Natural History of Moderate Aortic Stenosis with Preserved and Low Ejection Fraction

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Background: There is a shortage of data concerning the natural history of patients with moderate aortic stenosis (AS). The aim of this study was to assess the effect of moderate AS on mortality in the general population and in the subgroups of patients with moderate AS and reduced ejection fractions (EF) and patients with moderate AS and low aortic valve gradients. The study was not designed to address the applicability of treatment in this population.

Methods: Outcomes were compared between patients with moderate AS and a propensity-matched cohort (1:3 ratio) without AS. The primary outcome was survival until end of follow-up.

Results: Among approximately 40,000 patients who underwent echocardiographic evaluations between 2011 and 2016, 952 had moderate AS. Median follow-up duration was 181 weeks (interquartile range, 179–182 weeks) for the entire cohort and 174 weeks (interquartile range, 169–179 weeks) for the propensity-matched groups. Propensity matching successfully balanced most preexisting clinical differences. Increased mortality was observed in the group of patients with moderate AS before propensity matching and persisted following propensity matching (median survival 4.1 vs 5.2 years, $P = .008$). Survival rates and corresponding standard errors at 1, 2, 3, and 5 years were 80 ± 1% versus 82 ± 0.7%, 70 ± 1.5% versus 74 ± 0.8%, 62 ± 1.7% versus 66 ± 0.9%, and 47 ± 2.4% versus 52 ± 1.3%, respectively. A survival difference was similarly observed for the subgroup analyses of moderate AS and reduced ejection fraction ($P = .028$) and moderate AS and low aortic valve gradients ($P = .039$).

Conclusions: Moderate AS is associated with increased mortality. The increased mortality was also observed in the subgroups of patients with either reduced ejection fraction or low aortic valve gradients. (J Am Soc Echocardiogr 2021;34:735-43.)

Keywords: Aortic stenosis, Gradients, Ejection fraction, Stroke volume, Survival

Aortic stenosis (AS) is a progressive disease affecting approximately 10% of the population older than 75 years in its moderate to severe forms.[1] The number of patients is rising and is expected to be multiplied by a factor of 2 to 3 over the next 50 years.[2] Once symptoms develop, prognosis is poor.[3,4] The standard of care for patients with severe symptomatic AS is valve replacement, either surgical aortic valve (AV) replacement or transcatheter AV replacement (TAVR).[5-7]

The European Society of Cardiology and American Heart Association/American College of Cardiology guidelines define moderate AS as an AV area (AVA) of 1.0 to 1.5 cm^2, an indexed AVA (AVAI) of 0.6 to 0.85 cm^2/m^2, or a mean aortic gradient of 20 to 40 mm Hg in the presence of normal flow.[8] Current accepted guidelines recommend AV replacement strictly for severe AS,[9,10] excluding moderate AS, although it may harbor a risk for adverse implications.[11]

It is unclear, however, whether patients with moderate AS actually have increased mortality due to their valvular disease or simply due to their background illnesses.

Using our institutional echocardiography registry, we aimed to evaluate whether moderate AS is associated with increased mortality in comparison with propensity-matched patients, stratified by ejection fraction (EF), and transaortic gradient, potentially justifying AV intervention by TAVR. The key outcome of this study was to compare survival between patients with moderate AS and a propensity-matched cohort of the general population and in two subgroups of interest: patients with moderate AS and reduced EFs and those with moderate AS with low AV gradients. Importantly, the study was not designed to address the applicability of treatment, either surgical or percutaneous, in this population.

METHODS

Database

Our database includes all patients who underwent echocardiographic examinations (for any indication) at the Tel Aviv Sourasky Medical Center between 2011 and 2016.

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Abbreviations

AS = Aortic stenosis

AV = Aortic valve

AVA = Aortic valve area

AVA-I = Indexed aortic valve area

EF = Ejection fraction

IQR = Interquartile range

LV = Left ventricular

MR = Mitral regurgitation

RV = Right ventricular

SV = Stroke volume

TAVR = Transcatheter aortic valve replacement

TR = Tricuspid regurgitation

In addition to detailed echocardiographic measurements regarding systolic, diastolic, valvular, and right-sided functions and sizes, we also documented extensive clinical details of the patients, including demographics, hospitalization details, background illnesses, and follow-up data regarding invasive interventions and mortality. The end of follow-up was the predefined ending time point of the study, April 1, 2018. Clinical outcomes were retrieved from patients' charts.

Echocardiography was performed in a standard manner using the same equipment (iE33; Philips Medical Systems, Bothell, WA) for all patients, with measurements conducted according to accepted guidelines.[8,12] Measurements of mitral inflow included the peak early filling (E-wave) and late diastolic filling (A-wave) velocities, the E/A ratio, and the deceleration time of early filling velocity. Early diastolic mitral annular velocities (e′) were measured in the apical four-chamber view. In patients in sinus rhythm, all measurements were averages of at least three cardiac cycles. In patients with atrial fibrillation, all measurements were averages of at least seven cardiac cycles. Left atrial volume was calculated using the biplane area-length method at end-systole. The severity of AS was defined by AVA, calculated using the standard continuity equation. Moderate AS was defined as AVA-I between 0.6 and 0.85 cm^2/m^2 or AVA between 1 and 1.5 cm^2 in the rare occasions when body surface area measurements were unavailable to calculate AVA-I.[8] Forward stroke volume (SV) was calculated from left ventricular (LV) outflow tract with subsequent calculation of cardiac output and index. LV EF was calculated as SV divided by LV end-diastolic volume. Right ventricular (RV) qualitative size and function assessments were based on multiple views of the right ventricle (short-axis parasternal at the basal, mid, and apical levels; lower parasternal RV inflow view; apical four-chamber view and if possible RV long-axis view; and subcostal short-axis and four-chamber views). Using these multiple views, an overall qualitative grading was determined by the interpreting physician.

