

BMJ Open Prognostic impact of combined non-severe aortic stenosis and mitral regurgitation on clinical outcomes: a single-centre retrospective study

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ABSTRACT

Objectives Though the concomitant occurrence of non-severe aortic stenosis (AS) and mitral regurgitation (MR) is highly prevalent, there are limited data to guide clinical decision-making in this condition. Here, we attempt to determine an aortic valve area (AVA) cut-off value associated with worse clinical outcomes in patients with combined non-severe AS and MR.

Methods Single-centre, retrospective analysis of consecutive patients who underwent echocardiography examination between 2010 and 2021 with evidence of combined non-severe AS and MR. We excluded patients with ≥moderate aortic valve regurgitation or mitral stenosis, as well as patients who underwent any aortic or mitral intervention either prior or following our assessment (n=372).

Results The final cohort consisted of 2933 patients with non-severe AS, 506 of them with >mild MR. Patients with both pathologies had lower cardiac output and worse diastolic function.

Patients with an AVA ≤1.35 cm² in the presence of >mild MR had the highest rates of heart failure (HF) hospitalisations (HR 3.1, IQR 2.4–4, p<0.001) or mortality (HR 2, IQR 1.8–2.4, p<0.001), which remained significant after adjusting for clinical and echocardiographic parameters.

Conclusion Patients with combined non-severe AS and MR have a higher rate of HF hospitalisations and mortality. An AVA≤1.35 cm² in the presence of >mild MR is associated with worse clinical outcomes.

INTRODUCTION

Multiple valvular heart disease (mVHD) is defined as the combination of stenotic or regurgitant lesions occurring in ≥2 cardiac valves.¹ The presence of mVHD may significantly affect the evaluation of each valvular lesion severity by affecting left ventricular (LV) filling pressures, preload and afterload. Moreover, mVHD was associated with worse outcomes. In the Euro Heart Survey, mVHD was observed in 20% of the patients with native VHD,² whereas in a Swedish nationwide study, mVHD was present in 11% of

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Single-centre retrospective analysis of patients who underwent echocardiography examination between 2010 and 2021 which demonstrated combined non-severe aortic stenosis and mitral regurgitation.
- ⇒ Patients with other significant left-sided valvular abnormalities and those in whom an aortic or mitral valve intervention was done were excluded from the analysis.
- ⇒ Classification and regression trees modelling was used to identify the optimal aortic valve area cut-off value predictive of heart failure hospitalisation or all-cause mortality.
- ⇒ Further studies are warranted to validate this cut-off value.

patients, with high prevalence of combined aortic stenosis (AS) and mitral regurgitation (MR).³ Notably, definition and specific cut-off values for mVHD currently lack and are based on local practice or registries.

As the impact of combined non-severe mVHD has not been appropriately defined or evaluated, contemporary guideline documents^{4,5} focus mainly on mVHD in which at least one of the lesions involved is defined as severe. Therefore, in this study, we chose to evaluate the presence and the impact of non-severe mVHD on patients' outcomes in a large tertiary centre and seek an aortic valve area (AVA) cut-off value associated with worse clinical outcomes.

MATERIAL AND METHODS

We used a retrospective analysis performed in a single university-affiliated large tertiary care hospital.

Study population

Adult patients who underwent an echocardiography at our centre between January 2010

and March 2021, with evidence of less than severe AS combined with less than severe MR, were included in the initial cohort.

Patients with \geq moderate aortic valve regurgitation (AR) or \geq moderate mitral stenosis and those in whom an aortic or mitral valve intervention was done (n=372) were excluded from the analysis.

Doppler echocardiography

To evaluate the presence of mVHD, all patients underwent a comprehensive two-dimensional (2D) and Doppler echocardiographic study with multiple windows during the same examination. Echocardiography was performed according to contemporary European Society of Cardiology (ESC) guideline.⁶ All measurements were retrieved from the echocardiography reporting system.

Stroke volume was calculated as the product of LV outflow tract (LVOT) area and the time-velocity integral of the aortic flow velocity. Cardiac output (CO) measured as stroke volume multiplied by heart rate.

