JACC: CARDIOVASCULAR IMAGING VOL. ■, NO. ■, 2021

PUBLISHED BY ELSEVIER

NEW RESEARCH PAPER

Functional Mitral Regurgitation Outcome and Grading in Heart Failure With Reduced Ejection Fraction

Giovanni Benfari, MD, Clémence Antoine, MD, Benjamin Essayagh, MD, Roberta Batista, MD, Joseph Maalouf, MD, Andrea Rossi, MD, Francesco Grigioni, MD, Prabin Thapa, MS, Hector I. Michelena, MD, Maurice Enriquez-Sarano, MD

ABSTRACT

OBJECTIVES This study aims to define excess-mortality linked to functional mitral regurgitation (FMR) quantified in routine-practice.

BACKGROUND Appraisal of FMR in heart failure with reduced ejection fraction (HFrEF) is challenging because risks of excess mortality remain uncertain and guidelines diverge.

METHODS Cases of HFrEF (ejection-fraction <50%) Stage B-C that were diagnosed between 2003 and 2011 and had routine-practice FMR quantitation (FMR cohort, n = 6,381) were analyzed for excess mortality thresholds/rates within the cohort and in comparison to the general population. These were also compared to those of a degenerative mitral regurgitation (DMR) simultaneous cohort (DMR cohort, n = 2,416).

RESULTS In the FMR cohort (age: 70 ± 11 years, ejection fraction: 36 ± 10%, effective regurgitant orifice area [EROA]: 0.09 ± 0.13 cm^2), EROA distribution was skewed towards low-values (≥0.40 cm^2 in only 8% vs 38% for the DMR cohort; $P < 0.0001$). One-year mortality was high (15.6%), increasing steeply from 13.3% without FMR to 28.5% with EROA ≥0.30 cm^2 (adjusted odds ratio: 1.57 [95% CI: 1.19-2.97]; $P = 0.001$). In the long term, 3,538 FMR cohort patients died with excess mortality threshold ∼0.10 cm^2 (vs ∼0.20 cm^2 in the DMR cohort), with 0.10 cm^2 EROA increments independently associated with considerable mortality increment (adjusted HR: 1.11 [95% CI: 1.08-1.15]; $P < 0.0001$) and with no detectable interaction. Compared to the general population, FMR excess mortality increased exponentially with higher EROA (risk ratio point estimates 2.8, 3.8, and 5.1 at EROA 0.20, 0.30, and 0.40 cm^2, respectively), and was much steeper than that of the DMR cohort ($P < 0.0001$). In nested models, individualized EROA was the strongest FMR survival marker, and a new expanded FMR grading scale based on 0.10 cm^2 EROA increments provided incremental power over current American Heart Association–American College of Cardiology/European Society of Cardiology guidelines (all $P <$ 0.03).

CONCLUSIONS In HFrEF, FMR is skewed towards smaller EROA. Nevertheless, when measured in routine practice, EROA is the strongest independent FMR determinant of survival after diagnosis. Excess mortality increases exponentially above the threshold of 0.10 cm^2, with a much steeper slope than in DMR, for any EROA increment. An expanded EROA-based stratification, superior to existing grading schemes in determining survival, should allow guideline harmonization. (J Am Coll Cardiol Img 2021;■:■–■) © 2021 by the American College of Cardiology Foundation.

From the Department of Cardiovascular Diseases, Mayo Clinic, Mayo Clinic, Rochester, Minnesota, USA.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received December 21, 2020; revised manuscript received May 18, 2021, accepted May 21, 2021.

ISSN 1936-878X/$36.00 https://doi.org/10.1016/j.jcmg.2021.05.017

ABBREVIATIONS AND ACRONYMS

ACC = American College of Cardiology

AHA = American Heart Association

DMR = degenerative mitral regurgitation

EROA = effective regurgitant orifice area

ESC = European Society of Cardiology

FMR = functional mitral regurgitation

HFrEF = heart failure with reduced ejection fraction

LV = left ventricular

RVol = regurgitant volume

Mitral regurgitation is the most frequently valve disease (1,2). Functional mitral regurgitation (FMR) with structurally normal leaflets most often forms in association with left ventricular dysfunction (3). High mortality and heart failure events reported in FMR have contrasted with generally low regurgitation volume and have raised concerns that FMR may only mirror ventricular dysfunction or be a surrogate (4-8). Moreover, observational studies have reported marked FMR improvement with medical treatment without benefit to mitral surgery and divergent results from small clinical trials of surgical repair/replacement have perpetuated uncertainty (9-12). Doubts regarding FMR persist with conflicting reports and variable guidelines. Discordant trials of interventional treatment (ie, positive COAPT [Cardiovascular Outcomes Assessment of the MitraClip in Patients with Heart Failure and Secondary Mitral Regurgitation] and negative Mitra-FR [Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation]) are difficult to reconcile (13,14). Pilot FMR outcome studies with positive results supporting the prognostic impact of effective regurgitant orifice area (EROA) have conflicted with multiple methodological criticisms (4-7,15-17). Widely divergent 5-year EROA-linked survival rates have amplified uncertainties surrounding FMR outcome (18,19). Interaction reports have suggested alternatively that FMR affects survival only with relatively preserved ejection fraction (EF), or with small ventricular size, or by combining regurgitant fraction with EROA (18,20,21). Although these reports were based on small samples or theoretical constructs, confusion has ensued (18,20,21). Most troubling are the guidelines fluctuations. US recommendations were initially divergent from European ones, which defined severe FMR with lower EROA, but then became aligned using low EROA thresholds, and finally reversed severe FMR to high EROA thresholds, which are identical to severe degenerative mitral regurgitation (DMR) (22-28). To help resolve the FMR outcome and severity grading uncertainty, we gathered new data from a large cohort with comprehensive regurgitation quantification and clinical characterization and have analyzed survival and patterns of excess-mortality versus the general population, including comparison of FMR to DMR.

METHODS

ELIGIBILITY FOR FMR COHORT. Patients eligible for the FMR cohort were first diagnosed with heart failure with reduced ejection fraction (HFrEF) Stage B or C with transthoracic echocardiography performed at the Mayo Clinic between 2003 and 2011, aged ≥50 years at diagnosis, with comprehensive clinical characterization and FMR quantitation if present. Exclusion criteria included: 1) organic mitral disease (prolapse, flail-leaflet, prosthetic valve, or greater than or equal to trivial rheumatic or degenerative mitral valve thickening/calcification); 2) aortic stenosis/regurgitation greater than or equal to moderate (sclerosis not excluded); 3) mitral stenosis greater than or equal to moderate; 4) organic tricuspid valve disease; 5) pericardial, congenital, hypertrophic, or infiltrative (amyloidosis, hemochromatosis, or sarcoidosis) heart-disease; 6) previous valve surgery; and 7) history of cancer. FMR absence, constituting the reference regarding FMR EROA outcome impact, was not excluded. The DMR cohort was formed from patients with mitral valve prolapse whose cases were diagnosed between 2003 and 2011 with similar inclusion (age ≥50 years with quantified DMR) and exclusion criteria (no cancer, no other valve, pericardial, infiltrative, and hypertrophic diagnosis). The Mayo Clinic Institutional Review Board approved the protocol and waived informed consent requirement.

CLINICAL AND ECHOCARDIOGRAPHIC DATA. Patients' medical histories and clinical characteristics documented by physicians at our institution were retrieved unaltered from electronic records. Vital signs were measured at echocardiography. Atrial fibrillation was diagnosed by electrocardiogram. Comorbidities were summated using the Charlson index.

