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ORIGINAL INVESTIGATIONS

Concomitant Mitral Regurgitation in Patients With Chronic Aortic Regurgitation

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ABSTRACT

BACKGROUND Etiology, mechanisms, and survival of mitral regurgitation (MR) plus hemodynamically-significant chronic aortic regurgitation (AR) are mostly unknown.

OBJECTIVES The purpose of this study was to investigate the prevalence, mechanisms, etiologies, and survival impact of coexistent ≥ moderate MR in AR patients.

METHODS Consecutive patients with ≥ moderate-severe AR were retrospectively identified between 2004 and 2019.

RESULTS Of 1,239 eligible patients (61 ± 18 years, 80% men), 1,072 (86%) had pure AR, and 167 (14%) had AR + MR (9% functional mitral regurgitation [FMR] [84% nonischemic] and 5% organic mitral regurgitation [OMR] [62% degenerative]). At baseline transthoracic echocardiogram, pure AR versus AR + OMR versus AR + FMR exhibited differences in age (59 ± 18, 62 ± 16, and 73 ± 14 years, respectively), female sex (18%, 27%, and 39%, respectively), symptoms (36%, 41%, and 64%, respectively), atrial fibrillation (5%, 17%, and 36%, respectively), left ventricular (LV) ejection fraction (59%, 58%, and 46%, respectively), LV end-systolic dimension and volume index, ≥ moderate tricuspid regurgitation (TR) (7%, 35%, and 53%, respectively), and right ventricular systolic pressure (32 ± 11, 45 ± 15, and 50 ± 14 mm Hg, respectively), all $p < 0.0001$. After a median follow-up of 5.2 years (interquartile range: 2.2 to 10.0 years) and adjusting for demographics, New York Heart Association functional class, aortic valve surgery, LV ejection fraction, LV end-systolic dimension and volume index, presence of FMR was independently associated with all-cause mortality ($p \leq 0.004$). Compared with pure AR, AR + MR + TR exhibited the highest adjusted risk of death (2.4-fold; $p < 0.0001$). When compared with expected population survival, excess mortality risks of pure AR, AR + OMR, and AR + FMR were 1.25-fold, 1.76-fold, and 2.34-fold, respectively (all $p \leq 0.02$).

CONCLUSIONS In hemodynamically significant AR, coexistent MR is not uncommon (approximately 14%) and mostly comprises FMR and less commonly OMR. As compared with pure AR, AR + MR + TR exhibit the largest mortality risk. Both AR + OMR and AR + FMR carry a survival penalty compared with the general population, but AR + FMR is associated with the largest excess mortality and represents an advanced stage within the AR clinical spectrum.
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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

AR = hemodynamically-significant chronic aortic regurgitation

AVS = aortic valve surgery

LVEF = left ventricular ejection fraction

LVESDi = left ventricular end-systolic diameter index

MR = mitral regurgitation

TTE = transthoracic echocardiogram

Patients with significant left-sided valvular disease may carry a survival penalty (1), particularly when "downstream" pathophysiological cardiac consequences arise. For example, in patients with severe aortic stenosis (AS), the presence of ≥ moderate mitral regurgitation (MR) represents "disease progression" with associated poor prognosis (2,3). Patients with pure, hemodynamically significant chronic aortic regurgitation (AR) incur excess mortality (4). However, unlike AS, there is no contemporary textbook description of downstream cardiac consequences of AR beyond those specifically related to the left ventricle (i.e., dilatation and systolic dysfunction) (5,6); thus, determining whether MR can occur concomitantly or in advanced stages of AR has remained largely neglected. Furthermore, whether patients with significant AR and MR carry a survival penalty is mostly unknown because most studies in AR excluded patients with ≥ moderate MR (4,7). One exception is the study by Pai et al. (8), which explored older decades (i.e., 1990s to 2000s) and reported an inflated prevalence of coexistent ≥ moderate MR (45%) in AR patients, possibly due to a limited/nonintegrated definition of severe AR. In addition, it did not define the etiology/mechanisms of MR, yet reported worse prognosis in those with combined MR and AR. In AS, clinicians have become more aware of the impact of MR on survival because of the increased use of transcatheter AV replacement. Most studies, however, do not have details regarding quantitative MR assessment, etiologies, and mechanisms of MR (2,3,9), making it difficult to identify the prevalence of specific MR types.

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Because the pathophysiological hallmark in patients with AR is a dilated left ventricle, which may tether mitral leaflets resulting in functional mitral regurgitation (FMR), we hypothesize that MR mechanisms in AR may be different from those in AS, which commonly presents with normal left ventricular (LV) size and function and various degrees of mitral leaflet or annular calcification (9).

Therefore, in patients with ≥ moderate-severe chronic AR, we sought to: 1) describe the prevalence, etiologies, and mechanisms of coexistent ≥ moderate MR; and 2) analyze survival and its determinants in patients with AR + MR.

METHODS

STUDY POPULATION AND CLINICAL DATA. Between 2004 and 2019, all consecutive patients age ≥18 years with ≥ moderate-severe chronic AR by transthoracic echocardiogram (TTE) were retrospectively identified from our electronic echo database. All cases were manually reviewed to determine eligibility. Exclusion criteria included: no research authorization, > mild mitral stenosis, > mild AS, prior mitral/aortic surgery, complex cyanotic congenital heart disease, carcinoid heart disease, and acute AR (dissection, trauma, active endocarditis) (Supplemental Figure 1). Non-U.S. residents were excluded due to incomplete follow-up. After exclusions, 1,239 patients constituted the study cohort (820 patients with < moderate concomitant MR belong to our previous cohort) (10). All patients had comprehensive cardiology and/or cardiovascular surgery evaluations within 30 days of TTE. Baseline symptoms, independently recorded by treating physicians, were meticulously abstracted from the electronic medical record. Asymptomatic patients were those without typical symptoms (heart failure symptoms, chest pain, dyspnea, and exercise intolerance). Patients with atypical symptoms (i.e., palpitations, fatigue) were also considered asymptomatic. Comorbid conditions recorded during AR consultation were electronically extracted using International Classification of Diseases-9th and -10th revision codes. Charlson comorbidity index was calculated. Ischemic heart disease was defined as prior myocardial infarction, coronary artery bypass grafting, coronary artery disease, or history of ischemic cardiomyopathy.

This study was approved by the institutional review board.

ECHOCARDIOGRAPHY. In patients with multiple TTEs, the first eligible study was used as baseline for analysis. TTE was performed by trained sonographers and reviewed by cardiologists with level III echocardiography training, using commercially available echocardiography systems. LV volumes were derived from the biplane disk-summation method or single-plane if biplane not feasible (11). Other chamber quantification, quantitative (effective regurgitant orifice area and regurgitant volume [RVol]), and semiquantitative measurements (vena contracta width, time-velocity integral of descending aorta reversed-flow, and pulmonary vein flow reversal) were performed using an integrated, comprehensive approach according to guidelines (11,12).

Mechanisms and etiologies of MR, including mitral leaflet motion by the Carpentier classification (13), were determined by de novo review of electronically stored TTE images by experienced cardiologists (L.T.Y. and H.I.M.) as previously described (14): MR due to structurally abnormal mitral leaflets (i.e.,

prolapse, flail, calcification, endocarditis, congenital defects) was defined as organic mitral regurgitation (OMR) while MR due to LV/left atrial (LA) remodeling (i.e., ischemic/nonischemic cardiomyopathy, dilated annulus, atrial fibrillation [AF]) was defined as FMR. The etiologies of MR were determined also based on clinical history and/or intraoperative and pathological findings, if applicable. Mitral annulus calcification (MAC) was subjectively graded as no, mild, and prominent based on multiple views from TTE, including but not limited to parasternal long- and short-axis views. Definitions regarding mechanisms of AR were as described earlier (15).

OUTCOMES. Our primary endpoint was all-cause death. Observation time was between baseline TTE and death or last follow-up. Mortality status and dates of death and last follow-up were retrieved using electronic medical records. For subjects not known to be deceased, linkage to mortality was done using Accurint (LexisNexis Risk Solutions), a proprietary resource gathering multiple national sources, on November 30, 2019. Subjects who were linked to Accurint and were not found to be deceased were censored on May 31, 2019.

