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NEW RESEARCH PAPER

STRUCTURAL

Staging Heart Failure Patients With Secondary Mitral Regurgitation Undergoing Transcatheter Edge-to-Edge Repair

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ABSTRACT

BACKGROUND Secondary mitral regurgitation (SMR) is a progressive disease with characteristic pathophysiological changes that may influence prognosis. Although the staging of SMR patients suffering from heart failure with reduced ejection fraction (HFrEF) according to extramitral cardiac involvement has prognostic value in medically treated patients, such data are so far lacking for edge-to-edge mitral valve repair (M-TEER).

OBJECTIVES This study sought to classify M-TEER patients into disease stages based on the phenotype of extramitral cardiac involvement and to assess its impact on symptomatic and survival outcomes.

METHODS Based on echocardiographic and clinical assessment, patients were assigned to 1 of the following HFrEF-SMR groups: left ventricular involvement (Stage 1), left atrial involvement (Stage 2), right ventricular volume/pressure overload (Stage 3), or biventricular failure (Stage 4). A Cox regression model was implemented to investigate the impact of HFrEF-SMR stages on 2-year all-cause mortality. The symptomatic outcome was assessed with New York Heart Association functional class at follow-up.

RESULTS Among a total of 849 eligible patients who underwent M-TEER for relevant SMR from 2008 until 2019, 9.5% (n = 81) presented with left ventricular involvement, 46% (n = 393) with left atrial involvement, 15% (n = 129) with right ventricular pressure/volume overload, and 29% (n = 246) with biventricular failure. An increase in HFrEF-SMR stage was associated with increased 2-year all-cause mortality after M-TEER (HR: 1.39; CI: 1.23-1.58; $P < 0.01$). Furthermore, higher HFrEF-SMR stages were associated with significantly less symptomatic improvement at follow-up.

CONCLUSIONS The classification of M-TEER patients into HFrEF-SMR stages according to extramitral cardiac involvement provides prognostic value in terms of postinterventional survival and symptomatic improvement.
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Secondary mitral regurgitation (SMR) is a multifaceted valve disorder with a strong impact on life expectancy and quality of life.[1,2] Apart from a small subset of SMR patients with preserved left ventricle (LV) function,[3,4] the majority of SMR patients suffer from heart failure with reduced ejection fraction (HFrEF). A considerable number of patients with HFrEF-SMR are not suitable for conventional surgical therapy caused by concomitant diseases or advanced age. According to current guidelines, mitral valve transcatheter edge-to-edge repair (M-TEER) is the treatment of choice on top of guideline-directed medical therapy (GDMT) and device therapy in these patients.[5,6]

A growing body of literature emphasizes the critical importance of careful patient selection before M-TEER to further optimize treatment outcomes.[7-12] Knowledge of the natural history of SMR is important for determining the optimal timing of intervention. The mutual interplay of impaired LV function, progressive LV dilation, and SMR leads to increasing enlargement of the left atrium (LA). Sustained volume overload of the LA favors the occurrence of atrial fibrillation (AF) and eventually leads to an affection of pulmonary circulation in the form of secondary pulmonary hypertension. The prolonged hemodynamic stress may eventually promote the development of secondary tricuspid regurgitation (TR) and in the final stage, may lead to the impairment of right ventricle (RV) function and subsequently biventricular failure.

The concept of staging heart failure according to the extent of cardiac damage was first introduced by Généreux et al[13] for patients with aortic stenosis. It was recently demonstrated that grouping GDMT-treated HFrEF-SMR patients into the aforementioned pathophysiological stages has significant prognostic relevance.[14] Patients with LV dilation alone and those with additional LA enlargement or AF showed a comparable 3-year survival rate of approximately 85%, whereas survival was reduced to approximately 75% at 3 years in the presence of additional TR or involvement of pulmonary circulation. Patients presenting with manifest right ventricular dysfunction (RVD) had the worst prognosis (3-year survival rate of 60%).[14]

The aim of this study was to apply the aforementioned staging concept of HFrEF-SMR to surgical high-risk patients undergoing M-TEER. Furthermore, we sought to assess the prognostic implications of this classification in terms of symptomatic outcome and survival prognosis.

METHODS

STUDY COHORT AND PROCEDURAL TECHNIQUE. Data basis for this study was the EuroSMR (European Registry of Transcatheter Repair for Secondary Mitral Regurgitation) registry, which from 2008 to 2019 retrospectively included patients who underwent M-TEER treatment at 11 cardiac centers across Europe. The study was registered at Deutsches Register Klinischer Studien (DRKS00017428), received ethical approval at each participating center, and its protocol is in accordance with the principles of the 1975 Declaration of Helsinki.

Patients who remained symptomatic after the application of GDMT and, if applicable, cardiac resynchronization therapy were discussed in an interdisciplinary heart team meeting at the respective study center. Treatment indications for interventional treatment were established by heart team

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

GDMT = guideline-directed medical therapy

HFrEF = heart failure with reduced ejection fraction

LA = left atrium

LV = left ventricle

LVEF = left ventricular ejection fraction

MR = mitral regurgitation

M-TEER = mitral valve transcatheter edge-to-edge repair

NYHA = New York Heart Association

RV = right ventricle

RVD = right ventricular dysfunction

RVPAc = right ventricular to pulmonary artery coupling

SMR = secondary mitral regurgitation

sPAP = systolic pulmonary artery pressure

TAPSE = tricuspid annular plane systolic excursion

TR = tricuspid regurgitation

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TABLE 1 Definition of HFrEF-SMR stages

Stage 1 (LV involvement)	LVEF <50% LVEDV ≥ 159 mL
Stage 2 (LA involvement)	Indexed LA volume > 34 mL/m^2 Atrial fibrillation or flutter
Stage 3 (RV pressure/volume overload)	TR ≥ 3+ sPAP > 65 mm Hg
Stage 4 (biventricular failure)	RVPAc < 0.274 mm/mm Hg

HFrEF = heart failure with reduced ejection fraction; LA = left atrium; LV = left ventricle; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; RV = right ventricle; RVPAc = right ventricular to pulmonary artery coupling; sPAP = systolic pulmonary artery pressure; TR = tricuspid regurgitation.

consensus considering individual history, comorbidities, and age. The M-TEER treatment technique using the MitraClip device (Abbott Structural Heart) has been described previously.[15-17]

The present analysis included all patients with significant HFrEF-SMR, which was defined as impaired left ventricular ejection fraction (LVEF) < 50% with concomitant symptomatic SMR.

