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ORIGINAL PAPER

Prognostic implications of moderate aortic stenosis with concomitant aortic regurgitation in degenerative aortic valve disease: insights from a multicentre cohort

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See the editorial comment for this article "Double trouble': when mixed moderate aortic valve disease turns out in a severe clinical issue', by P. Springhetti *et al.*, https://doi.org/10.1093/ehjci/jeaf255.

Aims Mixed aortic valve disease poses unique haemodynamic challenges. This study compared the clinical outcomes of concomitant moderate aortic stenosis (AS) and moderate aortic regurgitation to isolated AS.

Methods and results We analysed a multicentre cohort of valvular heart disease between 2008 and 2022 at three tertiary centres. The entire cohort was divided into three groups: moderate AS accompanied by moderate aortic regurgitation (moderate ASR), isolated severe AS, and isolated moderate AS. The primary outcome was a composite of cardiac death and hospitalization for heart failure. The final analysis included 4395 patients (median age: 76 years, 50.8% male), comprising 224 patients with moderate ASR, 1996 with severe AS, and 2175 with moderate AS. Over a median follow-up of 3.4 years, aortic valve replacement (AVR) rates were 11.1, 57.2, and 7.8 per 100 person-years in the moderate ASR, severe AS, and moderate AS groups, respectively ($P < 0.001$). Patients with moderate ASR had a significantly higher risk of the primary outcome compared with moderate AS [adjusted hazard ratio (aHR) 1.49; 95% confidence interval (CI) 1.15–1.92; $P = 0.002$] and a risk comparable to severe AS (aHR 1.28; 95% CI 1.00–1.64; $P = 0.052$). These results remained consistent even when AVR was included as a time-varying covariate. Older age, male sex, renal dysfunction, and lower left ventricular ejection fraction were independent predictors of the primary outcome in patients with moderate ASR.

Conclusion Moderate ASR should not be considered a benign condition, as it is associated with poor clinical outcomes comparable to those of severe AS.

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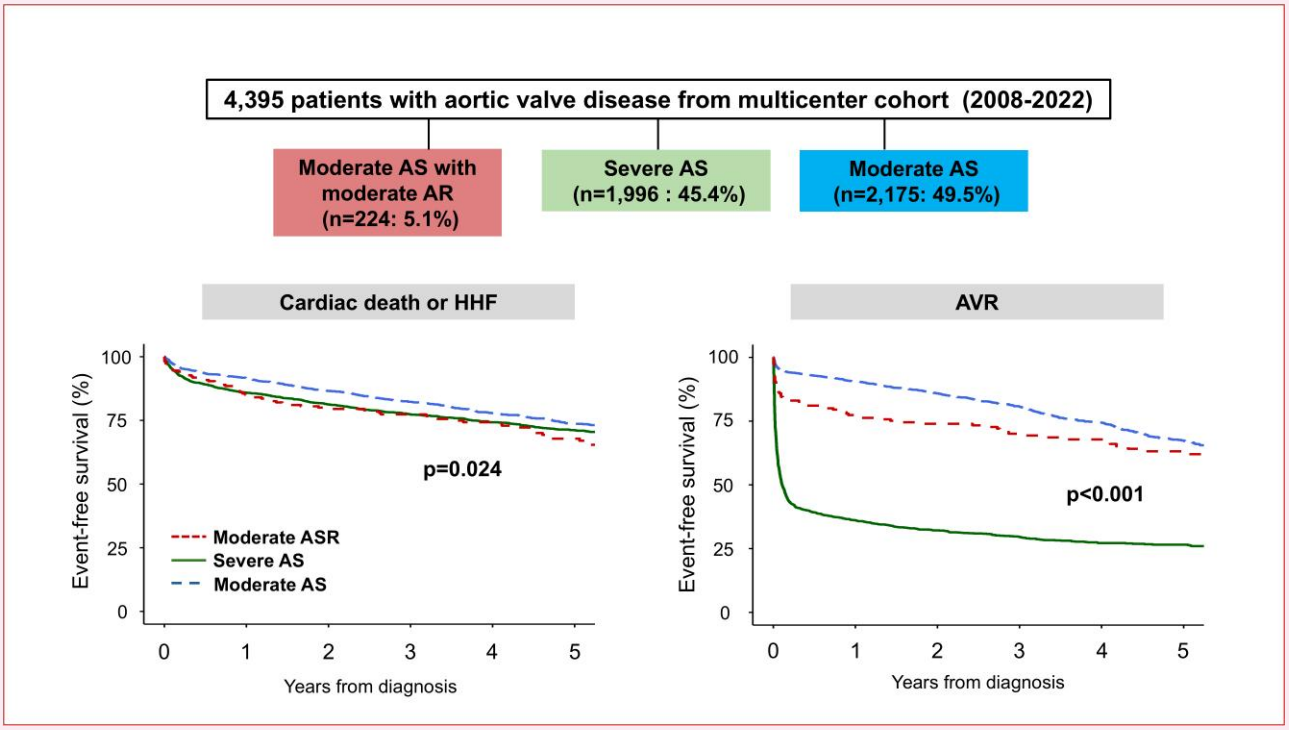
Graphical Abstract



Prognostic implications of moderate aortic stenosis with concomitant aortic regurgitation. In this multicentre cohort of valvular heart disease, moderate aortic stenosis with regurgitation (ASR) was associated with a significantly higher risk of cardiac death or hospitalization for heart failure than isolated moderate aortic stenosis (AS), and the risk was comparable to that observed in isolated severe AS. AS, aortic stenosis; ASR, aortic stenosis with regurgitation; AVR, aortic valve replacement; HHF, hospitalization for heart failure.