All echocardiographic examinations were performed in routine clinical practice by multiple trained sonographers (>100) and reviewed by cardiologists (>30) at the Mayo Clinic (Rochester, Minnesota) using diverse, commercially available machines. Measurements were guided by clinical recommendations for regurgitation and cardiac cavities assessment (23,29). At the conclusion of echocardiography, mitral regurgitation was graded by the cardiologist as none/trivial, mild, moderate, or severe by integrating all signs/measures recommended by guidelines, including quantitation of EROA and regurgitant volume (RVol), which were considered null with no/trivial regurgitation (23). Echocardiographic data (qualitative and

TABLE 1 Clinical and Echocardiographic Characteristics of Patients With Left Ventricular Dysfunction

			FMR-EROA			
	Overall (N = 6,381)	No FMR (60%, n = 3,823)	FMR-EROA 0.01-0.19 (20%, n = 1,262)	FMR-EROA 0.20-0.39 (17%, n = 1,103)	FMR-EROA ≥0.40 (3%, n = 193)	*P* for Trend
Clinical characteristics						
Age, y	70 ± 11	68 ± 7	73 ± 11	72 ± 10	70 ± 10	0.2
Female, %	31	25	45	34	31	<0.0001
BMI, kg/m^2	29.1 ± 6.5	29.9 ± 6.8	27.9 ± 6.0	28.1 ± 5.5	28.2 ± 6.9	0.002
Atrial fibrillation, %	20 (1,239)	14	26	33	30	<0.0001
Heart rate, beats/min	76 ± 18	75 ± 18	75 ± 17	78 ± 17	80 ± 16	<0.0001
Systolic BP, mm Hg	121 ± 21	122 ± 21	128 ± 22	118 ± 19	106 ± 18	<0.0001
Diastolic BP, mm Hg	69 ± 12	69 ± 13	71 ± 14	68 ± 13	65 ± 13	<0.0001
Diabetes	1,724 (28)	1,058 (28)	294 (24)	324 (30)	48 (25)	0.8
Systemic hypertension	3,716 (58)	2,293 (60)	749 (59)	591 (54)	83 (43)	<0.0001
Dyslipidemia	3,196 (50)	2,034 (53)	601 (48)	484 (44)	77 (40)	0.0001
CAD	4,379 (69)	2,613 (68)	865 (69)	761 (69)	140 (73)	0.2
Charlson comorbidity index	2.44 ± 1.94	2.36 ± 1.94	2.44 ± 1.89	2.70 ± 1.98	2.72 ± 1.91	0.002
Symptoms						
Dyspnea	3,363 (53)	1,702 (45)	734 (58)	744 (67)	160 (83)	<0.0001
Angina	1,722 (27)	1,132 (30)	302 (24)	236 (21)	52 (27)	0.3
Palpitation	787 (12)	439 (12)	163 (13)	157 (14)	28 (15)	0.2
Echocardiographic characteristics						
LVEDD, mm	59 ± 9	54 ± 7	58 ± 9	61 ± 9	66 ± 10	<0.0001
LVESD, mm	46 ± 10	43 ± 7	43 ± 8	52 ± 10	57 ± 12	<0.0001
LVEDD index, mm/m^2	29 ± 5	27 ± 4	31 ± 5	32 ± 5	34 ± 6	<0.0001
LVESD index, mm/m^2	24 ± 5	21 ± 4	25 ± 5	27 ± 6	29 ± 7	<0.0001
LVEF, %	36 ± 10	38 ± 9	33 ± 10	30 ± 10	28 ± 10	<0.0001
WMSI	2.01 ± 0.44	1.91 ± 0.42	2.11 ± 0.44	2.22 ± 0.43	2.30 ± 0.36	<0.0001
LV SV-index, mL/m^2	38 ± 10	39 ± 10	37 ± 11	34 ± 10	31 ± 9	<0.0001
E, m/s	0.81 ± 0.29	0.70 ± 0.25	0.90 ± 0.26	0.96 ± 0.26	1.17 ± 0.33	<0.0001
E/A	1.22 ± 0.86	0.94 ± 0.57	1.46 ± 0.97	1.88 ± 1.03	2.52 ± 1.30	<0.0001
DTE, ms	193 ± 63	213 ± 62	180 ± 58	157 ± 46	147 ± 37	<0.0001
E/e'	17.13 ± 9.47	14 ± 7	21 ± 10	22 ± 10	28 ± 11	<0.0001
EROA, cm^2	0.09 ± 0.13	0 ± 0	0.14 ± 0.04	0.28 ± 0.05	0.51 ± 0.11	<0.0001
RVol, mL	14 ± 19	0 ± 0	24 ± 8	42 ± 11	67 ± 19	<0.0001
MR severe by integrative grading, %	11	0	3	42	94	<0.0001
S-PAP, mm Hg	42 ± 15	36 ± 12	45 ± 15	50 ± 14	57 ± 14	<0.0001
Medical therapy						
ACE inhibitors /ARB	5,008 (78)	2,922 (76)	1,026 (81)	903 (82)	157 (81)	<0.0001
Beta blockers	5,928 (83)	3,063 (80)	1,098 (87)	969 (88)	168 (87)	<0.0001
Diuretics	4,316 (68)	2,243 (59)	963 (76)	931 (84)	179 (93)	<0.0001
Aspirin	4,999 (78)	3,018 (79)	987 (78)	843 (76)	151 (78)	0.12
Statin	4,109 (64)	2,513 (66)	783 (62)	699 (63)	114 (59)	0.01
Spironolactone	1,024 (17)	473 (12)	227 (18)	256 (23)	68 (35)	<0.0001
Cardiac resynchronization therapy	170 (2.7)	59 (1.5)	33 (2.6)	57 (5.2)	21 (10.9)	<0.0001

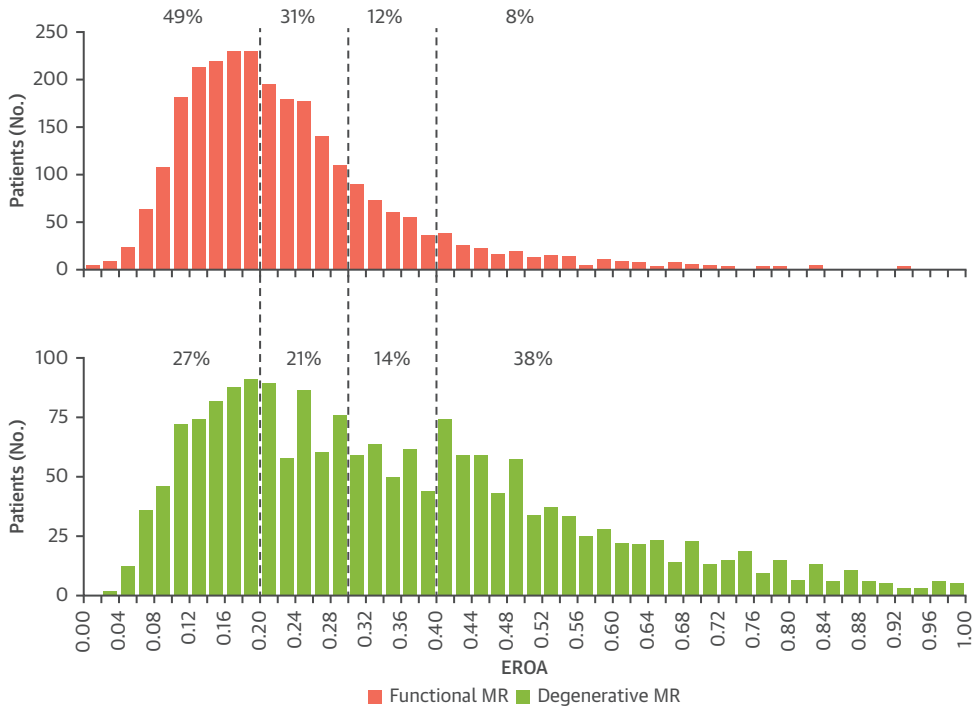
Values are n (%), unless otherwise specified.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blockers; BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; DTE = mitral inflow E-wave deceleration time; EROA = effective regurgitant orifice area; FMR = functional mitral regurgitation; LV SV = left ventricular stroke volume (by left ventricular outflow tract pulsed Doppler method); LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; MR = mitral regurgitation; RVol = regurgitant volume; S-PAP = systolic pulmonary arterial pressure; WMSI = wall motion score index.

quantitative) were retrieved unaltered from original reports via electronic transfer.

