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Complete List of Authors:	Granot, Yoav; affiliated to the Faculty of Medicine, Department of Cardiology; Icahn School of Medicine at Mount Sinai Sapir, Orly Ran; Tel Aviv Sourasky Medical Center, Department of Cardiology; Mayo Clinic, Department of Cardiovascular Medicine Laufer-Perl, Michal; Tel Aviv Sourasky Medical Center Cardiology Division Viskin, Dana; Tel Aviv Sourasky Medical Center, Cardiology Banai, Shmuel; Tel-Aviv Medical Centre, Department of Cardiology Topilsky, Yan; Tel Aviv Sourasky Medical Center, Cardiology Havakuk, Ofer; Tel Aviv Sourasky Medical Center
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The Effect of Combined Non-Severe Aortic Stenosis and Mitral Regurgitation on Clinical Outcomes

Yoav Granot, MD[1] [2], Orly Ran Sapir[1] [3], MD[1], Michal Laufer Perl MD[1], Dana Viskin MD[1], Shmuel Banai MD[1], Yan Topilsky, MD[1] and Ofer Havakuk MD[1]

From [1] Department of Cardiology, Tel Aviv Medical Center, Tel Aviv, Israel, affiliated to the Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

[2] Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai,New York, NY, United States

[3] Division of preventive Cardiology, Department of Cardiovascular Medicine, Mayo Clinic

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Corresponding author: Yoav Granot, MD, Department of Cardiology, Tel Aviv Medical Center, 6 Weizmann Street. Tel Aviv 6423906, Israel. Email: yoavgran@gmail.com

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 cut-off values associated with worse clinical outcomes in patients with combined non-severe AS and MR

Methods: Included were consecutive patients who underwent echocardiography examination in 2010-2021 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. Patient with both pathologies had lower cardiac output and worse diastolic function. Patients with an aortic valve area (AVA) ≤1.35cm² in the presence of >mild MR had the highest rates of HF hospitalizations (HR 3.1, IQR 2.4-4, P < 0.001) or mortality (HR 2, IQR 1.8-2.4, P<0.001), that remained significant after adjusting for clinical and echocardiographic parameters.

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

Keywords: Aortic stenosis, Mitral regurgitation, Heart failure, Mortality

Key messages

What is already known on this topic – Current guidelines recommend intervention only when these valvular lesions are severe and limited data exist for the management of patients with combined non-severe AS and MR

What this study adds – In patients with combined non-severe AS and MR, an AVA between 1.0-1.35cm² in the presence of >mild MR is associated with worse clinical outcomes

How this study might affect research, practice or policy – We suggest an AVA cutoff value of 1.35cm² for further evaluation and careful consideration of early intervention

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 filling pressures, preload and afterload. Moreover, mVHD was associated with worse outcomes. In the Euro Heart Survey (EHS), mVHD was observed in 20% of the patients with native VHD [2], whereas in a Swedish nationwide study, mVHD was present in 11% of patients, with high prevalence of combined aortic stenosis (AS) and mitral regurgitation (MR) [3]. Notably, definition and specific cutoff 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 center.

Material and Methods

We used a retrospective analysis performed in a single university-affiliated large tertiary care hospital. The study was reviewed and approved by the Institutional Review Board with a waiver of informed consent.

Study Population

Adult patients who underwent an echocardiography at our center 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 ≥moderate aortic valve regurgitation (AR) or ≥moderate mitral stenosis (MS) 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 and Doppler echocardiographic study with multiple windows during the same examination. Echocardiography was performed according to contemporary ESC guideline [6]. All measurements were retrieved from the echocardiography reporting system.

Stroke volume was calculated as the product of left ventricular 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.

Aortic valve area (AVA) was calculated using continuity equation from the flow through the LVOT with respect to the flow through the aortic valve. Aortic valve velocities were obtained from multiple windows for the highest obtained peak velocity and mean gradient. Severe AS was defined as a peak velocity >4m/s, mean gradient >40mmHg or estimated AVA<1cm^2.

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 these patients into: MR≤mild and MR>mild.

Pulsed-wave Doppler was performed in the apical 4-chamber view to obtain mitral inflow velocities to assess LV filling. A 1-mm to 3-mm sample volume was placed between the mitral leaflet tips at end-expiration and during diastole after optimizing spectral gain, wall filter

settings, and setting sweep speeds of 100 mm/s. Recordings were averaged over 3 consecutive cardiac cycles during sinus rhythm and over 5 cycles during atrial fibrillation (AF).

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') was measured in the apical 4-chamber view. The e' was measured from septal and lateral annulus. The ratio of peak E to peak e' was calculated (mitral E/e' ratio) from the average of at least 3 cardiac cycles. Left atrium volume was calculated by tracing the endocardial borders at end-systole in the apical four-and two-chamber views, with LA volume index calculated by adjusting to the patient's body surface index (BSA).

Systolic pulmonary arterial pressure (sPAP) was determined by the maximal tricuspid regurgitant velocity (calculated based on the simplified Bernoulli equation) 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 specialized imaging cardiologist responsible for the echocardiographic study.

Clinical data and outcome measures

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

Statistical Analysis

Categorical variables are reported as numbers and percentages, and continuous variables are reported as means and standard deviations or medians and interquartile ranges (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 test, post-hoc Bonferroni correction applied to analyze subgroup comparison. Categorical variables were compared using Chi-square test or Fisher's exact test, post-hoc Bonferroni correction applied to analyze subgroup comparison.

The AVA was divided into categories by means of a classification and regression model (CART) for the prediction of HF hospitalization, 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 hospitalization) 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, ischemic heart disease (IHD), AF, HF, 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 hemodynamic consequences leading to HF hospitalization, these parameters we evaluated in the COX regression model separately.

All statistical tests were two-sided, and a P-value of < .05 was considered statistically significant. SPSS software was used for all statistical analysis (IBM SPSS statistics, version 25, Armnok, NY, USA, 2017).

Results

Patient Clinical Characteristics

The study cohort included 2933 patients with non-severe AS. Of whom, 2427 had ≤mild MR and 506 >mild MR. Table 1 provides the patients' clinical characteristics.

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 a HF hospitalization. Compared with patients with ≤mild MR, patient with >mild MR 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 >mild MR were more likely to have a history of AF (36.8% versus 22.4%, P < 0.001), CRF (21.7% versus 12.9, P < 0.001), hypertension (71.3% versus 62.5%, P < 0.001) and IHD (45.5% versus 37.1%, P < 0.001).

Examining outcomes, patient with >mild MR experienced a higher rate of HF hospitalizations (23.9% versus 12.9%, P < 0.001) and increased all-cause mortality (66.2% versus 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 >mild MR had slightly lower cardiac output values (5.03ml/m2, IQR 4.29-6.18 versus 5.64 (IQR 4.78-6.61, P < 0.001) and a greater left ventricle end-systolic (31mm, IQR 26-38, versus 28, IQR 25-33, P < 0.001) and end-diastolic diameters (49mm, IQR 45-54 versus 47, IQR 43-51, P < 0.001).

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

As expected, patients with >mild MR had an overall worse diastolic indices with a larger LA volume index, shorter deceleration time, higher E/A ratio and elevated SPAP compared with patient with ≤mild MR. 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 >mild MR (Table 2).

Aortic valve area optimal cutoff value

In patients with >mild MR, a classification tree analysis revealed a cutoff value of 1.35cm² to be predictive for HF hospitalizations. Accordingly, we further divided both MR groups according to the suggested AS cutoff value. Patients' clinical and echocardiographic measurements in these 4 sub-groups are presented in table 3.

Hemodynamic impact of AVA in patient with >mild MR

Among patients with >mild MR, those with AVA≤1.35cm² were older compared with patients with AVA>1.35cm² (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 sub-groups.

Patient with AVA≤1.35 cm² had lower CO compared with patients with an AVA>1.35cm² (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 (49mmHg, IQR 39-59 compared with 42mmHg, 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 hospitalizations within each subgroup is presented in table 4.

In univariate Cox regression analysis (Figure 1), patients with >mild MR and an AVA≤1.35cm² had the highest rate of HF hospitalizations compared with patients ≤mild MR and an AVA>1.35cm² (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>1.35cm² was associated with increased rates of HF hospitalizations in univariate analysis (group 1 versus 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≤1.35cm² had a higher HF hospitalizations rate.

Analysis concerning all-cause mortality is available in Table S1 and Figure 1S. Patients with >mild MR and AVA≤1.35cm² had higher mortality rates compared with patients with ≤mild MR and AVA>1.35cm², even after adjusting for clinical and/or echocardiographic parameters

The effect of diastolic function on outcome is presented in table 4 and the effect of surgical AV replacement on outcomes is presented in tables S2,S3 and figure S2.

Discussion

This study sought to describe the clinical outcomes of patients with combined non-severe AS and low-grade MR. Our major findings are:

- These patients have lower CO with worse diastolic function.
- AVA between 1.0-1.35cm² in the presence of >mild MR is associated with worse clinical outcomes even after adjusting for clinical and/or echocardiographic parameters.
- In contrast, patients with an AVA>1.35cm² have similar clinical outcomes regardless of (non-severe) MR grade.

AS and MR are the most prevalent valvular heart diseases 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 hemodynamic effects of AS result from chronic increased afterload that leads to LV hypertrophy, diastolic dysfunction and increased systolic intra-ventricular 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.

