# Clinical and Echocardiographic Predictors of Outcomes in Patients With Moderate (Mean Transvalvular Gradient 20 to 40 mm Hg) Aortic Stenosis

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**Risk factors for adverse clinical outcomes in patients with moderate aortic stenosis are not well defined. Previous studies have suggested that certain patients with moderate AS may be at an increased risk of heart failure (HF) or death. All patients with moderate AS seen in our institution during the study period (6/1/2014 to 6/30/2017) with a minimum 1-year follow-up were included. Clinical and echocardiographic data were collected retrospectively. End points were defined as HF hospitalization, aortic valve replacement (AVR), or death. Kaplan-Meier and multivariable Cox proportional hazard models analyses were conducted using composite outcomes of (1) HF hospitalization or AVR and (2) HF hospitalization, AVR, or all-cause death. A total of 151 subjects met the inclusion criteria. The most significant risk factors associated with the composite outcomes were an ejection fraction (EF) <50% ((1) hazard ratio [HR]: 4.1; 95% confidence interval [CI]: 2.34, 7.12; (2) HR: 3.8; 95% CI: 2.2, 6.6), atrial fibrillation ((1) HR: 2.0; 95% CI: 1.2, 3.2; (2) HR: 2.1; 95% CI: 1.43, 3.2), left ventricular hypertrophy ((1) HR: 5.85; 95% CI: 2.0, 15.8; (2) HR: 3.2; 95% CI: 1.4, 7.4), aortic valve area ((1) HR: 0.3; 95% CI: 0.1, 0.6; (2) HR: 0.32; 95% CI: 0.1, 0.65), and abnormal right ventricular function ((1) HR: 4.3; 95% CI: 2.5, 7.5; (2) HR: 5.5; 95% CI: 3.0, 9.8). In conclusion, presence of reduced ejection fraction, atrial fibrillation, left ventricular hypertrophy, and abnormal right ventricular function are associated with an increased risk of HF hospitalization, AVR, and death in patients with moderate aortic stenosis.**  **(Am J Cardiol 2019;124:1924−1931)**

Surgical aortic valve replacement (SAVR) or transcatheter aortic valve implantation (TAVI) is indicated for patients with severe symptomatic AS. Monitoring with serial follow-up is recommended for patients with mild and moderate AS.[1] Several previous studies have shown that patients with moderate AS have higher mortality compared with the general population, but the risk factors for clinical deterioration are not well defined.[2,3] In this study, we sought to characterize patients with moderate aortic stenosis at our institution to identify risk factors for death, heart failure (HF) hospitalization, and aortic valve replacement (AVR).

## Methods

We retrospectively screened electronic health records at Oregon Health & Science University for patients with a diagnosis of moderate AS. Eligible patients were age ≥18 years, had an ICD code for "nonrheumatic aortic (valve) stenosis" (ICD-10 code: I35.0) recorded at an inpatient or outpatient visit, and had an echocardiogram obtained between June 1, 2014 and June 30, 2017 showing moderate AS. The first study indicating moderate AS during this study period was considered the index echocardiogram. For patients who met inclusion criteria, index echocardiogram images were reviewed to confirm they met all of the following parameters defining moderate AS: peak transvalvular velocity of 3.0 to 4.0 m/s, mean transvalvular pressure gradient of 20 to 40 mm Hg, dimensionless index between 0.25 and 0.50, and calculated valve area 1.0 to 1.5 $cm^2$. Left ventricular systolic dysfunction was defined as left ventricular ejection fraction (LVEF) <50% and left ventricular mass index was calculated based on echocardiographic data using the Devereux formula. RV dysfunction was defined as a tricuspid annular plane systolic excursion (TAPSE) <1.5 cm or tissue Doppler S' velocity <12 cm/s. Patients were excluded if they had previous SAVR, TAVI, other major aortic surgery, complex congenital heart disease or incomplete clinical or echocardiographic data. Baseline clinical data at the time of index echocardiogram were obtained through chart review of medical records. The study protocol was approved by the

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Table 1
Baseline clinical characteristics by outcome

