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RESEARCH ARTICLE

Right ventricular dysfunction predicts outcome after transcatheter mitral valve repair for primary mitral valve regurgitation

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Aims Right ventricular dysfunction (RVD), as expressed by right ventricular to pulmonary artery coupling, has recently been identified as a strong outcome predictor in patients undergoing mitral valve edge-to-edge repair (M-TEER) for secondary mitral regurgitation (MR). The aim of this study was to define RVD in patients undergoing M-TEER for primary MR (PMR) and to evaluate its impact on procedural MR reduction, symptomatic development and 2-year all-cause mortality.

Methods and results This multicentre study included patients undergoing M-TEER for symptomatic PMR at nine international centres. The study cohort was divided into a derivation (DC) and validation cohort (VC) for calculation and validation of the best discriminatory value for RVD. A total of 648 PMR patients were included in the study. DC and VC were comparable regarding procedural success and outcomes at follow-up. Sensitivity analysis identified RVD as an independent predictor for 2-year mortality in the DC (hazard ratio [HR] 2.37, 95% confidence interval [CI] 1.47–3.81, $p < 0.001$), which was confirmed in the VC (HR 2.06, 95% CI 1.36–3.13, $p < 0.001$). Procedural success

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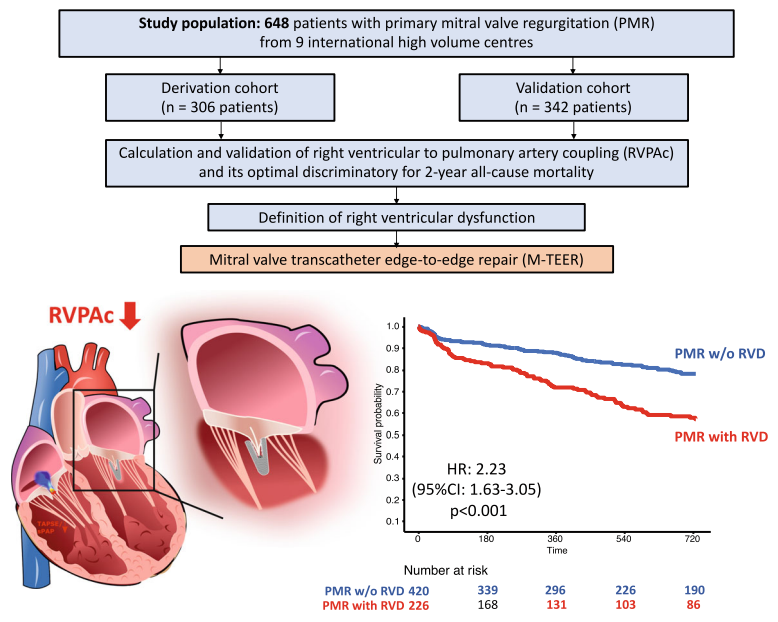
(MR ≤2+) and symptomatic improvement at follow-up (New York Heart Association [NYHA] class ≤II) were lower in PMR patients with RVD (MR ≤2+: 82% vs. 93%, $p = 0.002$; NYHA class ≤II: 57.3% vs. 66.5%, $p = 0.09$ for with vs. without RVD). In all PMR patients, the presence of RVD significantly impaired 2-year survival after M-TEER (HR 2.23, 95% CI 1.63−3.05, $p < 0.001$).

Conclusions Mitral valve edge-to-edge repair is an effective treatment option for PMR patients. The presence of RVD is associated with less MR reduction, less symptomatic improvement and increased 2-year mortality. Accordingly, RVD might be included into pre-procedural prognostic considerations.

Graphical Abstract



RVD predicts outcome after M-TEER for PMR. CI, confidence interval; HR, hazard ratio; PMR, primary mitral regurgitation; RVD, right ventricular dysfunction.

Keywords Transcatheter mitral valve repair • Primary mitral valve regurgitation • Right ventricular dysfunction • Edge-to-edge repair

Introduction

Originally, the 'clip' device was developed to mimic the surgical edge-to-edge repair technique which was performed in selected patients with primary (PMR) and secondary mitral regurgitation (SMR). Recently, mitral valve transcatheter edge-to-edge repair (M-TEER) has become a guideline-recommended therapy for SMR patients with heart failure and reduced left ventricular ejection fraction.[1] For PMR patients at prohibitive surgical risk, M-TEER has emerged as an effective and safe treatment alternative.[2]

Several studies have shown that pre-procedural presence of right ventricular dysfunction (RVD) as assessed by right ventricular to pulmonary artery coupling (RVPAc) is an important outcome predictor in a broad variety of cardiologic pathologies including aortic stenosis,[3] pulmonary hypertension[4] and heart failure with preserved ejection fraction.[5] Additionally, in patients treated with transcatheter or surgical aortic valve replacement, RVD has shown to be an important prognostic marker for all-cause mortality.[6–8] Beyond that, the multicenter European SMR (EuroSMR) registry and a recent secondary subgroup analysis from the COAPT trial confirmed the prognostic importance of RVD also in the setting of M-TEER for SMR.[9,10]

So far, prevalence and impact of RVD on outcomes in PMR patients undergoing M-TEER remain unknown. Therefore, this study aimed at defining and validating RVD in M-TEER treated PMR

patients and evaluating its impact on procedural and symptomatic outcomes and 2-year mortality in a large observational multicentre analysis.