Recent data show that compared with no or mild AS, moderate AS was found to be associated with increased mortality risk [10-11]. A recent meta-analysis by Coisne et al. [12] showed that

the rate difference of all-cause mortality was -3.9 (95% CI: -6.7 to -1.1) for no or mild AS compared with moderate AS. An additional retrospective analysis of 148 patients with moderate AS [13] studied predictors of poor clinical outcomes (composite of CV death, HF admission and AV replacement), and showed that ≥moderate MR, as well as lower range AVA was associated with worse outcomes. A study by Tastet et al. [14] retrospectively analyzed 735 patient with at least moderate aortic stenosis (AVA<1.5cm²) followed in the heart valve clinics of four high-volume centers. The patients were classified according to degree of cardiac structural abnormalities; with stage 2 classified as either LA enlargement or >mild MR (9 patients in total), both shown to predict higher all-cause mortality rates. A follow-up study by Amanullah et al [15] showed that stage 2 patients (~20% of them with significant MR) had worse clinical outcomes including increased all-cause mortality and HF events. Finally, Benfari et al. [16] showed that in patients with trans-aortic velocity>2.5m/s and AVA>1cm², an MR ERO area >0.1cm² was associated with a higher rates of HF hospitalizations or death.

In clinical practice, it is challenging to determine the optimal timing for valvular correction of mVHD. Our data, encompassing almost 3,000 patients with comprehensive echocardiographic evaluation and valid clinical outcomes, suggest that patients with combined >mild MR and AVA≤1.35cm² 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-center 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. Last, as we excluded patient with other left sided valvular abnormalities, the current finding should not be applied to other mVHD.

In conclusion, combined low grade AS with MR is associated with adverse outcomes. We suggest an AVA cutoff value of 1.35cm² for further evaluation and careful consideration of early intervention.

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Table 1 | Patients' clinical Characteristics in the entire cohort and according to severity of mitral regurgitation

	All patients (n=2933)	Patients with up to mild MR (n=2427)	Patient with greater than mild MR (n=506)	P value
Age (years) [a]	80.64 (73.16-86.7)	80.11 (72.42-86.24)	83.15 (76.3-88.57)	<0.001
Follow-up (days) [a]	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

[a]Median and interquartile range. All other values represent the number of patients and percentages

AF – Atrial fibrillation; CRF – Chronic renal failure; DM – Diabetes mellitus; CVA – Cerebrovascular accident; TIA – transient ischemic attack; IHD – Ischemic heart disease; COPD – Chronic obstructive pulmonary disease

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

		All patients (n=2933)	Patients with up to mild MR (n=2427)	Patient with greater than mild MR (n=506)	P value
Ejection Fraction a		60 (55-60)	60 (55-60)	55 (45-60)	<0.001
Cardiac output (liter/min) a		5.56 (4.67-6.53)	5.64 (4.78-6.61)	5.03 (4.29-6.18)	<0.001
LVEDd (mm) a		47 (43-51)	47 (43-51)	49 (45-54)	<0.001
LVESd (mm) a		29 (25-34)	28 (25-33)	31 (26-38)	<0.001
Aortic valve area (cm2) a		1.4 (1.2-1.6)	1.4 (1.2-1.7)	1.3 (1.1-1.5)	<0.001
Peak aortic gradient (mmHg) a		26 (21-34)	27 (22-35)	26 (21-33)	0.045
Mean aortic gradient (mmHg) a		15 (12-20)	15 (12-20)	15 (11-19)	0.018
LAVI (ml/m2) a		42.7 (33.5-53.5)	40.3 (32.2-50.8)	53.1 (44-65.7)	<0.001
Deceleration time (ms) a		219 (174-274)	225 (180-275)	187 (153-241)	<0.001
E/e' a		14.02 (10.97-18.34)	13.62 (10.54-17.7)	17.05 (13.18-22.39)	<0.001
Average e' a		6 (4.93-7.21)	6 (4.96-7.2)	6 (4.73-7.35)	0.452
E/A ratio a		0.8 (0.7-1.1)	0.8 (0.6-1.1)	1.1 (0.9-1.6)	<0.001
sPAP (mmHg) a		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)	

[a]Median and interquartile range. All other values represent the number of patients and percentages

LVEDd – Left ventricle end diastolic diameter; LVESd – Left ventricle end systolic diameter; LAVI – Left atrial volume index; sPAP – Systolic pulmonary artery pressure;

Table 3 | Patients' clinical and echocardiographic measurements according to MR severity and Aortic valve area of 1.35cm²

	MR <= mild			MR > Mild					
	AVA > 1.35	AVA ≤1.35		AVA > 1.35	AVA ≤1.35				
	Group 1 N=1333	Group 2 N=1094	P	Group 3 N=211	Group 4 N=295	P	P Group 2-4	P Group 1-3	P All groups
Age (years) [a]	79.29 (70.70-85.62)	81.46 (74.49-86.71)	<0.001	81.17 (73.62-87.38)	84.42 (77.51-89.21)	0.002	<0.001	0.027	<0.001
Follow-up (days) [a]	1392.46 (540.49-2178.28)	1107.03 (431.58-1955.41)	0.002	1005.51 (242.21-1750.63)	573.56 (111.7-1249.36)	0.003	<0.001	<0.001	<0.001
Sex (Female)	527 (39.5)	584 (53.4)	<0.001	103 (48.8)	165 (55.9)	NS	NS	NS	<0.001
Deceased during Follow-up	647 (48.4)	589 (53.8)	<0.001	124 (58.8)	211 (71.5)	0.017	<0.001	0.035	<0.001
Heart Failure admission	176 (13.2)	138 (12.6)	NS	38 (18)	83 (28.1)	0.024	<0.001	NS	<0.001
AF	257 (19.3)	214 (19.6)	NS	78 (37)	108 (36.6)	NS	0.012	<0.001	<0.001
CRF	172 (12.9)	141 (12.9)	NS	51 (24.2)	59 (20)	NS	0.012	<0.001	<0.001
Malignancy	295 (22.1)	233 (21.3)		45 (21.3)	69 (23.4)				0.879
HTN	853 (64)	663 (60.6)	NS	145 (68.7)	216 (73.2)	NS	<0.001	NS	<0.001
DM	439 (32.9)	362 (33.1)		70 (33.2)	94 (31.9)				0.982
CVA/TIA	167 (12.5)	138 (12.6)		26 (12.3)	48 (16.3)				0.35
CHD	512 (38.4)	389 (35.6)	NS	99 (46.9)	131 (44.4)	NS	0.032	NS	0.002
COPD	139 (10.4)	84 (7.7)		15 (7.1)	31 (10.5)				0.067
LV EF [a]	60 (55-60)	60 (55-60)	1	60 (45-60)	55 (45-60)	0.514	<0.001	0.001	<0.001
Cardiac output (liter/min) [a]	6.05 (5.13-7)	5.01 (4.3-5.93)	<0.001	5.93 (4.85-6.62)	4.77 (4.03-5.7)	<0.001	0.058	0.001	<0.001
LVEDd (mm) [a]	47 (43-51)	46 (42-51)	0.019	50 (46-55)	48 (44-54)	0.18	<0.001	<0.001	<0.001

LVESd (mm) [a]		29 (25-33)	28 (25-33)	0.334	31 (27-39)	31 (26-38)	1	<0.001	<0.001	<0.001
Aortic valve area (cm²) [a]		1.6 (1.5-1.9)	1.2 (1.1-1.3)	<0.001	1.6 (1.4-1.8)	1.13 (1.08-1.26)	<0.001	1	0.725	<0.001
Peak aortic gradient (mmHg) [a]		24 (20-30)	31 (24-40)	<0.001	23 (19-29)	29 (22-38)	<0.001	0.001	0.491	<0.001
Mean aortic gradient (mmHg) [a]		14 (11-17)	18 (14-24)	<0.001	13 (11-16)	17 (13-21)	<0.001	<0.001	0.294	<0.001
LAVI (ml/m²) [a]		40 (32.1-50.6)	40.8 (32.4-51)	1	54.1 (44.66.2)	52.1 (44.2-65)	1	<0.001	<0.001	<0.001
Deceleration time (ms) [a]		225 (182-275)	224 (180-277)	1	208 (162-254)	180 (148-229)	0.056	<0.001	0.001	<0.001
E/e' [a]		13.23 (10.18-17.07)	14 (11-18.16)	0.001	16.3 (12.56-21.95)	17.58 (14.03-22.64)	0.425	<0.001	<0.001	<0.001
Average e' [a]		6.2 (5.1-7.4)	5.8 (4.7-7)	<0.001	6 (4.7-7.5)	6 (4.7-7.2)	1	1	1	<0.001
E/A ratio [a]		0.8 (0.7-1.1)	0.8 (0.6-1.1)	1	1.1 (0.8-1.5)	1.2 (0.9-1.7)	0.451	<0.001	<0.001	<0.001
SPAP (mmHg) [a]		34 (28-43)	35 (29-45)	0.089	42 (34-54)	49 (39-59)	<0.001	<0.001	<0.001	<0.001
MR ERO (cm²) [a]		NA	NA		0.1 (0.1-0.2)	0.1 (0.1-0.2)	0.148			
MR Rvol (ml) [a]		NA	NA		25 (17-35)	26 (17-34)	0.893			
AR	None	739 (55.4)	549 (50.2)	NS	82 (38.9)	115 (39)	NS	0.005	<0.001	<0.001
	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)				
RV function	Normal	1245 (93.4)	1019 (93.1)	NS	173 (82)	231 (78.3)	NS	<0.001	<0.001	<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)				
RV size	Normal	1221 (91.6)	987 (90.2)	NS	167 (79.1)	218 (73.9)	NS	<0.001	<0.001	<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)				

