

## ORIGINAL ARTICLE



# Atrial Dysfunction in Significant Atrial Functional Mitral Regurgitation: Phenotypes and Prognostic Implications

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**BACKGROUND:** Atrial functional mitral regurgitation (AFMR) is associated with increased morbidity and mortality. Left atrial (LA) size and function in AFMR are poorly characterized. We aimed to assess LA function by reservoir strain (LASr) and estimated reservoir work (LAWr) and their impact on outcome in AFMR.

**METHODS:** Consecutive patients at our institution between 2001 and 2019 and with significant (moderate or greater) AFMR were examined. LAWr was estimated as LASr×LA reservoir volume, and patients were grouped by median LASr and LAWr. Outcomes were all-cause death or heart failure hospitalizations.

**RESULTS:** Five hundred fifteen AFMR patients were followed up for 5 (1–17) years. Patients had previously documented atrial fibrillation (AF; 37%), heart failure with preserved ejection fraction (HFpEF) without AF (24%), or both (HFpEF+AF, 39%). LA volume was largest in AF, while LA function parameters were most impaired in the combined HFpEF+AF group.

During follow-up, patients with low LASr or LAWr had higher risk of death ( $P<0.001$ ) and heart failure hospitalization ( $P<0.05$ ). In Cox regression analyses, low LASr and LAWr, but not LA volume or left ventricular function, were associated with a higher risk of death (LASr: hazard ratio, 2.3 [95% CI, 1.6–3.5]; LAWr: hazard ratio, 3.4 [95% CI, 2.4–4.9]; both  $P<0.001$ ) after adjustment for clinical and echocardiographic confounders. Low LASr and LAWr were strongest associated with death in HFpEF and HFpEF+AF.

**CONCLUSIONS:** LA reservoir function but not LA size is a robust predictor of outcome in significant AFMR. This provides mechanistic insights into the interplay of functional versus geometric LA changes in AFMR.

**GRAPHIC ABSTRACT:** A [graphic abstract](#) is available for this article.

**Key Words:** atrial function, left ■ echocardiography ■ mitral valve ■ mitral valve insufficiency ■ mortality

### See Editorial by Vannan et al

Functional mitral regurgitation (MR) is caused by geometric changes of the mitral apparatus without concomitant structural leaflet pathology. A common type of secondary MR is associated with left ventricular (LV) remodeling in the context of ischemic heart disease or dilated cardiomyopathy. More recently, atrial functional MR

(AFMR) has been recognized as a type of secondary MR with distinct mechanisms and clinical features than that due to ischemic or myopathic LV remodeling. AFMR is mostly described in patients with normal LV size and preserved ejection fraction (EF), mitral leaflets with normal echocardiographic appearance, and dilated left atrium (LA).<sup>1</sup>

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## CLINICAL PERSPECTIVE

In a large cohort of patients with moderate and greater atrial functional mitral regurgitation (AFMR), we found that AFMR is commonly associated with heart failure with preserved ejection fraction or atrial fibrillation. Depending on the linked pathology, we identified distinct patterns of left atrial remodeling in AFMR, with more severely dilated atria with higher storage capacity in patients with atrial fibrillation and smaller, noncompliant atria in heart failure with preserved ejection fraction. Patients with significant AFMR experienced a high number of adverse events, including a 38% mortality and 30% first-time heart failure hospitalizations during a 5-year follow-up. Impaired left atrial function assessed by either the reservoir strain or the product of reservoir strain $\times$ left atrial reservoir volume (a simplified index of left atrial reservoir work) was a strong predictor of death in AFMR, particularly in the setting of heart failure with preserved ejection fraction. The maximum left atrial volume—a guideline-recommended criterion for grading and considering intervention in chronic mitral regurgitation—was not related to outcome in significant AFMR. The current findings support future investigations to evaluate different treatment strategies addressing both the mitral regurgitation and the left atrial dysfunction in AFMR.

## Nonstandard Abbreviations and Acronyms

<b>AF</b>	atrial fibrillation
<b>AFMR</b>	atrial functional mitral regurgitation
<b>EF</b>	ejection fraction
<b>GLS</b>	global left ventricular longitudinal strain
<b>HF</b>	heart failure
<b>HFpEF</b>	heart failure with preserved ejection fraction
<b>LA</b>	left atrium
<b>LASr</b>	left atrial reservoir strain
<b>LAVmax</b>	maximum left atrial volume
<b>LAVmin</b>	minimum left atrial volume
<b>LAWr</b>	left atrial reservoir work
<b>LV</b>	left ventricle
<b>MR</b>	mitral regurgitation

AFMR is common in elderly individuals with atrial arrhythmias but is also associated with heart failure (HF) with preserved EF (HFpEF).<sup>2</sup> The clinical impact of this secondary MR subtype will escalate due to the aging of the population worldwide and the ongoing obesity and atrial fibrillation (AF) epidemic. The mortality risk of AFMR is comparable to that of degenerative MR.<sup>3</sup> However, its mechanisms and clinical presentation are

poorly defined, and in the recent European Society of Cardiology/ European Association for Cardio-Thoracic Surgery and American Heart Association/American College of Cardiology valvular heart disease guidelines, AFMR is recognized mainly in the context of AF and lacks separate recommendations for grading, follow-up, and treatment.<sup>4,5</sup>

Mechanistically, AFMR is commonly attributed to adverse LA remodeling such as increased LA and annular size. However, the impact of atrial mechanics has been scarcely described. Atrial mechanical function may be an important contributor to clinical outcome in AFMR.<sup>6</sup> We aim to characterize LA function and remodeling patterns in a large population of patients with significant AFMR and assess the independent impact of atrial mechanics on the patients' long-term outcome.

## METHODS

### Study Population

Patients with AFMR examined at the Massachusetts General Hospital in the period 2001 to 2019 were identified in the institutional echocardiographic database. The definition of AFMR was significant (moderate or greater) MR with normal-sized LV and LV function (LV EF,  $\geq 50\%$ ; Carpentier type I).<sup>6</sup> Patients with LV wall motion abnormalities or other MR mechanisms were excluded. The echocardiographic evaluation that was the basis for inclusion is referred to as the index examination. Only patients followed up at the Massachusetts General Hospital were included in the study. MR severity was graded using a standardized and integrative method based on combined qualitative, semiquantitative, and quantitative evaluation<sup>7</sup> performed by cardiologists with specialized expertise in echocardiography. Patients with evidence of structural mitral valve pathology, other severe valve disease, hypertrophic or dilated cardiomyopathy, congenital heart disease, pulmonary embolism, or constrictive pericarditis were excluded.