Methods

Study design

We retrospectively analysed a cohort of 306 M-TEER treated PMR patients between 2011 and 2020 at the University Hospitals of Hamburg, Mainz, Paris, Munich and the Heart Center Leipzig. In the following, these patients are referred to as the 'derivation cohort' (DC). For external validation, a large international multicentre cohort (Québec, Technical University of Munich) of 342 M-TEER treated PMR patients was used. This cohort is referred to as the 'validation cohort' (VC). A total of 22 patients with concomitant transcatheter tricuspid valve edge-to-edge repair and 290 with missing parameters for RVPAc were excluded.

All patients showed severe heart failure-related symptoms despite optimal medical treatment. An interdisciplinary heart team recommended M-TEER after careful consideration of comorbidities, surgical risk, optimal medical therapy, life expectancy and feasibility of the procedure in line with recent guidelines.[11] The M-TEER procedures were performed under general anaesthesia with 2- and 3-dimensional transoesophageal echocardiography as well as fluoroscopic guidance as previously described.[12] Primary outcome was 2-year survival; secondary outcomes were success (defined as implantation of ≥1 dedicated device resulting in a post-procedural mitral regurgitation [MR] ≤2+) and New York Heart Association (NYHA) functional class at follow-up. The study was conducted according to international rules for scientific studies as well as the Declaration of Helsinki.[13] Informed written consent was obligatory for all patients.

Data collection and procedural techniques

Collected data included demographic data (age, sex and body mass index), medical history, echocardiographic and clinical parameters. All echocardiograms were performed and analysed by experienced physicians at each study site according to current echocardiographic guidelines. Baseline MR severity was assessed according to current recommendations of the European Association of Echocardiography.[14] Right ventricular (RV) parameters were assessed through a right ventricle-focused apical four-chamber view.[15–17] RVPAc was assessed using the tricuspid annular plane systolic excursion (TAPSE) to systolic pulmonary artery pressure (sPAP) ratio, as previously described.[2,3,9,18–20]

Follow-up

Data collection at follow-up was performed according to protocols of the participating sites and was approved by each centres' local ethics committee. Follow-up was completed on the last medical interview date, the last examination date, or the date when an endpoint event was observed, whichever came first. At follow-up examinations, we assessed NYHA functional class and survival status.

Statistical analysis

Normality of data distribution was assessed graphically and using the Shapiro–Wilk test. For descriptive statistics, continuous data were presented as means with standard deviation (SD) and medians with interquartile ranges (IQR), respectively. Categorical data were presented as proportions. Comparisons between groups were performed using the Chi-squared test for categorical variables, and Student's *t*-test or Mann–Whitney U test for unpaired continuous variables, and Wilcoxon rank sum test for paired variables, according to data distribution. The receiver operating characteristic (ROC) analysis was performed in the DC in order to identify the optimal cut-off value for dichotomizing RVPAc according to its discriminatory value for 2-year all-cause mortality. The predictive value of the established cut-off was externally validated in the VC. Cumulative survival after 2 years was estimated and graphically displayed using Kaplan–Meier curves. The risk of mortality was assessed using Cox multivariate regression analysis with backward elimination and expressed as hazard ratios (HR), 95% confidence intervals (95% CI), and *p*-value.

The statistical tests applied yielded a 2-sided *p*-value with a level of significance (alpha) of <0.05 to determine statistical significance. The statistical software used for data analysis and visualization was R version 3.6.2 (The R Foundation for Statistical Computing).

Results

A total of 648 M-TEER treated PMR patients was included in this study. Out of these, 306 patients treated between 2011 and 2020 at the University Hospitals of Hamburg, Mainz, Paris, Munich and the Heart Center Leipzig were assigned to the DC. For external validation, a cohort of 342 patients from the University Hospitals of Quebec, Munich TU, Bern and Cologne was used and assigned to the VC accordingly. *Tables 1* and *2* display clinical characteristics, echocardiographic parameters and procedural outcomes for the entire study population as well as for the DC and VC subcohorts in detail.

In the DC, median patient age was 81 (77–84) years and 4.2% were female. Surgical risk was high as estimated by a median log EuroSCORE of 14.8 (7.6–26.0)%. Mean left ventricular ejection fraction was preserved (54 ± 12.5%) and the majority of patients presented with MR 3+ or 4+ with a mean MR regurgitant volume) and effective regurgitant orifice area (EROA) of 62 ± 31.3 ml and 50 ± 36 mm^2, respectively. Overall procedural success was achieved in 90.9% of patients and 61.8% showed MR ≤1+ after M-TEER (*Figure 1A*).