STUDY VARIABLES. The collected clinical patient characteristics included demographic data (age and sex), comorbidities (diabetes mellitus, arterial hypertension, myocardial infarction, stroke/transient ischemic attack, coronary artery bypass grafting, percutaneous coronary intervention, AF, and chronic obstructive pulmonary disease), renal function (estimated glomerular filtration rate), information on GDMT (renin-angiotensin system inhibitors, mineralocorticoid receptor antagonists, and beta-blockers), and New York Heart Association (NYHA) functional class.

Echocardiographic evaluation was performed by experienced operators at each study site in line with the respective guidelines.[18] Each patient underwent both transthoracic and transesophageal echocardiography. Mitral regurgitation (MR) severity was evaluated using an integrative approach including the effective regurgitant orifice area, the regurgitant volume derived from the proximal isovelocity surface area method, and vena contracta. LV function and dimensions were described by LVEF and LV end-systolic and -diastolic diameter and volume. RV fractional area change and tricuspid annular plane systolic excursion (TAPSE) were used to quantify RV function, whereas RV midventricular diameter and tricuspid annular diameter served as parameters of RV size. Systolic pulmonary artery pressure (sPAP) was estimated by the addition of peak systolic TR pressure gradient with estimated right atrial pressure derived from the inferior vena cava width. Right ventricular to pulmonary artery coupling (RVPAc) was calculated as the ratio of TAPSE and sPAP as described previously.[10,19] Accordingly, RVD was defined by an RVPAc < 0.247 mm/mm Hg. Depending on the protocol of the individual study centers, follow-up was conducted either during regular patient visits or by telephone interview with the patients or their next of kin. Follow-up included at least NYHA functional class and survival status.

STAGES OF HFrEF-SMR AND STUDY ENDPOINTS. All HFrEF-SMR patients in the EuroSMR registry were assigned to the following 4 stages[10,14,20] (**Table 1**): LV involvement (Stage 1, left ventricular end-diastolic volume ≥159 mL and/or LVEF <50%), LA involvement (Stage 2, history of AF and/or indexed LA volume > 34 mL/m^2), RV pressure/volume overload (Stage 3, TR ≥ 3+ and/or sPAP >65 mm Hg), and biventricular failure (Stage 4, RVPAc <0.274 mm/mm Hg).[10] In the presence of more than 1 fulfilled criterion, the highest stage was decisive for classification. If a patient fulfilled criteria for a certain stage, the patient was included despite missing information regarding parameters of lower stages. If the criterion of a certain level was met, the patient was only included if there was information that he or she did not qualify for a higher level. Details regarding the patient selection process are displayed in Supplemental Figure 1. Patients with heart failure with preserved ejection fraction (n = 272) were excluded. Missing data regarding RVPAc, TR/sPAP, and AF/left atrial volume index led to the exclusion of 420, 6, and 79 patients, respectively. The endpoints assessed in this study were 2-year all-cause mortality and symptomatic outcome as expressed by NYHA functional class at follow-up.

STATISTICAL ANALYSIS. Continuous data were expressed as mean ± SD or median with IQR. Nominal and ordinal data were displayed as number and percentage. Multiple independent samples were analyzed using the Kruskal-Wallis or Pearson chi-square test as appropriate. For the comparison of 2 paired samples, the Wilcoxon test was applied. Survival was displayed by Kaplan-Meier curves and tested by means of the log-rank test and the test for linear trend of factor levels. Parameters showing statistical significance in the univariate Cox regression models were included into the multivariate regression model with backward variable elimination. Cox regression results were presented as HR, 95% CI, and *P* value. Parameters already defining the different HFrEF-SMR stages were excluded from the multivariate model. The level of statistical significance was set to $P = 0.05$. Statistical analyses were performed using R (version 4.0.4, R Foundation for Statistical Computing) and SPSS (version 25, IBM Corp) software.

TABLE 2 Patient Characteristics

	Overall Cohort (N = 849)
Clinical data	
Age, y	72.9 ± 10.0
Sex, male	606 (71.4)
BSA, m^2	1.9 ± 0.2
BMI, kg/m^2	26.3 ± 4.7
Log EuroSCORE	21.8 ± 16.6
eGFR, mL/min	47.1 ± 21.9
Coronary artery disease	441 (56.3)
Diabetes	297 (35.0)
Hypertension	587 (72.9)
Myocardial infarction	270 (32.1)
PCI	279 (42.1)
CABG	172 (21.1)
Stroke or TIA	81 (9.6)
COPD	133 (15.7)
Atrial fibrillation or flutter	535 (63.0)
NYHA class baseline	
I	1 (0.1)
II	115 (13.6)
III	536 (63.4)
IV	194 (22.9)
HFrEF-SMR stage	
1	81 (9.5)
2	393 (46.3)
3	129 (12.5)
4	246 (29.0)
Medication	
RAS-I	645 (76.3)
Beta-blocker	735 (87.0)
MRA	493 (58.3)
Echocardiography	
MR vena contracta, mm	6.0 ± 2.7
MR EROA, cm^2	0.33 ± 0.28
MR RegVol, mL	42.0 ± 21.8
MR severity baseline	
2+	32 (3.8)
3+	403 (47.5)
4+	414 (48.4)
LVEDV, mL	193.8 ± 75.4
LVESV, mL	134.2 ± 63.4
LVEDD, mm	63.4 ± 9.6
LVESD, mm	49.1 ± 25.2
LVEF, %	31.3 ± 8.8
LA volume index, mL/m^2	57.7 ± 37.8
TAPSE, mm	16.7 ± 4.6
RVPAc, mm/mm Hg	0.380 ± 0.179
TAD, mm	38.6 ± 6.6
RV mid-diameter, mm	36.3 ± 9.3
RV EDA, cm^2	23.0 ± 7.9
RV ESA, cm^2	15.9 ± 6.1
RV FAC	0.33 ± 0.11
TR max PG, mm Hg	38.2 ± 15.6
sPAP, mm Hg	48.5 ± 13.8
TR severity baseline	
0+	11 (1.3)
1+	292 (34.4)
2+	353 (41.6)
3+	181 (21.3)
4+	12 (1.4)

