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ORIGINAL RESEARCH

Staging of Cardiac Adverse Remodeling in Moderate or Severe Aortic Regurgitation

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ABSTRACT

BACKGROUND A recently proposed staging system for cardiac structural and functional abnormalities demonstrated incremental prognostic value in aortic stenosis.

OBJECTIVES The authors investigate a staging system incorporating cardiac magnetic resonance (CMR) in moderate or severe aortic regurgitation (AR).

METHODS Patients prospectively enrolled in DEBAKEY-CMR (DeBakey Cardiovascular Magnetic Resonance Study; NCT04281823) between 2009 and 2020 who had moderate or severe AR by CMR were studied. We excluded patients with a primary cardiomyopathy (eg, hypertrophic cardiomyopathy, amyloidosis, sarcoidosis) or prior valve intervention. The stages were defined as stage 0: no cardiac remodeling; stage 1: left ventricular (LV) remodeling; stage 2: mitral valve or left atrial abnormalities; and stage 3: right heart remodeling. The outcome was all-cause mortality.

RESULTS The authors studied 395 patients, median age 62 years (Q1-Q3: 51-72 years); 79.2% were male, and 25.8% had bicuspid aortic valve. Thirty-two patients (8.10%) were classified as stage 0, 146 (37.0%) as stage 1, 77 (19.5%) as stage 2, and 140 (35.4%) as stage 3. Over a mean follow-up period of 3.9 ± 2.9 years, the annualized mortality rate was 0.68% per year in stage 0, 2.25% per year in stage 1, 3.76% per year in stage 2, and 7.25% per year in stage 3 (P for trend of mortality <0.001). The extent of cardiac remodeling was independently associated with increased hazard for mortality (adjusted HR: 1.69 per increment of stage [95% CI: 1.28-2.23]; $P < 0.001$) after adjusting for regurgitation severity, aortic valve replacement (AVR), and EuroSCORE II (European System for Cardiac Operative Risk Evaluation). Patients with right heart remodeling had the highest hazard for events.

CONCLUSIONS A cardiac remodeling staging system incorporating CMR findings provides incremental prognostication in AR after adjusting for surgical risk, AVR, and regurgitation severity. Right heart remodeling in AR was associated with the highest mortality. Further research can determine whether the staging system could aid in guiding patient management and the timing of intervention. (JACC Cardiovasc Imaging. 2025;18:1093-1103) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

AR = aortic regurgitation

AVR = aortic valve replacement

CMR = cardiac magnetic resonance

LGE = late gadolinium enhancement

LV = left ventricle

LVEF = left ventricular ejection fraction

LVESD = left ventricular end-systolic diameter

LVESV = left ventricular end-systolic volume

Guidelines for the treatment of aortic regurgitation (AR) recommend aortic valve replacement (AVR) in the presence of symptoms or in asymptomatic patients with left ventricular (LV) dysfunction and/or excessive dilatation.[1] Patients with AR meeting these guidelines for surgery may incur long-term residual risk even after AVR.[2-4] As a result, predictors of poor outcomes in patients with AR continue to be investigated with the objective of improving long-term survival.[5,6] Patients included in the original natural history studies of AR were generally younger and may differ from contemporary cohorts of older patients with associated comorbid conditions.[7-10]

The downstream effects of valvular heart disease and extravalvular cardiac remodeling have attracted increasing attention recently with the advent of percutaneous valve replacement approaches with reduced procedural risk than surgical replacement. In AR, the presence of concomitant mitral regurgitation and tricuspid regurgitation were previously shown to be associated with increased mortality risk.[11] A recently proposed staging system for aortic stenosis has demonstrated incremental prognostic value in symptomatic, asymptomatic, and post-transcatheter AVR patients.[12-15] In this study, we propose and assess a cardiac remodeling staging system for AR patients that uses cardiac magnetic resonance (CMR) along with echocardiographic and clinical parameters. CMR has favorable reproducibility in quantifying AR,[16] it is the current noninvasive reference standard for cardiac remodeling assessment, and its use is supported by outcome data in the management of patients with AR.[17-20]

METHODS

PATIENT SELECTION. We included consecutive patients who were prospectively enrolled in DEBAKEY-CMR (DeBakey Cardiovascular Magnetic Resonance Study; NCT04281823) between 2009 and 2020 and were found to have moderate or severe AR on CMR, defined as a regurgitant volume ≥30 mL or regurgitant fraction ≥30% measured on phase contrast imaging. Patients were excluded if they had: 1) cardiomyopathy deemed unrelated to AR (eg, hypertrophic cardiomyopathy, amyloidosis, sarcoidosis); 2) previous aortic or mitral valve surgery or intervention; 3) complex congenital heart disease or intracardiac shunts; 4) metastatic cancer; or 5) greater than moderate aortic stenosis (**Figure 1**). We performed a thorough baseline patient interview and review of medical records at the time of imaging. The study was approved by the Institutional Review Board at the Houston Methodist Research Institute, and the patients gave written informed consent.

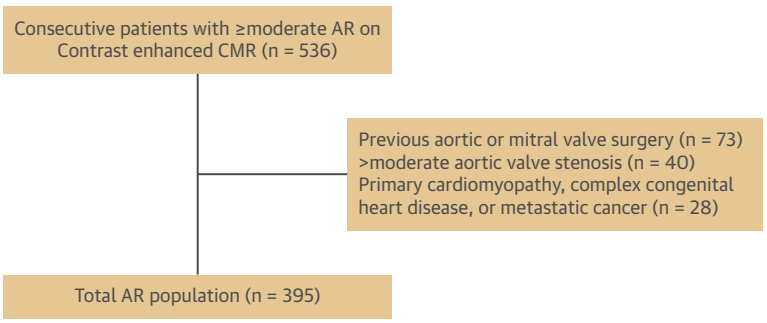
CMR STUDY PROTOCOL. CMR studies were acquired using either 1.5-T or 3.0-T clinical scanners (Aera, Verio, Avanto, or Skyra; Siemens) with a phased-array coil system. Examinations began with cine-CMR for anatomic and functional assessment in a short-axis stack and standard 2-, 3-, and 4-chamber views using a steady-state free-precession (SSFP) sequence with typical flip angle of 65° to 85°; repetition time of 3.0 ms; echo time of 1.3 ms; in-plane spatial resolution of 1.7 to 2.0 mm × 1.4 to 1.6 mm; slice thickness of 6 mm with 4-mm interslice gap; and temporal resolution of 35 to 40 ms. A high-resolution, small field of view cine-CMR was used to evaluate aortic valve morphology, using a parallel series of at least 3 thin (4-5 mm) slices in short axis of the aortic valve, prescribed from the 3-chamber view and coronal left ventricular outflow views.

