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The Natural History of Atrial Functional Mitral Regurgitation

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ABSTRACT

BACKGROUND The natural history of moderate/severe atrial functional mitral regurgitation (AFMR) is unknown.

OBJECTIVES The authors sought to study the incidence of left ventricular (LV) systolic dysfunction (LVSD), progression or regression of ≥mild-moderate AFMR, and impact on mortality.

METHODS Adults with left atrial (LA) volume index ≥40 mL/m^2, ≥mild-moderate AFMR, and follow-up echocardiogram were followed for incident LVSD (ejection fraction <50% and ≥10% lower than baseline), progression of mild-moderate/moderate AFMR to severe, and persistent regression of AFMR to no/trivial. Relation of AFMR progression or regression as time-dependent covariates with all-cause mortality was studied. Incidence of LVSD was compared with patients with no/mild AFMR matched on age, sex, comorbidities and ejection fraction. Patients were followed until mitral intervention, myocardial infarction, or last follow-up.

RESULTS A total of 635 patients (median age 75 years, 51% female, 96% mild-moderate/moderate AFMR, 4% severe AFMR) were included. Over a median 2.2 years (Q1-Q3: 1.0-4.3 years), incidence rates per 100 person-years were 3.2 for LVSD ($P = 0.52$ vs patients with no/mild AFMR), 1.9 for progression of AFMR, and 3.9 for regression. Female sex and larger LA volume index were independently associated with progression, whereas younger age, male sex, absent atrial fibrillation, and higher LA emptying fraction were independently associated with regression. Neither AFMR progression nor regression was independently associated with mortality. Instead, independent risk factors for mortality included older age, concentric LV geometry, and higher estimated LV filling and pulmonary pressures.

CONCLUSIONS In patients with predominantly mild-moderate/moderate AFMR, regression of MR was more common than progression, but neither was associated with mortality. Instead, diastolic function abnormalities were more important. Over a median 2-year follow-up, LVSD risk was not increased. (J Am Coll Cardiol 2024;■:■-■)

Atrial functional mitral regurgitation (AFMR) constitutes one-quarter of cases of ≥moderate MR in the community[1] and develops in the setting of mitral annular dilation and left atrial (LA) enlargement but relatively preserved left ventricular (LV) size and systolic function. Recent studies have characterized the prevalence, incidence, and risk factors of AFMR, which included older age, female sex, atrial fibrillation (AF), and diastolic dysfunction.[2,3] The presence of AFMR is associated with increased mortality, even when mild,[1-3] and rhythm control of AF is associated with both a decreased risk of incident AFMR and regression of established AFMR.[2,4,5] However, detailed understanding of the natural history of AFMR including progression and regression rates is lacking. Furthermore, primary MR causes LV volume overload resulting in LV enlargement and, eventually, LV systolic

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

AFMR = atrial functional mitral regurgitation

EF = ejection fraction

HFpEF = heart failure with preserved ejection fraction

ICD = International Classification of Diseases

LA = left atrial

LAEF = left atrial emptying fraction

LAVI = left atrial volume index

LV = left ventricular

LVSD = left ventricular systolic dysfunction

PISA = proximal isovelocity surface area

TR = tricuspid regurgitation

TTE = transthoracic echocardiogram

dysfunction (LVSD).[6] To our knowledge, no study has estimated the extent to which LVSD develops in the setting of AFMR.

In this study, we aimed to: 1) characterize incidence of new-onset LVSD in patients with mild-moderate, moderate, or severe AFMR compared with patients with mild or no AFMR; 2) investigate progression and regression rates of ≥mild-moderate AFMR and associated risk factors; 3) analyze echocardiographic changes associated with progression or regression of AFMR; and 4) study the impact of progression and regression of AFMR on all-cause mortality.

METHODS

STUDY POPULATION. The study was approved by the Mayo Clinic Institutional Review Board. The main study cohort constituted of consecutive adults with documented LA volume index (LAVI) ≥40 mL/m^2 and ≥mild-moderate MR on a transthoracic echocardiogram (TTE) performed between 2010 and 2021, identified retrospectively. Patients who had current/previous low ejection fraction (EF) <50%, >mild LV enlargement (LV end-systolic dimension >38 mm in women and >43 mm in men or end-diastolic dimension >56 mm in women and >63 mm in men[7]), regional wall motion abnormalities, primary mitral disease, rheumatic, radiation, or carcinoid heart disease, hypertrophic/infiltrative cardiomyopathy, congenital heart disease, systemic lupus erythematosus, previous cardiac procedures, ≥moderate aortic stenosis/regurgitation, or no follow-up TTE were excluded (Figure 1). Reports of all available transesophageal echocardiograms were also reviewed to exclude primary mitral valve disease. Baseline TTE was defined as first TTE with LAVI ≥40 mL/m^2 and ≥mild-moderate AFMR in the study period.

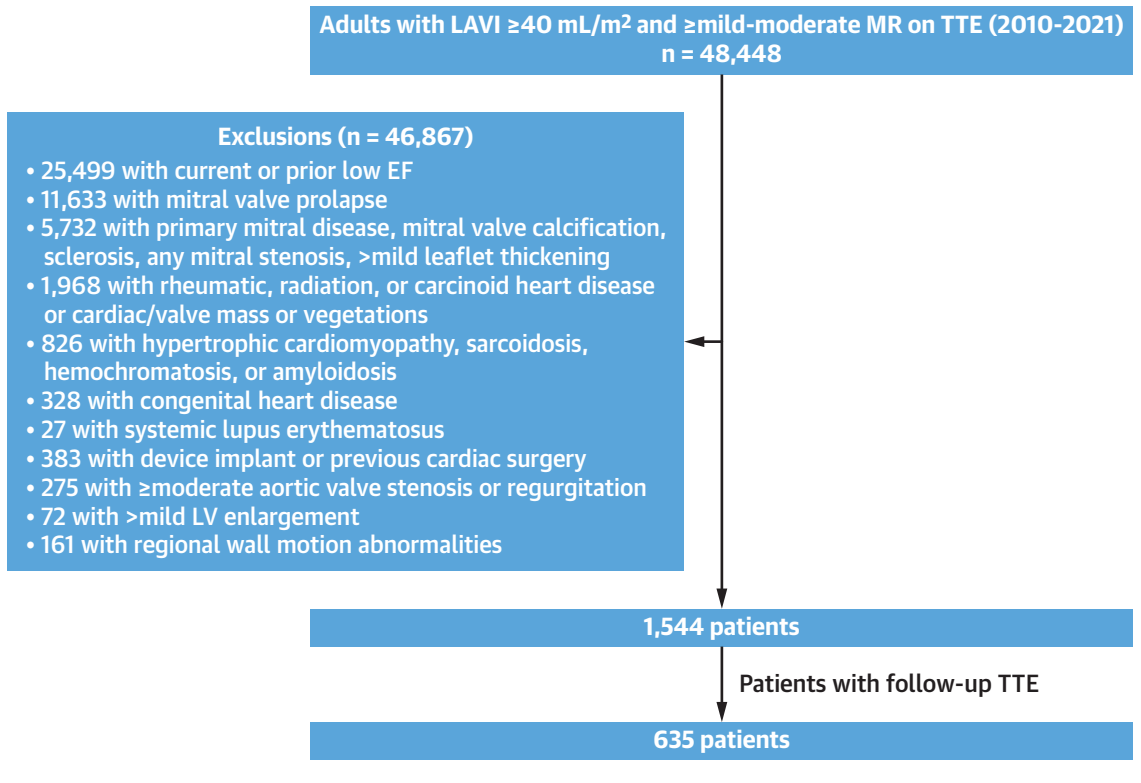
COMPARISON GROUP WITHOUT SIGNIFICANT AFMR. A comparison group of patients with LAVI ≥40 mL/m^2 and no/mild AFMR between 2010 and 2021 with otherwise identical inclusion criteria to the main cohort were identified. The main purpose of this comparison group was to provide a reference for incidence of LVSD in patients without significant AFMR (see later in the text).

