Original research

Echocardiographic cardiac damage classification and clinical outcomes in atrial functional mitral regurgitation

Taiji Okada ,[1] Nobuyuki Kagiyama ,[2] Tomohiro Kaneko,[2] Masashi Amano ,[3] Yukio Sato,[4] Yohei Ohno,[5] Masaru Obokata ,[6] Kimi Sato ,[7] Kojiro Morita ,[8] Tomoko Machino-Ohtsuka ,[7] Yukio Abe ,[9] Yutaka Furukawa[1]

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/heartjnl-2024-325240).

For numbered affiliations see end of article.

Correspondence to
Dr Taiji Okada;
t.dakao@gmail.com and Dr Nobuyuki Kagiyama;
kgnb_27_hot@yahoo.co.jp

Received 14 October 2024
Accepted 21 January 2025
Published Online First
6 February 2025

ABSTRACT

Background Atrial functional mitral regurgitation (AFMR) arises from left atrial (LA) dilation, commonly associated with atrial fibrillation, and leads to progressive cardiac damage. This study evaluated the prognostic value of a novel echocardiographic cardiac damage classification system for patients with moderate or severe AFMR.

Methods In a retrospective multicentre study, 1007 patients with AFMR were stratified into four groups based on echocardiographic findings: group 1, LA damage (dilation); group 2, left ventricular damage (reduced ejection fraction and/or dilation); group 3, right heart damage (tricuspid regurgitation and/or pulmonary hypertension); and group 4, combined left and right heart damage. The primary outcome was a composite of all-cause death, heart failure hospitalisations and mitral valve (MV) interventions over a median follow-up of 3.0 years.

Results The cohort's mean age was 78±10 years, with 56% female. Event rates for the primary outcome were progressively higher across groups 1–4 (31.0%, 38.0%, 46.3% and 57.2%, respectively; p<0.001). After multivariable adjustment, group 4 was associated with a significantly higher risk of the primary outcome compared with group 1 (HR 1.65, 95% CI 1.29 to 2.11, p<0.001). This classification consistently stratified risks for individual components of the composite endpoint, particularly in patients without MV intervention.

Conclusions A cardiac damage classification system based on echocardiographic parameters provides prognostic insights in patients with AFMR, identifying subgroups at higher risk of adverse outcomes. Future studies are needed to validate its use in guiding therapeutic decisions.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Atrial functional mitral regurgitation (AFMR) is a subtype of mitral regurgitation (MR) driven by left atrial dilation, distinct from other functional MR types.
⇒ While cardiac damage classification systems exist for other valve diseases, there has been no specific system for AFMR.

WHAT THIS STUDY ADDS

⇒ A novel cardiac damage classification for AFMR based on echocardiographic parameters stratifies patients by risk of adverse outcomes.
⇒ Combined left and right heart damage is associated with the highest risk of all-cause death, heart failure hospitalisations and MV intervention.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This classification system could enhance risk stratification and inform management strategies for patients with AFMR.
⇒ Prospective studies are required to determine its utility in clinical decision-making and its potential impact on patient outcomes.

INTRODUCTION

Atrial functional mitral regurgitation (AFMR) is recognised as a significant subtype of mitral regurgitation (MR), frequently associated with atrial fibrillation (AF) or underlying heart failure (HF) with preserved ejection fraction. These conditions lead to atrial enlargement, which causes the dilatation of the mitral annulus and subsequent MR development.[1] The mechanisms underlying AFMR are multifaceted, with various factors influencing MR severity. Several studies have identified left atrium (LA) dilatation and mitral annular dilatation as common mechanisms.[2 3]

The influence of AFMR can extend beyond the LA to other chambers of the heart. Although AFMR is generally characterised with preserved left ventricular (LV) size and function, volume overload by significant MR can lead to mild LV enlargement and slight LV systolic and diastolic dysfunction.[4] Additionally, progression of left-sided HF causes pulmonary hypertension (PH) and functional tricuspid regurgitation (TR). TR can also occur by tricuspid annular dilatation due to AF.[5] Consequently, AFMR identifies an under-recognised, high-risk subgroup, especially those with LV dilatation, concomitant TR and right ventricular dysfunction.[6 7]

However, the exact cascade of cardiac damage of AFMR remains undetermined. The prognosis in asymptomatic moderate and/or severe valvular heart disease is determined by the extent of cardiac

To cite: Okada T, Kagiyama N, Kaneko T, *et al*. *Heart* 2025;**111**:532–540.

damage associated with the valve disease.[8] Although cardiac damage staging has provided independent and incremental prognostic value in patients with degenerative MR and ventricular functional MR,[9 10] the progression of cardiac damage in AFMR may differ from that in degenerative MR and ventricular functional MR. We hypothesised that a cardiac damage classification could enhance risk stratification in patients with AFMR. Furthermore, we assumed that damage to the right heart might pose a greater concern. This study aimed to assess the relationship between a novel cardiac damage classification and the clinical background overall and by severity of AFMR.

METHODS

Study population

The REal-world obserVational study for invEstigAting the prevaLence and therapeutic options for Atrial Functional Mitral Regurgitation (REVEAL-AFMR) was a multicentre, retrospective study that enrolled consecutive patients with AFMR across 26 centres in Japan, including 17 university hospitals, 1 national centre, 3 public hospitals and 5 private hospitals. The study protocols were in accordance with the Declaration of Helsinki, and received approval from the institutional review board of Juntendo University, Japan, with each participating centre also approving the execution of the study. Given its retrospective, observational and non-invasive nature, the requirement for written informed consent was waived, and opt-out consent was used instead. Study details information, including the objectives, inclusion and exclusion criteria, clinical event, and names of the participating hospitals, were published on the publicly available University Hospital Information Network (UMIN-CTR, unique identifier: UMIN000046146), prior to patient enrolment. The design and patient enrolment of the REVEAL-AFMR has been previously described.[11] Adult (≥20 years) patients with at least moderate AFMR in a stable condition, which was defined with the absence of primary changes on the mitral valve (MV), preserved LV ejection fraction (LVEF) ≥50% without regional wall motion abnormality, and an LA dilatation (LA volume index (LAVI) ≥38 mL/m^2 for men, ≥41 mL/m^2 for women; based on a previous report of the normal values of Japanese people[12]), were enrolled in a REDCap database between April and November 2022.