FOLLOW-UP. The outcome endpoint was mortality under medical management (all-cause). Patients were censored at cardiac surgery/transplantation or at the time of defibrillator/ventricular assist devices implantation. Procedures performed during follow-up were electronically identified using clinical notes and procedure codes. Occurrence and dates of death were retrieved using Accurint, a proprietary resource gathering multiple national sources. For

FIGURE 1 Distribution of Mitral Regurgitation EROA



Distribution of effective regurgitant orifice area (EROA) in patients with regurgitation in functional mitral regurgitation (FMR) **(upper-graph/red)** and degenerative mitral regurgitation (DMR) **(lower-graph/green)** mitral regurgitation. FMR displays markedly skewed distribution towards low EROA vs. DMR with exceptionally EROA ≥0.40 cm^2. MR = mitral regurgitation.

patients considered alive by Accurint assessment, last follow-up was marked 6 months earlier than the Accurint interrogation to account for any possible delay in recording of death events. To account for possible under-detection of censoring interventions, overall mortality was also analyzed as an alternate endpoint.

STATISTICAL ANALYSIS. Continuous variables were expressed as mean ± SD or median (interquartile range). Group comparisons were performed using analysis of variance with appropriate post hoc multiple comparisons. Trends were tested using the Cochran-Armitage trend test or regression analysis.

Logistic regression models assessed the odds ratio for 1-year mortality. Long-term survival rates were estimated using the Kaplan-Meier method and were compared using the log-rank test. Cox proportional hazards models were used to assess the association with FMR survival presented as HR (95% CI). The models were unadjusted and comprehensively adjusted for age, sex, EF, systolic blood pressure, dyspnea, and comorbidity index with nested models (compared using chi-square difference test) assessing incremental power attached to FMR measures/grading. Modeling used continuous variables covariates as such and was repeated with interaction terms as continuous variables. FMR and DMR survival rates were compared (using 1-sample log-rank) to age- and sex-specific expected survival (using census bureau life tables) and spline curves were built of excess mortality. Analyses were performed using JMP14, SAS9.4 (SAS Institute Inc) and R3.6.2 (R Foundation for Statistical Computing). A 2-tailed a priori alpha level of <0.05 was considered significant.

RESULTS

BASELINE CHARACTERISTICS. The cohort included 6,381 patients (age 70 ± 11 years; 31% women) with HFrEF (EF: 36 ± 10%) Stage B or C. The features found were typical for HFrEF (Table 1) and included frequent symptoms, history of hypertension, diabetes, coronary disease, atrial fibrillation, and considerable comorbidity burden with high Charlson comorbidity index. Medical treatment use was high and comparable to recent clinical trials.

TABLE 2 Cox Proportional Analysis for ERO Subgroup Models and ERO Continuous Increase[a]

	Long-Term Mortality Risk Under Medical Management							
	ERO Groups vs No FMR						ERO Continuous Increase vs No FMR	
Model	Expanded Grading, cm^2	HR (95% CI); *P* Value	ACC/AHA Grading, cm^2	HR (95% CI); *P* Value	ESC Grading, cm^2	HR (95% CI); *P* Value	Increase, cm^2	HR (95% CI); *P* Value
Unadjusted	0.01-0.09	1.28 (1.05-1.55); 0.01	0.01-0.19	1.39 (1.27-1.52); <0.0001	0.01-0.19	1.39 (0.27-1.52); <0.0001	Per 0.10	1.24 (1.20-1.27); <0.0001
	0.10-0.19	1.41 (1.29-1.55); <0.0001						
	0.20-0.29	1.69 (1.52-1.89); <0.0001	0.20-0.39	1.76 (1.60-1.94); <0.0001	≥0.20	1.86 (1.70-2.03); <0.0001		
	≥0.30	2.20 (1.93-2.51); <0.0001	≥0.40	2.77 (2.23-3.41); <0.0001				
Adjusted	0.01-0.09	1.08 (0.88-1.33); 0.40	0.01-0.19	1.09 (0.99-1.20); 0.07	0.01-0.10	1.09 (0.99-1.20); 0.07	Per 0.10	1.11 (1.08-1.15); <0.0001
	0.10-0.19	1.09 (0.98-1.21); 0.08						
	0.20-0.29	1.13 (1.01-1.27); 0.04	0.20-0.39	1.21 (1.09-1.34); 0.0005	≥0.20	1.27 (1.15-1.41); <0.0001		
	≥0.30	1.61 (1.40-1.86); <0.0001	≥0.40	2.00 (1.61-2.48); <0.0001				

[a]The endpoint is mortality under medical management. Adjusted model accounts for age, sex, ejection fraction, systolic blood pressure, dyspnea, and comorbidity index.
Abbreviations as in Table 1.

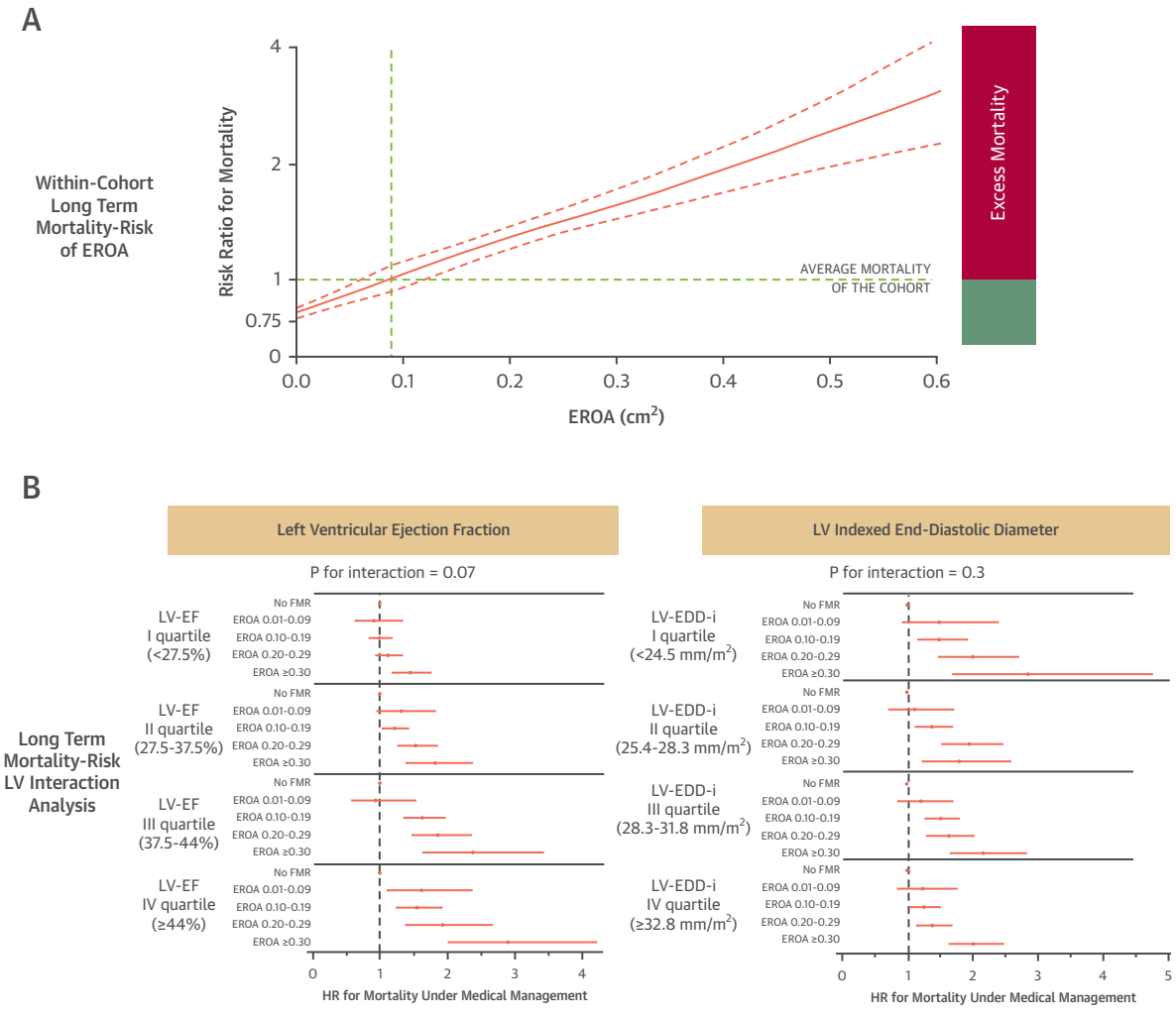
The EROA was 0.09 ± 0.13 cm^2 (0.22 ± 0.12 cm^2 in those with FMR) and RVol was 14 ± 19 mL (35 ± 16 mL in those with FMR) with EROA distribution shown in Figure 1. Only 3% of the entire cohort (8% of those with FMR) had EROA ≥0.40 cm^2, whereas lower EROA was much more frequent, so that 20% of FMR involved EROA ≥0.30 cm^2. Baseline characteristics according to U.S. guidelines-based quantitative subsets are presented Table 1. Although age, history of diabetes or coronary disease, and symptoms of angina or palpitations were similar between FMR quantitative grades, all other characteristics showed statistically significant differences; however, clinically relevant differences were limited. History of hypertension was less frequent with the largest FMR, which is possibly consistent with known lower blood pressure in this context. Important collinearities showed atrial fibrillation, comorbidity, and HFrEF severity increasing with FMR severity, with more dyspnea, larger ventricle, lower EF, lower stroke volume index, higher E/e', and pulmonary pressure (Table 1). Conversely, treatment use was also higher with larger FMR. Similar associations are noted with FMR stratified along an expanded quantitative grading (Supplemental Table 1).