Continued in the next column

TABLE 2 Continued

	Overall Cohort (N = 849)
Follow-up data	
MR severity postprocedural	
1+	556 (65.6)
2+	235 (27.7)
3+	42 (5.0)
4+	15 (1.8)
NYHA class follow-up	
I	74 (16.4)
II	228 (50.6)
III	126 (27.9)
IV	23 (5.1)

BMI = body mass index; BSA = body surface area; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; EDA = end-diastolic area; eGFR = estimated glomerular filtration rate; ESA = end-systolic area; EROA = effective regurgitant orifice area; FAC = fractional area change; HFrEF = heart failure with reduced ejection fraction; LA = left atrium; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic diameter; MR = mitral regurgitation; MRA = mineralocorticoid receptor antagonist; NYHA = New York Hear Association functional class; PCI = percutaneous coronary intervention; RAS-I = renin angiotensin aldosterone system inhibitor; RegVol = regurgitant volume; RV = right ventricle; RVPAc = right ventricular to pulmonary artery coupling; SMR = secondary mitral regurgitation; sPAP = systolic pulmonary artery pressure; TAD = tricuspid annular diameter; TAPSE = tricuspid annular plane systolic excursion; TIA = transient ischemic attack; TR = tricuspid regurgitation; TR max PG = tricuspid regurgitation maximum pressure gradient.

