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A Unifying Concept for the Quantitative Assessment of Secondary Mitral Regurgitation

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ABSTRACT

BACKGROUND Diverging guideline definitions for the quantitative assessment of severe secondary mitral regurgitation (sMR) reflect the lacking link of the sMR spectrum to mortality and has introduced a source of uncertainty and continuing debate.

OBJECTIVES The current study aimed to define improved risk-thresholds specifically tailored to the complex nature of sMR that provide a unifying solution to the ongoing guideline-controversy.

METHODS This study enrolled 423 heart failure patients under guideline-directed medical therapy and assessed sMR by effective regurgitant orifice area (EROA), regurgitant volume (RegVol), and regurgitant fraction (RegFrac).

RESULTS Measures of sMR severity were consistently associated with 5-year mortality with a hazard ratio of 1.42 for a 1-SD increase (95% confidence interval [CI]: 1.25 to 1.63; $p < 0.001$) for EROA, 1.37 (95% CI: 1.20 to 1.56; $p < 0.001$) for RegVol, and 1.50 (95% CI: 1.30 to 1.73; $p < 0.001$) for RegFrac. Results remained statistically significant after bootstrap- or clinical confounder-based adjustment. Spline-curve analyses showed a linearly increasing risk enabling the ability to stratify into low-risk (EROA <20 mm^2 and RegVol <30 ml), intermediate-risk (EROA 20 to 29 mm^2 and RegVol 30 to 44 ml), and high-risk (EROA ≥ 30 mm^2 and RegVol ≥ 45 ml) groups. In the intermediate-risk group, a RegFrac $\geq 50\%$ as indicator for hemodynamic severe sMR was associated with poor outcome ($p = 0.017$). A unifying concept based on combined assessment of the EROA, the RegVol, and the RegFrac showed a significantly better discrimination compared with the currently established algorithms.

CONCLUSIONS Risk-based thresholds tailored to the pathophysiological concept of sMR provide a unifying solution to the ongoing guideline controversy. An algorithm based on the combined assessment of the unifying cutoffs for EROA, RegVol, and RegFrac improves risk prediction compared with currently established grading.
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Diverging guideline definitions for the quantitative assessment of severe secondary mitral regurgitation (sMR) (1,2) reflect the lack of data that link the spectrum of sMR to mortality and introduced uncertainty, inconsistency, and continuing debate (3,4). A diagnosis of severe sMR entails subsequent decision making for surgical and transcatheter repair. Therefore, cutoffs need to account for the competing risks between the procedure and the potential benefit of reducing long-term mortality. Lower thresholds may expose a significant proportion of patients to unnecessary risk of futile procedures, but higher thresholds may withhold potentially life-extending therapies. The spectrum of sMR begins at mild degrees, often compensated and stable under guideline-directed medical therapy (GDMT). Increasing regurgitant load augments wall stress and stimulates adverse left ventricular (LV) remodeling if it exceeds specific thresholds that are beyond the compensatory potential (5). Those

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thresholds represent the point where heart failure transits toward valvular-driven heart failure and the regurgitant load exceeds the compensatory potential of the ventricle driving excess mortality.

The present study aimed to define risk thresholds specifically tailored to the contemporary pathophysiological concept of sMR to improve risk stratification as compared with established grading algorithms.

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METHODS

STUDY POPULATION. We enrolled consecutive adult patients with chronic heart failure with reduced ejection fraction (HFrEF) in compensated clinical condition at the heart failure outpatient clinic of the Vienna General Hospital, a university-affiliated tertiary center in this observational, noninterventional study. HFrEF was defined in line with the respective guideline (6). All patients underwent a comprehensive echocardiographic exam according to a prespecified protocol at least 3 months after uptitration of guideline-directed medical therapy. The echocardiographic time point served as the index time for time-to-event analyses, and baseline variables were collected at the time of the index echocardiographic exam. The study was approved by the ethics committee of the Medical University of Vienna.

CLINICAL MEASURES AND FOLLOW-UP. Medical history, current medication, and electrocardiogram recordings were collected at study enrollment. Routine laboratory parameters were analyzed from venous blood samples according to the local laboratory's standard procedure. All-cause mortality during 5-year follow-up was defined as primary endpoint and obtained via retrieval query from the Austrian Death Registry.

ECHOCARDIOGRAPHIC ASSESSMENT. Echocardiograms were performed using commercially available equipment (Vivid7, GE-Healthcare, Chicago, Illinois). Left atrial volume index and LV ejection fraction including stroke volume were assessed according to American Society of Echocardiography (ASE) guideline recommendations (7). Mitral regurgitation (MR) was assessed by a multiparametric approach using complementary techniques: sMR was quantified by an integrated approach comprising mitral valve morphology, vena contracta width (VCW), the proximal isovelocity surface area (PISA) method including the effective regurgitant orifice area (EROA), and the regurgitant volume (RegVol) (1). Proximal flow convergence was assessed with a baseline downward shift toward optimized visualization of the hemispheric shell from standard 4-chamber zoomed view of the MR jet. Measurement of proximal flow convergence radius was performed at the same time point as the peak velocity during the regurgitant phase. Beat-to-beat variability in patients with atrial fibrillation during the echocardiographic exam was addressed by multibeat analysis. Regurgitant fraction (RegFrac) was calculated as the ratio of mitral regurgitant volume to global stroke volume and expressed in percentages (8). Raw data were stored digitally and analyzed using GE EchoPac software, version 201 (GE Vingmed, Horten, Norway).

STATISTICAL METHODS. Discrete data were presented as count and percentage, and analyzed by a chi-square test. Continuous data were presented as median and interquartile range, and compared by the Kruskal-Wallis test. Cox proportional hazard regression analysis was applied to assess the effect of sMR severity on survival. To account for potential confounding effects, we formed a confounder cluster encompassing age, sex, body mass index, ischemic etiology of heart failure, New York Heart Association (NYHA) functional class, hypertension, diabetes, creatinine, LV end-diastolic diameter, LV function, LA diameter, right ventricular end-diastolic diameter, right ventricular function, right atrial diameter, renin-angiotensin system (RAS) antagonists, beta-blockers, mineralocorticoid antagonist therapy, and cardiac resynchronization therapy. A stepwise bootstrap resampling procedure including all aforementioned variables was used to identify best-fitting variables for the final multivariable Cox-regression model. Five-hundred repeats with a p value of 0.05 for selection were performed, and variables, selected in 80% of all repeats, were included in the final confounder model (i.e., age and creatinine). Additionally, we adjusted for a clinical confounder model encompassing etiology of heart failure, LV end-diastolic diameter, LV function, NYHA functional class, and severity of tricuspid regurgitation (≥moderate). Hazard ratios (HR) refer to a 1-SD increase in continuous variables and to an increase of 1 category of semiquantitative sMR assessment. The pattern of quantitatively assessed sMR linking sMR severity to mortality was analyzed by spline curves (9) that display the relative risk on the y-axis versus the metric used to quantify sMR on the x-axis, whereby a relative risk of 1 represents the risk of

