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Impact of tricuspid regurgitation on survival in patients with chronic heart failure: unexpected findings of a long-term observational study

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Aims Tricuspid regurgitation (TR) is common in patients with chronic heart failure (CHF) but its prognostic impact is unclear.

Methods and results A total of 576 consecutive patients with CHF were prospectively included. The impact of moderate and severe (significant) TR on the combined endpoint death/heart transplantation/left ventricular-assist device implantation was assessed. Patients were followed for 5.8 ± 4.2 (maximum 14.4) years. Kaplan–Meier analysis showed a worse outcome of patients with significant TR ($P < 0.0001$). By multivariable analysis, amino terminal pro B-type natriuretic peptide (NT-proBNP) ($P = 0.0028$), systolic left ventricular function (LVF) ($P = 0.0014$), serum sodium, NYHA functional class, systolic blood pressure, right atrial size (all $P = 0.0001$), but not TR were significantly related with the outcome. However, as soon as the strong interaction between TR and LVF was included in the model, significant TR determined outcome as well ($P = 0.0059$). Therefore, in a second analysis patients were stratified for LVF. In patients with mildly or moderately impaired LVF, TR was significantly related with the outcome (HR: 1.368, CI: 1.070–1.748, $P = 0.0125$), whereas in patients with severely depressed LVF it was not ($P = 0.1401$). As a proof of concept, we additionally stratified patients according to serum NT-proBNP concentrations. In patients with NT-proBNP concentrations below the median (≤280 fmol/mL), TR was related with the outcome (HR: 2.512, CI: 1.127–5.597, $P = 0.0242$) but it was not in patients with NT-proBNP concentrations above the median ($P = 0.3935$).

Conclusion The prognostic impact of TR depends on the severity of CHF. While TR was significantly related with excess mortality in mild to moderate CHF, it provided no additive value in advanced disease when compared with established risk factors.

Keywords Tricuspid regurgitation • Chronic heart failure • Outcome

Introduction

Although significant tricuspid regurgitation (TR) is a common finding, data about its prognostic relevance in chronic heart failure (CHF) are sparse.

Two retrospective studies from the 1990s reported a considerably increased mortality risk of CHF patients with moderate and severe TR.[1,2] However, the interpretation of these studies today is difficult due to the lack of important co-variables like serum levels of natriuretic peptides or renal function. One more recent retrospective study on >5000 patients also demonstrated increased mortality rates among patients with significant TR, independent of left ventricular ejection fraction or pulmonary artery pressure.[3] The major limitation of that study, though, is the lack of information on patient characteristics or co-morbidities other than gender and age.

Except for these few publications, no relevant literature about the prognostic impact of significant TR in CHF patients is available.

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This question, however, is important since TR may be surgically corrected.

Very recently, a study on factors associated with an adverse outcome after tricuspid valve replacement was published in 'Circulation', reflecting the great interest of the scientific community in treatment options in patients with tricuspid valve disease.[4] Operative mortality in that study was high (10%), and the late outcome was determined by the severity of heart failure. However, a beneficial effect of tricuspid valve surgery on clinical outcomes particularly in CHF patients remains uncertain.[5]

To clarify the prognostic value of significant TR in CHF, we performed the present prospective long-term observational study on a well-characterized contemporary cohort of CHF patients, treated according to current heart failure guidelines[6,7] in a tertiary heart failure clinic.

Methods

Between 1995 and 2003, 576 consecutive patients with systolic heart failure who presented to our tertiary care heart failure clinic and agreed to participate were included in this observational, non-interventional study. All data were collected prospectively. According to the study design (non-interventional, purely observational study, initiated in 1995 prior to the publication of the Declaration of Helsinki 1996), written informed consent was not demanded.

Systolic heart failure was defined according to current guidelines.[6] Patients with more than mild aortic or mitral stenosis were excluded. The Ethics Committee of the Medical University of Vienna approved the study protocol.

Patient evaluation and follow-up

Baseline assessment included medical history, assessment of current medication, physical examination, ECG recording, blood tests, and a transthoracic echocardiogram. Patients were re-evaluated at regular intervals every 3 to 9 months, including reassessment as appropriate.

The study endpoint was a combined endpoint consisting of death, heart transplantation, or implantation of a left ventricular-assist device. None of the patients included in this study underwent tricuspid annuloplasty.