Defining the right ventricular dysfunction cut-off and its impact on survival

In the DC, the median follow-up time was 666 (275–1134) days. Mortality was observed in 69 of 306 DC patients at 2 years. Accordingly, the estimated 2-year survival rate was 74.3% (95% CI 69–80%). ROC analysis and Youden's J identified RVPAc <0.307 mm/mmHg as optimal predictor for 2-year all-cause mortality within the DC. Accordingly, RVD with a RVPAc <0.307 mm/mmHg was observed in 93 (30%) DC patients, while 213 (70%) DC patients presented without RVD (online supplementary *Figure S1*). In the Kaplan–Meier analysis, the presence of RVD was associated with significantly impaired 2-year survival (HR 2.37, 95% CI 1.47–3.81, $p < 0.001$ in the DC; *Figure 2A*).

Table 1 Baseline clinical characteristics of patients

	Overall (n = 648)	Derivation cohort (n = 306)	Validation cohort (n = 342)	p-value
Age, years	81.00 [76.01–84.29]	81.0 [77.0–84.0]	81.01 [76.00–84.49]	0.782
Male sex	362 (55.9)	177 (57.8)	185 (54.1)	0.379
BMI, kg/m^2	24.62 [22.09–27.48]	24.7 [22.5–27.3]	24.50 [21.86–27.63]	0.559
Log EuroSCORE II, %	14.82 [7.62–25.98]	14.82 [7.62–25.98]	NA	NA
EuroSCORE II, %	4.30 [2.49–6.66]	4.11 [2.57–6.33]	4.46 [2.41–7.15]	0.848
eGFR, ml/min	49.00 [36.00–62.00]	49.2 [36.4–63.3]	47.53 [35.00–62.00]	0.369
NYHA class				0.002
II	79 (12.6)	30 (10.4)	50 (14.7)	
III	427 (68.2)	194 (67.6)	233 (68.7)	
IV	109 (17.4)	63 (22.0)	46 (13.6)	
History of atrial fibrillation/flutter	412 (65.7)	208 (73.0)	204 (59.6)	0.001
Coronary artery disease	266 (45.2)	105 (42.5)	161 (47.1)	0.310
Previous stroke	64 (10.2)	26 (9.1)	38 (11.1)	0.476
COPD	108 (17.2)	52 (18.2)	56 (16.4)	0.609
Previous cardiac surgery	93 (14.4)	25 (8.2)	68 (19.9)	<0.001
Previous ICD/CRT	36 (13.9)	36 (13.9)	NA	NA
ACE-inhibitor/ARB	413 (67.3)	180 (66.2)	233 (68.1)	0.670
Beta-blocker	452 (74.0)	202 (74.0)	250 (74.0)	1.000
Aldosterone antagonist	107 (24.0)	56 (21.1)	51 (28.5)	0.092
NT-proBNP, pg/ml	2225 [1110–5159]	2765 [1235–5711]	2120 [1005–4985]	<0.001

Qualitative data are presented as n (%); quantitative data are presented as median [interquartile range].
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter defibrillator; NA, not available; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

Table 2 Baseline echocardiographic characteristics of patients

	Overall	Derivation cohort	Validation cohort	p-value
LVEF, %	55.25 (11.20)	53.9 (12.5)	56.45 (9.68)	0.005
LVEDV (Simpson), ml	115.66 (45.60)	121.49 (48.60)	110.09 (41.91)	0.010
LVESV (Simpson), ml	52.92 (28.36)	57.26 (32.56)	48.90 (23.17)	0.002
MR grade				0.025
2+	4 (0.6)	4 (1.3)	0 (0.0)	
3+	106 (16.8)	59 (19.4)	47 (14.4)	
4+	520 (82.5)	241 (79.3)	279 (85.6)	
MR volume, ml	67.37 (31.61)	62.3 (31.3)	71.15 (31.39)	0.009
EROA, cm^2	0.51 (0.32)	0.50 (0.36)	0.52 (0.28)	0.533
MR VC (biplane), mm	0.57 (0.58)	0.9 (1.0)	1.01 (0.48)	<0.001
LA volume index (biplane), ml	73.00 (35.32)	129.5 (60.4)	73.17 (36.10)	0.893
Tricuspid regurgitation grade				0.037
0	23 (3.6)	8 (2.7)	15 (4.4)	
1+	268 (41.9)	124 (41.5)	144 (42.2)	
2+	218 (34.1)	97 (32.4)	121 (35.5)	
3+	103 (16.1)	53 (17.7)	50 (14.7)	
4+	28 (4.4)	17 (5.7)	11 (3.3)	
TAPSE, mm	19.07 (5.51)	19.5 (5.4)	18.70 (5.62)	0.065
sPAP, mmHg	51.94 (17.09)	50.6 (15.5)	53.18 (18.32)	0.051
RVPAc, mm/mmHg	0.42 (0.23)	0.44 (0.2)	0.41 (0.24)	0.152

Qualitative data are presented as n (%); quantitative data are presented as mean (standard deviation).
EROA, effective regurgitant orifice area; LA, left atrium; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MR, mitral regurgitation; RVPAc, right ventricular to pulmonary artery coupling; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; VC, vena contracta.