ABBREVIATIONS AND ACRONYMS

ACC = American College of Cardiology

AHA = American Heart Association

ASE = American Society of Echocardiography

CI = confidence interval

EROA = effective regurgitant orifice area

ESC/EACTS = European Society of Cardiology/ European Association for Cardio-Thoracic Surgery

GDMT = guideline-directed medical therapy

HFrEF = heart failure with reduced ejection fraction

HR = hazard ratio

LV = left ventricular

MR = mitral regurgitation

NYHA = New York Heart Association

PISA = proximal isovelocity surface area

RegFrac = regurgitant fraction

RegVol = regurgitant volume

sMR = secondary mitral regurgitation

VCW = vena contracta width

TABLE 1 Baseline Characteristics of Total Study Population (N = 423) According to Severity of MR

	Total Study Population (N = 423)	No/Mild sMR (n = 204)	Moderate sMR (n = 118)	Severe sMR (n = 101)	p Value
Baseline characteristics					
Age, yrs	66 (57–73)	63 (52–70)	68 (58–76)	68 (61–76)	**<0.001**
Male	334 (79)	162 (79)	97 (82)	75 (74)	0.35
BMI, kg/m^2	27 (24–29)	27 (24–30)	27 (24–29)	26 (23–29)	**<0.001**
Hypertension	222 (53)	117 (57)	59 (50)	46 (46)	0.16
Diabetes	116 (27)	51 (25)	37 (31)	28 (28)	0.48
Ischemic etiology of HF	165 (39)	82 (40)	47 (40)	36 (36)	0.62
NYHA functional class					**0.02**
II	90 (21)	53 (26)	25 (21)	12 (12)	
III	176 (42)	85 (42)	46 (23)	45 (45)	
IV	49 (12)	16 (8)	13 (6)	20 (20)	
Creatinine, mg/dl	1.2 (1.0–1.6)	1.2 (1.0–1.4)	1.4 (1.1–1.7)	1.4 (1.1–1.8)	**<0.001**
Blood urea nitrogen, mg/dl	23 (17–36)	20 (16–28)	26 (17–42)	31 (21–46)	**<0.001**
Echocardiographic characteristics					
Left ventricular end-diastolic diameter, mm	60 (54–66)	57 (51–64)	60 (57–66)	63 (58–68)	**<0.001**
Left ventricular function					**<0.001**
Moderately reduced (EF 30%–40%)	143 (34)	70 (34)	40 (34)	33 (33)	
Severely reduced (LVEF <30%)	236 (56)	92 (45)	78 (66)	66 (65)	
LVEF, %	26 (19–34)	27 (20–35)	25 (18–34)	25 (18–33)	0.27
Left atrial diameter, mm	63 (56–70)	58 (52–65)	67 (61–72)	68 (61–75)	**<0.001**
Left atrial volume index, ml/m^2	47 (35–63)	43 (30–55)	46 (38–61)	56 (45–73)	**<0.001**
Right ventricular end-diastolic diameter, mm	37 (31–44)	35 (30–39)	40 (35–46)	41 (35–48)	**<0.001**
Right ventricular function					**<0.001**
Moderately reduced	46 (11)	12 (6)	13 (11)	21 (21)	
Severely reduced	29 (7)	7 (3)	13 (11)	9 (9)	
Right atrial diameter, mm	58 (51–66)	54 (48–60)	62 (55–68)	63 (56–73)	**<0.001**
sMR vena contracta, cm	4.0 (2.8–5.2)	2.7 (1.9–4.0)	3.9 (3.2–5.0)	4.8 (3.9–6.2)	**<0.001**
sMR effective regurgitant orifice area, mm^2	12.8 (7.9–20.5)	6.9 (4.5–10.0)	12.2 (9.3–16.7)	21.9 (14.4–32.0)	**<0.001**
sMR regurgitant volume, ml/beat	19 (12–31)	12 (6–15)	19 (14–25)	33 (23–47)	**<0.001**
sMR regurgitant fraction, %	24 (0.3–55)	0.27 (0.1–18)	39 (19–67)	58 (35–87)	**<0.001**
Tricuspid regurgitation ≥ moderate,	158 (37)	38 (19)	58 (49)	62 (61)	**<0.001**
Systolic pulmonary artery pressure, mm Hg	49 (36–60)	39 (32–50)	51 (40–60)	54 (44–64)	**<0.001**
Medication					
RAS antagonist	377 (89)	182 (89)	104 (88)	91 (90)	0.87
Beta-blockers	333 (79)	146 (72)	101 (86)	86 (85)	**0.002**
Mineralocorticoid antagonist	216 (51)	82 (40)	70 (59)	64 (63)	**<0.001**
Furosemide	258 (61)	116 (57)	75 (64)	67 (66)	0.07
Cardiac resynchronization therapy	226 (53)	95 (47)	78 (66)	53 (52)	**0.003**

Values are median (interquartile range) or n (%). **Bold** p values are significant.

BMI = body mass index; EF = ejection fraction; HF = heart failure; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; NYHA = New York Heart Association; RAS = renin-angiotensin system; sMR = secondary mitral regurgitation.

patients without or with minimal sMR. We tested for collinearity in the multivariable model using the variance inflation factor. The proportional hazards assumption was tested and satisfied in all cases using Schoenfeld residuals. Interactions between surrogates of MR severity and all variables included in the multivariable model were tested by entering interaction terms in the Cox proportional hazard regression models. Kaplan-Meier analysis (log rank test) was applied to assess the discriminative power of quantitative measures of sMR severity. Severe sMR was graded according to American Heart Association (AHA)/American College of Cardiology (ACC) guidelines (EROA ≥40 mm^2 or RegVol ≥60 ml/beat) (2), European Society of Cardiology/European Association for Cardio-Thoracic Surgery (ESC/EACTS) guidelines (EROA ≥20 mm^2 or RegVol ≥30 ml/beat) (1), and ACC/ASE expert consensus for elliptical orifice (EROA ≥30 mm^2 or RegVol ≥45 ml/beat or RegFrac ≥40%) (8,10). The discriminatory power of each definition was assessed using receiver-operating characteristic analysis, and improvement in individual risk prediction was examined by the integrated discrimination index. Two-sided p values <0.05 were

TABLE 2 Crude and Multivariable Cox Regression Model Assessing the Impact of Surrogates of MR Severity on Long-Term Mortality (N = 423)