Patient and public involvement

Patients and the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

Cardiac damage classification

Patients who underwent transthoracic echocardiography from 1 January to 31 December 2019 were hierarchically classified into the following categories (figure 1A): group 1, LA damage, as defined by LVEF ≥60% and LA dilatation (LAVI ≥38 mL/m^2 for men, ≥ 41 mL/m^2 for women); group 2, LV damage, as defined by LVEF between 50% and 60% and/or LV End-Diastolic Volume (LVEDV) Index >74 mL/m^2 for men, > 61 mL/m^2 for women;[13] group 3, right heart damage, as defined by the presence of moderate-severe or severe TR and/or the presence of PH (pulmonary artery systolic pressure (PASP) ≥50 mm Hg); and group 4, left and right heart damage, defined as fulfilling both group 2 and group 3 criteria.

LVEF and volumes and LAVI were calculated using the biplane disk summation methods. E/e' was calculated using the mean value of lateral and septal e'. PASP was calculated from TR pressure gradient and the size of inferior vena cava, and TR was graded with qualitative and quantitative methods as recommended.[14] The numbers of missing data for LAVI, E/e', LVEF, LVEDV Index, PH, and the presence of TR were 62, 67, 0, 5, 168 and 0 patients, respectively. A core laboratory independently re-analysed 100 randomly selected echocardiographic studies to ensure the reliability of echocardiographic data. This verification process revealed excellent concordance between the core laboratory and site measurements, with intraclass correlation coefficients ranging from 0.82 to 0.99, underscoring the high quality of the echocardiographic data used in the study.[11]

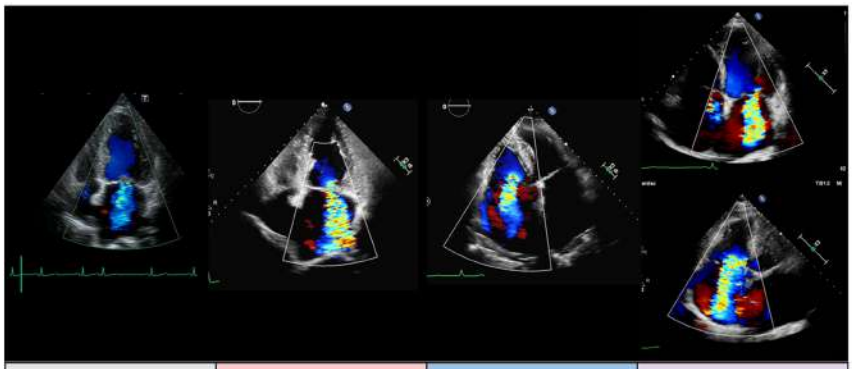
Study outcomes

The primary outcome comprised a composite of all-cause death, HF hospitalisation and the clinical requirement of MV interventions (including surgical MV repair, MV replacement and mitral transcatheter edge-to-edge repair), data regarding which were derived from electronic medical records. The electronic records used in our Cox models were collected during the period between April and November 2022. Additionally, secondary outcomes included all-cause death, cardiac death, HF hospitalisation and MV interventions assessed individually. Definitions for cardiac death and HF hospitalisation followed the American College of Cardiology/American Heart Association key data elements and definitions for cardiovascular endpoint events in clinical trials.[15] Telephone surveys were conducted with patients to confirm endpoints if over a year had elapsed since the patient's last follow-up, and the data were based on the patients' responses, which can be considered approximate.

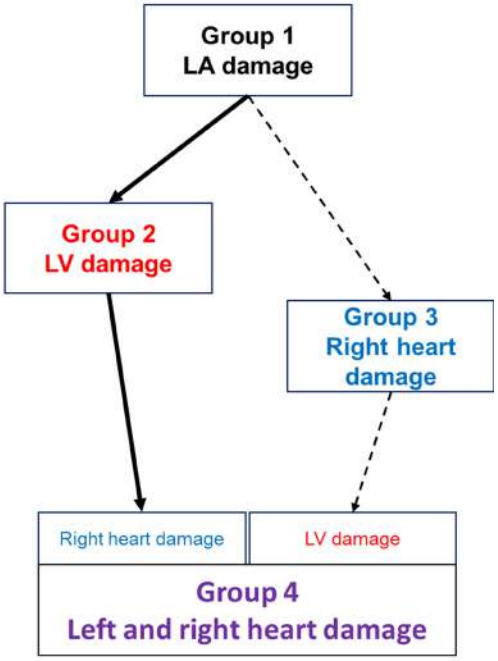
Statistical analysis

Data were presented based on the type of variable, with continuous variables shown as mean±SD or medians (IQR), and categorical variables as frequencies (%). The Jonckheere–Terpstra trend test was used to compare continuous variables, and the Cochran–Armitage trend test was employed to compare proportions and investigate the trend of variables in cardiac damage classification. Kaplan–Meier curves visualised outcomes, with the log-rank test assessing differences. An exploratory analysis was conducted to assess the influence of AFMR severity on the relationship between cardiac damage classification and the primary outcome. This analysis involved stratifying the data based on AFMR severity. Moreover, all-cause death and its composite with HF hospitalisation were analysed, excluding patients who underwent MV intervention. This exclusion was made in acknowledgement of prior evidence indicating a significant impact of such interventions on these endpoints.[11] Cox regression analysis was performed to determine the impact of cardiac damage classification, categorising for analysis. To account for clustering within participating hospitals, we applied a robust variance estimator in the Cox regression model. The multivariable Cox regression models incorporated cardiac staging and variables that were used in the previous analyses of this cohort.[11] These were prespecified based on their association with the primary outcome in patients with HF. These variables included age, sex, body mass index, systolic blood pressure, New York Heart Association (NYHA) functional class II/III/IV, previous history of HF, EuroSCORE II, serum levels of haemoglobin and creatinine, and MR severity. The Cox regression findings were presented as HRs, 95% CIs and p values. Notably, 83 patients were excluded from the Cox regression analysis due to incomplete data on key variables, including essential echocardiographic parameters. An additional analysis was conducted focusing on patients who did not undergo MV intervention, aiming to further investigate the