Phase contrast CMR was performed at the level of the sinotubular junction, left ventricular outflow tract, mid-ascending aorta, and the pulmonary artery. The typical parameters were flip angle of 25° to 30°, repetition time of ∼5 ms, echo time of 2.4 ms, reconstructed in-plane spatial resolution of ∼2.0 × 2.4 mm, slice thickness of 6 mm, and temporal resolution of ∼40 ms.

Late gadolinium enhancement (LGE) imaging was performed using a magnitude and phase-sensitive segmented inversion-recovery sequence approximately 10 minutes after intravenous gadolinium contrast administration (gadopentetate dimeglumine or gadoterate meglumine, 0.15 mmol/kg). The parameters were in-plane spatial resolution of 1.8 × 1.3 mm and slice thickness of 6 mm, with inversion time adjusted to null normal myocardium. Cine- and LGE-CMR images were obtained in matching short- and long-axis planes. Shimming and delta frequency adjustments were applied to minimize off-resonance artifacts.

DATA COLLECTION AND ANALYSIS. All CMR image analysis was done on the same software (Precession, Heart Imaging Technologies). LV and right ventricular (RV) end-diastolic volume, end-systolic volume, ejection fraction (left ventricular ejection fraction [LVEF] and right ventricular ejection fraction), and LV mass were measured consistently with guidelines.[21] The aortic regurgitation volume was calculated using the direct method from phase contrast

FIGURE 1 Patient Enrollment



AR = aortic regurgitation; CMR = cardiac magnetic resonance.

imaging at the level of the sinotubular junction. The aortic regurgitant fraction was calculated as: (reverse volume/forward stroke volume × 100%).[22]

Mitral and tricuspid regurgitant volumes were calculated as the difference between the ventricular stroke volume and forward stroke volume in the aorta and pulmonary artery, respectively. Mitral and tricuspid regurgitant fractions were calculated as: (regurgitant volume / [ventricular stroke volume − aortic or pulmonic regurgitant volume] × 100).

The presence and extent of myocardial scar was assessed on LGE imaging in all LV segments according to the 17-myocardial-segment model. To mitigate the effect of imaging artifacts, scar was only considered present if it was visually identified on 2 contiguous or orthogonal slices and seen on both magnitude and phase-sensitive image reconstruction.[21] Our previously described semiquantitative method was used to rapidly calculate the burden of myocardial scar (as a percentage of the left ventricle) by summing segmental scores, weighted by the midpoint of the range of LGE, and dividing by the total number of LV regions.[23-26]

ECHOCARDIOGRAPHY, LABORATORY, AND CARDIAC CATHETERIZATION DATA. Findings on imaging and laboratory studies done within 6 months of CMR were collected. Data on diastolic function were collected from echocardiographic studies, which were available in 222 of 395 patients (56%). Pulmonary artery systolic pressure data were obtained by echocardiography and/or cardiac catheterization, whichever was done closest to the CMR date (available in 249 of 395 patients [48.3%]). Categories of pulmonary artery systolic pressure (<30 mm Hg, 31-55 mm Hg, >55 mm Hg) were defined similar to the EuroSCORE II (European System for Cardiac Operative Risk Evaluation) calculation. Brain natriuretic peptide level data were available in 176 of 395 patients (44.5%).

STAGING OF CARDIAC REMODELING. The presence and extent of cardiac remodeling beyond the aortic valve was evaluated by integrating CMR, echocardiographic, and laboratory findings. Patients were classified into 4 stages as proposed by Généreux et al[15] with minor modifications. Stage 0 is no cardiac remodeling. Stage 1 is LV remodeling (any of the following: LVEF ≤55%, indexed LV end-systolic volume ≥45 mL/m^2, presence of myocardial scar, or LV hypertrophy based on CMR criteria for age and gender).[27] Stage 2 is mitral valve or left atrium abnormalities (any of the following: mitral regurgitation fraction ≥30%, severe left atrium dilatation by CMR, grade III diastolic dysfunction on echocardiography, or elevated brain natriuretic peptide >150 mg/dL). Stage 3 is right heart remodeling (systolic pulmonary artery pressure ≥55 mm Hg on echocardiography or catheterization, tricuspid regurgitation fraction ≥30%, or right ventricular ejection fraction ≤45%). Patients were classified according to the highest criteria of the staging they met.

FOLLOW-UP. Clinical follow-up was initiated from the time of CMR imaging. Event data and last follow-up date were gathered from medical record review; from telephone interviews with the patients, relatives, or their health care providers; and from the SSDI (Social Security Death Index) database. Management plans including surgery vs medical surveillance were ascertained. The primary outcome was all-cause mortality.

STATISTICAL ANALYSIS. Descriptive data were reported as median (Q1-Q3) for continuous variables