		Univariable Model		Bootstrap-Adjusted Confounder Model*		Clinical Confounder Model†	
Surrogates of sMR Severity	SD	Crude HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value
sMR semiquantitative assessment	–	1.70 (1.42–2.03)	**<0.001**	1.51 (1.25–1.83)	**<0.001**	1.45 (1.16–1.80)	**0.001**
sMR EROA	11.0	1.42 (1.25–1.63)	**<0.001**	1.31 (1.13–1.51)	**<0.001**	1.28 (1.09–1.51)	**0.003**
sMR regurgitant volume	17.0	1.37 (1.20–1.56)	**<0.001**	1.25 (1.08–1.44)	**0.002**	1.22 (1.04–1.43)	**0.013**
sMR vena contracta width	2.4	1.37 (1.19–1.57)	**<0.001**	1.27 (1.09–1.48)	**0.002**	1.22 (1.04–1.45)	**0.018**
sMR regurgitant fraction	31.0	1.50 (1.30–1.73)	**<0.001**	1.36 (1.16–1.59)	**<0.001**	1.31 (1.11–1.56)	**0.001**

Hazard ratios (HR) refer to a 1-SD increase in continuous variables and to an increase of 1 category of semiquantitative MR assessment. **Bold** p values are significant. *Adjusted for: age and creatinine. †Adjusted for: etiology of heart failure, left ventricular end-diastolic diameter, left ventricular function, NYHA functional class, and severity of tricuspid regurgitation (≥moderate).

CI = confidence interval; EROA = effective regurgitant orifice area; other abbreviations as in Table 1.

used to indicate statistical significance. The STATA11 software package (StataCorp, College Station, Texas) and SPSS 24.0 (IBM, Armonk, New York) were used for all analyses.

RESULTS

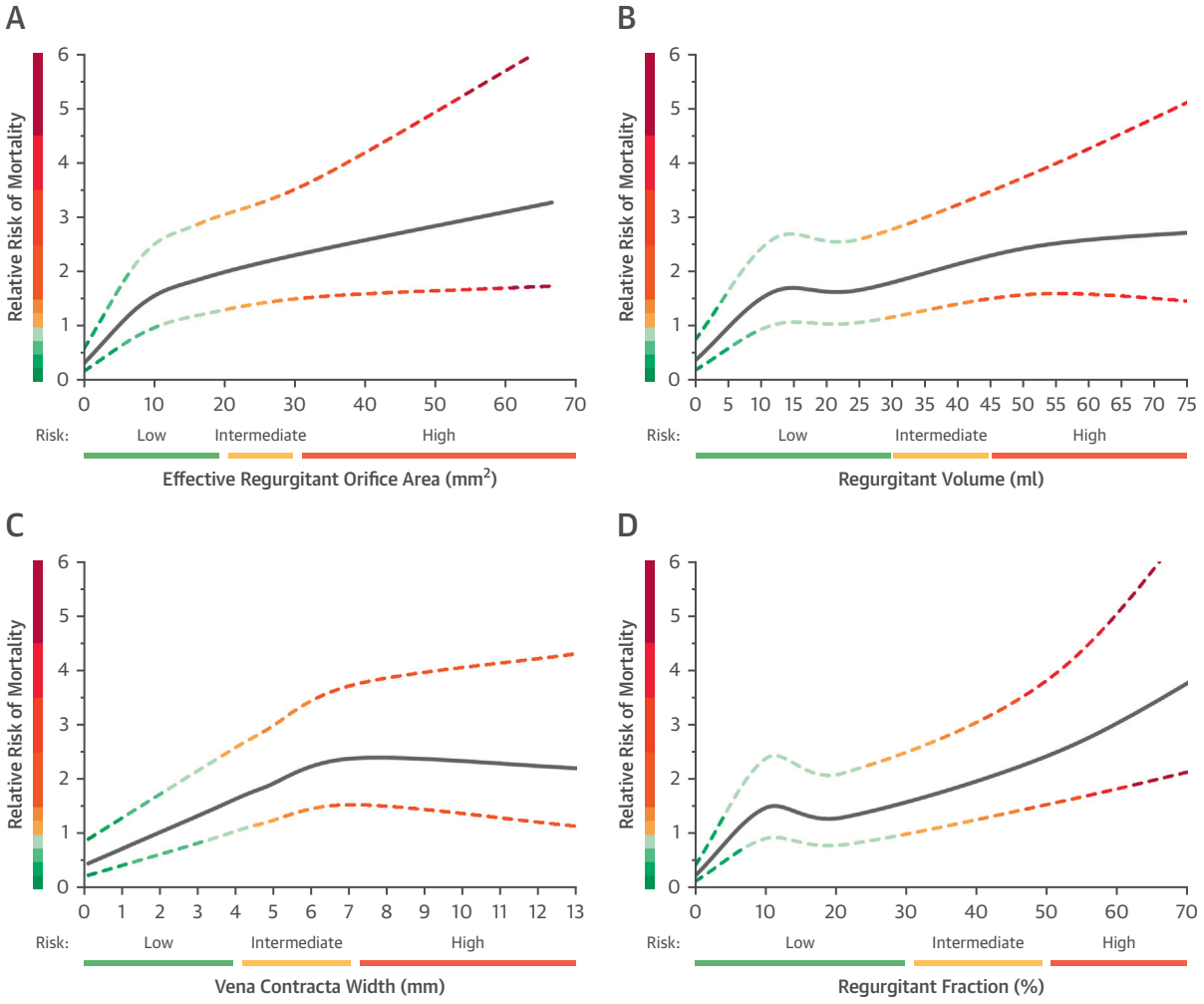
BASELINE CHARACTERISTICS. We enrolled 423 patients with chronic HFrEF with a median age of 66 years (interquartile range 57 to 73 years). Detailed baseline characteristics of the study population are displayed in Table 1. Forty-two percent (n = 176) were in NYHA functional class III, and 12 (n = 49) in NYHA functional class IV. With respect to heart failure therapy, 377 patients (89%) received RAS antagonists up-titrated to a median dose of 100% of the maximal guideline recommended dosages, 333 patients (79%) received beta-blockers up-titrated to a median dose of 50% of the maximal guideline-recommended dosages, 216 patients (51%) were treated with a mineralocorticoid receptor antagonist, and 226 patients (53%) underwent cardiac resynchronization therapy.

FEATURES OF sMR SEVERITY. Baseline characteristics according to sMR severity are detailed in Table 1. Briefly, with increasing sMR severity prevalence of atrial fibrillation increased. Increasing MR severity was associated with larger LV end-diastolic diameters ($p < 0.001$), larger left atrial diameter ($p < 0.001$), higher systolic pulmonary artery pressures ($p < 0.001$), and poorer LV function ($p < 0.001$).

