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ORIGINAL PAPER

The estimated plasma volume status is an independent predictor for mortality in patients undergoing transcatheter mitral valve repair

Moritz Haus[1] · Franziska Grewe[1] · Valeska Bienert[1] · Christian Schach[1] · Andreas Luchner[2] · Christoph Birner[3] · Lars S. Maier[1] · Bernhard Unsöld[1,4] · Michael Paulus[1] · Christine Meindl[1] · Kurt Debl[1]

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Abstract

Introduction Fluid overload and congestion are common in patients with mitral regurgitation and are associated with poor outcome and increased mortality. However, assessment for subclinical congestion in patients undergoing transcatheter edge-to-edge mitral valve repair (M-TEER) remains challenging. Besides the established natriuretic peptides like NT-proBNP, the estimated plasma volume status (ePVS) has emerged as a prognostic marker for intravascular congestion in heart failure and valvular heart disease. This study evaluated the prognostic impact of preprocedural ePVS in patients undergoing M-TEER.

Methods 311 patients undergoing M-TEER were prospectively enrolled. The ePVS as the difference between actual and ideal plasma volume was calculated based on Hakim's formula using hematocrit, body weight and sex dependent constants. Follow-up data were collected regularly after M-TEER. Based on 1-year mortality, cut-off values for ePVS and NT-proBNP were calculated.

Results Median ePVS was -3.8% (IQR -10.3% to 3.6%). An elevated ePVS above the cut-off was associated with higher Kaplan–Meier-estimated mortality at 1 year (14.4% vs. 4.7%) and 5 years (63.0% vs. 26.0%; log-rank $p<0.001$). Elevated ePVS and NTproBNP remained independently associated with mortality after multivariable adjustment (ePVS: HR 2.38, 95%CI 1.20-4.74; $p=0.013$; NT-proBNP: HR 4.30, 95%CI 1.50-12.31; $p=0.007$). Their combined assessment provided further risk stratification, with the highest risk in patients with both markers elevated compared with neither (HR 14.27, 95%CI 3.19-63.89; $p<0.001$).

Conclusion Elevated preprocedural ePVS and NT-proBNP were independent predictors of mortality after M-TEER. Their combined assessment provided further risk stratification and may improve risk assessment in this heterogeneous population.

✉ Moritz Haus
Moritz.Haus@klinik.uni-regensburg.de; moritz.haus@ukr.de

[1] Department of Internal Medicine II, University Hospital Regensburg, Franz-Josef-Strauß-Allee 11, 9193053 Regensburg, Germany

[2] Department of Cardiology, Hospital Barmherzige Brüder Regensburg, Regensburg, Germany

[3] Department of Internal Medicine I, Klinikum St. Marien, Amberg, Germany

[4] Medical Clinic I, Cardiology and Angiology, Justus-Liebig-University Giessen, Giessen, Germany

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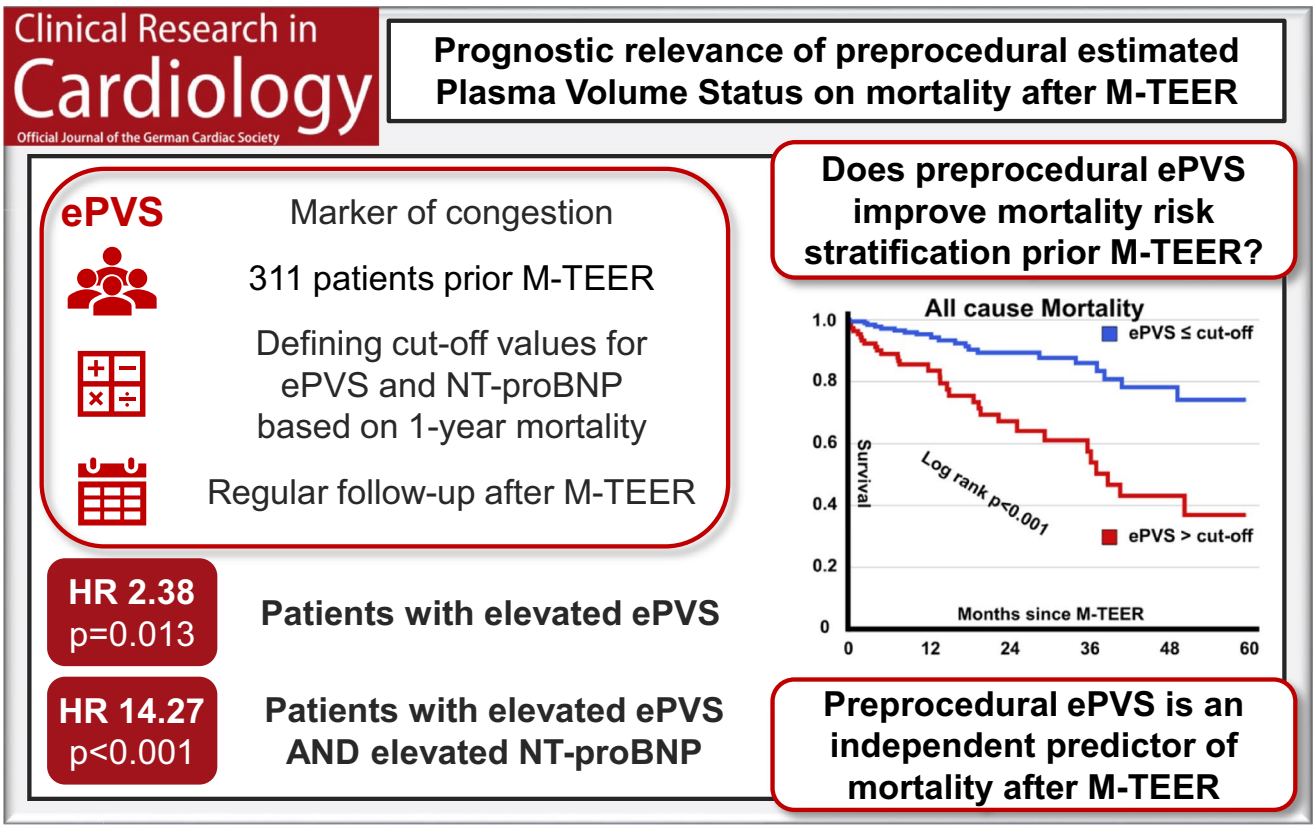
Graphical abstract



Keywords M-TEER · Congestion · ePVS · NT-proBNP · Heart failure

Introduction

Transcatheter edge to edge mitral valve repair (M-TEER) has emerged as an established therapeutic option for patients with severe mitral regurgitation who are considered high risk for conventional surgical intervention due to older age or comorbidities [1–6]. In these patients, hypervolemia and congestion are common and represent major determinants of mortality and morbidity [7–11]. Beyond overt signs of volume overload, intravascular congestion, hemodilution and pseudoanemia due to an expanded plasma volume [12], contribute to adverse organ effects and impaired prognosis in both heart failure [11, 13–16] and transcatheter aortic valve replacement (TAVR) populations [17–20]. Subclinical congestion frequently persists despite apparently compensated clinical status [8, 9, 11, 12, 16]. However, assessment for subclinical congestion remains challenging and clear risk stratification, particularly for patients under evaluation for M-TEER, is currently lacking.

