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Initial changes in peak aortic jet velocity and mean gradient predict progression to severe aortic stenosis

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ABSTRACT

Background: There is significant interindividual variability in the rate of aortic stenosis (AS) progression that is not accounted for in the current surveillance algorithms. We sought to examine the association between changes in peak aortic jet velocity (Vmax) and mean gradient (MG) among patients with mild or moderate AS and risk of progression to severe disease.

Methods: Adult subjects referred for echocardiography at a single academic referral center with a diagnosis of mild or moderate AS and ≥2 additional surveillance echocardiograms were included in the study. Changes in Vmax and MG between the first two echocardiograms were indexed to time and tested for association with future progression to severe AS.

Results: Among three hundred and sixty-four subjects, the median time between first and second echocardiograms was 1.3 years and initial changes in Vmax and MG indexed to time were +0.16 m/s per year and +1.44 mmHg per year, respectively. Fifty-three (15%) and fifty-six (15%) subjects progressed to severe AS defined by Vmax and MG, respectively. In multivariable logistic regression, initial increase in Vmax (OR = 4.19, 95% CI 1.93–9.10, p < 0.001) and initial increase in MG (OR = 1.12, 95% CI 1.06–1.18, p < 0.001) were associated with progression to severe AS.

Conclusions: Initial changes in Vmax and MG among patients with mild or moderate AS are strongly associated with risk of progression to severe AS and may help guide individualized surveillance strategies.

1. Introduction

Aortic stenosis (AS) is the most common valvular heart disease in the developed world, affecting up to 10% of elderly patients [1,2]. Clinically, AS is classified as mild, moderate, or severe based on degree of hemodynamic obstruction, with severe AS further characterized as asymptomatic or symptomatic [3,4]. AS is generally regarded as a progressive condition and severe AS (particularly when symptomatic) has a dire prognosis without valvular intervention [5,6].

Current guidelines recommend routine monitoring of asymptomatic AS with echocardiography, where the frequency of surveillance is determined by disease severity [4].

These recommendations are based on average rates of change in the echocardiographic parameters that define severity of AS, even though the tempo of progression varies widely [3,7]. There is significant interindividual variability in the rate of AS progression that is not accounted for in the current surveillance algorithms based on average changes in echocardiographic parameters. Identifying predictors of disease progression could help estimate individualized risk and inform optimal surveillance strategies.

We sought to examine the association of initial changes in echocardiographic measures of hemodynamic obstruction, namely peak aortic jet velocity (Vmax) and mean gradient (MG), in patients with mild or moderate AS with risk of disease progression to severe stage. We hypothesized that initial changes in these

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echocardiographic parameters may help better estimate individualized risk of AS progression.

2. Methods

2.1. Population & study design

We performed a retrospective observational study of all adult subjects with mild or moderate AS and longitudinal echocardiographic surveillance data in the Vanderbilt University Medical Center's Synthetic Derivative [8,9]. The Synthetic Derivative is a de-identified image of the electronic health record (EHR), containing more than 20 years of records [8,9]. The inclusion criteria for the study were: 1) diagnosis of mild or moderate AS, 2) ≥2 additional surveillance echocardiograms spaced ≥6 months apart, 3) without progression to severe stage at the time of first repeat echocardiography. The study was approved by the Vanderbilt University institutional review board (IRB).

In accordance with published guidelines, AS severity was determined by Vmax and MG, with mild AS defined as a Vmax of 2.6–2.9 m/s and MG of <20 mmHg and moderate AS defined as a Vmax of 3.0–3.9 m/s or MG of 20–39 mmHg [3]. Similarly, severe AS was defined as Vmax of ≥4 m/s or MG ≥40 mmHg [3]. The Vmax and MG were compared between the first two echocardiograms to define *Initial change in Vmax* (m/s per year) and *initial change in MG* (mmHg per year), respectively. *Initial increase in Vmax* and *initial increase in MG* as categorical measures are also reported.