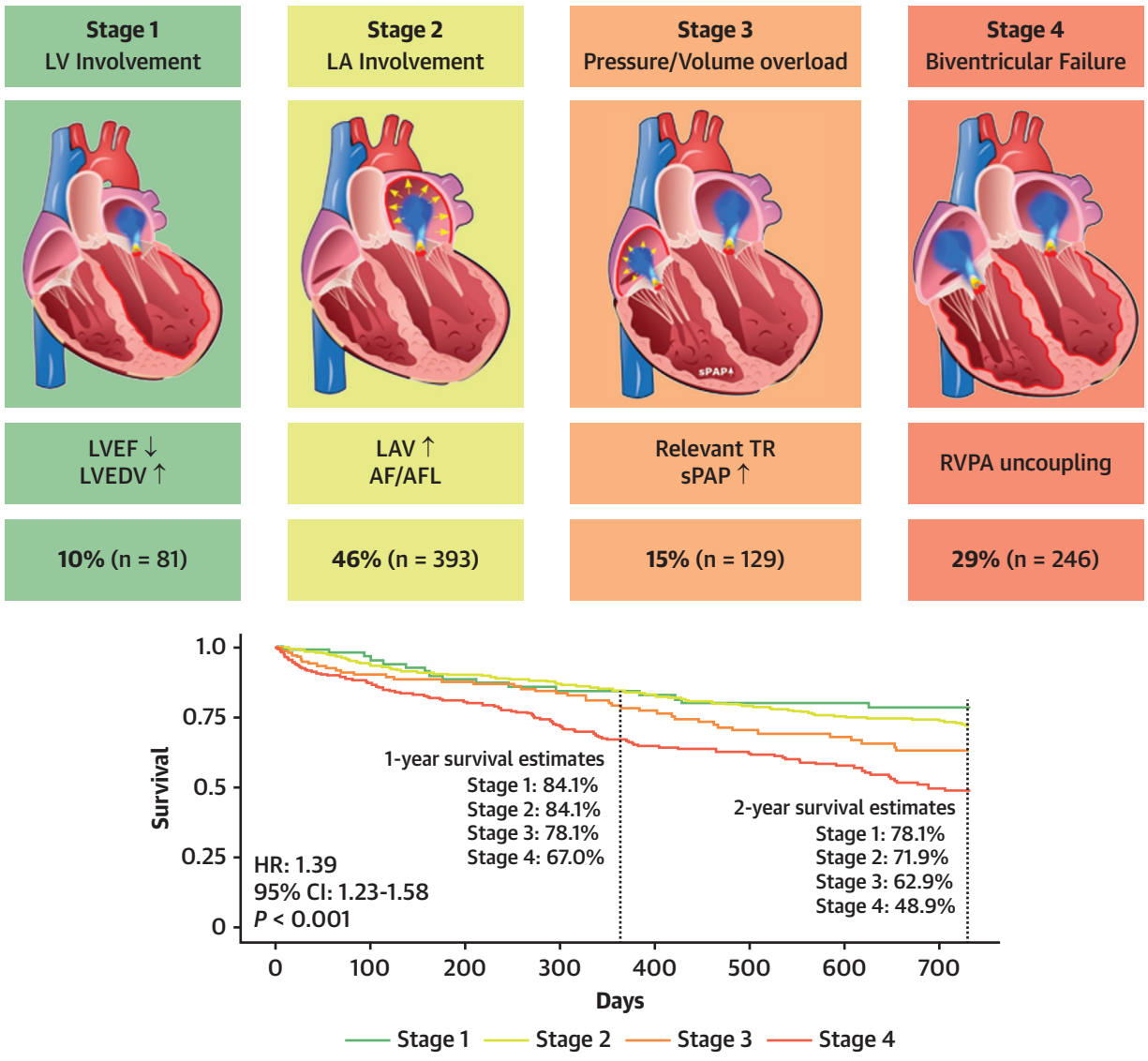
RESULTS

OVERALL STUDY COHORT. Among a total of 1,626 registered patients who underwent M-TEER between 2008 and 2019, 84.2% (1,354 patients) presented with HFrEF-SMR, with 63.0% (849 patients, mean age = 72.7 ± 10.2 years, 71.6% male) fulfilling the previously mentioned inclusion criteria. A comparison of the included and excluded HFrEF-SMR patients is provided in Supplemental Table 1. Baseline characteristics of the study cohort are provided in **Table 2**. Patients presented with high surgical risk (LogEuroSCORE = 21.8% ± 16.6%) and progressive heart failure symptoms (NYHA functional class ≥ III in 86.3%, 378 patients). LV function was significantly impaired as represented by a mean LVEF of 31.3% ± 8.8%. Overall, the LV dimensions indicated significant ventricular enlargement (left ventricular end-diastolic volume = 193.8 ± 75.4 mL). RVD was present in 29.0% (246 patients, mean RVPAc = 0.38 ± 0.18 mm/mm Hg).

M-TEER reduced MR severity to ≤2+ in 93.3% (794 patients) and ≤1+ in 65.6% of individuals (556 patients). Symptomatic follow-up was available in 53% (451 patients). NYHA functional class at follow-up was ≤II in 67.0% (302 patients). The overall survival estimates at 1 and 2 years were 78.2% and 64.6%, respectively. The median duration of follow-up regarding 2-year survival was 560 (IQR: 308-730) days.

HFrEF-SMR STAGES. As illustrated in the **Central Illustration**, 9.5% of patients (81 patients) presented in HFrEF-SMR Stage 1 (LV involvement), 46% (393 patients) in Stage 2 (LA involvement), 15% (129

CENTRAL ILLUSTRATION **Distribution of Secondary Mitral Regurgitation Stages Within the Overall Population (n = 849) and its Impact on Survival Prognosis**



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AF = atrial fibrillation; AFL = atrial flutter; LA = left atrium; LAV = atrial volume; LV = left ventricle; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; RPVA = right ventricular-pulmonary artery coupling; sPAP = systolic pulmonary artery pressure; TR = tricuspid regurgitation.

patients) in Stage 3 (RV pressure/volume overload), and 29% (246 patients) in Stage 4 (biventricular failure). HFrEF-SMR Stage 4 was associated with a considerably increased surgical risk (Log EuroSCORE = 24.3% ± 18.3%), a high prevalence of ischemic HFrEF-SMR (coronary artery disease: 61.8% [n = 139], myocardial infarction: 34.7% [n = 84]), and severely reduced RV function (TAPSE = 12.9 ± 3.3 mm, RVPAc 0.22 ± 0.04 mm/mm Hg) (Table 3). In contrast, LVEF and LV dimensions were comparable between all 4 groups (Table 3). Figure 1 shows the Kaplan-Meier charts for 2-year survival of the 4 HFrEF-SMR subgroups. At the 2-year follow-up, the survival curves of the corresponding subgroups separated with

TABLE 3 Patient Characteristics by HFrEF-SMR Stages

	Stage 1 (n = 81)	Stage 2 (n = 393)	Stage 3 (n = 129)	Stage 4 (n = 246)	*P* Value[a]
Clinical data					
Age, y	72.2 ± 10.3	73.4 ± 9.8	72.7 ± 9.5	72.4 ± 10.3	0.467
Male	58 (71.6)	270 (68.7)	91 (70.5)	187 (76.0)	0.260
BSA, m^2	1.8 ± 0.2	1.9 ± 0.2	1.8 ± 0.2	1.9 ± 0.20	<0.001
BMI, kg/m^2	24.8 ± 6.4	26.6 ± 4.4	25.8 ± 4.9	26.4 ± 4.9	0.013
Log EuroSCORE	18.0 ± 13.7	21.1 ± 15.7	22.6 ± 17.7	24.3 ± 18.3	0.062
eGFR, mL/min	46.3 ± 23.4	49.1 ± 20.7	43.7 ± 21.8	45.8 ± 22.6	0.028
Coronary artery disease	40 (50.0)	192 (54.7)	70 (55.1)	139 (61.8)	0.165
Diabetes	24 (29.6)	131 (33.4)	45 (34.9)	97 (39.4)	0.311
Hypertension	47 (59.5)	286 (77.1)	88 (71.5)	166 (71.6)	0.013
Myocardial infarction	33 (40.7)	115 (29.6)	38 (29.7)	84 (34.7)	0.165
PCI	27 (38.0)	131 (42.3)	41 (42.3)	80 (43.2)	0.900
CABG	20 (24.7)	71 (18.5)	24 (19.4)	57 (24.9)	0.227
Stroke	5 (6.2)	36 (9.2)	17 (13.3)	23 (9.3)	0.361
COPD	17 (21.0)	64 (16.3)	18 (14.1)	34 (13.9)	0.450
Afib	0 (0.0)	290 (73.8)	84 (65.1)	161 (65.4)	<0.001
NYHA functional class baseline					0.013
I	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	
II	16 (19.8)	54 (13.8)	17 (13.4)	28 (11.4)	
III	59 (72.8)	253 (64.5)	80 (63.0)	144 (58.8)	
IV	6 (7.4)	84 (21.4)	30 (23.6)	74 (30.1)	
Medication					
RAS-I	50 (61.7)	315 (80.8)	92 (71.3)	188 (76.7)	0.001
Beta-blocker	67 (82.7)	350 (89.7)	105 (81.4)	213 (86.9)	0.058
MRA	59 (72.8)	220 (56.4)	70 (54.3)	144 (58.8)	0.037
Echocardiography					
MR vena contracta, mm	5.5 ± 2.1	5.7 ± 2.7	5.9 ± 3.1	6.6 ± 2.5	0.014
MR EROA, cm^2	0.36 ± 0.32	0.31 ± 0.20	0.39 ± 0.51	0.33 ± 0.18	0.596
MR RegVol, mL	46.4 ± 34.7	42.0 ± 19.3	40.8 ± 23.4	42.4 ± 24.4	0.731

