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Right Ventricular Dysfunction Predicts Outcome After Transcatheter Mitral Valve Repair For Primary Mitral Valve Regurgitation

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/ejhf.2661

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Manuscript word count: 2433 (excluding references and figure legends)

Abstract word count: 244

Abstract

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. 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 multicenter study included patients undergoing M-TEER for symptomatic PMR at 9 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.

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 (HR: 2.37, 95%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 (MR ≤2+) and symptomatic at follow-up (NYHA≤II) were lower in PMR patients with RVD (MR≤2+: 82% vs. 93% p=0.002; NYHA≤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

M-TEER 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 preprocedural prognostic considerations.

Key words:

Transcatheter mitral valve repair, Primary mitral valve regurgitation, Right ventricular dysfunction, Edge-to-edge repair, TMVR

Abbreviation list:

M-TEER = transcatheter edge-to-edge mitral valve repair; **SMR** = Secondary mitral regurgitation; **PMR** = Primary mitral regurgitation; **RVD** = Right ventricular dysfuntion; **NYHA** = New York Heart Association; **DC** = Derivation cohort; **VC** = Validation cohort; **RVPAc** = right ventricular to pulmonary artery coupling

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 (SMR) mitral regurgitation. 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 (LV) ejection fraction (HFrEF)(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 allcause 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 multicenter analysis.

Methods

Study design. We retrospectively analyzed 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, Cologne, Bern) 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 (OMT). An interdisciplinary heart team recommended M-TEER after careful consideration of comorbidities, surgical risk, OMT, 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 postprocedural 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 analyzed 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). RV parameters were assessed through an RV-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,](18-20)[3, 21, 22].

Follow-up. Data collection at follow-up was performed according to protocols of the participating sites and was approved by each centers' local ethics committee. The study complies with the Declaration of Helsinki. 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. 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-values 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, Vienna, Austria).

Results

A total number 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 derivation cohort (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 validation cohort (VC) accordingly. Table 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 logEuroScore 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 (RegVol) and effective regurgitant orifice area (EROA) of 62 ±31.3 ml and of 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 RVD 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 to 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, *Supplementary Figure 1*. In the Kaplan-Maier 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)*.

Validation of RVD 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 (73% vs. 60% for DC vs. VC, p=0.001) with lower rates of NYHA IV (22% vs. 14% for DC vs. VC).

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, *Supplementary figure 2*). 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-Maier 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*).

Impact of RVD on Outcomes

All 648 patients were considered for the evaluation of RVD 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 lower estimated GFR, a higher rate of coronary artery disease, a reduced LV ejection fraction as well as a more severe preprocedural TR (*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 postprocedural 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 ≤II at follow-up was lower in RVD patients (NYHA ≤II at FU: 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 VC: HR: 1.79, 95%CI: 1.26-2.54, p=0.001, *Table 4*).
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 primary MR. 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 preprocedural MR and lower eGFR. In addition, we identified RVD and impaired renal function as 2 strong independent predictors for 2-year mortality. PMR patients with RVD showed a more than 2.2-fold increase in the 2-year all-cause mortality as well as less symptomatic improvement after M-TEER.

While surgical mitral valve repair remains the reference standard therapy for patients with PMR(23-25), some PMR patients have prohibitive risk for surgery. These patients can be successfully treated with M-TEER(26),[2]. 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 three-day duration of hospitalization[2]. Yet, the degree of MR reduction as compared to open mitral valve (MV) 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[27], which appears to be acceptable in the absence of alternative treatment options. The procedural benefit is mirrored by improvements in functional status and quality of life after M-TEER(28, 29)and prospective randomized clinical trials are ongoing to confirm these results(30-32). 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.

RVD and RVPA 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 RV, 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 RV and the pulmonary circulation. In the presence of balanced RVPAc, the RV 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, RVPA uncoupling showed to be associated with worse outcome in patient cohorts with aortic stenosis(3), pulmonary hypertension(4), HFpEF(5) or SMR(20, 33). In this context, RVD and its clinical relevance regarding the patients' outcome after M-TEER has been obviously underestimated in the past.