Obesity was defined as a body mass index  $\geq 30$  kg/m<sup>2</sup>. Relevant comorbidities, including HFpEF, daily medication, including HF treatment, and symptoms at presentation were obtained via chart review. History of AF was assessed by manual review of all resting electrocardiograms (available in all patients), 24-hour Holter registrations (available in 11% of the study population), and charts prior to the index examination. Type of heart rhythm during echocardiography was also assessed.

The study was approved by the institutional review board and was conducted in accordance with the revised Declaration of Helsinki. Due to the retrospective nature of the study, informed consent was not required. The data that support the findings of this study are available from the corresponding author upon reasonable request.

### Echocardiographic Measurements

Comprehensive transthoracic echocardiograms were performed by experienced sonographers and analyzed on Syngo Dynamics stations (Siemens Medical Solutions Munich, Germany) equipped with 2-dimensional speckle tracking software (2D Cardiac Performance Analysis; Tomtec Arena 2.42, Unterschleissheim, Germany).

## LA Size and Function

LA volume was measured in dedicated apical 4- and 2-chamber views at 3 different time points: end diastole (the frame just after mitral valve closure), onset of atrial contraction (identified by the P wave on ECG), and end systole (the frame just before mitral valve opening), rendering minimum LA volume (LAVmin), pre-LA, and maximum LA volume (LAVmax), respectively.<sup>8</sup> LA appendage and the ostia of pulmonary veins, if visible, were excluded from the volumes. LA dilatation was assessed based on LAVmax indexed for body surface area. The increase in LA volume from minimum to maximum during the reservoir phase defined the LA reservoir volume (also referred to as the total emptying LA volume in the literature).<sup>9</sup> The LA emptying fraction was calculated as the ratio of the LA reservoir volume and LAVmax.

LA strain was measured using specific software (2D Cardiac Performance Analysis; Tomtec Arena 2.42) and end diastole as the zero-strain reference point.<sup>9</sup> LA reservoir function was assessed by the reservoir strain (LASr) and additionally estimated from the product LASr (as a surrogate of LA pressure change<sup>10–12</sup>) $\times$ LA reservoir volume<sup>13–15</sup>—a simplified index of LA reservoir work (LAWr).

Additionally, the LA expansion index—a previously proposed marker of reservoir function—was deducted from the ratio of LA reservoir volume to LAVmin.<sup>16</sup> In patients in sinus rhythm at the index examination, LA strain during the atrial contraction phase was also quantified.<sup>9</sup> In patients in AF, both LA size and function were assessed in 3 consecutive cardiac cycles during reasonably regular rhythm and averaged.<sup>9</sup>

Of note, the ratio of mitral peak E-wave velocity and mitral annular e' velocity is not reported as it is not recommended to be used in functional analyses in patients with significant MR and preserved LV EF.<sup>17,18</sup>

## LV Size and Function

LV size was evaluated by the 2-dimensional wall and cavity linear dimensions and by triplane volumes following the joint American Society of Echocardiography and European Association of Cardiovascular Imaging guidelines.<sup>19</sup> LV hypertrophy was identified as recommended in populations with higher prevalence of obesity as LV mass indexed for height<sup>27</sup>  $\geq 49.2$  g/m<sup>2.7</sup> in men and  $\geq 46.7$  g/m<sup>2.7</sup> in women.<sup>20–22</sup> The ratio of LV end-diastolic posterior wall thickness/internal diameter (the relative wall thickness) indicated concentric LV geometry when  $\geq 0.43$ .<sup>23</sup>

LV systolic function was assessed by both EF and global left ventricular longitudinal strain (GLS; low if less negative than  $-16.7\%$  in men and  $< -17.8\%$  in women) using all 3 standard apical views.<sup>19,24</sup>

## Echocardiographic Control Group

To examine the individual impact of AFMR on LA function, we additionally measured LA size and reservoir function in a separate, contemporary cohort (examined between 2017 and 2022) of patients with an established HFpEF diagnosis, none or trace MR, no history of atrial arrhythmias and sinus rhythm at the index examination, and echocardiographic data suitable for speckle tracking analysis. The exclusion criteria were otherwise similar as for the main study population. A group of 100

controls with a comparable age and sex composition as the main study population was identified and used as a comparison sample in analyses of echocardiographic data.

## Outcomes

We examined the prognostic value of measures of LA reservoir function in relation to all-cause mortality and HF hospitalizations. Patients were followed up beginning with the day of the index examination and up to 2021. All deaths were ascertained from medical records and the social security death index. Hospitalization for HF was ascertained from chart reviews.

## Statistical Analyses

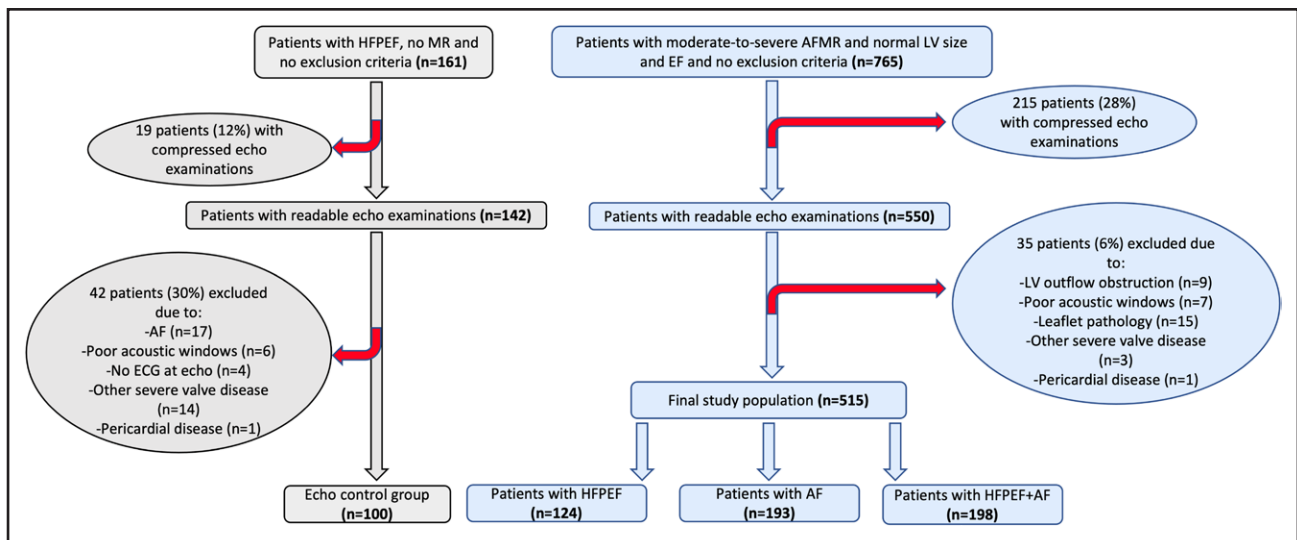
All statistical analyses were performed using IBM SPSS Statistics 28.0 (IBM Corp, Armonk, NY). Between-group differences were assessed by unpaired *t* tests, 1-way ANOVA with Sidak post hoc test,  $\chi^2$  test, or Fisher exact test as appropriate. Due to fundamentally different atrial mechanics, atrial size and function are reported separately for patients in sinus rhythm and AF at the index examination. Findings are reported as mean $\pm$ SD and median values with error bars for the 95% CIs for continuous variables and percentages for categorical variables.

