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ORIGINAL RESEARCH

Definition and Validation of Prognostic Phenotypes in Moderate Aortic Stenosis

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ABSTRACT

BACKGROUND Adverse outcomes from moderate aortic stenosis (AS) may be caused by progression to severe AS or by the effects of comorbidities. In the absence of randomized trial evidence favoring aortic valve replacement (AVR) in patients with moderate AS, phenotyping patients according to risk may assist decision making.

OBJECTIVES This study sought to identify and validate clusters of moderate AS that may be used to guide patient management.

METHODS Unsupervised clustering algorithms were applied to demographics, comorbidities, and echocardiographic parameters in a training data set in patients with moderate AS (n = 2,469). External validation was obtained by assigning the defined clusters to an independent group with moderate AS (n = 1,358). The primary outcome, a composite of cardiac death, heart failure hospitalization, or aortic valve (AV) intervention after 5 years, was assessed between clusters in both data sets.

RESULTS Four distinct clusters—cardiovascular (CV)-comorbid, low-flow, calcified AV, and low-risk—with significant outcomes (log-rank $P < 0.0001$ in both data sets) were identified and replicated. The highest risk was in the CV-comorbid cluster (validation HR: 2.00 [95% CI: 1.54-2.59]; $P < 0.001$). The effect of AVR on cardiac death differed among the clusters. There was a significantly lower rate of outcomes after AVR in the calcified AV cluster (validation HR: 0.21 [95% CI: 0.08-0.57]; $P = 0.002$), but no significant effect on outcomes in the other 3 clusters. These analyses were limited by the low rate of AVR.

CONCLUSIONS Moderate AS has several phenotypes, and multiple comorbidities are the key drivers of adverse outcomes in patients with moderate AS. Outcomes of patients with noncalcified moderate AS were not altered by AVR in these groups. Careful attention to subgroups of moderate AS may be important to define treatable risk.
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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis

AVA = aortic valve area

AVR = aortic valve replacement

CV = cardiovascular

DBSCAN = density-based spatial clustering of applications with noise

DSI = dimensionless severity index

HDBSCAN = hierarchical density-based scan

LVEF = left ventricular ejection fraction

LVOT = left ventricular outflow tract

PAM = partition around medoids

ROC = receiver-operating characteristic

TAVR = transcatheter aortic valve replacement

V_{max} = peak velocity

VTI = velocity-time integral

Aortic stenosis (AS) is a major public health burden, affecting at least 12% of people aged >75 years.[1] As this population continues to grow, frailty and complex comorbidities such as renal failure, concurrent mitral valve disease, left ventricular (LV) and right ventricular dysfunction, and raised filling pressure in older adult AS patients will augment the complexity of risk assessment for aortic valve replacement (AVR), either surgical AVR or transcatheter AVR (TAVR).[2-4]

These considerations may be crucial in patients with moderate AS, but the current classification relies on echocardiographic criteria without adequately capturing noncardiac disease heterogeneity.[4,5] As a result, the diagnosis of moderate AS provides ambiguous management implications. A 5- to 6-year event-free survival of 53% to 56% has been reported and was longer than in severe AS in studies using aortic valve area (AVA) and aortic valve (AV) morphology to define moderate AS.[6] Notwithstanding, a mortality ratio of 2.43 (95% CI: 2.17-2.72) has been reported compared with the general population. However, several studies have suggested that moderate AS is associated with poor outcomes, approaching those of severe AS.[6-12] Many of these recent studies reporting unexpectedly poor outcomes in patients with moderate AS were derived from echocardiographic databases, with limited clinical data.[6-12] In the absence of clinical and demographic information, it is impossible to discern the principal drivers of adverse outcomes. Better phenotyping to categorize patients with moderate AS, on the basis of demographics, and comorbidities, as well as echocardiographic parameters, could inform a tailored treatment approach. Moreover, the presence of external validation would ensure that such an approach would be generalizable. Accordingly, we used an unsupervised machine learning strategy to identify distinct clinical phenotypes of moderate AS, on the basis of clinical and echocardiographic variables, to associate these phenotypes with clinical outcomes, with external validation.

METHODS

STUDY DESIGN. This cohort study included adults aged at least 18 years with moderate AS who were identified from the Metro South Health echocardiographic database (Brisbane, Australia) from January 1, 2009, to August 1, 2023. Using the Queensland Cardiac Outcomes Registry, demographic, clinical, and imaging data of these patients were obtained from hospital data sets (cardiac catheterization laboratory, cardiac surgery, echocardiography, electrophysiology, International Classification of Diseases-10th edition [ICD-10] codes, and death registry data set). This registry was also used to track outcomes over 7.4 years. A separate validation group was obtained from Western Health (Melbourne, Australia).[13]

The Melbourne Health Human Research Ethics Committee (HREC/49236/MH-2018), along with Research Governance at the Metro South Research Office and the Western Health Office for Research, granted approval for this study. This study was conducted in accordance with the National Statement on Ethical Conduct in Human Research 2007 (updated 2018), the Australian Code for the Responsible Conduct of Research, and the principles outlined in the Declaration of Helsinki.

CLINICAL VARIABLES. At baseline (ie, at the first identification of moderate AS), we assessed 54 predictive variables, thus aiming to identify adverse outcomes (Supplemental Methods). These variables included demographic characteristics, clinical variables, comorbidities (including heart failure [HF], ischemic heart disease, myocardial infarction, hypertension, diabetes mellitus, hyperlipidemia, cardiomyopathy, systolic and diastolic blood pressures, atrial fibrillation, and atrial flutter, as defined on the basis of ICD-10 codes), echocardiographic variables (see later), and procedures (pacemaker implantation or revascularization).

