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Atrial Functional Mitral Regurgitation

Effect of Phenotype Definition on Classification, Valve Features, and Prognosis

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ABSTRACT

BACKGROUND Atrial functional mitral regurgitation (AfMR) is a distinct entity of functional mitral regurgitation (fMR) with substantial clinical implications. Variation among published definitions introduces uncertainty regarding prevalence, morphology, and mortality, precluding consistent clinical decision making. A JACC Expert Consensus proposed a definition that was recently challenged by the European Society of Cardiology (ESC) valve guidelines. A unified, broadly applicable definition requires systematic evaluation of existing criteria.

OBJECTIVES The authors undertook sensitivity analyses of previously published AfMR definitions regarding classification, valve features, population characteristics, and prognosis, with a particular focus on the JACC Expert Consensus and the ESC guidelines definitions.

METHODS PubMed, Embase, and Web of Science were systematically searched for publications on AfMR. All identified definitions were applied to an independent single-center database of severe fMR patients (n = 581). Moderate fMR (n = 6,755) served as comparator group. Sensitivity analyses evaluated the robustness of results across definition specifications.

RESULTS Seventy-two unique AfMR definitions were identified. There was considerable variability in prevalence (2%-62%), valve features (annular diameter: 31.5-37.1 mm; tenting area: 146-229 mm^2; Carpentier classification IIIb: 0%-49%), and outcome (HR: 1.17-2.42). Clustering by ejection fraction, left atrial dilation, and atrial fibrillation demonstrated that conceptually similar definitions frequently classified distinct populations. The JACC and ESC definitions showed similar overall prevalence but defined heterogeneous populations with differences in left atrial thresholds (40 mL/m^2 in JACC vs 34 mL/m^2 in ESC) and inclusion of 25% Carpentier IIIb cases with JACC (ESC: Carpentier type I only). Both were associated with higher mortality vs moderate fMR (JACC HR: 2.08 [95% CI: 1.42-3.04; $P < 0.001$]; ESC HR: 1.88 [95% CI: 1.26-2.82; $P = 0.002$]). After multivariate adjustment and correction for multiple testing, the JACC Expert Consensus definition remained significant, whereas the ESC guidelines definition did not.

CONCLUSIONS AfMR definitions show considerable variability in prevalence, valve features, and prognostic performance. Although the ESC guidelines and JACC Expert Consensus definitions yield similar prevalence, the JACC definition demonstrated robust prognostic validity and adaptability to a wider morphologic spectrum, including restrictive posterior leaflet (Carpentier IIIb) configurations. The robustness and flexibility indicate that the JACC definition provides a solid foundation for a unified, clinically applicable AfMR definition. (JACC. 2026;87:3277-3292)

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

Af = atrial fibrillation

AfMR = atrial functional mitral regurgitation

EF = ejection fraction

fMR = functional mitral regurgitation

HFmrEF = heart failure with mildly reduced ejection fraction

HFpEF = heart failure with preserved ejection fraction

LA = left atrial

LV = left ventricular

LVEDV = left ventricular end-diastolic volume

NT-proBNP = N-terminal pro-B-type natriuretic peptide

Functional mitral regurgitation (fMR) is a prevalent condition associated with a poor quality of life, high hospitalization rates, and unfavorable outcomes.[1-3] Traditionally, the development of fMR has been attributed to dysfunction and alterations in the geometry of the left ventricle (LV), known as ventricular fMR. More recent studies have identified another distinct subtype—atrial fMR (AfMR)—characterized by mitral regurgitation due to left atrial (LA) and consequently mitral annular dilation in the absence of LV remodeling-induced leaflet tethering. As AfMR enters guidelines[4,5] and clinical decision making, inconsistent definitions now risk fragmenting the evidence base, obscuring treatment effects, and misclassifying patients at the point of care. Establishing a clear definition is essential and requires a comprehensive assessment and comparison of existing frameworks, with particular attention to patient selection, detailed morphologic evaluation, and clinical relevance. Rather than proposing yet another definition, we sought to understand how existing definitions behave when applied to the same patients, and what principles consistently identify clinically meaningful AfMR. Across definitions, we hypothesized that morphology-based criteria would outperform rhythm-based criteria in identifying AfMR phenotypes with consistent structural and prognostic profiles.

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METHODS

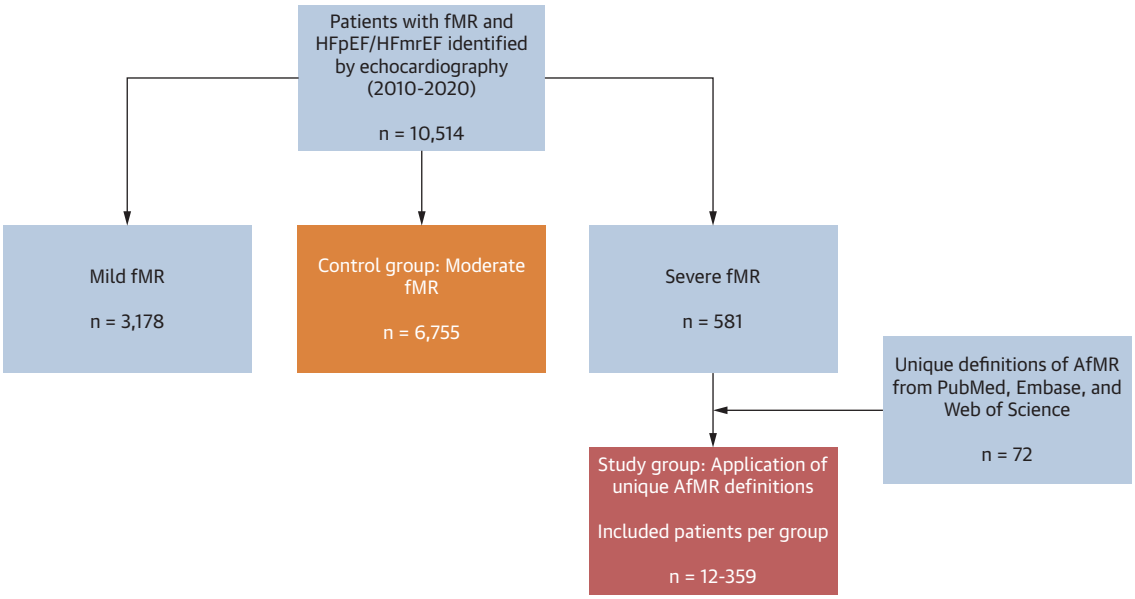
STUDY DESIGN AND POPULATION. In this large-scale study, all adult patients with fMR and heart failure with preserved (HFpEF) or mildly reduced ejection fraction (HFmrEF) that had received echocardiography in our tertiary care center from 2010 to 2020 were enrolled. Exclusion criteria comprised significant primary mitral or tricuspid valve disease, rheumatic valve disease, endocarditis, congenital heart disease, any mitral/tricuspid annular calcification with signs of inflow obstruction or more than moderate-severe mitral/tricuspid annular calcification without stenotic effects, any other significant (moderate or more) primary valve disease, and poor image quality. This resulted in a cohort of 10,514 patients with fMR, of whom 581 had severe fMR, 6,755 moderate fMR, and 3,178 mild fMR. A flow diagram of the patient categorization is shown in **Figure 1**.

LITERATURE SEARCH STRATEGY AND SELECTION CRITERIA. A systematic data search of PubMed, Embase, and Web of Science of studies assessing AfMR, published up to September 26, 2025, was performed. The search algorithm is presented in detail in Supplemental Methods 1, and the search strategy is detailed in Supplemental Figure 1. Trials were included if they were original articles and provided a definition of AfMR. In addition, the proposed definitions from the 2025 ESC guidelines and from the 2022 JACC Expert Consensus were included. In the ESC guidelines, a key criterion of AfMR is defined as fMR occurring in the setting of preserved or mildly dilated LV geometry, in the absence of leaflet tethering. Although the ESC guidelines acknowledge the potential for overlap between AfMR and ventricular mechanisms at advanced stages, such cases are not included within the AfMR framework as applied in clinical practice and illustrative figures. Therefore, in the present analysis, patients with marked leaflet tethering including pronounced restriction of the posterior leaflet were not included for this definition.

DATA ANALYSIS AND SYSTEMATIC IMPLEMENTATION OF AfMR DEFINITIONS. AfMR definitions were extracted with the use of a standardized data form and analyzed by 2 authors (S.K. and C.J.). Any discrepancies were resolved by consensus of 2 other authors (P.E.B. and C.N.). The definitions were grouped according to ejection fraction (EF) clusters (≥50%, ≥45%, >40%). As the majority of definitions required an EF ≥50%, this group was further subdivided according to clusters of LA dilation and atrial fibrillation (AF) mandatory requirements: mandatory LA dilation and AF, mandatory LA dilation only, mandatory AF only, or neither mandatory for the definition. All extracted definitions were then applied to the aforementioned comprehensive and independent reference database,[1,6] and sensitivity analyses were performed in terms of classification, valve features, and prognosis.

