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Prevalence and Prognostic Implications of Moderate or Severe Mitral Regurgitation in Patients with Bicuspid Aortic Valve

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Background: Significant (moderate or greater) mitral regurgitation (MR) could augment the hemodynamic effects of aortic valvular disease in patients with bicuspid aortic valve (BAV), imposing a greater hemodynamic burden on the left ventricle and atrium, possibly culminating in a faster onset of left ventricular dilation and/or symptoms. The aim of this study was to determine the prevalence and prognostic implications of significant MR in patients with BAV.

Methods: In this large, multicenter, international registry, a total of 2,932 patients (mean age, 48 ± 18 years; 71% men) with BAV were identified. All patients were evaluated for the presence of significant primary or secondary MR by transthoracic echocardiography and were followed up for the end points of all-cause mortality and event-free survival.

Results: Overall, 147 patients (5.0%) had significant primary (1.5%) or secondary (3.5%) MR. Significant MR was associated with all-cause mortality (hazard ratio [HR], 2.80; 95% CI, 1.91-4.11; $P < .001$) and reduced event-free survival (HR, 1.97; 95% CI, 1.58-2.46; $P < .001$) on univariable analysis. MR was not associated with all-cause mortality (adjusted HR, 1.33; 95% CI, 0.85-2.07; $P = .21$) or event-free survival (adjusted HR, 1.10; 95% CI, 0.85-1.42; $P = .49$) after multivariable adjustment. However, sensitivity analyses demonstrated that significant MR not due to aortic valve disease retained an independent association with mortality (adjusted

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HR, 1.81; 95% CI, 1.04-3.15; P = .037). Subgroup analyses demonstrated an independent association between significant MR and all-cause mortality for individuals with significant aortic regurgitation (HR, 2.037; 95% CI, 1.025-4.049; P = .042), although this association was not observed for subgroups with significant aortic stenosis or without significant aortic valve dysfunction.

Conclusions: Significant MR is uncommon in patients with BAV. Following adjustment for important confounding variables, significant MR was not associated with adverse prognosis in this large study of patients with BAV, except for the patient subgroup with moderate to severe aortic regurgitation. In addition, significant MR not due to aortic valve disease demonstrated an independent association with all-cause mortality. (J Am Soc Echocardiogr 2023;36:402-10.)

Keywords: Aortic stenosis, Aortic regurgitation, Primary, Secondary, Mitral regurgitation

Abbreviations
BAV = Bicuspid aortic valve
HR = Hazard ratio
IQR = Interquartile range
LV = Left ventricular
LVEF = Left ventricular ejection fraction
MR = Mitral regurgitation

Bicuspid aortic valve (BAV) is frequently associated with other congenital cardiac abnormalities, such as aortic coarctation, hypoplastic left heart syndrome, Shone's syndrome, and reversal of coronary artery dominance.[1-5] In addition, several studies have suggested an association between BAV and primary mitral regurgitation (MR), although further research is required to confirm this relationship.[6-9] Severe aortic stenosis or regurgitation due to BAV may also be associated with left ventricular (LV) remodeling and dysfunction, which can lead to secondary MR.

In patients with BAV, significant (moderate or greater) MR could augment the hemodynamic effects of coexistent aortic valvular disease,[10,11] imposing a greater hemodynamic burden on the left ventricle and atrium, conceivably culminating in a faster onset of LV dilation or symptoms or a poorer long-term outcome.[12] Although previous studies have demonstrated that significant MR is independently associated with an adverse prognosis in the general population,[13,14] until now, the prognostic importance of significant MR in patients with BAV had not been investigated.

In this context, the aims of this study were (1) to determine the prevalence of significant primary and secondary MR in patients with BAV and (2) to investigate the association of significant MR with overall survival and event-free survival in individuals with BAV.

METHODS

Study Population

From an international, multicenter registry of patients with BAV, patients with MR were identified.[15] Individuals with previous aortic or mitral valve surgery, endocarditis of the mitral valve or complex congenital heart disease were excluded. Demographic (including age, sex, and body surface area calculated using the Mosteller[16] method), clinical data, and cardiovascular risk factors (hypertension, dyslipidemia, diabetes, and smoking history[17-19]) were collected from medical records at the time of the first diagnosis of BAV by transthoracic echocardiography. Coronary artery disease was defined as a history of myocardial infarction or revascularization or coronary artery stenosis ≥50% on coronary angiography. Data were collected according to the regulations approved by the institutional review board of each research center and retrospectively analyzed. Because of the retrospective study design and anonymous handling of clinical data, the ethics committees of participating centers waived the need to obtain written informed consent. This investigation conformed to the principles outlined in the Declaration of Helsinki. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Echocardiography