STATISTICAL ANALYSIS. Continuous variables, expressed as mean ± SD or median (interquartile range [IQR]) according to data distribution, were compared using the Student's *t*-test or Wilcoxon rank sum test, as appropriate based on distributional assumptions. Categorical data, presented as count and percentages, were compared using the chi-square test. Generalized linear and logistic regression models, both binary and ordinal, were used to compare continuous and categorical variables, respectively, between groups with adjustment for covariates as needed. Survival was estimated using the Kaplan-Meier method and compared using the log-rank statistic. The primary endpoint of mortality was analyzed using the Cox-proportional hazard model, where variables with clinical and pathophysiological relevance plus univariate p value <0.05 were chosen for multivariable analyses; the time-dependent effect of aortic valve surgery (AVS) was also estimated. Proportional hazards assumptions were evaluated both visually by looking for trends in plots of scaled Schoenfeld residual versus time and formally by testing for correlations between residual and the log of time. Expected mortality was estimated based on the mortality of subjects in the general population of similar age and gender and compared using one sample log-rank test. To compare outcomes in those with significant MR to pure AR alone, a matched group (approximately 1:3 matching based on age, sex, and AR severity) was created using a greedy matching algorithm. All statistical analyses were performed using commercially available software (JMP 11 and SAS 9.4, SAS Institute Inc., Cary, North Carolina). A 2-sided p value <0.05 was considered statistically significant.

RESULTS

BASELINE CHARACTERISTICS. Baseline characteristics are displayed in Table 1. The final study cohort included 1,239 ≥ moderate-severe AR patients (mean age 61 ± 18 years; 80% men), of whom 167 (14%) patients had ≥ moderate MR and the remainder had < moderate or no MR. Patients with AR plus ≥ moderate MR were older, with less bicuspid AV, worse functional class, more AF, more ≥ moderate TR, higher estimated pulmonary pressure, higher resting heart rate, larger LV/LA size (dimensions and volumes), and lower left ventricular ejection fraction (LVEF) (Table 1).

Interestingly, compared with those with pure AR (n = 1,072), patients with ≥ moderate MR had similar AR effective regurgitant orifice area but smaller AR regurgitant volume, likely due to higher baseline heart rate and a smaller stroke volume due to a combination of reduced LVEF and MR. In multivariable analysis adjusted for age, factors independently associated with baseline ≥ moderate MR included: women (odds ratio [OR]: 2.9; 95% confidence interval [CI]: 2.21 to 6.07), AF (OR: 4.1; 95% CI: 1.91 to 6.02), absence of bicuspid aortic valve (OR: 2.3; 95% CI: 1.04 to 3.35), lower LVEF (OR per 1%: 0.97; 95% CI: 0.95 to 0.99), larger LVEDD (OR per 1 mm: 1.05; 95% CI: 1.01 to 1.08), and larger left atrial volume index (LAVi) (OR per 1 mm/m^2: 1.03; 95% CI: 1.02 to 1.06), all p ≤ 0.026.

ETIOLOGY AND MECHANISMS OF MR. Of 167 patients having AR plus ≥ moderate MR, 107 (64%) had AR + FMR while 60 (36%) had AR + OMR (Figure 1). Compared with AR + FMR, AR + OMR patients were younger; were less symptomatic; and had less AF, better LV function, more severe MR, and less severe TR (Table 1). Figure 1 shows MR mechanisms and etiologies. AR + FMR mechanisms based on leaflet movement (13) were type I in 25% and type IIIB in 75%. FMR (n = 107) was largely due to LV remodeling (n = 84 [67 nonischemic and 17 ischemic]) and less frequently due to pure atrial remodeling (n = 23). Of 107 patients with FMR, prominent and mild MAC were noted in 7 and 21 patients, respectively; the remainder (n = 79; 74%) had no MAC.

In AR + OMR patients (n = 60), MR mechanisms were type I in 7%, type II in 62%, type IIIA in 23%,

TABLE 1 Baseline Clinical and Echocardiographic Characteristics in All Patients

	Total (n = 1,239)	Pure AR (n = 1,072)	AR + ≥ Moderate MR (n = 167)	p Value*	AR + FMR (n = 107)	AR + OMR (n = 60)	p Value†
Age, yrs	61 ± 18	59 ± 18	69 ± 16	**<0.0001**	73 ± 14	62 ± 16	**<0.0001**
Women	250 (20)	189 (18)	58 (35)	**<0.0001**	42 (39)	16 (27)	0.09
Systolic blood pressure, mm Hg	130 ± 20	130 ± 20	128 ± 22	0.35	127 ± 23	131 ± 21	0.25
Diastolic blood pressure, mm Hg	63 ± 13	64 ± 13	62 ± 14	0.19	62 ± 15	63 ± 12	0.57
Resting heart rate, beats/min	65 ± 13	64 ± 12	73 ± 16	**<0.0001**	74 ± 15	73 ± 17	0.64
Body surface area, m^2	2.00 ± 0.25	2.01 ± 0.24	1.90 ± 0.25	**<0.0001**	1.85 ± 0.24	2.00 ± 0.26	**0.0005**
Baseline symptoms (n = 1,226)	478 (39)	387 (36)	91 (55)	**<0.0001**	67 (64)	24 (41)	**0.004**
NYHA functional class (n = 1,214)				**0.0003**			0.08
I + II	1,072 (88)	942 (90)	130 (79)		79 (75)	51 (86)	
III + IV	142 (12)	108 (10)	34 (21)		26 (25)	8 (14)	
Medical history							
Hypertension (n = 1,192)	591 (50)	490 (47)	101 (64)	**0.0001**	71 (70)	30 (52)	**0.019**
Diabetes mellitus (n = 1,192)	153 (13)	126 (12)	27 (17)	0.10	19 (19)	8 (14)	0.41
Hyperlipidemia (n = 1,192)	442 (37)	381 (37)	61 (38)	0.71	42 (42)	19 (33)	0.26
Prior myocardial infarction (n = 1,192)	65 (5)	51 (5)	14 (9)	0.06	10 (10)	4 (7)	0.57
Prior CABG (n = 1,192)	45 (4)	33 (3)	12 (8)	**0.01**	10 (10)	2 (3)	0.21
Coronary artery disease (n = 1,192)	113 (9)	85 (8)	28 (18)	**0.0005**	21 (21)	7 (12)	0.15
Atrial fibrillation at time of echo	105 (8)	56 (5)	49 (30)	**<0.0001**	39 (36)	10 (17)	**0.006**
Chronic kidney disease > stage 3 (n = 1,192)	89 (7)	72 (7)	17 (11)	0.11	14 (14)	3 (5)	0.11
Creatinine (n = 1,081)	1.2 ± 0.7	1.2 ± 0.7	1.3 ± 0.9	0.07	1.4 ± 1.0	1.1 ± 0.4	**0.027**
Charlson index (n = 1,192)	1.15 ± 1.31	1.06 ± 1.25	1.74 ± 1.56	**<0.0001**	1.9 ± 1.6	1.5 ± 1.5	0.17
Echo parameters							
Bicuspid aortic valve	399 (32)	377 (36)	22 (13)	**<0.0001**	8 (7)	14 (23)	**0.004**
LV ejection fraction, %	57 ± 10	59 ± 9	50 ± 15	**<0.0001**	46 ± 15	58 ± 11	**<0.0001**
LV ejection fraction <50%	195 (16)	129 (12)	66 (40)	**<0.0001**	55 (51)	11 (18)	**<0.0001**
LVESD, mm (n = 1,192)	41 ± 8	40 ± 7	45 ± 10	**<0.0001**	47 ± 10	42 ± 8	**0.0008**
LVESD >50 mm (n = 1,192)	118 (10)	76 (7)	42 (27)	**<0.0001**	36 (36)	6 (11)	**0.0007**
LVESDi, mm/m^2 (n = 1,192)	20.7 ± 4.3	20.2 ± 3.8	24.1 ± 5.8	**<0.0001**	25.5 ± 5.5	21.5 ± 5.5	**<0.0001**
LVESDi >25 mm/m^2 (n = 1,192)	162 (14)	107 (10)	55 (36)	**<0.0001**	46 (46)	9 (17)	**0.0003**
LVEDD, mm (n = 1,219)	61 ± 7	60 ± 7	63 ± 8	**0.0003**	63 ± 8	63 ± 8	0.78
LVEDD >65 mm (n = 1,219)	274 (22)	221 (21)	53 (33)	**0.001**	35 (33)	18 (32)	0.85
LVEDDi, mm/m^2 (n = 1,218)	30.7 ± 4.3	30.3 ± 4.1	33.3 ± 4.8	**<0.0001**	34.0 ± 4.5	31.9 ± 5.2	**0.010**
LVEDV (disk summation), ml (n = 1,162)‡	210 ± 71	208 ± 68	218 ± 83	0.16	213 ± 83	227 ± 84	0.28
LVEDVi (disk summation), ml/m^2 (n = 1,162)‡	105 ± 32	103 ± 31	113 ± 38	**0.002**	113 ± 39	113 ± 37	0.98
LVESV (disk summation), ml (n = 1,158)‡	83 ± 46	89 ± 41	116 ± 62	**<0.0001**	122 ± 67	105 ± 51	**0.06**
LVESVi (disk summation), ml/m^2 (n = 1,158)‡	46 ± 22	44 ± 20	61 ± 32	**<0.0001**	65 ± 34	53 ± 26	**0.011**
Doppler-derived SVi, ml/m^2 (n = 1,111)	71 ± 19	73 ± 18	58 ± 19	**<0.0001**	56 ± 17	63 ± 21	**0.02**
LAVi, ml/m^2 (n = 1,151)	43 ± 19	40 ± 15	62 ± 27	**<0.0001**	63 ± 25	60 ± 30	0.53
LV mass index, ml/m^2	144 ± 42	141 ± 40	158 ± 46	**<0.0001**	160 ± 46	154 ± 47	0.44
MR EROA, mm^2 (n = 127)	–	–	34 ± 19	–	29 ± 14	43 ± 23	**0.001**
MR RVol (n = 127)	–	–	55 ± 26	–	49 ± 19	66 ± 32	**0.002**
MR severity ≥ moderately-severe	–	–	87 (52)	–	47 (44)	40 (67)	**0.004**
Tricuspid regurgitation ≥ moderate	153 (12)	73 (7)	78 (47)	**<0.0001**	57 (53)	21 (35)	**0.015**
Tricuspid regurgitation velocity >2.8 m/s	227 (18)	137 (13)	90 (54)	**<0.0001**	66 (62)	24 (40)	**0.006**
RVSP, mm Hg (n = 955)	35 ± 13	32 ± 11	48 ± 14	**<0.0001**	50 ± 14	45 ± 15	0.05
E velocity (n = 1,137)	0.76 ± 0.29	0.71 ± 0.25	1.05 ± 0.37	**<0.0001**	0.99 ± 0.31	1.15 ± 0.44	**0.025**
E/e′ (n = 1,096)	12 ± 6	11 ± 5	18 ± 7	**<0.0001**	18 ± 7	17 ± 8	0.28
Aortic annulus, mm (n = 1,224)	26 ± 3	26 ± 3	24 ± 3	**<0.0001**	24 ± 3	25 ± 4	**0.015**
Sinus of Valsalva (n = 1,152)	40 ± 6	41 ± 6	39 ± 7	**0.014**	39 ± 7	39 ± 6	0.71
Mid-ascending aorta, mm (n = 1,112)	41 ± 7	41 ± 7	40 ± 8	0.17	40 ± 9	38 ± 7	0.12