DEFINITIONS. AFMR was defined as functional MR meeting all the following criteria: EF ≥50%; the absence of >mild LV enlargement; LAVI ≥40 mL/m^2; and dilated mitral annulus (systolic anteroposterior diameter ≥35 mm).[8] Comorbidities including sleep apnea, coronary artery disease, chronic kidney disease, chronic lung disease, diabetes mellitus, hypertension, ischemic strokes, and transient ischemic attacks were extracted using the International Classification of Diseases (ICD) codes. AF was identified using ICD codes, electrocardiograms, echocardiograms (rhythm recorded by cardiologists during the study), and continuous cardiac monitoring. AF was classified as paroxysmal if there was evidence of spontaneous conversion to sinus rhythm and persistent otherwise. Rhythm control of AF included successful catheter ablation, cardioversion, or use of antiarrhythmic medications for ≥30 days. Heart failure with preserved ejection fraction (HFpEF) was defined using: 1) Framingham criteria identified by manual examination of the electronic medical records; 2) ICD codes; or 3) a diagnosis assessed by a board-certified cardiologist, as indicated in the clinical notes. In all these cases, EF was preserved ≥50%.

PROBABILITY OF HFpEF USING THE CONTINUOUS H_2FPEF SCORE. To estimate the probability of HFpEF, the H_2FPEF continuous score was calculated in the study population as previously described.[9,10]

ECHOCARDIOGRAPHY. All TTEs were performed in routine clinical practice by trained sonographers and reviewed by level III board-certified echocardiologists, according to the guidelines.[11] Chamber size measurements were performed according to guidelines.[7] Mitral annulus dilation was assessed using the systolic anteroposterior diameter measured in the parasternal long-axis view using 2-dimensional imaging. LVEF measured using the biplane method was used when possible. When not available, the linear measurement was used. LA volume was measured using the biplane disk summation method at end-systole for maximum LA volume and at end-diastole for minimum LA volume. Left atrial emptying fraction (LAEF) was then calculated by subtracting the 2 measurements and dividing by LA maximum size. MR severity was graded using an integrative approach with both qualitative (color Doppler flow mapping including proximal flow convergence, vena contracta width, jet/LA ratio, jet density and contour on continuous Doppler, pulmonary vein systolic reversal) and quantitative (proximal isovelocity surface area [PISA], as available) assessments and was classified as mild-moderate, moderate, or severe, according to guidelines.[12] Mild-moderate MR was considered when at least 2 criteria arguing against mild MR existed (eg, vena contracta >3 mm, a dense/complete jet on continuous wave Doppler, medium-sized jet), and in cases when PISA was performed, when measurements were discordant between mild

FIGURE 1 Study Population Overview



Among 48,448 patients with left atrial volume index (LAVI) ≥40 mL/m² and ≥mild-moderate mitral regurgitation (MR) between 2010 and 2021, 635 patients met the final inclusion criteria. See text for more details. EF = ejection fraction; LV = left ventricle; TTE = transthoracic echocardiography.

and moderate. Therefore, these cases remained indeterminate between mild and moderate.

Interobserver agreement for the systolic anteroposterior diameter of the mitral annulus, maximum LA volume, and minimum LA volume was assessed using the intraclass correlation coefficient in a random 10-patient-sample.

FOLLOW-UP. Patients were followed using all available TTEs until last follow-up under conservative management (ie, before mitral valve intervention) and before myocardial infarction to avoid including ventricular functional MR. The primary outcomes were: 1) LVSD, defined as decrease in EF to <50% and an absolute decrease of ≥10% from baseline; 2) progression of AFMR from mild-moderate/moderate to severe; and 3) regression of AFMR, defined as persistent decrease of AFMR to no/trivial grade without reincrease until last available follow-up. In evaluation of LVSD, the same EF measurement approach was considered both at baseline and follow-up (ie, if only linear measurement-based EF was available at follow-up, the linear measurement EF was compared at baseline in the same patient).

Additional secondary endpoints included persistent regression of ≥moderate AFMR to ≤mild and all-cause mortality in relation to progression or regression of AFMR. In analysis of all-cause mortality, patients with malignancy (other than basal cell carcinoma and squamous cell carcinoma of the skin) were excluded.

STATISTICAL ANALYSIS. Statistical analyses were performed with JMP Pro software version 16.2.0 (SAS Institute) and R version 4.2.2 (R Foundation for Statistical Computing). Two-sided P values <0.05 were considered significant. Continuous variables are reported as median (Q1-Q3) and categorical variables as number (percentage). Baseline characteristics were compared using the Student's t-test or the Wilcoxon test for continuous variables, as appropriate, and the chi-square test or the Fisher exact test for categorical variables. Incidence rates were calculated by dividing the number of events by total follow-up time until the

TABLE 1 Baseline Characteristics of the Study Cohort With ≥Mild-Moderate AFMR Compared With Matched Patients With No or Mild AFMR

	≥Mild-Moderate AFMR (n = 635)	Mild or No AFMR (n = 1,905)	*P* Value
Age, y	75 (66-81)	74 (66-81)	0.62
Female	321 (51)	922 (48)	0.37
BMI, kg/m^2	27.4 (23.9-31.6)	27.7 (24.4-31.6)	0.79
Sleep apnea	114 (18)	347 (18)	0.93
Coronary artery disease	163 (26)	478 (25)	0.81
HFpEF	168 (28)	509 (27)	0.63
Chronic kidney disease	163 (26)	464 (24)	0.54
Chronic lung disease	75 (12)	222 (12)	0.97
Diabetes mellitus	191 (30)	570 (30)	0.98
Hypertension	439 (69)	1,293 (68)	0.59
Nonskin cancer	179 (28)	499 (26)	0.33
History of ischemic stroke	36 (6)	116 (6)	0.77
History of TIA	46 (7)	141 (7)	0.97
Atrial fibrillation	382 (60)	1140 (60)	0.94
Ejection fraction, %	62 (58-65)	62 (58-65)	0.67

Values are median (Q1-Q3) or n (%).