Comorbidities and medications at time of first echocardiogram were extracted from the EHR. Left ventricular ejection fraction (LVEF) is reported as a percentage for the initial and the final echocardiograms. Duration of follow-up was calculated as the time between first and last echocardiograms. The primary outcome of the study was progression to severe AS defined by Vmax or MG.

2.2. Statistical analysis

Statistical analyses were performed using Stata Statistical Software: Release 14 (College Station, TX, USA) and R statistical software (Vienna, Austria) [10,11]. Descriptive statistics are expressed as median with interquartile ranges (IQR) for continuous variables and frequencies (percentages) for categorical variables. Univariate analyses were performed using the Pearson's chi-squared test and Wilcoxon rank sum test for categorical and continuous variables, respectively. Receiver operating characteristic (ROC) curves were created to compare the predictive accuracy of initial Vmax and MG in addition to initial changes in Vmax and MG in predicting progression to severe AS. The area under the curve (AUC) with 95% confidence intervals (CI) and ideal cutoff points, determined using the Youden method, are also shown where appropriate. Multivariable logistic regression was used to test for independent association of rate of change of Vmax or MG with progression to severe AS, adjusting for age, diabetes mellitus, chronic kidney disease, and initial Vmax or initial MG. ROC analysis was also performed to compare multivariable models with and without initial changes in Vmax and MG. All tests were two-tailed and a p-value of less than or equal to 0.05 was considered statistically significant.

3. Results

Nine hundred and twenty subjects were initially identified with mild or moderate AS. Five hundred and thirty-nine subjects did not have sufficient echocardiographic follow-up and 17 subjects had progressed to severe AS at time of initial repeat echocardiography. These patients were thus excluded from further analysis. Three hundred and sixty-four (N = 364) subjects met inclusion criteria for the study. Baseline demographic and clinical features are shown in Table 1. At initial echocardiography, the median Vmax was 2.7 m/s (IQR 2.3–3.2 m/s) and median MG was 15 mmHg (IQR 11–21 mmHg). During a median interval of 1.3 years (IQR 1–2.2 years) between the first two echocardiograms, the median change in Vmax and MG were +0.11 m/s per year (IQR −0.09 to +0.32 m/s per year) and +1.44 mmHg per year (IQR −0.34 to +4.00 mmHg per year), respectively, Fig. 1. One hundred and ninety-five (54%) and 242 (66%) subjects had an initial increase in Vmax and MG, respectively. One hundred and seventy-seven

Table 1
Baseline demographic and clinical features.

		Vmax			MG		
	Overall (N = 364)	Progression to Severe AS – NO (N = 311)	Progression to Severe AS – YES (N = 53)	P Value	Progression to Severe AS – NO (N = 308)	Progression to Severe AS – YES (N = 56)	P Value
Age – years	70 (62–77)	69 (62–76)	73 (64–77)	0.087[a]	70 (62–76)	74 (69–79)	0.090[a]
Male (%)	200 (55%)	172 (55%)	28 (53%)	0.738[b]	171 (56%)	29 (52%)	0.605[b]
Caucasian (%)	337 (93%)	292 (94%)	45 (85%)	0.021[b]	288 (94%)	49 (88%)	0.056[b]
Tobacco use (%)	142 (39%)	124 (40%)	18 (34%)	0.415[b]	119 (39%)	23 (41%)	0.731[b]
Hypertension (%)	356 (98%)	303 (97%)	53 (100%)	0.238[b]	301 (98%)	55 (98%)	0.819[b]
Hyperlipidemia (%)	167 (46%)	138 (44%)	29 (55%)	0.162[b]	138 (45%)	33 (59%)	0.051[b]
Diabetes mellitus (%)	162 (45%)	133 (43%)	29 (55%)	0.106[b]	134 (44%)	28 (50%)	0.233[b]
Chronic kidney disease (%)	97 (27%)	80 (26%)	17 (32%)	0.334[b]	77 (25%)	20 (36%)	0.095[b]
Coronary artery disease (%)	264 (73%)	222 (71%)	42 (79%)	0.236[b]	219 (71%)	45 (80%)	0.154[b]
Cerebrovascular accident (%)	31 (9%)	26 (8%)	5 (9%)	0.796[b]	27 (9%)	4 (7%)	0.689[b]
Beta-blocker (%)	298 (82%)	258 (83%)	40 (75%)	0.191[b]	250 (81%)	48 (86%)	0.417[b]
ACE inhibitor or ARB (%)	306 (84%)	262 (84%)	44 (83%)	0.822[b]	258 (84%)	48 (86%)	0.714[b]
Statin (%)	286 (79%)	245 (79%)	41 (77%)	0.816[b]	242 (79%)	44 (79%)	1.000[b]
Bisphosphonate (%)	10 (3)	10 (3)	0 (0%)	0.186[b]	10 (3%)	0 (0%)	0.172[b]
Left ventricular ejection fraction - %	55 (55–60)	55 (55–60)	55 (55–55)	0.854[a]	55 (55–60)	55 (55–60)	0.912[a]
Duration of follow-up – years	4.0 (2.8–6.3)	4.1 (2.7–6.4)	4.0 (3.1–5.9)	0.903[a]	3.9 (2.7–6.1)	5.5 (3.5–7.7)	0.031[a]

