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The Effect of Combined Non-Severe Aortic Stenosis and Mitral Regurgitation on Clinical Outcomes

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3 The Effect of Combined Non-Severe Aortic Stenosis and Mitral Regurgitation on Clinical
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6 Outcomes
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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 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 \geq 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) $\leq 1.35\text{cm}^2$ 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 $\leq 1.35\text{cm}^2$ 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.

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3 Patients with \geq moderate aortic valve regurgitation (AR) or \geq moderate mitral stenosis (MS) and
4 those in whom an aortic or mitral valve intervention was done (n=372) were excluded from the
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6 analysis.
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9 10 Doppler Echocardiography

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12 To evaluate the presence of mVHD, all patients underwent a comprehensive two-dimensional
13 and Doppler echocardiographic study with multiple windows during the same examination.
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15 Echocardiography was performed according to contemporary ESC guideline [6]. All
16
17 measurements were retrieved from the echocardiography reporting system.
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20 Stroke volume was calculated as the product of left ventricular outflow tract (LVOT) area and
21
22 the time-velocity integral of the aortic flow velocity. Cardiac output (CO) measured as stroke
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24 volume multiplied by heart rate.
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26

27 Aortic valve area (AVA) was calculated using continuity equation from the flow through the
28
29 LVOT with respect to the flow through the aortic valve. Aortic valve velocities were obtained
30
31 from multiple windows for the highest obtained peak velocity and mean gradient. Severe AS was
32
33 defined as a peak velocity >4 m/s, mean gradient >40 mmHg or estimated AVA <1 cm².
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36 MR severity was determined by an integrative, semi-quantitative and quantitative approach,
37
38 including assessment of vena contracta width, valve morphology, chamber size, jet area, jet
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40 density and contour, and when available, effective orifice area (ERO) and regurgitant volume.
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43 After excluding those defined as severe MR, we grouped those these patients into: MR \leq mild and
44
45 MR $>$ mild.
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48 Pulsed-wave Doppler was performed in the apical 4-chamber view to obtain mitral inflow
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50 velocities to assess LV filling. A 1-mm to 3-mm sample volume was placed between the mitral
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52 leaflet tips at end-expiration and during diastole after optimizing spectral gain, wall filter
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3 settings, and setting sweep speeds of 100 mm/s. Recordings were averaged over 3 consecutive
4 cardiac cycles during sinus rhythm and over 5 cycles during atrial fibrillation (AF).
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7 Measurements of mitral inflow included the peak early filling (E wave) and late diastolic filling
8 (A wave) velocities, the E/A ratio, and deceleration time (DT) of early filling velocity. Early
9 diastolic mitral annular velocities (e') was measured in the apical 4-chamber view. The e' was
10 measured from septal and lateral annulus. The ratio of peak E to peak e' was calculated (mitral
11 E/e' ratio) from the average of at least 3 cardiac cycles. Left atrium volume was calculated by
12 tracing the endocardial borders at end-systole in the apical four-and two-chamber views, with LA
13 volume index calculated by adjusting to the patient's body surface index (BSA).
14

15
16 Systolic pulmonary arterial pressure (sPAP) was determined by the maximal tricuspid
17 regurgitant velocity (calculated based on the simplified Bernoulli equation) and an estimation of
18 right atrial pressure according to the vena cava width and responsiveness.
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21 LV diameters including left ventricle end systolic and diastolic diameter (LVESd, LVEDd) were
22 measured using lineal 2D echocardiography or M-mode parallel to the mitral valve annulus.
23

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25 Right ventricular (RV) size and function assessment was based on multiple views of the RV. An
26 integrative qualitative grading of RV function was formulated by a specialized imaging
27 cardiologist responsible for the echocardiographic study.
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30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 Clinical data and outcome measures

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

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

14 Patient Clinical Characteristics

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17 The study cohort included 2933 patients with non-severe AS. Of whom, 2427 had \leq mild MR and
18
19 506 >mild MR. Table 1 provides the patients' clinical characteristics.
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22 The median follow-up time of the entire cohort was 1127 days (IQR 392-1999), during which
23
24 1572 patients (53.6%) had died and 435 patients (14.8%) had experienced a HF hospitalization.
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26 Compared with patients with \leq mild MR, patient with >mild MR were older (80.1 years, IQR
27
28 72.4-86.2 vs 83.2 years, IQR 76.3-88.6, $P < 0.001$), with a predominance female population
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30 (45.8% vs 53%, $P = 0.03$) respectively.
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33 In addition, patients with >mild MR were more likely to have a history of AF (36.8% versus
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35 22.4%, $P < 0.001$), CRF (21.7% versus 12.9, $P < 0.001$), hypertension (71.3% versus 62.5%, $P <$
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37 0.001) and IHD (45.5% versus 37.1%, $P < 0.001$).
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40 Examining outcomes, patient with >mild MR experienced a higher rate of HF hospitalizations
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42 (23.9% versus 12.9%, $P < 0.001$) and increased all-cause mortality (66.2% versus 53.6%,
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44 $P < 0.001$).
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47 Patient echocardiographic measurements

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49 Patients' echocardiographic measurements in the entire cohort and according to severity of MR
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51 are presented in table 2.
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3 Patients with >mild MR had slightly lower cardiac output values (5.03ml/m², IQR 4.29-6.18
4 versus 5.64 (IQR 4.78-6.61, P < 0.001) and a greater left ventricle end-systolic (31mm, IQR 26-
5 38, versus 28, IQR 25-33, P < 0.001) and end-diastolic diameters (49mm, IQR 45-54 versus 47,
6 IQR 43-51, P < 0.001).
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12 Proximal isovelocity hemispheric surface area (PISA) data were available only in a portion of
13 patients with >mild MR. These patients had an ERO area of 0.1cm² (IQR 0.1-0.2, n=184/514)
14 with a regurgitant volume of 26ml (IQR 17-35ml, n=105/330).
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19 As expected, patients with >mild MR had an overall worse diastolic indices with a larger LA
20 volume index, shorter deceleration time, higher E/A ratio and elevated SPAP compared with
21 patient with ≤mild MR. The average e' for the entire cohort was mildly reduced (6, IQR 4.93-
22 7.21), with no difference between MR severity groups.
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28 Higher rates of RV dysfunction and RV dilatation were found in patients with >mild MR (Table
29 2).
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33 **Aortic valve area optimal cutoff value**

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

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49 Among patients with >mild MR, those with AVA ≤ 1.35cm² were older compared with patients
50 with AVA > 1.35cm² (84.4 years, IQR 77.5-89.2 vs 81.2 years, IQR 73.6-87.3 respectively, P =
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0.002). There were no other statistically significant differences in baseline clinical characteristics between these two sub-groups.

Patient with $AVA \leq 1.35 \text{ cm}^2$ had lower CO compared with patients with an $AVA > 1.35 \text{ cm}^2$ (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 $AVA \leq 1.35 \text{ cm}^2$ had the highest rate of HF hospitalizations compared with patients \leq mild MR and an $AVA > 1.35 \text{ cm}^2$ (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 $AVA > 1.35 \text{ cm}^2$ 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 $AVA \leq 1.35 \text{ cm}^2$ had a higher HF hospitalizations rate.