QUANTITATIVE APPROACH TO sMR AND OUTCOME. During the 5-year follow-up period, 169 patients died. Mortality in patients with severe sMR was 59% compared with 34% in patients with nonsevere sMR. We observed a significant impact of sMR severity on long-term outcome with a crude HR of 1.70 (95% confidence interval [CI]: 1.42 to 2.03; $p < 0.001$) for semiquantitative assessment, of 1.42 (95% CI: 1.25 to 1.63; $p < 0.001$) for a 1-SD increase in EROA, of 1.37 (95% CI: 1.20 to 1.56; $p < 0.001$) for a 1-SD increase in regurgitant volume, of 1.38 (95% CI: 1.20 to 1.60; $p < 0.001$) for a 1-SD increase in VCW, and of 1.50 (95% CI: 1.30 to 1.73; $p < 0.001$) for a 1-SD increase in regurgitant fraction (Table 2). Detailed results after adjustment for the bootstrap-selected confounder model and the clinical confounder model are displayed in Table 2. The proportional hazards assumption was satisfied, and we did not detect a significant collinearity in our multivariable models. We then further explored the association between quantitative measures of sMR severity and outcome using spline analysis to describe intermediate- and high-risk groups in order to define new reference values for sMR (Figure 1). The lower 95% CI served as the threshold for further analysis (9). According to previously observed risk ranges (5,11), the current relative risk range of sMR (low, intermediate, and high risk) was assigned to the following numeric partitions: the cutpoint of the lower 95% CI with a relative risk between 1 and 1.5 defined the intermediate-risk subset, and a cutpoint of the lower 95% CI with a relative risk above 1.5 defined the high-risk subset. Kaplan-Meier analysis demonstrated a significant increase in mortality in patients with sMR with increasing EROA (log rank $p < 0.001$) (Figure 2A), RegVol (log rank $p < 0.001$) (Figure 2B), VCW (log rank $p = 0.006$) (Figure 2C), and RegFrac (log rank $p < 0.001$). Intraobserver and interobserver variability for quantitative measures of sMR severity displayed good reproducibility as detailed in Online Table 1. Bland-Altman plots for quantitative measures of sMR are displayed in Online Figures 1 and 2.

HEMODYNAMIC SEVERITY OF sMR IN THE INTERMEDIATE-RISK GROUP. A total of 59 patients (14%) were allocated to the intermediate-risk group according to this comprehensive algorithm (Figure 3) defined as sMR with an EROA of 20 to 29 mm^2 or a RegVol of 30 to 44 ml. We then assessed the hemodynamic severity of sMR on the basis of the regurgitant fraction for further risk stratification in this

FIGURE 1 **Relative Risk of Mortality According to Spline Analysis in Patients With sMR According to the EROA, RegVol, VCW, and RegFrac**

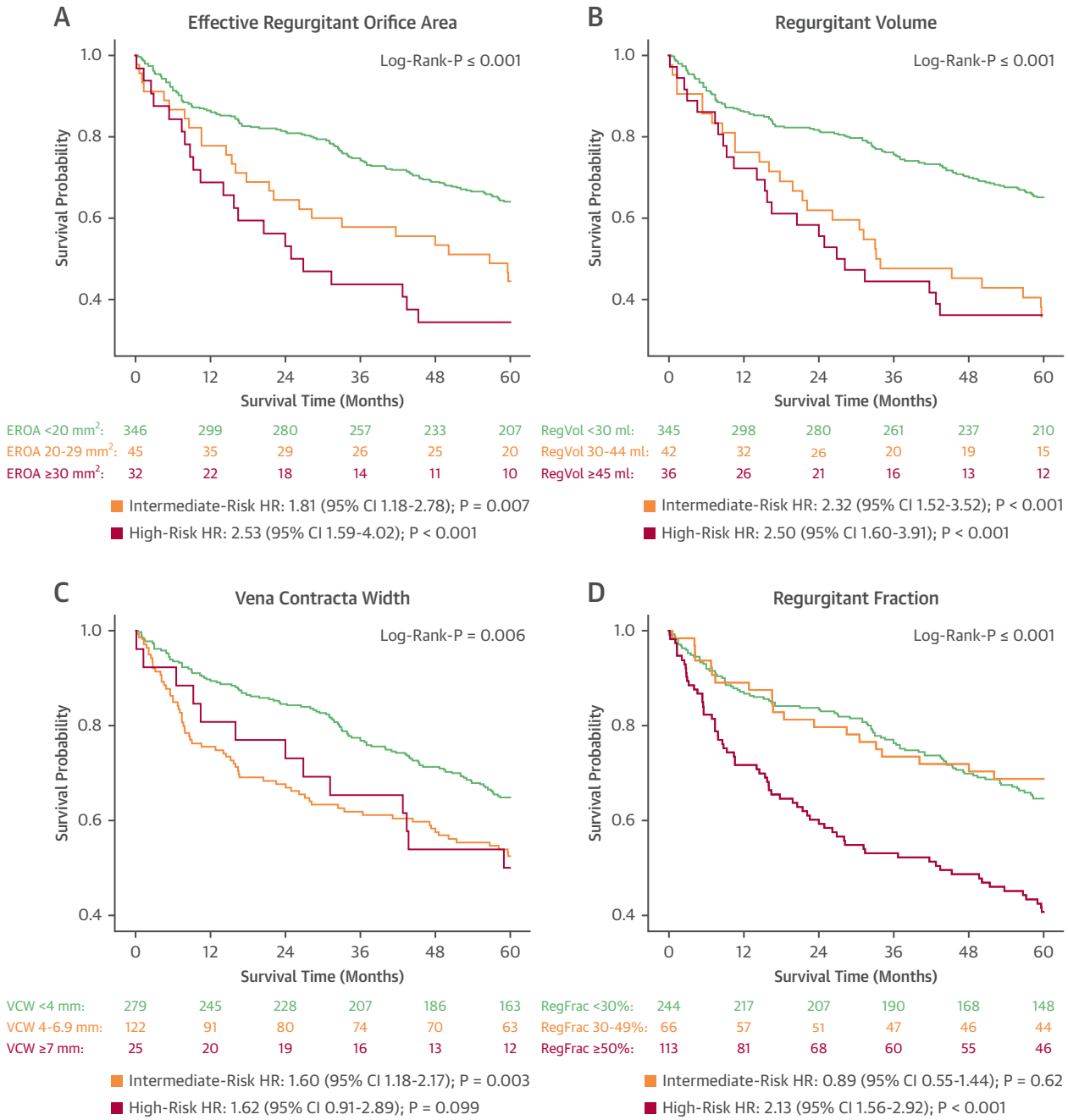


Spline curves of relative risk of mortality according to EROA **(A)**, RegVol **(B)**, VCW **(C)**, and RegFrac **(D)**. **Dashed lines** are 95% confidence intervals and are color coded according to risk indicated by the color bar of the y-axes. Bars below the x-axes represent the subsequently defined risk zones (**green** = low risk, **yellow** = intermediate risk, and **red** = high risk). EROA = effective regurgitant orifice area; RegFrac = regurgitant fraction; RegVol = regurgitant volume; sMR = secondary mitral regurgitation; VCW = vena contracta width.

