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# Prognostic comparison of atrial and ventricular functional mitral regurgitation

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## ABSTRACT

**Objective** Atrial functional mitral regurgitation (A-FMR) has been suggested as a new aetiology of functional MR (MR); however, its prognosis and prognostic predictors are not fully elucidated. Aim of this study was to investigate the prognosis and prognostic predictors of A-FMR in comparison with ventricular functional MR (V-FMR).

**Methods** Three hundred and seventy-eight consecutive patients with moderate-to-severe or severe functional MR were studied. Functional MR was classified into V-FMR (N=288) and A-FMR (N=90) depending on the alterations of left ventricle (LV) or left atrium (LA) along with clinical context and diagnosis of ischaemic heart disease or cardiomyopathy.

**Results** During a median follow-up of 4.1 (2.0–6.7) years, all-cause mortality, cardiovascular mortality and heart failure (HF) hospitalisation occurred in 98 (26%), 81 (21%) and 177 (47%) patients, respectively, and rates of these events and the composite end point of all-cause mortality and HF hospitalisation were consistently higher in V-FMR than A-FMR (unadjusted HR 1.762 (95% CI 1.250 to 2.438), p<0.001; adjusted HR 1.654 (95% CI 1.027 to 2.664), p=0.038, for the composite end point). Further analysis showed different prognostic predictors between V-FMR and A-FMR; while age and LA volume index were independent prognostic predictors of both V-FMR and A-FMR, systolic blood pressure and B-type natriuretic peptide were also those of V-FMR, and estimated glomerular filtration rate, LV end-systolic dimension and tricuspid regurgitation were also those of A-FMR.

**Conclusions** The prognosis of V-FMR was significantly worse than that of A-FMR, and prognostic predictors were different between V-FMR and A-FMR. Our study suggests the importance of discriminating A-FMR and V-FMR, and that different treatment strategies may be considered for each aetiology.

## Key questions

### What is already known about this subject?

► Atrial functional mitral regurgitation (A-FMR) has been recently suggested as a new aetiology of functional MR. Data regarding the prognosis and prognostic predictors of A-FMR are limited.

### What does this study add?

► Our study reports that the prognosis of ventricular functional MR (V-FMR) was significantly worse than that of A-FMR, and prognostic predictors were different between V-FMR and A-FMR.

### How might this impact on clinical practice?

► The current guidelines do not emphasise the importance of discriminating A-FMR and V-FMR; however, our study suggests the importance to discriminate A-FMR and V-FMR, and that different treatment strategies may be considered for each aetiology.

## INTRODUCTION

Functional mitral regurgitation (MR) is recognised as MR that occurs in structurally normal leaflets without significant degenerative changes. Classically, it has been recognised to be observed in the severely dilated left ventricle (LV) or ischaemic LV with mitral leaflet tethering due to a displaced papillary muscle (recently recognised as ventricular functional MR (V-FMR)), and coexistence of V-FMR in heart failure (HF) with reduced ejection fraction (EF) is associated with worse clinical outcomes.[1–5]

In contrast, recent studies have suggested a new aetiology of functional MR in patients with dilated left atrium (LA) or mitral annulus without obvious LV systolic dysfunction, typically in the context of atrial fibrillation (AF) and/or HF with preserved EF. This novel type of functional MR has been recently recognised as atrial functional MR (A-FMR).[6–8] Although suggested mechanisms of A-FMR include LA dilatation, atriogenic leaflet tethering, mitral annular dilation, insufficient leaflet remodelling and reduced annular contractility, its precise mechanisms remain unclear.[9–13] As A-FMR has been under-recognised until recently as a cause of functional MR, its prognosis and prognostic predictors (especially in comparison with V-FMR, in which the prognosis is also associated with the underlying LV disease) are not fully elucidated.