Five hundred fifteen patients had apparent discrepancies in stenosis severity as defined by the mean gradient compared with the calculated valve area. In these patients, to verify the accuracy of the echocardiographic data, we evaluated SV, LV end-diastolic size, and EF. If SV was low because of small ventricular chamber or a low EF, a low AS mean gradient was still considered compatible with moderate AS. Of note, in all the discrepant patients, we also compared SV calculated from the LV outflow tract diameter and velocity with SV measured on two-dimensional echocardiography. SV measured on two-dimensional echocardiography was calculated as the difference of LV end-diastolic volume and end-systolic volume, calculated using the biplane method of disks summation (modified Simpson method), or the Quinones method, to confirm a low transaortic volume flow rate. When review of data confirmed accuracy of measurements and there was no clinical evidence for a low-flow state, patients with very low mean aortic pressure gradients (<20 mm Hg) and valve areas of 1.0 to 1.5 cm^2 were considered to have mild AS and were excluded from the analysis.

All measurements were abstracted from clinical reports. Echocardiographic measurements and AS grading criteria remained consistent throughout the study period, with the same criteria used for all patients examined, ensuring that all diagnoses were standardized and centralized.

In patients undergoing surgical ($n = 74$) or percutaneous ($n = 111$) AV replacement, censoring was defined as the day of procedure. We repeated the analyses, defining AV intervention as a competing risk, and again without censoring at the day of the procedure to ensure robustness of our findings.

Statistical Methods

To compare survival of patients with moderate AS with that of the general population, while controlling for the baseline differences in risk factors between the groups, we performed propensity score matching with a 3:1 ratio. The selection of variables for matching was done individually for each analysis (for all patients with moderate AS and for subgroups with moderate AS and reduced EF and with moderate AS and high AV gradients) in two stages: first, we examined baseline differences between the groups and selected all unbalanced features (defined as a standardized mean difference > 0.2). Among these unbalanced features, we then filtered out the redundant ones (those with significant inherent overlaps [i.e., cardiac output, cardiac index, EF, and SV]; in such cases one presentative feature was selected on the basis of clinical considerations or magnitude of imbalance). First, the entire moderate AS group was analyzed (matched with non-AS control subjects in a 1:3 ratio for signal optimization). We iteratively performed the analyses for patients with moderate AS and LV systolic dysfunction (EF < 50%) and for patients with moderate AS with relatively low gradients across the AV (i.e., mean pressure gradient < 27 mm Hg). Optimal cutoff for the low-gradient group was identified by the maximally selected rank method, which calculates the threshold value with the most significant relation to the outcome.

Collinear parameters were removed in upstream analysis. Matching was done on the following features using a nearest neighbor algorithm with a 1:3 ratio: Norton activity score,[13] history of ischemic heart disease or angina, atrial fibrillation or flutter, diabetes mellitus, hypertension, hyperlipidemia, renal dysfunction, mitral stenosis, age, left atrial index, intraventricular septal diameter in diastole, LV mass index, SV, tricuspid regurgitation (TR) velocity, mitral valve E/E′ average, systolic pulmonary artery pressure, and tricuspid annular plane systolic excursion. Assessment of balance was performed using the methods described by Ho *et al.*[14] and by inspecting resulting standardized mean differences (values < 0.2 were considered small). Variance inflation > 5 was considered large. Parameters on which to match were chosen separately for each analysis on the basis of the considerations specified above. Full specification of parameters used in each of the three analyses is available in the Supplemental Material.

Continuous, normally distributed variables are presented as mean ± SD and were compared using Student's *t* test. Ordinal and/or non-normally distributed variables are presented as median and interquartile range (IQR) and were compared using the Wilcoxon rank-sum test. Normality was assessed using the Shapiro-Wilk test and visual inspection of quantile-quantile plots and skews. Categorical variables were compared using the χ^2 test. We used a random forest classifier to impute the missing data. We performed

HIGHLIGHTS

- Patients with moderate AS have increased mortality compared with matched controls.
- Detrimental effect of moderate AS applies to patients with reduced and preserved EFs.
- Patients with moderate AS and low gradients also suffer increased mortality.
- Future studies are needed to examine the use of aortic valve replacement in this population.

Kaplan-Meier and log-rank tests to assess time to mortality from the date the echocardiographic study was done. Interactions between groups and EF, SV, and gradients were assessed by performing a Cox proportional-hazards regression test.

Comparing life expectancies between our cohort and the local population was done using the Ederer exact method,[15-19] using Israeli Central Bureau of Statistics mortality data as a reference.

All analyses were made using R version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria), with the following packages: imputations with the missForest package, propensity matching with the matchIt package, and survival analysis with the Survival and Survminer packages.

RESULTS

In total, our data set comprised 37,037 examinees with data suitable for analysis. Nine hundred fifty-two patients had moderate AS. The average AVA-I and mean pressure gradient for the moderate AS group were 0.71 ± 0.08 cm^2/m^2 and 20.5 ± 9.3 mm Hg, respectively, and median follow-up time was 181 weeks (IQR, 179–182 weeks).

For the outcome variables of survival under medical management (from diagnosis to surgery or TAVR or death), there were no missing data in the original data set. As for the partitioning feature for grouping (i.e., presence of moderate AS), only original data were used.

Basic characteristics varied substantially between the groups with moderate AS and the group without AS (Table 1). Patients with moderate AS tended to be older ($P < .001$), to have a higher burden of cardiovascular risk factors, to have higher comorbidity indexes, to have higher rates of ischemic heart disease ($P < .001$) and renal dysfunction ($P < .001$), to have worse RV function and pulmonary hypertension ($P < .001$), to have more systolic and diastolic dysfunction, and, not surprisingly, to have lower survival rates (with corresponding standard errors): 80 ± 1% versus 90 ± 0.1%, 70 ± 1.5% versus 86 ± 0.1%, 62 ± 1.7% versus 82% ± 0.2%, and 47 ± 2.4% versus 25% ± 0.3% at 1, 2, 3, and 5 years, respectively ($P < .0001$).