TABLE 1 Baseline Characteristics

	Total (N = 395)	Stage 0 (n = 32)	Stage 1 (n = 146)	Stage 2 (n = 77)	Stage 3 (n = 140)	*P* Value
Clinical findings						
Age, y	62.0 (51.0-72.0)	62.0 (41.5-71.5)	56.0 (49.0-66.0)	64.0 (54.0-73.0)	66.00 (56.50-76.00)	<0.001
Sex						0.65
Female	82 (20.8)	4 (12.5)	33 (22.6)	16 (20.8)	29 (20.7)	
Male	313 (79.2)	28 (87.5)	113 (77.4)	61 (79.2)	111 (79.3)	
Systolic BP, mm Hg	132.0 (120.0-146.0)	131.0 (118.0-138.0)	132.0 (122.0-146.0)	139.0 (123.0-156.0)	128.00 (117.00-146.00)	0.017
Diastolic BP, mm Hg	69.0 (62.0-78.0)	68.0 (63.0-82.0)	69.0 (62.0-77.0)	70.0 (60.0-79.0)	68.00 (61.00-79.00)	0.88
Heart rate, beats/min	68.0 (60.0-78.0)	70.0 (61.5-81.5)	65.5 (60.0-72.0)	64.0 (57.0-76.0)	72.00 (62.00-83.00)	<0.001
CAD	82 (20.8)	1 (3.1)	18 (12.3)	18 (23.4)	45 (32.1)	<0.001
History of MI	45 (11.4)	0 (0.0)	11 (7.5)	8 (10.4)	26 (18.6)	0.004
Diabetes	49 (12.5)	1 (3.1)	15 (10.3)	11 (14.5)	22 (15.8)	0.18
Hyperlipidemia	202 (51.7)	13 (40.6)	67 (46.5)	34 (44.7)	88 (63.3)	0.007
Hypertension	279 (71.4)	21 (65.6)	93 (64.6)	55 (72.4)	110 (79.1)	0.048
Current or previous smoking	144 (37.9)	11 (34.4)	49 (35.3)	29 (38.7)	55 (41.0)	0.76
NYHA functional class						<0.001
I	243 (61.5)	26 (81.3)	108 (74.0)	52 (67.5)	57 (40.7)	
II	103 (26.1)	6 (18.8)	32 (21.9)	17 (22.1)	48 (34.3)	
III	43 (10.9)	0 (0.0)	5 (3.4)	8 (10.4)	30 (21.4)	
IV	6 (1.5)	0 (0.0)	1 (0.7)	0 (0.0)	5 (3.6)	
EuroSCORE II	1.42 (0.69-2.75)	0.7 (0.5-1.1)	0.9 (0.6-1.7)	1.6 (0.9-2.9)	2.32 (1.29-4.08)	<0.001
PASP, mm Hg	35.0 (28.0-45.0)	25.0 (21.5-28.0)	30.0 (25.0-35.0)	37.0 (31.9-41.3)	43.00 (32.75-55.00)	<0.001
BNP, mg/dL	251.50 (102.00-645.00)	48.5 (11.5-107.2)	59.5 (24.0-97.0)	486.0 (264.0-772.0)	309.00 (161.00-963.00)	<0.001
Medications						
Antiplatelet agents	160 (42.0)	10 (31.3)	44 (30.6)	37 (49.3)	69 (53.1)	<0.001
Beta-blockers	207 (53.1)	16 (50.0)	56 (38.6)	44 (57.9)	91 (66.4)	<0.001
ACEIs/ARB	186 (48.3)	12 (37.5)	69 (48.3)	41 (53.9)	64 (47.8)	0.48
CMR findings						
LVEF	58.0 (48.0-65.0)	66.5 (63.0-69.8)	61.0 (54.4-66.0)	57.0 (50.0-64.0)	49.77 (38.49-59.09)	<0.001
RVEF	51.7 (46.0-56.2)	55.5 (52.4-57.5)	54.0 (50.0-58.0)	54.0 (49.4-59.0)	42.69 (34.90-49.00)	<0.001
LVEDV index	114.6 (89.6-145.0)	90.6 (72.9-100.0)	114.3 (90.5-137.9)	131.1 (98.4-151.9)	120.94 (89.83-162.30)	<0.001
RVEDV index	80.5 (65.6-97.0)	75.2 (64.5-83.0)	78.2 (63.0-91.1)	80.7 (67.3-97.6)	84.33 (67.48-103.51)	0.014
LVESV index	48.2 (32.3-69.0)	29.0 (22.4-34.5)	44.9 (31.6-61.4)	54.6 (35.8-72.8)	59.79 (39.48-92.07)	<0.001
RVESV index	38.4 (29.9-49.3)	33.5 (27.4-37.0)	35.2 (27.7-43.0)	38.1 (28.4-45.2)	47.09 (35.95-67.18)	<0.001
LVESD index	2.1 (1.7-2.4)	1.7 (1.5-1.8)	1.9 (1.7-2.3)	2.2 (1.9-2.4)	2.26 (1.78-2.67)	<0.001
LV mass index	93.6 (74.2-114.7)	69.2 (59.5-78.6)	90.6 (78.0-107.1)	103.5 (83.5-121.3)	100.00 (77.64-124.31)	<0.001
LA volume index	57.1 (44.4-73.5)	44.0 (34.7-54.3)	50.2 (40.6-58.8)	74.1 (60.1-85.9)	67.45 (51.74-95.39)	<0.001
Aortic regurgitation						
Volume, mL	39.0 (30.0-60.0)	32.5 (26.0-40.5)	43.5 (33.0-65.0)	44.0 (34.0-70.0)	34.00 (23.50-53.00)	<0.001
Fraction, %	38.0 (32.0-45.0)	32.0 (29.0-37.0)	37.0 (32.0-47.0)	38.0 (33.0-45.0)	39.50 (33.00-45.00)	<0.001
Mitral regurgitation						
Volume, mL	21.0 (15.0-28.0)	16.0 (10.0-20.0)	19.0 (13.0-22.0)	22.0 (18.0-33.0)	22.00 (17.00-32.00)	0.003
Fraction, %	25.0 (18.0-35.0)	18.0 (15.0-21.0)	19.0 (13.0-22.0)	26.0 (19.0-34.0)	30.50 (22.00-41.00)	<0.001
Tricuspid regurgitation						
Volume, mL	20.0 (14.0-30.0)	16.0 (8.0-17.0)	17.0 (11.0-26.0)	20.0 (15.0-29.0)	23.00 (17.00-34.00)	0.023
Fraction, %	25.00 (17.00-32.00)	15.0 (9.0-16.0)	17.5 (15.0-23.0)	20.0 (14.0-23.0)	31.00 (25.00-38.00)	<0.001
Leaflet morphology						<0.001
Trileaflet	293 (74.2)	20 (62.5)	90 (61.6)	61 (79.2)	122 (87.1)	
Bicuspid	102 (25.8)	12 (37.5)	56 (38.4)	16 (20.8)	18 (12.9)	
Myocardial scarring on LGE imaging						<0.001
No	261 (67.1)	32 (100.0)	113 (77.4)	46 (62.2)	70 (51.1)	
Yes	128 (32.9)	0 (0.0)	33 (22.6)	28 (37.8)	67 (48.9)	

Values are n (%) or median (Q1-Q3), unless otherwise indicated.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BNP = brain natriuretic peptide; BP = blood pressure; CAD = coronary artery disease; CMR = cardiac magnetic resonance; EuroSCORE = European System for Cardiac Operative Risk Evaluation; LA = left atrium; LGE = late gadolinium enhancement; LV = left ventricle; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; LVESV = left ventricular end-systolic volume; MI = myocardial infarction; PASP = pulmonary artery systolic pressure; RVEDV = right ventricular end-diastolic volume; RVEF = right ventricular ejection fraction; RVESV = right ventricular end-systolic volume.

and as frequencies and proportions for categorical variables. Differences between groups were compared using the chi-square or Fisher's exact tests for categorical variables and Kruskal-Wallis test for continuous variables. The probability of death across the stages was presented using Kaplan-Meier curves. Differences between stages were compared using the log-rank test. The annualized mortality rates in each of the stages were calculated by adding the number of deaths divided by the total duration of follow-up observation for each group and were reported as a percentage.

Nonparametric trend test was used to evaluate the trend of annualized mortality across stages. Univariable and multivariable Cox proportional-hazards models were used to determine the contribution of potential prognostic variables to the patient outcome. The selection of covariates was conducted using Stata's Lasso command with the cross-validation selection option[28,29] and also based on prognostic factors established in AR patients.[1,18,30] The time-dependent effect of AVR was also estimated. Schoenfeld residuals (using the Stata's *phtest* command) and deviance residuals were used to test for proportional hazards and nonlinearity assumptions to ensure these assumptions were met in all final models.