AFMR = atrial functional mitral regurgitation; BMI = body mass index; HFpEF = heart failure with preserved ejection fraction; TIA = transient ischemic attack.

event of interest or until patients were censored. Patients were censored at last follow-up if they did not experience the event of interest (last TTE for progression or regression of AFMR and LVSD; last clinical follow-up for mortality), at the time of mitral valve intervention, or at the time of myocardial infarction if occurred, whichever was earliest.

To evaluate whether ≥mild-moderate AFMR is independently associated with development of LVSD, we compared the incidence of LVSD in patients with ≥mild-moderate AFMR to that in propensity-matched patients with mild or no AFMR from the comparison group described earlier in the text using Kaplan-Meier survival analysis. The propensity score was estimated using logistic regression (generalized linear method [glm] in the 'MatchIt' package in R using greedy nearest neighbor matching) based on age, sex, body mass index, comorbidities, baseline EF, and years of follow-up, and was used to match patients with ≥mild-moderate AFMR in a 1:3 ratio to patients with ≤mild AFMR. The median matching distance was 0.10 (Q1-Q3: 0.05-0.16). Cox proportional hazards regression was used to identify factors associated with progression of AFMR, regression of AFMR, and all-cause mortality. The proportional hazards assumption was tested using the cox.zph() function from the 'survival' package in R. Time-dependent covariate analysis was used to study the association between regression and progression of AFMR with all-cause mortality, to study the association between AF at baseline or follow-up (and whether it was persistent or paroxysmal) with outcomes, and to study the association of rhythm control with regression of AFMR. In multivariable analysis, factors entered into the model were chosen based on knowledge of the a priori relationships with AFMR or mortality, and backward elimination was used until an average of ~10 events per variable was achieved to avoid overfitting. Complete case analysis was performed when missing values existed. Variables with >20% missing values were not considered.

A mixed effect linear model was used to compare changes in echocardiographic parameters between patients with and without progression (or regression) of AFMR using baseline and last follow-up TTEs (ie, at time of event if occurred or when patients were censored). This analysis was performed using the lme function from the 'lme4' package in R, and the estimated annual change along with 95% CIs were reported.

RESULTS

INCIDENT LVSD. Overall, 635 patients met the eligibility criteria and were included. Median age was 75 years (Q1-Q3: 66-81 years), 51% were women, 75% had mild-moderate AFMR, 21% had moderate, 4% had severe AFMR, and 60% had AF, which was persistent in 60% of cases. Baseline demographics and echocardiographic characteristics are presented in Tables 1 and 2. HFpEF was present in 168 patients (28%). In 458 patients without an established diagnosis of HFpEF at baseline, 130 patients developed incident HFpEF over a median 3.0 years (Q1-Q3: 1.4-5.7 years) (7.4 per 100 person-years). Interestingly, the median continuous H_2FPEF score was 90% (Q1-Q3: 72%-96%) at baseline, and 50% of patients had a H_2FPEF score ≥90%, indicating high-risk of masked HFpEF.

These patients had a mean 2.3 ± 2.0 follow-up TTEs. LVSD developed in 60 of 635 patients over a median 2.2 years (Q1-Q3: 1.0-4.3 years) with incidence rate of 3.2 per 100 person-years. When stratifying by severity of AFMR, LVSD occurred in 58 of 610 patients with mild-moderate/moderate AFMR over a median 2.2 years (Q1-Q3: 1.0-4.2 years) (3.2 per 100 person-years) and in 2 of 25 patients with severe AFMR over a median 1.2 years (Q1-Q3: 0.5-4.9 years) (3.0 per 100 person-years; P = 0.95 vs mild-moderate/moderate AFMR).

Matched patients with no/mild AFMR had a mean 2.2 ± 1.9 follow-up TTEs (Table 1). Incident LVSD developed in 197 of 1,905 patients with no/mild AFMR over a median 2.3 years (Q1-Q3: 1.0-4.3 years) with similar incidence rate of 3.5 per 100 person-years (log-rank P = 0.52) (Central Illustration). In these

patients with no/mild AFMR, mild AFMR was present in 741 patients (39%) (Table 1).

PROGRESSION OF AFMR. Overall, 595 patients with mild-moderate/moderate AFMR had follow-up with assessment for MR severity before mitral valve intervention or myocardial infarction events (Table 3). Progression to severe MR occurred in 36 patients over a median 2.5 years (Q1-Q3: 1.1-4.6 years) (1.9 per 100 person-years). Absolute change in systolic or diastolic blood pressure at time of the follow-up TTE compared with baseline TTE was not different between patients with and without AFMR progression ($P = 0.48$ and $P = 0.93$, respectively). Furthermore, none of the progression events happened during a hospitalization for acute heart failure.

Factors associated with progression of AFMR are shown in Table 3. Independent factors included female sex (HR: 2.66; 95% CI: 1.27-5.58; $P = 0.01$) and larger LAVI (HR: 1.02 per 1 mL/m^2; 95% CI: 1.002-1.04 per 1 mL/m^2; $P = 0.03$). Notably, AF was not associated with progression of AFMR, likely due to low event rate. Interestingly, although LAEF was not associated with progression to severe AFMR, subgroup analysis in patients with and without AF revealed that a higher LAEF was associated with lower risk of progression (HR: 0.96 per 1%; 95% CI: 0.92-0.99 per 1%; $P = 0.049$; 13 progression events) in 237 patients without AF, but not in 345 patients with an established diagnosis of AF (HR: 1.03; 95% CI: 0.99-1.05; $P = 0.10$; 23 progression events).

Duration of follow-up was similar between patients with and without progression of AFMR ($P = 0.31$). Patients who had progression of AFMR had significantly larger increases in LV end-diastolic dimension and tricuspid regurgitation (TR) velocity, and had numerically larger increases in LAVI and LV mass index, although the latter 2 did not achieve statistical significance (Supplemental Table 1).