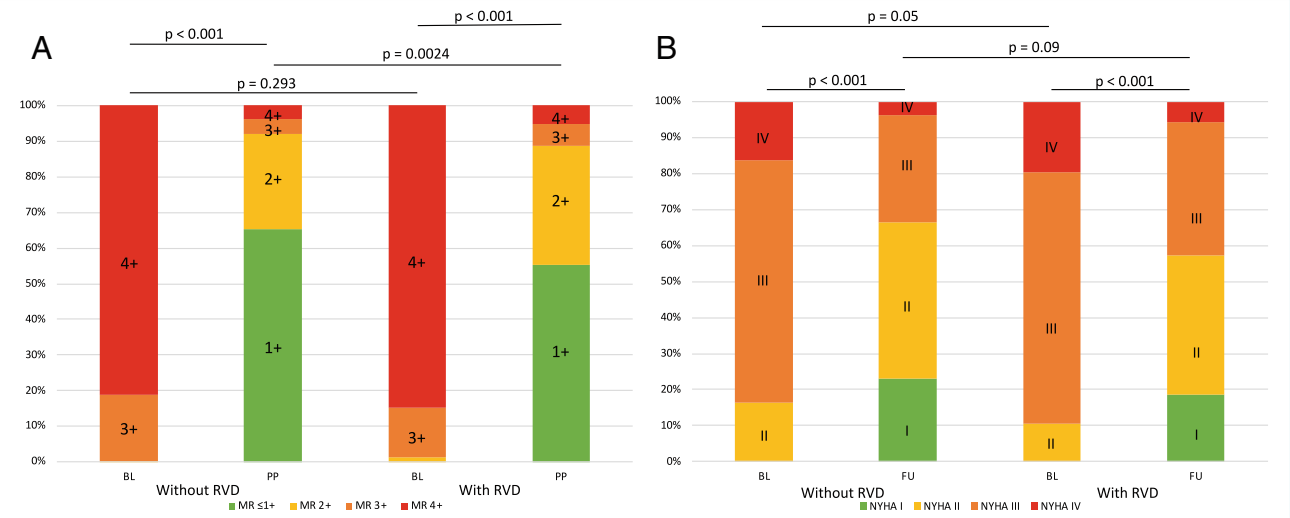


Figure 1 Symptomatic and procedural success. (*A*) Post-procedural mitral regurgitation (MR) reduction after mitral valve edge-to-edge repair in patients with and without right ventricular dysfunction (RVD). (*B*) The according degree of New York Heart Association (NYHA) functional class at follow-up.

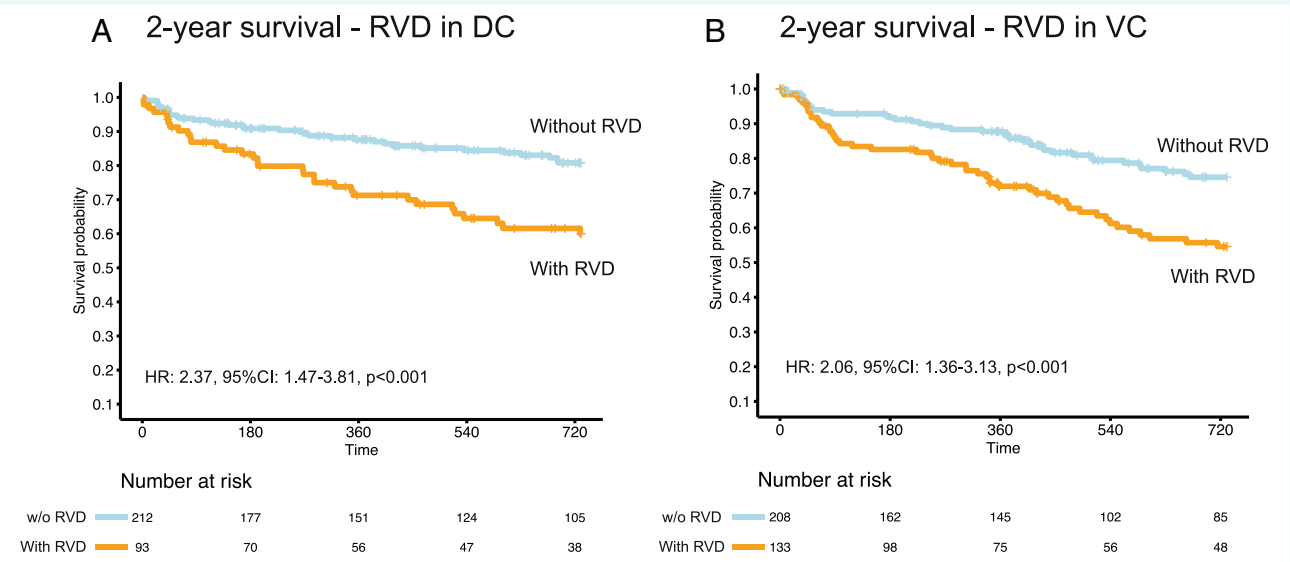


Figure 2 Two-year survival according to the presence of right ventricular dysfunction (RVD) in the derivation (*A*) and validation cohort (*B*). CI, confidence interval; HR, hazard ratio.