A



Group 1	Group 2	Group 3	Group 4
LA damage	LV damage	Right heart damage	Left and right heart damage
LAV↑	LVEF↓ LVEDV index↑	PASP↑ TR↑	Group 2 and Group 3
30.7% (n = 303)	40.3% (n = 406)	9.9% (n = 100)	19.7% (n = 198)



B

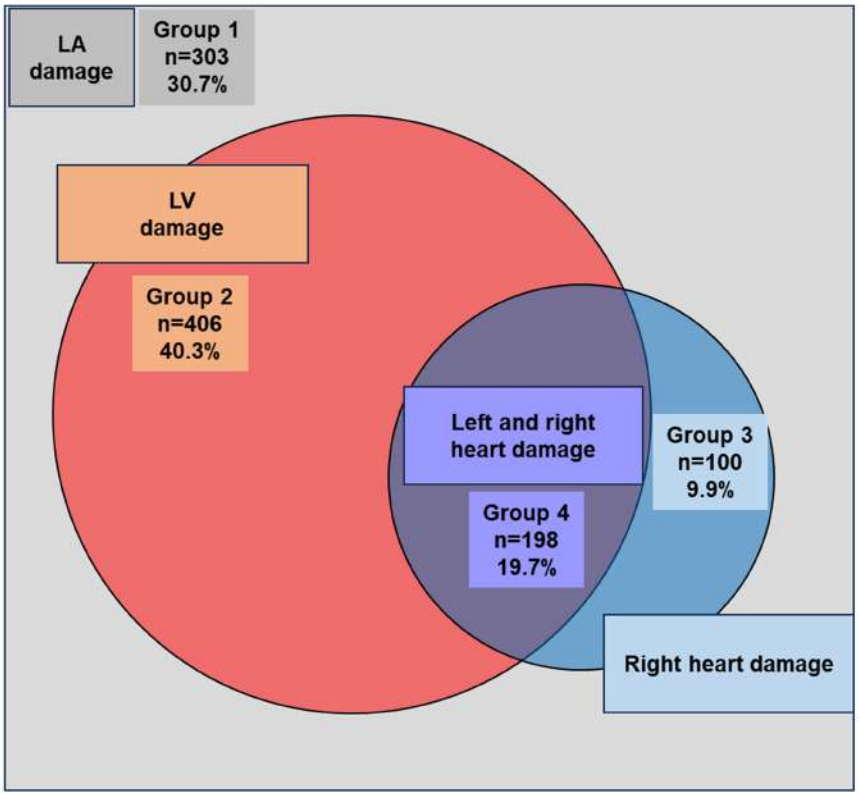


Figure 1 Definition of cardiac damage classification and distribution. A definition and progression schema of cardiac damage classification based on echocardiographic characteristics, including LA size (LAVI), LV function (LVEF, LVEDV), PASP and TR presence in patients with AFMR (A) and distribution (B). AFMR, atrial functional mitral regurgitation; LA, left atrium; LAVI, left atrial volume index; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; PASP, pulmonary artery systolic pressure; TR, tricuspid regurgitation.

Table 1 Characteristics of the study population divided by cardiac damage classification

	N	Group 1 (n=303)	Group 2 (n=406)	Group 3 (n=100)	Group 4 (n=198)	P value*
Age, years	1007	78±9	76±11	81±7	79±9	0.001
Female	1007	170 (56)	230 (57)	54 (54)	107 (54)	0.637
Body surface area, m^2	1002	1.55±0.18	1.54±0.21	1.51±0.17	1.52±0.19	0.204
Body mass index, kg/m^2	1002	22.3±3.2	22.3±3.7	21.8±3.5	21.5±3.3	0.018
Systolic BP, mm Hg	946	130±19	128±20	127±21	121±18	<0.001
Heart rate, /min	996	73±15	72±18	72±15	73±17	0.756
Haemoglobin, g/dL	988	12.2±1.8	11.9±2.1	11.4±2.2	11.2±1.9	<0.001
BUN, mg/dL	979	22±11	24±13	25±11	26±15	0.001
Creatinine, mg/dL	989	1.22±1.15	1.27±1.23	1.24±1.15	1.25±0.93	0.022
EuroSCORE II, %	1007	1.9 (1.3–3.7)	2.1 (1.3–3.5)	3.1 (2.1–4.7)	2.9 (1.7–5.2)	<0.001
Permanent AF	1007	174 (57)	217 (53)	79 (79)	167 (84)	<0.001
Duration of AF, month	706	60 (12–120)	48 (12–108)	91 (35–156)	108 (48–204)	<0.001
BNP, pg/mL	542	160 (97–311)	193 (110–352)	327 (127–616)	215 (125–413)	0.001
NT-proBNP, pg/mL	342	1083 (428–2,094)	1123 (540–2,245)	1372 (375–2613)	1822 (750–3934)	0.012
NYHA class I	345	140 (46)	149 (37)	23 (23)	33 (17)	<0.001
II	557	141 (47)	225 (55)	57 (57)	134 (67)	
III	86	16 (5)	26 (6)	14 (14)	30 (15)	
IV	19	6 (2)	6 (2)	6 (6)	1 (1)	
Hypertension	1007	253 (84)	347 (86)	85 (85)	164 (83)	0.988
Prior HF admission	1007	47 (16)	105 (26)	33 (33)	86 (43)	<0.001
RAS-I	1007	130 (43)	190 (47)	44 (44)	96 (49)	0.250
Beta-blocker	1007	143 (47)	206 (51)	53 (53)	98 (50)	0.441
Loop diuretics	1007	127 (42)	204 (50)	70 (70)	147 (74)	<0.001
Echocardiography						
IVSd, mm	1007	10±2	10±2	10±2	10±2	0.192
LVEDV, mL	1007	78±23	111±36	74±22	109±38	<0.001
LVEDV Index, mL/m^2	1007	50±11	72±20	49±12	71±22	<0.001
LVESV, mL	1007	27±9	45±15	26±9	43±15	<0.001
LVEF, %	1007	65±4	59±6	65±4	60±6	<0.001
LA diameter, mm	1005	48±9	49±9	53±10	58±12	<0.001
LAVI, mL/m^2	945	77±35	88±64	100±49	131±78	<0.001
PASP, mm Hg	839	33±8	33±8	49±13	50±13	<0.001
Mitral E wave, cm/s	996	98±28	98±27	107±24	112±28	<0.001
Mean E/e'	940	18±8	18±9	19±8	17±7	0.650
Moderate-severe/severe MR	1007	57 (19)	110 (27)	28 (28)	84 (42)	<0.001
Moderate-severe/severe TR	1007	0 (0)	0 (0)	73 (73)	148 (75)	<0.001