intermediate-risk group. Forty-three patients showed hemodynamic severe sMR in the intermediate-risk group on the basis of a RegFrac of ≥50%. We observed a significant impact on long-term mortality in this intermediate-risk group with a HR of 3.02 (95% CI: 1.17 to 7.80; p = 0.023) when comparing patients with a regurgitant fraction ≥50% with patients with <50%. Kaplan-Meier analysis further underlined the significant increase of mortality in intermediate-risk patients with hemodynamically severe sMR defined as a regurgitant fraction ≥50% (log-rank p = 0.017) (**Figure 4**). We then investigated various echocardiographic markers (encompassing triangular-shaped continuous-wave Doppler spectrum, E-wave dominance, E-wave velocity >1.2 m/s, stroke volume, stroke distance, LV ejection fraction, EROA, and RegVol) to identify additional modes of stratification, but none of the markers obtained statistically significant results (Online Figure 3).

COMPARISON WITH ESTABLISHED DEFINITIONS OF SEVERE sMR. According to AHA/ACC guidelines, severe sMR was present in 38 patients; according to the ESC/EACTS guidelines, in 115 patients; according to

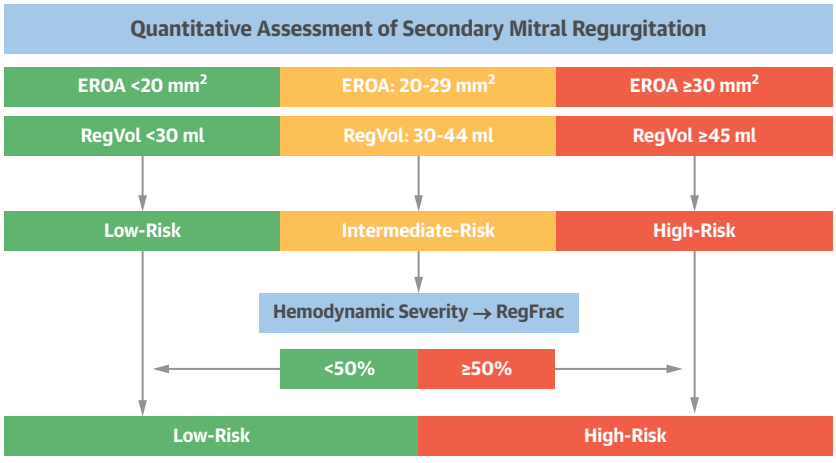
FIGURE 2 **Kaplan-Meier Estimates of Mortality According to Quantitatively Assessed sMR and Subsequent Defined Thresholds of Risk**



Kaplan-Meier estimates of mortality in patients with **(A)** an EROA <20 mm^2 **(green)**, an EROA of 20 to 29 mm^2 **(yellow)**, and an EROA ≥30 mm^2 **(red)** ($p \leq 0.001$), **(B)** a RegVol <30 ml **(green)**, a RegVol of 30 to 44 ml **(yellow)**, and a RegVol of ≥45 ml **(red)** ($p \leq 0.001$), **(C)** a VCW <4 mm **(green)**, a VCW of 4 to 6.9 mm **(yellow)**, and a VCW ≥7 mm **(red)** ($p = 0.006$), and **(D)** a RegFrac<30% **(green)**, a RegFrac of 30% to 49% **(yellow)**, and a RegFrac ≥50% **(red)** ($p \leq 0.001$). HRs are derived from a univariable Cox regression model. CI = confidence interval; HR = hazard ratio; other abbreviations as in Figure 1.

ASE/ACC expert consensus, in 143 patients; and according to the presented unifying concept, in 68 patients. We observed the strongest association with outcome for the unifying concept with a HR of 3.76 (95% CI: 2.71 to 5.23; $p < 0.001$) (Table 3). Furthermore, the discriminatory ability of the presented unifying concept was significantly better compared to all 3 alternative definitions of severe sMR (Table 3).

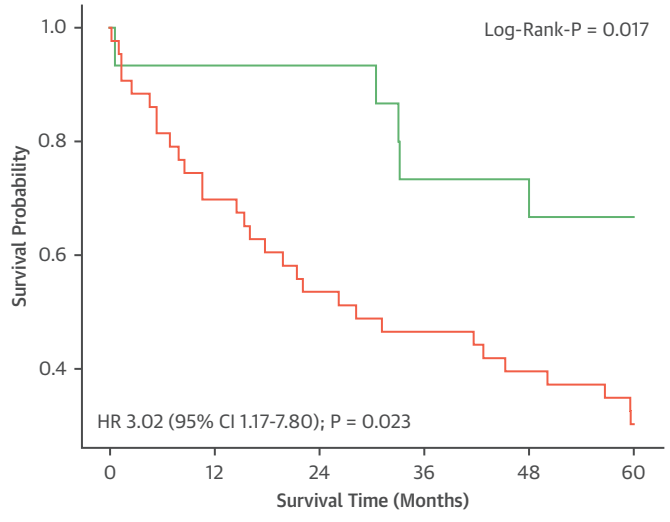
FIGURE 3 A Risk-Based Algorithm for Quantitative Assessment of sMR



A comprehensive algorithm for a risk-based quantitative assessment of sMR. On the basis of EROA and RegVol, patients are subclassified into low-, intermediate-, and high-risk groups. In intermediate-risk patients, the RegFrac might provide an additional tool for subsequent risk classification. Abbreviations as in Figure 1.

Additionally, integrated discrimination index showed a significant improvement in individual risk classification compared to the AHA/ACC and ESC/EACTS recommendations and the ACC/ASE expert consensus.

FIGURE 4 Kaplan-Meier Estimates of Mortality in Intermediate-Risk Patients



Kaplan-Meier estimates of mortality in intermediate-risk patients. (as classified by an EROA of 20 to 29 mm² or a RegVol of 30 to 44 ml) according to a RegFrac of <50% **(green)** or a RegFrac ≥50% **(red)**; p = 0.017. Abbreviations as in Figures 1 and 2.

