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Atrial functional mitral regurgitation: prevalence, characteristics and outcomes from the National Echo Database of Australia

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ABSTRACT

Aims Atrial functional mitral regurgitation (AFMR) is characterised by left atrial and consequent mitral annular dilatation causing mitral regurgitation. AFMR is likely to become more common with population ageing, alongside increases in atrial fibrillation and heart failure with preserved ejection fraction; conditions causing atrial dilatation. Here, we aim to define the prevalence and characterise the patient and survival characteristics of AFMR in the National Echocardiographic Database of Australia (NEDA).

Methods and results 14 004 adults with moderate or severe FMR were identified from NEDA. AFMR or ventricular FMR (VFMR) was classified by LA size, LV size and LVEF. AFMR was found in 40% (n=5562) and VFMR in 60% (n=8442). Compared with VFMR, the AFMR subgroup were significantly older (mean age 78±11 years), with a higher proportion of females and of AF. Participants were followed up for a median of 65 months (IQR 36–116 months). After adjustment for age, sex, AF, and pulmonary hypertension, the prognosis for VFMR was significantly worse than for AFMR (HR 1.57, 95% CI 1.47 to 1.68 for all-cause and 1.73, 95% CI 1.60 to 1.88, p<0.001 for both). After further adjustment for LVEF, mortality rates were similar in VFMR and AFMR patients (HR 0.93, p=NS), though advancing age and pulmonary hypertension remained independently associated with prognosis.

Conclusions AFMR is a common cause of significant functional MR that predominantly affects elderly female patients with AF. Advancing age and pulmonary hypertension independently associated with survival in FMR. Prognosis was better in AFMR compared with VFMR; however, this difference was accounted for by LV systolic impairment and not by MR severity.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Atrial functional mitral regurgitation (AFMR) is a common aetiology of secondary mitral regurgitation, however to date, studies have used data derived from small, single-centre cohorts.

WHAT THIS STUDY ADDS

⇒ This large, multicentre study using the world's largest echocardiographic database provides generalisable insights into the prevalence, characteristics and relative prognosis of AFMR.

⇒ AFMR patients are older, more likely to be female, and have more atrial fibrillation versus entricular FMR (VFMR).

⇒ VFMR has a poorer prognosis than AFMR, due to the impact of LV systolic impairment.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ We hope to increase clinician awareness of AFMR and its unique clinical features, to facilitate diagnosis and encourage development of targeted treatment strategies for this increasingly prevalent condition.

INTRODUCTION

Mitral regurgitation (MR) is the most common valvular heart disease in developed nations, with increasing prevalence strongly associated with advancing age.[1 2] As the population aged over 80 years is expected to triple in developed countries by 2050, a commensurate increase in the burden of clinically significant MR is anticipated.[3]

Primary MR refers to structural abnormality of the mitral valve itself, while secondary or functional MR (FMR) is due to mitral annular dilatation and/or incomplete leaflet closure, with a structurally normal mitral valve. Ventricular FMR (VFMR) is due to left ventricular (LV) dilatation and/or dysfunction, causing mitral regurgitation through papillary muscle displacement and/or dysfunction, ventricular dilatation of the mitral annulus (leading to tethered and poorly coapting leaflets) and reduced mitral valve systolic closing force due to reduced LV contractility.[4]

The concept of atrial FMR (AFMR) has been introduced more recently.[5 6] In AFMR, left atrial (LA) dilatation due to chronically elevated LA pressure leads to mitral annular
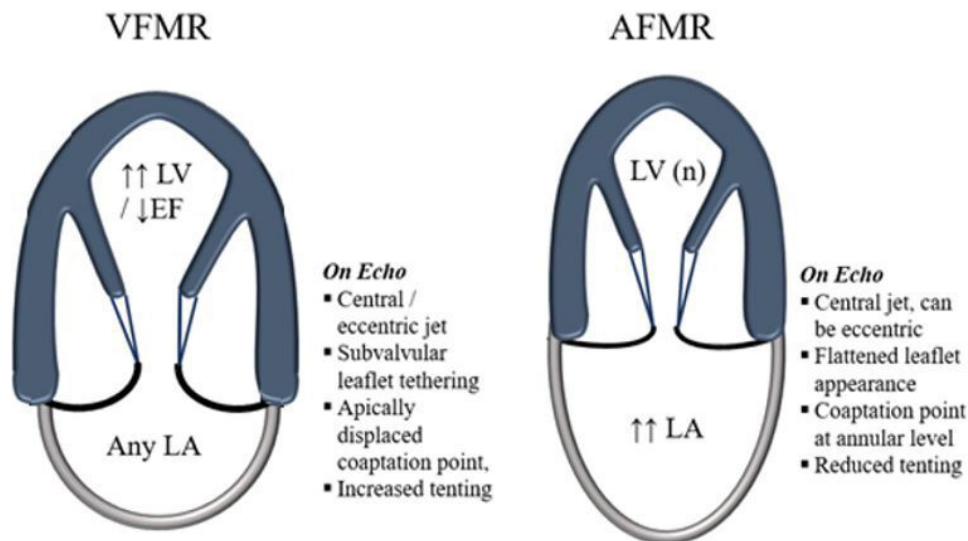
Figure 1 Illustration of VFMR (left) and AFMR (right) with their diagnostic echocardiographic features. Echo data cut-offs described in online supplemental appendix 2. AFMR, atrial functional mitral regurgitation; EF, ejection fraction; LA, left atrium; LV, left ventricle; VFMR, ventricular FMR.