The prevalence of RVD in PMR patients (approx. 30%) was comparable to those undergoing M-TEER for SMR (26%(34); 30%(33)). 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 in other studies(35, 36). According to the present data, PMR patients with RVD may represent a sub-group of patients with progressed disease comprising higher grades of MR and TR, higher NTproBNP serum levels and most importantly an impaired LV ejection fraction. Higher prevalence of CAD and an increased rate of previous MI may further hint at chronic myocardial ischemia, 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 TR in RVD patients. Concomitant transcatheter tricuspid valve repair (T-TEER) might be a therapeutic option for these high risk patients with progressed heart failure(37), if such therapies prove to be of prognostic benefit. The clinical research on noval

interventional therapeutic options remains ongoing and may provide opportunities for interventional mitral valve replacement in the future.

Several limitations have to be acknowledged and maintly 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 interobserver 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.

Funding: None

Conflicts of interest:

D. Braun, M. Orban, N Karam and M. Nabauer received speaker honoraria from Abbott Vascular. M.Orban received speaker fees from TOMTEC Imaging Systems. Daniel Kalbacher received speaker Honoria from Abbott Vascular as well as lecture and proctor fees from Edwards Lifesciences. Niklas Schofer received proctor fees from Edwards Lifesciences. Hausleiter received speaker honoraria from and serves as consultant for Abbott Vascular and Edwards Lifesciences. S. Higuhi has received lecture fees from Medtronic Japan, Daiichi Sankyo, and Ono Pharmaceutical Company. Speaker honoraria (D. Kalbacher, R. Pfister), consultant fees (C. Iliadis,), travel expenses (R. Pfister, C. Iliadis, D. Kalbacher) were disbursed by Abbott Medical. Speaker honoraria (D. Kalbacher), consultant fees (CI), travel expenses (D. Kalbacher), proctor fees (D. Kalbacher) were disbursed by Edwards LifeSciences.

All other authors report no relevant conflicts of interest in the context of this manuscript.

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Legends

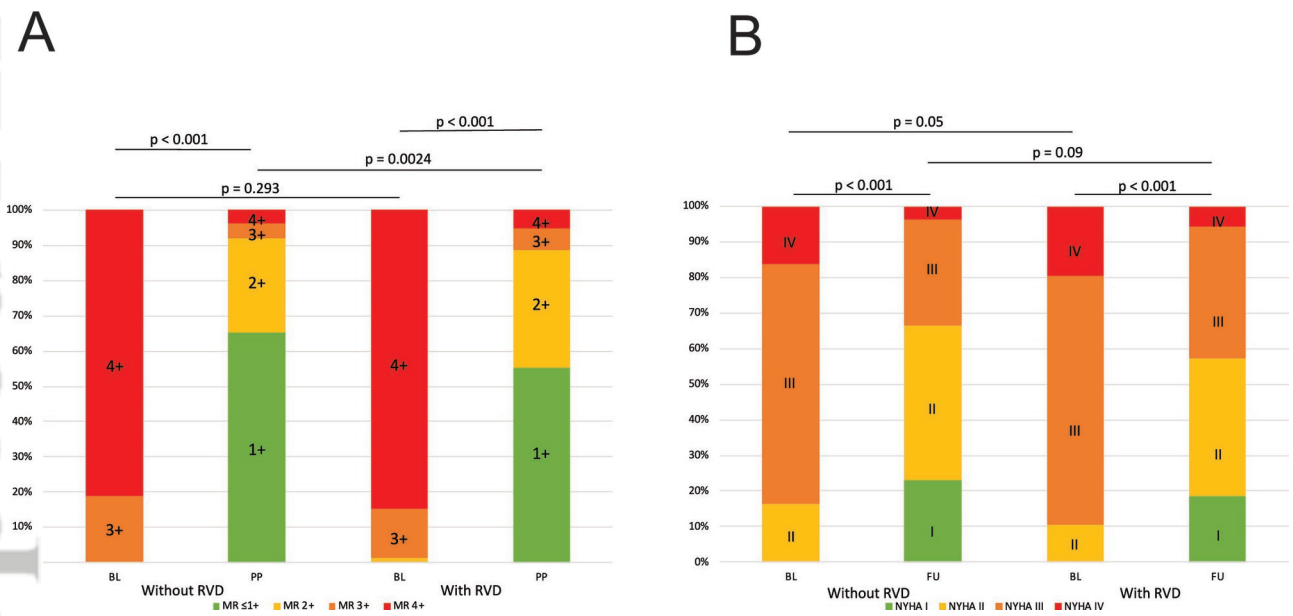
Figure 1: Symptomatic and procedural success. A shows the postprocedural MR reduction after M-TEER in patients with and without RVD. B demonstrates the according degree of NYHA functional class at follow-up.

