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Original article

Post-procedural tricuspid regurgitation predicts long-term survival in patients undergoing percutaneous mitral valve repair

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ABSTRACT

Background: Functional tricuspid regurgitation (TR) is frequently present in patients with severe mitral regurgitation and is associated with worse outcome. While percutaneous mitral valve repair (PMVR) is on the increase, the role of TR in those patients is unclear. This study aimed to compare pre- and post-procedural TR and investigated the impact of post-procedural TR and major clinical risk factors on long-term survival in patients undergoing PMVR.

Methods: In this retrospective observational cohort study, data from 213 consecutive patients at a tertiary care center undergoing PMVR from 2010 to 2016 were analyzed. Two different groups, dichotomized according to the degree of TR (none/mild and moderate/severe) were compared. Multivariable analyses were performed assessing predictors for long-term survival adjusting for major risk factors.

Results: Following PMVR TR was significantly reduced by at least 1 grade in 23.0% ($p = 0.001$), while echocardiographic pulmonary pressure was decreased (TR Vmax 3.21 ± 0.49 m/s vs. 2.98 ± 0.53 m/s; $p = <0.001$). Patients with moderate or severe TR presented with worse New York Heart Association functional class and elevated N-terminal pro B-type natriuretic peptide levels compared to patients with none or mild TR. Median survival time was 1458 days. Proportional hazards model, adjusted for major risk factors, revealed post-procedural TR grade (HR 2.055, CI 1.317–3.206, $p = 0.02$), severely impaired left ventricular function (HR 3.145, CI 1.199–8.250, $p = 0.020$), and chronic kidney disease [glomerular filtration rate (GFR) 30–60 ml/min HR 1.917, CI 1.109–3.314, $p = 0.020$; GFR < 30 ml/min HR 3.969, CI 1.981–7.951, $p < 0.001$] as independent predictors for long-term survival.

Conclusion: Post-procedural moderate and severe TR predicts worsened long-term survival in patients undergoing PMVR and is associated with adverse clinical outcome. Whether outcome might be improved by interventional reduction of post-procedural TR has to be investigated in the future.

Introduction

Tricuspid regurgitation (TR) is frequently present in patients with severe mitral regurgitation (MR), approximately one-third exhibit moderate or severe TR [1,2]. Most commonly, TR is functional, secondary to tricuspid annular dilation, right ventricular enlargement, and dysfunction [3]. Left-sided valve disease is the most prevalent cause. Backwards failure leads to increased pulmonary pressure. Pressure overload consequently causes right ventricular impairment and results in tricuspid annular dilation and tethering of papillary muscles. As the leaflets are pulled apart, the coaptation area is reduced and a gap is created. TR evolves. In such conditions TR is further worsened by volume overload [4]. Besides that pacemaker or ICD leads and atrial fibrillation can also contribute to the evolution of TR [5,6].

Current guidelines suggest tricuspid valve (TV) repair in presence of at least moderate TR if patients undergo left-sided heart surgery since it is associated with worse survival, a high

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incidence of heart failure, and reduced functional capacity [7–9]. Delayed surgery must be avoided given the risk of irreversible right ventricular damage and poor results of later surgical intervention. Concomitant TV repair during left-sided heart surgery was associated with a reduction in mortality; recommendation is given even for mild or moderate TR in presence of a dilated TV annulus [10,11]. This approach appreciates the fact of progressive TR and right heart failure in patients where annular dilation has already occurred. Patients not referable to open-heart surgery because of a high perioperative risk have been increasingly admitted to percutaneous edge-to-edge mitral valve repair (PMVR) using the MitraClip system (Abbott Vascular, Abbott Park, IL, USA) [12]. This is a catheter-based technology that mimics the Alfieri technique where the middle scallops of the anterior and the posterior leaflet of a regurgitant mitral valve are connected [13]. For that a catheter is placed into the left atrium. Under echocardiographic and fluoroscopic guidance, the mid portion of the anterior and posterior leaflets grasped and approximated by a clip. A double orifice is formed. The clip is then detached and the catheter withdrawn [14]. This novel procedure has been shown to be effective for reduction in MR, clinical symptoms, and even survival [15,16]. First data from Transcatheter Mitral valve Interventions (TRAMI) and Getting Reduction of Mitral Insufficiency by Percutaneous Clip Implantation (GRASP) registries suggest, pre-interventional severe TR to be an independent predictor for 1-year mortality [17,18]. It seems reasonable to take into account the experience regarding concomitant TR in patients undergoing mitral valve surgery in the past and translate these findings into those patients who are now admitted for PMVR and investigate this concept in detail.