| | Composite: Surgery/hospitalization | | Composite: Surgery/hospitalization/death | | |
|---|---|---|---|---|---|
| | With outcome 93 (61%) | Without outcome 58 (39%) | With outcome 99 (66%) | Without outcome 52 (34%) | Overall n = 151 |
| Men | 59 (63%) | 35 (60%) | 62 (62%) | 32 (62%) | 94 (62%) |
| Ejection fraction >50% | 76 (82%) | 57 (98%) | 82 (83%) | 51 (98%) | 133 (88%) |
| Mean age (y) | 75.4 ± 11 | 72.7 ± 14 | 75.5 ± 11 | 72.3 ± 14 | 74.4 ± 12 |
| Mean body surface area ($m^2$) | 2.0 ± 0.3 | 1.9 ± 0.3 | 2.0 ± 0.3 | 1.9 ± 0.3 | 2.0 ± 0.2 |
| Hypertension | 74 (80%) | 43 (74%) | 79 (80%) | 38 (73%) | 117 (78%) |
| Coronary artery disease | 44 (47%) | 20 (35%) | 47 (48%) | 17 (33%) | 64 (42%) |
| Chronic obstructive pulmonary disease | 21 (23%) | 2 (3%) | 21 (21%) | 2 (4%) | 23 (15%) |
| Stroke or transient ischemic event | 7 (8%) | 8 (14%) | 7 (7%) | 8 (15%) | 15 (10%) |
| Atrial fibrillation | 29 (31%) | 5 (9%) | 30 (30%) | 4 (8%) | 34 (23%) |
| Diabetes mellitus | 25 (27%) | 20 (35%) | 28 (28%) | 17 (33%) | 45 (30%) |
| Peripheral arterial disease | 12 (13%) | 16 (28%) | 16 (16%) | 12 (23%) | 28 (19%) |
| Prior coronary artery bypass graft | 13 (14%) | 6 (10%) | 16 (16%) | 3 (6%) | 19 (13%) |
| Prior percutaneous intervention | 12 (13%) | 4 (7%) | 13 (13%) | 3 (6%) | 16 (11%) |
| Mean sodium (mmol/L) | 138.2 ± 4 | 138.7 ± 3 | 138.2 ±4 | 138.9 ± 3 | 138 ± 4 |
| Median creatinine (mg/dL) (interquartile range) | 1.0 (0.8, 1.3) | 1.0 (0.8, 1.2) | 1.0 (0.8, 1.4) | 1.0 (0.8, 1.2) | 1.0 (0.8, 1.3) |
| Mean albumin (g/dL) | 3.7 ± 0.5 | 3.6 ± 0.6 | 3.7 ± 0.6 | 3.6 ± 0.6 | 3.7 ± 0.6 |
| Mean hemoglobin (g/dL) | 12.8 ± 1.7 | 12.5 ± 2.1 | 12.7 ± 1.8 | 12.7 ± 2.1 | 12.7 ± 1.9 |
| Mean hematocrit (%) | 38.2 ± 4.8 | 37.4 ± 5.9 | 37.8 ± 5.0 | 38.1 ± 5.8 | 37.9 ± 5.2 |
| Mean platelet count (per $mm^3$) | 219.0 ± 86 | 200.4 ± 80 | 215.5 ± 86 | 204.9 ± 79 | 211.9 ± 84 |
| Beta blocker | 49 (53%) | 18 (31%) | 52 (53%) | 15 (29%) | 67 (44%) |
| Angiotensin-converting enzyme inhibitor / angiotensin receptor blocker | 45 (48%) | 27 (47%) | 49 (50%) | 23 (44%) | 72 (48%) |
| Calcium channel blocker | 29 (31%) | 12 (21%) | 29 (29%) | 12 (23%) | 41 (27%) |
| Statin | 55 (59%) | 31 (53%) | 59 (60%) | 27 (52%) | 86 (57%) |
| Thiazide | 12 (13%) | 4 (7%) | 12 (12%) | 4 (7%) | 16 (11%) |
| Loop diuretic | 37 (40%) | 18 (31%) | 39 (39%) | 16 (31%) | 55 (36%) |
| Warfarin | 19 (20%) | 4 (7%) | 20 (20%) | 3 (6%) | 23 (15%) |
| Novel anticoagulant | 1 (1%) | 2 (3%) | 1 (1%) | 2 (4%) | 3 (2%) |

institutional review board at our institution. Patients were not required to provide written informed consent as this was a retrospective chart review study. Data were collected from the time of index echocardiogram through June 30, 2018, allowing each patient to have a minimum of 1 year of follow-up. The study end points were composites of (1) HF hospitalization or AVR (TAVI or SAVR) and (2) HF hospitalization, AVR, or all-cause death. HF hospitalization was defined as a hospital admission with HF as a primary diagnosis. All individual outcomes including HF hospitalization, AVR, or death were considered terminal events for our study model. Categorical variables are reported as n (%) and continuous variables as mean (standard deviation [SD]) or median (interquartile range [IQR]) where appropriate. Kaplan-Meier analysis was conducted to estimate the time to event for each outcome. Multivariable Cox proportional hazards analysis was conducted to determine independent risk factors of each composite end point using a best subset approach based on minimizing Bayes information criteria for variable selection. Schoenfeld residuals were used to assess the validity of the proportional hazard assumption. Hazards ratios (HR) with 95% confidence intervals (CI) are reported from the final model. A p value $<0.05$ was considered statistically significant. Analyses were performed in SAS v9.4 (SAS Institute, Inc.; Cary, NC) and R (R Core Team; Vienna, Austria).