[a]Median and interquartile range. All other values represent the number of patients and percentages

AF – Atrial fibrillation; CRF – Chronic renal failure; DM – Diabetes mellitus; CVA – Cerebrovascular accident; TIA – transient ischemic attack; IHD – Ischemic heart disease; COPD – Chronic obstructive pulmonary disease; LVEDd – Left ventricle end diastolic diameter; LVESd – Left ventricle end systolic diameter; LAVI – Left atrial volume index; sPAP – Systolic pulmonary artery pressure; MR - Mitral Regurgitation; RV – Rigth Ventricle; AR – Aortic regurgitation; LV EF – Left ventricle ejection fraction

Table 4 | Impact of MR grade and Aortic valve area on heart failure hospitalization

	HR	95% CI	P
Up to mild MR + AVA ≤ 1.35cm² versus AVA > 1.35cm²			
Univariate analysis	1.036	0.829-1.295	0.754
Greater than mild MR + AVA ≤ 1.35cm² versus AVA > 1.35cm²			
Univariate	1.893	1.288-2.781	0.001
Adjusted for all clinical*	1.941	1.309-2.880	<0.001
Adjusted for all echocardiographic†	1.672	1.097-2.548	0.017
Adjusted for both *†	1.774	1.157-2.72	0.009
Adjusted for Diastolic parameter # + Cardiac output	1.555	0.833-2.904	0.166
AVA > 1.35cm² + MR up to mild versus greater than mild			
Univariate analysis	1.624	1.143-2.308	0.007
Adjusted for all clinical*	1.249	0.873-1.788	0.223
Adjusted for all echocardiographic†	0.992	0.652-1.508	0.969
Adjusted for both *†	0.881	0.572-1.358	0.567
Adjusted for Diastolic parameter # + Cardiac output	0.645	0.356-1.168	0.148
AVA ≤ 1.35cm² + MR greater than mild versus up to mild			
Univariate analysis	3.056	2.324-4.018	<0.001
Adjusted for all clinical*	2.241	1.689-2.973	<0.001
Adjusted for all echocardiographic†	2.162	1.545-3.025	<0.001
Adjusted for both *†	1.625	1.163-2.271	0.004
Adjusted for Diastolic parameter # + Cardiac output	1.816	1.135-2.906	0.013
Greater than mild MR + AVA ≤ 1.35cm² versus Up to mild MR + AVA > 1.35cm²			
Univariate analysis	3.089	2.374-4.019	<0.001
Adjusted for all clinical*	2.164	1.641-2.852	<0.001
Adjusted for all echocardiographic†	1.67	1.205-2.314	0.002
Adjusted for both *†	1.296	0.941-1.784	0.112
Adjusted for Diastolic parameter # + Cardiac output	1.175	0.708-1.948	0.533

* For clinical variables – Age, Sex, Atrial fibrillation, chronic renal failure Hypertension, Ischemic 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

Table S1 | Impact of MR grade and Aortic valve area on mortality

	HR	95% CI	P
Up to mild MR + AVA ≤ 1.35cm² versus AVA > 1.35cm²			
Univariate	1.223	1.094-1.368	<0.001
Adjusted for all clinical*	1.15	1.027-1.288	0.015
Adjusted for all echocardiographic†	1.168	1.032-1.321	0.014
Adjusted for both *†	1.116	0.984-1.266	0.087
Adjusted for Diastolic parameter # + Cardiac output	0.985	0.815-1.191	0.878
Greater than mild MR + AVA ≤ 1.35cm² versus AVA > 1.35cm²			
Univariate	1.426	1.142-1.78	0.002
Adjusted for all clinical*	1.324	1.053-1.664	0.016
Adjusted for all echocardiographic†	1.242	0.969	1.592
Adjusted for both *†	1.23	0.954-1.586	0.11
Adjusted for Diastolic parameter # + Cardiac output	1.176	0.818-1.689	0.382
AVA > 1.35cm² + MR up to mild versus greater than mild			
Univariate analysis	1.431	1.181-1735	<0.001
Adjusted for all clinical*	1.22	1.003-1.484	0.046
Adjusted for all echocardiographic†	1.317	1.057-1.639	0.014
Adjusted for both *†	1.191	0.95-1.493	0.129
Adjusted for Diastolic parameter # + Cardiac output	1	0.74-1.353	0.998
AVA ≤ 1.35cm² + MR up to mild versus greater than mild			
Univariate analysis	1.684	1.438-1.972	<0.001
Adjusted for all clinical*	1.388	1.18-1.632	<0.001
Adjusted for all echocardiographic†	1.409	1.167-1.701	<0.001
Adjusted for both *†	1.196	0.99-1.444	0.064
Adjusted for Diastolic parameter # + Cardiac output	1.055	0.798-1.395	0.706
Greater than mild MR + AVA ≤ 1.35cm² versus Up to mild MR + AVA > 1.35cm²			
Univariate analysis	2.049	1.753-2.396	<0.001

Adjusted for all clinical*	1.543	1.312-1.815	<0.001
Adjusted for all echocardiographic†	1.737	1.446-2.086	<0.001
Adjusted for both *†	1.377	1.144-1.657	<0.001
Adjusted for Diastolic parameter # + Cardiac output	1.127	0.84-1.513	0.425

* For clinical variables – Age, Sex, Atrial fibrillation, chronic renal failure Hypertension, Ischemic 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

Table S2 | Patients' clinical and echocardiographic measurements according to Intervention (Surgical AVR) in patient with MR>mild and AVA≤1.35cm²

	MR > mild + AVA≤1.35cm²		
	No intervention (n=295)	SAVR (n=10)	P
Age (years) [a]	84.42 (77.51-89.21)	65.77 (63.3-68.93)	<0.001
Sex (Female)	165 (55.9)	5 (50)	0.71
Deceased during Follow-up	211 (71.5)	4 (40)	0.032
Heart Failure admission	83 (28.1)	1 (10)	0.207
AF	108 (36.6)	5 (50)	0.389
CRF	59 (20)	2 (20)	1
Malignancy	69 (23.4)	0	0.082
HTN	216 (73.2)	7 (70)	0.821
DM	94 (31.9)	5 (50)	0.228
CVA/TIA	48 (16.3)	0	0.165
IHD	131 (44.4)	6 (60)	0.33
COPD	31 (10.5)	0	0.279
LV EF [a]	55 (45-60)	60 (45-60)	0.485
Cardiac output (liter/min)	4.77 (4.03-5.7)	5.42 (4.45-7)	0.174
LVEDd (mm) [a]	48 (44-54)	51 (49-57)	0.097
LVESd (mm) [a]	31 (26-38(	31 (28-37)	0.888
Aortic valve area (cm2) [a]	1.13 (1.08-1.26)	1.15 (1.1-1.2)	0.775
Peak aortic gradient (mmHg) [a]	29 (22-38(	39 (37-45)	0.01
Mean aortic gradient (mmHg) [a]	17 (13-21)	23 (18-28)	0.009
LAVI (ml/m2) [a]	52.1 (44.2-65)	47.5 (46.8-48.4)	0.442
Deceleration time (ms) [a]	180 (148-229)	197 (173-235)	0.327
E/e' [a]	17.58 (14.03-22.64)	19.37 (17.92-23.93)	0.092

E/A ratio [a]		1.2 (0.9-1.7)	1.2 (1-2.9)	0.6
sPAP (mmHg) [a]		49 (39-59)	40 (38-50)	0.107
AR	None	115 (39)	3 (30)	0.762
	minimal	69 (23.4)	2 (20)	
	mild	81 (27.5)	3 (30)	
	mild to moderate	30 (10.2)	2 (20)	
RV function	Normal	231 (78.3)	10 (100)	0.433
	Mild	45 (15.3)	0	
	Moderate	16 (5.4)	0	
	Severe	3 (1)	0	
RV size	Normal	218 (73.9)	10 (100)	0.322
	Mild	59 (20)	0	
	Moderate	13 (4.4)	0	
	Severe	5 (1.7)	0	

[a]Median and interquartile range. All other values represent the number of patients and percentages

AF – Atrial fibrillation; CRF – Chronic renal failure; DM – Diabetes mellitus; CVA – Cerebrovascular accident; TIA – transient ischemic attack; IHD – Ischemic heart disease; COPD – Chronic obstructive pulmonary disease; LVEDd – Left ventricle end diastolic diameter; LVESd – Left ventricle end systolic diameter; LAVI – Left atrial volume index; sPAP – Systolic pulmonary artery pressure; MR - Mitral Regurgitation; RV – Rigth Ventricle; AR – Aortic regurgitation; LV EF – Left ventricle ejection fraction

Table S3 | Impact of Intervention (Surgical AVR) in patient with MR>mild and AVA≤1.35cm²

HF hospitalization	HR	95% CI	P
Univariate	0.21	0.029-1.513	0.121
Adjusted *	0.372	0.048-2.895	0.345
All-Cause Mortality			
Univariate	0.286	0.106-0.774	0.014
Adjusted *	0.508	0.177-1.461	0.209

* For Age, Left ventricle end diastolic diameter, Aortic valve Peak and mean gradient, Average E/e' ratio

Figure legend:

Figure 1 – Univariate Cox regression analysis for HF hospitalization according to severity of MR and AVA

Figure S1 – Univariate Cox regression analysis for mortality according to severity of MR and AVA