Additionally mitral valve (MV) repair has been shown to improve functional TR [18,19]. However the role of post-procedural TR has not been investigated so far. Whereas the negative influence of TR on outcome in surgical patients is clear and TV repair is suggested during the same operative procedure, the relevance of post-procedural TR in those undergoing PMVR remains elusive. In the present study we therefore sought to investigate the impact of post-procedural TR and major clinical risk factors regarding long-term survival in patients undergoing PMVR.

Methods

Patient population

In a retrospective observational cohort study with prospective patient follow-up we analyzed data from 213 consecutive patients presenting at a tertiary care center specialized in interventional cardiology, who underwent PMVR using the MitraClip system from 01/2010 to 07/2016 for severe MR. Of those patients 146 (68.5%) received one, 66 (30.9%) two, and 1 patient (0.5%) three clips.

The patient flow through the study is shown in Fig. 1.

Data collection and outcome definition

Demographic and clinical data including laboratory results and echocardiographic parameters were collected at baseline and within 3 months after PMVR. Transthoracic echocardiography was used to assess valvular and cardiac chamber function as well as sizes. TR determination was conducted in line with current recommendations and guidelines using primarily effective regurgitant orifice area (EROA) measurement [7,11,20]. When not feasible vena contracta or color flow Doppler jet area were used. To measure proximal isovelocity surface area the Nyquist limit was set to 40 cm/s. The flow convergence zone was traced, TR Vmax determined, and EROA calculated. TR was graded in 4 stages: none, mild, moderate, and severe. MR quantification was conducted

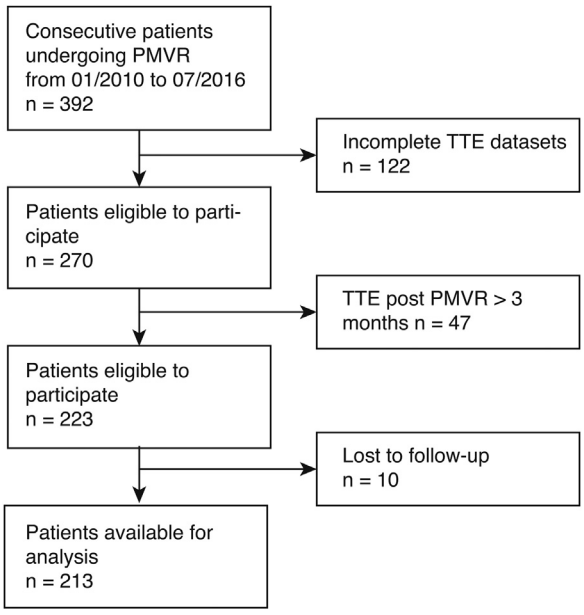

Fig. 1. Patient flow through the study. Figure shows patients included and excluded in the study with a number of *n* individuals at each step and for final analysis. PMVR, percutaneous mitral valve repair; TTE, transthoracic echocardiography.

accordingly. TV annulus, right ventricular (RV) end-diastolic area and left atrial (LA), as well as right atrial (RA) end-systolic area were measured in four-chamber view. Left ventricular diameters were determined in parasternal long-axis view. Ejection fraction was calculated from end-diastolic volume and end-systolic volume estimates as described previously [21]. Only patients with functional TR have been included.

Chronic kidney disease (CKD) was defined according to kidney damage with glomerular filtration rate <60 ml/min/1.73 m^2 using CKD-Epidemiology Collaboration creatinine equation for estimation, irrespective of cause [22,23]. Data for survival rates was collected from hospital database and primary care physicians.

Primary endpoint was defined as survival after PMVR with regard to post-procedural TR grade. Secondary endpoints were post-procedural changes of TR, echocardiographic pulmonary pressure, ventricular function and diameters, as well as evaluation of New York Heart Association (NYHA) functional class and N-terminal pro B-type natriuretic peptide (NT-proBNP) serum levels, again with respect to post-procedural TR grade.

The study was approved by the local Ethics Committee of the State Brandenburg (AS 155(bB)/2017) and was conducted in accordance with the Declaration of Helsinki. The Strengthening the Reporting of Observational Studies in Epidemiology recommendations for reporting observational studies were applied [24].

Statistics

Statistical analysis was performed using SPSS Statistics Version 23.0 (SPSS Inc., Chicago, IL, USA, 2015). Continuous variables are reported as mean with standard deviation if normally distributed or median with interquartile range respectively, if not normally distributed. Categorical variables are expressed as absolute numbers and/or percentages. Two different groups, dichotomized according to the degree of TR (none/mild and moderate/severe), were analyzed. Paired and unpaired Student's *t*, Mann–Whitney *U*, Wilcoxon, and chi-square test were used when appropriate to test for differences between groups. Correlation analysis was conducted to determine variables' relationship. Variables with possible impact on survival were tested in a univariate analysis first. Then multivariable analysis for long-term survival using Cox

regression was performed including variables with univariate p-value ≤0.200. Results are presented as adjusted hazard ratios. A p-value ≤0.05 was considered statistically significant.