Analysis concerning all-cause mortality is available in Table S1 and Figure 1S. Patients with $>$ mild MR and $AVA \leq 1.35 \text{ cm}^2$ had higher mortality rates compared with patients with \leq mild MR and $AVA > 1.35 \text{ cm}^2$, even after adjusting for clinical and/or echocardiographic parameters

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3 The effect of diastolic function on outcome is presented in table 4 and the effect of surgical AV
4 replacement on outcomes is presented in tables S2,S3 and figure S2.
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11 12 **Discussion**

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14 This study sought to describe the clinical outcomes of patients with combined non-severe AS and
15 low-grade MR. Our major findings are:
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- 18 - These patients have lower CO with worse diastolic function.
- 19 - AVA between 1.0-1.35cm² in the presence of >mild MR is associated with worse clinical
20 outcomes even after adjusting for clinical and/or echocardiographic parameters.
- 21 - In contrast, patients with an AVA>1.35cm² have similar clinical outcomes regardless of
22 (non-severe) MR grade.
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30 AS and MR are the most prevalent valvular heart diseases in high-income countries [7].

31 However, unless the patient is planned for an aortic or coronary surgery, current guidelines

32 recommend intervention only when these valvular lesions are severe [4-5] and limited

33 recommendations exist for the management of patients with combined non-severe AS and MR.

34 The hemodynamic effects of AS result from chronic increased afterload that leads to LV

35 hypertrophy, diastolic dysfunction and increased systolic intra-ventricular pressures. MR, on the

36 other hand, reduces afterload, SV and CO, but increases preload. The net effect of both lesions

37 will reduce the net forward flow with augmentation of diastolic pressures [8-9], a finding

38 compatible with our results.
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40 Recent data show that compared with no or mild AS, moderate AS was found to be associated

41 with increased mortality risk [10-11]. A recent meta-analysis by Coisne et al. [12] showed that
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3 the rate difference of all-cause mortality was -3.9 (95% CI: -6.7 to -1.1) for no or mild AS
4 compared with moderate AS. An additional retrospective analysis of 148 patients with moderate
5 AS [13] studied predictors of poor clinical outcomes (composite of CV death, HF admission and
6 AV replacement), and showed that \geq moderate MR, as well as lower range AVA was associated
7 with worse outcomes. A study by Tastet et al. [14] retrospectively analyzed 735 patient with at
8 least moderate aortic stenosis ($AVA < 1.5\text{cm}^2$) followed in the heart valve clinics of four high-
9 volume centers. The patients were classified according to degree of cardiac structural
10 abnormalities; with stage 2 classified as either LA enlargement or $>$ mild MR (9 patients in total),
11 both shown to predict higher all-cause mortality rates. A follow-up study by Amanullah et al [15]
12 showed that stage 2 patients ($\sim 20\%$ of them with significant MR) had worse clinical outcomes
13 including increased all-cause mortality and HF events. Finally, Benfari et al. [16] showed that in
14 patients with trans-aortic velocity $> 2.5\text{m/s}$ and $AVA > 1\text{cm}^2$, an MR ERO area $> 0.1\text{cm}^2$ was
15 associated with a higher rates of HF hospitalizations or death.
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33 In clinical practice, it is challenging to determine the optimal timing for valvular correction of
34 mVHD. Our data, encompassing almost 3,000 patients with comprehensive echocardiographic
35 evaluation and valid clinical outcomes, suggest that patients with combined $>$ mild MR and
36 $AVA \leq 1.35\text{cm}^2$ have worse clinical outcomes and as such could benefit from close follow-up
37 visits and frequent serial evaluation by a multidisciplinary heart valve team. It remains to be
38 seen, however, whether early interventions could improve the clinical outcome of these patients.
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49 Several important limitations should be addressed. First, this is a single-center retrospective
50 study; thus, prospective data are needed to further establish its findings. Second, due to relatively
51 small number of patient with combined non-severe AS and MR we did not divide our cohort into
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3 a learning and validation groups, consequently reducing the internal validity of the study. Last,
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5 as we excluded patient with other left sided valvular abnormalities, the current finding should not
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7 be applied to other mVHD.
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10 In conclusion, combined low grade AS with MR is associated with adverse outcomes. We
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12 suggest an AVA cutoff value of 1.35cm² for further evaluation and careful consideration of early
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14 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

^aMedian 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 (cm ²) 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/m ²) 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)	

^aMedian 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)				0.874
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
GVA/TIA	167 (12.5)	138 (12.6)		26 (12.3)	48 (16.3)				0.35
HD	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
V 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)	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

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3	LVESd (mm) ^a		29 (25-33)	28 (25-33)	0.334	31 (27-39)	31 (26-38)	1	<0.001	<0.001	<0.001
4	Aortic valve area (cm ²) ^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
5	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
6	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
7	E/A ratio ^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
8	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
9	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
10	PAP (mmHg) ^a		34 (28-43)	35 (29-45)	0.089	42 (34-54)	49 (39-59)	<0.001	<0.001	<0.001	<0.001
11	MR ERO (cm ²) ^a		NA	NA		0.1 (0.1-0.2)	0.1 (0.1-0.2)	0.148			
12	MR Rvol (ml) ^a		NA	NA		25 (17-35)	26 (17-34)	0.893			
13	AR	None	739 (55.4)	549 (50.2)	NS	82 (38.9)	115 (39)	NS	0.005	<0.001	<0.001
14		minimal	253 (19)	225 (20.6)		30 (14.2)	69 (23.4)				
15		mild	266 (20)	266 (24.3)		72 (34.1)	81 (27.5)				
16		mild to moderate	75 (5.6)	54 (4.9)		27 (12.8)	30 (10.2)				
17	RV function	Normal	1245 (93.4)	1019 (93.1)	NS	173 (82)	231 (78.3)	NS	<0.001	<0.001	<0.001
18		Mild	72 (5.4)	59 (5.4)		31 (14.7)	45 (15.3)				
19		Moderate	15 (1.1)	14 (1.3)		6 (2.8)	16 (5.4)				
20		Severe	1 (0.1)	2 (0.2)		1 (0.5)	3 (1)				
21	RV size	Normal	1221 (91.6)	987 (90.2)	NS	167 (79.1)	218 (73.9)	NS	<0.001	<0.001	<0.001

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3	Mild	83 (6.2)	82 (7.5)		33 (15.6)	59 (20)				
4	Moderate	24 (1.8)	17 (1.6)		9 (4.3)	13 (4.4)				
5	Severe	5 (0.4)	8 (0.7)		2 (0.9)	5 (1.7)				

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^aMedian 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 – Right 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 \leq 1.35cm ² versus AVA > 1.35cm ²			
Univariate analysis	1.036	0.829-1.295	0.754
Greater than mild MR + AVA \leq 1.35cm ² versus AVA > 1.35cm ²			
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 > 1.35cm ² + 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 \leq 1.35cm ² + 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 \leq 1.35cm ² versus Up to mild MR + AVA > 1.35cm ²			
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

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4 * For clinical variables – Age, Sex, Atrial fibrillation, chronic renal failure Hypertension, Ischemic
5 heart disease, COPD

