

CLINICAL RESEARCH

Impact of Proportionality of Secondary Mitral Regurgitation on Outcome After Transcatheter Mitral Valve Repair

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ABSTRACT

OBJECTIVES The purpose of this paper was to evaluate the impact of proportionality of secondary mitral regurgitation (SMR) in a large real-world registry of transcatheter edge-to-edge mitral valve repair (TMVr)

BACKGROUND Differences in the outcomes of recent randomized trials of TMVr for SMR may be explained by the proportionality of SMR severity to left ventricular (LV) volume.

METHODS The ratio of pre-procedural effective regurgitant orifice area (EROA) to LV end-diastolic volume (LVEDV) was retrospectively assessed in patients undergoing TMVr for severe SMR between 2008 and 2019 from the EuroSMR registry. A recently proposed SMR proportionality scheme was adapted to stratify patients according to EROA/LVEDV ratio in 3 groups: MR-dominant (MD), MR-LV-co-dominant (MLCD), and LV-dominant (LD). All-cause mortality was assessed as a primary outcome, secondary heart failure (HF) outcomes included hospitalization for HF (HHF), New York Heart Association (NYHA) functional class, N-terminal pro-B-type natriuretic peptide (NT-proBNP), 6-min-walk distance, quality of life and MR grade.

RESULTS A total of 1,016 patients with an EROA/LVEDV ratio were followed for 22 months after TMVr. MR was reduced to grade $\leq 2+$ in 92%, 96%, and 94% of patients (for MD, MLCD, and LD, respectively; $p = 0.18$). After adjustment for covariates including age, sex, diabetes, kidney function, body surface area, LV ejection fraction, and procedural MR reduction (grade $\leq 2+$), adjusted rates of 2-year mortality in MD patients did not differ from those for MLCD patients (17% vs. 18%, respectively), whereas it was higher in LD patients (23%; $p = 0.02$ for comparison vs. MD+MLCD). The adjusted first HHF rate differed between groups (44% in MD, 56% in MLCD, 29% in LD; $p = 0.01$) as did the adjusted time for first death or HHF rate (66% in MD, 82% in MLCD, 68% in LD; $p = 0.02$). Improvement of NYHA functional class was seen in all groups ($p < 0.001$). Values for 6-min-walk distances, quality of life and NT-proBNP improved in most patients.

CONCLUSIONS MD and MLCD patients had a comparable, adjusted 2-year mortality rate after TMVr which was slightly better than that of LD patients. Patients treated with TMVr had symptomatic improvement regardless of EROA/LVEDV ratio. (J Am Coll Cardiol Img 2020;■:■-■) © 2020 by the American College of Cardiology Foundation.

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ABBREVIATIONS
AND ACRONYMS**EF** = ejection fraction**EROA** = effective regurgitant orifice area**HFrEF** = heart failure with reduced ejection fraction**LV** = left ventricle/ventricular**LV-EF** = left ventricular ejection fraction**LVEDV** = left ventricular end-diastolic volume**MR** = mitral regurgitation**NT-proBNP** = N-terminal pro-B-type natriuretic peptide**NYHA** = New York Heart Association**TMVr** = transcatheter mitral valve repair

Patients with severe secondary mitral regurgitation (SMR) due to heart failure with reduced ejection fraction (HFrEF) are frequently hospitalized and have an impaired prognosis (1). Beyond optimal medical therapy and cardiac resynchronization therapy, edge-to-edge transcatheter mitral valve repair (TMVr) is an interventional treatment approach in patients at prohibitive surgical risk (2,3).

Two recent randomized trials, MITRA-FR (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) and COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation), have shown conflicting results of TMVr in patients with SMR and HFrEF (4,5). The MITRA-FR study did not demonstrate a reduction of the primary combined endpoint of all-cause death and hospitalization for heart failure (HHF) at 2-year follow-up (6). In contrast, the COAPT trial demonstrated significant reductions in HHF and all-cause mortality over a 2-year follow-up. Of note, the baseline effective regurgitant orifice area (EROA) of the SMR and left ventricular end-diastolic volume (LVEDV) differed substantially between the 2 studies (7). Among others, these important determinants of left HF are thought to explain the observed discrepant outcomes between both trial results. A recent concept by Grayburn et al. (8) proposed to stratify SMR into proportionality of EROA to that of LVEDV, thereby providing a possible explanation for why patients with a high EROA/LVEDV ratio (as in COAPT) benefitted particularly from TMVr in terms of reductions in mortality and repeated hospitalizations (9–11). Based on this concept, a recent analysis of patients with SMR undergoing guideline-directed medical therapy (GDMT) found an association between a high EROA/LVEDV ratio and a worse outcome (12). Accordingly, it has been hypothesized that patients with a predominantly high EROA/LVEDV ratio will clinically benefit from TMVr procedures, whereas

the benefit in patients with lower EROA/LVEDV ratios is uncertain compared with those treated with GDMT. The aim of this retrospective study was to investigate the impact of different EROA/LVEDV ratios on mortality and symptomatic outcome in a large international multicenter registry of patients with HFrEF and SMR treated with TMVr.