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a significant difference between the different stages (Stage 1: 78.1%, Stage 2: 71.9%, Stage 3: 62.9%, Stage 4: 48.9%; log-rank test $P < 0.01$). Because HFrEF-SMR patients in Stages 1 and 2 present with comparable survival rates, Supplemental Figure 2 depicts another Kaplan-Meier chart merging Stages 1 and 2. Subsequent uni- and multivariate Cox regression analyses identified renal function (estimate glomerular filtration rate per 10 mL/min decrease; HR: 1.09; 95% CI: 1.02-1.17; $P < 0.01$), diabetes mellitus (HR: 1.34; 95% CI: 1.03-1.73; $P = 0.03$), age (HR: 1.02; 95% CI: 1.01-1.04; $P < 0.01$), NYHA functional class IV (HR: 1.55; 95% CI: 1.17-2.05; $P < 0.01$), postprocedural MR severity ≥3+ (HR: 1.85; 95% CI: 1.21-2.83; $P < 0.01$), and increasing HFrEF-SMR stage (HR: 1.39; 95% CI: 1.23-1.58; $P < 0.01$) as predictors of 2-year all-cause mortality (**Table 4,** Supplemental Table 2, **Figure 2**).

NYHA functional class at baseline showed a trend toward more severe heart failure symptoms with increasing stage of HFrEF-SMR without reaching statistical significance (**Table 2, Figure 3**). From baseline to follow-up, NYHA functional class significantly improved in all HFrEF-SMR stages (all $P < 0.001$) (**Figure 3**). Nevertheless, HFrEF-SMR stages were significantly associated with NYHA functional class at the follow-up examination (**Figure 3**).

DISCUSSION

The present study assigned HFrEF-SMR patients into 4 disease stages according to extramitral cardiac involvement based on a recently published concept and pathophysiological considerations.[13,14,21] In summary, this study revealed a HFrEF-SMR stage-dependent increase in 2-year mortality after M-TEER and identified patients in HFrEF-SMR Stage 3 (RV pressure/volume overload) and Stage 4 (biventricular failure) to have a significantly increased 2-year mortality risk and more severe heart failure symptoms at the follow-up examination.

PATHOPHYSIOLOGY AND NATURAL DISEASE COURSE OF SMR. SMR is usually the consequence of either ventricular or atrial pathologies[22] leading to

TABLE 3 Continued

	Stage 1 (n = 81)	Stage 2 (n = 393)	Stage 3 (n = 129)	Stage 4 (n = 246)	*P* Value[a]
MR severity baseline					0.004
2+	1 (1.2)	18 (4.6)	4 (3.1)	9 (3.7)	
3+	30 (37.0)	212 (53.9)	60 (46.5)	101 (41.1)	
4+	50 (61.7)	163 (41.5)	65 (50.4)	136 (55.3)	
LVEDV, mL	203.6 ± 64.5	191.4 ± 71.2	183.4 ± 79.2	199.8 ± 82.5	0.098
LVESV, mL	139.2 ± 50.0	131.4 ± 60.1	125.1 ± 64.6	141.5 ± 71.2	0.102
LVEDD, mm	65.0 ± 8.7	63.1 ± 9.7	62.2 ± 10.2	63.9 ± 9.4	0.122
LVESD, mm	53.1 ± 10.4	48.4 ± 33.6	45.7 ± 18.5	50.3 ± 15.2	0.015
LVEF, %	31.3 ± 7.0	31.9 ± 8.9	31.6 ± 8.7	30.1 ± 9.1	0.117
LA volume index, mL/m^2	17.7 ± 5.3	66.1 ± 36.6	59.0 ± 37.7	62.1 ± 36.7	<0.001
TAPSE, mm	18.6 ± 3.4	18.1 ± 4.3	18.7 ± 6.4	12.9 ± 3.3	<0.001
RVPAc, mm/mm Hg	0.47 ± 0.17	0.45 ± 0.17	0.41 ± 0.16	0.22 ± 0.04	<0.001
TAD, mm	36.3 ± 6.1	38.7 ± 7.0	39.2 ± 6.4	39.1 ± 6.3	0.018
RV mid-diameter, mm	32.7 ± 8.0	35.3 ± 9.2	39.7 ± 9.5	37.6 ± 9.2	<0.001
RV EDA, cm^2	20.3 ± 6.0	22.1 ± 7.4	24.3 ± 10.2	24.9 ± 7.3	<0.001
RV ESA, cm^2	13.1 ± 4.9	14.9 ± 5.7	16.2 ± 6.7	18.2 ± 5.8	<0.001
RV FAC	0.36 ± 0.11	0.35 ± 0.11	0.34 ± 0.10	0.27 ± 0.10	<0.001
TR max Pg, mm Hg	35.7 ± 10.7	33.2 ± 14.3	36.6 ± 15.4	47.8 ± 14.6	<0.001
sPAP, mm Hg	43.3 ± 11.8	42.5 ± 10.7	48.7 ± 13.4	59.8 ± 12.0	<0.001
TR severity baseline					<0.001
0+	1 (1.2)	9 (2.3)	1 (0.8)	0 (0.0)	
1+	26 (32.1)	200 (50.9)	4 (3.1)	62 (25.2)	
2+	54 (66.7)	184 (46.8)	7 (5.4)	108 (43.9)	
3+	0 (0.0)	0 (0.0)	110 (85.3)	71 (28.9)	
4+	(0.0)	0 (0.0)	7 (5.4)	5 (2.0)	
Follow-up data					
MR severity postprocedural					0.449
1+	49 (60.5)	269 (68.6)	83 (64.3)	155 (63.0)	
2+	28 (34.6)	103 (26.3)	37 (28.7)	67 (27.2)	
3+	3 (3.7)	16 (4.1)	6 (4.7)	17 (6.9)	
4+	1 (1.2)	4 (1.0)	3 (2.3)	7 (2.8)	
NYHA functional class follow-up					0.035
I	19 (29.7)	35 (17.7)	5 (7.7)	15 (12.1)	
II	31 (48.4)	95 (48.0)	37 (56.9)	65 (52.4)	
III	12 (18.8)	60 (30.3)	20 (30.8)	34 (27.4)	
IV	2 (3.1)	8 (4.0)	3 (4.6)	10 (8.1)	