Despite being described for a while in various formulations, the estimated plasma volume status (ePVS) has been established as a simple surrogate marker of intravascular volume expansion and systemic congestion in recent years. The often used Hakim formula derived from hematocrit and bodyweight [9, 15, 21] is easy to assess and has demonstrated its capability to predict congestion and worse outcome in various populations [9, 18, 22–24]. In contrast, the well-established natriuretic peptides (B-type natriuretic peptide (BNP), N-terminal proBNP (NT-proBNP)) primarily reflect a mechanical end-diastolic myocardial wall stress due to intracardial volume and/ or pressure overload and are closely linked to cardiac function and heart failure [25–30]. Consequently, ePVS and NT-proBNP presumably represent distinct phenotypes of congestion as a reflection of the fundamental differences in their underlying pathophysiological mechanisms [13, 21, 29, 31, 32].

Besides the well-known poor prognostic implications of elevated natriuretic peptides [25–28, 33], a high ePVS as a surrogate of intravascular congestion has been consistently

associated with unfavourable outcomes in heart failure and TAVR populations [9, 18, 19]. Yet, the impact of pre-procedural, intravascular congestion and fluid overload on outcomes after M-TEER and the resulting implications for adequate stratification of risk and postprocedural benefit, remain an area of active investigation. The present study from the ongoing Regensburg Trial on TMVR Techniques in Mitral Regurgitation (RETORT-MR) is a prospective evaluation on the impact of preprocedural increased ePVS on outcome and mortality in patients undergoing M-TEER due to severe mitral regurgitation.

Methods

Regensburg Trial on TMVR Techniques in Mitral Regurgitation (RETORT-MR)

Three hundred-eleven patients with severe mitral regurgitation who were deemed eligible for M-TEER were prospectively enrolled from December 2017 to March 2024 as part of the ongoing Regensburg Trial on TMVR Techniques in Mitral Regurgitation (RETORT-MR). This single-center study was conducted in the cardiology department of University Hospital Regensburg, Germany. All patients gave informed consent before participating in the trial, which was approved by the local ethics committee of the University of Regensburg (approval no. Z-2017–0862-10).

After initial, preprocedural assessment of the well compensated patients without clinical signs of hypervolemia and congestion, follow-up data were collected at regular intervals after M-TEER. The collected data consisted of general information about the patients and their medical history as well as clinical, functional, laboratory and echocardiographic parameters. All data was collected prospectively and pseudonymized. Supplementary Fig. S1 and Table S7 present a detailed overview of patient inclusion, availability of biomarker data, and follow-up status.

Transcatheter edge to edge mitral valve repair (M-TEER)

All M-TEER procedures were performed under general anesthesia by experienced interventional cardiologists according to standard techniques [1, 2, 35, 36]. Fluoroscopic and three-dimensional transesophageal echocardiography were used for periprocedural guidance. Either the MitraClip system (NT, NTW, XT, XTW; Abbott Vascular, Menlo Park, CA, USA) or the PASCAL system (PASCAL P10, PASCAL Ace; Edwards Lifesciences, Irvine, CA, USA) was chosen for the procedure depending on patient anatomy and procedural strategy.

Calculating the estimated Plasma Volume Status (ePVS)

The estimated plasma volume status, an estimate of the proportional deviation from ideal plasma volume, was calculated based on the established formulas for the ideal plasma volume after Longo et al. [34] and the actual plasma volume according to Hakim et al. [21].

- Actual plasma volume (aPV): $aPV = (1 - \text{hematocrit}) * [a + (b * \text{weight})]$
  - a: 864 for female; 1,530 for male patients
  - b: 47.9 for female; 41.0 for male patients
- Ideal plasma volume (iPV):$iPV = c \times \text{weight}$
  - weight [kg], c: 40 for women and 39 for men
- Estimated plasma volume status (ePVS):$ePVS = [(aPV-iPV)/iPV] * 100$

Statistical analysis

Most statistical analyses were performed using IBM SPSS software Version 29 (IBM Corp., Armonk, NY, USA) and Microsoft Excel Version 2108 (Microsoft Corp., Redmond, WA, USA). Integrated discrimination improvement and continuous net reclassification improvement were performed using the survIDINRI package Version 1.1–2 [35] in RStudio Version 2026.7.1.147 (Posit Software, PBC, Boston, MA) [36]. Graphical processing of the displayed figures was carried out in Affinity Designer 2 Version 2.3.1 (Serif Ltd., Nottingham, UK). *P*-values < 0.05 were considered statistically significant. Continuous variables are presented as median with interquartile range. Categorical variables are reported as counts and percentages. Comparison between two groups was done using the Mann–Whitney-*U* test for continuous and ordinal and the Pearson's chi-square test for categorial variables. As the grading of mitral (MR) and tricuspid regurgitation (TR) as well as the left ventricular ejection fraction (LVEF) can be categorized as both, ordinal and categorial variables, both *p*-values are presented.

To assess the predictive value of the ePVS on mortality and to compare it with NT-proBNP, receiver operating characteristic (ROC) curve analyses were performed, based on 1-year-mortality. Optimal cut-off values were calculated using Youden's index [37] as well as the closest top left metric [38] and corresponding binary variables were generated. A combined risk variable was also introduced, coded as 0 (no marker elevated), 1 (one marker elevated), and 2 (both markers elevated).

Survival analysis was conducted using Kaplan–Meier (KM) estimates to compare time-to-event outcomes across groups stratified by ePVS, NT-proBNP and the combined risk variable. The log-rank test was used to evaluate

statistical significance between survival curves. To explore associations between clinical parameters and various endpoints, univariable Cox proportional hazards regression models were applied. Variables with a p-value < 0.05 in the univariable analysis were subsequently entered into multivariable cox regression models to identify independent outcome predictors. Hazard ratios (HR) are presented with 95% confidence intervals (CI) and corresponding p-values.

To assess the incremental prognostic value of ePVS beyond hematocrit, additional nested multivariable Cox regression models were constructed using the same adjustment covariates as the primary multivariable analysis and comparatively evaluated by likelihood-ratio chi-square tests. Hematocrit was assessed continuously per 5-percentage-point increase and dichotomized as a sex-specific cut-off of 40% (male) or 37% (female) [39–41]. Time-dependent incremental prognostic performance of ePVS was additionally assessed at 1, 1.5, and 2 years using the integrated discrimination improvement (IDI) and continuous net reclassification improvement (NRI) [42], with 95% confidence intervals and p-values calculated from 2000 perturbations.

Results

Baseline characteristics and ROC-derived cut-off analysis

A total of 311 patients undergoing transcatheter mitral valve repair (M-TEER) were prospectively enrolled in the ongoing RETORT-MR trial. Baseline characteristics of the overall cohort and stratified values according to the ePVS cut-off are presented in Table 1. Preprocedural ePVS could be calculated in all patients (100%), with a median value of − 3.8% (IQR −10.3%−3.6%). NT-proBNP levels were available in 293 patients (94%), with a median concentration of 2221 pg/mL (IQR 1064–4655 pg/mL). In three patients, the procedure was unsuccessful and no device was implanted. The remaining 308 patients with successful implantation of at least one device were included in the follow-up, with a median follow-up duration of 12.0 months (IQR 7.6–24.0).

Fifty-one patients died during follow-up, median time until death was 422 days (IQR 134–878 days). To identify prognostic cut-off values, receiver operating characteristic cut-off analyses were performed based on the 1-year mortality of 248 (100%; ePVS) and 236 (95%; NT-proBNP) patients who completed 1-year follow-up (n = 227; 91.5%) or died within 12 months after M-TEER (n = 21; 8.5%). Baseline characteristics stratified by the NT-proBNP cut-off and by 1-year mortality are presented in Supplementary Table S1 *(NT-proBNP)* and S2 *(1-year mortality)*. Based on their Youden index [37] and closest top left value [38] in the ROC curve, the optimal cut-off values to determine 1-year-mortality in this cohort were identified as + 0.36% for ePVS and 2794 pg/mL for NT-proBNP. These thresholds were applied for all subsequent outcome analyses.

