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ORIGINAL RESEARCH

# Cardiac Remodeling and Outcomes of Patients With Combined Aortic and Mitral Regurgitation

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## ABSTRACT

**BACKGROUND** Management of patients with combined aortic and mitral regurgitation (AR and MR) is largely based on expert opinion. Specifically, the outcomes of patients with combined moderate AR and moderate MR under medical surveillance are uncertain.

**OBJECTIVES** This study aimed to evaluate cardiac remodeling using cardiac magnetic resonance (CMR) in patients with combined AR/MR compared with isolated AR, to assess degree of MR associated with adverse outcomes, and evaluate the outcomes of asymptomatic patients with combined moderate AR and moderate MR under medical surveillance.

**METHODS** The authors conducted a multicenter observational outcome study of patients with moderate or severe AR on CMR, and evaluated the etiology and degree of concomitant MR in patients with combined AR and MR. They excluded patients if they had prior valvular surgery, > mild valve stenosis, hypertrophic or infiltrative cardiomyopathy, or congenital heart disease except bicuspid aortic valve. The authors evaluated ventricular volumes and function across the spectrum of regurgitation severity. Receiver-operating characteristic analyses for the association of concomitant MR severity with outcomes were performed. The primary outcome was all-cause death. Secondary outcome was all-cause death or heart failure (HF) hospitalization. Patients were censored at the time of valvular surgery or intervention. Propensity score matching was done between isolated AR and the combined AR/MR groups.

**RESULTS** The authors studied 915 patients with a median age of 61 years (Q1-Q3: 49-72 years), 79.5% male, 29% with bicuspid aortic valve, and a median AR fraction of 38% (Q1-Q3: 32%-45%). In 251 of 915 patients (27.4%) with concomitant MR, the median MR fraction was 24% (Q1-Q3: 17%-35%). The presence of concomitant ≥moderate MR (14.2% of the total population) was associated with a greater increase in ventricular volumes per unit increase in AR severity, and a decline in ventricular function ($P$ for interaction ≤0.01). During a median follow-up of 3.0 years (Q1-Q3: 1.1-5.6 years), there were 152 deaths. Presence of concomitant ≥moderate MR was associated with an increased hazard for all-cause death (HR: 2.77; 95% CI: 1.91-4.01; $P < 0.001$), and the secondary outcome of death or HF (HR: 2.62; 95% CI: 1.87-3.67; $P < 0.001$). In asymptomatic or minimally symptomatic patients undergoing medical surveillance, the presence of combined moderate AR and moderate MR was independently associated with a higher hazard for the primary and secondary outcomes compared with isolated AR, independent of age, sex, comorbidities, ejection fraction, and end-systolic volume. Findings were consistent in the propensity matched cohort.

**CONCLUSIONS** The presence of combined AR and MR on CMR is associated with a greater extent of ventricular remodeling and increased hazard for adverse outcomes, compared with isolated AR. Asymptomatic patients with combined moderate AR and MR under medical surveillance are at higher risk for death and HF, and warrant further study. (JACC Cardiovasc Imaging. 2026;19:180–193) © 2026 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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Patients with multivalvular disease present challenges in assessment, quantitation of lesion severity, and management. With the aging population, the burden of valvular disease is expected to increase, and multivalvular disease is not uncommon.[1,2] Guidelines highlight significant knowledge gaps regarding multivalvular disease; and treatment recommendations are often based on expert opinion and treating the dominant lesion.[3-5]

Patients with combined aortic and mitral regurgitation (AR and MR) experience left ventricular (LV) pressure and volume overload due to AR, and the additional volume overload of MR.[6] Presence of concomitant MR in patients with AR was associated with excess LV remodeling and a higher risk of adverse outcomes in 2 prior studies.[7,8] However, the degree of MR at which outcomes differ from the general AR population is unclear, and specific MR severity thresholds for guiding the management of patients with combined AR/MR are uncertain. In addition, there is a lack of data on the outcomes of asymptomatic patients with 2 moderate lesions (moderate AR with moderate MR), where neither lesion is severe, and the indications for intervention in such cases are unknown.

The presence of multivalvular disease makes the assessment of valvular regurgitation more complex, and guidelines highlight that cardiac magnetic resonance (CMR) can offer advantages over other methods in assessment of severity.[9] It is also the current reference standard for assessment of LV volumes, function, and mass, which are the principal parameters for evaluating cardiac remodeling in valvular disease.

We conducted a multicenter observational study with the following aims: 1) to evaluate cardiac remodeling using CMR in patients with combined AR/MR compared with isolated AR; 2) to assess MR etiologies and severity of MR associated with adverse outcomes; and 3) to evaluate the outcomes of asymptomatic or minimally symptomatic patients with combined moderate AR and moderate MR under medical surveillance.

## METHODS

**PATIENT SELECTION.** We included consecutive and unique patients, from 4 U.S. medical centers, with moderate or greater AR (AR volume ≥30 mL or AR fraction ≥30%) measured by phase-contrast imaging. Studies were performed between 2006 and 2022. We excluded patients with: 1) > mild aortic or mitral stenosis; 2) any prior valve intervention or surgery; 3) hypertrophic or infiltrative cardiomyopathy; 4) congenital disease except bicuspid valve; and 5) end-stage systemic disease with competing mortality risk (eg, end-stage cirrhosis or cancer). No patients with acute AR (eg, due to aortic dissection), primary tricuspid regurgitation, or > mild pulmonic valve disease were included. A subgroup of this cohort (n = 458) was previously described.[10] The enrollment process is summarized in Figure 1. Institutional review board approval for use of the data encompassed in this study was obtained at each site.

**MULTICENTER DATA AGGREGATION AND ANALYSIS.** The study was performed through the SCMR Registry (Society for Cardiovascular Magnetic Resonance Registry Resource). Four centers participated in this study (Houston Methodist Hospital, Duke University, Atrium Health, and Piedmont Healthcare). Houston Methodist Hospital was the data coordinating center. Patients underwent a baseline interview and review of medical records at the time of CMR at each institution. Collected data included demographic characteristics, risk factors, comorbidities, and NYHA functional class. Each of the participating centers used the same software (Precession; Heart Imaging Technologies).

**ABBREVIATIONS AND ACRONYMS**

**AR** = aortic regurgitation
**AVR** = aortic valve replacement
**CAD** = coronary artery disease
**CMR** = cardiac magnetic resonance
**HF** = heart failure
**LV** = left ventricular
**LVEDV** = left ventricular end-diastolic volume
**LVEF** = left ventricular ejection fraction
**LVESV** = left ventricular end-systolic volume
**MR** = mitral regurgitation
**M-TEER** = mitral transcatheter edge of edge repair
**MV** = mitral valve

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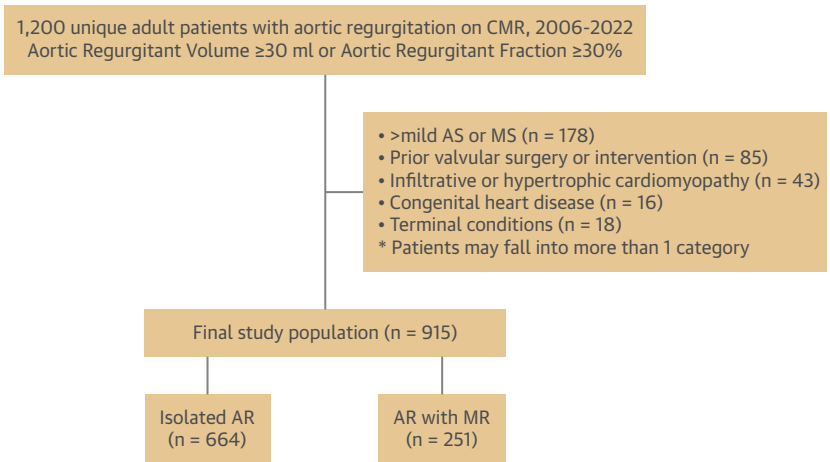
**FIGURE 1 Overview of Patient Enrollment**




AR = aortic regurgitation; AS = aortic stenosis; CMR = cardiac magnetic resonance; MR = mitral regurgitation; MS = mitral stenosis.