Clinical data

Baseline clinical data included: age, gender, height, weight, NYHA functional class, blood pressure, presence of leg oedema, hypercholesterolaemia (total cholesterol >200 mg/dL or patient on lipid-lowering therapy at study entry), diabetes mellitus (fasting blood glucose >126 mg/dL or use of antidiabetic medication/insulin), presence of atrial fibrillation, history of hypertension, presence of coronary artery disease. Serum electrolytes, creatinine, and blood urea nitrogen were routinely measured. To calculate the estimated creatinine-clearance, the Cockcroft-Gault formula was used. Serum amino terminal pro B-type natriuretic peptide (NT-proBNP) was determined using a commercially available test (Elecsys Systems, Roche Diagnostics). NT-proBNP levels are given in fmol/mL, to convert from fmol/mL to pg/mL multiply by 8.457.

Echocardiography

All patients underwent a comprehensive echocardiographic examination by board certified physicians using high-end scanners, such as Siemens Acuson Sequoia C512 and GE Vivid 5 and Vivid 7. The evaluation included M-mode echocardiography, two-dimensional echocardiography, and conventional and colour Doppler ultrasonography according to current recommendations.[8–10] Left ventricular ejection fraction was assessed with the biplane Simpson's method. Right ventricular function was assessed visually in all patients, in 224 patients tricuspid annular plane systolic excursion (TAPSE) was also measured.

Tricuspid regurgitation was quantified by an integrated approach. Echocardiographic parameters used for grading included tricuspid valve morphology; right ventricular, right atrial, and inferior vena cava size; vena contracta width; proximal flow convergence radius; and hepatic venous flow pattern.[9–13]

Moderate and severe TR were considered significant TR and were compared with trace and mild TR. The graduation into non-significant TR (trace/mild) and significant TR (moderate/severe) was chosen to account for inaccuracies due to the semi-quantitative assessment of TR by echocardiography and has previously been deemed reasonable.[2,3,14,15]

Mitral regurgitation was also graded semi-quantitatively, including valve morphology, size of left atrium and left ventricle, proximal regurgitant jet width, proximal flow convergence, and pulmonary venous flow pattern.[9,10]

Statistical analysis

Statistical analysis was performed using SAS 9.1 for Windows. Continuous variables were expressed as mean $\pm$ standard deviation, median and quartiles, and categorical variables were expressed as percentages. Bivariate Kendall Tau correlation coefficients between influence variables were computed.

Differences in baseline characteristics were calculated using the *t*-test and Wilcoxon-test for continuous data, and a χ^2 test for categorical data.

Freedom from death, heart transplantation, and left ventricular-assist device implantation (combined endpoint) was estimated by Kaplan-Meier analysis, using a log-rank test.

A multivariable Cox regression was performed to identify parameters associated with the combined endpoint.

The following parameters were assessed:

(1) Renal function: glomerular filtration rate, serum creatinine, sodium, potassium, blood urea nitrogen.
(2) Neurohormones: NT-proBNP.
(3) Clinical signs of heart failure: NYHA functional class, leg oedema.
(4) Cardiac signs/haemodynamics: presence of atrial fibrillation/sinus rhythm, heart rate, systolic blood pressure.
(5) Co-morbidities: diabetes mellitus, hyperlipidaemia, coronary artery disease, history of arterial hypertension.
(6) Demographics: age, gender, body mass index.
(7) Echocardiographic measurements: left and right ventricular end-diastolic diameter, left and right atrial size, left and right ventricular systolic function, severity of mitral and TR, estimated systolic pulmonary artery pressure.

Groups (1)–(7) were formed because many parameters were significantly correlated. First, a stepwise multivariable Cox regression analysis within each group was performed. In addition, a joint non-stepwise multivariable analysis including all baseline variables was done. Only parameters with multivariate significant influence within each group and with a *P*-value <0.15 in the joint non-stepwise multivariable analysis remained in the final model. A cut-off of 0.15 was chosen not to miss parameters with a potential influence, but also to limit the number of variables in the final multivariable model. For the final multivariable analysis, the significance level was set to 0.05.

In a second analysis, the interaction between left ventricular function and TR was included in the model. To further assess the prognostic impact of TR at different stages of heart failure, patients were divided into groups (i) according to left ventricular systolic function and (ii) according to median serum NT-proBNP concentrations. Multivariable analyses were repeated within these subgroups.

Results

Baseline patient characteristics and echocardiographic data

In a first step, we performed a Kaplan–Meier analysis to compare the outcome in patients with no/mild, moderate, and severe TR (*Figure 1*). This analysis revealed no difference in the outcome between patients with moderate and severe TR. Accordingly patients were divided into a group with no/mild and a group with moderate/severe TR (defined as significant TR).

Baseline patient characteristics according to TR severity are shown in *Table 1*. *Table 2* displays baseline characteristics according to the outcome.