A comparison of quantitative and integrative mitral regurgitation grading is indicated in Table 1. Although association was strong (gamma: 0.92 [95% CI: 0.90-0.94]), 42% of patients with EROA 0.20 cm^2 to 0.39 cm^2 were labelled "severe FMR" and 76% of EROA 0.01-0.19 were labelled "moderate FMR."

1-YEAR MORTALITY. During the first year post-diagnosis, 897 patients died under medical management, and 66 died after receiving mitral surgery, defibrillator, or left ventricular assist device/transplantation procedure. One-year mortality under medical management was high (15.6%) and increased with FMR-EROA from 13.3% (no FMR) to 15.4% with EROA 0.01 cm^2-0.19 cm^2 ranging from 13.7% with EROA 0.01 cm^2-0.09 cm^2 to 15.8% with EROA 0.10 cm^2-0.19 cm^2. With EROA ≥0.20 cm^2, 1-year mortality was 23.8%, stratifying at 21.4% for EROA 0.20 cm^2-0.39 cm^2, rising to 28.5% for EROA ≥0.30 cm^2 and 39.7% for EROA ≥0.40 cm^2. This sharp increase in short-term mortality is demonstrated with a spline curve of 1-year absolute mortality by EROA, showing 1-year mortality elevated in all EROA subsets which is steeply accelerating with higher EROA ranges (Supplemental Figure 1). The odds ratio for 1-year mortality with EROA ≥0.40 cm^2 versus no FMR was 2.58 (95% CI: 1.83-3.57) unadjusted $P < 0.0001$ and 1.64 (95% CI: 1.11-2.39) comprehensively adjusted $P = 0.01$. Odds ratios for EROA ≥0.30 cm^2 versus no FMR were 2.59 (95% CI: 2.03-3.30) unadjusted $P < 0.0001$ and 1.57 (95% CI: 1.19-2.97) comprehensively adjusted $P = 0.001$.

LONG-TERM MORTALITY. During a follow-up period of 4.1 years (1.1 years-7.1 years), 3,538 patients died, 3,124 of whom were under medical management. Absolute mortality was 39 ± 1% at 5 years and 64 ± 1% at 10 years with excess mortality versus expected

FIGURE 2 Mortality Within the FMR Cohort



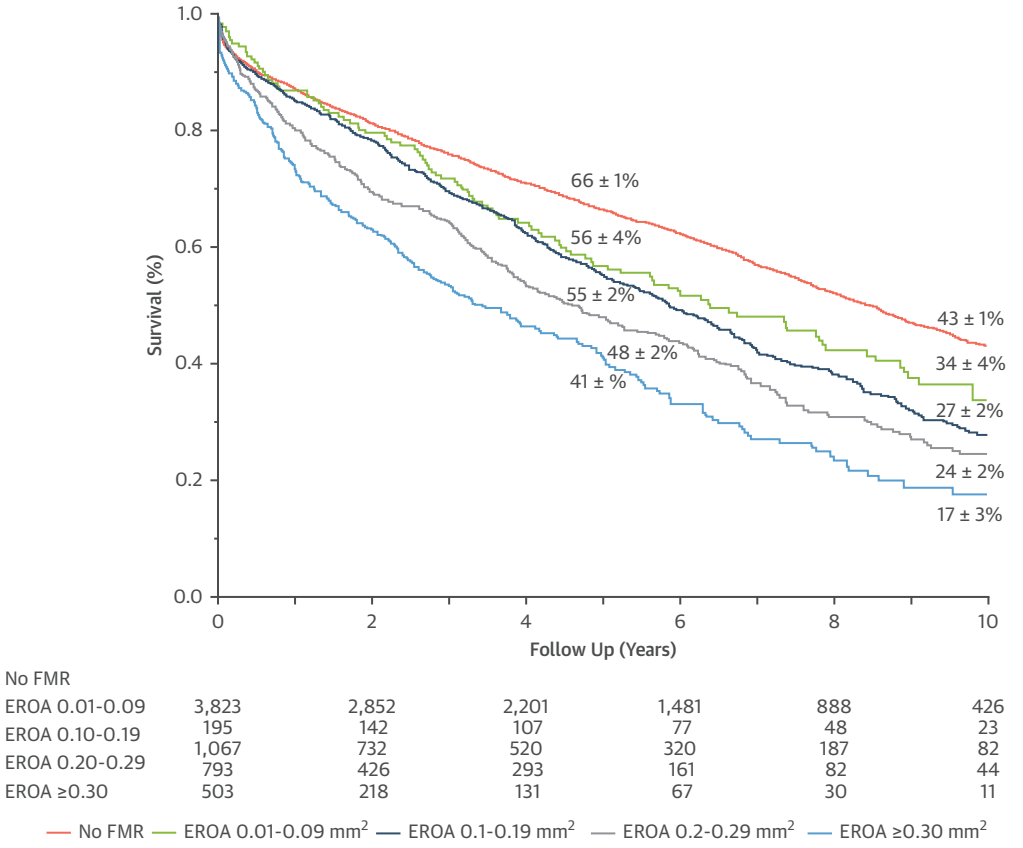
(A) Spline curve of mortality under medical management within FMR cohort. The dashed line showing a HR of 1 represents the average cohort mortality. Excess mortality (HR: >1) among FMR appears for low EROA ~0.10 cm^2, then increases steadily without plateau. **(B)** Interaction analysis of EROA with left ventricular (LV) characteristics for mortality risk under medical management. Patients are stratified according to ejection fraction (EF) **(left)** and LV dimension normalized to body surface area **(right)**. In each, cartouche HRs attached to expanded EROA ranges are indicated. Despite the large cohort size, no significant interaction is noted. EDD-i = end-diastolic diameter index; other abbreviations as in Figure 1.

mortality for a matched Minnesota population (risk ratio [RR]: 2.57 [95% CI: 2.48-2.67]; $P < 0.0001$).