CLINICAL MEASURES AND FOLLOW-UP. Baseline examination included demographic data, past medical history, routine laboratory values, and transthoracic echocardiographic assessment. The diagnosis of comorbidities was obtained from ICD-10 codes. The primary endpoint was all-cause mortality. Mortality data were obtained from the national death registry, listing all deceased Austrian citizens in Austria and abroad. Causes of death were classified according to the authority vital statistic coding system as cardiovascular or noncardiovascular. The study was approved by the Institutional Ethics Review Board of the Medical University of Vienna

FIGURE 1 Flow Diagram of the Cohort



The flow diagram illustrates patient selection for the study. Among 10,514 patients with fMR and HFpEF/HFmrEF, 581 had severe fMR; 72 published definitions of AfMR, identified through systematic PubMed, Embase, and Web of Science searches, were applied to this cohort, resulting in 72 AfMR subgroups containing 12-359 patients. This diagram summarizes the derivation of AfMR cohorts used for comparative analyses. AfMR = atrial functional mitral regurgitation; fMR = functional mitral regurgitation; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction.

(EK no. 2137/2018), and informed consent was waived according to the Institutional Review Board. All authors had full access to all study data and are responsible for its integrity and data analysis.

ECHOCARDIOGRAPHIC ASSESSMENT. All transthoracic echocardiographic examinations were performed in accordance with societal guidelines.[4,5] The studies were performed with commercially available ultrasound systems (Vivid E7 and E9 [GE Healthcare] and Acuson S2000 [Siemens]) and were interpreted by board-certified cardiologists. For the assessment of cardiac dimensions, diameters and volumes were measured in the 2-chamber and 4-chamber views. LV EF was quantified according to the biplane method of disks (modified Simpson rule). Right ventricular function was quantitatively assessed by experienced echocardiographers using multiple acoustic windows and graded according to current recommendations.[7] Standard parameters from the local echocardiography laboratory, including tricuspid annular plane systolic excursion, pulsed-wave Doppler S′ velocity, and RV free-wall strain, were integrated to classify dysfunction as mild, moderate, or severe.[7] Comprehensive mitral valvular measurements were performed offline blinded to patient data, including annular diameter (3-chamber and 4-chamber views), tenting height, tenting area (3-chamber and 4-chamber view), and tethering angles of the mitral leaflets (3-chamber view). A detailed description of the methodology used for valve morphology assessment is provided in Supplemental Methods 2. The severity of fMR was graded with an integrative approach in accordance with prevailing guidelines.[8] Parameters included in the study were mitral valve morphology, vena contracta width, pulmonary venous flow pattern, and calculation of the effective regurgitant orifice area, regurgitant volume by the proximal isovelocity surface area method, and regurgitant fraction. Severe fMR was defined by an effective regurgitant orifice area ≥0.40 mm^2 and/or regurgitant volume ≥60 mL. A vena contracta width ≥7 mm and a regurgitant fraction ≥50% were considered to be supportive of severe fMR. Systolic pulmonary artery pressure was calculated according to the simplified Bernoulli equation plus right atrial pressure estimated. Central venous pressure, as an estimate of right-side filling pressure, was graded as normal (<5 mm Hg), mildly (5 to <10), moderately (10 to <15), or severely abnormal (≥15).

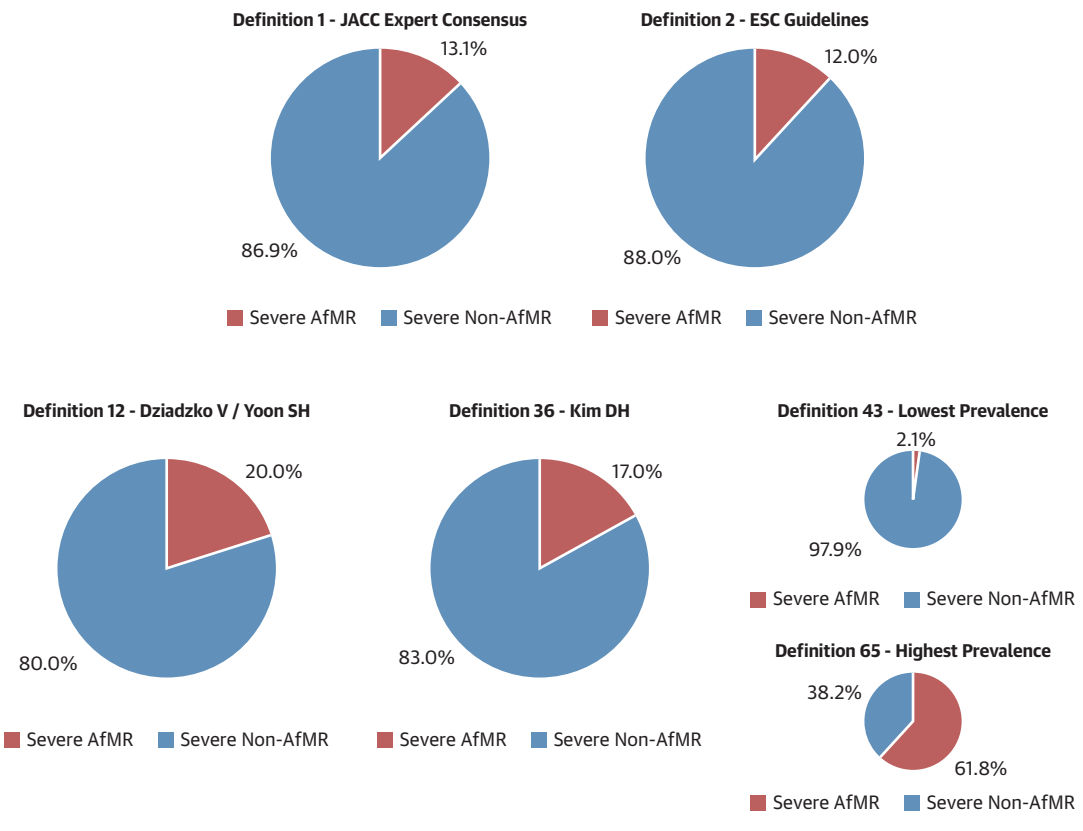
TABLE 1 Key Inclusion Criteria of Selected AfMR Definitions

Definition and Requirements	EF Threshold	No Regional Wall Motion Abnormalities	No LV Dilation	Mild or Less LV Dilation	Less Than Severe LV Dilation	LA Dilation	AF	Mitral Annular Dilation	Carpentier Type I	No or Mild Leaflet Tethering	No Coronary Artery Disease
1. JACC Expert Consensus[9]	≥50%	X	X indexed LVEDV ≤78 mL/m² F, ≤85 mL/m² M			X ≥ moderate, Indexed LA volume ≥40 mL/m²		X		X	
2. ESC Guidelines[5]	≥50%	X	X Indexed LVEDV <71 mL/m² F, <79 mL/m² M			X ≥ mild, Indexed LA volume >34 mL/m²		X	X	X	
12. Yoon et al[10] + Dziadzko et al[11]	≥54% F, ≥52% M			X		X ≥ moderate, Indexed LA volume ≥40 mL/m²					
36. Kim et al[12]	≥50%	X	X Indexed LVEDV ≤75 mL/m²				X				
All definitions, 1-72	≥40% to ≥55%					X/not applicable					

Matrix table summarizing the diagnostic criteria applied in the 4 definitions from the main analysis of AfMR evaluated in this study. Each row represents 1 definition and each column a specific diagnostic criterion. An "X" indicates that the feature is included in that definition. For each variable the overall minimum and maximum value was chosen, to show the wide variability across AfMR definitions. This table highlights the heterogeneity in key parameters such as AF, LA dilation, mitral annular dilation, and LV size and function across the main AfMR definitions.

AF = atrial fibrillation; AfMR = atrial functional mitral regurgitation; EF = ejection fraction; F = female; LA = left atrial; LV = left ventricle; LVEDV = left ventricular end-diastolic volume; M = male.

FIGURE 2 Prevalence of Severe AfMR Across Definitions



The first 4 pie charts display the 4 AfMR definitions used in the main analysis, highlighting variation in classification. The last 2 pie charts show the full range of prevalence across all 72 definitions, with definition 43 showing the lowest and definition 65 the highest prevalence of severe AfMR. AfMR = atrial functional mitral regurgitation.