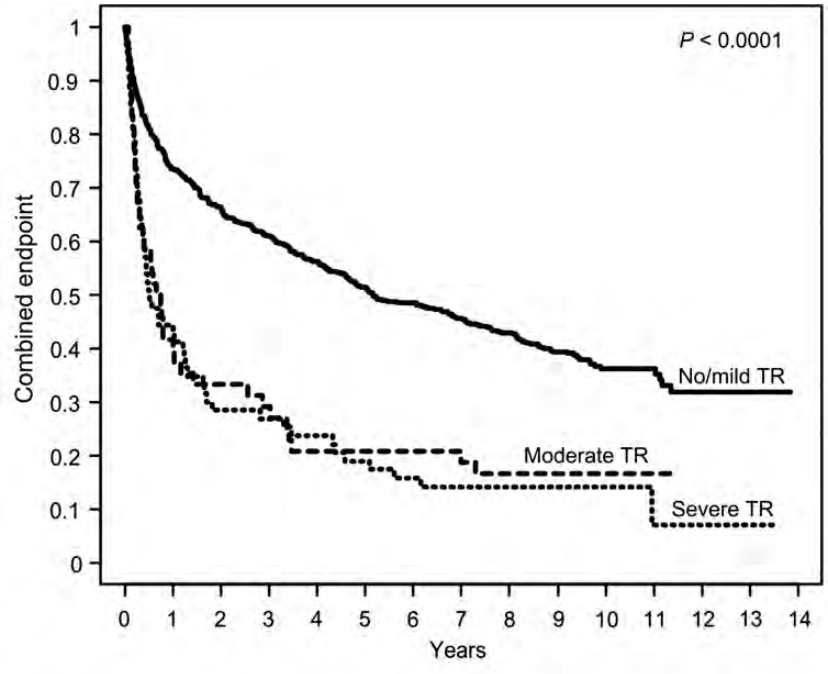
Table 3 shows echocardiographic data at baseline.

Late outcome

Patients were followed for 69.18 ± 50.24 months. Three hundred and eighty-six patients (67%) reached the combined endpoint, which was defined as death, heart transplantation, or left ventricular-assist device implantation. Among these 330 died (cardiac death 84% of deaths), 85 patients underwent heart transplantation, and 34 had a left ventricular-assist device implanted. Fifteen patients underwent heart transplantation after left ventricular-assist device implantation. The overall outcome as estimated by Kaplan–Meier analysis was considerably worse in patients with significant TR with 1-, 3-, 5-, and 7-year survival rates of 43, 27, 19, and 14% compared with 71, 58, 49, and 43% in patients without significant TR (Log-rank test, $P < 0.0001$, *Figure 1*).

Parameters related to outcome

By multivariable Cox regression analysis, serum sodium ($P < 0.0001$), NT-proBNP ($P = 0.0028$), NYHA functional class ($P < 0.0001$), systolic blood pressure ($P < 0.0001$), right atrial size ($P = 0.0001$), and LV function ($P = 0.0014$), but not TR ($P = 0.8518$) were significantly related to the combined endpoint.



Year	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Mild TR (*n*=465)														
Endpoint	123	158	181	203	225	239	253	265	279	287	287	291	291	291
N.at Risk	342	307	284	262	240	226	212	187	136	77	35	17	5	0
Moderate TR (*n*=48)														
Endpoint	28	32	34	38	38	38	39	40	40	40	40	40	40	40
N.at Risk	20	16	14	10	10	10	9	5	4	4	1	0	0	0
Severe TR (*n*=63)														
Endpoint	36	45	46	48	51	53	54	54	54	54	55	55	55	55
N.at Risk	27	18	17	15	12	10	9	6	5	3	1	1	1	0

Figure 1 Kaplan–Meier curves for overall survival. Numbers at the bottom indicate the number of patients at risk and the number of events at each follow-up year.