During follow-up, cardiac surgery was performed in 502 patients with only 181 receiving mitral valve interventions (repair 57%, replacement 43%). Defibrillators were implanted in 864 patients, and interventions for imminent death (ventricular assist device or cardiac transplantation) were performed in 36 (<1%) patients.

In univariable and multivariable models (Table 2), EROA as a continuous variable was associated with increased hazards of mortality under medical management, with powerful chi-square similar to EF. The spline curve of mortality risk within the FMR cohort (RR: 1 represents average mortality of FMR cohort) versus EROA (continuous variable) shows excess mortality appearing around 0.1 cm^2 with steep increase thereafter with further EROA increments with no plateau (Figure 2). Consequent to continuous mortality increment with increasing EROA, univariable and multivariable survival analysis is presented Table 2 by American College of

FIGURE 3 **Survival of HFrEF by FMR EROA Strata**

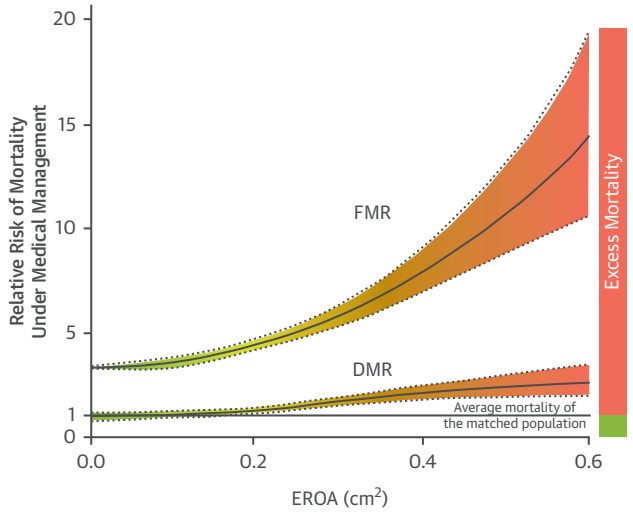


Kaplan-Meier curves showing survival under medical management stratified by expanded strata of FMR EROA. Each EROA increment is associated with marked mortality increase, appearing early and sustained through 5 y postdiagnosis. HFrEF = heart failure with reserved ejection fraction; other abbreviations as in **Figure 1**.

Cardiology (ACC)/American Heart Association (AHA) grades, European Society of Cardiology (ESC) grades (summarized in Supplemental Table 2) and by expanded grading based on EROA ranges. An EF mortality spline curve is provided for completeness (Supplemental Figure 2). All FMR quantitative stratifications were strongly associated with long-term mortality; however, with comprehensive adjustment, nested models showed that the expanded EROA FMR stratification provided incremental power over ACC/AHA stratification ($P = 0.03$) and over ESC stratification ($P = 0.0007$). Hence, survival after HFrEF diagnosis according to this expanded stratification is presented in **Figure 3** showing notable mortality even without FMR with markedly increasing mortality in all increasing EROA subsets: short-term and sustained up to 5-year and beyond. Survival after HFrEF diagnosis according to the ACC/AHA stratification (EROA 0 cm^2, 0.01 cm^2-0.19 cm^2, 0.20 cm^2-0.40 cm^2, and ≥40 cm^2) and by ESC stratification (EROA 0, 0.01-0.19, and ≥0.20 cm^2) are presented in Supplemental Figure 3.

In nested models, the addition of EROA as a continuous variable provides incremental model power over all 3 EROA FMR stratifications (all $P < 0.0001$) demonstrating the importance of reporting and considering in risk prediction and individual EROA values. Mitral integrative grading, regurgitant fraction, RVol, or ratio of EROA to estimated end-diastolic left ventricular volume univariately were also associated with long-term mortality, but in models including EROA they lost their association to increased mortality and displayed no interaction with EROA (all $P > 0.20$) as shown in Supplemental Table 3. In all models, EROA remained highly associated with

FIGURE 4 Spline Curves Linking EROA to Excess Mortality (Versus Matched Population) in FMR and DMR



Spline curves representing risk of long-term excess-mortality (vs expected mortality of the Minnesota general population specific for each cohort) according to EROA for FMR and DMR. A risk ratio of 1 represents long-term mortality equivalent to that expected in the Minnesota general population matched to FMR and DMR cohorts. In FMR, from 0 cm^2 0.10 cm^2 risk ratios >1 indicate excess mortality caused by the ventricular disease, with then sustained and exponentially steeper increase in risk with even modest EROA increases. Conversely, in DMR, excess mortality appears for higher EROA (~0.20 cm^2) and increases at a linear and slower pace. Abbreviations as in Figure 1.

excess mortality (all $P < 0.0001$), and in nested models it always improved the model's power (all $P < 0.0001$).

Association of EROA with mortality was unaffected by additional adjustment for mitral deceleration time (adjusted HR: 1.11 [95% CI: 1.06-1.15] per 0.1 cm^2; $P < 0.0001$), E/e' ratio (adjusted HR: 1.09 [95% CI: 1.05-1.13] per 0.1 cm^2; $P < 0.0001$), and left ventricular end-systolic (adjusted HR: 1.12 [95% CI: 1.08-1.16] per 0.1 cm^2; $P < 0.0001$) and end-diastolic (adjusted HR: 1.13 [95% CI: 1.09-1.16] per 0.1 cm^2; $P < 0.0001$) diameter-indexes (Supplemental Table 4).