Results

Baseline characteristics

Of 213 consecutive patients undergoing PMVR, 4 (1.9%) were found to exhibit no, 97 (45.5%) mild, 92 (43.2%) moderate, and 20 (9.4%) severe functional TR at time of examination pre-procedurally (median 23 days, IQR 36) (Fig. 2A). Upon examination post PMVR (median 5 days, IQR 33) 4 (1.9%) showed no, 125 (58.7%) mild, 67 (31.5%) moderate, and 17 (8.0%) severe TR. In comparison TR was significantly reduced by at least 1 grade in 23.0% of patients, while TR remained unchanged in 63.8% and showed progression in 13.1% of patients ($p = 0.001$). Especially those with moderate or severe TR improved distinctly (Fig. 2B). MR was reduced in 77.7% of patients after the procedure. It remained unchanged in 21.7% and was worse in 0.6%. There was a significant positive correlation between post-procedural reduction in MR and improvement in TR ($r_S = 0.216$; $p = 0.003$). TR Vmax was reduced after the procedure (TR Vmax 3.23 ± 0.49 m/s vs. 2.98 ± 0.51 m/s; $p < 0.001$) (Fig. 2C). There were no changes in ventricular dimension or RV function.

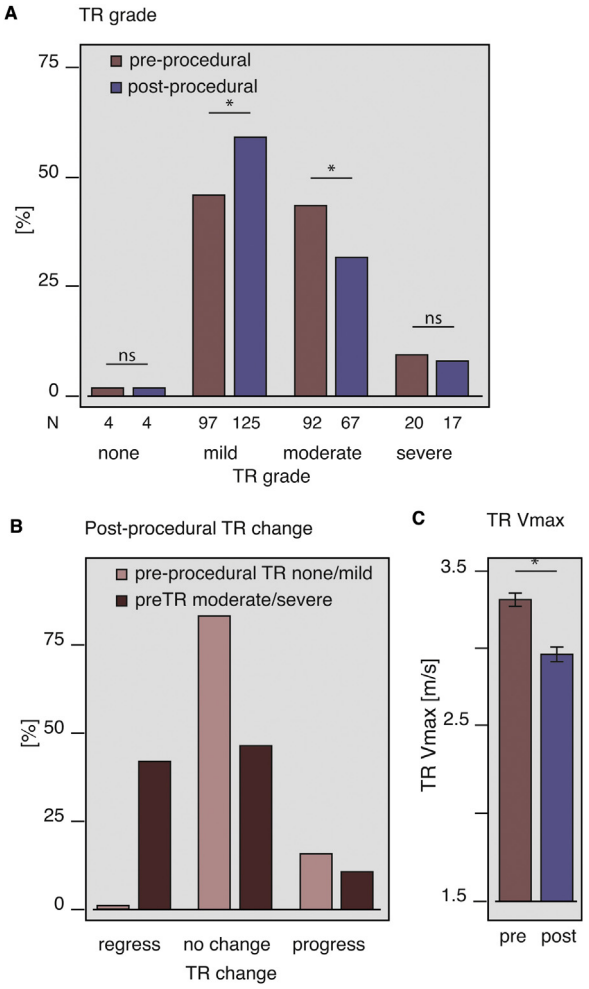

Fig. 2. (A) Prevalence of pre- and post-procedural tricuspid regurgitation (TR) in patients undergoing percutaneous mitral valve repair. Grades are defined as none (0), mild (I), moderate (II), and severe (III). Wilcoxon rank sum test, $p = 0.001$, chi-square test for differences between groups, $^*p \leq 0.05$. Values are percentages. (B) Prevalence of TR change (regress, no change, progress) according to pre-procedural TR grade. (C) Pre- and post-procedural TR Vmax as surrogate for pulmonary arterial pressure. Paired t-test, $p < 0.001$. Values denote mean ± SEM.

Reduced functional capacity with respect to worse NYHA class was observed in patients who showed post-procedural moderate or severe TR ($p = 0.050$) (Fig. 3A). Median NT-proBNP levels were significantly higher in patients with at least moderate TR compared to none or mild (3500 pg/ml IQR 5981 vs. 2571 pg/ml IQR 3099; $p < 0.024$) (Fig. 3B). Patients with moderate and severe TR had more often a history of atrial fibrillation and less often of coronary artery disease (CAD) and dyslipidemia. Patients' characteristics according to degree of TR are shown in Table 1.