ECHOCARDIOGRAMS. A complete echocardiogram was obtained in all patients on the basis of a standard examination protocol, as described by the American Society of Echocardiography.[4] Measurements included left ventricular outflow tract (LVOT) diameter, LVOT velocity-time integral (VTI), AV VTI, AV mean gradient, AVA, left ventricular ejection fraction (LVEF) <50%, moderate or severe tricuspid or mitral regurgitation, and valve morphology. Moderate AS was defined by an AVA of 1 to 1.5 cm^2, a peak velocity (V_{max}) of 3 to 4 m/s, or a dimensionless severity index (DSI) of 0.25 to 0.50. Calcification was determined on the basis of text mined data in AV summaries or conclusions made from clinical interpretation of echocardiographic reports.

CLINICAL OUTCOMES. The primary endpoint was a 5-year composite of cardiac death, AV intervention (surgical or catheter-based), or HF hospitalization. Cardiac mortality was defined as the primary cause of death attributable to heart disease, myocardial ischemia and infarction, HF, cardiac arrest,

cardiomyopathy, amyloidosis, arrhythmias, endocarditis, heart block, valvular heart disease, coronary obstruction, myopericarditis, pericardial effusion, or cardiorenal syndrome. HF was defined by 1 or more hospitalizations with the following ICD-10 code: I110, I130, I132, I50, I500, I501, I509, U822, or I255 (Supplemental Methods). Secondary outcomes included a composite of cardiac death and HF hospitalization, individual components of composite endpoints and all-cause mortality (ie, death attributable to any cause), and the same outcomes within 3 or 10 years.

DATA ANALYSIS. Exploratory data analyses were conducted by visualizing distributions of each variable through the use of bar charts for categorical variables and histograms for continuous variables, and then summarizing the frequency and percentage of each categorical variable and mean ± SD (or median [Q1-Q3] ranges for non-normally distributed data) of continuous variables.

DATA PREPROCESSING. Outliers of continuous variables that were >4 times the SD or a clinically meaningful prespecified threshold for each variable were excluded. Variables that had >20% of missing values were excluded except for blood pressure. Imputation was applied on the included variables by using a random forest with an iterative imputer consisting of 1,000 iterations and a random forest regressor with 300 trees.[14,15]

UNSUPERVISED ANALYSIS. Unsupervised machine learning on the basis of clustering algorithms, including k-means,[16] partition around medoids (PAM),[17] agglomerative hierarchical clustering a using complete-linkage method,[18] density-based spatial clustering of applications with noise (DBSCAN),[19] and hierarchical density-based scan (HDBSCAN),[20]as well as another unsupervised learning algorithm, dimensionality reduction using principle components analysis, t-distributed stochastic neighbor embedding, and uniform manifold approximation and projection,[21,22] were used to gain an understanding of the data distribution of the clinical variables (no outcomes were used). More details of each algorithm are described in Supplemental Methods. The optimal number of clusters was identified initially using silhouette width[23] and the Davies-Bouldin score,[24] but the final decision for selection of the number of clusters was made on the basis of obtaining clinically interpretable clusters by comparing clinical variables of the clustering outputs. More details on each method are described in the Supplemental Methods.

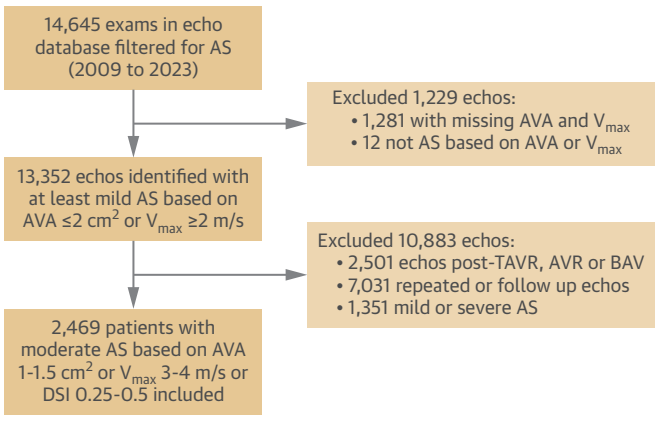
INTERPRETATION OF POST HOC CLUSTERING ANALYSIS. A heatmap was created to visualize the clusters of variables in the training data set. The means of continuous variables and the proportions of categorical variables were determined and scaled on the basis of each column (representing the variable) using the *z*-score. The importance of every variable in each cluster was evaluated and explained by means of local model-agnostic methods such as SHAP (SHapley Additive exPlanations)[25] using XGBoost (Extreme Gradient Boosting), a highly efficient gradient boosting implementation.[26] The top variables and SHAP values were compared among the clusters. The SHAP values are based on a game theory approach, which is a concept used to distribute fairly the total payoff of a cooperative game among its players, by taking into account each player's contribution and the interactions among the players, an approach that then helps provide an understanding of the influence of each variable to create a predictive model.[25]

SUPERVISED ANALYSES. Supervised learning algorithms that were easier to interpret, including multivariable logistic regression and Cox proportional hazards, were used to find the ideal algorithm for phenotypic differentiation and associations between identified clusters and clinical outcomes. Examples of parameters that were expected to affect survival included echocardiographic parameters (eg, AVA, peak mean gradient) and clinical variables (eg, hypertension, atrial fibrillation). Outcomes assessed included all-cause or cardiovascular mortality, HF, and the need for AV intervention. Cardiac death, HF readmission, and AV intervention were also remodeled using competing risk regression analysis, and mortality from other causes was considered a competing risk. The subdistribution hazard derived from the cumulative incidence function was used and corrected for competing risk estimated using Fine-Gray regression.[27]

Differences in the 52 variables and outcomes among clusters were determined using analysis of variance and chi-squared tests as appropriate. HRs for mortality per cluster were computed, and the *P* value for comparison against the full cohort was calculated using the log-rank test.