Data are presented as median (IQR) for continuous variables and number (percentage) of subjects for categorical variables. Severity of AS is shown both based on peak aortic jet velocity (Vmax) and mean gradient (MG).

[a] Wilcoxon rank sum test.

[b] Pearson's chi-squared test.

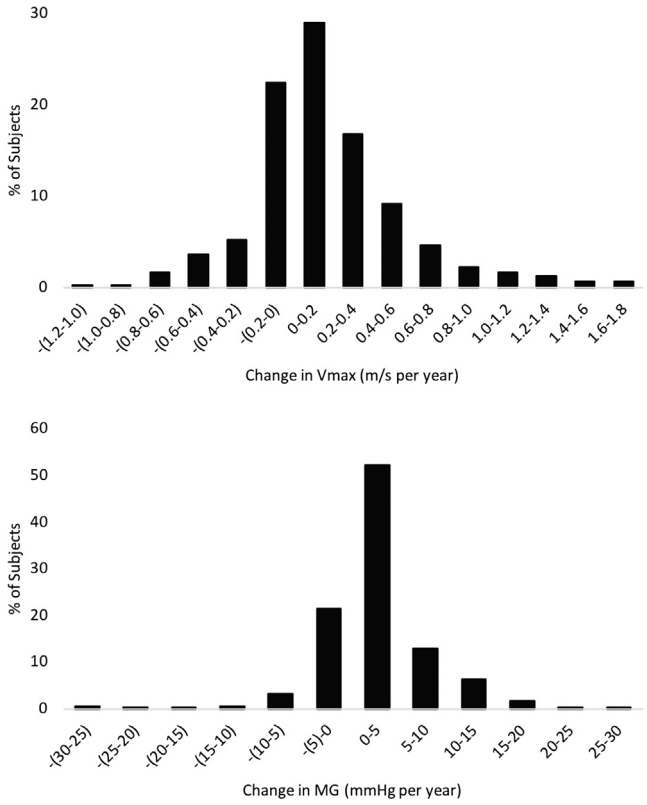

Fig. 1. Initial changes in Vmax (top panel) and MG (bottom panel).

(49%) subjects had an initial increase in both Vmax and MG and 104 (29%) subjects had no initial increase in either Vmax or MG.

The median duration of follow-up between first and last echocardiograms was 4.0 years (IQR 2.8–6.3 years). There was no statistically significant difference in LVEF between the first echocardiogram (median 55%, IQR 55–60%) and the final echocardiogram (median 55%, IQR 55–60%), p = 0.872. Fifty-three (15%) and fifty-six (15%) subjects progressed to severe AS defined by Vmax and MG, respectively. The majority of these subjects (N = 31) met both Vmax and MG criteria for progression to severe AS. Initial Vmax and MG values in addition to initial changes in Vmax and MG were compared with risk of progression to severe AS via ROC curves, Fig. 2. Summary of the sensitivity and specificity of selected cutoff points of initial changes of Vmax and MG in predicting progression to severe AS is provided in Table 2.