Stratified baseline characteristics showed that patients with an elevated ePVS were slightly but significantly older (79 vs. 78 years, p = 0.004) and exhibited a significantly lower estimated glomerular filtration rate (eGFR) (39.5 vs. 51.0 ml/min/1.73 m^2; p = 0.003). They also presented a significantly lower body mass index (BMI) and hemoglobin and hematocrit levels were also significantly lower in this group. Notably, both body weight and hematocrit (and thus indirectly hemoglobin) are components of the ePVS calculation. Regarding medication, patients with elevated ePVS received a higher median furosemide-equivalent loop diuretic dose (80 mg/day IQR 40–120) than those with lower ePVS (60 mg/day IQR 40–100; p = 0.011). Angiotensin Converting Enzyme (ACE-) Inhibitors, Angiotensin-Receptor Blockers (ARB) and Angiotensin-Receptor-Neprilysin-Inhibitors (ARNI) (76.3% vs. 65.5%; p = 0.048) and beta-blocker therapy (81.3% vs. 70.8%; p = 0.035) were more frequent in the lower-ePVS group. MRA use was comparable between groups (35.9% vs. 33.6%; p = 0.713).

In contrast to the ePVS-stratified, which did not reveal significant differences in cardiac function parameters, preprocedural NT-proBNP above the calculated cut-off (Supplementary Table S1) was significantly associated with impaired cardiac function. Elevated NT-proBNP was also associated with a higher prevalence of secondary mitral regurgitation (64.8% vs. 42.2%; p < 0.001). Markers of cardiac dysfunction included a higher prevalence of heart failure with reduced ejection fraction (HFrEF) (44.4% vs. 18.0%; p < 0.001), lower left ventricular ejection fraction (LVEF) (45% vs. 55%; p < 0.001) and a reduced tricuspid annular plane systolic excursion (TAPSE) (17 mm vs. 19 mm; p < 0.001). In addition, NYHA functional class III–IV was more frequent in patients with elevated NT-proBNP (81.7% vs. 70.7%; p = 0.039), whereas no significant differences were observed across ePVS-stratified groups.

A preprocedural elevated ePVS is an independent predictor for an increased mortality in patients undergoing M-TEER

Cut-off based survival analysis of ePVS, NT-proBNP and a combined congestion variable

To evaluate the effect of an elevated preprocedural ePVS on mortality from any cause, a Kaplan–Meier survival analysis was conducted (Fig. 1). Elevated ePVS above the ROC-derived cut-off was significantly associated with increased cumulative 1-year (14.4% for elevated vs. 4.7% for low ePVS) and 5-year KM estimated mortality rate (63.0% vs.

Table 1 Baseline characteristics of the overall cohort and stratified values by a preprocedural ePVS cut-off

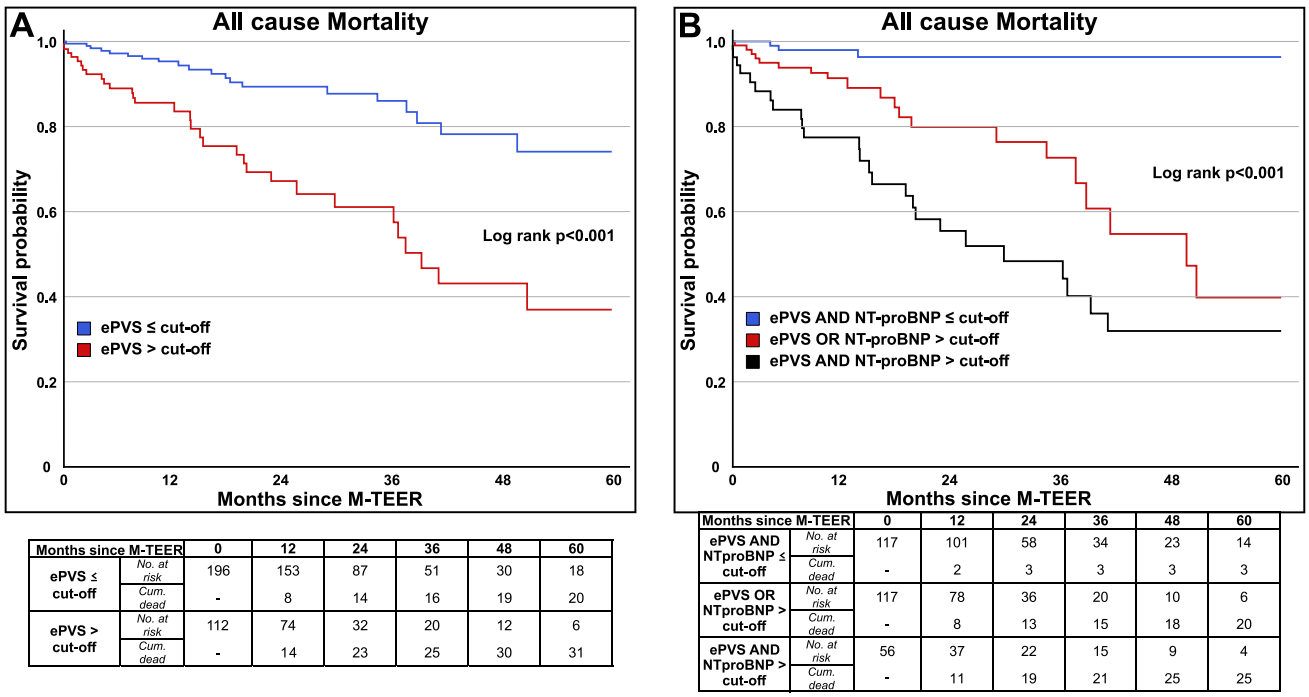
Patients	**All** *n=311 (100)*	**ePVS ≤ 0.36%** *n=198 (63.7)*	**ePVS > 0.36%** *n=113 (36.3)*	***p***
Age (Years)	79 [73–82]	78 [72–81]	79 [76–83]	**0.004**
Male sex	192 (61.7)	119 (60.1)	73 (64.6)	0.468
BMI (kg/m²)	25.5 [22.9–28.7]	26.8 [24.3–30.1]	23.5 [21.2–25.6]	**< 0.001**
HFrEF	91 (29.3)	65 (32.8)	26 (23.0)	0.071
CAD	190 (61.1)	115 (58.1)	75 (66.4)	0.183
Prior MI	69 (22.2)	38 (19.2)	31 (27.4)	0.118
Prior PCI	117 (37.6)	69 (34.8)	48 (42.5)	0.224
Prior CABG	34 (10.9)	22 (11.1)	12 (10.6)	1.000
Atrial Fibrillation	209 (67.2)	130 (65.7)	79 (69.9)	0.455
COPD	36 (11.6)	23 (11.6)	13 (11.5)	1.000
Diabetes mellitus	80 (25.7)	48 (24.2)	32 (28.3)	0.500
M-TEER Device *	*n=308)*			
Mitra-Clip	215 (69.1)	140 (70.7)	75 (66.4)	0.446
PASCAL	96 (30.9)	58 (29.3)	38 (33.6)	
MR etiology				
Primary	117 (37.6)	70 (35.4)	47 (41.6)	0.569
Secondary	156 (50.2)	103 (52.0)	53 (46.9)	
Mixed	38 (12.2)	25 (12.6)	13 (11.5)	
MR grade pre				
III	71 (22.8)	48 (24.2)	23 (20.4)	0.484
IV	240 (77.2)	150 (75.8)	90 (79.6)	
MR grade post *	*n=308*	*n=196*	*n=112*	
I	183 (59.4)	117 (59.7)	66 (58.9)	0.753/0.722
II	111 (36.0)	72 (36.7)	39 (34.8)	
III	11 (3.6)	5 (2.6)	6 (5.4)	
IV	3 (1.0)	2 (1.0)	1 (0.9)	
TR grade pre	*n=309*	*n=196*	*n=113*	
≤ I	94 (30.4)	68 (34.7)	26 (23.0)	**0.015**/0.072
II	104 (33.7)	66 (33.7)	38 (33.6)	
III	111 (35.9)	62 (31.6)	49 (43.4)	
LVEF (%)	52 [38–58]	51 [37–58]	53 [43–59]	0.128
LVEF ≥ 50%	173 (55.6)	104 (52.5)	69 (61.1)	
LVEF 41–49%	47 (15.1)	29 (14.6)	18 (15.9)	0.150/0.110
LVEF 30–40%	41 (13.2)	33 (16.7)	8 (7.1)	
LVEF < 30%	50 (16.1)	32 (16.2)	18 (15.9)	
TAPSE (mm)	*n=292*	*n=184*	*n=108*	0.309
	18 [16–21]	19 [16–22]	18 [16–21]	
ePVS (%)	–3.8 [–10.3–3.6]	–8.3 [–13.2—4.2]	6.0 [2.7–11.6]	**<0.001**
NT-proBNP (pg/mL)	*n=293*	*n=188*	*n=105*	
	2221 [1064–4655]	2077 [1062–3806]	3071 [1226–7725]	**0.025**
Hb (g/dL)	12.7 [11.0–13.8]	13.4 [12.5–14.2]	10.6 [9.6–11.6]	**< 0.001**
Hematocrit (%)	37.9 [33.4–41.2]	40.2 [38.0–42.7]	32.2 [29.4–34.8]	< 0.001
eGFR (ml/min/1.73m²)	47.0 [32.0–64.0]	51.0 [35.0–65.0]	40.0 [29.0–58.0]	**0.003**
Betablocker therappy	241 (77.5)	161 (81.3)	80 (70.8)	**0.035**
ACE-Inhibitor/ AT1-Receptor-Antagonist/ ARNI therapy	225 (72.3)	151 (76.3)	74 (65.5)	**0.048**