INTERNAL VALIDATION OF CLUSTERING. Using the most common split set method with 80% of data randomly selected for training and 20% for the internal validation set,[28] the prediction of cluster assignment was performed using multinominal logistic regression with the least absolute shrinkage and

FIGURE 1 Flowchart for Patient Inclusion



AS = aortic stenosis; AVA = aortic valve area; AVR = aortic valve replacement; BAV = bicuspid aortic valve; DSI = dimensionless severity index; echo = echocardiogram; TAVR = transcatheter aortic valve replacement; V_{max} = peak velocity.

selection operator to select the optimal set of variables. This trained model was used to predict the phenotypes in the internal validation cohort. Discrimination of this model evaluated the ability of the scores to distinguish among phenotypic clusters using the area under the receiver-operating characteristic curve (ROC AUC) and C-statistics with CIs on the basis of 1,000 bootstrap runs.[29,30]

EXTERNAL VALIDATION. The aforementioned steps were repeated for training on the original whole data set and to predict cluster assignment in an external, geographically separated, manually validated data set including 1,358 patients with moderate AS by using the same AS severity definition and validated echocardiographic parameters from Western Health (Melbourne, Australia), the external validation cohort. The clinical variables of the 4 clusters in the external validation data set were compared, and the associations between the clusters and outcomes were evaluated using Cox proportional hazards models. The HRs and cumulative hazard plots between the internal and external validation data sets were then compared. Cumulative hazard plots were plots of the cumulative hazard, $H(t_i)$ vs the time of the i-th failure, where $H(t_i)$ is equivalent to $-\log S(t_i)$, and $S(t_i)$ is the survival function.[31] A value of $P < 0.05$ was considered statistically significant. All analyses were performed using the R statistical platform version 4.3.1 (R Foundation).

EFFECT OF AV INTERVENTION ON OUTCOMES IN EACH CLUSTER. Cox proportional hazards models were used to derive unadjusted and adjusted HRs for evaluating the effect of AV intervention within each cluster on the composite of cardiac death or HF (or individual components with death from other causes as competing risk). Adjusted analyses included cardiac surgical risk factors assessed by the Parsonnet score at baseline from the time of echocardiographic examination.[32,33]

INCREMENTAL BENEFIT OF CLUSTERS TO CARDIAC DAMAGE SCORING. Net reclassification improvement was used to assess correct reassignment among risk subgroups in a base model using stages of cardiac damage alone[34]compared with the base model in addition to the clusters. The risk categories or thresholds used were based on the distribution of patients over the range of predicted scores, which included <50% (low risk), 50% to <60% (medium low risk), 60% to <70% (intermediate risk), and ≥70% (high risk). Bootstrapping was used to determine the 95% CI.

RESULTS

PATIENT COHORT. A total of 2,469 patients (median age, 75 years; 67% male) with moderate AS (AVA: 1-1.5 cm^2; or V_{max}: 3-4 m/s; or DSI: 0.25-0.5) were included (Figure 1). These patients had a median AVA of 1.40 cm^2 (Q1-Q3: 1.27-1.59 cm^2), a median V_{max} of 2.62 m/s (Q1-Q3: 2.20-3.10 m/s), and a median DSI of 0.37 (Q1-Q3: 0.31-0.43) (Table 1). The most common type of AS was degenerative calcified AS (65%). Only 9% were bicuspid AVs, and 4% had rheumatic heart disease. There were 329 patients (13.3%) who underwent AV intervention during the follow-up period after an average of 4 years from diagnosis, with 57 patients (2.3%) who underwent AV intervention within a year.

CLUSTERING RESULTS. Five different clustering algorithms were assessed and compared (k-means, PAM, agglomerative hierarchical clustering, DBSCAN, and HDBSCAN). By using silhouette width and the Davies-Bouldin index, several clusters were identified from k-means, PAM, agglomerative hierarchical clustering, DBSCAN, and HDBSCAN. When comparing the number of patients in each cluster and the differences in characteristics, PAM identified most clinically distinct subgroups with meaningful differences. Although based on silhouette width or the Davies-Bouldin index, 3 (or 2) clusters seemed to be the optimal number for the PAM-derived clustering model (Supplemental Figure 1); 4 clusters were selected because they reflected clinically significant groups. The 4 distinct clusters are as follows: cluster #1, low-risk; cluster #2, calcified AV morphology;

TABLE 1 Selected Characteristics of the 4 Clusters in 2,469 Patients With Moderate Aortic Stenosis in the Training Set