AVA was calculated using continuity equation from the flow through the LVOT with respect to the flow through the aortic valve. Multiple windows were used for the highest velocity. Severe AS was defined as a peak velocity >4 m/s, mean gradient >40 mm Hg or estimated AVA <1 cm². Both classical low-flow-low gradient and paradoxical low-flow low gradient AS were not included in the current study.

MR severity was determined by an integrative, semi-quantitative and quantitative approach, including assessment of vena contracta width, valve morphology, chamber size, jet area, jet density and contour, and when available, effective orifice area (ERO) and regurgitant volume. After excluding those defined as severe MR, we grouped those patients into MR \leq mild and MR $>$ mild.

Measurements of mitral inflow included the peak early filling (E wave) and late diastolic filling (A wave) velocities, the E/A ratio and deceleration time (DT) of early filling velocity. Early diastolic mitral annular velocities (e') were measured from both septal and lateral annulus. Left atrium volume was calculated by tracing the endocardial borders at end-systole in the apical four-chamber and two-chamber views, with LA volume index calculated by adjusting to the patient's body surface area.

Systolic pulmonary arterial pressure (sPAP) was determined by the maximal tricuspid regurgitant velocity and an estimation of right atrial pressure according to the vena cava width and responsiveness.

LV diameters including left ventricle end systolic and diastolic diameter (LVESd, LVEDd) were measured using lineal 2D echocardiography or M-mode parallel to the mitral valve annulus.

Right ventricular (RV) size and function assessment was based on multiple views of the RV. An integrative qualitative grading of RV function was formulated by a specialised imaging cardiologist responsible for the echocardiographic study.

Clinical data and outcome measures

Baseline characteristics including age, sex and major comorbidities were extracted from the electronic health record (EMR). Hospitalisation for heart failure (HF) which occurred at our medical centre alone was retrieved from the electronic health record. The date of mortality (if occurred) was automatically updated in the hospital records via the Ministry of Health.

All the data obtained in the study were retrieved from the hospital anonymised database that includes all clinical and echocardiographic information.

Statistical analysis

Categorical variables are reported as numbers and percentages, and continuous variables are reported as means and SD or medians and IQRs, as appropriate. Continuous variables were tested for normal distribution using histograms, Q-Q plots and normality tests (Kolmogorov-Smirnov and Shapiro-Wilk). Continuous variables were compared between groups using independent Mann-Whitney U test, post hoc Bonferroni correction applied to analyse subgroup comparison. Categorical variables were compared using χ^2 test or Fisher's exact test, post hoc Bonferroni correction applied to analyse subgroup comparison.

The AVA was divided into categories by means of a classification and regression trees model for the prediction of HF hospitalisation, with a minimum of 100 cases in parent node and minimum of 50 cases in child node. The analysis selects the best predictor for splitting the data into child nodes. A p value is given for each branch.

Long-term outcome (all-cause mortality or HF hospitalisation) assessed using a Cox regression model, also adjusted for clinical and echocardiographic parameters. The following variables were included:

Clinical variables: Age, sex, chronic renal failure (CRF), hypertension, ischaemic heart disease (IHD), AF, HF and chronic obstructive pulmonary disease (COPD).

Echocardiographic variables: Ejection fraction (EF), LVEDd, LVESd, degree of AR, RV function and RV size. Of note, due to the expected effect of mVHD on LV filling indices and forward flow (stroke volume), as the major haemodynamic consequences leading to HF hospitalisation, these parameters we evaluated in the Cox regression model separately.

All statistical tests were two sided, and a $p < 0.05$ was considered statistically significant. SPSS software was used for all statistical analysis (IBM SPSS statistics, V.25).

RESULTS

Patient clinical characteristics

The study cohort included 2933 patients with non-severe AS. Of whom, 2427 had \leq mild MR and 506 $>$ mild MR. Data regarding the aetiology of $>$ MR were available in 59% (299 patients), in whom 22 secondary and 277 with primary MR. [Table 1](#) provides the patients' clinical characteristics.