STATISTICAL ANALYSIS. For a focused comparison, 4 definitions were compared: those from the 2025 ESC guidelines,[5] 2022 JACC expert consensus,[9] Dziadzko et al[10]/Yoon et al,[11] and Kim et al.[12] These definitions were chosen because they represent major reference standards and key criteria commonly used for inclusion. The study by Kim et al was not designed to establish a definition of AfMR, but rather to investigate leaflet remodeling in patients with AfMR and AF. Nevertheless, it was selected as a representative example of AfMR definitions that mandate the presence of AF. In addition, the ranges of characteristics across all definitions are given. Information on characteristics of all definitions are detailed in Supplemental Table 1.

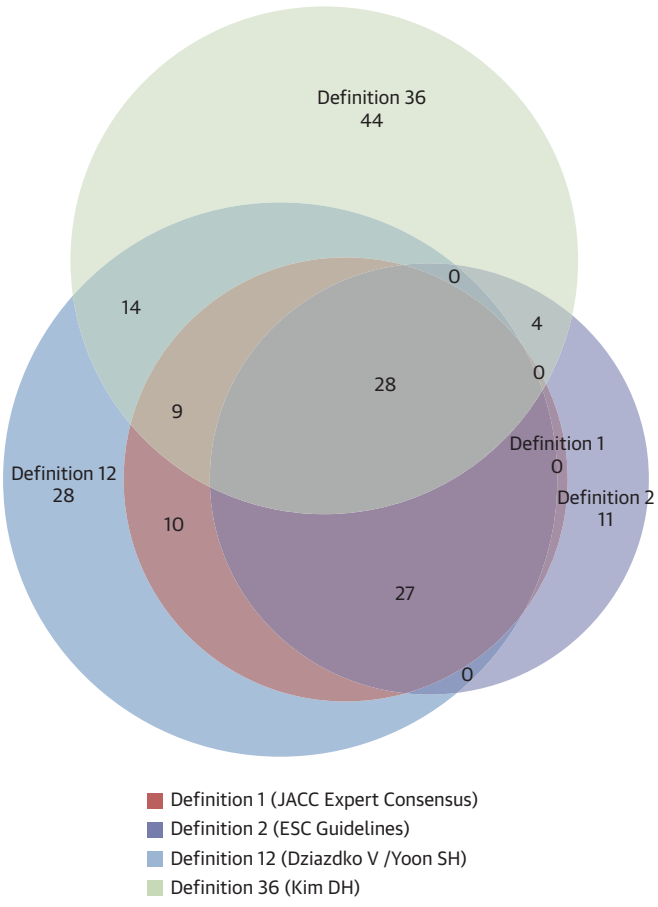
The data are presented as median (Q1-Q3) for continuous variables, and n (%) for discrete data. Due to the large number of groups (n = 72) and small sample sizes, statistical comparisons of baseline characteristics between groups were not performed, and results are presented descriptively. Kaplan-Meier estimates, univariable and multivariable Cox proportional hazard regression analyses were performed to assess the impact of severe AfMR on survival for each definition, respectively. The comparator groups consisted of moderate fMR. The results are presented as log-rank test and hazard ratio with 95% CI. For definitions with a small number of included patients (n < 30) or a low event rate (n < 10), prevalence and characteristics were reported descriptively. The multivariable Cox model was adjusted for age, sex, and N-terminal pro-B-type natriuretic peptide (NT-proBNP). Patients that received mitral valve intervention during the observation period were censored at the time of intervention. *P* values were adjusted for multiple testing with the use of the Benjamini-Hochberg procedure, yielding *q* values. To compare cardiovascular and noncardiovascular survival across the 4 main definitions, Fine-Gray analysis with cumulative incidence curves and Gray's test for equality of cumulative incidence functions across group were performed. To assess potential temporal heterogeneity, additional Cox regression models were performed with adjustment for the date of echocardiography, allowing evaluation of potential era-related effects. A 2-sided *P* value of <0.05 was considered to be statistically significant. Statistical analyses were performed with the use of R Studio Version 4.4.3.

RESULTS

AfMR PREVALENCE. As detailed in the Methods, this analysis centers on 4 clinically relevant definitions of AfMR: those from the JACC expert consensus (definition 1), the ESC guidelines (definition 2), Dziadzko et al/Yoon et al (definition 12), and Kim et al (definition 36).[5,9,11,12]

A total of 72 distinct definitions of AfMR were identified. Of these, 6 required an EF ≥40%, 6 an EF ≥45%, and 60 an EF ≥50%. Within the EF ≥50% group, 7 definitions required both AF and LA dilation, 25 required LA dilation alone, 15 required AF alone, and 13 did not specify either criterion. **Table 1** summarizes the 4 selected definitions and their respective diagnostic features, key inclusion criteria for all 72 definitions are provided in Supplemental Table 1. Common inclusion parameters included EF, the absence of regional wall motion abnormalities, LA and LV enlargement, AF, mitral

FIGURE 3 Overlap of AfMR Definitions



Venn diagram visualizing the shared and unique patient subsets (absolute numbers) identified by the 4 representative AfMR definitions, further emphasizing the variability in classification depending on the applied criteria. AfMR = atrial functional mitral regurgitation.

TABLE 2 Baseline Characteristics of AfMR Definitions

	Definition 1—JACC Expert Consensus[9] (n = 76)	Definition 2—ESC Guidelines[5] (n = 70)	Definition 12—Dziadzko et al[10]/Yoon et al[11] (n = 116)	Definition 36—Kim et al[12] (n = 99)	All Definitions 1-72, Range (n = 12-359)
Characteristics					
Age, y	74 (66-78)	75 (69-79)	75 (68-81)	75 (68-84)	72-78
Female	39 (51)	37 (53)	65 (56)	61 (62)	0%-71%
Body surface area, m^2	1.82 (1.72-2.01)	1.85 (1.71-2.01)	1.80 (1.68-1.98)	1.85 (1.69-2.03)	1.77-2.00
Comorbidities					
Coronary artery disease	18 (24)	20 (29)	31 (27)	36 (36)	0%-53%
Diabetes	10 (13)	9 (13)	17 (15)	22 (22)	10%-28%
AF	39 (51)	33 (47)	58 (50)	99 (100)	40%-100%
Hypertension	26 (34)	25 (36)	46 (40)	60 (61)	28%-70%
Hyperlipidemia	9 (12)	10 (14)	20 (17)	22 (22)	7.5%-38%
Chronic obstructive pulmonary disease	9 (12)	10 (14)	11 (9.5)	15 (15)	5%-19%
Peripheral artery disease	13 (17)	15 (21)	21 (18)	22 (22)	10%-44%
Carotid artery disease	12 (27)	7 (16)	19 (28)	14 (25)	10%-57%
HFpEF	79 (100)	70 (100)	116 (100)	99 (100)	49%-100%
Laboratory measurements					
Hemoglobin, g/dL	12.05 (10.15-13.50)	11.70 (10.50-13.20)	12.00 (10.30-13.30)	12.00 (10.40-13.30)	11.70-12.60
Creatinine, mg/dL	1.02 (0.85-1.27)	1.05 (0.87-1.28)	1.05 (0.86-1.30)	1.05 (0.85-1.28)	1.00-1.17
Blood urea nitrogen, mmol/L	19 (14-25)	19 (15-26)	20 (15-28)	18 (14-25)	17-21
Albumin, g/L	40 (33-43)	39.2 (33.043.3)	39 (36-43)	39 (33-42)	37.6-40
Bilirubin, μmol/L	0.66 (0.45-0.97)	0.71 (0.45-1.08)	0.64 (0.45-0.96)	0.66 (0.46-0.92)	0.61-0.81
γ-Glutamyltransferase, U/L	54 (35-96)	55 (35-93)	50 (29-85)	49 (32-100)	33-62
NT-proBNP	1,970 (986-3,651)	1,976 (1,056-3,725)	2,041 (1,047-3,701)	2,014 (1,038-3,738)	1,681-2,956
Echocardiographic characteristics					
LA diameter, mm	70 (65-79)	70 (65-79)	69 (63-78)	65 (60-73)	31.5-75
Indexed LA volume, mL/m^2	54 (47-70)	52 (42-68)	52 (46-62)	41 (31-52)	36-62
Right atrial diameter, mm	68 (60-76)	69 (60-79)	64 (58-76)	61 (56-71)	33.4-70.0
Indexed LV end-diastolic diameter, mm	29.4 (26.7-32.6)	29.3 (26.1-32.6)	29.3 (26.2-32.5)	27.7 (24.3-30.8)	25.5-31.6
Indexed LV end-diastolic volume, mL/m^2	49 (37-59)	48 (36-57)	48 (36-57)	42 (34-53)	38-56
Right ventricular end-diastolic diameter, mm	36.0 (32.0-41.0)	37.0 (33.0-41.0)	36 (32-41)	35 (31-39)	34-39
Mitral annulus diameter, 4-chamber view, mm	39.7 (36.7-42.6)	39.4 (36.6-42.3)	37 (33-42)	34.4 (31.4-39.6)	33.4-40.8
Mitral annulus diameter, 3-chamber view, mm	36.7 (33.6-39.8)	37.1 (34.4-39.9)	34.2 (30.4-38.3)	33 (29-37)	31.5-37.1
Tenting height, 4-chamber view, mm	4.95 (3.60-6.25)	4.55 (3.30-6.00)	4.75 (3.25-6.00)	4.60 (3.30-6.60)	4.1-6.15
Tenting height, 3-chamber view, mm	7.80 (5.75-9.15)	6.95 (5.10-8.30)	7.35 (5.10-9.05)	7.20 (5.10-9.10)	6.2-8.95
Tenting area, 4-chamber view, mm^2	125 (83-171)	118 (84-158)	117 (78-161)	115 (78-162)	99-131
Tenting area, 3-chamber view, mm^2	209 (127-283)	196 (121-261)	193 (117-257)	168 (120-224)	146-229
Angle anterior, 3-chamber view, °	19 (15-22)	16.7 (13.4-20.7)	20 (15-23)	21 (15-25)	16.7-22
Angle posterior, 3-chamber view, °	28 (22-35)	25 (21-29)	29 (22-36)	29 (22-36)	23-34
Carpentier classification					
I	57 (75)	70 (100)	85 (73)	70 (71)	51%-100%
IIIb	19 (25)	0 (0)	31 (27)	29 (29)	0%-49%
Systolic pulmonary artery pressure, mm Hg	54 (41-64)	56 (44-65)	56 (43-65)	51 (44-62)	51-56
≥ moderately reduced right ventricular function	13 (17)	13 (19)	17 (15)	13 (14)	9.1%-29%
≥ moderate tricuspid regurgitation	60 (80)	60 (86)	93 (81)	83 (85)	67%-90%