	Cluster #1 (Low-Risk) (n = 539)	Cluster #2 (Calcified AV) (n = 940)	Cluster #3 (Low-Flow) (n = 571)	Cluster #4 (CV-Comorbid) (n = 419)	Overall (N = 2,469)	*P* Value
Demographics						
Age, y	75 ± 11	71 ± 0.2	75 ± 10	73 ± 10	73 ± 11	<0.001
Male	45 (8)	823 (88)	473 (83)	317 (76)	1,658 (67)	<0.001
Height, cm	159 ± 7	173 ± 8	172 ± 8	170 ± 9	169 ± 10	<0.001
Weight, kg	74 ± 18	90 ± 20	84 ± 18	86 ± 18	85 ± 20	<0.001
Body mass index, kg/m^2	20 ± 7	30 ± 7	29 ± 6	30 ± 6	29 ± 6	<0.001
Echocardiographic parameters						
AV mean gradient, mm Hg	21 ± 7	21 ± 7	14 ± 6	18 ± 6	19 ± 7	<0.001
AV VTI, cm	65 ± 15	63 ± 15	49 ± 12	57 ± 15	59 ± 16	<0.001
AVA, cm^2	1.3 ± 0.2	1.4 ± 0.2	1.6 ± 0.3	1.4 ± 0.3	1.4 ± 0.3	<0.001
V_{max}, m/s	2.8 ± 0.62	2.8 ± 0.66	2.3 ± 0.48	2.5 ± 0.62	2.7 ± 0.64	<0.001
DSI	0.39 ± 0.1	0.44 ± 1.3	0.48 ± 1.1	0.45 ± 0.96	0.44 ± 1.0	0.027
LA volume, mL	78 ± 27	82 ± 25	101 ± 37	82 ± 25	86 ± 30	<0.001
LV diastolic dimension, cm	4 ± 0.6	5 ± 0.7	5 ± 0.7	5 ± 0.7	5 ± 0.7	<0.001
LV posterior wall diastole, cm	0.9 ± 0.2	1.1 ± 0.2	1.1 ± 0.2	1.1 ± 0.2	1 ± 0.2	<0.001
LV septum diastole, cm	1.1 ± 0.2	1.2 ± 0.2	1.2 ± 0.2	1.2 ± 0.2	1.2 ± 0.2	<0.001
LVEF, %	58 ± 11	54 ± 12	53 ± 13	52 ± 14	54 ± 13	<0.001
LVOT diameter, cm	2.1 ± 0.2	2.3 ± 0.2	2.3 ± 0.2	2.3 ± 0.2	2.2 ± 0.2	<0.001
LVOT VTI, cm	24 ± 5	22 ± 4	20 ± 5	21 ± 5	22 ± 5	<0.001
Stroke volume index, mL/m^2	47.9 ± 11.4	43.8 ± 10.8	42.2 ± 12.6	43.0 ± 10.6	44.2 ± 11.5	<0.001
Low flow stroke volume index <35 mL/m^2	60 (11.1)	185 (19.7)	172 (30.1)	93 (22.2)	510 (20.7)	<0.001
MV E wave, cm/s	96 ± 43	72 ± 37	85 ± 39	71 ± 41	80 ± 41	<0.001
RA area, cm^2	16 ± 4	19 ± 5	20 ± 6	18 ± 5	18 ± 5	<0.001
Systolic BP, mm Hg	138 ± 16	136 ± 16	141 ± 58	138 ± 14	138 ± 31	0.032
Diastolic BP, mm Hg	72 ± 8	73 ± 8	75 ± 8	73 ± 7	73 ± 8	<0.001

Continued on the next page

cluster #3, low-flow AS; and cluster #4, cardiovascular (CV)-comorbid. Additional characteristics of each cluster are described in Supplemental Table 1. A heatmap visualized the 4 clusters of top variables in the data (**Figure 2**, Supplemental Figure 2). **Table 1** summarizes the selected variables of the 4 clusters derived from PAM.

The distribution of variable contributions to the cluster output was further assessed using SHAP values of each variable for every observation, to determine which variables had the strongest influence on the clustering results (Supplemental Figures 3 and 4). The top global variables that differed among the 4 groups were sex, ischemic heart disease, hyperlipidemia, atherosclerosis, height, acute coronary syndrome, weight, calcification, mitral E wave, and diabetes with complications.

For each cluster, there were distinct differences in multiple variables, as follows:

- The low-risk cluster (#1) was typified by women (92%) with preserved LV function (mean LVEF 58%) and low levels of CV-comorbid disease.
- The calcified AV cluster (#2) was typically defined by overweight (mean weight, 90 kg) men (88%), with the highest mean body mass index of 30.1 kg/m^2, and with calcified valves (80%), gradients more prominent than valve areas, low levels of multimorbidity.
- The low-flow cluster (#3) had among the oldest patients (mean: 75 years), with low gradients and low flow (largest proportion with stroke volume index <35 mL/m^2 [30%]), despite noncalcified valves (67%), and concurrent valvular disease (highest proportion with mitral or tricuspid regurgitation).
- The CV-comorbid cluster (#4) had positive contributions from ischemic heart disease (73%), hyperlipidemia (61%), atherosclerosis including coronary artery disease and peripheral artery disease (80%), diabetes with complications (67%), hypertension (94%), and very high cardiovascular risk. The individuals in this cluster also had the largest proportion of obesity, with a mean body mass index 30 kg/m^2.

INTERNAL VALIDATION OF CLUSTERS. A multinomial logistic regression model was used to predict cluster assignment (Supplemental Table 2, Supplemental Figure 5). The main independent