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7 † For Echocardiographic variables – Ejection fraction, Left ventricle end diastolic diameter, Left
8 ventricle end systolic diameter, Aortic valve regurgitation grade, right ventricle size, right
9 ventricle function

10 # For Diastolic parameter – LAVI, DT, Average E/e', E/A ratio, sPAP
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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 \leq 1.35cm ² versus AVA > 1.35cm ²			
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 \leq 1.35cm ² versus AVA > 1.35cm ²			
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 > 1.35cm ² + MR up to mild versus greater than mild			
Univariate analysis	1.431	1.181-1.735	<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 \leq 1.35cm ² + 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 \leq 1.35cm ² versus Up to mild MR + AVA > 1.35cm ²			
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 \leq 1.35cm²

	MR > mild + AVA \leq 1.35cm ²		
	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
QVA/TIA	48 (16.3)	0	0.165
PHD	131 (44.4)	6 (60)	0.33
COPD	31 (10.5)	0	0.279
LVEF ^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 (cm ²) ^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
AVI (ml/m ²) ^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

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3	E/A ratio ^a		1.2 (0.9-1.7)	1.2 (1-2.9)	0.6
4					
5	sPAP (mmHg) ^a		49 (39-59)	40 (38-50)	0.107
6					
7	AR	None	115 (39)	3 (30)	0.762
8		minimal	69 (23.4)	2 (20)	
9		mild	81 (27.5)	3 (30)	
10		mild to moderate	30 (10.2)	2 (20)	
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13	RV function	Normal	231 (78.3)	10 (100)	0.433
14		Mild	45 (15.3)	0	
15		Moderate	16 (5.4)	0	
16		Severe	3 (1)	0	
17					
18					
19	RV size	Normal	218 (73.9)	10 (100)	0.322
20		Mild	59 (20)	0	
21		Moderate	13 (4.4)	0	
22		Severe	5 (1.7)	0	
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^aMedian 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 – Righth Ventricle; AR – Aortic regurgitation; LV EF – Left ventricle ejection fraction

Table S3 | Impact of Intervention (Surgical AVR) in patient with MR>mild and AVA \leq 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:

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3 Figure 1 – Univariate Cox regression analysis for HF hospitalization according to severity of MR
4 and AVA
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7 Figure S1 – Univariate Cox regression analysis for mortality according to severity of MR and
8 AVA
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11 Figure S2 – Univariate Cox regression analysis for the Impact of Intervention (Surgical AVR) in
12 patient with MR>mild and AVA \leq 1.35cm²
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Figure 1