## Results

A total of 413 patients were screened for inclusion through the electronic chart review process and 151 subjects were included in analysis (Figure S1). The primary reasons for exclusion were insufficient clinical data or nonmoderate aortic stenosis (n = 262). Baseline clinical characteristics are shown in Table 1 and baseline echocardiographic data are shown in Table 2. Patients had a median follow-up time of 18 months (IQR: 11 to 27).

SAVR or TAVI was the most frequent outcome, occurring in 77/151 patients (51%), followed by HF hospitalization (n = 30/151, 20%) and all-cause death (n = 13/151, 9%). Two patients (1.3%) died due to complications of either SAVR or TAVI. Kaplan-Meier plots showing time to events for each composite outcome are shown in Figures 1 and 2. The estimated median time from index echocardiogram to hospitalization or AVR was 24 (95% CI: 21, 27) months; it was 22 (95% CI: 19, 26) months for the composite outcome of hospitalization, AVR, or death. Two-year mortality for the cohort was 7.9% (12/151). A total of 17.9% (27/151) were hospitalized and 41.1% (62/151) had an AVR within 2 years as well.

The composite outcome of AVR or HF hospitalization was met by 93/151 (61%) of patients during the study period. On multivariable analysis, this outcome was significantly associated with reduced ejection fraction (HR: 4.1; 95%

Table 2
Baseline echocardiographic characteristics by outcome

| | Composite: Surgery/hospitalization | | Composite: Surgery/hospitalization/death | | |
|---|---|---|---|---|---|
| | With outcome 93 (61%) | Without outcome 58 (39%) | With outcome 99 (66%) | Without outcome 52 (34%) | Overall n = 151 |
| Mean left ventricular outflow tract diameter (cm) | 2.2 ± 0.2 | 2.1 ± 0.2 | 2.2 ± 0.2 | 2.1 ± 0.2 | 2.2 ± 0.2 |
| Mean left ventricular outflow tract velocity interval time (cm) | 22.0 ± 6 | 22.7 ± 5 | | 22.8 ± 6 | 22.3 ± 6 |
| Mean stroke volume index (mL/m$^2$) | 40.8 ± 12 | 43.4 ± 10 | 40.8 ± 12 | 43.8 ± 10 | 41.8 ± 11 |
| Median interventricular septal diameter (cm) (interquartile range) | 1.2 (1.1, 1.4) | 1.1 (1.0, 1.3) | 1.2 (1.1,1.4) | 1.1 (1.0, 1.3) | 1.2 (1.0, 1.4) |
| Mean left ventricular end diastolic diameter (cm) | 4.6 ± 0.8 | 4.6 ± 0.7 | 4.6 ± 0.8 | 4.6 ± 0.7 | 4.6 ± 0.8 |
| Mean left ventricular posterior wall end diastolic diameter (cm) | 1.2 ± 0.2 | 1.1 ± 0.2 | 1.2 ± 0.2 | 1.1 ± 0.2 | 1.1 ± 0.2 |
| Median left ventricular mass index (g/m$^2$) (interquartile range) | 104.0 (85.1, 132.2) | 99.5 (79.8, 121.1) | 104.5 (85.1, 134.5) | 97.5 (79.8, 120.4) | 101.2 (81.1, 128.6) |
| Mean aortic valve peak velocity (m/s) | 3.4 ± 0.5 | 3.2 ± 0.6 | 3.3 ± 0.5 | 3.2 ± 0.6 | 3.3 ± 0.6 |
| Mean aortic valve gradient (mm Hg) | 26.9 ± 8 | 23.8 ± 6 | 26.5 ± 8 | 24.3 ± 8 | 25.7 ± 8 |
| Mean aortic valve area (cm$^2$) | 1.1 ± 0.3 | 1.2 ± 0.3 | 1.1 ± 0.3 | 1.2 ± 0.3 | 1.1 ± 0.3 |
| Mean Doppler velocity index | 0.29 ± 0.06 | 0.34 ± 0.10 | 0.30 ± 0.07 | 0.33 ± 0.10 | 0.31 ± 0.08 |
| Mitral insufficiency | 38 ± 41 | 14 ± 24 | 41 ± 41 | 11 ± 21 | 52 ± 34 |
| Tricuspid insufficiency | 46 ± 50 | 13 ± 22 | 49 ± 50 | 10 ± 19 | 59 ± 39 |
| Mean left atrial diameter (cm) | 4.2 ± 0.9 | 4.0 ± 0.7 | 4.2 ± 0.8 | 3.9 ± 0.6 | 4.1 ± 0.8 |
| Abnormal right ventricular function | 14 ± 15 | 0 ± 0.0 | 14 ± 14 | 0 ± 0.0 | 14 ± 9 |