All echocardiograms were obtained using commercially available equipment and were retrospectively analyzed by experienced investigators at each center. The first transthoracic echocardiogram confirming a diagnosis of BAV was considered as the index study. The phenotype of BAV was defined according to the classification proposed by Sievers and Schmidtke[20]: type 0, valve without raphe; type 1, valve with one raphe (which is further subclassified according to the orientation of the raphe in relation to the coronary sinuses); and type 2, valves with two raphes. The presence of either aortic valve stenosis and/or regurgitation was assessed and graded as none, mild, moderate, or severe according to current guidelines, where moderate or severe grading was considered as significant.[21,22] MR was assessed and classified according to the mechanism: primary (organic or structural intrinsic mitral valve disease) or secondary (without evident structural abnormality of the mitral valve). The severity of MR was graded as none, mild, moderate, or severe according to guideline recommendations, integrating qualitative, semiquantitative, and quantitative parameters.[23] Vena contracta width was measured from an apical four-chamber view at the narrowest portion of the regurgitant flow at the regurgitant orifice. The effective regurgitation orifice area and regurgitant volume were calculated using the proximal isovelocity surface area method.[23] Mitral valve prolapse was evaluated in the parasternal long-axis window and was defined as systolic displacement of the mitral leaflet(s) into the left atrium of ≥2 mm from the mitral annular plane.[23] A mixed etiology of significant MR was defined as including components of both primary and secondary MR.[23] The diameter of the aortic root and ascending aorta (4-5 cm distal to the sinotubular junction) were measured using two-dimensional echocardiography on the parasternal long-axis view using the leading edge–to–leading edge convention in an end-diastolic frame.[24] The aortic dilatation configurations were reported following the classification of Fazel *et al.*[25]: aortic root dilatation only, ascending aortic dilatation only, and diffuse involvement of both aortic root and ascending aorta. LV end-diastolic diameter and LV end-systolic diameter were calculated using the linear two-dimensional approach. LV ejection fraction (LVEF) and LV end-diastolic volume were calculated using the biplane Simpson method.[24] All other standard measurements were performed according to European Association of Cardiovascular Imaging and American Society of Echocardiography guidelines.[24]

HIGHLIGHTS

- In this international registry of 2,932 patients with BAV, 5.0% had significant MR.
- A total of 1.5% had significant primary MR and 3.5% significant secondary MR.
- Significant MR was not independently related to outcomes in patients with BAV.
- Significant MR not related to AV disease was associated with all-cause mortality.
- Significant MR was associated with mortality in patients with significant AR and BAV.

Follow-Up

The primary end point of the study was all-cause mortality. Follow-up started at the time of the index echocardiographic examination confirming the diagnosis of BAV. The secondary end point was a composite of aortic valve repair or replacement and all-cause mortality (event-free survival). Indications for aortic valve surgery were based on contemporary guidelines.[26,27] Data of all patients were included up to the last date of follow-up.

Statistical Analysis

Categorical variables are presented as counts and percentages and were compared using the Pearson χ^2 test. Adherence to a normal distribution was evaluated by comparing histograms to overlaid normal probability curves. Normally distributed continuous variables are presented as mean ± SD and were compared using Student's *t* test or one-way analysis of variance, while non-normally distributed parameters are presented as median (interquartile range [IQR]) and were compared using the Mann-Whitney *U* or Kruskal-Wallis test. Multiple comparisons were tested using Bonferroni correction. The association between BAV morphology and significant primary MR with prolapse of the anterior mitral valve leaflet was evaluated using logistic regression.

Cumulative 1- and 5- year survival rates were estimated using the Kaplan-Meier method and compared using the log-rank test. Univariable Cox proportional hazards regression analysis was performed to investigate the association of significant MR with all-cause mortality and event-free survival. Hazard ratios (HRs) and 95% CIs are reported. Prespecified clinical and echocardiographic variables known to be associated with all-cause mortality or event-free survival were entered into the respective multivariable models, with additional adjustment for aortic root or ascending aortic dilation in the model evaluating the combined end point. Aortic root or ascending aortic diameter ≥ 50 mm was defined as aortic root or ascending aortic dilation to reflect current guideline indications for surgical intervention.[28] Sensitivity analyses incorporating aortic valve surgery as a time-dependent covariate were performed for each multivariable Cox regression model that evaluated all-cause mortality as the end point. In addition, further sensitivity analyses evaluating the prognostic implications of significant MR stratified according to etiology (due to aortic valve disease or not) were performed. The proportional hazards assumption was verified with the evaluation of scaled Schoenfeld residuals.