Figure S2 – Univariate Cox regression analysis for the Impact of Intervention (Surgical AVR) in patient with MR>mild and AVA≤1.35cm²

Figure 1

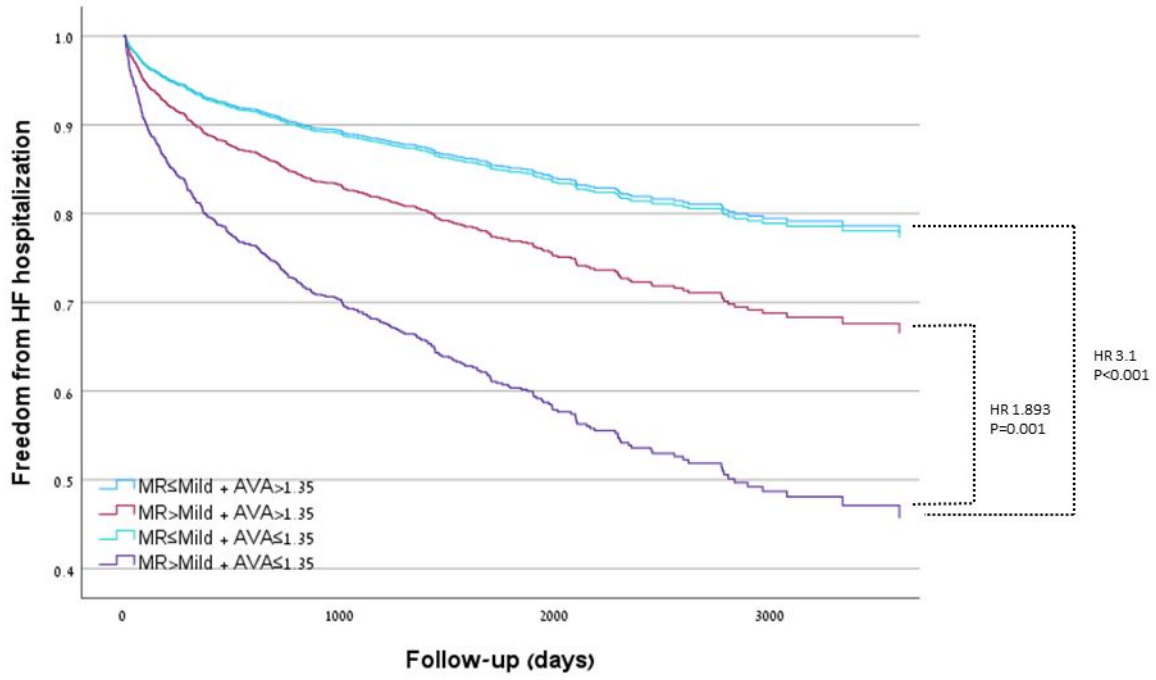


Figure S1

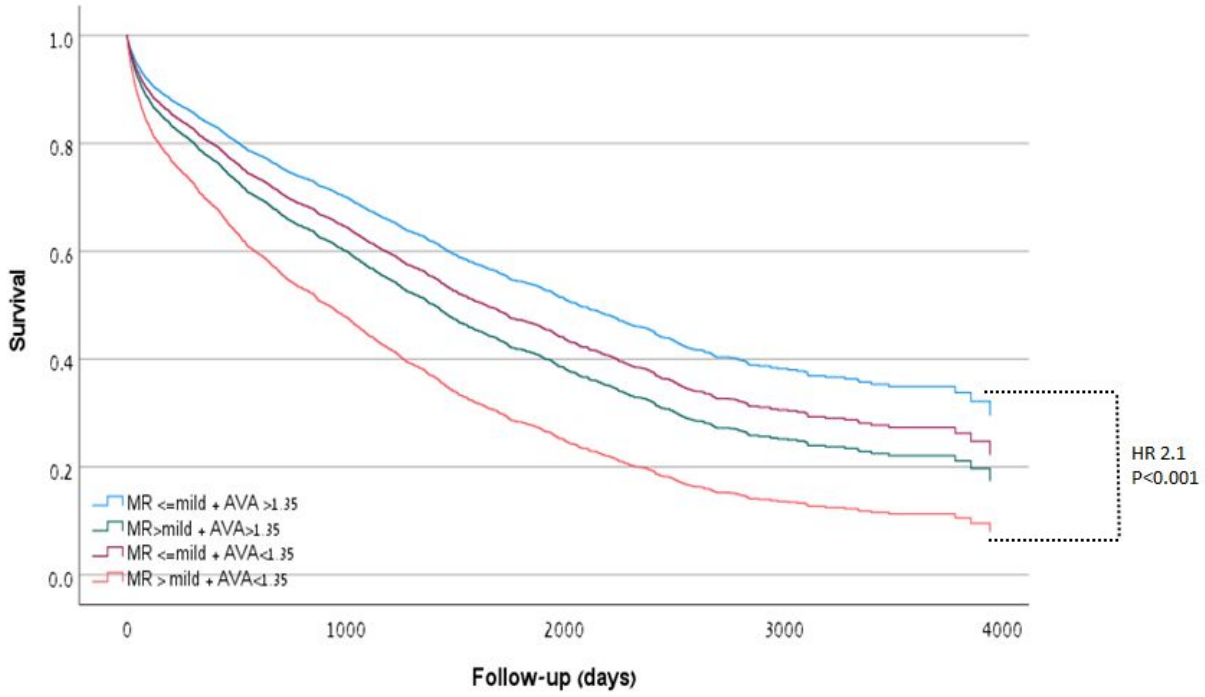
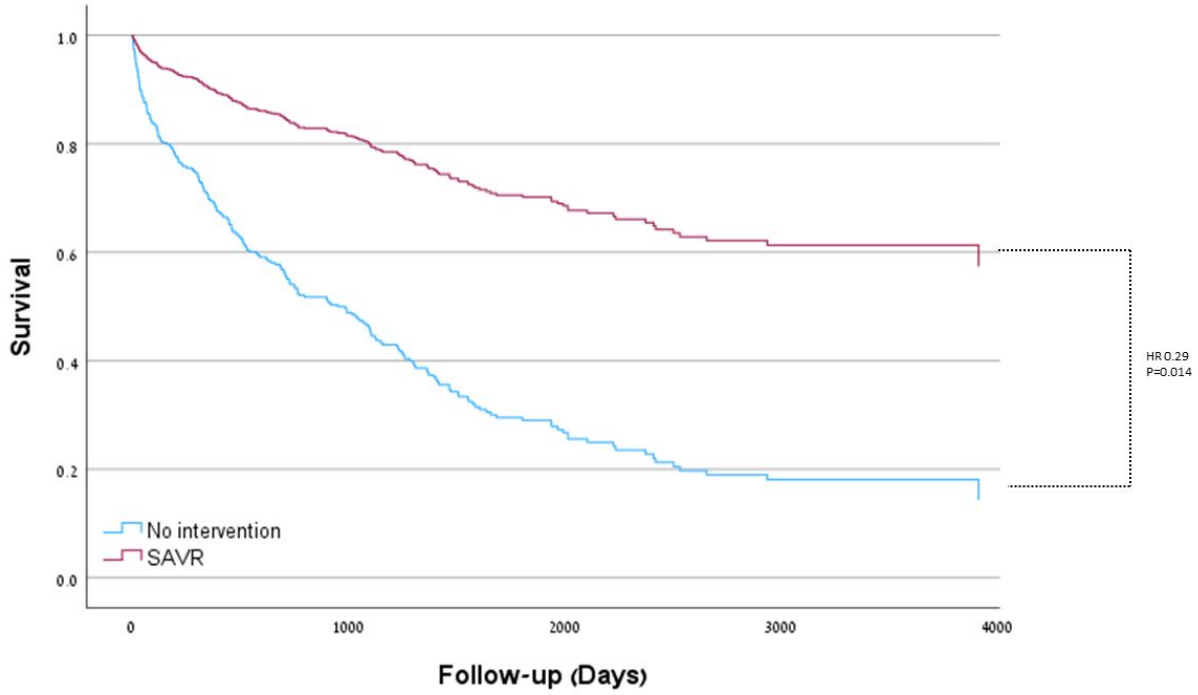


Figure S2



Data Availability Statement

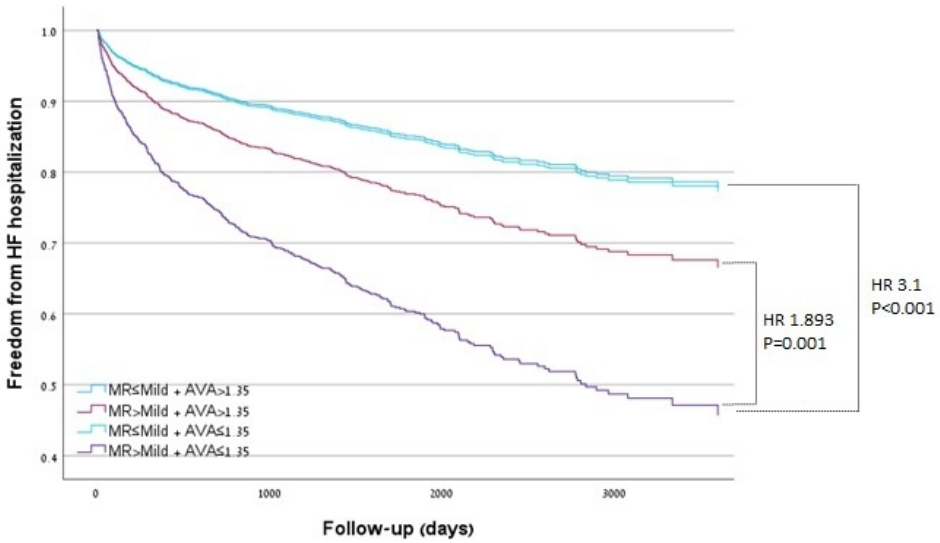
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Consent