dilatation and remodelling, with consequent leaflet malcoaptation and MR (figure 1).[5 7 8]

Compared with VFMR, there are very few studies to date describing the prevalence and outcomes of AFMR; most from small, single-centre cohorts.[9 10] These smaller mechanistic studies provide cohort-specific clinical details; large-scale studies are required to make robust observations of disease prevalence and outcomes, complementing the clinical granularity of small cohort studies with the statistical power and generalisability of 'big data'. Here, we report on over 5500 patients with AFMR, from the National Echo Database of Australia.

METHODS
Study participants
National Echocardiographic Database of Australia (NEDA) is a large database containing demographic and detailed echocardiographic data from more than 650 000 individuals from 25 centres around Australia, including inpatient, outpatient, urban and regional centres. NEDA is the world's largest echo database[11] that is linked with mortality, via Australia's National Death Index (NDI), which includes date and causes of death.

NEDA data censored at May 2019 were used to identify the last recorded echocardiogram for 652 243 participants aged ≥18 years. (figure 2) Subjects were excluded from primary analysis for any of the following prospectively defined exclusions:

1. Less than moderate MR (616 883 excluded).
2. Incomplete data for all of LA size, LV size and LV ejection fraction (EF) (13 364 excluded).
3. 'Non-FMR' (7709 excluded), comprising:
   i. Primary MR (2276 excluded), as defined by echocardiogram report text (string text codes) listed in online supplemental appendix.

   ii. 'Non-functional' MR (4, 983 excluded) defined by none of severe LA dilatation, moderate or severe LV dilatation, or EF <50%
4. Previous mitral valve replacement, mitral annuloplasty or coexisting severe aortic stenosis (AS) (283 excluded) .

All individuals were followed up from the date of the echocardiogram to the point of death or censorship on 21 May 2019.

Ethics approval
Institutional ethics approval has been obtained for all participating centres. The data collection process is described in detail elsewhere.[12 13] The NEDA project has undergone extensive ethical review throughout each state and territory of Australia, and by the University of Notre Dame Human Research and Ethics Committee. The project has been approved by the lead ethics committee at the Royal Prince Alfred Hospital in Sydney, overseeing all Public Institutions operating under the National Mutual Agreement in NSW, QLD, VIC, SA and ACT. Private practices are covered either by the University of Notre Dame HREC or under their own local HREC and governance arrangement.

Approval to obtain linkage with the National Deaths Index has been approved by the Australian Institute for Health and Welfare (AIHW) Human Research and Ethics Committee. All research is governed by appropriate guidelines and the NHMRC statement on ethical conduct of human research.

Echocardiographic parameters
We used diagnostic echocardiographic criteria for chamber quantification from the American Society of Echocardiography and the European Association of Cardiovascular Imaging[14–16] (see online supplemental
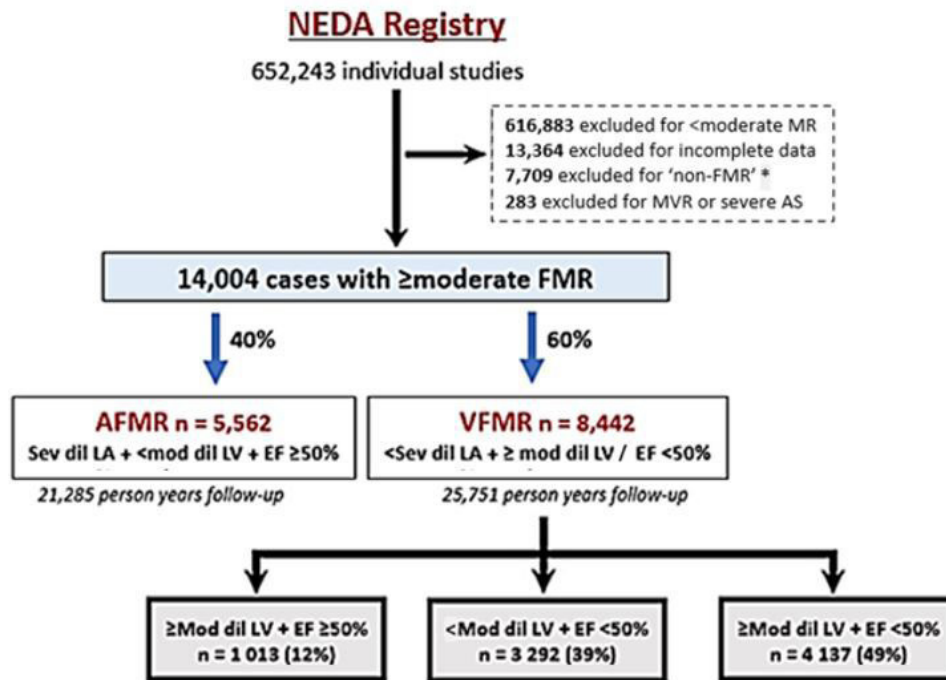
Figure 2 Flow chart of FMR subgroup definition and characteristics. *'Non-functional MR' was defined as studies that could not be clearly attributed to an atrial or ventricular functional aetiology, having neither significant LA/LV dilatation or LV systolic impairment, or those cases define as primary MR by presence of string text variables (see the Methods section). AF, atrial fibrillation; AFMR, atrial functional mitral regurgitation; AS, aortic stenosis; dil, dilated; EF, ejection fraction; LA, left atrium; LV, left ventricle; mod, moderate; Sev, severe; VFMR, ventricular FMR.

