricuspid regurgitation

regurgitation do not always coexist and other mechanisms such as a fibrous skeleton of the tricuspid annulus with less structural integrity or senescent annular degeneration may contribute to the development of isolated TR (14, 17).

Presentation and evaluation of tricuspid regurgitation

Tricuspid regurgitation is a relatively common disease, with an estimated prevalence of moderate and severe tricuspid regurgitation of 0.5-0.8% in the general population, which increases with age (11, 18). The prevalence of concomitant tricuspid regurgitation in patients with mitral valve disease is >30% (19, 20). Mild tricuspid regurgitation is far more widespread in the general population (65-80%), but as mild tricuspid regurgitation is well tolerated and patients often remain completely asymptomatic in early stages of the disease, these patients often stay unnoticed (4). When tricuspid regurgitation severity progresses, morphological changes of not only the tricuspid valve, but of the complete right heart are related to the onset of symptoms: patients present with right heart failure. Right heart failure is a clinical diagnosis characterized by reduced exercise capacity and/or signs of right-sided decompensation in combination with structural and/or functional abnormalities of the right heart (21, 22). A decrease in cardiac output due to a leftward shift of the interventricular septum because of volume overload of the right ventricle is responsible for complaints of fatigue, exertional dyspnea and decreased functional capacity (21). Signs of right-sided decompensation are peripheral edema, abdominal fullness, congestive hepatomegaly and ascites. In the late stages of tricuspid regurgitation, severe venous congestion can lead to liver and renal dysfunction (23-25). Rarely, a holosystolic murmur can be heard upon physical examination (4).

Patients with tricuspid regurgitation can be evaluated with various non-invasive imaging techniques: 2-dimensional and 3-dimensional transthoracic or transesophageal echocardiography, magnetic resonance imaging, and computed tomography imaging. Currently, transthoracic 2-dimensional echocardiography is the technique of choice for the initial evaluation of the etiology and the severity of tricuspid regurgitation, and therefore used in the current thesis (Figure 2). As described in the current recommendations, tricuspid regurgitation can be graded as none/trivial, mild, moderate and severe by a multiparametric, integrative approach based qualitative, semiquantitative and quantitative color Doppler flow data, continuous-wave Doppler data of the regurgitant jet, and assessment of the right atrial and right ventricular dimensions (26, 27). As the pathophysiology of tricuspid regurgitation involves a complex interaction between the tricuspid valve, the right side of the heart and the pulmonary vasculature, echocardiographic evaluation of tricuspid regurgitation should not only include grading the

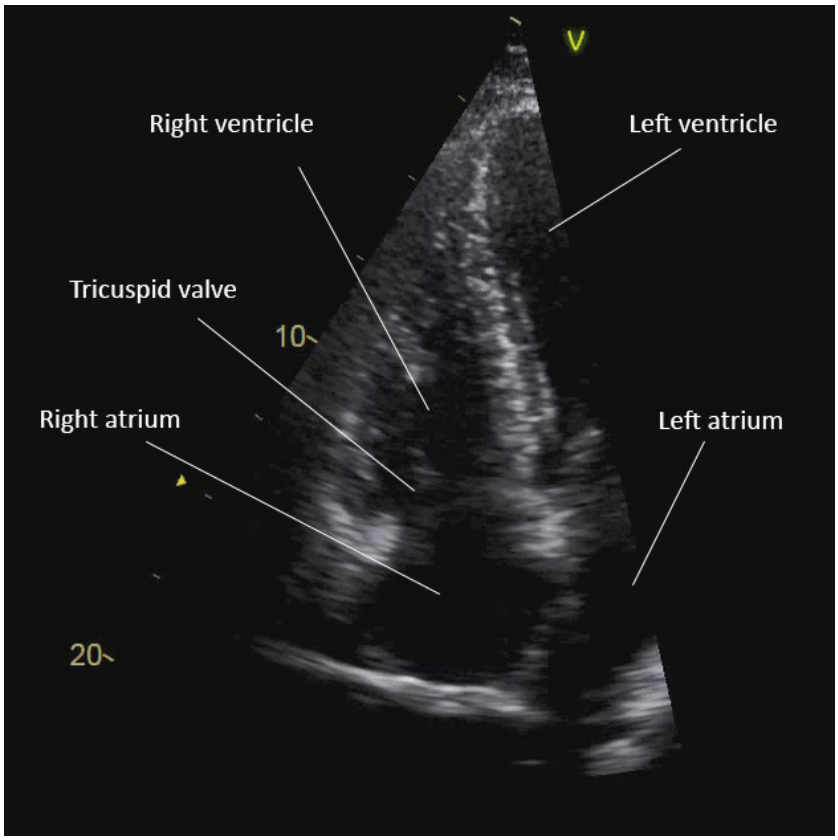


Figure 2. Visualization of the right heart and the tricuspid valve on a right ventricle-focused apical 4-chamber view on 2-dimensional transthoracic echocardiography

severity, but also visualizing the tricuspid annulus and leaflets, assessing right ventricular size and function, and estimating right atrial filling pressures.

Certain limitations in the assessment of tricuspid regurgitation by 2-dimensional transthoracic echocardiography should be considered. Identifying the leaflets of such a complex 3-dimensional structure with strong anatomical variations is challenging on transthoracic echocardiography. In case of poor quality views or endocarditis, transesophageal echocardiography may be required to better visualize the tricuspid leaflets. Transesophageal echocardiographic imaging also plays an essential role in guiding transcatheter interventions. Furthermore, 2-dimensional transthoracic echocardiography may underestimate the tricuspid annulus diameter (28) and vena contracta area (29). Use of 3-dimensional echocardiography and computed tomography may allow more accurate

measurements of the tricuspid annular shape, size, and function (6). Integration of cardiac magnetic resonance imaging, as gold standard to assess right ventricular morphology and function, may likewise be of additive value in the evaluation of tricuspid regurgitation (4).

Natural history of tricuspid regurgitation

Trivial or mild tricuspid regurgitation, usually regarded as benign, may progress into significant (moderate or severe) tricuspid regurgitation over time due to the vicious circle of volume overload that enhances right ventricular dilation and dysfunction, which again worsens the tricuspid regurgitation. Factors associated with a fast development of significant tricuspid regurgitation are older age, the presence of a pacemaker or defibrillator lead, right ventricular dilation and dysfunction and left-sided valve surgery without concomitant tricuspid surgery (30). If left untreated, tricuspid regurgitation is independently associated with increased mortality, as was demonstrated by several natural history studies (3, 31). However, prognosis of patients with tricuspid regurgitation is confounded by the etiology of tricuspid regurgitation and the patient's comorbidities and hemodynamic profile. Some even claim that secondary tricuspid regurgitation, in the context of other cardiac diseases, is not the cause of worse prognosis, but a surrogate for the associated comorbidities (32). Right ventricular dilation and dysfunction are also thought to play an important role in outcome of patients with secondary tricuspid regurgitation, but results in various patient populations have been inconsistent (25, 33, 34).

Isolated tricuspid regurgitation has a better prognosis compared to other types of secondary tricuspid regurgitation, due to the lack of left-sided cardiac comorbidities (11). Nevertheless, even isolated tricuspid regurgitation seems to adversely impact prognosis, although studies are scarce and significant variation in the definition of isolated TR challenge the interpretation of discrepant results (35-37).

Regarding primary tricuspid regurgitation, Messika-Zeitoun et al. (38) demonstrated an excess of mortality and morbidity in patients with significant tricuspid regurgitation caused by flail leaflets, which could be improved by surgical treatment.

Treatment of tricuspid regurgitation

Conservative treatment of tricuspid regurgitation includes optimization of right ventricular preload and afterload and targeting the underlying etiology (39). Although diuretic use may improve symptoms and reduce right heart failure hospitalizations, it is unclear if they alter the progression of tricuspid regurgitation and improve survival of patients (12, 40). Therefore, tricuspid valve surgery is the designated therapy for tricuspid regurgitation.

However, less than 5% of patients with severe tricuspid regurgitation are estimated to receive surgical intervention (41, 42). This low referral rate is most probably caused by lack of clear guidelines, a paucity of supportive data and reported in-hospital mortality rates for isolated tricuspid valve surgery as high as 8.8% (6, 12, 43). Nevertheless, European and American guidelines for the management of tricuspid regurgitation agree that severe tricuspid regurgitation should be treated at the time of left-sided heart valve surgery (class IC indication – level of evidence C) (39, 44). Even mild or moderate tricuspid regurgitation in the presence of a tricuspid annulus of >40mm should be considered to treat during left-sided heart valve surgery (class IIA indication - level of evidence B/C) (39, 44). This recommendation is based on data that concomitant preventative tricuspid valve surgery at the time of mitral valve surgery may prevent the development of significant tricuspid regurgitation and improve clinical outcome, although long-term outcome data are lacking (45-47).

Indications for isolated tricuspid valve surgery are even less well supported by the literature (class IIB indications – level of evidence C). The decision to intervene in tricuspid regurgitation patients that do not require left-sided heart valve surgery mostly depends on the presence of right ventricular dilation and dysfunction and the presence of symptoms of right heart failure (44). Current guidelines advise to intervene before the development of severe right ventricular dysfunction. However, the paucity of supportive data and high in-hospital mortality rates leads to significant delay in referral by clinicians, even though recent studies have shown that an acceptable mortality rate can be reached in patients without RV dysfunction or pulmonary hypertension (48). Axtell et al. (49) showed that 72% of patients with tricuspid regurgitation had evidence of right heart failure at the time of diagnosis, but that more than a quarter experienced a delay of more than a year before surgical referral.

Transcatheter therapies are currently being investigated as alternatives to surgical approaches in high-risk patients. Early outcome data provide some insight into the feasibility, safety, and efficacy of a variety of devices for percutaneous tricuspid valve replacement or repair (50-52). Although the results of these prospective trials are promising, they also demonstrate that defining the appropriate patient population for each transcatheter device as to achieve procedural success remains a challenge. Ongoing and future clinical research are of utmost importance to refine our understanding of the pathophysiology, progression, and prognostic impact of tricuspid regurgitation in order to optimize timing of surgery or transcatheter intervention and improve outcome in these patients.

OBJECTIVE AND OUTLINE OF THIS THESIS

The aim of this thesis is to provide new insights in the characterization of tricuspid regurgitation and its clinical and prognostic implications. Part I of the thesis focusses on the relationship between secondary tricuspid regurgitation and the right ventricle. In chapter 2, the relation between right ventricular remodeling and survival in patients with significant secondary tricuspid regurgitation is assessed. Chapter 3 demonstrates the prognostic impact of a staging system for right heart failure, which combines right ventricular dysfunction with clinical signs of right heart failure, in patients with significant secondary tricuspid regurgitation. Chapter 4 evaluates the long-term impact of concomitant preventative tricuspid valve annuloplasty at the time of mitral valve annuloplasty on right ventricular remodeling in patients with primary mitral regurgitation.

Part II is designated to various types of tricuspid regurgitation in specific patient populations. In chapter 5, the prognostic impact of significant isolated tricuspid regurgitation in patients with atrial fibrillation is investigated. Chapter 6 reports on differences between men and women in the etiology and prognosis of significant tricuspid regurgitation. Chapter 7 provides more insight in the impact of increased body mass index on right ventricular remodeling and prognosis in patients with significant tricuspid regurgitation.

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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

Marlieke F Dietz, MD; Edgard A Prihadi, MD; Pieter van der Bijl, MBChB, MMed; Laurien Goedemans, MD; Bart JA Mertens, PhD; Erhan Gursoy, MD; Olton van Genderen, BSc; Nina Ajmone Marsan, MD; Victoria Delgado, MD; Jeroen J Bax, MD

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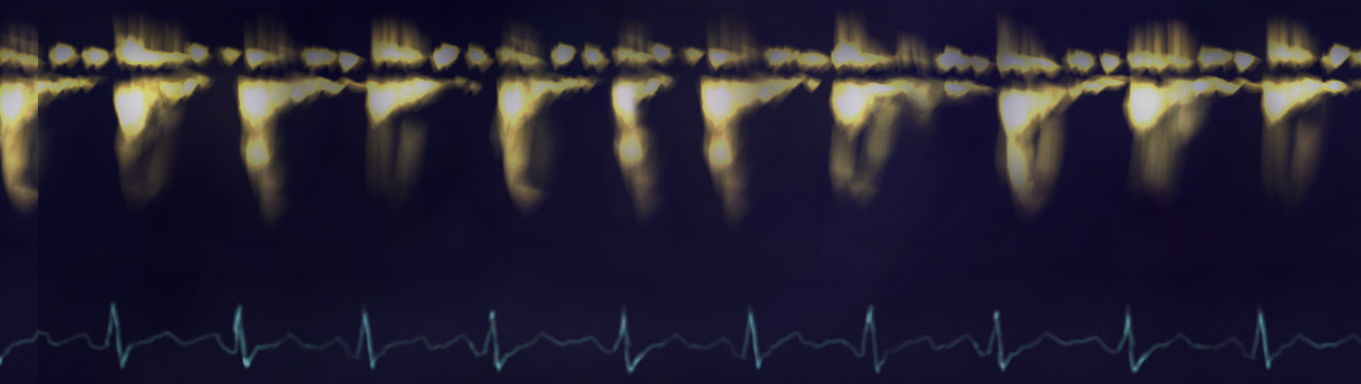


ABSTRACT

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

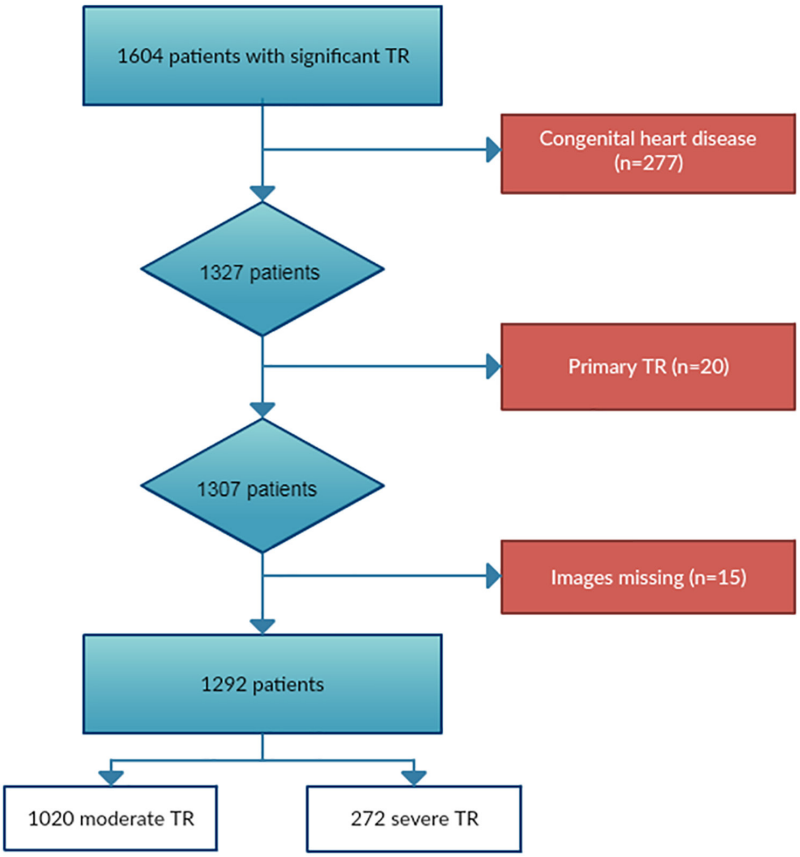


Figure 1. Flowchart of inclusion of patients with significant secondary tricuspid regurgitation
TR = tricuspid regurgitation

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).

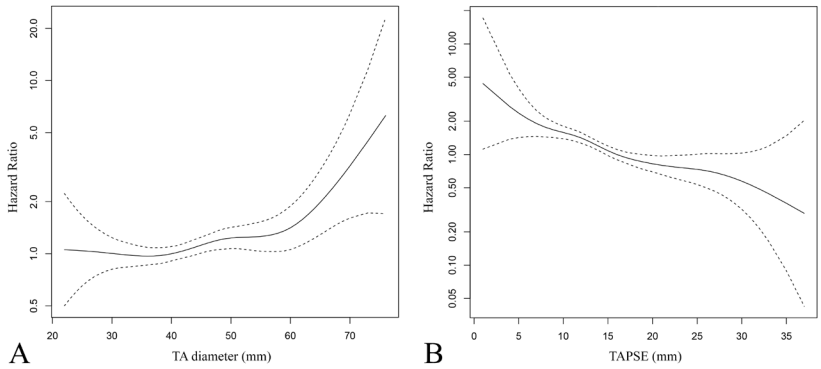


Figure 2. Spline curves for TA diameter and TAPSE vs. all-cause mortality

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

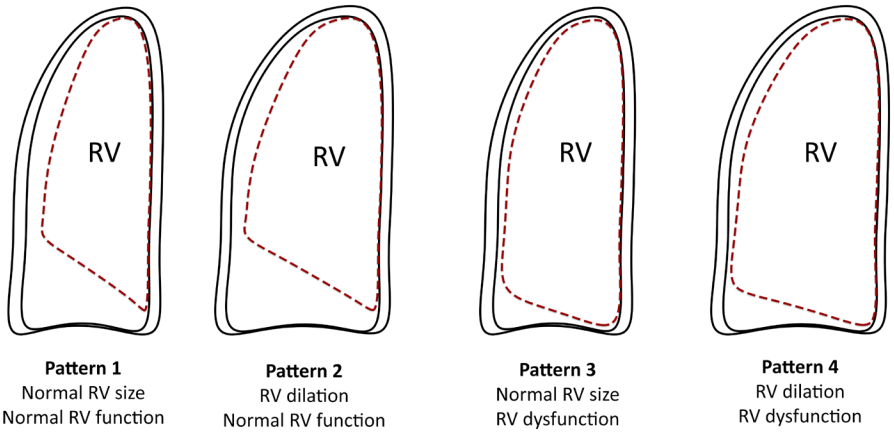


Figure 3. RV remodeling patterns as defined with the cut-off values derived from the spline curves of TA diameter and TAPSE vs. all-cause mortality

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

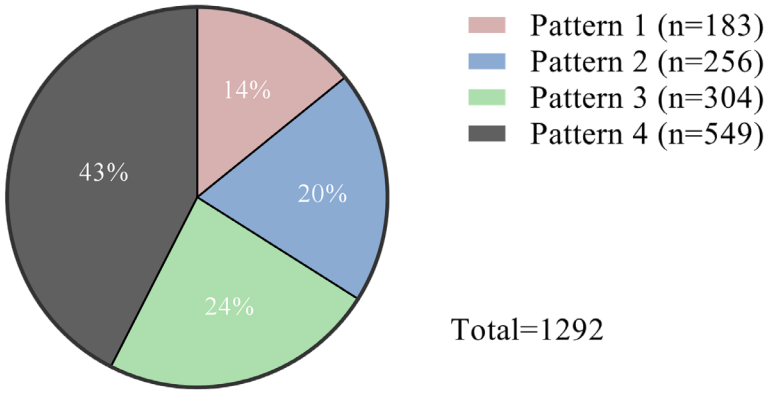


Figure 4. Distribution of right ventricular remodeling patterns in patients with significant secondary tricuspid regurgitation

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

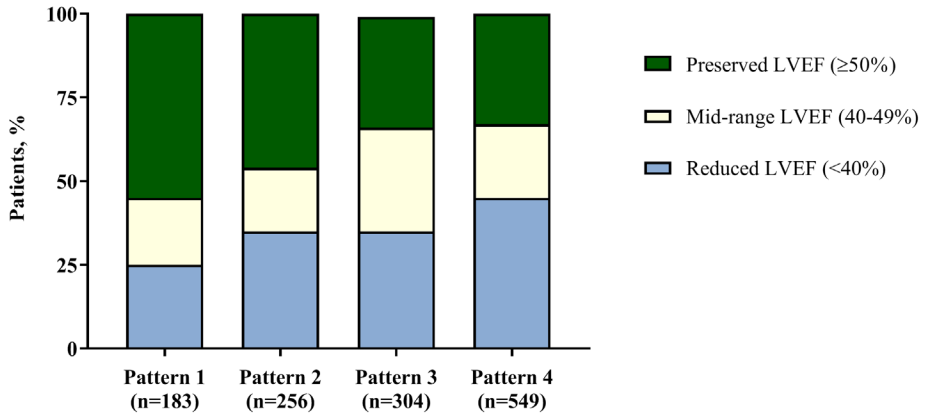


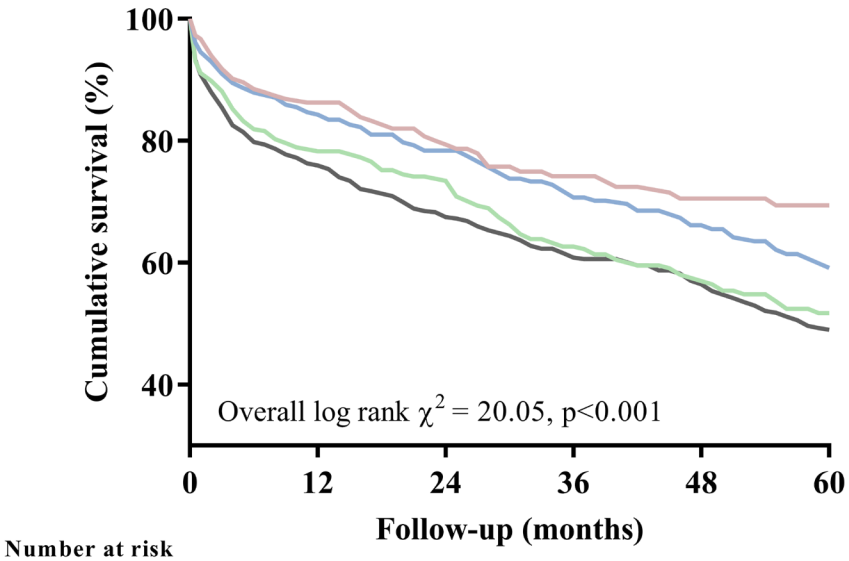
Figure 5. Association between left ventricular ejection fraction and patterns of right ventricular remodeling
LVEF = left ventricular ejection fraction

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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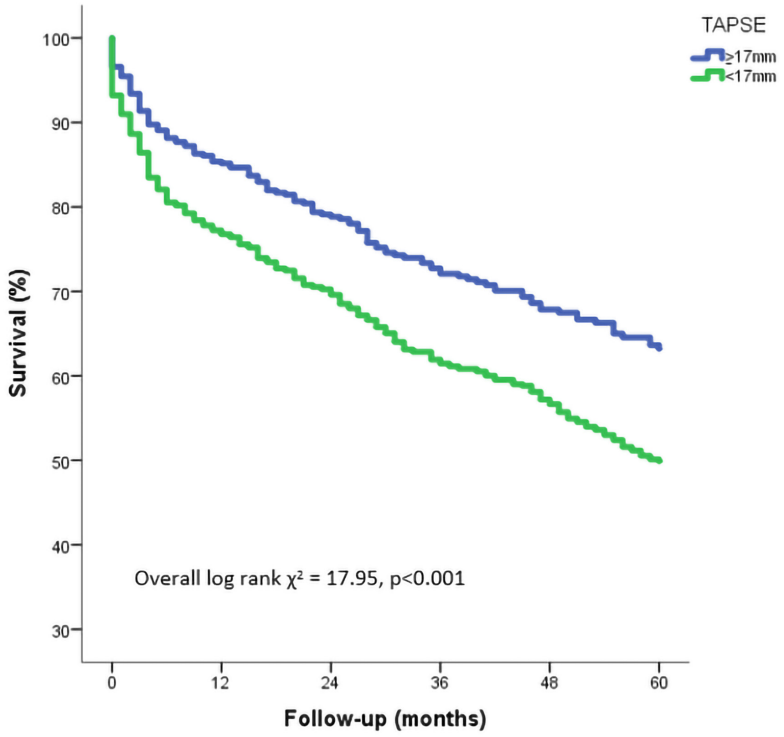
SUPPLEMENTAL MATERIAL



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

Chapter 3

Prognostic implications of staging right heart failure in patients with significant secondary tricuspid regurgitation

Marlieke F Dietz, MD; Edgard A Prihadi, MD; Pieter van der Bijl, MBChB, MMed; Nina Ajmone Marsan, MD; Victoria Delgado, MD; Jeroen J Bax, MD

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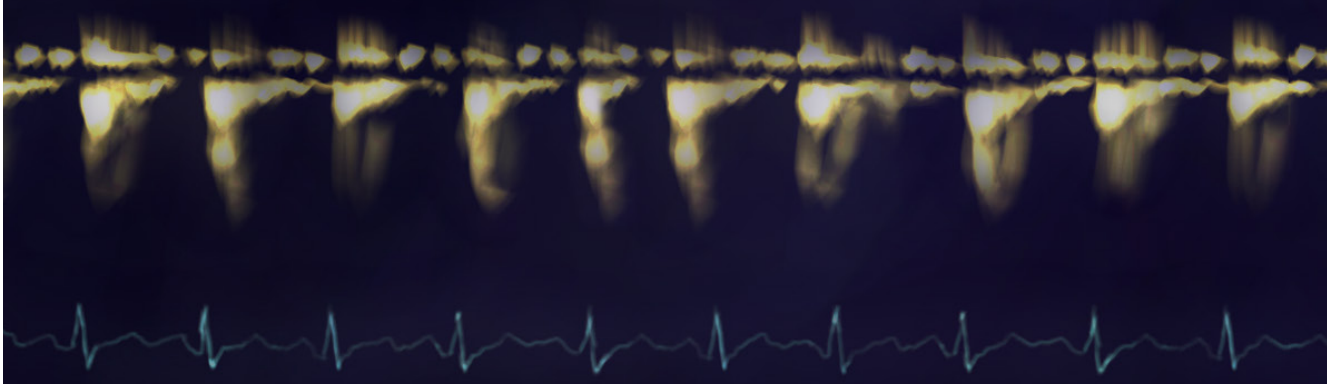


ABSTRACT

Objective: We aimed to evaluate the prognostic value of staging right heart failure (RHF) in patients with significant secondary tricuspid regurgitation (TR).

Background: Right ventricular dysfunction (RVD, defined as tricuspid annular plane systolic excursion <17mm) and clinical signs of RHF (defined as NYHA≥II, edema or use of diuretics) do not always coincide in patients with significant secondary TR and may have different prognostic implications.

Methods: A total of 1311 patients with significant secondary TR (median age 71 (62-78), 50% male) were classified into 4 RHF stages according to the presence or absence of RVD and clinical signs of RHF: stage 1) no RVD, no signs of RHF; stage 2) RVD, but no signs of RHF; stage 3) RVD, and signs of RHF; stage 4) RVD, and refractory signs of RHF at rest. Five-year mortality rates were compared across the 4 stages of RHF and the independent associates of mortality were identified using multivariable Cox proportional hazards models.

Results: One hundred one (8%) patients were classified as stage 1, 124 (10%) as stage 2, 683 (52%) as stage 3 and 403 (31%) as stage 4. Patients in higher stages of RHF had more comorbidities and worse renal and left ventricular systolic function. Cumulative 5-year survival was 54%. Stages 3 and 4 of RHF were independently associated with increased mortality compared to stage 1 (Hazard Ratio 2.110 (1.163-3.828) and 3.318 (1.795-6.133), respectively).

Conclusion: In patients with significant secondary TR, higher stages of RHF are independently associated with all-cause mortality at long-term follow-up.