EROA was significantly larger ($0.41 \pm 0.26\ cm^2$ vs. $0.20 \pm 0.14\ cm^2$; $p < 0.001$) and TV annular diameters were increased (40.7 ± 5.6 mm vs. 38.1 ± 5.8 mm; $p = 0.001$) if post-procedural TR was at least moderate. Patients also showed dilated right atrium ($p < 0.001$) and right ventricle ($p < 0.001$) as well as impaired right ventricular function measured by TAPSE ($p < 0.024$). Groups did not differ regarding systolic left ventricular function, LVEDD, LVESD, MR, or mitral stenosis (MS), and TR Vmax (Table 2).

Long-term survival

Overall survival rate was 79.3% (169 patients) at 1 and 63.4% (135 patients) at 2 years following PMVR. In patients with no or mild TR post-procedurally survival rate was 85.3% (1 year) and 68.2% (2 years) compared to 70.2% (1 year) and 56.0% (2 years) in those with moderate or severe TR ($p = 0.011$ and $p = 0.025$ respectively). Median survival time was 1458 days.

TR grade, left ventricular function, CKD, and chronic obstructive pulmonary disease appeared to be relevant variables upon univariate analysis for further evaluation ($p \leq 0.200$), whereas age, sex, MR and MS grade, right ventricular function, echocardiographic pulmonary hypertension, CAD, and arterial hypertension did not. Proportional hazards model revealed post-procedural TR grade ($p = 0.002$), CKD ($p = 0.001$), and systolic left ventricular function ($p = 0.024$) as independent predictors for long-term survival (Fig. 4 and Table 3). However, there was no significant effect with respect to pre-procedural TR in this cohort (HR 1.364, CI 0.878–2.118; $p = 0.167$).

Discussion

In this study we investigated changes in pre- and post-procedural TR and the impact of post-procedural TR on long-term survival in patients undergoing PMVR.

TR is present in a significant number of patients with MR. Upon follow-up 23.0% improved by at least 1 degree in TR after the procedure. Moderate and severe TR was associated with adverse clinical outcome assessed by NYHA functional class and elevated NT-proBNP levels as a sign of neurohumoral response in the organism. Our findings regarding the prevalence of TR in MV disease are in line with previous studies [1,2,17,25]. However, this is the first study to show that post-procedural TR in patients undergoing PMVR is independently associated with long-term survival besides generally known risk factors such as CKD and systolic heart failure [26–28].

Resolving TR after mitral and aortic valve surgery has been reported previously. Ohno et al. further showed reduction of TR in patients following PMVR in the early phase (up to 12 months) [18]. In our study we observed similar results of post-procedural TR improvement. Here we found a significant decrease of TR upon follow-up within the first three months after the intervention. The understanding that TR generally resolves after treatment of left-sided heart disease however has been misleading in the past. This is particularly important, as data previously demonstrated acute

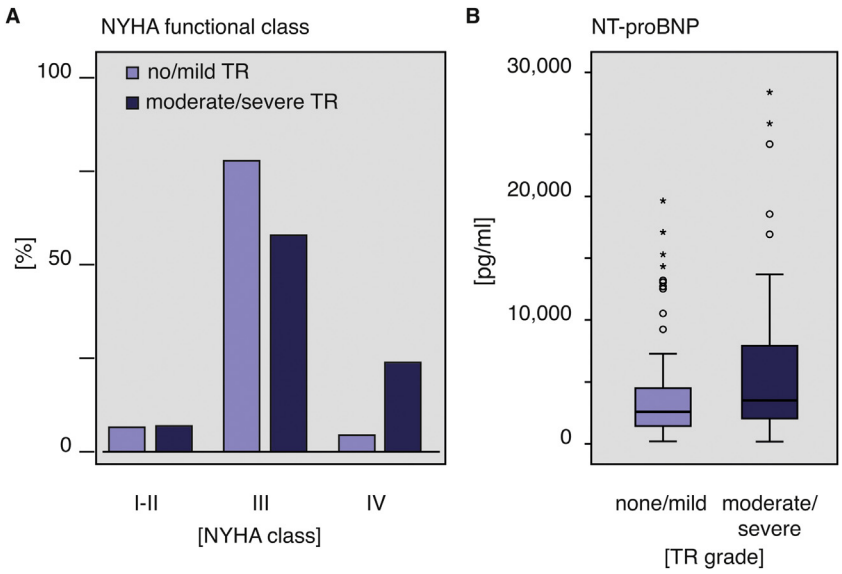

Fig. 3. (A) New York Heart Association (NYHA) functional class according to post-procedural tricuspid regurgitation (TR) grade no/mild versus moderate/severe in transthoracic echocardiography (TTE). $p = 0.050$. (B) N-terminal pro B-type natriuretic peptide (NT-proBNP) serum levels according to post-procedural TR grade no/mild versus moderate/severe in TTE. $p = 0.024$.