**CMR STUDY PROTOCOL AND ANALYSIS.** CMR was performed using 1.5-T or 3.0-T scanners (Siemens Healthineers). A typical aortic valve and mitral valve (MV) assessment by CMR was previously described.[10]

Left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), left ventricular ejection fraction (LVEF), and LV mass were measured in accordance with SCMR guidelines.[11] Measures were indexed to body surface area. AR volume was calculated using the direct method from phase-contrast imaging at the level of the sinotubular junction. AR fraction was calculated as (aortic regurgitant volume / forward aortic stroke volume × 100%). Phase-contrast imaging in the ascending aorta, and the difference between aortic and net pulmonic forward stroke volume were used as secondary checks for AR volume quantitation.

Mitral regurgitant volume was calculated as the difference between the LV stroke volume and forward stroke volume in the aorta. Mitral regurgitant fraction was calculated as (mitral regurgitant volume / [LV stroke volume − aortic regurgitant volume] × 100).[9] In patients with atrial fibrillation, we used multiaverage free breathing phase-contrast. In cases of frequent ectopy, arrhythmia rejection or prospective gating with a short RR interval was utilized to derive systolic flow volumes in the aorta and pulmonary artery. Severe MR and AR were defined as regurgitant volume ≥60 mL or regurgitant fraction ≥50%, according to guidelines.[3,4]

In patients with concomitant MR, etiology was evaluated by consensus of 2 of the authors (M.M. and D.J.S.), who were blinded to outcomes. Patients were categorized as primary MR, secondary MR, or mixed etiology. Patients with primary MR were further classified into Carpentier type II MR (prolapse or flail), and Carpentier type IIIa MR (leaflet degeneration or restriction). Patients with secondary MR were classified into secondary ventricular MR due to LV/annular dilation or ischemic MR (Carpentier type IIIb), or atrial secondary MR (Carpentier type I) due to severe left atrial dilation with preserved LVEF and relatively preserved LV volume (nonsevere LV dilation).

**CLINICAL FINDINGS AND OUTCOME ASSESSMENT.** Each site updated patient mortality by comparing local patient identifiers to the U.S. Social Security Death Index. Mortality events were also collected and verified through health record review and/or calls with patients' relatives. Investigators at each site collected ancillary findings and comorbid conditions. Management decisions and timing were recorded, including surgical or transcatheter aortic valve replacement/repair (AVR), surgical MV replacement or repair, and mitral transcatheter edge of edge repair (M-TEER). The EuroSCORE II (European System for Cardiac Operative Risk Evaluation) risk score was calculated. Clinical follow-up was initiated from the time of CMR imaging.

The primary outcome was all-cause death. Secondary outcome was a composite outcome of death or heart failure (HF) hospitalization. HF hospitalization was determined according to the criteria by

**TABLE 1 Baseline Patient Characteristics**

| | Total (N = 915) | Isolated AR (n = 664) | Combined AR/MR (n = 251) | *P* Value |
|---|---|---|---|---|
| Clinical findings | | | | |
| Age, y | 61.0 (49.0-72.0) | 60.0 (47.8-71.0) | 64.7 (54.2-72.2) | 0.001 |
| Female | 188 (20.5) | 128 (19.3) | 60 (23.9) | 0.14 |
| Caucasian race | 650 (71.0) | 462 (69.6) | 188 (74.9) | 0.13 |
| Heart rate, beats/min | 68.5 (61.0-78.0) | 68.0 (60.8-76.0) | 70.0 (61.0-80.0) | 0.11 |
| SBP, mm Hg | 136 (122-150) | 135.0 (122.0-149.0) | 137.0 (122.3-152.0) | 0.48 |
| DBP, mm Hg | 68 (61-77) | 68.0 (61.0-77.0) | 68.0 (61.0-77.0) | 0.95 |
| In sinus rhythm during CMR | 868 (94.9) | 634 (95.5) | 234 (93.2) | 0.22 |
| Body surface area, $m^2$ | 2.0 ± 0.3 | 2.0 ± 0.3 | 2.0 ± 0.3 | 0.02 |
| Body mass index, $kg/m^2$ | 27.4 (24.6-31.1) | 27.7 (24.7-31.2) | 26.6 (24.4-30.9) | 0.06 |
| Coronary artery disease | 176 (19.2) | 107 (16.1) | 69 (27.5) | <0.001 |
| Diabetes | 98 (10.7) | 63 (9.5) | 35 (13.9) | 0.06 |
| Hyperlipidemia | 439 (48.0) | 302 (45.5) | 137 (54.6) | 0.01 |
| Hypertension | 610 (66.7) | 422 (63.6) | 188 (74.9) | 0.002 |
| Current or previous smoking | 285 (31.1) | 209 (31.5) | 76 (30.3) | 0.78 |
| History of atrial fibrillation/flutter | 167 (18.3) | 110 (16.6) | 57 (22.7) | 0.04 |
| EuroSCORE II | 1.07 (0.68-2.21) | 0.95 (0.62-1.92) | 1.34 (0.83-3.35) | <0.001 |
| NYHA functional class | | | | |
| I | 673 (73.6) | 513 (77.3) | 160 (63.7) | <0.001 |
| II | 164 (17.9) | 113 (17.0) | 51 (20.3) | |
| III | 69 (7.5) | 35 (5.3) | 34 (13.5) | |
| IV | 9 (1.0) | 3 (0.5) | 6 (2.4) | |
| Medications | | | | |
| Beta-blockers | 343 (37.5) | 214 (32.2) | 129 (51.4) | <0.001 |
| RAAS inhibitors | 396 (43.3) | 314 (47.3) | 82 (32.7) | <0.001 |
| Antiplatelet agents | 347 (37.9) | 273 (41.1) | 74 (29.5) | 0.002 |
| Anticoagulation | 120 (13.1) | 77 (11.6) | 43 (17.1) | 0.03 |

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

AR = aortic regurgitation; CMR = cardiac magnetic resonance; DBP = diastolic blood pressure; MR = mitral regurgitation; RAAS = renin-angiotensin-aldosterone; SBP = systolic blood pressure.

Hicks et al,[12] based upon hospital discharge records. To study the natural history of concomitant AR/MR, patients were censored at the time of MV and/or aortic valve intervention in outcome analysis. The event status (censor date) for patients was checked until September 2023. An additional sensitivity outcome analysis was performed using the total duration of follow-up while including valve intervention as an adjustment variable.

**STATISTICAL ANALYSIS.** Continuous variables were tested for normality using the Shapiro-Wilk test. Descriptive statistics are reported as median (Q1-Q3) or mean ± SD for continuous variables, and as frequencies and proportions for categorical variables. Group differences were assessed using the chi-square or Fisher exact test for categorical variables, and the Kruskal-Wallis test or unpaired Student's *t*-test for continuous variables, depending on their distribution. Receiver-operating characteristic curves were constructed, and the Youden index[13] was used to identify the optimal thresholds of MR severity in discriminating outcomes. Fractional polynomial spline curves were used to present variation in cardiac remodeling across the spectrum AR severity, stratified by MR severity. The interaction between AR and MR in the association with remodeling variables was tested using fractional polynomial regression by incorporating the interaction term between AR severity and concomitant MR. We selected the functional form based on the best-fitting fractional polynomial transformation using deviance minimization criteria. The chosen model adequately captured the nonlinear relationship between the predictor and outcome, as supported by improved model fit compared to linear alternatives.