Continued on the next page

and miscellaneous in 8% (including prior endocarditis without perforation in 4 cases). Mitral valve (MV) degeneration was the most common noted in 37 (62%) (flail leaflet in 13 [2 anterior, 9 posterior, and 2 bileaflet] and prolapse in 24 [9 anterior, 7 posterior, and 8 bileaflet]), healed endocarditis in 7, calcification in 5, rheumatic in 4, congenital in 1 (bicuspid AV with double-orifice MV), others

TABLE 1 Continued

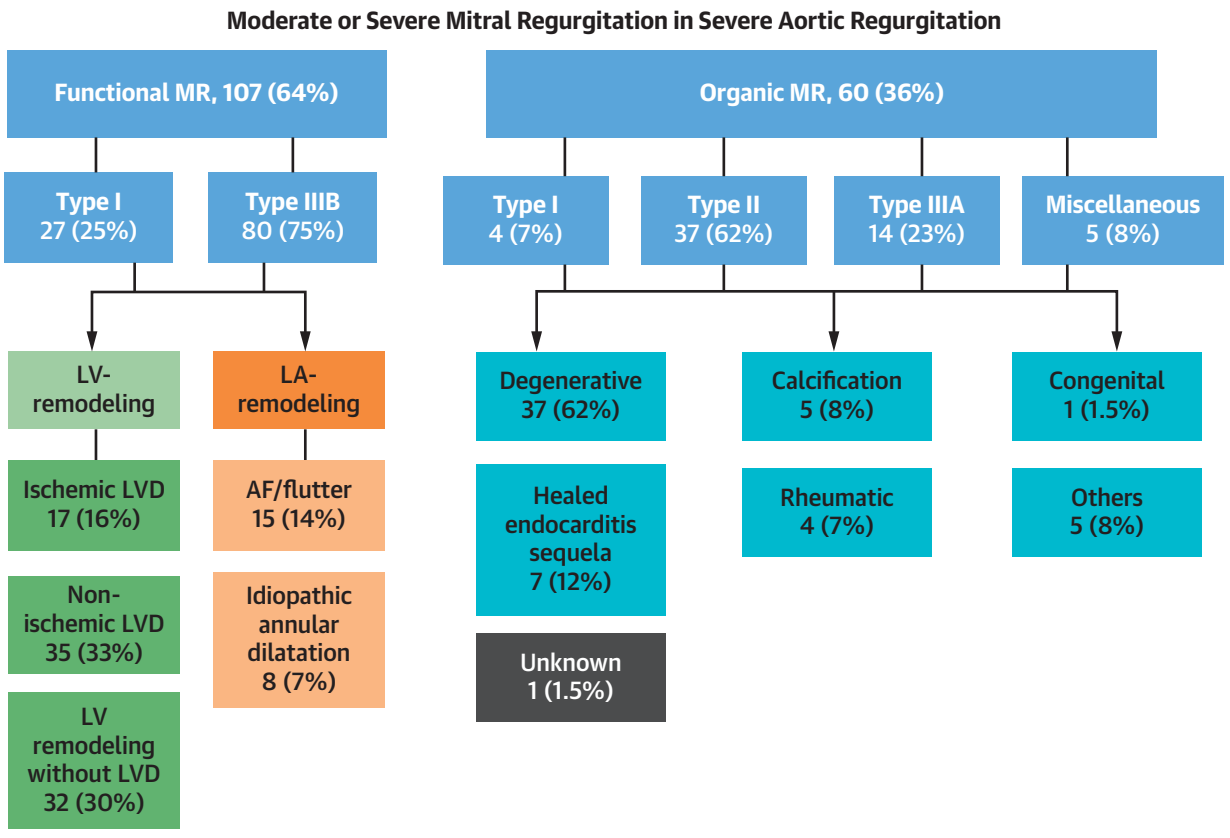
	Total (n = 1,239)	Pure AR (n = 1,072)	AR + ≥ Moderate MR (n = 167)	p Value*	AR + FMR (n = 107)	AR + OMR (n = 60)	p Value†
AR quantification							
Regurgitant volume, ml (n = 1,003)	70 ± 25	70 ± 25	62 ± 21	**0.0003**	60 ± 18	68 ± 30	0.16
EROA, mm^2 (n = 951)	30 ± 12	30 ± 12	31 ± 12	0.16	32 ± 12	30 ± 12	0.58
TVI of reversal flow in descending aorta (n = 973)	15 ± 5	15 ± 5	14 ± 5	**0.04**	13 ± 5	15 ± 5	0.12
Vena contracta, mm (n = 812)	6.0 ± 1.6	6.0 ± 1.6	5.8 ± 1.4	0.42	5.8 ± 1.4	5.9 ± 1.3	0.73
AR severity (severe)	714 (57)	628 (59)	84 (50)	**0.04**	54 (50)	30 (50)	0.95

Values are mean ± SD or n (%). **Bold** p values are significant. *p value for comparison between pure AR and AR + ≥ moderate MR. †p value for comparison between AR + FMR and AR + OMR. ‡LV volumes were derived from biplane and single-plane disk-summation method in 86% and 14%, respectively.