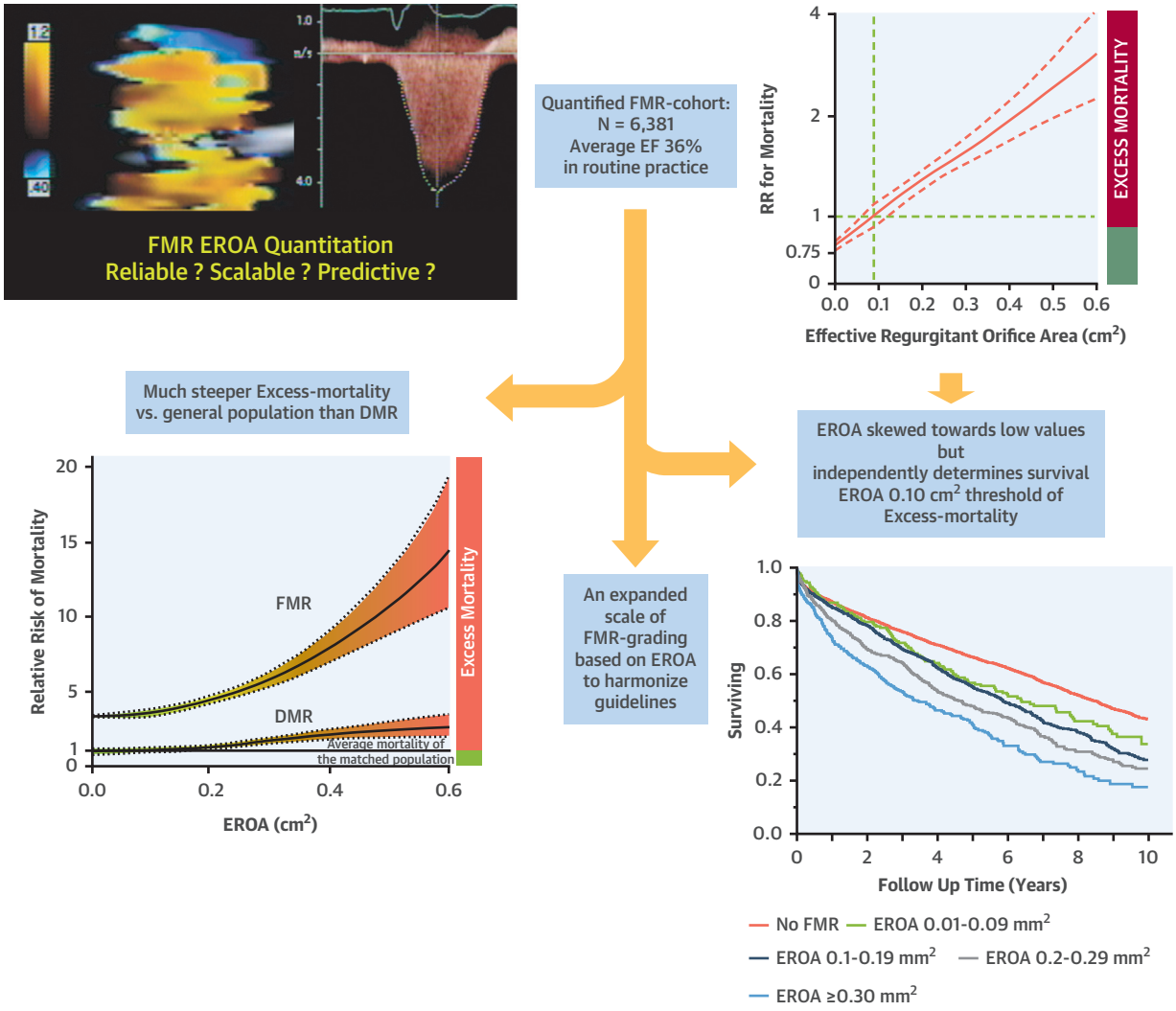
No interactions were noted with left ventricular size (both $P > 0.10$) and EF ($P = 0.07$) in age-/sex-adjusted models (Figure 2). Survival curves for left ventricular size or function subgroups stratified by FMR (EROA threshold 0.3 cm^2) are shown in Supplemental Figure 4. EROA impact on survival was unaffected by medications received (angiotensin-converting enzyme inhibitors/beta blockers/diuretics/spironolactone) and remained highly associated with excess mortality ($P < 0.0003$ for all). Subgroup analysis using Forrest plot (Supplemental Figure 5) shows stable mortality HRs of EROA in all subgroups. Additionally, severe right ventricular dysfunction/tricuspid regurgitation showed no interaction and sustained EROA prognostic value (HR for EROA 0.1 cm^2 increment: 1.10 [95% CI: 1.05-1.14]; P < 0.0001 adjusting for right-ventricular dysfunction, P for interaction 0.08; Hazard-ratio for EROA 0.1 cm^2 increment 1.10 [95% CI: 1.06-1.14]; P < 0.0001 adjusting for tricuspid regurgitation, P for interaction 0.7). Furthermore, results were stable using overall mortality (medical + postintervention) as endpoint (adjusted HR: 1.10 [95% CI: 1.07-1.13]; $P < 0.0001$ for EROA 0.1 cm^2 increment).

An essential analysis uses comparison of observed versus expected survival of the matched Minnesota population (Figure 4). In the HFrEF-cohort, excess-mortality was present even without FMR (RR 2.33 [95% CI: 2.21-2.44]; $P < 0.0001$); Excess-mortality steeply and exponentially increased with EROA, with RR 2.48 [95% CI: 2.30-2.68]; $P < 0.0001$ for EROA 0.01 cm^2-0.19 cm^2, with RR 3.33 [95% CI: 3.06-3.62]; $P < 0.0001$ for EROA 0.20 cm^2-0.39 cm^2 and with RR 8.06 [95% CI: 6.58-9.88]; $P < 0.0001$ for EROA ≥0.40 cm^2. Spline curve (Figure 4) relating excess mortality to EROA (continuous variable) is flat up to 0.10 cm^2, thereafter showing higher excess mortality with increasing EROA, steepening exponentially with EROA values ≥0.20 cm^2 emphasizing the importance of individual EROA values in estimating excess mortality risk. Spline curve analysis after matching for age and sex FMR versus DMR cohorts (N = 1,588 pairs) led to similar results (Supplemental Figure 6).

COMPARISON TO DMR. Within the study period, 2,416 patients were diagnosed with isolated, quantified DMR and identical eligibility criteria. The DMR cohort and the FMR cohort displayed expected considerable differences in characteristics (Supplemental Table 5) and outcome. EROA distribution was remarkably different, with much smaller proportion of patients with EROA ≥0.4 cm^2 in FMR versus DMR and skewed distribution towards low EROA in FMR (Figure 1). Hence, applying EROA ≥0.4 cm^2 criterion in HFrEF would yield only 3% (8% with regurgitation) of the FMR cohort versus 28% (38% with regurgitation) in the DMR cohort.

The most significant differences involve mortality after diagnosis. For 1-year mortality, spline curves as shown in Supplemental Figure 1 (absolute rates) under medical management according to EROA for FMR (upper curve) versus DMR (lower curve) show a steeper increase of mortality with EROA increments (P for slope <0.0001). Thus, the 1-year mortality increment between no-mitral regurgitation (MR) and

CENTRAL ILLUSTRATION **Outcome and Harmonized Grading of Functional Mitral Regurgitation Effective Regurgitation Orifice Area in Heart Failure With Reserved Ejection Fraction**



Benfari, G. et al. J Am Coll Cardiol Img. 2021;■(■):■–■.

(Top left) Example of effective regurgitant orifice area (EROA) measurement. **(Top right)** Spline curve of mortality under medical management within the heart failure with reserved ejection fraction cohort. Excess mortality (HR >1) appears for low EROA ~0.10 cm^2, then increases steadily with increasing EROA values without plateau. **(Lower right)** Survival under medical management stratified by expanded strata of EROA in functional mitral regurgitation (FMR). **(Lower left)** Spline curves representing excess mortality risk (vs expected mortality of the Minnesota general population specific for each cohort) according to EROA values for FMR and degenerative mitral regurgitation (DMR). A risk ratio of 1 represents mortality equivalent to that expected in Minnesota. FMR curve displays earlier rise with sustained and exponentially steeper increase in risk with even modest increases in EROA versus linear and slower pace in DMR.

EROA 0.20 cm^2-0.39 cm^2 was 8.1% in FMR versus 3.0% in DMR, and between no-MR and EROA ≥0.40 cm^2 it was 26.4% for FMR versus 10.8% for DMR. Long-term, spline curves of excess mortality versus the general population show much steeper increase in excess mortality with each EROA increment in FMR versus DMR, with curves of risk exponential for FMR versus linear for DMR (Figure 4). Hence, comparison of FMR to DMR shows very different entities, with widely different EROA distributions, whereby DMR severity criteria would apply to a tiny minority of FMR and also regarding MR-related excess mortality appearing for lower thresholds in FMR (0.10 cm^2 vs 0.20 cm^2) and increasing

much more steeply in FMR than DMR for short- and long-term mortality.

DISCUSSION

This study which extensively characterized consecutive HFrEF cohorts with uniform FMR quantitation performed in routine practice linked to clinical outcome provides novel insights (**Central Illustration**). FMR is frequently found in HFrEF, but with distribution skewed towards low EROA values. Despite these low values, FMR measured by EROA strongly determines excess mortality short- and long-term independently of all performed adjustments. These results indicate FMR quantitative severity as a strong and independent determinant of outcome. In view of previous methodological criticisms, it is also important that EROA could be measured in routine practice in a large number of patients and that this measure is highly predictive of survival. Excess mortality starts at low EROA (~0.1 cm^2), implying that FMR below this level is mild. Subsequent EROA increments are associated with a steep increase in excess mortality, becoming considerable before the US guidelines-based 0.40 cm^2 threshold. Furthermore, an expanded EROA FMR stratification based on the 0.1 cm^2 increment provides supplemental power for outcome prediction over current ACC/AHA/ESC-divergent recommendations. EROA impact on mortality is unaffected by interactions with left ventricular size or EF, despite considerable cohort power, so that modulating FMR grading based on these variables does not appear useful. EROA in FMR is radically different from DMR by its lower and skewed distribution, but most importantly by yielding excess mortality at lower EROA values and with much steeper, exponential risk increase for any EROA increment. These new findings warrant reporting patients' EROA of FMR consistently in routine practice for individualized risk assessment and clinical decision-making, and warrant harmonizing guidelines along a unified, expanded FMR grading scale.