Cox proportional-hazards models were built to evaluate the association between potential

**TABLE 2 Baseline Patient Characteristics, Propensity Score Matched Cohort**

| | Total (N = 416) | Isolated AR (n = 208) | Combined AR/MR (n = 208) | SMD | *P* Value |
|---|---|---|---|---|---|
| Clinical findings | | | | | |
| Age, y | 65.0 (53.0-74.2) | 65.0 (51.5-76.0) | 64.6 (54.0-72.0) | 0.05 | 0.62 |
| Female | 102 (24.5) | 51 (24.5) | 51 (24.5) | 0.00 | 1.00 |
| Caucasian race | 320 (76.9) | 162 (77.9) | 158 (76.0) | 0.05 | 0.64 |
| Heart rate, beats/min | 70.0 (61.0-79.0) | 70.0 (60.0-78.5) | 70.0 (61.5-80.0) | −0.07 | 0.49 |
| SBP, mm Hg | 137.0 (123.0-153.0) | 137.0 (122.5-154.0) | 137.0 (123.0-152.0) | 0.05 | 0.64 |
| DBP, mm Hg | 68.0 (61.0-76.0) | 67.0 (60.5-76.0) | 68.0 (61.0-76.0) | 0.00 | 0.96 |
| In sinus rhythm during CMR | 387 (93.0) | 191 (91.8) | 196 (94.2) | −0.09 | 0.34 |
| Body surface area, $m^2$ | 2.0 ± 0.2 | 1.9 ± 0.2 | 2.0 ± 0.3 | −0.11 | 0.27 |
| Body mass index, $kg/m^2$ | 26.7 (24.2-30.7) | 27.0 (24.1-30.2) | 26.6 (24.3-31.1) | −0.11 | 0.27 |
| Coronary artery disease | 110 (26.4) | 53 (25.5) | 57 (27.4) | −0.04 | 0.66 |
| Diabetes | 51 (12.3) | 23 (11.1) | 28 (13.5) | −0.07 | 0.46 |
| Hyperlipidemia | 211 (50.7) | 104 (50.0) | 107 (51.4) | −0.03 | 0.77 |
| Hypertension | 297 (71.4) | 144 (69.2) | 153 (73.6) | −0.10 | 0.33 |
| Current or previous smoking | 137 (32.9) | 66 (31.7) | 71 (34.1) | −0.05 | 0.60 |
| History of atrial fibrillation/flutter | 103 (24.8) | 57 (27.4) | 46 (22.1) | 0.12 | 0.21 |
| EuroSCORE II | 1.3 (0.8-3.0) | 1.3 (0.7-2.6) | 1.3 (0.8-3.4) | −0.07 | 0.49 |
| NYHA functional class | | | | | |
| I | 276 (66.3) | 141 (67.8) | 135 (64.9) | 0.14 | 0.54 |
| II | 88 (21.2) | 45 (21.6) | 43 (20.7) | | 0.81 |
| III | 47 (11.3) | 19 (9.1) | 28 (13.5) | | 0.16 |
| IV | 5 (1.2) | 3 (1.4) | 2 (1.0) | | 0.65 |
| Medications | | | | | |
| Beta-blockers | 205 (49.3) | 104 (50.0) | 101 (48.6) | 0.03 | 0.77 |
| RAAS inhibitors | 142 (34.1) | 68 (32.7) | 74 (35.6) | −0.06 | 0.54 |
| Antiplatelet agents | 136 (32.7) | 72 (34.6) | 64 (30.8) | 0.08 | 0.40 |
| Anticoagulation | 77 (18.5) | 39 (18.8) | 38 (18.3) | 0.01 | 0.90 |

Values are median (Q1-Q3), n (%), or mean ± SD, unless otherwise indicated.
SMD = standardized mean differences; other abbreviations as in Table 1.

prognostic variables with the risk of adverse outcomes. HRs and 95% CIs are reported. Predicted 5-year outcomes under medical surveillance corresponding to different MR fraction and AR fraction levels were estimated for the entire cohort following the univariable Cox regression and plotted in a 3-dimensional spline graph. The selection of covariates for the multivariable Cox models was based on clinically relevant variables and variables with values of $P < 0.05$ on univariable analysis. Variables included were age, sex, EuroSCORE II, diabetes mellitus, indexed LVESV, LVEF, and regurgitation severity. Additional multivariable analysis was performed excluding patients with history of coronary artery disease (CAD) or ischemic pattern LV scar on CMR. The proportional hazards assumption (based on the Schoenfeld residuals test) and interaction testing were conducted. All presented models met the proportional hazards assumption, and no significant interactions were found. In addition, we performed propensity score matching between the AR/MR and isolated AR groups using all baseline variables listed in Table 1. We used the nearest neighbors matching approach without replacement with a caliper width of 0.4. To balance covariates while preserving sample size, we used a standardized mean difference threshold of <0.2. Survival analyses were also performed in the propensity score-matched group. All analyses were performed on Stata software version 18.5 (StataCorp). A 2-sided *P* value of <0.05 was considered statistically significant.

## RESULTS

**STUDY POPULATION.** We studied 915 patients with a median age of 61.0 years (Q1-Q3: 49.0-72.0 years), 79.5% male, and 29% with a bicuspid valve. Baseline characteristics for the entire cohort and the propensity score-matched cohort are listed in Tables 1 and 2. CMR findings are summarized in Table 3. In total, there were 297 of 915 patients (32.4%) with severe AR and 618 of 915 (67.54%) with moderate AR.

**TABLE 3 CMR Findings and Rates of Valvular Intervention**

| | Total (N = 915) | Isolated AR (n = 664) | Combined AR/MR (n = 251) | *P* Value |
|---|---|---|---|---|
| CMR findings | | | | |
| LVEF, % | 59.3 (51.0-65.6) | 60.57 (53.0-66.0) | 57.22 (47.2-64.0) | <0.001 |
| Indexed LVEDV, mL/m$^2$ | 112.3 (90.9-139.2) | 109.2 (88.5-133.9) | 126.7 (102.0-151.6) | <0.001 |
| Indexed LVESV, mL/m$^2$ | 44.5 (33.0-63.1) | 42.6 (31.7-58.1) | 53.1 (39.9-74.1) | <0.001 |
| Indexed LVESD, cm/m$^2$ | 1.99 (1.7-2.3) | 1.94 (1.68-2.29) | 2.10 (1.7-2.4) | 0.001 |
| Indexed LV mass, g/m$^2$ | 88.9 (73.3-108.6) | 87.8 (72.2-106.3) | 94.8 (76.9-115.2) | 0.003 |
| Indexed LA volume, mL/m$^2$ | 50.0 (38.2-66.4) | 46.0 (35.2-59.3) | 64.4 (47.6-86.9) | <0.001 |
| Presence of LGE | 244 (26.7) | 147 (22.1) | 97 (38.6) | <0.001 |
| Non-CAD pattern scar | 126 (51.6) | 74 (50.3) | 52 (53.6) | 0.62 |
| CAD pattern scar | 118 (48.4) | 73 (49.7) | 45 (46.4) | — |
| LGE extent, % of LV | 3 (2-8) | 3 (2-8) | 3.1 (2-8) | 0.61 |
| Bicuspid aortic valve | 265 (29.0) | 215 (32.4) | 50 (19.9) | <0.001 |
| Regurgitation quantification | | | | |
| Aortic regurgitant volume, mL | 41 (32-61) | 43.0 (32.0-62.0) | 37.0 (30.0-59.5) | 0.001 |
| Aortic regurgitant fraction, % | 38 (32-46) | 38.0 (32.0-46.0) | 39.0 (32.0-45.8) | 0.99 |
| Mitral regurgitant volume, mL | 20 (14-29) | 6.0 (5.3-8.0) | 21.0 (15.0-30.5) | — |
| Mitral regurgitant fraction, % | 23 (16-34) | 7.0 (6.0-9.0) | 24.0 (17.0-35.0) | — |
| Intervention during follow-up[a] | | | | |
| Aortic valve intervention | 363 (41.2) | 264 (40.9) | 99 (41.9) | 0.78 |
| Mitral valve intervention | n/a | n/a | 36 (14.3)[b] | — |

Values are median (Q1-Q3) or n (%), unless otherwise indicated. [a]Complete follow-up available in 881/915 (96.2%) of patients. [b]MV intervention in 36 of 130 patients (28%) with AR and ≥moderate MR.