Table 1
Patients' baseline characteristics.

	No/mild TR $n = 129$	Moderate/severe TR $n = 84$	Overall $n = 213$	p-Value
Age [years]	75.3 ± 8.9	75.8 ± 8.9	75.5 ± 8.9	0.694
Male [%]	71.3	60.7	67.1	0.135
BMI [kg/m^2]	26.7 ± 4.3	26.0 ± 4.6	26.5 ± 4.4	0.342
NYHA class [%]				0.050*
I–II	7.3	7.7	7.5	
III	87.8	65.4	79.1	
IV	4.9	26.9	13.4	
Comorbidities				
CAD [%]			65.7	0.013*
Single vessel	18.6	20.2		
Double vessel	18.6	10.7		
Triple vessel	34.9	25.0		
Atrial fibrillation [%]			70.4	0.016*
Paroxysmal	22.5	28.6		
Persistent	4.7	9.5		
Permanent	35.7	44.0		
DCM [%]	16.3	25.0	20.6	0.168
COPD [%]	20.9	25.0	22.5	0.506
Pulmonary hypertension [%]				0.566
Unlikely	33.0	36.6	34.5	
Possible	47.4	47.9	47.6	
Likely	19.6	15.5	17.9	
Arterial hypertension [%]	96.9	95.2	96.2	0.715
Dyslipidemia [%]	80.6	67.9	75.6	0.049*
Type 2 diabetes [%]	31.0	33.3	31.9	0.765
CKD [%]				0.471
1–2	35.2	30.3	33.2	
3	50.0	47.6	51.1	
4	14.8	15.5	15.8	
5				
Implantable cardiac device [%]	43.4	53.6	47.4	0.162
EROA [cm^2]	0.18 ± 0.13	0.38 ± 0.29	0.29 ± 0.26	<0.001*
PISA [mm]	0.46 ± 0.16	0.66 ± 0.21	0.57 ± 0.21	<0.001*
TV-annulus [mm]	37.6 ± 5.9	40.8 ± 5.7	39.2 ± 6.0	<0.001*
TR Vmax [m/s]	3.2 ± 0.5	3.2 ± 0.5	3.2 ± 0.5	0.733
TAPSE [mm]	19.3 ± 5.2	16.8 ± 4.9	18.0 ± 5.2	0.002*
LV-EF [%]	39.7 ± 15.9	37.1 ± 15.2	38.4 ± 15.6	0.348
LVEDD [mm]	57.4 ± 10.5	58.4 ± 10.1	57.9 ± 10.3	0.609

Table1 (*Continued*)