AR = aortic regurgitation; CABG = coronary artery bypass grafting; E/e' = early mitral diastolic velocity to mitral annulus tissue velocity; EROA = effective regurgitant orifice area; FMR = functional mitral regurgitation; LAVi = left atrial volume index; LV = left ventricular; LVEDD = left ventricular end-diastolic dimension; LVEDDi = left ventricular end-diastolic dimension index; LVEDV = left ventricular end-diastolic volume; LVEDVi = left ventricular end-diastolic volume index; LVESD = left ventricular end-systolic dimension; LVESDi = left ventricular end-systolic dimension index; LVESV = left ventricular end-systolic volume; LVESVi = left ventricular end-systolic volume index; MR = mitral regurgitation; NYHA = New York Heart Association functional class; OMR = organic mitral regurgitation; RVol = regurgitant volume; RVSP = right ventricular systolic pressure; SVi = stroke volume index; TVI = time-velocity integral.

(post-radiation, ergot valve disease, rheumatoid arthritis) in 5, and unknown in 1 (Figure 1). Baseline characteristics according to type of MR are shown in Supplemental Table 1 (type IIIA was excluded due to small sample size); patients with type I MR had the highest prevalence of AF, hypertension, and more severe TR. In contrast, type IIIB patients had the largest LV size, lowest LVEF, and highest

FIGURE 1 Etiology and Mechanisms of ≥ Moderate MR in Patients With Hemodynamically Significant Chronic AR



Mitral regurgitation (MR) was classified as functional MR and organic MR, followed by mechanisms of MR based on Carpentier classification and etiologies. Predominant left ventricular (LV) remodeling is shown in **green**, predominantly atrial remodeling in **orange**, and organic MR etiologies in **teal**. Four patients with prior healed endocarditis were classified as miscellaneous because it was unknown whether the mitral valve was perforated. AF = atrial fibrillation; AR = aortic regurgitation; LA = left atrial; LVD = left ventricular dysfunction.

TABLE 2 Cardiac Remodeling at Interval TTE in Patients With Pure AR Who Developed FMR

	Baseline AR + Type IIIB FMR With a Prior TTE Showing MR < Moderate (n = 34)			Baseline Pure AR With Development of ≥ Moderate FMR at Follow-Up (n = 10)		
	Prior TTE	Baseline TTE	p Value	Baseline TTE	Follow-Up TTE	p Value
LVEF, %	54 ± 12	39 ± 13	<0.0001	55 ± 14	43 ± 17	0.0041
LVEDD, mm	56 ± 7	64 ± 7	<0.0001	59 ± 8	64 ± 11	0.022
LVESD, mm	38 ± 6	51 ± 9	<0.0001	41 ± 8	49 ± 13	0.0012
LVESDi, mm/m^2	21.2 ± 4.2	27.9 ± 6.2	<0.0001	21.8 ± 4.0	26.3 ± 6.5	0.0017
LAVi, ml/m^2	49 ± 19	72 ± 31	0.001	46 ± 13	62 ± 14	0.0001

Values are mean ± SD.
LVEF = left ventricular ejection fraction; other abbreviations as in Table 1.

estimated pulmonary pressure. Of 80 cases with type IIIB FMR at baseline-TTE, 37 had previous TTEs (median of 6.7 years prior to baseline TTE); 34 (92%) cases had < moderate MR and LV/LA were less remodeled (Table 2), suggesting that MR became more severe as the LV gradually enlarged. Likewise, of 206 patients having pure AR at baseline TTE, a follow-up TTE at least 2.5 years from baseline revealed that 10 (5%) patients developed ≥ moderate FMR at follow-up TTE (median of 5.7 years [IQR: 3.2 to 12.1 years] from baseline) accompanied with worse cardiac remodeling (Table 2).

MECHANISMS OF AR. Of 1,239 patients, 7 had quadricuspid AV, 5 had unicuspid AV, and in 80 patients, the mechanism of AR was unknown. In the remaining 1,147 patients, the mechanisms of AR (15) included single mechanisms in 732 (64%) (dilatation of annulus/sinotubular junction in 403, cusp prolapse in 140, cusp restriction/retraction in 150, and cusp fenestration or perforation in 39), and mixed mechanisms (i.e., a combination of the aforementioned) in 415 (36%). Overall, cusp prolapse and dilatation of annulus/sinotubular junction were more common in patients with pure AR compared with those with ≥ moderate MR (both p < 0.0001).

SURGICAL PROCEDURES, TRIGGERS OF SURGERY, AND LV REMODELING. The distribution of surgical procedures is shown in Table 3. At a median follow-up of 5.2 year (IQR: 2.2 to 10.0 years), 650 of 1,239 (52%) patients underwent AVS, including 98 with ≥ moderate MR (of which 74 of 98 had concomitant MV surgery). The 8-year incidence of AVS was higher in those with concomitant MR versus AR alone (70% vs. 55%; p = 0.0005) and higher in OMR versus FMR (91% vs. 54%; p = 0.0003). Those who had pure AR were more likely to have AV repair and aorta surgery, reflected by their younger age and larger root (Table 1). Patients with coexistent OMR had more MV surgery performed, congruent with more severe MR in this subset (Table 1). In multivariable analysis, ≥ moderate-severe MR (OR: 9.82; 95% CI: 2.87 to 33.5; p < 0.0001) was the only factor associated with concomitant MV surgery, while the presence of OMR showed a trend toward concomitant MV surgery (OR: 3.03; 95% CI: 0.86 to 10.65; p = 0.07). Of 98 patients with ≥ moderate MR undergoing AVS without concomitant MV surgery (n = 24), the MR severity at pre-dismissal TTE (median 5 days post-AVS) decreased to ≤ mild-to-moderate in 21 (88%) patients (Table 3). Of 51 FMR patients having AVS,

TABLE 3 Aortic Valve and Concomitant Surgeries

Patients Undergoing AV Surgery in Entire Cohort (n = 650)*				
	Pure AR (n = 552 of 1,072)	AR + FMR (n = 51 of 107)	AR + OMR (n = 47 of 60)	p Value
AV repair	122 (22)	4 (8)	3 (6)	**0.0008**
Aorta surgery	175 (32)	8 (16)	8 (17)	**0.005**
Mitral repair/replacement	10 (2)	32 (63)	42 (89)	**<0.0001**
Tricuspid valve repair/replacement	11 (2)	10 (20)	7 (15)	**<0.0001**
Concomitant CABG	86 (16)	9 (18)	7 (15)	0.91