CAD = coronary artery disease; LA = left atrial; LGE = late gadolinium enhancement; LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; LVESV = left ventricular end-systolic volume; other abbreviations as in Table 1.

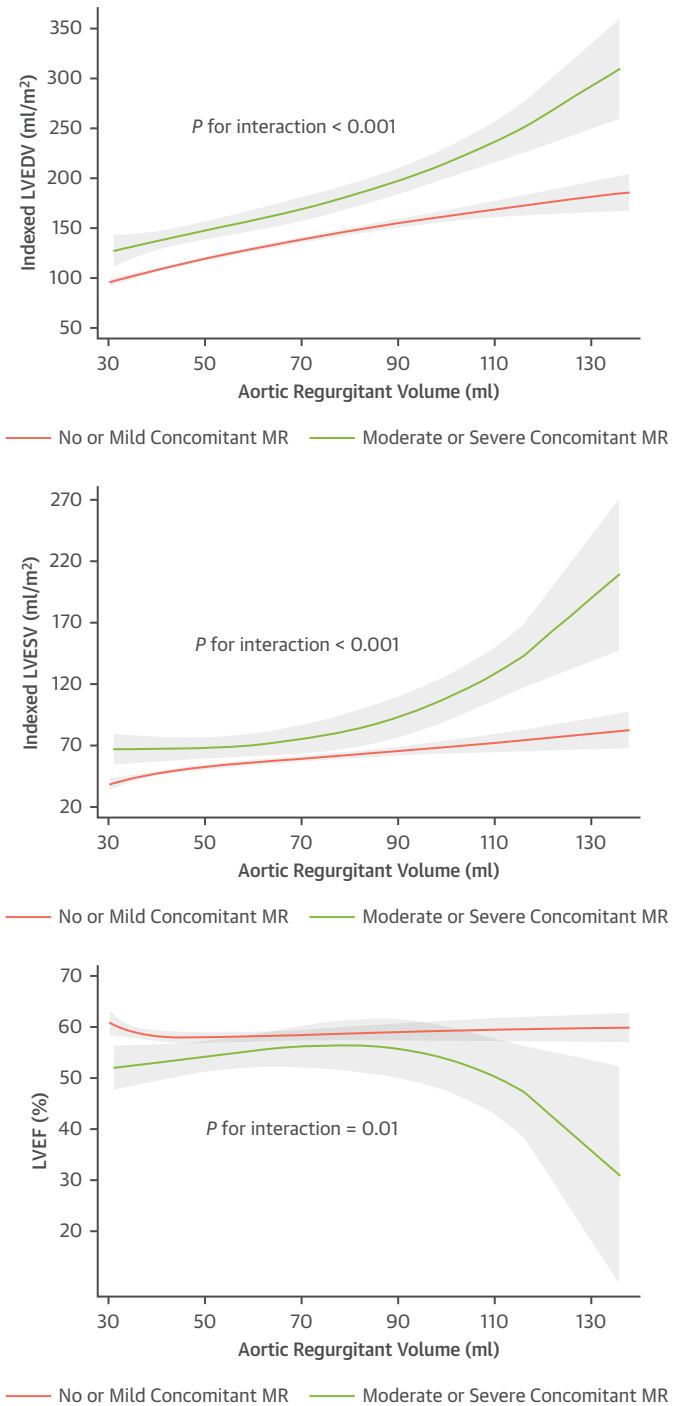
The median AR fraction was 38% (Q1-Q3: 32%-46%). There were 251 of 915 patients (27.4%) with combined AR/MR, of whom there were 104 of 251 (41.4%) with MR volume ≥30 mL or MR fraction ≥30%, and 21 of 251 patients (8.3%) with MR volume ≥60 mL or MR fraction ≥50%. Based on receiver-operating characteristic analysis, the MR fraction threshold that was associated with the outcome of death was 25% (Youden index = 0.28, area under the curve at the cut point = 0.64); and thus 26 additional patients with MR fraction between 25% and 30% were also considered to have moderate—potentially hemodynamically significant—MR (total of 130/251 [51.7%] of patients with ≥ moderate MR). Distribution of AR and MR severity is summarized in Supplemental Table 1. We also stratified the cohort to patients with isolated moderate AR, isolated severe AR, and patients with combined moderate AR and moderate MR (excluding patients with severe MR) (Supplemental Tables 2 and 3). Overall, patients with combined AR/MR were older, had a higher burden of advanced symptoms (NYHA functional class III/IV), more comorbidities, higher prevalence of atrial fibrillation/flutter, greater LV volumes, and lower LVEF.

**CARDIAC REMODELING FINDINGS IN AR/MR PATIENTS.** Across the spectrum of AR severity, presence of concomitant ≥ moderate MR was associated with greater increases for indexed LVEDV and indexed LVESV per unit of AR volume compared with those with isolated AR or AR and mild MR (*P* for interaction < 0.001 for indexed LVEDV; *P* for interaction < 0.001 for indexed LVESV). The LVEF decreased with increasing AR severity in patients with concomitant ≥ moderate MR relative to patients with isolated AR (*P* for interaction = 0.01) (Figure 2). The group of combined AR/MR had a higher prevalence of LV scarring on CMR (38.6% vs 22.1% in isolated AR) (Table 3). There was no statistically significant difference in the burden of scar or type of scar (CAD vs non-CAD scarring) between the 2 groups of isolated AR and combined AR/MR.

**CHARACTERIZATION AND MANAGEMENT OF AR/MR PATIENTS.** In 130 patients with combined AR and ≥ moderate MR, etiology of MR was type IIIb (ventricular secondary MR) in 69 patients (53%), type II (prolapse or flail) in 16 patients (12.3%), type IIIa (leaflet degeneration/restriction) in 26 (20%), mixed etiology in 16 (12.3%), and type 1 (atrial secondary) in 3 patients (2.3%). In the remainder of the 251 patients with AR/MR (n = 121), the mitral valve was structurally normal, and all those patients had mild MR.

Of 915 patients, 34 (3.7%) did not have information regarding procedures (either lost to follow-up after CMR or given recommendations on surgery but lost

**FIGURE 2 Cardiac Remodeling Findings**




Changes in indexed left ventricular end-diastolic volume (LVEDV) (top), indexed left ventricular end-systolic volume (LVESV) (middle), and left ventricular ejection fraction (LVEF) (bottom) across degrees of AR severity, stratified by the presence or absence of moderate or severe concomitant MR. Abbreviations as in Figure 1.

to follow-up). Of the remaining 881 patients, 363 (41.2%) underwent AVR (344 had surgical AVR, 9 had AV repair, and 11 had transcatheter AVR). The rates of AVR were 67.5% in the isolated severe AR group, 26.5% in the isolated moderate AR group, and 33.8% in the combined moderate AR/MR group. There were 36 patients who underwent MV intervention, 16 patients had MV repair, 15 had MV replacement, and 5 patients underwent M-TEER.