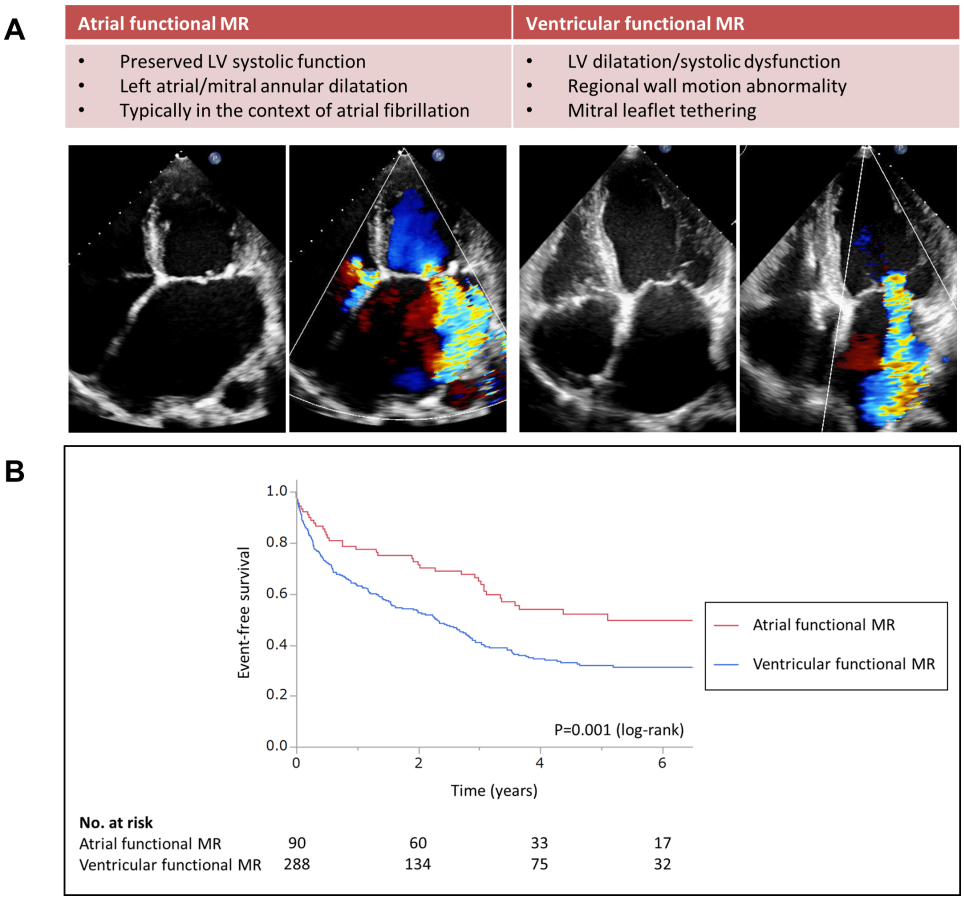



**Figure 1** Characteristics of atrial and ventricular functional mitral regurgitation and prognostic comparison. (A) Characteristics of atrial functional mitral regurgitation (MR) and ventricular functional MR. (B) Kaplan-Meier analysis for the composite end point of all-cause mortality and heart failure hospitalisation showed that ventricular functional MR had significantly higher event rates compared with atrial functional MR (p=0.001, log-rank). LV, left ventricle.

Since different pathophysiology and mechanisms have been suggested between V-FMR and A-FMR, we hypothesised that the prognosis and prognostic predictors may differ between these two aetiologies.

## METHODS

This study was performed from a cohort of consecutive MR patients identified from our institutional echocardiography database. The details of this cohort have been published previously.[14] Briefly, we identified 4049 transthoracic echocardiography examinations performed in 1312 patients with grade 3+ (moderate-to-severe) or 4+ (severe) MR from January 2012 to December 2015. For the current study, patients with degenerative MR, moderate or greater aortic valve disease or mitral stenosis, previous valve surgery or transcatheter aortic valve replacement were excluded, and 378 consecutive patients with functional MR were studied. Functional MR was further classified into V-FMR (N=288) and A-FMR (N=90) depending on the alterations of LV or LA (functional MR with moderate or severe LV remodelling (enlargement or dysfunction or both) were classified as V-FMR; functional MR with nor or mild ventricular remodelling but moderate or severe atrial remodelling were classified as A-FMR) along with clinical context and diagnosis of ischaemic heart disease or cardiomyopathy, as previously described.[15] In detail, we classified functional MR with EF <40% or EF ≥40% with regional wall motion abnormality as V-FMR along with clinical diagnosis of ischaemic heart disease or non-ischaemic cardiomyopathy, and functional MR with EF ≥50% or EF 40%–50% with LA dilatation (LA volume index >48 mL/m$^2$)[16] and no regional wall motion abnormality as A-FMR (figure 1A). All patients in the A-FMR group had LA volume index >48 mL/m$^2$ and no patients remained unclassified. For determination of the MR aetiology and mechanism, echocardiography and clinical data were reviewed by two experienced cardiologists (CO and AO).