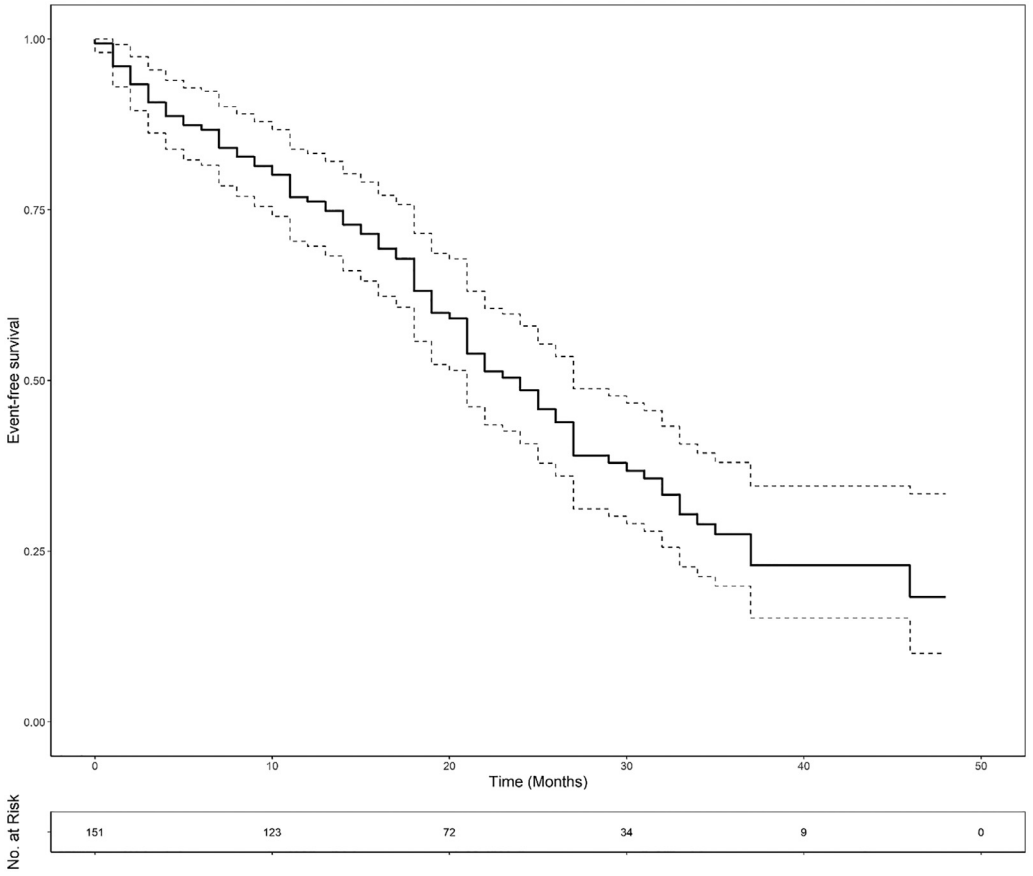


Figure 1. Kaplan-Meier survival curve for the composite outcome of aortic valve replacement and heart failure hospitalization.