Data are expressed as mean±SD or median (IQR) or number (%).
*Values of p indicate the trend of variables in cardiac damage classification using the Jonckheere–Terpstra trend test for the continuous variables and the Cochran–Armitage trend test for the proportions.
AF, atrial fibrillation; BNP, B-type natriuretic peptide; BP, blood pressure; BUN, blood urea nitrogen; HF, heart failure; IVSd, interventricular septum dimension; LA, left atrium; LAVI, left atrial volume index; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MR, mitral regurgitation; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; NT pro-BNP, N-terminal prohormone brain natriuretic peptide; RAS-I, renin angiotensin aldosterone system inhibitor; TR, tricuspid regurgitation.

relationship between classification and natural prognosis. All statistical analyses were performed using SPSS Statistics Desktop V.28.0 (IBM, Armonk, New York). The reported p values were two-tailed with statistical significance established at $p<0.05$.

RESULTS

Trends in baseline characteristics across cardiac damage stages

Table 1 and online supplemental table 1 present the baseline characteristics of a total of 1007 participants, stratified by cardiac damage classification. The cohort had a mean age of 78±10 years, 56% were female and 72% had moderate MR. Distribution of cardiac damage classification was as follows: group 1, 30.1% (303 patients); group 2, 40.3% (406 patients); group 3, 9.9% (100 patients); and group 4, 19.7% (198 patients) (figure 1B). Trend analysis revealed significant correlations of advanced cardiac damage classification with increased age, decreased body mass index, and lower blood pressure. Notably, haemoglobin and albumin levels declined, while creatinine and blood urea nitrogen levels increased with the classification of right heart damage. An increase in the EuroSCORE II was observed, reflecting an increased surgical risk with the classification of right heart damage. Furthermore, the prevalence of permanent AF increased, and the duration of AF was longer, with more frequent anticoagulation use. B-type natriuretic peptide (BNP) and N-terminal

pro-BNP levels were elevated, aligning with worsening HF symptoms, paralleled by increased diuretics use. On echocardiographic findings, the classification of left and right heart damage correlated with greater LV and LA enlargement, reduced LVEF, and more pronounced PH and TR, without a consistent trend in E/e'. Additionally, MR severity incidents also tended to escalate with the progression of right heart damage.

Cardiac damage classification and study outcome

The median follow-up duration was 3.0 years (IQR: 2.0–3.2 years) and the follow-up rate was 99.3% (997/1007). During follow-up, 387 patients experienced the primary outcome (189 all-cause death, 69 cardiac death, 141 HF hospitalisation and 143 MV intervention). Trend analysis demonstrated an increasing incidence of primary outcomes, all-cause death, cardiac deaths, HF hospitalisations, and clinically indicated MV interventions with the progression of right heart damage (online supplemental table 2). Kaplan–Meier analysis of the total population revealed that classification significantly stratified the incidence of primary endpoints (3-year event rates of 31.0%, 38.0%, 46.3% and 57.2% for groups 1, 2, 3 and 4, respectively; log-rank test, $p<0.001$; figure 2A). Group 4 consistently exhibited high incidence rates across separate analyses of HF hospitalisation, MV intervention (figure 2B–D) and cardiac death (online supplemental figure 1). A Cox multivariable hazard model (table 2), including the 11 variables, demonstrated a