The impact of LA function on outcomes was tested in Kaplan-Meier survival analyses with log-rank test for the overall analysis, as well as in univariable and multivariable Cox regression analyses. Additionally, the strength of the relationship between different indexes of LA function and death was assessed in the receiver operating characteristic analysis with comparison between the areas under the curve of the different parameters. For survival analyses, patients were grouped according to the median value of LASr and LAWr, and the association with all-cause death was assessed univariably in the whole AFMR population and in the 3 AFMR subgroups: HFpEF, AF, and HFpEF+AF. Multivariable Cox regression models were additionally run in the whole AFMR population and covariates selected based both on clinical relevance and a  $P < 0.1$  level of significance for the association with the dependent variables in univariable analyses. Results are reported as hazard ratios with 95% CIs. A 2-tailed  $P \leq 0.05$  was considered significant both in univariable and multivariable analyses.

## RESULTS

### Study Population

A total of 515 patients with significant AFMR (97% with moderate and 3% with severe AFMR) were included (Figure 1). Among them, 124 (24%) had previously documented HFpEF but no atrial arrhythmias, 193 (38%) had a history of AF, and 198 (38%) had both HFpEF and AF (HFpEF+AF). While the groups had comparable distribution of sexes and equally high prevalence of hypertension, patients with HFpEF+AF were significantly older and had higher prevalence of chronic obstructive pulmonary disease and peripheral vascular disease (Table 1). The AF group had less comorbidities including less diabetes, chronic kidney disease, and clinical vascular



**Figure 1. Study enrollment flowchart.**

AF indicates atrial fibrillation; AFMR, atrial functional mitral regurgitation; EF, ejection fraction; HFpEF, heart failure with preserved ejection fraction; LV, left ventricle; and MR, mitral regurgitation.

disease, slightly higher hemoglobin, and lower creatinine than the other 2 groups. Combined HFpEF+AF was associated with a higher prevalence of symptoms at the

index examination, particularly dyspnea and chest pain, and these patients used more often  $\beta$ -blockers, diuretics, and mineralocorticoid receptor antagonists (Table 1).

**Table 1. Demographics and Clinical Characteristics**

	All (n=515)	HFpEF (n=124)	AF (n=193)	HFpEF+AF (n=198)	P value
Age, y	71±12	66±14*	71±9*	74±12*	<0.001
Female sex	56%	57%	52%	58%	0.42
Obesity	26%	33%	23%	25%	0.13
Heart rate, bpm	71±18	68±14	72±20	73±19	0.06
Hypertension	82%	84%	79%	83%	0.44
Hypercholesterolemia	38%	35%	35%	44%	0.09
Diabetes	30%	35%	23%	34%	0.03
Chronic kidney disease	20%	31%	8%	25%	<0.001
COPD	14%	11%	6%	22%	<0.001
Previous myocardial infarction	7%	11%	3%	8%	0.005
Previous stroke	7%	7%	5%	10%	0.12
Peripheral vascular disease	12%	13%	7%	16%	0.03
Dyspnea	47%	52%	36%	55%	<0.001
Chest pain	55%	55%	48%	63%	0.009
Palpitations	36%	23%	38%	41%	0.003
Hemoglobin, g/dL	11.8±2.2	11.1±2.2*	12.5±1.9*	11.7±2.1*	<0.001
Creatinine, mg/dL	1.3±1.0	1.7±1.5*	1.1±0.5†	1.3±0.8†	<0.001
<b>Medication</b>					
$\beta$ -Blocker	65%	55%	62%	75%	<0.001
ACE inhibitor or ARB	42%	43%	40%	44%	0.71
Diuretic	52%	54%	35%	67%	<0.001
MRA	5%	4%	2%	9%	0.007

Values are mean±SD or percentage. The P value in the last table column indicates the statistical significance when testing the overall group differences (by ANOVA for continuous variables and  $\chi^2$  or Fisher exact test for categorical variables). ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; HFpEF, heart failure with preserved ejection fraction; and MRA, mineralocorticoid receptor antagonist.

\* $P$ <0.05 vs all the other groups by Sidak post hoc test.

† $P$ <0.05 vs the HFpEF group by Sidak post hoc test.

## Ventricular Size and Function

Patients had on average normal LV cavity size, mass, and EF with no between-group differences (Table 2). Concentric LV remodeling was a frequent finding in this study population but with an even distribution among the 3 groups. Of note, LV mass index was similar in HFpEF patients with and without AF, underlining the multifactorial nature of increased LV filling pressure in HFpEF.

LV GLS was on average at the lower limit of normal in the whole population (Table 2). In patients in sinus rhythm during the index echocardiography, the mean LV GLS value was normal and comparable between groups:  $-18.9\pm 3.9\%$ / $-19.1\pm 3.5\%$ / $-18.5\pm 3.8\%$  in the HFpEF/AF/HFpEF+AF group, respectively. Considering only patients with AF at the index examination, LV GLS was similarly impaired in the AF and HFpEF+AF groups:  $-15.2\pm 3.6\%$  versus  $-15.7\pm 3.7\%$ . Furthermore, patients with combined HFpEF+AF had more frequently a dilated right ventricle with impaired global systolic function (Table 2).

## LA Function and Phenotypes of LA Remodeling

In the whole study population, LAVmax was increased (LAVmax/body surface area,  $\geq 35$  mL/m<sup>2</sup>) in 90% of patients and severely increased (LAVmax/body surface

area,  $\geq 60$  mL/m<sup>2</sup>) in 37%. LASr and LAW<sub>r</sub> were both severely impaired (Table 3). Patients with LASr and LAW<sub>r</sub> below the median values were older, had a longer AF history, had a higher heart rate, used more often a diuretic, had larger LAVmax and LAVmin, and more often combined HFpEF+AF.

The pattern of LA remodeling differed between the 3 AFMR groups. In the AF and HFpEF+AF groups, patients with AF at the index examination (61% and 59% of the AF and HFpEF+AF groups, respectively) had the largest LAVs of the whole population and concomitantly severely impaired reservoir function by either LASr, LAW<sub>r</sub>, and LA expansion index (Table 3; Figure 2). When comparing only patients in sinus rhythm at echocardiography, the HFpEF and AF groups had significant differences in LAVmax, LAVmin, and LA reservoir volume, with the HFpEF patients having the smallest LA volumes and the AF group the largest ones. Moreover HFpEF patients had comparable LASr, but lower LASr normalized for heart rate and lower LAW<sub>r</sub> than the AF group. The HFpEF+AF patients had intermediate LA size but the most severe atrial dysfunction by either LASr or LAW<sub>r</sub> (Table 3; Figure 2).