The study was reviewed and approved by the Institutional Review Board with a waiver of informed consent. Approval number – TLV-0111-18

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research



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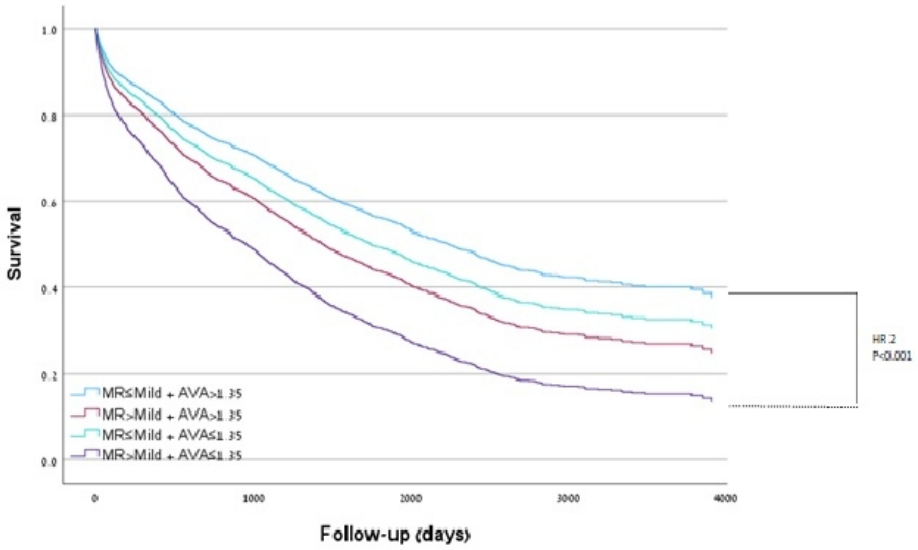

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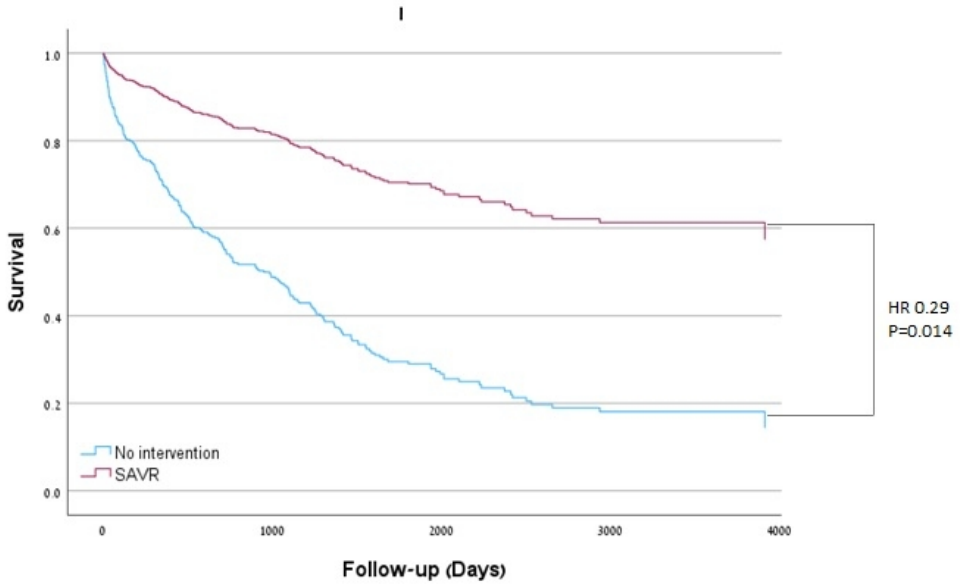

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	5-6
Study size	10	Explain how the study size was arrived at	5-6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	7
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	8

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9-10
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9-10
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12-13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Prognostic Impact of Combined Non-severe Aortic Stenosis and Mitral Regurgitation on Clinical Outcomes: A Single-Center Retrospective Study

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Complete List of Authors:	Granot, Yoav; affiliated to the Faculty of Medicine, Department of Cardiology; Icahn School of Medicine at Mount Sinai Sapir, Orly Ran; Tel Aviv Sourasky Medical Center, Department of Cardiology; Mayo Clinic, Department of Cardiovascular Medicine Laufer-Perl, Michal; Tel Aviv Sourasky Medical Center Cardiology Division Viskin, Dana; Tel Aviv Sourasky Medical Center, Cardiology Banai, Shmuel; Tel-Aviv Medical Centre, Department of Cardiology Topilsky, Yan; Tel Aviv Sourasky Medical Center, Cardiology Havakuk, Ofer; Tel Aviv Sourasky Medical Center
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Prognostic Impact of Combined Non-severe Aortic Stenosis and Mitral Regurgitation on Clinical Outcomes: A Single-Center Retrospective Study

Yoav Granot, MD[1 2], Orly Ran Sapir[1 3], MD[1], Michal Laufer Perl MD[1], Dana Viskin MD[1], Shmuel Banai MD[1], Yan Topilsky, MD[1] and Ofer Havakuk MD[1]

From [1] Department of Cardiology, Tel Aviv Medical Center, Tel Aviv, Israel, affiliated to the Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

[2] Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai,New York, NY, United States

[3] Division of preventive Cardiology, Department of Cardiovascular Medicine, Mayo Clinic

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Corresponding author: Yoav Granot, MD, Department of Cardiology, Tel Aviv Medical Center, 6 Weizmann Street. Tel Aviv 6423906, Israel. Email: yoavgran@gmail.com

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 center, retrospective analysis of consecutive patients who underwent echocardiography examination between 2010-2021 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. Patient with both pathologies had lower cardiac output and worse diastolic function. Patients with an aortic valve area (AVA) ≤1.35cm² in the presence of >mild MR had the highest rates of HF hospitalizations (HR 3.1, IQR 2.4-4, P < 0.001) or mortality (HR 2, IQR 1.8-2.4, P<0.001), that remained significant after adjusting for clinical and echocardiographic parameters.

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

Keywords: Aortic stenosis, Mitral regurgitation, Heart failure, Mortality

Strengths and limitations of this study

- Single center retrospective analysis of patients who underwent echocardiography examination between 2010-2021 which demonstrated combined non severe AS and MR
- 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.
- CART modeling was used to identify the optimal aortic valve area (AVA) cutoff value predictive of heart failure hospitalization or all-cause mortality
- Further studies are warranted to validate this cutoff value."

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 filling pressures, preload and afterload. Moreover, mVHD was associated with worse outcomes. In the Euro Heart Survey (EHS), mVHD was observed in 20% of the patients with native VHD [2], whereas in a Swedish nationwide study, mVHD was present in 11% of patients, with high prevalence of combined aortic stenosis (AS) and mitral regurgitation (MR) [3]. Notably, definition and specific cutoff 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 center and seek an AVA cutoff value associated with worse clinical outcomes.

Material and Methods

We used a retrospective analysis performed in a single university-affiliated large tertiary care hospital. The study was reviewed and approved by the Institutional Review Board with a waiver of informed consent.

Study Population

Adult patients who underwent an echocardiography at our center 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 ≥moderate aortic valve regurgitation (AR) or ≥moderate mitral stenosis (MS) 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 and Doppler echocardiographic study with multiple windows during the same examination. Echocardiography was performed according to contemporary ESC guideline [6]. All measurements were retrieved from the echocardiography reporting system.

Stroke volume was calculated as the product of left ventricular 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.

Aortic valve area (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 >4m/s, mean gradient >40mmHg or estimated AVA<1cm^2. Both classical low flow-low gradient and paradoxical low-flow low gradient aortic stenosis 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 these patients into: MR≤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') was measured from both septal and lateral annulus. Left atrium volume was calculated by tracing the endocardial borders at end-systole in the apical four-and two-chamber views, with LA volume index calculated by adjusting to the patient's body surface index (BSA).

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 specialized imaging cardiologist responsible for the echocardiographic study.

Clinical data and outcome measures

Baseline characteristics including age, sex and major co-morbidities were extracted from the electronic health record (EMR). Hospitalization for heart failure (HF) which occurred at our medical center alone were 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 anonymized 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 standard deviations or medians and interquartile ranges (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 test, post-hoc Bonferroni correction applied to analyze subgroup comparison. Categorical variables were compared using Chi-square test or Fisher's exact test, post-hoc Bonferroni correction applied to analyze subgroup comparison.

The AVA was divided into categories by means of a classification and regression model (CART) for the prediction of HF hospitalization, 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 hospitalization) 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, ischemic heart disease (IHD), AF, HF, 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 hemodynamic consequences leading to HF hospitalization, these parameters we evaluated in the COX regression model separately.

All statistical tests were two-sided, and a P-value of $< .05$ was considered statistically significant. SPSS software was used for all statistical analysis (IBM SPSS statistics, version 25, Armnok, NY, USA, 2017).

Results

Patient Clinical Characteristics

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

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 a HF hospitalization.

Compared with patients with ≤mild MR, patient with >mild MR 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 >mild MR were more likely to have a history of AF (36.8% versus 22.4%, P < 0.001), CRF (21.7% versus 12.9, P < 0.001), hypertension (71.3% versus 62.5%, P < 0.001) and IHD (45.5% versus 37.1%, P < 0.001).