Keywords mixed valve disease • aortic stenosis • aortic regurgitation • outcomes

Introduction

Mixed valve disease refers to the coexistence of stenosis and regurgitation in the same valve, creating complex haemodynamic consequences. In particular, mixed aortic valve disease (MAVD), characterized by the combination of aortic stenosis (AS) and aortic stenosis with regurgitation (ASR), is frequently encountered in patients with aortic valve (AV) pathologies. A Swedish nationwide study reported that aortic regurgitation (AR) was the most frequent lesion among patients diagnosed with AS, and vice versa, highlighting the frequent coexistence of these conditions.[1] Currently, moderate-to-severe AR is present in ~13% of patients undergoing transcatheter AV replacement (TAVR) for severe AS.[2,3]

Haemodynamically, MAVD imposes both pressure and volume overload from AS and AR, leading to accelerated left ventricular (LV) remodeling and an increased risk of adverse outcomes. Despite this, the optimal management strategy for MAVD—particularly in patients with moderate AS and moderate AR—remains poorly defined. Several observational studies suggest that even moderate MAVD is associated with a prognosis comparable to that of severe AS.[4–6] However, these studies were predominantly single centre, included younger patients (with a mean age in the 50–60s), and often reported a high prevalence of bicuspid AV, which limits the generalizability of their findings to contemporary degenerative MAVD. There is a critical gap in large-scale, real-world data assessing the clinical trajectory of moderate MAVD, particularly among older populations with degenerative valve disease. Given the uncertainty surrounding the optimal timing for intervention, a clearer understanding of prognostic risk factors in moderate ASR is urgently needed to guide clinical decision-making. Therefore, this study aimed to compare the long-term clinical outcomes of moderate ASR with those of isolated severe AS and moderate AS in a large, multicentre cohort, with a focus on identifying high-risk subgroups and evaluating the impact of AVR.

Methods

Study population

This retrospective real-world, multicentre observational study was conducted on consecutive patients diagnosed with at least moderate valvular heart disease at their initial echocardiographic evaluation across three major tertiary centres in the Republic of Korea between January 2008 and October 2020. Among the initial cohort of 6275 patients, we included only those with moderate AS combined with moderate AR (moderate ASR), isolated severe AS, or isolated moderate AS. Patients presenting severe AS combined with moderate AR or severe AR combined with moderate AS were specifically excluded. Mild AR or mild AS were not considered clinically significant in defining MAVD; thus, patients with severe AS accompanied by mild AR were categorized within the isolated severe AS group. Patients were excluded if they were younger than 19 years old, had moderate or severe mitral valve disease, had undergone previous valve

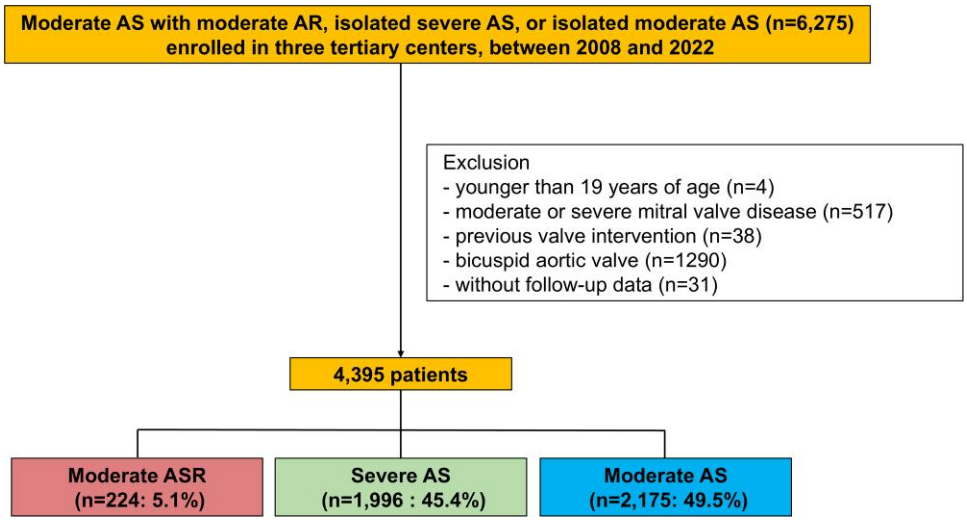


Figure 1 Study flow. AS, aortic stenosis; ASR, aortic stenosis with regurgitation.

intervention, had a bicuspid AV, or lacked follow-up data (*Figure 1*). The exclusion of bicuspid AV patients was intended to create a more homogenous study population, as bicuspid AV represents a distinct congenital entity with different disease progression and treatment implications. No explicit exclusion was made for low-flow, low-gradient AS as our study intentionally included a wide spectrum of LV systolic function. A detailed overview of the entire AS cohort is provided in Supplementary data online, *Figure S1*.

Definition

Clinical, laboratory, and echocardiographic data were retrospectively collected from individual centres and centrally processed at the core centre (Seoul National University Hospital). Detailed data processing procedures are provided in the Supplementary materials. The definitions of AS and severity were based on current guidelines from the American Society of Echocardiography (ASE).[7] Severe AS was defined as a peak AV velocity ≥ 4 m/s or a mean pressure gradient ≥ 40 mmHg and an AV area (AVA) < 1 cm^2. Moderate AS was defined as a peak AV velocity ≥ 3 m/s or a mean pressure gradient ≥ 20 mmHg and an AVA ≥ 1 cm^2 but <1.5 cm^2. The diagnosis and grading of AR were performed in accordance with current ASE guidelines, using both quantitative and qualitative approaches.[7] Moderate AR was diagnosed comprehensively using the following criteria: (i) specific criteria for severe AR (e.g. flail valve, prominent holodiastolic flow reversal in the descending aorta, large flow convergence, or marked enlarged LV with normal systolic function) were not met; (ii) the pressure half-time was between 200 and 500 ms, the vena contracta width was ≥0.3 cm but <0.6 cm, or the regurgitant jet width was ≥25% but <65% of LV outflow tract, and (iii) the effective regurgitant orifice area was ≥0.1 cm^2 but <0.3 cm^2, the regurgitant volume was ≥30 mL but <60 mL, or the regurgitant fraction was ≥30% but <50%. The aetiology of the AV disease was determined by expert review of echocardiographic images. Left ventricular hypertrophy was defined using the left ventricular mass index and relative wall thickness, in accordance with current recommendations.[8] Low-flow low-gradient severe AS was defined as AVA < 1.0 cm^2 (indexed AVA < 0.6 cm^2/m^2), low-flow status (stroke volume index < 35 mL/min/m^2), peak transaortic velocity (<4 m/s), and mean pressure gradient (<40 mmHg).[9]

Symptoms were defined as the presence of one or more of the following: dyspnoea, chest pain, oedema, palpitation, or syncope. The presence of comorbidities, including hypertension, diabetes, dyslipidaemia, atrial fibrillation, previous myocardial infarction, or previous cerebrovascular accident, was defined as either a documented history of disease or ongoing treatment for it. Discharge medications, including renin–angiotensin–aldosterone system blocker, beta-blocker, oral anticoagulant, antiplatelets, diuretics, or statins, were recorded.