METHODS

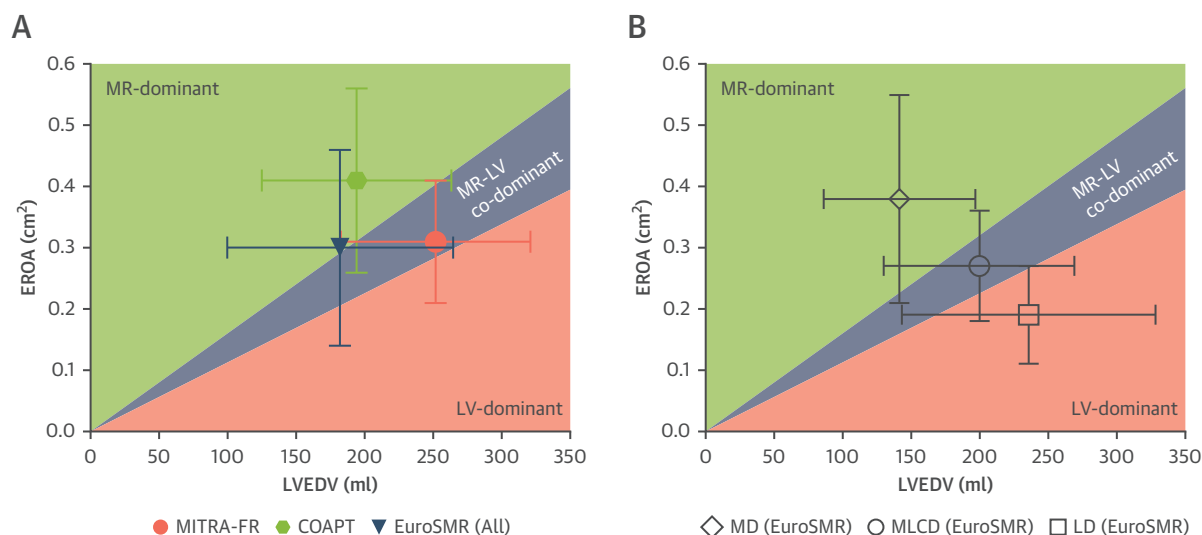
STUDY POPULATION AND ENDPOINT ANALYSIS.

Anonymized patients of the EuroSMR (European Registry of Transcatheter Repair for Secondary Mitral Regurgitation) registry (registered at German Clinical Trials Register; [DRKS00017428](#)) with severe SMR treated with TMVr in 8 academic centers across Europe were analyzed between November 2008 and January 2019. All patients were deemed to be at high or prohibitive surgical risk. TMVr was performed by an interdisciplinary heart team, which considered SMR severity, cardiac function, and history, current status, and life expectancy of the patient. Before the TMVr procedure, patients were treated with standard GDMT. Changes to the medication after TMVr were left to the discretion of the treating physicians at the respective centers and referring or treating general practitioners. Available follow-up data included mortality data, HHF after TMVr (HHF data were available in 7 of 8 centers), assessment of New York Heart Association (NYHA) functional class, 6-min walk distance (6MWD), quality of life (according to the Minnesota Living with Heart Failure Questionnaire [MLHFQ]), and N-terminal pro-B-type natriuretic peptide (NT-proBNP) and an evaluation of MR grade. The present study chose a 2-year follow-up analysis for evaluation of mortality, similar to that of the COAPT study. All data collection and analysis were performed with approval of the institutional review board of the respective academic center.

PROCEDURAL TECHNIQUE. TMVr was performed using either MitraClip NT, NTR or XTR (Abbott Structural Heart, Santa Clara, California) by a standard protocol, as described previously (13).

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FIGURE 1 Stratification of Patients According to Their EROA/LVEDV Ratio

Patient cohorts treated with TMVr are depicted according to their mean baseline EROA (y-axis) and LVEDV (x-axis). **(A)** Data from all EuroSMR centers combined (triangle), COAPT (hexagon) and MITRA-FR trial (dot) are provided. **(B)** EuroSMR patients were grouped according to MR proportionality (MD - diamond, MLCD - circle, and LV - rectangle) adapting a concept by Grayburn et al (9). Error bars represent SD. COAPT = Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation; EROA = effective regurgitant orifice area; EuroSMR = European Registry of Transcatheter Repair for Secondary Mitral Regurgitation; LD = LV-dominant; LVEDV = left ventricular end-diastolic volume; LV-EF = left ventricular ejection fraction; MD = MR-dominant; MITRA-FR = (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation); MLCD = MR-LV-co-dominant.

ECHOCARDIOGRAPHIC ANALYSIS. All echocardiograms were performed and analyzed by experienced operators at each site. All patients underwent transthoracic and transesophageal echocardiography before TMVr. SMR severity was assessed, applying an integrative approach of quantitative, semi-quantitative, and qualitative parameters according to the European recommendations for assessment of native valvular regurgitation (8,14). Baseline evaluation of MR by transthoracic echocardiography included quantitative (EROA and regurgitant volume by proximal isovelocity surface area [PISA] method) and semiquantitative parameters (vena contracta width, 3D vena contracta area from multiplanar reconstruction by transesophageal echocardiography, if applicable). LV volumes (LVEDV and LV end-systolic volume) and function (LV ejection fraction [LV-EF]) were assessed by using Simpson's biplane method (15). Patients were then stratified according to their EROA/LVEDV ratio into 3 groups, adapting the concept from Grayburn et al. (8) where MR-dominant (MD, high EROA/LVEDV ratio ≥ 0.165 cm² per 100 ml of LVEDV, also referred to as "disproportionate MR"), MR-LV-co-dominant (MLCD, intermediate EROA/LVEDV

ratio < 0.165 and ≥ 0.115 cm²/per 100 ml of LVEDV, also referred to as "proportionate MR") and LV-dominant (LD, low EROA/LVEDV ratio < 0.115 cm² per 100 ml of LVEDV, also referred to as "non-severe MR") (9). The cutoff values are shown in Figure 1, derived from the report by Grayburn et al. (8). The cohort was also divided into tertiles of EROA/LVEDV ratio, and respective analyses were performed.