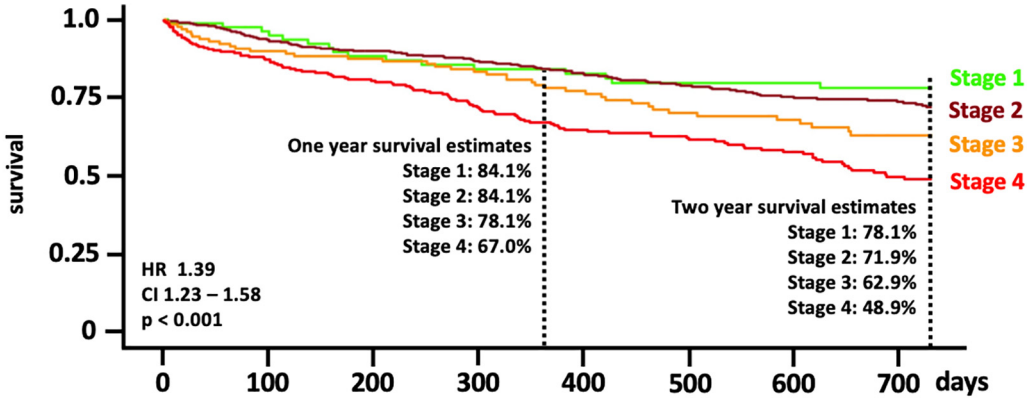
Values are mean ± SD or n (%). [a]Kruskal-Wallis test.

BMI = body mass index; BSA = body surface area; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; EDA = end-diastolic area; eGFR = estimated glomerular filtration rate; ESA = end-systolic area; EROA = effective regurgitant orifice area; FAC = fractional area change; HFrEF = heart failure with reduced ejection fraction; LA = left atrium; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic diameter; MR = mitral regurgitation; MRA = mineralocorticoid receptor antagonist; NYHA = New York Hear Association functional class; PCI = percutaneous coronary intervention; RAS-I = renin angiotensin aldosterone system inhibitor; RegVol = regurgitant volume; RV = right ventricle; RVPAc = right ventricular to pulmonary artery coupling; SMR = secondary mitral regurgitation; sPAP = systolic pulmonary artery pressure; TAD = tricuspid annular diameter; TAPSE = tricuspid annular plane systolic excursion; TIA = transient ischemic attack; TR = tricuspid regurgitation; TR max PG = tricuspid regurgitation maximum pressure gradient.

insufficient mitral valve leaflet closure during systole. Regurgitant blood flow into the LA leads to reduced effective forward stroke volume. In the early stages of the disease, inotropic stimulation, activation of the renin-angiotensin-aldosterone system, and LV hypertrophy[23] compensate the hemodynamic stress of MR. Hence, LV dilation is a good indicator for patients with progressive MR in whom compensatory mechanisms are no longer sufficient to prevent the hemodynamic consequences of reduced forward stroke volume and thus HF symptoms. Persistent regurgitant blood flow leads to dilation of the LA, which is often associated with Afib, a known contributor to adverse events in M-TEER patients.[24,25]

PROGNOSTIC UTILITY OF STAGING HFrEF-SMR. Although HFrEF-SMR Stages 1 and 2 were defined similarly to the initial concept of Généreux et al[13,21] and the adoptive work of Singh et al,[14] we used impaired RVPAc (TAPSE/sPAP <0.274 mm/mm Hg) as the definition for RVD and hence biventricular failure (Stage 4). This decision was based on repeated studies showing prognostic superiority of RVPAc compared with TAPSE alone as the definition for RVD in the setting of M-TEER.[10,26] Consequently, in our patient cohort, only 29% were in HFrEF-SMR Stage 4, whereas Singh et al[14] reported a 47% rate of biventricular failure. As expected, additional RVD was associated with excessive mortality rates in the first 2 years after

FIGURE 1 **Impact of HFrEF Stages on 2-Year Survival**



Stage 1: LA/LV Involvement	81 (100)	73 (90)	65 (80)	60 (74)	56 (69)	52 (64)	51 (63)	48 (59)
Stage 2: LA Involvement	393 (100)	357 (91)	336 (85)	316 (80)	250 (64)	227 (58)	198 (50)	174 (44)
Stage 3: RV Pressure/Volume overload	129 (100)	111 (86)	106 (82)	99 (77)	79 (61)	67 (52)	57 (44)	47 (36)
Stage 4: Biventricular Failure	246 (100)	206 (84)	188 (76)	168 (68)	131 (53)	116 (47)	93 (38)	70 (28)

Kaplan-Meier curves for 2-year survival in patients undergoing mitral valve transcatheter edge-to-edge repair for SMR. The log-rank test for linear trend of factor levels showed significant association of increasing heart failure with reduced ejection fraction–secondary mitral regurgitation stages with 2-year all-cause mortality. LA = left atrial; LV = left ventricle; RV = right ventricle.