REGRESSION OF AFMR. Regression to no/trivial AFMR. Of 620 patients with ≥mild-moderate AFMR with follow-up for MR severity (Table 4), 74 patients had persistent regression of AFMR to no/trivial over a median 2.3 years (Q1-Q3: 1.0-4.4 years) (3.9 per 100 person-years). Absolute change in systolic or diastolic blood pressure at time of the follow-up TTE compared with baseline was not different between patients with and without regression ($P = 0.22$ and $P = 0.67$, respectively). Notably, none of the 24 patients with severe AFMR had spontaneous regression to no/trivial AFMR.

Factors associated with regression to no/trivial AFMR are shown in Table 4. AF was associated with a lower rate of regression. This was the case in both paroxysmal (HR: 0.36; 95% CI: 0.20-0.64; $P < 0.001$) and persistent AF (HR: 0.17; 95% CI: 0.08-0.33; $P < 0.001$) vs sinus rhythm. Furthermore, patients with persistent AF tended to have a lower rate of regression vs paroxysmal AF (HR: 0.46; 95% CI: 0.21-1.00; $P = 0.05$). Independent factors associated with regression included younger age (HR: 0.96 per year; 95% CI: 0.94-0.98 per year; $P < 0.001$), male sex (HR: 1.67; 95% CI: 1.04-2.70; $P = 0.03$), AF (HR: 0.45; 95% CI: 0.16-0.49; $P = 0.01$, where absence of AF was favorable), and higher LAEF (HR: 1.04 per unit; 95% CI: 1.02-1.06 per unit; $P < 0.001$). In the multivariable analysis, 607 patients had complete data and were included, whereas 13 were excluded; a comparison between patients with and without missing data is shown in Supplemental Table 2.

In 371 patients with AF at baseline, 58 underwent rhythm control, performed at a median 0.3 years (Q1-Q3: 0.1-1.5 years) from baseline. Rhythm control was associated with regression of AFMR (age- and sex-adjusted HR: 3.13; 95% CI: 1.18-8.28; $P = 0.02$).

Duration of follow-up was similar between patients with and without regression to no/trivial AFMR ($P = 0.26$). Patients who had regression of AFMR had

TABLE 2 Baseline Echocardiographic Parameters

	≥Mild-Moderate AFMR (n = 635)	Mild or No AFMR (n = 1,905)	*P* Value
Mild MR, vs no/trivial	–	741 (39)	–
Severe MR, vs mild-moderate or moderate	25 (4)	–	–
MR EROA by PISA, cm^2	0.18 (0.14-0.23)[a]	–[b]	–
MR regurgitant volume, mL	33 (25-41)[a]	–[b]	–
Vena contracta width, mm	4.2 (3.5-5.1)[a]	–[b]	–
LVEDD, mm	49 (45.5-53)[a]	48 (44-52)[c]	<0.001
LVESD, mm	32 (29-34)[a]	31 (28-34)[c]	0.002
Ejection fraction, %	62 (58-65)	62 (58-65)	0.67
LV mass index, g/m^2	98.5 (84-117)[a]	96 (82-112)[c]	0.20
Mitral E velocity, m/s	0.9 (0.8-1.1)[a]	0.8 (0.7-1.0)[c]	<0.001
Mitral medial E/e' ratio	12.9 (10-17.1)[a]	11.4 (8.9-14.3)[c]	<0.001
TR velocity, m/s	2.8 (2.5-3.1)[a]	2.6 (2.4-2.8)[c]	<0.001
LAVI, mL/m^2	49 (44-57)	45 (42-50)	<0.001
Mitral medial e', cm/s	7 (6-8)[a]	7 (6-9)[c]	0.15
RV enlargement	111 (24)[a]	334 (18)[c]	0.003
TR severity	–[a]	–[c]	<0.001
No/trivial	103 (22)	892 (47)	
Mild	206 (44)	720 (38)	
Moderate	125 (37)	232 (12)	
Severe	35 (7)	43 (2)	

Values are n (%) or median (Q1-Q3). [a]Variables with missing values in patients with ≥mild-moderate AFMR. Available numbers are as follows: mitral regurgitation (MR) effective regurgitant orifice area (EROA) by proximal isovelocity surface area (PISA): 243 patients; MR regurgitant volume: 239; vena contracta width: 622; left ventricular (LV) end-diastolic dimension (LVEDD): 615; left ventricular end-systolic dimension (LVESD): 583; LV mass index: 602; mitral E velocity: 604; mitral medial E/e' ratio: 578; tricuspid regurgitation (TR) velocity: 601; mitral medial e': 582 patients; right ventricular (RV) enlargement: 165; TR severity: 469. [b]Values not included, given that no/trivial MR constituted the majority of these patients. [c]Variables with missing values in patients with no or mild AFMR. Available numbers are as follows: LVEDD: 1,864; LVESD: 1,787; LV mass index: 1,850; mitral E velocity: 1,860; mitral medial E/e' ratio: 1,818; TR velocity: 1,662; mitral medial e': 1,826 patients; RV enlargement: 1,902; TR severity: 1,887.

Abbreviations as in Table 1.

TABLE 3 Factors Associated With Progression of AFMR From Mild-Moderate/Moderate to Severe