Table 1 Baseline characteristics according to tricuspid regurgitation severity

Variable	All patients, *n* = 576	No/mild TR, *n* = 465 (81%)	Moderate/severe TR, *n* = 111 (19%)	*P*-value
Demographic data				
Male (%)	83	82	84	0.723
Age (years)	56.4 ± 11.2	56.3 ± 10.9	56.9 ± 12.4	0.630
BMI (kg/m^2 BSA)	26.6 ± 4.1	26.9 ± 4.2	25.7 ± 3.3	0.002
Clinical data				
Systolic blood pressure (mmHg)	116.2 ± 22.3	118.8 ± 22.2	105.6 ± 19.4	<0.001
Heart rate (b.p.m.)	74.5 ± 16.0	73.9 ± 15.8	77.1 ± 16.9	0.061
Atrial fibrillation (%)	21	19	30	0.009
Coronary artery disease (%)	39	42	27	0.004
Hypertension (%)	49	53	32	<0.001
Diabetes mellitus (%)	23	24	16	0.075
Hyperlipidaemia (%)	41	44	26	0.001
NYHA functional class (%)				<0.001
NYHA I (%)	12	13	6	
NYHA II (%)	26	29	13	
NYHA III (%)	41	42	39	
NYHA IV (%)	21	16	42	
Leg oedema (%)	16	12	31	<0.001
GFR (mg/dL)	77 ± 30	79 ± 30	70 ± 28	0.005
Creatinine (mg/dL)	1.3 ± 0.8	1.3 ± 0.9	1.4 ± 06	0.001[a]
Blood urea nitrogen (mg/dL)	26 ± 15	24 ± 15	31 ± 17	<0.001
Sodium (mmol/L)	139 ± 4	139 ± 4	137 ± 5	<0.001
Potassium (mmol/L)	4.4 ± 0.5	4.4 ± 0.5	4.2 ± 0.6	0.016
NT-proBNP (fmol/mL)	488 ± 645	400 ± 546	858 ± 863	0.004[a]
Medical treatment				
RAAS antagonist (%)	96	95	97	0.346
Beta-blocker (%)	71	73	66	0.161
Aldosterone antagonist (%)	33	30	45	0.002
Furosemide (%)	75	70	92	<0.001
Furosemide (mg)	51 ± 74	44 ± 69	78 ± 90	<0.001[a]
Amiodarone (%)	19	17	28	0.008
Rhythm device				
ICD (%)	12	11	14	0.379
Pacemaker (%)	17	16	25	0.015

Values are mean ± SD or % of patients.
Categorical numbers were calculated using a χ^2 test; continuous data were calculated using *t*-tests.
[a]Continuous data were calculated using Wilcoxon-test.
TR, tricuspid regurgitation; BMI, body mass index; BSA, body surface area; NYHA, New York Heart Association; GFR, glomerular filtration rate; NT-proBNP, amino terminal pro B-type natriuretic peptide; RAAS antagonist, angiotensin-converting enzyme inhibitor or angiotensin receptor 1 antagonist; ICD, implanted cardioverter defibrillator.

However, an interaction between TR and LV systolic function ($P = 0.0054$) was present. After including the interaction term into the model, TR was significantly related to the outcome (significant main effect: $P = 0.0059$, *Table 4*).

Prognostic value of tricuspid regurgitation severity at different stages of heart failure

To further assess the interaction between LV systolic function and TR, we divided our study population into two groups: patients with mild and moderately reduced LV systolic function and patients with severely reduced LV function.

Kaplan–Maier analysis within these subgroups revealed a significant impact of TR in both patients with mild and moderately impaired LV function ($P < 0.0001$) and in patients with severely reduced LV function ($P = 0.0005$, *Figure 2*). However, by multivariable Cox regression analysis of the two subgroups accounting for the same variables as used in the basic model, TR was significantly related to outcome only in patients with mild/moderately impaired LV function ($n = 248$; HR: 1.368, CI: 1.070–1.748, $P = 0.0125$). In patients with severely impaired LV function ($n = 318$), TR had no

Table 2 Baseline characteristics according to outcome

Variable	All patients, n = 576	Endpoint, n = 386 (67%)	No Endpoint, n = 190 (33%)	P-value
Demographic data				
Male (%)	83	85	78	0.079
Age (years)	56.4 ± 11.2	57.7 ± 10.8	53.9 ± 11.6	<0.001
BMI ((kg/m^2 BSA)	26.6 ± 4.1	26.5 ± 3.9	26.9 ± 4.5	0.213
Clinical data				
Systolic blood pressure (mmHg)	116.2 ± 22.3	111.2 ± 20.7	124.9 ± 23.0	<0.001
Heart rate (b.p.m.)	74.5 ± 16.0	75.4 ± 15.9	72.7 ± 16.2	0.061
Atrial fibrillation (%)	21	24	13	0.002
Coronary artery disease (%)	39	41	35	0.204
Hypertension (%)	49	48	52	0.376
Diabetes mellitus (%)	23	23	22	0.751
Hyperlipidaemia (%)	41	37	47	0.024
NYHA functional class (%)				<0.001
NYHA I (%)	12	7	20	
NYHA II (%)	26	22	37	
NYHA III (%)	41	42	38	
NYHA IV (%)	21	29	5	
Leg oedema (%)	16	21	6	<0.001
GFR (mg/dL)	77 ± 30	72 ± 28	87 ± 30	<0.001
Creatinine (mg/dL)	1.3 ± 0.8	1.4 ± 0.9	1.2 ± 0.4	<0.001[a]
Blood urea nitrogen (mg/dL)	26 ± 15	28 ± 17	21 ± 9	<0.001
Sodium (mmol/L)	139 ± 4	138 ± 4	140 ± 3	<0.001
Potassium (mmol/L)	4.4 ± 0.5	4.4 ± 0.5	4.4 ± 0.5	0.332
NT-proBNP (fmol/mL)	488 ± 645	615 ± 709	231 ± 378	<0.001[a]
Medical treatment				
RAAS antagonist (%)	96	96	95	0.515
Beta-blocker (%)	71	67	80	0.001
Aldosterone antagonist (%)	33	35	28	0.089
Furosemide (%)	75	85	54	<0.001
Furosemide dose (mg)	51 ± 74	64 ± 76	24 ± 62	<0.001[a]
Amiodarone (%)	19	24	10	<0.001
Rhythm device				
ICD (%)	12	9	7	0.812
Pacemaker (%)	17	20	13	0.036
Any device (%)	25	28	18	0.016
Moderate/severe TR (%)	19	86	14	<0.001