Figure 2: 2-year survival according to RVD. A demonstrates the 2-year survival in the DC according to the presence of RVD. **B** displays the according 2-year survival rates in the VC.

Figure 3: RVD predicts outcome after M-TEER in patients with PMR. This figure compares the 2-year survival of all PMR patients according to the presence of RVD.

Supplementary Figure 1: RVD distribution among PMR patients. Supplementary Figure 1 displays the distribution of RVD among PMR patients evaluated by the established cut-off for RV-PA Uncoupling.

Supplementary Figure 2: 2-year survival – DC vs. VC. This figure demonstrates the 2-year survival rates with Kaplan-Meier curves of the DC and VC.



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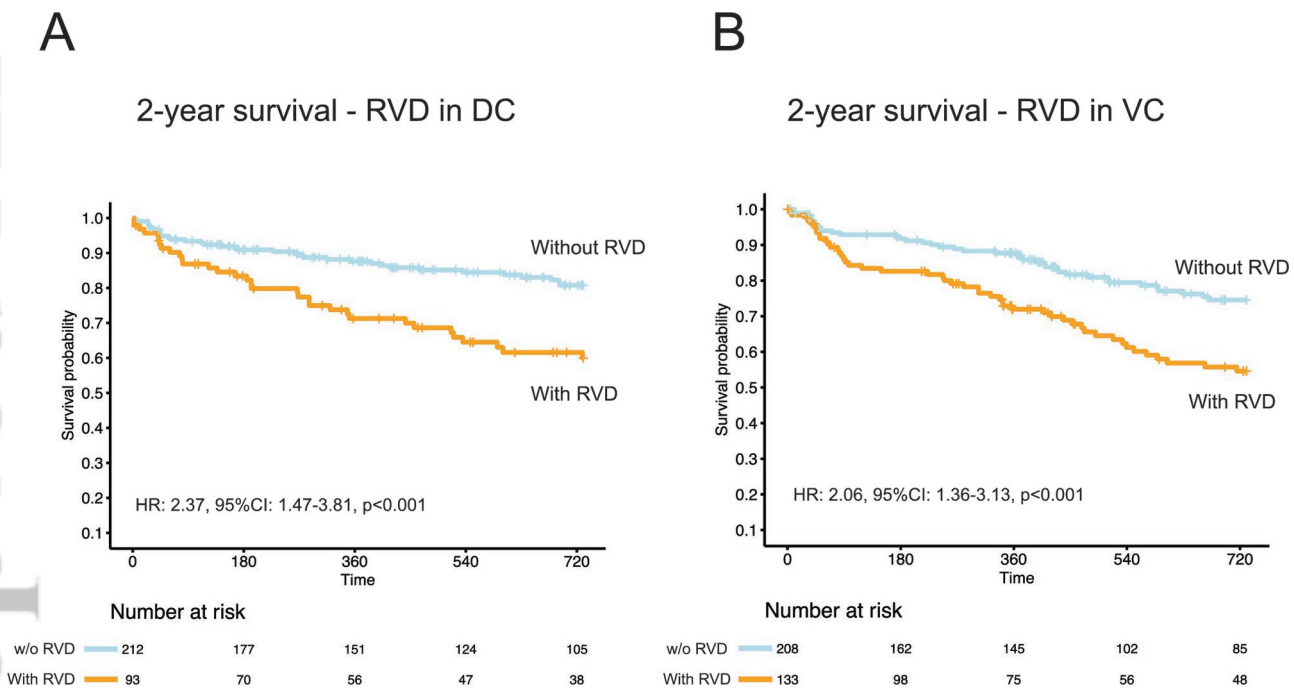