Examining outcomes, patient with >mild MR experienced a higher rate of HF hospitalizations (23.9% versus 12.9%, P < 0.001) and increased all-cause mortality (66.2% versus 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 >mild MR had slightly lower cardiac output values (5.03ml/m2, IQR 4.29-6.18 versus 5.64 (IQR 4.78-6.61, P < 0.001) and a greater left ventricle end-systolic (31mm, IQR 26-

38, versus 28, IQR 25-33, P < 0.001) and end-diastolic diameters (49mm, IQR 45-54 versus 47, IQR 43-51, P < 0.001).

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

As expected, patients with >mild MR had an overall worse diastolic indices with a larger LA volume index, shorter deceleration time, higher E/A ratio and elevated SPAP compared with patient with ≤mild MR. 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 >mild MR (Table 2).

Aortic valve area optimal cutoff value

In patients with >mild MR, a classification tree analysis revealed a cutoff value of 1.35cm² to be predictive for HF hospitalizations. Accordingly, we further divided both MR groups according to the suggested AS cutoff value. Patients' clinical and echocardiographic measurements in these 4 sub-groups are presented in table 3.

Hemodynamic impact of AVA in patient with >mild MR

Among patients with >mild MR, those with AVA≤1.35cm² were older compared with patients with AVA>1.35cm² (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 sub-groups.

Patient with AVA≤1.35 cm² had lower CO compared with patients with an AVA>1.35cm² (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 (49mmHg, IQR 39-59 compared with 42mmHg, 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 hospitalizations within each subgroup is presented in table 4.

In univariate Cox regression analysis (Figure 1), patients with >mild MR and an AVA≤1.35cm² had the highest rate of HF hospitalizations compared with patients ≤mild MR and an AVA>1.35cm² (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>1.35cm² was associated with increased rates of HF hospitalizations in univariate analysis (group 1 versus 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≤1.35cm² had a higher HF hospitalizations rate.

Analysis concerning all-cause mortality is available in Table S1 and Figure 1S. Patients with >mild MR and AVA≤1.35cm² had higher mortality rates compared with patients with ≤mild MR and AVA>1.35cm², 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≤1.35cm² (n=10, one patient with concomitant mitral valve intervention) on outcomes is presented in tables S2,S3 and figure S2.

Discussion

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

- Patients with combined non-severe AS and low-grade MR had lower cardiac output and impaired diastolic function compared to those without these conditions.
- AVA between 1.0-1.35 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 valvular heart diseases 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 hemodynamic effects of AS result from chronic increased afterload that leads to LV hypertrophy, diastolic dysfunction and increased systolic intra-ventricular 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 to 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 ≥moderate MR, as well as lower range AVA [13] or stage 2 cardiac structural abnormalities such as either LA enlargement or >mild MR (only 9 patients in total) [14-15]. Notably, Benfari et al. [16] showed that in patients with trans-aortic velocity>2.5m/s and AVA>1cm2, an MR ERO area >0.1cm² was associated with a higher rates of HF hospitalizations 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. Our cohort's all-cause mortality rate was higher compared to existing studies on severe [17] or moderate AS [18]. While baseline co-morbidities 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 3,000 patients with comprehensive echocardiographic evaluation and valid clinical outcomes, suggest that patients with combined >mild MR and AVA≤1.35cm² 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-center 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 patient with other left sided valvular abnormalities, the current finding should not be applied to other mVHD.

Our study suggests that combined non-severe aortic stenosis (AS) and low-grade mitral regurgitation (MR) may be associated with worse clinical outcomes, particularly when the aortic valve area (AVA) falls below 1.35 cm². 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

Contributorship statement

YG., YT., OH. contributed to the design and implementation of the research, to the analysis of the results and to the writing of the manuscript. MLP. and SB. were involved in planning and supervised the work. YG, ORS and DV were involved in data acquisition and creation of the database. All authors discussed the results and commented on the manuscript.

Competing interests

none declared

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Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Consent

The study was reviewed and approved by the Institutional Review Board with a waiver of informed consent. Approval number – TLV-0111-18

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research

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Table 1 | Patients' clinical Characteristics in the entire cohort and according to severity of mitral regurgitation

	All patients (n=2933)	Patients with up to mild MR (n=2427)	Patient with greater than mild MR (n=506)	P value
Age (years) [a]	80.64 (73.16-86.7)	80.11 (72.42-86.24)	83.15 (76.3-88.57)	<0.001
Follow-up (days) [a]	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

[a]Median and interquartile range. All other values represent the number of patients and percentages

AF – Atrial fibrillation; CRF – Chronic renal failure; DM – Diabetes mellitus; CVA – Cerebrovascular accident; TIA – transient ischemic attack; IHD – Ischemic heart disease; COPD – Chronic obstructive pulmonary disease

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

		All patients (n=2933)	Patients with up to mild MR (n=2427)	Patient with greater than mild MR (n=506)	P value
Ejection Fraction a		60 (55-60)	60 (55-60)	55 (45-60)	<0.001
Cardiac output (liter/min) a		5.56 (4.67-6.53)	5.64 (4.78-6.61)	5.03 (4.29-6.18)	<0.001
LVEDd (mm) a		47 (43-51)	47 (43-51)	49 (45-54)	<0.001
LVESd (mm) a		29 (25-34)	28 (25-33)	31 (26-38)	<0.001
Aortic valve area (cm2) a		1.4 (1.2-1.6)	1.4 (1.2-1.7)	1.3 (1.1-1.5)	<0.001
Peak aortic gradient (mmHg) a		26 (21-34)	27 (22-35)	26 (21-33)	0.045
Mean aortic gradient (mmHg) a		15 (12-20)	15 (12-20)	15 (11-19)	0.018
LAVI (ml/m2) a		42.7 (33.5-53.5)	40.3 (32.2-50.8)	53.1 (44-65.7)	<0.001
Deceleration time (ms) a		219 (174-274)	225 (180-275)	187 (153-241)	<0.001
E/e' a		14.02 (10.97-18.34)	13.62 (10.54-17.7)	17.05 (13.18-22.39)	<0.001
Average e' a		6 (4.93-7.21)	6 (4.96-7.2)	6 (4.73-7.35)	0.452
E/A ratio a		0.8 (0.7-1.1)	0.8 (0.6-1.1)	1.1 (0.9-1.6)	<0.001
sPAP (mmHg) a		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)	

[a]Median and interquartile range. All other values represent the number of patients and percentages

LVEDd – Left ventricle end diastolic diameter; LVESd – Left ventricle end systolic diameter; LAVI – Left atrial volume index; sPAP – Systolic pulmonary artery pressure;

Table 3 | Patients' clinical and echocardiographic measurements according to MR severity and Aortic valve area of 1.35cm²

	MR <= mild			MR > Mild				
	AVA > 1.35	AVA ≤1.35		AVA > 1.35	AVA ≤1.35			
	Group 1 N=1333	Group 2 N=1094	P	Group 3 N=211	Group 4 N=295	P	P Group 2-4	P Group 1-3
Age (years) [a]	79.3 (70.7-85.6)	81.46 (74.5-86.7)	<0.001	81.2 (73.6-87.4)	84.4 (77.5-89.2)	0.002	<0.001	0.027
Follow-up (days) [a]	1393 (541-2178)	1107 (432-1955)	0.002	1006 (242-1751)	574 (112-1249)	0.003	<0.001	<0.001
Sex (Female)	527 (39.5)	584 (53.4)	<0.001	103 (48.8)	165 (55.9)	NS	NS	NS
Deceased during follow-up	647 (48.4)	589 (53.8)	<0.001	124 (58.8)	211 (71.5)	0.017	<0.001	0.035
Heart Failure admission	176 (13.2)	138 (12.6)	NS	38 (18)	83 (28.1)	0.024	<0.001	NS
AF	257 (19.3)	214 (19.6)	NS	78 (37)	108 (36.6)	NS	0.012	<0.001
CRF	172 (12.9)	141 (12.9)	NS	51 (24.2)	59 (20)	NS	0.012	<0.001
Malignancy	295 (22.1)	233 (21.3)	NS	45 (21.3)	69 (23.4)	NS	NS	NS
HTN	853 (64)	663 (60.6)	NS	145 (68.7)	216 (73.2)	NS	<0.001	NS
DM	439 (32.9)	362 (33.1)	NS	70 (33.2)	94 (31.9)	NS	NS	NS
CVA/TIA	167 (12.5)	138 (12.6)	NS	26 (12.3)	48 (16.3)	NS	NS	NS
IHD	512 (38.4)	389 (35.6)	NS	99 (46.9)	131 (44.4)	NS	0.032	NS
COPD	139 (10.4)	84 (7.7)	NS	15 (7.1)	31 (10.5)	NS	NS	NS
LV EF [a]	60 (55-60)	60 (55-60)	1	60 (45-60)	55 (45-60)	0.514	<0.001	0.001
Cardiac output (liter/min) [a]	6.05 (5.1-7)	5.01 (4.3-5.9)	<0.001	5.9 (4.9-6.6)	4.8 (4.0-5.7)	<0.001	0.058	0.001
LVEDd (mm) [a]	47 (43-51)	46 (42-51)	0.019	50 (46-55)	48 (44-54)	0.18	<0.001	<0.001
LVESd (mm) [a]	29 (25-33)	28 (25-33)	0.334	31 (27-39)	31 (26-38)	1	<0.001	<0.001
Aortic valve area (cm²) [a]	1.6 (1.5-1.9)	1.2 (1.1-1.3)	<0.001	1.6 (1.4-1.8)	1.13 (1.08-1.26)	<0.001	1	0.725
Peak aortic gradient (mmHg) [a]	24 (20-30)	31 (24-40)	<0.001	23 (19-29)	29 (22-38)	<0.001	0.001	0.491
Mean aortic gradient (mmHg) [a]	14 (11-17)	18 (14-24)	<0.001	13 (11-16)	17 (13-21)	<0.001	<0.001	0.294
LAVI (ml/m²) [a]	40 (32.1-50.6)	40.8 (32.4-51)	1	54.1 (44.66.2)	52.1 (44.2-65)	1	<0.001	<0.001
Deceleration time (ms) [a]	225 (182-275)	224 (180-277)	1	208 (162-254)	180 (148-229)	0.056	<0.001	0.001
E/e' [a]	13.2 (10.2-17.1)	14 (11-18.2)	0.001	16.3 (12.6-22)	17.6 (14-22.6)	0.425	<0.001	<0.001
Average e' [a]	6.2 (5.1-7.4)	5.8 (4.7-7)	<0.001	6 (4.7-7.5)	6 (4.7-7.2)	1	1	1