Values are mean ± SD or % of patients.
Categorical numbers were calculated using a χ^2 test; continuous data were calculated using *t*-tests
[a]Continuous data were calculated using Wilcoxon-test.
BMI, body mass index; BSA, body surface area; NYHA, New York Heart Association; GFR, glomerular filtration rate; NT-proBNP, amino terminal pro B-type natriuretic peptide; RAAS antagonist, angiotensin-converting enzyme inhibitor or angiotensin receptor 1 antagonist; ICD, implanted cardioverter defibrillator.

significant impact on the outcome (HR: 0.876, CI: 0.734–1.045, $P = 0.1401$).

As NT-proBNP is the standard parameter to estimate the severity of CHF, we repeated this subgroup analysis using the median serum NT-proBNP concentration (280 fmol/mL) to divide our patient population.

Again, Kaplan–Meier analysis showed a significant impact of TR in both patients with NT-proBNP concentrations below the median ($P = 0.0023$) and above the median ($P = 0.0013$) (*Figure 3*). By multivariable analysis of the subgroups, stratified for a median NT-proBNP, TR severity was significantly related to the outcome in patients with serum NT-proBNP concentrations below the median (HR: 2.512, CI: 1.127–5.597, $P = 0.0242$), while it was not in patients with NT-proBNP concentrations >280 fmol/mL (HR: 1.397, CI: 0.648–3.010, $P = 0.3935$).

Table 3 Echocardiographic findings according to tricuspid regurgitation severity

Variable	All patients, $n = 576$	No/mild TR, $n = 465$ (81%)	Moderate/severe TR, $n = 111$ (19%)	*P*-value
LVEDD (mm)	64 ± 10	64 ± 11	66 ± 9	0.009
RVEDD (mm)	37 ± 8	35 ± 7	43 ± 7	<0.001
LA (mm)	64 ± 10	63 ± 9	71 ± 8	<0.001
RA (mm)	59 ± 11	58 ± 10	67 ± 11	<0.001
sPAP (mmHg)	47 ± 12	45 ± 12	52 ± 13	<0.001
TAPSE (mm)	19 ± 4	18 ± 4	19 ± 4	0.378
LVEF (%)				<0.001
LVEF >50% (%)	17	19	3	
LVEF 35–50% (%)	27	30	17	
LVEF <35% (%)	56	51	80	
MR (%)				<0.001
No/mild MR (%)	67	75	28	
Moderate MR (%)	23	20	40	
Severe MR (%)	10	5	32	

Values are mean ± SD or % of patients.
TR, tricuspid regurgitation; LVEDD, left ventricular end-diastolic diameter, apical four chamber view; RVEDD, right ventricular end-diastolic diameter, apical four chamber view; LA, left atrial longitudinal diameter, apical four chamber view; RA, right atrial longitudinal diameter, apical four chamber view; TAPSE, tricuspid annular plane systolic excursion, $n = 224$; sPAP, estimated systolic pulmonary artery pressure; LVEF, left ventricular ejection fraction; MR, mitral regurgitation.