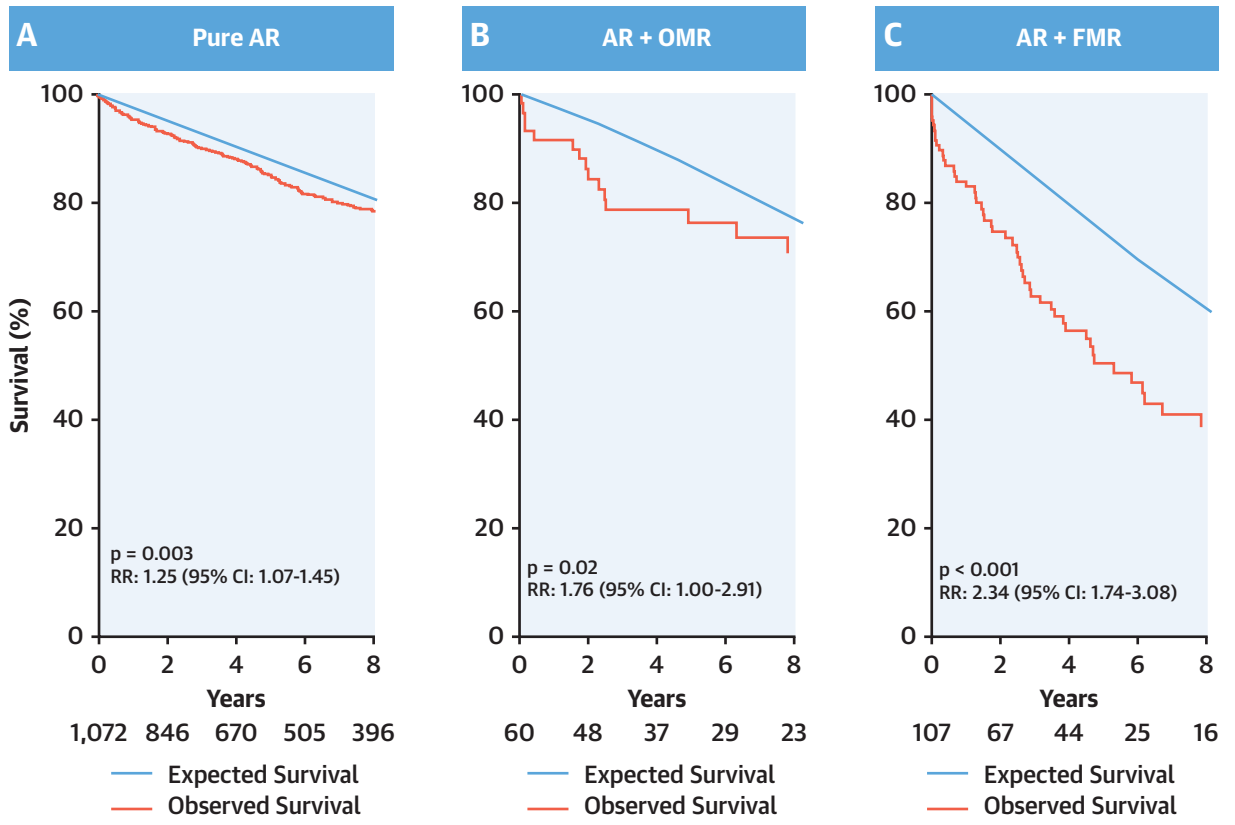
Patients With AR + ≥ Moderate MR Undergoing AV Surgery* (N = 98)			
	Concomitant MV Surgery		
	Yes	No†	p Value
Baseline moderate MR (n = 41)	21 (51) [FMR 13 + OMR 8]‡	20 (49) [FMR 16 + OMR 4]‡	**<0.0001**
Baseline > moderate MR (n = 57)	53 (93) [FMR 19, + OMR 34]‡	4 (7)§ [FMR 3 + OMR 1]‡	

Values are n (%). **Bold** p values are significant. *One patient with OMR undergoing heart transplantation was excluded from this analysis. †Of 24 without concomitant MV surgery, post-AVR pre-dismissal TTE showed no/trivial MR in 4, mild in 7, mild-moderate in 10, moderate in 2, and moderate-severe in 1. ‡The number of patients belonging to FMR or OMR was shown. §Of 3 FMR patients, MR decreased to ≤moderate perioperatively and 1 had transcatheter AV replacement. The MR in OMR patient decreased to mild-moderate perioperatively.
AV = aortic valve; other abbreviations as in Table 1.

FIGURE 2 **LV Remodeling and Surgical Triggers**

LV remodeling was based on transthoracic echocardiograms (TTEs) closest to aortic valve surgery (AVS) (77% the same as baseline TTE). **(A)** At time of AVS, AR + functional mitral regurgitation (FMR) had the largest left ventricular end-systolic diameter index (LVESDi) and lowest left ventricular ejection fraction (LVEF). Surgical triggers in the entire cohort **(B)** and asymptomatic patients **(C)** showed similar distribution of Class I, Class II, and early surgery; however, patients with coexistent MR had significantly more symptoms and LVEF <50% as Class I triggers. AR + FMR had largest proportion of LVESDi >20 mm/m^2 and LVESDi >25 mm/m^2. *Asymptomatic patients refers to those who did not have dyspnea, chest pain, or heart failure symptoms at baseline TTEs. LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; OMR = organic mitral regurgitation; other abbreviations as in Figure 1.

FIGURE 3 Expected Versus Observed Survival by AR Patient Type



Excess mortality is expressed as relative risk (RR) and 95% confidence interval (CI) in each panel. When compared with expected population survival, patients with **(A)** pure AR, **(B)** AR + OMR, and **(C)** AR + FMR had incremental excess risk of death. Abbreviations as in Figures 1 and 2.

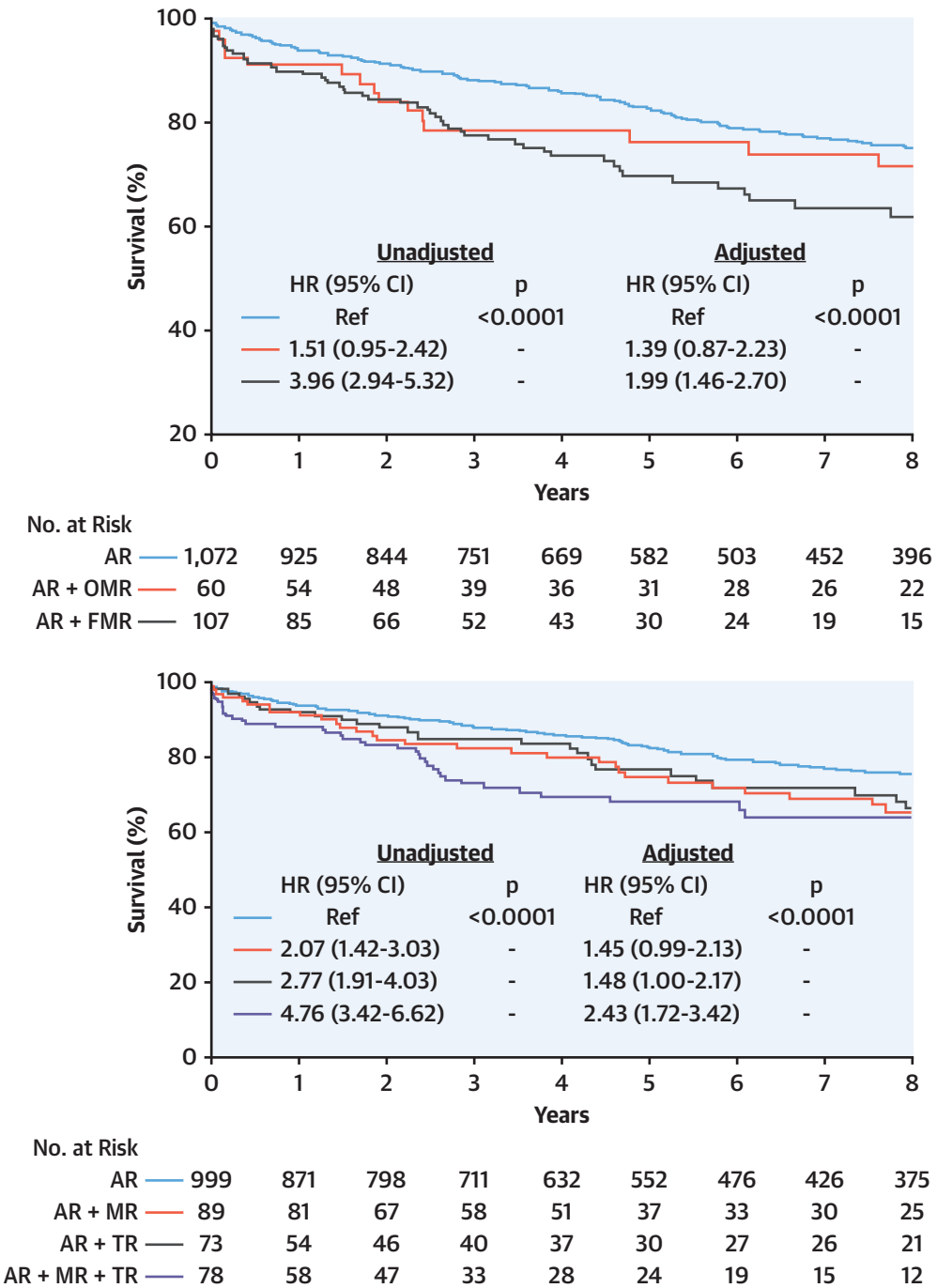
post-AVS MR at follow-up TTE (median 0.8 months [0.2 to 37 months) post-AVS) remained ≥moderate in 5 of 32 patients having concomitant MV surgery versus 5 of 19 patients without MV surgery (p = 0.35).