Validation of right ventricular dysfunction for survival

Clinical characteristics, echocardiographic parameters and procedural outcomes of patients from the VC are summarized in *Tables 1* and *2*. Characteristics and parameters differed to some extent between DC and VC. Patients in the VC had a lower rate of atrial fibrillation (60% vs. 73%, $p = 0.001$) with lower rates of NYHA class IV (14% vs. 22%).

In the VC, the median follow-up time was 562 (341–1334) days. The estimated 2-year survival rate was 67% (95% CI 61–73%) and did not differ between DC and VC ($p = 0.1$ by log-rank test) (online supplementary *Figure S2*). Applying the established RVD threshold (RVPAc <0.307 mm/mmHg) to the VC, 133 (39%) and 209 (61%) patients presented with or without RVD. The discriminatory effect of RVD on 2-year survival was confirmed in the Kaplan–Meier analysis of VC patients. The presence of RVD was associated with a similar impaired 2-year survival (HR 2.06, 95% CI 1.36–3.13, $p < 0.001$; *Figure 2B*).

Table 3 Characteristics of patients according to the presence of right ventricular dysfunction

	Overall (n = 648)	Without RVD (n = 422)	With RVD (n = 226)	p-value
Baseline characteristics				
Age, years	81.0 [76.0–84.3]	81.0 [76.0–84.1]	81.5 [76.1–85.0]	0.527
Male sex	362 (55.9)	237 (56.2)	125 (55.3)	0.901
BMI, kg/m^2	24.62 [22.1–27.5]	25.00 [22.41–27.71]	24.09 [21.80–26.64]	0.019
log EuroSCORE II, %	8.0 [4.0–17.7]	6.1 [3.1–14.6]	10.7 [5.2–23.4]	<0.001
EuroSCORE II, %	4.5 [2.4–7.2]	3.3 [2.0–5.3]	5.9 [4.4–10.1]	<0.001
eGFR, ml/min	49.0 [36.0–62.0]	52.5 [38.6–66.0]	44.0 [30.5–56.0]	<0.001
NYHA class				0.201
II	79 (12.6)	59 (14.5)	20 (9.1)	
III	427 (68.2)	274 (67.3)	153 (69.9)	
IV	109 (17.4)	66 (16.2)	43 (19.6)	
History of atrial fibrillation/flutter	412 (65.7)	255 (62.7)	157 (71.4)	0.035
Coronary artery disease	266 (45.2)	141 (37.3)	125 (59.2)	<0.001
Previous stroke	64 (10.2)	43 (10.6)	21 (9.5)	0.770
COPD	108 (17.2)	66 (16.3)	42 (19.0)	0.447
Previous cardiac surgery	93 (14.4)	32 (7.6)	61 (27.0)	<0.001
Previous ICD/CRT	36 (13.9)	25 (14.0)	11 (13.8)	1.000
ACE-inhibitor/ARB	413 (67.3)	272 (68.0)	141 (65.9)	0.659
Beta-blocker	452 (74.0)	280 (70.5)	172 (80.4)	0.011
Aldosterone antagonist	107 (24.0)	66 (23.1)	41 (25.8)	0.600
NT-proBNP, pg/ml	2765 [1235–5711]	1638 [700–3458.50]	3621 [1880–8108]	<0.001
Echocardiographic parameters				
LVEF, %	55.25 (11.20)	56.91 (10.36)	52.18 (12.04)	<0.001
LVEDV (Simpson), ml	115.66 (45.60)	117.69 (47.73)	112.15 (41.58)	0.226
LVESV (Simpson), ml	52.92 (28.36)	51.45 (28.02)	55.44 (28.84)	0.160
MR grade				0.092
2+	4 (0.6)	1 (0.2)	3 (1.3)	
3+	106 (16.8)	75 (18.5)	31 (13.8)	
4+	520 (82.5)	330 (81.3)	190 (84.8)	
MR volume, ml	67.37 (31.61)	69.96 (33.34)	62.57 (27.63)	0.036
EROA, cm^2	0.51 (0.32)	0.51 (0.32)	0.51 (0.33)	0.951
MR VC (biplane), mm	0.57 (0.58)	0.50 (0.55)	0.67 (0.60)	0.015
LA volume index (biplane), ml	73.00 (35.32)	71.47 (36.03)	75.60 (34.01)	0.227
Tricuspid regurgitation grade				<0.001
0	23 (3.6)	17 (4.1)	6 (2.7)	
1+	268 (41.9)	209 (50.1)	59 (26.5)	
2+	218 (34.1)	123 (29.5)	95 (42.6)	
3+	103 (16.1)	53 (12.7)	50 (22.4)	
4+	28 (4.4)	15 (3.6)	13 (5.8)	
TAPSE, mm	19.07 (5.51)	21.40 (4.76)	14.72 (3.96)	<0.001
sPAP, mmHg	51.94 (17.09)	44.30 (12.41)	66.21 (15.42)	<0.001
RVPAc, mm/mmHg	0.42 (0.23)	0.53 (0.22)	0.23 (0.05)	<0.001