INTRODUCTION

In heart failure patients, evaluating the presence of symptoms and signs of right heart failure (RHF) is key in decision making and risk stratification. RHF is a clinical diagnosis characterized by reduced exercise capacity and/or signs of right-sided decompensation (1). Comparable to left heart failure, RHF is a progressive disease that can be classified into stages (2, 3). Based on the staging system for left heart failure, a similar staging system that combines right ventricular (RV) dysfunction and clinical signs of RHF was proposed by Haddad et al. (3) and adapted by Gorter et al. (1). This staging system recognizes the progressive nature of the disease in the presence of established risk factors such as tricuspid regurgitation (TR). Significant (moderate and severe) TR is often associated with RV remodeling and dysfunction due to volume overload. Recent studies have demonstrated the independent prognostic influence of RV dysfunction in patients with significant TR (4). However, the prognostic impact of staging RHF in patients with secondary TR is unknown. Accordingly, we evaluated the impact of staging RHF on survival of patients with significant secondary TR.

METHODS

Study population and design

The data that support the findings of this study are available upon reasonable request to the corresponding author. Patients diagnosed with significant TR between June 1995 and September 2016 were identified from the departmental echocardiographic database of the Leiden University Medical Center (Leiden, the Netherlands). Significant TR was defined as moderate and severe TR, measured by an integrative approach using qualitative, semi-quantitative and quantitative echocardiographic parameters of the regurgitant jet, tricuspid valve morphology, right atrial and RV dimensions, as recommended by the current guidelines (5). Patients with congenital heart disease, primary TR or previous surgery of the tricuspid valve were excluded from the analysis.

Based on the staging system for RHF as proposed by Haddad et al. (3), patients were divided into 4 groups of progressive disease according to the presence or absence of RV dysfunction in combination with clinical signs of RHF. RV dysfunction was evaluated by transthoracic echocardiography and defined as a tricuspid annular plane systolic excursion (TAPSE) of <17mm (6). Clinical signs of RHF included New York Heart Association (NYHA) functional class >II, use of diuretics and the presence of peripheral edema.

Transthoracic echocardiograms were analyzed and demographic and clinical data were retrospectively retrieved from the departmental Cardiology Information System (EPD-Vision; Leiden University Medical Center, Leiden, the Netherlands). The study endpoint was all-cause mortality. Outcome was analyzed from time of first diagnosis of significant secondary TR until death or last follow-up to August 2017. Date of death for all patients was ascertained from the departmental Cardiology Information System and the Social Security Death Index. In addition, the prevalence of tricuspid valve surgery during follow-up was evaluated. The institutional review board of the Leiden University Medical Center approved the observational design and retrospective analysis of clinically acquired data. For retrospective analysis of anonymized clinically acquired data, the need for written informed consent was waived.

Clinical and echocardiographic variables

Baseline data included demographic, clinical and echocardiographic characteristics at the time of first diagnosis of significant TR by transthoracic echocardiography. Demographic characteristics included age, sex and body surface area. Clinical variables comprised cardiovascular risk factors (hypertension, hypercholesterolemia, diabetes mellitus, smoking habit), relevant medical history and comorbidity (coronary artery disease, chronic kidney disease, pacemaker or implantable cardioverter defibrillator [ICD], atrial fibrillation, chronic obstructive pulmonary disease), clinical signs of RHF (dyspnea, peripheral edema, NYHA functional class), medication (aspirin, beta-blocker, angiotensin-converting enzyme [ACE] inhibitor, aldosterone antagonist, statin, diuretic) and biochemical analysis (hemoglobin, creatinine, urea, bilirubin). Significant coronary artery disease was defined as previous myocardial infarction or >70% stenosis of a coronary artery on invasive coronary angiography.

Transthoracic echocardiographic data were obtained in a standard manner using the available equipment (Vivid 7 and E9 systems; GE-Vingmed, Horton, Norway). All images were digitally stored for offline analysis (EchoPAC version 113.0.3 and 202; GE-Vingmed, Horten, Norway). The evaluation included M-mode, 2-dimensional and color, continuous and pulsed wave Doppler data, obtained during the same examination on multiple windows, following current recommendations (5, 7, 8). Left ventricular (LV) ejection fraction was derived from LV volumes measured on apical 2- and 4-chamber views with the Simpson's method (6). Left atrial volume was measured at end-systole on the apical 4-chamber view and normalized for BSA (6). Aortic and mitral valve function was based on qualitative, semi-quantitative and quantitative parameters evaluated on color, continuous and pulsed wave Doppler data and graded according to current recommendations (5, 8,

9). Right atrial and RV dimensions as well as the tricuspid annular end-diastolic diameter were measured on a RV focused apical 4-chamber view and RV function was evaluated by TAPSE, measured by M-mode as the total displacement of the tricuspid annulus from end-diastole to end-systole. In addition, RV end-systolic and end-diastolic areas were traced and RV fractional area change (FAC) was derived (6). As recommended by current guidelines, TR severity was measured by an integrative assessment of the valve using qualitative, semi-quantitative and quantitative approaches (8). Tricuspid valve tenting height and area were measured at mid-systole. Systolic pulmonary artery pressures were estimated by Doppler echocardiography recording the tricuspid regurgitant jet peak velocity from any view with continuous wave Doppler (modified Bernoulli equation) (7).

Stages of right heart failure

The development of RHF was classified into 4 progressive stages of disease as proposed by Haddad et al. (3) (Figure 1). Patients categorized as being in stage 1 are at risk for RHF without RV dysfunction or symptoms of RHF (defined as TAPSE ≥17 mm, NYHA class I, no peripheral edema and no use of diuretics). Stage 2 includes patients with RV dysfunction, but without symptoms of RHF (defined as TAPSE <17 mm, NYHA class I, no peripheral

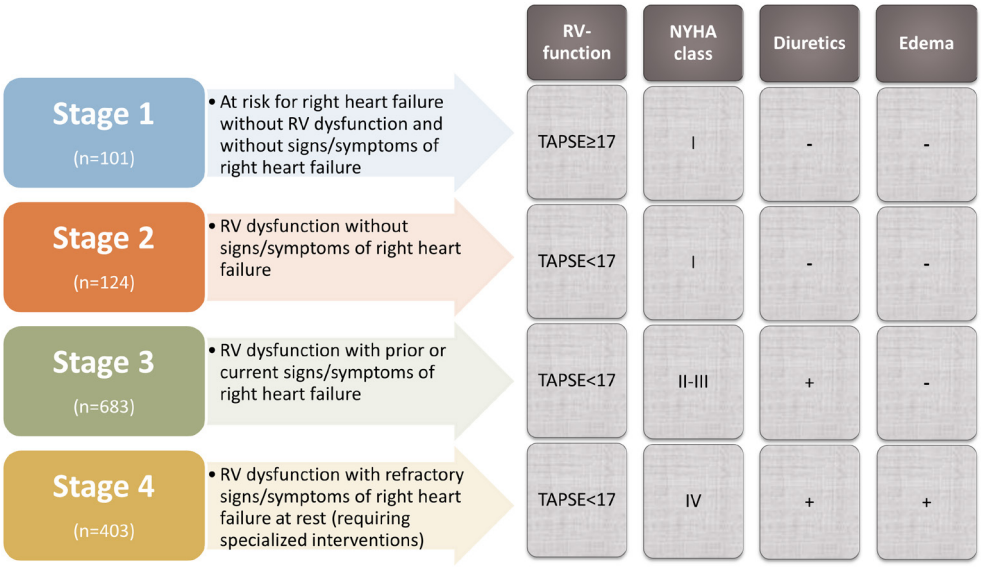


Figure 1. Stages of right heart failure defined by clinical and echocardiographic variables

NYHA = New York Heart Association; RV = right ventricular; TAPSE = tricuspid annular plane systolic excursion

edema and no use of diuretics). Stage 3 includes patients with RV dysfunction and prior or current symptoms of RHF (defined as TAPSE <17 mm, NYHA class II-III, no peripheral edema with use of diuretics) and stage 4 comprises patients with RV dysfunction and refractory signs of RHF or symptoms at rest (defined as TAPSE <17 mm, NYHA class IV, peripheral edema despite the use of diuretics). Patients were classified according to the parameter that defined the highest stage.

Statistical analysis

Continuous variables with Gaussian distribution are summarized as mean ± standard deviation and were compared using the one-way analysis of variance (ANOVA). Continuous variables without a Gaussian distribution are presented as median (interquartile range [IQR]) and were compared using the Kruskal-Wallis test. Categorical variables are expressed as numbers and percentages and differences between groups were analyzed using the Pearson's chi-square test. Multiple comparisons of continuous variables were tested with Bonferroni correction. Long-term survival rates were calculated according to the Kaplan-Meier method and differences between groups were compared by means of the log-rank test. A multivariable Cox proportional hazards regression analysis was performed to identify parameters independently associated with all-cause mortality. The entry criteria for the multivariable regression analysis were a significant correlation in univariable analysis ($p<0.05$) and the amount of missing values not exceeding 10% of the total study population. In addition, correlation factor analysis was used to determine if any pairs of variables were correlated. No collinearity (correlation coefficient >0.7) was detected for the variables that met the entry criteria for multivariable regression analysis. Variables with missing data exceeding 10% were not included (BSA, hemoglobin, urea and bilirubin levels, E/A ratio, left atrial volume and significant aortic stenosis). Hazards ratios (HR) and 95% confidence intervals (CI) were calculated. All p-values were two-sided and values <0.05 were considered significant. All data were analyzed using SPSS for Windows, version 23 (SPSS Inc, Armonk, NY:IBM Corp).

RESULTS

Distribution of RHF stages

A total of 1311 patients with significant secondary TR (median age 71 years [IQR 62-78], 50% male) were included in the analysis. At the time of first diagnosis of significant TR on echocardiography, 101 patients (8%) were in stage 1 (at risk), 124 patients (10%) were in stage 2 (RV dysfunction without clinical symptoms of RHF), 683 patients (52%) were in stage 3 (RV dysfunction with symptoms of RHF) and 403 patients (31%) were in stage 4 (RV dysfunction with refractory signs of RHF) (Figure 2). Patients with severe TR on

echocardiography (N=276; 21%) presented with more advanced stages of RHF compared to patients with moderate TR (37% in stage 4 vs 29%, respectively; p=0.027; Figure 2).

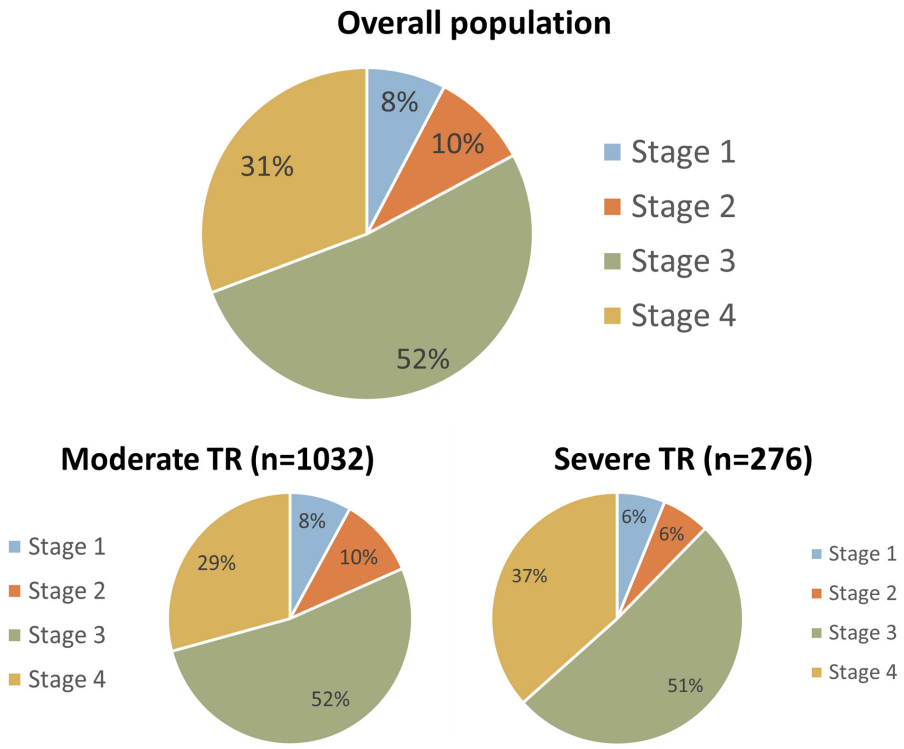


Figure 2. Distribution of patients with significant secondary tricuspid regurgitation across stages of right heart failure for the overall population and according to severity of tricuspid regurgitation

TR = tricuspid regurgitation

Clinical characteristics

Clinical characteristics of the overall population, stratified according to RHF stage are presented in Table 1. Most patients had hypertension (81%) and 521 patients (40%) had a history of coronary artery disease, of whom 300 had a previous myocardial infarction. Half of the patients (50%) had atrial fibrillation and 471 (37%) had a pacemaker or ICD. Almost two thirds of the patients used beta-blockers, ACE-inhibitors and diuretics at the time of first diagnosis of significant TR.

Table 1. Clinical characteristics of the total population and according to stages of right heart failure

	Overall (n=1311)	Stage 1 (n=101)	Stage 2 (n=124)	Stage 3 (n=683)	Stage 4 (n=403)	P-value
Demographic characteristics						
Age (years)	71 (62-78)	67 (59-75) §	73 (63-79)	71 (62-78)	71 (63-78) *	**0.041**
Male sex	651 (50)	49 (49)	71 (57)	333 (49)	198 (49)	0.364
Body surface area (m^2)	1.9 ± 0.2	1.9 ± 0.2	1.9 ± 0.2	1.9 ± 0.2	1.9 ± 0.3	0.355
Medical history						
NYHA class						**<0.001**
NYHA I	267 (22)	79 (100)	84 (100)	86 (13)	18 (5)	
NYHA II	383 (32)	0 (0)	0 (0)	313 (48)	70 (18)	
NYHA III	379 (31)	0 (0)	0 (0)	257 (39)	122 (31)	
NYHA IV	185 (15)	0 (0)	0 (0)	0 (0)	185 (47)	
Dyspnea	729 (57)	6 (6)	13 (12)	285 (58)	319 (79)	**<0.001**
Edema	296 (24)	0 (0)	0 (0)	0 (0)	296 (74)	**<0.001**
Hypertension	977 (81)	65 (73)	78 (78)	537 (83)	297 (80)	0.098
Hypercholesterolemia	574 (48)	30 (34)	48 (48)	307 (47)	189 (51)	**0.036**
Diabetes mellitus	240 (20)	6 (7)	11 (11)	113 (18)	110 (30)	**<0.001**
(Ex-)smoker	381 (32)	26 (30)	27 (27)	200 (31)	128 (35)	0.398
Coronary artery disease	521 (40)	14 (14)	41 (35)	289 (42)	177 (44)	**<0.001**
Pacemaker/ICD	471 (37)	36 (27)	40 (33)	272 (40)	133 (34)	**0.024**
Chronic kidney disease	227 (19)	6 (7)	12 (12)	116 (18)	93 (25)	**<0.001**
Atrial fibrillation	611 (50)	39 (42)	56 (54)	318 (48)	198 (52)	0.190
Chronic obstructive pulmonary disease	167 (14)	6 (7)	6 (6)	90 (14)	65 (17)	**0.005**
Laboratory values						
Hemoglobin (mmol/L)	7.9 (6.8-8.7)	8.4 (7.6-9.2) ‡ §	8.5 (7.3-9.1) ‡ §	7.9 (6.9-8.7) * †	7.6 (6.5-8.5) * †	**<0.001**

Creatinine (µmol/L)	93 (74-124)	79 (67-90) ‡ §	86 (75-103) §	92 (73-121) * §	105 (79-145) * † ‡	**<0.001**
Urea (mmol/L)	8.5 (6.3-12.2)	6.3 (5.1-8.5) ‡ §	7.2 (5.5-9.7) ‡ §	8.4 (6.2-11.8) * † §	10.3 (7.2-17.2) * † ‡	**<0.001**
Bilirubin (µmol/L)	12 (9-18)	13 (9-17)	12 (10-16)	11 (8-16) §	16 (10-23) ‡	**<0.001**
Medication						
Aspirin	254 (22)	14 (16)	23 (24)	145 (23)	72 (20)	0.355
Beta-blocker	736 (62)	47 (53)	55 (56)	422 (66)	212 (58)	**0.010**
ACE-inhibitor	758 (64)	48 (55)	60 (61)	423 (66)	227 (62)	0.133
Aldosterone antagonist	256 (22)	3 (3)	2 (2)	149 (23)	102 (28)	**<0.001**
Statin	543 (46)	26 (30)	49 (51)	293 (46)	175 (48)	**0.012**
Diuretics	763 (60)	0 (0)	0 (0)	458 (68)	305 (76)	**<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. Stage 1, †p < 0.05 vs. Stage 2, ‡p < 0.05 vs. Stage 3, § p < 0.05 vs. Stage 4). ACE = angiotensin-converting enzyme; ICD = implantable cardioverter-defibrillator; NYHA = New York Heart Association*

Analysis of the differences between the 4 stages of RHF showed that patients in stage 4 were significantly older than patients in stage 1, while no significant differences in sex were observed between stages. Inherent to the definitions of the stages in this study, a significant difference between the stages was observed in NYHA functional class, peripheral edema and diuretic use. Notably, only half of patients (47%) classified in stage 4 of RHF had NYHA class IV symptoms. As expected, patients in more advanced stages of RHF more often presented with dyspnea. A similar trend was detected for the presence of comorbidities such as diabetes mellitus, chronic obstructive pulmonary disease and worse renal function. Interestingly, no significant difference was observed across groups for the prevalence of atrial fibrillation at first diagnosis of TR.

Echocardiographic variables

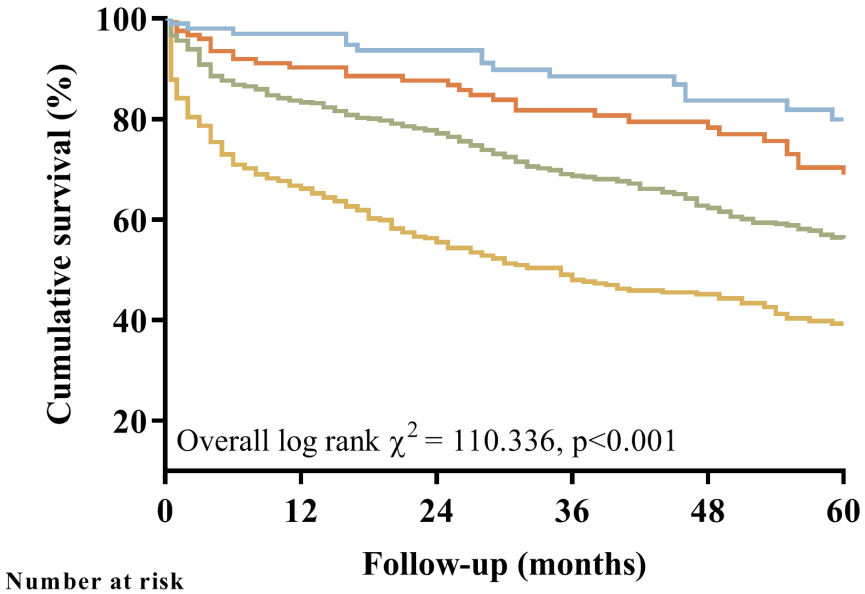
The echocardiographic characteristics of the patients are summarized in Table 2. The mean heart rate was 79 ± 19 beats per minute and 375 patients (29%) had atrial fibrillation during echocardiographic assessment. The mean LV ejection fraction was 44 ± 16% and concomitant significant aortic stenosis or mitral regurgitation were present in 25% and 29% of patients, respectively.

In per-group analysis, concomitant left-sided valvular disease was generally more prevalent in more advanced stages of RHF. Furthermore, patients in stage 4 had significantly larger LV and RV dimensions, larger right atrial area, lower LV ejection fraction, higher RV systolic pressure and larger tricuspid leaflet tenting height and area compared to all other stages of right heart failure.

Prognostic impact of RHF stages

During a median follow-up of 34 months (IQR 15-66 months) after diagnosis of significant secondary TR, 602 deaths (46%) occurred. The cumulative survival rates were 80% and 54% at 1 and 5 years, respectively. During follow-up, only 103 patients (8%) underwent tricuspid valve surgery. Ninety-one percent of these patients were in stage 3 and 4 of RHF.

The Kaplan-Meier curves for overall survival according to the 4 stages of RHF are shown in the Central Illustration. Five-year survival rates were significantly worse in more advanced stages of RHF: 80%, 70%, 57% and 39% for stage 1, 2, 3 and 4, respectively (log-rank chi-square 110.336; $p<0.001$). Five-year survival rates for patients who underwent tricuspid valve surgery were higher in all stages of RHF compared to the overall population: 100%, 80%, 71% and 52% for stage 1, 2, 3 and 4, respectively.



Number at risk

Stage 1	101	94	79	63	48	41
Stage 2	124	110	96	77	63	51
Stage 3	683	566	472	356	268	202
Stage 4	403	266	197	146	111	77

Central illustration. Kaplan-Meier curves for survival according to stages of right heart failure

In a total population of 1311 patients with significant secondary tricuspid regurgitation, higher stages of right heart failure (RHF) were associated with significantly lower 5-year survival rates. Patients in stage 1 had normal right ventricular (RV) function and no symptoms of RHF; stage 2 included patients with RV dysfunction but without symptoms of RHF; stage 3 included patients with RV dysfunction and prior or current symptoms of RHF and stage 4 comprised patients with RV dysfunction and refractory signs of RHF.

Uni- and multivariable Cox regression analyses for all-cause mortality are presented in Table 3. Age, coronary artery disease, worse renal function, lower LV ejection fraction, higher RV systolic pressure and the stages of RHF were significantly associated with worse survival. Sex and the presence of a pacemaker or ICD were not independently associated with survival in patients with significant TR in the current study.

Table 2. Echocardiographic characteristics of the total population and according to stages or right heart failure

	Overall (n=1311)	Stage 1 (n=101)	Stage 2 (n=124)	Stage 3 (n=683)	Stage 4 (n=403)	P-value
Heart rhythm						
AF	375 (29)	17 (17)	34 (27)	193 (28)	131 (33)	**0.019**
Rate (bpm)	79 ± 19	75 ± 17 §	76 ± 18 §	79 ± 18 §	82 ± 20 * † ‡	**<0.001**
LV, LA and left-sided valvular disease						
LV end-diastolic diameter (mm)	49 ± 12	45 ± 8 ‡ §	44 ± 9 ‡ §	49 ± 11 * † §	51 ± 13 * † ‡	**<0.001**
LV end-systolic diameter (mm)	39 ± 13	33 ± 9 ‡ §	34 ± 9 ‡ §	39 ± 13 * † §	42 ± 15 * † ‡	**<0.001**
LV end-diastolic volume (ml)	114 (80-171)	103 (78-135) §	102 (78-138) ‡ §	111 (80-176) †	127 (83-194) * †	**<0.001**
LV end-systolic volume (ml)	61 (38-108)	45 (34-71) ‡ §	53 (35-75) ‡ §	60 (38-114) * † §	75 (43-133) * † ‡	**<0.001**
LV ejection fraction (%)	44 ± 16	51 ± 12 ‡ §	48 ± 14 §	45 ± 15 * §	40 ± 16 * † ‡	**<0.001**
E/A ratio	1.6 (1.0-2.7)	1.2 (0.9-1.8) ‡ §	1.3 (0.9-2.4) §	1.6 (1.0-2.6) *	2.0 (1.1-3.0) * †	**<0.001**
Left atrial maximum volume, indexed (ml/m^2)	51 (34-70)	41 (26-57) ‡ §	48 (30-66)	52 (34-70) *	55 (37-73) *	**<0.001**
Significant (moderate and severe) AS	292 (25)	9 (10)	26 (23)	160 (26)	97 (29)	**<0.001**
Significant (moderate and severe) MR	374 (29)	22 (22)	24 (20)	176 (26)	152 (38)	**<0.001**
RV and RA						
RV basal dimension (mm)	45 ± 8	43 ± 8 §	44 ± 7 §	45 ± 8 §	47 ± 9 * † ‡	**<0.001**
RV end-diastolic area (mm^2)	24 (19-30)	20 (17-27) ‡ §	21 (19-27) §	23 (18-29) * §	26 (20-33) * † ‡	**<0.001**
RV fractional area change (%)	35 ± 13	39 ± 14 §	36 ± 13	36 ± 12 §	33 ± 12 * ‡	**0.001**
RV systolic pressure (mmHg)	36 ± 15	31 ± 12 §	32 ± 11 §	35 ± 15	38 ± 17 * †	**<0.001**
TAPSE (mm)	15 ± 5	21 ± 4 † ‡ §	13 ± 2 * ‡ §	15 ± 5 * † §	14 ± 5 * † ‡	**<0.001**
Right atrial maximum area (mm^2)	26 (20-34)	24 (19-30) §	25 (20-32) §	26 (20-33) §	28 (22-35) * † ‡	**<0.001**
Tricuspid valve						
Moderate TR	1035 (79)	84 (83)	107 (86)	542 (80)	302 (75)	**0.028**
Severe TR	276 (21)	17 (17)	17 (14)	141 (21)	101 (25)	**0.028**

Valvular annulus diameter (mm)	42 ± 8	41 ± 8 §	42 ± 7	42 ± 8	43 ± 8 *	**0.014**
Leaflet tenting height (mm)	10 (0-14)	5 (0-12) ‡ §	9 (0-13) §	10 (0-14) * §	11 (4-16) * † ‡	**<0.001**
Leaflet tenting area (mm^2)	2.5 (0-4.2)	0.9 (0-3.2) ‡ §	2.3 (0-3.7) §	2.5 (0-4.2) * §	3.0 (0.6-4.8) * † ‡	**<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. Stage 1, †p < 0.05 vs. Stage 2, ‡p < 0.05 vs. Stage 3, § p < 0.05 vs. Stage 4). AF = atrial fibrillation; AS = aortic stenosis; E/A = ratio of mitral inflow peak early diastolic flow-velocity to atrial contraction peak-velocity; LA = left atrium; LV = left ventricle; MR = mitral regurgitation; RV = right ventricle; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation*

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

Variable	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Age (years)	1.021 (1.015-1.028)	**<0.001**	1.024 (1.016-1.033)	**<0.001**
Male sex	1.210 (1.031-1.421)	**0.019**	1.090 (0.898-1.324)	0.383
BSA (m^2)	0.555 (0.360-0.854)	**0.007**		
Dyspnea	1.573 (1.328-1.863)	**<0.001**	0.986 (0.806-1.207)	0.891
Diabetes mellitus	1.787 (1.477-2.161)	**<0.001**	1.144 (0.921-1.421)	0.225
Hypercholesterolemia	1.065 (0.902-1.257)	0.458		
Coronary artery disease	1.620 (1.379-1.902)	**<0.001**	1.212 (1.003-1.464)	**0.046**
Atrial fibrillation	1.025 (0.870-1.207)	0.771		
Pacemaker/ICD	1.261 (1.071-1.486)	**0.005**	1.092 (0.904-1.319)	0.363
COPD/asthma	1.537 (1.230-1.921)	**<0.001**	1.164 (0.911-1.487)	0.224
Hemoglobin (mmol/L)	0.846 (0.791-0.905)	**<0.001**		
Creatinine (µmol/L)	1.004 (1.003-1.004)	**<0.001**	1.003 (1.002-1.004)	**<0.001**
Urea (mmol/L)	1.013 (1.010-1.017)	**<0.001**		
Bilirubin (µmol/L)	1.014 (1.010-1.020)	**<0.001**		
Beta-blocker	0.943 (0.794-1.120)	0.505		
Aldosterone antagonist	1.362 (1.127-1.645)	**0.001**	1.037 (0.840-1.280)	0.736
Statin	1.116 (0.944-1.319)	0.200		
LV ejection fraction (%)	0.985 (0.979-0.990)	**<0.001**	0.992 (0.986-0.998)	**0.010**
E/A ratio	1.121 (1.035-1.214)	**0.005**		
LAVI (ml/m^2)	1.006 (1.003-1.009)	**<0.001**		
Significant AS	1.443 (1.194-1.745)	**<0.001**		
Significant MR	1.377 (1.162-1.633)	**<0.001**	0.991 (0.815-1.205)	0.929
Tricuspid annulus diameter (mm)	1.011 (1.001-1.021)	**0.034**	1.005 (0.990-1.021)	0.489
RV systolic pressure (mmHg)	1.018 (1.013-1.023)	**<0.001**	1.010 (1.004-1.016)	**0.001**
Right atrial maximum area (cm^2)	1.008 (1.000-1.016)	**0.037**	0.995 (0.984-1.007)	0.440
Severe TR	1.139 (0.938-1.383)	0.187		
Leaflet tenting height (mm)	1.014 (1.002-1.026)	**0.017**	1.006 (0.991-1.021)	0.430
Stages overall		**<0.001**		**<0.001**
Stage 1 (reference)	……	……	……	……
Stage 2	1.753 (0.989-3.107)	0.055	1.439 (0.727-2.849)	0.297
Stage 3	3.097 (1.899-5.050)	**<0.001**	2.110 (1.163-3.828)	**0.014**
Stage 4	5.545 (3.388-9.076)	**<0.001**	3.318 (1.795-6.133)	**0.001**

AS = aortic stenosis; BSA = body surface area; CI = confidence interval; COPD = chronic obstructive pulmonary disease; ICD = implantable cardiac defibrillator; LAVI = left atrial volume index; LV = left ventricular; MR = mitral regurgitation; RV = right ventricle; TR = tricuspid regurgitation

DISCUSSION

The main finding of the present, large retrospective study is the independent association between stages of RHF and survival in patients with significant secondary TR.