The discrimination power of the predicting models was assessed using the C-statistic. The performance of the models was compared using Stata's lincom function. Survival of each cardiac remodeling stage was compared against age- and gender-matched U.S. population data during the same time frame using the life table data downloaded from the U.S. Centers for Disease Control and Prevention's website.[31] All the analyses were performed on Stata version 18.5 (StataCorp LLC). A value of $P < 0.05$ was considered statistically significant.

RESULTS

STUDY POPULATION. Baseline characteristics of the cohort and each stage are displayed in Table 1. The median age was 62 years (Q1-Q3: 51-72 years), and 79.2% were male. Median aortic valve regurgitant volume was 39 mL (Q1-Q3: 30-60 mL), and median regurgitant fraction was 38% (Q1-Q3: 32%-45%). Leaflet morphology was bicuspid in 102 patients (25.8%). There were 49 patients (12.4%) with NYHA functional class III/IV symptoms. The median EuroSCORE II was 1.4 (Q1-Q3: 0.7-2.8). Age, comorbidities burden, and surgical risk (EuroSCORE II) were higher in the advanced stages of cardiac remodeling. Patients in higher stages of cardiac remodeling were also more likely to have coronary artery disease and a greater increase in biventricular remodeling and LV dysfunction. The regurgitant fraction was also higher in the more advanced stages. The rates of each component of the staging system are available in Table 2.

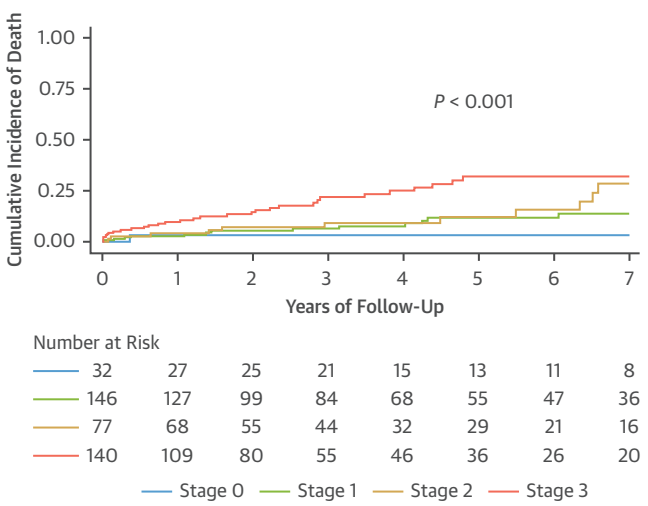
TABLE 2 Prevalence of Individual Components in Each Stage

	Stage 0 (n = 32)	Stage 1 (n = 146)	Stage 2 (n = 77)	Stage 3 (n = 140)
Stage 1				
LVEF ≤55%	0 (0.0)	42 (28.8)	29 (37.7)	90 (64.3)
Presence of LGE	0 (0.0)	33 (22.6)	28 (37.8)	67 (48.9)
LV hypertrophy	0 (0.0)	122 (83.6)	61 (79.2)	114 (81.4)
Indexed LVESV ≥45 mL/m^2	0 (0.0)	82 (56.2)	49 (63.6)	95 (67.9)
Stage 2				
Grade III diastolic dysfunction[a]	0 (0.0)	0 (0.0)	1 (2.6)	8 (9.5)
BNP >150 mg/dL[b]	0 (0.0)	0 (0.0)	43 (87.8)	66 (77.6)
Severe LA enlargement	0 (0.0)	0 (0.0)	44 (57.1)	60 (42.9)
Mitral regurgitant fraction ≥30%	0 (0.0)	0 (0.0)	12 (15.6)	42 (30.0)
Stage 3				
RVEF ≤45%	0 (0.0)	0 (0.0)	0 (0.0)	92 (65.7)
Tricuspid regurgitant fraction ≥30%	0 (0.0)	0 (0.0)	0 (0.0)	38 (27.1)
PASP ≥55 mm Hg[c]	0 (0.0)	0 (0.0)	0 (0.0)	47 (49)

Values are n (%). [a]Diastolic function data available in 222 of 395 patients (56%). [b]BNP data available in 176 of 395 patients (44.5%). [c]Pulmonary artery systolic pressure data available in 249 of 395 patients (48.3%).
Abbreviations as in Table 1.

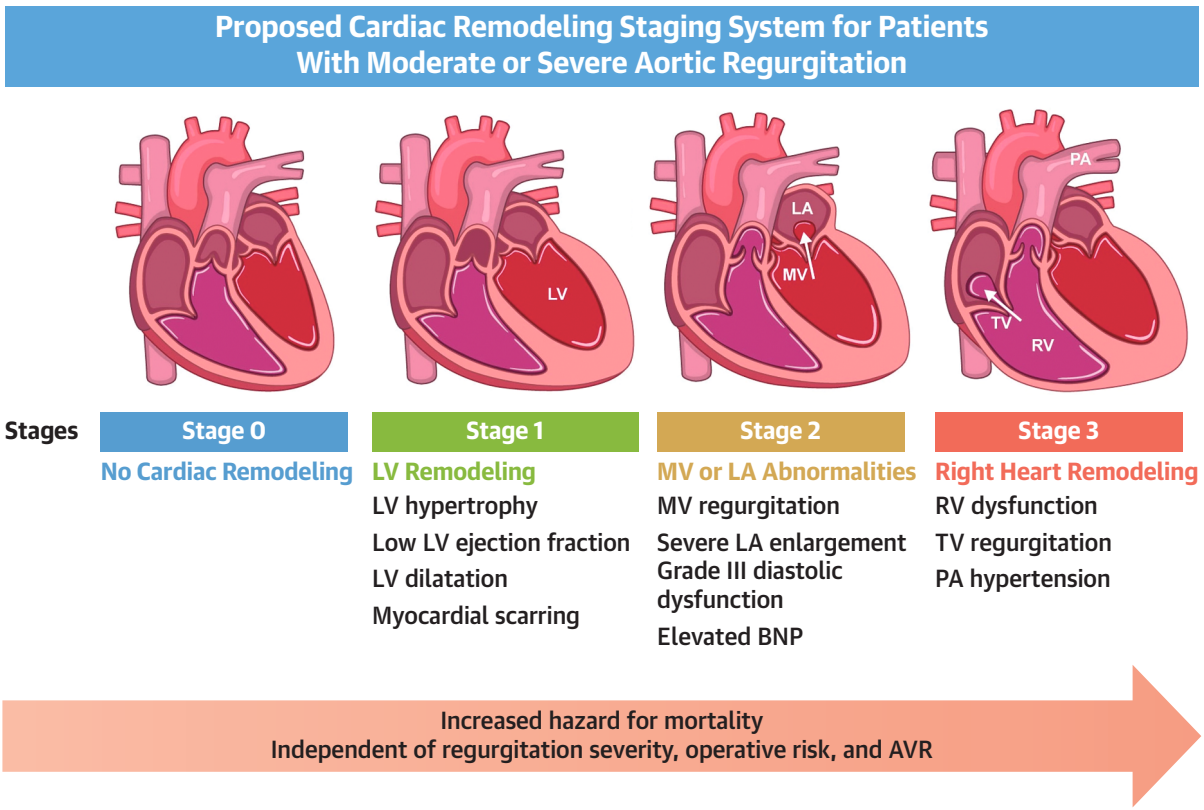
MANAGEMENT AND FOLLOW-UP. Patients were followed for up to 11.2 years (3.9 ± 2.9 years). Follow-up on management strategy was able to be ascertained