appendix 2 for details). Participants with moderate or severe FMR were prospectively characterised as follows (figure 1):

1. AFMR: severe LA dilatation and no or mild LV dilatation and LVEF ≥50%.
2. VFMR: any LA size and moderate or severe LV dilatation and/or LVEF <50%

While moderate LA dilatation may in some cases result in significant AFMR, only severe LA dilatation was included in the diagnostic criteria to improve specificity and criterion validity of FMR subgroup classification, for example, those with moderate LA dilatation and mild LV dilatation were excluded as 'non-functional' MR.

Qualitative echocardiographic assessment of MR severity by clinician judgement was used preferentially, as echocardiographic assessment by semiquantitative MR parameters in AFMR is highly prone to error[17]; assessment of PISA using vena contraction and regurgitant volume is affected by beat-to-beat variation in LV contractility in AF, and severe LA dilatation reduces the reliability of both jet area relative to LA size and pulmonary venous flow reversal.

Baseline echocardiographic parameters were defined as categorical variables by presence or absence of: severe AS by aortic valve area <1.0 cm^2; qualitative right ventricular (RV) dysfunction as 'moderate' or 'severe' from report text; pulmonary hypertension as estimated right ventricular systolic pressure ≥45 mm Hg; and LVEF in decile groups (<30%, 30–40%, 40–50%, 50–60% and >60%). Cardiac rhythm (sinus, atrial fibrillation (AF) or flutter, or paced rhythm) at the time of echocardiogram was derived from echo report text.[18]

Statistical analysis

Categorical variables were presented as numbers and percentages, and continuous variables were presented as the mean and SD or median and IQR based on their distributions. Unless otherwise specified, between-group comparisons were assessed by Student's t-test, χ^2 test (with calculation of OR and 95% CI), or analysis of variance with post-hoc Tukey test, where appropriate.

Actuarial annualised survival rates for all-cause and cardiovascular mortality (defined by ICD codes I00-I09, I10-13, I15, I20-I51) were calculated in the cases with complete follow-up at 1-year, 3-year and 5-year time points. Unadjusted survival analysis was performed using Kaplan-Meier analysis, and differences in survival between the predefined FMR subgroups of AFMR and VFMR were examined with the log-rank test.

A multivariate Cox proportional hazards model was used to derive adjusted HR for all-cause and cardiovascular mortality during follow-up, adjusted for potentially confounding variables identified in bivariate analysis to be significantly associated with mortality. A separate model adjusting for LVEF was then used to assess the association of LVEF with all-cause and cardiovascular mortality between FMR subgroups.

All analyses were performed with SPSS software V.24.0 (IBM) and two-tailed pvalues <0.05 were considered statistically significant.

Table 1 Demographic characteristics of the FMR subgroups

Type of FMR	AFMR n=5562 (40)	VFMR n=8442 (60)	Overall n=14 004	P value
Male	2314 (42)	5339 (63)	7653 (55)	<0.001
Age (years)	78±11	74±13	76±12	<0.001
BMI	27±5.6	27±5.8	27±5.7	NS
Sinus	2292 (42)	3737 (48)	6029 (46)	<0.001
Atrial fibrillation	2745 (51)	2994 (39)	5739 (44)	<0.001
Paced	384 (7)	1037 (13)	1421 (11)	<0.001

Data are n (%), median (IQR) or mean±SD unless otherwise specified.
AFMR, atrial FMR; BMI, body mass index; FMR, functional mitral regurgitation; NS, not significant; VFMR, ventricular FMR.