The primary outcome was a composite of cardiac death or hospitalization for heart failure (HHF). Vital status and cause of death were determined using medical records and official death certification data from the Statistics Korea at the Ministry of Strategy and Finance of South Korea. Admissions and their aetiology were identified through careful chart reviews. The secondary outcomes included cardiac death, HHF, all-cause death, and a composite of all-cause death or AVR.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation or median (interquartile range), depending on distribution normality (assessed by the Shapiro–Wilk test). Between-group comparisons were performed using the Student's *t*-test or the Mann–Whitney *U* test for continuous variables and the χ^2 test for categorical variables. For missing data, case-wise deletion was performed (see Supplementary data online, *Table S1*). The cumulative incidence of each outcome was estimated using the Kaplan–Meier method, with log-rank tests used for between-group comparisons. Cox proportional hazards models were used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs), adjusting for age, sex, and baseline comorbidities (hypertension, diabetes, dyslipidaemia, atrial fibrillation, renal dysfunction, chronic obstructive pulmonary disease, prior myocardial infarction, and prior cerebrovascular accident). Renal dysfunction was defined as an estimated glomerular filtration rate of <60 mL/min/1.72 m^2 calculated using the Chronic Kidney Disease Epidemiology Collaboration formula.[10] Due to missing values for estimated glomerular filtration rate, Cox regression analyses were performed both with and without the inclusion of renal dysfunction. The results excluding renal function are presented in Supplementary data online, *Tables S2–S4*. Plots of the log–log survival function were used for proportional hazards assumption. Since AVR was performed during the follow-up period, a time-dependent Cox model was applied to adjust for AVR as a time-varying covariate. Independent predictors of the primary outcome and AVR in patients with moderate ASR were identified using multivariable Cox regression analysis, incorporating variables with $P < 0.1$ from the univariable analysis.

A subgroup analysis was performed comparing the primary outcome between moderate ASR and moderate AS, stratified by sex and left ventricular ejection fraction (LVEF; <55% vs. ≥55%), both of which were identified as

independent predictors of the primary outcome. To assess the continuous relationship between LVEF and the risk of the primary outcome, we employed a generalized additive model to capture non-linear associations between the covariate and outcome. This analysis adaptively determined the smooth relationship without relying on pre-specified knots and identified a clinically relevant LVEF cutoff of ~55% (see Supplementary data online, *Figure S2*).

Statistical significance was set at $P < 0.05$ and all tests were two sided. All statistical analyses were conducted using R software (version 4.3.2; R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics

A total of 4395 patients were included in the final analysis; moderate ASR ($n = 224$), severe AS ($n = 1996$), and moderate AS ($n = 2175$). Significant differences were observed in age, symptom burden, and comorbidities at the time of baseline echocardiography among the three groups (*Table 1*). Patients with moderate ASR were the youngest, with a median age of 74 years, compared with 77 years in severe AS and 76 years in moderate AS. The proportion of male patients did not differ significantly between groups ($P = 0.426$). In terms of echocardiographic parameters, patients with moderate ASR exhibited the largest LV end-diastolic and end-systolic dimensions, as well as the highest LV mass, resulting in the highest prevalence of eccentric left ventricular hypertrophy—suggesting greater volume overload compared with the other groups. Notably, the prevalence of low-flow status, defined as stroke volume index < 35 mL/m^2, was substantially lower in the moderate ASR group (2.9%) compared with the severe AS (14.2%) and moderate AS groups (10.2%).

Clinical outcomes

The median follow-up duration was 3.4 years (1.3–6.2 years). During this period, 1162 primary events of cardiac death or HHF occurred, with incidence rates of 7.3, 7.3, and 6.3 per 100 person-year for moderate ASR, severe AS, and moderate AS, respectively (log rank $P = 0.024$; *Figure 2A*). For patients with moderate ASR, the risk of cardiac death or HHF was significantly higher than that in moderate AS group [adjusted HR (aHR) 0.67; 95% CI 0.52–0.87; $P = 0.002$,

Table 1 Baseline characteristics

Variables	Moderate ASR ($n = 224$)	Severe AS ($n = 1996$)	Moderate AS ($n = 2175$)	*P* value
Age	74.0 [65.0, 80.0]	77.0 [70.0, 81.0]	76.0 [70.0, 81.0]	**<0.001**
Male	114 (50.9)	992 (49.7)	1125 (51.7)	0.426
Height	160.0 [152.8, 166.0]	158.0 [151.0, 165.0]	160.0 [152.4, 166.0]	**0.001**
Weight	60.0 [53.0, 67.0]	60.0 [52.0, 68.0]	61.0 [54.0, 69.0]	**<0.001**
Body mass index, kg/m^2	23.4 [21.7, 25.5]	24.0 [21.7, 26.3]	24.2 [22.0, 26.5]	**0.001**
Body surface area, m^2	1.6 [1.5, 1.8]	1.6 [1.5, 1.8]	1.6 [1.5, 1.8]	**<0.001**
Systolic blood pressure, mmHg	130.0 [115.0, 144.0]	128.0 [114.0, 140.0]	132.0 [119.0, 146.0]	**<0.001**
Diastolic blood pressure, mmHg	69.0 [60.0, 78.0]	69.0 [61.0, 77.0]	70.0 [62.0, 79.0]	**<0.001**
Symptoms	122 (54.5)	1286 (64.5)	1002 (46.1)	**<0.001**
Dyspnoea	91 (41.6)	1034 (53.0)	707 (34.1)	**<0.001**
Chest pain	28 (12.8)	313 (16.0)	265 (12.8)	**0.011**
Oedema	8 (3.7)	98 (5.0)	97 (4.7)	0.640
Palpitation	9 (4.1)	37 (1.9)	49 (2.4)	0.095
Syncope	7 (3.2)	81 (4.1)	58 (2.8)	0.064
Comorbidities				
Hypertension	115 (51.3)	1136 (56.9)	1450 (66.7)	**<0.001**
Diabetes	50 (22.3)	653 (32.7)	766 (35.2)	**<0.001**
Dyslipidaemia	51 (22.8)	539 (27.0)	780 (35.9)	**<0.001**
Atrial fibrillation	28 (12.5)	179 (9.0)	290 (13.3)	**<0.001**
COPD	31 (13.8)	280 (14.0)	326 (15.0)	0.652
Prior myocardial infarction	9 (4.0)	119 (6.0)	162 (7.5)	**0.043**
Prior cerebrovascular accident	23 (10.3)	164 (8.2)	290 (13.3)	**<0.001**
eGFR, mL/min/1.73 m^2	77.5 [56.7, 91.8]	76.4 [55.7, 89.5]	73.8 [52.2, 89.5]	**0.014**
Renal dysfunction (eGFR < 60)	56 (26.9)	540 (28.9)	635 (32.4)	**0.028**
Medications				
Beta-blockers	22 (10.0)	157 (8.0)	235 (11.0)	**0.005**
RAAS blockers	74 (33.6)	627 (31.9)	769 (36.0)	**0.022**
Statins	59 (26.8)	631 (32.1)	683 (32.0)	0.270
Diuretics	71 (32.3)	581 (29.6)	460 (21.5)	**<0.001**
Oral anticoagulants	20 (9.1)	219 (11.1)	210 (9.8)	0.315