All patients underwent echocardiography by experienced technicians using commercially available ultrasonography systems. Assessments of cardiac function and valvular disease were performed in accordance to the guidelines of the American Society of Echocardiography.[16 17] The severity of the MR was defined using a multiparametric approach, including an assessment of the colour Doppler-derived jet area, regurgitant volume, regurgitant fraction and effective regurgitant orifice area using Doppler-derived method and the proximal isovelocity surface area method and the pulmonary vein flow pattern. The severity of TR was defined using a multiparametric approach, including an assessment

**Table 1** Patient characteristics

| | Ventricular functional MR N=288 | Atrial functional MR N=90 | P value |
|---|---|---|---|
| Age, years | 70 (58–77) | 76 (69–82) | <0.001 |
| Male, n (%) | 188 (65) | 32 (36) | <0.001 |
| Body surface area, $m^2$ | 1.59±0.19 | 1.53±0.18 | 0.004 |
| NYHA functional class, n (%) | | | <0.001 |
| I/II | 213 (74) | 86 (96) | |
| III/IV | 75 (26) | 4 (4) | |
| Previous HF hospitalisation, n (%) | 205 (71) | 49 (55) | 0.005 |
| Atrial fibrillation, n (%) | | | <0.001 |
| None | 168 (58) | 11 (12) | |
| Paroxysmal | 47 (16) | 12 (13) | |
| Persistent/chronic | 73 (25) | 67 (74) | |
| Hypertension, n (%) | 132 (46) | 54 (60) | 0.019 |
| Dyslipidaemia, n (%) | 150 (52) | 36 (40) | 0.045 |
| Diabetes, n (%) | 62 (22) | 16 (18) | 0.44 |
| Ischaemic heart disease, n (%) | 84 (29) | 7 (8) | <0.001 |
| Cardiac resynchronisation therapy, n (%) | 48 (17) | 0 (0) | <0.001 |
| Heart rate, bpm | 70 (60–81) | 70 (61–81) | 0.83 |
| Systolic blood pressure, mm Hg | 107 (92–126) | 120 (108–135) | <0.001 |
| Diastolic blood pressure, mm Hg | 65 (56–77) | 70 (60–74) | 0.08 |
| **Laboratory data** | | | |
| Haemoglobin, g/L | 124±20 | 122±19 | 0.37 |
| Estimated glomerular filtration rate, mL/min/1.73 $m^2$ | 51 (36–65) | 53 (35–67) | 0.58 |
| B-type natriuretic peptide, pg/mL | 447 (213–952) | 169 (101–318) | <0.001 |
| **Medications during follow-up** | | | |
| Beta-blocker, n (%) | 239 (83) | 48 (53) | <0.001 |
| ACE-I/ARB, n (%) | 226 (79) | 54 (60) | <0.001 |
| Mineralocorticoid receptor antagonist, n (%) | 156 (54) | 24 (27) | <0.001 |
| Loop diuretic, n (%) | 217 (75) | 59 (66) | 0.07 |

Numeric values are expressed as mean±SD or median (IQR).
ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; HF, heart failure; MR, mitral regurgitation; NYHA, New York Heart Association.

of the colour Doppler-derived jet area, the continuous wave Doppler-derived jet density and contour, and the hepatic vein flow pattern. The methods for the assessments of these valvular regurgitations were selected for each patients by careful consideration of the methodological advantages and limitations according to the guidelines, and MR and TR was graded as 0 (none), 1+ (mild), 2+ (moderate), 3+ (moderate to severe) or 4+ (severe). Grade 3+ (moderate to severe) or 4+ (severe) TR was considered as significant TR.

Persistent AF was defined as continuous AF sustained for >7 days, and paroxysmal AF as AF that spontaneously terminated within 7 days. Blood pressures were obtained at the beginning of echocardiography examination. Laboratory data were collected from electronic charts obtained at the closest date from echocardiography (the median difference between date of echocardiography and laboratory data was 0 (0–2) days). Estimated glomerular filtration rate (eGFR) was determined using the abbreviated Modification of Diet in Renal Disease equation.

### Clinical events during follow-up

All-cause mortality, cardiovascular (CV) mortality, HF hospitalisation and the composite end point of all-cause mortality and HF hospitalisation were evaluated as clinical events in this study. CV mortality included deaths that resulted from acute myocardial infarction, sudden cardiac death, death due to HF, death due to stroke, death due to CV procedures, death due to CV haemorrhage and death due to other CV causes. HF hospitalisation was defined as unplanned hospitalisation due to worsening HF symptoms and physical findings requiring hospitalisation, diagnosed based on the Framingham criteria by an experienced cardiologist. Patients were followed from the date of echocardiography and censored at the time of the last hospital visit. Data regarding mitral