In addition, subgroup analyses of patients with BAV with significant aortic regurgitation, with significant aortic stenosis, and without significant aortic valvular disease were performed. The relationship of significant MR with all-cause mortality and event-free survival were examined for each subgroup in univariable and multivariable Cox regression models. Multivariable subgroup analyses were limited to adjustment of four prespecified variables (age, diabetes mellitus, LV end-diastolic volume, and LVEF) because of the risk for model overfitting.[29] All tests were two sided, and *P* values <.05 were considered to indicate statistical significance. Statistical analysis was performed using SPSS version 25.0 (IBM) and R version 4.0.1 (R Foundation for Statistical Computing).

RESULTS

Patient Population

A total of 2,932 patients with BAV (mean age, 48 ± 18 years; 71% men) met the study inclusion criteria (Figure 1). Significant MR was identified in 148 patients (5%), with primary MR observed in 44 patients (1.5%) and secondary MR in 104 patients (3.5%). Individuals with significant MR were older and more likely to have diabetes mellitus. Overall, the most frequently encountered BAV morphology was type 1 with raphe fusion between the right and left coronary cusps (Table 1). Patients with significant primary MR were more likely to have type 1 raphe with left and noncoronary cusp fusion compared with patients without significant primary MR (19.0% vs 4.6%, $P < .001$; Figure 2). Furthermore, the presence of type 1 raphe with left and noncoronary cusp fusion was associated with a significantly higher prevalence of significant MR due to prolapse of the anterior mitral valve leaflet compared with patients with other BAV morphologies (odds ratio, 6.76; 95% CI, 2.42-18.90; $P < .001$). Etiologies of significant primary MR included mitral valve prolapse (57%), leaflet calcification (18%), rheumatic heart disease (5%), leaflet billowing (5%), mitral valve cleft (2%), parachute mitral valve (2%), and mixed (11%). Of those with secondary MR, the etiology was aortic valve disease in 76 (73%), nonischemic cardiomyopathy in 11 (11%), ischemic cardiomyopathy in eight (8%), hypertensive cardiomyopathy in three (3%), atrial functional MR in two (2%), and unclear etiology in four (4%). The clinical and demographic characteristics of the total population are summarized in Table 1.

Echocardiographic Characteristics

The echocardiographic characteristics of the population are presented in Table 2. The mean LVEF for the total population was 60.8 ± 11.8%, and the median LV end-diastolic volume was 122 mL (IQR, 94-154 mL). Patients with significant secondary MR had lower LVEFs and larger LV dimensions compared with those with significant primary MR and those without significant MR (Supplemental Tables 1 and 2). In addition, a higher proportion of patients with significant secondary MR had moderate or severe aortic regurgitation (45.2% vs 27.3%, $P < .001$) and aortic stenosis (54.8% vs 35.4%, $P < .001$) compared with those without significant MR. Individuals with significant secondary MR had larger ascending aortas (39.0 ± 8.0 vs 36.4 ± 7.3 mm, $P = .001$) and sinus of Valsalva diameters (37.2 ± 7.2 vs 34.6 ± 6.2 mm, $P < .001$) compared with those without significant MR, while aortic annulus and sinotubular junction diameters were similar between the two groups.

Survival Analysis

Over a median follow-up time of 51 months (IQR, 18-95 months), 223 patients (7.6%) died. In total, 84 patients (38%) had cardiovascular causes of death, 67 (30%) patients had noncardiovascular causes of death, and 72 patients (32%) had unknown causes of death. One- and 5-year cumulative survival rates were 97% and 93%, respectively. Analysis using the Kaplan-Meier method demonstrated a reduction in survival for patients with significant MR compared with their counterparts (91% and 81% vs 97% and 93% at 1- and 5-year follow-up, respectively; $\chi^2 = 29.95$, $P < .001$). To further evaluate the association between significant MR and all-cause mortality, univariable and multivariable Cox regression analyses were performed (Supplemental Table 3). In the unadjusted model, significant MR was associated with all-cause mortality (HR, 2.80; 95% CI, 1.91-4.11; $P < .001$). However, following adjustment for age, smoking, hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, LV end-diastolic volume, and LVEF, significant MR was not associated with the primary outcome (HR, 1.33; 95% CI, 0.85-2.07; $P = .21$; Figure 3). When stratified by etiology of MR, significant secondary MR due to aortic valve disease was not associated with all-cause mortality (adjusted HR, 0.99; 95% CI, 0.54-1.83; $P = .98$), whereas significant MR not due to aortic valve disease was independently associated with worse survival (adjusted HR, 1.81; 95% CI, 1.04-3.15; $P = .037$; Supplemental Table 4). For the analysis of the secondary end point of event-free survival, after a median follow-up of 23 months (IQR, 3-67 months), 996 patients (34.0%) died ($n = 161$ [5.5%]) or underwent aortic valve surgery ($n = 835$ [28.5%]). Univariable analysis demonstrated that significant MR was associated with a reduction in event-free survival (Supplemental Table 3), although this association was not observed following adjustment (adjusted HR, 1.10; 95% CI, 0.85-1.42; $P = .49$).