Continued

Table 1 Continued

Variables	Moderate ASR ($n = 224$)	Severe AS ($n = 1996$)	Moderate AS ($n = 2175$)	*P* value
Echocardiography				
LVEDD, mm	53.0 [48.0, 57.0]	48.0 [45.0, 52.0]	48.0 [44.0, 52.0]	**<0.001**
LVESD, mm	34.0 [30.0, 38.0]	30.0 [27.0, 34.0]	29.0 [26.0, 32.5]	**<0.001**
LVEF, %	63.0 [56.0, 68.5]	64.0 [57.0, 69.0]	64.6 [59.0, 69.0]	**0.001**
Stroke volume index, mL/m^2	54.0 [46.5, 64.2]	46.7 [38.9, 54.2]	48.5 [41.2, 56.0]	**<0.001**
< 35 mL/m^2	6 (2.9%)	273 (14.2%)	208 (10.2%)	**<0.001**
IVS thickness, mm	11.0 [10.0, 12.0]	12.0 [10.6, 13.0]	10.7 [9.4, 12.0]	**<0.001**
LVPW thickness, mm	10.6 [9.8, 12.0]	11.0 [10.0, 12.0]	10.0 [9.0, 11.0]	**<0.001**
Relative wall thickness	0.4 [0.4, 0.5]	0.5 [0.4, 0.5]	0.4 [0.4, 0.5]	**<0.001**
LV mass, g	215.7 [179.1, 264.4]	209.0 [171.6, 249.8]	178.2 [147.8, 213.9]	**<0.001**
LV hypertrophy	172 (82.3)	1486 (79.0)	1085 (54.8)	**<0.001**
Concentric	75 (35.9)	1114 (59.3)	619 (31.2)	
Eccentric	97 (46.4)	372 (19.8)	466 (23.5)	
LA dimension, mm	43.9 [38.0, 48.5]	43.0 [38.0, 48.0]	43.0 [38.0, 48.0]	0.561
Medial *E*/*e*′	15.6 [12.5, 20.2]	17.7 [13.3, 23.5]	15.0 [11.7, 20.0]	**<0.001**
TR maximal velocity, m/s	2.6 [2.4, 2.9]	2.7 [2.4, 3.0]	2.6 [2.4, 2.9]	**0.013**
AV peak velocity, m/s	3.5 [3.2, 4.0]	4.5 [4.1, 5.0]	3.4 [3.1, 3.7]	**<0.001**
AV mean PG, mmHg	28.0 [22.9, 36.9]	48.3 [40.1, 61.0]	26.0 [22.0, 31.0]	**<0.001**
AV area, cm^2	1.2 [1.1, 1.3]	0.8 [0.6, 0.9]	1.1 [1.0, 1.2]	**<0.001**
Semi-quantitative parameters				
Pressure half-time, ms	457 [389, 527]	—	—	—
Vena contracta width, cm	0.43 [0.34, 0.47]	—	—	—

Values are *n* (%) or presented as mean ± standard deviations or median [interquartile range]. Bold values indicate statistical significance ($P < 0.05$).
AV, aortic valve; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; IVS, interventricular septal; LA, left atrial; LV, left ventricular; LVEF, left ventricular ejection fraction; LVED(S)D, left ventricular end-diastolic(systolic) dimension; LVPW, left ventricular posterior wall; PG, pressure gradient; RAAS, renin–angiotensin–aldosterone system; TR, tricuspid regurgitation.

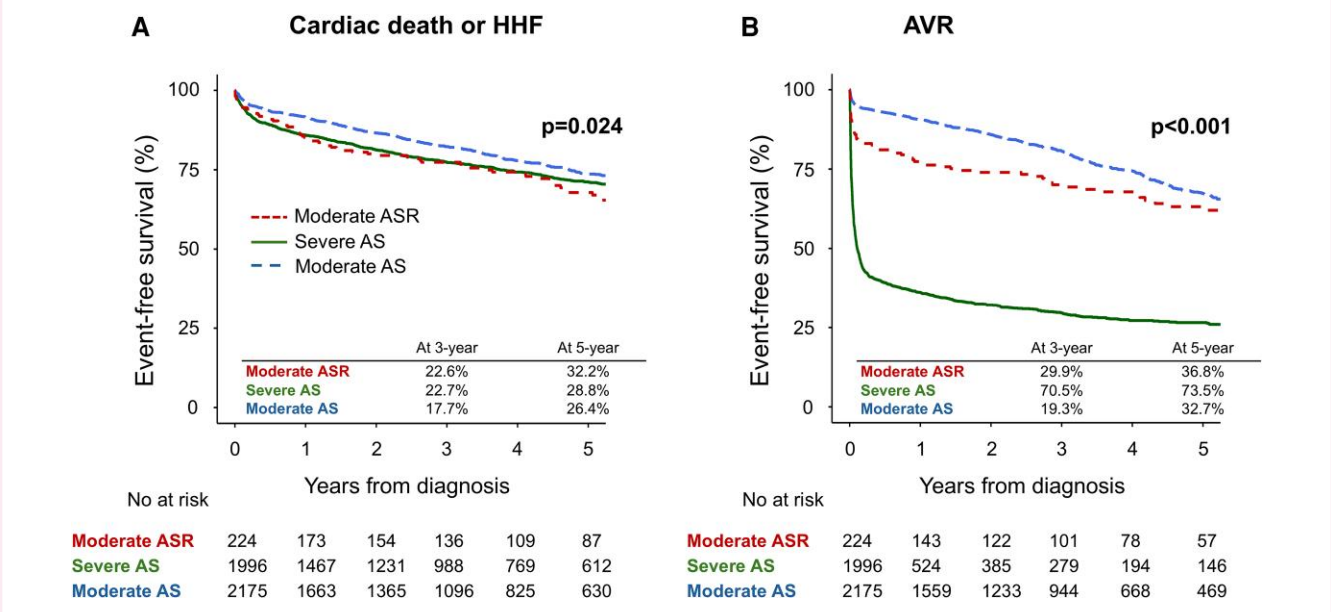


Figure 2 Event-free survival. The incidence of cardiac death or HHF (*A*) and AVR (*B*) among the patients with moderate ASR, severe AS, or moderate AS. AS, aortic stenosis; ASR, aortic stenosis with regurgitation; AVR, aortic valve replacement; HHF, hospitalization for heart failure.