Values are median (Q1-Q3) or n (%), unless otherwise indicated. Baseline demographic, clinical, and echocardiographic characteristics of patients with severe AfMR, stratified by the 4 definitions from the main analysis (JACC Expert Consensus,[9] ESC Guidelines,[5] Dziadzko et al[10]/Yoon et al,[11] and Kim et al[12]) and summarized across all 72 published definitions. The "All Definitions" column displays the ranges of medians across all definitions, illustrating variability in patient selection and phenotype among AfMR criteria.

AF = atrial fibrillation; AfMR = atrial functional mitral regurgitation; HFpEF = heart failure with preserved ejection fraction; LA = left atrial; LV = left ventricular; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

TABLE 3 Univariate and Multivariate Cox Regression Models

AfMR Definition	Univariate				Multivariate			
	HR	95% CI	*P* value	FDR, *q*[a]	HR	95% CI	*P* value	FDR, *q*[a]
Moderate fMR	Reference				Reference			
1 (JACC)[5]	2.08	1.42-3.04	<0.001	<0.001	1.79	1.22-2.62	0.003	0.027
2 (ESC)[9]	1.88	1.26-2.82	0.002	0.006	1.46	0.98-2.18	0.066	0.216
12 (Dziadzko et al[10]/Yoon et al[11])	1.72	1.25-2.36	<0.001	0.003	1.38	1.00-1.89	0.047	0.171
36 (Kim et al)[12]	1.49	1.03-2.14	0.034	0.042	1.14	0.79-1.65	0.48	0.689
All definitions 1-72	1.17-2.42	0.69-3.5	<0.001- 0.56	<0.001- 0.56	0.9-1.99	0.57-4.4	<0.001-0.99	0.002-0.99

Cox proportional hazard regression analyses evaluating the association between severe AfMR and long-term all-cause mortality, compared with moderate fMR as the reference group. Univariate and multivariate models are shown for the 4 definitions from the main analysis (JACC Expert Consensus,[9] ESC Guidelines,[5] Dziadzko et al[10]/Yoon et al[11], and Kim et al[12]). Multivariate models were adjusted for age, sex, and N-terminal pro-B-type natriuretic peptide. The ranges across all 72 definitions are provided for comparison, highlighting the variability in hazard ratio and statistical significance across published AfMR definitions. [a]Benjamini and Hochberg correction for multiple testing was applied.

AfMR = atrial functional mitral regurgitation; fMR = functional mitral regurgitation; FDR = false discovery rate.

annular dilatation, leaflet motion (Carpentier classification), no or only mild leaflet tethering, and the absence of coronary artery disease. The prevalence of severe AfMR varied substantially depending on the definition applied, ranging from 12 (2%) to 359 (62%) patients. **Figure 2** illustrates the distribution of severe AfMR and severe non-AfMR across the 4 selected definitions, as well as the definitions yielding the lowest (definition 43) and highest (definition 65) prevalence.

The prevalence of severe AfMR was similar when applying the JACC expert consensus (definition 1) and the ESC guidelines (definition 2), yielding 13.1% and 12%, respectively. Despite the similar prevalence, 25% (JACC) and 27% (ESC) of patients were nonoverlapping, representing distinct patient subsets. Both definitions require an EF ≥50%, absence of regional wall motion abnormalities, absence of LV dilation, presence of LA dilation, and mitral annular dilatation. Differences arise mainly in the interpretation of LA/LV enlargement and leaflet motion. The ESC guidelines define LA dilation as any enlargement, whereas the JACC expert consensus requires at least moderate LA dilation. LV enlargement thresholds also slightly differ, defined as an indexed LV end-diastolic volume (LVEDV) ≤85 mL/m^2 in men and ≤78 mL/m^2 in women by the JACC expert consensus, and ≤79 mL/m^2 and ≤71 mL/m^2, respectively, by the ESC guidelines. In terms of leaflet motion, the ESC guidelines restrict inclusion to Carpentier type I (normal motion), whereas the JACC expert consensus permits Carpentier type I and type IIIb (restricted leaflet motion in systole), provided leaflet tethering is mild.

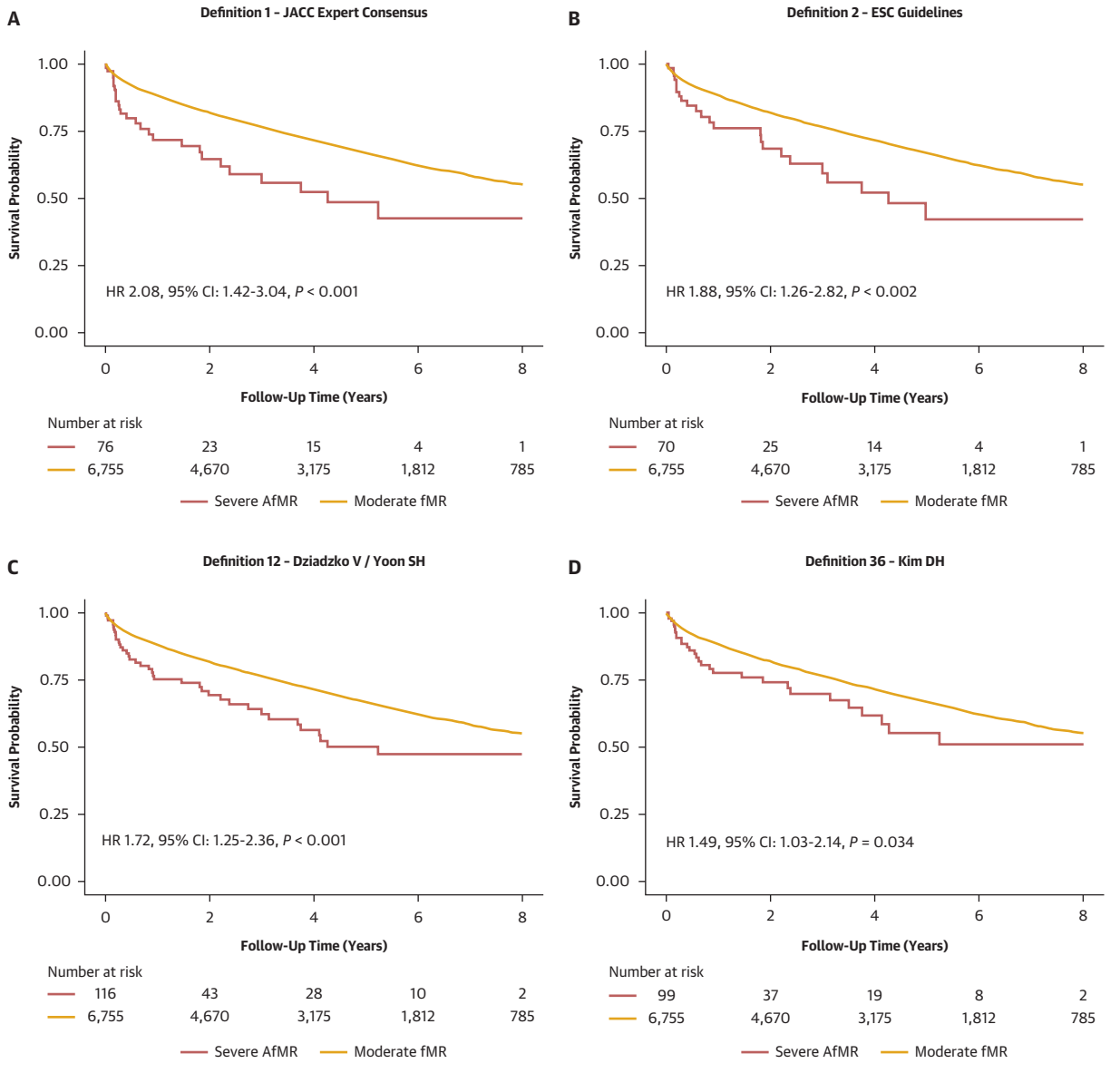
Definition 12 (Dziadzko et al/Yoon et al) specifies preserved LV function, no more than mild LV dilation, and moderate or more LA dilation. Definition 36 (Kim et al) includes an EF ≥50%, no regional wall motion abnormalities, indexed LVEDV ≤75 mL/m^2, and AF. The corresponding prevalences of severe AfMR were 20% and 17%, respectively.