Table 1 (continued)

Patients	All *n=311 (100)*	ePVS ≤ 0.36% *n=198 (63.7)*	ePVS > 0.36% *n=113 (36.3)*	*p*
Mineralocorticoid receptor antagonist therapy	109 (35.0)	71 (35.9)	38 (33.6)	0.713
Loop diuretic dose (Furosemide-equivalent in mg)	60 [40–120]	60 [40–100]	80 [40–120]	**0.011**
NYHA class ≥ III	235 (75.6)	148 (74.7)	86 (76.1)	0.891

BMI Body Mass Index; *HFrEF* Heart Failure with reduced Ejection Fraction; *CAD* Coronary Artery Disease; *MI* Myocardial Infarction; *PCI* Percutaneous Coronary Intervention; *CABG* Coronary Artery Bypass Grafting; *COPD* Chronic Obstructive Pulmonary Disease; *M-TEER* Mitral valve Transcatheter Edge to Edge Repair; *MR* Mitral Regurgitation; *TR* Tricuspid Regurgitation; *LVEF* Left Ventricular Ejection Fraction; *TAPSE* Tricuspid Annular Plane Systolic Excursion; *ePVS* estimated Plasma Volume Status; *NT-proBNP* N-Terminal pro–Brain Natriuretic Peptide; *Hb* Hemoglobin; *eGFR* estimated Glomerular Filtration Rate; *ACE-Inhibitor* Angiotensin Converting Enzyme-Inhibitor; *ARB* Angiotensin-Receptor Blockers; *ARNI* Angiotensin-Receptor-Neprilysin-Inhibitor; *MRA* Mineralocorticoid-Receptor-Antagonist; *NYHA* New York Heart Association. Mitral regurgitation is graded from I to IV; Tricuspid regurgitation is graded from I to III; Loop-diuretic doses were converted to daily furosemide-equivalent doses, with 10 mg torasemide considered equivalent to 40 mg furosemide. Patients not receiving diuretics were assigned a dose of 0 mg/day. SGLT2 inhibitors were not analyzed because they were not available throughout the entire enrollment period. Bold values indicate statistical significance ($p < 0.05$)

*The used M–TEER Device and the postprocedural mitral regurgitation was only assessed in the 308 patients with successful implantation of at least 1 clip device



Months since M-TEER		0	12	24	36	48	60
ePVS ≤ cut-off	No. at risk	196	153	87	51	30	18
	Cum. dead	-	8	14	16	19	20
ePVS > cut-off	No. at risk	112	74	32	20	12	6
	Cum. dead	-	14	23	25	30	31

Months since M-TEER		0	12	24	36	48	60
ePVS AND NTproBNP ≤ cut-off	No. at risk	117	101	58	34	23	14
	Cum. dead	-	2	3	3	3	3
ePVS OR NTproBNP > cut-off	No. at risk	117	78	36	20	10	6
	Cum. dead	-	8	13	15	18	20
ePVS AND NTproBNP > cut-off	No. at risk	56	37	22	15	9	4
	Cum. dead	-	11	19	21	25	25

Fig. 1 Kaplan Meier survival analysis for all-cause mortality stratified by preprocedural ePVS and a combined congestion variable based on preprocedural ePVS and NT-proBNP

26.0%). Figure 1A demonstrates the corresponding significant separation of survival curves, with highly significant log-rank test ($p < 0.001$). Similarly, elevated NT-proBNP above the respective cut-off (Supplementary Fig. S2) was also associated with significantly higher cumulative 1-year KM estimated mortality rate (14.6% for elevated NT-proBNP vs. 3.5% for low NT-proBNP), with a significant log-rank test ($p < 0.001$).

To assess the combined prognostic value of both biomarkers, the patients were stratified in three groups according to their ePVS and NT-proBNP status:

- ePVS AND NT-proBNP ≤ cut-off (reference group)
- ePVS OR NT-proBNP > cut-off
- ePVS AND NT-proBNP > cut-off

Table 2 Uni- and multivariable Cox regression analysis for mortality from any cause