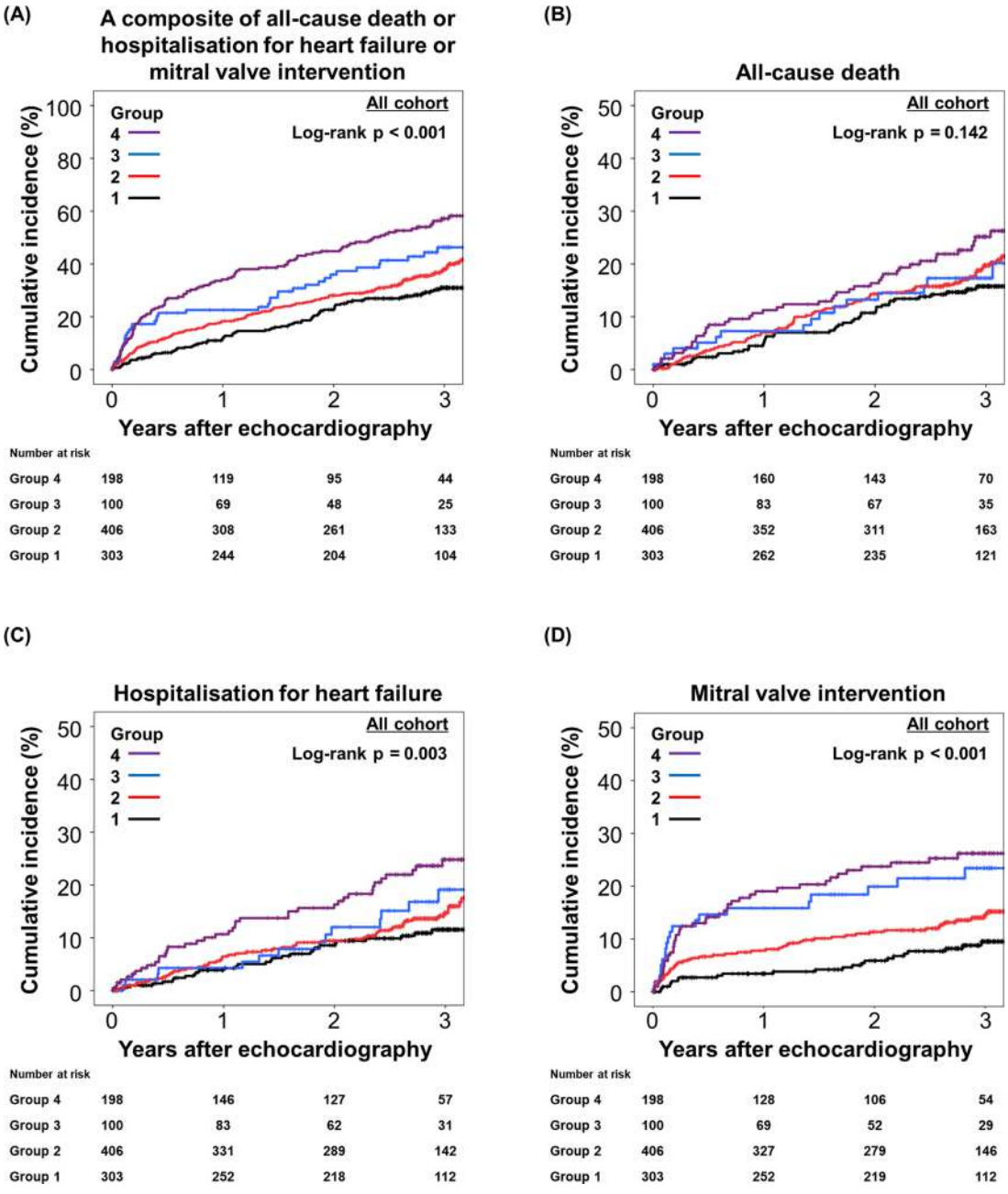


Figure 2 Kaplan–Meier analyses for clinical outcomes by cardiac damage classification. Cumulative incidence rates for the primary composite outcome (A), all-cause death (B), hospitalisation for heart failure (C) and mitral valve intervention (D), stratified by cardiac damage classification. Group 4 consistently shows the highest rates across all outcomes.

Table 2 Univariable and multivariable analyses for primary endpoint in the entire cohort

	Univariate analysis		Multivariable analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Group 1 (reference)				
Group 2	1.40 (1.07 to 1.82)	0.009	1.35 (0.96 to 1.90)	0.079
Group 3	1.78 (1.23 to 2.57)	0.002	1.48 (1.01 to 2.09)	0.041
Group 4	2.43 (1.83 to 3.23)	<0.001	1.65 (1.29 to 2.11)	< 0.001
Age	1.02 (1.01 to 1.03)	0.002	1.01 (0.99 to 1.02)	0.161
Female	0.79 (0.65 to 0.97)	0.023	0.65 (0.50 to 0.83)	0.001
Systolic BP, mm Hg	0.99 (0.98 to 0.99)	<0.001	0.99 (0.99 to 0.99)	0.004
Body mass index, kg/m^2	0.95 (0.93 to 0.98)	0.003	0.98 (0.96 to 1.01)	0.250
NYHA functional class II/III/IV	1.92 (1.52 to 2.43)	<0.001	1.38 (1.02 to 1.87)	0.034
Prior HF hospitalisation	2.19 (1.78 to 2.69)	<0.001	1.48 (1.15 to 1.91)	0.002
Haemoglobin, mg/dL	0.85 (0.81 to 0.90)	<0.001	0.90 (0.85 to 0.95)	< 0.001
Creatinine, mg/dL	1.10 (1.02 to 1.18)	0.012	1.04 (0.96 to 1.12)	0.369
EuroSCORE II, %	1.06 (1.05 to 1.08)	<0.001	1.03 (1.00 to 1.05)	0.045
Moderate-severe/Severe MR	2.38 (1.94 to 2.92)	<0.001	1.97 (1.55 to 2.45)	< 0.001

BP, blood pressure; HF, heart failure; MR, mitral regurgitation; NYHA, New York Heart Association.

significant association between cardiac damage group 4 and the primary outcomes, with an HR of 1.65 (95% CI 1.29 to 2.11, p<0.001).

Exploratory analysis on cardiac damage classification

Kaplan–Meier curves for the primary outcomes based on the cardiac damage classification stratified in patients with moderate MR and those in patients with severe MR are shown in online supplemental figure 1. Regardless of MR severity, cardiac damage group 4 were significantly associated with an increased risk of the composite of all-cause death, HF hospitalisation and MV intervention (online supplemental figure 2A,B). The natural history of the disease analysed in the 864 patients who did not undergo MV intervention revealed 244 composite outcomes of all-cause death and HF hospitalisation (168 all-cause death and 113 HF hospitalisation). Kaplan–Meier analysis of this group showed that group 4 consistently exhibited high incidence rates across analyses of the composite of all-cause death and HF hospitalisation, all-cause death, and HF hospitalisation (figure 3A–C). Furthermore, the cardiac damage group 4 was significantly associated with the composite of all-cause death and HF hospitalisation (HR of 1.59, 95%CI 1.06 to 2.37, p=0.025) in this group (online supplemental table 3). Conversely, in patients with MV intervention, no significant relationship was observed between cardiac damage classification and clinical events (log-rank test, p=0.489; figure 3D). The median duration from enrolment to MV intervention was 580 days in group 1, 197 days in group 2, 53 days in group 3 and 111 days in group 4.

DISCUSSION

In this extensive multicentre retrospective observational study, we systematically classified patients with AFMR into cardiac damage classification based on echocardiographic characteristics across a cohort of 1007 patients. Our exploration of the associations between cardiac damage classification, clinical characteristics and their impact on clinical outcomes has provided significant insights. Crucially, cardiac damage classification has emerged as an independent prognostic predictor for clinical events. This prognostic significance remained robust even after adjusting for confounding factors, such as HF manifestations, EuroSCORE II and MR severity, highlighting its substantial predictive value.

Baseline characteristics and cardiac damage classification

AFMR is primarily characterised as LA dilatation and mitral annular dilatation,[2 16 17] distinguishing it from the other subtype of functional MR that begins with LV dysfunction. AFMR is commonly observed in older patients, who have a higher prevalence of AF and have a larger LA than other aetiologies of MR.[7 18] This predominance of LA damage in AFMR differs significantly from other studies focused on cardiac damage which often starts with LV dysfunction.[8–10 19]

The progression of cardiac damage in AFMR is significantly influenced by factors such as ageing and the presence of permanent AF, which are closely associated with worsening clinical manifestations. Moreover, AF is associated with increased dilation of the tricuspid annulus, resulting in TR irrespective of MR severity.[20] This makes it difficult to interpret the association between the present group and TR in patients with AFMR. The incidence of functional TR associated with AF increases over time, with an incidence of 7.9 per 1000 person-years.[21] In our present results, the proportion of patients in group 3, that is, patients with isolated TR and/or PH, was 9.9%. These patients may indicate that right heart disorders do not necessarily succeed LV damage, as we had hypothesised in figure 1. However, as the prognosis of this group was between groups 2 and 4, it suggested that right heart damage may have a greater impact on prognosis than left heart damage.