Figure 3 depicts the overlap between these 4 AfMR definitions. The JACC and ESC definitions captured partly similar patient subsets, whereas the others showed marked divergence, reflecting the heterogeneity in current diagnostic criteria. The UpSet plot in Supplemental Figure 2 illustrates the prevalence and intersection of patient cohorts classified as AfMR.

BASELINE CHARACTERISTICS. Across all definitions, the median age ranged from 72 to 78 years, with 0% to 71% female. Coronary artery disease was present in 0%-53%, AF in 40%-100%, and hypertension in 28%-70%. Median NT-proBNP ranged from 1,681 pg/mL to 2,956 pg/mL, and HFpEF was present in 49%-100% of patients. Echocardiographic characteristics showed broad variability, with indexed LA volume ranging from 36 mL/m^2 to 62 mL/m^2 and indexed LVEDV from 38 mL/m^2 to 56 mL/m^2; right ventricular measures were similar across groups. Valvular morphology showed substantial numeric variability, with mitral annular diameters 31.5-37.1 mm, tenting heights 6.2-8.95 mm, tenting areas 146 to 229 mm^2, and leaflet angles anterior 16.7° to 22° and posterior 23° to 34°. Carpentier type IIIb leaflet motion occurred in 0%-49%, and moderate tricuspid regurgitation was frequent (67%-90%). Reported values reflect medians across groups. Detailed data are provided in Supplemental Table 2. Baseline characteristics of the entire study population and of subgroups defined by fMR severity (mild, moderate, severe) are summarized in Supplemental Table 3.

Baseline characteristics were broadly similar across the 4 main definitions (**Table 2**). Median age

FIGURE 4 Kaplan-Meier Survival Analysis



Kaplan-Meier curves illustrating long-term survival among patients with moderate fMR and severe AfMR. (A to D) The four AfMR definitions used in the main analysis, demonstrating variation in survival outcomes across classification criteria. (E) The range of hazard estimates across all definitions, with definition 37 showing the lowest and definition 72 the highest long-term mortality hazard. AfMR = atrial functional mitral regurgitation; fMR = functional mitral regurgitation.

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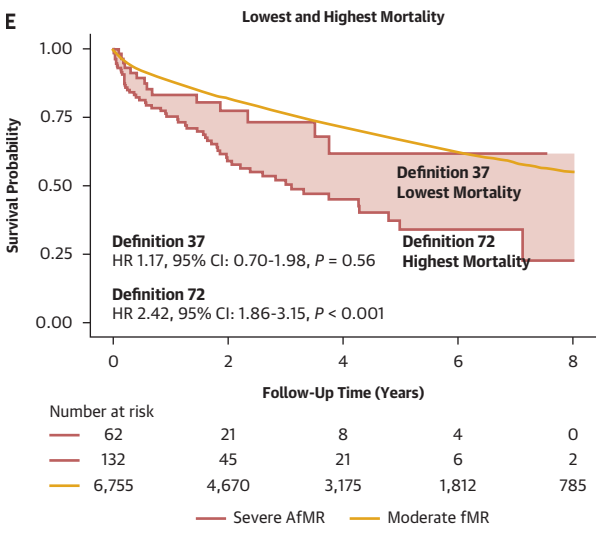
was 74 to 75 years, and 51% to 62% were female. Coronary artery disease was present in 24% to 36%, diabetes in 13% to 22%, and hypertension in 34% to 61%. AF was a prerequisite in definition 36 (Kim et al) and present in approximately one-half of patients in the other definitions. All patients had HFpEF. Median NT-proBNP levels showed only small numeric differences among the 4 definitions. Echocardiographic characteristics substantially differed, with median indexed LA volume ranging from 41 to 54 mL/m^2, being lowest in definition 36 (Kim et al) and largest in the JACC definition. Mitral annular diameter in the 3-chamber view was largest in definitions 1 and 2 (36.6 and 37.1 mm) and smaller in definitions 12 and 36 (34.2 and 33 mm). Tenting height and area, respectively, ranged from 4.55 mm to 4.95 mm and 115 mm^2

to 125 mm² (4-chamber view), and from 6.95 mm to 7.8 mm and from 168 mm² to 209 mm² (3-chamber view). The ESC definition included only Carpentier type I motion, whereas the others also allowed type IIIb (25%-29%). At least moderate tricuspid regurgitation was common across all definitions (80%-86%).

DEFINITIONS AND SURVIVAL. Across all 72 definitions of severe AfMR, univariate HRs for all-cause mortality ranged from 1.17 to 2.42, and multivariable HRs in the clinical risk factor-adjusted model ranged from 0.90 to 1.99, illustrating substantial variability in mortality depending on the applied definition (Supplemental Table 4). Two definitions (definitions 43 and 63) were excluded from Cox regression analysis owing to the small numbers of included patients. Normalized adjusted HRs across all definitions are shown in Supplemental Figure 3 for visualization of the variability in mortality.

In the main analyses in **Table 3**, the JACC definition (definition 1) demonstrated the highest mortality hazard (univariate HR: 2.08; 95% CI: 1.42-3.04; $P < 0.001$, $q < 0.001$). The ESC definition (definition 2) showed a similar trend (univariate HR: 1.88; 95% CI: 1.26-2.82; $P = 0.002$; $q = 0.006$) but did not remain significant after adjustment for clinical risk factors. Definitions by Dziadzko et al/Yoon et al (definition 12) and Kim et al (definition 36) showed numerically lower risk than the society-proposed definitions (univariate HRs: Dziadzko et al/Yoon et al: 1.72 [95% CI: 1.25-2.36; $P < 0.001$; $q = 0.003$]; Kim et al: 1.49 [95% CI: 1.03-2.14; $P = 0.034$; $q = 0.042$]). Kaplan-Meier analysis (**Figure 4**) demonstrated the highest mortality for definition 1 (JACC expert consensus) and the lowest for definition 36 (Kim et al), with intermediate outcomes for definitions 2 and 12. **Figure 4** also illustrates the range of mortality across all 72 definitions, emphasizing the wide variability in mortality hazard. In Fine-Gray competing risk analysis (**Figure 5**, Supplemental Table 5), significantly higher rates in cardiovascular death were observed in definitions 1, 2, and 13, whereas noncardiovascular death was not significantly different compared with moderate fMR. In definition 36, neither cardiovascular nor noncardiovascular death showed a significant difference. Among these, the JACC definition (definition 1) demonstrated one of the most pronounced differences in cardiovascular mortality (Gray's test statistic = 12.6; $P < 0.001$), underscoring its strong discriminatory capacity for cardiovascular outcomes and supporting its robustness and prognostic precision. **Figure 6** illustrates adjusted HRs for mortality across the 4 definitions from the main analysis,