RESULTS

We found 35 360 (5.4%) individuals had at least moderate MR reported by qualitative assessment. Of these, 21 713 individuals had sufficient data for quantification of chamber size and a recorded LVEF. LA volume was available in all included cases, and used to determine the degree of LA dilatation. Using these measures, FMR was identified in 14 004 (64.5%) and non-FMR (including DMR and 'mixed' MR) in 7709 (35.5%) of cases. Of the FMR subgroup, 45% were female (mean age 76±12 years) with a mean LVEF of 48±19% (figure 2: describes the study flowchart and FMR subgroups). AFMR and VFMR were identified in 40% and 60% of the FMR cohort, respectively.

Demographic, clinical and echocardiographic characteristics of AFMR Patients

Table 1 summarises the baseline demographic characteristics of the study cohort by FMR subgroup. The AFMR group were 58% female with a mean age of 78±11 years; the VFMR group were 37% female with a mean age 74±13 years (p<0.001). Distribution of MR severity was similar between groups; with 77% moderate and 23% severe

(p=NS). The AFMR cohort had a higher rate of AF (51%) than VFMR (39%) (p<0.001), and the VFMR cohort had a higher rate of paced rhythm (13%) than AFMR (7%) (p<0.001). The rate of sinus rhythm was 42% in AFMR and 48% in VFMR (p<0.001).

Baseline echocardiographic parameters are summarised in table 2. Mean LVEF was 37%±14% in the VFMR group and 66%±10% in the AFMR group (p<0.001). Moderate or worse right heart dysfunction was present in 15% of VFMR and 3% of AFMR (p<0.001), moderate or worse TR in 56% of AFMR and 54% of VFMR (p=0.005) and significant pulmonary hypertension in 35% of VFMR and 38% of AFMR (p=0.008). As EROA data were only available for a small subset of cases, these data were excluded from analysis.

Prognosis of AFMR

Over a median follow-up of 65 months (IQR 36–116), cardiovascular death occurred in 51% of AFMR and 57% of VFMR. Median survival from time of echocardiogram was 2.6 years (IQR 1.2–5.4) for AFMR and 1.9 years (IQR 0.6–4.3) for VFMR.

Table 2 Baseline echocardiographic parameters of the FMR subgroups

Type of FMR	AFMR n=5562	VFMR n=8442	Overall n=14 004	P value
Moderate LA dilatation	–	1353 (16)	–	–
Severe LA dilatation	5562 (100)	5454 (65)	11 016 (79)	<0.001
Moderate LV dilatation	–	2178 (26)	–	–
Severe LV dilatation	–	2189 (26)	–	–
LV EF (%)	66±10	37±14	48±19	<0.001
Moderate MR	4289 (77)	6512 (77)	10 801 (77)	NS
Severe MR	1273 (23)	1930 (23)	3203 (23)	NS
≥Moderate RV dysfunction	72 (3)	473 (15)	545 (10)	<0.001
≥Moderate TR	2112 (56)	2388 (53)	4500 (54)	0.005
eRVSP ≥45 mm Hg	662 (35)	1232 (38)	1894 (37)	0.008

Data are n (%), median (IQR) or mean±SD unless otherwise specified.
eRVSP, estimated right ventricular systolic pressure; LA, left atrium; LVEF, Left ventricular ejection fraction; MR, mitral regurgitation; NS, not significant; RV, right ventricular; TR, tricuspid regurgitation.

Table 3 Bivariate Cox regression analysis—all-cause and cardiovascular mortality

	All-cause mortality			Cardiovascular mortality		
	HR	95% CI	P value	HR	95% CI	P value
Age (vs <65 years)						
65–75 years	1.78	1.32 to 2.39		1.51	0.93 to 1.42	NS
75–85 years	2.52	1.93 to 3.30	<0.001	2.11	1.43 to 3.12	<0.001
>85 years	4.12	3.13 to 5.42		3.78	2.55 to 5.61	<0.001
Male (vs female)	1.25	1.09 to 1.45	0.002	1.16	1.08 to 1.25	<0.001
AF (vs no AF)	1.11	1.04 to 1.19	0.003	1.26	1.04 to 1.54	0.02
eRVSP ≥45 mm Hg (vs <45 mm Hg)	2.34	1.87 to 2.93	<0.001	1.91	1.51 to 2.41	<0.001
≥Moderate TR	1.25	0.99 to 1.57	NS	1.37	1.12 to 1.68	0.002
≥Moderate RV dysfunction	1.46	1.18 to 1.8	NS	1.05	0.74-1.50	NS
LV EF (vs EF >60%)						
50%–60%	1.01	0.91 to 1.17	NS	1.02	0.89 to 1.21	NS
40%–50%	1.18	1.07 to 1.31	<0.001	1.23	1.09 to 1.39	<0.001
30%–40%	1.65	1.65 to 1.83	<0.001	1.56	1.39 to 1.80	<0.001
<30%	2.23	2.02 to 2.46	<0.001	2.74	2.46 to 3.05	<0.001
VFMR (vs AFMR)	1.57	1.47 to 1.68	<0.001	1.73	1.60 to 1.88	<0.001

AFMR, atrial functional mitral regurgitation; EF, ejection fraction; eRVSP, estimated right ventricular systolic pressure; LV, left ventricular; NS, not significant; RV, right ventricular; TR, tricuspid regurgitation; VFMR, ventricular FMR.