Table 1 Patients' clinical characteristics in the entire cohort and according to severity of mitral regurgitation (MR)

	All patients (n=2933)	Patients with up to mild MR (n=2427)	Patients with greater than mild MR (n=506)	P value
Age (years)*	80.64 (73.16–86.7)	80.11 (72.42–86.24)	83.15 (76.3–88.57)	<0.001
Follow-up (days)*	1127.54 (392.45–1998.65)	1227.27 (488.60–2100.26)	721.52 (150.39–1471.61)	<0.001
Sex (female)	1379 (47)	1111 (45.8)	268 (53)	0.03
Deceased during Follow-up	1571 (53.6)	1236 (50.9)	335 (66.2)	<0.001
Heart failure admission	435 (14.8)	314 (12.9)	121 (23.9)	<0.001
AF	657 (22.4)	471 (19.4)	186 (36.8)	<0.001
CRF	423 (14.4)	313 (12.9)	110 (21.7)	<0.001
Malignancy	642 (21.9)	528 (21.8)	114 (22.5)	0.702
Hypertension	1877 (64)	1516 (62.5)	361 (71.3)	<0.001
DM	965 (32.9)	801 (33)	164 (32.4)	0.796
CVA/TIA	379 (12.9)	305 (12.6)	74 (14.6)	0.209
IHD	1131 (38.6)	901 (37.1)	230 (45.5)	<0.001
COPD	269 (9.2)	223 (9.2)	46 (9.1)	0.945

*Median and IQR. All other values represent the number of patients and percentages.

AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; CVA, cerebrovascular accident; DM, diabetes mellitus; IHD, ischaemic heart disease; TIA, transient ischaemic attack.

The median follow-up time of the entire cohort was 1127 days (IQR 392–1999), during which 1572 patients (53.6%) had died and 435 patients (14.8%) had experienced an HF hospitalisation.

Compared with patients with \leq mildMR, patients with $>$ mildMR were older (80.1 years, IQR 72.4–86.2 vs 83.2 years, IQR 76.3–88.6, $p<0.001$), with a predominance female population (45.8% vs 53%, $p=0.03$), respectively.

In addition, patients with $>$ mildMR were more likely to have a history of AF (36.8% vs 22.4%, $p<0.001$), CRF (21.7% vs 12.9, $p<0.001$), hypertension (71.3% vs 62.5%, $p<0.001$) and IHD (45.5% vs 37.1%, $p<0.001$).

Examining outcomes, patients with $>$ mildMR experienced a higher rate of HF hospitalisations (23.9% vs 12.9%, $p<0.001$) and increased all-cause mortality (66.2% vs 53.6%, $p<0.001$).

Patient echocardiographic measurements

Patients' echocardiographic measurements in the entire cohort and according to severity of MR are presented in table 2.

Patients with $>$ mildMR had slightly lower CO values (5.03 mL/m², IQR 4.29–6.18 vs 5.64 (IQR 4.78–6.61, $p<0.001$) and a greater left ventricle end-systolic (31 mm, IQR 26–38, vs 28, IQR 25–33, $p<0.001$) and end-diastolic diameters (49 mm, IQR 45–54 vs 47, IQR 43–51, $p<0.001$).

Proximal isovelocity hemispheric surface area data were available only in a portion of patients with $>$ mildMR. These patients had an ERO area of 0.1 cm² (IQR 0.1–0.2, n=184/514) with a regurgitant volume of 26 mL (IQR 17–35 mL, n=105/330).

As expected, patients with $>$ mildMR had an overall worse diastolic indices with a larger LA volume index,

shorter DT, higher E/A ratio and elevated SPAP compared with patients with \leq mildMR. The average e' for the entire cohort was mildly reduced (6, IQR 4.93–7.21), with no difference between MR severity groups.

Higher rates of RV dysfunction and RV dilatation were found in patients with $>$ mildMR (table 2).

AVA optimal cut-off value

In patients with $>$ mildMR, a classification tree analysis revealed a cut-off value of 1.35 cm² to be predictive for HF hospitalisations. Accordingly, we further divided both MR groups according to the suggested AS cut-off value. Patients' clinical and echocardiographic measurements in these four subgroups are presented in table 3.

Haemodynamic impact of AVA in patients with $>$ mild MR

Among patients with $>$ mildMR, those with AVA \leq 1.35 cm² were older compared with patients with AVA $>$ 1.35 cm² (84.4 years, IQR 77.5–89.2 vs 81.2 years, IQR 73.6–87.3, respectively, $p=0.002$). There were no other statistically significant differences in baseline clinical characteristics between these two subgroups.