Qualitative data are presented as n (%); quantitative data are presented as mean (standard deviation) or median [interquartile range].
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; EROA, effective regurgitant orifice area; ICD, implantable cardioverter defibrillator; LA, left atrium; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MR, mitral regurgitation; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; RVD, right ventricular dysfunction; RVPAc, right ventricular to pulmonary artery coupling; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; VC, vena contracta.

Impact of right ventricular dysfunction on outcomes

All 648 patients were considered for the evaluation of RVD or regular RV function (RVr on procedural outcomes and symptomatic improvement after M-TEER as well as for the uni- and multivariate Cox proportional hazard models for 2-year mortality. The mean number of clips implanted was 1.47 (±0.67) and did not differ between patients with and without RVD. *Table 3* summarizes the clinical characteristics, echocardiographic parameters and procedural outcomes of all patients stratified by presence of RVD. In comparison, patients with RVD presented with

Table 4 Univariate and multivariable Cox regression analysis for 2-year mortality

Characteristic	Univariable			Multivariable		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age, years	1.00	0.98–1.02	>0.9			
Male sex	0.67	0.49–0.92	0.013			
BMI, kg/m^2	0.95	0.91–0.99	0.013			
eGFR, ml/min	0.98	0.97–0.99	<0.001	**0.99**	**0.97–1.00**	**0.038**
Previous stroke	0.97	0.57–1.66	>0.9			
Coronary artery disease	1.32	0.95–1.83	0.10			
Previous cardiac surgery	1.79	1.22–2.62	0.003			
COPD	1.22	0.82–1.81	0.3			
History of atrial fibrillation/flutter	1.17	0.83–1.66	0.4			
Echocardiographic parameters						
LVEF, %	0.98	0.97–0.99	0.003			
LVEDV (Simpson), ml	1.00	0.99–1.00	0.4			
LVESV (Simpson), ml	1.00	1.00–1.01	0.6			
LA volume index (biplane), ml	1.00	1.00–1.01	0.2			
MR volume, ml	0.99	0.98–1.00	0.026			
EROA, cm^2	0.44	0.18–1.07	0.069			
MR VC (biplane), mm	2.16	1.56–2.97	<0.001	**1.79**	**1.26–2.54**	**0.001**
Tricuspid regurgitation >3+	1.47	1.02–2.11	0.037			
TAPSE, mm	0.93	0.90–0.96	<0.001			
sPAP, mmHg	1.01	1.00–1.02	0.046			
RVPAc, mm/mmHg	0.18	0.07–0.44	<0.001			
Right ventricular dysfunction	2.23	1.63–3.05	<0.001	**1.79**	**1.11–2.90**	**0.018**

BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; EROA, effective regurgitant orifice area; HR, hazard ratio; ICD, implantable cardioverter defibrillator; LA, left atrium; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MR, mitral regurgitation; NYHA, New York Heart Association; RVPAc, right ventricular to pulmonary artery coupling; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; VC, vena contracta.

lower estimated glomerular filtration rate (eGFR), a higher rate of coronary artery disease, a reduced left ventricular ejection fraction as well as a more severe preprocedural tricuspid regurgitation (*Table 3*). M-TEER effectively reduced MR irrespective of RVD (82% vs. 93% for RVD vs. RVreg, $p = 0.002$). However, procedural success defined as post-procedural MR ≤2+ was significantly lower in RVD patients compared to patients without RVD.

Symptomatic improvement as assessed by NYHA functional class at follow-up was observed in patients with and without RVD. However, the rate of patients with NYHA class ≤II at follow-up was lower in RVD patients (57.3% vs. 66.5% for with vs. without RVD, $p = 0.09$; *Figure 1B*).

Table 4 summarizes the results of the univariate and multivariate Cox proportional hazard models for 2-year mortality. RVD, low eGFR and increased MR vena contracta were identified as strong and independent predictors for 2-year mortality (RVD: HR 1.79, 95% CI 1.11–2.90, $p = 0.018$; eGFR: HR 0.99, 95% CI 0.97–1.00, $p = 0.038$; MR vena contracta: HR 1.79, 95% CI 1.26–2.54, $p = 0.001$). Comparable results for RVD were obtained when the Cox proportional hazard models were restricted to the DC or VC (RVD in DC: HR 2.37, 95% CI 11.47–3.81, $p < 0.001$; RVD in VC: HR 1.68, 95% CI 1.09–2.59, $p = 0.018$). The presence of RVD in PMR patients was associated with a significantly impaired 2-year survival (HR 2.23, 95% CI 1.63–3.05, $p < 0.001$; *Figure 3*).