In total, 373 of 881 patients (42.3%) underwent AVR and/or MV intervention. The median time to valve intervention was 1.8 months (Q1-Q3: 0.63-5.0 months). In the 36 patients who had MV intervention, 24 had concomitant AVR and MV intervention, 10 had MV intervention without AVR, 1 patient had M-TEER followed later by transcatheter AVR, and another had AVR then developed progression of MR severity requiring MV surgery 5 years later. In those who had MV intervention without AVR, the AR volume was ≤40 mL in all 10 patients. In the 363 patients who underwent AVR, the main indication was symptoms in 159 patients (43.8%), LVEF <50% in 26 (7.1%), LV remodeling criteria in 158 (43.5%), and aortic aneurysm surgery in 20 patients (5.5%). All who underwent MV intervention or AV/MV intervention were symptomatic; and 9 of 36 patients (25%) had advanced NYHA functional class III/IV symptoms. By contrast, 43 of 363 patients (11.8%) undergoing isolated AVR had NYHA functional class III/IV symptoms at the time of CMR.

**OUTCOMES IN THE TOTAL STUDY COHORT.** After a median follow-up of 3.0 years (Q1-Q3: 1.1-5.6 years), there were 152 deaths (17.2%) and 54 HF hospitalizations (6.1%). On univariable Cox regression analysis, presence of ≥ moderate MR was associated with a higher hazard for death (HR: 2.77; 95% CI: 1.91-4.01; $P < 0.001$), and the secondary outcome (HR: 2.62; 95% CI: 1.87-3.67; $P < 0.001$). The MR fraction as a continuous variable was significantly associated with the primary outcome (HR per 5% increase: 1.16; 95% CI: 1.05-1.28; $P = 0.002$) and the secondary outcome (HR per 5% increase: 1.11; 95% CI: 1.02-1.21; $P = 0.01$).

Restricted cubic spline analysis censored at MV intervention showed that the HR for all cause death increased in a linear fashion for MR fraction, and survival curves adjusted for age and sex demonstrated a higher risk for the primary and secondary outcomes according to the presence of concomitant ≥ moderate MR (Figure 3). Consistent findings were noted in the propensity score matched cohort (Figure 4). The 5-year predicted outcomes according to grades

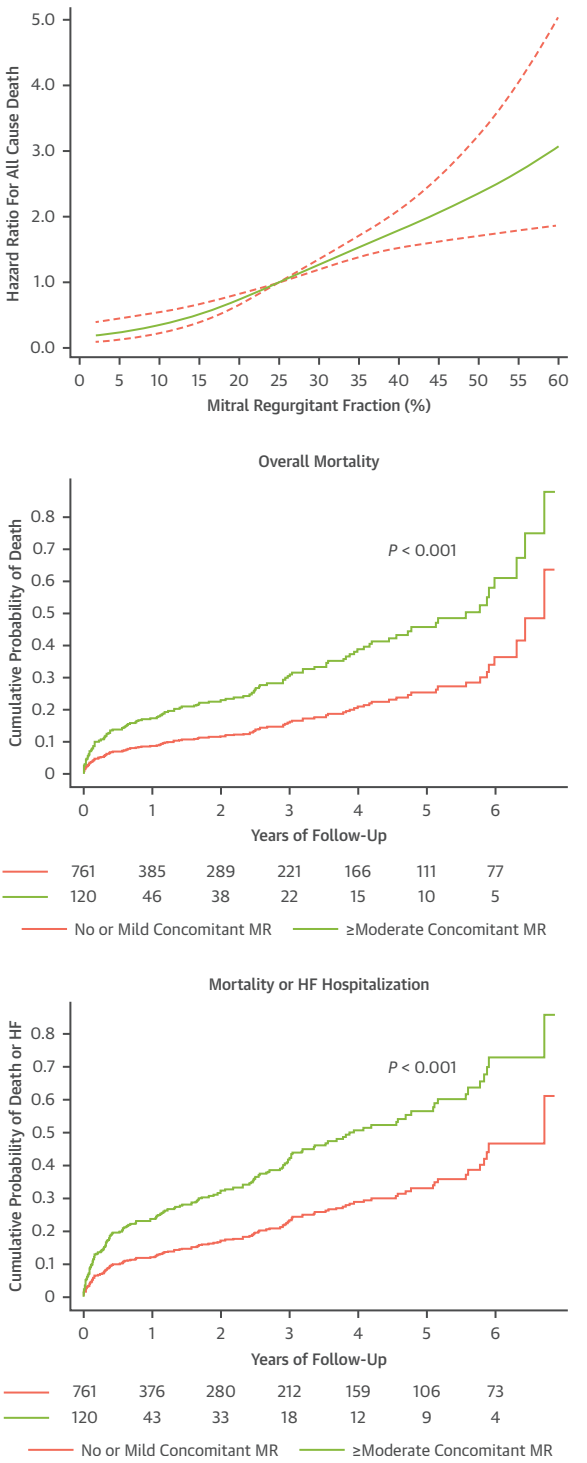
of AR fraction and MR fraction are displayed in a 3-dimensional graph in **Figure 5**, showing a continuous increase in event rates with increasing AR and MR fraction, with the highest risk in patients with high AR and MR fractions.

Outcomes according to etiology of MR in patients with combined AR/MR are shown in Supplemental Figure 1. Patients with secondary or mixed etiology MR were at higher risk of adverse outcomes compared with patients with primary MR and MR with a structurally normal mitral valve. Outcomes according to MV intervention vs medical surveillance are shown in Supplemental Figure 2. Patients with ≥ moderate MR under medical surveillance were at the highest risk, whereas patients with ≥ moderate MR who underwent MV intervention were at intermediate risk compared with patients with no or mild MR. In adjusted analysis for age, sex, AVR, and NYHA functional class, patients with ≥ moderate MR who underwent MV intervention were at similar risk as those with isolated AR.

Echocardiography was available within 6 months of CMR in 626 of 915 patients (68.4%) and the median time between the 2 studies was 12 days. The exact grade agreement between echocardiography and CMR on AR severity was 40.7%, Kappa = 0.16; $P < 0.001$. The agreement between echocardiography and CMR on MR severity grading was 66.8%, Kappa 0.41; $P < 0.001$ (Supplemental Figure 3). Kaplan-Meier survival curves according to MR severity by echocardiography are shown in Supplemental Figure S4, and showed overall consistent findings with the main results.

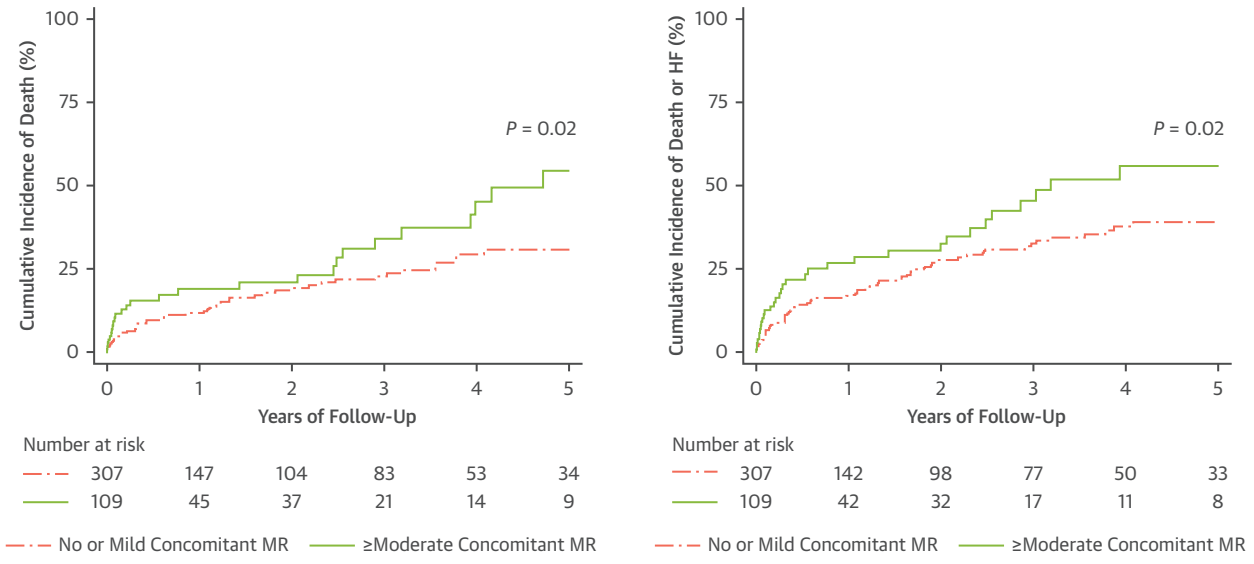
**OUTCOMES OF PATIENTS WITH COMBINED MODERATE AR/MODERATE MR.** Excluding patients with NYHA functional class III/IV symptoms, we found that asymptomatic or mildly symptomatic patients with combined moderate AR and moderate MR had a higher hazard for the primary and secondary outcomes while under medical surveillance, compared with patients with isolated AR (**Figure 6**). Consistent differences were noted in the propensity matched cohort (**Figure 7**). On multivariable Cox regression analysis (**Table 4**), patients with combined moderate AR/MR were at higher risk for the primary and secondary outcomes in adjusted analysis for age, sex, EuroSCORE II, diabetes mellitus, indexed LVESV, and LVEF (HR for the primary outcome: 2.20; 95% CI: 1.31-3.67; $P = 0.003$; HR for the secondary composite outcome: 1.76; 95% CI: 1.09-2.85; $P = 0.02$). Excluding patients with history of CAD and ischemic pattern LV scar demonstrated that patients with combined AR/MR were at higher risk of the primary