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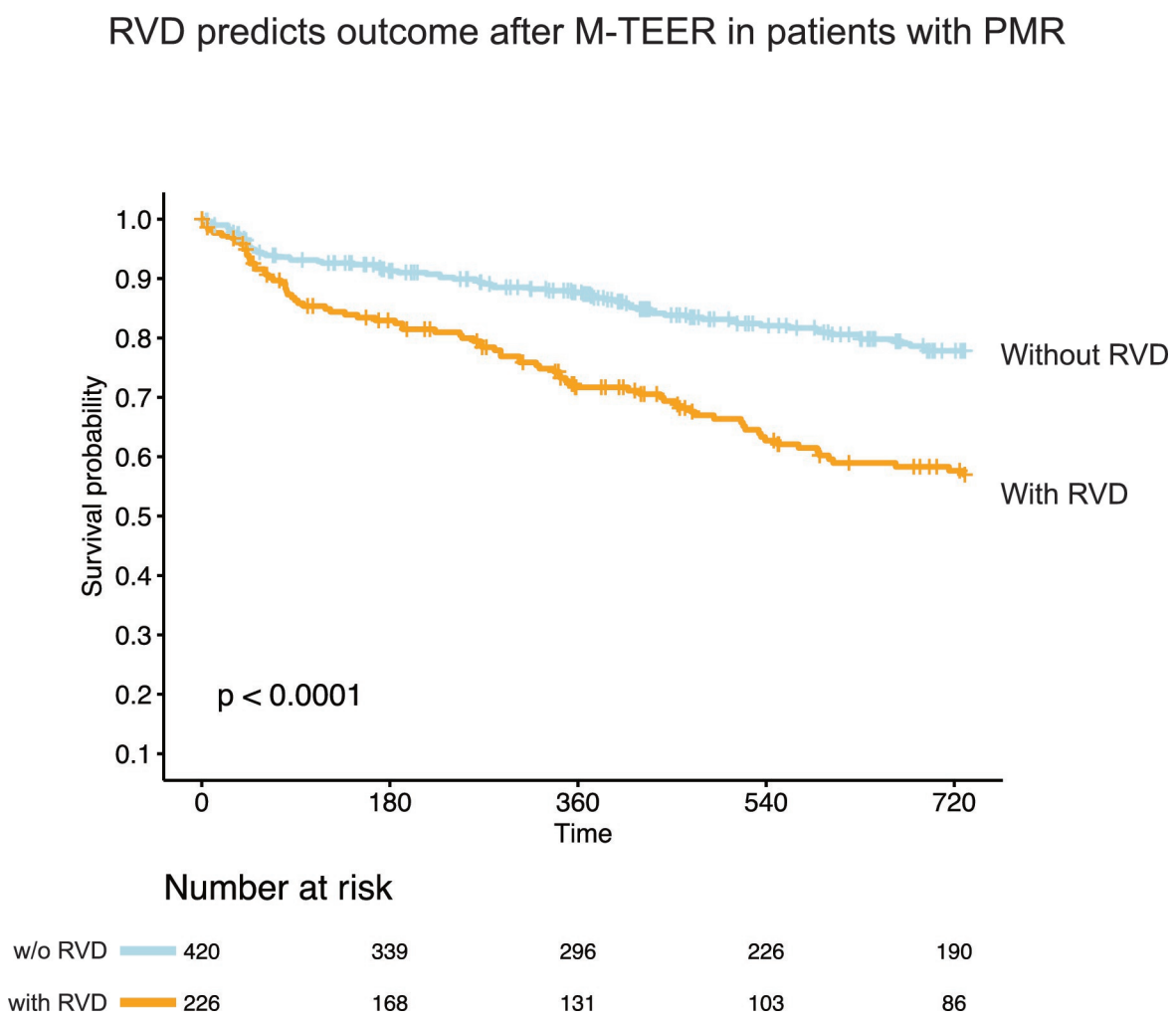