To assess the contribution of AFMR to atrial remodeling, the AFMR patients were compared to a contemporary cohort of HFpEF subjects with similar sex and age distribution, but with no or only trace MR. LAVmax

**Table 2. Cardiac Structure and Function**

	All (n=515)	HFpEF (n=124)	AF (n=193)	HFpEF+AF (n=198)	P value
LV EDD, mm	46±5	46±5	46±5	46±5	0.59
LV ESD, mm	30±4	30±4	31±4	31±5	0.80
LV mass, g	177±47	178±49	177±48	177±46	0.97
LV mass index, g/h <sup>2.7</sup>	43±10	45±12	42±8*	44±11	0.03
LV hypertrophy	31%	40%	22%	33%	0.009
LV relative wall thickness	0.45±0.09	0.45±0.1	0.45±0.08	0.46±0.09	0.23
LV concentric geometry	57%	58%	54%	59%	0.63
LV EDV, mL	117±35	124±34	120±36	110±33*	0.001
LV EF, %	65±7	66±7	65±7	64±8*	0.03
LV GLS, %	-17.3±4.1	-19.0±3.9†	-16.7±4.0	-16.9±4.0	<0.001
Low GLS	50%	32%	55%	57%	<0.001
LV GCS, %	-26.8±5.5	-28.4±5.0‡	-25.5±5.3†	-27.0±5.6‡	<0.001
Dilated right ventricle§	17%	9%	15%	23%	0.04
Right ventricular systolic dysfunction§	7%	6%	4%	10%	0.16
Mild/moderate tricuspid regurgitation	82%	74%	83%	83%	<0.001
Estimated SPAP, mm Hg	45±13	49±16‡	41±9	46±13‡	<0.001

Values are mean±SD or percentage. The P value in the last table column indicates the statistical significance when testing the overall group differences (by ANOVA for continuous variables and  $\chi^2$  or Fisher exact test for categorical variables). AF indicates atrial fibrillation; EDD, end-diastolic diameter; EDV, end-diastolic volume; EF, ejection fraction; ESD, end-systolic diameter; GCS, global circumferential strain; GLS, global longitudinal strain; HFpEF, heart failure with preserved ejection fraction; LV, left ventricular; and SPAP, systolic pulmonary artery pressure.

\*P<0.05 vs the HFpEF group by Sidak post hoc test.

†P<0.05 vs all the other groups by Sidak post hoc test.

‡P<0.05 vs the AF group by Sidak post hoc test.

§Based on qualitative assessment.

**Table 3. LA Size and Function**

	HFpEF controls without MR (n=100)	All patients (n=515)	HFpEF (n=124)	AF (n=193)		HFpEF+AF (n=198)		P value
				Sinus rhythm at echo	AF at echo	Sinus rhythm at echo	AF at echo	
LAVmax, mL	86±28	106±36	85±24*	105±27†‡	124±38	96±29†‡	118±42	<0.001
LAVmax/BSA, mL/m <sup>2</sup>	46±14	56±18	45±12*	55±14†‡	64±17	52±14†‡	64±23	<0.001
LAVmax/BSA ≥35 mL/m <sup>2</sup>	80%	90%	78%	95%	94%	94%	95%	<0.001
LAVmax/BSA ≥60 mL/m <sup>2</sup>	12%	37%	11%	32%	61%	24%	54%	<0.001
LAVmin, mL	34±18§	70±34	47±21*	61±22†‡	96±32	58±25†‡	85±36	<0.001
LAVmin/BSA, mL/m <sup>2</sup>	18±9§	37±18	25±11*	32±12†‡	50±15	31±13†‡	46±21	<0.001
LA reservoir volume, mL	52±16§	36±15	38±14	44±15†‡	27±11	39±15‡	33±17	0.07
LA emptying fraction, %	62±11§	36±15	46±15	43±11‡	23±8	41±14†‡	29±12	<0.001
LA expansion index, %	186±86§	66±49	102±64*	80±32‡	31±14	79±46‡	45±27	<0.001
LASr, %	29.1±8.1§	14.8±7.6	19.9±8.6	19.4±5.8†	9.4±3.5	16.5±6.6*‡	10.6±5.1	<0.001
LAWr, %×mL	1550±685§	596±482	822±507*	907±522†	275±176	714±507‡	392±310	<0.001
LASct, %	-12.3±6.2§	-3.5±4.5	-7.2±4.7	-6.7±4.2†	NA	-4.9±3.6*‡	NA	<0.001

Values are mean±SD or percentage. HFpEF controls without AFMR were compared with the subgroup of patients with HFpEF and AFMR using independent samples *t* test. The *P* value in the last table column indicates the statistical significance when testing the overall group differences by ANOVA. AF indicates atrial fibrillation; AFMR, atrial functional mitral regurgitation; BSA, body surface area; HFpEF, heart failure with preserved ejection fraction; LA, left atrial; LASct, left atrial contraction strain; LASr, left atrial reservoir strain; LAVmax, maximum left atrial volume; LAVmin, minimum left atrial volume; LAW<sub>r</sub>, left atrial reservoir work; MR, mitral regurgitation; and NA, not applicable.

\**P*<0.05 vs all the other groups by Sidak post hoc test.

†*P*<0.05 vs the HFpEF group by Sidak post hoc test.

‡*P*<0.001 between patients in sinus rhythm and patients in AF at the echocardiographic examination in the AF and HFpEF+AF groups, respectively, by independent samples *t* test.

§*P*<0.001 between the HFpEF controls without MR and the HFpEF patient group with AFMR by independent samples *t* test.

||*P*<0.05 vs the AF group by Sidak post hoc test.

|||*P*<0.05 vs the HFpEF+AF group by Sidak post hoc test.

was comparable between patients with HFpEF with and without MR, but subjects with HFpEF and no MR had smaller LAVmin, larger reservoir volume, and significantly higher LA function by either LASr, LAW<sub>r</sub>, LA emptying fraction, and expansion index (Table 3; Figure 2).