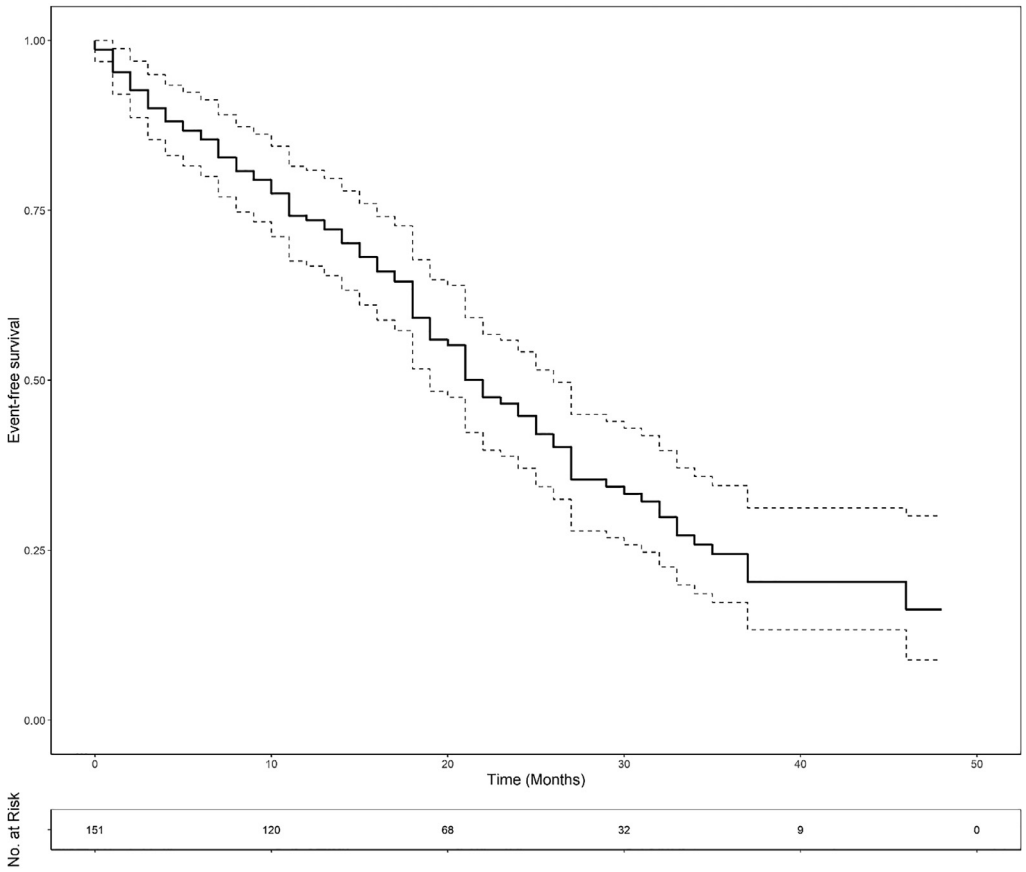


Figure 2. Kaplan-Meier survival curve for the composite outcome of aortic valve replacement, heart failure hospitalization, and all-cause mortality.

CI: 2.3, 7.1; p ≤0.001), atrial fibrillation (HR: 2.0; 95% CI: 1.2, 3.2; p = 0.006), increased left ventricular posterior wall thickness (LVPWD) (HR: 5.6; 95% CI: 2.0, 15.8; p = 0.001), abnormal RV function (HR: 5.5; 95% CI: 3.0, 9.8; p ≤0.001), reduced aortic valve area (HR: 0.3; 95% CI: 0.1, 0.6; p = 0.003), and increased aortic valve mean gradient (HR: 1.06; 95% CI: 1.03, 1.09; p ≤0.001; Table 3).

A total of 99/151 patients (66%) met the composite outcome of AVR, HF hospitalization, or all-cause death within the follow-up period. Reduced ejection fraction (HR: 3.8; 95% CI 2.2, 6.6; p ≤0.001), atrial fibrillation (HR: 2.1; 95% CI: 1.4, 3.2; p = 0.001), increased interventricular septal dimension (HR: 3.2; 95% CI: 1.4, 7.4; p = 0.006), increased mean gradient across the aortic valve (HR: 1.05; 95% CI: 1.02, 1.08; p = 0.001), reduced aortic valve area (HR: 0.25; 95% CI: 0.1, 0.6; p = 0.001), and abnormal RV function (HR: 4.3; 95% CI: 2.5, 7.5; p ≤0.001) were significantly associated with the composite outcome (Table 4). Kaplan-Meier plots stratified by the presence of atrial fibrillation, reduced ejection fraction, and right ventricular dysfunction are shown in Figures 3 to 5.

Table 3
Risk factors from multivariable Cox proportional hazards model for composite outcome of aortic valve replacement surgery or heart failure hospitalization

| Predictor | HR | (95% CI) | p Value |
|---|---|---|---|
| Ejection fraction ≤50% | 4.06 | (2.33, 7.06) | <0.001 |
| Chronic obstructive pulmonary disease | 1.56 | (0.88, 2.77) | 0.126 |
| Atrial fibrillation | 1.99 | (1.22, 3.23) | 0.006 |
| Left ventricular posterior wall thickness at end-diastole (per mm) | 5.55 | (1.95, 15.77) | 0.001 |
| Abnormal right ventricular function | 5.46 | (3.02, 9.84) | <0.001 |
| Aortic valve area (per $cm^2$) | 0.28 | (0.12, 0.65) | 0.003 |
| Aortic valve mean gradient (per mm Hg) | 1.06 | (1.03, 1.09) | <0.001 |

CI = confidence interval; HR = hazard ratio.

## Discussion

Previous studies have found that patients with moderate AS have higher mortality rates than the general population,

Table 4
Risk factors from multivariable Cox proportional hazards model for composite outcome of aortic valve replacement surgery, heart failure hospitalization, or all-cause death

| Predictor | HR | (95% CI) | p Value |
|---|---|---|---|
| Ejection fraction ≤50% | 3.79 | (2.17, 6.62) | <0.001 |
| Atrial fibrillation | 2.09 | (1.35, 3.23) | 0.001 |
| Interventricular septal dimension (per mm) | 3.23 | (1.41, 7.39) | 0.006 |
| Aortic valve mean gradient (per mm Hg) | 1.05 | (1.02, 1.08) | 0.001 |
| Aortic valve area (per $cm^2$) | 0.25 | (0.11, 0.57) | 0.001 |
| Abnormal right ventricular function | 4.30 | (2.48, 7.45) | <0.001 |

CI = confidence interval; HR = hazard ratio.