STATISTICAL ANALYSIS. Continuous variables are mean \pm SD, if the Shapiro-Wilk test for normality has been passed, or median interquartile range [IQR]. The chi-squared test was applied to compare categorical variables (unpaired). For continuous variables, statistics were tested using the Kruskal-Wallis test (unpaired). The McNemar test was applied for nominal, paired variables and Wilcoxon's rank sum test for continuous, paired variables. Kaplan-Meier estimates were applied for overall mortality after TMVr. The log-rank (Mantel-Cox) test was used for comparison of unadjusted mortality. Mortality curves were adjusted for baseline parameters with significant differences between groups using a Cox proportional hazards regression model to fit data. Hazard ratios and multivariate analysis to test for

TABLE 1 Baseline Characteristics

	All Patients (N = 100 [100%])	MD (n = 506 [50%])	MLCD (n = 209 [20%])	LD (n = 301 [30%])	p Value
Age, yrs	73 ± 10	75 ± 10	72 ± 10	72 ± 10	<0.001
Males	650 (64)	269 (53)	162 (78)	219 (73)	<0.001
Diabetes mellitus (on insulin therapy)	279 (32)	120 (28)	63 (35)	96 (38)	0.02
Arterial hypertension	644 (75)	310 (72)	132 (73)	202 (79)	0.07
Previous myocardial infarction	249 (25)	118 (24)	56 (27)	75 (25)	0.56
Previous PCI	329 (43)	178 (44)	63 (39)	88 (44)	0.51
Previous CABG	163 (17)	87 (18)	31 (16)	45 (17)	0.82
Previous stroke	95 (9)	45 (9)	20 (10)	30 (10)	0.88
COPD	165 (16)	79 (16)	29 (14)	57 (19)	0.27
History of atrial fibrillation or flutter	656 (65)	351 (69)	117 (56)	188 (62)	<0.01
Body mass index, kg/m ²	26.1 ± 7.0	25.9 ± 9.0	26.0 ± 4.5	26.6 ± 4.5	<0.01
Body surface area, m ²	1.85 ± 0.32	1.78 ± 0.38	1.92 ± 0.26	1.92 ± 0.20	<0.001
GFR, ml/min	49.1 ± 21.9	47.3 ± 21.8	48.6 ± 21.7	52.4 ± 22.1	0.01
eGFR ≤60 ml/min	692 (73)	355 (77)	132 (69)	185 (65)	<0.01
EuroSCORE II %	9.2 ± 8.0	9.2 ± 7.7	8.4 ± 6.6	9.8 ± 9.1	0.41
Logistic EuroSCORE %	20.2 ± 15.7	19.9 ± 14.4	19.2 ± 14.2	21.9 ± 19.1	0.82
Ischemic MR	490 (51)	232 (49)	100 (52)	158 (56)	0.12
NYHA functional class					0.07
II	107 (11)	60 (12)	27 (13)	20 (7)	
III	674 (67)	333 (66)	139 (67)	202 (67)	
IV	228 (22)	108 (22)	42 (20)	78 (26)	
Previous CRT	154 (19)	61 (14)	42 (25)	51 (26)	<0.001
Previous ICD	165 (25)	61 (16)	43 (33)	61 (36)	<0.001
MR severity					<0.001
2+	42 (4)	8 (2)	7 (3)	27 (9)	
3+	592 (58)	298 (59)	122 (58)	172 (57)	
4+	382 (38)	200 (39)	80 (38)	102 (34)	
LV-EF %	35.1 ± 12.8	39.6 ± 13.2	32.6 ± 11.1	29.5 ± 10.2	<0.001
LVEDV, ml	182.3 ± 82.6	142.0 ± 55.4	200.4 ± 69.6	236.8 ± 92.8	—
LVESV, ml	122 ± 71.1	88.0 ± 47.3	135.5 ± 62.6	168.1 ± 79.3	<0.001
MR EROA (PISA), cm ²	0.30 ± 0.16	0.38 ± 0.17	0.27 ± 0.09	0.19 ± 0.08	—
MR EROA/LVEDV, cm ² per 100 ml of LVEDV	0.20 ± 0.14	0.29 ± 0.14	0.14 ± 0.01	0.08 ± 0.02	<0.001
MR volume (PISA), ml	42.6 ± 22	53.5 ± 22.7	39.0 ± 15.5	27.6 ± 13.3	<0.001
vena contracta, cm	0.72 ± 2.11	0.73 ± 0.20	0.73 ± 0.27	0.71 ± 0.19	0.68

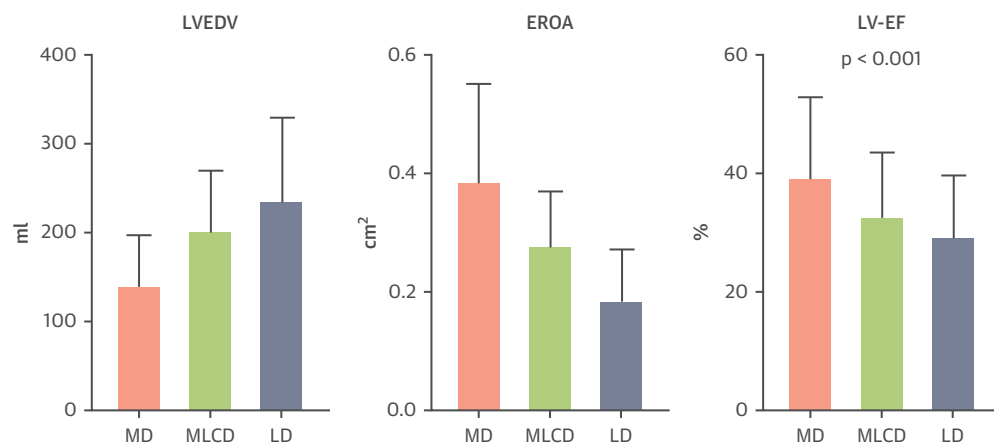
Values are mean ± SD or n (%). Table data show baseline characteristics of the study population. Patient number with baseline information: diabetes (n = 864), hypertension (n = 863), previous myocardial infarction (n = 1,002), previous PCI (n = 763), previous CABG (n = 949), eGFR (n = 942) EuroSCORE II (n = 769), logistic EuroSCORE (n = 848), ischemic MR (n = 952), previous CRT (n = 806), previous ICD (n = 672). Text in **bold** indicates p < 0.05.