Figure 2 shows the degree of LV remodeling and surgical triggers in those having AVS. Regarding LV remodeling at the time of AVS (n = 651), preoperative TTEs showed larger left ventricular end-systolic diameter index (LVESDi) and lower LVEF in AR + FMR (Figure 2A). Compared with pure AR, in both the entire cohort and asymptomatic subgroup, AR + OMR and AR + FMR had more "symptoms" (development of new symptoms, typical or atypical) and "LVEF <50%" as Class I triggers for AVS, as well as more LVESDi >25 mm/m^2 (Figures 2B and 2C). AR + FMR had the highest proportion of LVESDi >20 mm/m^2 or >25 mm/m^2, albeit smaller MR quantification (Table 1) than AR + OMR, which suggests late AVS referral for AR in these patients.

SURVIVAL. Median follow-up was 5.2 years (IQR: 2.2 to 10.0 years) and up to 15.6 years, during which 299 died (186 deaths under medical management and 113 deaths after AVS). The 8-year survival in those with pure AR, AR + OMR, and AR + FMR was 78 ± 2%, 71 ± 7%, and 39 ± 6%, respectively. Age- and sex-adjusted Kaplan-Meier curves showed that those with AR + FMR had significant excess death as compared to pure AR (p < 0.0001) (Figure 4). When compared to age- and sex-matched general population, 1.25-fold, 1.76-fold, and 2.34-fold excess mortality was observed in those with pure AR, AR + OMR, and AR + FMR, respectively (all p ≤ 0.02) (Figure 3).

Multivariable modeling of factors associated with death is presented in Table 4. When adjusted for demographics, comorbidities, New York Heart Association functional class, time dependent-AVS, LVEF, LVESDi, and LV end-systolic volume index, presence of ≥ moderate MR or FMR was independently

FIGURE 4 Age- and Sex-Adjusted Survival Curves



(A) After adjustment for age and sex, patients with AR and AR + OMR had similar survival; AR + FMR had 2-fold increased mortality. **(B)** When patients were stratified based on the number of valves involved, those with AR + TR + MR had a 2.4-fold excess risk of death. HR = hazard ratio; other abbreviations as in Figures 1 to 3.

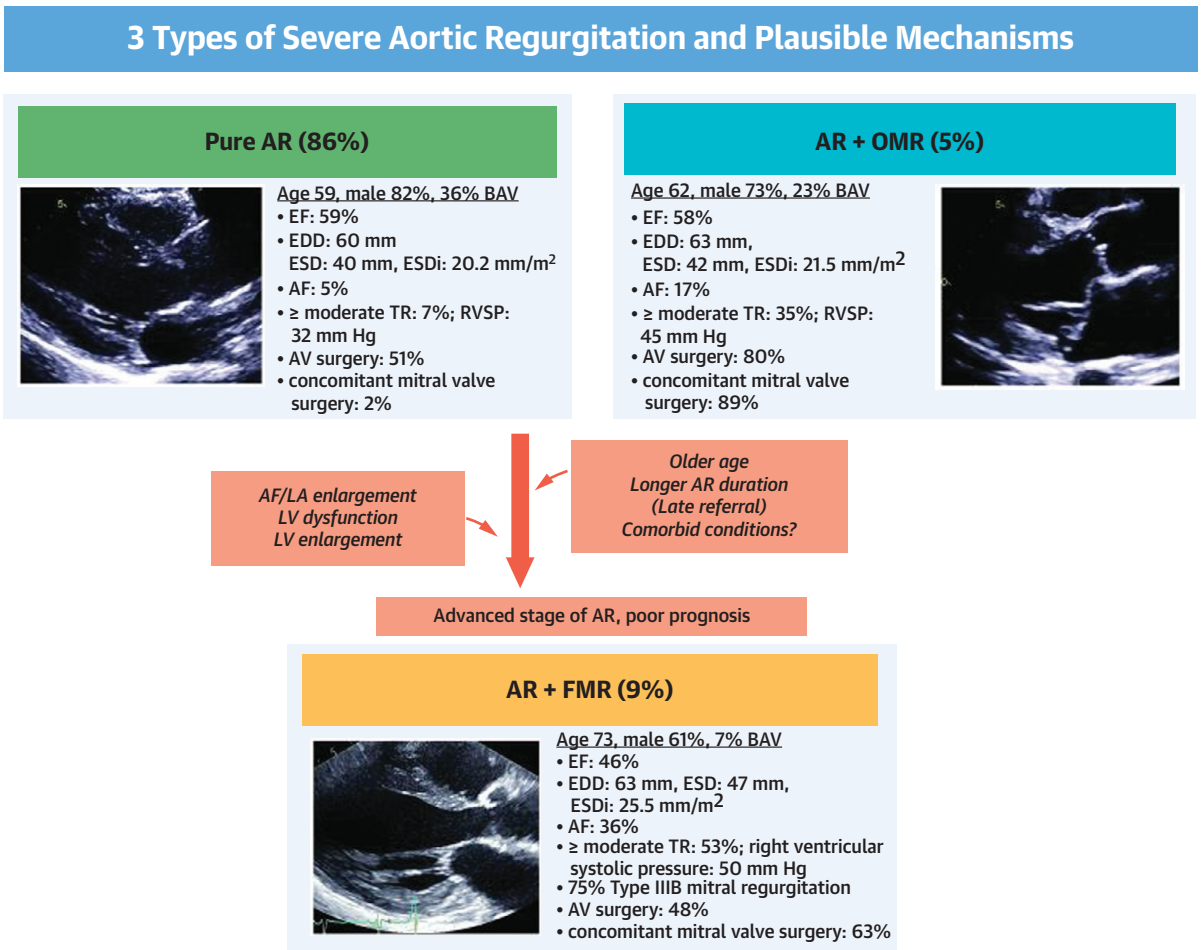
TABLE 4 Multivariate Analyses for Determinants of Survival in the Entire Cohort and Combinations of Mixed Valvular Disease

	HR (95% CI)	p Value
Overall survival (n = 1,239; 299 deaths)		
Pure AR, AR + OMR, or AR + FMR		
Model 1: LVEF model*†		
Age	1.06 (1.04–1.07)	**<0.0001**
Male	1.01 (0.77–1.32)	0.96
Charlson score	1.29 (1.19–1.39)	**<0.0001**
LV ejection fraction per 10%	0.90 (0.82–0.99)	**0.04**
Time dependent AV surgery	0.63 (0.49–0.82)	**0.0005**
NYHA functional class III/IV	2.54 (1.90–3.39)	**<0.0001**
Pure AR	Ref	Ref
AR + OMR	1.23 (0.76–1.99)	0.50
AR + FMR	1.70 (1.22–2.37)	**0.002**
Model 2: LVESDi model*		
Age	1.06 (1.04–1.07)	**<0.0001**
Male	1.04 (0.80–1.36)	0.78
Charlson score	1.30 (1.20–1.41)	**<0.0001**
LVESDi per 5-mm/m^2 increase	1.17 (1.03–1.32)	**0.02**
Time-dependent AV surgery	0.61 (0.47–0.79)	**0.0002**
NYHA functional class III/IV	2.61 (1.96–3.48)	**<0.0001**
Pure AR	Ref	Ref
AR + OMR	1.15 (0.71–1.87)	0.57
AR + FMR	1.63 (1.16–2.27)	**0.004**
Model 3: LVESVi model*; adjusted for age, sex, Charlson, NYHA functional class III/IV, AV surgery		
LVESVi per 5-ml/m^2 increase	1.03 (1.01–1.06)	**0.009**
Pure AR	Ref	Ref
AR + OMR	1.20 (0.74–1.94)	0.46
AR + FMR	1.67 (1.19–2.34)	**0.003**
Pure AR, AR + MR, AR + TR, or AR + TR + MR		
Model 4: adjusted for age, sex, Charlson, NYHA functional class III/IV, AV surgery, LVEF		
Pure AR	Ref	Ref
AR + MR	1.29 (0.86–1.92)	0.21
AR + TR	1.45 (0.99–2.13)	0.06
AR + TR + MR	2.02 (1.40–2.90)	**0.0002**
Model 5: adjusted for age, sex, Charlson, NYHA functional class III/IV, AV surgery, LVESDi		
Pure AR	Ref	Ref
AR + MR	1.16 (0.77–1.74)	0.48
AR + TR	1.52 (1.04–2.23)	**0.03**
AR + TR + MR	1.99 (1.39–2.85)	**0.0002**
Model 6: adjusted for age, sex, Charlson, NYHA functional class III/IV, AV surgery, LVESVi		
Pure AR	Ref	Ref
AR + MR	1.21 (0.80–1.81)	0.37
AR + TR	1.39 (0.94–2.04)	0.10
AR + TR + MR	2.02 (1.41–2.89)	**0.0001**
Survival in FMR (n = 107; 56 deaths)		
Age	1.04 (1.01–1.06)	**0.01**
NYHA functional class III/IV	3.39 (1.83–6.31)	**0.0001**
Tricuspid regurgitation velocity >2.8 m/s	1.73 (0.94–3.18)	0.08
Charlson score	1.25 (1.02–1.52)	**0.03**
Time dependent AV surgery	0.66 (0.35–1.27)	0.22
Atrial fibrillation‡	2.50 (1.37–4.58)	**0.003**