DISCUSSION

This large-scale long-term observational study defines the continuous relationship between quantitative Doppler echocardiographic measures of sMR and outcome. Thresholds reflecting high-risk (an EROA ≥30 mm² and RegVol ≥45 ml) might serve as valuable tools for subsequent decision making. In the intermediate-risk subset (EROA 20 to 29 mm², RegVol 30 to 44 ml), a RegFrac of ≥50% might emerge as a valuable tool for further risk discrimination. A unifying concept based on combined assessment of the EROA, the RegVol, and the RegFrac showed a significantly better discrimination compared with the currently established algorithms.

QUANTITATIVE DEFINITION OF sMR: A MATTER OF DEBATE. A limited number of studies addressed the predictive value of quantitatively assessed sMR (5,12-14). Pioneering studies (5,12) introduced the revolutionary concept of lower EROA thresholds in ischemic sMR to be associated with excessive mortality. Main limitations are inclusion of solely ischemic sMR 2 to 3 decades ago at the advent of GDMT and cardiac resynchronization therapy, both of which might significantly halter disease progression and reduce cardiac susceptibility to the hemodynamic burden of sMR (11,15,16), and the adapted cutoffs for EROA and RegVol thresholds calibrated according to angiographic grading (17). Nevertheless, those series had the undisputed merit of raising the

TABLE 3 Comparison of the Unifying Concept With the ACC/AHA, ESC/EACTS and ACC/ASE Expert Consensus Definitions of sMR by Cox Regression, ROC, and IDI

	Cox Regression Analysis		ROC Analysis		IDI Analysis	
Definition of Severe sMR	HR (95% CI)	p Value	ROC	p Value for Comparison	IDI	p Value
Unifying concept	3.76 (2.71–5.23)	**<0.001**	0.63	–	–	–
ACC/AHA definition	3.20 (2.14–4.78)	**<0.001**	0.57	**<0.001**	0.06	**<0.001**
ESC/EACTS definition	1.52 (1.10–2.09)	**0.01**	0.55	**<0.001**	0.13	**<0.001**
ACC/ASE expert consensus	1.89 (1.40–2.56)	**<0.001**	0.59	**0.04**	0.08	**<0.001**

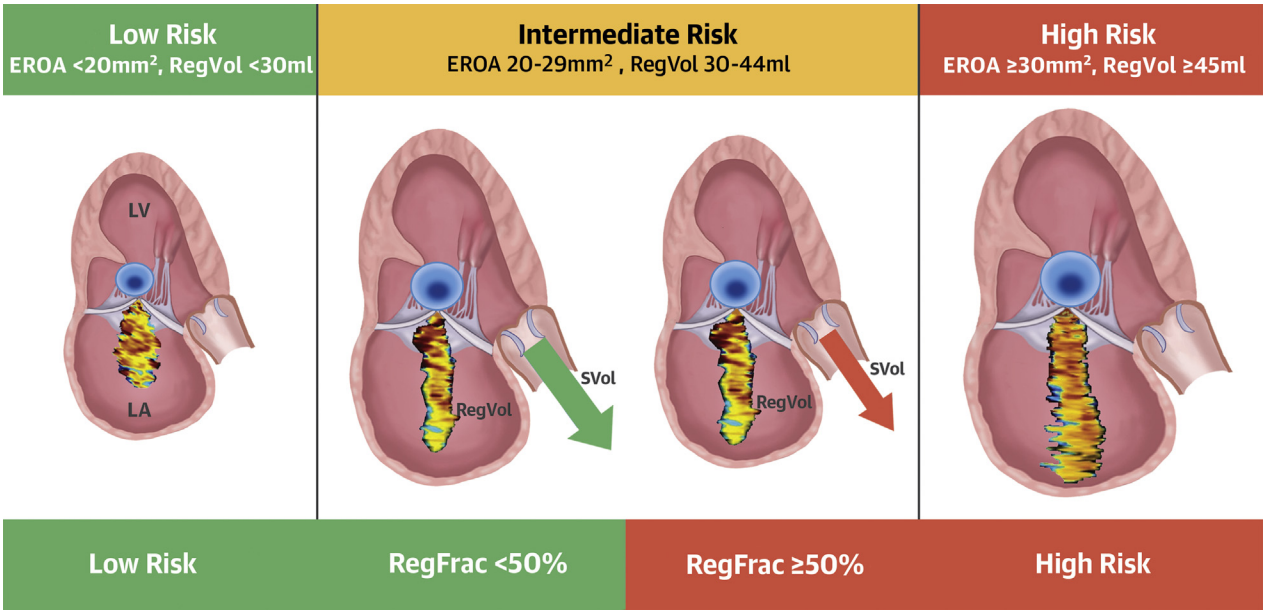
Bold p values are significant.

ACC = American College of Cardiology; AHA = American Heart Association; ASE = American Society of Echocardiography; ESC/EACTS = European Society of Cardiology/European Association for Cardio-Thoracic Surgery; IDI = integrated discrimination index; ROC = receiver-operating characteristic; other abbreviations as in Table 1 and 2.

hypothesis of the need for lower cutoff values in sMR subsequently expanded to the entire spectrum of HFrEF (13) and adopted by the ESC/EACTS guidelines (1). Whereas the AHA/ACC guidelines have revised the definition of severe sMR to an EROA ≥40 mm^2 and a RegVol ≥60 ml, the ESC/EACTS guidelines have kept their initial definition that is considerably lower: an EROA ≥20 mm^2 and a RegVol ≥30 ml. Initially, both guidelines recommended the lower thresholds due to important differences between secondary MR as compared with primary MR: 1) the geometric assumptions of the proximal flow convergence do not fit the anatomic orifice in sMR, which is often crescent-shaped, leading to an underestimation of disease severity; 2) the primarily failing heart might be more susceptible to the regurgitant burden; and 3) a universal definition is challenging because there is significant causal interference with competing risks of heart failure and disease-modifying factors such as GDMT (3). Surgical valve repair or replacement conveys significant procedural risk that needs to be outweighed by the potential benefit. Data from the Cardiothoracic Surgical Trials Network showed no survival benefit of valve repair on top of revascularization in patients with an EROA cutoff for inclusion of ≥20 mm^2 but with increased supraventricular arrhythmias and neurological events (18). Contemporary definition of severe sMR, however, also entails subsequent decision making for transcatheter repair, and recently published results of the 2 randomized controlled trials, MITRA-FR (Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation) (19) and COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) (20), have shown that patient selection is crucial for successful treatment of sMR. Among many differences in the selection of patients between the 2 trials, MITRA-FR used the lower cutoffs as a trigger to treat sMR by transcatheter valve repair (an EROA of ≥20 mm^2) and showed no significant reduction in heart failure rehospitalizations on top of GDMT. The COAPT trial used an EROA of ≥30 mm^2 and showed a significant reduction of death from any cause, with a HR of 0.62. Although transcatheter therapies have been developed as low-risk alternatives to surgery, it has to be noted that there still remains a risk of periprocedural adverse events reported with approximately 5.6% in MITRA-FR encompassing cardiogenic shock resulting in intravenous inotropic support, cardiac embolism including gas embolism and stroke, and tamponade. A lower threshold, that is, an EROA ≥20 mm^2, may expose a significant proportion of patients to unnecessary risk of futile procedures and higher thresholds; that is, an EROA ≥40 mm^2 may withhold potentially life-extending therapies. An EROA cutoff at 30 mm^2 for high risk therefore seems reasonable. Whether an interventional repair strategy can reduce mortality and heart failure hospitalizations in selected patients in the intermediate-risk group remains to be demonstrated. Moreover, sMR grading was only 1 of the differences between the 2 trials, and the outcome difference cannot be attributed exclusively to this difference. Further considerations that might explain the different results include the differences in medical therapies, as well differential LV remodeling patterns between the 2 trials.