**Table 2** Echocardiographic variables

| | Ventricular functional MR N=288 | Atrial functional MR N=90 | P value |
|---|---|---|---|
| LV end-diastolic dimension, mm | 64 (58–72) | 52 (48–57) | <0.001 |
| LV end-systolic dimension, mm | 55 (48–64) | 34 (31–37) | <0.001 |
| LV ejection fraction, % | 28 (19–35) | 55 (50–60) | <0.001 |
| Interventricular septal thickness, mm | 8.1±2.2 | 8.9±1.6 | 0.003 |
| Posterior wall thickness, mm | 8.3±2.0 | 9.0±1.5 | <0.001 |
| LA diameter, mm | 48 (43–54) | 52 (47–61) | <0.001 |
| LA volume index, mL/m$^2$ | 73 (57–91) | 99 (73–137) | <0.001 |
| Tricuspid regurgitation, n (%) | 28 (10) | 35 (39) | <0.001 |
| Tricuspid regurgitation pressure gradient, mm Hg | 33 (23–43) | 30 (25–38) | 0.18 |
| Quantitative MR severity | | | |
| Volumetric method | | | |
| Regurgitant volume, mL | 47 (37–59) | 45 (41–60) | 0.61 |
| Regurgitant fraction, % | 50 (45–56) | 46 (38–55) | 0.08 |
| PISA method | | | |
| Regurgitant volume, mL | 48 (40–61) | 49 (39–65) | 0.77 |
| Effective regurgitant orifice area, cm$^2$ | 0.32 (0.26–0.40) | 0.31 (0.24–0.45) | 0.95 |

Numeric values are expressed as mean±SD or median (IQR).
LA, left atrium; LV, left ventricle; MR, mitral regurgitation; PISA, proximal isovelocity surface area.

valve intervention, left ventricular assist device implantation and heart transplantation during the follow-up period were also collected, and patients who were referred for these interventions without the clinical events were handled as not reaching an endpoint and these cases were censored. Clinical outcomes, including mortality, adverse events and details of mitral valve interventions, were retrieved from hospital patient records and from primary care physicians.

### Patient and public involvement

Patients were involved in prioritising the research question but due to the nature of the study using an electronic echocardiography database, they were not involved further in the design, conduct or reporting of this work.

### Statistical analysis

Values were expressed as mean±SD if the variable was normally distributed, or median (IQR) if not. Groups were compared using Student's t-test or Wilcoxon test for continuous values and $\chi^2$ test for categorical data, as appropriate. Shapiro-Wilk's test was used to assess whether data were normally distributed or not. All tests were two sided, and $p<0.05$ was considered statistically significant. Kaplan-Meier analysis was used to evaluate clinical events during follow-up,

**Table 3** Events during follow-up

| | Ventricular functional MR N=288 | Atrial functional MR N=90 | P value |
|---|---|---|---|
| Events, n (%) | | | |
| All-cause mortality | 84 (29) | 14 (16) | 0.010 |
| Cardiovascular mortality | 72 (25) | 9 (10) | 0.002 |
| HF hospitalisation | 145 (50) | 32 (36) | 0.014 |
| Composite end point, n (%) | | | |
| All-cause mortality or HF hospitalisation | 177 (61) | 40 (44) | 0.005 |
| Other interventions, n (%) | | | |
| Mitral valve interventions | 28 (10) | 22 (24) | <0.001 |
| Surgical mitral valve plasty | 15 (5) | 9 (10) | |
| Surgical mitral valve replacement | 8 (3) | 10 (11) | |
| Transcatheter mitral valve repair | 5 (2) | 3 (3) | |
| LVAD implantation | 34 (12) | 0 (0) | 0.001 |
| Heart transplantation | 18 (6) | 0 (0) | 0.015 |

HF, heart failure; LVAD, left ventricular assist device; MR, mitral regurgitation.