M-TEER. From a pathophysiological point of view, this is a consequence of the RV's inability of adapting contractile function to increasing pulmonary resistance, which ultimately leads to excessive symptoms of heart failure. Patients with relevant concomitant TR (Stage 3) as a sign of significant RV volume overload or elevated sPAP as a sign of pressure overload presented with better survival compared with HFrEF-SMR Stage 4 patients. Patients in HFrEF-SMR Stage 4 presented with significantly larger left and right ventricular end-systolic dimensions, whereas end-diastolic measurements were statistically comparable. This fits well into the pathophysiological concept that patients in HFrEF-SMR Stage 3 already suffer from significant volume overload (end-diastolic volume increase), but RVPAc is intact. In HFrEF-SMR Stage 4, RV function further declines, and the right ventricle cannot contract properly because of increased afterload. This finally leads to increased end-systolic dimensions and RVPA uncoupling.

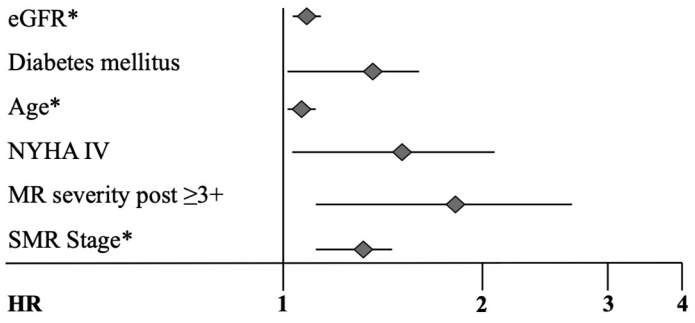
TABLE 4 **Multivariate Predictors of 2-Year All-Cause Mortality**

	Univariate			Multivariate		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Age, per 1 y	1.026	1.012-1.039	<0.001	**1.023**	**1.009-1.038**	**0.001**
eGFR, per 10 mL/min decrease	1.152	1.084-1.225	<0.001	**1.093**	**1.024-1.166**	**0.007**
Diabetes	1.386	1.083-1.775	0.010	**1.335**	**1.034-1.725**	**0.027**
CABG	1.405	1.056-1.870	0.020	1.286	0.961-1.720	0.091
NYHA functional class IV	1.761	1.351-2.294	<0.001	**1.552**	**1.173-2.052**	**0.002**
MR severity post ≥3+	1.805	1.195-2.726	0.005	**1.853**	**1.214-2.829**	**0.004**
HFrEF-SMR per 1-stage increase	1.445	1.279-1.632	<0.001	**1.392**	**1.226-1.581**	**<0.001**

Bold values indicate significant multivariate 2-year survival predictors.

CABG = coronary artery bypass grafting; eGFR = estimated glomerular filtration rate; HFrEF = heart failure with reduced ejection fraction; MR = mitral regurgitation; NYHA = New York Heart Association; SMR = secondary mitral regurgitation.

FIGURE 2 Multivariate Predictors of 2-Year All-Cause Mortality After M-TEER



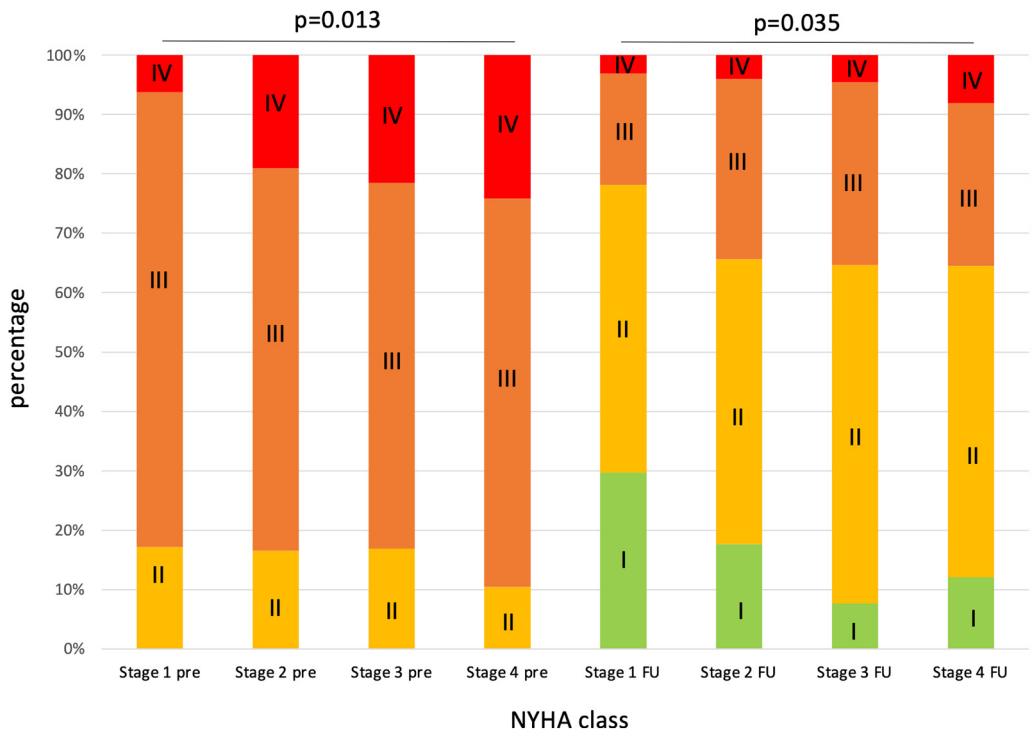
Decreased estimated glomerular filtration rate (eGFR) (per 10 mL/min), diabetes mellitus, age, New York Heart Association (NYHA) functional class IV, moderate to severe or severe postprocedural mitral regurgitation (MR), and increasing heart failure with reduced ejection fraction–secondary mitral regurgitation (HFrEF-SMR) stage were associated with 2-year all-cause mortality in patients undergoing mitral valve transcatheter edge-to-edge repair for HFrEF-SMR. *eGFR per 10 mL/min decrease, age per 1-year increase, and HFrEF-SMR stage per 1-stage increase. SMR = secondary mitral regurgitation.