Table 2 Hazard ratios for clinical outcomes according to the type of valvular heart disease

Outcome	Event (Incidence rate per 100 PY)	Unadjusted	Adjusted[a]		Adjusted for AVR[b]	
		HR (95% CI)	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Cardiac death or HHF						
Moderate ASR	75 (7.3)	Reference	Reference		Reference	
Severe AS	563 (7.3)	0.97 (0.76–1.23)	0.78 (0.61–1.00)	0.052	0.83 (0.65–1.06)	0.127
Moderate AS	524 (6.3)	0.83 (0.65–1.05)	0.67 (0.52–0.87)	**0.002**	0.66 (0.52–0.84)	**<0.001**
Cardiac death						
Moderate ASR	56 (5.0)	Reference	Reference		Reference	
Severe AS	391 (4.7)	0.91 (0.69–1.21)	0.72 (0.54–0.97)	**0.029**	0.80 (0.60–1.06)	0.121
Moderate AS	373 (4.2)	0.82 (0.62–1.08)	0.66 (0.49–0.89)	**0.005**	0.63 (0.48–0.84)	**0.002**
HHF						
Moderate ASR	29 (2.8)	Reference	Reference		Reference	
Severe AS	221 (2.9)	0.95 (0.65–1.41)	0.89 (0.59–1.34)	0.568	0.80 (0.52–1.23)	0.307
Moderate AS	200 (2.4)	0.79 (0.53–1.16)	0.72 (0.48–1.09)	0.124	0.74 (0.49–1.13)	0.165
Death						
Moderate ASR	101 (9.1)	Reference	Reference		Reference	
Severe AS	786 (9.4)	1.02 (0.83–1.26)	0.82 (0.66–1.01)	0.065	0.97 (0.79–1.20)	0.812
Moderate AS	909 (10.3)	1.11 (0.91–1.37)	0.90 (0.73–1.12)	0.351	0.84 (0.69–1.04)	0.103
Death or AVR						
Moderate ASR	156 (21.5)	Reference	Reference		Reference	
Severe AS	1736 (74.3)	2.55 (2.16–3.01)	2.62 (2.21–3.11)	**<0.001**	NA	NA
Moderate AS	1309 (19.0)	0.85 (0.72–1.01)	0.83 (0.70–0.99)	**0.040**	NA	NA

Bold values indicate statistical significance ($P < 0.05$).
AS, aortic stenosis; ASR, aortic stenosis with regurgitation; AVR, aortic valve replacement; CI, confidence interval; HHF, hospitalization for heart failure; HR, hazard ratio; NA, not available; PY, person-year.
[a]Adjusted for age, sex, hypertension, diabetes, dyslipidaemia, atrial fibrillation, renal dysfunction, chronic obstructive pulmonary disease, prior myocardial infarction, and prior cerebrovascular event.
[b]Further adjustment for AVR as a time-varying variable.

compared with moderate ASR), whereas it was comparable to that in severe AS (aHR 0.78; 95% CI 0.61–1.00; $P = 0.052$, compared with moderate ASR; *Table 2*). In contrast, all-cause mortality rates did not differ significantly among the three groups.

During follow-up, AVR was performed in 1954 patients, with significant differences in incidence among the groups (log rank $P < 0.001$; *Figure 2B*). AVR rates per 100 person-years were 11.1 for moderate ASR, 57.2 for severe AS, and 7.8 for moderate AS ($P < 0.001$), corresponding to 3-year incidences of 29.9%, 70.5%, and 19.3%, respectively. The median times to AVR were 0.4 years [0–3.1] for moderate ASR, 0 years [0–0.1] for severe AS, and 2.0 years [0.3–4.0] for moderate AS. Among those who underwent AVR, 1280 (65.5%) underwent surgical AVR and 674 (34.5%) underwent TAVR. Even after time-dependent adjustment for AVR, the moderate ASR group continued to show a significantly higher risk of cardiac death or HHF compared with moderate AS, while maintaining comparable risk to severe AS (*Table 2*). However, patients with low-flow low-gradient severe AS—a distinct subgroup comprising 3.7% (72 patients) of the severe AS group—had a significantly higher risk of cardiac death or HHF compared with the moderate ASR group (aHR 1.78; 95% CI 1.09–2.93; $P = 0.022$).

Predictors of the primary outcome in moderate ASR

In the multivariable Cox regression analysis (*Table 3*), the following factors were identified as independent predictors of cardiac death or HHF in patients with moderate ASR: older age (aHR 1.07 per year; 95% CI 1.03–1.08; $P < 0.001$), male sex (aHR 1.81; 95% CI 1.09–3.01; $P = 0.022$), renal dysfunction (aHR 2.86; 95% CI 1.72–4.74; $P < 0.001$), and lower LVEF (per 1% increase, aHR 0.97; 95% CI 0.95–0.99; $P = 0.010$). After further adjustment for AVR as a time-varying variable, these associations remained significant. Furthermore, AVR itself was associated with a 60% reduction in the risk of cardiac death or HHF (aHR 0.42; 95% CI 0.20–0.87; $P = 0.020$) in this multivariable analysis.

Patients with low-flow status had a significantly higher incidence of the primary outcome (see Supplementary data online, *Table S5*). However, low-flow status was not included in the multivariable analysis due to its low prevalence and substantial overlap with reduced LVEF.