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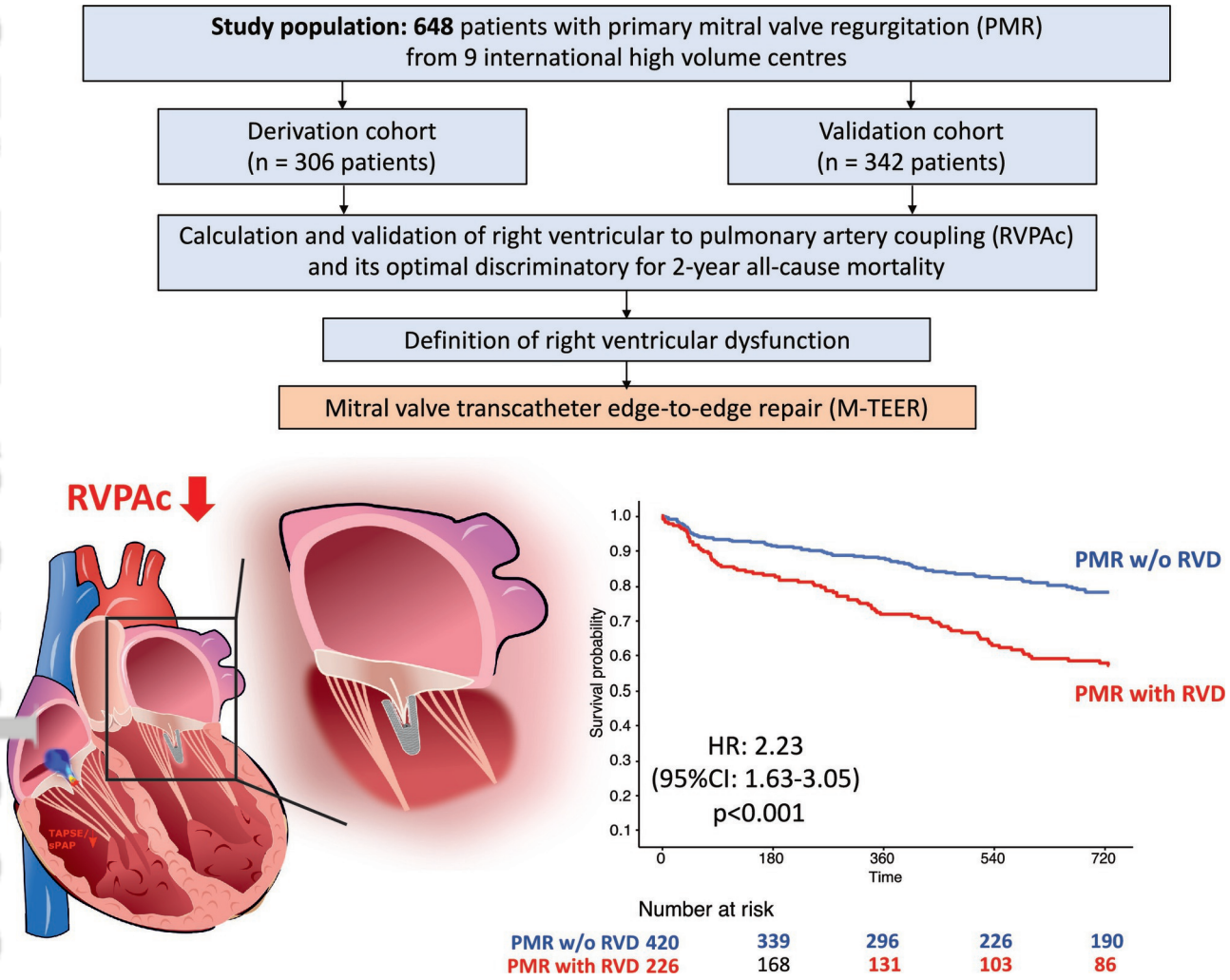