	No/mild TR $n=129$	Moderate/severe TR $n=84$	Overall $n=213$	p-Value
LVESD [mm]	52.3 ± 9.2	47.8 ± 13.3	49.4 ± 12.1	0.316
RA dilatation [%]				<0.001
None	57.0	22.7	40.1	
Mild	27.0	35.1	31.0	
Moderate	12.0	25.8	18.8	
Severe	4.0	16.5	10.2	
LA dilatation [%]				0.006
None	7.8	2.1	5.0	
Mild	35.0	25.8	30.5	
Moderate	31.1	29.9	30.5	
Severe	26.2	42.3	34.0	
RV dilatation [%]				<0.001
None	80.4	50.5	65.8	
Mild	12.7	30.9	21.6	
Moderate	3.9	15.5	9.5	
Severe	2.9	3.1	3.0	
MR [%]				0.692
None	0	0	0	
Mild	0	0	0	
Moderate	13.2	11.2	12.2	
Severe	86.8	88.8	87.8	
MS [%]				0.843
None	95.7	96.4	96.0	
Mild	2.9	3.6	3.2	
Moderate	1.4	0	0.8	
Severe	0	0	0	
Laboratory results				
CKD-EPI eGFR [ml/min]	50.9 ± 20.0	48.5 ± 19.4	49.9 ± 19.7	0.472
Serum creatinine [μmol/l]	127.6 ± 46.6	128.2 ± 49.8	127.9 ± 47.9	0.940
Urea [mmol/l]	11.2 ± 6.2	11.7 ± 4.6	11.5 ± 5.6	0.677
Hemoglobin [mmol/l]	7.7 ± 0.9	7.7 ± 1.2	7.7 ± 1.1	0.782
Leucocytes [Gpt/l]	7.6 ± 1.9	7.4 ± 1.7	7.5 ± 1.8	0.528
CRP [mg/l]	7.7 ± 12.8	9.6 ± 15.8	8.6 ± 14.2	0.465
HbA1c [%]	6.2 ± 0.9	6.2 ± 0.9	6.2 ± 0.9	0.935
NT-proBNP [pg/ml]	2571 IQR 3099	3500 IQR 5981	2919 IQR 3803	<0.024*
Total bilirubin [μmol/l]	19.3 ± 21.0	25.0 ± 13.4	22.1 ± 17.7	0.376
AST [μkat/l]	0.69 ± 0.82	0.65 ± 0.26	0.67 ± 0.61	0.812
ALT [μkat/l]	0.47 ± 0.42	0.55 ± 0.84	0.50 ± 0.64	0.537
Potassium [mmol/l]	4.5 ± 0.5	4.5 ± 0.7	4.5 ± 0.6	0.975
Sodium [mmol/l]	139.0 ± 2.8	138.3 ± 4.0	138.7 ± 3.4	0.249
Troponin I [ng/ml]	0.036 ± 0.071	0.035 ± 0.023	0.035 ± 0.052	0.949
Diuretics				
Torasemide [%] ([mg])	85.0 (17.6 ± 13.4)	87.3 (21.4 ± 14.2)	86.2 (19.2 ± 13.8)	(0.068)
Furosemide [%] ([mg])	5.8 (153.8 ± 244.2)	5.0 (42.5 ± 5.0)	5.4 (116.7 ± 202.4)	(0.395)
Aldosterone antagonist [%] ([mg])	41.7 (25.8 ± 11.6)	50.6 (25.9 ± 10.1)	46.2 (25.9 ± 10.9)	(0.979)
Hydrochlorothiazide [%]([mg])	20.8 (16.3 ± 5.9)	15.2 (17.7 ± 6.4)	18 (16.8 ± 6.0)	(0.523)
Sulfonamide (Xipamide) [%] ([mg])	5.0 (11.6 ± 3.5)	11.4 (14.0 ± 10.5)	8.2 (12.9 ± 8.1)	(0.540)

Table shows patients' baseline demographic, functional, and echocardiographic characteristics.
BMI, body mass index; NYHA, New York Heart Association; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DCM, dilated cardiomyopathy; CKD, chronic kidney disease; EROA, effective regurgitant orifice area; PISA, proximal isovelocity surface area; TV, tricuspid valve; TR, tricuspid regurgitation; TAPSE, tricuspid annular plane systolic excursion; LV, left ventricular; LVEDD, left ventricular enddiastolic diameter; LVESD, left ventricular endsystolic diameter; RA, right atrial; LA, left atrial; RV, right ventricular; MR, mitral regurgitation; MS, mitral stenosis; eGFR, estimated glomerular filtration rate calculated by serum creatinine; CRP, C-reactive protein; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; AST, aspartate transaminase; ALT, alanine transaminase. Values denote percentages, mean ± standard deviation (SD), or median with interquartile range (IQR) as indicated.
* A p-value ≤0.05 was considered statistically significant.

reduction but late progression of TR in patients who underwent surgery for severe functional MR where TR had been left untreated [1]. Even if TR improves after MV repair it predicts for poor survival in this cohort. Different mechanisms play a role in early and late stages: hemodynamic changes, such as reduction in LA and pulmonary pressure, can occur immediately. We found a significant reduction of TR Vmax as surrogate for pulmonary arterial pressure post-procedurally. This may be a relevant reason for improvement of TR as described by Toyama et al. [29]. On the other hand delayed irreversible right ventricular and TV annular dilatation that lead to leaflet malcoaptation are insidious and develop in the later phase of TR evolution due to chronic remodeling processes [30,31]. TV repair is suggested at time of left-sided heart surgery to improve outcomes and avoid multiple operations [32,33]. Both European and US guidelines recommend simultaneous TV repair if patients undergo mitral valve surgery and significant TR or TV annular dilatation is present [7,20]. High-risk patients however are no longer admitted for complex surgical procedures, where concomitant TV disease can be simultaneously addressed. Today's interventional procedures such as PMVR and

Table 2
Post-procedural echocardiographic characteristics.

