Characterization of tricuspid regurgitation and its prognostic implications

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Chapter 3

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

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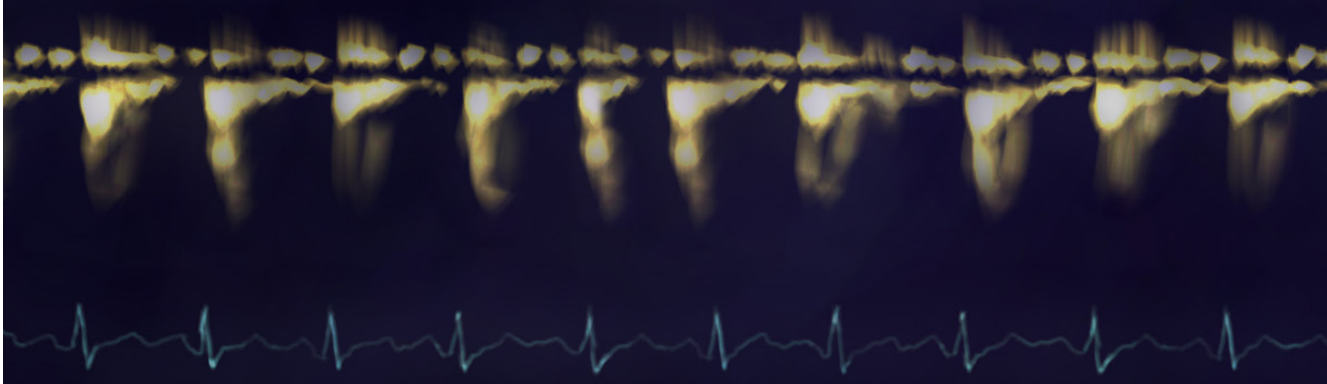


ABSTRACT

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

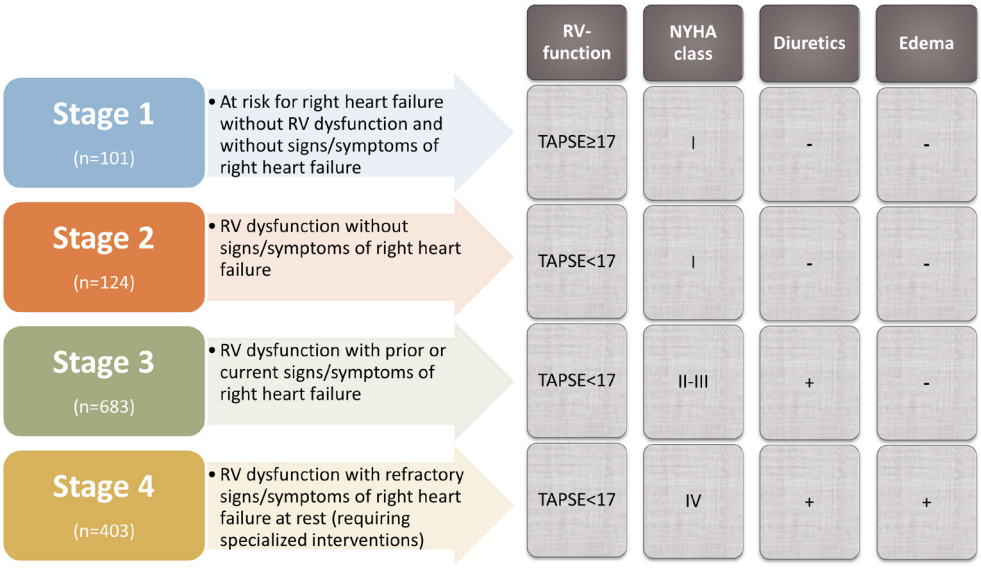


Figure 1. Stages of right heart failure defined by clinical and echocardiographic variables

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).