Before propensity matching, survival curves differed significantly between patients with moderate AS and control subjects (Figure 1).

Propensity matching was performed with a 1:3 ratio and resulted in 952 patients in the moderate AS cohort matched with 2,856 control subjects, with good overall balancing of preexisting differences. The C statistic for the propensity score was 0.845. Several differences in baseline parameters remained between the groups. However, these were generally small, for example, presence of mitral regurgitation (MR) (4.6% vs 2.9%, $P = .04$), cardiac index (2.9 vs 3.1 L/min/m^2, $P < .01$), and EF (54% vs 55.5%, $P < .01$). A detailed description of all the differences in baseline characteristics following propensity matching is provided in Table 2.

Median follow-up duration in this cohort was 174 weeks (IQR, 169–179 weeks). Survival differences under medical management (from diagnosis until end of follow-up, intervention, or death) were still significantly different following propensity matching (Figure 2), with a median survival time of 220 weeks (IQR, 204–276 weeks) in the moderate AS group versus 269 weeks (IQR, 253–322 weeks) in the control group ($P = .008$). Survival rates and corresponding standard errors at 1, 2, 3, and 5 years were 80 ± 1% versus 82 ± 0.7%, 70 ± 1.5% versus 74 ± 0.8%, 62 ± 1.7% versus 66 ± 0.9%, and 47 ± 2.4% versus 52 ± 1.3%, respectively. Love plots and quantile-quantile plots displaying covariate balance improvements following propensity matching are found in the Supplemental Material.

As a sensitivity analysis, we performed a direct comparison between survival of our cohort of patients with moderate AS and the regular life expectancy of the local population of Israel at the relevant time period of data gathering. The mean age of patients with moderate AS in our cohort was 78 years. At that age, life expectancy in Israel is 11.4 years (95% CI, 11.4–11.5 years) for women and 10.3 years (95% CI, 10.2–10.3 years) for men. Patients with moderate AS had lower survival rates compared with the general population. Relative survival rates at 1, 3, and 5 years were 92%, 78%, and 66%, respectively. Additionally, we performed two separate analyses, defining AV intervention as a competing risk, and again without censoring at the day of the procedure, to ensure the robustness of our findings. Excess mortality in the moderate AS group was still apparent compared with matched control subjects ($P = .0145$ and $P = .009$, respectively).

Moderate AS with Reduced EF

To assess for possible difference in outcomes in the high-risk subgroup of patients with reduced EF and moderate AS, we identified 145 patients with moderate AS and EFs < 50% and matched them using a 1:3 ratio with 435 control subjects who also had EFs < 50% but without AV pathology. Matching was done to balance the groups on nonredundant covariates with baseline differences between the groups, without controlling for EF, as previously specified. Following matching, preexisting differences in patient risk factors between the two groups were almost entirely balanced.

Details regarding matching quality and balance between the groups following propensity matching are presented in Table 3. Data before propensity matching are presented in Supplemental Table 1.

Median follow-up in this matched cohort was 166 weeks (IQR, 151–176 weeks). A survival difference was observed in the group with moderate AS and reduced EFs compared with control (median survival times of 147 weeks [95% CI, 95–215 weeks] vs 190 weeks [95% CI, 169–250 weeks], $P = .04$) (Figure 3). Survival rates with corresponding standard errors at 1, 2, 3, and 5 years were 68 ± 3.9% versus 74 ± 2% ($P = .13$), 55 ± 4.3% versus 65 ± 2.3% ($P = .05$), 47 ± 4.7% versus 58 ± 2.5% ($P = .04$), and 30 ± 6.3% versus 42 ± 3.6% ($P = .04$), respectively.

Cox proportional-hazards analysis, including interactions for EF above or below 50% and the presence of moderate AS,