BSA = body surface area; CABG = coronary-artery bypass grafting; COPD = chronic obstructive pulmonary disease; CRT = cardiac resynchronization therapy; eGFR = estimated glomerular filtration rate; EROA = effective regurgitant orifice area; ICD; implantable cardioverter-defibrillator; LD = LV-dominant; LVEDV = left ventricular end-diastolic volume; LV-EF = left ventricular ejection fraction; MD = MR-dominant; MLCD = MR-LV-co-dominant; MR = mitral regurgitation; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; PISA = proximal isovelocity surface area.

independent predictors of 2-year mortality were calculated using a Cox proportional hazard model. All variables that showed a p value <0.10 in the univariate Cox proportional hazard analysis were included in the multivariate model. A p value <0.05 was considered statistically significant. Statistical analysis was performed using Prism version 8.0.1 software (GraphPad Software, San Diego, California), SPSS version 1.0.0.1213 software (IBM, Armonk, New York) for Cox proportional hazard model, and the survplot method from the rms application of R version 3.5.1 software (R Project for Statistical Computing, Vienna, Austria) for adjusting survival curves.

RESULTS

In 8 European heart valve centers, 1,237 patients were treated with TMVr for severe SMR between 2008 and 2019 and were included in the EuroSMR registry. Of the total EuroSMR registry cohort, 1,016 patients with quantified EROA and LVEDV parameters were included in the current analysis. The baseline characteristics of those patients are summarized in **Table 1**. The mean age was 73 ± 10 years; 36.0% were women; 19% had previously undergone cardiac resynchronization therapy; and 25% had implantable cardioverter-defibrillators. The cause of

FIGURE 2 Echocardiographic Baseline Parameters

Echocardiographic baseline parameter from three different groups of EROA/LVEDV ratio. Columns represent mean with SD. EROA = effective regurgitant orifice area; LD = LV-dominant; LVEDV = left ventricular end-diastolic volume; LV-EF = left ventricular ejection fraction; MD = MR-dominant; MLCD = MR-LV-co-dominant.

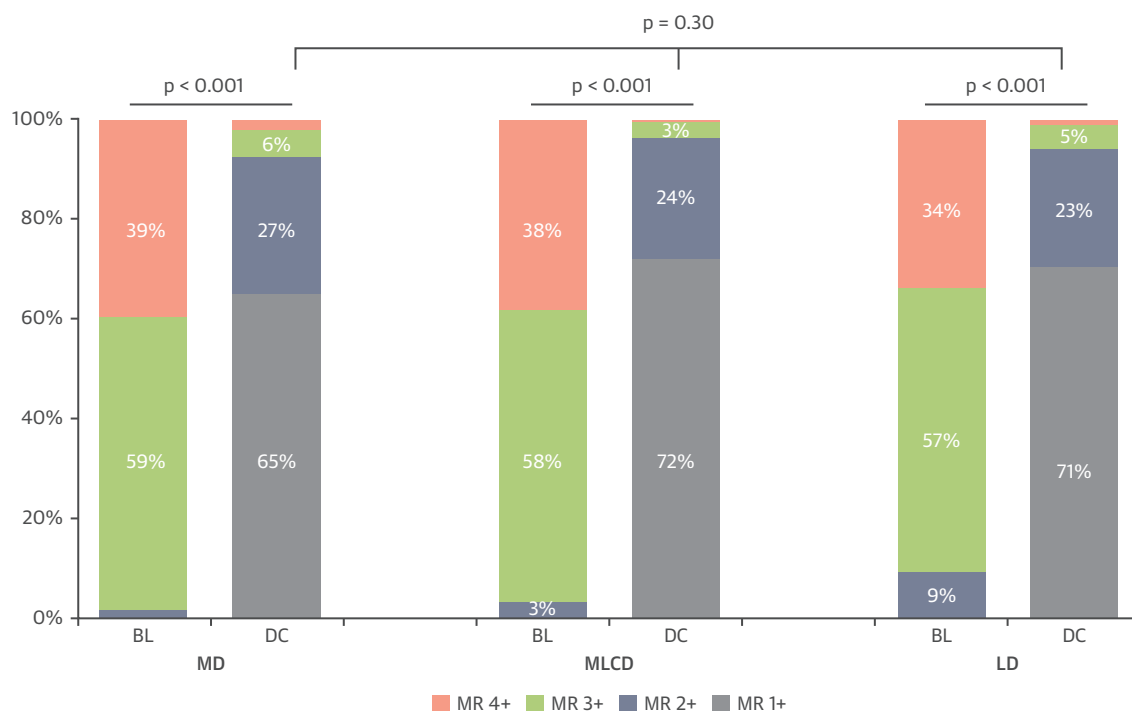
cardiomyopathy was ischemic in 51% of patients, and the mean Logistic EuroSCORE was $20.2 \pm 15.7\%$. The mean LV-EF was $35.1\% \pm 12.8\%$, and the mean EROA and LVEDV were $0.30 \pm 0.16 \text{ cm}^2$ and $182.3 \pm 82.6 \text{ ml}$, respectively (Figure 1A). Before TMVr, MR grade was 3+ in 592 patients (58%) and 4+ in 382 patients (38%). At discharge, MR grade was 1+ or lower in 696 patients (69%), 2+ in 254 patients (25%), 3+ in 50 patients (5%), and 4+ in 14 patients (1%).