Predictors of AVR in moderate ASR

Among 224 patients with moderate ASR, AVR was performed in 81 individuals. The cumulative incidence of AVR was 22.6% at 1 year, 29.9% at 3 years, and 36.8% at 5 years. Baseline characteristics of patients with moderate ASR, stratified by AVR status, are presented in Supplementary data online, *Table S6*. In univariable analysis, factors associated with AVR utilization included the presence of symptoms, prior myocardial infarction, larger LV end-diastolic dimension and LV mass, lower LVEF, higher peak AV velocity, and higher mean pressure gradient (*Table 4*). In multivariable analysis, the three strongest independent predictors of AVR were presence of symptoms (aHR 2.26; 95% CI 1.35–3.79; $P = 0.002$), prior myocardial infarction (aHR 3.03; 95% CI

Table 3 Predictors of the primary outcome in patients with moderate ASR

	Univariable analysis		Multivariable analysis		Multivariable analysis including AVR	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Clinical						
Age, +1 year	1.06 (1.04–1.09)	<0.001	1.07 (1.03–1.08)	**<0.001**	1.05 (1.02–1.09)	**<0.001**
Male	1.61 (1.02–2.55)	0.041	1.81 (1.09–3.01)	**0.022**	1.85 (1.09–3.15)	**0.023**
Symptoms	1.05 (0.67–1.66)	0.831				
Hypertension	1.09 (0.69–1.71)	0.716				
Diabetes	1.56 (0.93–2.61)	0.091	1.04 (0.57–1.88)	0.902	1.01 (0.56–1.83)	0.963
Dyslipidaemia	1.44 (0.87–2.39)	0.154				
Renal dysfunction	3.74 (2.33–6.00)	<0.001	2.86 (1.72–4.74)	**<0.001**		
Atrial fibrillation	1.75 (0.94–3.26)	0.080	1.40 (0.71–2.978	0.335	1.42 (0.75–2.66)	0.278
COPD	1.67 (0.87–3.19)	0.121				
Prior MI	2.26 (0.91–5.61)	0.080	1.80 (0.65–4.95)	0.257	2.28 (0.66–7.89)	0.193
Prior CVA	1.75 (0.89–3.41)	0.104				
Echocardiographic						
LVEDD, +1 mm	0.99 (0.96–1.03)	0.669				
LVEF, +1%	0.97 (0.95–0.99)	<0.001	0.97 (0.95–0.99)	**0.010**	0.97 (0.94–0.99)	**0.002**
LV mass, +1 g	1.00 (1.00–1.00)	0.947				
LA dimension, +1 mm	1.01 (0.98–1.03)	0.669				
Medial $E/e' \geq 15$	1.36 (0.80–2.32)	0.252				
AV peak velocity, m/s	0.68 (0.45–1.02)	0.061	0.67 (0.43–1.03)	0.069	0.86 (0.54–1.36)	0.519
AV mean PG, mmHg	0.98 (0.96–1.01)	0.157				
AV area, cm^2	0.36 (0.10–1.32)	0.124				

Bold values indicate statistical significance ($P < 0.05$).
AV, aortic valve; ASR, aortic stenosis with regurgitation; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; HR, hazard ratio; LA, left atrial; LV, left ventricular; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PG, pressure gradient.

1.27–7.20; $P = 0.012$), and higher peak AV velocity (per 1 m/s increase, aHR 3.51; 95% CI 2.36–5.20; $P < 0.001$).

Subgroup analysis comparing moderate ASR and moderate AS

Compared with moderate AS, female patients with moderate ASR had a comparable risk of cardiac death or HHF (HR 0.91; 95% CI 0.64–1.29; $P = 0.584$). However, male patients with moderate ASR had a significant higher risk (HR 1.60; 95% CI 1.17–2.20; $P = 0.004$; *Figure 3A*).

When stratified by LVEF (≥55% vs. <55%), patients with moderate ASR and preserved LVEF (≥55%) had a similar incidence of cardiac death or HHF compared with those with moderate AS (HR 0.98; 95% CI 0.74–1.30; $P = 0.888$). However, patients with LVEF < 55% had a significantly higher incidence of cardiac death or HHF than the moderate AS group (HR 2.56; 95% CI 1.67–3.93; $P < 0.001$; *Figure 3B*).

Discussion

In this large, multicentre cohort, we found that patients with moderate ASR had a risk of cardiac death or HHF comparable to those with severe AS, despite a significantly lower AVR rate. In contrast, moderate ASR patients had significantly worse outcomes than those with moderate AS. These findings underscore the need for heightened surveillance and potentially earlier intervention in selected high-risk patients with moderate ASR. Three key predictors of adverse outcomes in moderate ASR were older age, male sex, and lower LVEF. Notably, patients with an LVEF ≥ 55% had outcomes comparable to those with moderate AS, whereas those with an LVEF < 55% had significantly higher risks of cardiac death or HHF, suggesting that LV systolic function may be a critical determinant for risk stratification.

Clinical challenges in managing moderate ASR

Management decisions in MAVD are often guided by the predominant lesion when either AS or AR is severe. However, when both AS and AR are moderate, clinical decision-making becomes more complex because the haemodynamic burden is difficult to quantify. Therefore, understanding the characteristics and prognosis of moderate ASR is critical for refining treatment strategies. The prevalence of concomitant AS and AR remains poorly defined. A Swedish nationwide registry reported that 6.8% of patients with AS had concurrent AR,[1] but the study was limited by its reliance on International Classification of Diseases codes, which do not provide precise severity grading. In our study cohort, which excluded patients with significant mitral valve disease, the prevalence of moderate ASR among patients with significant AS was 5.1% (224 out of 4395 patients), reflecting contemporary real-world practice.

Comparison with prior studies and study strengths

The findings of this study are consistent with previous research suggesting that moderate ASR carries a prognosis comparable to that of severe

Table 4 Predictors of the aortic valve replacement in patients with moderate ASR

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Clinical				
Age, +1 year	1.00 (0.98–1.02)	0.921		
Male	1.48 (0.95–2.29)	0.083	1.11 (0.67–1.86)	0.676
Symptoms	2.74 (1.69–4.42)	<0.001	2.26 (1.35–3.79)	**0.002**
Hypertension	0.02 (0.52–1.24)	0.320		
Diabetes	0.88 (0.50–1.56)	0.667		
Dyslipidaemia	0.62 (0.34–1.12)	0.115		
Renal dysfunction	1.47 (0.86–2.48)	0.156		
Atrial fibrillation	0.91 (0.46–1.83)	0.801		
COPD	0.95 (0.46–1.98)	0.893		
Prior MI	2.58 (1.12–5.98)	0.027	3.03 (1.27–7.20)	**0.012**
Prior CVA	1.35 (0.64–2.81)	0.431		
Echocardiographic				
LVEDD, +1 mm	1.05 (1.02–1.09)	0.003	1.00 (0.95–1.06)	0.937
LVEF, +1%	0.98 (0.96–1.00)	0.044	0.98 (0.95–1.01)	0.132
LV mass, +1 g	1.00 (1.00–1.01)	0.005	1.00 (1.00–1.00)	0.779
LA dimension, +1 mm	1.02 (0.99–1.04)	0.201		
Medial *E*/*e*′, +1	1.01 (0.98–1.04)	0.677		
AV peak velocity, m/s	2.78 (2.03–3.81)	<0.001	3.51 (2.36–5.20)	**<0.001**
AV mean PG, mmHg	1.07 (1.05–1.08)	<0.001		
AV area, cm^2	0.39 (0.09–1.57)	0.183		

Bold values indicate statistical significance ($P < 0.05$).
AV, aortic valve; ASR, aortic stenosis with regurgitation; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; HR, hazard ratio; LA, left atrial; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PG, pressure gradient.