**FIGURE 3 Outcomes in Patients With Isolated AR and Combined AR/MR**




Cubic spline curves for the HR for all cause death against MR fraction values (top). Cumulative probability for the outcome of death (middle) and the composite of death or heart failure (HF) (bottom), adjusted for age and sex and stratified by concomitant MR categories. Abbreviations as in **Figure 1**.

**FIGURE 4 Outcomes in the Propensity Score–Matched Cohort**




Cumulative probability for the outcome of death (left) and the composite of death or HF (right) and stratified by concomitant MR categories. Abbreviations as in Figures 1 and 3.

and secondary outcomes in adjusted analysis (Table 4).

Sensitivity analyses using the current criteria for moderate MR are in the Supplemental Appendix (Supplemental Table 4) and were consistent with the primary results. An additional sensitivity analysis evaluating outcomes for the total duration of follow-up and adjusting for aortic valve/MV intervention is shown in Supplemental Table 5. The results were also consistent with the primary findings. Female sex was independently associated with the secondary outcome in multivariable analysis, and we evaluated the clinical and CMR findings of patients with combined AR/MR stratified by sex (Supplemental Tables 6 and 7). Women had smaller median LV volumes in conjunction with smaller AR volume and similar AR fraction as men. The median LVEF was similar, and the burden of symptoms was overall not significantly different between men and women. Mitral regurgitation volume was slightly lower in women, and MR fraction was not significantly different between men and women. The absolute rates of aortic and mitral intervention were not significantly different between men and women.

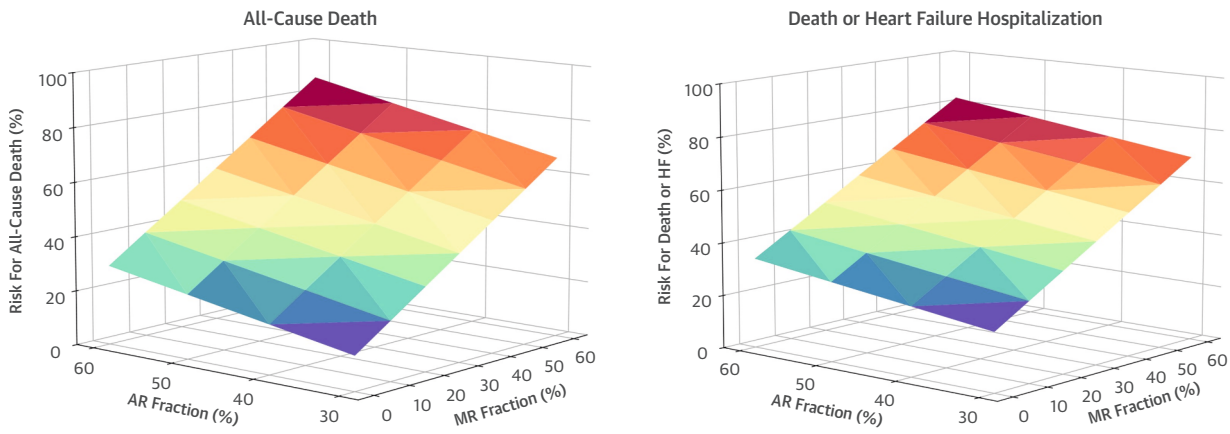
**MR SEVERITY IN PATIENTS WITH COMBINED AR/MR AFTER SURGERY.** In the 130 patients with combined AR and ≥ moderate MR, 24 patients underwent AVR and MV intervention (combined surgery or staged transcatheter intervention), 12 patients underwent MV intervention without AVR, 35 underwent isolated AVR, 51 were recommended medical surveillance, and 7 patients were lost to follow-up.

In the 35 patients with AR/MR who underwent isolated AVR, follow-up echocardiography showed persistent moderate MR in 4 patients, and reduction to mild MR in the remainder. The MR etiology in those with improved MR severity after isolated AVR was secondary ventricular or mixed etiology (whereas the primary MV prolapse/flail patients underwent MV intervention).

## DISCUSSION

Our study highlights patients with combined AR/MR as a unique high-risk population with a higher burden of comorbidities, symptoms, and greater extent of LV remodeling compared with isolated chronic AR. In asymptomatic or minimally symptomatic patients, patients with combined moderate AR and MR were at a higher hazard for mortality and HF under medical surveillance, after adjustments for clinical and imaging findings. We found that coexisting MR with AR has an effect on LV volumes and systolic performance reflected by pronounced increases of LV volumes and lower ejection fraction, particularly at high grades of regurgitation

**FIGURE 5** **Outcomes Based on AR and MR Severity**

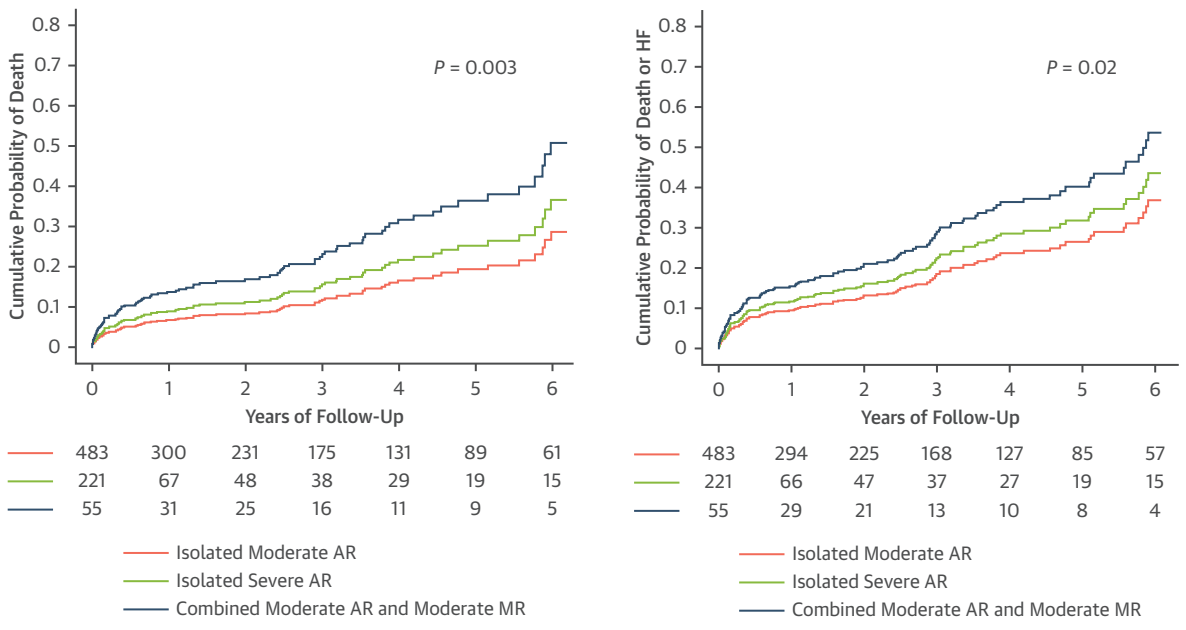



Three-dimensional plot of the 5-year risk of death (left) and death or HF (right) across degrees of AR fraction and MR fraction. Abbreviations as in Figures 1 and 3.