A UNIFYING, RISK-BASED, QUANTITATIVE APPROACH TO sMR. The present data introduce the continuous relationship of quantitatively assessed sMR and mortality. Spline-curve analyses (**Figure 1**) show a continuous increasing risk with increasing EROA and RegVol. An EROA <20 mm^2 and a RegVol <30 ml are associated with a favorable prognosis. In those patients, sMR is not the disease-driving factor, and the therapeutic focus should be GDMT. The subset of patients with an EROA of 20 to 29 mm^2 and a RegVol of 30 to 44 ml is an intermediate-risk group approaching the thresholds where the regurgitant load starts fueling the disease.

CENTRAL ILLUSTRATION **A Unifying Concept for the Quantitative Assessment of sMR**



Bartko, P.E. et al. J Am Coll Cardiol. 2019;73(20):2506–17.

Based on the relationship of the effective regurgitant orifice area (EROA) and the regurgitant volume (RegVol) with relative risk of mortality, 3 risk categories can be defined: low, intermediate, and high risk. An EROA <20 mm^2 and a RegVol <30 ml is associated with the lowest risk **(left, green panel)** whereas an EROA ≥30 mm^2 and a RegVol ≥45 ml indicates the highest risk subset **(right, red panel)**. Patients with an EROA of 20 to 29 mm^2 and a RegVol of 30 to 44 ml are at an intermediate risk **(center, yellow panel)** because sMR will be the leading contender in some, but not all, patients. Among other things such as the failure phenotype, impact on heart failure progression and mortality (i.e., hemodynamic severity) depends upon ventricular adaptation to the volume load by the lesion (larger LV cavity size and relatively preserved EF **[center panel, left])** will maintain forward stroke volume, whereas smaller LV cavity size and more reduced EF **[center panel, right]** will indicate failure of compensation to volume overload and reduced cardiac output). This is a clinical dilemma because the EROA and the RegVol within the blue spectrum do not specify whether sMR is the leading contender of heart failure progression and mortality. The ratio of total stroke volume to RegVol however—as expressed by the regurgitant fraction (RegFrac) in percent—can guide clinicians in this challenging subset of patients because a RegFrac of <50% indicates that the patient can be restratified to the low-risk group **(left, green panel)**, whereas a RegFrac of ≥50% suggests hemodynamically significant sMR, and those patients can be re-stratified to the high-risk subset **(right, red panel)**. sMR = secondary mitral regurgitation.

This subset represents the patients where heart failure progression is driven by the valvular lesion. Specifically, the EROA shows a linear relationship between its increase and the relative risk (Figure 1A), corroborating its use on top of the integrated algorithm as a clinically robust grading tool.

The subset with an EROA ≥30 mm^2 and a RegVol ≥45 ml represents those patients where sMR drives the disease, and efforts to reduce this potentially treatable lesion might be beneficial beyond pure symptom reduction. Those thresholds are exactly within the grey zone defined by the mismatch of the AHA/ACC (2) and ESC/EACTS (1) guidelines on valvular heart disease, indicating a potentially resolvable debate. Indeed, the recommendations for the evaluation of valve regurgitation by the ASE (8) as well as the ACC expert consensus on the management of mitral regurgitation (10) have effectively lowered the EROA cutoff for sMR to ≥30 mm^2 in the presence of an elliptical orifice, which is almost invariably the case in sMR. The present data corroborate this approach by providing outcome-based evidence in support of the EROA ≥30 mm^2 cutoff for sMR. Among previous recommendations for sMR grading (Table 3), the ASE algorithm has the highest predictive power.

In contrast to EROA and RegVol, VCW discriminates less well for intermediate- and high-risk patients (Figure 1C). This is reflected by the current ASE guidelines (8) that note a substantial overlap of VCW values between MR grades and therefore the need for additional measurements such as EROA and RegVol.

SPLINE ANATOMY OF VARIOUS QUANTITATIVE APPROACHES TO sMR. Several observations stand out in the association of quantitative sMR with the relative risk of mortality. First, and most importantly,

the association is distinctly different from previously published reports on organic mitral regurgitation where a steep increase of EROA can be observed. This is in line with the pathophysiological concept of sMR where the volume load due to the lesion is not the sole driving force of mortality. In fact, there are many competing risks in this multimorbid patient cohort that need careful consideration in the clinical setting. Eventually, sMR becomes the critical contender specifically in those patients with an intermediate failure phenotype and more severe degrees of sMR. In addition to the pathophysiological considerations, technical limitations of the metrics need to be considered. The ASE recommendations have previously described substantial overlap of intermediate VCW values between MR grades. The spline anatomy is suggestive that a VCW <4 mm is valuable as a rapid measure to rule out moderate or severe sMR as previously suggested (14); however, the flattening in higher VCW ranges limits its use for more concise risk stratification in the disease spectrum (**Figure 1C**). This might be attributable to technical factors but also the relatively small sample size of the present cohort of patients with a VCW ≥7 mm. Albeit to a lesser extent, a flatter course of the association between RegVol amount and the relative risk can also be observed (**Figure 1B**), which might be due to a low driving force often observed in HFrEF patients potentially leading to an underestimation of lesion severity by RegVol as also previously suspected by the ASE recommendations. The present data, therefore, support the limitations outlined by the ASE recommendations and provides a reasonable basis to use the EROA on the top of a grading approach because it shows the most uniform increase in risk with increasing EROA.