Freedom from all-cause mortality at 1, 3 and 5 years was 82%, 63% and 50% for AFMR; and 69%, 49% and 38% for VFMR; and freedom from cardiovascular death was 92%, 82% and 75% for AFMR, and 81%, 69% and 61% for VFMR (Wilcoxon test p<0.001; p<0.001 for all pairwise comparisons). Cumulative 5-year all-cause and cardiovascular death were thus higher in VFMR compared with AFMR subjects (62% vs 50% and 49% vs 25%, p<0.001 for pairwise comparison).

Survival analysis
Bivariate regression analysis demonstrated that increasing age (increasing risk for each decade above 65 years vs <65 years), male sex, pulmonary hypertension, presence of AF, reduced LVEF (increasing risk for each decile below 60% vs above 60%) and VFMR (vs AFMR) were independently associated with all-cause and cardiovascular mortality. Moderate or worse TR was associated with cardiovascular survival only, and MR severity (moderate 3+ vs severe 4+) was not associated with all-cause or cardiovascular mortality. Advancing age and severe LV dysfunction demonstrated the strongest independent associations with both all—cause and cardiovascular survival (table 3).

Multivariate Cox regression modelling for all-cause and cardiovascular mortality with adjustment for age, sex, AF, and pulmonary hypertension, demonstrated that VFMR (vs AFMR) remained independently associated with all-cause and cardiovascular mortality, as did advancing age and pulmonary hypertension (p<0.001 for all) (figure 3).
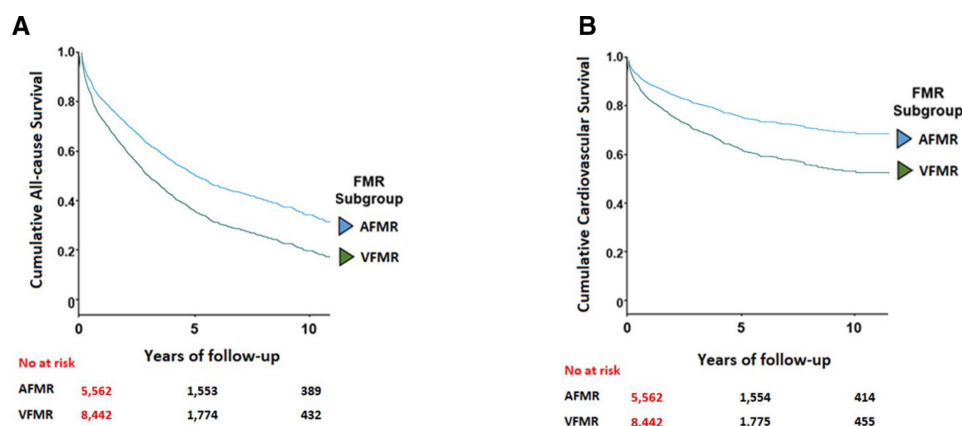

Figure 3 (A, B) Adjusted all-cause and cardiovascular survival by FMR subgroup. (Adjusted for age, sex, AF, and pulmonary hypertension). AFMR, atrial FMR; FMR, functional mitral regurgitation; VFMR, ventricular FMR.

Table 4 HR for 1-year and 5-year survival, adjusted for age, sex, AF and pulmonary hypertension

	All-cause mortality						Cardiovascular mortality					
	1 year			5 years			1 year			5 years		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
VFMR (vs AFMR)	1.09	0.98 to 1.22	NS	1.30	1.16 to 1.45	<0.001	1.23	1.04 to 1.45	0.016	1.48	1.25 to 1.75	<0.001

AF, atrial fibrillation; AFMR, atrial functional mitral regurgitation; VFMR, ventricular FMR.

After the addition of LV EF to the multivariate model, VFMR (vs AFMR) was no longer significantly associated with all-cause or cardiovascular mortality, whilst advancing age and pulmonary hypertension remained independently associated with both (p<0.001 for all), as did worsening LVEF (p<0.001 for all).

With regard to 1 year (short-term) and 5 years (medium-term) mortality, after adjustment for age, sex, AF and pulmonary hypertension, VFMR (vs AFMR) was significantly associated with 5 years all-cause mortality (HR 1.3, 95% CI 1.16 to 1.45, p<0.001), and both 1-year and 5-year cardiovascular mortality (HR1.23, 95% CI 1.04 to 1.45, p=0.016, and HR 1.48, 95% CI 1.25 to 1.75, p<0.001, respectively). After addition of LVEF to the multivariate model, the risk of all-cause and CV mortality was only significant different for VFMR (vs AFMR) for 5-year all cause mortality (HR 1.27, 95% CI 1.03 to 1.57, p=0.027) (tables 4 and 5).