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Table 1

	Overall	Derivation Cohort	Validation Cohort	p-value
n	**648**	**306**	**342**	
Age (years)	81.00 [76.01, 84.29]	81.0 [77.0, 84.0]	81.01 [76.00, 84.49]	0.782
Sex (male)	362 (55.9)	177 (57.8)	185 (54.1)	0.379
BMI	24.62 [22.09, 27.48]	24.7 [22.5, 27.3]	24.50 [21.86, 27.63]	0.559
logEUROScore II	14.82 [7.62, 25.98]	14.82 [7.62, 25.98]	NA [NA, 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				0.002
NYHA II	79 (12.6)	30 (10.4)	50 (14.7)	
NYHA III	427 (68.2)	194 (67.6)	233 (68.7)	
NYHA 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 arterie 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)	(NaN)	NaN
ACE-Inhibitor/AT1-Receptor antagonist	413 (67.3)	180 (66.2)	233 (68.1)	0.670
Betablocker	452 (74.0)	202 (74.0)	250 (74.0)	1.000
Aldosterone antagonist	107 (24.0)	56 (21.1)	51 (28.5)	0.092
NTproBNP	2225 [1110, 5159]	2765 [1235, 5711]	2120 [1005, 4985]	<0.001

Qualitative data are presented as n (%); Quantitative data are presented as means (SD) or medians [IQR]; eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association; COPD, chronic pulmonary artery disease; ICD, implantable cardioverter defibrilator; CRT, cardiac resynchronization therapy

Table 2

	Overall	**Derivation Cohort**	**Validation Cohort**	**P-value**
LV-EF, %	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
Mitral regurgitation 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
RV/PA-Coupling, 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 (SD)

LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LA, left atrium; VC, vena contracta; TAPSE, tricuspid annular plane systolic excursion; EROA, effective regurgitant orifice area; MR, mitral regurgitation; RV, right ventricle;, systolic pulmonary artery pressure; PA, pulmonary artery

Table 3

	Overall	Without RVD	With RVD	p-value
n	**648**	**422**	**226**	
Baseline Characteristics				
Age (years)	81.0 [76.0, 84.3]	81.0 [76.0, 84.1]	81.5 [76.1, 85.0]	0.527
Sex (male)	362 (55.9)	237 (56.2)	125 (55.3)	0.901
BMI	24.62 [22.1, 27.5]	25.00 [22.41, 27.71]	24.09 [21.80, 26.64]	0.019
logEUROScore 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				0.201
NYHA II	79 (12.6)	59 (14.5)	20 (9.1)	
NYHA III	427 (68.2)	274 (67.3)	153 (69.9)	
NYHA 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 arterie 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/AT1-Receptor antagonist	413 (67.3)	272 (68.0)	141 (65.9)	0.659
Betablocker	452 (74.0)	280 (70.5)	172 (80.4)	0.011

Aldosterone antagonist	107 (24.0)	66 (23.1)	41 (25.8)	0.600
NTproBNP	2765 [1235, 5711]	1638 [700, 3458.50]	3621 [1880, 8108]	<0.001
Echocardiographic parameters				
LV-EF, %	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
Mitral regurgitation 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
RV/PA-Coupling, 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 means (SD) or medians [IQR];

eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association; COPD, chronic pulmonary artery disease; ICD, implantable cardioverter defibrilator; CRT, cardiac resynchronization therapy; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LA, left atrium; VC, vena contracta; TAPSE, tricuspid annular plane systolic excursion; EROA, effective regurgitant orifice area; MR, mitral regurgitation; RV, right ventricle; sPAP, systolic pulmonary artery pressure; PA, pulmonary artery

Table 4

Characteristic	Univariable			Multivariable		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Age (years)	1.00	0.98, 1.02	>0.9			
Sex (male)	0.67	0.49, 0.92	0.013			
BMI	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 arterie 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						
LV-EF, %	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**
TR >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			
RV/PA-Coupling, 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; eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association; ICD, implantable cardioverter defibrilator; CRT, cardiac resynchronization therapy; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LA, left atrium; VC, vena contracta; TAPSE, tricuspid annular plane systolic excursion; EROA, effective regurgitant orifice area; MR, mitral regurgitation; RV, right ventricle; sPAP, systolic pulmonary artery pressure; PA, pulmonary artery