The association between significant TR and mortality has initially been demonstrated by Nath et al. (10) and confirmed by several studies since (11). However, patients with significant TR are not frequently referred for surgery and the majority of tricuspid valve repair interventions are performed concomitantly to left-sided valve surgery (12). Isolated TR intervention is associated with high in-hospital mortality (8-10%) in small and heterogenous study populations (13). The outcomes of these studies were confirmed in a recent larger study by Zack et al. (12) including 5,005 isolated secondary tricuspid valve operations over a 10-year period. During this period, the number of operations increased significantly, but the in-hospital mortality remained consistently high (8.8%). In contrast, Hamandi et al. (14) demonstrated that in-hospital mortality for isolated primary and secondary tricuspid valve surgery can be as low 3.2% and suggested that this difference is predominantly caused by improved patient selection.

RV function is one of the main determinants of postoperative outcome in patients with secondary TR (15). However, there are no recommendations on specific values of RV functional parameters to predict the outcome of isolated tricuspid valve intervention and it is difficult to characterize with two-dimensional echocardiography due to the complex geometry of the right ventricle and the interaction between RV myocardial performance and loading conditions (16). In addition, volume overload is well tolerated by the RV compared to pressure overload and RV remodeling may precede RV dysfunction until advanced stages of TR (16). We recently demonstrated that RV dysfunction (based on TAPSE) was associated with poor outcomes in patients with significant secondary TR, regardless of the RV dilation (17). However, signs of RHF were not included in the analysis. The present results are incremental, as they demonstrate that not only RV dysfunction but also signs of RHF which may be related to the severity of TR should be considered in the risk stratification of these patients.

Current transcatheter therapies for severe TR are being tested in patients with symptoms, large coaptation defects and regurgitant volumes and have demonstrated promising results (18). Treating patients with severe TR who are asymptomatic and have normal RV systolic function may prevent further damage of the RV and improve survival. This needs to be demonstrated in large studies where safety and efficacy are shown and the risk of mortality is proven to be much lower than the surgical risk.

International heart failure associations proposed a staging strategy to characterize RHF, combining signs and symptoms of RHF and RV dysfunction (1). In the presence of established risk factors such as TR, RHF may progress from asymptomatic RV dysfunction to refractory RHF in 4 consecutive stages of disease. The staging system provides a tool for risk stratification and helps clinicians optimally manage their patients with stage-specific treatments to reduce morbidity and mortality. However, the proposed RHF staging system has never been validated in patients with significant secondary TR.

Multiple studies have demonstrated the prognostic value of RV dysfunction in heterogenous populations of patients with TR (4, 19). In addition, a significant interaction between the presence of symptoms and outcome of significant TR in patients with preserved LV ejection fraction and pulmonary hypertension was demonstrated by Bar and colleagues (20). However, only one study has described the entity RHF in patients with TR and LV systolic dysfunction (21). The definition of RHF in this study was based on the Framingham criteria and the prognostic implications were not assessed. To our knowledge, the current study is the first to assess the distribution and prognostic implications of stages of RHF as proposed by the international heart failure associations in patients with significant secondary TR. Given the clear association between higher stages of RHF and all-cause mortality in this study, application of multi-parametric staging of RHF might be useful in future recommendations for risk stratification of patients with significant secondary TR. In addition, our study can be used as a benchmark for later studies assessing optimal timing and outcomes of tricuspid valve interventions. Further research is needed to investigate if surgery is effective in patients with significant secondary TR at an earlier stage, prior to the onset of symptomatic RHF.

AF and significant MR are frequently observed in patients with heart failure and are associated with poor prognosis (22, 23). Significant secondary TR may be observed in these patients and may indicate a more advanced stage of the disease. In the current study, significant MR and AF were observed in 29% and 50% of the patients, respectively. The presence of significant MR was significantly associated with all-cause mortality in the univariable Cox regression analysis, but not in the multivariable analysis. Notwithstanding, comparison of HR for the RHF stages in a model with and without adjustment for significant MR shows a confounding effect of MR on the association between RHF stages and mortality, although small (HR for RHF stage 4 vs. stage 1 without adjustment for MR: 3.333, 95% CI 1.804-6.159). AF was not significantly associated with survival in univariable Cox regression analysis. This differs from the results of the study by Benfari et al. (24) in patients with heart failure with reduced LV ejection fraction, of which a subgroup of

patients with severe TR had similar AF rates (48%). However, in multivariable analysis AF was not significantly associated with mortality, while the presence of moderate or severe TR was. Similar to our results, this could suggest that the presence of significant TR represents a more advanced stage of disease and is significantly associated with increased all-cause mortality, even after adjustment for known associates of poor survival such as MR and AF.

Study limitations

Firstly, the current study is a retrospective cohort study from a single tertiary center. Future prospective trials are needed to confirm the prognostic value of the described classification system. Secondly, it is important to acknowledge certain limitations of the staging system. In the current study, the echocardiographic variable TAPSE with a cut-off value of <17 mm for RV dysfunction was used since this is the most validated method in two-dimensional echocardiography (7). However, TAPSE is dependent on volume overload and may be influenced by the tricuspid regurgitant volume. Moreover, RHF is a subjective clinical diagnosis, while signs and symptoms may change over short periods of time, resulting in a low reproducibility. We therefore have chosen a multiparametric approach to define the stages of RHF. Prior symptoms of RHF were considered by including diuretic use in stage 3 and 4 of RHF. It should be noted that diuretic use as well as reduced exercise capacity could be caused by left heart failure instead of RHF. To correct for this confounder in the evaluation of the prognostic implications of RHF, we included LV ejection fraction in the multivariate Cox proportional hazard model. Additionally, some studies claim that NYHA class correlates better with RHF through ventricular interdependence than with left heart failure (25, 26). Specific signs of RHF such as hepatomegaly, jugular venous distention and ascites were not widely available in our retrospective database, but could complement the current staging system. We did not compare this classification of RHF with other established risk scores such as MAGGIC risk score (27) due to the specific characteristics of the study population, including patients with secondary significant TR and not only patients with left-sided heart failure.

Conclusion

The introduction of a staging system for RHF is potentially valuable in the risk stratification of patients with significant secondary TR. In this large cohort of patients with significant secondary TR, symptomatic RHF (stage 3 and 4) was present in approximately 80% of the population and was independently associated with worse survival.

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3

Chapter 4

Long-term impact of preventive tricuspid valve annuloplasty on right ventricular remodeling

Marlieke F. Dietz*, MD; Aniek L. van Wijngaarden*, MD; Michael J. Mack, MD; Jerry Braun, MD; Nina Ajmone Marsan, MD; Victoria Delgado, MD; Robert Klautz, MD; Jeroen J. Bax, MD

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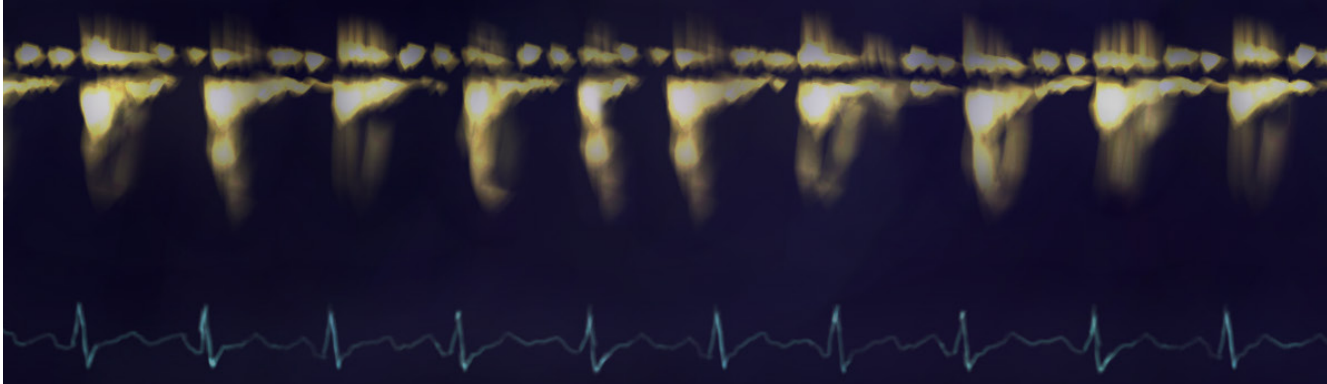
* Shared first authorship



ABSTRACT

Background: In patients with primary mitral regurgitation (MR), concomitant tricuspid valve (TV) annuloplasty at the time of left-sided valve surgery is indicated in case of a dilated TV annulus ≥40 mm independent of the presence or severity of tricuspid regurgitation (TR). However, the long-term impact on right ventricular (RV) adverse remodeling is less well established and the benefit of preventive TV annuloplasty remains controversial. The aim of the study was to assess differences in long-term RV adverse remodeling and the development of significant TR in those patients.

Methods: In total, 98 patients (mean age 65±11 years, 85% male) with significant primary MR and TV annulus dilatation ≥40 mm without significant TR who underwent mitral valve (MV) repair with or without concomitant TV annuloplasty were included. Of the 98 patients, 28 patients underwent isolated MV repair without TV annuloplasty and 70 patients received concomitant TV annuloplasty at the time of MV surgery.

Results: The RV basal diameter (p=0.03), RV long axis diameter (p=0.04), RV end-diastolic area (p<0.01) and RV end-systolic area (p=0.03) showed less adverse remodeling at follow-up in patients with concomitant TV annuloplasty compared to patients without TV annuloplasty. Additionally, 4 patients (14%) in the subgroup without TV annuloplasty developed significant TR during follow-up in contrast to 0 patients in the subgroup with TV annuloplasty (p=0.001).

Conclusion: Concomitant preventive TV annuloplasty during mitral valve surgery in patients with primary MR, no significant TR and a tricuspid annulus (≥40 mm), prevented RV adverse remodeling and the development of significant TR at long-term follow-up.

INTRODUCTION

Secondary tricuspid regurgitation (TR) in patients with concomitant left-sided valve disease was initially thought to decrease or even resolve once surgery had corrected the primary left-sided problem (1). However, patients with increased right ventricular (RV) afterload due to left-sided heart valve disease may develop a vicious circle of tricuspid valve (TV) annulus dilatation, worsening TR and adverse RV remodeling (2). Studies have shown that a conservative approach of a dilated TV annulus without significant TR (<2+) during left-sided valve surgery does not stop the progression of this process: up to one-third of patients develop late significant TR after mitral valve (MV) surgery if the dilated annulus is not addressed (3). Significant TR and the associated RV adverse remodeling is associated with poor prognosis (4). Additionally, surgical intervention in patients with late isolated TR can be a high-risk procedure with high morbidity and mortality (5). Accordingly, current guidelines recommend concomitant TV annuloplasty at the time of left-sided valve surgery in patients with a dilated TV annulus of ≥40 mm independent of the presence or severity of TR (6). Although various studies have confirmed reduction of TR after this procedure, the long-term impact on RV adverse remodeling and clinical outcomes is less well established and the benefit of preventive TV annuloplasty remains controversial (7-10). Therefore, the aim of the current study was to assess differences in long-term RV adverse remodeling and clinical outcomes in patients with significant primary mitral regurgitation (MR) and TV annulus dilatation ≥40 mm without significant TR who underwent MV surgery with versus without concomitant preventive TV annuloplasty.

METHODS

Patients who underwent MV repair for primary MR due to fibro-elastic deficiency or Barlow's disease with or without concomitant TV annuloplasty at the Leiden University Medical Center (Leiden, The Netherlands) between 2000-2017 were included. TV annuloplasty was performed by inserting an annular ring in the position of the TV annulus. The following exclusion criteria were used: unavailable echocardiogram pre-operative or at long-term follow-up (≥2 years), pre-operative TR grade ≥3 (significant TR), pre-operative TV annulus diameter <40 mm and age <18 years. Patients were divided into 2 groups 1) patients who did not undergo concomitant TV annuloplasty ("no TV annuloplasty") and 2) patients who underwent concomitant TV annuloplasty ("TV annuloplasty"). Pre-operative demographic and clinical characteristics of patients were collected from the hospital information system (HIX 6.1; ChipSoft BV, Amsterdam, The Netherlands) and the patient electronic record used by the cardiology department (EPD-Vision®; Leiden University Medical Center, Leiden, The Netherlands). The following information

was obtained: demographic characteristics, cardiovascular risk factors, concomitant cardiovascular disease, concomitant surgical procedures and clinical follow-up data. The following endpoints were assessed: all-cause mortality and adverse events after surgery which included the implantation of a pacemaker or implantable cardioverter-defibrillator, new onset of atrial fibrillation, surgical intervention on the mitral or tricuspid valve, hospitalization for heart failure, myocardial infarction, out-of-hospital cardiac arrest and stroke. Date of death was verified by reviewing the hospital records, which are connected to the governmental death registry database. For retrospective analysis of clinically acquired data and anonymously handled the Institutional Review Board waived the need of written patient informed consent.

Standard transthoracic 2D echocardiography was performed in all patients before surgery and at long-term follow-up (≥2 years) using commercially available ultrasound devices (Vivid 5, Vivid 7, System 5 and E9, GE Healthcare, Vingmed, Horten, Norway). Conventional 2D, M-mode, pulsed and continuous wave and color Doppler images were acquired in parasternal and apical views with the patients in left lateral decubitus position. Data were digitally stored and analyzed offline using EchoPAC (version 112, 202 and 203 GE Medical Systems, Horten, Norway). The right atrial maximum dimension, TV annular diameter and RV dimensions and areas were measured on the focused RV 4-chamber apical view (11, 12). In addition, the fractional area change was derived from the RV end-diastolic and end-systolic areas traced on the focused RV 4-chamber apical view (12). The RV systolic pressure was determined using the peak velocity of the TR jet (12). Left ventricular dimensions (end-diastolic and end-systolic diameter) were assessed from the parasternal long-axis view and were used to calculate fractional shortening (11). From the apical 2- and 4-chamber views, the left ventricular end-diastolic and end-systolic volumes were measured using the Simpson's biplane method; left ventricular ejection fraction was subsequently calculated (11). The maximum left atrial diameter was assessed in the parasternal long-axis view at end-systole. Left atrial volumes were measured at end-systole in the apical 2- and 4-chamber views using the Simpson's biplane method and indexed for body surface area (left atrial volume index) (11). MR and TR were graded according to current guidelines using a multi-parametric approach (13, 14). Additionally, TR was quantitatively assessed according to current recommendations (13).

Categorical variables are expressed as absolute numbers and percentages. Continuous variables are presented as mean±standard deviation (SD) when normally distributed and as median with interquartile range (IQR) when not normally distributed. The Kolmogorov-Smirnov test and the Shapiro Wilk test were used to assess for normality of

data distribution. The chi-square test, unpaired Student's T-test, Mann-Whitney U test and Kruskal-Wallis test were used for the analysis of the continuous and categorical clinical and echocardiographic variables as appropriate. Repeated-measure analysis-of-variance (ANOVA) was used to analyze the trend of right and left cardiac chamber dimensions, volumes and function during follow-up and to investigate the effect of preventive TV annuloplasty on adverse RV remodeling. Multiple pairwise comparisons within groups were performed with the paired Student's T-test, Wilcoxon signed-rank test or McNemar test as appropriate. Kaplan-Meier analysis was performed to evaluate the differences in all-cause mortality and the Log-rank test was used to compare the 2 groups. The chi-square test was used to analyze the other end-points. To evaluate the reproducibility for the TV annular measurements, the intra-class correlation coefficient (ICC) was calculated for inter- and intra-observer agreement in 10 randomly selected patients. Statistical analysis was performed using SPSS version 23.0 (IBM Corp., Armonk, NY, USA). For all tests, a 2-sided p-value <0.05 was considered statistically significant.

RESULTS

A total of 98 patients met the inclusion criteria; 28 of these patients underwent isolated MV repair without TV annuloplasty and 70 patients received concomitant TV annuloplasty at the time of MV surgery. Clinical characteristics at the time of MV surgery of all patients and for the 2 subgroups (with and without concomitant TV annuloplasty) are summarized in Table 1. The mean age of the overall population at the time of surgery was 65±11 years and 83 patients (85%) were men. More than half of the patients had pre-existing atrial fibrillation (55%) for which most patients underwent a maze procedure during surgery. In per-group analysis, no statistically significant differences were noted between patients with and without concomitant TV annuloplasty except in preoperative logistic EuroSCORE (3.0% [1.7-4.5] vs. 1.3% [0.8-3.4], respectively; p<0.001) as expected due to the additional TV annuloplasty. The echocardiographic characteristics at the time of MV surgery of all patients and according to the 2 subgroups are summarized in Table 2. Approximately two-third (68%) of the patients had MR grade 4 before surgery. Consequently, the left atrium was severely dilated in the overall population (LA diameter 48±9 mm and LA volume index 56 [45-76] ml/mm^2). Per design of the study, the TV annulus was dilated in all patients (43±3 mm) at baseline. Additionally, RV basal diameter was dilated (50±5 mm) compared to the normal range (25-41 mm)(11), while RV midventricular diameter (32±6 mm) and longitudinal diameter (78±10 mm) were within the normal range (19-35 mm and 59-83 mm, respectively) (11). Both subgroups with and without preventive TV annuloplasty were comparable at baseline in terms of echocardiographic characteristics,

Table 1. Baseline clinical characteristics

Variable	Total population (n=98)	TV annuloplasty (n=70)	No TV annuloplasty (n=28)	P-value
Age at surgery (years)	65±11	66±10	63±13	0.172
Men	83 (85%)	62 (89%)	21 (75%)	0.092
NYHA Class				0.251
I	19 (19%)	15 (21%)	4 (14%)	
II	57 (58%)	42 (60%)	15 (51%)	
III	21 (21%)	13 (19%)	8 (29%)	
IV	1 (1%)	0 (0%)	1 (4%)	
Atrial fibrillation	53 (55%)	38 (54%)	15 (56%)	0.910
Diabetes mellitus	2 (2%)	2 (3%)	0 (0%)	0.366
Hypertension	42 (43%)	30 (43%)	12 (43%)	1.000
Chronic obstructive pulmonary disease	5 (5%)	4 (6%)	1 (4%)	0.663
Smoker	39 (40%)	32 (46%)	7 (25%)	0.052
Coronary artery disease	29 (30%)	22 (31%)	7 (26%)	0.596
Out of hospital cardiac arrest	3 (3%)	2 (3%)	1 (4%)	0.853
Pacemaker/ICD	5 (5%)	2 (3%)	3 (11%)	0.099
eGFR, ml/min/1.73m^2	81±25	82±25	79±24	0.536
Logistic EuroSCORE (%)	2.8 (1.4-3.8)	3.0 (1.7-4.5)	1.3 (0.8-3.4)	**<0.001**
Maze procedure	41 (42%)	31 (44%)	10 (36%)	0.437

Values are mean±SD, median (IQR) or n (%).
eGFR = estimated glomerular filtration rate; ICD = implantable cardioverter-defibrillator; NYHA = New York Heart Association

although pre-operative RV function was more preserved in patients without TV annuloplasty compared to those with TV annuloplasty (RV fractional area change 38% [33-44] vs. 33% [22-45], respectively; p=0.05). The ICC for repeated measurements of the TV annular diameter at baseline by the same observer (intra-observer agreement) was excellent (ICC=0.96), the ICC for measurements between two different observers (inter-observer agreement) was also good (ICC=0.89).

Supplementary Tables 1 and 2 summarize the echocardiographic characteristics at baseline and long-term follow-up for the subgroup with TV annuloplasty and the subgroup without TV annuloplasty, respectively. The median time between baseline and follow-up echocardiography in the overall population was 6.4 (3.9-9.3) years. The median follow-up duration was not significantly different between patients with and without concomitant TV

Table 2. Baseline echocardiographic characteristics

Variable	Total population (n=98)	TV annuloplasty (n=70)	No TV annuloplasty (n=28)	P-value
Heart rate (bpm)	70 (60-83)	70 (61-82)	73 (60-83)	0.452
Atrial fibrillation	34 (35%)	27 (39%)	7 (25%)	0.144
RV basal diameter (mm)	50±5	50±5	50±5	0.777
RV mid diameter (mm)	32±6	32±6	31±5	0.470
RV long axis diameter (mm)	78±10	78±11	77±9	0.467
RV end-diastolic area (cm^2)	27 (23-30)	27 (22-31)	26 (24-28)	0.345
RV end-systolic area (cm^2)	17 (14-21)	17 (14-22)	15 (13-17)	0.146
RV fractional area change (%)	36 (24-45)	33 (22-45)	38 (33-44)	**0.050**
RA maximum diameter (mm)	56±8	57±7	56±9	0.796
TR vena contracta (mm)	3.7±2.2	3.7±2.3	3.7±2.3	0.938
TR PISA radius (cm)	0.39±0.21	0.40±0.21	0.36±0.21	0.479
TR EROA (mm^2)	6.5 (2.7-10.2)	6.4 (2.4-9.7)	9.3 (3.8-12.7)	0.312
TR regurgitant volume (ml/beat)	4.6 (2.3-9.1)	4.5 (2.0-8.3)	5.2 (2.9-9.8)	0.584
TR gradient (mmHg)	29 (21-34)	30 (23-40)	28 (16-31)	0.056
TR velocity (m/sec)	2.7±0.6	2.8±0.5	2.5±0.6	**0.021**
TV annulus (mm)	43±3	43±3	42±2	**0.023**
TR grade				0.333
0	11 (11%)	8 (11%)	3 (11%)	
1	52 (53%)	34 (49%)	18 (64%)	
2	35 (36%)	28 (40%)	7 (25%)	
LA diameter (mm)	48±9	48±8	48±10	0.922
LA volume index (ml/mm^2)	56 (45-76)	56 (46-74)	56 (38-88)	0.760
LV end-diastolic diameter (mm)	57±7	58±7	56±6	0.400
LV end-systolic diameter (mm)	36±7	37±8	35±6	0.222
LV fractional shortening (%)	37±9	37±10	38±9	0.409
LV end-diastolic volume (ml)	146 (116-174)	146 (116-174)	144 (111-175)	0.917
LV end-systolic volume (ml)	53 (42-67)	55 (44-69)	49 (38-61)	0.200
LV ejection fraction (%)	62±9	61±9	65±8	0.084
MR grade				0.303
3	31 (32%)	20 (29%)	11 (39%)	
4	67 (68%)	50 (71%)	17 (61%)	

Values are mean±SD, median (IQR) or n (%).

EROA = effective regurgitant orifice area; LA = left atrium; LV = left ventricle; MR = mitral regurgitation; PISA = proximal isovelocity surface area; RA = right atrium; RV = right ventricle; TR = tricuspid regurgitation; TV = tricuspid valve

annuloplasty (6.1 [3.9-9.4] years vs. 6.7 [3.8-9.1] years, respectively; p=0.89). As expected after MV repair, a significant reduction in MR severity and LA size was observed in both subgroups (p<0.01 for all). In patients who underwent concomitant TV annuloplasty, no significant RV dilatation was observed at follow-up in contrast to the patients who did not undergo concomitant TV annuloplasty, who did develop RV dilatation. In patients without TV annuloplasty, the RV midventricular diameter, longitudinal diameter, end-diastolic and end-systolic areas were significantly larger at follow-up (p<0.01 for all). Additionally, 4 patients (14%) in the subgroup without TV annuloplasty developed significant TR during follow-up in contrast to zero patients (0%) in the subgroup with TV annuloplasty (p=0.001). Only in patients who underwent TV annuloplasty, was there a significant reduction (vs baseline) in right atrial diameter observed (baseline right atrial diameter 57±7 mm; follow-up 52±7 mm; p<0.01), with significant reduction in TR grade (93% of patients having no residual TR or TR grade 1, p<0.01). To evaluate whether concomitant TV annuloplasty had an impact on the change in different echocardiographic parameters over time, repeated measure ANOVA was performed (Table 3 and Figure 1). This analysis showed that concomitant TV annuloplasty was associated with less adverse RV remodeling. The RV basal diameter (p=0.03), RV long axis diameter (p=0.04), RV end-diastolic area (p<0.01) and RV end-systolic area (p=0.03) showed less adverse remodeling at follow-up in patients with concomitant TV annuloplasty compared to patients without TV annuloplasty. RV function was more preserved at baseline in patients without TV annuloplasty, but did not change over time in both subgroups, showing no interaction between TV annuloplasty and RV function (p=0.49). As expected, TV annuloplasty was not associated with changes over time in left-sided echocardiographic variables.

Clinical outcome data of the total population, and of the patients with versus without concomitant TV annuloplasty are shown in Table 4. During the median follow-up of 6.4 (3.9-9.3) years, 9 patients (13%) with TV annuloplasty and 7 patients (25%) without TV annuloplasty died. Kaplan–Meier analysis showed no significant differences in survival rates between patients with and without TV annuloplasty (log-rank chi-square 0.56; p=0.45). The most frequent adverse events during follow-up were the need of a pacemaker or implantable cardioverter-defibrillator (21%) and new onset atrial fibrillation (10%). No significant differences in incidence of these or other outcomes between patients with versus without TV annuloplasty were observed.