Patients with AVA \leq 1.35 cm² had lower CO compared with patients with an AVA $>$ 1.35 cm² (4.77 L/min, IQR 4.03–5.7 vs 5.93 L/min, IQR 4.85–6.62, respectively, $p<0.001$) and had elevated sPAP values (49 mm Hg, IQR 39–59 compared with 42 mm Hg, IQR 34–54, $p<0.001$), whereas other diastolic or RV function indices did not significantly differ between the two groups (table 3).

Effect of AVA and MR severity on clinical outcomes

The impact of MR grade and AVA on HF hospitalisations within each subgroup is presented in table 4.

Table 2 Patients' echocardiographic measurements in the entire cohort and according to severity of mitral regurgitation (MR)

		All patients (n=2933)	Patients with up to mild MR (n=2427)	Patients with greater than mild MR (n=506)	P value
Ejection fraction*		60 (55–60)	60 (55–60)	55 (45–60)	<0.001
Cardiac output (liter/min)*		5.56 (4.67–6.53)	5.64 (4.78–6.61)	5.03 (4.29–6.18)	<0.001
LVEDd (mm)*		47 (43–51)	47 (43–51)	49 (45–54)	<0.001
LVESd (mm)*		29 (25–34)	28 (25–33)	31 (26–38)	<0.001
Aortic valve area (cm ²)*		1.4 (1.2–1.6)	1.4 (1.2–1.7)	1.3 (1.1–1.5)	<0.001
Peak aortic gradient (mm Hg)*		26 (21–34)	27 (22–35)	26 (21–33)	0.045
Mean aortic gradient (mm Hg)*		15 (12–20)	15 (12–20)	15 (11–19)	0.018
LAVI (mL/m ²)*		42.7 (33.5–53.5)	40.3 (32.2–50.8)	53.1 (44–65.7)	<0.001
Deceleration time (ms)*		219 (174–274)	225 (180–275)	187 (153–241)	<0.001
E/e*		14.02 (10.97–18.34)	13.62 (10.54–17.7)	17.05 (13.18–22.39)	<0.001
Average e*		6 (4.93–7.21)	6 (4.96–7.2)	6 (4.73–7.35)	0.452
E/A ratio*		0.8 (0.7–1.1)	0.8 (0.6–1.1)	1.1 (0.9–1.6)	<0.001
sPAP (mm Hg)*		36 (30–47)	34 (29–44)	46 (37–58)	<0.001
Aortic valve regurgitation	None	1485 (50.6)	1288 (53.1)	197 (38.9)	<0.001
	Minimal	577 (19.7)	478 (19.7)	99 (19.6)	
	Mild	685 (23.4)	532 (21.9)	153 (30.2)	
	Mild to moderate	186 (6.3)	129 (5.3)	57 (11.3)	
Right ventricle function	Normal	2668 (91)	2264 (93.3)	404 (79.8)	<0.001
	Mild dysfunction	207 (7.1)	131 (5.4)	76 (15)	
	Moderate dysfunction	51 (1.7)	29 (1.2)	22 (4.3)	
	Severe dysfunction	7 (0.2)	3 (0.1)	4 (0.8)	
Right ventricle size	Normal	2593 (88.4)	2208 (91)	385 (76.1)	<0.001
	Mild dilatation	257 (8.8)	165 (6.8)	92 (18.2)	
	Moderate dilatation	63 (2.1)	41 (1.7)	22 (4.3)	
	Severe dilatation	20 (0.7)	13 (0.5)	7 (1.4)	

*Median and IQR. All other values represent the number of patients and percentages.

E/A, Early diastolic flow velocity (E velocity) divided by late diastolic transmitral flow velocity (A velocity); LAVI, Left Atrial Volume Index; LVEDd, left ventricle end diastolic diameter; LVESd, left ventricle end systolic diameter; sPAP, Systolic pulmonary artery pressure.

In univariate Cox regression analysis (figure 1), patients with >mild MR and an AVA \leq 1.35 cm² had the highest rate of HF hospitalisations compared with patients \leq mild MR and an AVA $>$ 1.35 cm² (HR 3.1, IQR 2.4–4, p<0.001).