	No. of Events	N	Baseline Characteristics	Univariate Analysis		Multivariable Analysis (36 Events; N = 595)	
				HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age, y[a,b]	36	595	75 (66-81)	1.00 (0.97-1.03)	0.76	0.98 (0.95-1.02)	0.32
Female[b]	36	595	300 (50)	2.42 (1.16-3.33)	0.02	2.66 (1.27-5.58)	0.01
BMI, kg/m^2[a,b]	36	595	27.5 (23.9-31.7)	1.03 (0.97-1.08)	0.29		
Sleep apnea	36	595	109 (18)	1.28 (0.60-2.72)	0.53		
Coronary artery disease	36	595	152 (26)	0.70 (0.31-1.60)	0.39		
HFpEF[b]	36	595	168 (28.2)	1.57 (0.80-3.11)	0.19		
Chronic kidney disease	36	595	153 (26)	1.69 (0.84-3.38)	0.14		
Chronic lung disease	36	595	72 (12)	1.08 (0.43-2.74)	0.85		
Diabetes mellitus	36	595	184 (31)	1.11 (0.39-3.13)	0.85		
Hypertension[b]	36	595	418 (70)	1.03 (0.52-2.04)	0.96		
History of ischemic stroke[b]	36	595	34 (6)	0.67 (0.16-2.78)	0.59		
History of TIA[b]	36	595	43 (7)	0.87 (0.21-3.64)	0.85		
Nonskin cancer	36	595	170 (28.6)	1.81 (0.93-3.51)	0.08		
Atrial fibrillation[b,c]	36	595	355 (60.0)	1.58 (0.72-3.52)	0.26	1.74 (0.74-4.07)	0.21
LAVI, mL/m^2[a,b]	36	595	49 (44-57)	1.02 (1.002-1.04)	0.03	1.02 (1.002-1.04)	0.03
LA emptying fraction, %[a,b]	36	582	32.5 (20.1-44.8)	1.00 (0.98-1.02)	0.85		
LV mass index, g/m^2[a,b]	31	564	99 (84-117)	1.00 (0.99-1.01)	0.82		
Mitral E velocity, m/s[a,b]	35	568	0.9 (0.8-1.1)	1.01 (0.61-1.05)	0.88		
Mitral medial e', cm/s[a,b]	32	548	7 (6-8)	1.01 (0.84-1.21)	0.88		
Mitral medial E/e' ratio[a,b]	32	544	12.9 (10-16.8)	1.04 (0.98-1.10)	0.18		
TR velocity, m/s[a,b]	32	564	2.8 (2.5-3.1)	1.29 (0.55-2.86)	0.54		
EF, %[a,b]	36	595	62 (58-65)	0.99 (0.92-1.05)	0.67		
LVEDD, mm[a]	32	576	49 (45.8-53)	0.97 (0.91-1.03)	0.27		
LVESD, mm[a]	31	545	32 (29-34)	0.93 (0.86-1.01)	0.07		
LV hypertrophy, vs normal[b]	31	564					
Concentric remodeling			143 (25.4)	1.45 (0.54-3.87)	0.46		
Concentric hypertrophy			149 (25.8)	1.53 (0.57-4.10)	0.39		
Eccentric hypertrophy			80 (14.2)	2.23 (0.81-6.18)	0.12		

Values are median (Q1-Q3) or n (%), unless otherwise indicated. [a]HR is presented per a unit increase. [b]Included in the multivariable model based on a priori knowledge of factors associated with atrial functional MR; however, backward elimination was performed to allow ~1 variable per 10 events including age and sex, to avoid overfitting. [c]Analyzed as time-dependent covariate.

EF = ejection fraction; other abbreviations as in Tables 1 and 2.

significantly larger decreases in LAVI, LV end-diastolic dimension, LV mass index, and E/e′ ratio as well as a numerically larger increase in EF (Supplemental Table 3).

Regression of ≥moderate AFMR to ≤mild. Of 159 patients with ≥moderate AFMR, 50 patients regressed to ≤mild over a median 1.9 years (Q1-Q3: 0.9-3.8 years) (11.3 per 100 person-years). Of 24 patients with severe AFMR, 2 patients regressed to mild over a median 1.1 years (Q1-Q3: 0.5-4.5 years) (3.2 per 100 person-years). Factors associated with regression of ≥moderate AFMR to ≤mild are shown in Supplemental Table 4. In the multivariable analysis, 145 patients had complete data and were included, whereas 14 were excluded; a comparison between patients with and without missing data is shown in Supplemental Table 5.

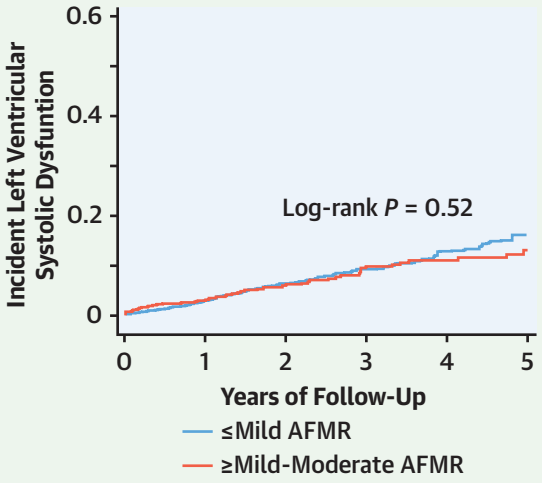
ALL-CAUSE MORTALITY. In 425 patients with mild-moderate/moderate AFMR eligible for mortality analysis, 116 patients died over a median 3.7 years (Q1-Q3: 1.7-6.2 years), with a mortality rate of 5.9 per 100 person-years (3.7% at 1-year follow-up; 21% at 5-year follow-up). Progression to severe AFMR was associated with increased mortality (12 events in 36 patients with progression vs 164 in 559 patients without progression; age and sex-adjusted HR: 2.42; 95% CI: 1.24-4.73; $P = 0.01$). However, this did not remain significant at the multivariable level when including baseline comorbidities and echocardiographic parameters. Similarly, in 445 patients with ≥mild-moderate AFMR, persistent regression to no/trivial of AFMR was not associated with improved survival (17 events in 74 patients with regression and 165 events in patients without regression; $P = 0.36$).

CENTRAL ILLUSTRATION The Natural History of Atrial Functional Mitral Regurgitation

The Natural History of ≥Mild-Moderate Atrial Functional Mitral Regurgitation (AFMR)

Incidence of left ventricular systolic dysfunction is 3.2 per 100 person-years

Not different from matched patients with no/mild AFMR



	Progression of AFMR	Regression of AFMR
Definition	Progression of moderate to severe AFMR	Persistent regression of AFMR to no/trivial
Incidence rate	1.9 per 100 person-years	3.9 per 100 person-years
Risk factors at baseline	Female ↑LAVI ↓LAEF (when no AF)	Younger age Male No AF (or rhythm control) ↑LAEF
Association of incident event with mortality	Only at the univariate level	No

Factors Associated With Mortality

- Older age
- Chronic lung disease
- Ischemic strokes
- LV filling pressure (E/e' ratio)
- RV systolic pressure
- Concentric LV geometry

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(Top) Incidence of left ventricular (LV) systolic dysfunction was similar in patients with ≥mild-moderate atrial functional mitral regurgitation (AFMR) as compared with patients with no/mild AFMR over a median follow-up of 2.3 years, as demonstrated in Kaplan-Meier curves. (Middle) Definitions, incidence rates, risk factors, and association of each of progression and regression of AFMR with mortality are shown. (Bottom) Factors independently associated with mortality in patients with ≥mild-moderate AFMR are shown. AF = atrial fibrillation; LAVI = left atrial volume index; RV = right ventricle.