AS.[5,11,12] However, this study offers several contributions by addressing the limitations of prior investigations, thereby enhancing the generalizability and robustness of its conclusions. First, unlike previous studies that included a high prevalence of bicuspid AV disease,[5,6] the present study focused exclusively on degenerative MAVD. Bicuspid AV is a congenital condition with distinct pathophysiological characteristics and a different natural disease progression compared with degenerative AV disease.[13,14] By excluding patients with bicuspid AV, we eliminated a major source of heterogeneity, allowing for a more accurate assessment of the prognosis and clinical course of degenerative moderate ASR. Secondly, this study included an older patient cohort, which more accurately reflects contemporary real-world populations with MAVD. Prior studies predominantly enrolled younger patients, with a mean age in the 50s or 60s.[5,6] In contrast, the median age in this study was 76 years, which aligns with the demographic profile of patients typically seen in clinical practice. Given the increasing prevalence of degenerative AV disease in ageing populations, these findings are relevant to current clinical decision-making. Thirdly, this study incorporated AVR as a time-dependent covariate in the survival analysis, a methodological improvement that enhances the validity of the findings. Many prior studies treated AVR as a static event, which may have led to biased estimates of long-term outcomes. By applying time-varying Cox regression models, this study provides a more accurate representation of the natural disease course in untreated moderate ASR, ensuring that the prognostic implications are less confounded by variations in AVR timing or selection bias for intervention. By focusing on degenerative MAVD, an older population, and time-varying AVR adjustment, this study provides clinically relevant insights that may refine risk stratification and inform future treatment guidelines for moderate ASR.

AVR utilization in moderate ASR: is there underuse?

The incidence of AVR in moderate ASR was significantly lower than in severe AS (11.1 vs. 57.2 per 100 person-years, $P < 0.001$). Given that the risk associated with moderate ASR is comparable to that in severe AS, concerns arise regarding the potential underutilization of AVR in moderate ASR. Compared with prior studies, our AVR rate in moderate ASR was higher than that reported by Patel *et al.*[12]—likely due to more severe haemodynamic profiles in our cohort—but lower than the 80% AVR rate reported by Egbe *et al.*,[5] which included younger patients and a high proportion of bicuspid AV and was conducted before the widespread adoption of TAVR. After adjusting for AVR as a time-varying variable, moderate ASR continued to exhibit a higher incidence of cardiac death or HHF compared with moderate AS, reinforcing the clinical significance of untreated moderate ASR.

Predictors of AVR in moderate ASR

The decision to perform AVR in moderate ASR remains poorly defined. In our study, symptoms, prior myocardial infarction, and higher peak AV velocity emerged as the strongest predictors of AVR. These findings align with prior research on MAVD,[6,11] suggesting that coronary artery disease and haemodynamic burden play key roles in AVR

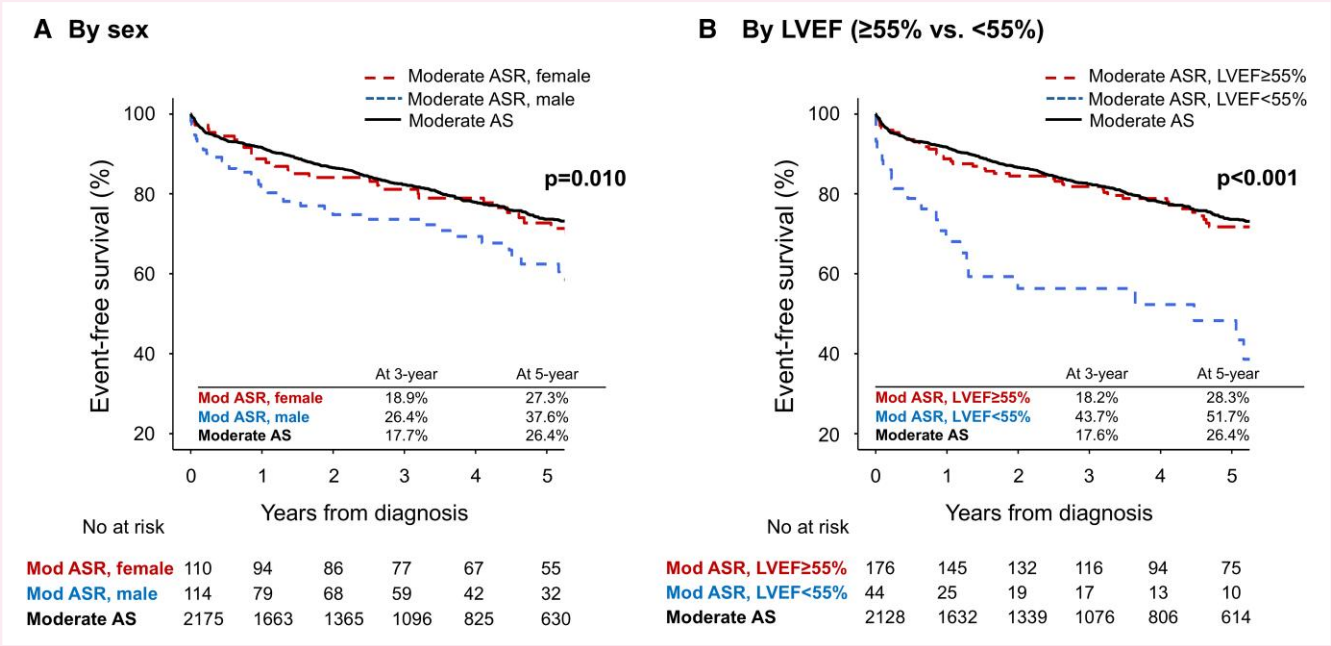


Figure 3 Incidence of cardiac death or HHF: a comparison between patients with moderate ASR and moderate AS. Compared with patients with moderate AS, male patients with moderate ASR exhibited worse outcomes, while female patients did not (*A*). Moderate ASR patients with an LVEF < 55% had a significantly higher risk of cardiac death or HHF than patients with moderate AS (*B*). AS, aortic stenosis; ASR, aortic stenosis with regurgitation; AVR, aortic valve replacement; HHF, hospitalization for heart failure; LVEF, left ventricular ejection fraction.

decision-making. Notably, age was not a predictor of AVR, likely due to widespread availability of TAVR, which has expanded AVR eligibility across age groups. Given that higher peak AV velocity was associated with more frequent AVR—a potential trigger for early intervention—the prognostic impact of peak AV velocity on the primary outcome may have been attenuated, as supported by the association between AVR and a lower risk of the primary outcome.