FIGURE 4 Continued



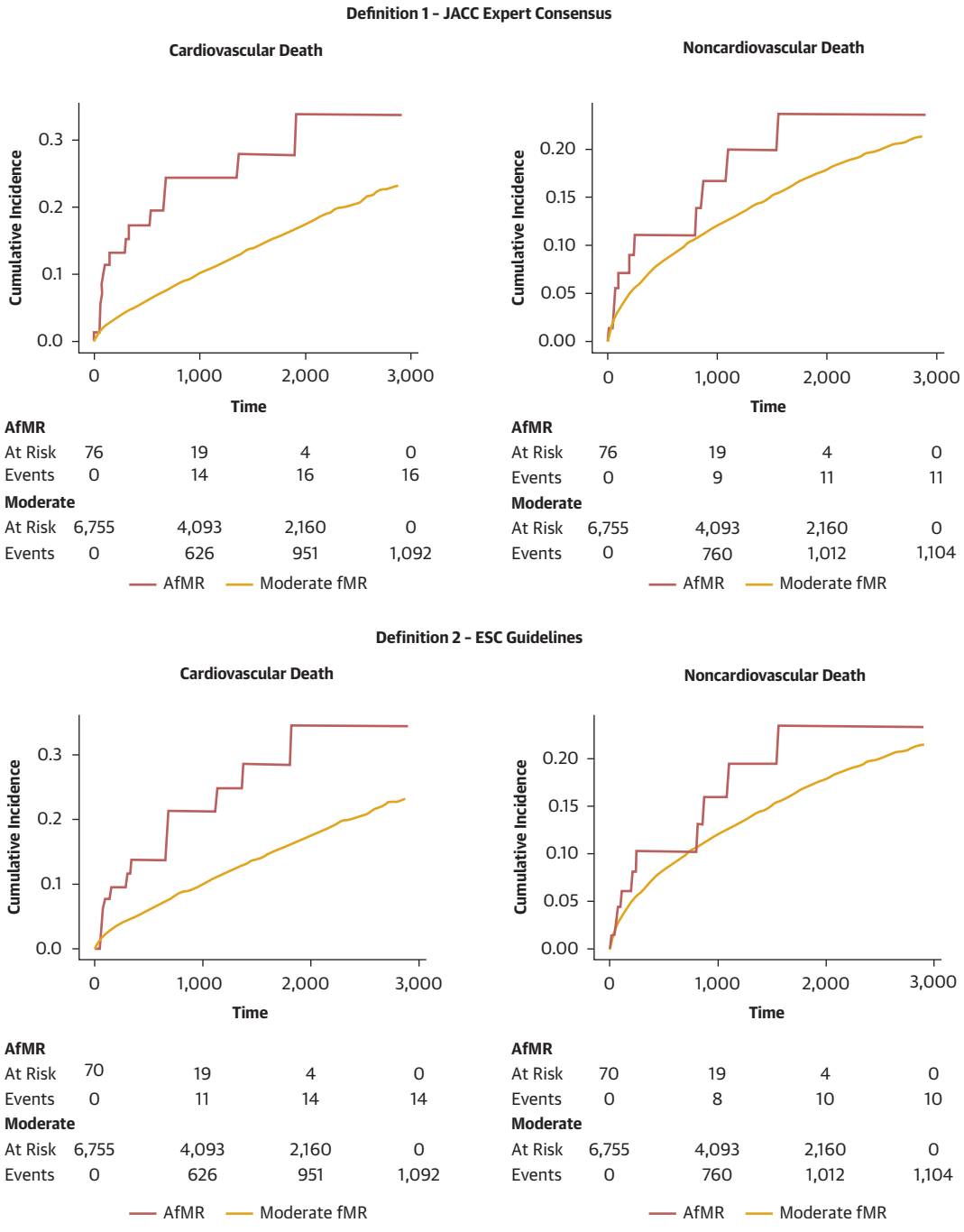
alongside the lowest and highest estimates. Cox regression models adjusted for the date of echocardiography yielded results consistent with the primary analyses, confirming the temporal stability of the associations between the 4 AfMR definitions and mortality (Supplemental Table 6).

Overall, mortality hazard across severe AfMR varied substantially depending on the definition applied. This variability was consistent across Cox regression, Kaplan-Meier, and Fine-Gray analyses, underscoring the strong influence of definition components on survival in severe AfMR.

DISCUSSION

AfMR is an increasingly recognized clinical entity that is conceptually clearly delineated from ventricular fMR. Despite a clear conceptual framework, AfMR remains inconsistently defined, with numerous diagnostic definitions. Across published frameworks, AfMR definitions show marked heterogeneity, with 72 unique definitions identified in the present analysis. These differences translate into substantial variation in prevalence, valve morphology, and clinical outcomes, underscoring the clinical consequences of definitional heterogeneity. Although major consensus definitions and guidelines share broad conceptual features, they diverge in key diagnostic components, particularly regarding atrial remodeling, leaflet motion, and ventricular thresholds, resulting in partially overlapping patient populations with differing prognostic profiles. In our comprehensive comparison of AfMR definitions, 3

FIGURE 5 Cumulative Incidence Curves of Cardiovascular and Noncardiovascular Death



Analyses are shown for the 4 definitions from the main analysis: JACC Expert Consensus (definition 1), ESC Guidelines (definition 2), Dziadzko et al/Yoon et al (definition 12), and Kim et al (definition 36). Fine-Gray competing-risk models were used to account for noncardiovascular mortality as a competing event. Across definitions 1, 2, and 12, patients with severe AfMR exhibited higher cumulative incidence of cardiovascular death compared with those with moderate fMR. AfMR = atrial functional mitral regurgitation; fMR = functional mitral regurgitation.

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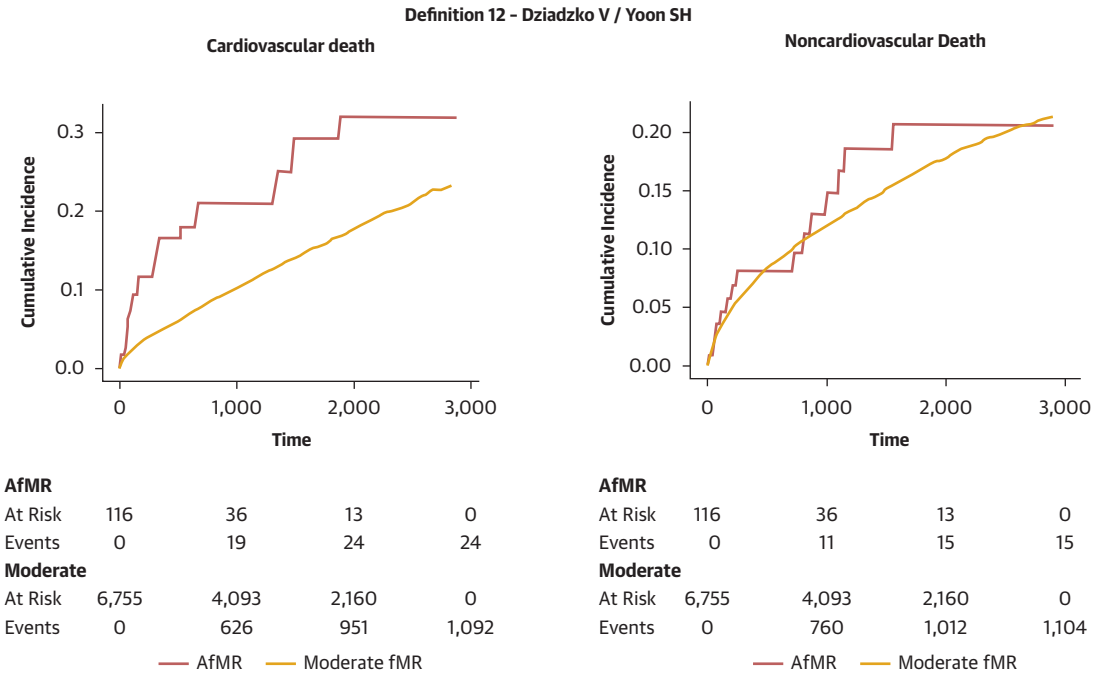
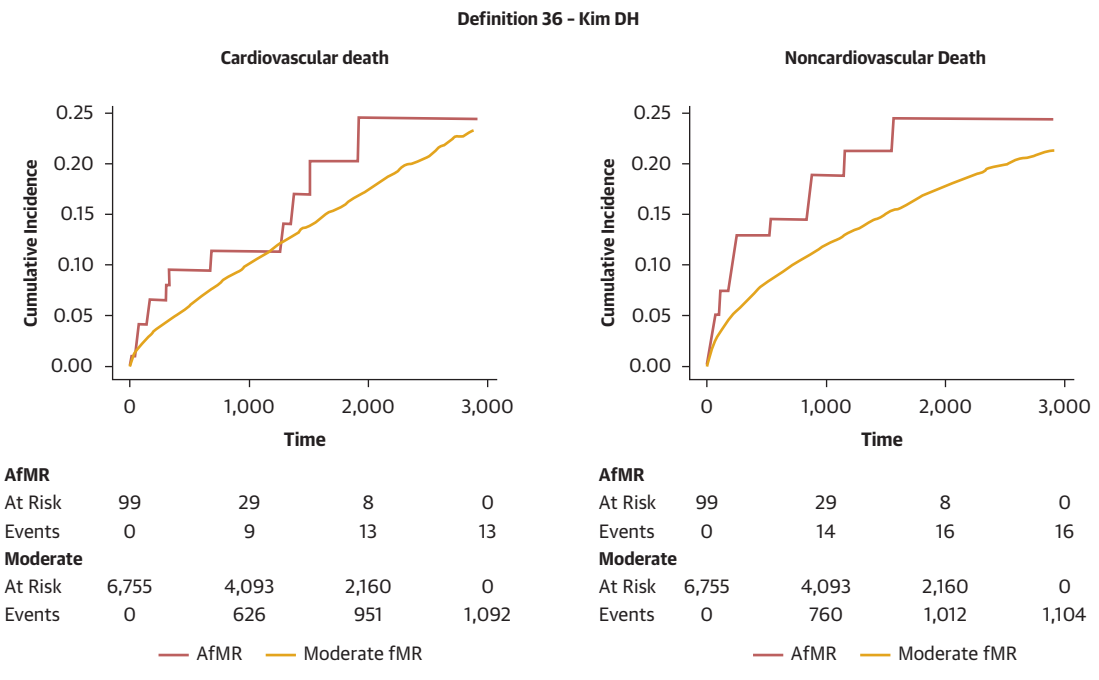
FIGURE 5 Continued