DISCUSSION

Our analysis, using the world's largest echocardiographic database, demonstrates that AFMR is a relatively common underlying cause of moderate or severe FMR, comprising 40% of this group. AFMR subjects were more likely to be female, older aged and have AF at the time of their echo, when compared with VFMR subjects.

Consistent with our findings, recent studies of FMR subtypes report a ratio of VFMR to AFMR of 1.5-2:1. Kim et al report on a Japanese cohort of 898 patients with ≥3+ MR; of the 579 individuals (64%) with FMR, AFMR was found in 32% and VFMR in 68%.[19] Dziadzko et al reported on 727 patients with moderate or severe MR from Olmstead County; of the 475 (65%) patients with FMR, 59% were classified as VFMR and 41% as AFMR.[10]

Significant AFMR has been observed in 8% of patients with AF and no underlying structural heart disease,[20] in 28% of patients with longstanding AF,[10] and in 20% of patients with heart failure with preserved left ventricular ejection fraction (HFpEF).[21] The presence of significant AFMR in HFpEF ('disproportionate' FMR) has been associated with greater haemodynamic severity of disease and poorer functional capacity,[22] as well as high morbidity and mortality.[18 19 23]

Our data demonstrate poor long-term survival in AFMR, although relatively better all-cause and cardiovascular survival compared with VFMR. The relatively poorer prognosis in VFMR compared with AFMR was closely associated with reduced LVEF, as adjusting for LVEF in multivariate modelling neutralised the survival difference between AFMR and VFMR. This finding suggests that left ventricular systolic impairment accounts for the poorer survival in VFMR vs AFMR. In the overall FMR cohort, left ventricular impairment, age and pulmonary hypertension, but not MR severity, AF, presence of significant TR, or RV dysfunction, conferred the most important prognostic impact on survival in FMR.[16 24 25]

Okamoto et al recently reported prognostic comparisons between AFMR and VFMR in a single-centre Japanese cohort of 378 consecutive FMR patients (288 VFMR and 90 AFMR), demonstrating higher event rates for all-cause mortality, cardiovascular mortality and HF hospitalisation in VFMR, as well as identifying distinct prognostic predictors of the composite endpoint that highlighted the importance of clinically discriminating these unique FMR aetiologies.[26] Our comparative prognostic data support the findings of this small cohort, enhancing the generalisability and validity of these observations to broader clinical contexts.

Despite the significant prevalence in the general population, particularly among older individuals, the relative under-reporting of AFMR compared with VFMR indicates that AFMR is an underappreciated and therefore likely undiagnosed subgroup of MR.[9 27] In highlighting the demographic and survival differences between AFMR

Table 5 HR for 1-year and 5-year survival, adjusted for age, sex, AF, pulmonary hypertension and LV EF

	All-cause mortality						Cardiovascular mortality					
	1 year			5 years			1 year			5 years		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
VFMR (vs AFMR)	1.21	0.98 to 1.49	NS	1.27	1.03 to 1.57	0.027	1.23	0.90 to 1.69	NS	1.32	0.96 to 1.82	NS

AF, atrial fibrillation; AFMR, atrial functional mitral regurgitation; EF, ejection fraction; LV, left ventricular; NS, not significant; VFMR, ventricular FMR.

and VFMR, our study seeks to increase awareness of AFMR as a distinct and important entity, in order to enhance recognition and diagnosis, inform clinical discussions regarding prognosis, and encourage further studies into medical management and intervention.

Defining AFMR

There have been no published echocardiographic guidelines to define the parameters and features that identify AFMR as a subgroup of FMR, with varied definitions used in prior studies.[5 19 20 28] In individuals with moderate or worse FMR, we defined VFMR by LVEF <50% and/or moderate or worse LV dilatation, and AFMR as severe LA dilatation in the absence of these LV changes (as illustrated in figure 1). These simple and readily applied definitions can be applied prior to more detailed anatomical assessment to facilitate FMR subgroup categorisation (ie, into 'atrial', 'ventricular' or 'mixed' FMR) in a primary care setting. Due to the evolution of recommendations over the inclusion period of this study, we accepted both two-dimensional and three-dimensional chamber quantification measurements, however, we strongly recommend the use of indexed volumes for chamber quantification in all future AFMR studies as per current echocardiography guidelines.[14 16]

Clinical implications

Understanding the underlying aetiology of MR is critical in guiding optimal clinical management, and relies on careful transthoracic and/or transoesophageal echocardiographic assessment. Significant MR in the setting of preserved LV function, normal mitral valve leaflet appearance and a dilated mitral annulus likely represents AFMR, particularly in elderly female patients with a history of AF. Clinicians making this diagnosis should be aware of mechanisms and relative prognosis compared with VFMR, use medical management including addressing lifestyle factors, diuretics and blood pressure control,[5 29] and evaluate suitability for potentially effective interventions in symptomatic AFMR, such as AF ablation, surgical repair (mitral annuloplasty),[23 30] and transcatheter edge-to-edge repair.[23 31 32] Mitral edge-to-edge repair has been demonstrated to be safe and effective in AFMR cohorts, demonstrating durable reduction in MR severity, positive mitral annular remodelling and rates of a composite outcome of all-cause death or HF hospitalisations ranged between 55% and 78%.[23 33 34] Reduction of AFMR through targeted intervention may represent a potential therapeutic avenue for patients with HFpEF and AF; future studies are needed to explore this hypothesis further.