AVA had more impact on patients' outcomes since the presence of significant MR in patients with an AVA $>$ 1.35 cm² was associated with increased rates of HF hospitalisations in univariate analysis (group 1 vs group 3, HR 1.6, IQR 1.1–2.3, p=0.007), this effect was lost after adjusting for echocardiographic parameters and/or clinical parameters. Furthermore, following adjustment for either clinical comorbidities or echocardiographic parameters only patients with a combination of >mild MR and AVA \leq 1.35 cm² had a higher HF hospitalisations rate.

Analysis concerning all-cause mortality is available in online supplemental table S1, figure S1. Patients with >mild MR and AVA \leq 1.35 cm² had higher mortality rates

compared with patients with \leq mild MR and AVA $>$ 1.35 cm², even after adjusting for clinical and/or echocardiographic parameters

The effect of diastolic function on outcome is presented in table 4.

The effect of surgical AV replacement in patients with >mild MR and AVA \leq 1.35 cm² (n=10, one patient with concomitant mitral valve intervention) on outcomes is presented in online supplemental tables S2,S3 and figure S2.

DISCUSSION

This study investigated the clinical outcomes of patients with combined non-severe AS and low-grade MR. We found two key findings:

Table 3 Patients' clinical and echocardiographic measurements according to MR severity and aortic valve area (AVA) of 1.35 cm²

	MR≤mild				MR>mild					
	AVA>1.35		AVA≤1.35		AVA>1.35		AVA≤1.35			
	Group 1 N=1333	Group 2 N=1094	Group 3 N=211	Group 4 N=295	P value	Group 3 N=211	Group 4 N=295	P value		
Age (years)*	79.3 (70.7–85.6)	81.46 (74.5–86.7)	81.2 (73.6–87.4)	84.4 (77.5–89.2)	<0.001	81.2 (73.6–87.4)	84.4 (77.5–89.2)	0.002	<0.001	0.027
Follow-up (days)*	1393 (541–2178)	1107 (432–1955)	1006 (242–1751)	574 (112–1249)	0.002	1006 (242–1751)	574 (112–1249)	0.003	<0.001	<0.001
Sex (female)	527 (39.5)	584 (53.4)	103 (48.8)	165 (55.9)	<0.001	103 (48.8)	165 (55.9)	NS	NS	NS
Deceased during Follow-up	647 (48.4)	589 (53.8)	124 (58.8)	211 (71.5)	<0.001	124 (58.8)	211 (71.5)	0.017	<0.001	0.035
Heart failure admission	176 (13.2)	138 (12.6)	38 (18)	83 (28.1)	NS	38 (18)	83 (28.1)	0.024	<0.001	NS
AF	257 (19.3)	214 (19.6)	78 (37)	108 (36.6)	NS	78 (37)	108 (36.6)	NS	0.012	<0.001
CRF	172 (12.9)	141 (12.9)	51 (24.2)	59 (20)	NS	51 (24.2)	59 (20)	NS	0.012	<0.001
Malignancy	295 (22.1)	233 (21.3)	45 (21.3)	69 (23.4)	NS	45 (21.3)	69 (23.4)	NS	NS	NS
HTN	853 (64)	663 (60.6)	145 (68.7)	216 (73.2)	NS	145 (68.7)	216 (73.2)	NS	<0.001	NS
DM	439 (32.9)	362 (33.1)	70 (33.2)	94 (31.9)	NS	70 (33.2)	94 (31.9)	NS	NS	NS
CVA/TIA	167 (12.5)	138 (12.6)	26 (12.3)	48 (16.3)	NS	26 (12.3)	48 (16.3)	NS	NS	NS
IHD	512 (38.4)	389 (35.6)	99 (46.9)	131 (44.4)	NS	99 (46.9)	131 (44.4)	NS	0.032	NS
COPD	139 (10.4)	84 (7.7)	15 (7.1)	31 (10.5)	NS	15 (7.1)	31 (10.5)	NS	NS	NS
LV EF*	60 (55–60)	60 (55–60)	60 (45–60)	55 (45–60)	1	60 (45–60)	55 (45–60)	0.514	<0.001	0.001
Cardiac output (L/min)*	6.05 (5.1–7)	5.01 (4.3–5.9)	<0.001	4.8 (4.0–5.7)	<0.001	5.9 (4.9–6.6)	4.8 (4.0–5.7)	<0.001	0.058	0.001
LVEDd (mm)*	47 (43–51)	46 (42–51)	0.019	48 (44–54)	0.019	50 (46–55)	48 (44–54)	0.18	<0.001	<0.001
LVESd (mm)*	29 (25–33)	28 (25–33)	0.334	31 (26–38)	0.334	31 (27–39)	31 (26–38)	1	<0.001	<0.001
Aortic valve area (cm ²)*	1.6 (1.5–1.9)	1.2 (1.1–1.3)	<0.001	1.13 (1.08–1.26)	<0.001	1.6 (1.4–1.8)	1.13 (1.08–1.26)	<0.001	1	0.725
Peak aortic gradient (mm Hg)*	24 (20–30)	31 (24–40)	<0.001	29 (22–38)	<0.001	23 (19–29)	29 (22–38)	<0.001	0.001	0.491
Mean aortic gradient (mm Hg)*	14 (11–17)	18 (14–24)	<0.001	17 (13–21)	<0.001	13 (11–16)	17 (13–21)	<0.001	<0.001	0.294
LAVI (mL/m ²)*	40 (32.1–50.6)	40.8 (32.4–51)	1	52.1 (44.2–65)	1	54.1 (44.66.2)	52.1 (44.2–65)	1	<0.001	<0.001
Deceleration time (ms)*	225 (182–275)	224 (180–277)	1	180 (148–229)	1	208 (162–254)	180 (148–229)	0.056	<0.001	0.001
E/e**	13.2 (10.2–17.1)	14 (11–18.2)	0.001	17.6 (14–22.6)	0.001	16.3 (12.6–22)	17.6 (14–22.6)	0.425	<0.001	<0.001
Average e**	6.2 (5.1–7.4)	5.8 (4.7–7)	<0.001	6 (4.7–7.2)	<0.001	6 (4.7–7.5)	6 (4.7–7.2)	1	1	1
E/A ratio*	0.8 (0.7–1.1)	0.8 (0.6–1.1)	1	1.2 (0.9–1.7)	1	1.1 (0.8–1.5)	1.2 (0.9–1.7)	0.451	<0.001	<0.001
sPAP (mm Hg)*	34 (28–43)	35 (29–45)	0.089	49 (39–59)	0.089	42 (34–54)	49 (39–59)	<0.001	<0.001	<0.001
MR ERO (cm ²)*	NA	NA	0.1 (0.1–0.2)	0.1 (0.1–0.2)	0.148	0.1 (0.1–0.2)	0.1 (0.1–0.2)	0.148		
MR Rvol (mL)*	NA	NA	25 (17–35)	26 (17–34)	0.893	25 (17–35)	26 (17–34)	0.893		
AR	739 (55.4)	549 (50.2)	NS	115 (39)	NS	82 (38.9)	115 (39)	NS	0.005	<0.001