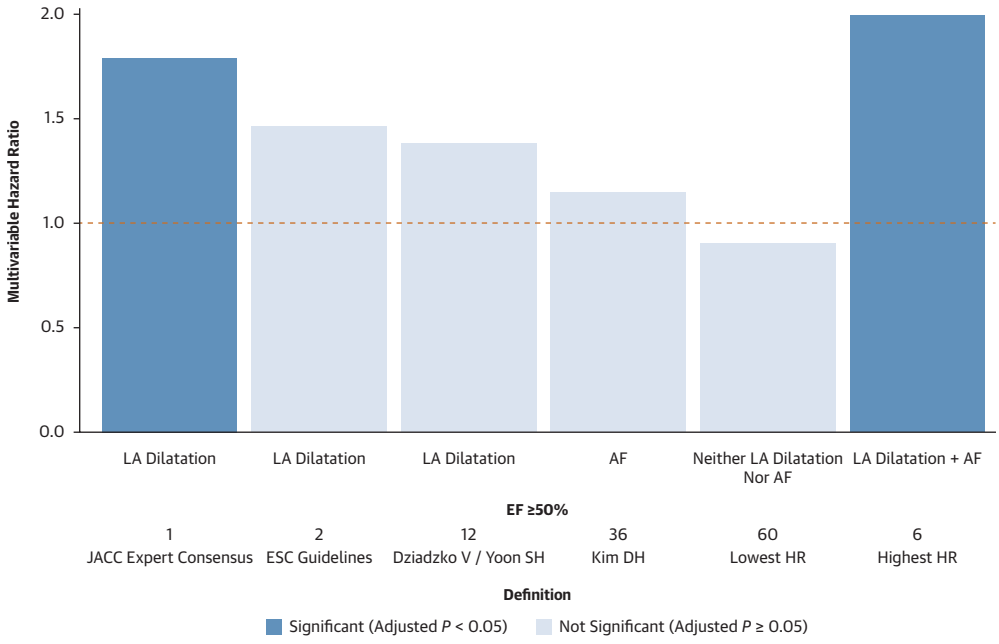




consistent findings emerged: Atrial remodeling is central, AF alone is insufficient, and small definitional differences meaningfully alter prognosis. Together, these findings highlight the impact of definitional heterogeneity in severe AfMR and its influence on patient classification, morphology, and outcomes, reinforcing the need for harmonization across frameworks.

CURRENT DEFINITIONS AND CLINICAL IMPACT. The conceptual framework of AfMR is multifactorial, integrating morphologic aspects alongside with an understanding of individual disease trajectories.

FIGURE 6 Adjusted HRs



Bar chart displaying multivariate HRs (adjusted for age, sex, and N-terminal pro-B-type natriuretic peptide) for long-term mortality across the four main definitions of severe AfMR as well as the definition with the highest and lowest multivariable HR, with moderate fMR as the reference. Each bar represents 1 AfMR definition: Blue bars indicate definitions with statistically significant associations after correction for multiple testing. The red dashed line marks the reference HR of 1.0. AF = atrial fibrillation; AfMR = atrial functional mitral regurgitation; EF = ejection fraction; fMR = functional mitral regurgitation; LA = left atrial.

Translating this conceptual framework into a universal definition is challenging, because disease trajectories are often unclear and other cardiac pathologies frequently coexist. As societal guidelines[4,5] increasingly emphasize AfMR as a distinct entity with different treatment recommendations, the need for a standardized, universally accepted definition becomes essential. The application of stringent criteria is crucial, especially in the light of overlapping types; however, the correct parameters must be determined.

Although the JACC[9] and ESC[5] definitions appear nearly identical, with both requiring preserved LV systolic function, no regional wall motion abnormalities or LV dilation, LA dilation, and mitral annular dilatation, they differ in critical details. The JACC definition allows mild leaflet tethering, is not limited exclusively to Carpentier type I, and mandates at least moderate LA dilation, whereas the ESC definition restricts inclusion to normal leaflet motion (Carpentier type I) and accepts even mild LA enlargement (indexed LA volume >34 mL/m^2) with lower cutoffs for normal LV size. Consequently, the JACC criteria capture a broader and more heterogeneous population. Despite similar valvular morphology, the main difference is the inclusion of 25% of patients exhibiting Carpentier type IIIb with the JACC definition, whereas that group was excluded from the ESC definition. That subgroup is often characterized by atriogenic tethering of the posterior mitral leaflet ("atriogenic hamstringing"), a distinct subtype of AfMR.[13-16] The ESC guidelines recognize that at advanced disease stages, overlapping ventricular features may be present. However, within the current guideline framework as implemented in clinical practice, AfMR is defined by the presence of normal leaflet motion. Consequently, atriogenic leaflet tethering consistent with Carpentier IIIb morphology falls outside the current operational AfMR definition. Such atriogenic tethering likely represents a manifestation along the AfMR continuum and warrants consideration to avoid potential misclassification. This finding illustrates how subtle differences can meaningfully influence patient selection and risk stratification.

Definitions 12 (Dziadzko et al/Yoon et al)[10,11] and 36 (Kim et al)[12] further illustrate how inclusion criteria influence cohort composition. Both require preserved LV function, yet definition 12 emphasizes structural atrial remodeling with mandatory moderate or more LA dilation, whereas definition 36 relies primarily on the presence of AF without a requirement for LA enlargement. Thus, definition 12 identified patients with more pronounced LA and mitral annular remodeling, and definition 36 included patients uniformly in AF but with smaller LA. These contrasting approaches represent conceptual perspectives on AfMR—atrial structural remodeling and electrical remodeling[15,17]—yet both yielded similar clinical profiles.

Across all 72 definitions, consistent morphologic patterns emerged aligned with inclusion criteria. Definitions emphasizing LA enlargement (eg, JACC, ESC, Dziadzko et al/Yoon et al.) identified patients with larger LA and more advanced mitral annular remodeling, and AF-based definitions (eg, Kim et al) captured smaller LA. These findings indicate that LA dilation represents a central structural prerequisite for defining AfMR, whereas AF may occur as an associated but nonmandatory manifestation of atrial remodeling. It is challenging to determine whether excessive LA dilation has occurred because of chronic volume overload in already existing AfMR or if it has been present before the onset and hence has been a contributing factor of such.[18] Previous studies have investigated the role of the LA in fMR and found that its dysfunction led to a greater hemodynamic severity of fMR, poorer functional capacity,[19] and increased mortality and hospitalizations for HF;[20] however, the latter was the case only for LA function and not for LA size.

The clustering framework captures the principal axes along which AfMR definitions diverge, namely LV function and the relative emphasis on AF vs LA dilation. Definitions that prioritized atrial structure consistently identified patients with larger LA size and annular remodeling, whereas AF-only criteria were less specific. Despite substantial definitional heterogeneity, AfMR uniformly occurred in the setting of a widely preserved LV size without advanced dilation, reaffirming that AfMR fundamentally occurs with preserved LV size.

The heterogeneity in definitions yields important implications for guidelines, trials, and clinical practice. Inconsistent AfMR criteria may lead to heterogeneous patient populations, limiting comparability across studies and potentially obscuring treatment effects in pharmacologic or interventional trials. Harmonization of AfMR definitions will therefore improve diagnostic consistency, guide patient selection for interventions, and inform future guideline recommendations.

IMPACT ON MORTALITY. Across all 72 definitions, the association between AfMR and mortality varied markedly, emphasizing that survival estimates are highly dependent on the applied diagnostic framework. Structurally anchored definitions with an EF ≥50%, namely, those requiring preserved LV function with either LA dilation or LA dilation plus AF, consistently identified patients at highest risk of mortality, whereas definitions relying solely on AF showed no independent prognostic relevance, even in the univariate analysis. Patients in the category with EF ≥50% that required neither LA dilation nor AF had the lowest HRs, of which many showed no significant survival difference compared with moderate fMR in the univariate analysis.