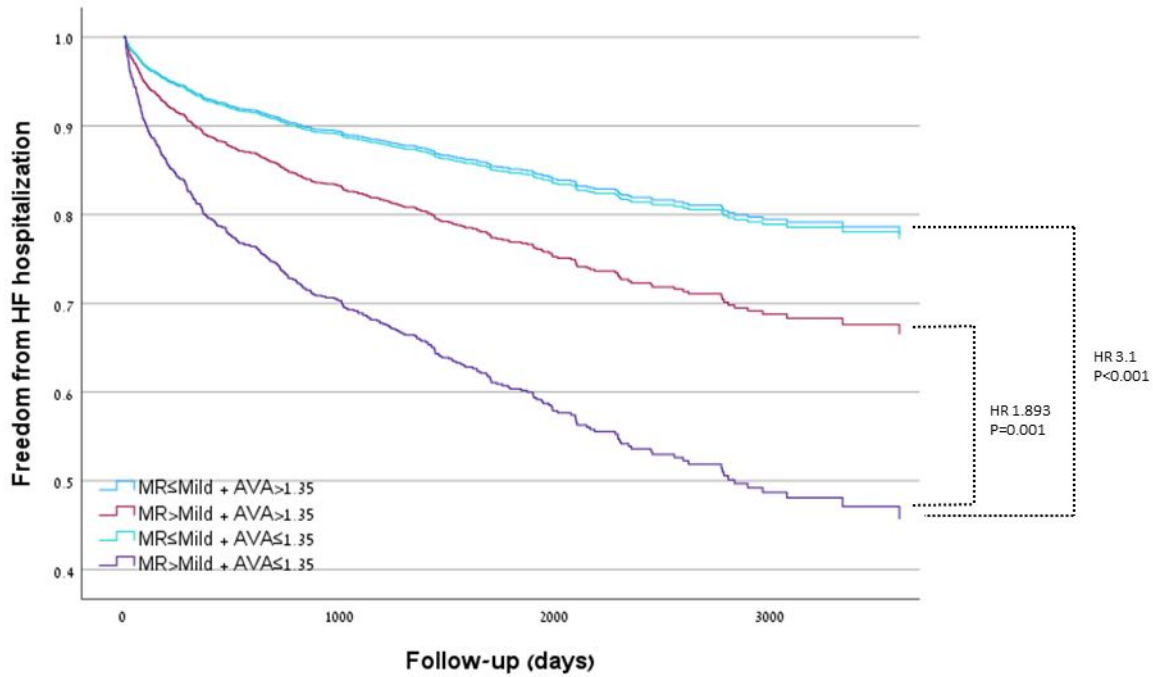


Figure S1

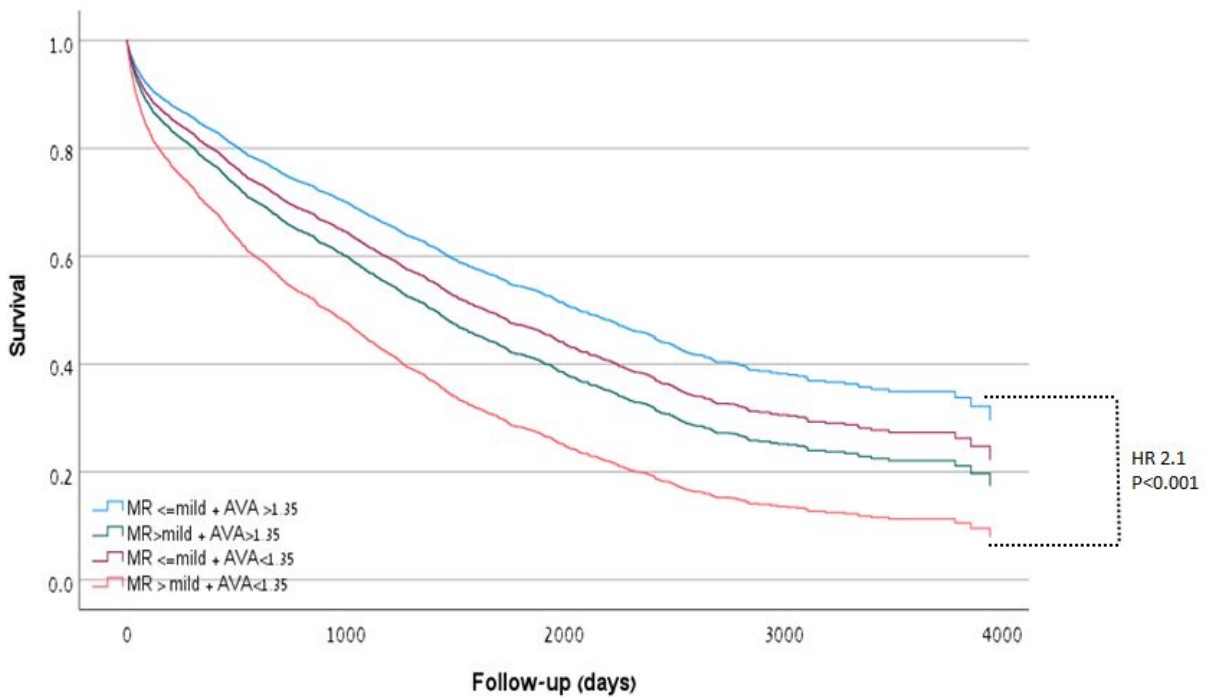
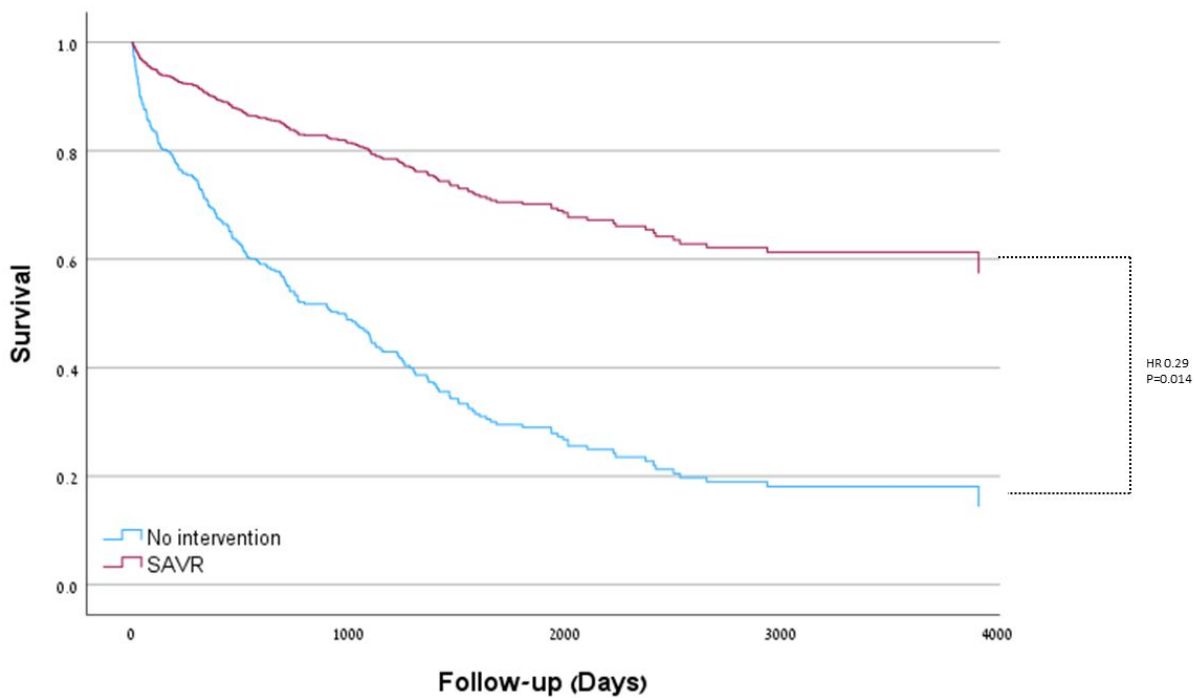


Figure S2



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4 Data Availability Statement
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6 The data that support the findings of this study are available from the corresponding author
7 upon reasonable request.
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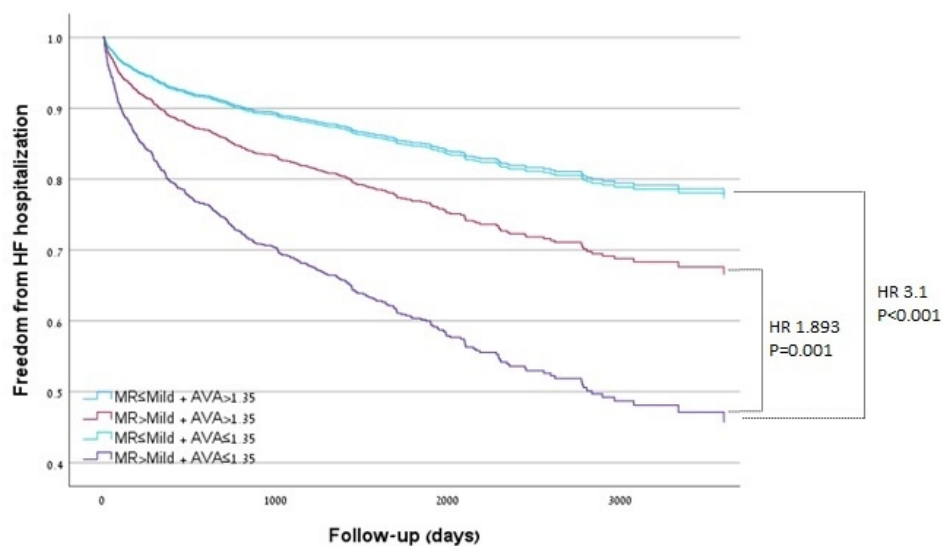
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13 Consent
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15 The study was reviewed and approved by the Institutional Review Board with a waiver of
16 informed consent. Approval number – TLV-0111-18
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22 Patient and Public Involvement
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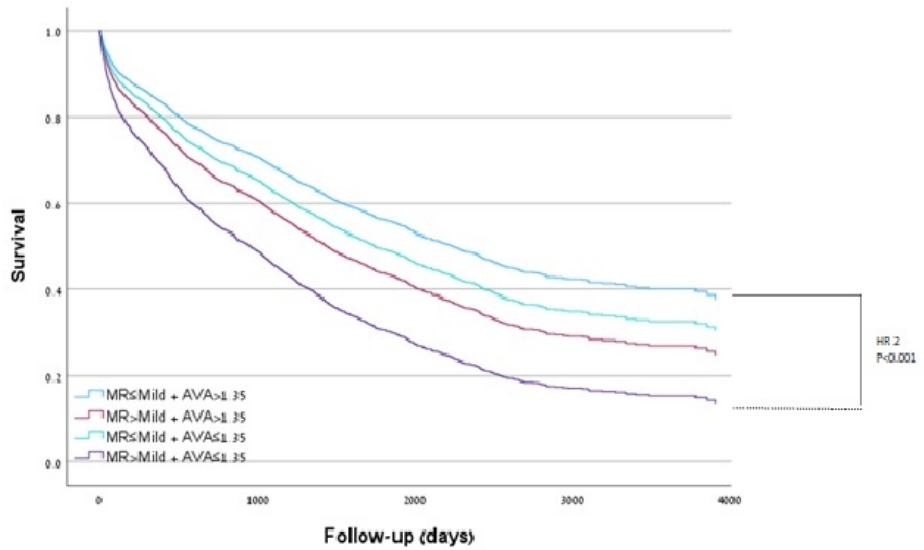
24 Patients or the public were not involved in the design, or conduct, or reporting, or
25 dissemination plans of our research
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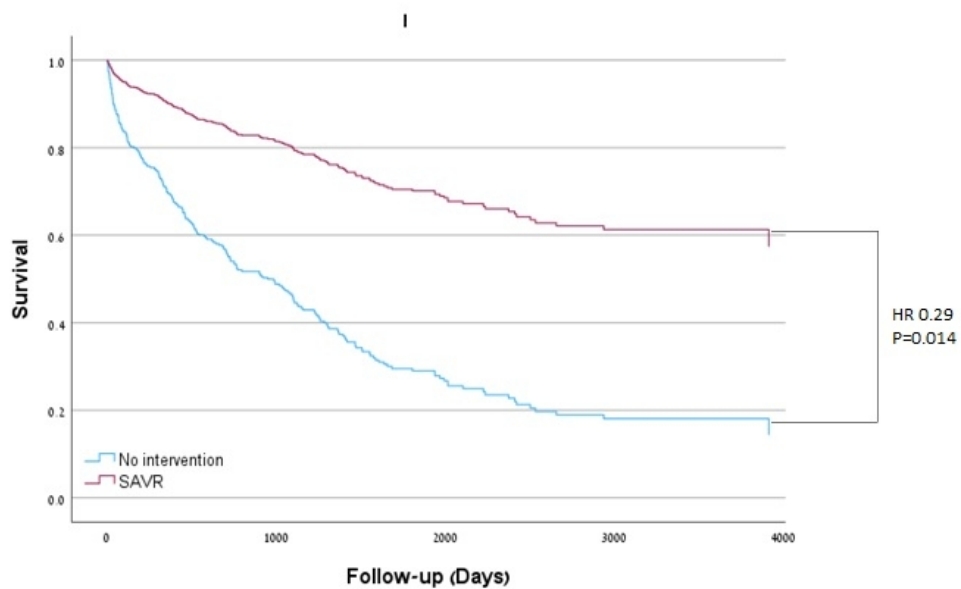
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STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	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