A total of 506 patients (50%) were grouped in MD, 209 (20%) in MLCD, and 301 (30%) in LD (Figure 1B). Most patients in all 3 groups were in NYHA functional class \geq III at baseline (88% in MD, 87% in MLCD, 93% in LD; $p = 0.07$). Significant differences were observed between baseline LVEDV and EROA between groups (LVEDV: 142.0 ± 55.4 vs. 200.4 ± 69.6 vs. $236.8 \pm 92.8 \text{ ml}$; EROA: 0.38 ± 0.17 vs. 0.27 ± 0.09 vs. $0.19 \pm 0.08 \text{ cm}^2$, for MD vs. MLCD vs. LD, respectively; both $p < 0.001$) (Table 1, Figure 2). Also, the LV-EF was significantly different among the 3 groups, with MD having the least impaired LV-EF ($39.6 \pm 13.2\%$ vs. $32.6 \pm 11.1\%$ vs. $29.5 \pm 10.2\%$, for MD vs. MLCD vs. LD, respectively; $p < 0.001$) (Table 1, Figure 2). In addition to these echocardiographic differences, the 3 groups differed significantly in age, sex, history of diabetes taking insulin, history of atrial fibrillation, cardiac resynchronization therapy, and rates of cardioverter-defibrillators implantation, estimated glomerular filtration rate (eGFR), body mass index, and body surface area (BSA) (Table 1). Except for a higher proportion of loop diuretic intake in MLCD, HF medication did not differ among the

groups at baseline (Supplemental Table 1). TMVr led to a successful procedural reduction in at least MR 2+ in 468 patients (92%) with MD, 200 patients (96%) with MLCD, and 282 patients (94%) with LD (all $p < 0.001$ for comparison to baseline). Postprocedural distribution of MR grades did not differ among groups ($p = 0.30$ for intergroup comparison) (Figure 3).

MORTALITY AFTER TMVr. Mean follow-up for all patients was 22 months. A total of 156 patients did not have a full 2-year follow-up for vital status, and the mean duration of follow-up in those patients was 13 months. One- and 2-year mortality rates in the entire patient cohort were 20% and 32%, respectively. There were no differences in mortality among the groups at 30 days (4% in MD, 3% in MLCD, 2% in LD, respectively), after 12 months (18%, 22%, 22%) and after 24 months (31%, 34%, 35%; $p = 0.41$ for log-rank test) (Supplemental Figure 1).

A univariate Cox proportional hazards model identified relevant associations of pre-procedural clinical and echocardiographic variables with the 2-year mortality in the entire patient group (Table 2). Associations with mortality with a p value < 0.10 included age, diabetes mellitus on insulin therapy, BSA, kidney function, NYHA functional class IV, LV-EF, and a post-procedural MR grade $\leq 2+$. EROA and LVEDV or the EROA/LVEDV ratio were not identified as univariate predictors for mortality. Receiver operating characteristics analysis revealed an area under the curve value of 0.51 for the EROA/LVEDV ratio (Supplemental Figure 2). In the multivariate Cox

FIGURE 3 Procedural Reduction of Mitral Regurgitation

Procedural reduction of MR from baseline to discharge in 3 different groups of EROA/LVEDV ratio. BL = baseline; DC = discharge; EROA = effective regurgitant orifice area; LD = LV-dominant; LVEDV = left ventricular end-diastolic volume; MD = MR-dominant; MLCD = MR-LV-co-dominant; MR = mitral regurgitation; TMVr = transcatheter edge-to-edge mitral valve repair.

proportional hazards model, all of the above-mentioned parameters remained as independent predictors for 2-year mortality after TMVr ($p < 0.05$) (Table 2).

After adjustment for different baseline characteristics including age, sex, history of diabetes on insulin, eGFR, BSA, LV-EF, and MR reduction to grade $\leq 2+$, the Cox regression analysis revealed significant differences in mortality among the 3 EROA/LVEDV groups. Each group was compared against the other 2 groups. Although the mortality rates did not differ between the MD and MLCD patient groups, patients in the LD group had the highest mortality rate ($p = 0.02$) compared with the MD and MLCD groups (Figure 4, Central Illustration). Similar results for mortality were obtained when the patient cohort was divided into tertiles of the EROA/LVEDV ratio (Supplemental Figure 3, Supplemental Table 2).

HEART FAILURE-RELATED OUTCOME AFTER TMVr. There were no differences in unadjusted 2-year first HHF rate (24% in MD, 31% in MLCD, 18% in LD; $p = 0.11$) (Supplemental Figure 4). After adjustment,

2-year first HHF rate differed among the groups (44% in MD, 56% in MLCD, 29% in LD; $p = 0.01$ for LD vs. MD+MLCD). There were no differences in unadjusted time to first death or HHF rate at 2 years (42% in MD, 54% in MLCD, 47% in LD; $p = 0.18$) (Supplemental Figure 5). The adjusted time to first death or HHF rate was higher in MLCD (82%) than in MD patients (66%) and LD patients (68%) ($p = 0.02$ for MLCD vs. MD+LD). Competing risk analysis showed that LD patients had a higher death/HHF ratio (Supplemental Figure 6).

Patients in all 3 groups improved in NYHA functional class after TMVr (Supplemental Figure 7). The proportion of NYHA functional class $\leq II$ at follow-up was 65% in MD, 60% in MLCD, and 58% in LD (all $p < 0.001$ for comparison to baseline). The distribution of NYHA functional classes at follow-up was not different among the groups ($p = 0.39$).

Significant improvements were seen in the 6MWD (+37 m) results, quality of life (as assessed by the MLHFQ [-6 points]), and NT-proBNP levels (-688 pg/ml) at follow-up (all $p < 0.001$). A detailed analysis with respect to the MR proportionality

TABLE 2 Univariate and Multivariate Cox Proportional Hazards Model of Mortality After TMVr in All SMR Patients

	Cox Regression Model			
	Univariate		Multivariate	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Age, y	1.01 (1.00-1.03)	0.052	1.02 (1.00-1.04)	0.01
Male	0.86 (0.67-1.09)	0.22	—	—
Diabetes, taking insulin therapy	1.52 (1.16-2.00)	<0.01	1.53 (1.15-2.04)	<0.01
Previous myocardial infarction	1.11 (0.85-1.45)	0.45	—	—
Previous CABG	1.11 (0.81-1.53)	0.50	—	—
Previous stroke	1.31 (0.89-1.93)	0.17	—	—
History of atrial fibrillation or flutter	1.11 (0.86-1.43)	0.45	—	—
Body mass index	0.99 (0.96-1.01)	0.34	—	—
Body surface area	0.68 (0.50-0.92)	0.01	0.68 (0.47-0.98)	0.04
Kidney function eGFR, ml/min	0.99 (0.98-0.99)	<0.001	0.99 (0.98-0.99)	<0.01
Ischemic MR	0.97 (0.75-1.25)	0.81	—	—
NYHA functional class IV	1.88 (1.33-2.12)	<0.001	1.78 (1.30-2.43)	<0.001
Previous CRT	1.29 (0.95-1.75)	0.10	—	—
Previous ICD	1.17 (0.84-1.64)	0.35	—	—
LV-EF	0.99 (0.98-1.00)	0.053	0.99 (0.97-0.99)	0.02
LVEDV	1.00 (0.99-1.00)	0.73	—	—
MR EROA (PISA)	0.75 (0.34-1.67)	0.49	—	—
MR EROA/100 ml of LVEDV continuous	1.11 (0.47-2.65)	0.81	—	—
MR reduction, postprocedural MR $\leq 2+$	0.56 (0.37-0.85)	0.01	0.52 (0.31-0.87)	0.01