Subgroup analyses were performed to investigate the association between significant MR and outcomes for patients with significant aortic regurgitation, significant aortic stenosis, and for those without significant aortic valvular disease (Figure 4). Significant MR was independently associated with all-cause mortality in the subgroup with moderate or severe aortic regurgitation (adjusted HR, 2.037; 95% CI, 1.025-4.049; $P = .042$). However, no independent association with all-cause mortality was observed in patients with significant aortic stenosis or without significant aortic valvular disease. Moreover, there was no independent association between significant MR and the end point of event-free survival in any subgroup.

In addition, sensitivity analyses incorporating aortic valve surgery as a time-dependent covariate were performed for all multivariable Cox regression models using all-cause mortality as the end point. The results of all sensitivity analyses were consistent with the main analysis (Supplemental Table 5).

DISCUSSION

In this large, international BAV registry, significant primary and secondary MR were uncommon, with prevalence rates of 1.5% and 3.5%, respectively. Significant MR was not independently associated with either all-cause mortality or event-free survival on multivariable analysis. However, when stratified by the etiology of MR, significant MR not due to aortic valve disease was independently associated with worse survival. Subgroup analyses suggested an independent association between significant MR and all-cause mortality for individuals with significant aortic regurgitation, although not for subgroups with significant aortic stenosis or without significant aortic valve disease.

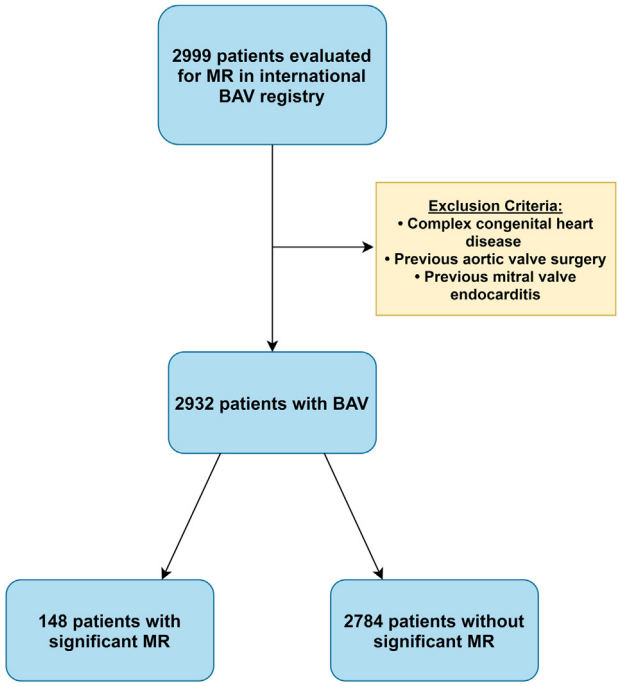

Figure 1 Study flowchart.

Prevalence of Primary and Secondary MR in BAV

The association between BAV and primary MR remains somewhat contentious.[6,7,9] Previously, in a retrospective study of 1,820 patients referred for surgery for significant BAV disease, Lad *et al.*[6] demonstrated a prevalence of significant primary MR of 1.6%, similar to that observed in the present study. In another smaller study of 191 patients with BAV, the prevalence of significant primary MR was 2.0%.[7] In comparison, in a large community cohort study of the general adult population, the prevalence of significant primary MR was approximately 0.26%.[13] However, despite evidence suggesting a higher prevalence of primary MR in individuals with BAV compared with the general population, a large study of approximately 360,000 patients did not demonstrate an increased prevalence of mitral valve prolapse in individuals with BAV.[9] However, the authors did not report on the frequency of significant MR due to mitral valve prolapse, which may explain this discrepancy. Interestingly, an association between mitral valve prolapse and BAV has previously been described by several authors, who reported an increased prevalence of large and myxomatous anterior mitral valve leaflets in those with BAV.[6-9] In the present study, the prevalence of significant primary MR due to mitral valve prolapse was 0.9%. Although a prevalence of significant secondary MR of 3.5% was observed in the present study, this could be an overestimation and not representative of the general BAV population, because of referral center bias and the associated higher rate of significant aortic valve disease, which may influence LV remodeling that leads to secondary MR.