	No/mild TR $n=129$	Moderate/severe TR $n=84$	p-Value
EROA [cm^2]	0.20 ± 0.14	0.41 ± 0.26	<0.001*
PISA [mm]	4.8 ± 1.6	6.3 ± 2.1	<0.001*
TV-annulus [mm]	38.1 ± 5.8	40.7 ± 5.6	0.001*
TR Vmax [m/s]	3.0 ± 0.6	2.9 ± 0.5	0.363
TAPSE [mm]	18.3 ± 4.6	16.6 ± 5.0	0.024*
LV-EF [%]	35.7 ± 15.3	35.6 ± 14.9	0.969
LVEDD [mm]	57.5 ± 9.8	58.7 ± 11.6	0.487
LVESD [mm]	48.7 ± 13.6	46.5 ± 14.1	0.592
RA dilatation [%]			<0.001*
None	55.9	20.0	
Mild	24.6	27.5	
Moderate	17.8	33.8	
Severe	1.7	18.8	
LA dilatation [%]			0.114
None	6.3	6.3	
Mild	31.0	20.0	
Moderate	36.7	38.8	
Severe	27.0	35.0	
RV dilatation [%]			<0.001*
None	78.3	43.2	
Mild	13.2	34.6	
Moderate	3.9	19.8	
Severe	1.6	2.5	
MR [%]			0.121
None	2.7	1.7	
Mild	62.2	50.8	
Moderate	32.4	40.7	
Severe	2.7	6.8	
MS [%]			0.863
None	64.2	66.7	
Mild	30.9	17.6	
Moderate	4.9	15.7	
Severe	0	0	

Table shows patients' *post*-procedural echocardiographic characteristics.
EROA, effective regurgitant orifice area; PISA, proximal isovelocity surface area; TV, tricuspid valve; TR, tricuspid regurgitation; TAPSE, tricuspid annular plane systolic excursion; LV, left ventricular; RA, right atrial; LA, left atrial; LVEDD, left ventricular enddiastolic diameter; LVESD, left ventricular endsystolic diameter; RV, right ventricular; MR, mitral regurgitation; MS, mitral stenosis.
Values denote percentages or mean ± standard deviation (SD) as indicated.
* A p-value ≤0.05 was considered statistically significant.

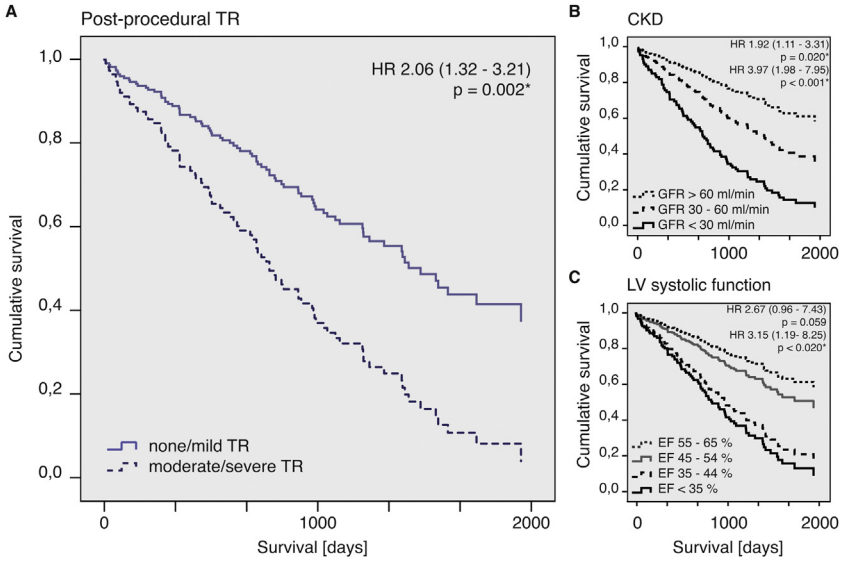

Fig. 4. Cox regression for long-term survival in patients undergoing percutaneous mitral valve repair (PMVR). (A) Survival according to post-procedural grade of tricuspid regurgitation (TR). (B) Survival according to stage of chronic kidney disease (CKD). (C) Survival according to left ventricular (LV) systolic function. Values denote adjusted hazard ratios (HR) and confidence interval (CI). *A p-value ≤0.05 was considered statistically significant.

Table 3
Multivariable regression analysis for survival.