FIGURE 2 Cumulative Mortality According to the Stages



Kaplan-Meier curves of the cumulative incidence of death in each cardiac remodeling stage. *P* value is for the log rank test.

CENTRAL ILLUSTRATION **Overview of the Staging System of Cardiac Remodeling in AVR**



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AVR = aortic valve replacement; BNP = brain natriuretic peptide levels; LA = left atrium; LV = left ventricle; MV = mitral regurgitation; PA = pulmonary artery; RV = right ventricle; TV = tricuspid valve.

in 373 patients (94.4%). There were 182 patients (48.8%) who underwent AVR (175 surgical AVR and 7 transcatheter AVR), and 191 patients were managed medically. The median time to AVR was 0.9 months (Q1-Q3: 0.3-2.8 months). Patients in higher stages underwent AVR at a higher rate. The annualized rate of AVR was 5.42% per year in stage 0, 12.16% per year in stage 1, 13.46% per year in stage 2, and 13.92% per year in stage 3 (P trend = 0.02).

In the 182 patients who underwent AVR, there were 116 with Class I indications for surgery at the time of CMR and 36 with Class II indications for surgery (16 based on LV diameter criteria and 20 based on concomitant surgery criteria). An additional 30 patients later developed indications for surgery or underwent surgery before meeting the guideline indications. In the medical therapy group (n = 191), there were 4 patients who had an indication for surgery but were deemed high risk and referred for advanced heart failure therapies; there were 5 patients who were recommended for surgery but were lost to follow-up. There were 16 patients who had symptoms deemed nonattributable to AR after evaluation in the context of a smaller regurgitant volume ~30-40 mL with a high regurgitant fraction >40% due to a small LV stroke volume.

OUTCOMES. There were 60 deaths in the overall cohort: 36 deaths occurred in the medical therapy group (18.8% of patients managed medically), and 22 deaths occurred in the group who underwent AVR (12% of patients undergoing AVR). Additional deaths were identified through the SSDI in patients whose management strategy was uncertain due to loss of follow-up. The annualized mortality rate was 2.59% per year in the AVR group and 6.08% per year in the medical therapy group. The annualized mortality rate increased progressively with each cardiac stage: 0.68% per year in stage 0, 2.25% per year in stage 1,

TABLE 3 Multivariable Cox Proportional Hazard Models for Mortality

	Model 1		Model 2		Model 3		Model 4		Model 5	
	Adjusted HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value
Staging										
Stage 0	–	–	–	–	(Ref.)	–	–	–	–	–
Stage 1	–	–	–	–	4.65 (0.60-36.16)	0.14	–	–	–	–
Stage 2	–	–	–	–	7.80 (1.00-61.09)	0.051	–	–	–	–
Stage 3	–	–	–	–	11.37 (1.53-84.39)	0.02	–	–	–	–
Staging per each increment in stage	–	–	–	–	–	–	1.69 (1.28-2.23)	<0.001	–	–
Stage 3 vs stage 0-2	–	–	–	–	–	–	–	–	2.36 (1.40-3.99)	0.001
LVEF ≤50%	1.19 (0.59-2.37)	0.63	–	–	–	–	–	–	–	–
LVEF <55%	–	–	1.80 (0.85-3.79)	0.12	–	–	–	–	–	–
iLVESD ≥2.5, cm/m^2	1.53 (0.76-3.08)	0.24	–	–	–	–	–	–	–	–
iLVESV >45, mL/m^2	–	–	1.11 (0.52-2.38)	0.79	–	–	–	–	–	–
AVR	0.26 (0.14-0.51)	<0.001	0.26 (0.14-0.51)	<0.001	0.26 (0.14-0.49)	<0.001	0.27 (0.14-0.51)	<0.001	0.28 (0.15-0.53)	<0.001
EuroSCORE II, %	1.10 (1.06-1.14)	<0.001	1.09 (1.05-1.13)	<0.001	1.10 (1.06-1.14)	<0.001	1.10 (1.06-1.14)	<0.001	1.10 (1.06-1.14)	<0.001
Aortic regurgitant fraction, per 5% increase	1.14 (1.00-1.31)	0.06	1.15 (1.00-1.32)	0.049	1.12 (0.97-1.29)	0.11	1.13 (0.98-1.30)	0.09	1.14 (0.99-1.32)	0.06
C-statistic	0.71 (0.63-0.78)		0.70 (0.62-0.78)		0.74 (0.68-0.81)		0.74 (0.67-0.81)		0.73 (0.67-0.80)	

AVR = aortic valve replacement; iLVESD = indexed left ventricular end-systolic diameter; iLVESV = indexed left ventricular end-systolic volume; Ref. = Reference; other abbreviations as in Table 1.

3.76% per year in stage 2, and 7.25% per year in stage 3 (P for trend of mortality < 0.001) (Figure 2, Central Illustration).

Univariable Cox regression analyses are presented in the appendix (Supplemental Table 1). The interaction between AVR and time to AVR was not statistically significant ($P = 0.71$), so AVR is presented as a time-independent variable in multivariable analysis. Patients with NYHA functional class I, LVEF >50%, and indexed LVESD <2.5 cm/m^2 still incurred stage 1 remodeling (69 of 178; 38.7%), stage 2 remodeling (38 of 178; 21.3%), and stage 3 remodeling (29 of 178; 16.2%). Supplemental Table 2 shows a comparison of the baseline characteristics and distribution of the stages in patients who underwent AVR vs medical surveillance. Supplemental Table 3 demonstrates clinical and imaging characteristics stratified by moderate vs severe AR.