Table 1 Clinical and BAV characteristics of patients divided according to MR mechanism

	Total population (n = 2,932)	No significant MR (n = 2,784)	Significant MR (n = 148)	P
Clinical characteristics				
Age, y	47.9 ± 17.7	47.3 ± 17.5	59.0 ± 17.5	<.001
Gender, male	2,065 (70.5)	1,961 (70.5)	104 (70.3)	.960
Prior CAD	216 (8.0)	198 (7.8)	18 (12.6)	.040
BSA, m^2	1.90 ± 0.26	1.90 ± 0.27	1.87 ± 0.22	.27
Hypertension	950 (34.7)	891 (34.4)	59 (41.3)	.092
Dyslipidemia	741 (26.2)	695 (25.9)	46 (31.1)	.162
Diabetes mellitus	285 (10.5)	262 (10.2)	23 (15.9)	.032
Current smoker	447 (16.5)	421 (16.4)	26 (17.9)	.638
BAV characteristics				
No raphe	397 (14.6)	386 (15.0)	11 (7.5)	<.001
Type 1 raphe (L-R)	1,759 (64.6)	1,657 (64.3)	102 (69.9)	
Type 1 raphe (R-N)	422 (15.5)	405 (15.7)	17 (11.6)	
Type 1 raphe (L-N)	132 (4.8)	116 (4.5)	16 (11.0)	
Type 2 raphe	13 (0.5)	13 (0.5)	0 (0.0)	

Data are expressed as mean ± SD or number (percentage). Percentages are calculated on the basis of data availability.
BSA, Body surface area; *CAD*, coronary artery disease; *L*, left coronary cusp; *N*, noncoronary cusp; *R*, right coronary cusp.

Association of MR with BAV Morphology and Aortic Root Dimensions

In the present study, an association between primary MR with prolapse of the anterior mitral valve leaflet and the type 1 left and noncoronary cusp fusion BAV raphe phenotype was observed. In contrast to the findings of our study, Schaefer *et al.*[7] observed an association between primary MR due to mitral valve prolapse and a type 1 raphe with right and noncoronary cusp fusion, although in a limited number of patients. Several mechanisms may explain the association between primary MR and BAV. Individuals with BAV may have an extension of the degenerative process that results in dilation of the aortic root to the anterior mitral valve leaflet, either mediated anatomically through the fibrous aortic-mitral continuity or because of a common embryological origin.[6,30,31] This could potentially manifest as an enlarged, myxomatous anterior mitral valve leaflet, as described earlier.

In addition, we also observed an association between secondary MR and larger sinus of Valsalva and ascending aortic dimensions. This may be explained by the common relationship among significant aortic regurgitation, secondary MR, and aortic root dilation in BAV

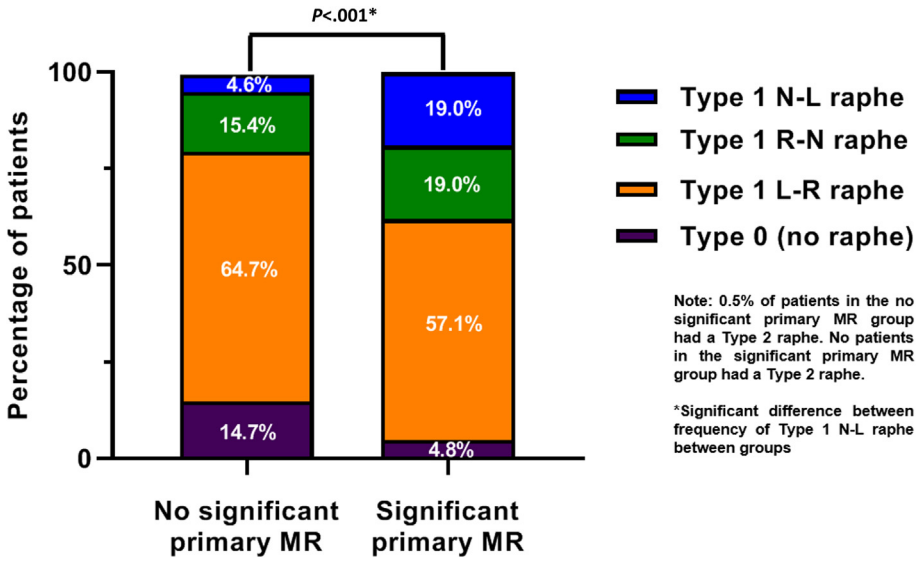

Figure 2 Distribution of BAV raphe phenotype according to the presence or absence of significant primary MR. *L*, Left coronary cusp; *N*, noncoronary cusp; *R*, right coronary cusp.