Categorical change in Vmax and MG were also tested for association with progression to severe AS. Thirty-eight (19%) subjects with initial increase in Vmax progressed to severe AS compared to 15 (9%) subjects without an initial increase in Vmax (p = 0.004). Fifty (21%) subjects with an initial increase in MG and 7 (6%) subjects without an initial increase in MG progressed to severe AS (p < 0.001), Fig. 3.

In multivariable logistic regression, initial Vmax (OR = 4.77, 95% CI 2.42–9.41, p < 0.001) and initial increase in Vmax (OR = 4.19, 95% CI 1.93–9.10, p < 0.001) were associated with progression to severe AS defined by Vmax. In a similar analysis, initial MG (OR = 1.11, 95% CI 1.06–1.15, p < 0.001) and initial increase in MG (OR = 1.12, 95% CI 1.06–1.18, p < 0.001) were associated with progression to severe AS defined by MG, Table 3. In ROC analyses, models including initial change in Vmax and MG provided increased accuracy compared to models including baseline values and other covariates alone (Vmax: AUC 77.0% vs 70.2%; MG: AUC 76.1% vs 69.5%), Fig. 4.

4. Discussion

The primary finding of this study is that the initial changes in Vmax and MG during surveillance of patients with mild and moderate AS are strongly associated with risk of progression to severe stage, independent of other potential predictors of progression including initial Vmax and MG. Accounting for these initial changes may help better predict individualized risk of AS progression.

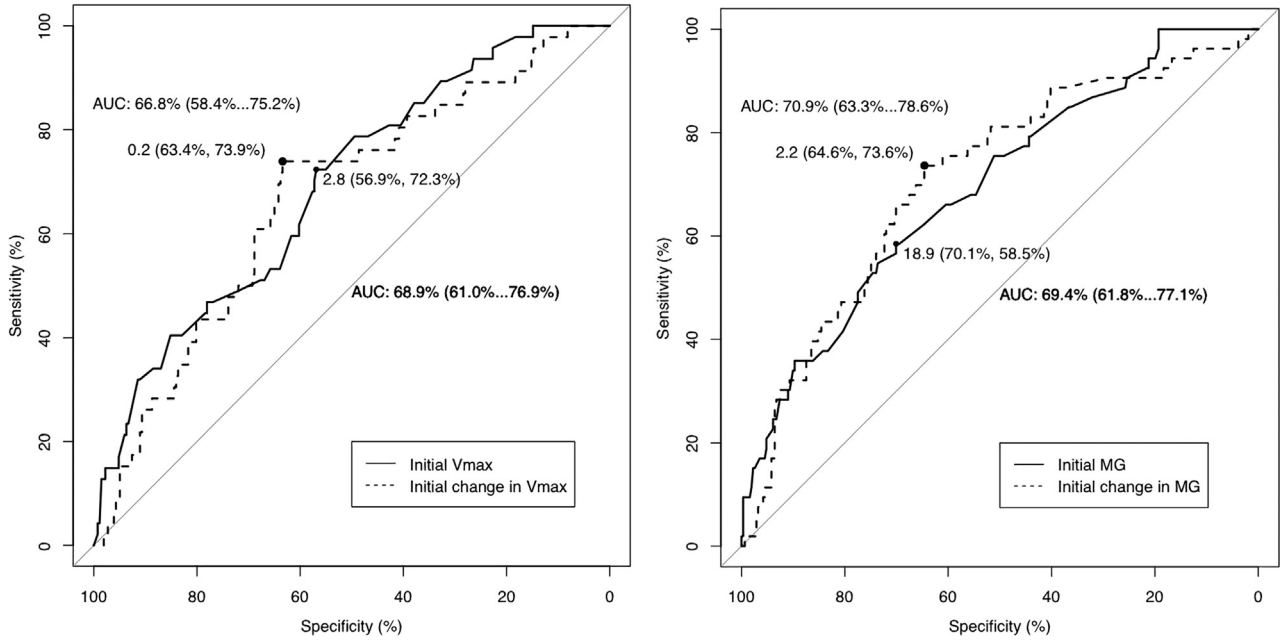

Fig. 2. ROC curves depicting accuracy of initial Vmax and initial change in Vmax (left) in addition to initial MG and initial change in MG (right) in predicting risk of progression to severe AS. AUC with 95% CI are shown next to each curve. Ideal cutoff point using the Youden method are shown with black dots and the adjacent caption for each curve.