E/A ratio [a]		0.8 (0.7-1.1)	0.8 (0.6-1.1)	1	1.1 (0.8-1.5)	1.2 (0.9-1.7)	0.451	<0.001	<0.001
sPAP (mmHg) [a]		34 (28-43)	35 (29-45)	0.089	42 (34-54)	49 (39-59)	<0.001	<0.001	<0.001
MR ERO (cm²) [a]		NA	NA		0.1 (0.1-0.2)	0.1 (0.1-0.2)	0.148		
MR Rvol (ml) [a]		NA	NA		25 (17-35)	26 (17-34)	0.893		
AR	None	739 (55.4)	549 (50.2)	NS	82 (38.9)	115 (39)	NS	0.005	<0.001
	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)			
RV function	Normal	1245 (93.4)	1019 (93.1)	NS	173 (82)	231 (78.3)	NS	<0.001	<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)			
RV size	Normal	1221 (91.6)	987 (90.2)	NS	167 (79.1)	218 (73.9)	NS	<0.001	<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)			

[a]Median and interquartile range. All other values represent the number of patients and percentages

AF – Atrial fibrillation; CRF – Chronic renal failure; DM – Diabetes mellitus; CVA – Cerebrovascular accident; TIA – transient ischemic attack; IHD – Ischemic heart disease; COPD – Chronic obstructive pulmonary disease; LVEDd – Left ventricle end diastolic diameter; LVESd – Left ventricle end systolic diameter; LAVI – Left atrial volume index; sPAP – Systolic pulmonary artery pressure; MR - Mitral Regurgitation; RV – Rigth Ventricle; AR – Aortic regurgitation; LV EF – Left ventricle ejection fraction

Table 4 | Impact of MR grade and Aortic valve area on heart failure hospitalization

	HR	95% CI	P
Up to mild MR + AVA ≤ 1.35cm² versus AVA > 1.35cm²			
Univariate analysis	1.036	0.829-1.295	0.754
Greater than mild MR + AVA ≤ 1.35cm² versus AVA > 1.35cm²			
Univariate	1.893	1.288-2.781	0.001
Adjusted for all clinical*	1.941	1.309-2.880	<0.001
Adjusted for all echocardiographic†	1.672	1.097-2.548	0.017
Adjusted for both *†	1.774	1.157-2.72	0.009
Adjusted for Diastolic parameter # + Cardiac output	1.555	0.833-2.904	0.166
AVA > 1.35cm² + MR up to mild versus greater than mild			
Univariate analysis	1.624	1.143-2.308	0.007
Adjusted for all clinical*	1.249	0.873-1.788	0.223
Adjusted for all echocardiographic†	0.992	0.652-1.508	0.969
Adjusted for both *†	0.881	0.572-1.358	0.567
Adjusted for Diastolic parameter # + Cardiac output	0.645	0.356-1.168	0.148
AVA ≤ 1.35cm² + MR greater than mild versus up to mild			
Univariate analysis	3.056	2.324-4.018	<0.001
Adjusted for all clinical*	2.241	1.689-2.973	<0.001
Adjusted for all echocardiographic†	2.162	1.545-3.025	<0.001
Adjusted for both *†	1.625	1.163-2.271	0.004
Adjusted for Diastolic parameter # + Cardiac output	1.816	1.135-2.906	0.013
Greater than mild MR + AVA ≤ 1.35cm² versus Up to mild MR + AVA > 1.35cm²			
Univariate analysis	3.089	2.374-4.019	<0.001
Adjusted for all clinical*	2.164	1.641-2.852	<0.001
Adjusted for all echocardiographic†	1.67	1.205-2.314	0.002
Adjusted for both *†	1.296	0.941-1.784	0.112
Adjusted for Diastolic parameter # + Cardiac output	1.175	0.708-1.948	0.533

* For clinical variables – Age, Sex, Atrial fibrillation, chronic renal failure Hypertension, Ischemic 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

Figure legend:

Figure 1 – Univariate Cox regression analysis for HF hospitalization according to severity of MR and AVA

Figure S1 – Univariate Cox regression analysis for mortality according to severity of MR and AVA

Figure S2 – Univariate Cox regression analysis for the Impact of Intervention (Surgical AVR) in patient with MR>mild and AVA≤1.35cm²

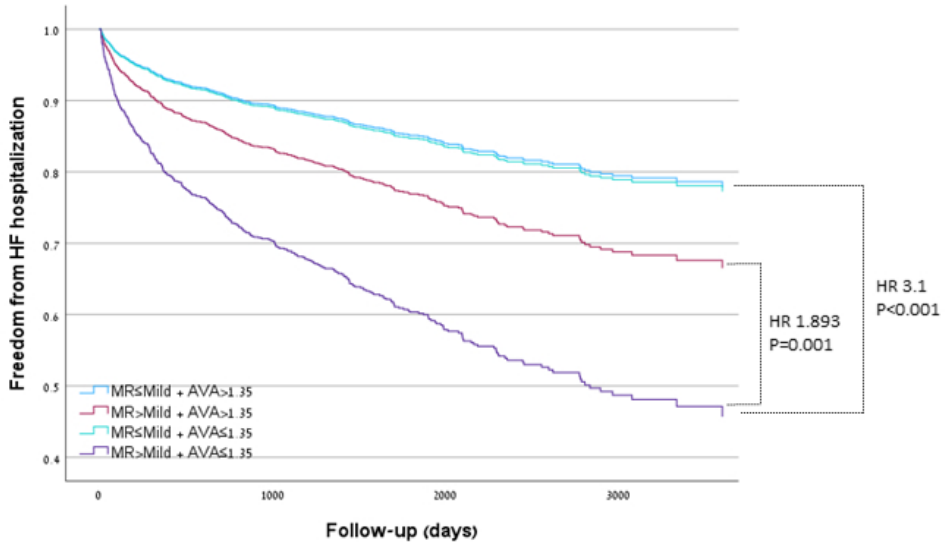

Figure 1

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Table S1 | Impact of MR grade and Aortic valve area on mortality

	HR	95% CI	P
Up to mild MR + AVA ≤ 1.35cm² versus AVA > 1.35cm²			
Univariate	1.223	1.094-1.368	<0.001
Adjusted for all clinical*	1.15	1.027-1.288	0.015
Adjusted for all echocardiographic†	1.168	1.032-1.321	0.014
Adjusted for both *†	1.116	0.984-1.266	0.087
Adjusted for Diastolic parameter # + Cardiac output	0.985	0.815-1.191	0.878
Greater than mild MR + AVA ≤ 1.35cm² versus AVA > 1.35cm²			
Univariate	1.426	1.142-1.78	0.002
Adjusted for all clinical*	1.324	1.053-1.664	0.016
Adjusted for all echocardiographic†	1.242	0.969	1.592
Adjusted for both *†	1.23	0.954-1.586	0.11
Adjusted for Diastolic parameter # + Cardiac output	1.176	0.818-1.689	0.382
AVA > 1.35cm² + MR up to mild versus greater than mild			
Univariate analysis	1.431	1.181-1735	<0.001
Adjusted for all clinical*	1.22	1.003-1.484	0.046
Adjusted for all echocardiographic†	1.317	1.057-1.639	0.014
Adjusted for both *†	1.191	0.95-1.493	0.129
Adjusted for Diastolic parameter # + Cardiac output	1	0.74-1.353	0.998
AVA ≤ 1.35cm² + MR up to mild versus greater than mild			
Univariate analysis	1.684	1.438-1.972	<0.001
Adjusted for all clinical*	1.388	1.18-1.632	<0.001
Adjusted for all echocardiographic†	1.409	1.167-1.701	<0.001
Adjusted for both *†	1.196	0.99-1.444	0.064
Adjusted for Diastolic parameter # + Cardiac output	1.055	0.798-1.395	0.706
Greater than mild MR + AVA ≤ 1.35cm² versus Up to mild MR + AVA > 1.35cm²			
Univariate analysis	2.049	1.753-2.396	<0.001

Adjusted for all clinical*	1.543	1.312-1.815	<0.001
Adjusted for all echocardiographic†	1.737	1.446-2.086	<0.001
Adjusted for both *†	1.377	1.144-1.657	<0.001
Adjusted for Diastolic parameter # + Cardiac output	1.127	0.84-1.513	0.425