Data show relationship between baseline clinical and echocardiographic characteristics and 2-y mortality after TMVr. **Bold** text indicates p values < 0.05.

BSA = body surface area; CABG = coronary-artery bypass grafting; CI = confidence interval; CRT = cardiac resynchronization therapy; eGFR = estimated glomerular filtration rate; EROA = effective regurgitant orifice area; HR = hazard ratio; ICD = implantable cardioverter-defibrillator; MR = mitral regurgitation; NYHA = New York Heart Association; LVEDV = left ventricular end-diastolic volume; LV-EF = left ventricular ejection fraction; PISA = proximal isovelocity surface area; TMVr = transcatheter mitral valve repair.

groups is provided in [Supplemental Figure 8](#) and the [Central Illustration](#).

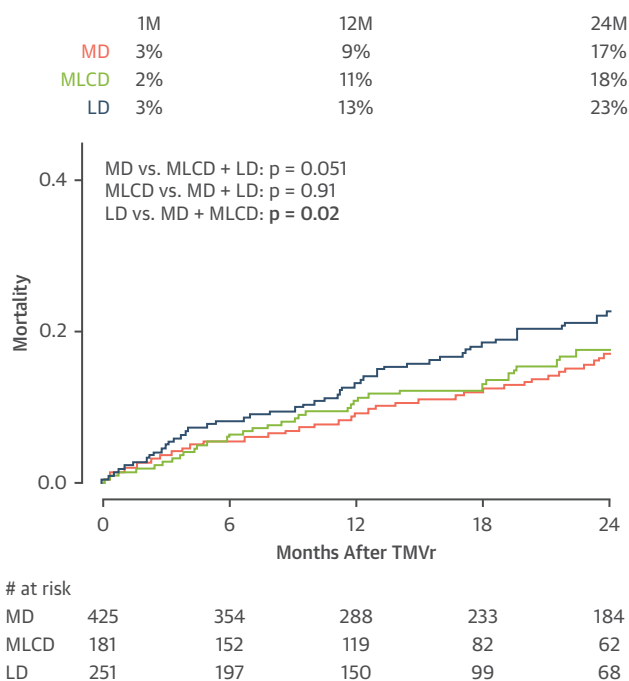
At echocardiographic follow-up (median 447 days for MD, 349 days for MLCD, 365 days for LD; $p = 0.1$), 89% (236 of 264 patients with follow-up) of MD, 92% (108 of 118 patients with follow-up) of MLCD, 93% (139 of 149 patients with follow-up) of LD patients presented with a durable MR reduction to grade $\leq 2+$ (all $p < 0.001$ for comparison to BL) ([Central Illustration](#), [Supplemental Figure 9](#)). Distribution of MR grades at follow-up did not differ between groups ($p = 0.48$ for intergroup comparison).

DISCUSSION

Until recently, compelling evidence was lacking for whether interventional treatment of SMR, specifically TMVr, could impact the prognosis of patients with HFrEF. Published in 2018, the MITRA-FR and COAPT studies were the first randomized controlled trials to examine TMVr for SMR in patients with symptomatic HFrEF in addition to GDMT and device therapy (4,5). Although MITRA-FR revealed no differences in the risk of death or HFrEF at 2-year follow-up, COAPT demonstrated significant reductions in both the mortality and HFrEF rates over a 2-year follow-up. A

variety of plausible reasons, which may explain the apparently discordant findings from 2 randomized trials, have been discussed (9,16). Among those, Grayburn et al. (8) developed a novel pathophysiologic hypothesis using the EROA/LVEDV ratio, which may provide guidance for selecting patients for TMVr treatment. They hypothesized that patients with a high EROA/LVEDV ratio may benefit in particular from TMVr procedures, whereas patients with a low EROA/LVEDV ratio may not derive a similar benefit.

Whether this hypothesis can explain different outcomes after TMVr treatment in a wide spectrum of EROA/LVEDV ratio has not been shown yet. Therefore, this retrospective analysis of patients undergoing TMVr for SMR in a real-world setting of the multicenter EuroSMR registry was undertaken. The EuroSMR centers treated patients with smaller EROAs than in COAPT, which is explained by the differences between the European and American guideline recommendations for the assessment of SMR severity. Furthermore, EuroSMR centers treated patients with smaller LVEDVs than in MITRA-FR but comparable to COAPT ([Figure 1A](#)). This indicates that MITRA-FR patients may be more likely end-stage patients with HFrEF, which are potentially not representative of patients treated in real-world settings. In contrast to

FIGURE 4 Adjusted Curves for Cumulative All-Cause Mortality 2 Years After TMVr With Adjustment for Baseline Parameters

Adjusted cumulative all-cause mortality curves 2 years after TMVr in 3 different groups of EROA/LVEDV ratio. Mortality rate at the respective time points above, number at risk below the graph. Mortality curves were adjusted for age, sex, diabetes on insulin, eGFR, BSA, LV-EF and MR reduction to grade $\leq 2+$. Patients without information on these covariates were excluded. Note that y-axis is curtailed. BSA = body surface area; eGFR = estimated glomerular filtration rate; EROA = effective regurgitant orifice area; LD = LV-dominant; LVEDV = left ventricular end-diastolic volume; LV-EF = left ventricular ejection fraction; MD = MR-dominant; MLCD = MR-LV-co-dominant; MR = mitral regurgitation; TMVr = transcatheter edge-to-edge mitral valve repair.