1	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	9-10
2			(b) Report category boundaries when continuous variables were categorized	
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
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9	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9-10
10				
11	Discussion			
12				
13	Key results	18	Summarise key results with reference to study objectives	11
14	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
15				
16	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13
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18				
19	Generalisability	21	Discuss the generalisability (external validity) of the study results	13
20				
21	Other information			
22	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
23				
24				

*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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Keywords:	Heart failure < CARDIOLOGY, Adult cardiology < CARDIOLOGY, Echocardiography < CARDIOLOGY, Valvular heart disease < CARDIOLOGY

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3 **Prognostic Impact of Combined Non-severe Aortic Stenosis and Mitral Regurgitation on**
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5 **Clinical Outcomes: A Single-Center Retrospective Study**
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10 Yoav Granot, MD^{1 2}, Orly Ran Sapir^{1 3}, MD¹, Michal Laufer Perl MD¹, Dana Viskin MD¹,
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31 All authors take responsibility for all aspects of the reliability and freedom from bias of the data
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33 presented and their discussed interpretation
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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 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 \geq 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) $\leq 1.35\text{cm}^2$ 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 $\leq 1.35\text{cm}^2$ 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.

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3 Patients with \geq moderate aortic valve regurgitation (AR) or \geq moderate mitral stenosis (MS) and
4 those in whom an aortic or mitral valve intervention was done (n=372) were excluded from the
5
6 analysis.
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9 10 Doppler Echocardiography

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12 To evaluate the presence of mVHD, all patients underwent a comprehensive two-dimensional
13 and Doppler echocardiographic study with multiple windows during the same examination.
14

15 Echocardiography was performed according to contemporary ESC guideline [6]. All
16
17 measurements were retrieved from the echocardiography reporting system.
18
19

20 Stroke volume was calculated as the product of left ventricular outflow tract (LVOT) area and
21
22 the time-velocity integral of the aortic flow velocity. Cardiac output (CO) measured as stroke
23
24 volume multiplied by heart rate.
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26

27 Aortic valve area (AVA) was calculated using continuity equation from the flow through the
28
29 LVOT with respect to the flow through the aortic valve. Multiple windows were used for the
30
31 highest velocity. Severe AS was defined as a peak velocity >4 m/s, mean gradient >40 mmHg or
32
33 estimated AVA <1 cm². Both classical low flow-low gradient and paradoxical low-flow low
34
35 gradient aortic stenosis were not included in the current study.
36
37

38 MR severity was determined by an integrative, semi-quantitative and quantitative approach,
39
40 including assessment of vena contracta width, valve morphology, chamber size, jet area, jet
41
42 density and contour, and when available, effective orifice area (ERO) and regurgitant volume.
43
44

45 After excluding those defined as severe MR, we grouped those these patients into: MR \leq mild and
46
47 MR $>$ mild.
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49

50 Measurements of mitral inflow included the peak early filling (E wave) and late diastolic filling
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52 (A wave) velocities, the E/A ratio, and deceleration time (DT) of early filling velocity. Early
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3 diastolic mitral annular velocities (e') was measured from both septal and lateral annulus. Left
4 atrium volume was calculated by tracing the endocardial borders at end-systole in the apical
5 four-and two-chamber views, with LA volume index calculated by adjusting to the patient's
6 body surface index (BSA).
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12 Systolic pulmonary arterial pressure (sPAP) was determined by the maximal tricuspid
13 regurgitant velocity and an estimation of right atrial pressure according to the vena cava width
14 and responsiveness.
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18
19 LV diameters including left ventricle end systolic and diastolic diameter (LVESd, LVEDd) were
20 measured using lineal 2D echocardiography or M-mode parallel to the mitral valve annulus.
21

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23
24 Right ventricular (RV) size and function assessment was based on multiple views of the RV. An
25 integrative qualitative grading of RV function was formulated by a specialized imaging
26 cardiologist responsible for the echocardiographic study.
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30 31 32 33 Clinical data and outcome measures

34
35 Baseline characteristics including age, sex and major co-morbidities were extracted from the
36 electronic health record (EMR). Hospitalization for heart failure (HF) which occurred at our
37 medical center alone were retrieved from the electronic health record. The date of mortality (if
38 occurred) was automatically updated in the hospital records via the Ministry of Health.
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42 All the data obtained in the study were retrieved from the hospital anonymized database that
43 includes all clinical and echocardiographic information.
44

45 46 47 48 49 Statistical Analysis

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52 Categorical variables are reported as numbers and percentages, and continuous variables are
53 reported as means and standard deviations or medians and interquartile ranges (IQRs), as
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3 appropriate. Continuous variables were tested for normal distribution using histograms, Q-Q
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5 Plots and normality tests (Kolmogorov-Smirnov and Shapiro-Wilk). Continuous variables were
6
7 compared between groups using independent Mann-Whitney test, post-hoc Bonferroni correction
8
9 applied to analyze subgroup comparison. Categorical variables were compared using Chi-square
10
11 test or Fisher's exact test, post-hoc Bonferroni correction applied to analyze subgroup
12
13 comparison.
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16
17 The AVA was divided into categories by means of a classification and regression model (CART)
18
19 for the prediction of HF hospitalization, with a minimum of 100 cases in parent node and
20
21 minimum of 50 cases in child node. The analysis selects the best predictor for splitting the data
22
23 into child nodes. A P value is given for each branch.
24
25