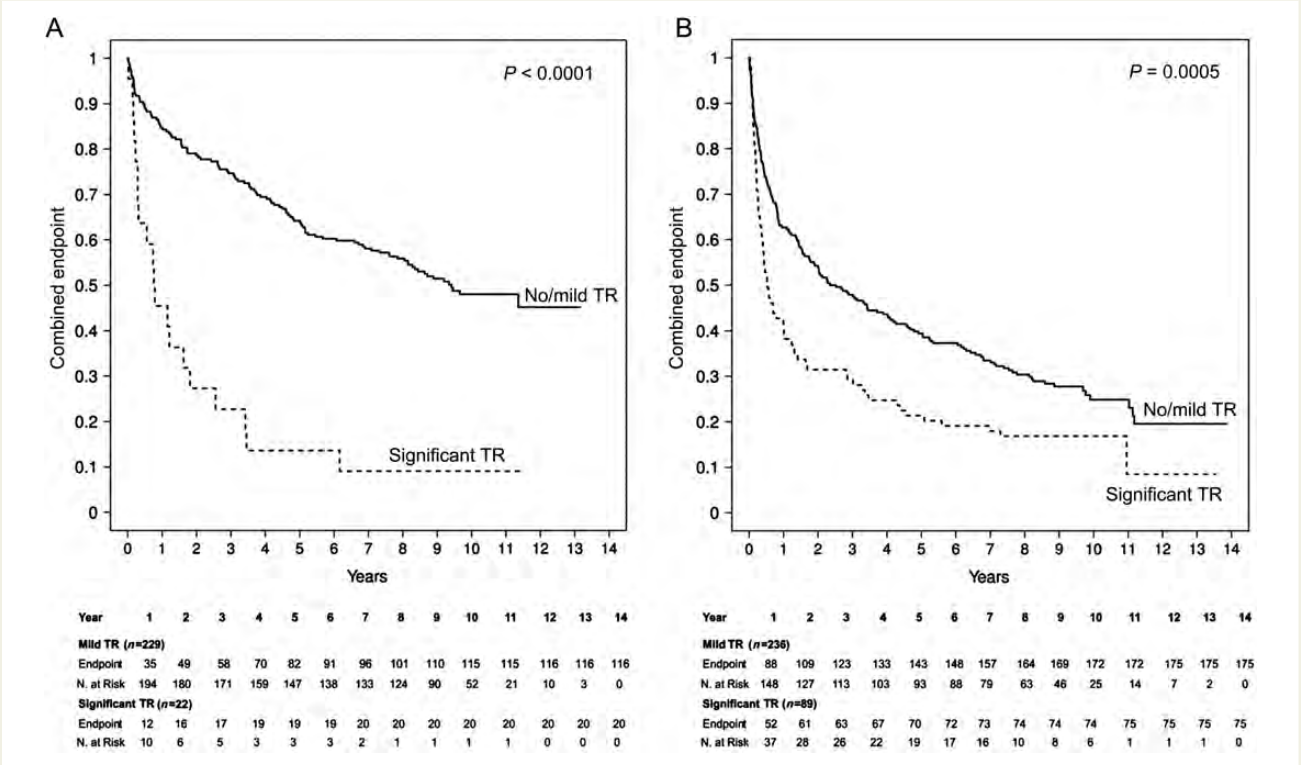


Figure 2 (*A*) Kaplan–Meier curves for survival in patients with mildly or moderately depressed left ventricular function. Significant tricuspid regurgitation indicates moderate and severe tricuspid regurgitation. (*B*) Kaplan–Meier curves for survival in patients with severely depressed left ventricular function. Numbers at the bottom indicate the number of patients at risk and the number of events at each follow-up year.