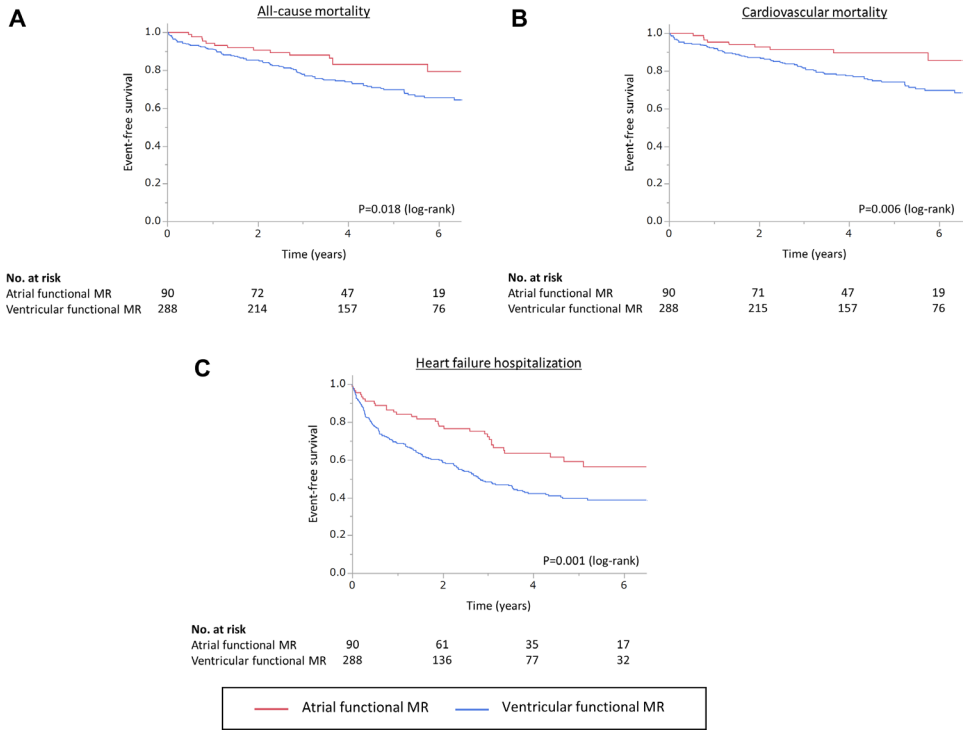



**Figure 2** Kaplan-Meier analysis for all-cause mortality, cardiovascular mortality and heart failure hospitalisation Kaplan-Meier analysis showed that event rates of (A) all-cause mortality, (B) cardiovascular mortality and (C) heart failure hospitalisation were consistently higher in ventricular functional mitral regurgitation (MR) compared with atrial functional MR.

and differences in survival curves were tested with log-rank test (Mantel-Cox). Cox proportional hazard analysis was performed to evaluate the influence of variables on events. Variables for analysis were selected based on clinical relevance and data from previous literature. Multivariable Cox regression analysis was performed using covariates that significantly predicted each end point in the univariable analysis and established prognostic risk factors for HF. Multivariable models were created using stepwise selection method (backwards elimination, removing all variables with a p>0.20). For all variables, we assessed the assumption of proportional hazards by testing for a nonzero slope in a plot of scaled Schoenfeld residuals against time. Multicollinearity among the variables in the model was assessed by calculation of the variance inflation factor and correlation coefficient. All statistical analyses were performed with JMP V.12 (SAS Institute) and SPSS V.26 (SPSS) software.

## RESULTS

The patients' characteristics are shown in table 1. A-FMR patients had significantly older age, higher female ratio, smaller body surface area and lower New York Heart Association functional class compared with V-FMR. Further, they had a lower rate of previous HF hospitalisation, higher rates of persistent/chronic AF and hypertension and lower rates of dyslipidaemia and ischaemic heart disease. Systolic blood pressure was significantly higher in A-FMR. Laboratory data showed that A-FMR had lower B-type natriuretic peptide (BNP) level. Medication during the follow-up included significantly higher rates of beta-blockers, ACE inhibitors and angiotensin II receptor blockers, and mineralocorticoid receptor antagonists in V-FMR compared with A-FMR.

Table 2 shows a comparison of echocardiographic variables. In A-FMR, LV end-diastolic and end-systolic dimensions were significantly smaller, and LV EF, interventricular septal thickness, posterior wall thickness, LA size and rate of significant TR were higher than V-FMR. There were no significant differences in quantitative MR severity of regurgitant volume and effective regurgitant orifice area, although regurgitant fraction tended to be higher in V-FMR.

### Clinical events during follow-up

Table 3 lists the events observed during a median follow-up of 4.1 (2.0–6.7) years. Follow-up periods were comparable between A-FMR and V-FMR (4.0 (2.5–5.7) vs 4.2 (1.6–6.1) years, p=0.88). Rates of all-cause mortality, CV mortality and HF hospitalisation were all significantly higher in the V-FMR group, and the composite end point of all-cause mortality and HF hospitalisation occurred in 177 (61%) of V-FMR and 40 (44%) of A-FMR patients (p=0.005). Mitral valve interventions were performed in 28 (10%) of V-FMR and 22 (24%) of A-FMR patients (p<0.001). Left ventricular assist device implantation and heart transplantation were performed in 34 (12%) and 18 (6%) V-FMR patients, respectively, and in no A-FMR patients.