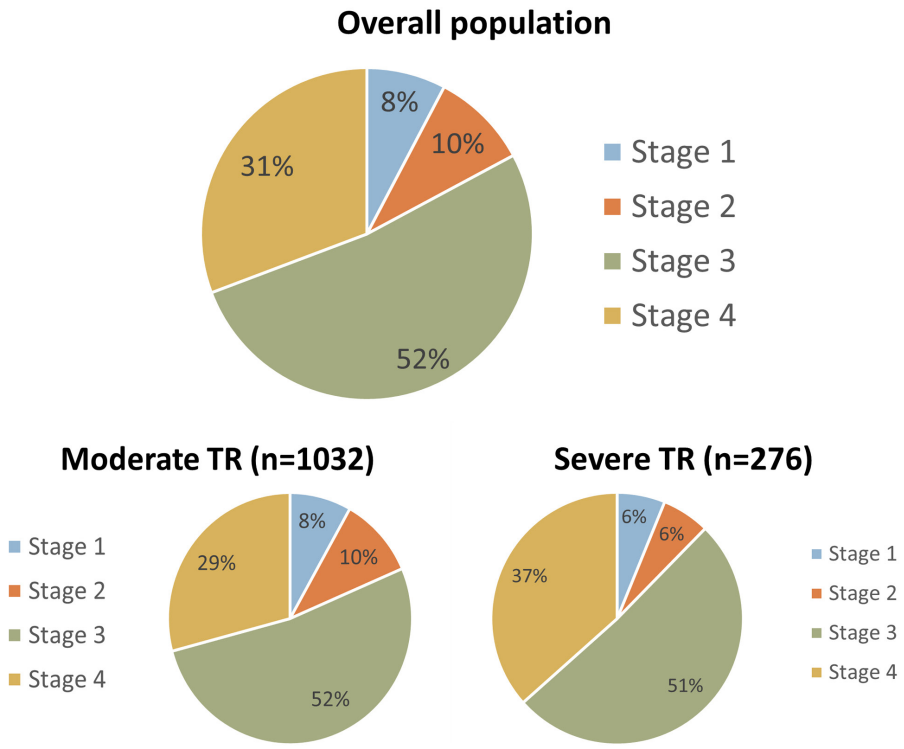


Figure 2. Distribution of patients with significant secondary tricuspid regurgitation across stages of right heart failure for the overall population and according to severity of tricuspid regurgitation

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

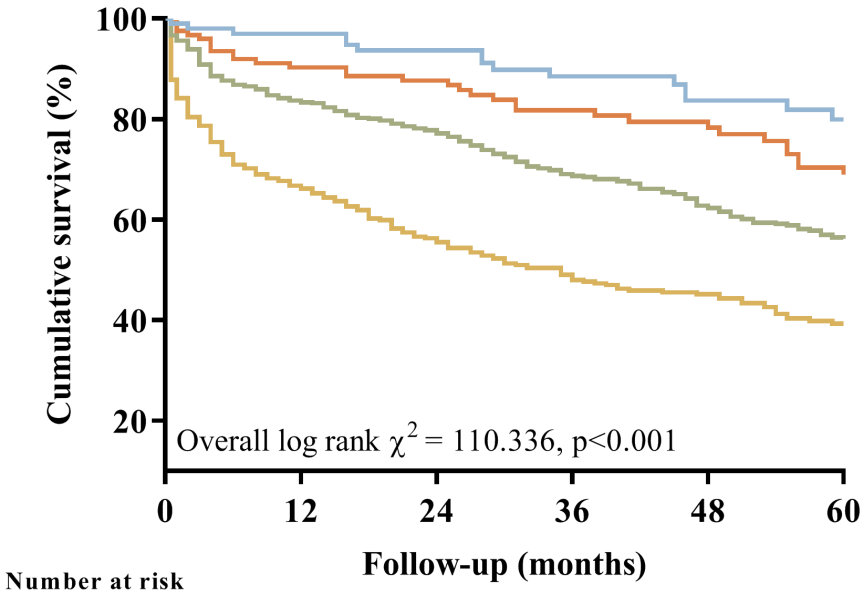
The echocardiographic characteristics of the patients are summarized in Table 2. The mean heart rate was 79 ± 19 beats per minute and 375 patients (29%) had atrial fibrillation during echocardiographic assessment. The mean LV ejection fraction was 44 ± 16% and concomitant significant aortic stenosis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