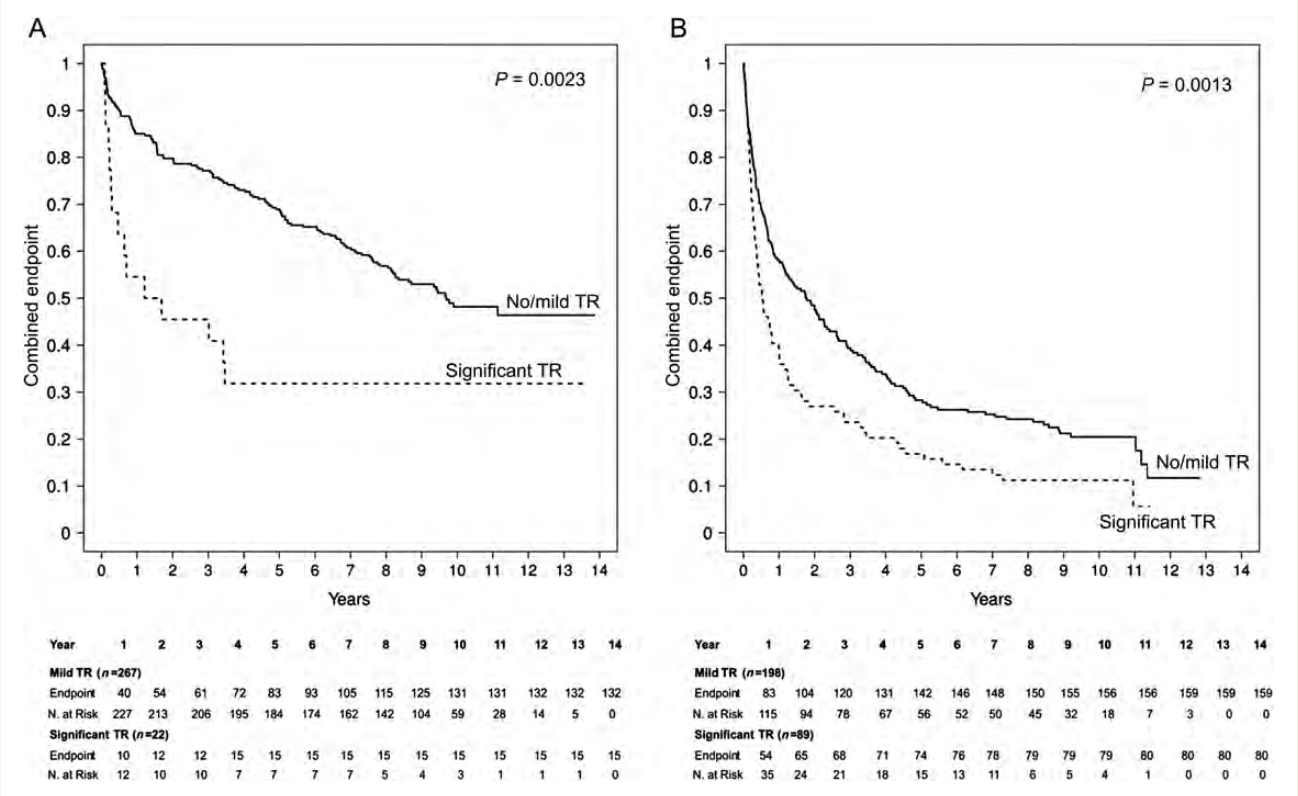


Figure 3 (*A*) Kaplan–Meier curves for survival in patients with NT-proBNP concentrations below the median (≤280 fmol/mL). Significant tricuspid regurgitation indicates moderate and severe tricuspid regurgitation. (*B*) Kaplan–Meier curves for survival in patients with NT-proBNP concentrations above the median (>280 fmol/mL). Numbers at the bottom indicate the number of patients at risk and the number of events at each follow-up year.

Table 4 Simple and multivariable Cox regression model

	Univariate			Multivariate		
	Hazard ratio	95% Hazard ratio confidence limits	*P*-value	Hazard ratio	95% Hazard ratio confidence limits	*P*-value
Creatinine	1.183	1.108–1.263	<0.0001	1.096	0.985–1.220	0.0938
Sodium	0.634	0.574–0.700	<0.0001	0.791	0.713–0.878	<0.0001
NT-proBNP	1.321	1.237–1.411	<0.0001	1.188	1.069–1.321	0.0014
NYHA functional class	1.806	1.600–2.039	<0.0001	1.417	1.244–1.614	<0.0001
Systolic blood pressure	0.619	0.549–0.698	<0.0001	0.706	0.622–0.802	<0.0001
Age	1.171	1.058–1.295	0.0023	1.076	0.965–1.200	0.1880
RA	1.582	1.425–1.757	<0.0001	1.293	1.142–1.463	<0.0001
LVEF	1.557	1.349–1.798	<0.0001	1.547	1.247–1.918	<0.0001
TR	1.665	1.488–1.863	<0.0001	2.068	1.233–3.469	0.0059
Interaction LVEF with TR				0.765	0.634–0.924	0.0054

NYHA, New York Heart Association; RA, right atrial longitudinal diameter, apical four chamber view; LVEF, left ventricular ejection fraction; TR, tricuspid regurgitation.

Discussion

Tricuspid regurgitation is not a benign disorder and carries a significant impact on morbidity and mortality.[3,5] In advanced CHF TR is mostly 'functional' in nature: elevated left ventricular end-diastolic pressure leads to a rise in pulmonary arterial pressure, resulting in right ventricular dilatation, and the development of TR. The occurrence of TR initiates a vicious cycle propagating further right ventricular dilatation, tricuspid annular dilatation, and, consequently, worsening of TR. Little is known about the prevalence and the prognostic significance of moderate and severe TR in CHF. The few existing studies indicate a strong impact of TR on the clinical outcome in these patients.[1–3] Koelling *et al.*[1] included 1421 patients, who were retrospectively collected between 1995 and 1998. Tricuspid regurgitation was significantly related with mortality, but the study lacks information on symptoms, biomarkers, and kidney function. Another retrospective study by Hung *et al.*[2] investigated 306 CHF patients. By multivariable analysis, NYHA functional class and TR were the only predictors of the outcome. Although both studies do convey an important message, their interpretation today is limited due to the lack of modern risk markers. One large more recent retrospective analysis also reported a significantly increased mortality rate among patients with moderate and severe TR, which was independent of left ventricular ejection fraction or pulmonary artery pressure.[3] However, aside from age and gender, the patient population of that study was not well characterized.