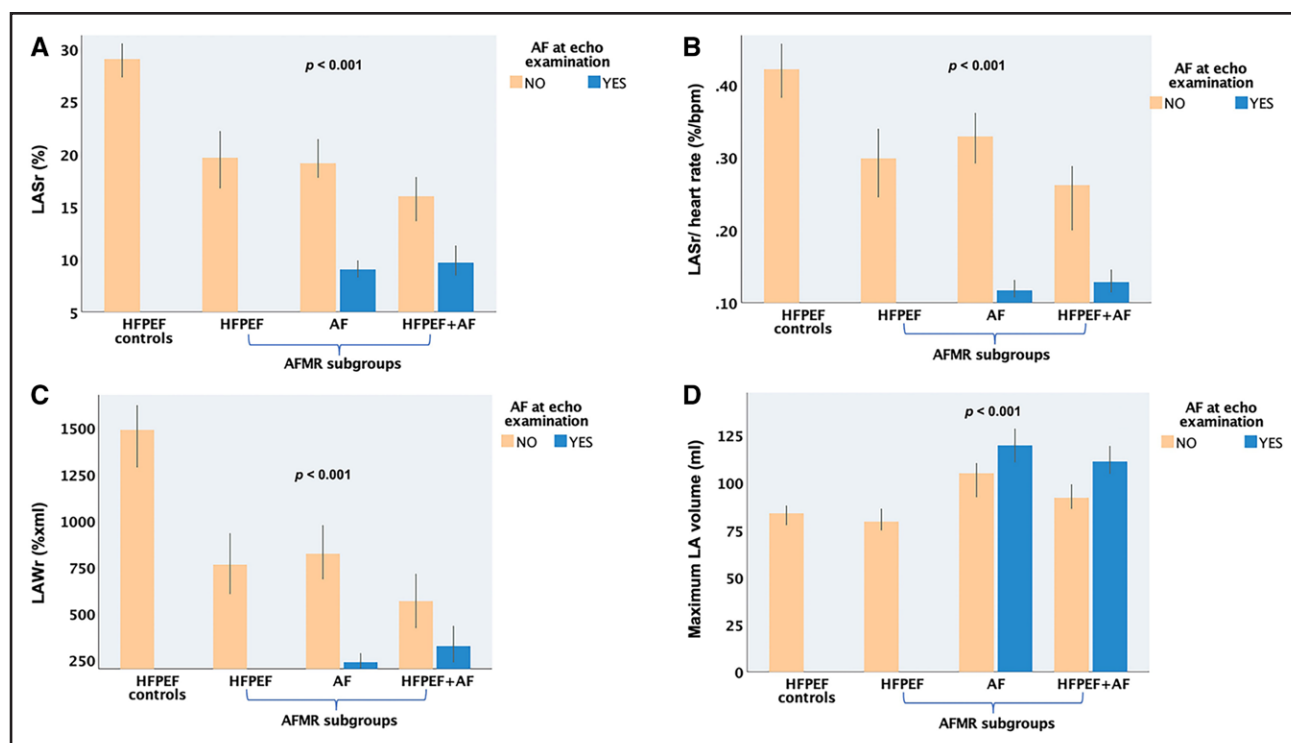
### Impact of Atrial Function on Outcomes

During the median follow-up of 5 (1–17) years, the AFMR patients experienced a high number of adverse events, including 197 (38%) deaths and 153 (30%) first-time HF hospitalizations. Only 14 patients (2.7%) underwent mitral valve surgery. The AF group had lower mortality (24%) and hospitalizations for HF symptoms (20%), while adverse events were most common in the HFpEF+AF group with 49% mortality and 33% first-time HF hospitalizations during the study period (*P*<0.001).

Of all the atrial functional indexes, LAW<sub>r</sub> followed by LASr had the strongest association with all-cause death (Figure 3). When the whole patient population was grouped according to the median value of either LASr or LAW<sub>r</sub>, low atrial function by either parameter was strongly associated

with higher risk of death over time (Figure 4) and with a higher probability of HF hospitalization (Figure 5).

In univariable Cox regression analyses, low LAW<sub>r</sub> and low LASr predicted a 4.1-fold and 3.9-fold higher risk of all-cause death (Table 4). In subgroup analyses, low LAW<sub>r</sub> and low LASr were strongly associated with death in the HFpEF+AF group (Table 5). Concentric LV geometry and lower LA reservoir volume, as well as higher age, chronic obstructive pulmonary disease, chronic kidney disease, peripheral vascular disease, HF treatment, or being in the HFpEF+AF subgroup predicted also higher risk of death. Importantly, neither LV function nor LAVmax was associated with outcome in patients with significant AFMR. Having AF at index examination did not predict outcome. After adjustment for these confounders in multivariable models, LAW<sub>r</sub> below the median value of 450.1%×mL remained the strongest independent predictor carrying a 3.4-fold higher risk of death. LARs under the median value of 13% translated into an independent 2.3-fold higher risk of all-cause death (Table 4). When LAVmax was forced into the multivariable models, the results remained unchanged.



**Figure 2.** Comparison of atrial function and size between heart failure with preserved ejection fraction (HFpEF) controls and the 3 atrial functional mitral regurgitation (AFMR) subgroups: HFpEF, atrial fibrillation (AF), and HFpEF+AF.

**A,** Left atrial reservoir strain (LASr). **B,** LASr normalized for heart rate. **C,** Left atrial reservoir work (LAWr). **D,** Maximum left atrial (LA) volume. *P* value for comparison between groups by 1-way ANOVA with Sidak post hoc test.

## DISCUSSION

In a large cohort of patients with moderate and greater AFMR, we found that AFMR is associated with either AF alone or HFpEF with or without AF. We demonstrate that these commonly AFMR-linked pathologies are associated with partially different patterns of LA remodeling, with more severely dilated atria with higher storage capacity in AFMR patients with AF alone and smaller, stiffer atria in HFpEF. LA function assessed by LASr or LAW<sub>r</sub>—a simplified index of the passive LA work in the reservoir phase—had a strong impact on patients' mortality risk after correction for multiple confounders and was a particularly powerful predictor of death in the HFpEF groups. On the contrary, LAV<sub>max</sub>—a guideline-recommended criterion for grading and considering intervention in chronic MR—had no impact on outcome in patients with significant AFMR. Finally, LAV<sub>max</sub> did not distinguish between HFpEF subjects with or without AFMR, in contrast to atrial function, which was significantly lower in the presence of AFMR.