Table 1 Patient characteristics before propensity score matching

	Control (*n* = 36,085)	Moderate AS (*n* = 952)	*P*
Age, y	62.57 ± 18.3	77.89 ± 11.9	<.001
Female gender	16,113 (44.7)	476 (50.0)	.001
Body mass index, kg/m^2	25.99 ± 4.09	26.68 ± 4.3	<.001
Body surface area, m^2	1.82 ± 0.2	1.84 ± 0.2	<.001
Congestive heart failure	1,701 (4.7)	92 (9.7)	<.001
Chronic lung disease	1,905 (5.3)	91 (9.6)	<.001
Ischemic heart disease	4,173 (11.6)	229 (24.1)	<.001
Pacemaker/ICD	559 (1.5)	35 (3.7)	<.001
Atrial fibrillation/flutter	2,640 (7.3)	137 (14.4)	<.001
Diabetes mellitus	6,180 (17.1)	269 (28.3)	<.001
Obesity	5,303 (14.7)	184 (19.3)	<.001
Hypertension	12,501 (34.6)	560 (58.8)	<.001
Hyperlipidemia	9,203 (25.5)	372 (39.1)	<.001
Smoking	2,981 (8.3)	74 (7.8)	.63
Renal dysfunction	1,684 (4.7)	102 (10.7)	<.001
Family history of ischemic heart disease	501 (1.4)	9 (0.9)	.31
History of venous thromboembolism	155 (0.4)	8 (0.8)	.101
Malignancy	1,261 (3.5)	46 (4.8)	.03
Stroke/transient ischemic event	678 (1.9)	24 (2.5)	.19
Norton scale: activity			<.001
0	946 (2.6)	18 (1.9)	
1	1,420 (3.9)	48 (5.0)	
2	2,470 (6.8)	142 (14.9)	
3	20,227 (56.1)	437 (45.9)	
4	11,022 (30.5)	307 (32.2)	
TR grade	4.43 ± 1.50	4.02 ± 1.5	<.001
Mitral stenosis	878 (2.4)	128 (13.4)	<.001
MR	662 (1.8)	28 (2.9)	.02
Left atrial volume index, mL/m^2	33.67 ± 13.4	45.32 ± 17.9	<.001
AV VTI, cm	37.63 ± 3.0	61.30 ± 16.3	<.001
LV mass index, g/m^2	106.31 ± 24.0	127.26 ± 22.2	<.001
LV end-diastolic diameter, mm	46.96 ± 5.9	47.54 ± 6.8	.003
LV end-systolic diameter, mm	29.34 ± 6.9	30.46 ± 7.6	<.001
Cardiac index, L/min/m^2	2.79 ± 0.6	3.05 ± 0.7	<.001
Cardiac output, L/min	5.04 ± 1.2	5.51 ± 1.4	<.001
SV, mL/beat	73.82 ± 17.1	80.44 ± 20.7	<.001
EF, %	56.15 ± 8.1	55.40 ± 8.2	.01
TR velocity, m/sec	2.62 ± 0.40	2.81 ± 0.4	<.001
Mitral valve deceleration time, msec	180.79 ± 69.7	199.98 ± 84.5	<.001
Lateral e′ wave, cm/sec	9.03 ± 3.1	7.11 ± 2.2	<.001
Septal e′ wave, cm/sec	6.77 ± 2.2	5.32 ± 1.6	<.001
MV e′ wave, average, cm/sec	7.39 ± 2.9	6.16 ± 1.8	<.001
MV E/e′ average	9.74 ± 4.9	14.96 ± 7.5	<.001
MV a wave, maximum velocity, cm/sec	0.77 ± 0.3	0.95 ± 0.4	<.001
MV e wave, maximum velocity, cm/sec	0.80 ± 0.3	0.97 ± 0.3	<.001
e/a	1.12 ± 0.5	1.09 ± 0.6	.24
AVA index, cm^2/m^2	1.49 ± 0.1	0.71 ± 0.1	<.001
AVA, cm^2	1.85 ± 0.1	1.31 ± 0.1	<.001
AV mean pressure gradient, mm Hg	10.99 ± 1.0	20.46 ± 9.3	<.001
AV maximum velocity, m/sec	1.45 ± 0.2	2.94 ± 0.6	<.001
RA area, cm^2	16.96 ± 4.0	19.32 ± 5.4	<.001
Estimated RA pressure, mm Hg	6.93 ± 3.0	7.33 ± 3.9	<.001
Systolic pulmonary artery pressure, mm Hg	33.55 ± 8.9	38.63 ± 12.1	<.001
Calculated RA pressure, mm Hg	6.58 ± 3.6	7.73 ± 5.0	<.001
Tricuspid annular plane systolic excursion, mm	22.98 ± 3.2	21.99 ± 3.9	<.001
TV systolic diameter, mm	11.09 ± 1.8	10.99 ± 2.3	.07
TR pressure gradient, mm Hg	22.71 ± 9.6	27.66 ± 13.0	<.001
TR vena contracta, mm	9.15 ± 2.1	7.23 ± 1.8	<.001

Data are expressed as mean ± SD or as number (percentage).
ICD, Implantable cardioverter-defibrillator; *MV*, mitral valve; *RA*, right atrial; *TV*, tricuspid valve; *VTI*, velocity-time integral.

demonstrated that EF (≤50% or >50%) did not interact with the impact of moderate AS on survival ($P = .27$).

Moderate AS with Low Gradients

Low AV gradients are assumed to be associated with low risk for mortality in patients with AS. We performed propensity matching for the subgroup of patients with AVA in the moderate range and relatively low pressure gradients across the AV (<27 mm Hg, chosen as an optimal cutoff value for outcome discrimination by the maximally selected ranking method). We identified 702 such patients and matched them using a 1:3 ratio with 2,106 control subjects without AV pathology. Again, matching was done on the basis of unbalanced nonredundant covariates as specified earlier to best balance the

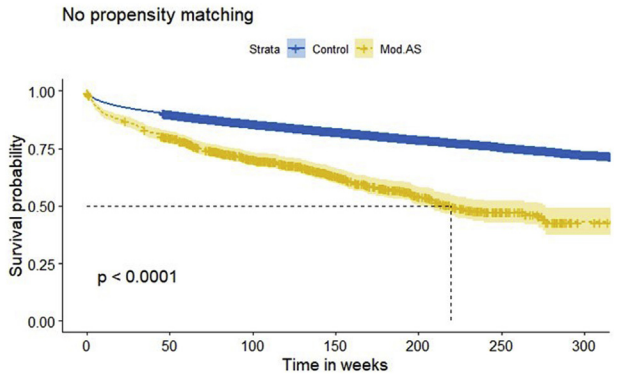

Figure 1 Survival curve before propensity matching demonstrating increased mortality in the moderate AS group.

groups. After a successful matching process, preexisting differences in patient risk factors between the groups greatly diminished (details regarding matching quality and balance between the groups following propensity matching can be seen in Table 4). Data before propensity matching can be seen in Supplemental Table 2.

Median follow-up duration in this matched cohort was 163 weeks (IQR, 155–169 weeks). Figure 4 demonstrates that survival rates significantly differed between the moderate AS with low transaortic gradient and control groups after propensity matching (median survival times of 208 weeks [95% CI, 174–264 weeks] vs 247 weeks [95% CI, 224–276 weeks], $P = .03$). Survival rates and corresponding standard errors at 1, 2, 3 and 5 years were 78 ± 1.5% versus 80 ± 0.8% ($P = .29$), 68 ± 1.8% versus 72 ± 1% ($P = .09$), 59 ± 2% versus 64 ± 1% ($P = .03$), and 44 ± 2.9% versus 49 ± 1.5% ($P = .03$), respectively.