Our trend analysis indicated that progression through cardiac damage classification was consistently associated with ageing,[22] worsening HF symptoms, increased diuretic use and elevated BNP levels. Additionally, the increasing prevalence of permanent AF correlated with diverse clinical manifestations in our cohort, further complicating the management of these patients. LA enlargement, MR severity and LV enlargement were also correlated with the progression through the cardiac damage classification. The progression of MR severity may be linked to the progression of both LV dilation and LA enlargement, as previously reported.[4 23] These trends may explain that the progression through cardiac damage classification was closely linked to worsening clinical outcomes.

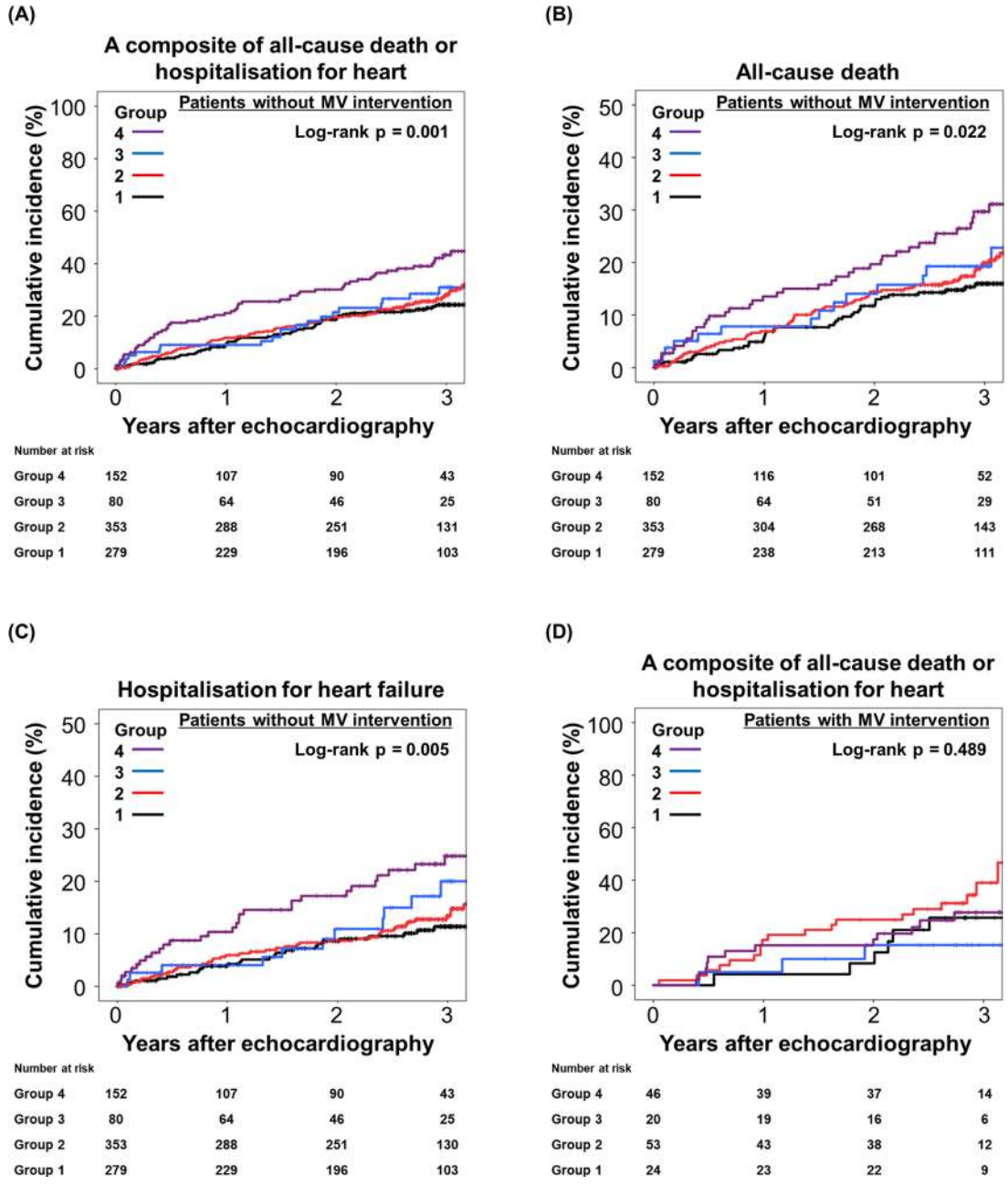


Figure 3 Outcomes by cardiac damage classification in subgroups with/without intervention. Cumulative incidence rates for the composite of all-cause death and hospitalisation for heart failure (A), all-cause death (B), hospitalisation for heart failure (C), patients without mitral valve intervention, and the composite of all-cause death and hospitalisation for heart failure in patients with mitral valve intervention (D). In the subgroup without MV intervention, group 4 consistently demonstrates the highest rates of adverse outcomes; among patients who underwent MV intervention, the outcomes across different damage groups did not show significant differences. MV, mitral valve.

Association between cardiac damage classification and clinical outcomes

Our study indicated a significant association between cardiac damage classification as the clinical condition and outcomes in AFMR, including all-cause death, cardiac death, HF hospitalisations and MV intervention. Few studies have addressed these clinical events in AFMR, emphasising the novelty of our findings in a multicentre large cohort. Previous research by Abe *et al*[1] supports our findings, showing that factors such as age, NYHA functional class, prior HF hospitalisation, AFMR severity and TR severity are linked to increased clinical adverse events. This correlation underscores the importance of cardiac damage classification, which is associated with these factors, in predicting patient outcomes.