DISCUSSION

The main finding of the current study was that in patients with significant primary MR and a dilated tricuspid annulus (≥40 mm) without significant TR (<2+) at baseline who

Table 3. Changes over time in echocardiographic parameters after mitral valve repair with versus without tricuspid valve annuloplasty

	Baseline	Follow-up	P-value
RV basal diameter (mm)			**0.032**
TV annuloplasty	50±5	49±8	
No TV annuloplasty	50±5	52±7	
RV mid diameter (mm)			0.079
TV annuloplasty	32±6	33±6	
No TV annuloplasty	31±5	36±7	
RV long axis diameter (mm)			**0.038**
TV annuloplasty	78±11	81±9	
No TV annuloplasty	77±9	84±8	
RV end-diastolic area (cm^2)			**0.004**
TV annuloplasty	27 (22-31)	27 (23-32)	
No TV annuloplasty	26 (24-28)	30 (26-35)	
RV end-systolic area (cm^2)			**0.033**
TV annuloplasty	17 (14-22)	17 (14-23)	
No TV annuloplasty	15 (13-17)	18 (15-22)	
RV fractional area change (%)			0.489
TV annuloplasty	33 (22-45)	33 (26-42)	
No TV annuloplasty	38 (33-44)	37 (31-47)	
RA maximum diameter (mm)			0.109
TV annuloplasty	57±7	52±7	
No TV annuloplasty	56±9	55±6	
TR gradient (mm)			0.264
TV annuloplasty	30 (23-40)	19 (15-24)	
No TV annuloplasty	28 (16-31)	22 (17-26)	
LV end-diastolic volume (ml)			0.135
TV annuloplasty	146 (116-174)	136 (113-160)	
No TV annuloplasty	144 (111-175)	118 (99-142)	
LV end-systolic volume (ml)			0.453
TV annuloplasty	55 (44-69)	61 (51-75)	
No TV annuloplasty	49 (38-61)	53 (46-69)	
LV ejection fraction (%)			0.330
TV annuloplasty	61±9	52±8	
No TV annuloplasty	65±8	53±7	
LA volume index (ml/mm^2)			0.835
TV annuloplasty	56 (46-74)	43 (30-59)	
No TV annuloplasty	56 (38-88)	41 (32-58)	

Values are mean±SD or median (IQR). LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle; TR = tricuspid regurgitation; TV = tricuspid valve

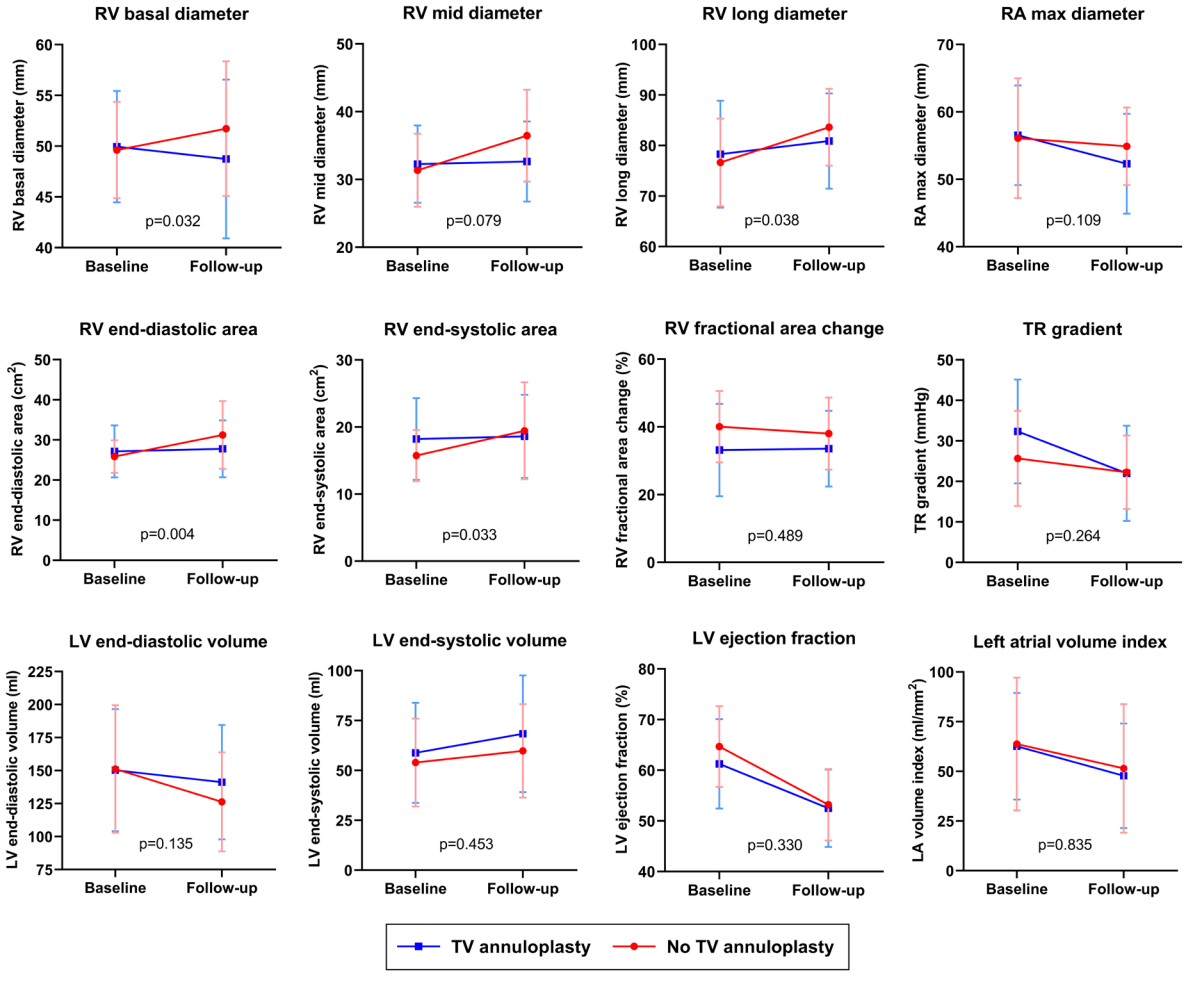


Figure 1. Changes over time in echocardiographic parameters after MV repair with (blue line) or without TV annuloplasty (red line)
LV = left ventricular; RA = right atrial; RV = right ventricular; TR = tricuspid regurgitation; TV = tricuspid valve

Table 4. Outcome data of the overall population of patients who underwent mitral valve surgery and the subgroups with and without tricuspid valve annuloplasty

Variable	Total population (n=98)	TV annuloplasty (n=70)	No TV annuloplasty (n=28)	P-value
All-cause mortality	16 (16%)	9 (13%)	7 (25%)	0.142
Surgical reintervention MV	8 (8%)	6 (9%)	2 (7%)	0.816
Surgical reintervention TV	1 (1%)	0 (0%)	1 (4%)	0.112
Heart failure hospitalization	8 (8%)	6 (9%)	2 (7%)	0.816
Myocardial infarction	2 (2%)	1 (1%)	1 (4%)	0.498
Out of hospital cardiac arrest	2 (2%)	1 (1%)	1 (4%)	0.498
Cerebrovascular accident	6 (6%)	2 (3%)	4 (14%)	0.087
Pacemaker/ implantable cardio-verter-defibrillator	21 (21%)	13 (19%)	8 (29%)	0.276
New onset atrial fibrillation	10 (10%)	6 (9%)	4 (14%)	0.399

Values are n (%).
MV = mitral valve; TV = tricuspid valve

underwent MV surgery, preventive TV annuloplasty was effective in preserving RV size and preventing the development of significant TR at long-term follow-up.

Previous studies have demonstrated that patients with RV dilatation who underwent TV annuloplasty during MV surgery were protected from development of significant TR and associated adverse RV remodeling in the first years after surgery (7, 15, 16). Bertrand et al. (15) showed that TV annuloplasty during MV surgery prevented postoperative RV dilatation in patients with a dilated TV annulus, although this effect was more pronounced in patients with moderate TR at baseline. Benedetto et al. (7) and Van de Veire et al. (16) reported RV reverse remodeling and prevention of TR progression in patients with less than moderate TR at 1 and 2 years after preventive TV annuloplasty at the time of MV surgery. In contrast, a recent randomized controlled trial analyzing 106 patients with less than severe TR demonstrated no impact of concomitant TV annuloplasty during MV surgery on RV dimensions during a median follow-up of 3.8 (3-5.6) years (8). However, these patients were not selected based on the presence of a dilated TV annulus, which suggests that TV annuloplasty may not be necessary to prevent RV dilatation in patients with normal preoperative TV annulus dimensions. Furthermore, secondary TR may slowly progress and TV annuloplasty does not reverse RV dilatation in secondary TR, but may only slow down the remodeling process that causes and results from TR (17). Therefore, the follow-up time in the previous studies may not be sufficient to analyze the effect

of TV annuloplasty on subsequent development of TR and adverse RV remodeling. The current study is the first to assess late adverse RV remodeling with a median follow-up of 6.4 (3.9-9.3) years in patients with primary MR. The results confirm and extend previous findings by demonstrating that concomitant TV annuloplasty during MV surgery was effective in preventing TR progression and adverse RV remodeling at long-term follow-up. Regarding RV systolic function, no significant changes between baseline and long-term follow-up were demonstrated in patients with TV annuloplasty as well as in patients without TV annuloplasty in the current study. Previous studies showed conflicting results. Chikwe et al. (18) investigated longitudinal changes in qualitatively assessed RV function up to 5 years after surgery in 645 patients who underwent MV repair (for degenerative MR) with or without TV annuloplasty in the presence of significant TR or a dilated tricuspid annulus (≥40 mm). After initial deterioration of RV function postoperatively in both groups, a more rapid recovery and improvement of RV function was observed in patients who underwent TV annuloplasty. Desai et al. (19) found similar late improvement of RV function in patients with preoperative severe TR. Patients with non-significant TR did not receive TV annuloplasty in this study. In contrast, others studies have demonstrated no impact of TV annuloplasty on RV function at follow-up as measured qualitatively (20) and by fractional area change (8, 21), which is concordant with the findings in the current study. Explanation for these varying results may relate to differences in patient population, baseline RV function or pulmonary artery pressures. Isolated MV surgery reduces pulmonary pressures and RV afterload, whereas correcting TR increases RV afterload, which may impair RV function but may also conceal changes in RV myocardial contractility. RV-pulmonary artery coupling could be a more useful parameter to accurately assess RV function, but non-invasive measurements of RV-pulmonary artery coupling still need further validation (22).

Badhwar et al. (9) reported that the addition of TV annuloplasty to MV surgery was associated with an increased risk of 30-day mortality in a large cohort of patients from The Society of Thoracic Surgeons Adult Cardiac Database. Most likely, the more advanced heart disease in the TV annuloplasty group accounted for this increased 30-day mortality, since adjustment for baseline characteristics neutralized the negative impact of TV annuloplasty on 30-day mortality. Moreover, multiple studies assessing long-term follow-up demonstrated no increased mortality in patients undergoing preventive TV annuloplasty (8, 10, 18, 20). Similarly, in the current study no significant differences were observed in all-cause mortality and morbidity during long-term follow-up in patients with versus without TV annuloplasty. The sample size of the current study and some previous studies may be too small to demonstrate significant differences in clinical outcomes.

However, the current results demonstrate that TV annuloplasty was effective in preventing the development of significant TR, which is an independent predictor of worse survival in general (4) and after MV surgery. Since TV annuloplasty in patients with a dilated TV annulus is not associated with incremental risk of mortality while reoperation of late significant TR is associated with high morbidity and mortality (5), a more widespread use of preventive TV annuloplasty might be justifiable. Large prospective studies are needed to clarify the clinical benefit of preventive TV annuloplasty during mitral valve surgery and to establish selection criteria for patients who may benefit most from preventive TV annuloplasty. A recent international randomized controlled trial assigned 401 patients with severe degenerative MR and grade ≤2 TR who underwent MV surgery to receive a procedure with or without TV annuloplasty. After a follow-up period of 2 years, the patients who underwent concomitant TV annuloplasty had less frequent progression to severe TR. The occurrence of major adverse events and the overall survival were similar in the groups with and without TV annuloplasty (23).

The current study is a retrospective cohort study from a single tertiary center with limitations inherent to its design. Due to the strict inclusion criteria, the sample size was relatively small. As the event rate of clinical outcomes was low, the current study was possibly underpowered to detect statistically significant differences. Because we were interested in the long-term outcome of TV annuloplasty, we excluded patients without available follow-up more than 2 years after surgery, inducing a selection bias. Furthermore, 2-dimensional transthoracic echocardiography may not be ideal for assessment of TV annulus dimensions, whereas 3-dimensional echocardiography may provide more accurate measurements of the tricuspid annulus.

In conclusion, the present study demonstrated that concomitant TV annuloplasty during MV surgery in patients with primary MR, no significant TR and a tricuspid annulus (≥40 mm), prevented adverse RV remodeling and the development of significant TR at long-term follow-up. Conversely, patients with isolated MV surgery and a dilated TV annulus who did not undergo TV annuloplasty showed significant RV dilatation with progression of TR. These results underscore that preventive TV annuloplasty may be effective in reducing late development of TR and RV dilatation. No effect of concomitant TV annuloplasty on outcomes was demonstrated, which may relate to the limited sample size. Larger randomized controlled trials with long-term follow-up are needed to provide further insight whether the preventive TV annuloplasty approach is associated with improved clinical outcomes.

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Supplementary Table 1. Echocardiographic characteristics at baseline and long-term follow-up of the subgroup of patients with concomitant tricuspid valve annuloplasty

Variable	Baseline	Follow-up	P-value
Heart rate (bpm)	70 (61-82)	69 (61-80)	0.916
Atrial fibrillation	27 (39%)	27 (39%)	1.000
RV basal diameter (mm)	50±5	49±8	0.224
RV mid diameter (mm)	32±6	33±6	0.665
RV long axis diameter (mm)	78±11	81±9	**0.031**
RV end-diastolic area (cm^2)	27 (22-31)	27 (23-32)	0.562
RV end-systolic area (cm^2)	17 (14-22)	17 (14-23)	0.296
RV fractional area change (%)	33 (22-45)	33 (26-42)	0.914
RA maximum diameter (mm)	57±7	52±7	**<0.001**
TR vena contracta (mm)	3.7±2.3	1.7±2.0	**<0.001**
TR PISA radius (cm)	0.40±0.21	0.25±0.28	**0.004**
TR EROA (mm^2)	6.4 (2.4-9.7)	0 (0-9.6)	0.092
TR RVol (ml/beat)	4.5 (2.0-8.3)	0 (0-6.5)	**0.029**
TR gradient (mmHg)	30 (23-40)	19 (15-24)	**0.006**
TV annulus (mm)	43±3	30±5	**<0.001**
TR grade			**<0.001**
0	8 (11%)	33 (47%)	
1	34 (49%)	32 (46%)	
2	28 (40%)	5 (7%)	
LA diameter (mm)	48±8	43±8	**<0.001**
LA volume index (ml/mm^2)	56 (46-74)	43 (30-59)	**<0.001**
LV end-diastolic diameter (mm)	58±7	55±7	**0.002**
LV end-systolic diameter (mm)	37±8	37±9	0.794
LV fractional shortening (%)	37±10	33±11	**0.009**
LV end-diastolic volume (ml)	146 (116-174)	136 (113-160)	0.138
LV end-systolic volume (ml)	55 (44-69)	61 (51-75)	**0.007**
LV ejection fraction (%)	61±9	52±8	**<0.001**
MR grade			**<0.001**
0	0 (0%)	25 (36%)	
1	0 (0%)	35 (50%)	
2	0 (0%)	8 (11%)	
3	20 (29%)	2 (3%)	
4	50 (71%)	0 (0%)	

Values are mean ±SD, median (IQR) or n (%). P-value by paired Student's T-test or Wilcoxon signed-rank test for Gaussian and non-Gaussian distributed continuous variables, respectively. P-value by McNemar test for categorical variables. EROA = effective regurgitant orifice area; IQR = interquartile range; LA = left atrium; LV = left ventricle; MR = mitral regurgitation; PISA = proximal isovelocity surface area; RA = right atrium; RV = right ventricle; RVol = regurgitant volume; SD = standard deviation; TR = tricuspid regurgitation; TV = tricuspid valve

Supplementary Table 2. Echocardiographic characteristics at baseline and long-term follow-up of the subgroup of patients without concomitant tricuspid valve annuloplasty

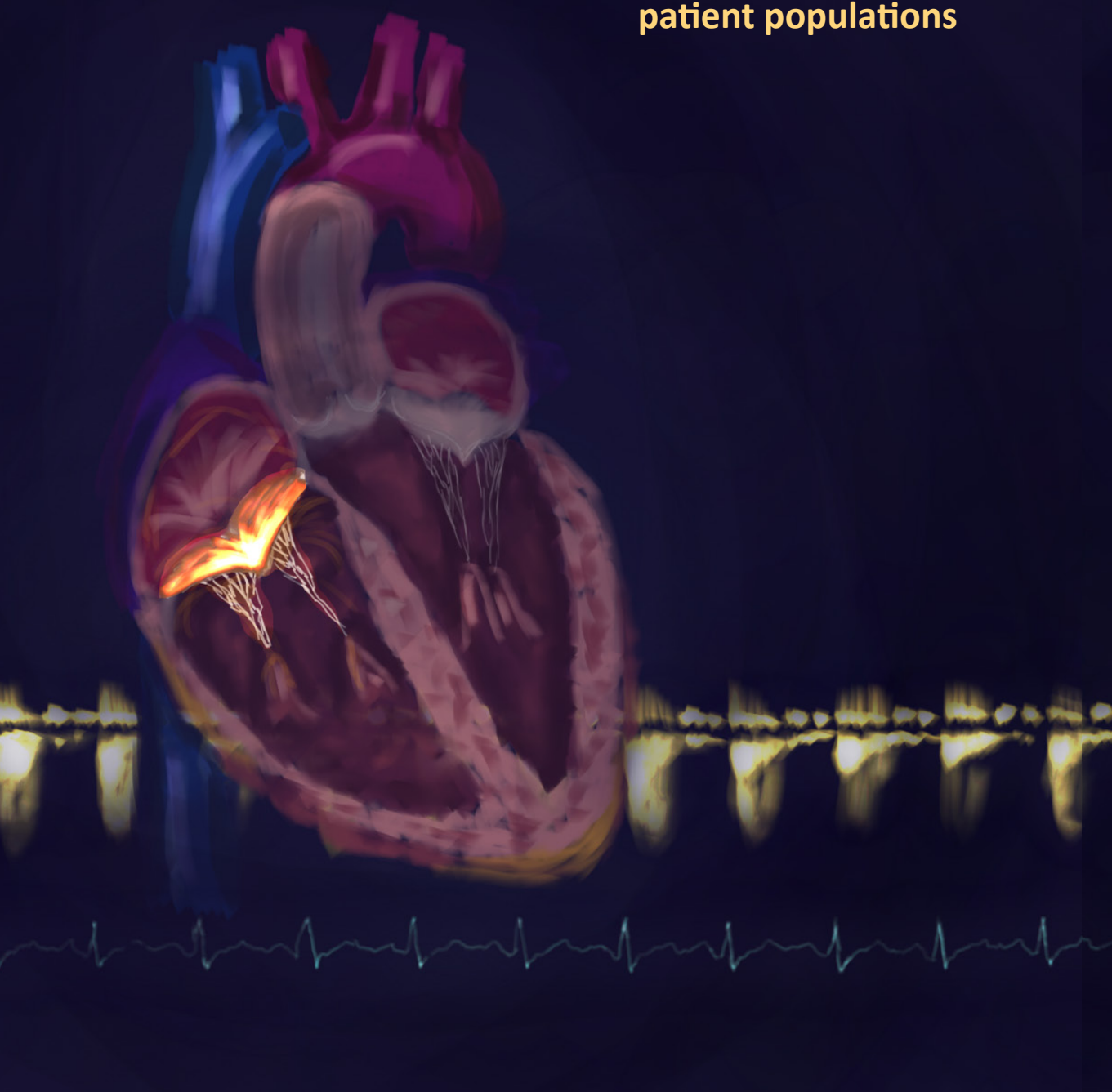
Variable	Baseline	Follow-up	P-value
Heart rate (bpm)	73 (60-83)	69 (63-76)	0.696
Atrial fibrillation	7 (25%)	7 (25%)	1.000
RV basal diameter (mm)	50±5	52±7	0.196
RV mid diameter (mm)	31±5	36±7	**0.001**
RV long axis diameter (mm)	77±9	84±8	**0.001**
RV end-diastolic area (cm^2)	26 (24-28)	30 (26-35)	**0.002**
RV end-systolic area (cm^2)	15 (13-17)	18 (15-22)	**0.006**
RV fractional area change (%)	38 (33-44)	37 (31-47)	0.456
RA maximum diameter (mm)	56±9	55±6	0.318
TR vena contracta (mm)	3.7±2.3	3.1±2.8	0.416
TR PISA radius (cm)	0.36±0.21	0.34±0.25	0.711
TR EROA (mm^2)	9.3 (3.8-12.7)	6.0 (3.3-11.8)	0.272
TR RVol (ml/beat)	5.2 (2.9-9.8)	3.7 (0.8-8.1)	0.117
TR gradient (mmHg)	28 (16-31)	22 (17-26)	0.085
TV annulus (mm)	42±2	42±5	0.973
TR grade			**<0.001**
0	3 (11%)	3 (11%)	
1	18 (64%)	12 (43%)	
2	7 (25%)	9 (32%)	
3	0 (0%)	4 (14%)	
LA diameter (mm)	48±10	43±9	**< 0.001**
LA volume index (ml/mm^2)	56 (38-88)	41 (32-58)	**< 0.001**
LV end-diastolic diameter (mm)	56±6	53±6	**0.012**
LV end-systolic diameter (mm)	35±6	36±8	0.184
LV fractional shortening (%)	38±9	32±10	**0.004**
LV end-diastolic volume (ml)	144 (111-175)	118 (99-142)	**0.007**
LV end-systolic volume (ml)	49 (38-61)	53 (46-69)	0.118
LV ejection fraction (%)	65±8	53±7	**<0.001**
MR grade			**<0.001**
0	0 (0%)	9 (32%)	
1	0 (0%)	15 (54%)	
2	0 (0%)	2 (7%)	
3	11 (39%)	2 (7%)	
4	17 (61%)	0 (0%)	

Values are mean ±SD, median (IQR) or n (%). P-value by paired Student's T-test or Wilcoxon signed-rank test for Gaussian and non-Gaussian distributed continuous variables, respectively. P-value by McNemar test for categorical variables. EROA = effective regurgitant orifice area; IQR = interquartile range; LA = left atrium; LV = left ventricle; MR = mitral regurgitation; PISA = proximal isovelocity surface area; RA = right atrium; RV = right ventricle; RVol = regurgitant volume; SD = standard deviation; TR = tricuspid regurgitation; TV = tricuspid valve

4

Part II

Tricuspid regurgitation in specific patient populations



Chapter 5

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

Marlieke F Dietz, MD; Edgard A Prihadi, MD; Pieter van der Bijl, MBChB, MMed; Federico Fortuni, MD; Ana Isabel Marques, MD; Nina Ajmone Marsan, MD; Jeroen J Bax, MD; Victoria Delgado, MD

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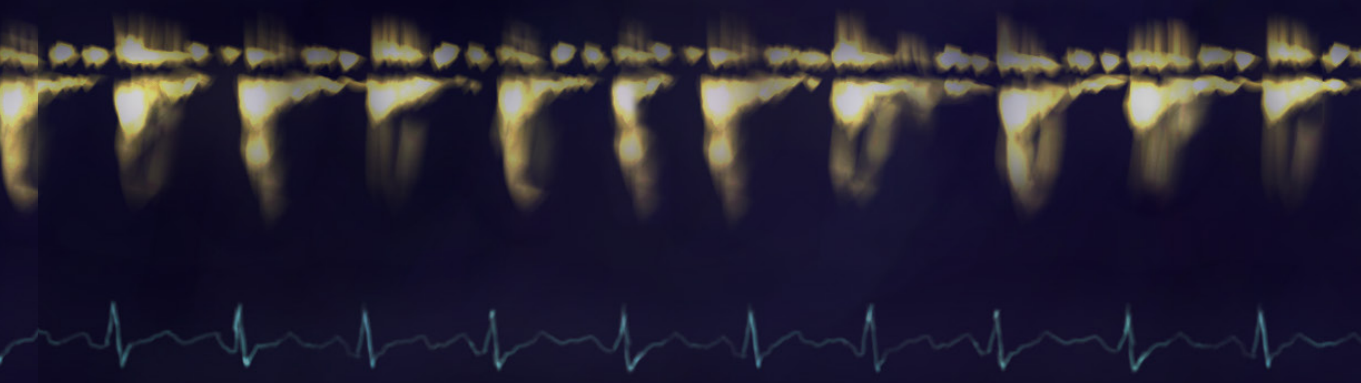

ABSTRACT

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.