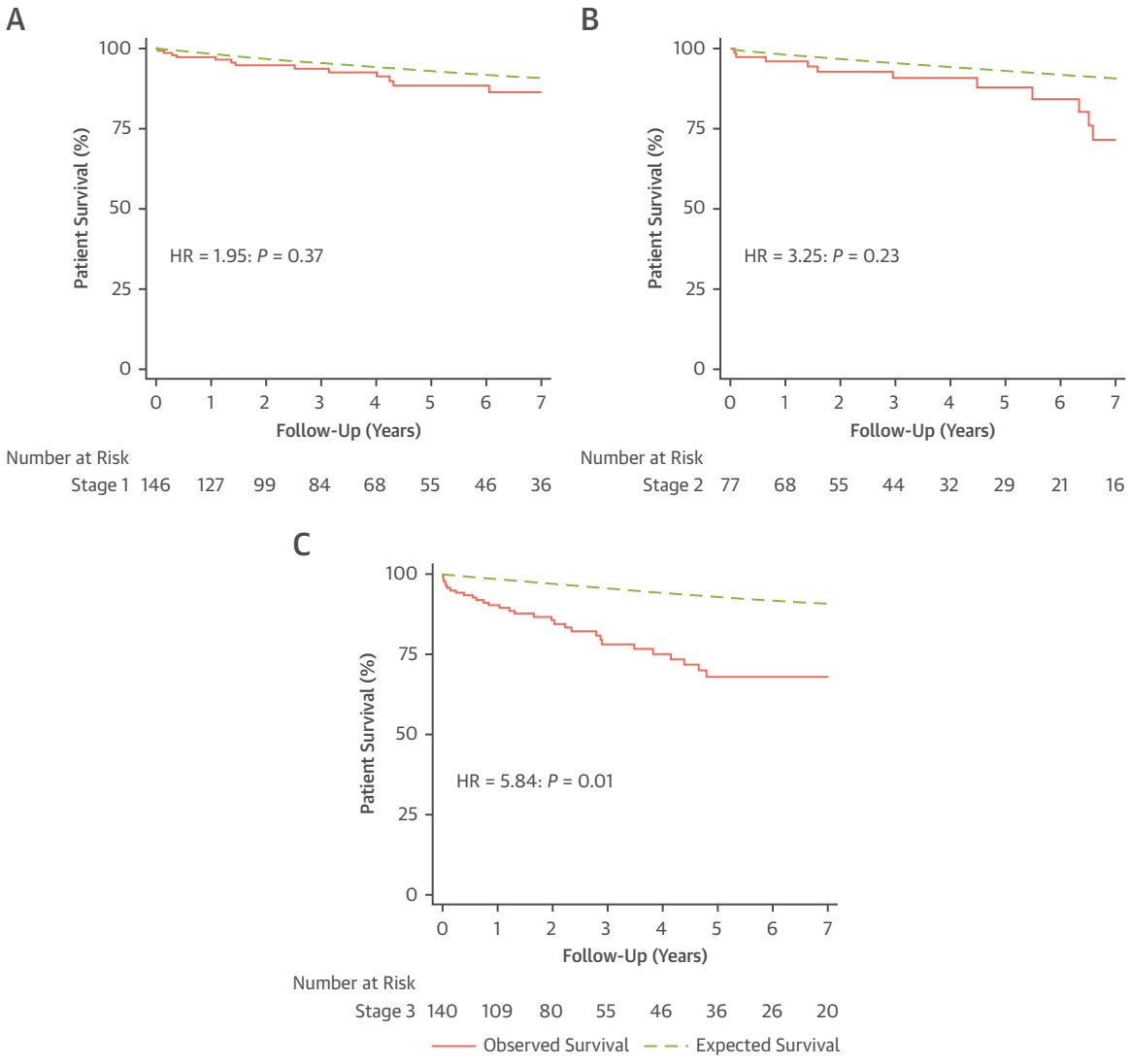
We constructed multivariable Cox regression models (Table 3) adjusting for AVR, EuroSCORE II (which includes age, sex, comorbidities, and NYHA functional class symptoms), aortic regurgitant fraction, and traditional risk markers in AR (LVEF ≤50% and indexed LVESD ≥2.5 cm/m^2; model 1). We also assessed newer thresholds of LVEF <55% and indexed LVESV >45 mL/m^2 (model 2). The staging system of cardiac remodeling incorporating the LVEF <55% and indexed LVESV thresholds was independently associated with an increased hazard for mortality (adjusted HR: 1.69 per increment of stage [95% CI: 1.28-2.23]; $P < 0.001$); and the highest hazard was for stage 3 (multivariable models 3 through 5) (Table 3). The area under the curve of the multivariable model using traditional measures of risk stratification in the guidelines was 0.71. The area under the curve of a multivariable model incorporating the staging system was 0.74. Compared to the age- and sex-matched general population, 1.95-fold ($P = 0.37$), 3.25-fold ($P = 0.23$), and 5.84-fold ($P = 0.01$) excess hazard for mortality was observed in those with stages 1 through 3, respectively (Figure 3).

DISCUSSION

In this study, we evaluated a staging system for cardiac valvular and extravalvular abnormalities in patients with moderate or severe aortic regurgitation. Each increment of the cardiac remodeling stages was associated with a 69% relative increase in the risk of death. Right heart remodeling (right ventricular dysfunction, ≥ moderate tricuspid regurgitation, and pulmonary hypertension) was associated with the highest risk of mortality.

CURRENT SCOPE OF AORTIC REGURGITATION AND NEED FOR FURTHER PROGNOSTICATION. The prevalence of clinically significant valvular heart disease is expected to increase, particularly in older

FIGURE 3 Observed vs Expected Survival Rates



Comparison of survival in stage 1 (A), stage 2 (B), and stage 3 (C) against an age- and sex-matched U.S. population.

adults,[10,32] and this carries important public health implications. An aging population is also more likely to have comorbidities, and thus attribution of symptoms to AR vs other conditions may be difficult. Patients included in the natural history studies of AR were generally young, and their outcomes might differ from current practice,[7,9] and the presence of extravalvular cardiac remodeling in these patients was not evaluated systematically. Current guidelines emphasize symptoms and left ventricular remodeling as the key parameters in evaluating and treating patients with AR. However, the sequelae of AR on the remainder of the heart are less emphasized due to insufficient data, and AR patients treated prior to meeting the traditional guideline indications appear to have a better long-term outcome, as previously shown.[2]

In our study, we noted that patients with AR may have cardiac remodeling or structural changes even when not meeting any of the traditional criteria for LV decompensation. Patients with NYHA functional class I, LVEF >50%, and indexed LVESD <2.5 cm/m^2 still had stage 1 remodeling (69 of 178; 38.7%), stage 2 remodeling (38 of 178; 21.3%), and stage 3 remodeling (29 of 178; 16.2%). Thus, patients can present clinically relevant cardiac remodeling before reaching the

guideline thresholds. The potential benefit of elective intervention on these patients requires further study.