Kaplan-Meier analysis showed that rates of all-cause mortality, CV mortality, HF hospitalisation and the

**Table 4** Multivariable Cox regression hazard analysis for risk of the composite end point

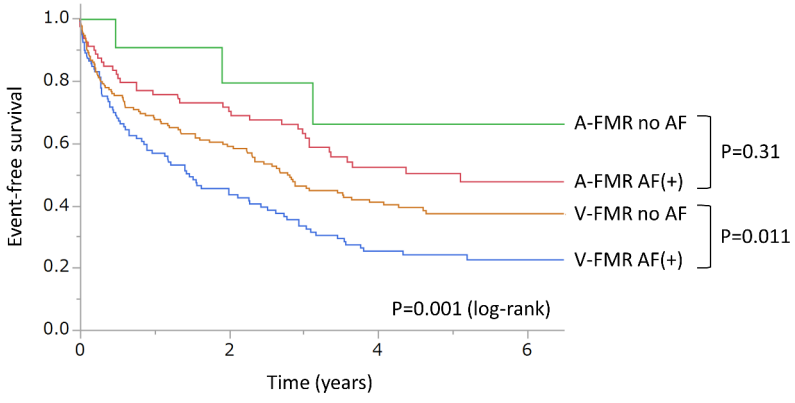
| | Univariable | | Multivariable | |
|---|---|---|---|---|
| | HR (95% CI) | P value | HR (95% CI) | P value |
| V-FMR/A-FMR | 1.762 (1.250 to 2.438) | <0.001 | 1.654 (1.027 to 2.664) | 0.038 |
| Age, 1 year | 1.015 (1.005 to 1.026) | 0.004 | 1.027 (1.015 to 1.040) | <0.001 |
| Male sex | 1.255 (0.953 to 1.654) | 0.11 | | |
| NYHA functional class III/IV | 1.394 (1.016 to 1.912) | 0.039 | | |
| Atrial fibrillation | 1.161 (0.888 to 1.517) | 0.28 | 1.437 (1.046 to 1.973) | 0.025 |
| Systolic blood pressure, 1 mm Hg | 0.992 (0.985 to 0.998) | 0.015 | | |
| Log B-type natriuretic peptide, 1 pg/mL | 1.453 (1.289 to 1.637) | <0.001 | 1.332 (1.162 to 1.526) | <0.001 |
| Estimated glomerular filtration rate, 1 mL/min/1.73 $m^2$ | 0.985 (0.978 to 0.991) | <0.001 | | |
| LV end-systolic dimension, 1 mm | 1.014 (1.005 to 1.023) | 0.002 | 1.017 (1.002 to 1.031) | 0.025 |
| LV ejection fraction, 1% | 0.983 (0.974 to 0.992) | <0.001 | | |
| LA volume index, 1 mL/$m^2$ | 1.004 (1.002 to 1.006) | <0.001 | 1.004 (1.002 to 1.007) | 0.001 |
| Tricuspid regurgitation | 1.012 (0.710 to 1.442) | 0.95 | | |
| MR regurgitant volume, 1 mL | 1.012 (0.998 to 1.026) | 0.10 | | |

LV ejection fraction were not adjusted for multivariable regressions because of collinearity (between LV end-systolic dimension and LV ejection fraction, R=−0.80).
A-FMR, atrial functional mitral regurgitation; LA, left atrium; LV, left ventricle; MR, mitral regurgitation; NYHA, New York Heart Association; V-FMR, ventricular functional mitral regurgitation.

composite end point were consistently higher in V-FMR (figures 1B and 2). Cox regression hazard analysis for the composite end point (table 4) showed significant hazard ratios of V-FMR over A-FMR (unadjusted HR 1.762 (95% CI 1.250 to 2.438), p<0.001, adjusted HR 1.654 (95% CI 1.027 to 2.664), p=0.038).

Figure 3 shows the event rates of the composite end point stratified by the presence of AF. The figure shows that there was no significant difference between A-FMR with and without AF (p=0.31), while V-FMR with AF had a significantly worse prognosis compared with V-FMR with no AF (p=0.011). Patients' characteristics of A-FMR patients between AF and no AF in are shown in online supplemental table 1.

Table 5 shows further analysis of individual prognostic predictors of V-FMR and A-FMR for the composite end point by multivariable Cox regression hazard analysis. While age and LA volume index were independent prognostic predictors of both V-FMR and A-FMR, systolic blood pressure and Log BNP were also those of V-FMR and eGFR, LV end-systolic dimension and TR were also those of A-FMR. Kaplan-Meier analyses of A-FMR stratified by median values of age and echocardiographic variables are shown in online supplemental figure 1. There




| No. at risk | | | | |
|---|---|---|---|---|
| A-FMR no AF | 11 | 8 | 5 | 2 |
| A-FMR AF(+) | 79 | 53 | 29 | 16 |
| V-FMR no AF | 168 | 88 | 54 | 23 |
| V-FMR AF(+) | 120 | 47 | 24 | 10 |

**Figure 3** Kaplan-Meier analysis for composite end point stratified by atrial fibrillation. There were no significant differences between atrial functional mitral regurgitation (A-FMR) with and without atrial fibrillation (AF) (p=0.31), while ventricular FMR (V-FMR) with AF had a significantly worse outcome compared with V-FMR with no AF (p=0.011).