Continued

Table 3 Continued

	MR \leq mild			MR>mild		
	AVA>1.35	AVA \leq 1.35	AVA>1.35	AVA>1.35	AVA \leq 1.35	AVA>1.35
	Group 1 N=1333	Group 2 N=1094	Group 3 N=211	Group 4 N=295	Group 3 N=211	Group 4 N=295
Minimal	253 (19)	225 (20.6)	30 (14.2)	69 (23.4)		
Mild	266 (20)	266 (24.3)	72 (34.1)	81 (27.5)		
Mild to moderate	75 (5.6)	54 (4.9)	27 (12.8)	30 (10.2)		
Normal	1245 (93.4)	1019 (93.1)	173 (82)	231 (78.3)	NS	<0.001
Mild	72 (5.4)	59 (5.4)	31 (14.7)	45 (15.3)		
Moderate	15 (1.1)	14 (1.3)	6 (2.8)	16 (5.4)		
Severe	1 (0.1)	2 (0.2)	1 (0.5)	3 (1)		
Normal	1221 (91.6)	987 (90.2)	167 (79.1)	218 (73.9)	NS	<0.001
Mild	83 (6.2)	82 (7.5)	33 (15.6)	59 (20)		
Moderate	24 (1.8)	17 (1.6)	9 (4.3)	13 (4.4)		
Severe	5 (0.4)	8 (0.7)	2 (0.9)	5 (1.7)		

*Median and IQR. All other values represent the number of patients and percentages.