	Univariable Analysis *		Model 1: ePVs and NT-proBNP isolated **		Model 2: ePVs and NT-proBNP combined **	
	HR [95%CI]	*p*	HR [95%CI]	*p*	HR [95%CI]	*p*
ePVS (per 1% increase)	**1.0 [1.01–1.06]**	**0.004**	-		-	-
ePVS > + 0.36%	**3.4 [1.94–5.99]**	**< 0.001**	**2.38 [1.20–4.74]**	**0.013**	-	-
NT-proBNP (per 1000 pg/mL increase)	**1.1 [1.04–1.11]**	**< 0.001**	-		-	-
NT-proBNP > 2794 pg/ml	**7.9 [3.55–17.69]**	**< 0.001**	**4.30 [1.50–12.31]**	**0.007**	-	-
ePVS AND NT-proBNP ≤ cut-off (reference)	**1.0**	-	-	-	**1.0**	-
ePVS OR NT-proBNP > cut-off	**9.3 [2.76–31.33]**	**< 0.001**	-	-	**6.67 [1.47–30.27]**	**0.014**
ePVS AND NT-proBNP > cut-off	**19.5 [5.88–64.52]**	**< 0.001**	-	-	**14.27 [3.19–63.89]**	**< 0.001**
Age (per 1 year increase)	0.99 [0.96–1.02]	0.586	-	-	-	-
Male Sex	1.29 [0.72–2.31]	0.389	-	-	-	-
BMI (per 1 kg/m^2 increase)	1.01 [0.95–1.07]	0.790	-	-	-	-
HFrEF	**1.99 [1.15–3.5]**	**0.014**				
CAD	1.35 [0.75–2.43]	0.313	-	-	-	-
Atrial Fibrillation	1.03 [0.57–1.84]	0.933	-	-	-	-
COPD	1.66 [0.83–3.32]	0.151	-	-	-	-
Diabetes mellitus	**2.59 [1.48–4.53]**	**< 0.001**	1.39 [0.70–2.73]	0.347	1.45 [0.73–2.87]	0.286
PASCAL-Device (Reference MitraClip)	1.19 [0.56–2.50]	0.656	-	-	-	-
Secondary or mixed MR	1.41 [0.75–2.65]	0.287	-	-	-	-
Preprocedural MR grade IV/IV (reference grade III/IV)	1.47 [0.69–3.12]	0.321	-	-	-	-
Severe residual MR (III-IV/IV)	**4.12 [1.75–9.69]**	**0.001**	**3.41 [1.29–9.01]**	**< 0.001**	**5.81 [2.25–14.99]**	**< 0.001**
Severe preprocedural TR (III/III)	**2.80 [1.59–4.90]**	**< 0.001**	**2.03 [1.07–3.84]**	**0.030**	**1.93 [1.02–3.67]**	**0.045**
LVEF (per 5% increase)	**0.86 [0.79–0.94]**	**< 0.001**	**0.85 [0.76–0.96]**	**0.006**	**0.88 [0.79–0.97]**	**0.012**
TAPSE (per mm increase)	**0.89 [0.83–0.97]**	**0.006**	1.03 [0.94–1.13]	0.544	1.02 [0.95–1.12]	0.606
Preprocedural NYHA class III/IV	2.14 [0.76–6.02]	0.149	-	-	-	-
eGFR (per 5 ml/min/1.73m^2 increase)	**0.80 [0.73–0.88]**	**< 0.001**	0.92 [0.84–1.02]	0.109	0.92 [0.83–1.01]	0.080
Hematocrit (per 5% increase)	**0.67 [0.54–0.84]**	**< 0.001**	-	-	-	-
Hb (per 1 g/dL increase)	**0.78 [0.68–0.90]**	**< 0.001**	-	-	-	-

ePVS estimated Plasma Volume Status, *NT-proBNP* N-Terminal pro-Brain Natriuretic Peptide, *BMI* Body Mass Index, *HFrEF* Heart Failure with reduced Ejection Fraction, *CAD* Coronary Artery Disease, *COPD* Chronic Obstructive Pulmonary Disease, *M-TEER* Mitral valve Transcatheter Edge to Edge Repair, *MR* Mitral Regurgitation, *VC* Vena Contracta, *TR* Tricuspid Regurgitation, *LVEF* Left Ventricular Ejection Fraction, *TAPSE* Tricuspid Annular Plane Systolic Excursion, *eGFR* estimated Glomerular Filtration Rate, *Hb* hemoglobin. Mitral regurgitation is graded from I to IV, Tricuspid regurgitation is graded from I to III. Hazard ratios (HR) are presented with 95% confidence intervals (CI) and corresponding *p*-values. Bold values indicate statistical significance ($p < 0.05$)

* univariable cox regression included all 308 patients with implanted clips, except the analyses for severe preprocedural TR ($n = 306$) and TAPSE ($n = 289$)

** multivariable cox regression included only patients with complete data for the included variables ($n = 273$)

Baseline characteristics stratified by these subgroups are summarized in Supplementary Table S3. Kaplan–Meier analysis (Fig. 1B) demonstrated a stepwise decline in survival across the three groups (log-rank $p < 0.001$).

Compared to the patients with both ePVS and NT-proBNP below the cut-off, those with elevation of one biomarker already exhibited a significantly higher 1-year (8.2% for one vs. 1.9% for no elevated biomarker) and 5-year cumulative KM estimated mortality rate (57.3% vs. 3.5%). Patients with both biomarkers above the cut-off showed the worst outcome, with a rate of 21.5% for the 1-year and a rate of 64.8% for the 5-year cumulative KM estimated mortality.

Cox regression models for ePVS and NT-proBNP dependent mortality

The results of the Cox regression analysis are summarized in Table 2. Univariable cox regression showed a significantly increased mortality risk for both ePVS (HR 3.4, 95%CI 1.94–5.99; $p < 0.001$) and NT-proBNP (HR 7.9, 95%CI 3.55–17.69; $p < 0.001$) when elevated above their respective cut-off. Assessment of the combined variable again indicated a highly significant increase in mortality risk, with a hazard ratio of 9.3 (95%CI 2.76–31.33) for patients with one and a hazard ratio of 19.5 (95%CI

5.88–64.52) for patients with both biomarkers above cut-off (both $p < 0.001$).

In parallel, several other mortality influencing risk factors were identified in the univariable analysis, including left (HR 0.86, 95%CI 0.79–0.94; per 5% increase in LVEF; $p < 0.001$) and right heart (HR 0.89, 95%CI 0.83–0.97; per mm increase in TAPSE; $p = 0.006$), as well as kidney function (HR 0.80, 95%CI 0.73–0.88; per 5 ml/min/1.73 m^2 increase in eGFR; $p < 0.001$). Severe (grade III/III) preprocedural tricuspid regurgitation (HR 2.80, 95%CI 1.59–4.90; $p < 0.001$), severe (grade III-IV/IV) residual mitral regurgitation (HR 4.12, 95%CI 1.75–9.69; $p = 0.001$) after M-TEER as well as preexisting diabetes mellitus (HR 2.59, 95%CI 1.48–4.53; $p < 0.001$). Reduced hemoglobin (HR 0.78, 95%CI 0.68–0.90; per 1 g/dL Hb increase; $p < 0.001$) and hematocrit (HR 0.67, 95%CI 0.54–0.84; per 5% hematocrit increase; $p < 0.001$) were also associated with a higher mortality risk in the univariable analysis.

Except for hemoglobin and hematocrit (as direct/ indirect part of the ePVS calculation), all significant variables of the univariable regression were subsequently used to create two multivariable Cox regression models, one with separated dichotomous variables for NT-proBNP and ePVS and one with a combined trichotomous variable.

In the first model with separated variables, both ePVS (HR 2.38, 95%CI 1.20–4.74; $p = 0.013$) and NT-proBNP (HR 4.30, 95%CI 1.50–12.31; $p = 0.007$) were independently associated with a significantly increased mortality risk. Apart from these, only the LVEF (HR 0.85, 95%CI 0.79–0.94; per 5% increase in LVEF; $p < 0.001$), a severe residual mitral regurgitation after M-TEER (HR 3.41, 95%CI 1.29–9.01; $p < 0.001$) as well as a severe preprocedural tricuspid regurgitation (HR 2.03, 95%CI 1.59–4.90; $p = 0.030$) indicated a significant influence on mortality risk in the multivariable analysis. The second multivariable model included the combined biomarker variable. Compared to the patients with neither ePVS, nor NT-proBNP above the respective cut-off, the patients with one positive biomarker experienced a significant higher mortality (HR 6.67, 95%CI 1.47–30.27; $p = 0.014$). Patients with both markers above the cut off showed an even higher mortality risk (HR 14.27, 95%CI 3.19–63.89; $p < 0.001$). Adjustment for the same covariates remained consistent with the first model with similar hazard ratios for a severe residual mitral regurgitation and the preprocedural LVEF. Impaired kidney and right ventricular function and diabetes mellitus showed a tendency towards a higher mortality in both regression models, but without reaching significance.