**Table 5** Multivariable Cox regression hazard analysis for individual prognostic predictors of ventricular functional mitral regurgitation (V-FMR) and atrial functional mitral regurgitation (A-FMR)

| | Univariable | | Multivariable | |
|---|---|---|---|---|
| | HR (95% CI) | P value | HR (95% CI) | P value |
| **(A) V-FMR** | | | | |
| Age, 1 year | 1.019 (1.007 to 1.030) | 0.001 | 1.024 (1.012 to 1.036) | <0.001 |
| Male sex | 1.175 (0.854 to 1.616) | 0.32 | | |
| NYHA functional class III/IV | 1.173 (0.840 to 1.638) | 0.35 | | |
| Atrial fibrillation | 1.468 (1.092 to 1.973) | 0.011 | | |
| Systolic blood pressure, 1 mm Hg | 0.995 (0.988 to 1.002) | 0.17 | 0.991 (0.983 to 0.999) | 0.028 |
| Log B-type natriuretic peptide, 1 pg/mL | 1.361 (1.191 to 1.554) | <0.001 | 1.325 (1.154 to 1.523) | <0.001 |
| Estimated glomerular filtration rate, 1 mL/min/1.73 $m^2$ | 0.989 (0.982 to 0.995) | 0.001 | | |
| LV end-systolic dimension, 1 mm | 1.004 (0.992 to 1.016) | 0.54 | | |
| LV ejection fraction, 1% | 0.989 (0.975 to 1.003) | 0.12 | | |
| LA volume index, 1 mL/$m^2$ | 1.005 (1.002 to 1.008) | <0.001 | 1.004 (1.001 to 1.007) | 0.008 |
| Tricuspid regurgitation | 0.955 (0.579 to 1.574) | 0.86 | | |
| MR regurgitant volume, 1 mL | 1.011 (0.996 to 1.028) | 0.16 | | |
| **(B) A-FMR** | | | | |
| Age, 1 year | 1.057 (1.015 to 1.101) | 0.008 | 1.056 (1.002 to 1.114) | 0.043 |
| Male sex | 0.972 (0.512 to 1.846) | 0.93 | | |
| NYHA functional class III/IV | 2.864 (0.688 to 7.993) | 0.13 | | |
| Atrial fibrillation | 1.821 (0.561 to 5.907) | 0.32 | | |
| Systolic blood pressure, 1 mm Hg | 0.993 (0.975 to 1.011) | 0.44 | | |
| Log B-type natriuretic peptide, 1 pg/mL | 1.837 (1.234 to 2.735) | 0.003 | | |
| Estimated glomerular filtration rate, 1 mL/min/1.73 $m^2$ | 0.963 (0.947 to 0.979) | <0.001 | 0.979 (0.961 to 0.997) | 0.025 |
| LV end-systolic dimension, 1 mm | 1.057 (1.006 to 1.110) | 0.027 | 1.082 (1.022 to 1.145) | 0.007 |
| LV ejection fraction, 1% | 0.964 (0.922 to 1.008) | 0.11 | | |
| LA volume index, 1 mL/$m^2$ | 1.006 (1.003 to 1.010) | <0.001 | 1.005 (1.001 to 1.008) | 0.022 |
| Tricuspid regurgitation | 1.990 (1.067 to 3.709) | 0.030 | 2.389 (1.185 to 4.816) | 0.015 |
| MR regurgitant volume, 1 mL | 1.018 (0.985 to 1.053) | 0.29 | | |

LA, left atrium; LV, left ventricle; MR, mitral regurgitation; NYHA, New York Heart Association.

were associations between larger LV end-systolic dimension, LA volume index and MR severity in A-FMR (online supplemental table 2).

## DISCUSSION

In the current analysis of 378 functional MR patients, there were two main findings. First, the rates of all-cause mortality, CV mortality and HF hospitalisation were consistently higher in V-FMR than in A-FMR. Second, prognostic predictors were different between V-FMR and A-FMR; while age and LA volume index were independent prognostic predictors of both V-FMR and A-FMR, systolic blood pressure and BNP were also those of V-FMR, and eGFR, LV end-systolic dimension and TR were also those of A-FMR.