AF, atrial fibrillation; AR, aortic regurgitation; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; CVA, cerebrovascular accident; DM, diabetes mellitus; E/A, Early diastolic flow velocity (E velocity) divided by late diastolic transmitral flow velocity (A velocity); ERO, effective orifice area; IHD, ischaemic heart disease; LAVI, Left Atrial Volume Index; LVEDd, left ventricle end diastolic diameter; LV EF, left ventricle ejection fraction; LVESd, left ventricle end systolic diameter; MR, mitral regurgitation; NA, not available; NS, not significant; RV, right ventricle; sPAP, systolic pulmonary artery pressure; TIA, transient ischaemic attack.

Table 4 Impact of MR grade and aortic valve area (AVA) on heart failure hospitalisation

	HR	95% CI	P value
Up to mild MR+AVA \leq 1.35 cm ² vs AVA>1.35 cm ²			
Univariate analysis	1.036	0.829 to 1.295	0.754
Greater than mild MR+AVA \leq 1.35 cm ² vs AVA>1.35 cm ²			
Univariate	1.893	1.288 to 2.781	0.001
Adjusted for all clinical*	1.941	1.309 to 2.880	<0.001
Adjusted for all echocardiographic†	1.672	1.097 to 2.548	0.017
Adjusted for both*†	1.774	1.157 to 2.72	0.009
Adjusted for diastolic parameter # +cardiac output	1.555	0.833 to 2.904	0.166
AVA>1.35 cm ² + MR up to mild vs greater than mild			
Univariate analysis	1.624	1.143 to 2.308	0.007
Adjusted for all clinical*	1.249	0.873 to 1.788	0.223
Adjusted for all echocardiographic†	0.992	0.652 to 1.508	0.969
Adjusted for both*†	0.881	0.572 to 1.358	0.567
Adjusted for diastolic parameter # +cardiac output	0.645	0.356 to 1.168	0.148
AVA \leq 1.35 cm ² + MR greater than mild vs up to mild			
Univariate analysis	3.056	2.324 to 4.018	<0.001
Adjusted for all clinical*	2.241	1.689 to 2.973	<0.001
Adjusted for all echocardiographic†	2.162	1.545 to 3.025	<0.001
Adjusted for both*†	1.625	1.163 to 2.271	0.004
Adjusted for diastolic parameter # +cardiac output	1.816	1.135 to 2.906	0.013
Greater than mild MR+AVA \leq 1.35 cm ² vs Up to mild MR+AVA>1.35 cm ²			
Univariate analysis	3.089	2.374 to 4.019	<0.001
Adjusted for all clinical*	2.164	1.641 to 2.852	<0.001
Adjusted for all echocardiographic†	1.67	1.205 to 2.314	0.002
Adjusted for both*†	1.296	0.941 to 1.784	0.112

Continued

Table 4 Continued

	HR	95% CI	P value
Adjusted for diastolic parameter # +cardiac output	1.175	0.708 to 1.948	0.533

*For clinical variables—age, sex, atrial fibrillation, chronic renal failure hypertension, ischaemic heart disease, COPD.

†For echocardiographic variables—ejection fraction, left ventricle end diastolic diameter, left ventricle end systolic diameter, aortic valve regurgitation grade, right ventricle size, right ventricle function # For diastolic parameter—LAVI, DT, average E/e', E/A ratio, sPAP.

COPD, chronic obstructive pulmonary disease; DT, deceleration time; E/A, Early diastolic flow velocity (E velocity) divided by late diastolic transmitral flow velocity (A velocity); LAVI, Left Atrial Volume Index; MR, mitral regurgitation.

- ▶ Patients with combined non-severe AS and low-grade MR had lower CO and impaired diastolic function compared with those without these conditions.
- ▶ AVA between 1.0 and 1.35 cm² in the presence of more than mild MR was associated with worse clinical outcomes, even after accounting for other relevant factors. Conversely, patients with an AVA greater than 1.35 cm² had clinical outcomes comparable to those without AS, regardless of the degree of non-severe MR.

AS and MR are the most prevalent VHDs in high-income countries.⁷ However, unless the patient is planned for an aortic or coronary surgery, current guidelines recommend intervention only when these valvular lesions are severe^{4,5} and limited recommendations exist for the management of patients with combined non-severe AS and MR.