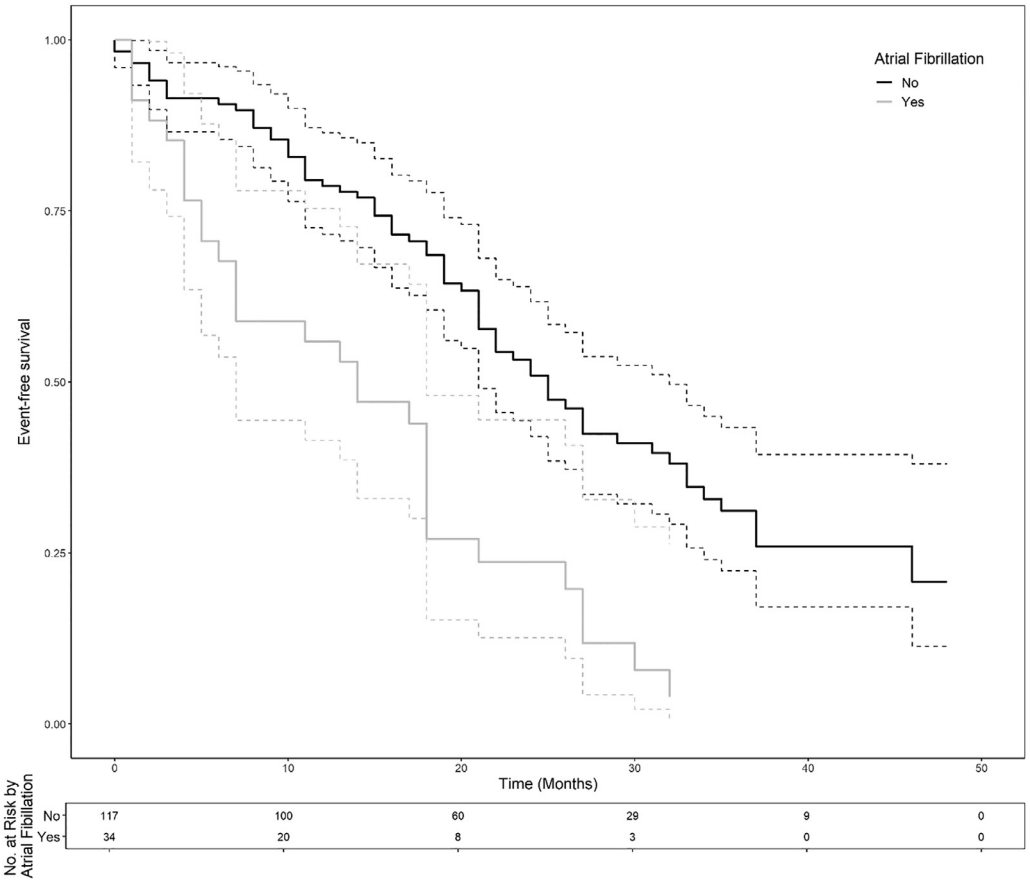


Figure 3. Kaplan-Meier survival curve for the composite outcome of aortic valve replacement, heart failure hospitalization, and all-cause mortality stratified by atrial fibrillation.

but none have comprehensively examined clinical and echocardiographic risk factors associated with adverse outcomes.[2,3] In this study, we identified left ventricular hypertrophy, reduced LVEF, atrial fibrillation, aortic valve mean gradient, and abnormal RV function as factors associated with death, HF hospitalization, or AVR. The risk factors identified in this study are consistent with those seen in severe AS and are biologically plausible and intuitive predictors of adverse outcomes.

Left ventricular hypertrophy can manifest as concentric hypertrophy or increased septal or posterior wall thickness. Previous studies have shown that patients with severe AS and left ventricular hypertrophy have a worse prognosis.[4] Septal hypertrophy is common in patients with moderate AS and associated with higher aortic valve velocity, hypertension, and diabetes mellitus.[5] In this study of patients with moderate AS, left ventricular posterior wall thickness was significantly associated with the composite outcome of AVR or HF hospitalization, whereas interventricular septal thickness was significantly associated with the composite outcome of AVR, HF hospitalization, or death. Increased septal or posterior wall hypertrophy is most often related to chronic excessive afterload, which negatively impacts ventricular performance and diastolic function, and contributes to the development of HF.

Atrial fibrillation is common in patients with AS and occurs more frequently as AS severity increases.[6] In patients with severe AS, it has been shown to be a predictor of mortality, even in those who are asymptomatic.[7,8] In this study, atrial fibrillation was present in 20% of patients and was significantly associated with both composite outcomes. These findings are consistent with a recent study by Delesalle et al, which found that a previous diagnosis of atrial fibrillation was associated with increased all-cause mortality in patients with moderate AS.[3] Atrial fibrillation in the context of moderate AS may be a marker of poor ventricular health and chronically elevated ventricular filling pressures.