Bold p values are significant. *When Charlson index was replaced with ischemic heart disease (i.e., coronary artery disease, prior myocardial infarction, or prior coronary artery bypass grafting), similar findings were noted: the hazard ratio (HR) and 95% confidence interval (CI) for AR + FMR was 1.65 (1.18–2.32) in the LVEF model, 1.61 (1.15–2.26) in the LVESDi model, and 1.64 (1.16–2.32) in the LVESVi-model, respectively (both p ≤ 0.006). †The presence of ≥ moderate MR was associated with all-cause death (HR: 1.53; 95% CI: 1.14–2.04) adjusted for age, sex, Charlson, NYHA functional class III/IV, LVEF, and AV surgery. ‡Results were similar when atrial fibrillation was replaced with left atrial volume index (HR per 10 ml/ m^2: 1.19; 95% CI: 1.06–1.32; p = 0.002) except that tricuspid regurgitation velocity >2.8 m/s became significant (p = 0.04).

TR = tricuspid regurgitation; other abbreviations as in Table 1.

CENTRAL ILLUSTRATION **3 Types of Aortic Regurgitation Patients According to Presence of ≥ Moderate Mitral Regurgitation**



Yang, L.-T. et al. J Am Coll Cardiol. 2020;76(3):233-46.

Patients with aortic regurgitation (AR) + functional mitral regurgitation (MR) included older patients and more women than the prior 2 types, had the largest left ventricles, lower LV EF, the highest right heart pressures, and high prevalence of tricuspid regurgitation and atrial fibrillation. AF = atrial fibrillation; AR = aortic regurgitation; AV = aortic valve; BAV = bicuspid aortic valve; EDD = end-diastolic diameter; ESD = end-systolic diameter; ESDi = end-systolic diameter index; EF = ejection fraction; FMR = functional mitral regurgitation; LV = left ventricular; OMR = organic mitral regurgitation; RVSP = right ventricular systolic pressure; TR = tricuspid regurgitation.

associated with all-cause death (Table 4, models 1 to 3). Substitution of Charlson score with coronary artery disease (footnotes, Table 4) showed similar results. To understand whether presence of tricuspid regurgitation (TR) contributed to the excess mortality that MR carried, patients were also stratified according to presence of ≥TR (Figure 4, Table 4). Unadjusted survival showed stepwise increase in mortality for pure AR, AR + MR, AR + TR, and AR + MR + TR (Figure 4). After multiple adjustments, patients with AR + MR + TR exhibited the highest risk of death versus pure AR (Table 4, models 4 to 6, and Figure 4).

In patients with AR + FMR (n = 107) exclusively, the presence of AF and LAVi were more robust determinants of death than TR velocity >2.8 m/s (Table 4). Importantly, univariate analysis revealed that in patients with AR + MR (n = 167), AVS plus MV surgery was protective (HR: 0.36; 95% CI: 0.20 to 0.62; p = 0.0002) versus AVS alone (p = 0.23), but not in multivariable analysis.

SURVIVAL IN THE MATCHED COHORT. In pure AR and AR plus ≥ moderate MR cohorts matched for age,

sex, and AR severity, MR patients still had more symptoms, more comorbidities, larger LV size, lower LVEF, more AF, more tricuspid regurgitation, and higher estimated systolic pulmonary pressure (Supplemental Table 2). Evidently, this translated into worse survival during total follow-up (Supplemental Figure 2).

DISCUSSION

In this large contemporary cohort of hemodynamically significant chronic AR, we report for the first time a comprehensive assessment of the prevalence, mechanisms, and survival impact of coexistent MR in these patients. Our principal findings are: 1) coexistent MR was not uncommon, with 14% of AR patients having ≥ moderate MR, and FMR being more common (9%) than OMR (5%); 2) FMR in AR was primarily due to nonischemic LV remodeling; 3) the presence of coexistent MR was associated with excess death compared with pure AR, with a larger and stronger death association for FMR than OMR in age-sex-adjusted multivariate comparisons, as well as compared with the general population; 4) within FMR, the presence of AF or large LAVi was associated with excess death; 5) when comparing single (pure AR) versus double (AR + MR) versus triple regurgitant valvular disease (AR + MR + TR), triple valve disease exhibited the highest risk of death; and 6) our observations suggest that FMR likely represents an advanced stage within the clinical spectrum of AR.

MR IN AS AND AR. In patients with severe AS undergoing transcatheter AV replacement, significant concomitant MR (≥ moderate) has been reported in 15% to 20%, with a highly variable (17% to 62%) prevalence of FMR (9,16). This variability relates to different selection criteria and the caveat that mechanisms and quantifications of MR in these AS studies were not unified. We show that the prevalence of ≥ moderate MR (14%) in AR is less than AS (yet not insignificant), mostly related to FMR (64%, only 16% ischemic) and less commonly to OMR (36%) (Figure 1). There are 3 major differences in MR mechanism between severe AS and AR. First, patients in AS potentially have more mixed etiologies of MR (9,16) because their mitral leaflets, annulus, and subvalvular apparatus are usually calcified to some degree. Indeed, of our patients with FMR, only 7% had prominent MAC, and of our OMR patients, only 8% had valvular calcification, whereas most were degenerative (62%), making mixed MR mechanisms in AR less likely than in AS. Second, patients with AR have more LV dilatation than AS (3), which results in more type IIIB MR. This is supported by our findings that 75% of FMR had type IIIB mechanism due to enlarged LV and tethered MV (Figure 1). Third, the lower prevalence of MR in AR as compared to AS, may be due to improved sealing as a result of mitral leaflet enlargement as an adaptive mechanism to LV dilatation (17).

PURE AR VERSUS AR + OMR VERSUS AR + FMR. Herein we have reported 3 types of AR patients (Central Illustration):

1. Patients with pure AR, a population most previous studies focused on (4,7,10), which is younger, male-predominant, and with preserved EF, < moderate or no MR, low left and right heart pressures, low prevalence of ≥moderate TR, and rarely requiring concomitant MV surgery.
2. Those with AR + OMR, predominantly due to degenerative MV disease, which constitutes a group with preserved LVEF but larger LV and LA, higher right heart pressures, more TR, and more AF. This group had the highest incidence of both AV and MV surgery, likely due to the presence of severe double-valve disease, and the technical feasibility and proven outcome benefit of early MV repair (18). Importantly, the prevalence of coexistent OMR is higher than that described for the general population (5% vs. 2.4%) (19).
3. Those with AR + FMR, with a demographic composition that included older patients and more women than the prior 2 types, had the largest left ventricles, lower LVEF, the highest right heart pressures, and the highest TR and AF prevalence (Central Illustration). In this group, presence of AF and/or large left atria was independently associated with death (Table 3).

The mechanisms and pathophysiology of FMR in chronic AR are incompletely understood; a recent sheep-model study with induced AR proposed that attenuated MV enlargement caused by myocardial infarction contributed to development of FMR in AR (20), but our high prevalence of nonischemic FMR (Figure 1) suggests there are likely other pathways for AR + FMR. Indeed, the presence of significantly smaller LV/LA diameters in TTEs prior to baseline TTE in patients with AR + FMR, the development of FMR at follow-up TTEs in those with pure AR at baseline TTE (Table 2), the significantly larger LV/LA diameters in AR + MR patients (particularly AR + FMR) (Table 1, Figure 2), and only 16% ischemic FMR all suggest that FMR represents an advanced stage within the AR natural history, where LV/LA remodeling are key pathophysiologies of MR mechanisms (Central Illustration).