TABLE 1 Continued

	Cluster #1 (Low-Risk) (n = 539)	Cluster #2 (Calcified AV) (n = 940)	Cluster #3 (Low-Flow) (n = 571)	Cluster #4 (CV-Comorbid) (n = 419)	Overall (N = 2,469)	*P* Value
Comorbidities						
AF or atrial flutter	106 (20)	185 (20)	193 (34)	127 (30)	611 (25)	<0.001
Atherosclerosis, CAD, and PAD	75 (14)	161 (17)	91 (16)	333 (80)	660 (27)	<0.001
Bicuspid valve	30 (6)	100 (11)	51 (9)	30 (7)	211 (9)	0.014
Calcified valve	383 (71)	748 (80)	190 (33)	277 (66)	1,598 (65)	<0.001
CKD	94 (17)	144 (15)	107 (19)	165 (39)	510 (21)	<0.001
Diabetes with complications	127 (24)	253 (27)	145 (25)	281 (67)	806 (33)	<0.001
Diabetes without complications	61 (11)	113 (12)	71 (12)	119 (28)	364 (15)	<0.001
EF <50%	63 (12)	238 (25)	168 (29)	145 (35)	614 (25)	<0.001
Heart failure	94 (17)	144 (15)	125 (22)	124 (30)	487 (20)	<0.001
Hyperlipidemia	29 (5)	61 (7)	29 (5)	256 (61)	375 (15)	<0.001
Hypertension	221 (41)	331 (35)	255 (45)	392 (94)	1,199 (49)	<0.001
IHD	44 (8)	56 (6)	44 (8)	305 (73)	449 (18)	<0.001
MR severity						
Mild	299 (56)	447 (48)	313 (55)	208 (50)	1,267 (51)	<0.001
Moderate	31 (6)	45 (5)	44 (8)	21 (5)	141 (6)	
Severe or critical	10 (1.9)	5 (0.5)	5 (0.9)	3 (0.7)	23 (0.9)	
Myocardial infarction	69 (13)	138 (15)	104 (18)	329 (79)	640 (26)	<0.001
Obesity	28 (5)	95 (10)	35 (6)	93 (22)	251 (10)	<0.001
TR severity						
Mild	446 (83)	793 (84)	449 (79)	342 (82)	2,030 (82)	0.007
Moderate	36 (7)	38 (4)	36 (6)	12 (3)	122 (5)	
Severe or critical	6 (1.1)	3 (0.3)	11 (2)	5 (1.2)	25 (1)	
Parsonnet score, %	18.9 (13.4)	14.9 (13.2)	18.7 (13.8)	21.3 (15)	17.7 (13.9)	<0.001
Parsonnet score categories						<0.001
Good (0-4)	90 (16.7)	243 (25.9)	97 (17.0)	39 (9.3)	469 (19.0)	
Fair (5-9)	51 (9.5)	131 (13.9)	54 (9.5)	48 (11.5)	284 (11.5)	
Poor (10-14)	83 (15.4)	135 (14.4)	77 (13.5)	57 (13.6)	352 (14.3)	
High (15-19)	74 (13.7)	127 (13.5)	87 (15.2)	85 (20.3)	373 (15.1)	
Extremely high (20+)	241 (44.7)	304 (32.3)	256 (44.8)	190 (45.3)	991 (40.1)	
Procedures						
CABG at baseline only	4 (0.7)	29 (3)	15 (3)	46 (11)	94 (4)	<0.001
CABG at baseline and follow-up	22 (4)	95 (10)	36 (6)	67 (16)	220 (9)	<0.001
SAVR	46 (9)	142 (15)	24 (4)	24 (6)	236 (9.6)	<0.001
TAVR	31 (6)	36 (4)	10 (2)	16 (4)	93 (4)	
CABG and SAVR	10 (2)	52 (6)	9 (2)	10 (2)	81 (3)	<0.001
Time to AVR, y	4.5 ± 3.1	4.1 ± 3	5.8 ± 3.3	4.6 ± 3.4	4.4 ± 3.1	0.051

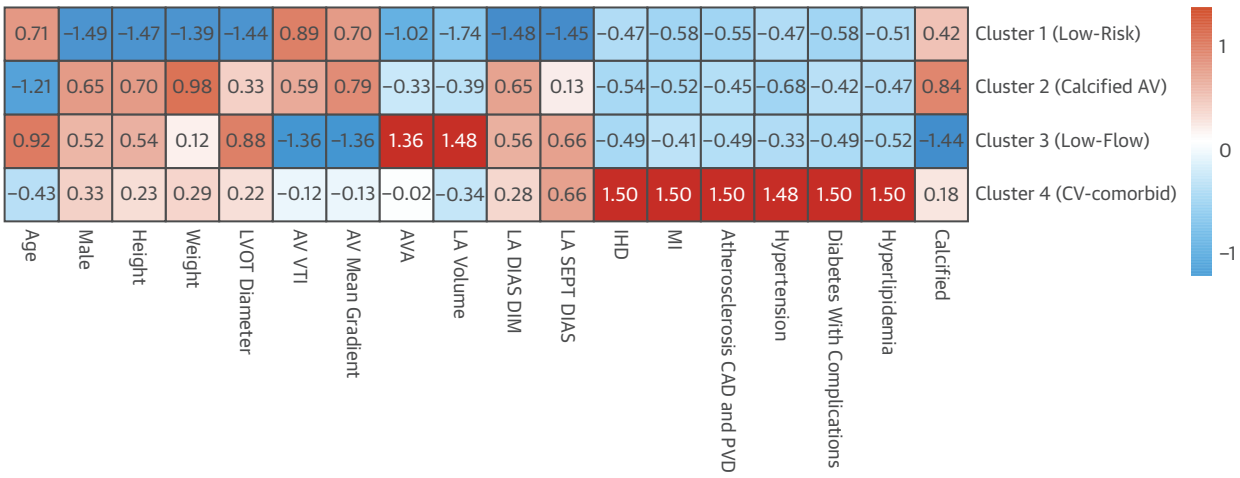
Values are mean ± SD or n (%).