Abnormal RV function was significantly associated with the composite outcomes in this study. Previous studies have identified RV dysfunction as being associated with an increase in cardiovascular mortality in patients with severe AS.[9] RV dysfunction can be a manifestation of pulmonary hypertension (PH), which is common in patients with aortic stenosis and may reflect HF and a decompensated state of the disease.[10] The presence of PH has been associated with worse outcomes in patients who receive AVR, but may be reversible depending on the chronicity and extent of pulmonary vascular remodeling.[11,12] Although strongly associated with the composite outcomes in our study, it is not clear if

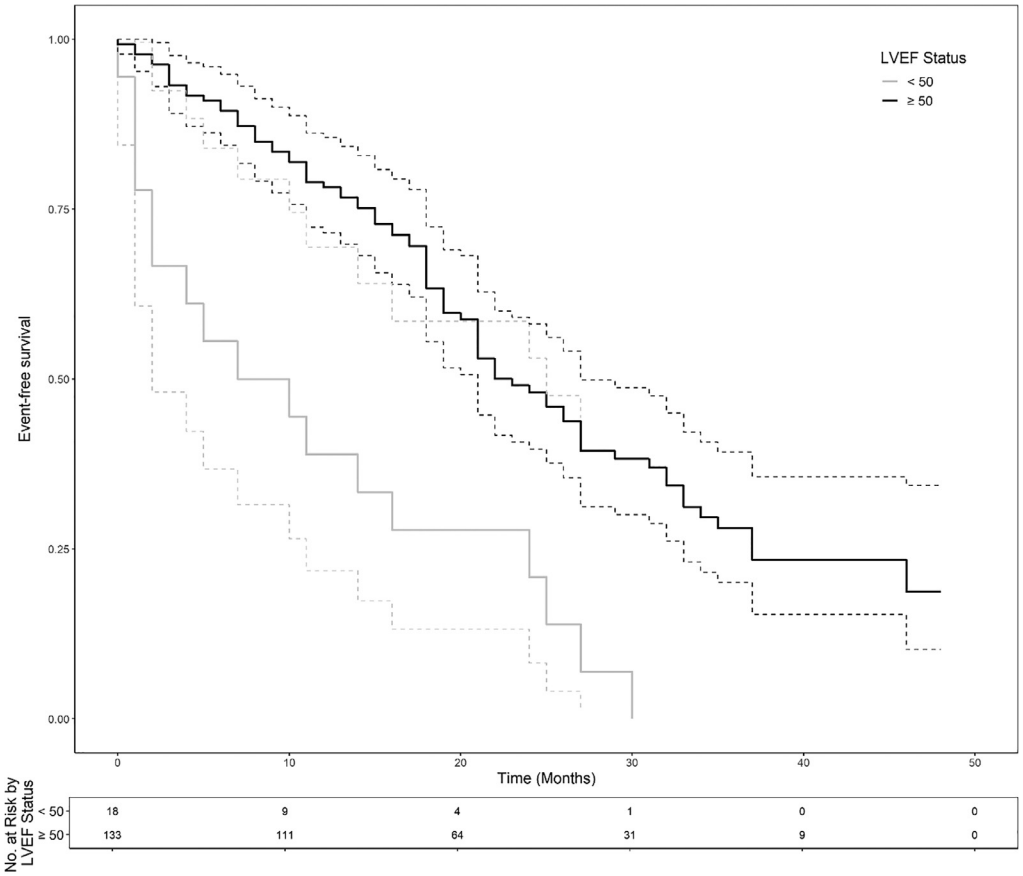


Figure 4. Kaplan-Meier survival curve for the composite outcome of aortic valve replacement, heart failure hospitalization, and all-cause mortality stratified by left ventricular ejection fraction.

the presence of RV dysfunction was part of the downstream cascade of AS or due to other reasons.

Previous studies have demonstrated a relation between reduced LVEF and increased rates of death and HF hospitalization in severe AS patients.[13,14] A recent study found that the decline in LVEF starts before AS becomes severe and accelerates after AVA reaches 1.2 $cm^2$.[15] One retrospective analysis of patients with moderate AS and LVEF <50% found that over half reached the end point of death or HF hospitalization within 4 years, with higher rates of HF hospitalization than are observed in patients with reduced LVEF alone.[15] Our study demonstrates that patients with moderate AS and reduced LVEF are more likely to have adverse outcomes, confirming previous studies' findings.

Patients with reduced LVEF are more vulnerable to any degree of LV outflow tract obstruction, such as that seen in moderate AS. This concept is the basis for the UNLOAD trial (clinicaltrials.gov # NCT02661451), which is an ongoing randomized trial investigating the outcomes on TAVI with the Sapien transcatheter heart valve in patients with impaired LVEF and moderate AS, compared with optimal HF therapy. TAVI has emerged as a much less invasive treatment option for AS and has shown similar clinical results when compared with surgical AVR in intermediate-risk and low-risk severe AS patients.[16–18] It is possible that TAVI may evolve as a treatment for moderate AS in patients with HF or those at an increased risk of HF. The co-morbid conditions identified in this study should next be evaluated in a prospective investigation with serial follow-up to monitor symptoms, cardiac remodeling, and clinical outcomes in patients with moderate AS to identify those who might benefit from earlier intervention.