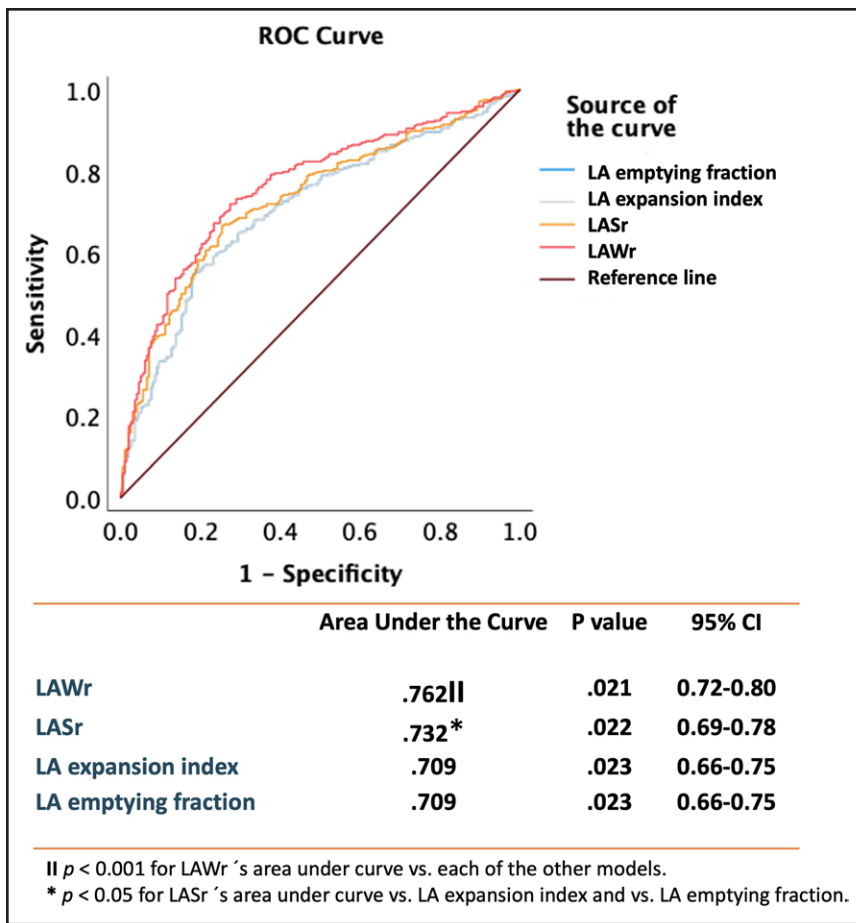
### AFMR Clinical Presentation

Functional MR in patients with normal LV size and EF but dilated LA has received increased clinical attention during the last years due to its escalating prevalence and recognition. AFMR commonly occurs in patients with a

history of AF.<sup>1,25</sup> Recent American Heart Association/American College of Cardiology and European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines for the management of valvular heart disease describe AFMR as an MR subtype associated with long-standing AF and attribute its etiology to atrial annular dilatation.<sup>4,5</sup> However, AFMR has also been described previously in HFpEF patients albeit in a limited number of studies and mostly in patients with mild MR.<sup>6,26</sup> In the present cohort, we show that HFpEF is highly associated with AFMR being present in 63% of our patients. Interestingly, LA was rarely severely dilated in the AFMR patients with HFpEF but no history of AF (11% of this group), implying that annular dilation is not the sole mechanisms behind significant MR in this clinical setting.

### Phenotypes of Atrial Remodeling in AFMR

AF and HFpEF increase in prevalence with age, have similar risk factors and clinical features, and are physiopathologically linked in complex and still incompletely understood ways.<sup>27</sup> In 285 patients with HFpEF, Reddy et al<sup>28</sup> described a continuum of disease with increasing AF burden, from none to paroxysmal and then permanent, in parallel with increasing LA myopathy assessed by LASr or LA compliance. In contrast, in AFMR, we did not see a continuum pattern with development of

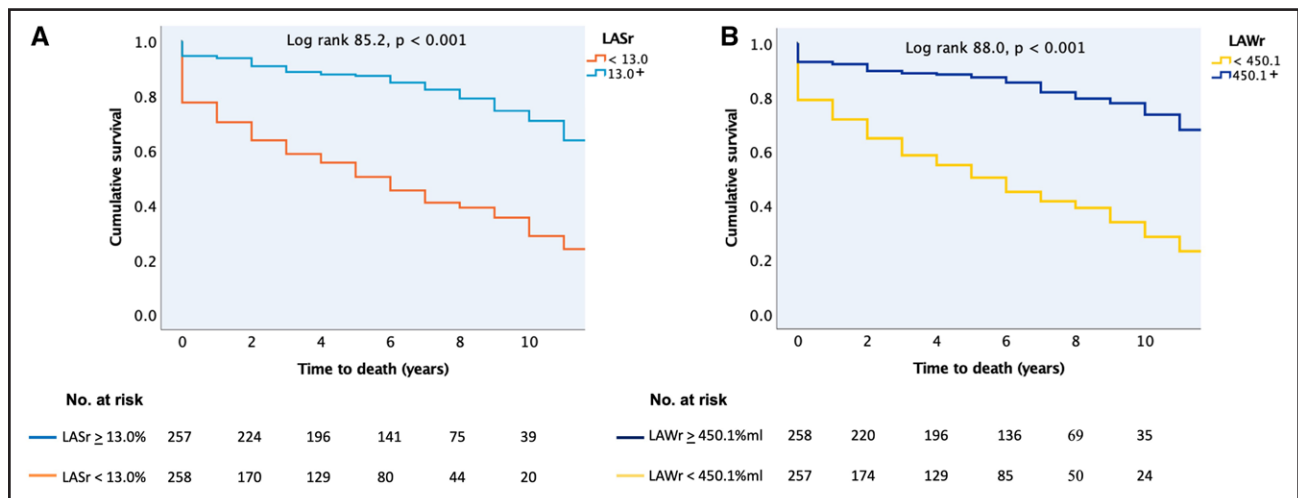


**Figure 3. Receiver operating characteristic (ROC) analysis showing the strength of the univariable relationship between different indexes of left atrial (LA) reservoir function (LA reservoir work [LAWr], LA reservoir strain [LASr], LA emptying fraction, and LA expansion index) and all-cause death.**

The table shows the areas under the curve (column 2) with the *P* value for the association between each index of LA reservoir function and all-cause death (column 3) and the 95% CIs (column 4). Additionally, the *P* values for the comparison between the areas under the curve of the 4 indexes of LA reservoir function are indicated by the symbols || and \*. || $P < 0.001$  for LAWr area under the curve vs each of the other models. \* $P < 0.05$  for LASr area under the curve vs LA expansion index and vs LA emptying fraction.