26 Long-term outcome (all-cause mortality or HF hospitalization) assessed using a Cox regression
27
28 model, also adjusted for clinical and echocardiographic parameters. The following variables
29
30 were included:
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33 Clinical variables: Age, sex, chronic renal failure (CRF), hypertension, ischemic heart disease
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35 (IHD), AF, HF, chronic obstructive pulmonary disease (COPD).
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38 Echocardiographic variables: ejection fraction (EF), LVEDd, LVESd, degree of AR, RV
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40 function and RV size. Of note, due to the expected effect of mVHD on LV filling indices and
41
42 forward flow (stroke volume), as the major hemodynamic consequences leading to HF
43
44 hospitalization, these parameters we evaluated in the COX regression model separately.
45
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47 All statistical tests were two-sided, and a P-value of $< .05$ was considered statistically significant.
48

49 SPSS software was used for all statistical analysis (IBM SPSS statistics, version 25, Armonk,
50
51 NY, USA, 2017).
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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 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 \leq 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-

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3 38, versus 28, IQR 25-33, $P < 0.001$) and end-diastolic diameters (49mm, IQR 45-54 versus 47,
4
5 IQR 43-51, $P < 0.001$).

6
7 Proximal isovelocity hemispheric surface area (PISA) data were available only in a portion of
8
9 patients with >mild MR. These patients had an ERO area of 0.1cm^2 (IQR 0.1-0.2, $n=184/514$)
10
11 with a regurgitant volume of 26ml (IQR 17-35ml, $n=105/330$).

12
13 As expected, patients with >mild MR had an overall worse diastolic indices with a larger LA
14
15 volume index, shorter deceleration time, higher E/A ratio and elevated SPAP compared with
16
17 patient with \leq mild MR. The average e' for the entire cohort was mildly reduced (6, IQR 4.93-
18
19 7.21), with no difference between MR severity groups.

20
21 Higher rates of RV dysfunction and RV dilatation were found in patients with >mild MR (Table
22
23 2).

24 25 26 27 28 **Aortic valve area optimal cutoff value**

29
30 In patients with >mild MR, a classification tree analysis revealed a cutoff value of 1.35cm^2 to be
31
32 predictive for HF hospitalizations. Accordingly, we further divided both MR groups according to
33
34 the suggested AS cutoff value. Patients' clinical and echocardiographic measurements in these 4
35
36 sub-groups are presented in table 3.

37 38 39 40 41 42 Hemodynamic impact of AVA in patient with >mild MR

43
44 Among patients with >mild MR, those with $\text{AVA} \leq 1.35\text{cm}^2$ were older compared with patients
45
46 with $\text{AVA} > 1.35\text{cm}^2$ (84.4 years, IQR 77.5-89.2 vs 81.2 years, IQR 73.6-87.3 respectively, $P =$
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48 0.002). There were no other statistically significant differences in baseline clinical characteristics
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50 between these two sub-groups.
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3 Patient with $AVA \leq 1.35 \text{ cm}^2$ had lower CO compared with patients with an $AVA > 1.35 \text{ cm}^2$ (4.77
4 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
5 values (49mmHg, IQR 39-59 compared with 42mmHg, IQR 34-54 $p < 0.001$), whereas other
6 diastolic or RV function indices did not significantly differ between the two groups (Table 3).
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15 Effect of AVA and MR severity on clinical outcomes

16
17 The impact of MR grade and AVA on HF hospitalizations within each subgroup is presented in
18 table 4.
19

20
21 In univariate Cox regression analysis (Figure 1), patients with >mild MR and an $AVA \leq 1.35 \text{ cm}^2$
22 had the highest rate of HF hospitalizations compared with patients \leq mild MR and an
23 $AVA > 1.35 \text{ cm}^2$ (HR 3.1, IQR 2.4-4, $P < 0.001$).
24
25

26
27 AVA had more impact on patients' outcomes, since the presence of significant MR in patients
28 with an $AVA > 1.35 \text{ cm}^2$ was associated with increased rates of HF hospitalizations in univariate
29 analysis (group 1 versus group 3, HR 1.6, IQR 1.1-2.3, $P = 0.007$), this effect was lost after
30 adjusting for echocardiographic parameters and/or clinical parameters. Furthermore, following
31 adjustment for either clinical comorbidities or echocardiographic parameters only patients with a
32 combination of >mild MR and $AVA \leq 1.35 \text{ cm}^2$ had a higher HF hospitalizations rate.
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42 Analysis concerning all-cause mortality is available in Table S1 and Figure 1S. Patients with
43 >mild MR and $AVA \leq 1.35 \text{ cm}^2$ had higher mortality rates compared with patients with \leq mild MR
44 and $AVA > 1.35 \text{ cm}^2$, even after adjusting for clinical and/or echocardiographic parameters
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51 The effect of diastolic function on outcome is presented in table 4.
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3 The effect of surgical AV replacement in patients with >mild MR and $AVA \leq 1.35 \text{ cm}^2$ (n=10, one
4 patient with concomitant mitral valve intervention) on outcomes is presented in tables S2,S3 and
5
6 figure S2.
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10 11 12 13 14 15 **Discussion**

16
17 This study investigated the clinical outcomes of patients with combined non-severe aortic
18 stenosis (AS) and low-grade mitral regurgitation (MR). We found two key findings:
19

- 20
21 • Patients with combined non-severe AS and low-grade MR had lower cardiac output and
22 impaired diastolic function compared to those without these conditions.
23
- 24 • AVA between 1.0-1.35 cm^2 in the presence of more than mild MR was associated with
25 worse clinical outcomes, even after accounting for other relevant
26 factors. Conversely, patients with an AVA greater than 1.35 cm^2 had clinical outcomes
27 comparable to those without AS, regardless of the degree of non-severe MR.
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35 AS and MR are the most prevalent valvular heart diseases in high-income countries [7].

36 However, unless the patient is planned for an aortic or coronary surgery, current guidelines
37 recommend intervention only when these valvular lesions are severe [4-5] and limited
38 recommendations exist for the management of patients with combined non-severe AS and MR.
39