STAGING OF CARDIAC REMODELING IN AORTIC REGURGITATION. Our modifications to the staging system described by Généreux et al[15] integrate a multimodality approach with CMR and echocardiography, as well as laboratory markers. The strengths of CMR in AR include its reproducibility, myocardial scarring assessment, accurate and reproducible quantitation of right ventricular function, and independent quantitation of coexisting valvular lesions.

The variables selected into each of the cardiac remodeling stages and their thresholds were mainly derived from the initial study of aortic stenosis by Généreux et al, not AR. Some of the newer components beyond LV parameters chosen in our staging system have established prognostic value in AR, such as brain natriuretic peptide,[5] myocardial scarring on CMR,[30] and pulmonary hypertension.[3,33] Others were chosen based on non-AR based studies such as secondary tricuspid regurgitation[34] and left atrial volume index.[35]

Female sex was associated with a higher hazard for death in univariable analysis in our study and was controlled for in the multivariable analysis using EuroSCORE II which includes sex. We note that prior studies demonstrated that women with AR have differences in cardiac remodeling and may have a worse prognosis potentially due to delayed referral to AVR.[36-38] Further studies are needed to investigate sex differences in AR and whether sex-specific thresholds for intervention are needed.

We did not include atrial fibrillation in the staging system because it was not associated with mortality on univariable analysis. However, atrial fibrillation patients may be less likely to be referred to CMR, and the occurrence of atrial fibrillation can still be relevant in AR patients.

CLINICAL IMPLICATIONS. The staging system described herein demonstrates incremental prognostic value beyond traditional markers of risk in AR, particularly stage 3 patients with right heart remodeling. Patients with right heart remodeling generally have higher surgical risk and burden of comorbid conditions, but they may be candidates for studies investigating percutaneous interventions for AR. Patients with multivalvular heart disease warrant further study as more percutaneous intervention options become available for treatment of mitral regurgitation and tricuspid regurgitation.

Our patient cohort had a higher burden of LV dysfunction and comorbidities (26.8% with LVEF <50% and 20.8% prevalence of coronary artery disease) in comparison with a recent large study of AR which had a coronary artery disease prevalence of 9% and LV dysfunction prevalence of 16%.[11] In either case, an important question to answer in large multicenter cohorts is whether the presence of comorbidities, or potentially advanced age, may decrease the tolerability of the pressure and volume load of AR, in comparison with younger, otherwise healthy adults who may tolerate AR for many years.

STUDY LIMITATIONS. This is a single-center study of patients referred to CMR with potential selection biases and may not represent the general AR population. Echocardiographic data and brain natriuretic peptide levels were not available on all patients (approximately half of patients) because many patients were referred to CMR from outside practices. We chose to include them in the staging system to incorporate as complete of an assessment as available.

We note that pulmonary artery systolic pressure cannot be estimated on numerous echocardiographic studies in real-world practice, and right heart catheterization is not routinely performed in all valvular heart disease patients. Although AR severity progressively increased at higher stages of cardiac remodeling in this study, it is challenging to determine whether all the observed parameters of valvular and extravalvular remodeling are attributable to AR. For example, the presence of diastolic dysfunction and secondary mitral regurgitation can certainly impact pulmonary artery pressures.

The severity of AR varied among different stages in terms of regurgitant volume, and patients in stage had lower regurgitant volume but similar regurgitant fraction to other stages. We suspect this to be due to the high prevalence of LV dysfunction and lower stroke volume in stage 3, leading to a higher regurgitant fraction measure. We included patients with regurgitant volume ≥30 mL or fraction ≥30% to attempt to capture all the "significant AR" population and to allow assessment for the fact that downstream cardiac remodeling may impact the ability to tolerate an aortic regurgitant load and affect clinical outcomes.

Assessment of the prognostic value of the staging system in those not meeting indications for surgery or other subgroups was limited by the number of patients in the study. We also did not assess cause of death due to the relatively lower number of deaths and difficulty of ascertainment of cause of death. Some of the components of the staging system were already shown to be associated with outcomes in AR

such as pulmonary artery systolic pressure and concomitant mitral regurgitation and tricuspid regurgitation. However, this staging system includes numerous other variables that were not included in previous studies of AR outcomes.

CONCLUSIONS

We evaluate a cardiac remodeling staging system for aortic regurgitation that takes into account imaging, clinical, and laboratory data. The staging system provides incremental prognostication beyond the traditional markers of prognosis in AR. Right heart remodeling (right ventricular dysfunction, advanced tricuspid regurgitation, and pulmonary hypertension) was associated with the highest risk of mortality.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: A cardiac remodeling staging system incorporating CMR findings provides incremental prognostication in AR beyond traditional risk markers. Right heart remodeling in AR is associated with the highest mortality.

TRANSLATIONAL OUTLOOK: Further research is needed to evaluate whether the staging system could aid in decision-making for AR patients.

REFERENCES

1. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *J Am Coll Cardiol*. 2021;77:e25–e197.

2. De Meester C, Gerber BL, Vancraeynest D, et al. Do guideline-based indications result in an outcome penalty for patients with severe aortic regurgitation? *JACC Cardiovasc Imaging*. 2019;12:2126–2138.

3. Mentias A, Feng K, Alashi A, et al. Long-term outcomes in patients with aortic regurgitation and preserved left ventricular ejection fraction. *J Am Coll Cardiol*. 2016;68:2144–2153.

4. Yang LT, Michelena HI, Scott CG, et al. Outcomes in chronic hemodynamically significant aortic regurgitation and limitations of current guidelines. *J Am Coll Cardiol*. 2019;73:1741–1752.

5. Pizarro R, Bazzino OO, Oberti PF, et al. Prospective validation of the prognostic usefulness of B-type natriuretic peptide in asymptomatic patients with chronic severe aortic regurgitation. *J Am Coll Cardiol*. 2011;58:1705–1714.

6. Alashi A, Mentias A, Abdallah A, et al. Incremental prognostic utility of left ventricular global longitudinal strain in asymptomatic patients with significant chronic aortic regurgitation and preserved left ventricular ejection fraction. *JACC Cardiovasc Imaging*. 2018;11:673–682.

7. Bonow RO, Lakatos E, Maron BJ, Epstein SE. Serial long-term assessment of the natural history of asymptomatic patients with chronic aortic regurgitation and normal left ventricular systolic function. *Circulation*. 1991;84, 1625-1535.