The additive prognostic value of ePVS beyond hematocrit

To assess whether the ePVS provides additional prognostic information over the hematocrit, multiple additional nested Cox proportional hazard models, with consecutive likelihood ratio tests were constructed (Supplementary Table S4). These included ePVS, as well as one continuous or one dichotomized, sex-dependent hematocrit variable together with all other variables from the primary multivariable regression analysis. In a multivariable model containing hematocrit instead of ePVS, a lower hematocrit was not independently associated with a higher mortality (HR 0.80, 95%CI 0.60–1.08; per 5% increase; $p = 0.148$) with no significant improvement of the model fit ($\Delta\chi^2 = 2.44$; df = 1; $p = 0.118$). When both ePVS and continuous hematocrit were included, the ePVS remained independently associated with all-cause mortality (HR 2.68, 95%CI 1.05–6.86; $p = 0.039$), whereas hematocrit was not independently associated with mortality (HR 1.08, 95%CI 0.72–1.63; per 5% increase; $p = 0.712$). Adding ePVS into the model significantly improved model fit compared to both, the model without hematocrit ($\Delta\chi^2 = 6.78$; df = 1; $p = 0.009$) as well as the model containing hematocrit ($\Delta\chi^2 = 4.44$, df = 1; $p = 0.035$). The analyses including the dichotomized, sex-dependent hematocrit variable yielded similar results, showing no independent association with mortality and no significant improvement in model fit by adding the hematocrit to a multivariable model.

In a time-dependent incremental prognostic performance analysis (Supplementary Table S5), addition of ePVS to a basic model with or without hematocrit, narrowly missed significance for IDI and continuous NRI at 1 or 1.5 years. At 2 years, addition of ePVS significantly improved IDI in the analysis without (0.058, 95%CI 0.006–0.155; $p = 0.018$) and with continuous hematocrit (0.041, 95%CI 0.003–0.118; $p = 0.025$), whereas continuous NRI did not reach statistical significance (0.678, 95%CI −0.008–1.074; $p = 0.054$). Compared to a model containing the dichotomized hematocrit variable, both IDI (0.050, 95%CI 0.007–0.118; $p = 0.019$) and NRI (0.602, 95%CI 0.013–1.001; $p = 0.045$) were significant at 2 years.

Subgroup analysis regarding MR etiology

Subgroup analyses according to MR etiology (Supplementary Fig. 3) yielded consistent findings. In patients with primary MR (univariable HR 6.26, 95%CI 1.72–22.82; $p = 0.005$; log-rank test $p = 0.001$) and those with secondary/mixed MR (univariable HR 2.95, 95%CI 1.55–5.59; $p < 0.001$; log-rank test $p < 0.001$), an elevated ePVS was significantly associated with higher all-cause mortality in time-dependent survival analyses. The combined ePVS/NT-proBNP risk variable also significantly stratified mortality in both etiologic subgroups (both log-rank tests $p < 0.001$). Patients with a secondary/mixed MR showed a significantly increased mortality risk when one (univariable HR 5.82, 95%CI 1.68–20.12; $p = 0.005$) or both (HR 10.86, 95%CI

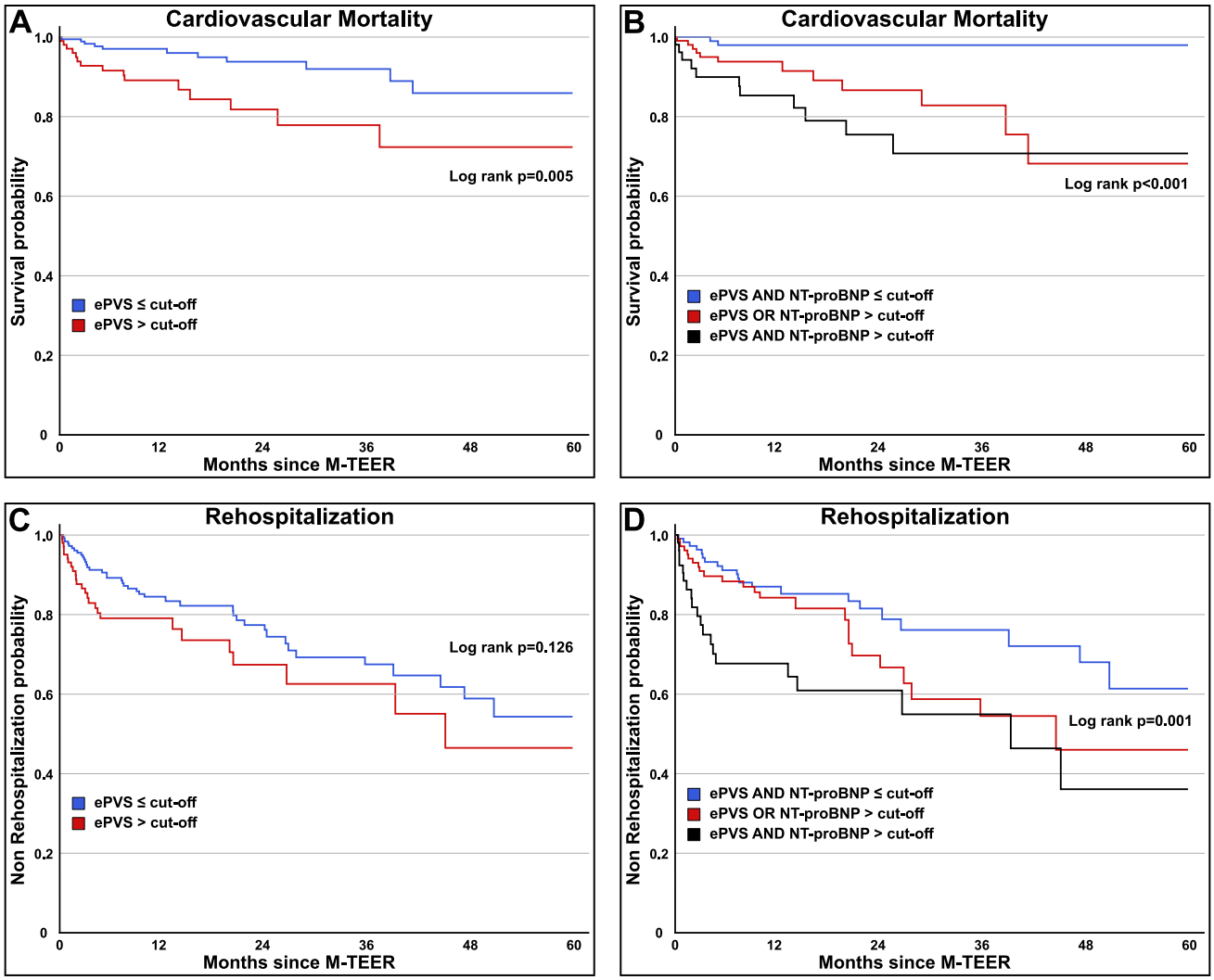


Fig. 2 Kaplan Meier survival analysis for cardiovascular mortality and heart failure rehospitalizations stratified by the preprocedural ePVS and a combined congestion variable based on preprocedural ePVS and NT-proBNP

3.18–37.07; $p < 0.001$) markers were elevated above their respected cut-off. Cox regression could not be calculated for the primary etiology analysis since no events occurred in the patients with low ePVS and NT-proBNP.

Risk for cardiovascular death and rehospitalization in patients with high ePVS or high NT-proBNP

The time dependent risk for a cardiovascular death as well as for the first postprocedural rehospitalization due to heart failure was also assessed in this collective.

From 51 patients who died during follow-up, a cardiovascular cause of death was observed in 26 patients. A preprocedural elevated ePVS above the cut-off was significantly associated with an increased risk for a cardiovascular death (Fig. 2A; log rank $p = 0.005$, univariable HR 2.91, 95%CI 1.33–6.34; $p = 0.07$). This was also observed in the patients with an elevated NT-proBNP (Supplementary Fig. 4A; log rank $p < 0.001$, univariable HR 5.37, 95%CI 2.02–14.33; $p < 0.001$).