40 The hemodynamic effects of AS result from chronic increased afterload that leads to LV
41 hypertrophy, diastolic dysfunction and increased systolic intra-ventricular pressures. MR, on the
42 other hand, reduces afterload, SV and CO, but increases preload. The net effect of both lesions
43 will reduce the net forward flow with augmentation of diastolic pressures [8-9], a finding
44 compatible with our results.
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3 While previous studies demonstrated increased mortality risk in moderate AS compared to no or
4 mild AS [10-12], the impact of combined non-severe AS and low-grade MR remained less
5 explored. Similar to our finding, smaller studies found predictors of poor outcome in this
6 population, including \geq moderate MR, as well as lower range AVA [13] or stage 2 cardiac
7 structural abnormalities such as either LA enlargement or $>$ mild MR (only 9 patients in total)
8 [14-15]. Notably, Benfari et al. [16] showed that in patients with trans-aortic velocity >2.5 m/s
9 and AVA >1 cm², an MR ERO area >0.1 cm² was associated with a higher rates of HF
10 hospitalizations or death. Our study adds to this evidence by highlighting the specific association
11 between AVA size and clinical outcomes in the context of non-severe AS and low-grade MR.
12 Our cohort's all-cause mortality rate was higher compared to existing studies on severe [17] or
13 moderate AS [18]. While baseline co-morbidities and the presence of MR in our cohort might
14 contribute to this finding, the most likely explanation is the older age of our study population
15 (80.1 vs. 77.8 years in severe AS and 74 years in moderate AS cohorts).
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33 In clinical practice, it is challenging to determine the optimal timing for valvular correction of
34 mVHD. Our data, encompassing almost 3,000 patients with comprehensive echocardiographic
35 evaluation and valid clinical outcomes, suggest that patients with combined $>$ mild MR and
36 AVA ≤ 1.35 cm² have worse clinical outcomes and as such could benefit from close follow-up
37 visits and frequent serial evaluation by a multidisciplinary heart valve team. It remains to be
38 seen, however, whether early interventions could improve the clinical outcome of these patients.
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49 Several important limitations should be addressed. First, this is a single-center retrospective
50 study; thus, prospective data are needed to further establish its findings. Second, due to relatively
51 small number of patient with combined non-severe AS and MR we did not divide our cohort into
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3 a learning and validation groups, consequently reducing the internal validity of the study. Third,
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5 due to the observational nature of the design, we cannot definitively prove a causal relationship
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7 between the valvular abnormalities or their individual impact on outcomes. Last, as we excluded
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9 patient with other left sided valvular abnormalities, the current finding should not be applied to
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11 other mVHD.
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14 Our study suggests that combined non-severe aortic stenosis (AS) and low-grade mitral
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16 regurgitation (MR) may be associated with worse clinical outcomes, particularly when the aortic
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18 valve area (AVA) falls below 1.35 cm². This finding highlights the need for further investigation
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20 into the potential benefits of early intervention for these patients. Future studies could explore
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22 whether early intervention strategies, such as valve replacement or repair, can improve patients
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24 outcomes in this specific population
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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

^aMedian 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 (cm ²) 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/m ²) 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)	

^aMedian 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
CUA/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 (cm ²) ^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/m ²) ^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

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3	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	
4	sPAP (mmHg) ^a	34 (28-43)	35 (29-45)	0.089	42 (34-54)	49 (39-59)	<0.001	<0.001	<0.001	
5	MR ERO (cm ²) ^a	NA	NA		0.1 (0.1-0.2)	0.1 (0.1-0.2)	0.148			
6	MR Rvol (ml) ^a	NA	NA		25 (17-35)	26 (17-34)	0.893			
7	AR	None	739 (55.4)	549 (50.2)	NS	82 (38.9)	115 (39)	NS	0.005	<0.001
8		minimal	253 (19)	225 (20.6)		30 (14.2)	69 (23.4)			
9		mild	266 (20)	266 (24.3)		72 (34.1)	81 (27.5)			
10		mild to moderate	75 (5.6)	54 (4.9)		27 (12.8)	30 (10.2)			
11	RV function	Normal	1245 (93.4)	1019 (93.1)	NS	173 (82)	231 (78.3)	NS	<0.001	<0.001
12		Mild	72 (5.4)	59 (5.4)		31 (14.7)	45 (15.3)			
13		Moderate	15 (1.1)	14 (1.3)		6 (2.8)	16 (5.4)			
14		Severe	1 (0.1)	2 (0.2)		1 (0.5)	3 (1)			
15	RV size	Normal	1221 (91.6)	987 (90.2)	NS	167 (79.1)	218 (73.9)	NS	<0.001	<0.001
16		Mild	83 (6.2)	82 (7.5)		33 (15.6)	59 (20)			
17		Moderate	24 (1.8)	17 (1.6)		9 (4.3)	13 (4.4)			
18		Severe	5 (0.4)	8 (0.7)		2 (0.9)	5 (1.7)			

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^aMedian and interquartile range. All other values represent the number of patients and percentages

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

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

	HR	95% CI	P
Up to mild MR + AVA \leq 1.35cm ² versus AVA > 1.35cm ²			
Univariate analysis	1.036	0.829-1.295	0.754
Greater than mild MR + AVA \leq 1.35cm ² versus AVA > 1.35cm ²			
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 > 1.35cm ² + 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 \leq 1.35cm ² + 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 \leq 1.35cm ² versus Up to mild MR + AVA > 1.35cm ²			
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

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4 * For clinical variables – Age, Sex, Atrial fibrillation, chronic renal failure Hypertension, Ischemic
5 heart disease, COPD

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7 † For Echocardiographic variables – Ejection fraction, Left ventricle end diastolic diameter, Left
8 ventricle end systolic diameter, Aortic valve regurgitation grade, right ventricle size, right
9 ventricle function

10 # For Diastolic parameter – LAVI, DT, Average E/e', E/A ratio, sPAP
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8 Figure 1 – Univariate Cox regression analysis for HF hospitalization according to severity of MR
9 and AVA
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12 Figure S1 – Univariate Cox regression analysis for mortality according to severity of MR and
13 AVA
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17 Figure S2 – Univariate Cox regression analysis for the Impact of Intervention (Surgical AVR) in
18 patient with MR>mild and AVA \leq 1.35cm²
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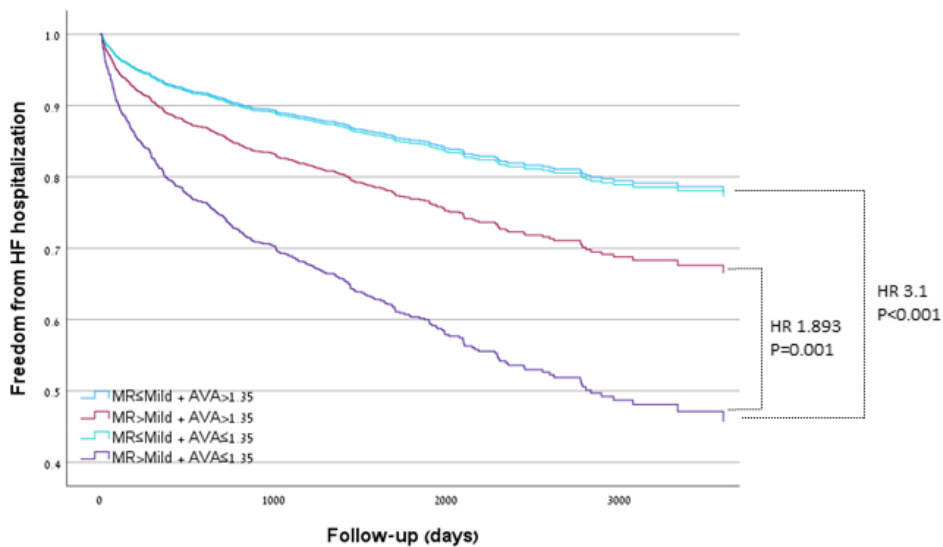