Thus, although TR seems to have a strong impact on the outcome in CHF prospective data are completely lacking. Furthermore, it is still unclear whether significant TR should be (surgically) treated, whether specific groups of patients would benefit more than others, and what the optimum timing of the treatment/intervention should be.

In the present study, we prospectively followed 576 CHF patients. The detailed data of this large cohort allowed us to comprehensively examine the prognostic relevance of TR in light of modern risk markers.[16–22]

Tricuspid regurgitation was not predictive of the outcome in a multivariable model including established biomarkers. What we did find, however, was an extremely close association between TR and LV systolic function. After consideration of this interaction, TR was significantly related with the outcome in the Cox model (*Table 4*). To better understand this relationship, we used LV function to dichotomize our cohort into mild and advanced heart failure.

This resulted in an unexpected inverse association: By multivariable analysis, TR had a strong impact on the outcome in patients with mild to moderate heart failure, characterized by only moderately decreased LV function, but did not substantially modify outcome in advanced heart failure with severely impaired LV function.

To investigate this in more detail, we used serum NT-proBNP to stratify our cohort into mild and advanced disease and got the same results: In mild heart failure characterized by NT-proBNP values below the median (280 fmol/mL), the severity of TR was related to the outcome by Cox regression analysis, whereas in advanced disease, characterized by serum NT-pro BNP $>$280 fmol/mL, the presence of severe TR did not alter the already dismal prognosis.

Although TR is mostly functional in CHF, it may in some cases also be a complication of pacemaker or cardiac defibrillator leads. Retrospective studies have postulated a potentially harmful effect of pacemaker and cardioverter defibrillator leads on tricuspid valve function and right heart haemodynamics.[23–25] In our cohort, pacemakers were a more common feature of patients with significant TR, whereas implantable cardioverter defibrillators were not (*Table 1*). As the existing studies have not focused on CHF patients, the interpretation of these results is difficult and warrants further investigation in CHF populations.

According to current guidelines,[26,27] surgical correction of functional TR is indicated in symptomatic patients with severe TR, and at the time of left-sided valve surgery even when only mild or moderate TR with associated annular dilatation is present. However, our actual knowledge about the optimal timing and mode of TR surgery as well as appropriate indications for surgical treatment are much more limited than in aortic or mitral valve disease. This is reflected by a high frequency of residual and recurrent TR after surgical correction and a relatively high perioperative mortality rate.[4,28,29]

Very recently, Topilsky *et al.*[4] published the outcome data of 189 patients who underwent tricuspid valve replacement between 1997 and 2007. The results of that study support our findings, as good outcomes of tricuspid valve replacement appeared achievable in patients who were not highly symptomatic and haemodynamically stable. However, important limitations of that study were the lack of a control group managed conservatively, lack of serum biomarkers like NT-proBNP, and the exclusion of patients who underwent repair. Even in patients with less severe symptoms restoration of a normal life expectancy was not achieved by surgery, stressing the need for a more sensitive preoperative risk stratification.

Our study identifies a subgroup of CHF patients in whom the presence of significant TR is associated with an impaired outcome. Whether these patients may benefit from a surgical correction of TR is unknown. Further prospective studies are needed to test whether a surgical intervention in patients with CHF and significant TR is beneficial.

Limitations

Eighty-three per cent of our patients were male, and the average age of 56 was relatively young. Although a high proportion of young male patients is not uncommon, neither for tertiary centres nor for heart failure studies, it should be stressed that our findings cannot be extrapolated to all heart failure populations.

Presented data have been collected in a single-centre setting. Therefore, a centre-specific bias cannot be excluded. However, the major advantages of limiting data collection to a single centre are (i) inclusion of a homogenous patient population, (ii) adherence to a constant clinical routine, (iii) constant quality of echocardiographic work-up, and (iv) constant follow-up over a time-period of 15 years. However, the present study is limited by the lack of data on re-hospitalization for heart failure.

Accurate determination of right ventricular dysfunction in the presence of significant TR is difficult as right ventricular unloading

due to TR may be misleading, on top of technical limitations of 2D echocardiography for the assessment of the right ventricle. Visual assessment of right ventricular function by 2D echo was included in the multivariable analysis but failed to show a significant impact on the combined endpoint. However, it cannot be excluded that TR is simply a marker of right ventricular dysfunction, or failure. Nevertheless, TR appears to be an important variable as it can be quantified reliably by transthoracic echocardiography and adds prognostic information.

Conclusion

The impact of TR on the outcome in CHF patients depends on the severity of heart failure. While TR provides no additive value in advanced disease, it is associated with excess mortality in mild to moderate CHF. Whether these patients may benefit from surgical correction of TR has to be addressed in further prospective, randomized studies.

Conflict of interest: none declared.

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