AF signaling an end-stage process but rather distinct phenotypes with important mechanistic insights about the interplay between atrial function and atrial structural remodeling. The AF-alone patients had larger LA reservoir volumes suggesting more compliant atria with higher storage reserves and hence greater accommodation of

the AFMR-related LA volume overload. In contrast, the HFpEF-alone patients had lower LA reservoir volumes suggesting smaller, stiffer atria.<sup>29</sup> This was associated with higher estimated pulmonary pressures and worse outcomes, denoting the adverse prognostic impact of a noncompliant LA. By cardiac magnetic resonance

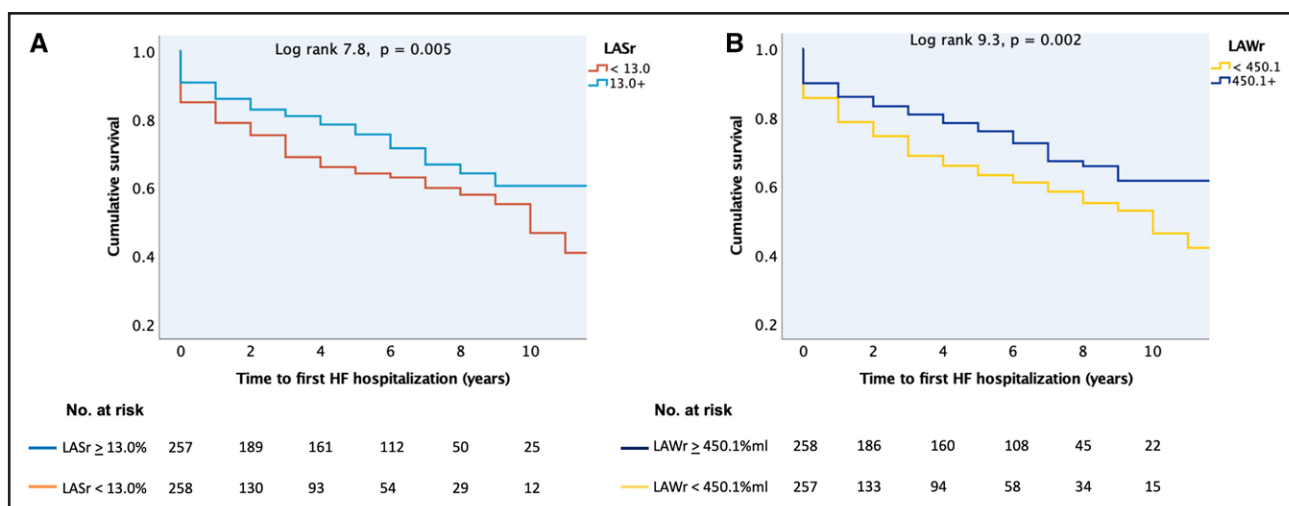


**Figure 4. Kaplan-Meier curves for time to all-cause death.**

**A**, In patients with left atrial reservoir strain (LASr) less than/greater than or equal to the median value of 13.0%. **B**, In patients with left atrial reservoir work (LAWr) less than/greater than or equal to the median value of 450.1% $\times$ mL. The value of the log-rank test is given for the overall analysis with the respective *P* value.

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**Figure 5. Kaplan-Meier curves for time to first heart failure (HF) hospitalization after inclusion in the study.**

**A**, In patients with left atrial reservoir strain (LASr) less than/greater than or equal to the median value of 13.0%. **B**, In patients with left atrial reservoir work (LAWr) less than/greater than or equal to the median value of 450.1% $\times$ mL. The value of the log-rank test is given for the overall analysis with the respective  $P$  value.

imaging, myocardial fibrosis has previously been shown to be common in HFpEF patients,<sup>30</sup> but its distribution in the cardiac chambers has been less characterized. Our findings suggest that HFpEF patients who develop significant AFMR might be an HFpEF subgroup with excessive fibrosis of the LA.<sup>29</sup> This requires, however, further elucidation by histopathological and imaging studies.

Atrial mechanical function was significantly lower in our AFMR patients than in previously published healthy individuals of similar age.<sup>31</sup> Additionally, in HFpEF patients without AF, atrial function was lower in those with AFMR than in those without MR from our control group, consistent with previously described cohorts.<sup>2</sup>

Of note, assessment of both LA and LV strain was significantly influenced by the presence of AF, with impaired LV GLS in patients with AF compared with normal values in those in sinus rhythm at the index examination and concomitantly severely impaired LASr and LAW. AF causes both loss of atrial contraction and atrial relaxation, and LA function should ideally be assessed in sinus rhythm in patients with still paroxysmal AF and otherwise reported separately for patients in different types of cardiac rhythms at echocardiography.

### Atrial Dysfunction and Outcome in AFMR

Reduced atrial deformation in the reservoir phase has recently been identified as a predictor of worse outcome in patients with HF,<sup>32</sup> including patients with HFpEF,<sup>2</sup> as well as in patients with primary MR referred to mitral valve repair<sup>33,34</sup> and patients with secondary MR of ventricular cause.<sup>35</sup>

Atrial function has not been previously characterized in relation to outcome in AFMR of more than mild

degree. This study examined a large AFMR cohort with a high number of adverse events during long-term follow-up, including a 38% mortality. This confirms previous findings of comparable excess mortality in patients with primary MR and AFMR.<sup>3</sup> We additionally found that reduced LASr was a predictor of both all-cause death and higher risk of HF hospitalization in patients with AFMR. Moreover, combining LASr and LA reservoir volume in LAW improved both prediction of death and the distinction between the AFMR phenotypes. As such, low LAW in AFMR was strongly related to worse survival in patients with HFpEF, highlighting the important negative prognostic impact of LA noncompliance.

Of note, LASr and LAW performed better in risk prediction analyses than other previously proposed markers of LA function, including the LA expansion index.<sup>16</sup>

Neither maximum LA size nor LV function as assessed by LV EF and GLS had an impact on prognosis in our study population. This challenges the common belief that LA enlargement is both the cause and the determinant of outcome in AFMR patients.<sup>4,36,37</sup>

### Clinical Implications

AFMR has been etiologically attributed to atrial and annular dilation, with later studies also demonstrating an additional role of incomplete leaflet remodeling and atriogenic posterior leaflet tethering.<sup>25,38–40</sup> The role of abnormal atrial mechanical function has not been previously examined. Our study included patients with established moderate or greater AFMR so we could not address the initial cause of the regurgitation. However, in significant AFMR, it is noteworthy that LA dilation, assessed as maximum LA volume at end systole, had no impact on prognosis and that only 37% of the whole