POTENTIAL ROLE OF MULTIPARAMETRIC QUANTITATIVE ASSESSMENT IN sMR. The intermediate-risk subset is specifically challenging because it is composed of a subset of patients in whom the PISA-determined measurements might not reflect the hemodynamic severity of the regurgitant lesion. Nevertheless, in a significant proportion, the regurgitation might drive mortality, whereas some patients might be stable under contemporary GDMT, indicating the need for a measurement that reflects the hemodynamic severity in this subset of patients: the RegFrac, a hybrid parameter that calculates as the ratio of the RegVol to total stroke volume, has been previously proposed to determine the hemodynamic severity specifically in sMR (8). This parameter is of specific interest for this intermediate-risk group because it includes information, not only on the severity of regurgitant load, but also on its relation to cardiac size and function. **Figure 1D** shows that it might specifically well discriminate between the 3 risk subsets and might be of importance for subsequent management of patients with an EROA of 20 to 29 mm^2 and a RegVol of 30 to 44 ml. Essentially, as shown in **Figure 4**, RegFrac might be a possible solution to assess the hemodynamic severity in patients with sMR in the intermediate-risk group as previously specified by the ASE recommendations for valve regurgitation (8). Therefore, a reasonable approach to sMR is to quantitatively assess its severity by EROA and RegVol into subsequent risk groups (low, intermediate, and high risk) and then use the RegFrac for assessment of hemodynamic severity of sMR in the intermediate-risk group. If this parameter is below 50%, a low-risk management strategy might be advocated (**Figure 3, Central Illustration**), whereas if it exceeds 50%, more aggressive treatment might be indicated in an attempt to shift the ratio of total stroke volume to wasted backflow in favor of the forward stroke volume. The recommendations for the evaluation of valve regurgitation by the ASE have incorporated this aspect into the integrated algorithm and a RegFrac of ≥50% would qualify as severe. An additional challenge in the intermediate-risk group is discordance between the EROA and the RegFrac. Only 27% of the patients in this group had a RegFrac of <50% giving rise to a grading and potentially clinical management dilemma because EROA is suggestive of a nonsevere lesion in the range of 20 to 29 mm^2, whereas RegFrac ≥50% suggests the presence of a severe lesion. Given that the EROA appears to be a more robust measurement, it seems clinically reasonable to use this parameter for quantitative assessment and then add complementary metrics such as the RegFrac specifically in the intermediate-risk group. Of note, signs in support of more severe sMR such as a triangular-shaped Doppler spectrum or an E-velocity ≥1.2 m/s were not useful for risk stratification in the intermediate-risk group (Online Figure 3), underlining the diagnostic challenge in this subgroup and corroborating the use of RegFrac as an additional tool for risk stratification.

POTENTIAL IMPLICATIONS FOR CURRENT CLINICAL PRACTICE IN sMR. The current data provide the evidence for a contemporary risk-based quantitative approach to sMR (**Central Illustration, Figure 3**). This algorithm provides a clinically robust tool, and the majority of patients can be adjudicated to the

unambiguous risk categories low- or high-risk solely on the basis of EROA and RegVol. An EROA of <20 mm^2 and a RegVol of <30 ml are excellent indicators for a lower risk. and subsequent management strategies in those patients include a regular follow-up in heart failure or valvular heart failure clinics. Those patients generally can be managed well by GDMT; however, a proportion of roughly 20% might encounter disease progression as previously reported (16). Importantly, the follow-up timing should be adapted according to previously identified predictors of sMR progression (16), including a regular re-assessment of GDMT and re-evaluation of CRT indications (15). Patients with an EROA of 20 to 29 mm^2 and a RegVol of 30 to 44 ml are a challenging subset because subsequent management might be controversial. An integrated approach might be the key to subsequent treatment decisions. The RegFrac is a promising parameter in this subset to guide the decision process because a RegFrac of <50% indicates a good prognosis (**Figure 4**) and compensated disease, and regular follow-up is indicated similarly to low-risk patients. Contrarily, patients with an EROA of 20 to 29 mm^2 and a RegVol of 30 to 44 ml that also show a RegFrac of ≥50% have a high risk (**Figure 4**), indicating the need for a multidisciplinary discussion on subsequent management. The heart team can potentially address further strategies in those patients with the use of low-risk transcatheter strategies or with surgical strategies.

The subset of patients where the valve lesion drives excessive mortality is well defined by an EROA of ≥30 mm^2 and a RegVol of ≥44 ml in the current series. Those patients should be assessed by a multidisciplinary heart team because they have, not only a high risk of mortality, but also a high perioperative risk.

STUDY LIMITATIONS. The present data represent the most comprehensive contemporary information about quantitative measures of sMR. However, a validation of the proposed algorithm in different patient populations remains outstanding. The elliptical shape of the regurgitant orifice in sMR might lead to underestimation of lesion severity by the proximal flow convergence method. Three-dimensional imaging techniques might potentially offer complementary information. Furthermore, the PISA method is not reflective of the dynamic variations of the orifice, which is commonly observed in secondary MR, and therefore might lead to underestimation of the mitral regurgitant stroke volume. In addition, the RegFrac is limited by its derivation from multiple measurements that are often imprecise and therefore subject to compound error. Cardiac magnetic resonance imaging as a complementary tool for assessment of RegFrac might help to add the necessary precision to discriminate within the intermediate-risk subset and further improve risk stratification.

CONCLUSIONS

A contemporary quantitative risk-based approach to sMR reflects the continuous spectrum of disease severity in sMR. The present algorithm specifies thresholds for quantitatively assessed sMR that defines the risk according to 3 groups: 1) low risk, defined by an EROA <20 mm^2 and a RegVol <30 ml; 2) intermediate risk, defined by an EROA of 20 to 29 mm^2 and a RegVol of 30 to 44 ml; and 3) high risk, defined by an EROA ≥30 mm^2 and a RegVol ≥45 ml. In the intermediate-risk group, a RegFrac ≥50% indicated hemodynamic severe sMR and was used for further stratification. Those risk-based thresholds might evolve as a valuable tool for subsequent therapeutic decisions and might help to resolve an ongoing controversy between divergent cutoff values because they provide a unifying concept for the quantification of sMR. A unifying concept based on combined assessment of the EROA, the RegVol, and the RegFrac showed a significantly better discrimination compared with the currently established algorithms.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Secondary mitral regurgitation is associated with an increased risk of mortality despite guideline-directed therapy for heart failure. Echocardiographic correlates of highest risk include an EROA ≥30 mm^2 and regurgitant volume (RegVol) ≥45 ml. An EROA <20 mm^2 and RegVol <30 ml are associated with more favorable prognosis.

TRANSLATIONAL OUTLOOK: Future studies should compare these EROA and RegVol indices with conventional criterial for selection of patients for surgical valve repair.

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KEY WORDS effective regurgitant orifice area, heart failure with reduced ejection fraction, mitral insufficiency, proximal isovelocity surface area, regurgitant fraction, regurgitant volume, secondary mitral regurgitation

APPENDIX For an expanded Methods section as well as supplemental figures and a table, please see the online version of this paper.