LIMITATIONS

The major limitation of the NEDA database is that clinical data including comorbidities, pharmacological treatment, New York Heart Association (NYHA) functional class, HF hospitalisations or biochemical parameters[11 12 18] are not currently linked to the detailed echocardiographic and robust mortality data. The effects of medical treatment or CRT-pacing for LV dysfunction, for example, cannot be assessed using this echocardiographic database, at the current time. The use of therapies for LV dysfunction may have relatively altered the observed survival outcomes in VFMR compared with AFMR subjects, which while unable to be quantified in this study highlights the relative lack of available treatments for AFMR currently.

As a database of 'real-world' echocardiographic studies (from community and hospital-based echo centres, in urban and rural areas), we accepted chamber size measurements recorded in a number of different ways (such as diameter, area and/or volume). Ideally, chamber quantification would be assessed using uniform, volumetric, indexed parameters.

As semiquantitative or quantitative measures of MR severity were available for ~10% of studies, qualitative grading was used to define lesion severity. Ideally, MR severity would be assessed with both combined qualitative and qualitative data, where PISA is measurable.

AF was defined by AF at the time of the echo study, thus cases of paroxysmal AF in sinus rhythm at the time of the echo would not be defined as AF. This may underestimate the prevalence of AF in each group, though is unlikely to cause significant bias.

As many centres contributed to echocardiographic data collection, there is a potential for lack of standardisation in measurement and reporting; however, we believe that these aspects were unlikely to have introduced any systematic biases and instead is more reflective of real-world echocardiographic imaging, improving the generalisability of these findings.

As the definition for primary/DMR used in this study was dependent on string text variables being present in echo reports, not all DMR cases may have been captured for exclusion, however this likely represents only a minority of cases.

Finally, there are significant advantages to this 'big data' approach, despite the limitations noted above. The large number of AFMR cases (at over 5500 such patients, more than 10-fold the number reported in any other AFMR study, to the best of our knowledge) provides highly powered statistical data on prevalence, characteristics and outcomes, although with less clinically granular information about each case.

CONCLUSIONS

Our data demonstrate that AFMR is a prevalent subgroup of significant functional MR, in a broad variety of settings. AFMR predominantly affects elderly female patients with AF, and carries a poor long-term prognosis, although not as poor as VFMR. The poorer prognosis of VFMR vs AFMR was accounted for by lower LVEF in this group of patients, rather than by the severity of the MR.