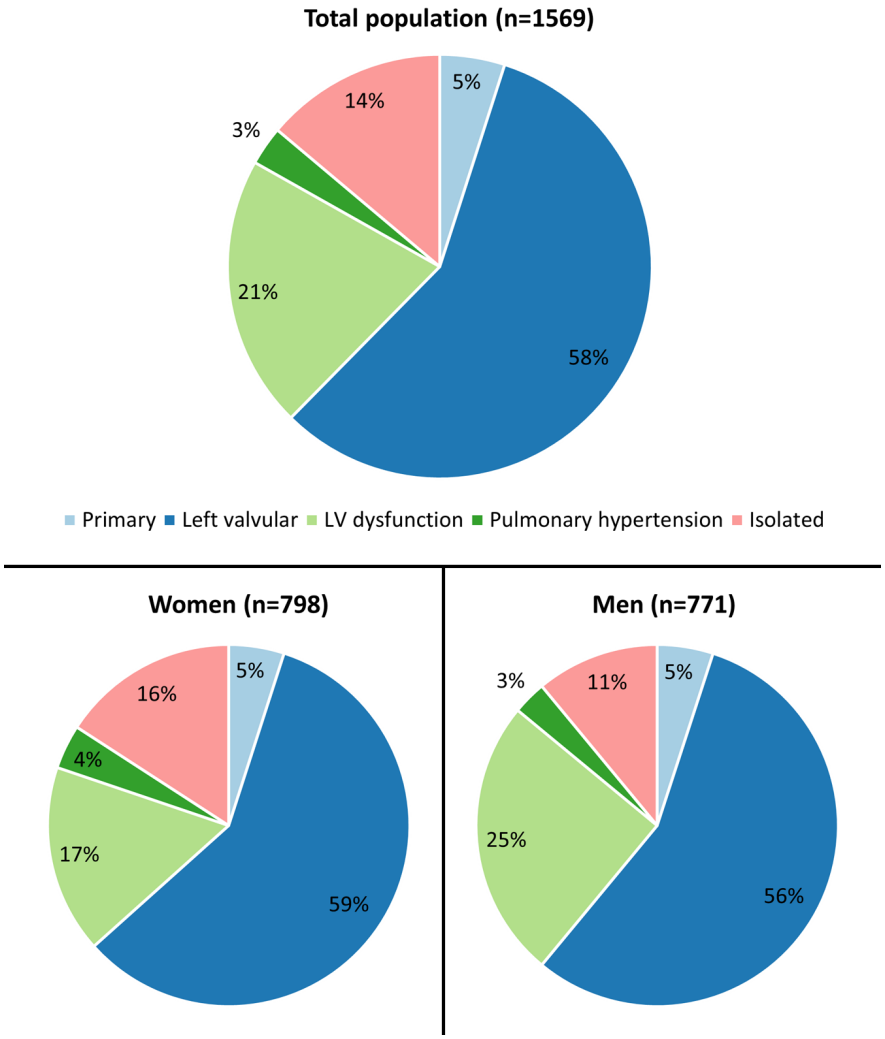

Figure 1. Distribution of tricuspid regurgitation (TR) etiologies in the total unmatched population of patients with moderate and severe TR and the differences between men and women

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

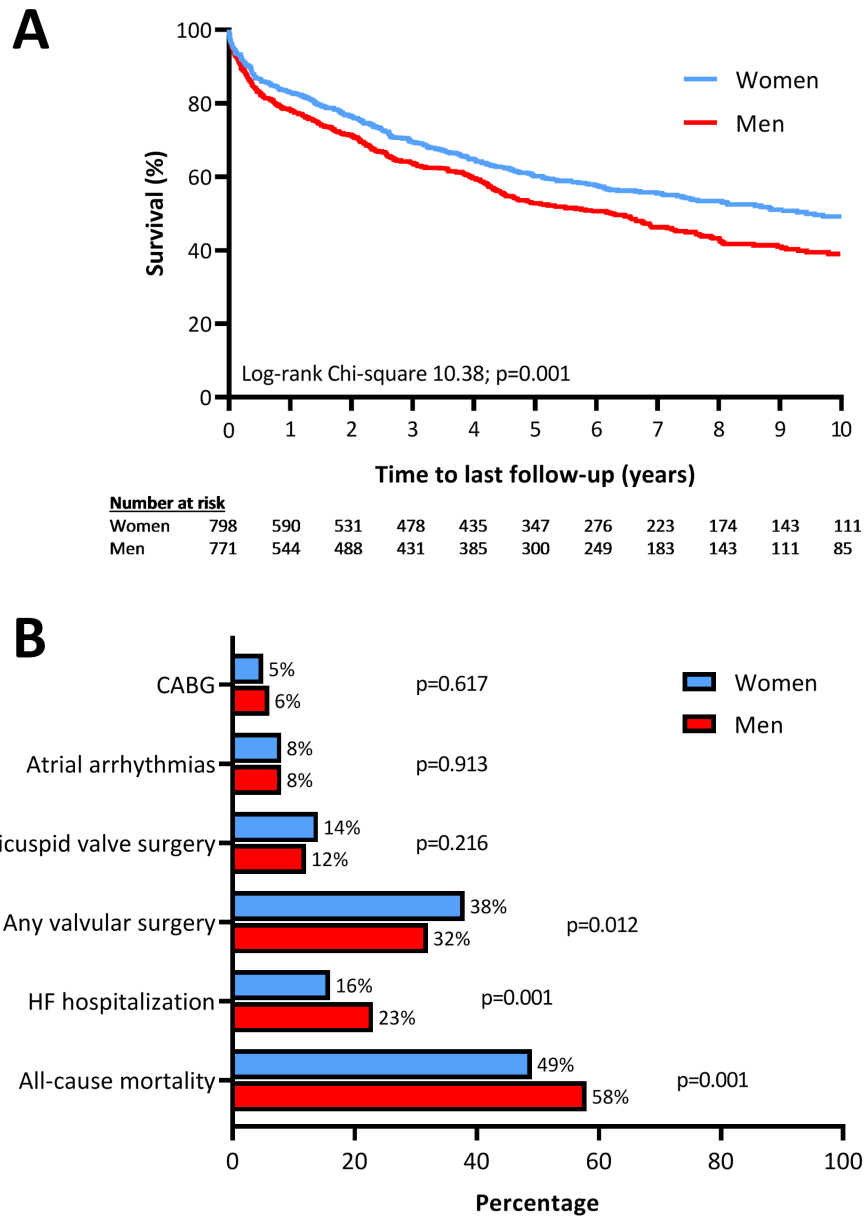

Figure 2. Outcomes according to sex for the total unmatched population of patients with moderate and severe tricuspid regurgitation

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

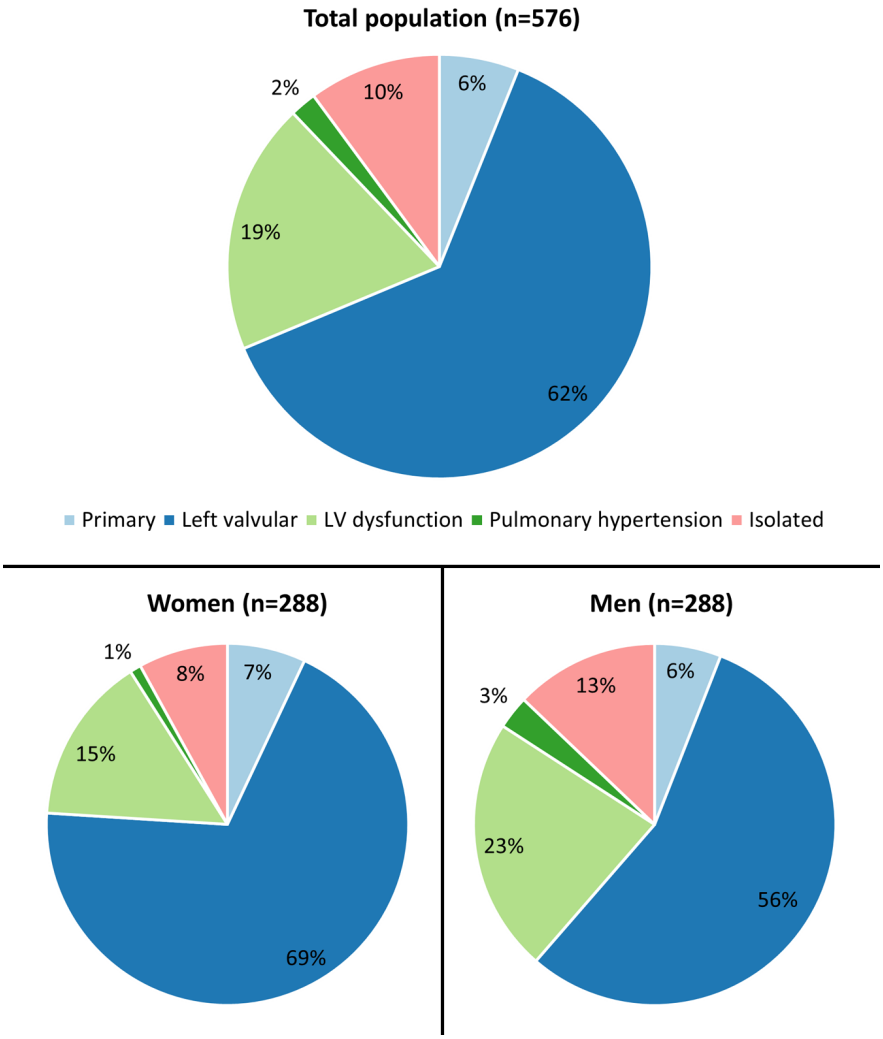

Figure 3. Distribution of tricuspid regurgitation (TR) etiologies in the propensity score matched population of patients with moderate and severe TR and the differences between men and women

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

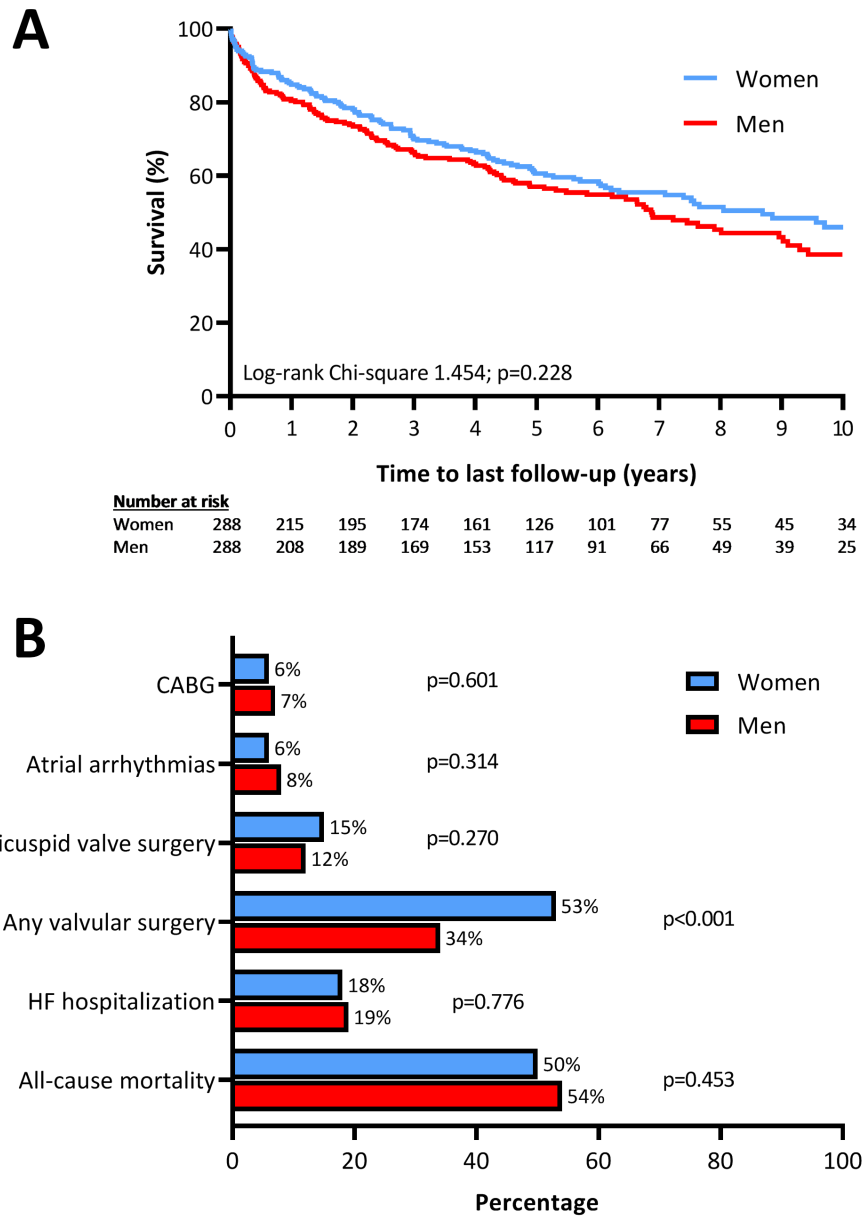

Figure 4. Outcomes according to sex for the propensity score matched population of patients with moderate and severe tricuspid regurgitation

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

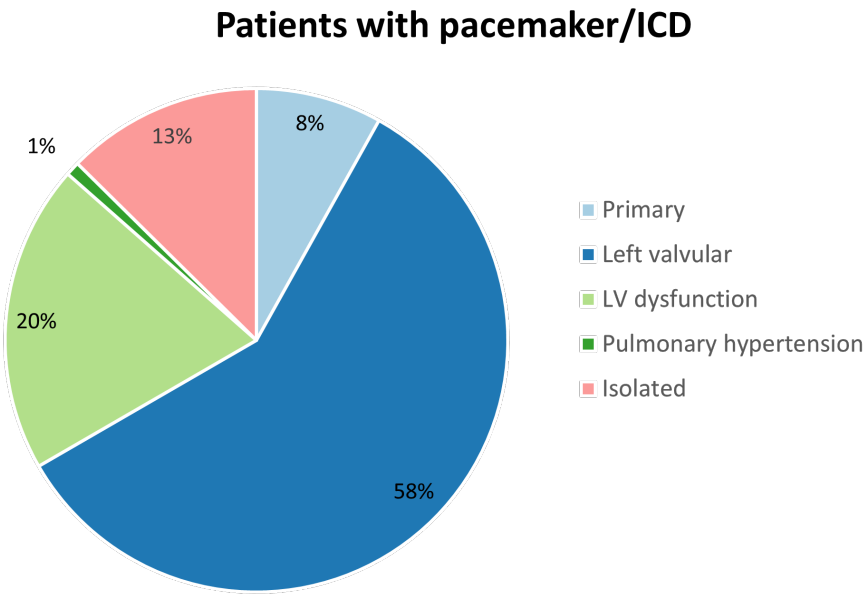
Clinical variables	Echocardiographic variables
Age (years)	LV end diastolic volume (ml/m^2)
Body mass index (kg/m^2)	LV ejection fraction (%)
Hypertension	LA maximum volume (ml/m^2)
Hypercholesterolemia	Significant aortic stenosis
Diabetes mellitus	Significant mitral regurgitation
(Ex-)smoker	RV end 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

Chapter 6

Prognostic implications of significant isolated tricuspid regurgitation in patients with atrial fibrillation without left-sided heart disease or pulmonary hypertension

Marlieke F Dietz, MD; Laurien Goedemans, MD; N Mai Vo, MD; Edgard A Prihadi, MD; Pieter van der Bijl, MBChB, MMed; Bernard J Gersh, MBChB, DPhil; Nina Ajmone Marsan, MD; Victoria Delgado, MD; Jeroen J Bax, MD

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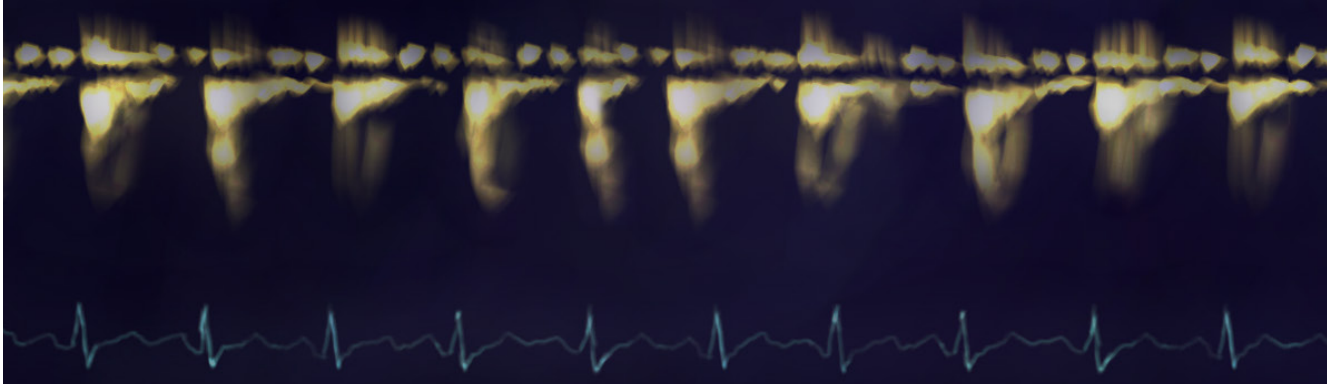

ABSTRACT

Background: The prognostic impact of isolated tricuspid regurgitation (TR) in patients with atrial fibrillation (AF) has not been investigated. The purpose of this study was to investigate the prognostic implications of significant isolated TR in AF patients without left-sided heart disease, pulmonary hypertension or primary structural abnormalities of the tricuspid valve.

Methods: A total of 63 AF patients with moderate and severe TR were matched for age and gender to 116 AF patients without significant TR. Patients were followed for the occurrence of all-cause mortality, hospitalization for heart failure and stroke.

Results: Patients with significant isolated TR (mean age 71±8 years, 57% men) more often had paroxysmal AF as compared to patients without TR (mean age 71±7 years, 60% men) (60% vs. 43%, p=0.028). In addition, right atrial volumes and tricuspid annular diameter were significantly larger in patients with significant isolated TR compared to their counterparts. During follow-up (median 62 [34-95] months), 53 events for the combined endpoint occurred. One- and 5-year event-free survival rates for patients with significant isolated TR were 76% and 56%, compared to 92% and 85% for patients without significant TR, respectively (Log rank Chi-Square p<0.001). The presence of significant isolated TR was independently associated with the combined endpoint (HR, 2.853; 95% CI, 1.458-5.584; p=0.002).

Conclusion: In the absence of left-sided heart disease and pulmonary hypertension, significant isolated TR is independently associated with worse event-free survival in patients with AF.

INTRODUCTION

Isolated tricuspid regurgitation (TR) is an increasingly recognized subtype of TR, which is defined by the absence of concomitant left-sided heart disease or pulmonary hypertension and which is frequently associated with the presence of atrial fibrillation (AF) (1). Isolated TR accounts for 6-10% of all patients with significant (moderate and severe) TR (2, 3). However, due to lack of outcome studies, the management of isolated TR is not clearly addressed in current guidelines (4, 5). Similar to atrial functional mitral regurgitation (6), a significant proportion of patients with isolated TR have AF (7). The prognostic implications of isolated significant TR in patients with AF have not been extensively studied. The aim of this study was therefore to assess the prognostic influence of isolated significant TR in patients with AF in the absence of left-sided heart disease, pulmonary hypertension or primary structural abnormalities of the tricuspid valve.

METHODS

Of 1604 patients with a diagnosis of significant (moderate or severe) TR in the departmental echocardiographic database at the Leiden University Medical Center (LUMC) between June 1995 and September 2016, patients with AF and isolated TR were selected. To identify those patients, a query was performed based on a history of AF. As per current guidelines (8), AF was diagnosed either on 12-lead ECG or during 24-hour Holter ECG monitoring. Subsequently, patients with any of the following conditions which could lead to primary or secondary TR were excluded: structural abnormalities of the tricuspid valve leaflets, significant (moderate or severe) aortic and/or mitral valve disease, previous cardiac surgery, congenital heart disease, left ventricular (LV) ejection fraction <50%, systolic pulmonary artery pressure >40 mmHg, pacemaker or implantable cardioverter defibrillator leads and new onset AF (defined as AF that has not been diagnosed before, irrespective of the duration) (8).

Patients with isolated significant TR were matched for age and gender in a 1:2 ratio by computer-generated frequency matching to patients who underwent echocardiographic evaluation for AF between June 1995 and September 2016, who did not show significant TR and in whom the same exclusion criteria as the significant TR group were applied.

Baseline data included demographic and clinical characteristics at the time of echocardiographic evaluation. Clinical data comprised cardiovascular risk factors, medication use, thyroid hormone levels, creatinine levels, New York Heart Association (NYHA) functional class and type of AF (paroxysmal AF vs. persistent/permanent AF)

(8). Coronary artery disease was defined as previous myocardial infarction or diagnosis of significant stenosis of an epicardial coronary artery (>70%) by invasive coronary angiography.

Data were analyzed retrospectively from the departmental Cardiology Information System (EPD-Vision; Leiden University Medical Center, Leiden, the Netherlands). The institutional review board of the Leiden University Medical Center authorized the study design and waived the need for patient written informed consent for retrospective analysis of anonymously handled data.

Transthoracic echocardiography was performed systematically according to institutional clinical protocols utilizing commercially available ultrasound systems (Vivid 7, E9 and E95 systems; GE-Vingmed, Horton, Norway). All images were digitally stored for offline analysis (EchoPAC version 113.0.3 and 202; GE-Vingmed, Horten, Norway). Parasternal, apical and subcostal views were used to acquire M-mode and 2D images and color, continuous and pulsed wave Doppler data according to the current recommendations (5, 9-11). TR severity was classified using a multiparametric approach based on qualitative, semiquantitative and quantitative assessment (10). Patients were divided into two groups according to TR grade: non-significant (none to mild) TR vs. significant (moderate to severe) TR. LV and left atrial (LA) volumes were measured on the apical 2- and 4-chamber views by the Simpson's biplane method. LV ejection fraction was calculated and expressed as percentage (12). The peak velocity of the transmitral early diastolic flow (E) and late diastolic flow (A) in patients with sinus rhythm were measured and the E/A ratio calculated. The tricuspid annular diameter, right atrial (RA) dimensions, right ventricular (RV) dimensions and RV areas were measured on a focused RV apical view (12). All left and right ventricular and atrial size measurements were indexed for body surface area (BSA) (12). To assess RV systolic function, tricuspid annular plane systolic excursion (TAPSE) was measured on Mmode recordings of the lateral tricuspid annulus in a focused RV apical view. In addition, fractional area change (%) was derived from the RV end-systolic and end-diastolic areas traced on a focused RV apical view (12). The systolic pulmonary artery pressure was estimated based on the TR jet velocity, adding 3, 8 or 15 mmHg based on the inferior vena cava collapsibility (9).

All-cause mortality data were ascertained from the departmental Cardiology Information system, which is updated based on municipal civil registry data. All-cause mortality data were complete for all patients. Last follow-up date corresponded to the date of death or last recorded visit. The primary endpoint for this study was a composite of all-cause

mortality, hospitalization for heart failure and stroke. Secondary endpoints were catheter ablation for AF and tricuspid valve surgery.

Continuous variables are expressed as mean ± SD, or median (interquartile range) in case of Gaussian or non-Gaussian distributions, respectively. Categorical variables are presented as numbers and percentages. Differences between groups were evaluated by the unpaired T-test for normally distributed continuous variables, by the Mann-Whitney U test for continuous variables with skewed distribution and by the chi-square test for categorical variables. Event rates of the composite endpoint (all-cause mortality, hospital admission for heart failure and stroke) were estimated by the Kaplan-Meier method and compared between groups by the Log-rank test. Multivariable Cox proportional hazards regression analysis was performed to determine the clinical and echocardiographic factors that were independently associated with prognosis. The variables included in the multivariable analysis were selected based on the sample size and number of events at follow-up. Variables with a p-value <0.05 in univariable Cox regression analysis and considered of clinical significance were entered into the multivariable model. Odds ratios and 95% confidence intervals (CI) were calculated. P-values were two-sided and values <0.05 were considered of statistical significance. All statistical analyses were performed using SPSS for Windows, version 23 (SPSS Inc, Armonk, NY:IBM Corp).

RESULTS

Of the 1604 patients with significant TR evaluated within the study period, a total of 79 patients (4.9%) were classified as having isolated TR and AF. Sixty-three of these patients could be matched for age and gender by computer-generated frequency matching with 116 AF patients without significant TR, resulting in a total study population of 179 patients (mean age 71±7 years, 59% male).

The baseline clinical characteristics of the overall population and for patients with versus without isolated significant TR are summarized in Table 1. Per design of the study, no significant differences in age and gender were observed between the two groups. The prevalence of hypertension in the overall population was high (84%) and 49% of the patients had hypercholesterolemia. Patients with isolated significant TR were more likely to be on rhythm control, as these patients had more often paroxysmal AF compared to patients without TR (60% vs. 43%, p=0.028). In addition, patients with isolated significant TR less frequently had coronary artery disease, but more often had NYHA functional class >2 heart failure symptoms. In terms of cardiovascular risk factors and medication use, no differences were observed between patients with and without significant TR. Hemoglobin

levels were significantly lower and renal function was worse in patients with significant TR compared to patients without significant TR.

Table 1. Clinical characteristics of the total population with atrial fibrillation and according to tricuspid regurgitation severity

Variable	Overall (n=179)	Tricuspid regurgitation		P-value
		None/mild (n=116)	Moderate/severe (n=63)	
Age (years)	71±7	71±7	71±8	0.940
Men	106 (59%)	70 (60%)	36 (57%)	0.677
Body surface area (m^2)	1.96 ± 0.23	1.98 ± 0.22	1.92 ± 0.25	0.081
Paroxysmal atrial fibrillation	88 (49%)	50 (43%)	38 (60%)	**0.028**
Coronary artery disease	51 (29%)	40 (35%)	11 (18%)	**0.022**
Obstructive pulmonary disease	21 (12%)	14 (12%)	7 (12%)	1.000
NYHA class >2	25 (14%)	7 (6%)	18 (31%)	**<0.001**
Hypertension	143 (84%)	96 (83%)	47 (86%)	0.656
Hypercholesterolemia	83 (49%)	60 (52%)	23 (42%)	0.226
Diabetes mellitus	25 (15%)	17 (15%)	8 (14%)	0.949
(Ex-)smoker	38 (22%)	28 (24%)	10 (18%)	0.352
Medications				
Anticoagulants	129 (76%)	87 (75%)	42 (78%)	0.693
Beta-blockers	114 (67%)	81 (70%)	33 (61%)	0.260
ACE-inhibitors	90 (53%)	58 (50%)	32 (59%)	0.260
Aldosterone antagonists	12 (7%)	6 (5%)	6 (11%)	0.159
Calcium channel antagonists	36 (21%)	24 (21%)	12 (22%)	0.820
Statins	78 (46%)	53 (46%)	25 (46%)	0.941
Diuretics	59 (34%)	37 (32%)	22 (37%)	0.525
Laboratory values				
Hemoglobin (mmol/L)	8.8 (8.0-9.5)	9.0 (8.4-9.2)	8.3 (6.1-9.2)	**<0.001**
Total cholesterol (mmol/L)	4.7 (4.1-5.8)	4.7 (4.2-5.7)	4.9 (3.6-6.4)	0.720
Total cholesterol (mg/dL)	85 (74-105)	85 (76-103)	88 (65-115)	0.720
TSH (mU/L)	1.8 (1.2-3.0)	1.8 (1.2-3.1)	1.8 (1.4-3.0)	0.931
T4 (pmol/L)	17 (15-19)	16 (15-19)	17 (15-21)	0.610
Creatinine (µmol/L)	85 (73-102)	81 (73-96)	95 (73-114)	**0.030**

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; IQR = interquartile range; NYHA = New York Heart Association; SD = standard deviation; TSH = thyroid-stimulating hormone; TR = tricuspid regurgitation

Table 2 shows the echocardiographic characteristics of the overall population with AF and the comparison between the two groups with vs. without isolated significant TR. As per inclusion/exclusion criteria of the current study, LV ejection fraction was normal and subsequently did not differ significantly between groups (no/mild TR: 58% [55-64] vs. moderate/severe TR: 57% [54-62], p=0.335). Right atrial maximum dimensions were significantly larger in patients with isolated significant TR compared to patients without significant TR. As expected, the tricuspid annular diameter was more dilated in patients with isolated significant TR. Interestingly, RV basal and midventricular dimensions were

Table 2. Echocardiographic characteristics of the total population with atrial fibrillation and according to tricuspid regurgitation severity

Variable	Overall (n=179)	Tricuspid regurgitation		P-value
		None/mild (n=116)	Moderate/severe (n=63)	
Heart rate (bpm)	72 (61-85)	69 (59-82)	75 (65-90)	**0.020**
LV end-diastolic volume (ml/m^2)	48 ± 14	48 ± 13	48 ± 16	0.967
LV end-systolic volume (ml/m^2)	20 ± 7	20 ± 6	20 ± 8	0.597
LVEF (%)	58 (54-63)	58 (55-64)	57 (54-62)	0.335
E/A ratio	1.1 (0.8-1.5)	1.0 (0.8-1.3)	1.5 (1.0-2.6)	**<0.001**
LA maximum volume (ml/m^2)	42 (30-56)	41 (31-50)	48 (29-60)	0.145
Tricuspid annular diameter (mm)	38 ± 8	35 ± 5	43 ± 9	**<0.001**
RV basal dimension (mm/m^2)	23 ± 4	22 ± 3	24 ± 4	**<0.001**
RV mid dimension (mm/m^2)	18 ± 3	17 ± 3	19 ± 4	**<0.001**
RV longitudinal dimension (mm/m^2)	38 ± 5	38 ± 5	37 ± 6	0.065
RV end-diastolic area (cm^2/m^2)	12 (10-14)	12 (10-14)	12 (10-14)	0.642
RV end-systolic area (cm^2/m^2)	7 (6-8)	7 (6-8)	7 (6-9)	0.608
RV fractional area change (%)	39 ± 12	38 ± 11	39 ± 13	0.535
TAPSE (mm)	20 ± 6	21 ± 6	17 ± 5	**<0.001**
Systolic pulmonary artery pressure (mmHg)	30 (25-35)	32 (27-36)	27 (24-33)	**0.001**
RA maximum area (cm^2/m^2)	11 (9-15)	10 (9-11)	16 (13-19)	**<0.001**
RA long-axis dimension (mm/m^2)	29 (26-33)	27 (25-31)	34 (30-38)	**<0.001**
RA short-axis dimension (mm/m^2)	23 (21-27)	22 (19-24)	28 (25-32)	**<0.001**

Values are mean ±SD, median (IQR) or n (%). P-value by unpaired t-test or Mann-Whitney U test for non-Gaussian and Gaussian distributed continuous variables, respectively. P-value by chi-square test for categorical variables. AF = atrial fibrillation; E/A = ratio of mitral inflow peak early diastolic flow-velocity to atrial contraction peak-velocity; IQR = interquartile range; LA = left atrium; LV = left ventricular; RA = right atrial; RV = right ventricular; SD = standard deviation; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation

significantly larger in patients with TR, while no significant differences in RV areas and fractional area change were observed between groups. However, RV function measured with TAPSE was significantly less in patients with significant TR.