TABLE 4 Factors Associated With Regression of ≥Mild-Moderate AFMR to No/Trivial

	No. of Events	N	Baseline Characteristics	Univariate Analysis		Multivariable Analysis (73 Events; N = 607)	
				HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age, y[a,b]	74	620	75 (66-81)	0.95 (0.93-0.96)	<0.001	0.96 (0.94-0.98)	<0.001
Male[b]	74	620	306 (49.4)	1.46 (0.92-2.31)	0.11	1.67 (1.04-2.70)	0.03
BMI, kg/m^2[a,b]	74	620	27.4 (23.9-31.5)	1.03 (0.99-1.07)	0.15	1.03 (0.99-1.07	0.06
Sleep apnea	74	620	112 (18.1)	1.32 (0.78-2.25)	0.30		
Coronary artery disease	74	620	158 (25.5)	0.78 (0.44-1.37)	0.38		
HFpEF[b]	74	620	176 (28.4)	1.38 (0.0.85-2.22)	0.21		
Chronic kidney disease	74	620	161 (26.0)	2.59 (1.63-4.11)	<0.001		
Chronic lung disease	74	620	74 (11.9)	0.78 (0.34-1.79)	0.55		
Diabetes mellitus	74	620	191 (30.8)	1.17 (0.73-1.88)	0.52		
Hypertension[b]	74	620	433 (69.8)	1.20 (0.71-2.04)	0.50	1.52 (0.87-2.65)	0.14
Nonskin cancer	74	620	175 (28.2)	1.15 (0.70-0.89)	0.57		
History of ischemic stroke[b]	74	620	35 (5.6)	0.69 (0.22-2.20)	0.53		
History of TIA[b]	74	620	44 (7.1)	1.96 (0.94-4.08)	0.07	2.40 (0.82-7.03)	0.13
Atrial fibrillation[b,c]	74	620	371 (60.0)	0.24 (0.15-0.40)	<0.001	0.45 (0.24-0.83)	0.01
Severe MR at baseline[b]	74	620	24 (3.9)	-	0.99		
LVEDD, mm[a]	70	600	49 (45-53)	1.07 (1.02-1.11)	0.003		
LVESD, mm[a]	67	569	32 (29-34)	1.09 (1.03-1.15)	0.003		
LV mass index, g/m^2[a,b]	69	588	99 (84-117)	1.01 (1.00-1.02)	0.002		
Mitral E velocity, m/s[a,b]	71	590	0.9 (0.8-1.1)	1.00 (0.90-1.13)	0.94		
Mitral medial e', cm/s[a,b]	70	569	7 (6-8)	1.04 (0.93-1.17)	0.48		
Mitral medial E/e' ratio[a,b]	68	565	13 (10-17)	1.00 (0.96-1.05)	0.89		
TR velocity, m/s[a,b]	69	589	2.8 (2.5-3.1)	0.81 (0.46-1.44)	0.47		
RV systolic pressure, mm Hg	69	588	38 (32-47)	1.00 (0.98-1.02)	0.85		
LAVI, mL/m^2[a,b]	74	620	49 (44-57)	0.98 (0.96-1.00)	0.12		
LA emptying fraction, %[a,b]	73	607	32.2 (19.8-44.4)	1.05 (1.03-1.06)	<0.001	1.04 (1.02-1.06)	<0.001
EF, %[a,b]	74	620	62 (58-65)	0.97 (0.92-1.01)	0.13	0.96 (0.92-1.00)	0.06
LV hypertrophy, vs normal[b]	69	588					
Concentric remodeling			153 (26.05)	1.21 (0.63-2.33)	0.57		
Concentric hypertrophy			153 (26.0)	1.75 (0.90-3.26)	0.12		
Eccentric hypertrophy			84 (14.3)	1.49 (0.70-3.16)	0.30		

Values are median (Q1-Q3) or n (%), unless otherwise indicated. [a]HR is presented per a unit increase. [b]Included in the multivariable model based on a priori knowledge of factors associated with atrial functional MR; however, backward elimination was performed to allow ~1 variable per 10 events including age and sex, to avoid overfitting. [c]Analyzed as time-dependent covariate.

Abbreviations as in Tables 1 to 3.

Instead, independent risk factors associated with mortality in patients with ≥mild-moderate AFMR were older age, chronic lung disease, history of ischemic stroke, a higher E/e′ ratio and TR velocity, and concentric LV geometry (Table 5). In the multivariable analysis, 362 patients had complete data and were included, whereas 94 were excluded; a comparison between patients with and without missing data is shown in Supplemental Table 6. Notably, patients with ≥mild-moderate AFMR had increased mortality compared with matched patients with no/mild AFMR (HR: 1.29; 95% CI: 1.05-1.61; $P = 0.02$).

INTEROBSERVER VARIABILITY IN MITRAL ANNULUS AND LA VOLUME. In a 10-patient sample randomly selected for measurement by 2 observers, the intraclass correlation coefficient showed good reliability (0.89 for maximum LA volume; 0.94 for minimum LA volume; and 0.88 for mitral annulus anteroposterior diameter).

DISCUSSION

In this study, which investigated the natural history of ≥mild-moderate AFMR, patients with ≥mild-moderate AFMR developed LVSD at a rate of 3.2 per 100 person-years, but this was similar to the rate in patients with no/mild AFMR, indicating no additional risk imposed by AFMR for development of LVSD over a median 2.2 years. Furthermore, progression from mild-moderate/moderate to severe AFMR was uncommon, occurring at a rate of 1.9 per 100 person-years, and was associated with female sex, larger LA size, and lower LAEF in patients without AF. On the other hand, a larger number of patients with ≥mild-moderate AFMR experienced regression

of AFMR to no/trivial grades (3.9 per 100 person-years) with favorable factors including younger age, male sex, a higher LAEF, the absence of AF, and rhythm control in patients with AF. Interestingly, there were no statistically significant associations between progression or regression of AFMR and all-cause mortality; instead, factors associated with diastolic dysfunction (concentric LV geometry and higher LV filling and pulmonary pressures) were more important.