Discussion

For the first time, the impact of RVD was systematically analysed in a large international cohort of M-TEER treated patients with PMR. Additionally, we were able to validate these results in a large international PMR cohort. The presence of RVD found in 30% of patients was associated with higher pre-procedural MR and lower eGFR. In addition, we identified RVD and impaired renal function as two strong independent predictors for 2-year mortality. PMR patients with RVD showed a more than 2.2-fold increase in 2-year all-cause mortality as well as less symptomatic improvement after M-TEER (*Graphical Abstract*).

While surgical mitral valve repair remains the reference standard therapy for patients with PMR,[21–23] some PMR patients have prohibitive risk for surgery. These patients can be successfully treated with M-TEER[2,24] Despite the increased risk and a large variety of comorbidities, M-TEER showed high rates of procedural success (up to 95%), few device-related complications and a median 3-day duration of hospitalization.[2] Yet, the degree of MR reduction as compared to open mitral valve surgery has been discussed critically. In this prohibitive risk cohort, 90.9% of the patients showed a MR reduction to ≤2+ and 61.8% showed MR ≤1+ following M-TEER. Other studies previously demonstrated the durability of MR reduction,[25] which appears to be acceptable in the absence of alternative

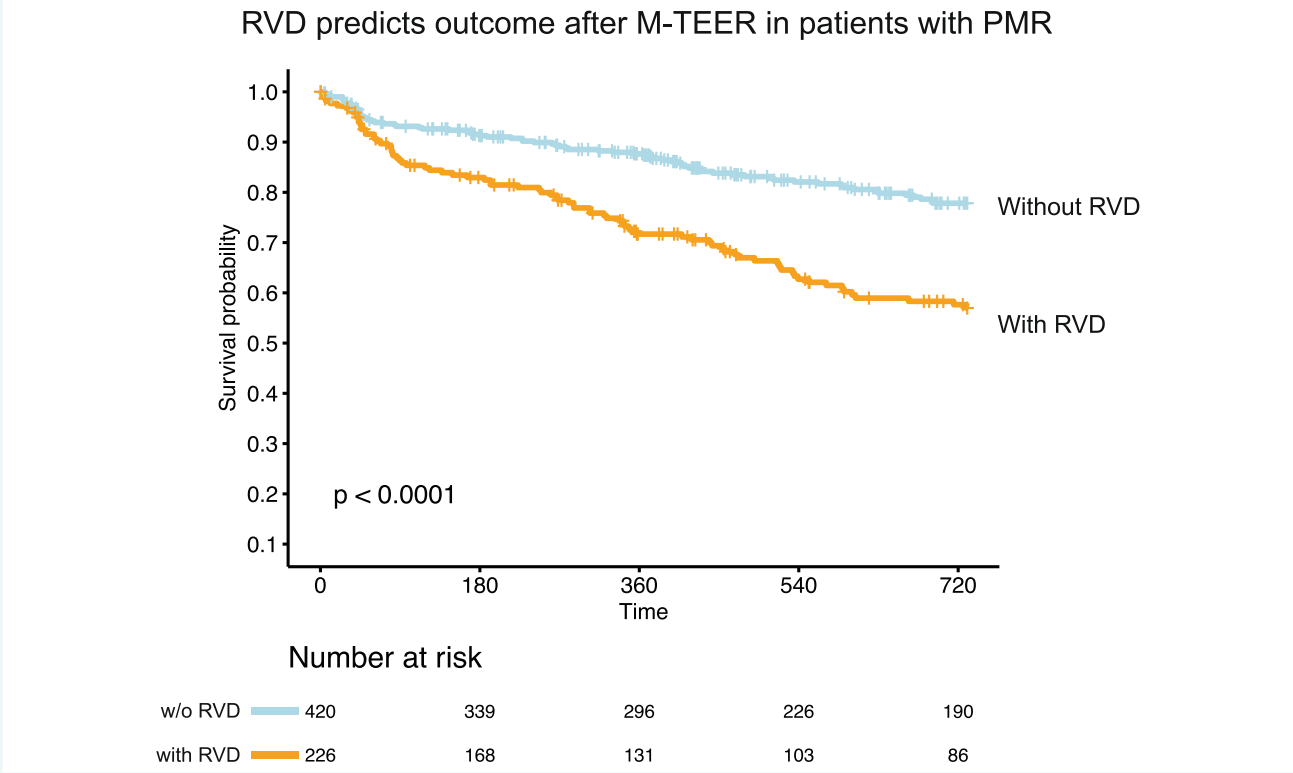


Figure 3 Right ventricular dysfunction (RVD) predicts outcome after mitral valve edge-to-edge repair (M-TEER) in patients with primary mitral regurgitation (PMR). This figure compares the 2-year survival of all primary mitral regurgitation patients according to the presence of RVD.

treatment options. The procedural benefit is mirrored by improvements in functional status and quality of life after M-TEER[26,27] and prospective randomized clinical trials are ongoing to confirm these results.[28–30] Nevertheless, results from several registries and randomized trials underlined the diversity of this prohibitive risk M-TEER cohort. Accordingly, the body of evidence regarding survival prediction in M-TEER treated PMR patients is small.