In turn, this LV and LA remodeling are likely the result of chronic AR (likely of longer duration and late surgical referral) (**Table 2, Figure 2**), increasing age, increasing AF prevalence, and possibly more comorbid conditions (**Central Illustration**).

AR + MR AND SURVIVAL. We have previously identified a survival penalty in contemporary patients with pure-AR (10). We now report that coexistent ≥ moderate MR in AR is independently associated with excess death as compared to pure AR. When compared to the general population, both AR + OMR and AR + FMR had worse-than-expected survival with AR + FMR exhibiting the largest excess death (**Figure 3**). These 2 novel AR patient types with coexistent MR have been excluded from most previous AR studies, likely resulting in overestimation of survival, limiting the exploration of pathophysiologic downstream consequences of AR (FMR), and hindering the documentation of associated degenerative MR (OMR). Although AR + FMR patients had less severe MR than AR + OMR (**Table 1**), they had the worst cardiac remodeling (**Figure 2**) at the time of surgery, suggesting late surgical-referral for AR. Nonetheless, our study suggests that the worse survival in AR + FMR is multifactorial (**Central Illustration**), including the presence of ≥ moderate TR. Indeed, the combination of AR + MR + TR exhibited the worst survival by adjusted Kaplan-Meier analyses and comprehensive multivariable models (**Figure 4, Table 4**). These findings mirror the proposed staging concept in severe AS (2,3), where advancing stages present higher prevalence of MR and TR; in our study, 47% AR + MR patients had significant TR versus 7% in pure AR. However, ≥ moderate TR could also be related to pure AR without MR (i.e., AR + TR) (**Figure 4, Table 4**); these patients had a higher prevalence of AF (19% vs. 4%; $p < 0.0001$).

Whether surgery or contemporary percutaneous treatments of FMR in AR patients can attenuate this survival penalty (21) requires future study; yet, univariate analysis revealing AVS plus MV surgery to be survival protective versus AVR alone (see Results section) seems a hopeful start.

Besides AVS with or without MV surgery, management of patients with AR + FMR should also focus on associated comorbid conditions (i.e., coronary artery disease, hypertension, AF). For contemporary clinicians and imagers, it becomes important to identify MV morphology and the coexistence of ≥ moderate MR in AR patients, distinguish MR mechanisms and etiologies, and report echocardiographic signs of worsening LV chamber size and function as well as downstream cardiac damage (i.e., MR, LAVi, AF, TR, and pulmonary hypertension). Current guidelines (22) do not address the "downstream" effects of chronic AR and their clinical implications, or the significance of concomitant OMR or FMR in AR patients, all of which may inform clinical decision-making.

STUDY LIMITATIONS. This is a single tertiary-referral center report, and observations could be different in the community. However, it represents consecutive contemporary patients with significant AR and coexistent MR who are usually referred to and managed in tertiary centers. The retrospective nature of our study increases the potential for referral and selection bias, which could affect prevalence and outcomes of significant MR in AR. Given the relatively low number of AR + MR patients, evaluation of the association of concomitant mitral surgery with survival and evaluation of determinants for MR reduction after AVS was limited and inconclusive. We reported all-cause mortality but not cardiac death, because retrospective analysis of cause-of-death data derived from death certificates may be subject to inconsistencies and biases (23). We observed large differences between groups for some characteristics and it is possible that statistical adjustment could not completely account for these differences; therefore, we cannot completely rule out the possibility of residual confounding. Our study comprised adult patients who were predominantly of white European ancestry.

CONCLUSIONS

In hemodynamically-significant AR, coexistent ≥ moderate MR is not uncommon, occurring in 14% of patients, and mostly comprised nonischemic FMR followed by OMR. Both AR + OMR and AR + FMR carry a survival penalty compared with the general population, but AR + FMR is associated with the largest excess mortality. AR + FMR represents an advanced stage within the AR clinical spectrum, with more advanced LV and LA remodeling, AF, pulmonary hypertension and TR, and it is associated with excess death independently of LVEF, LVESDi and LV end-systolic volume index.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Moderate or severe MR occurs in nearly 15% of patients with significant AR, and the mechanism is most often nonischemic FMR. Although both FMR and OMR in patients with AR are associated with reduced survival, patients with FMR typically have more advanced LV and atrial remodeling, atrial fibrillation, pulmonary hypertension, tricuspid regurgitation, and adverse prognosis, independent of ventricular enlargement or systolic dysfunction.

TRANSLATIONAL OUTLOOK: Because patients with concomitant MR and AR are often older and have comorbidities that limit candidacy for cardiac surgery, future research should evaluate alternative treatment strategies, including percutaneous transcatheter interventions.

REFERENCES

1. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. Lancet 2006;368:1005–11.

2. Tastet L, Tribouilloy C, Marechaux S, et al. Staging cardiac damage in patients with asymptomatic aortic valve stenosis. J Am Coll Cardiol 2019;74:550–63.

3. Vollema EM, Amanullah MR, Ng ACT, et al. Staging cardiac damage in patients with symptomatic aortic valve stenosis. J Am Coll Cardiol 2019;74:538–49.

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;73:1741–52.

5. Lindman BR, Bonow RO, Otto CM. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. Eleventh Edition. New York: Elsevier, 2019.

6. Tornos P, Lansac E. ESC Textbook of Cardiovascular Medicine. Third Edition. London: Oxford University Press, 2019.

7. 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;68:2144–53.

8. Pai RG, Varadarajan P. Prognostic implications of mitral regurgitation in patients with severe aortic regurgitation. Circulation 2010;122:S43–7.

9. Sannino A, Grayburn PA. Mitral regurgitation in patients with severe aortic stenosis: diagnosis and management. Heart 2018;104:16–22.

10. Yang LT, Pellikka PA, Enriquez-Sarano M, et al. Diastolic blood pressure and heart rate are independently associated with mortality in chronic aortic regurgitation. J Am Coll Cardiol 2020;75:29–39.

11. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440–63.

12. Zoghbi WA, Adams D, Bonow RO, et al. Recommendations for noninvasive evaluation of native valvular regurgitation: a report from the American Society of Echocardiography Developed in Collaboration with the Society for Cardiovascular Magnetic Resonance. J Am Soc Echocardiogr 2017;30:303–71.

13. Carpentier A. Cardiac valve surgery—the "French correction". J Thorac Cardiovasc Surg 1983;86:323–37.

14. Dziadzko V, Dziadzko M, Medina-Inojosa JR, et al. Causes and mechanisms of isolated mitral regurgitation in the community: clinical context and outcome. Eur Heart J 2019;40:2194–202.

15. Yang LT, Michelena HI, Maleszewski JJ, Schaff HV, Pellikka PA. Contemporary etiologies, mechanisms, and surgical approaches in pure native aortic regurgitation. Mayo Clin Proc 2019;94:1158–70.

16. Nombela-Franco L, Ribeiro HB, Urena M, et al. Significant mitral regurgitation left untreated at the time of aortic valve replacement: a comprehensive review of a frequent entity in the transcatheter aortic valve replacement era. J Am Coll Cardiol 2014;63:2643–58.

17. Beaudoin J, Handschumacher MD, Zeng X, et al. Mitral valve enlargement in chronic aortic regurgitation as a compensatory mechanism to prevent functional mitral regurgitation in the dilated left ventricle. J Am Coll Cardiol 2013;61:1809–16.

18. Suri RM, Vanoverschelde JL, Grigioni F, et al. Association between early surgical intervention vs watchful waiting and outcomes for mitral regurgitation due to flail mitral valve leaflets. JAMA 2013;310:609–16.

19. Freed LA, Levy D, Levine RA, et al. Prevalence and clinical outcome of mitral-valve prolapse. N Engl J Med 1999;341:1–7.

20. Marsit O, Clavel MA, Cote-Laroche C, et al. Attenuated mitral leaflet enlargement contributes to functional mitral regurgitation after myocardial infarction. J Am Coll Cardiol 2020;75:395–405.

21. Stone GW, Lindenfeld J, Abraham WT, et al. Transcatheter mitral-valve repair in patients with heart failure. N Engl J Med 2018;379:2307–18.

22. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:e57–185.

23. Lauer MS, Blackstone EH, Young JB, Topol EJ. Cause of death in clinical research: time for a reassessment? J Am Coll Cardiol 1999;34:618–20.

KEY WORDS aortic regurgitation, mechanism, mitral regurgitation, survival

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