Cox proportional-hazards analysis, including interaction terms for mean AV pressure gradients > 27 mm Hg or <27 mm Hg and presence of moderate AS, revealed that the mean gradient did not interact with the impact of moderate AS on survival ($P = .40$).

Because SV is also associated with poorer survival in patients with severe AS,[20] we performed a Cox proportional-hazards analysis, including interaction terms for SV index > 35 mL/m^2 or <35 mL/m^2 and presence of moderate AS. This analysis revealed that SV index did not interact with the impact of moderate AS on survival ($P = .70$).

DISCUSSION

Our study demonstrates that patients with moderate AS have increased mortality rates compared with control subjects in an unadjusted analysis. These results are similar to those recently presented by researchers in Australia.[21] We show that following propensity matching with patients without AS, survival analysis continues to demonstrate a difference in survival. Although several statistically significant differences remain in the propensity-matched groups, the differences are minor and clinically insignificant.

Coexistence of severe or moderate AS in patients with heart failure with reduced EF is common. Severe and even moderate AS increases afterload, whereas pharmacologic reduction of afterload is a pillar of contemporary heart failure management. In severe AS, deteriorating LV function is caused by the increased afterload from the stenotic valve,[22] increasing mortality in these patients. A similar mechanism might therefore exist as well in moderate AS.[23,24] On the basis of these hemodynamic concepts, an ongoing trial has speculated that unloading the left ventricle by reducing the

Table 2 Propensity-matched patient characteristics

	Control (*n* = 2,856)	Moderate AS (*n* = 952)	*P*
Age, y	78.41 ± 11.1	77.89 ± 11.9	.43
Female gender	1,296 (45.4)	476 (50.0)	.02
Body mass index, kg/m^2	26.80 ± 4.8	26.68 ± 4.3	.21
Body surface area, m^2	1.81 ± 0.3	1.84 ± 0.2	.14
Body mass index, kg/m^2	26.80 ± 4.8	26.68 ± 4.3	.57
Body surface area, m^2	1.81 ± 0.3	1.84 ± 0.2	.001
Congestive heart failure	291 (10.2)	92 (9.7)	.69
Chronic lung disease	206 (7.2)	91 (9.6)	.02
Ischemic heart disease	716 (25.1)	229 (24.1)	.56
Pacemaker/ICD	102 (3.6)	35 (3.7)	.96
Atrial fibrillation/flutter	414 (14.5)	137 (14.4)	.98
Diabetes mellitus	858 (30.0)	269 (28.3)	.32
Obesity	526 (18.4)	184 (19.3)	.56
Hypertension	1,717 (60.1)	560 (58.8)	.50
Hyperlipidemia	1,147 (40.2)	372 (39.1)	.58
Smoking	198 (6.9)	74 (7.8)	.42
Renal dysfunction	339 (11.9)	102 (10.7)	.37
Family history of ischemic heart disease	14 (0.5)	9 (0.9)	.18
History of venous thromboembolism	15 (0.5)	8 (0.8)	.40
Malignancy	139 (4.9)	46 (4.8)	1.00
Stroke/transient ischemic event	96 (3.4)	24 (2.5)	.24
Norton scale: activity			.22
0	75 (2.6)	18 (1.9)	
1	156 (5.5)	48 (5.0)	
2	352 (12.3)	142 (14.9)	
3	1,346 (47.1)	437 (45.9)	
4	927 (32.5)	307 (32.2)	
TR grade	4.08 ± 1.5	4.02 ± 1.5	.31
Mitral stenosis	350 (12.3)	128 (13.4)	.36
MR	130 (4.6)	28 (2.9)	.04
Left atrial volume index, mL/m^2	45.34 ± 17.98	45.32 ± 17.93	.98
AV VTI, cm	38.45 ± 4.88	61.30 ± 16.30	.36
LV mass index, g/m^2	128.27 ± 22.24	127.26 ± 22.18	.22
LV end-diastolic diameter, mm	48.20 ± 6.83	47.54 ± 6.84	.01
LV end-systolic diameter, mm	31.08 ± 7.88	30.46 ± 7.56	.03
Cardiac index, L/min/m^2	2.92 ± 0.69	3.05 ± 0.70	<.001
Cardiac output, L/min	5.31 ± 1.48	5.51 ± 1.43	<.001
SV, mL/beat	79.70 ± 23.45	80.44 ± 20.66	.38
EF, %	53.96 ± 9.36	55.40 ± 8.18	<.001

(*Continued*)

Table 2 (*Continued*)