(Central Illustration). Due to its independent and reproducible quantitation of regurgitant lesions, as well as accurate assessment of ventricular volumes, CMR is well positioned for evaluation of patients with combined AR/MR, particularly when echocardiographic quantitation is uncertain or challenging.

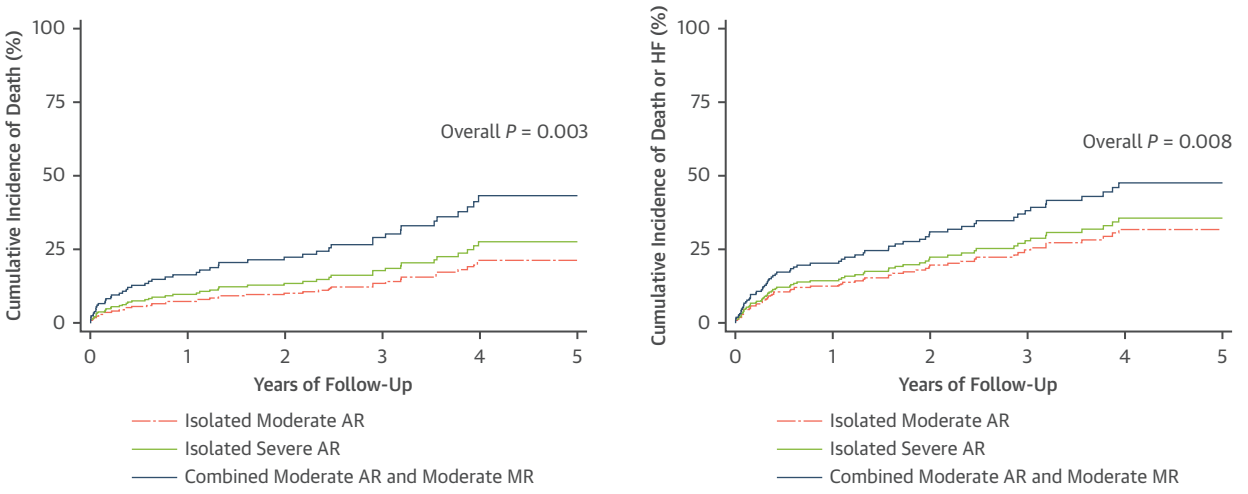
Recent studies suggest that the population of multivalvular heart disease is expected to grow,

**FIGURE 6** **Adjusted Cumulative Probability of Adverse Outcomes Based on Grades of AR and Concomitant MR, in Asymptomatic or Minimally Symptomatic Patients**




Adjusted cumulative probability for outcome of death (left) and the composite of death or heart failure (right) under medical surveillance in patients with NYHA functional class I and II. Adjustment made for age, sex, diabetes, EuroSCORE II, LVEF, and indexed LVESV. Abbreviations as in Figures 1, 2, and 3.

**FIGURE 7 Adjusted Cumulative Incidence of Adverse Outcomes Based on Grades of AR and Concomitant MR, in Asymptomatic or Minimally Symptomatic Patients of the Propensity Matched Cohort**



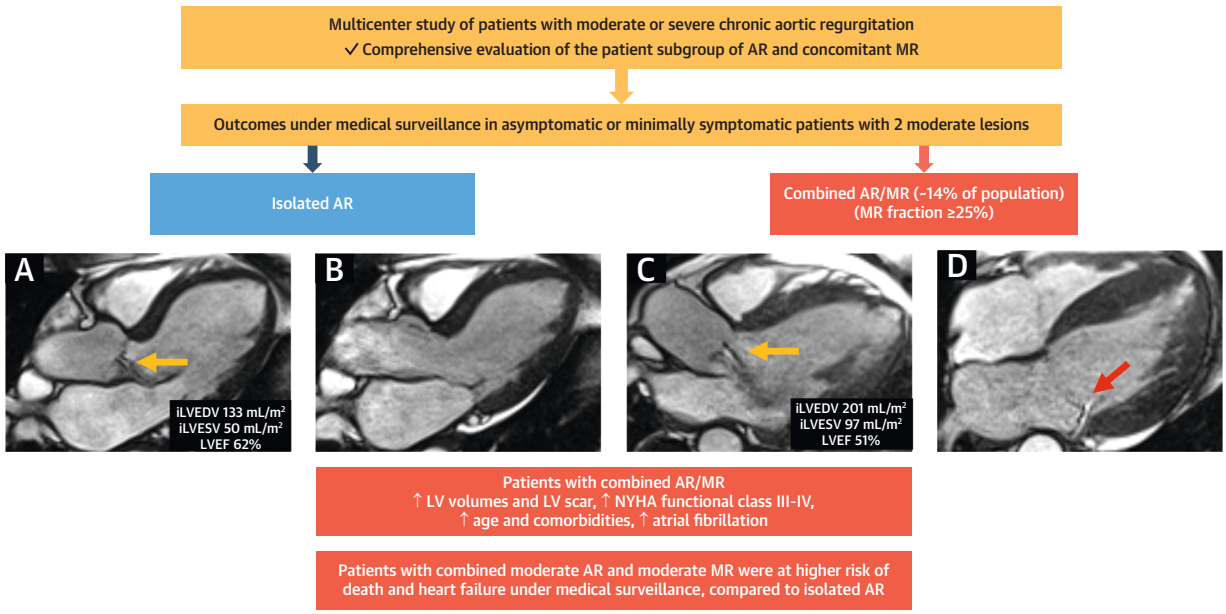

Adjusted cumulative incidence for outcome of death (left) and the composite of death or heart failure (right) under medical surveillance in patients with NYHA functional class I and II. Adjusted for the same variables as Figure 6. Abbreviations as in Figures 1 and 3.

**TABLE 4 Multivariable Cox Regression Analysis for the Primary Outcome of All-Cause Death, and the Secondary Outcome of All-Cause Death or Heart Failure Hospitalization**