Table 2
Sensitivity and specificity of selected cutoffs in increase of peak aortic jet velocity (Vmax) and mean gradient (MG) in predicting progression to severe AS.

	Sensitivity (%)	Specificity (%)
Initial change in Vmax (m/s per year)		
0.1	85	14
0.2*	74*	63*
0.3	48	66
0.4	27	85
0.5	17	88
Initial change in MG (mmHg per year)		
1	87	23
2*	74*	65*
3	55	71
4	31	83
5	16	86

* Denotes ideal cutoff points using the Youden method.

Table 3
Adjusted odds ratios for progression to severe AS.

Progression to Severe AS (Vmax ≥4 m/s)			
Characteristic	OR	95% CI	P value
Age (years)	1.01	0.98–1.04	0.517
Diabetes mellitus	1.22	0.61–2.46	0.575
Chronic kidney disease	1.39	0.67–2.88	0.372
Initial Vmax (m/s)	4.77	2.42–9.41	<0.001
Initial change in Vmax (m/s per year)	4.19	1.93–9.10	<0.001
Progression to Severe AS (MG ≥40 mmHg)			
Characteristic	OR	95% CI	P value
Age (years)	1.01	0.99–1.04	0.374
Diabetes mellitus	1.11	0.58–2.09	0.756
Chronic kidney disease	1.60	0.82–3.12	0.172
Initial MG (mmHg)	1.11	1.06–1.15	<0.001
Initial change in MG (mmHg per year)	1.12	1.06–1.18	<0.001

CI, confidence interval; OR, odds ratio.

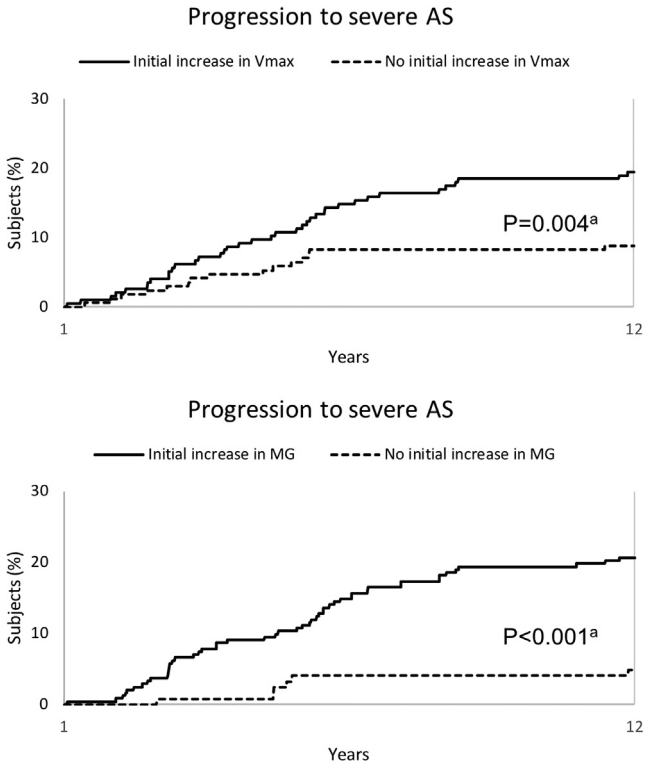

Fig. 3. Progression to severe AS based on initial change in echocardiographic parameters. The top panel shows progression to AS defined by Vmax and the bottom panel shows progression to AS defined by MG. [a]Pearson's chi-squared test.