The severity of cardiac damage in AFMR significantly impacted clinical outcomes, with group 4, representing both left and right heart damage, showing the strongest association with adverse results. Group 4 was associated with an increased risk of all-cause death, and HF among patients who did not undergo MV intervention. In contrast, group 3 was predominantly associated with higher rates of early MV interventions, possibly due to surgical intervention for TR or PH complications.[1]

Outcomes after MV intervention were similar among different cardiac damage states. This may indicate that there is no 'point of no return', although the number of events to draw robust conclusions was limited. To enhance the predictive accuracy of cardiac damage classification for treatment outcomes, further

large-scale studies are essential, especially those that assess patients immediately before intervention.

Limitations

This study had several limitations. First, despite the multicentre observation involving 26 hospitals, all patients were Asian, potentially limiting the generalisability of our findings to other ethnicities. Future studies should include diverse populations to enhance applicability across various clinical settings and validate the classification system. Furthermore, the classification in this study was based on a cross-sectional observation, and it does not necessarily reflect the longitudinal progression of AFMR. Longitudinal studies are needed to assess the dynamic progression of AFMR and refine stage transitions. Next, the diagnosis of AFMR and TR severity primarily relied on transthoracic echocardiography, supplemented by transoesophageal echocardiography when feasible. However, all transthoracic echocardiographic analyses were carefully reviewed by cardiologists specialising in echocardiography, who received dedicated training equivalent to level III echocardiography training. To ensure diagnostic accuracy, we also validated the AFMR diagnosis in a subset of randomly selected patients, all of whom were confirmed to exhibit significant AFMR. Next, echocardiographic analyses were conducted onsite, yet validation at a core laboratory corroborated the measurements, demonstrating excellent concordance with the initial assessments.[11] Additionally, patients with LV enlargement, a group often excluded from prior studies, were included to broaden the understanding of the spectrum of AFMR. However, further longitudinal studies are needed to clarify whether such cases should be classified within AFMR or excluded under revised definitions. Moreover, the LVEF threshold of 50%–60%, used to define LV damage in this study, was exploratory and adapted from degenerative MR criteria. Future research should evaluate this threshold in the context of AFMR to better reflect its unique pathophysiology. Furthermore, the right ventricular function, commonly used in cardiac damage classification, could not be assessed. Future research should incorporate detailed assessments of RV and RA function to develop a more comprehensive classification system that better captures the complexity of AFMR. Lastly, this retrospective study is subject to potential survivor bias, as patients with severe conditions who did not survive follow-up were excluded. The absence of propensity score analysis to address this bias should be considered when interpreting the findings. Nonetheless, our approach highlights the potential variability in progression from LA damage and elucidates differences across classification, underscoring the novel contributions despite these limitations.

In conclusion, this cardiac damage classification in AFMR, based on echocardiographic assessment of atrial and ventricular dysfunction, was closely associated with the progression of HF symptoms, AF and MR severity. Furthermore, this cardiac damage classification was significantly associated with adverse clinical outcomes in AFMR. However, further studies are needed to explore the potential for patient management using this classification in AFMR.

Author affiliations
[1]Department of Cardiovascular Medicine, Kobe City Medical Center General Hospital, Kobe, Japan
[2]Department of Cardiovascular Biology and Medicine, Juntendo University Graduate School of Medicine, Bunkyo-ku, Japan
[3]Department of Heart Failure and Transplantation, National Cerebral and Cardiovascular Center Hospital, Suita, Japan
[4]Department of Cardiology, St Marianna University School of Medicine, Kawasaki, Japan
[5]Department of Cardiology, Tokai University School of Medicine, Isehara, Japan
[6]Department of Cardiovascular Medicine, Gunma University Graduate School of Medicine, Maebashi, Japan
[7]Department of Cardiology, Institute of Medicine, University of Tsukuba, Tsukuba, Japan
[8]Department of Nursing Administration and Advanced Clinical Nursing, Division of Health Sciences and Nursing, Graduate School of Medicine, The University of Tokyo, Bunkyo, Japan
[9]Department of Cardiology, Osaka City General Hospital, Osaka, Japan

Acknowledgements The authors thank Naoki Hoshino, Kentaro Yamashita, Yuko Katsuta, Yuki Izumi, Mitsuhiko Ota, Yasuhide Mochizuki, Kaoruko Sengoku, Shunsuke Sasaki, Fukuko Nagura, Nanaka Nomura, Ryo Nishikawa, Nahoko Kato, Takahiro Sakamoto, Noriko Eguchi, Maiko Senoo, Mariko Kitano, Yoichi Takaya and Yoshihito Saijo for their contributions for data acquisition.

Contributors TO and NK structured and drafted the manuscript. All other authors drafted, reviewed and edited the manuscript. TO and NK are the guarantors of this manuscript and accept full responsibility for the integrity of the work, including the accuracy of the data and the analysis. The authors used ChatGPT, an AI language model, for editing and refining the text of this manuscript. Additionally, the manuscript was proofread by a professional editing company. All final content was reviewed and approved by the authors to ensure accuracy and compliance with research integrity.

Funding This study was partially supported by the Uehara Memorial Foundation and by the Japanese Japan Society for the Promotion of Science KAKENHI (grant number 22K20895).

Competing interests NK received research grants from EchoNous Inc., AMI Inc., and AstraZeneca and speaker honoraria from Eli Lilly, Novartis, Otsuka pharmaceutical, and Nippon Boehringer-Ingelheim outside this work and is affiliated with a department funded by Paramount Bed Ltd. MO received research grants from the Fukuda Foundation for Medical Technology, the Mochida Memorial Foundation for Medical and Pharmaceutical Research, Nippon Shinyaku, Takeda Science Foundation, the Japanese Circulation Society, the Japanese College of Cardiology, JSPS KAKENHI 21K16078, AMED (23jm0210104h0002), AMI Inc., Boehringer-Ingelheim, and Janssen and speaker honoraria from AstraZeneca, Eli Lilly, Novartis, Otsuka pharmaceutical, and Boehringer-Ingelheim outside this work. KS belongs to an endowed department funded by Medtronic and DVX. TK receives research grants from the Japanese Circulation Society. YF has received speaker honoraria from Daiichi Sankyo and Bayer. YO is a clinical proctor of transcatheter edge-to-edge repair for Abbott Medical and has received speaker fees from Abbott Medical. Other authors have nothing to disclose regarding the submitted manuscript.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants. The study protocols were in accordance with the Declaration of Helsinki, and received approval from the institutional review board of Juntendo University, Japan, with each participating centre also approving the execution of the study. Given its retrospective, observational, and non-invasive nature, the requirement for written informed consent was waived, and opt-out consent was used instead. Study detail information, including the objectives, inclusion and exclusion criteria, clinical event, and names of the participating hospitals, were published on the publicly available University Hospital Information Network (UMIN-CTR, unique identifier: UMIN000046146), prior to patient enrolment. This study was conducted using an opt-out method, so explicit informed consent was not obtained from the participants.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The data that support the findings of this study are available from the corresponding authors, TO and NK, upon reasonable request. Due to privacy and ethical restrictions, the data are not publicly available. Access to the data can be granted upon request and with the approval of the relevant ethics committees.