	Control (*n* = 2,856)	Moderate AS (*n* = 952)	*P*
TR velocity, m/sec	2.80 ± 0.43	2.81 ± 0.42	.83
Mitral valve deceleration time, msec	188.32 ± 78.43	199.98 ± 84.46	<.001
Lateral e′ wave, cm/sec	7.16 ± 2.24	7.11 ± 2.22	.59
Septal e′ wave, cm/sec	5.39 ± 1.68	5.32 ± 1.56	.26
MV e′ wave, average, cm/sec	6.20 ± 1.92	6.16 ± 1.78	.55
MV E/e′ average	14.74 ± 7.22	14.96 ± 7.47	.41
MV a wave, maximum velocity, cm/sec	0.87 ± 0.32	0.95 ± 0.35	<.001
MV e wave, maximum velocity, cm/sec	0.94 ± 0.35	0.97 ± 0.32	.02
e/a	1.12 ± 0.59	1.09 ± 0.61	.35
AVA index, cm^2/m^2	1.47 ± 0.10	0.71 ± 0.08	<.001
AVA, cm^2	1.83 ± 0.05	1.31 ± 0.12	<.001
AV mean pressure gradient, mm Hg	11.08 ± 1.52	20.46 ± 9.31	<.001
AV maximum velocity, m/sec	1.53 ± 0.31	2.94 ± 0.63	<.001
RA area, cm^2	19.60 ± 5.02	19.32 ± 5.43	.15
Estimated RA pressure, mm Hg	7.67 ± 4.05	7.33 ± 3.94	.02
Systolic pulmonary artery pressure, mm Hg	38.61 ± 12.66	38.63 ± 12.13	.97
Calculated RA pressure, mm Hg	8.02 ± 4.94	7.73 ± 5.00	.12
Tricuspid annular plane systolic excursion, mm	21.89 ± 3.75	21.99 ± 3.88	.50
TV systolic diameter, mm	10.98 ± 2.02	10.99 ± 2.28	.98
TR pressure gradient, mm Hg	26.98 ± 13.45	27.66 ± 13.01	.17
TR vena contracta, mm	7.37 ± 1.82	7.23 ± 1.83	.05

Data are expressed as mean ± SD or as number (percentage).
ICD, Implantable cardioverter-defibrillator; *MV*, mitral valve; *RA*, right atrial; *TV*, tricuspid valve; *VTI*, velocity-time integral.

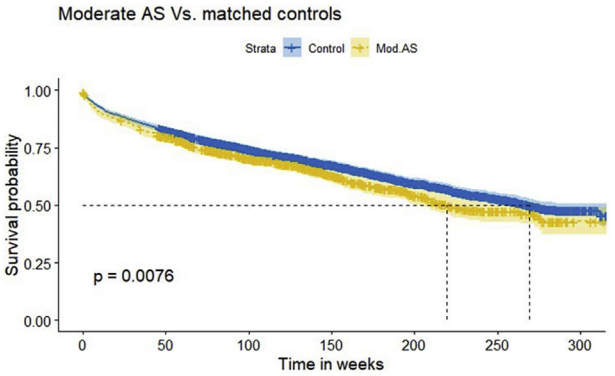

Figure 2 Survival curve following propensity matching. A survival difference persists between the groups.

transaortic gradient with TAVR may improve clinical outcomes in patients with moderate AS and heart failure with reduced EF.[25] Indeed, our analysis demonstrated excess mortality rates in patients with moderate AS compared with propensity-matched patients without AS. However, Cox proportional-hazards analysis, including interactions for EF > 50% or <50% and the presence of moderate AS, demonstrated that EF did not interact with the impact of moderate AS on survival. This lack of interaction suggests that the detrimental effect of moderate AS is not unique for patients with reduced EF and may apply to patients with preserved EFs. Previous hemodynamic trials showed that maneuvers that increase LV afterload, such as "hand grip," increase LV end-diastolic pressure and decrease SV, by increasing LV stiffness even in patients with preserved EFs. These hemodynamic insights support a potential detrimental role of increased afterload load applied by moderate AS even in the presence of preserved EF.[26-28]

Recent guidelines (European Society of Cardiology/European Association for Cardio-Thoracic Surgery valve guidelines[10]) suggest that a mean transaortic gradient < 30 mm Hg decreases the likelihood of clinically significant AS. Common practice is to ignore AVA once mean gradients are in the mild range. In this study, we show for the first time that even the subgroup of patients with moderate AS (AVA 1–1.5 cm^2) and low gradients experience increased mortality.

Interestingly, a recent report from the Mayo Clinic compared the outcomes of patients with moderate AS with age- and sex-matched expected mortality in the general population of Minnesota. They showed that patients with moderate AS and decreased LV EF and/or SV index are at high risk compared with the age- and sex-matched general population. Even if LV EF was preserved, the mortality ratio remained >2 times higher compared with reference. This was also the case for patients with SV index < 35 mL/m^2. The investigators concluded that moderate AS, even in the presence of preserved LV EF, or low SV, should not be seen as a benign condition, corroborating our propensity-matched analyses.[29]

The exact characteristics that drive this difference in mortality from the general populations remain unclear. We suggest that further studies, principally of prospective and randomized design, are needed to affirm our results.

It is important to acknowledge several limitations of our study. First, we were unable to assess causality, because of the nonrandomized or controlled nature of the study. Furthermore, we did not examine intervention by either surgical AV replacement or TAVR in patients with moderate AS and therefore cannot offer evidence to support the use of AV replacement in this population. An additional point is that we did not examine impact on quality of life. Last, we could not stratify valvular diseases other than AS (MR and TR) by severity because of a lack of data; less than severe MR and TR were not graded in our database. We could not compare the mean or distribution of MR and TR grades between the groups but only the prevalence of existence of any MR or TR (greater than mild), with no capacity to differentiate between the grades of mild to moderate or moderate MR or TR. Additionally, despite a considerable improvement in groups' balance, some patient features were not fully matched following propensity matching and multivariate analysis procedures. This could potentially contribute to the mortality differences observed.