AF = atrial fibrillation; AV = aortic valve; AVA = aortic valvular area; AVR = aortic valve replacement; BP = blood pressure; CABG = coronary artery bypass graft; CAD = coronary artery disease; CKD = chronic kidney disease; CV = cardiovascular; DSI = dimensionless severity index; EF = ejection fraction; HF = heart failure; IHD = ischemic heart disease; LA = left atrial; LV = left ventricular; LV DIAS DIM = left ventricular diastolic dimension; LV PW DIAS = left ventricular posterior wall end diastole; LV SEPT DIAS = left ventricular septal end diastole; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; MI = myocardial infarction; MR = mitral regurgitation; MV = mitral valve; PAD = peripheral artery disease; RA = right atrial; SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement; TR, tricuspid regurgitation; VTI = velocity-time integral.

variables of cluster components (on the basis of the highest β values) were the following comorbidities or risk factors: male sex, HF, ischemic heart disease, acute coronary syndrome, atherosclerosis, hypertension, diabetes with complications, hyperlipidemia, calcification, atrial fibrillation or atrial flutter, cardiomyopathy, height, weight, LVOT diameter, AV VTI, mean pressure gradient, AVA, mitral valve E wave, left atrial volume, right atrial area, LV septal diastolic dimension, and LV posterior wall at end-diastole.

The cluster score created from this analysis had moderate to high predictive performance when data were split to 80% training and 20% internal validation set on the basis of the ROC AUC, as shown in Supplemental Figure 6: Low-risk cluster (#1) score: AUC = 0.96 (95% CI: 0.96-0.97); calcified AV cluster (#2) score: AUC = 0.7 (95% CI: 0.68-0.72); low-flow cluster (#3) score: AUC = 0.92 (95% CI: 0.91-0.93); CV-comorbid cluster (#4) score: AUC = 0.99 (95% CI: 0.99-1).

FIGURE 2 **Heatmap Visualizing the 4 Clusters of Top Variables, With Values Scaled Using Z-Scores**



The low-risk cluster (#1) consisted mostly of female patients with low levels of cardiovascular (CV) comorbid disease. The calcified aortic valve (AV) cluster (#2) typically comprised overweight male patients with a calcified valve, but with low levels of multimorbidity. The low-flow cluster (#3) had among the oldest patients, with low gradients and mostly noncalcified valves. The cardiovascular-comorbid cluster (#4) had the highest proportions of ischemic heart disease (IHD), myocardial infarction (MI), atherosclerosis including coronary artery disease (CAD) and peripheral vascular disease (PVD), hypertension, diabetes with complications, and hyperlipidemia at very high cardiovascular risk. AVA = aortic valvular area; LA = left atrial; LV DIAS DIM = left ventricular diastolic dimension; LV SEPT DIAS = left ventricular septal end-diastole; LVOT = left ventricular outflow tract; VTI = velocity-time integral.

EXTERNAL VALIDATION OF CLUSTERS. The baseline characteristics of the external test set (n = 1,358) were compared with those of the training set in Supplemental Table 3. Several characteristics of the training and validation groups showed statistically significant differences, albeit not clinically significant, except for the proportion of patients with calcified valves (65% with calcified valves in the training test and 40% in the external validation set). The cluster assignment of each patient from the validation data set was predicted using the multinominal logistic regression model trained on the original data set (n = 1,358), and the differences in clinical characteristics were comparable to those in the original training set from the Queensland Cardiac Outcomes Registry (Supplemental Table 4). However, there were significantly fewer patients grouped in the low-risk cluster (#1).

OUTCOMES. The median follow-up duration in the training set was 8.8 years (Q1-Q3: 5.4-11.4 years). The overall outcomes included a composite of cardiac death, HF hospitalization, or AV intervention (59% in the training group; 75% in the external validation group), all-cause mortality (51% training; 56% external validation), or individual cardiac death (22% training; 23% validation), HF hospitalization (48% training; 69% external validation), or any AV interventions (14% training; 13% external validation) (**Table 2**, Supplemental Table 5).

The highest proportion of composite outcomes (cardiac death, HF hospitalization, or AV intervention) was found in the CV-comorbid cluster (#4) in both training (70%) and external validation (86%) groups. Individually, the CV-comorbid group had the highest proportion of all-cause death (60% training, and 65% validation), cardiac death (31% training and 32% validation), and HF hospitalization (60% training and 79% validation). The calcified AV cluster (#2) group, in turn, had the highest proportion of AV intervention in both the training (19%) and validation groups (20%). There were no differences in noncardiac death among the clusters over the entire follow-up.

The associations among clusters with 5-year all-cause mortality, cardiovascular mortality, HF diagnosis, and the need for AV intervention are summarized in **Table 3** for the external validation data set and in Supplemental Table 6 for the training data set. In comparison with the low-risk cluster (#1) in both training and validation data sets, the CV-comorbid cluster (#4) and, to a lesser degree, the low-flow cluster (#3), were disproportionately represented in death and hospitalization endpoints. In contrast, the calcified AV cluster (#2) was disproportionately represented in AV interventions. Cumulative hazard plots for each outcome at 5 years for the external validation data set are shown in **Figure 3** (and for the

TABLE 2 Clinical Endpoints Between Each Cluster Over the Full Follow-Up Period in the External Validation Data Set (N = 1,358)