COAPT and EuroSMR, the MITRA-FR study did not use an integrated approach beyond EROA or regurgitant volume to define severe SMR. Accordingly, the generalization of MITRA-FR to guide patient selection for TMVr appears to be of limited value. Interestingly, the estimated 1-year mortality rate of 20% in the EuroSMR registry seems to be comparable with the 19% in COAPT and lower than the 24% in MITRA-FR.

Besides MR severity and LV volumes, the 3 patient groups (MD, MLCD, and LD) differed significantly in terms of their baseline characteristics. On average, the LV-EF was 7% higher in the MD patients than in MLCD patients, but MD patients were also 3 years older, more often women, and presented with more impaired kidney function. Accordingly, an adjusted mortality analysis was performed to investigate the impact of MR severity and left ventricular volumes on 2-year mortality. A surprising finding of this study

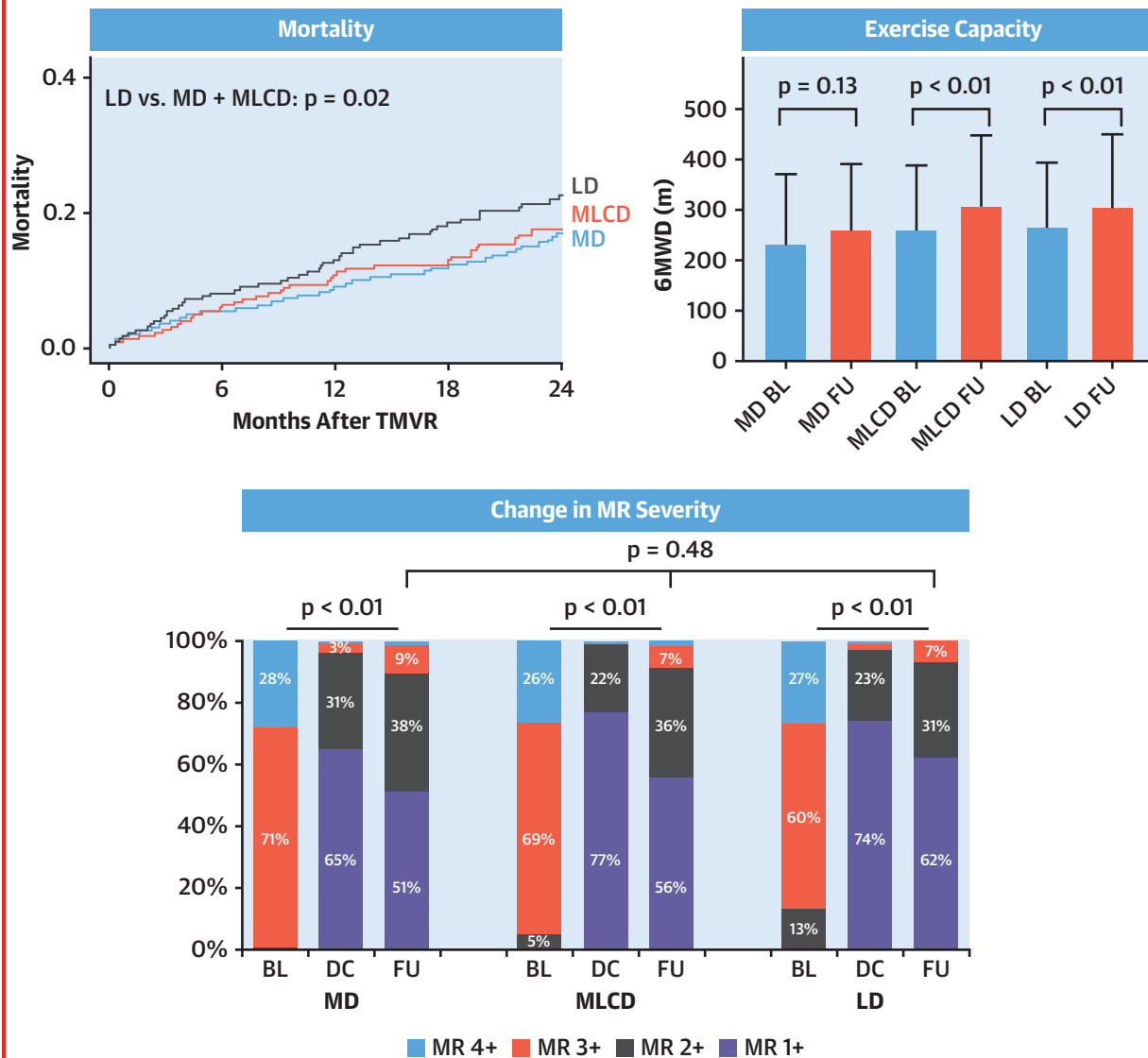
was that the adjusted 2-year mortality rates in EuroSMR did not differ between patients with MD and those with MLCD, as we expected a higher mortality in the MLCD patient group than in MD.

For 531 patients, MR grade at follow-up was determined and showed a stable MR reduction with 91% of patients with MR grade 2+ or less, which is comparable to the results from COAPT, which had 95% with MR grade 2+ or less and better than MITRA-FR with 82% of patients with MR grade 2+ or less at follow-up. Considering the 3 different EROA/LVEDV strata in the EuroSMR registry, MR reduction was comparable in all strata. Furthermore, patients with MD and MLCD demonstrated considerable improvement in NYHA functional class with 65% and 60% of patients being in class I or II at follow-up, respectively.