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REFERENCES

1 d'Arcy JL, Coffey S, Loudon MA, *et al*. Large-Scale community echocardiographic screening reveals a major burden of undiagnosed valvular heart disease in older people: the oxvalve population cohort study. *Eur Heart J* 2016;37:3515–22.
2 Nkomo VT, Gardin JM, Skelton TN, *et al*. Burden of valvular heart diseases: a population-based study. *Lancet* 2006;368:1005–11.
3 Kodali SK, Velagapudi P, Hahn RT, *et al*. Valvular heart disease in patients ≥80 years of age. *J Am Coll Cardiol* 2018;71:2058–72.
4 Enriquez-Sarano M, Akins CW, Vahanian A. Mitral regurgitation. *Lancet* 2009;373:1382–94.
5 Deferm S, Bertrand PB, Verbrugge FH, *et al*. Atrial functional mitral regurgitation. *J Am Coll Cardiol* 2019;73:2465–76.
6 O'Gara PT, Mack MJ. Secondary mitral regurgitation. *N Engl J Med* 2020;383:1458–67.
7 Deferm S, Dauw J, Vandervoort PM, *et al*. Atrial functional mitral and tricuspid regurgitation. *Curr Treat Options Cardio Med* 2020;22:10.
8 Delgado V, Bax JJ. Atrial functional mitral regurgitation: from mitral annulus dilatation to insufficient leaflet remodeling. *Circ Cardiovasc Imaging* 2017;10:e006239.
9 Mesi O, Gad MM, Crane AD, *et al*. Severe atrial functional mitral regurgitation: clinical and echocardiographic characteristics, management and outcomes. *JACC Cardiovasc Imaging* 2021;14:797–808.
10 Dziadzko V, Dziadzko M, Medina-Inojosa JR, *et al*. Causes and mechanisms of isolated mitral regurgitation in the community: clinical context and outcome. *Eur Heart J* 2019;40:2194–202.
11 Strange G, Celermajer DS, Marwick T, *et al*. The national echocardiography database australia (NEDA): rationale and methodology. *Am Heart J* 2018;204:186–9.
12 Strange G, Stewart S, Celermajer D, *et al*. Poor long-term survival in patients with moderate aortic stenosis. *J Am Coll Cardiol* 2019;74:1851–63.
13 Strange G, Stewart S, Celermajer DS, *et al*. Threshold of pulmonary hypertension associated with increased mortality. *J Am Coll Cardiol* 2019;73:2660–72.
14 Lang RM, Badano LP, Mor-Avi V, *et al*. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the american society of echocardiography and the european association of cardiovascular imaging. *J Am Soc Echocardiogr* 2015;28:1–39.
15 Nishimura RA, Otto CM, Bonow RO, *et al*. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of cardiology/american heart association Task force on clinical practice guidelines. *Circulation* 2017;135:e1159–95.
16 Nishimura RA, Otto CM, Bonow RO, *et al*. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the american college of cardiology/american heart association task force on practice guidelines. *J Am Coll Cardiol* 2014;63:e57–185.
17 Hagendorff A, Doenst T, Falk V. Echocardiographic assessment of functional mitral regurgitation: opening Pandora's box? *ESC Heart Fail* 2019;6:678–85.
18 Playford D, Strange G, Celermajer DS, *et al*. Diastolic dysfunction and mortality in 436 360 men and women: the National echo database Australia (NEDA). *Eur Heart J Cardiovasc Imaging* 2021;22:505–15.
19 Kim K, Kitai T, Kaji S, *et al*. Outcomes and predictors of cardiac events in medically treated patients with atrial functional mitral regurgitation. *Int J Cardiol* 2020;316:195–202.
20 Abe Y, Takahashi Y, Shibata T. A new disease entity: atrial functional mitral regurgitation. *J Cardiol* 2021;77:565–9.
21 Chioncel O, Lainscak M, Seferovic PM, *et al*. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC heart failure long-term registry. *Eur J Heart Fail* 2017;19:1574–85.
22 Tamargo M, Obokata M, Reddy YNV, *et al*. Functional mitral regurgitation and left atrial myopathy in heart failure with preserved ejection fraction. *Eur J Heart Fail* 2020;22:489–98.
23 Wagner CM, Brescia AA, Watt TMF, *et al*. Surgical strategy and outcomes for atrial functional mitral regurgitation: all functional mitral regurgitation is not the same! *J Thorac Cardiovasc Surg* 2022:00373-7.
24 Azzalini L, Millán X, Khan R, *et al*. Impact of left ventricular function on clinical outcomes of functional mitral regurgitation patients undergoing transcatheter mitral valve repair. *Catheter Cardiovasc Interv* 2016;88:1124–33.
25 Grayburn PA, Sannino A, Packer M. Proportionate and disproportionate functional mitral regurgitation: a new conceptual framework that reconciles the results of the MITRA-FR and COAPT trials. *JACC Cardiovasc Imaging* 2019;12:353–62.
26 Okamoto C, Okada A, Nishimura K, *et al*. Prognostic comparison of atrial and ventricular functional mitral regurgitation. *Open Heart* 2021;8:e001574.
27 Lancellotti P, Go YY. Atrial secondary mitral regurgitation: often overlooked, but never forgotten. *JACC Cardiovasc Imaging* 2021;14:809–11.
28 Saito C, Minami Y, Arai K, *et al*. Prevalence, clinical characteristics, and outcome of atrial functional mitral regurgitation in hospitalized heart failure patients with atrial fibrillation. *J Cardiol* 2018;72:292–9.
29 Izumi C, Eishi K, Ashihara K, *et al*. JCS/JSCS/JATS/JSVS 2020 guidelines on the management of valvular heart disease. *Circ J* 2020;84:2037–119.
30 Balogh Z, Mizukami T, Bartunek J, *et al*. Mitral valve repair of atrial functional mitral regurgitation in heart failure with preserved ejection fraction. *J Clin Med* 2020;9:3432.
31 Gertz ZM, Herrmann HC, Lim DS, *et al*. Implications of atrial fibrillation on the mechanisms of mitral regurgitation and response to mitraclip in the COAPT trial. *Circ Cardiovasc Interv* 2021;14:e010300.
32 Gertz ZM, Raina A, Saghy L, *et al*. Evidence of atrial functional mitral regurgitation due to atrial fibrillation: reversal with arrhythmia control. *J Am Coll Cardiol* 2011;58:1474–81.
33 Yoon S-H, Makar M, Kar S, *et al*. Outcomes after transcatheter edge-to-edge mitral valve repair according to mitral regurgitation etiology and cardiac remodeling. *JACC Cardiovasc Interv* 2022;15:1711–22.
34 Popolo Rubbio A, Testa L, Grasso C, *et al*. Transcatheter edge-to-edge mitral valve repair in atrial functional mitral regurgitation: insights from the multi-center MITRA-TUNE registry. *Int J Cardiol* 2022;349:39–45.