THE DEBATED FMR OUTCOME. Considerable doubts surround FMR's (a consequence of the ventricular disease) causality link to the HFrEF outcome (the ventricular disease). FMR improvement with medical treatment, divergent data on outcome, and negative surgical observational series and trials have suggested that FMR may be a surrogate of the ventricular disease or of other determinants of survival (7-10,12,30). Even in positive quantitative outcome studies, an FMR low volume of regurgitation caused uncertainty (4-6). According to ACC/AHA guidelines, FMR would be quantified as mild or at most moderate, raising concerns that collinear alterations may be responsible for poor outcome and not FMR itself. Conversely, dose effect between FMR volume/orifice and worse outcome and positive COAPT trial reporting that FMR treatment yielded marked reduction in heart failure incidence, transplantation requirements, and mortality were highly suggestive that FMR, in and by itself, is the determinant of excess mortality (7,13). However, discordance between positive COAPT and negative Mitra-FR trials left unresolved issues emphasizing the importance of defining risks attached to FMR ranges of severity (13,14). This risk characterization, undefinable by clinical trials, requires analysis of large and comprehensive cohorts because modestly sized series cannot address multiple collinearities. Furthermore, previous series and reviews suggesting various combinations of EROA with other factors (left ventricular volume, regurgitant fraction, EF) to modulate FMR grading generated confusion (18,20,31). In that regard, our cohort provides important clarifications. Despite considerable size/power, none of these interactions were of significance. FMR impacts outcome, without detectable interaction, independently of all possible confounders, and the EROA remains the most powerful FMR measure linked to outcome (although all FMR measures/grading are univariately linked to mortality). The singular power of larger EROA for poor outcome is linked to larger regurgitant volume but also to increased potential energy in atria of reduced compliance translating into higher atrial pressure, which explains the strong linkage of larger EROA to higher heart failure incidence (7,32).

Defining FMR risks is achieved using EROA measured by standard Doppler echocardiography in routine practice. Cases with FMR and EROA <0.10 cm^2 who do not incur FMR-related excess mortality (only low-EF risk) qualify as mild FMR. Between 0.10 and 0.20 cm^2 excess mortality appears and remains moderate. Greater than 0.2 cm^2 FMR consequences are significant, and such patients were enrolled in both FMR clinical trials, whereas patients with EROA ≥0.30 cm^2 display severe excess mortality (13,14). Thus, an expanded EROA-based FMR grading based on 0.10 cm^2 increments separates very distinctly survival of patients after diagnosis and is superior to that of AHA/ACC and ESC guidelines. Importantly, EROA individualized values provide incremental prognostic information shown by nested models, spline curves and by the fact that patients with EROA ≥0.40 cm^2, rarely encountered, incur considerable mortality very short-term. Therefore,

our present cohort defines risks attached to discreet EROA values and allows consideration for therapy, depending on safety/efficacy. This point is crucial to address generalized considerable FMR undertreatment (3).

CHALLENGING FMR ASSESSMENT. FMR quantitation concerns have been voiced, relating to orifice shape, flow dynamics, and scalability from experts to reliable routine practice (15-17). However, comparative methods carry their own limitations. Previous modestly sized studies combined with the present large cohort show a strong independent link to excess mortality, overall dispelling these reliability concerns (4-7,18,33). Furthermore, the present study shows FMR quantitation scalability to routine clinical practice of wide arrays of technicians/cardiologists in our institution. Although no measurement method is perfect, this considerable predictive power underscores the robustness of FMR Doppler echocardiographic measures.

Our study, the first to compare FMR and DMR in parallel analyses, also shows that EROA should be interpreted in MR causal context. FMR is characterized by low regurgitation volume, much lower than DMR. Is such a low volume an underestimation by the methods used? This is unlikely, as older studies measuring ventricular volumes and more recent trials show that total left ventricular stroke volume of FMR is small, implying an obligatory small regurgitant volume (13,14,34). Low-volume regurgitation is also secondary to reduced left atrial compliance tending to equalize ventricular and atrial pressure, reducing the driving force of regurgitation (31,35). Similarly, although EROA is smaller in FMR than DMR with distribution skewed towards low values, it nevertheless has profound outcome implications for excess mortality. Spline curves show steep mortality increase with any EROA increment, much steeper than for DMR, even considering higher background mortality in HFrEF. Therefore, EROA and RVol values must be interpreted in context of the causal disease. Differing interpretation of pathophysiological measures depending on clinical context is not new (eg, serum creatinine interpreted by sex and body mass). Thus, separating volumetric overload assessment (ie, is MR voluminous?) from outcome severity interpretation (ie, is MR associated with excess mortality?) appears reasonable. For example, EROA of 0.15 cm^2, benign in DMR, denotes excess mortality in FMR. Because the impact on clinical outcome fundamentally guides therapeutic attention (medical, interventional, or surgical), the framework of EROA interpretation must differ in FMR and DMR. Although EROA dominates clinical interpretation of FMR severity, no value should be accepted blindly. Careful analysis of all signs/measures is warranted to judge whether these are acceptable or require verification. Unfortunately, in FMR, these signs may be defective because left atrial enlargement has many causes, pulmonary venous flow rarely shows systolic reversals, and diastolic inflows are affected by diastolic ventricular dysfunction. Furthermore, FMR mechanisms such as localized aneurysms may cause persistence postrepair (36). This underscores the importance of careful FMR quantitation, which in routine practice can be powerfully connected to subsequent outcome, as achieved in our practice.

STUDY LIMITATIONS. Our cohort was not prospectively enrolled with protocolized care but identified retrospectively in a single referral center. However, all measurements were performed prospectively at diagnosis, unaltered for analysis, and patients were treated by their personal physicians based on these values. Hence, our cohorts are highly representative of routine clinical practice. It is also not a clinical trial and cannot report effectiveness of therapies. Conversely, the present considerable cohorts optimally define risks incurred by patients with HFrEF and links those independently to FMR. Comparison to the Minnesota population for assessing excess mortality, justified by regional patients' predominance, has also proved its value versus national valve diseases assessment (1). Furthermore, analyzing cohort relevance shows remarkable similarity with the COAPT trial (13). Patients with EROA ≥ 0.30 cm^2 in the present study (n = 503) versus COAPT had age 72 ± 10 years versus 73 ± 7 years; $P = 0.2$, EROA: 0.40 ± 0.10 cm^2 versus 0.41 ± 0.15 cm^2; $P = 0.2$ with minimal difference in EF of $29 \pm 11\%$ versus $31 \pm 10\%$; $P = 0.01$, and comparable survival rates in medically treated patients (29% vs. 31% at 2 years) underscoring our cohort's relevance. Additional strengths and limitations of the study are reported in the Supplemental Appendix.