### Definition of A-FMR and prognostic comparison of A-FMR and V-FMR

While A-FMR has been recently recognised as functional MR observed typically in the context of AF and/or HF without obvious LV systolic dysfunction, there has been no clear definition of A-FMR. Most previous studies have defined A-FMR as 'functional MR in patients with preserved EF' or 'functional MR in patients with AF and EF ≥50%'.[8–12 18–21] Two studies have reported prognosis of A-FMR and V-FMR by these definitions. Kajimoto *et al*[5] studied the prognostic impact of functional MR in 3357 patients admitted for acute HF, and reported that residual functional MR at discharge was significantly associated with a higher rate of composite events (all-cause mortality and readmission for HF) in both the EF >40% and EF ≤40% groups, suggesting that functional MR in patients with preserved EF as well as reduced EF is associated with a worse outcome. However, they did not compare the prognostic impact of functional MR between EF >40% and EF ≤40% (ie, the prognostic comparison between A-FMR and V-FMR). A small study by Saito *et al*,[21] of 189 hospitalised HF patients including 30 with A-FMR (defined as EF ≥50% with AF and moderate/severe functional MR), reported that there were no significant differences in CV events between A-FMR and V-FMR (defined as EF <50% with AF and moderate/severe functional MR). Our results are

in contrast to their study, although their data are limited by selection bias of the study population as well as their limited statistical power including a study population approximately one third the size of ours with alternative study outcomes.

We defined V-FMR and A-FMR depending on the alterations of LV or LA along with clinical context and diagnosis of ischaemic heart disease or cardiomyopathy, which was recently described by Dziadzko *et al*.[15] They reported that A-FMR and V-FMR patients both had worse survival compared with age-matched and sex-matched general populations; however, direct comparison of survival between A-FMR and V-FMR was not reported in their study. HF events were compared, and the rates of HF events were significantly higher in V-FMR compared with A-FMR, which was consistent with our study. Prognostic predictors of A-FMR and V-FMR were not reported.

The results of our study, showing that rates of all-cause mortality, CV mortality and HF hospitalisation were all consistently higher in V-FMR compared with A-FMR, emphasise the importance of discriminating A-FMR and V-FMR.

### Prognostic predictors of A-FMR

There are limited data regarding the prognostic predictors of A-FMR. We report that age, eGFR, LV end-systolic dimension, LA volume index and TR were independent prognostic predictors of A-FMR, which were different from those of V-FMR where the underlying LV disease is also associated with its prognosis. Interestingly, LV end-systolic dimension and LA volume index are two echocardiographic variables that are currently accepted for prognostic stratification and determining surgical indication in degenerative MR.[22 23]

We found association between larger LV end-systolic dimension, LA volume index and MR severity in A-FMR, which is in line with the recent study reported by Akamatsu *et al* which reported that LA dimension and LV end-systolic dimension were both associated with MR severity in A-FMR.[24] These two variables could be linked to MR severity, or perhaps reflect left-sided volume overload as in degenerative MR, and may be a prognostic predictor in A-FMR. MR severity itself could be but was not a significant prognostic predictor in our data; however, our data suggests that LA size and LV end-systolic dimension associated with MR severity could be a surrogate marker. Our study results suggest that these two variables may be considered for prognostic stratification of A-FMR and that they could be considered for determining indications of mitral valve interventions in A-FMR. However, further studies are needed to determine appropriate cut-off values which may be different from those of degenerative MR (LV end-systolic dimension of 40 or 45 mm and LA volume index of 60 mL/m$^2$), as median LV end-systolic dimension was 34 mm and median LA volume index was 99 mL/m$^2$ in our A-FMR group. While treatment strategies for V-FMR including optimal patient selection are starting to be reviewed,[25 26] outcome data of mitral valve intervention in A-FMR are very limited.[20 27–29] In addition, TR is often observed as a consequence of long-standing AF and atrial dilatation, which are common patient backgrounds in A-FMR and TR. Significant TR as a prognostic indicator in A-FMR may be important in considering transcatheter treatment strategies for A-FMR, as concomitant mitral and tricuspid interventions may be needed for patients with A-FMR and concomitant TR.[19 30 31] However, further prospective studies are required in this field.

Patients who had mitral valve interventions for A-FMR were limited in our study population, and the impact of mitral interventions on outcomes could not be evaluated. However, there are very limited data regarding the prognosis of A-FMR, especially in comparison with V-FMR, and our study suggests the need for future studies to evaluate the prognosis and impact of mitral interventions separately in A-FMR and V-FMR.

### Study limitations

Our study was a retrospective analysis from an echocardiography database in a single referral centre with a limited number of study patients and events, with potential selection bias of the study patients. Thus, the results of the current study need further validation and evaluation in a larger prospective study.

## CONCLUSION

In the current analysis of functional MR patients, the rates of all-cause mortality, CV mortality and HF hospitalisation were consistently higher in V-FMR compared with A-FMR, and there were different prognostic predictors between V-FMR and A-FMR. Our study suggests the importance of discriminating A-FMR and V-FMR, and that different treatment strategies may be considered for each aetiology.

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