Given this was a retrospective study, we were reliant on the accuracy of the electronic medical record to obtain all data. Additionally, the amount of time in which patients had moderate aortic stenosis before the index echocardiogram was likely variable and not accounted for in our time to event analysis. Our classification of subjects with AS was based on echocardiographic assessments, which can be subject to measurement or interpretation error. Subjects with low-flow, low-gradient AS are sometimes miscategorized as moderate AS, and it is possible that some were miscategorized on this basis. RV function and RVSP were estimated by echocardiography, so the presence of PH or abnormal pulmonary vascular resistance may have been missed as confirmation with invasive right heart catheterization was not performed. Finally, given that this study was conducted at a single quaternary center, it may not be generalizable to a broader population.

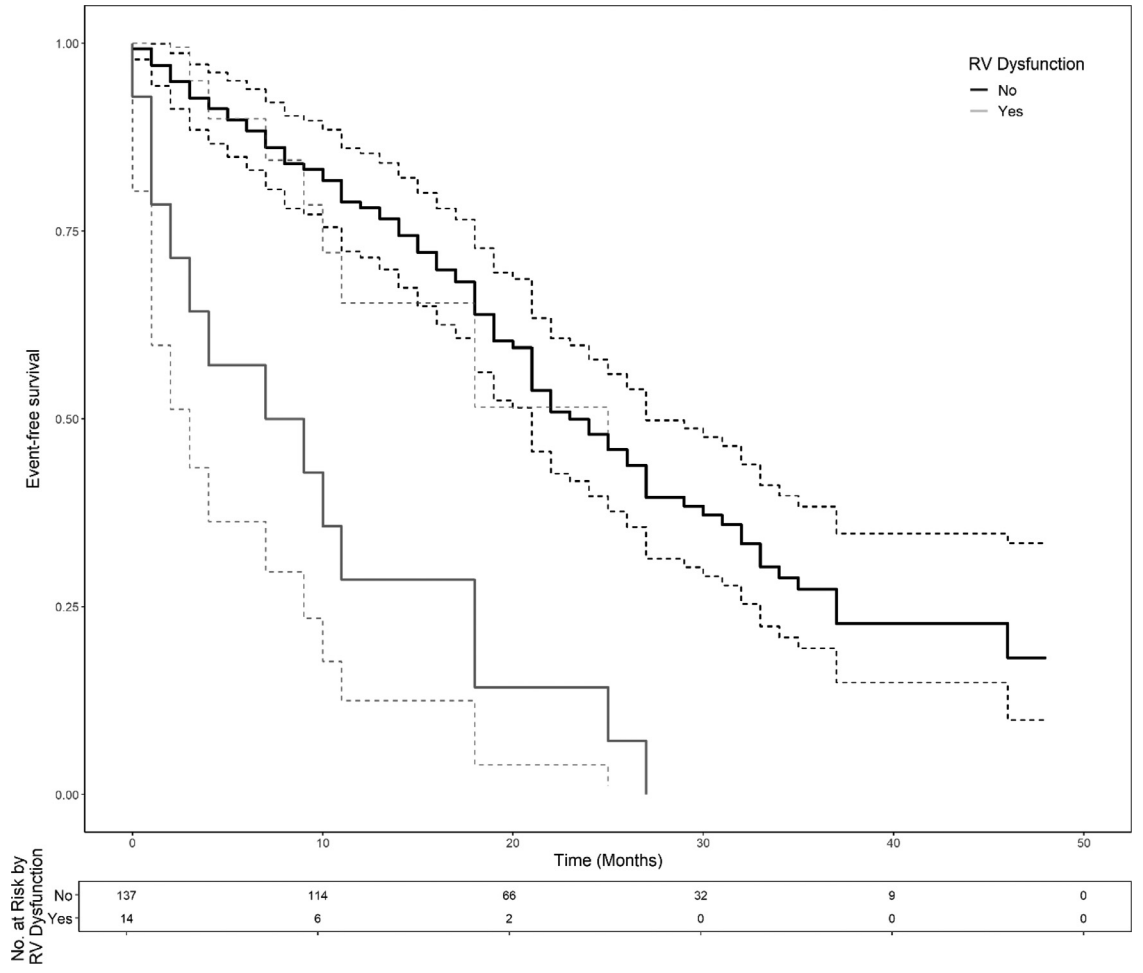


Figure 5. Kaplan-Meier survival curve for the composite outcome of aortic valve replacement, heart failure hospitalization, and all-cause mortality stratified by right ventricular dysfunction.

In conclusion, our study identified reduced LVEF, atrial fibrillation, left ventricular hypertrophy, and abnormal RV function as associated with HF hospitalization, AVR, or death in patients with moderate AS.

## Disclosures

The authors confirm there are no financial, personal, or professional relationships to disclose.

## Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.09.022.

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