AFMR develops in the setting of LA enlargement and myopathy with subsequent mitral annulus dilation but relatively preserved LV size and systolic function.[8] The association between diastolic dysfunction, AFMR, and HFpEF is well-established due to the shared underlying pathophysiological mechanism (ie, systemic inflammation with subsequent coronary microvascular dysfunction and myocardial changes in the atria leading to atrial myopathy and the ventricles leading to diastolic dysfunction) but also the direct impact of diastolic dysfunction and HFpEF on LA remodeling due to the increased LA pressure.[13,14] Indeed, our study shows that 28% of patients with ≥mild-moderate AFMR had HFpEF at time of the index TTE, and in patients without an established diagnosis at baseline, incident HFpEF was diagnosed in ~7.4% of patients every year, indicating a high risk of masked HFpEF in these patients. This was also indicated by a high baseline continuous H_2FPEF probability score, with around one-half of the patients having a score exceeding 90%. Notably, 14% of patients with ≥mild-moderate AFMR had eccentric hypertrophy. This finding is not necessarily surprising as an "eccentric phenotype" has been described to occur in ~12% of ambulatory patients with HFpEF in previous studies.[15]

DEVELOPMENT OF LV SYSTOLIC DYSFUNCTION IN AFMR. Chronic significant primary MR is known to lead to ventricular volume-overload, which over time results in adaptive remodeling of the LV.[6] Eventually, LVSD ensues and is considered a sign of an advanced decompensated stage in primary MR.[16] In this study, we show that around 3.2% of patients with ≥mild-moderate AFMR develop LVSD every year, not related to myocardial infarction. However, this was not different from matched patients with no/mild AFMR with otherwise similar inclusion criteria. This indicates that over a median 1 to 2 years, neither moderate nor severe AFMR is associated with increased risk of LVSD. Whether longer-term exposure to significant AFMR would result in increased risk of LVSD needs further investigation.

PROGRESSION VS REGRESSION OF AFMR. After median 2.2 years of follow-up, the progression of mild-moderate/moderate to severe AFMR was uncommon, occurring in 1.9% of patients every year. A lower LAEF in patients without AF and a larger LA size were important associated factors, which is not surprising since LA remodeling is cornerstone in the development of atriogenic mitral annular dilation and AFMR.[17] Women were at least twice as likely as men to experience progression of mild-moderate/moderate to severe AFMR. Previous studies have shown that women are also more likely to develop incident AFMR.[2] Several mechanisms have been proposed to explain this predisposition.[18] Women with AF were found to have a higher burden of atrial fibrosis compared with men,[19,20] which could be due to presentation at a later disease stage in the setting of atypical symptoms or different response to the inflammation underlying the AF as a result of sex hormones.[14,21,22] Sex hormones can also modify the response of fibroblasts to the stress inflicted by changes in mitral annular dynamics in AFMR and can be implicated in inadequate compensatory growth of the leaflets in the setting of LA enlargement.[23,24] Furthermore, the composition of mitral and tricuspid annuli is different between sexes, with less/absent myocardium and less collagen matrix and elasticity in females, potentially contributing to the propensity towards annular dilation in women.[25]

On the other hand, around 3.6% of patients with ≥mild-moderate AFMR experienced regression to no/trivial grades of AFMR every year. Not surprisingly, this was associated with younger age and male sex. Aging is associated with oxidative stress, chronic low-grade inflammation, and decreased cellular regenerative capacity, a constellation of changes that leads to structural changes in the heart, predisposing to LA myopathy and enlargement.[26] Our study confirms findings from previous studies that rhythm control in AF is associated with regression of AFMR,[4,5] and the absence of AF was a favorable factor for the regression of ≥mild-moderate AFMR.

AF was also shown to be an important factor associated with the development of incident AFMR.[2] The absence of association between AF and progression from mild-moderate/moderate to severe AFMR was likely in the setting of a low event rate. AF in these patients can be a manifestation reflecting the underlying atrial myopathy; furthermore, the associated loss of atrial contraction leads to further hemodynamic deterioration with increase in atrial pressure and subsequent remodeling, further exacerbating the atrial myopathy.[27]

TABLE 5 Factors Associated With All-Cause Mortality

			Univariate Analysis		Multivariable Analysis (93 Events; N = 362)	
	No. of Events	N	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age, per 10 y[a]	116	456	1.34 (1.10-1.63)	<0.001	1.34 (1.09-1.66)	0.005
Male[a]	116	456	0.99 (0.69-1.44)	0.97	1.57 (0.97-2.55)	0.07
BMI, kg/m^2[a,b]	116	456	0.98 (0.95-1.01)	0.24	0.96 (0.92-1.00)	0.05
Sleep apnea	116	456	0.62 (0.36-1.09)	0.10		
Coronary artery disease[a]	116	456	1.08 (0.71-1.65)	0.71		
HFpEF[a]	116	456	2.08 (1.42-3.04)	<0.001		
Chronic kidney disease[a]	116	456	2.07 (1.40-3.06)	<0.001		
Chronic lung disease[a]	116	456	2.65 (1.66-4.23)	<0.001	2.29 (1.26-4.16)	0.007
Diabetes mellitus[a]	116	456	1.45 (0.99-2.11)	0.05		
Hypertension[a]	116	456	1.28 (0.85-1.95)	0.24		
History of ischemic stroke[a]	116	456	1.91 (1.07-3.39)	0.03	4.11 (2.02-8.36)	<0.001
History of TIA[a]	116	456	1.39 (0.74-2.58)	0.30		
Atrial fibrillation[a,c]	116	456	1.40 (0.90-2.181)	0.14	1.36 (0.75-2.45)	0.31
Severe (vs moderate) MR[a]	116	456	1.18 (0.48-2.90)	0.71	0.48 (0.16-1.44)	0.20
LVEDD, mm[b]	111	440	0.95 (0.92-0.99)	0.005		
LVESD, mm[b]	105	412	0.94 (0.90-0.98)	0.006		
LV mass index, g/m^2[a,b]	111	432	1.00 (1.00-1.01)	0.48		
Mitral E velocity, m/s[a,b]	112	434	0.98 (0.93-1.05)	0.60		
Mitral medial e', cm/s[a,b]	105	418	0.87 (0.79-0.96)	0.007		
Mitral medial E/e' ratio[a,b]	105	416	1.06 (1.03-1.09)	<0.001	1.04 (1.00-1.08)	0.048
TR velocity, m/s[a,b]	112	430	3.42 (2.38-4.90)	<0.001	2.91 (1.93-4.39)	<0.001
MR EROA by PISA, per 0.01 cm^2[b]	43	171	1.02 (0.98-1.06)	0.30		
MR regurgitant volume, mL[b]	42	167	1.01 (0.99-1.04)	0.27		
Vena contracta width, mm[b]	115	444	1.15 (0.98-1.33)	0.07		
RV systolic pressure, mm Hg[b]	111	429	1.04 (1.03-1.05)	<0.001		
LV stroke volume index, mL/m^2[b]	98	399	1.00 (0.98-1.01)	0.60		
LAVI, mL/m^2[a,b]	116	456	1.02 (1.00-1.03)	0.02		
LA emptying fraction, %[a,b]	111	444	0.99 (0.97-0.999)	0.04	1.01 (0.99-1.03)	0.09
EF, %[a,b]	116	456	1.00 (0.97-1.04)	0.85		
LV hypertrophy, vs normal[a]	111	432				
Concentric remodeling/hypertrophy			2.09 (1.30-3.35)	0.002	2.03 (1.15-3.58)	0.01
Eccentric hypertrophy			1.13 (0.56-2.28)	0.74	1.16 (0.53-2.55)	0.71
RV enlargement[a]	116	450	1.77 (1.18-2.63)	0.005	1.51 (0.89-2.56)	0.13
≥Moderate TR[a]	115	453	1.83 (1.22-2.74)	0.004		
Regression of AFMR[a,c]	116	456	1.36 (0.70-2.63)	0.36		

[a]Included in the multivariable model based on a priori knowledge of factors associated with atrial functional MR; however, backward elimination was performed to allow ~one variable per 10 events including age and sex, to avoid overfitting. [b]HR is presented per a unit increase. [c]Analyzed as time-dependent covariate.