The haemodynamic effects of AS result from chronic increased afterload that leads to LV hypertrophy, diastolic dysfunction and increased systolic intraventricular pressures. MR, on the other hand, reduces afterload, SV and CO but increases preload. The net effect of both lesions will reduce the net forward flow with augmentation of diastolic pressures,^{8,9} a finding compatible with our results.

While previous studies demonstrated increased mortality risk in moderate AS compared with no or mild AS,^{10–12} the impact of combined non-severe AS and low-grade MR remained less explored. Similar to our finding, smaller studies found predictors of poor outcome in this population, including \geq moderate MR, as well as lower range AVA¹³ or stage 2 cardiac structural abnormalities such as either LA enlargement or >mild MR (only nine patients in total).^{14,15} Notably, Benfari *et al*¹⁶ showed that in patients with transaortic velocity >2.5 m/s and AVA>1 cm², an MR ERO area >0.1 cm² was associated with a higher rate of HF hospitalisations or death. Our study adds to this evidence by highlighting the specific association between AVA size and clinical outcomes in the context of non-severe AS and low-grade MR.

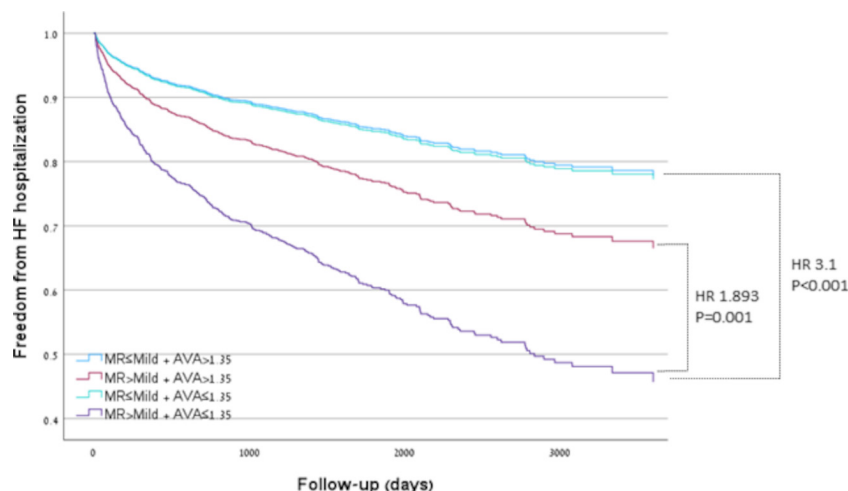


Figure 1 Univariate Cox regression analysis for heart failure (HF) hospitalisation according to severity of MR and AVA. AVA, aortic valve area; MR, mitral regurgitation.

Our cohort's all-cause mortality rate was higher compared with existing studies on severe¹⁷ or moderate AS.¹⁸ While baseline comorbidities and the presence of MR in our cohort might contribute to this finding, the most likely explanation is the older age of our study population (80.1 vs 77.8 years in severe AS and 74 years in moderate AS cohorts).

In clinical practice, it is challenging to determine the optimal timing for valvular correction of mVHD. Our data, encompassing almost 3000 patients with comprehensive echocardiographic evaluation and valid clinical outcomes, suggest that patients with combined >mild MR and $AVA \leq 1.35 \text{ cm}^2$ have worse clinical outcomes and as such could benefit from close follow-up visits and frequent serial evaluation by a multidisciplinary heart valve team. It remains to be seen, however, whether early interventions could improve the clinical outcome of these patients.

Several important limitations should be addressed. First, this is a single-centre retrospective study; thus, prospective data are needed to further establish its findings. Second, due to relatively small number of patient with combined non-severe AS and MR, we did not divide our cohort into a learning and validation groups, consequently reducing the internal validity of the study. Third, due to the observational nature of the design, we cannot definitively prove a causal relationship between the valvular abnormalities or their individual impact on outcomes. Last, as we excluded patients with other left-sided valvular abnormalities, the current finding should not be applied to other mVHD.

Our study suggests that combined non-severe AS and low-grade MR may be associated with worse clinical outcomes, particularly when the AVA falls below 1.35 cm^2 . This finding highlights the need for further investigation into the potential benefits of early intervention for these patients. Future studies could explore whether early intervention strategies, such as valve replacement or repair, can improve patients outcomes in this specific population.

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