* For clinical variables – Age, Sex, Atrial fibrillation, chronic renal failure Hypertension, Ischemic 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

Table S2 | Patients' clinical and echocardiographic measurements according to Intervention (Surgical AVR) in patient with MR>mild and AVA≤1.35cm²

	MR > mild + AVA≤1.35cm²		
	No intervention (n=295)	SAVR (n=10)	P
Age (years) [a]	84.42 (77.51-89.21)	65.77 (63.3-68.93)	<0.001
Sex (Female)	165 (55.9)	5 (50)	0.71
Deceased during Follow-up	211 (71.5)	4 (40)	0.032
Heart Failure admission	83 (28.1)	1 (10)	0.207
AF	108 (36.6)	5 (50)	0.389
CRF	59 (20)	2 (20)	1
Malignancy	69 (23.4)	0	0.082
HTN	216 (73.2)	7 (70)	0.821
DM	94 (31.9)	5 (50)	0.228
CVA/TIA	48 (16.3)	0	0.165
IHD	131 (44.4)	6 (60)	0.33
COPD	31 (10.5)	0	0.279
LV EF [a]	55 (45-60)	60 (45-60)	0.485
Cardiac output (liter/min)	4.77 (4.03-5.7)	5.42 (4.45-7)	0.174
LVEDd (mm) [a]	48 (44-54)	51 (49-57)	0.097
LVESd (mm) [a]	31 (26-38(	31 (28-37)	0.888
Aortic valve area (cm2) [a]	1.13 (1.08-1.26)	1.15 (1.1-1.2)	0.775
Peak aortic gradient (mmHg) [a]	29 (22-38(	39 (37-45)	0.01
Mean aortic gradient (mmHg) [a]	17 (13-21)	23 (18-28)	0.009
LAVI (ml/m2) [a]	52.1 (44.2-65)	47.5 (46.8-48.4)	0.442
Deceleration time (ms) [a]	180 (148-229)	197 (173-235)	0.327
E/e' [a]	17.58 (14.03-22.64)	19.37 (17.92-23.93)	0.092

E/A ratio [a]		1.2 (0.9-1.7)	1.2 (1-2.9)	0.6
sPAP (mmHg) [a]		49 (39-59)	40 (38-50)	0.107
AR	None	115 (39)	3 (30)	0.762
	minimal	69 (23.4)	2 (20)	
	mild	81 (27.5)	3 (30)	
	mild to moderate	30 (10.2)	2 (20)	
RV function	Normal	231 (78.3)	10 (100)	0.433
	Mild	45 (15.3)	0	
	Moderate	16 (5.4)	0	
	Severe	3 (1)	0	
RV size	Normal	218 (73.9)	10 (100)	0.322
	Mild	59 (20)	0	
	Moderate	13 (4.4)	0	
	Severe	5 (1.7)	0	

[a]Median and interquartile range. All other values represent the number of patients and percentages

AF – Atrial fibrillation; CRF – Chronic renal failure; DM – Diabetes mellitus; CVA – Cerebrovascular accident; TIA – transient ischemic attack; IHD – Ischemic heart disease; COPD – Chronic obstructive pulmonary disease; LVEDd – Left ventricle end diastolic diameter; LVESd – Left ventricle end systolic diameter; LAVI – Left atrial volume index; sPAP – Systolic pulmonary artery pressure; MR - Mitral Regurgitation; RV – Rigth Ventricle; AR – Aortic regurgitation; LV EF – Left ventricle ejection fraction

Table S3 | Impact of Intervention (Surgical AVR) in patient with MR>mild and AVA≤1.35cm²

HF hospitalization	HR	95% CI	P
Univariate	0.21	0.029-1.513	0.121
Adjusted *	0.372	0.048-2.895	0.345
All-Cause Mortality			
Univariate	0.286	0.106-0.774	0.014
Adjusted *	0.508	0.177-1.461	0.209

* For Age, Left ventricle end diastolic diameter, Aortic valve Peak and mean gradient, Average E/e' ratio

Figure S1

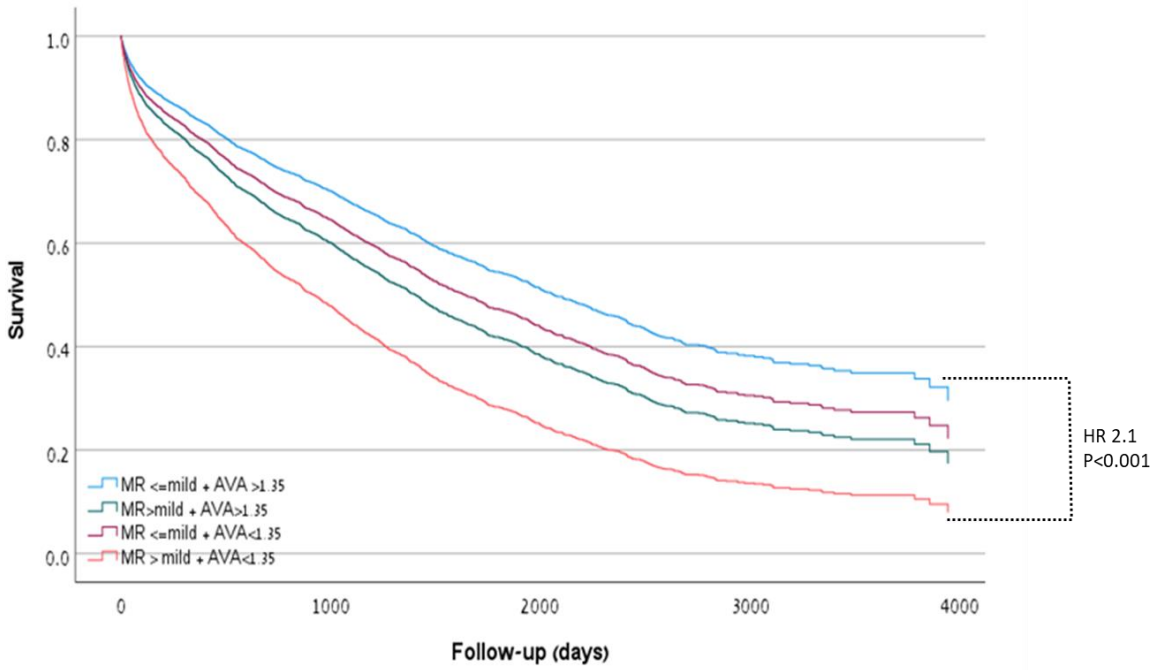
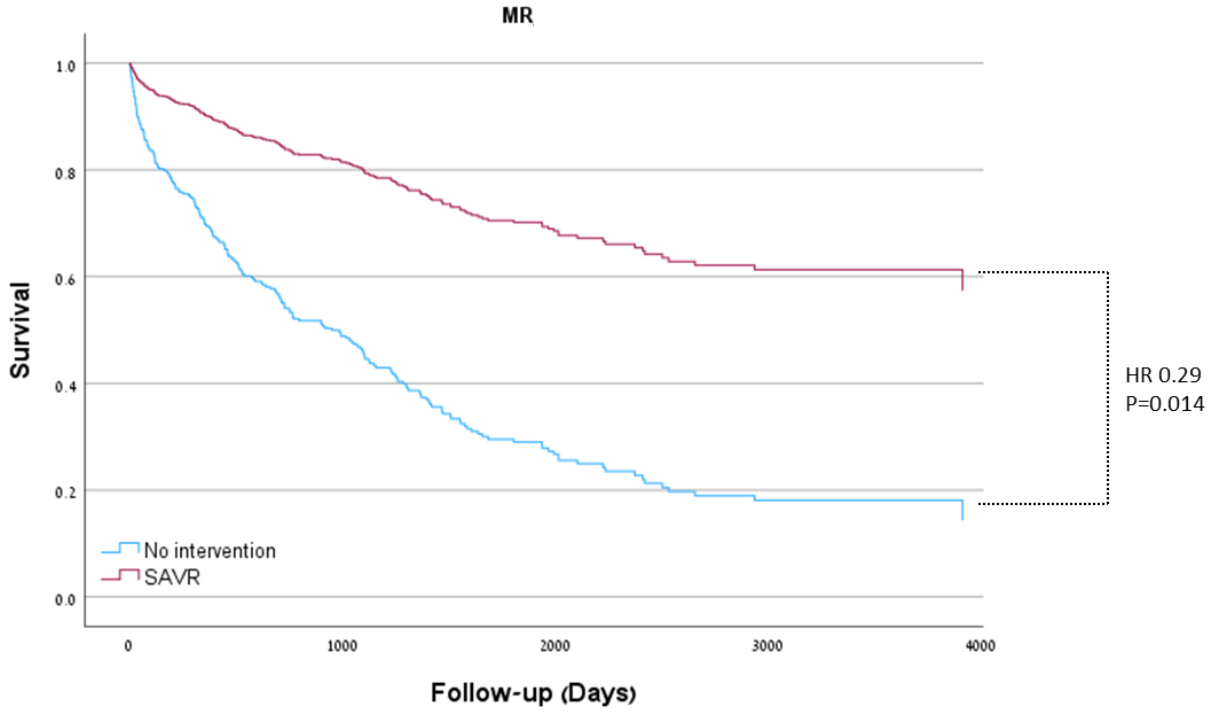


Figure S2



STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	5-6
Study size	10	Explain how the study size was arrived at	5-6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	7
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	8

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9-10
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9-10
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12-13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.