Table 2 Echocardiographic characteristics

Variable	Total population (*n* = 2,932)	No significant MR (*n* = 2,784)	Significant MR (*n* = 148)	*P*
Left ventricle				
LVEDD, mm	51.7 ± 8.7	51.3 ± 8.3	57.9 ± 12.3	<.001
LVESD, mm	34.4 ± 9.1	33.8 ± 8.4	43.6 ± 14.1	<.001
LVEDV, mL	122 (94-154)	120 (93-153)	154 (110-211)	<.001
LVEF, %	60.8 ± 11.8	61.5 ± 11.0	48.3 ± 17.8	<.001
Mitral inflow E velocity, m/sec	0.8 ± 0.3	0.8 ± 0.3	1.0 ± 0.4	<.001
Aortic valve and aortic root				
Aortic annular diameter, mm	23.0 ± 3.2	23.0 ± 3.2	23.5 ± 3.1	.081
SOV diameter, mm	34.7 ± 6.3	34.6 ± 6.2	36.4 ± 6.9	.001
STJ diameter, mm	30.5 ± 6.5	30.5 ± 6.4	31.0 ± 7.4	.321
Ascending aortic diameter, mm	36.5 ± 7.4	36.4 ± 7.3	38.0 ± 8.1	.014
Dilated aortic root or tubular aorta (≥ 40 mm)	1,125 (39.1)	1,058 (38.8)	67 (45.6)	.099
Dilated aortic root or tubular aorta (≥ 50 mm)	140 (4.9)	130 (4.8)	10 (6.8)	.255
Moderate or severe AS	1,054 (36.0)	984 (35.4)	70 (47.3)	.003
Moderate or severe AR	822 (28.1)	760 (27.3)	62 (41.9)	<.001

Data are expressed as mean ± SD, median (IQR), or number (percentage).
AR, Aortic regurgitation; *AS*, aortic stenosis; *LVEDD*, LV end-diastolic diameter; *LVEDV*, LV end-diastolic volume; *LVESD*, LV end-systolic diameter; *SOV*, sinus of Valsalva; *STJ*, sinotubular junction.

disease or, alternatively, could represent altered motion of the anterior mitral valve leaflet, attributable to changes in biomechanical forces transmitted through the aortic-mitral continuity in the presence of aortic root dilation.

Prognostic Implications of MR in Patients with BAV

In this large cohort of patients with BAV, no independent association between significant MR and all-cause mortality was observed. This contrasts with several large community studies of the general population that showed an independent association between significant MR and increased all-cause mortality.[13,14] However, in those studies, limited adjustment for important confounding variables were performed, notably for LV end-diastolic volume and LVEF. Moreover, the patients with significant MR in those studies were nearly 20 years older, and it is likely that the etiology of secondary MR differed dramatically from the BAV population in our study. Indeed, a substantial proportion of secondary MR in the present study was due to significant aortic valve disease, which typically has a more favorable prognosis than secondary MR due to LV systolic dysfunction or ischemic heart disease, particularly in the context of timely aortic valve intervention. Following aortic valve surgery, approximately 55% of patients with aortic stenosis and 70% of those with aortic regurgitation will have improvement in the grade of secondary MR, likely because of a combination of reverse LV remodeling and alterations in mitral valve hemodynamics.[32-34] In accordance with this hypothesis, when stratifying by the etiology of MR, we observed an independent association between significant MR not due to aortic valve disease and all-cause mortality, findings consistent with prior literature. In contrast, no association between all-cause mortality and significant secondary MR due to aortic valve disease was observed. This suggests that consideration of the etiology of significant MR is essential in the setting of treatable AV disease.

In the present study, the absence of a relationship between the composite end point of aortic valve repair or replacement and all-cause mortality with significant MR was unexpected, given the greater hemodynamic burden on the left ventricle in multiple left-sided valvular disease.[10] The combination of significant MR and aortic stenosis and/or aortic regurgitation may have been expected to culminate in additional LV and left atrial remodeling, earlier onset of symptoms, and therefore an earlier indication for aortic valve surgery.[10] However, there are several explanations for these findings. Significant MR may mask reductions in LVEF,[35] an important indication for intervention in aortic regurgitation and aortic stenosis, leading to a delay in referral. In addition, significant MR may lead to low-flow, low-gradient aortic stenosis and an underestimation of the hemodynamic severity of disease,[36] potentially delaying referral for surgery or intervention.