Nevertheless, Stage 3 HFrEF-SMR was also associated with significantly impaired survival as shown in our multivariate Cox regression model. Individuals in HFrEF-SMR Stages 1 and 2 were characterized by dysfunction limited to the left ventricle and/or LA. Nevertheless, dilated left atria and the presence of Afib might be indicators of longer standing MR compared with Stage 1 patients. Of note, patients with atrial SMR have been excluded from this analysis because they usually present with heart failure with preserved ejection fraction.[3,27]

Overall, the mortality rates observed in the current study are numerically higher compared with those presented in the study of Singh et al.[14] This is probably a consequence of a relatively high percentage of patients with moderate SMR in the later study (16% compared with 4% in EuroSMR).

The classification adapted here was primarily based on prognostic significance with respect to postintervention survival. Theoretically, one would also expect increasing LV dilation as the disease stage

FIGURE 3 NYHA Functional Class According to HFrEF-SMR Stages



From baseline to follow-up New York Heart Association (NYHA) functional class improved irrespective of heart failure with reduced ejection fraction–secondary mitral regurgitation (HFrEF-SMR) stage. Of note, HFrEF-SMR stage was significantly associated with NYHA functional class at baseline and follow-up examination. FU = follow-up.

progresses. However, this observation could neither be made in the current study nor in the work of Singh et al.[14] This raises the question of whether, within the classification proposed here, patients of different HFrEF-SMR subetiologies are hidden. In a recent study, Bartko et al[28] classified medically treated SMR patients into 4 groups based on a variety of echocardiographic parameters using complex statistical clustering. They also included a significant proportion of patients with absent or mild SMR (43%), which partly complicates the applicability to our study population in excessively progressed disease states. Nevertheless, the authors identified a subgroup of patients with worse survival, which was characterized by extensively dilated left ventricles, large effective regurgitant orifice areas, and high regurgitant volume. The median left ventricular end-diastolic volume in this subgroup was >315 mL, which shows similarity to the extensively dilated LVs in the MITRA-FR (Multicentre Randomized Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation) study.[8] Of note, the EuroSMR registry did not observe patients with this extent of LV dilation. Patients in HFrEF-SMR Stage 4 in our study had LV dimensions of about 200 mL in end-diastole, which was comparable to the HFrEF-SMR phenotype with the worst survival (phenotype 3) according to Bartko et al.[28] Consistent with our results, those phenotype 3 patients also showed the most distinct impairment of RV function parameters (TAPSE and RV fractional area change).[28]

The results of the current study show significantly impaired survival and functional outcome in advanced HFrEF-SMR stages. Nevertheless, whether early treatment of SMR (HFrEF-SMR Stages 1 or 2) might prevent progression of the disease to prognostically less favorable higher stages can only be determined by structured prospective trials. The optimal timing of M-TEER remains difficult considering that obvious parameters including LVEF and NYHA functional class did not differ between stages. Possibly, the staging of HFrEF-SMR patients may help to identify dedicated patient groups, which might be subjected to advanced therapies beyond M-TEER in the future. Beyond that, recent developments in the field of machine learning and artificial intelligence pave the way toward increasingly personalized medicine. Especially for M-TEER, there is the urgent need for the development of a dedicated risk score, which not only predicts postprocedural mortality but also identifies individual drivers for mortality as well as identifies patients in whom M-TEER procedures might be futile. Individual risk stratification could optimize patient selection and might identify concomitant treatment targets besides MR.

STUDY LIMITATIONS. The main limitations of the current study are related to the retrospective nature of this study. Echocardiographic data were not subject to core lab supervision, but the echocardiographic evaluation was performed by highly experienced imaging specialists. Furthermore, complete retrospective echocardiographic characterization was not feasible in every patient, which may possibly lead to selection bias. Beyond that, no detailed distinction between ischemic and nonischemic SMR was available.

CONCLUSIONS

Patients suffering from HFrEF-SMR present in different stages of the disease dependent on mitral, extramitral, and even extracardiac involvement, which needs to be considered when discussing patients in the heart team meeting. The application of the proposed SMR stages is easy to perform and is associated with significant differences in symptomatic and survival outcomes after M-TEER. Thus, staging HFrEF patients with symptomatic SMR may help to identify patients who may profit from an earlier M-TEER procedure.

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PERSPECTIVES

WHAT IS KNOWN? Stratifying medically treated SMR patients into disease stages according to mitral and extramitral cardiac involvement provided prognostic value in a recent study.

WHAT IS NEW? The assessment of extramitral cardiac changes allows for staging of the heart failure patients with SMR and M-TEER treatment, with advanced stages being associated with impaired survival and less symptomatic improvement.

WHAT IS NEXT? Prospective trials are needed to clarify whether the staging of SMR patients might enable a better characterization of the heart failure disease progress and allow for an earlier M-TEER treatment resulting in improved outcomes. Further studies are needed to continuously monitor the development of HFrEF-SMR patients over time. Understanding the natural disease course of HFrEF-SMR is essential for choosing the optimal therapy and optimizing treatment timing.

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APPENDIX For supplemental tables and figures, please see the online version of this paper.