Analysis of the combined variable also indicated a significant higher cardiovascular mortality (Fig. 2B; log rank $p < 0.001$) both in patients with one (univariable HR 7.74, 95%CI 1.73–34.66; $p = 0.007$) or two (univariable HR 12.82, 95%CI 2.84–57.86; $p < 0.001$) markers above their cut-off. Besides ePVS and NT-proBNP, preprocedural LVEF, eGFR, severe preprocedural tricuspid regurgitation as well as a residual severe mitral regurgitation postprocedure had significant impact on cardiovascular mortality in this cohort. The patients age and a pre-existing diabetes mellitus also showed a tendency but without reaching significance.

In the additional multivariable regression models, ePVS alone (HR 2.66, 95%CI 1.08–6.52; $p = 0.033$) and the combined variable (HR 9.20, 95%CI 1.14–74.45; $p = 0.037$ for

one and HR 17.07, 95%CI 2.11–138.18; $p=0.008$ for two variables above the cut off) could maintain significant impact on cardiovascular mortality. NT-proBNP alone (HR 3.18, 95%CI 0.94–10.76; $p=0.063$) showed a clear tendency, but without reaching significance.

When adjusting for the univariable significant covariates, in both regression models only LVEF and a severe residual MR after M-TEER maintained significant impact regarding cardiovascular mortality. As above, hemoglobin and hematocrit were not taken into account in the analysis due to the considerable overlap with the ePVS.

Full results of the uni- and multivariable regression analysis can be observed in Supplementary Table S6.

When looking at the time dependent risk for the first rehospitalization due to heart failure, in this collective, patients with an ePVS above the cut-off showed a trend but no significant risk alterations (Log-rank $p=0.126$; univariable HR 1.47, 95%CI 0.90–2.41; $p=0.128$; Fig. 2C). On the other hand, patients with a preprocedural NT-proBNP above the respected cut-off exhibited a significantly higher risk for a rehospitalisation (Log-rank $p<0.001$; univariable HR 2.33, 95%CI 1.42–3.83; $p<0.001$; Supplementary Fig. 4B). When considering both markers combined (Log-rank $p=0.001$; Fig. 2D), patients with one variable above the cut-off showed no significant risk elevation (univariable HR 1.60, 95%CI 0.89–2.89; $p=0.118$), whereas patients with both variables elevated, faced a significant increased rehospitalisation risk (univariable HR 2.72, 95%CI 1.47–5.03; $p=0.001$).

Time dependent survival curves stratified by the dichotomized estimated plasma volume status (ePVS) according to the ROC-derived cut-off (A) and the combined, trichotomous congestion variable based on ePVS and NT-proBNP status (B). For the ePVS-stratified analysis, all 308 patients with successful M-TEER and implantation of at least one clip device were included. For the combined analysis, all 290 patients with successful M-TEER and available NT-proBNP data were included.

Time dependent survival curves stratified by the dichotomized estimated plasma volume status (ePVS) according to the ROC-derived cut-off (A, B) and the combined, trichotomous congestion variable based on ePVS and NT-proBNP status (C, D). For the ePVS-stratified analysis, all 308 patients with successful M-TEER and implantation of at least one device were included. For the combined analysis, all 290 patients with successful M-TEER and available NT-proBNP data were included.

Discussion

This present study from the ongoing Regensburg Trial on TMVR Techniques in Mitral Regurgitation (RETORT-MR) evaluated the impact of preprocedural, intravascular, often subclinical congestion on outcome and mortality in a prospective cohort of patients undergoing M-TEER due to severe mitral regurgitation.

The assessed TMVR collective was heterogeneous and contained mostly patients with high surgical risk due to advanced age and substantial burden of comorbidities, favouring a transcatheter treatment approach [2, 4]. As optimal procedural conditions were aspired, all patients did not show overt signs of congestion before M-TEER. The estimated plasma volume status, an easily calculated surrogate marker for intravascular volume expansion and hemodilution [12], indicating deviation from ideal plasma volume [21, 34], was applied to assess for intravascular congestion. The impact of ePVS was assessed and compared to NT-proBNP, a well-established, quantitative plasma biomarker for the presence and severity of myocardial wall stress due to pressure and volume overload [25, 26, 29, 30, 33]. Based on one year mortality, cut-off values for both ePVS (+0.36%) and NT-proBNP (2794 pg/mL) were calculated and a combined risk variable of both markers was introduced.

Although ePVS and NT-proBNP are both associated with congestion and share substantial overlap, they reflect different underlying pathophysiological mechanisms [13, 21, 25, 28, 29, 31, 32, 43, 44], leading to distinct congestion phenotypes, as observed in this cohort. Patients with elevated NT-proBNP were characterized by significantly impaired cardiac function, including a higher prevalence of HFrEF, impaired TAPSE and a higher prevalence of a secondary mitral regurgitation. In these patients, advanced cardiac dysfunction seemed to be the dominant driver of biomarker elevation [26–29]. In contrast, an elevated ePVS was not primarily associated with markers of impaired cardiac systolic function, indicating a composite phenotype dominated by intravascular volume expansion, hemodilution, renal dysfunction as well as systemic congestion rather than myocardial wall stress alone [12, 13, 16, 24, 31, 43, 45]. This dissociation may explain why some patients present with high NT-proBNP but low ePVS (predominantly myocardial disease without major plasma volume expansion), whereas others show high ePVS but only moderately elevated NT-proBNP (predominantly intravascular congestion with limited myocardial wall stress) [44, 46–48].

Although patients were clinically compensated before M-TEER, those with elevated ePVS received higher diuretic doses and were less frequently treated with RAAS-Inhibitors or beta-blockers. This may reflect a greater disease burden and reduced tolerance of guideline-directed therapy, particularly given the older age and lower renal function in this group, whereas MRA use was comparable.

Kaplan-Maier survival analysis and subsequent univariable cox regression implied a significant increased mortality in both, patients with ePVS as well as patients with NT-proBNP above the proposed cut-off. These results could

be confirmed in a multivariable cox-regression model suggesting that both ePVS and NT-proBNP are independent predictors for a higher all-cause mortality in patients with severe MR undergoing M-TEER. These results are consistent with previous findings in comparable TMVR-, TAVR- or HF- collectives [9, 14–16, 18, 19, 22, 31, 49]. When combining the cut-off stratified, binary ePVS and NT-proBNP variables to a joint, trichotomous congestion variable, hazard estimates were even greater. Patients with both, ePVS and NT-proBNP above the proposed cut-off showed a markedly elevated mortality risk. On the other hand patients with both, ePVS and NT-proBNP below the cut-off showed a significantly better outcome after M-TEER. These results suggest a further improved prognostic value through integration of both myocardial and intravascular components of congestion as proposed before [13, 47, 50]. Consistent with previous findings [49], the prognostic associations of ePVS and the combined ePVS/NT-proBNP variable with an increased mortality risk were observed in both primary and secondary/mixed MR. However, given the limited number of events, these subgroup findings should be considered exploratory.

Several co-variates were associated with a higher mortality in the univariable analysis, yet only an impaired LVEF as well as a postprocedural residual severe mitral and severe preprocedural tricuspid regurgitation remained statistically significant in subsequent multivariable analysis. As many of the non-significant variables also showed significant and independent association with mortality in larger collectives [14, 18, 49], our results may be partly attributed to the smaller number of patients with a fewer number of deaths during follow-up in this prospective study setting. However, this underlines the prognostic significance of an elevated ePVS and NT-proBNP for mortality, even in a smaller cohort.