**Table 4. Predictors of All-Cause Death in Patients With Moderate and Greater Atrial Functional Mitral Regurgitation**

Variable	Univariable analyses		Multivariable analyses			
	HR (95% CI)	P value	Model 1		Model 2	
			HR (95% CI)	P value	HR (95% CI)	P value
Low LASr (<13%)	3.88 (2.81–5.35)	<0.001	2.32 (1.55–3.46)	<0.001	...	...
Low LAWr (<450.1%×mL)	4.06 (2.92–5.66)	<0.001			3.42 (2.41–4.85)	<0.001
Age, y	1.04 (1.03–1.05)	<0.001	1.02 (1.00–1.03)	0.04	1.02 (1.00–1.03)	0.02
Female sex	1.24 (0.94–1.64)	0.14				
Heart rate, bpm	1.01 (1.00–1.01)	0.11				
Obesity	0.91 (0.66–1.26)	0.59				
COPD	2.20 (1.57–3.07)	<0.001	1.36 (0.95–1.93)	0.09	1.50 (1.06–2.13)	0.02
AF at examination	1.22 (0.92–1.62)	0.16				
HFpEF+AF subgroup	1.81 (1.37–2.40)	<0.001	1.42 (1.04–1.93)	0.03	1.33 (0.99–1.81)	0.06
Hypertension	1.36 (0.90–2.06)	0.14				
Hypercholesterolemia	0.83 (0.62–1.11)	0.22				
Diabetes	1.21 (0.90–1.63)	0.20				
Chronic kidney disease	2.32 (1.71–3.15)	<0.001	2.20 (1.59–3.03)	<0.001	2.20 (1.60–3.03)	<0.001
Peripheral vascular disease	1.65 (1.14–2.39)	0.008	1.08 (0.73–1.58)	0.71	1.09 (0.74–1.59)	0.67
Diuretic	3.22 (2.36–4.39)	<0.001	2.76 (1.91–3.99)	<0.001	2.59 (1.80–3.73)	<0.001
ACE inhibitor or ARB	1.51 (1.14–2.02)	0.005	0.80 (0.58–1.10)	0.17	0.81 (0.59–1.11)	0.19
β-Blocker	1.88 (1.36–2.59)	<0.001	1.16 (0.81–1.67)	0.41	1.18 (0.83–1.69)	0.36
LV concentric geometry	1.36 (1.02–1.82)	0.04	1.03 (0.76–1.38)	0.87	1.04 (0.77–1.40)	0.82
LV EF, %	0.99 (0.98–1.02)	0.95				
LV GLS, %	1.02 (0.99–1.06)	0.26				
LAVmax, mL	1.00 (0.99–1.00)	0.20				
LA reservoir volume, mL	0.96 (0.95–0.97)	<0.001	0.98 (0.96–0.99)	<0.001	...	...

In the multivariable model, either LASr <13.0% and LA reservoir volume (model 1) or LAWr <450.1%×mL (model 2), in combination with the other variables, was used. ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; GLS, global longitudinal strain; HFpEF, heart failure with preserved ejection fraction; HR, hazard ratio; LA, left atrial; LASr, left atrial reservoir strain; LAVmax, maximum left atrial volume; LAWr, left atrial reservoir work; and LV, left ventricle.

cohort had severely dilated LA by standard criteria. Moreover, LAVmax was comparable between HFpEF patients with AFMR and HFpEF controls without MR. So, even if LA and annular dilation might be the kickoff of AFMR, its progression and prognosis are more closely related to atrial dysfunction.

While our data point to the important prognostic impact of low LA function in AFMR, they do not exclude that treating AFMR per se might improve outcomes. Strategies addressing both AFMR, rhythm control, and LA dysfunction such as an atrial shunt device

can be considered.<sup>41</sup> In our study, common medications that are recommended for HF with reduced EF such as angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, and β-blockers did not have independent prognostic value in AFMR, while the use of diuretics more than doubled the risk of death, perhaps reflecting, at least partially, their use in more advanced HF stages. This might suggest that optimal medical treatment for patients with HF with reduced EF, with demonstrated value in secondary MR of ventricular cause,<sup>42,43</sup> does not have the same advantages

**Table 5. Univariable Cox Analyses of the Association Between Low LASr and Low LAWr and All-Cause Death in Subgroups of Patients With Significant Atrial Functional Mitral Regurgitation**

Variable	HFpEF (n=124)		AF (n=193)		HFpEF+AF (n=198)	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Low LASr (<13%)	6.63 (3.77–11.66)	<0.001	1.65 (0.89–3.07)	0.11	9.39 (5.19–16.98)	<0.001
Low LAWr (<450.1%×mL)	5.46 (3.17–9.42)	<0.001	1.98 (1.04–3.77)	0.04	9.74 (5.18–18.30)	<0.001

Low LASr and low LAWr are defined as values below the median of 13.0% and 450.1%×mL, respectively. AF indicates atrial fibrillation; HFpEF, heart failure with preserved ejection fraction; HR, hazard ratio; LASr, left atrial reservoir strain; and LAWr, left atrial reservoir work.

in AFMR. Catheter AF ablation has previously been shown to reduce LA size and AFMR severity in selected AF patients.<sup>37</sup> However, ablations can increase LA stiffness through scar formation,<sup>44</sup> and one should probably be particularly careful in using this therapeutic strategy in patients with concomitant AF and HFpEF that have, as our data show, limited atrial expansibility and severe LA dysfunction.

Studies on the relative contribution of atrial dysfunction versus increasing MR volume to symptoms during exercise are lacking in AFMR patients. Exercise testing may unmask stiff LAs or worsening MR in symptomatic AFMR patients.

## Study Limitations

The present study is a retrospective follow-up of patients with significant AFMR and has the limitations inherent to this study design. However, it is the largest AFMR cohort characterized clinically and echocardiographically up to this date, and our findings contribute to better understanding of an increasingly prevalent MR subtype. Data on AFMR effective regurgitant orifice area and regurgitation volume were not available for the present analyses; however, the vast majority of the patients (97%) had moderate AFMR based on a comprehensive evaluation done by experienced echocardiologists. History of AF was based on review of all previous electrocardiograms and clinical charts, so one cannot exclude that some HFpEF patients might have had an undocumented AF episode. However, this would only reduce the observed differences between the AFMR phenotypes (bias toward the null). Similarly, even if none of our patients with AF had previous HF hospitalizations and this subgroup had significantly less dyspnea and use of diuretics, some of the patients with AF might have had earlier stages of HFpEF.<sup>27</sup> However, this would again only bias our results toward the null. Contemporary controls with AFMR and no MR were not followed up for the same duration of time as AFMR patients. The control group was though only selected for comparison of atrial remodeling between HFpEF with and without AFMR, as LA function in relation to outcome has been previously reported in patients with HFpEF with no significant MR.<sup>2,28</sup> Finally, LAW<sub>r</sub> requires further validation in both experimental and clinical settings.

## Conclusions

AFMR develops in patients with AF or HFpEF in whom it is associated with partially different LA remodeling patterns. LA mechanics does not parallel changes in LA size and is severely impaired in significant AFMR and particularly in patients with a history of HFpEF in whom it is a strong predictor of death. Neither maximum LA size nor

LV function are significant prognosticators in AFMR. The outcome of patients with AFMR is related to the degree of LA reservoir dysfunction independent of comorbidities and medical treatment.

## ARTICLE INFORMATION

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### Disclosures

None.

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