During a median follow-up of 62 (34-95) months, 53 adverse events for the combined endpoint occurred. Of the overall population, 19 patients (11%) were hospitalized for heart failure, 16 (10%) had a stroke and 37 patients (21%) died. All-cause mortality and the amount of hospitalizations for heart failure during follow-up were significantly higher in patients with isolated significant TR compared to patients without significant TR. During follow-up, 47 patients (27%) underwent catheter ablation and 6 patients with isolated significant TR received tricuspid valve annuloplasty (Table 3). In the overall population, the cumulative event-free survival for the combined endpoint at 1 year and 5 years was 87% and 75%, respectively. Figure 1 shows the Kaplan-Meier curves for event-free survival of the combined endpoint according to the presence or absence of isolated significant TR. At longterm follow up, the clinical outcome was significantly worse in patients with TR (Log rank Chi-Square: 18.694; p<0.001). One- and 5-year event-free survival rates for patients with isolated significant TR were 76% and 56%, compared to 92% and 85% in patients without significant TR, respectively.

Table 3. Follow-up variables for the overall population with atrial fibrillation and according to tricuspid regurgitation severity

Variable	Overall (n=179)	Tricuspid regurgitation		P-value
		None/mild (n=116)	Moderate/severe (n=63)	
All-cause mortality	37 (21%)	14 (12%)	23 (37%)	**<0.001**
Stroke	16 (10%)	7 (7%)	9 (15%)	0.085
Hospital admission for heart failure	19 (11%)	5 (4%)	8 (13%)	**0.039**
Catheter ablation	47 (27%)	30 (26%)	17 (28%)	0.774
TR surgery	6 (3%)	0 (0%)	6 (10%)	**0.001**

Values are n (%).

TR = tricuspid regurgitation

In the multivariable Cox proportional hazard model adjusted for age, gender, NYHA functional class >2, renal function and RV function, the presence of isolated significant TR was independently associated with the combined endpoint of all-cause mortality,

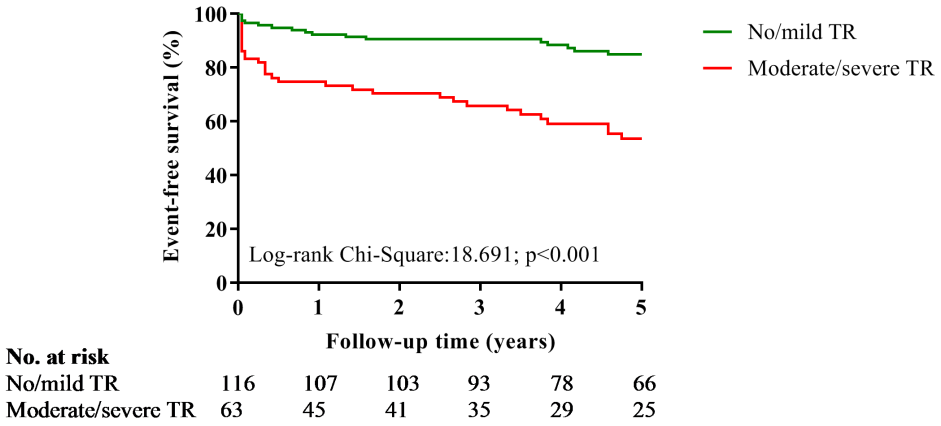

Figure 1. Kaplan-Meier curves for freedom of adverse events (death, hospital admission for heart failure, stroke) in atrial fibrillation patients with versus without significant isolated tricuspid regurgitation

In 179 age and gender matched atrial fibrillation patients without left-sided heart disease, pulmonary hypertension, or primary structural abnormalities of the tricuspid valve, isolated moderate and severe TR was associated with worse long-term prognosis in terms of mortality, hospitalization for heart failure and stroke compared to patients without isolated significant TR.

AE = adverse events; TR = tricuspid regurgitation

hospitalization for heart failure and stroke (Table 4). In addition, older age, NYHA functional class >2 and worse renal function were significantly associated with the combined endpoint.

DISCUSSION

TR is a heterogenous disease with diverse characteristics due to various underlying mechanisms. Isolated TR is a morphologic type of TR characterized by the absence of primary tricuspid valve abnormality, left-sided heart disease and pulmonary hypertension (1). Compared to left-sided heart disease-related TR, isolated TR is associated with older age, female sex and a high prevalence of AF (7, 13). Because longstanding AF leads to right atrial enlargement and subsequent tricuspid annular dilation, various studies have suggested AF to be a major cause of isolated TR (6, 14, 15). Park et al. (15) demonstrated in 89 patients with lone AF that persistent AF was independently associated with greater TR severity compared to paroxysmal AF. Interestingly, in the current study, patients with isolated significant TR more often had paroxysmal AF as compared to patients without significant TR. However, duration and burden of AF was not taken into account in the current study, which could be of influence on TR severity.

Table 4. Univariable and multivariable Cox proportional hazard models for freedom of adverse events (death, hospital admission for heart failure, stroke) for patients with atrial fibrillation

Variable	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Age	1.053 (1.012-1.095)	**0.012**	1.061 (1.012-1.113)	**0.015**
Male gender	0.959 (0.552-1.663)	0.881	0.676 (0.352-1.297)	0.239
BSA (m^2)	0.563 (0.160-1.990)	0.373		
Paroxysmal atrial fibrillation	1.431 (0.823-2.486)	0.204		
Coronary artery disease	1.142 (0.646-2.020)	0.647		
NYHA class >2	3.069 (1.685-5.589)	**<0.001**	2.179 (1.089-4.357)	**0.028**
Hemoglobin	0.698 (0.575-0.847)	**<0.001**		
Creatinine	1.007 (1.004-1.009)	**<0.001**	1.006 (1.003-1.010)	**<0.001**
Heart rate	1.009 (0.996-1.022)	0.181		
LVEF	1.003 (0.958-1.050)	0.902		
E/A ratio	1.275 (0.937-1.735)	0.122		
TAPSE	0.940 (0.898-0.985)	**0.010**	1.023 (0.968-1.081)	0.427
Systolic pulmonary artery pressure	0.975 (0.936-1.015)	0.213		
RA maximum area, indexed	1.048 (0.994-1.104)	0.080		
Tricuspid annulus diameter	1.049 (1.015-1.081)	**0.004**		
Significant TR	3.130 (1.810-5.415)	**<0.001**	2.853 (1.458-5.584)	**0.002**

BSA = body surface area; CI = confidence interval; E/A = ratio of mitral inflow peak early diastolic flow-velocity to atrial contraction peakvelocity; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; RA = right atrial; RV = right ventricular; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation

The strong association between AF and isolated significant TR is confirmed in the present study. Nevertheless, AF and isolated significant TR do not always coexist and other mechanisms such as a fibrous skeleton of the tricuspid annulus with less structural integrity or senescent annular degeneration may contribute to the development of isolated TR (13, 16).

Compared to other morphologic types of TR, prognosis in patients with isolated TR is relatively good (1, 2). It has been suggested that TR, in the context of other cardiac diseases, is not the cause of worse prognosis, but a surrogate for the associated comorbidities (17). The absence of cardiac comorbidities such as pulmonary hypertension, left-sided valvular disease or LV systolic dysfunction, suggests isolated TR to be the ideal etiology to investigate the prognostic implications of TR itself. However, previous studies investigating the prognostic impact of isolated TR are scarce and significant variation in the definition of isolated TR challenge the interpretation of discrepant results (14, 18, 19). The inclusion and exclusion criteria used by Topilsky et al. (20) are most congruent with the definition of isolated TR as described by Prihadi et al. (1) and therefore the most comparable to our study. In that study, AF patients with and without isolated significant TR were compared (similar to the current study), and the results confirmed that isolated TR has a significant influence on mortality and cardiac events in patients with AF, independent of RV size and function (20). A more recent study compared 89 patients with moderate to severe isolated TR (assessed qualitatively) to a group of healthy individuals matched for age, sex, LV ejection fraction, systolic pulmonary artery pressure and comorbidity index in a sub-analysis and demonstrated that isolated significant TR was associated with increased mortality after adjustment for AF(2). Interestingly, only 68% of patients with isolated significant TR had AF.

Tricuspid valve surgery for isolated TR is associated with high in-hospital mortality and morbidity due to complications, e.g. right-sided heart failure (21). However, recent studies have shown that an acceptable mortality rate can be reached in patients without RV dysfunction or pulmonary hypertension (22). AF patients with isolated TR may be the best candidates for tricuspid valve annuloplasty, since TR in these patients is mainly caused by annular dilation while other cardiac comorbidities are absent (16). Nevertheless, clinical decision making remains challenging with the limited data on prognosis in isolated TR at our disposal, leading to low referral rates for surgical treatment, which increase only after the onset of right heart failure. In the retrospective cohort described by Axtell et al (23), 72% of patients had evidence of right heart failure at the time of diagnosis, but more than a quarter experienced a delay of more than a year before surgical referral. Prospective

studies are needed to assess optimal timing for surgery in this particular group of patients. A clinical risk score for isolated tricuspid valve surgery as proposed by LaPar et al. could be useful but needs validation (24).

The present study is subject to the limitations inherent to a single-center retrospective cohort study. Assessing the stability of TR over time would have been subject to bias as follow-up echocardiography was not performed at fixed timepoints. Due to the strict definition of isolated TR, the final study population was limited to 179 patients. However, these exclusion criteria are necessary to minimize heterogeneity between patients and assess the true impact of TR on prognosis. The use of cut-off values for reduced LV systolic function and pulmonary hypertension are based on current guidelines (9, 12). However, they may have led to over- or underestimation of the total population of patients with isolated TR, since not all patients with a LV ejection fraction <50% or systolic pulmonary artery pressure >40 mmHg develop significant TR. The inevitable small number of events has led to a multivariable analysis with few variables to prevent overfitting of the model. The main challenge of a case-control study is the identification of an appropriate control-group. In the current study, we have chosen controls with AF without significant TR instead of healthy individuals to be able to demonstrate the added prognostic impact of TR and eliminate the confounding factor of AF. As AF may be asymptomatic, the duration of diagnosis is often difficult to determine, which is why we did not take AF duration into account in the current study.

In conclusion, patients with isolated moderate and severe TR showed more RA dilation and RV conical remodeling than patients with AF and without TR. Furthermore, isolated significant TR was independently associated with worse long-term prognosis in terms of mortality, hospitalization for heart failure and stroke compared to patients without isolated significant TR. These results emphasize the need for prospective studies investigating the effect of early intervention in patients with AF and isolated significant TR.

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Chapter 7

The obesity paradox in patients with significant tricuspid regurgitation: effects of obesity on right ventricular remodeling and long-term prognosis

Marlieke F Dietz, MD; Edgard A Prihadi, MD; Pieter van der Bijl, MBChB, MMed; Nina Ajmone Marsan, MD; Jeroen J Bax, MD; Victoria Delgado, MD

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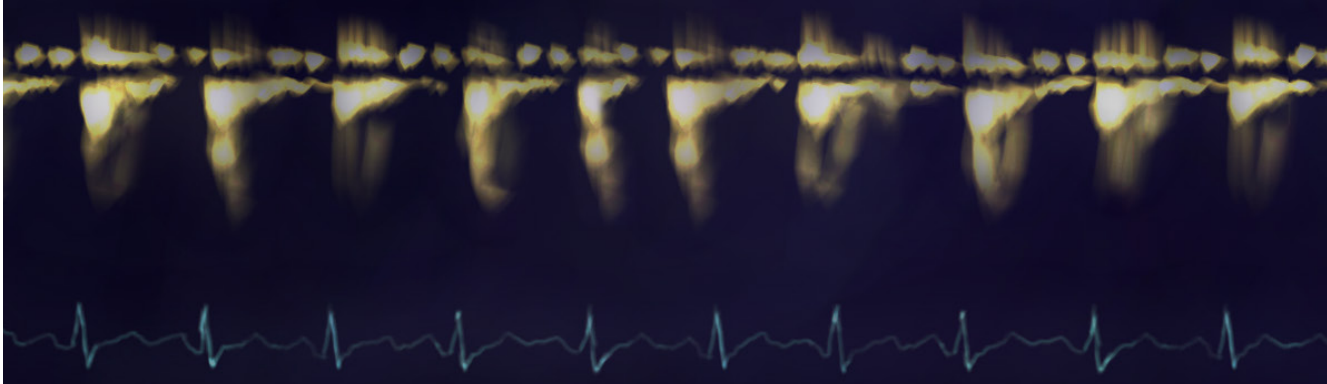


ABSTRACT

Background: Obesity may cause right ventricular (RV) remodeling due to volume overload. However, obesity is also associated with better prognosis compared to normal weight patients in various cardiac diseases.

Objective: The aim of this study was to assess the impact of obesity on RV remodeling and long-term prognosis in patients with significant (moderate and severe) tricuspid regurgitation (TR).

Methods: A total of 951 patients with significant TR (age 70 [61-77] years, 50% male) were divided into 3 groups according to body mass index (BMI): normal weight (BMI 18.5-24.9 kg/m^2), overweight (BMI 25-29.9 kg/m^2) and obese (BMI≥30 kg/m^2). Patients with congenital heart disease, peripheral edema, active endocarditis and BMI<18.5 kg/m^2 were excluded. RV size and function for each group were measured by transthoracic echocardiography and compared to reference values of healthy study populations. The primary endpoint was all-cause mortality. Event rates were compared across the 3 BMI categories.

Results: 476 (50%) patients with significant TR had a normal weight, 356 (37%) were overweight and 119 (13%) patients were obese. RV end-diastolic and end-systolic areas were larger in overweight and obese patients compared to normal weight patients. However, no differences in RV systolic function were observed. During a median follow-up of 5 years, 358 (38%) patients died. Five-year survival rates were significantly better in overweight and obese patients compared to patients with normal weight (65% and 67% compared to 58%, respectively, p<0.001 and p=0.005). In multivariable analysis, overweight and obesity were independently associated with lower rates of all-cause mortality compared to normal weight (HR, 0.628; 95% CI, 0.493-0.800 and HR, 0.573, 95% CI 0.387-0.848, respectively).

Conclusion: In patients with significant TR, overweight and obese patients demonstrated more RV remodeling compared to patients with normal weight. Nevertheless, a higher BMI was independently associated with better long-term survival, confirming the obesity paradox in this context.

INTRODUCTION

Obesity is a rapidly growing problem in the modern society and a known risk factor for the development of heart failure (1). Hemodynamic and metabolic changes due to excessive adipose tissue in patients with a high body mass index (BMI) may increase total blood volume and cardiac output (2). The resulting pressure and volume overload are associated with various changes in cardiac morphology and function in the general community, including right ventricular (RV) dilation and dysfunction (3). By a similar mechanism, significant (moderate or severe) tricuspid regurgitation (TR) causes volume overload of the RV and is often associated with RV dilation and/or dysfunction at first presentation (4). Whether a high BMI enhances RV remodeling and dysfunction in patients with significant TR has never been investigated.

Several studies have demonstrated the independent influence of RV dysfunction on prognosis in patients with significant TR (4, 5). The association between high BMI and RV dysfunction in different patient populations would suggest that obesity enhances the development of RV dysfunction and has a negative effect on prognosis in patients with significant TR (3, 6). However, in patients with certain established cardiovascular diseases, a higher BMI is associated with lower mortality, known as the obesity paradox (7). No studies to date have investigated if the obesity paradox exists in patients with significant TR.

More insight into the effects of BMI on RV remodeling and function and the influence on prognosis in patients with significant TR is needed. Therefore, the aim of the current study was to assess the impact of overweight and obesity on RV remodeling and long-term prognosis in a large cohort of patients with significant TR.

METHODS

Patients

A query was performed in the departmental echocardiographic database of the Leiden University Medical Center (Leiden, the Netherlands) whereby 1,598 patients with significant (moderate and severe) TR between June 1995 and September 2016 were selected. TR was diagnosed by a multiparametric approach in agreement with current recommendations, including qualitative, semi-quantitative and quantitative data of the regurgitant jet, tricuspid valve characteristics, right atrial (RA) and RV size (8, 9). Patients with congenital heart disease, previous tricuspid valve surgery or endocarditis of the tricuspid valve at baseline were excluded. For inclusion in the present study, patients were

required to have height and weight data documented at the time of first echocardiographic diagnosis of significant TR to derive baseline BMI by the following formula: body weight (kg) divided by height squared (m^2). Those patients with peripheral edema at baseline, which could lead to incorrect BMI measurements, were excluded. Patients were divided into BMI categories according to current guidelines (10). Because of the small number of underweight patients in the current database, 3 BMI categories were examined and compared in the final study population: patients with normal weight (BMI 18.5-24.9 kg/m^2), overweight (BMI 25-29.9 kg/m^2) and obesity (BMI ≥30 kg/m^2) (Figure 1).

The first transthoracic echocardiogram diagnosing significant (moderate and severe) TR marked the baseline time point for the subsequent survival analyses. Demographic and clinical data at baseline were collected retrospectively in the departmental Cardiology Information System (EPD-Vision; Leiden University Medical Center). Clinical characteristics included New York Heart Association (NYHA) functional class, cardiovascular risk factors, relevant comorbidities, laboratory values and medication use. The institutional review board of the Leiden University Medical Center approved the observational design of the current retrospective study of clinically acquired anonymized data and waived the need for written informed consent of the patients.

Echocardiography

Transthoracic 2-dimensional echocardiography was performed according to current recommendations (8, 11). Commercially available ultrasound systems (Vivid 7, E9 and E95 systems; GE-Vingmed) equipped with 3.5 MHz or M5S transducers were used. Images were digitally stored for offline analysis using EchoPAC version 113.0.3 and 202 software (GE-Vingmed, Horten, Norway). M-mode, bidimensional and color, continuous- and pulsed-wave Doppler data were obtained from parasternal long- and short-axis, apical and subcostal views. Left ventricular (LV) ejection fraction was derived from LV end-diastolic and end-systolic volumes measured on apical 2- and 4-chamber views by the Simpson method (11). The peak velocity of the early diastolic flow (E) and late diastolic flow (A) across the mitral valve in patients with sinus rhythm were measured and the E/A ratio was derived (12). Significant (moderate or severe) aortic stenosis was defined by an aortic valve area ≤ 1.5 cm^2 as calculated using the continuity equation (13). Mitral regurgitation and TR were assessed based on qualitative, semi-quantitative and quantitative measurements evaluated on bidimensional, color, continuous and pulsed wave Doppler data and graded according to current recommendations (8). All dimensions and areas of the RA, RV and the tricuspid valve annulus were measured on the RV focused apical 4-chamber view. RV systolic pressure was estimated based on the TR peak jet velocity with continuous wave

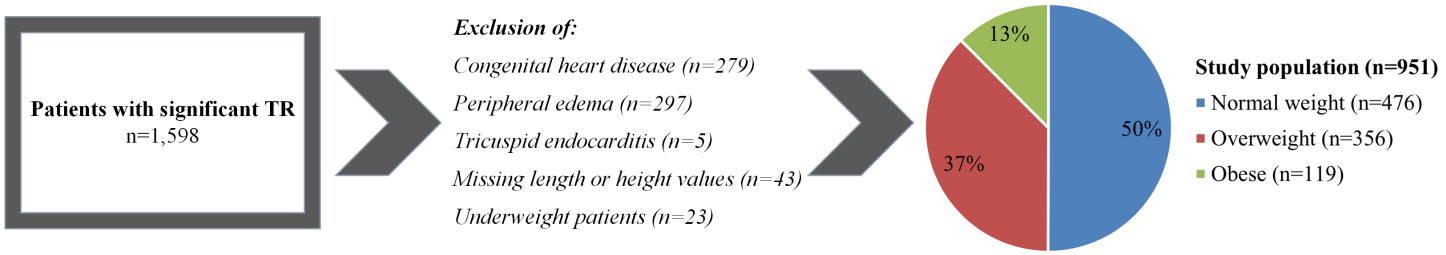


Figure 1. Flowchart of the selection of the study population and the distribution of body mass index categories in patients with significant tricuspid regurgitation

TR= tricuspid regurgitation

Doppler using the modified Bernoulli equation (14). RV systolic function was assessed by tricuspid annular plane systolic excursion (TAPSE), which was measured on M-mode recordings of the lateral tricuspid annulus in an RV focused apical 4-chamber view. Additionally, fractional area change was derived from RV end-diastolic and end-systolic areas (11). From the RV focused apical view, 2-dimensional RV free wall longitudinal strain was measured and calculated as the mean of the RV lateral basal, mid and apical segments and values are presented as absolute values (15). All left and right atrial and ventricular dimensions, areas and volumes were corrected for height for comparison across BMI categories. Furthermore, median RV end-diastolic areas of all groups were compared to reference values of the current recommendations, the Atherosclerosis Risk in Communities (ARIC) study and the Coronary Artery Risk Development in Young Adults (CARDIA) study, to define RV remodeling in patients with TR (3, 11, 16).

Outcome

Patient follow-up started on the day of first diagnosis of significant TR by echocardiography. The primary endpoint for the current study was all-cause mortality. Date of death was ascertained from the departmental Cardiology Information System and the Social Security Death Index and was available for all patients. Secondary endpoints were hospitalization for heart failure, tricuspid valve surgery and any other valve surgery and were obtained from the departmental Cardiology Information System.

Statistical analysis

Continuous variables with Gaussian distribution are presented as mean ± standard deviation. Non-normally distributed continuous variables are presented as median (interquartile range [IQR]). Categorical variables are presented as frequencies and percentages. Differences between BMI categories were analyzed using the one-way analysis of variance for continuous variables in case of Gaussian distribution, the Kruskal-Wallis test for continuous variables in case of non-Gaussian distribution and the Pearson χ^2 test for categorical variables. Post hoc correction for multiple comparisons between groups was performed by the Bonferroni method.

Kaplan-Meier curves were used to estimate cumulative 1- and 5-year survival rates. Differences between BMI categories were compared using the log-rank test. Likewise, Kaplan-Meier curves were composed for the combined endpoint of all-cause mortality and hospitalization for heart failure. Cox proportional hazards models were used to investigate the independent associates of all-cause mortality and of the combined endpoint of all-cause mortality and hospitalization for heart failure. Clinical and echocardiographic variables that were different between BMI categories at baseline and possible confounders

for the association between BMI and mortality in patients with TR were included in the univariable analysis. Variables with a P-value <0.1 in the univariable analysis were considered significant for entry in the multivariable analysis. A tolerance level of >0.5 was set to avoid multicollinearity between the univariable determinants. No collinearity was detected, thus all parameters that were significantly associated with all-cause mortality in univariable analysis were included in the multivariable model. The proportional-hazards assumption was confirmed using statistics and graphs on the basis of the Schoenfeld residuals. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated. All tests were 2-sided and P-values <0.05 were considered significant. Statistical analyses were performed with SPSS for Windows, version 25 (SPSS Inc, Armonk, NY:IBM Corp).

RESULTS

After the exclusion of patients with congenital heart disease (n=279), tricuspid valve endocarditis (n=5), peripheral edema (n=297), those with missing length or height values (n=43) and patients with a BMI <18.5 kg/m^2 (n=23), a total of 951 patients with significant TR were included in the final study population. In 49% of the cases, the patient was hospitalized at the time of the first diagnosis of significant TR. At the time of first diagnosis of significant TR, 476 patients (50%) had a normal weight, 356 patients (37%) were overweight and 119 (13%) patients were obese (Figure 1).

Clinical characteristics

The clinical characteristics of all patients and according to BMI categories are summarized in Table 1. The median age was 70 years (IQR 61-77) and 477 patients (50%) were male. Patients with significant TR were often limited in their physical activity, with 336 patients (39%) presenting in NYHA functional class III and IV heart failure symptoms. Pre-existing hypertension was common (81%) and approximately half of the patients had atrial fibrillation (48%).

In per-group analysis, obese patients were more often female (63%) and less tall (168 ± 9 cm) than those with normal weight (50% and 171 ± 10 cm, p=0.002 and p=0.003; respectively). Overweight and obese patients were more likely to have hypercholesterolemia and diabetes mellitus compared to patients with normal weight (p=0.009 and p<0.001, respectively). Furthermore, use of diuretics and statins was more prevalent in patients with a higher BMI (p=0.022 and p=0.015, respectively). No significant differences across BMI categories were observed in hemoglobin, creatinine and urea level.

Table 1. Baseline clinical characteristics of the overall population of patients with significant tricuspid regurgitation and according to body mass index

	Overall (n=951)	Normal weight (n=476)	Overweight (n=356)	Obese (n=119)	P-value
Age, years	70 (61-77)	71 (60-78)	69 (61-77)	69 (59-75)	0.282
Male sex	477 (50)	236 (50) ‡	197 (55) ‡	44 (37) *†	**0.002**
Weight, kg	75 ± 14	67 ± 10 †‡	80 ± 9 *‡	94 ± 12 *†	**<0.001**
Height, cm	171 ± 10	171 ± 10 ‡	172 ± 10 ‡	168 ± 9 *†	**0.003**
BSA, m^2	1.9 ± 0.2	1.8 ± 0.2 †‡	2.0 ± 0.2 *‡	2.1 ± 0.2 *†	**<0.001**
BMI, kg/m^2	26 ± 4	23 ± 2 †‡	27 ± 1 *‡	33 ± 3 *†	**<0.001**
NYHA class >II	336 (39)	160 (38)	126 (38)	50 (47)	0.175
Hypertension	714 (81)	354 (80)	266 (80)	94 (85)	0.532
Hypercholesterolemia	419 (47)	187 (42) †‡	171 (52) *	61 (55) *	**0.009**
Diabetes mellitus	148 (17)	51 (12) †‡	59 (18) *‡	38 (34) *†	**<0.001**
(Ex-)smoker	271 (31)	131 (30)	109 (33)	31 (28)	0.571
Coronary artery disease	362 (38)	169 (36)	147 (42)	46 (39)	0.264
Pacemaker/ICD	348 (37)	167 (36)	138 (39)	43 (36)	0.625
Atrial fibrillation	421 (48)	204 (46)	159 (48)	58 (52)	0.528
Chronic obstructive pulmonary disease	114 (13)	58 (13)	42 (13)	14 (13)	0.987
Hemoglobin, mmol/L	8.0 (6.9-8.8)	8.1 (7.1-8.8)	8.0 (6.9-8.9)	7.7 (6.4-8.6)	0.071
Creatinine, µmol/L	89 (73-116)	89 (72-114)	90 (77-117)	88 (69-123)	0.145
Urea, mmol/L	8.1 (6.0-11.3)	8.1 (6.0-11.3)	8.2 (6.3-11.5)	7.8 (5.7-10.9)	0.446
Diuretics	495 (54)	226 (49)	199 (57)	70 (60)	**0.022**
Statins	401 (46)	180 (41) †	164 (50) *	57 (53)	**0.015**

*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. normal weight, †p < 0.05 vs. overweight, ‡p < 0.05 vs. obese).*

BMI = body mass index; BSA = body surface area; ICD = implantable cardiac defibrillator; IQR = interquartile range; NYHA = New York Heart Association; SD = standard deviation

Echocardiographic characteristics

Table 2 summarizes the echocardiographic characteristics of the total population and the comparisons across BMI categories. The mean LV ejection fraction of the overall population was 45 ± 15% and highest in obese patients (48 ± 14%, p=0.041). Concomitant significant aortic stenosis or mitral regurgitation was present in 180 (21%) and 249 patients (26%), respectively.

After correction for height, patients with overweight had larger LV end-diastolic and end-systolic volumes compared to patients with normal weight and obesity (p=0.006 and p=0.003, respectively). In contrast, RV end-diastolic and end-systolic areas were significantly larger in both overweight and obese patients compared to those with normal weight (p<0.001). RV systolic function as measured by TAPSE was reduced in the overall study population (16 ± 5 mm) and did not differ significantly across BMI categories (p=0.153). In contrast, RV free wall strain was significantly more impaired in obese patients compared to patients with normal weight and overweight. The tricuspid annulus diameter and RV linear diameters as well as the left and right atrium were largest in obese patients.