The subgroup analysis suggested an independent association between significant MR and all-cause mortality in patients with moderate to severe aortic regurgitation. This finding is consistent with a previous study of 756 patients with severe aortic regurgitation due to a variety of etiologies, which also demonstrated an independent association between all-cause mortality and significant MR.[12] The relationship between mortality and significant MR in aortic regurgitation is probably mediated by increased LV dilation and eccentric hypertrophy, with poorer long-term LV functional recovery.[10] In addition, because of the absence of the premature mitral valve closure usually seen in severe aortic regurgitation, the combination of significant MR and aortic regurgitation may lead to elevated left atrial and pulmonary capillary wedge pressures and poor clinical tolerability.[10] In an additional subgroup analysis of patients with moderate or severe aortic stenosis, we did not observe an independent association between significant MR and all-cause mortality. Indeed, the association of significant MR with mortality in severe aortic stenosis remains contentious in the context of both surgical and transcatheter aortic valve interventions.[32,37] As discussed previously, the BAV population is typically much younger, with fewer comorbidities, and it is likely that the absence of an association with all-cause mortality in the aortic stenosis subgroup can be attributed to patients with BAV having etiologies of secondary MR with a more favorable prognosis. In addition, it

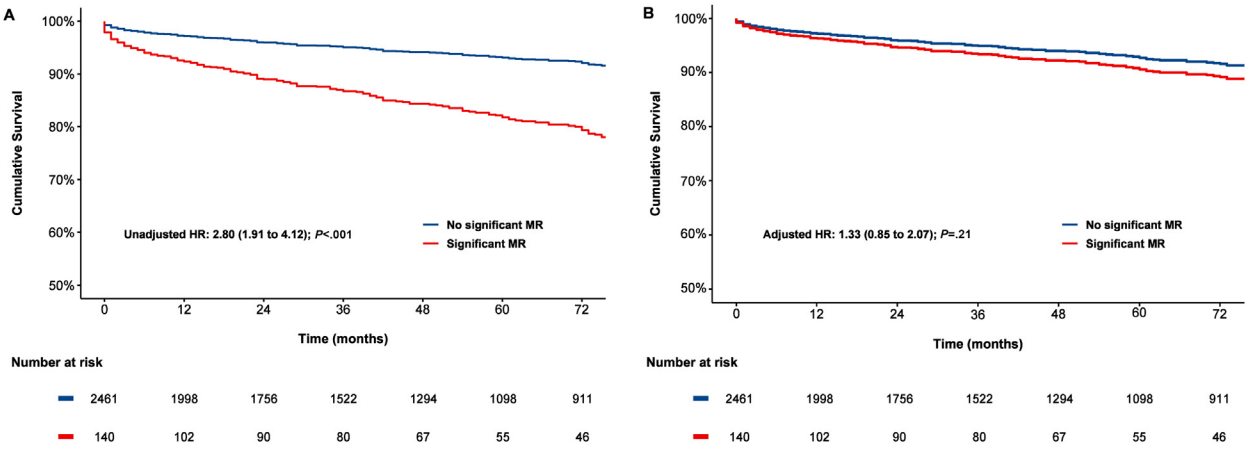

Figure 3 Cumulative survival estimates for all-cause mortality according to the presence or absence of significant MR in the overall population. **(A)** Significant MR is associated with all-cause mortality in an unadjusted model in patients with BAV. **(B)** However, significant MR was not associated with all-cause mortality in a model adjusted for important confounding variables. The model in **(B)** is adjusted on the basis of the average covariate values of the study population for age, diabetes mellitus, hypertension, smoking, dyslipidemia, coronary artery disease, LVEF, and LV end-diastolic volume.

is also conceivable that the concentric remodeling induced by severe pressure overload in aortic stenosis is fundamentally different and not additive to the severity of eccentric remodeling that is typically observed in significant MR (and vice versa). In contrast, volume overload secondary to both aortic regurgitation and MR may be additive, causing a greater degree of eccentric remodeling and severe LV dilatation, which could induce an earlier onset of LV systolic dysfunction and ultimately a poorer prognosis.[38,39]