Figure 1

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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 \leq 1.35cm ² versus AVA > 1.35cm ²			
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 \leq 1.35cm ² versus AVA > 1.35cm ²			
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 > 1.35cm ² + MR up to mild versus greater than mild			
Univariate analysis	1.431	1.181-1.735	<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 \leq 1.35cm ² + 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 \leq 1.35cm ² versus Up to mild MR + AVA > 1.35cm ²			
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≤1.35cm ²		
	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
QVA/TIA	48 (16.3)	0	0.165
IHD	131 (44.4)	6 (60)	0.33
COPD	31 (10.5)	0	0.279
LVEF ^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 (cm ²) ^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
LA VI (ml/m ²) ^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

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3	E/A ratio ^a		1.2 (0.9-1.7)	1.2 (1-2.9)	0.6
4					
5	PAP (mmHg) ^a		49 (39-59)	40 (38-50)	0.107
6					
7	AR	None	115 (39)	3 (30)	0.762
8		minimal	69 (23.4)	2 (20)	
9		mild	81 (27.5)	3 (30)	
10		mild to moderate	30 (10.2)	2 (20)	
11					
12					
13	RV function	Normal	231 (78.3)	10 (100)	0.433
14		Mild	45 (15.3)	0	
15		Moderate	16 (5.4)	0	
16		Severe	3 (1)	0	
17					
18	RV size	Normal	218 (73.9)	10 (100)	0.322
19		Mild	59 (20)	0	
20		Moderate	13 (4.4)	0	
21		Severe	5 (1.7)	0	
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^aMedian 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 – Righth Ventricle; AR – Aortic regurgitation; LV EF – Left ventricle ejection fraction

Table S3 | Impact of Intervention (Surgical AVR) in patient with MR>mild and AVA \leq 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

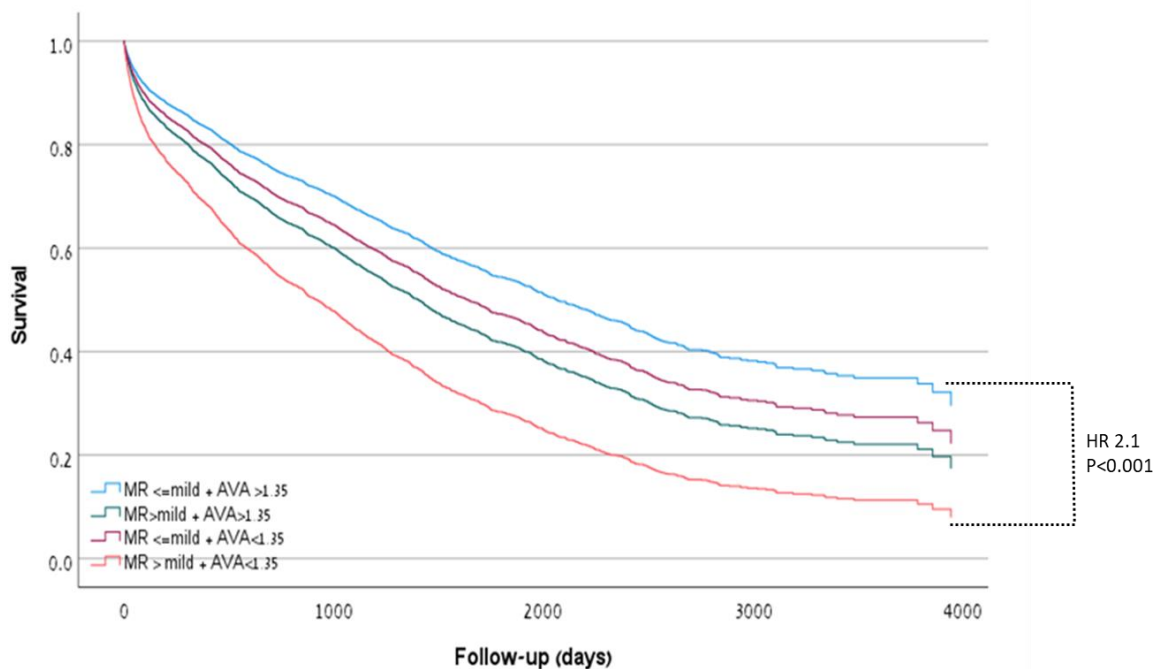
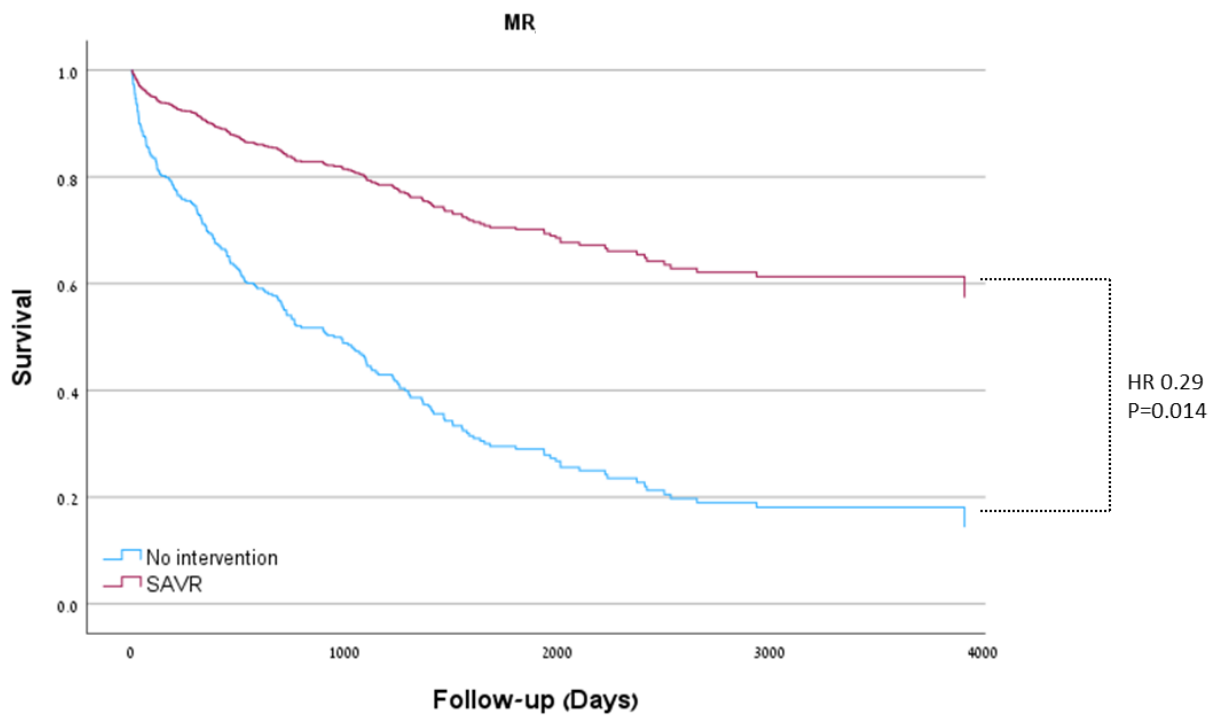


Figure S2



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

1	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	9-10
2			(b) Report category boundaries when continuous variables were categorized	
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
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9	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9-10
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11	Discussion			
12				
13	Key results	18	Summarise key results with reference to study objectives	11
14	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
15				
16	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13
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19	Generalisability	21	Discuss the generalisability (external validity) of the study results	13
20				
21	Other information			
22	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
23				
24				

*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>.