Right ventricular dysfunction and right ventricular to pulmonary artery coupling

Within the past few years, the importance of RVD in primarily left-sided heart failure increasingly came into clinical focus. Due to the unique anatomy, function and contraction pattern of the right ventricle, defining RVD by single echocardiographic parameters of RV function is a challenging task and highly prone to inter-observer variability. The concept of RVPAc not only takes into account RV function, but respects the mutual interdependence of the right ventricle and the pulmonary circulation. In the presence of balanced RVPAc, the right ventricle is capable of increasing contractility proportionate to increasing afterload. Using RVPAc as definition of RV function is clinically appealing as TAPSE and echo sPAP are easily assessable parameters of clinical routine. Recently, RV to pulmonary artery uncoupling showed to be associated with worse outcome in patient cohorts with aortic stenosis,[3] pulmonary hypertension,[4] heart failure with preserved ejection fraction[5] or SMR.[9,10] In this context, RVD and its clinical relevance regarding patient outcome after M-TEER has been obviously underestimated in the past.

The prevalence of RVD in PMR patients (approximately 30%) was comparable to those undergoing M-TEER for SMR (26%[9]; 30%[10]). The comparable, but slightly diverging cut-off value in our cohort compared to other larger M-TEER cohorts might be due to the fact that our cohort exclusively included PMR patients, which was not the case in other studies.[31,32] According to the present data, PMR patients with RVD may represent a subgroup of patients with progressed disease comprising higher grades of mitral and tricuspid regurgitation, higher N-terminal pro-B-type natriuretic peptide serum levels and most importantly an impaired left ventricular ejection fraction. Higher prevalence of coronary artery disease and an increased rate of previous myocardial infarction may further hint at chronic myocardial ischaemia, potentially contributing to the development of biventricular heart failure in PMR. As RVD is predominantly associated with progressive disease, an early surveillance of RV function and discussion of therapeutic options is crucial in these patients. By establishing an early diagnosis of concomitant RVD, increased further opportunities for optimized medical therapy may exist. In addition, we observed higher rates of moderate to severe tricuspid regurgitation in RVD patients. Concomitant transcatheter tricuspid valve repair might be a therapeutic option for these high-risk patients with progressed heart failure,[33] if such therapies prove to be of prognostic benefit.

The clinical research on novel interventional therapeutic options remains ongoing and may provide opportunities for interventional mitral valve replacement in the future.

Several limitations have to be acknowledged and mainly derive from the retrospective nature of this study. As this is an observational study, there was no central adjudication of clinical status and echocardiographic parameters, so a certain inter-observer variability has to be acknowledged. Some patients were lost to follow-up, as it is often the case in retrospective registries. Additionally, missing information on baseline diuretic therapy, additional perioperative risk scores, and heart failure hospitalization after M-TEER have to be acknowledged. Moreover, some patients have previously undergone cardiac surgery (14.4%), which may influence RV function parameters such as TAPSE. Nevertheless, this analysis represents the yet largest study on M-TEER treated PMR patients with additional external validation in an international cohort.

Conclusion

For the first time, the impact of RVD in PMR patients treated with M-TEER was investigated. While M-TEER proved to be effective irrespective of RVD, the presence of RVD itself was associated with reduced procedural success rate, less reduction of symptoms and most importantly increased mortality at follow-up. The results highlight the importance of detailed RV function assessment in PMR patients scheduled for M-TEER.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Conflict of interest: D.K. received speaker honoraria from Abbott Vascular as well as lecture and proctor fees from Edwards Lifesciences. M.O., D.B., M.N. and N.K. received speaker honoraria from Abbott Vascular. M.O. received speaker fees from TOMTEC Imaging Systems. S.H. has received lecture fees from Medtronic Japan, Daiichi Sankyo, and Ono Pharmaceutical Company. N.S. received proctor fees from Edwards Lifesciences. J.H. received speaker honoraria from and serves as consultant for Abbott Vascular and Edwards Lifesciences. Speaker honoraria (D.K., R.P.), consultant fees (C.I.), travel expenses (R.P., C.I., D.K.) were disbursed by Abbott Medical. Speaker honoraria (D.K.), consultant fees (C.I.), travel expenses (D.K.), proctor fees (D.K.) were disbursed by Edwards LifeSciences. All other authors have nothing to disclose.

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