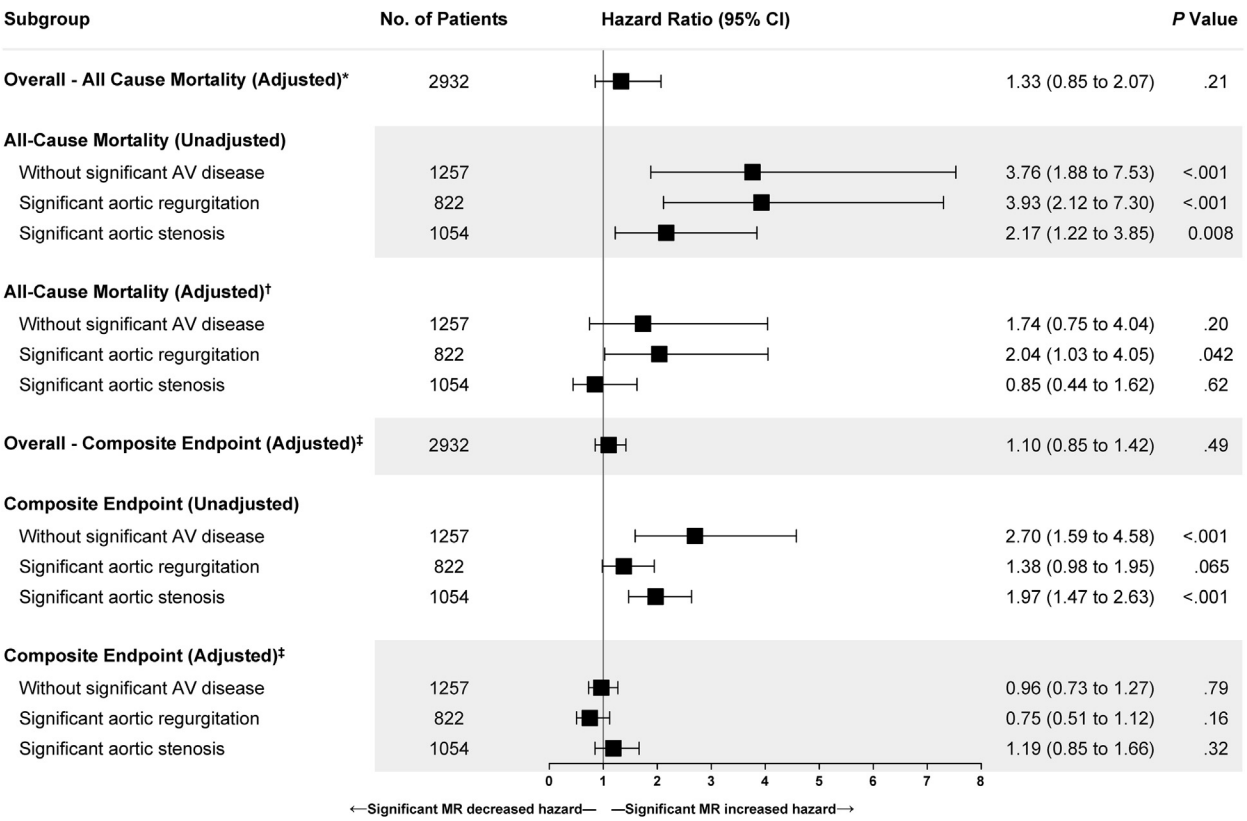

Figure 4 Forest plot of Cox regression models investigating the association between significant MR for the end points of all-cause mortality and event-free survival in patient subgroups. *Multivariable model adjusting for age, smoking, hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, LV end-diastolic volume (LVEDV), and LVEF. †Multivariable model adjusting for age, diabetes mellitus, LVEDV, and LVEF. ‡Multivariable model adjusting for age, smoking, hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, aortic root or ascending aortic dilation ≥50 mm, LVEDV, and LVEF. *AV*, Aortic valve.

Limitations

This study was subject to the inherent limitations of any observational, retrospective registry. Furthermore, because of the registry study design, clinical outcomes could have been underreported if a patient left the registry or was lost to follow-up, and although all centers followed guideline recommendations, assessment and treatment criteria may have varied across countries and centers. In addition, many of the participating international centers act as referral centers for their respective regions, resulting in increased complexity in the interpretation of epidemiologic data because of a higher prevalence of clinically significant aortic valve disease than in the general BAV population. Furthermore, data pertaining to the specific indication for aortic valve surgery were not available.

CONCLUSION

Significant MR is uncommon in patients with BAV. Following adjustment for important confounding variables, significant MR was not associated with adverse prognosis in this large study of patients with BAV, except for the patient subgroup with moderate to severe aortic regurgitation. In addition, significant MR not due to aortic valve disease demonstrated an independent association with all-cause mortality.

SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.echo.2022.10.019.

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