Univariate analysis				*p*-Value
Age				0.581
Sex				0.917
TR grade				*0.188*
MR grade				0.848
MS grade				0.247
LV systolic function				*0.061*
RV systolic function				0.663
Pulmonary hypertension				0.284
CAD				0.711
Atrial fibrillation				0.349
COPD				*0.190*
CKD				*0.160*
Arterial hypertension				0.362
Multivariable regression	**HR**	**95% CI**		***p*-Value**
Post-procedural TR grade (<II vs. ≥II)	2.055	1.317	3.206	0.002*
Post-procedural LV systolic function				0.024*
Mildly impaired	1.352	0.473	3.862	0.574
Moderately impaired	2.673	0.962	7.429	0.059
Severely impaired	3.145	1.199	8.250	0.020*
COPD	1.266	0.763	2.100	0.360
CKD				0.001*
GFR 30–60 ml/min	1.917	1.109	3.314	0.020*
GFR < 30 ml/min	3.969	1.981	7.951	<0.001*

Table shows patients' characteristics for univariate analysis and proportional hazards model.
TR, tricuspid regurgitation; MR, mitral regurgitation; MS, mitral stenosis; LV, left ventricular; RV, right ventricular; CAD, coronary artery disease, COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease.
Italized values signifies < 0.2
* A *p*-value ≤0.05 was considered statistically significant.

transcatheter aortic valve implantation (TAVI) intend only to repair an isolated valve. TR is then left untreated.

Besides TR, left ventricular dysfunction was associated with worsened survival in this cohort. Heart failure is a well-known predictor for increased mortality [27,28,34]. According to previous studies congestive heart failure increases with age and has a higher incidence in men than in women, which can be both found here. It occurs particularly in patients with CAD, hypertension, and type 2 diabetes [35]. But also MR, which is distinctly of interest in this study, burdens the left ventricle and leads to a series of compensatory adaptations such as chronic remodeling processes, enlargement of the left ventricular chamber, and eventually to ventricular dysfunction [36]. Patients with at least moderate TR less frequently presented with previous CAD but more frequently with dilated cardiomyopathy compared to those with no or mild TR in this study. Impaired renal function has been previously reported in patients with relevant TR [37,38]. The latter may contribute to renal dysfunction in patients with heart failure through elevated central and renal venous pressure. Yet chronic kidney disease has been generally associated with worse survival in several studies [26,39–41]. According to the hazards model in this study post-procedural TR grade, left ventricular function, and CKD appear to be potentially modifiable risk factors for long-term survival. Interestingly we found no significant effect of pre-procedural TR on survival in this cohort as described previously [17,25]. Of note, those studies compared groups on the basis of severe TR only and not moderate and severe, which may account for the observed effect. Only a small number of patients showed pre-procedural severe TR in this cohort, thus robust statistics for this subgroup did not seem to be reasonable. We speculate that if TR is still reversible due to immediate hemodynamic changes such as a decrease in pulmonary pressure, the disease will not likely be far advanced and may thus be less relevant for survival. On the contrary TR in virtue of irreversible right ventricular and TV-annulus dilatation with leaflet tethering may account for chronic heart failure, congestion, and increased mortality rates.

Pacemaker and implantable cardioverter defibrillator (ICD) leads have been reported to increase the risk for TR [42]. Hoke et al. observed significant lead-induced TR in the very high number of 38% of patients after placement of a right ventricular lead which was associated with worse long-term clinical outcomes in their study [43]. Here we found around half of the patients had an implantable cardiac device such as pacemaker, ICD, or cardiac resynchronization therapy device and pacemaker or defibrillator. Regarding the prevalence of an implantable cardiac device there were no differences in TR grade in this study. Atrial fibrillation is a known risk factor for TR [6]. This may explain the higher prevalence in patients who exhibited moderate or severe TR.

Study limitations

The study has several limitations. It was retrospectively performed at a single center. Sample size was relatively small. Assessment of TR grade included semi-quantitative and quantitative echocardiographic parameters. TR is known to fluctuate and to be load-dependent. Standards for evaluation of TR are less robust than for MR. All echo data were reanalyzed according to the accepted grading standards from well-trained cardiologists. Pulmonary hypertension was assessed via echocardiographic measurement of TR Vmax.

Clinical implications

According to the hazards model in this study post-procedural TR grade, left ventricular function, and CKD appear to be potentially modifiable risk factors for long-term survival. TR should be taken into account when patients undergo PMVR, including right ventricular characteristics and pulmonary pressure. A closer monitoring and follow-up in patients with residual moderate to severe TR seems reasonable. Beyond that, new strategies ought to be pursued in the future to reduce post-procedural TR. Interventional therapeutic approaches for TV repair may improve functional capacity and possibly even survival. Furthermore the interaction of TR and CKD should be investigated in future studies.

Conclusion

Post-procedural moderate and severe TR predicts worsened long-term survival in patients undergoing PMVR and is associated with adverse clinical outcome such as worse NYHA functional class and elevated NT-proBNP levels. Whether outcome might be improved by interventional reduction of post-procedural TR has to be investigated in the future.

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Conflict of interest

The authors declare that there is no conflict of interest.

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