Quantitative data on TR severity were available for 852 patients. Overweight and obese patients had more severe TR compared to normal weight patients based on quantitative parameters, but not according to the multiparametric approach (Table 2). A sensitivity analysis was performed to assess the relationship between BMI and RV size in different TR grades based on effective regurgitant orifice area (EROA). In patients with quantitatively assessed severe TR (EROA≥40mm^2), a similar progression of RV end-diastolic area along with increasing BMI was demonstrated as in the overall population (Supplemental Table 1).

RV remodeling according to BMI in patients with significant TR

According to the most recent recommendations, the normal range for RV end-diastolic area when indexed to body surface area (BSA) is 4.5-11.5 cm^2/m^2 for women and 5-12.6 cm^2/m^2 for men (11). Similar 95% reference limits were reported in the Coronary Artery Risk Development in Young Adults (CARDIA) study by Ogunyankin et al. (16) including a large population of healthy young adults. In the current study of patients with significant TR, RV dilation was frequent: median RV end-diastolic area of 11.5 cm^2/m^2 (IQR 9.3-14.0) for women and 12.9 cm^2/m^2 (IQR 10.8-16.0) for men. Linear dimensions also showed RV basal (47 ± 8 mm) and midventricular (36 ± 9 mm) dilation, as compared to current limits of normality (25-41 mm and 19-35 mm, respectively) (11). In contrast, the mean longitudinal diameter of the RV in patients with significant TR (75 ± 12 mm) was within the normal range summarized in the guidelines (59-83 mm) (11).

Table 2. Baseline echocardiographic characteristics of the overall population of patients with significant tricuspid regurgitation and according to body mass index

	Overall (n=951)	Normal weight (n=476)	Overweight (n=356)	Obese (n=119)	P-value
Heart rate, bpm	78 ± 18	79 ± 17	77 ± 18	80 ± 19	0.183
LV end-diastolic volume/height, mL/m	65 (47-97)	63 (45-91) †	69 (50-104) *	65 (46-94)	**0.006**
LV end-systolic volume/height, mL/m	34 (22-58)	32 (21-54) †	38 (24-68) *	31 (23-51)	**0.003**
LV ejection fraction, %	45 ± 15	46 ± 15	44 ± 15 ‡	48 ± 14 †	**0.041**
E/A ratio	1.5 (1.0-2.6)	1.3 (0.9-2.5)	1.6 (1.1-2.7)	1.8 (1.2-2.8)	**0.026**
LA maximum volume/height, mL/m	53 (34-75)	49 (33-74)	57 (36-74)	60 (39-78)	**0.029**
Significant aortic stenosis	180 (21)	94 (22)	65 (20)	21 (19)	0.715
Significant mitral regurgitation	249 (26)	128 (27)	97 (28)	24 (20)	0.273
Tricuspid annulus diameter/height, mm/m	24 ± 4	24 ± 5 ‡	25 ± 4	25 ± 4 *	**0.006**
RV basal diameter/height, mm/m	26 ± 5	26 ± 5	26 ± 4	27 ± 4	0.143
RV midventricular diameter/height, mm/m	20 ± 5	20 ± 5 ‡	20 ± 5	21 ± 5 *	**0.034**
RV longitudinal diameter/height, mm/m	42 ± 7	41 ± 6 †‡	42 ± 7 *	43 ± 7 *	**<0.001**
RV end-diastolic area/height, cm^2/m	13 (11-17)	13 (10-16) †‡	14 (11-17) *	15 (11-18) *	**<0.001**
RV end-systolic area/height, cm^2/m	8 (6-11)	8 (6-11) †‡	9 (7-12) *	9 (7-12) *	**<0.001**
RV systolic pressure, mmHg	32 (25-42)	31 (25-41)	33 (25-42)	33 (25-44)	0.615
RA maximum area/height, cm^2/m	15 (12-19)	15 (11-18) †‡	16 (12-20) *	16 (12-20) *	**0.001**
TAPSE, mm	16 ± 5	16 ± 5	15 ± 5	16 ± 5	0.153
RV fractional area change, %	36 ± 13	37 ± 13	35 ± 13	37 ± 12	0.310
RV free wall longitudinal strain (%)	15.6 ± 7.4	16.6 ± 7.3	15.5 ± 7.4	12.4 ± 7.1	**<0.001**
Severe tricuspid regurgitation	188 (20)	101 (21)	62 (17)	25 (20)	0.370
Leaflet tenting height, mm	10 (0-14)	8 (0-13) †‡	10 (0-15) *	12 (6-16) *	**<0.001**
PISA radius (mm)	12 ± 4	11 ± 4 †‡	12 ± 4 *	13 ± 4 *	**<0.001**
EROA (mm^2)	68 (45-102)	61 (42-93) †‡	72 (47-109) *	75 (49-131) *	**0.001**
RVol (ml/beat)	66 (41-102)	58 (37-91) †‡	71 (45-108) *	77 (47-120) *	**<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. normal weight, †p < 0.05 vs. overweight, ‡p < 0.05 vs. obese).*
E/A = ratio of mitral inflow peak early diastolic flow velocity to atrial contraction peak velocity; EROA = effective regurgitant orifice area; IQR = interquartile range; LA = left atrial; LV = left ventricular; PISA = proximal isovelocity surface area; RA = right atrial; RV = right ventricular; RVol = regurgitant volume; SD = standard deviation; TAPSE = tricuspid annular plane systolic excursion

Table 3. Occurrence of the outcome parameters in the overall population and according to body mass index during follow-up

	Overall (n=951)	Normal weight (n=476)	Overweight (n=356)	Obese (n=119)	P-value
Death	358 (38)	200 (42)	120 (34)	38 (32)	**0.019**
Hospital admission for heart failure	144 (15)	66 (14)	61 (17)	17 (14)	0.412
Tricuspid valve surgery	76 (8)	36 (8)	27 (8)	13 (11)	0.451
Any valve surgery	111 (12)	55 (12)	38 (11)	18 (16)	0.439

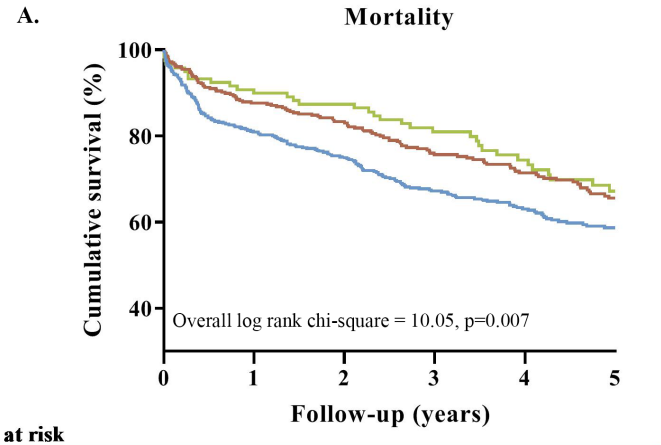
Values are n (%).

To the best of our knowledge, only the sub-study of the Atherosclerosis Risk in Communities (ARIC) trial (3) considered BMI to correct for cardiac abnormalities independent of comorbidities in obese patients in a population of 4343 patients aged 69-82 years who were free of coronary artery disease and heart failure. Overall, RV end-diastolic areas were larger in our population with significant TR (normal weight men, 25 cm^2 [IQR 20-31]; normal weight women, 19 cm^2 [16-24]) compared to patients in the ARIC study (normal weight men, 22 ± 5 cm^2; normal weight women; 16 ± 4 cm^2). The association between increasing BMI and larger RV end-diastolic area demonstrated in the ARIC study for both sexes is comparable to our findings: RV end-diastolic area in overweight men was 26 cm^2 (22-31) in patients with TR compared to 22 ± 5 cm^2 in patients of the ARIC sub-study and RV end-diastolic area in obese men was 28 cm^2 (23-37) compared to 23 ± 5 cm^2, respectively. In the current study, RV end-diastolic area was significantly larger in overweight and obese patients compared to normal weight patients in both men and women (p=0.005 and p<0.001, respectively).

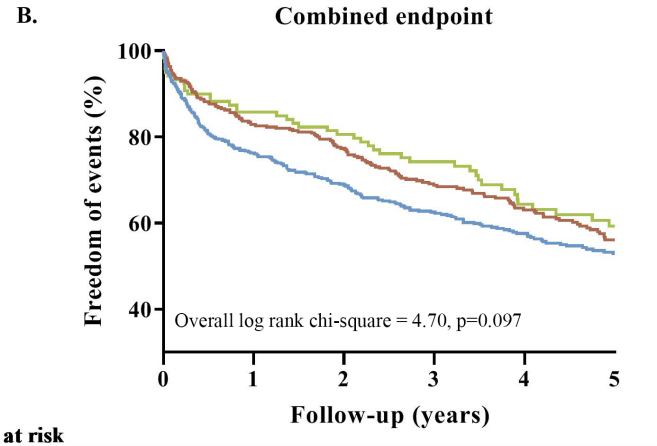
Long-term follow-up

During a median follow-up of 5 years (IQR 29-60 months), 358 patients (38%) died. In this period, 144 patients (15%) were hospitalized for heart failure. Only 76 patients (8%) received tricuspid valve annuloplasty or replacement while 111 out of 429 patients with concomitant valvular disease in this cohort had other valvular surgery during follow-up (Table 3). In the evaluation of outcome according to the BMI categories, the Kaplan-Meier analysis demonstrated a significant better survival for patients with overweight and obesity compared to those with normal weight (overall log rank Chi-square 10.05; p=0.007) (Figure 2A). One and 5-year survival rates were 81% and 58% in patients with normal weight, 87% and 65% in overweight patients, and 90% and 67% in obese patients, respectively. The Kaplan-Meier curves for the combined endpoint of all-cause mortality and hospital admissions for heart failure were similar across the BMI categories (overall log rank chi-square 4.70; p=0.097) (Figure 2B).

Univariable and multivariable Cox proportional hazard models for the primary endpoint are presented in Table 4. In multivariable analysis, overweight and obesity were independently associated with better survival compared to normal weight (HR, 0.628; 95% CI, 0.493-0.800; p<0.001 and HR, 0.573; 95% CI, 0.387-0.848; p=0.005, respectively). When introducing BMI as a continuous variable, higher BMI was also independently associated with better survival (HR, 0.934; 95% CI, 0.903-0.965; p<0.001). Additionally, older age, higher creatinine, diuretic use, larger LV end-diastolic volume and lower TAPSE were independently associated with all-cause mortality. Regarding the composite endpoint,



N. at risk						
Normal weight	476	381	318	235	177	138
Overweight	356	307	256	198	156	118
Obese	119	105	94	75	58	45



N. at risk						
Normal weight	476	363	309	248	189	143
Overweight	356	293	256	196	158	119
Obese	119	101	92	75	55	43

Figure 2. Kaplan-Meier curves for survival (A) and the combined endpoint of hospital admissions for heart failure and survival (B) according to body mass index in patients with significant tricuspid regurgitation

Table 4. Univariable and multivariable Cox proportional hazard models for mortality in patients with tricuspid regurgitation with BMI in categories (model 1) and BMI as continuous variable (Model 2)

Variable	Univariate analysis		Multivariate analysis – Model 1		Multivariate analysis – Model 2	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Age	1.024 (1.015-1.033)	**<0.001**	1.027 (1.017-1.037)	**<0.001**	1.026 (1.016-1.036)	**<0.001**
Male sex	1.290 (1.048-1.589)	**0.016**	1.010 (0.796-1.282)	0.936	0.988 (0.779-1.254)	0.924
Diabetes mellitus	1.702 (1.322-2.192)	**<0.001**	1.270 (0.951-1.696)	0.105	1.301 (0.977-1.733)	0.072
Hypercholesterolemia	1.074 (0.868-1.327)	0.512				
Creatinine	1.004 (1.003-1.005)	**<0.001**	1.003 (1.002-1.004)	**<0.001**	1.003 (1.002-1.004)	**<0.001**
Diuretics	1.931 (1.545-2.413)	**<0.001**	1.439 (1.118-1.852)	**0.005**	1.425 (1.106-1.836)	**0.006**
LV end-diastolic volume/ht	1.006 (1.004-1.008)	**<0.001**	1.004 (1.002-1.007)	**0.001**	1.004 (1.002-1.007)	**0.001**
LV ejection fraction	0.983 (0.977-0.990)	**<0.001**	0.994 (0.985-1.002)	0.132	0.994 (0.986-1.002)	0.159
E/A ratio	1.005 (0.989-1.022)	0.530				
TA diameter/ht	1.031 (1.007-1.056)	**0.013**	1.008 (0.982-1.035)	0.562	1.010 (0.983-1.037)	0.472
RV end-diastolic area/ht	1.010 (1.003-1.017)	**0.005**	1.006 (0.997-1.015)	0.190	1.006 (0.997-1.015)	0.226
TAPSE	0.952 (0.931-0.974)	**<0.001**	0.971 (0.948-0.995)	**0.017**	0.973 (0.950-0.997)	**0.026**
RV free wall longitudinal strain (each 1% decrease)	1.037 (1.020-1.054)	**<0.001**				
Severe TR	1.197 (0.933-1.535)	0.157				
BMI groups		**0.007**		**<0.001**	----------	-------
Normal weight (reference)	----------	-------	----------	-------	----------	-------
Overweight	0.734 (0.585-0.920)	**0.007**	0.628 (0.493-0.800)	**<0.001**	----------	-------
Obese	0.669 (0.473-0.947)	**0.023**	0.573 (0.387-0.848)	**0.005**	----------	-------
BMI (continuous)	0.951 (0.923-0.979)	**0.001**	----------	-------	0.932 (0.901-0.964)	**<0.001**

BMI = body mass index; CI = confidence interval; E/A = ratio of mitral inflow peak early diastolic flow velocity to atrial contraction peak velocity; ht = height; LV = left ventricular; RV = right ventricular; TA = tricuspid annulus; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation

multivariable analysis showed an independent association between overweight and obesity with better prognosis compared to normal weight (HR, 0.716; 95% CI, 0.573-0.895; p=0.003 and HR, 0.685; 95% CI, 0.483-0.971; p=0.034, respectively) (Supplemental Table 2).

DISCUSSION

The main findings of the current study of a large population of patients with moderate and severe TR are that a higher BMI is associated with a larger RV end-diastolic area, while no differences in RV systolic function were observed across BMI groups. In addition, overweight and obesity were independently associated with lower all-cause mortality compared to normal weight, confirming the existence of the obesity paradox in this cardiac condition. No significant differences in hospitalization for heart failure during follow-up were observed between patients with normal weight, overweight and obesity.

Association between right ventricular remodeling and obesity in patients with significant TR

Significant TR is often associated with RV dilation and dysfunction due to volume overload of the RV (4). Accordingly, the RV size of the overall population in the current study was larger compared to reference values of healthy study populations (11, 16, 17). Obesity may also impact RV structure and function by a multifactorial mechanism of increased RV afterload, increased circulating blood volume, metabolic and neuroendocrine influences, and direct obesity-related myocardial effects (2, 18). The additional impact of obesity on RV dilation and dysfunction in patients with significant TR has not previously been investigated.

Most studies to date investigated RV size in obesity without cardiovascular comorbidities using cardiovascular magnetic resonance imaging (CMR) (19-21). Foppa et al. (19) demonstrated in 1794 participants of the Framingham Heart study that increased BMI was associated with larger RV end-diastolic volume indexed for height in both men and women. In contrast, in 739 subjects without cardiovascular risk factors, women displayed increased RV end-diastolic volume per BMI point increase, while in men no association between RV end-diastolic volume and BMI was demonstrated (20). The MESA-Right Ventricle Study by Chahal et al. (21) is the largest study to date evaluating the association between BMI and RV dimensions. In 4127 individuals without clinical heart disease, overweight and obesity were independently associated with greater RV end-diastolic volume on CMR, even after adjustment for respective LV parameters. Studies using echocardiography to assess RV size in obese individuals are scarce. The only published data

comparing RV end-diastolic area measured by 2-dimensional echocardiography across various BMI categories in a healthy population originates from a sub-study of the ARIC trial by Bello et al. (3), which demonstrated a significantly larger RV end-diastolic area with increasing BMI. Tadic et al. (22) reported similar results for indexed RV volumes measured by 3-dimensional echocardiography in 127 patients with untreated hypertension.

The current study extends these findings by demonstrating the additive effect of overweight and obesity on RV dilation in both men and women with significant TR. Similar to the results presented by Chahal et al. (21) changes in RV size were more pronounced than changes in LV size, suggesting that RV dilation is more than a generalized cardiac adaptation to a larger body size in obese patients. In our population, this difference could be explained by the additional impact of TR on volume overload of the thin walled RV, which is already more susceptible to dilation than the LV.

Despite the association between RV remodeling and obesity, RV systolic function as measured by TAPSE and RV fractional area change was not more impaired in patients with increasing BMI in our data. However, when using speckle tracking echocardiography to assess RV free wall strain, we observed more impaired RV systolic function in patients with larger BMI. Previous studies on the influence of BMI on RV function in different patient populations have yielded conflicting results. Interestingly, the studies that reported RV dilation in individuals without structural heart disease as discussed previously, also reported a significant reduction in RV systolic function in higher BMI groups (3, 21, 22). Likewise, Wong et al. (23) demonstrated a reduction of RV free wall strain in overweight and obese subjects compared to normal weight subjects without overt heart disease. In contrast, 153 obese participants of the Obesity Weight Reduction and Remodeling Study had similar TAPSE as age and gender matched healthy controls (24). Additionally, Takiguchi et al. (25) reported no significant differences in RV fractional area change between all BMI groups in a population of 648 patients hospitalized for decompensated heart failure. In the context of acute myocardial infarction, obese patients even had a better RV function measured by TAPSE than non-obese patients (26). The heterogenous results of these studies may be explained by factors that were not accounted for, such as duration of obesity, or by differences between study populations. In our population, the enhanced RV dilation in obese patients may be an initial adaptive response to increased circulating blood volume in order to preserve RV function by the Frank Starling mechanism. As this mechanism may become maladaptive over time, prospective trials with systematic RV function analysis during follow-up are needed to elucidate if targeting obesity could prevent or reverse RV remodeling and dysfunction.

Association of prognosis and obesity in patients with significant TR

Obesity is associated with the development of various cardiovascular diseases due to hemodynamic, metabolic and neuroendocrine effects of adipose tissue that lead to an unfavorable profile (1). Concordant with these mechanisms, overweight and obese patients in our population had a higher prevalence of obesity-related comorbidities (hypercholesterolemia, diabetes mellitus) and larger left and right atrial and ventricular volumes and areas. Notwithstanding, the current study demonstrated a better long-term survival in overweight and obese patients compared to normal weight patients with significant TR. This 'obesity paradox' for mortality has been described in various patient populations, but the mechanism remains unclear (7, 27, 28). Investigators have suggested several hypotheses, such as the production of protective cytokines by the adipose tissue (29). Moreover, obese patients may have a greater metabolic reserve or could become symptomatic at less severe stages of heart failure, and thus present earlier (29). Others suggested that the prognosis might be impacted by unmeasured confounding factors, as non-purposeful weight loss, leading to worse survival in patients with a lower BMI (29, 30). Banack et al. (31) suggested that the obesity paradox in cardiovascular diseases may be entirely explained by collider stratification bias (a correlation between an exposure and an unmeasured confounder due to selection on a third variable [collider] that is caused by both, which induces a false association between the exposure and outcome in case the confounder also influences the outcome). However, in the current population of patients with significant TR, the role of collider bias is uncertain. Firstly, collider bias can only occur if obesity causes TR. Although obesity is known to increase the risk for cardiovascular diseases as myocardial infarction, hypertension and atrial fibrillation, there is no evidence that obesity causes TR. In subjects of the Framingham Heart Study (32) the severity and prevalence of TR even decreased as a function of increasing BMI. This reverse association makes the hypothesis unlikely that obesity causes TR. However, despite lacking evidence, one may argue that obesity can cause TR by the pathophysiological mechanism of volume overload which leads to RV dilation and tricuspid annulus dilation, thereby causing secondary TR. Assuming obesity does cause TR, collider bias is still not the only explanation for the obesity paradox. As demonstrated by Sperrin et al. (33), for obesity as collider to reverse the harmful effect, the unmeasured confounders must have a very strong effect on TR and mortality. It is unlikely that confounders with such a strong association with TR and mortality are still unknown to the current medical world and therefore not included in the analysis. Consequently, a true physiologic protective effect of obesity on mortality in patients with significant TR is more plausible. Preclinical trials, clinical studies and bias analyses might further elucidate the mechanisms for the obesity paradox.

Interestingly, in the current population of patients with significant TR, higher BMI was not associated with a higher risk for heart failure hospitalization during follow-up, but was independently associated with a lower risk for the combined endpoint of all-cause mortality and heart failure hospitalization. This in contrast to the increased risk of heart failure in overweight and obese subjects as demonstrated in 5,881 participants of the Framingham Heart Study (1). These contrasting results suggest that even though obesity is a risk factor for heart failure in healthy populations, a higher BMI in the presence of established cardiovascular disease like significant TR, is associated with a lower risk for heart failure hospitalization, confirming the presumption of an obesity paradox for heart failure as well.

To the best of our knowledge, the current study is the first to demonstrate the independent association between obesity and prognosis in patients with significant TR. These counterintuitive findings emphasize the need for further studies to confirm our results. Better understanding of the favorable phenotype of obese patients and the mechanism behind the obesity paradox may help clinicians in applying risk-reducing treatment in this patient population.

Study limitations

The current study is subject to limitations inherent to the retrospective and single center design. No information was available on physical activity, the duration of obesity, the distribution of adipose tissue and weight loss, all of which could influence RV remodeling and prognosis (7, 21). BMI, even though it is a surrogate for true body adiposity, is highly correlated to anthropometric measures of body fat (3, 21) and is an easy to use parameter for caregivers in risk stratification.

The presence of obstructive sleep apnea was not documented, even though this disease is associated with obesity and may increase afterload of the RV and thereby enhance RV remodeling due to pulmonary arterial hypertension (34). However, Wong et al. (23) found no relationship between sleep apnea severity and RV characteristics. Furthermore, pulmonary pressures were assessed in our study and did not differ significantly across BMI groups.

No healthy controls were included in the current study. To assess the impact of significant TR and obesity on RV remodeling compared to normal subjects, reference values of RV measurements in healthy subjects from the largest studies to date were used (3, 11, 16, 17). However, data on RV size are challenging to compare because data are inconsistently presented with and without indexation for BSA or height. Current recommendations

differentiate normal values for men and women, but do not specify different normal ranges for higher BMI groups (11). We chose to index RV parameters for height to correct for a generalized cardiac adaptation to a larger body size, but to prevent overcorrection for the effects of obesity. After correction for height, RV size was similar in both sexes in the current study. Explicit guidelines on how to present reference values on RV size could improve comparability across studies.

Measuring RV function by two-dimensional echocardiography is challenging. Given the higher blood volume and compensatory mechanisms that initially lead to increased stroke volume in obese patients, load dependent measurements as TAPSE are not ideal to assess RV systolic function in patients with higher BMI. However, TAPSE is the most validated method and most used in clinical practice (14). Furthermore, similar results were observed with RV fractional area change. Longitudinal data from sequential echocardiograms over time were not analyzed since the data were not gathered systematically (only at the discretion of the treating physician) and may introduce a significant bias.

Conclusion

In a large cohort of patients with moderate and severe TR, overweight and obesity were associated with more pronounced RV dilation compared to normal weight patients. This RV remodeling appears to be adaptive, since no significant differences across BMI groups were observed in RV systolic function. Additionally, higher BMI was independently associated with better survival during long term follow-up, supporting the concept of the 'obesity paradox' being applicable to patients with significant TR.

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Supplemental Table 1. The association between RV end-diastolic area in patients with normal weight, overweight and obesity according to quantitatively assessed TR grades

	Overall (n=852)	EROA<20 (n=44)	EROA 20-39 (n=125)	EROA≥40 (n=683)	P-value
RV end-diastolic area/height, cm^2/m	13 (11-17)	14 (10-17)	12 (10-15)	14 (11-17)	**0.001**
RVEDA/ht in normal weight	13 (10-16)	14 (10-16)	12 (9-14)	13 (11-16)	**0.038**
RVEDA/ht in overweight	14 (11-17)	13 (10-16)	13 (11-17)	14 (11-17)	0.335
RVEDA/ht in obese	15 (12-18)	17 (10-17)	12 (10-12)	15 (12-19)	**0.004**
P-value	**<0.001**	0.719	**0.046**	**<0.001**	

Values are median (IQR).

EROA = effective regurgitant orifice area; ht = height; RV = right ventricular; RVEDA = right ventricular end-diastolic area

Supplemental Table 2. Univariable and multivariable Cox proportional hazard models for the combined endpoint of hospital admissions for heart failure and all-cause mortality in patients with tricuspid regurgitation with BMI in categories (model 1) and BMI as continuous variable (Model 2)

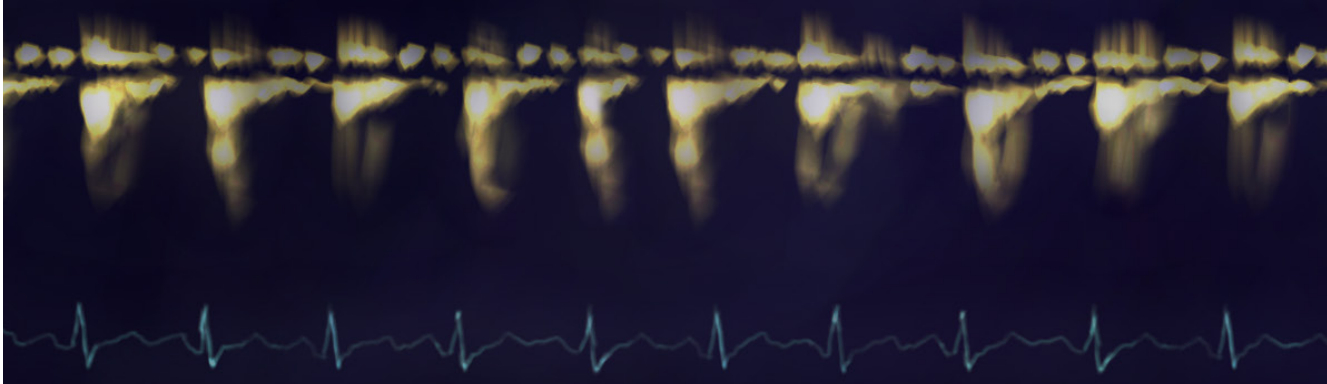
Variable	Univariate analysis		Multivariate analysis – Model 1		Multivariate analysis – Model 2	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Age	1.012 (1.004-1.020)	**0.002**	1.015 (1.006-1.023)	**0.001**	1.014 (1.006-1.023)	**0.001**
Male sex	1.341 (1.105-1.627)	**0.003**	1.034 (0.828-1.290)	0.770	1.015 (0.813-1.267)	0.894
Diabetes mellitus	1.655 (1.305-2.098)	**<0.001**	1.234 (0.934-1.629)	0.138	1.255 (0.951-1.655)	0.108
Hypercholesterolemia	1.225 (1.006-1.493)	**0.044**	0.923 (0.741-1.149)	0.472	0.919 (0.738-1.145)	0.452
Creatinine	1.003 (1.003-1.004)	**<0.001**	1.003 (1.002-1.004)	**<0.001**	1.003 (1.002-1.004)	**<0.001**
Diuretics	2.134 (1.733-2.629)	**<0.001**	1.613 (1.274-2.041)	**<0.001**	1.599 (1.262-2.025)	**<0.001**
LV end-diastolic volume/ht	1.008 (1.006-1.010)	**<0.001**	1.006 (1.004-1.008)	**<0.001**	1.006 (1.004-1.008)	**<0.001**
LV ejection fraction	0.980 (0.974-0.987)	**<0.001**	0.993 (0.986-1.001)	0.088	0.994 (0.982-1.001)	0.103
E/A ratio	1.004 (0.989-1.020)	0.582				
TA diameter/ht	1.031 (1.008-1.054)	**0.008**	1.006 (0.981-1.031)	0.657	1.007 (0.982-1.032)	0.586
RV end-diastolic area/ht	1.010 (1.003-1.017)	**0.004**	1.003 (0.994-1.014)	0.574	1.002 (0.994-1.011)	0.610
TAPSE	0.953 (0.934-0.973)	**<0.001**	0.977 (0.955-0.999)	**0.037**	0.978 (0.957-1.000)	0.052
RV free wall longitudinal strain (each 1% decrease)	1.039 (1.023-1.055)	**<0.001**				
Severe TR	1.140 (0.902-1.442)	0.272				
BMI groups		0.097		**0.005**	----------	-------
Normal weight (reference)	----------	-------	----------	-------	----------	-------
Overweight	0.830 (0.674-1.022)	0.079	0.714 (0.571-0.893)	**0.003**	----------	-------
Obese	0.763 (0.557-1.046)	0.093	0.683 (0.481-0.971)	**0.033**	----------	-------
BMI (continuous)	0.968 (0.943-0.994)	**0.016**	----------	-------	0.952 (0.923-0.981)	**0.002**

BMI = body mass index; CI = confidence interval; E/A = ratio of mitral inflow peak early diastolic flow velocity to atrial contraction peak velocity; ht = height LV = left ventricular; RV = right ventricular; TA = tricuspid annulus; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation

Chapter 8

Summary, conclusions and future perspectives

Samenvatting, conclusies en toekomstperspectieven



8

SUMMARY

The introduction of this thesis (**chapter 1**) provides a state-of-the-art on tricuspid regurgitation encompassing current evidence on epidemiology, mechanisms of disease, clinical presentation, evaluation, prognosis and treatment. New, minimally invasive, transcatheter techniques have demonstrated to be safe and effective in reducing tricuspid regurgitation and improving symptoms of patients with severe tricuspid regurgitation that were not eligible for surgical valve repair or replacement. These achievements have led to increased awareness among clinicians of the burden of severe tricuspid regurgitation in the general patient population and underscore that severe tricuspid regurgitation should not be neglected and should be timely treated.