| | All-Cause Death (n = 112) | | Death or Heart Failure (n = 151) | |
|---|---|---|---|---|
| | HR (95% CI) | *P* Value | HR (95% CI) | *P* Value |
| Multivariable models in the entire cohort | | | | |
| Age | 1.04 (1.03-1.06) | <0.001 | 1.03 (1.02-1.04) | <0.001 |
| Female | 1.48 (0.94-2.33) | 0.092 | 1.59 (1.06-2.39) | 0.024 |
| EuroSCORE II | 1.06 (1.02-1.11) | 0.004 | 1.05 (1.01-1.09) | 0.011 |
| Diabetes mellitus | 1.35 (0.81-2.27) | 0.248 | 1.50 (0.95-2.36) | 0.082 |
| LVEF | 0.99 (0.97-1.02) | 0.694 | 0.99 (0.96-1.01) | 0.413 |
| Indexed LVESV | 1.01 (0.99-1.02) | 0.435 | 1.01 (0.99-1.02) | 0.206 |
| Regurgitation severity | | | | |
| Isolated moderate AR | Reference | | Reference | |
| Isolated severe AR | 1.15 (0.68-1.97) | 0.600 | 1.11 (0.70-1.78) | 0.658 |
| Moderate AR plus moderate MR | 2.20 (1.31-3.67) | 0.003 | 1.76 (1.09-2.85) | 0.021 |
| | **All-Cause Death (n = 77)** | | **Death or Heart Failure (n = 93)** | |
| | **HR (95% CI)** | ***P* Value** | **HR (95% CI)** | ***P* Value** |
| Multivariable models excluding patients with CAD or ischemic LV scar | | | | |
| Age | 1.04 (1.02-1.06) | <0.001 | 1.03 (1.02-1.05) | <0.001 |
| Female | 1.49 (0.86-2.58) | 0.15 | 1.64 (1.00-2.70) | 0.05 |
| EuroSCORE II | 1.06 (1.01-1.11) | 0.02 | 1.04 (1.00-1.09) | 0.07 |
| Diabetes mellitus | 1.95 (1.00-3.80) | 0.05 | 1.90 (1.02-3.55) | 0.04 |
| LVEF | 1.00 (0.97-1.04) | 0.87 | 1.00 (0.96-1.03) | 0.93 |
| Indexed LVESV | 1.01 (0.99-1.03) | 0.53 | 1.01 (0.99-1.03) | 0.25 |
| Regurgitation severity | | | | |
| Isolated moderate AR | Reference | | Reference | |
| Isolated severe AR | 1.16 (0.64-2.14) | 0.62 | 1.19 (0.69-2.05) | 0.53 |
| Moderate AR plus moderate MR | 2.65 (1.23-5.70) | 0.01 | 2.64 (1.28-5.45) | 0.01 |

Abbreviations as in Tables 1 and 3.

**CENTRAL ILLUSTRATION** **Overview of Study Findings and Case Examples**




**Malahfji M, et al. JACC Cardiovasc Imaging. 2026;19(2):180–193.**

(A, B) Examples of a patient with isolated aortic regurgitation (AR). (C, D) Examples of a patient with combined AR/mitral regurgitation (MR). Yellow arrows point to the AR jet, and red arrow points to the MR jet. iLVEDV = indexed left ventricular end-diastolic volume; iLVESV = indexed left ventricular end systolic volume; LV = left ventricular; LVEF = left ventricular ejection fraction.

particularly in older adults. In a community screening study,[1] combined ≥ mild AR/MR was present in 25% of participants who were found to have AR on screening. Although many of these lesions may not advance to significant disease, increasing life expectancy may result in a higher prevalence of elderly individuals with hemodynamically significant combined AR/MR, who are often at high risk for surgery and can have a challenging symptom assessment.

The study highlights the varied etiologies of MR in the AR population, and challenges of treatment decisions of patients with combined AR/MR. In patients who underwent AVR and had ≥ moderate MR on CMR, 24 of 59 (41.1%) had a mitral intervention. Although guidelines recommend considering intervention in those with moderate or severe valvular disease when undergoing surgery for other indications, the recommendation is primarily based on expert opinion. One factor that may have influenced the decision to intervene is whether the MR was primary or secondary. Secondary MR due to isolated LV dilation could improve with correction of AR, but the proportion of patients whose MR improves, and the degree of improvement has varied in existing literature, which primarily studied MR combined with aortic stenosis. In a subset of patients with combined AR and ≥ moderate MR who underwent isolated AVR, most patients with moderate—mostly secondary—MR appear to have improved MR severity after isolated AVR, but this requires further study.

**CLINICAL IMPLICATIONS.** Given the recent progress in transcatheter therapies for both AR and MR, further investigation is warranted for patients with multivalvular disease, who are often at high risk for surgery, and quantitation of regurgitation severity and LV remodeling should be emphasized. Thresholds for defining hemodynamically significant MR in this population may be lower than the isolated MR population. Our findings suggest that patients with ≥ moderate primary MR would benefit from concomitant MV repair during AVR as recommended by the guidelines, as the MR is less likely to improve with isolated AVR. Treatment of patients with AR and secondary MR needs to be more individualized through a heart team discussion, where patients with AR and secondary severe MR (perhaps those with concomitant leaflet disease or ischemic MR) should be considered for double surgery with AVR and MV

intervention/replacement; whereas patients with AR and secondary MR with isolated annular dilatation can potentially undergo isolated AVR; and then MR could be reassessed for improvement (transcatheter or surgical intervention then considered for persistent MR). In view of our findings, strategies for early identification and referral of patients with multivalvular disease should be emphasized to avoid late referrals for intervention.

**STUDY LIMITATIONS.** Patients in this study were a select group referred to tertiary centers and to undergo CMR, and selection biases may apply beyond the general AR population. However, guidelines recommend considering CMR in patients with multivalvular disease, particularly when echocardiographic or clinical assessment are uncertain.[9] We note that the prevalence of AR/MR was similar in our study compared with echocardiography-based studies,[7] along with similar findings of patient differences between isolated AR and combined AR/MR. Patients with AR/MR had advanced symptoms, LV remodeling, and a higher burden of comorbidities reflecting the delays in their evaluation and treatment, and although adjustment for confounders and propensity score-matched analyses were performed, residual confounding cannot be excluded.

The quantitation of AR/MR using CMR relies on volumetric assessment and phase contrast imaging primarily. Although they are highly reproducible and acquired independently, prompting the guidelines recommendations, quantitation of combined AR/MR is less established given the lack of data in this area. The SCMR Registry participation agreement does not encompass sharing of echocardiographic images, and systematic evaluation of echo findings could not be done in a core lab fashion. However, our outcomes findings based on echo were overall consistent with the CMR findings. Because management decisions were made by physicians not blinded to CMR results, it is possible that CMR findings influenced the ultimate decision to intervene on the MV and/or the aortic valve. However, we note that thresholds for intervention based on CMR findings are not yet established during the study. All patients with AR/MR who underwent MV intervention had symptoms as the main indication rather than LV remodeling or severity of AR and/or MR. Due to the relatively limited number of patients with combined moderate AR and moderate MR, we could not comprehensively evaluate subgroups of moderate MR (primary vs secondary). However, given the potential benefit of intervention in secondary MR—after medical optimization—based on randomized trial findings,[14] both outcomes of primary and secondary MR are still relevant for further consideration in this understudied cohort. The study spans an extended period of time during which advancements in medical therapy of HF were made. Medical therapy with sodium-glucose cotransporter 2 inhibitors appears to have a positive effect on secondary MR.[15] We did not account for new medical therapies' introduction and potential association with outcomes; prospective studies to evaluate their potential effects on the progression and outcomes of multivalvular disease should be considered. Finally, due to lack of systematic follow-up with CMR in most patients, we were not able to fully evaluate the time course of progression of MR severity preoperatively or its course after isolated AR surgery. Future research will be needed to address these important questions.

## CONCLUSIONS

The presence of combined AR and MR on CMR is associated with a greater extent of ventricular remodeling and increased hazard for adverse outcomes, compared to isolated AR. Asymptomatic or minimally symptomatic patients with combined moderate AR and MR under medical surveillance are at higher risk for death and HF, and warrant further study.

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## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** The presence of combined AR and MR is associated with a greater extent of ventricular remodeling and increased hazard for adverse outcomes, compared with isolated AR. Asymptomatic patients with 2 moderate lesions of AR and MR are at higher risk for death and heart failure under medical surveillance, relative to isolated moderate or severe AR.

**TRANSLATIONAL OUTLOOK:** Further research is needed to study the course of mitral regurgitation after isolated aortic regurgitation correction, and how to best implement medical and surgical therapies—and their timing—in patients with combined moderate AR and MR.

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**KEY WORDS** aortic regurgitation, cardiac magnetic resonance, cluster analysis, machine learning

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