Table 3 Propensity-matched baseline characteristics for patients with reduced EF AS

	Control (*n* = 435)	Moderate AS (*n* = 145)	*P*
Age, y	78.69 ± 9.14	78.74 ± 10.63	.95
Female gender	149 (34.3)	49 (33.8)	1.00
Body mass index, kg/m^2	26.42 ± 3.64	26.74 ± 4.39	.37
Body surface area, m^2	1.84 ± 0.17	1.86 ± 0.19	.22
Congestive heart failure	101 (23.2)	39 (26.9)	.43
Chronic lung disease	61 (14.0)	23 (15.9)	.68
Ischemic heart disease	207 (47.6)	66 (45.5)	.74
Pacemaker/ICD	34 (7.8)	10 (6.9)	.86
Atrial fibrillation/flutter	76 (17.5)	26 (17.9)	1.00
Diabetes mellitus	182 (41.8)	54 (37.2)	.38
Obesity	80 (18.4)	31 (21.4)	.50
Hypertension	293 (67.4)	91 (62.8)	.36
Hyperlipidemia	214 (49.2)	68 (46.9)	.70
Smoking	53 (12.2)	19 (13.1)	.88
Renal dysfunction	75 (17.2)	24 (16.6)	.95
Family history of ischemic heart disease	4 (0.9)	1 (0.7)	1.00
History of venous thromboembolism	6 (1.4)	1 (0.7)	.83
Malignancy	17 (3.9)	5 (3.4)	1.00
Stroke/transient ischemic event	22 (5.1)	5 (3.4)	.57
Norton scale: activity			.84
0	4 (0.9)	2 (1.4)	
1	29 (6.7)	7 (4.8)	
2	55 (12.6)	20 (13.8)	
3	163 (37.5)	59 (40.7)	
4	184 (42.3)	57 (39.3)	
TR grade	3.97 ± 1.58	3.89 ± 1.63	.59
Mitral stenosis	38 (8.7)	12 (8.3)	1.00
MR	35 (8.0)	14 (9.7)	.67
Left atrial volume index, mL/m^2	53.16 ± 23.33	52.83 ± 19.59	.88
AV VTI, cm	38.05 ± 4.50	54.87 ± 14.44	<.001
LV mass index, g/m^2	133.55 ± 18.06	139.29 ± 10.84	<.001
LV end-diastolic diameter, mm	54.70 ± 9.41	54.93 ± 7.87	.79
LV end-systolic diameter, mm	39.71 ± 11.82	41.50 ± 8.80	.10
Cardiac index, L/min/m^2	2.58 ± 0.64	2.83 ± 0.70	<.001
Cardiac output, L/min	4.62 ± 1.33	5.05 ± 1.44	.00
SV, mL/beat	67.49 ± 20.29	71.01 ± 18.67	.07
EF, %	44.51 ± 13.98	39.27 ± 6.99	<.001
TR velocity, m/sec	2.94 ± 0.47	2.94 ± 0.44	.97
Mitral valve deceleration time, msec	178.26 ± 63.80	182.97 ± 64.30	.44
Lateral e′ wave, cm/sec	6.71 ± 2.24	6.79 ± 2.26	.71
Septal e′ wave, cm/sec	4.83 ± 1.59	4.70 ± 1.58	.39
MV e′ wave, average, cm/sec	5.75 ± 1.80	5.73 ± 1.81	.87
MV E/e′ average	17.21 ± 8.37	17.07 ± 8.51	.87
MV a wave, maximum velocity, cm/s	0.81 ± 0.34	0.87 ± 0.32	.08
MV e wave, maximum velocity, cm/s	0.99 ± 0.34	1.00 ± 0.32	.67
e/a	1.31 ± 0.80	1.25 ± 0.76	.48
AVA index, cm^2/m^2	1.48 ± 0.09	0.72 ± 0.07	<.001
AVA, cm^2	1.83 ± 0.05	1.33 ± 0.12	<.001
AV mean pressure gradient, mm Hg	10.96 ± 1.27	16.18 ± 7.37	<.001
AV maximum velocity, m/sec	1.49 ± 0.27	2.61 ± 0.56	<.001
RA area, cm^2	20.67 ± 5.50	21.07 ± 5.57	.45
Estimated RA pressure, mm Hg	9.45 ± 5.16	9.13 ± 5.21	.51
Systolic pulmonary artery pressure, mm Hg	42.76 ± 14.41	42.58 ± 12.31	.89
Calculated RA pressure, mm Hg	10.03 ± 5.76	9.59 ± 6.17	.43
Tricuspid annular plane systolic excursion, mm	19.20 ± 4.43	19.39 ± 4.27	.65
TV systolic diameter, mm	10.04 ± 2.27	9.74 ± 2.24	.17
TR pressure gradient, mm Hg	29.40 ± 15.50	30.48 ± 13.25	.45
TR vena contracta, mm	7.27 ± 1.70	7.16 ± 1.59	.52

Data are expressed as mean ± SD or as number (percentage).
ICD, Implantable cardioverter-defibrillator; *MV*, mitral valve; *RA*, right atrial; *TV*, tricuspid valve; *VTI*, velocity-time integral.

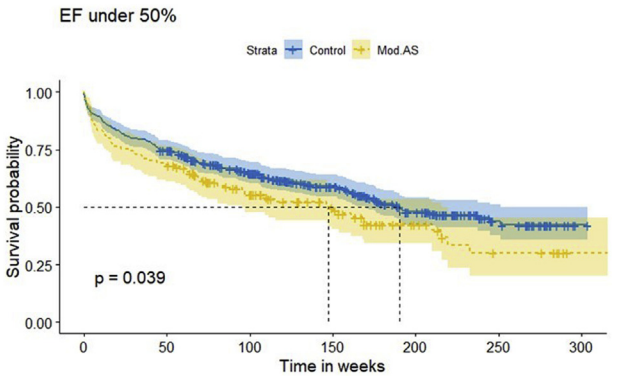

Figure 3 Survival curves following propensity matching for subgroups with reduced EF, demonstrating increased mortality in this subgroup.