Cluster	Management	Composite (Cardiac Death, HF, AV intervention)	Composite (Cardiac Death, HF)	Cardiac Death	HF Hospitalization	AV Intervention	Noncardiac Death
Overall	Medical	NA	844 (71.6)	293 (24.9)	810 (68.8)	0 (0)	402 (34.1)
	AV intervention		127 (70.6)	23 (12.8)	127 (70.6)	All	48 (26.7)
	All	1,024 (75.4)	971 (71.5)	316 (23.3)	937 (69.0)	180 (13.3)	450 (33.1)
Cluster #1 (low-risk)	Medical	NA	67 (59.8)	18 (16.1)	65 (58.0)	0 (0)	40 (35.7)
	AV intervention		7 (77.8)	1 (11.1)	7 (77.8)	All	1 (11.1)
	All	76 (62.8)	74 (61.2)	19 (15.7)	72 (59.5)	9 (7.4)	41 (33.9)
Cluster #2 (calcified AV)	Medical	NA	214 (64.7)	73 (22.1)	208 (62.8)	0 (0)	120 (36.3)
	AV intervention		52 (63.4)	6 (7.3)	52 (63.4)	All	20 (24.4)
	All	296 (71.7)	266 (64.4)	79 (19.1)	260 (63.0)	82 (19.9)	140 (33.9)
Cluster #3 (low-flow)	Medical	NA	331 (72.3)	105 (22.9)	318 (69.4)	0 (0)	152 (33.2)
	AV intervention		32 (74.4)	10 (23.3)	32 (74.4)	All	11 (25.6)
	All	374 (74.7)	363 (72.5)	115 (23.0)	350 (69.9)	43 (8.6)	163 (32.5)
Cluster #4 (CV-comorbid)	Medical	NA	232 (83.8)	97 (35.0)	219 (79.1)	0 (0)	90 (32.5)
	AV intervention		36 (78.3)	6 (13.0)	36 (78.3)	All	16 (34.8)
	All	278 (86.1)	268 (83.0)	103 (31.9)	255 (78.9)	46 (14.2)	106 (32.8)

Values are n (%) within each subgroup.
NA = not applicable; other abbreviations as in Table 1.

training data set in Supplemental Figure 7). Cumulative hazard plots for outcomes at 3 and 10 years are shown in Supplemental Figures 8 and 9. The separation in outcomes appears to be greater in the external validation set than in the training set.

CLUSTERS AND OUTCOMES WITH AND WITHOUT AV INTERVENTIONS. Selected clusters had a differential treatment effect for clinical outcomes according to AV intervention vs no AV intervention. As shown in **Table 2**, across the entire follow-up period, cardiac death was more common in the medical group than in the intervention group. However, there was no difference in noncardiac death between AV intervention and no AV intervention in each cluster. When examining results at 5 years only, there was a statistical significance in 5-year noncardiac death between AV intervention and no AV intervention (17.1% vs 30.8%; $P = 0.046$) within cluster #2 only. Nonetheless, HF (which included baseline HF) was similar or higher in the intervention group compared with the medical group in the validation data set. However, over time, the AV intervention group had generally a lower risk of HF, but it was significant only in cluster #2. This is shown in Supplemental Figure 10.

AV intervention showed no association with the outcome in the low-risk cluster (#1). In the calcified AV cluster (#2), the intervention was associated with a reduction of death or cardiac death in the validation data set (**Figure 4**) and in a reduction of the composite outcome and HF alone in the training group (Supplemental Figure 10). AV intervention was not associated with any benefit in the low-flow cluster (#3), although it was associated with a reduction of mortality in the CV-comorbid cluster (#4) only in the validation data set, possibly reflecting selection issues. Effects of AV intervention for each cluster over 3 years and 10 years were similar to those at 5 years (Supplemental Figures 11 and 12).

Among medically treated patients, the CV-comorbid cluster (#4) had the highest risk of composite outcomes (HR: 2.03 [95% CI: 1.54-2.69]; $P < 0.001$) in the validation group, and individually, cardiac death and HF hospitalization. The low-flow cluster (#3) had the second highest risk of composite outcomes (HR: 1.50 [95% CI: 1.15-1.96]; $P = 0.003$) and cardiac death alone (Supplemental Table 7).

When AV intervention that occurred only within 1 year from diagnosis was assessed as an exposure variable, a significant effect of AV intervention was maintained in the calcified AV cluster (#2) only with a specific effect on cardiac and all-cause mortality in the external validation data set (Supplemental Figure 13). Using Cox proportional hazards models with and without adjustment for Parsonnet score, 1-year AV intervention was associated with a lower risk of 5-year cardiac death (with death from other causes as a competing risk) in both the derivation data set (adjusted HR: 0.35 [95% CI: 0.15-0.82]; $P = 0.015$) and the validation data set (adjusted HR: 0.28 [95% CI: 0.10-0.77]; $P = 0.013$) only in the calcified AV cluster (#2) (**Table 4**).[32] However, in the CV-comorbid

TABLE 3 Overall Characteristics of the 4 Clusters in Patients With Moderate Aortic Stenosis and Association With 5-Year Clinical Outcomes (Cardiac Death, HF Hospitalization, or AV Intervention) in the External Validation Set

		Effect Size			
	n	Cardiac Death, HF, or AVR	Cardiac Death, HF	All-Cause Death	Cardiac Death (Other Cause Death as Competing Risk)
1. Low-risk	121	Ref.	Ref.	Ref.	Ref.
2. Calcified AV	413	1.20 (0.93-1.55); $P = 0.2$	1.12 (0.86-1.45); $P = 0.4$	1.09 (0.80-1.47); $P = 0.6$	1.28 (0.76-2.17); $P = 0.4$
3. Low-flow	501	1.46 (1.14-1.88); $P = 0.003$	1.49 (1.15-1.92); $P = 0.002$	1.24 (0.92-1.67); $P = 0.2$	1.60 (0.96-2.66); $P = 0.073$
4. CV-comorbid	323	2.00 (1.54-2.59); $P < 0.001$	1.95 (1.50-2.54); $P < 0.001$	1.60 (1.18-2.16); $P = 0.003$	2.40 (1.44-4.00); $P < 0.001$

TABLE 3 Continued

	Effect Size			
	HF Hospitalization	HF (Death as Competing Risk)	AV Intervention	AV Intervention (Death as Competing Risk)
1. Low-risk	Ref.	Ref.	Ref.	Ref.
2. Calcified AV	1.12 (0.86-1.47); $P = 0.4$	1.11 (0.89-1.38); $P = 0.4$	2.56 (1.28-5.12); $P = 0.008$	2.45 (1.24-4.84); $P = 0.010$
3. Low-flow	1.46 (1.13-1.89); $P = 0.004$	1.31 (1.06-1.62); $P = 0.012$	1.25 (0.61-2.57); $P = 0.5$	1.16 (0.57-2.36); $P = 0.7$
4. CV-comorbid	1.89 (1.44-2.47); $P < 0.001$	1.57 (1.26-1.94); $P < 0.001$	2.11 (1.03-4.32); $P = 0.042$	1.86 (0.92-3.77); $P = 0.086$

Values are HR (95% CI).
Ref. = Reference; other abbreviations as in Table 1.