Patients with LD are characterized with relatively small EROAs and very large left ventricular volumes. It must be acknowledged that the PISA method often underestimates EROA quantification in patients with SMR and may therefore not be sufficient to be the main echocardiographic determinant of SMR severity, although other methods are under investigation and may add prognostic value (17). Although the LD patients in EuroSMR may represent a group with advanced HFrEF, the adjusted mortality probability was only slightly, but significantly higher when compared with patients with MD and MLCD, consistent with the difference between MITRA-FR and COAPT. The nonsignificant trend of LD patients having the lowest HHF rate compared to MD and MLCD is somewhat counterintuitive and needs further evaluation with a stringent analysis of this endpoint.

Nevertheless, a considerable proportion of LD patients may still exhibit improvements in NYHA functional class, 6MWD results, quality of life, and NT-proBNP at follow-up. Thus, TMVr may still be considered in such patients with LD as symptomatic treatment, when treatment options such as heart transplantation or left-ventricular assist devices are not indicated, or as a bridge to transplantation. Importantly, a very recently published echocardiographic analysis of COAPT has shown comparable clinical benefits after TMVr reduction of severe SMR compared to GDMT alone in patients with small and moderately dilated left ventricles (18). However, COAPT did not enroll lesser degrees of MR and markedly dilated left ventricles (as did MITRA-FR), limiting this analysis.

The EROA/LVEDV ratio potentially identifies a group of LD with a higher mortality risk, which is probably explained by an advanced HF stage with among other factors: a considerably reduced LV-EF

CENTRAL ILLUSTRATION Stratification of TMVr-Treated Patients

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Stratification of TMVr-treated patients according to EROA/LVEDV ratio revealed a slightly higher mortality rate for the lowest EROA/LVEDV group (LV-dominant secondary MR). All groups had a comparable symptomatic improvement and MR reduction after TMVr. Mortality (**upper left**), exercise capacity (**upper right**), and change of MR severity (**bottom**) in patients with secondary MR treated with TMVr are shown according to 3 different groups of preprocedural LVEVD/EROA ratios. Cumulative 2-year all-cause mortality was adjusted for the covariates age, sex, diabetes and taking insulin, eGFR, BSA, LV-EF, and procedural MR reduction to grade ≤ 2 . 6MWD distances increased by +29 m in MD patients, +48 m in MLCD patients, and +37 m in LD patients. Persistent MR reduction to grade ≤ 2 at follow-up was achieved in 89% of MD, 92% of MLCD, and 93% of LD patients. 6MWD = 6-min walk distance; BSA = body surface area; CI = confidence interval; eGFR = estimated glomerular filtration rate; HR = hazard ratio; LD = LV-dominant; LVEDV = left ventricular end-diastolic volume; LV-EF = left ventricular ejection fraction; MD = MR-dominant; MLCD = MR-LV-co-dominant; MR = mitral regurgitation; TMVr = transcatheter edge-to-edge mitral valve repair.

and severely dilated left ventricles. Still, a reduction of regurgitation volume after TMVr in a patient with low forward stroke volume due to severely impaired LV-EF could potentially be of clinical benefit with

higher exercise capacity which translates into better quality of life, irrespective of EROA or LVEDV (19).

Of note, in light of the positive results from COAPT, the FDA recently approved the edge-to-edge TMVr in

patients with severe SMR and HFrEF regardless of their EROA/LVEDV ratio but emphasized the inclusion criteria of COAPT, which themselves support an integrative approach of SMR grading.

A combined patient-level analysis of the COAPT and MITRA-FR trials or the ongoing RESHAPE-HF-2 trial could potentially provide new insights into the prognostic value of TMVr. Whether both study approaches will gather enough data on the interesting patient cohort with MR severity of EROA < 0.3 cm² and less severely dilated left ventricles (COAPT-like LVEDVs) has to be shown.

STUDY LIMITATIONS. This was an observational, nonrandomized, retrospective but large and international registry, which did not contain a control group. Therefore, the authors could not examine the relative improvement (or non-improvement) of the 3 groups with TMVr treatment compared to GDMT only; neither could a placebo effect of TMVr be excluded. A potential patient selection bias cannot be excluded, but the indication for TMVr was approved for each individual patient by a local heart team as required by the respective health authorities in a real-world setting. In contrast to COAPT, which also included patients with low surgical risk, all patients in our study were deemed at high or prohibitive surgical risk. Patients with missing baseline characteristics were excluded from the multivariable statistical analysis and survival curve adjustments. HF medication at follow-up was not included in the registry. Although secondary HF-related endpoints and echocardiographic MR severity at follow-up were incomplete, differed in follow-up interval, and were not validated in a core laboratory analysis, the results were prospectively obtained in a large proportion of included patients according to standard of care at each participating center. Hospitalization for HF was assessed by all centers except one, without a central adjudication for determining the reason for hospitalization. Therefore, results of this endpoint should be interpreted with caution. With the absence of a core laboratory-based analysis, an interoperator variability cannot be excluded, but all measurements

including LV and MR parameters were performed according to current echocardiographic guidelines and recommendations. Left atrial and ventricular pressures were not assessed and collected.

CONCLUSIONS

The international EuroSMR registry demonstrated a 2-year mortality rate after TMVr in patients with MD, comparable to that in MLCD patients, even after adjustment for differences in baseline characteristics. LD patients had a slightly higher mortality rate. All patient groups benefited symptomatically from TMVr. Whether the SMR proportionality concept might partially explain the divergent prognostic findings of COAPT and MITRA-FR should be further investigated, especially for patients with an intermediate EROA/LVEDV ratio.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE:

TMVr is a treatment option for clinical improvement in real-world patients with severe SMR. MR-dominant and MR-LV-co-dominant patients with HFrEF have a similar mortality after TMVr. Proportionality of SMR measured by the EROA/LVEDV ratio identifies LV-dominant patients who have a slightly higher mortality.

TRANSLATIONAL OUTLOOK: Further investigations are warranted to determine echocardiographic criteria to identify patients for TMVr with the best possible clinical outcome.

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KEY WORDS echocardiography, heart failure, MR proportionality, secondary mitral regurgitation, transcatheter mitral valve repair

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