Identifying individuals at increased risk of rapid AS progression remains challenging [12]. A number of demographic and clinical features have been associated with AS progression including increased age, tobacco use, hyperlipidemia, diabetes mellitus, chronic kidney disease, coronary artery disease, and metabolic syndrome [13–16]. Similarly, echocardiographic parameters, particularly initial Vmax and MG, are strongly associated with risk of progression to severe AS and largely guide the currently recommended surveillance algorithms [2,3]. However, significant interindividual variability in the rate of change in these parameters makes it difficult to identify individuals at increased risk of accelerated AS progression from a single echocardiographic assessment [3,7].

In light of this variability, we sought to assess whether the initial rate of change in Vmax and MG could improve prediction of progression to severe AS among patients with mild to moderate disease. We found that the addition of these parameters to the multivariable models improved prediction compared to models including only baseline values. Previous smaller-sized studies have suggested changes in these parameters may be associated with rapid progression of AS [3,17]. This study confirms these findings in a larger cohort and also proposes candidate cutoff points of initial increases in Vmax (0.2 m/s per year) and MG (2.2 mmHg per year) in predicting progression to severe AS. While these cutoff points may seem clinically insignificant and potentially due to measurement variability, we emphasize that these numbers are indexed to the time difference between the 2 initial echocardiograms (measured in years). Additionally, the AUC of these ROC curves suggest potentially excellent predictive accuracy of initial changes of these echocardiographic parameters in predicting AS progression.

We also assessed categorical changes (i.e. any increase from baseline) in Vmax or MG with risk of future AS progression. Although these measures do not take into account the time between the echocardiograms, they may be easier to assess in a clinical setting. Subjects with an initial increase in Vmax or MG had a roughly two-fold and three-fold increased risk of future progression to severe AS, respectively. Given the relative ease of calculating initial change in Vmax and MG, this method may be a readily available tool for clinicians looking to further individualize risk stratification for AS progression.

The current surveillance schedules based solely on static measurements of AS severity may underestimate the risk of rapid progression in certain patients, such as those with significant initial increases in Vmax or MG. Alternatively, patients at lower risk for disease progression, such as those without an initial increase in Vmax or MG, may currently be undergoing excessive and unnecessary imaging surveillance. Although echocardiography is a relatively benign diagnostic modality, it is not without significant cost to the healthcare system, especially given the frequency of its utilization [18]. Overall, individualized surveillance using metrics such as initial changes in Vmax or MG may help identify patients in need of closer clinical follow-up and those for whom less frequent surveillance may be appropriate.

As mentioned above, there are a number of other clinical factors that are associated with risk of AS progression [13–16]. The predictive value of these variables when adjusted for the initial change in echocardiographic values such as Vmax or MG remains to be delineated. In this study, only initial Vmax and MG values in addition to initial changes in Vmax and MG were associated with progression to severe AS. Age, diabetes mellitus, and chronic kidney disease were not independently associated with progression to severe AS