Abbreviations as in Tables 1, 2, and 3.

ASSOCIATED CHANGES IN ECHOCARDIOGRAPHIC PARAMETERS. Patients who had progression from mild-moderate/moderate to severe AFMR concurrently experienced worse echocardiographic changes, including enlargement of LV and LA size, increase in LV mass index, and increase in TR velocity, compared with patients who did not have progression. On the other hand, patients with regression of AFMR to no/trivial experienced more decrease in LV and LA size, LV mass index, and mitral E/e' ratio and more increase in the EF. A cause vs result effect cannot be inferred from the current study, and a bidirectional relationship between AFMR and LV and LA remodeling is likely present. The favorable changes associated with regression of AFMR were shown after mitral valve interventions that resulted in decreased severity of AFMR, highlighting the role of AFMR in LV and LA remodeling.[28]

MORTALITY IN PATIENTS WITH ≥MILD-MODERATE AFMR. Interestingly, EF at baseline was not associated with mortality in patients with established AFMR. Instead, diastolic function abnormalities were more important including concentric LV geometry and elevated estimated LV filling and pulmonary pressures. Cramariuc et al[29] showed that measures of LA function were independent predictors of mortality in patients with moderate or severe AFMR, although

other diastolic function parameters were not examined.

We have previously demonstrated that the development of incident AFMR at follow-up in patients without structural heart disease (outside of diastolic dysfunction) or significant MR at baseline was independently associated with increased mortality both in patients with and without new-onset AF.[2] We have also shown that even mild AFMR was associated with increased mortality compared with no AFMR, although moderate and severe AFMR did not confer additional mortality compared with mild AFMR at the multivariable level.[3] In this latter study, AFMR severity during follow-up was examined, and patients contributed time at risk only to the most severe AFMR grade they have been diagnosed with (ie, once severe, always severe).[3] Therefore, the potential impact of regression of AFMR on mortality remained unknown. In this study, we show consistent findings that ≥mild-moderate AFMR is associated with increased mortality (vs no/mild AFMR). However, despite the favorable echocardiographic changes associated with regression of AFMR and the unfavorable changes associated with progression, we show that once patients develop moderate/severe AFMR, neither progression nor regression of AFMR had an independent impact on all-cause mortality. The lack of survival benefit, even with persistent regression of significant AFMR, raises the question of whether AFMR confers mortality in virtue of itself or because it is a marker of worse LA myopathy. This question has significant implications on management strategies in patients with significant AFMR: do we target the AFMR or the diastolic dysfunction and the atrial myopathy?

Previous observational studies evaluating mitral valve interventions in patients with AFMR demonstrated effectiveness of transcatheter edge-to-edge repair and indirect mitral annuloplasty in decreasing the severity of regurgitation in patients with significant AFMR and improving NYHA functional class and symptoms in these patients.[28,30-33] However, there was no comparison group of patients with AFMR treated conservatively, and the impact of these interventions on mortality could not be ascertained. Future studies to evaluate clinical outcomes after mitral valve interventions compared with medical treatment targeted towards diastolic dysfunction in patients with AFMR are needed.

STUDY LIMITATIONS. This is a retrospective study involving Mayo Clinic sites; some of these sites are tertiary referral centers with inherent limitations related to selection bias. All echocardiographic examinations were done in routine clinical practice based upon a clinical need. Therefore, follow-up echocardiographic evaluations were not standardized. To help mitigate this issue, we used survival analysis and mixed linear models to estimate annual change in echocardiographic measurements. Echocardiographic interpretation was performed by many cardiologists with potential interobserver variability. However, Mayo Clinic echocardiographic laboratories are accredited labs with level III board-certified cardiologists in echocardiography, advanced sonographers for quality control, and mandatory quarterly quality assessment to ensure consistency and adherence with guidelines. Only a small number of patients had severe AFMR, which may have affected some of the analyses due to low power. We included a mild-moderate category for MR severity due to the inability to determine retrospectively with certainty the exact grade (ie, mild or moderate). LA strain was not measured given the large number of patients, and future studies are needed to evaluate its role in predicting progression or regression of AFMR. However, LAEF as a measure of LA function was included and analyzed in this study. The included EF measurements were performed by the linear or the biplane methods. However, only 1 measurement method was considered in the same patient to avoid method-related variability. We used ICD codes to identify many comorbidities, with the potential of underestimation of their prevalence. However, both HFpEF and AF diagnoses were meticulously identified. The association between use of diuretic agents and regression of AFMR could not be evaluated due to the inaccuracies and challenges in obtaining data related to the initiation and dosage of diuretic agents by retrospective review of the electronic medical records, and future prospective studies are needed to evaluate such association.

CONCLUSIONS

In patients with ≥mild-moderate AFMR, approximately 3% of patients develop LVSD every year, but this rate was not different compared with patients with no/mild AFMR. Progression from mild-moderate/moderate to severe AFMR was uncommon, occurring in ~1.9% of patients every year and was associated with female sex, larger LA size, and lower LAEF in patients without AF. Regression occurred more commonly (~3.9% per year) and was associated with younger age, male sex, lower LAEF, the absence of AF, and rhythm control in patients with AF. Despite the fact that progression of AFMR was associated with unfavorable echocardiographic

changes and regression was associated with favorable changes, neither was independently associated with all-cause mortality. Instead, diastolic function abnormalities were more important. Future studies to evaluate the impact of mitral valve interventions on mortality in patients with AFMR are needed.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients with more than mild AFMR, left ventricular systolic function does not decline more than in patients without AFMR over time, but diastolic dysfunction may develop, resulting in heart failure with preserved ejection fraction as a key determinant of mortality.

TRANSLATIONAL OUTLOOK: Further research is needed to determine the impact on long-term clinical outcomes of mitral valve interventions compared with treatment directed at diastolic ventricular dysfunction and atrial myopathy in patients with AFMR.

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