ORCID iDs
Taiji Okada http://orcid.org/0000-0002-8878-3446
Nobuyuki Kagiyama http://orcid.org/0000-0002-2305-0049
Masashi Amano http://orcid.org/0000-0003-4095-1567
Masaru Obokata http://orcid.org/0000-0002-5473-0688
Kimi Sato http://orcid.org/0000-0003-4549-7770
Kojiro Morita http://orcid.org/0000-0002-2306-0669
Tomoko Machino-Ohtsuka http://orcid.org/0000-0003-1901-7112
Yukio Abe http://orcid.org/0000-0003-0241-1412

REFERENCES

1 Abe Y, Akamatsu K, Ito K, *et al*. Prevalence and Prognostic Significance of Functional Mitral and Tricuspid Regurgitation Despite Preserved Left Ventricular Ejection Fraction in Atrial Fibrillation Patients. *Circ J* 2018;82:1451–8.
2 Abe Y, Takahashi Y, Shibata T. A new disease entity: Atrial functional mitral regurgitation. *J Cardiol* 2021;77:565–9.
3 Kagiyama N, Mondillo S, Yoshida K, *et al*. Subtypes of atrial functional mitral regurgitation: imaging insights into their mechanisms and therapeutic implications. *JACC Cardiovasc Imaging* 2020;13:820–35.
4 Akamatsu K, Abe Y, Matsumura Y, *et al*. Etiology of Atrial Functional Mitral Regurgitation: Insights from Transthoracic Echocardiography in 159 Consecutive Patients with Atrial Fibrillation and Preserved Left Ventricular Ejection Fraction. *Cardiology* 2020;145:511–21.
5 Utsunomiya H, Itabashi Y, Mihara H, *et al*. Functional Tricuspid Regurgitation Caused by Chronic Atrial Fibrillation: A Real-Time 3-Dimensional Transesophageal Echocardiography Study. *Circ Cardiovasc Imaging* 2017;10:e004897.
6 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.
7 Doldi P, Stolz L, Orban M, *et al*. Transcatheter Mitral Valve Repair in Patients With Atrial Functional Mitral Regurgitation. *JACC Cardiovasc Imaging* 2022;15:1843–51.
8 Généreux P, Pibarot P, Redfors B, *et al*. Staging classification of aortic stenosis based on the extent of cardiac damage. *Eur Heart J* 2017;38:3351–8.
9 Bernard J, Altes A, Dupuis M, *et al*. Cardiac Damage Staging Classification in Asymptomatic Moderate or Severe Primary Mitral Regurgitation. *Struct Heart* 2022;6:100004.
10 Stolz L, Doldi PM, Orban M, *et al*. Staging Heart Failure Patients With Secondary Mitral Regurgitation Undergoing Transcatheter Edge-to-Edge Repair. *JACC Cardiovasc Interv* 2023;16:140–51.
11 Kagiyama N, Kaneko T, Amano M, *et al*. Clinical outcomes and impact of mitral valve surgery in atrial functional mitral regurgitation: the REVEAL-AFMR registry. *Eur Heart J* 2024;45.
12 Daimon M, Watanabe H, Abe Y, *et al*. Normal values of echocardiographic parameters in relation to age in a healthy Japanese population: the JAMP study. *Circ J* 2008;72:1859–66.
13 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.
14 Zoghbi WA, Adams D, Bonow RO, *et al*. Recommendations for Noninvasive Evaluation of Native Valvular Regurgitation: A Report from the American Society of Echocardiography Developed in Collaboration with the Society for Cardiovascular Magnetic Resonance. *J Am Soc Echocardiogr* 2017;30:303–71.
15 Hicks KA, Tcheng JE, Bozkurt B, *et al*. 2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards). *Circulation* 2015;132:302–61.
16 Kagiyama N, Hayashida A, Toki M, *et al*. Insufficient Leaflet Remodeling in Patients With Atrial Fibrillation: Association With the Severity of Mitral Regurgitation. *Circ Cardiovasc Imaging* 2017;10:e005451.
17 Machino-Ohtsuka T, Seo Y, Ishizu T, *et al*. Novel Mechanistic Insights Into Atrial Functional Mitral Regurgitation - 3-Dimensional Echocardiographic Study. *Circ J* 2016;80:2240–8.
18 Masiero G, Montonati C, Rubbio AP, *et al*. Impact of Transcatheter Edge-to-Edge Mitral Valve Repair on Atrial Functional Mitral Regurgitation from the GIOTTO Registry. *Am J Cardiol* 2024;211:219–27.
19 van Wijngaarden AL, Mantegazza V, Hiemstra YL, *et al*. Prognostic Impact of Extra-Mitral Valve Cardiac Involvement in Patients With Primary Mitral Regurgitation. *JACC Cardiovasc Imaging* 2022;15:961–70.
20 Ortiz-Leon XA, Posada-Martinez EL, Trejo-Paredes MC, *et al*. Tricuspid and mitral remodelling in atrial fibrillation: a three-dimensional echocardiographic study. *Eur Heart J Cardiovasc Imaging* 2022;23:944–55.
21 Kwak S, Lim J, Yang S, *et al*. Atrial Functional Tricuspid Regurgitation: Importance of Atrial Fibrillation and Right Atrial Remodeling and Prognostic Significance. *JACC Cardiovasc Imaging* 2023;16:575–87.
22 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.
23 Naser JA, Alexandrino FB, Harada T, *et al*. The Natural History of Atrial Functional Mitral Regurgitation. *J Am Coll Cardiol* 2024;83:1495–507.