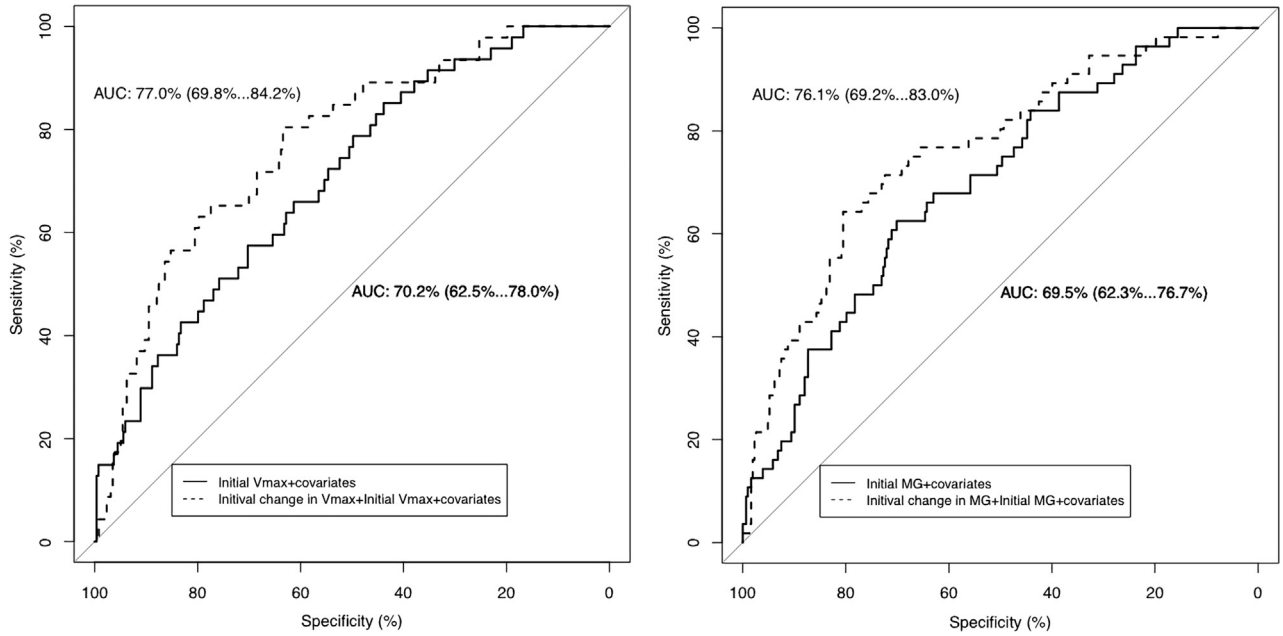

Fig. 4. ROC curves depicting accuracy of multivariable models based on the inclusion of initial change in Vmax (left) and initial change in MG (right) in predicting risk of progression to severe AS. AUC with 95% CI are shown next to each curve. Both models adjusted for age, diabetes mellitus, and chronic kidney disease.

in the multivariable analyses. However, statistical power is a concern in this study and larger scale studies are needed to evaluate demographic, clinical, and echocardiographic parameters for independent association with progression to severe AS. Ultimately, the identification of independent predictors of AS progression can potentially be used in the design of a risk calculator aimed at estimating individualized risk of disease progression and better guide an optimal surveillance regimen.

4.1. Study limitations

This study should be interpreted in the context of its limitations. The retrospective cohort design only allows for identification of association and cannot infer causation. Moreover, the size of our cohort limits statistical power to detect associations and constrains the number of covariates included in the multivariable analyses. A number of comorbidities and medications listed in Table 1 were not included in the multivariable models due to the constrains of the cohort size. There are potential biases, including attribution or mortality bias related to incomplete echocardiographic data and limited follow-up, that may challenge the internal validity of the findings reported in this study. Aortic valve area was not consistently available for many of the echocardiograms and hence not assessed in this study. However, Vmax and MG were available for all echocardiograms of the subjects included in the study and these variables are most commonly used to define AS severity in the pre-existing literature. Valve morphology (i.e. bicuspid vs tricuspid) was not assessed in this study. The available data also did not allow for an assessment of low-gradient severe AS which may have led to an underestimation of cases progressing to severe stage.

5. Conclusions

In this single institution cohort, initial changes in Vmax and MG were strongly associated with risk of AS progression to severe stage. Accounting for these initial changes may help better estimate individualized risk of AS progression and guide optimal surveillance strategies. There is a great need for larger-scale studies evaluating the association of clinical and echocardiographic variables with risk of AS progression.

Disclosures

None.

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CRediT authorship contribution statement

Arash Nayeri: Conceptualization, Data curation, Formal analysis. **Meng Xu:** Formal analysis. **Eric Farber-Eger:** Conceptualization, Data curation. **Marcia Blair:** Data curation. **Inderpreet Saini:** Supervision. **Kamran Shamsa:** Supervision. **Gregg Fonarow:** Supervision. **Tamara Horwich:** Conceptualization, Supervision. **Quinn S. Wells:** Conceptualization, Supervision.

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