The influence of sex on outcomes in moderate ASR

We found that male sex was associated with a significantly higher risk of cardiac death or HHF in moderate ASR, while female patients had a risk comparable to moderate AS. This finding aligns with prior research on AS progression, which suggests that women tend to have slower haemodynamic progression and lower cardiovascular mortality compared with men.[15,16] Potential explanations include better LV remodeling responses, a lower burden of myocardial fibrosis, and sex-based differences in MAVD pathophysiology.[17] These results underscore the importance of sex-based risk stratification in moderate ASR, indicating that male patients may require closer surveillance and earlier consideration for AVR.

The role of LV dysfunction in moderate ASR

Our study identified lower LVEF as an independent predictor of adverse outcomes in moderate ASR, reinforcing the importance of LV systolic function in risk stratification. Patients with LVEF ≥ 55% had similar outcomes to those with moderate AS, whereas those with LVEF < 55% experienced a significantly higher incidence of cardiac death or HHF (HR 2.56; $P < 0.001$). These findings are consistent with prior studies demonstrating that early myocardial dysfunction in MAVD is associated with a worse prognosis.[18] Although our study did not include global longitudinal strain analysis, previous research suggests that strain abnormalities may precede LVEF decline and serve as an early marker of subclinical LV dysfunction. These results emphasize the need for comprehensive monitoring of LV function in patients with moderate ASR, potentially incorporating global longitudinal strain alongside conventional echocardiographic parameters for improved risk stratification. Additionally, impaired LV systolic function in patients with moderate ASR may reduce transaortic velocity, which could have attenuated the prognostic significance of peak AV velocity in our study. This highlights the importance of a comprehensive assessment of conventional AS parameters in conjunction with underlying LV function to achieve more accurate clinical risk assessment. Although low-flow status was strongly associated with increased cardiac risk, its relatively low prevalence—likely influenced by concomitant AR-related higher stroke volumes—precluded its detailed inclusion in our multivariable outcome models. Nevertheless, recognizing low-flow status, even if infrequent, may further assist clinicians in risk stratification among patients with moderate ASR. Moreover, patients who met stringent criteria for low-flow low-gradient severe AS, characterized by low-flow status, exhibited significantly worse clinical outcomes compared with those in the moderate ASR group. This distinct subgroup of severe AS should be appropriately recognized and classified to facilitate more accurate prognostic assessment.

Limitations

This study has several limitations. As a retrospective observational analysis, first, inherent selection bias and missing data are possible. The timing of AVR was left to physician discretion, which may have influenced results, although robust statistical methods including time-dependent covariate adjustments were applied. Additionally, while referral bias at tertiary centres could lead to selective inclusion, the prevalence of MAVD in our cohort (15.2% among patients with moderate-to-severe AS) aligns with prior registries[1] and clinical imaging studies.[18] Therefore,

despite these potential limitations, our findings reflect contemporary clinical practice and provide valuable comparative insights between moderate ASR and isolated AS. Secondly, longitudinal echocardiographic data were not available, preventing the assessment of serial changes in key parameters, such as peak AV velocity, mean pressure gradient, diastolic function, and LV systolic function. Evaluating these changes over time could have provided valuable insights into disease progression and risk stratification in moderate ASR. Furthermore, given the multicentre and retrospective design, AR severity grading was performed at each centre's discretion, reflecting real-world practice variability in mixed valvular heart disease. Fully quantitative data were not consistently available, with semi-quantitative assessments performed in ~65.2% of patients within the moderate ASR group. Despite this variability, existing literature supports consistent prognostic significance across different AR grading methodologies.[6] Thirdly, several potentially important comorbidities, such as malignancies, were not systematically captured in our multicentre retrospective cohort, primarily due to the inherent design limitations of the study. While these conditions may have limited direct impact on our primary composite outcome (cardiac death or HHF), their absence may have attenuated the observed clinical significance of valvular heart diseases on overall patient outcomes. Furthermore, although prior myocardial infarction was included in our analysis, detailed information regarding the presence or severity of underlying coronary artery disease was not available, potentially introducing residual confounding despite adjustment for major cardiovascular risk factors. However, as prior myocardial infarction itself was not independently associated with our primary outcome in multivariable analyses, the impact of this missing data is unlikely to alter our main findings. Fourthly, because of the retrospective study design, mortality may have been underestimated, particularly for patients who were lost to follow-up or referred elsewhere. To mitigate this limitation, we incorporated national registry data to ensure a more comprehensive assessment of clinical outcomes. Despite these limitations, the median follow-up duration in this study was comparable to that of prior research,[12] with median follow-up times of 3.4 years for severe AS, 3.3 years for moderate AS, and 4.2 years for moderate ASR. The consistency of findings across groups suggests that any potential underestimation of events is unlikely to have biased the overall conclusions. Ultimately, this study provides important real-world insights into the risk profiles, haemodynamic characteristics, and clinical outcomes of moderate ASR, offering valuable guidance for clinical decision-making and informing future prospective studies aimed at optimizing its management.

Conclusions

In this large multicentre cohort, patients with moderate ASR exhibited a risk of cardiac death or HHF comparable to that of severe AS, despite a lower AVR rate. Older age, male sex, renal dysfunction, and lower LVEF (<55%) were identified as independent predictors of adverse outcomes, highlighting the importance of risk stratification in this population. These findings suggest that moderate ASR should not be considered a benign condition and that early identification of high-risk patients, along with timely consideration of AVR, is warranted.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

Author contributions

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author (S.-J.P.).

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