CONCLUSION

Patients with moderate AS have increased mortality rates in comparison with matched control subjects. This increased mortality is

Table 4 Propensity-matched baseline characteristics for patients with low-gradient AS

	Control (*n* = 2,106)	Moderate AS (*n* = 702)	*P*
Age, y	79.45 ± 10.2	78.82 ± 10.8	.16
Female gender	1,080 (51.3)	341 (48.6)	.23
Body mass index, kg/m^2	26.97 ± 5.0	26.95 ± 4.5	.93
Body surface area, m^2	1.82 ± 0.2	1.86 ± 0.2	<.001
Congestive heart failure	223 (10.6)	72 (10.3)	.86
Chronic lung disease	169 (8.0)	67 (9.5)	.24
Ischemic heart disease	574 (27.3)	192 (27.4)	1.00
Pacemaker/ICD	80 (3.8)	31 (4.4)	.54
Atrial fibrillation/flutter	347 (16.5)	110 (15.7)	.66
Diabetes mellitus	678 (32.2)	225 (32.1)	.98
Obesity	476 (22.6)	150 (21.4)	.53
Hypertension	1,363 (64.7)	446 (63.5)	.60
Hyperlipidemia	891 (42.3)	293 (41.7)	.83
Smoking	149 (7.1)	59 (8.4)	.28
Renal dysfunction	257 (12.2)	88 (12.5)	.87
Family history of ischemic heart disease	10 (0.5)	7 (1.0)	.21
History of venous thromboembolism	14 (0.7)	6 (0.9)	.80
Malignancy	112 (5.3)	40 (5.7)	.77
Stroke/transient ischemic event	77 (3.7)	19 (2.7)	.28
Norton scale: activity			.79
0	48 (2.3)	12 (1.7)	
1	139 (6.6)	43 (6.1)	
2	322 (15.3)	110 (15.7)	
3	939 (44.6)	305 (43.4)	
4	658 (31.2)	232 (33.0)	
TR grade	4.10 ± 1.6	3.99 ± 1.6	.12
Mitral stenosis	234 (11.1)	92 (13.1)	.17
MR	97 (4.6)	24 (3.4)	.22
Left atrial volume index, mL/m^2	45.58 ± 19.8	45.88 ± 18.6	.72
AV VTI, cm	38.51 ± 5.1	57.50 ± 12.2	<.001
LV end-diastolic diameter, mm	47.62 ± 6.9	47.59 ± 6.7	.91
LV end-systolic diameter, mm	30.89 ± 8.1	30.79 ± 7.6	.77
Cardiac index, L/min/m^2	2.75 ± 0.6	2.88 ± 0.6	<.001
Cardiac output, L/min	4.91 ± 1.2	5.20 ± 1.2	<.001
SV, mL/beat	72.08 ± 19.2	74.82 ± 16.6	.001
EF, %	54.56 ± 9.3	54.61 ± 8.6	.90
TR velocity, m/sec	2.82 ± 0.4	2.82 ± 0.4	.70
Mitral valve deceleration time, msec	200.69 ± 75.3	199.51 ± 80.8	.73
Lateral e′ wave, cm/sec	7.09 ± 2.2	7.12 ± 2.1	.78
Septal e′ wave, cm/sec	5.30 ± 1.6	5.26 ± 1.5	.58
MV e′ wave, average, cm/sec	6.12 ± 1.8	6.13 ± 1.7	.86
MV E/e′ average	14.78 ± 7.2	15.15 ± 7.4	.23
MV a wave, maximum velocity, cm/sec	0.86 ± 0.3	0.93 ± 0.3	<.001
MV e wave, maximum velocity, cm/sec	0.94 ± 0.4	0.98 ± 0.3	.01
e/a	1.12 ± 0.6	1.12 ± 0.6	.79
AVA index, cm^2/m^2	1.47 ± 0.1	0.72 ± 0.1	<.001
AVA, cm^2	1.83 ± 0.1	1.33 ± 0.1	<.001
AV mean pressure gradient, mm Hg	11.13 ± 2.1	16.12 ± 5.1	<.001
AV maximum velocity, m/sec	1.53 ± 0.3	2.68 ± 0.5	<.001
RA area, cm^2	19.53 ± 5.2	19.60 ± 5.6	.77
Estimated RA pressure, mm Hg	7.95 ± 4.3	7.48 ± 4.2	.01
Systolic pulmonary artery pressure, mm Hg	39.08 ± 12.7	38.98 ± 12.3	.85
Calculated RA pressure, mm Hg	8.28 ± 5.1	7.91 ± 5.2	.10
Tricuspid annular plane systolic excursion, mm	21.31 ± 3.7	21.49 ± 4.0	.29
TV systolic diameter, mm	10.70 ± 1.9	10.66 ± 2.3	.61
TR pressure gradient, mm Hg	27.17 ± 13.3	27.98 ± 13.1	.16
TR vena contracta, mm	7.31 ± 1.8	7.13 ± 1.7	.02

Data are expressed as mean ± SD or as number (percentage).
ICD, Implantable cardioverter-defibrillator; *MV*, mitral valve; *RA*, right atrial; *TV*, tricuspid valve; *VTI*, velocity-time integral.

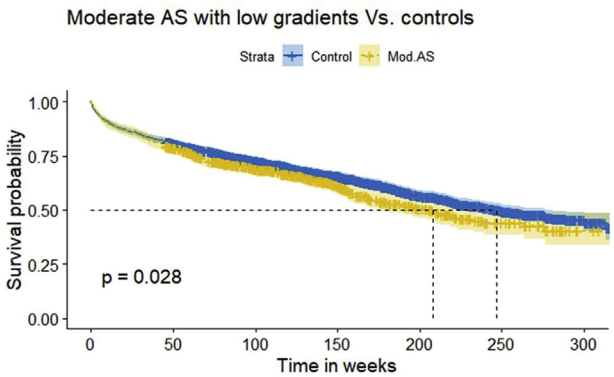

Figure 4 Survival curves following propensity matching for the subgroups with AV pressure gradients, demonstrating increased mortality rates in this subgroup.

observed in patients with low or preserved EFs and even in patients with low transaortic gradients.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.echo.2021.02.014.

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