Understanding tricuspid regurgitation begins with knowledge of the anatomy of the tricuspid valve and the mechanisms behind tricuspid regurgitation. In chapter 1, differences between mechanisms and characteristics of different types of tricuspid regurgitation are described. In addition, the role of echocardiography in the assessment of tricuspid regurgitation severity is introduced. What is currently known about the adverse impact on prognosis and the treatment options for tricuspid regurgitation are also presented. The aim of the current thesis is to increase the understanding of the disease by characterizing tricuspid regurgitation in relation to the right ventricle and the clinical context and by evaluating the associated prognostic implications.

Part I: the right ventricle in secondary tricuspid regurgitation

The first part of the thesis focusses on the relationship between secondary tricuspid regurgitation and the right ventricle. It is known that the right ventricle plays an important role in the vicious circle that causes, maintains and worsens tricuspid regurgitation. It has also been suggested that right ventricular dilation and dysfunction influence prognosis in patients with tricuspid regurgitation.

The aim of **chapter 2** was to characterize right ventricular remodeling and assess the prognostic impact of right ventricular dilation and dysfunction on long-term survival in a large cohort of patients with significant (moderate and severe) secondary tricuspid regurgitation. Patients were divided into four different patterns of right ventricular remodeling according to the presence or absence of right ventricular dilation (defined as a tricuspid annulus diameter ≥40mm) and dysfunction (defined as a tricuspid annular plane systolic excursion <17mm) at the first diagnosis of significant tricuspid regurgitation by transthoracic echocardiography. A combination of right ventricular dilation and dysfunction was present in 43% of the patients. At long-term follow-up, right ventricular

systolic dysfunction was independently associated with worse survival, regardless of the presence of right ventricular dilation.

Chapter 3 builds on the knowledge gained by the previous study. While the prognostic impact of right ventricular dysfunction had been established, the value of adding symptoms of right heart failure in the assessment of prognosis in patients with significant tricuspid regurgitation had never been investigated. In this study, 4 stages or right heart failure were defined in a population of patients with significant secondary tricuspid regurgitation. Patients in stage 1 had a preserved right ventricular function and no signs of right heart failure. In stage 2, patients had right ventricular dysfunction without symptoms of right heart failure. Stage 3 included patients with right ventricular dysfunction as well as right heart failure symptoms and patients in stage 4 presented with right ventricular dysfunction and refractory signs of right heart failure. Higher stages of right heart failure were independently associated with higher all-cause mortality at long-term follow-up. The introduction of this staging system in clinical practice could therefore be potentially valuable in risk stratification of patients with significant secondary tricuspid regurgitation.

Tricuspid valve annuloplasty during left-sided valve surgery is demonstrated to prevent development of significant tricuspid regurgitation and right ventricular dilation directly after surgery. The objective of the study presented in **chapter 4** was to extend this knowledge by assessing the long-term impact of preventative tricuspid valve annuloplasty during mitral valve surgery in patients with primary mitral regurgitation, a dilated tricuspid annulus (≥40mm) and no to mild tricuspid regurgitation. The results show that patients who received tricuspid valve annuloplasty had less right ventricular dilation and less severe tricuspid regurgitation at long-term follow-up. No significant differences in clinical outcome variables, such as all-cause mortality, surgical reintervention, heart failure hospitalization and pacemaker implantation, were demonstrated between patients with and without tricuspid valve annuloplasty, but as the sample size was relatively small, further randomized controlled trials are needed to establish the clinical relevance of preventative tricuspid valve annuloplasty during mitral valve annuloplasty in patients with primary mitral regurgitation.

Part II: tricuspid regurgitation in specific patient populations

In the second part of this thesis, various types of tricuspid regurgitation in specific patient populations are characterized. Tricuspid regurgitation is a heterogeneous disease and prognosis strongly depends on the etiology and clinical context. Therefore, it is important to investigate the clinical and echocardiographic characteristics and prognostic implications of significant tricuspid regurgitation in distinct populations.

In **chapter 5**, differences between men and women in characteristics and prognosis for all etiologies of tricuspid regurgitation are compared. Tricuspid regurgitation etiologies were defined as primary, left valvular disease related, left ventricular dysfunction related, pulmonary hypertension related, or isolated. The etiology of tricuspid regurgitation in women was more often left valvular disease related and isolated whereas men more often had left ventricular dysfunction related tricuspid regurgitation. In the total population, women had better 10-year survival compared to men. After propensity score matching, the influence of sex on survival was neutralized, but the tricuspid regurgitation etiologies remained significantly associated with all-cause mortality. Patients with significant tricuspid regurgitation related to left valvular disease or left ventricular dysfunction had lower survival compared to patients with primary tricuspid regurgitation. Etiology-specific approaches to detection and management of significant tricuspid regurgitation may improve prognosis in both men and women.

Chapter 6 focusses on isolated tricuspid regurgitation in patients with atrial fibrillation. By definition, these patients are free of left-sided heart diseases and pulmonary hypertension. Clinical and echocardiographic characteristics as well as long-term prognosis were compared between age- and gender matched patients with and without significant isolated tricuspid regurgitation. Atrial fibrillation patients with moderate or severe tricuspid regurgitation showed more right atrial dilation and right ventricular conical remodeling than atrial fibrillation patients without significant tricuspid regurgitation. Furthermore, significant isolated tricuspid regurgitation was independently associated with worse long-term prognosis in terms of all-cause mortality, heart failure hospitalizations and stroke. These results emphasize the need for prospective studies investigating the effect of early intervention in patients with atrial fibrillation and significant isolated tricuspid regurgitation.

In **chapter 7**, the impact of body mass index on right ventricular remodeling and prognosis in tricuspid regurgitation is investigated. A large cohort of patients with moderate and severe tricuspid regurgitation was divided into 3 groups according to body mass index: normal weight (body mass index 18.5-24.9 kg/m^2), overweight (body mass index 25-29.9 kg/m^2) and obese (body mass index ≥30kg/m^2). Underweight patients and those with active endocarditis or peripheral edema at baseline were excluded. Overweight and obesity were associated with more pronounced right ventricular dilation compared to normal weight patients. This right ventricular remodeling appears to be adaptive, as no significant differences across body mass index groups were observed in right ventricular

systolic function. Additionally, higher body mass index was independently associated with better survival during long-term follow-up, also known as the 'obesity paradox'.

CONCLUSIONS AND FUTURE PERSPECTIVES

The impact of tricuspid regurgitation in the general community should not be underestimated. Tricuspid regurgitation is typically a disease of the elderly in an ageing world population. Furthermore, the results of the current thesis demonstrate the adverse prognostic impact of moderate and severe tricuspid regurgitation in various contexts.

Two-dimensional transthoracic echocardiography is the preferred imaging method to diagnose tricuspid regurgitation and evaluate the associated right ventricular remodeling, since it is widely available, non-invasive and inexpensive. However, advanced imaging techniques like 3-dimensional echocardiography are emerging and may become the standard procedure to accurately measure tricuspid regurgitation severity and the interaction with the right heart. Assessment of this interaction is of utmost importance, as the right ventricle plays an essential role in the pathophysiology and outcome of tricuspid regurgitation. The development of right ventricular dilation and consequently significant tricuspid regurgitation can be prevented in patients with a dilated tricuspid annulus by performing tricuspid annuloplasty during left valvular surgery. Unfortunately, timing of intervention in patients who already show significant tricuspid regurgitation and right ventricular remodeling has proven difficult, and the high mortality rates after tricuspid valve surgery in current clinical practice demonstrate that we are often too late. The question remains: how early should we intervene in severe tricuspid regurgitation?

In patients with significant tricuspid regurgitation, right ventricular systolic dysfunction is associated with worse prognosis. The presence of symptoms of right heart failure further indicates the risk of mortality in these patients. Incorporation of stages of right heart failure in future risk stratification of patients with significant secondary tricuspid regurgitation may help to identify patients who will benefit from earlier tricuspid intervention. However, validation of this staging system in a broader perspective is needed, as prognosis of significant tricuspid regurgitation is strongly dependent on the etiology and patient characteristics. Appropriate patient selection is key in successful treatment, whether by surgery or transcatheter interventions.

A number of transcatheter tricuspid valve repair devices are currently under investigation. The first results of these studies are promising. Transcatheter therapy may be a solution

for high risk patients with tricuspid regurgitation in the near future, although additional long-term outcomes are needed.

In conclusion, treating patients with tricuspid regurgitation is challenging, but with ongoing and future research on etiology-specific evaluation, advanced imaging techniques, appropriate patient selection for intervention and new therapies, prognosis of patients with significant tricuspid regurgitation can be improved.

SAMENVATTING

De introductie van dit proefschrift (**hoofdstuk 1**) geeft een kort overzicht van de huidige kennis over tricuspidalisklepinsufficiëntie met betrekking tot de epidemiologie, mechanismes van de ziekte, klinische presentatie, evaluatie, prognose en behandeling. Toenemende onderzoeken naar de klinische relevantie van tricuspidalisklepinsufficiëntie in de afgelopen jaren heeft het besef onder clinici en onderzoekers versterkt dat de tricuspidalisklep niet moet worden onderschat. Echter, door een combinatie van langdurige desinteresse en het complexe, heterogene karakter van de ziekte is nog veel over tricuspidalisklepinsufficiëntie onbekend. Het begrijpen van tricuspidalisklepinsufficiëntie begint bij kennis van de anatomie van de tricuspidalisklep en de mechanismes achter tricuspidalisklepinsufficiëntie. Verschillen tussen deze mechanismes en karakteristieken tussen verschillende types tricuspidalisklepinsufficiëntie worden beschreven. Daarnaast wordt de rol van echocardiografie in de beoordeling van de ernst van tricuspidalisklepinsufficiëntie geïntroduceerd. Ook wordt gepresenteerd wat momenteel bekend is over de ongunstige prognose en de behandelingsopties. Het doel van dit proefschrift was om het begrip van de ziekte te vergroten door tricuspidalisklepinsufficiëntie te karakteriseren in relatie tot de rechter ventrikel en de klinische context, en door de daarbij geassocieerde prognose te evalueren.

Deel I: de rechter ventrikel in tricuspidalisklepinsufficiëntie

Het eerste deel van dit proefschrift focust op de verhouding tussen secundaire tricuspidalisklepinsufficiëntie en de rechter ventrikel. Het is bekend dat de rechter ventrikel een belangrijke rol speelt in de vicieuze cirkel die tricuspidalisklepinsufficiëntie veroorzaakt, onderhoudt en verergert. Daarbij wordt gesuggereerd dat rechter ventrikeldilatatie en -disfunctie de prognose van patiënten met tricuspidalisklepinsufficiëntie beïnvloeden.

Het doel van het in **hoofdstuk 2** beschreven onderzoek was het karakteriseren van rechter ventrikel remodellering en het analyseren van de prognostische impact van rechter ventrikeldilatatie en -disfunctie op lange termijn overleving in een groot cohort van patiënten met significante (matige of ernstige) tricuspidalisklepinsufficiëntie. Patiënten werden verdeeld in vier groepen met verschillende patronen van rechter ventriculaire remodellering corresponderend met de aan- of afwezigheid van rechter ventrikeldilatatie (gedefinieerd als tricuspidalisklep annulus diameter ≥40mm) en disfunctie (gedefinieerd als tricuspid annular plane systolic excursion <17mm) op het moment van diagnose van tricuspidalisklepinsufficiëntie door middel van transthoracale echocardiografie. Een combinatie van rechter ventrikeldilatatie en -disfunctie was aanwezig in 43% van de patiënten. Bij lange termijn follow-up was rechter ventrikeldisfunctie onafhankelijk

geassocieerd met slechtere overleving, ongeacht de aanwezigheid van rechter ventrikeldilatatie.

Het onderzoek dat in **hoofstuk 3** wordt gepresenteerd, bouwt voort op de kennis welke is opgedaan bij de vorige studie. De prognostische impact van rechter ventrikeldisfunctie werd aangetoond, maar de toegevoegde waarde van symptomen van rechtszijdig hartfalen bij het analyseren van prognose van patiënten met significante secundaire tricuspidalisklepinsufficiëntie is niet eerder onderzocht. In deze studie werden 4 stadia van rechtszijdig hartfalen gedefinieerd in een populatie van patiënten met significante secundaire tricuspidalisklepinsufficiëntie. Patiënten in stadium 1 hadden een behouden rechter ventrikelfunctie en geen tekenen van rechtszijdig hartfalen. In stadium 2 hadden patiënten rechter ventrikeldisfunctie zonder symptomen passend bij rechtszijdig hartfalen. Stadium 3 includeerde patiënten met zowel rechter ventrikeldisfunctie als tekenen van rechtszijdig hartfalen, en patiënten in stadium 4 hadden rechter ventrikeldisfunctie en refractaire symptomen van rechtszijdig hartfalen. Hogere stadia van rechtszijdig hartfalen waren onafhankelijk geassocieerd met hogere sterfte tijdens lange termijn follow-up. De introductie van dit systeem van stadiering in de klinische praktijk is daardoor van potentiele waarde voor de risicostratificatie van patiënten met significante secundaire tricuspidalisklepinsufficiëntie.

Tricuspidalisklep annuloplastiek tijdens linkszijdige klepchirurgie is aangetoond effectief in het voorkomen van de ontwikkeling van significante tricuspidalisklepinsufficiëntie en rechter ventrikeldilatatie direct na operatie. Het doel van de studie welke wordt gepresenteerd in **hoofdstuk 4** was om deze kennis uit te breiden door de lange termijn impact te onderzoeken van preventieve tricuspidalisklep annuloplastiek tijdens mitralisklepchirurgie bij patiënten met primaire mitralisklepinsufficiëntie, een gedilateerde tricuspidalisklep annulus en geen tot milde tricuspidalisklepinsufficiëntie. De resultaten tonen dat patiënten die een tricuspidalisklep annuloplastiek kregen, minder rechter ventrikeldilatatie en minder ernstige tricuspidalisklepinsufficiëntie bleken te ontwikkelden bij lange termijn follow-up. Geen significante verschillen in klinische uitkomstvariabelen werden gedemonstreerd tussen patiënten met en zonder tricuspidalisklep annuloplastiek. Omdat de steekproefomvang relatief klein was, zijn gerandomiseerde onderzoeken nodig om de klinische relevantie van preventieve tricuspidalisklep annuloplastiek tijdens mitralisklepchirurgie bij patiënten met primaire mitralisklepinsufficiëntie aan te tonen.

Deel II: tricuspidalisklepinsufficiëntie in specifieke patiëntenpopulaties

In het tweede deel van dit proefschrift worden verschillende types tricuspidalisklepinsufficiëntie gekarakteriseerd in specifieke patiëntenpopulaties. Tricuspidalisklepinsufficiëntie is

een heterogene ziekte en de prognose hangt sterk af van de etiologie en klinische context. Daarom is het belangrijk om de klinische en echocardiografische karakteristieken en prognostische implicaties van tricuspidalisklepinsufficiëntie in subgroepen te onderzoeken.

In **hoofdstuk 5** worden verschillen tussen mannen en vrouwen in karakteristieken en prognose voor alle bekende types tricuspidalisklepinsufficiëntie vergeleken. De verschillende etiologieën werden gedefinieerd als primair, gerelateerd aan linkszijdige klepziektes, gerelateerd aan linker ventrikeldisfunctie, gerelateerd aan pulmonale hypertensie of geïsoleerd. Bij vrouwen was de etiologie van tricuspidalisklepinsufficiëntie vaker gerelateerd aan linkszijdige klepziektes of geïsoleerd, terwijl mannen vaker linker ventrikeldisfunctie gerelateerde tricuspidalisklepinsufficiëntie hadden. In de totale populatie hadden vrouwen betere 10-jaarsoverleving dan mannen. Na propensity score matching werd de invloed van geslacht op overleving geneutraliseerd, maar bleven de etiologieën van tricuspidalisklepinsufficiëntie geassocieerd met sterfte door alle oorzaken. Zowel mannen als vrouwen met significante tricuspidalisklepinsufficiëntie gerelateerd aan linkszijdige klepziektes of linker ventrikeldisfunctie hadden een slechtere overleving dan patiënten met primaire tricuspidalisklepinsufficiëntie. Etiologie-specifieke benaderingen voor detectie en behandeling van significante tricuspidalisklepinsufficiëntie zou de prognose van zowel mannen als vrouwen kunnen verbeteren.

In **hoofdstuk 6** focust het onderzoek op geïsoleerde tricuspidalisklepinsufficiëntie bij patiënten met atriumfibrilleren. Per definitie hebben deze patiënten geen linkszijdige hartziektes of pulmonale hypertensie. Bij op leeftijd en geslacht gematchte patiënten met en zonder significante tricuspidalisklepinsufficiëntie werden zowel klinische en echocardiografische karakteristieken als lange termijn prognose vergeleken. Atriumfibrillatie patiënten met matige of ernstige tricuspidalisklepinsufficiëntie hadden meer rechter atriumdilatatie en rechter ventriculaire conische remodellering dan atriumfibrillatie patiënten zonder significante tricuspidalisklepinsufficiëntie. Daarnaast bleek significante geïsoleerde tricuspidalisklepinsufficiëntie onafhankelijk geassocieerd met slechtere lange termijn prognose aangaande sterfte door alle oorzaken, hartfalen hospitalisaties en beroertes. Deze resultaten benadrukken het belang van prospectieve studies die het effect van vroege interventie bij patiënten met atriumfibrilleren en significante geïsoleerde tricuspidalisklepinsufficiëntie onderzoeken.

In **hoofdstuk 7** wordt de impact van body mass index op rechter ventriculaire remodellering en prognose bij tricuspidalisklepinsufficiëntie onderzocht. Een groot cohort patiënten met matige en ernstige tricuspidalisklepinsufficiëntie werd verdeeld in 3 groepen op basis van body mass index: normaal gewicht (body mass index 18.5-24.9

kg/m^2), overgewicht (body mass index 25-29.9 kg/m^2) en obesitas (body mass index ≥30kg/m^2). Patiënten met ondergewicht en met actieve endocarditis op het moment van diagnose van tricuspidalisklepinsufficiëntie werden geëxcludeerd. Overgewicht en obesitas waren geassocieerd met meer uitgesproken rechter ventrikeldilatatie vergeleken met patiënten met een normaal gewicht. Deze rechter ventriculaire remodellering lijkt adaptief te zijn, gezien er geen significante verschillen tussen body mass index groepen werden geobserveerd in rechter ventrikelfunctie. Daarnaast was een hogere body mass index onafhankelijk geassocieerd met betere overleving op lange termijn, wat ook wel de 'obesitas paradox' wordt genoemd.

CONCLUSIES EN TOEKOMSTPERSPECTIEVEN

De impact van tricuspidalisklepinsufficiëntie voor de samenleving moet niet worden onderschat. Tricuspidalisklepinsufficiëntie is typisch een ouderdomsziekte, waardoor de prevalentie de komende jaren verder zal toenemen. Bovendien demonstreren de resultaten in het huidige proefschrift de ongunstige prognostische impact van matige en ernstige tricuspidalisklepinsufficiëntie in verschillende contexten.

Tweedimensionale echocardiografie is tot op heden de beeldvormingsmethode van voorkeur om tricuspidalisklepinsufficiëntie te diagnosticeren en geassocieerde rechter ventriculaire remodellering te evalueren, omdat het ruim beschikbaar, non-invasief en niet duur is. Echter, geavanceerde beeldvormingstechnieken zoals driedimensionale echocardiografie zijn in opkomst en kunnen de standaard procedure worden om accuraat de ernst van de tricuspidalisklepinsufficiëntie en de interactie met de rechter ventrikel te meten. Het evalueren van deze interactie is van groot belang door de essentiële rol die de rechter ventrikel speelt in de pathofysiologie en prognose van tricuspidalisklepinsufficiëntie. De ontwikkeling van rechter ventrikeldilatatie en derhalve significante tricuspidalisklepinsufficiëntie kan bij patiënten met tricuspidalisklep annulusdilatatie worden voorkomen door het uitvoeren van een tricuspidalisklep annuloplastiek ten tijde van een linkszijdige klepoperatie. Helaas is de timing van interventie bij patiënten die geen linkszijdige klepoperatie nodig hebben moeilijker, en de hoge sterftecijfers na tricuspidalisklep interventies in de huidige klinische praktijk tonen dat we vaak te laat zijn. De vraag blijft echter: wat is dan wel het juiste moment voor een interventie?

Bij patiënten met significante tricuspidalisklepinsufficiëntie zijn rechter ventrikeldilatatie en -disfunctie veelvoorkomend, maar alleen rechter ventrikeldisfunctie is geassocieerd met een slechtere prognose. De aanwezigheid van symptomen van rechtszijdig hartfalen kunnen het risico op mortaliteit verder indiceren. Incorporatie van stadia van rechtszijdig

hartfalen in toekomstige risicostratificatie van patiënten met significante secondaire tricuspidalisklepinsufficiëntie zou kunnen helpen om patiënten te identificeren die baat hebben bij vroegere chirurgie of nieuwe percutane behandelingen. Maar omdat de prognose van significante tricuspidalisklepinsufficiëntie sterk afhankelijk is van de etiologie en de patiënt, is het nodig om dit systeem van stadiëring te valideren in een breder perspectief. Selectie van geschikte patiënten is de sleutel tot succesvolle behandeling, zowel bij chirurgie als bij percutane interventies.

Verscheidene percutane tricuspidalisklep reparatie apparaten worden momenteel onderzocht. De eerste resultaten van deze studies zijn veelbelovend. Meer lange termijnuitkomsten zij nodig, maar percutane behandelingen zijn mogelijk een oplossing voor hoog risico patiënten met tricuspidalisklepinsufficiëntie in de nabije toekomst.

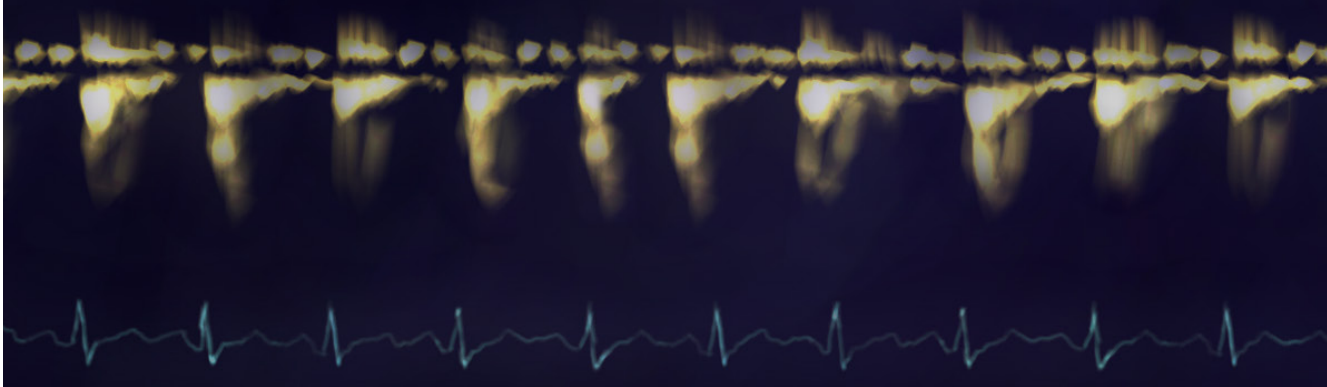
Concluderend is de behandeling van patiënten met tricuspidalisklepinsufficiëntie een uitdaging, maar met huidige en toekomstige onderzoeken naar etiologie-specifieke evaluatie, geavanceerde beeldvormingstechnieken, selectie van geschikte patiënten voor interventie, en nieuwe therapeutische mogelijkheden, kan de prognose van patiënten met significante tricuspidalisklepinsufficiëntie sterk worden verbeterd. De tricuspidalisklep is niet langer de vergeten klep.

8

List of publications

Curriculum vitae

Dankwoord



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**shared first authorship*

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CURRICULUM VITAE

Marlieke Francien Dietz werd geboren op 7 augustus 1992 te Tilburg. In 2010 behaalde zij cum laude haar atheneumdiploma aan het Theresialyceum te Tilburg. Van 2010 tot en met 2016 studeerde zij geneeskunde aan de Universiteit Leiden. Tijdens haar studie deed zij in het kader van haar wetenschappelijke stage onderzoek naar de kwaliteit van de zorg bij de behandeling van het myocardinfarct. Gedurende deze stage is haar speciale interesse voor de cardiologie ontstaan.

Aansluitend aan haar studie heeft Marlieke gewerkt als arts-assistent niet in opleiding op de afdeling cardiologie van het Leids Universitair Medisch Centrum. In 2017 startte zij op deze afdeling haar promotietraject naar tricuspidalisklepinsufficiëntie onder leiding van prof. dr. J.J. Bax en dr. V. Delgado, waarvan de resultaten in dit proefschrift staan beschreven. Tijdens haar promotietraject presenteerde Marlieke de resultaten van deelonderzoeken op verschillende internationale congressen. Op het *European Society of Cardiology Congress* in München in 2018 werd haar presentatie besproken in de hoogtepunten van het congres. In 2019 ontving zij een *best poster award* op het *American College of Cardiology Congress* in New Orleans.

Per 1 december 2020 is Marlieke begonnen met de opleiding Cardiologie vanuit het Leids Universitair Medisch Centrum (opleider dr. S.I.A.P. Trines). Momenteel is zij werkzaam als arts-assistent in opleiding op de afdeling Interne Geneeskunde in het Alrijne Ziekenhuis te Leiderdorp (opleider drs. L. Hardi).

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