Among the 4 definitions from the main analysis, the JACC Expert Consensus definition demonstrated the strongest and most robust association with mortality, both in Cox regression (univariate HR: 2.08; 95% CI: 1.4-3.0; $P < 0.001$; $q < 0.001$) and in Fine-Gray competing risk analysis (Gray test = 12.6; $P < 0.001$). These findings underscore that inclusion of LA dilation and mitral annular remodeling effectively captures a clinically meaningful, high risk phenotype. The ESC Guidelines definition yielded a significant univariate signal that attenuated after adjustment for clinical risk factors, suggesting that stricter morphologic constraints and restriction to Carpentier type I leaflet motion identify a more homogeneous, yet partly lower risk, population. Although the influence of Carpentier type IIIb in fMR on survival has not been investigated yet, studies suggest that patients exhibiting this kind of leaflet motion restriction show worse procedural and clinical outcomes after mitral edge-to-edge repair compared with those with Carpentier type I.[16]

Definition 12, which mandates at least moderate LA enlargement, remained borderline significant after multivariable adjustment, supporting that structural atrial remodeling conveys prognostic impact. In contrast, definition 36, anchored solely in the presence of AF, showed only a weak univariate association and no independent multivariable association with mortality, reaffirming that AF alone is insufficient to define an AfMR phenotype.

Cluster-based analyses corroborated these findings. Across the cohorts that had AF as a requirement for inclusion (definitions 33-47), associations with mortality remained weak, uniformly losing statistical

significance after adjustment for clinical risk factors. Conversely, LA-based definitions frequently remained significant. This pattern highlights LA enlargement as the key structural and prognostic criterion for AfMR, whereas AF lacks diagnostic and prognostic specificity.

Regarding heart failure subgroups, although all definitions excluded heart failure with reduced EF, those with HFmrEF more frequently demonstrated independent mortality associations. These definitions likely captured patients with an early transition toward mixed atrial-ventricular remodeling, as consistent with previous studies showing that impaired LV function in fMR leads to a higher mortality.[1] Consequently, rigid exclusion of patients with mildly reduced EF may underestimate the true burden of advanced AfMR and obscure its natural progression toward overlap phenotypes. This is supported by previous work showing that a subset of AfMR patients develop LV dysfunction over time.[21] Predominant atrial remodeling in severe fMR can be present even in patients with mildly reduced or reduced LV function, challenging the concept of AfMR occurring exclusively in HFpEF.[6] Thus, some entities classified as ventricular fMR may actually represent advanced AfMR stages with secondary LV involvement. Chen et al showed that one-fourth of patients with AfMR and more than one-half with ventricular fMR progressed to dual fMR (concomitant AfMR and ventricular fMR) over time.[22]

Taken together, survival analyses confirm that structurally defined AfMR, which is characterized by LA dilation and mitral annular remodeling with preserved geometry but not necessarily normal LV function, carries the clearest prognostic signal. Conversely, AF-only definitions lack discriminative power.

Future definitions should therefore prioritize LA structural remodeling and mitral annular dilation, rather than rhythm status, as core criteria, treat AF as an associated but nonmandatory feature, and acknowledge disease evolution toward combined atrial and ventricular forms to achieve both pathophysiologic precision and prognostic relevance. This is necessary for clinical trials, where heterogeneous populations may dilute treatment effects and limit comparability across studies.

All-cause and cardiovascular mortality were chosen as endpoints owing to their objective ascertainment, completeness, and robustness across health care settings. In contrast, heart failure hospitalizations are influenced not only by clinical deterioration but also by local admission practices, bed availability, and health system resources, limiting their objectivity and comparability as prognostic endpoint.

TOWARD A UNIFORM DEFINITION OF AfMR. A comprehensive definition has to fulfil certain requirements. First, adequate patient selection needs to be met. Definitions that select only a small number of patients in a large cohort over a 10-year inclusion period may not be clinically meaningful. On the other hand, a definition must be selective and has to separate subtypes of fMR. Second, a difference in survival, compared with moderate fMR, seems mandatory, because that defines and justifies potential invasive treatment strategies. The definition with the highest mortality, however, might not necessarily be the best AfMR definition, and particular emphasis needs to be placed on the valve morphology that ultimately defines potential treatment approaches.

Across definitions, the key differences lie in the degree of required atrial structural remodeling, the role of AF, restrictions regarding leaflet motion, and the treatment of early ventricular involvement. A unified definition of AfMR should be anchored in morphology and to a certain extent in prognosis. Across all examined frameworks, mandatory AF diagnosis lacked prognostic discrimination and therefore cannot constitute a mandatory feature. AF should be viewed as a frequent but nonessential marker of atrial disease. In contrast, LA remodeling, reflected by enlargement and mitral annular dilation, emerges as the central structural substrate of AfMR. These features were consistently identified, underscoring a shared structural substrate despite heterogeneity in operational criteria.

Restricting the definition to Carpentier type I does not provide the necessary flexibility to include patients with posterior leaflet tethering (Carpentier type IIIb, posterior leaflet hamstring morphology), a well-known subtype of AfMR that deserves further scientific focus. Moderate posterior leaflet tethering often accompanies LA and annular remodeling in the absence of LV dilation and is also known as atriogenic leaflet tethering, representing the natural spectrum of atrial disease.[12,15] Excluding such cases and including only Carpentier type I may omit clinically and prognostically relevant AfMR.

AfMR and ventricular fMR form a continuum, with overlapping phenotypes reflecting progressive atrial-

ventricular remodeling.[22] A unified framework may therefore acknowledge mild LV involvement without excluding an atrial phenotype.

Future studies need to clarify how specific clinical contexts, such as AF, coronary artery disease, previous mitral valve intervention, and patient age, affect the underlying mechanisms, phenotypic expression, and treatment response of AfMR.

The JACC Expert Consensus and ESC Guidelines provide a strong foundation for harmonization. A pragmatic and clinically relevant definition may require largely preserved LV geometry and function, absence of excessive regional wall motion abnormalities, include any LA enlargement (indexed LA volume >34 mL/m^2), and allow posterior leaflet tethering (Carpentier I + IIIb), regardless of AF. A morphologically anchored approach aligns structural integrity with prognostic significance, establishing a coherent basis for diagnosis, risk stratification, and future therapeutic trials, and provides a framework for guideline development and clinical decision-making. As AfMR increasingly influences clinical decision making, harmonizing definitions is no longer an academic exercise but a prerequisite for evidence-based care.

STUDY STRENGTHS AND LIMITATIONS. This study does not resolve treatment strategy or define intervention thresholds. Rather, it clarifies the phenotypic substrate on which such decisions must rest. It represents the experience of a single tertiary care center with a dedicated valve program, ensuring consistent clinical routines and adherence to guidelines. Although all echocardiographic analyses were performed in a single core laboratory, which potentially limits generalizability, this is the largest echocardiographic laboratory in Austria with long-standing expertise. Referral bias cannot be excluded. The cohort was defined by strict inclusion and exclusion criteria, which may limit external validation. Comorbidities were derived from ICD-10 coding and may be subject to misclassification. Data on EF were not available for all patients, so classification was based on heart failure subgroup. AF presence was used as an inclusion criterion without differentiation by type or duration. Patients with previous percutaneous coronary intervention, cardiac surgery, or pacemaker implantation were included. Although adjustment for echocardiography date showed consistent results, minor temporal bias due to evolving imaging or management practices cannot be entirely excluded. Some definition subgroups were small, restricting analyses and reinforcing the hypothesis-generating nature of the analysis. Finally, data on heart failure hospitalizations were not systematically captured across the full cohort, precluding robust analyses for this outcome. Moreover, heart failure hospitalization is a less objective endpoint, because admission decisions are influenced by local health care system factors and not just clinical deterioration, limiting comparability across studies. For these reasons, all-cause and cardiovascular mortality were prioritized as endpoints.

CONCLUSIONS

In this systematic analysis of 72 published definitions, AfMR emerged as a morphologically and prognostically heterogeneous entity whose characterization critically depends on the applied diagnostic framework. Definitions based on LA dilation yielded a clinically and prognostically relevant AfMR phenotype, whereas definitions based exclusively on AF failed to discriminate mortality hazard. The JACC Expert Consensus and ESC Guidelines definitions, although conceptually similar, differed in patient selection and outcome, underscoring that even subtle variations meaningfully influence prognosis. A consolidated and morphologically founded definition of AfMR should prioritize LA and annular remodeling, permit mild leaflet tethering and Carpentier type IIIb, and regard AF as an associated but non-compulsory feature. Such an approach would harmonize diagnostic criteria, improve prognostic stratification, and provide a coherent foundation for patient selection and therapeutic evaluation in future studies and clinical practice.

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KEY WORDS atrial functional mitral regurgitation, atrial secondary mitral regurgitation, definitions, guidelines, heart failure, valvular heart disease

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