8. Tornos MP, Olona M, Permanyer-Miralda G, et al. Clinical outcome of severe asymptomatic chronic aortic regurgitation: a long-term prospective follow-up study. *Am Heart J*. 1995;130:333–339.

9. Dujardin KS, Enriquez-Sarano M, Rossi A, Bailey KR, Seward JB. Echocardiographic assessment of left ventricular remodeling: are left ventricular diameters suitable tools? *J Am Coll Cardiol*. 1997;30:1534–1541.

10. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet*. 2006;368:1005–1011.

11. Yang LT, Enriquez-Sarano M, Scott CG, et al. Concomitant mitral regurgitation in patients with chronic aortic regurgitation. *J Am Coll Cardiol*. 2020;76:233–246.

12. Tastet L, Tribouilloy C, Marechaux S, et al. Staging cardiac damage in patients with asymptomatic aortic valve stenosis. *J Am Coll Cardiol*. 2019;74:550–563.

13. Vollema EM, Amanullah MR, Ng ACT, et al. Staging cardiac damage in patients with symptomatic aortic valve stenosis. *J Am Coll Cardiol*. 2019;74:538–549.

14. Fukui M, Gupta A, Abdelkarim I, et al. Association of structural and functional cardiac changes with transcatheter aortic valve replacement outcomes in patients with aortic stenosis. *JAMA Cardiol*. 2019;4:215–222.

15. Généreux P, Pibarot P, Redfors B, et al. Staging classification of aortic stenosis based on the extent of cardiac damage. *Eur Heart J*. 2017;38:3351–3358.

16. Cawley PJ, Hamilton-Craig C, Owens DS, et al. Prospective comparison of valve regurgitation quantitation by cardiac magnetic resonance imaging and transthoracic echocardiography. *Circ Cardiovasc Imaging*. 2013;6:48–57.

17. Kockova R, Linkova H, Hlubocka Z, et al. Multiparametric strategy to predict early disease decompensation in asymptomatic severe aortic regurgitation. *Circ Cardiovasc Imaging*. 2022;15:e014901.

18. Malahfji M, Crudo V, Kaolawanich Y, et al. Influence of cardiac remodeling on clinical outcomes in patients with aortic regurgitation. *J Am Coll Cardiol*. 2023;81:1885–1898.

19. Hashimoto G, Enriquez-Sarano M, Stanberry LI, et al. Association of left ventricular remodeling assessment by cardiac magnetic resonance with outcomes in patients with chronic aortic regurgitation. *JAMA Cardiol*. 2022;7:924–933.

20. Myerson SG, d'Arcy J, Mohiaddin R, et al. Aortic regurgitation quantification using cardiovascular magnetic resonance: association with clinical outcome. *Circulation*. 2012;126:1452–1460.

21. Schulz-Menger J, Bluemke DA, Bremerich J, et al. Standardized image interpretation and post-

processing in cardiovascular magnetic resonance—2020 update: Society for Cardiovascular Magnetic Resonance (SCMR) Board of Trustees Task Force on Standardized Post-Processing. *J Cardiovasc Magn Reson*. 2020;22:19.

22. 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;30:303–371.

23. Fine NM, Tandon S, Kim HW, et al. Validation of sub-segmental visual scoring for the quantification of ischemic and nonischemic myocardial fibrosis using late gadolinium enhancement MRI. *J Magn Reson Imaging*. 2013;38:1369–1376.

24. Klem I, Heiberg E, Van Assche L, et al. Sources of variability in quantification of cardiovascular magnetic resonance infarct size: reproducibility among three core laboratories. *J Cardiovasc Magn Reson*. 2017;19:62.

25. Kitkungvan D, Nabi F, Kim RJ, et al. Myocardial fibrosis in patients with primary mitral regurgitation with and without prolapse. *J Am Coll Cardiol*. 2018;72:823–834.

26. Tayal B, Debs D, Nabi F, et al. Impact of myocardial scar on prognostic implication of secondary mitral regurgitation in heart failure. *JACC Cardiovasc Imaging*. 2021;14:812–822.

27. Kawel-Boehm N, Maceira A, Valsangiacomo-Buechel ER, et al. Normal values for cardiovascular magnetic resonance in adults and children. *J Cardiovasc Magn Reson*. 2015;17:29.

28. Hastie T, Tibshirani R, Wainwright M. *Statistical Learning With Sparsity: The Lasso and Generalizations*. Chapman and Hall/CRC; 2015.

29. StataCorp. *Stata Lasso Reference Manual*. 16th release. Stata Press; 2019. https://www.stata.com/manuals16/lasso.pdf

30. Malahfji M, Senapati A, Tayal B, et al. Myocardial scar and mortality in chronic aortic regurgitation. *J Am Heart Assoc*. 2020;9:e018731.

31. Life Tables. Centers for Disease Control and Prevention. Accessed December 2, 2020. https://www.cdc.gov/nchs/products/life_tables.htm

32. D'Arcy JL, Coffey S, Loudon MA, et al. Large-scale community echocardiographic screening reveals a major burden of undiagnosed valvular heart disease in older people: the OxVALVE Population Cohort Study. *Eur Heart J*. 2016;37:3515–3522.

33. Anand V, Scott CG, Lee AT, et al. Prevalence and prognostic implications of pulmonary hypertension in patients with severe aortic regurgitation. *JACC Adv*. 2024;3:100827.

34. Zhan Y, Debs D, Khan MA, et al. Natural history of functional tricuspid regurgitation quantified by cardiovascular magnetic resonance. *J Am Coll Cardiol*. 2020;76:1291–1301.

35. Khan MA, Yang EY, Zhan Y, et al. Association of left atrial volume index and all-cause mortality in patients referred for routine cardiovascular magnetic resonance: a multicenter study. *J Cardiovasc Magn Reson*. 2019;21:4.

36. Klodas E, Enriquez-Sarano M, Tajik AJ, Mullany CJ, Bailey KR, Seward JB. Surgery for aortic regurgitation in women: contrasting indications and outcomes compared with men. *Circulation*. 1996;94:2472–2478.

37. Tower-Rader A, Mathias IS, Obuchowski NA, et al. Sex-based differences in left ventricular remodeling in patients with chronic aortic regurgitation: a multi-modality study. *J Cardiovasc Magn Reson*. 2022;24:1–13.

38. Yang LT, Enriquez-Sarano M, Pellikka PA, et al. Sex differences in outcomes of patients with chronic aortic regurgitation: closing the mortality gap. *Mayo Clin Proc*. 2021;96:2145–2156.

KEY WORDS aortic regurgitation, cardiac magnetic resonance, cardiac remodeling

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