CONCLUSIONS

This large and extensively characterized HFrEF cohort with uniform FMR quantitation in routine practice provides new insights. First, FMR is frequently found but skewed towards low EROA values. Most importantly, FMR quantified by EROA in routine practice strongly and independently determines excess mortality starting at EROA 0.1 cm^2 with each EROA increment associated with a

considerable excess mortality increment, increasing steeply before and through the US guideline-based threshold of 0.40 cm^2. EROA impact on mortality is unaffected by interactions; therefore, modulating FMR grading based on purported interactions is not justified. FMR is radically different from DMR in its skewed regurgitation distribution yielding excess mortality at lower EROA values and exponential risk increase for any EROA increment. These new findings warrant reporting patients' EROA of FMR consistently in routine practice, and warrant harmonizing guidelines along a unified FMR expanded grading scale.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

All contributors have been listed as coauthors. This work was supported by the Mayo Research Foundation. Dr Enriquez-Sarano received consulting fees from Edwards LLC, Mardil Inc, and Cryolife Inc All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Enriquez-Sarano, Department of Cardiovascular Diseases, Mayo Clinic College of Medicine, 200 First Street SW, Rochester, Minnesota 55905, USA. E-mail: sarano.maurice@gmail.com.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: FMR quantitation is indispensable, and EROA, powerfully linked to excess mortality in routine practice, should be measured and reported. An expanded EROA-based FMR grading allows the harmonization of current recommendations.

TRANSLATIONAL OUTLOOK: New clinical trials testing the benefit of FMR therapies in each EROA strata are warranted.

REFERENCES

1. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet*. 2006;368:1005-1011.

2. d'Arcy JL, Coffey S, Loudon MA, et al. Large-scale community echocardiographic screening reveals a major burden of undiagnosed valvular heart disease in older people: the OxVALVE Population Cohort Study. *Eur Heart J*. 2016;37:3515-3522.

3. Dziadzko V, Dziadzko M, Medina-Inojosa JR, et al. Causes and mechanisms of isolated mitral regurgitation in the community: clinical context and outcome. *Eur Heart J*. 2019;40:2194-2202.

4. Grigioni F, Enriquez-Sarano M, Zehr K, Bailey K, Tajik A. Ischemic mitral regurgitation: long-term outcome and prognostic implications with quantitative Doppler assessment. *Circulation*. 2001;103:1759-1764.

5. Rossi A, Dini FL, Faggiano P, et al. Independent prognostic value of functional mitral regurgitation in patients with heart failure. A quantitative analysis of 1256 patients with ischaemic and non-ischaemic dilated cardiomyopathy. *Heart*. 2011;97:1675-1680.

6. Lancellotti P, Gerard PL, Pierard LA. Long-term outcome of patients with heart failure and dynamic functional mitral regurgitation. *Eur Heart J*. 2005;26:1528-1532.

7. Grigioni F, Detaint D, Avierinos JF, Scott C, Tajik J, Enriquez-Sarano M. Contribution of ischemic mitral regurgitation to congestive heart failure after myocardial infarction. *J Am Coll Cardiol*. 2005;45:260-267.

8. Patel JB, Borgeson DD, Barnes ME, Rihal CS, Daly RC, Redfield MM. Mitral regurgitation in patients with advanced systolic heart failure. *J Card Fail*. 2004;10:285-291.

9. Stevenson L, Brunken R, Belil D, et al. Afterload reduction with vasodilators and diuretics decreases mitral regurgitation during upright exercise in advanced heart failure. *J Am Coll Cardiol*. 1990;15:174-180.

10. Wu AH, Aaronson KD, Bolling SF, Pagani FD, Welch K, Koelling TM. Impact of mitral valve annuloplasty on mortality risk in patients with mitral regurgitation and left ventricular systolic dysfunction. *J Am Coll Cardiol*. 2005;45:381-387.

11. Chan KM, Punjabi PP, Flather M, et al. Coronary artery bypass surgery with or without mitral valve annuloplasty in moderate functional ischemic mitral regurgitation: final results of the Randomized Ischemic Mitral Evaluation (RIME) trial. *Circulation*. 2012;126:2502-2510.

12. Smith PK, Puskas JD, Ascheim DD, et al. Surgical treatment of moderate ischemic mitral regurgitation. *N Engl J Med*. 2014;371:2178-2188.

13. Stone GW, Lindenfeld JA, Abraham WT, et al. transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med*. 2018;379:2307-2318.

14. Obadia JF, Messika-Zeitoun D, Leurent G, et al. Percutaneous repair or medical treatment for secondary mitral regurgitation. *N Engl J Med*. 2018;379:2297-2306.

15. Zeng X, Levine RA, Hua L, et al. Diagnostic value of vena contracta area in the quantification of mitral regurgitation severity by color Doppler 3D echocardiography. *Circ Cardiovasc Imaging*. 2011;4:506-513.

16. Yosefy C, Levine RA, Solis J, Vaturi M, Handschumacher MD, Hung J. Proximal flow convergence region as assessed by real-time 3-dimensional echocardiography: challenging the hemispheric assumption. *J Am Soc Echocardiogr*. 2007;20:389-396.

17. Biner S, Rafique A, Rafii F, et al. Reproducibility of proximal isovelocity surface area, vena contracta, and regurgitant jet area for assessment of mitral regurgitation severity. *J Am Coll Cardiol Img*. 2010;3:235-243.

18. Bartko PE, Arfsten H, Heitzinger G, et al. A unifying concept for the quantitative assessment of secondary mitral regurgitation. *J Am Coll Cardiol*. 2019;73:2506-2517.

19. Bartko PE, Hulsmann M, Goliasch G. Quantitative definition of severe functional mitral regurgitation. *J Am Coll Cardiol*. 2018;72:2934-2935.

20. Goliasch G, Bartko PE, Pavo N, et al. Refining the prognostic impact of functional mitral regurgitation in chronic heart failure. *Eur Heart J*. 2018;39:39-46.

21. Grayburn PA, Carabello B, Hung J, et al. Defining "severe" secondary mitral regurgitation: emphasizing an integrated approach. *J Am Coll Cardiol*. 2014;64:2792-2801.

22. Lancellotti P, Moura L, Pierard LA, et al. European Association of Echocardiography recommendations for the assessment of valvular regurgitation. Part 2: mitral and tricuspid regurgitation (native valve disease). *Eur J Echocardiogr*. 2010;11:307-332.

23. Zoghbi WA, Enriquez-Sarano M, Foster E, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr*. 2003;16:777-802.

24. Vahanian A, Alfieri O, Andreotti F, et al. Guidelines on the management of valvular heart disease (version 2012). *Eur Heart J*. 2012;33:2451-2496.

25. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of

patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129:e521–e643.

26. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J*. 2017;38:2739–2791.

27. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2017;70:252–289.

28. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2021;143:e35–e71.

29. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr*. 2005;18:1440–1463.

30. Acker MA, Parides MK, Perrault LP, et al. Mitral-valve repair versus replacement for severe ischemic mitral regurgitation. *N Engl J Med*. 2014;370:23–32.

31. Grayburn PA, Sannino A, Packer M. Proportionate and disproportionate functional mitral regurgitation: a new conceptual framework that reconciles the results of the MITRA-FR and COAPT trials. *J Am Coll Cardiol Img*. 2019;12:353–362.

32. MacIsaac AI, McDonald IG, Kirsner RL, Graham SA, Tanzer D. Left ventricular energy in mitral regurgitation: a preliminary report. *Aust N Z J Med*. 1992;22:532–540.

33. Mele D, Vandervoort P, Palacios I, et al. Proximal jet size by Doppler color flow mapping predicts severity of mitral regurgitation. *Circulation*. 1995;91:746–754.

34. Enriquez-Sarano M, Michelena HI, Grigioni F. Treatment of functional mitral regurgitation. *Circulation*. 2019;139:2289–2291.

35. Benfari G, Essayagh B, Nistri S, et al. Left atrial volumetric/mechanical coupling index: a novel predictor of outcome in heart failure with reduced ejection fraction. *Circ Cardiovasc Imaging*. 2021;14, e011608.

36. Kron IL, Hung J, Overbey JR, et al. Predicting recurrent mitral regurgitation after mitral valve repair for severe ischemic mitral regurgitation. *J Thorac Cardiovasc Surg*. 2015;149:752–761 e1.

KEY WORDS **Doppler-echocardiography, functional mitral regurgitation, prognosis, ventricular dysfunction**

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