As the hematocrit is directly included in the ePVS calculation and anemia is associated with adverse outcomes in heart failure [51], specific assessment of the additional prognostic value of the ePVS beyond hematocrit is indispensable. In comparatively nested adjusted Cox models including ePVS and hematocrit, elevated ePVS remained independently associated with mortality and significantly improved model fit when added to either continuous or dichotomized hematocrit. In contrast, hematocrit alone was neither independently associated with mortality nor improved model performance.

A complementary time-dependent reclassification analyses yielded more heterogeneous results with no significant improvement was observed at an event horizon of 1 or 1.5 years. Incremental discrimination was detected at 2 years, with a significant IDI in the primary continuous-hematocrit analysis and significant IDI and continuous NRI in the binary-hematocrit analysis. Hematocrit on the other hand did not show significant association with mortality or an improvement for the prediction models in either the nested multivariable Cox regression models, nor in the time-dependent IDI/NRI analyses. These results suggest, that ePVS may capture prognostic information beyond anemia and that it is rather the multifactorial causes of (pseudo-) anemia and hemodilution [9, 12, 16] that are responsible for the worsened outcome. Nevertheless, the mathematical relationship between ePVS and hematocrit as well as the limited number of events and the variation in reclassification results across time horizons warrant cautious interpretation and validation in a larger cohort with more adverse events.

Regarding cardiovascular mortality, only ePVS maintained statistical significance in the multivariable regression model, with significantly increased hazard estimates for both markers in the univariable analysis. As prior trials consistently showed an increased cardiovascular mortality for both markers in similar cohorts [15, 49], this was also most likely due to a low absolute amount of cardiovascular deaths in the studied cohort. The combined congestion variable also showed prognostic significance regarding cardiovascular mortality in a multivariable regression model, emphasizing the role of a joint, comprehensive assessment of congestion. Slightly diverging from the all-cause mortality analysis, only an impaired LVEF and a residual severe MR after M-TEER were found to be significant covariates. Nevertheless, an association between NT-proBNP and cardiovascular mortality seems plausible given the significantly worse cardiac function in those patients [27–29].

Given the pathophysiological differences described above, it is not surprising that in this small cohort only a considerably elevated NT-proBNP was significantly associated with postprocedural rehospitalization for heart failure. Patients with clinically overt congestion and high NT-proBNP are more likely to be readmitted for heart failure decompensation, whereas elevated ePVS appears to reflect a more subtle, subclinical form of congestion that may contribute to progressive organ dysfunction and mortality but less frequently triggers heart failure–driven rehospitalization [16, 22, 43]. These patients may instead be rehospitalized for non-cardiac causes such as worsening renal function, anemia, or general clinical deterioration [10, 23, 45]. Yet, intravascular congestion without overt congestion symptoms has shown to be already associated with elevated cardiac filling pressures [47] and is often experienced in advance of clinical congestion signs [48, 52]. As larger studies were already able to show an association between an elevated ePVS and a higher risk for rehospitalization [18, 22, 49], the non-significant results in this study may be again explained by the smaller number of patients and shorter median follow-up time.

As discussed, the estimated plasma volume depends on several different variables and integrates various pathophysiological processes. Therefore, it can only provide limited

information about the actual quantitative plasma volume and should not be viewed as imperative for therapy management [32, 53]. However, detecting both overt and subclinical congestion is complex and an integrative assessment for the various congestion phenotypes is needed to address the associated significantly worsened outcome [13, 16, 47, 50]. Besides preprocedural subclinical congestion, our study showed that a poor outcome was closely linked to impaired cardiac function and residual severe MR following the procedure as seen before [49]. This further emphasizes the importance of an optimal heart failure therapy and good procedural results for long-term survival and good outcomes.

Limitations

Some limitations of the present study should be acknowledged. First, as RETORT-MR is a single-center study, the overall number of patients included was relatively small compared with larger retrospective multi-center TAVR or M-TEER registries, which limits statistical power. In particular, the total number of deaths, and especially cardiovascular deaths, was low, which may have reduced the ability to detect differences in cause-specific mortality and may also have affected the analysis of rehospitalization outcomes. In particular, the IDI and NRI analyses are significantly limited in their interpretability by the small number of deaths. In a limited amount of patients, clinical or laboratory data were missing at random, mostly due to the clinical setting of study inclusion or technical constraints in routine clinical practice. The overall amount of missing data was low and there were no differences between patients with and without missing values regarding baseline characteristics and the evaluated endpoints (Supplementary Table S7). However, as the multivariable cox regression analyses were restricted to patients with complete data for all covariates included in the respective models, which resulted in a slightly decreased statistical power. Finally, a substantial proportion of patients was lost to follow-up, which may have introduced attrition bias and further limited the robustness of the long-term outcome analyses.

Conclusion

Congestion is a well-established determinant of poor outcome and mortality in patients with mitral regurgitation. However, assessment for subclinical, intravascular congestion in this heterogenous population remains challenging. In this prospective study, preprocedural elevation of both estimated plasma volume status as well as NT-proBNP were independent predictors of mortality in patients undergoing M-TEER due to severe mitral regurgitation. When integrated into a combined congestion variable, the prognostic significance of this prediction model was even further increased. As a comprehensive approach is required to capture the distinct phenotypes and pathophysiological mechanisms of congestion, the easy-to-assess ePVS adds substantial prognostic information on subclinical congestion to current preprocedural evaluation of patients considered for M-TEER.

Abbreviations *ACE*: Angiotensin Converting Enzyme (Inhibitor); *ARB*: Angiotensin-Receptor Blockers; *ARNI*: Angiotensin-Receptor-Neprilysin-Inhibitor; *BMI*: Body Mass Index; *BNP*: B-type natriuretic peptide; *CABG*: Coronary Artery Bypass Grafting; *CI*: Confidence Interval; *COPD*: Chronic Obstructive Pulmonary Disease; *CAD*: Coronary Artery Disease; *eGFR*: Estimated Glomerular Filtration Rate; *ePVS*: Estimated Plasma Volume Status; *Hb*: Hemoglobin; *HF (HFpEF/HFmrEF/HFrEF)*: Heart Failure with preserved/mildly reduced/ reduced Ejection Fraction; *HR*: Hazard Ratio; *IDI/NRI*: Integrated Discrimination Improvement/ Net Reclassification Improvement; *IQR*: Interquartile Range; *KM*: Kaplan-Meier; *LVEF*: Left Ventricular Ejection Fraction; *MI*: Myocardial Infarction; *MR*: Mitral Regurgitation; *MRA*: Mineralocorticoid-Receptor-Antagonist; *NT-proBNP*: N-terminal proBNP; *NYHA*: New York Heart Association.; *PCI*: Percutaneous Coronary Intervention; *RETORT-MR*: Regensburg Trial on TMVR Techniques in Mitral Regurgitation; *ROC*: Receiver operating characteristics; *TAPSE*: Tricuspid Annular Plane Systolic Excursion; *TAVR/TAVI*: Transcatheter Aortic Valve Replacement/ Implantation; *TMVR/M-TEER*: Transcatheter Edge to Edge Mitral Valve Repair; *TR*: Tricuspid Regurgitation

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Data Availability The data underlying this article will be shared on reasonable request to the corresponding author.

Declarations

Ethical standards statement The study involving human participants was reviewed and approved by the Ethics Committee of the University of Regensburg, Germany (approval number: Z-2017-0862-10). The study was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments, as well as with applicable national and institutional regulations. No animal studies were performed as part of this work. All participants provided written informed consent prior to inclusion in the study.

Conflict of interest The authors declare no competing interests.

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