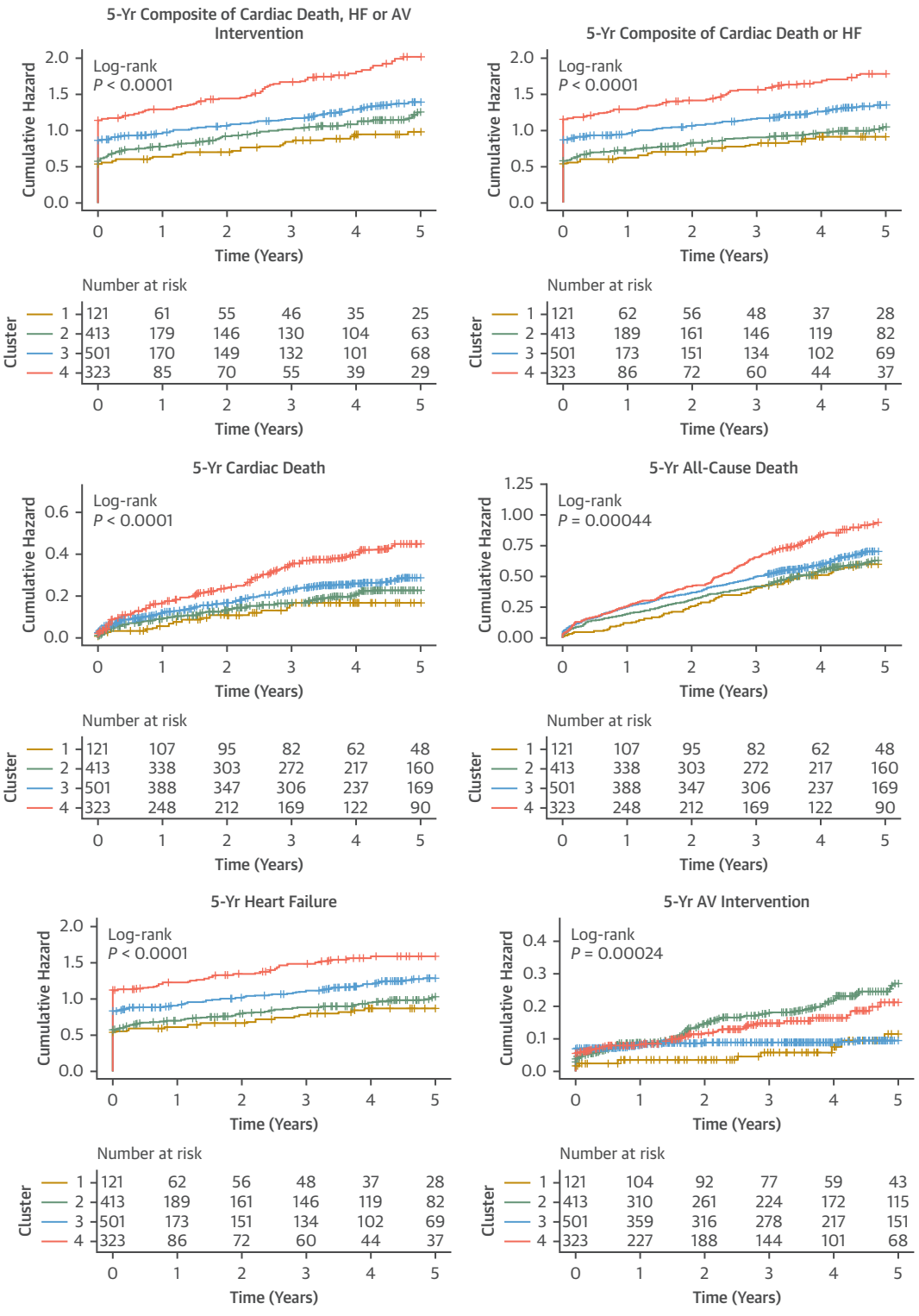
cluster (#4), the competing risk analysis showed a significantly lower risk of 5-year cardiac death in those patients with 1-year AV intervention in the external validation data set (adjusted HR: 0.36 [95% CI: 0.15-0.87]; $P = 0.022$) but not in the internal training set. Importantly, after adjustment for Parsonnet score, there was a significantly higher risk for composite of cardiac death or HF in low-flow cluster (#3) by using the training set and in the CV-comorbid cluster (#4) by using the validation set.

INCREMENTAL BENEFIT OF CLUSTERING GROUPS TO STAGES OF CARDIAC DAMAGE. The clusters provide additive information beyond the previously established cardiac damage stage and as evidenced by different proportions of different stages of cardiac damage in different clusters (Supplemental Table 8). The addition of cluster groups to the staging cardiac damage improved risk prediction of the primary composite outcome (net reclassification improvement: 0.17; 95% CI: 0.12-0.23) (Supplemental Figure 14).

DISCUSSION

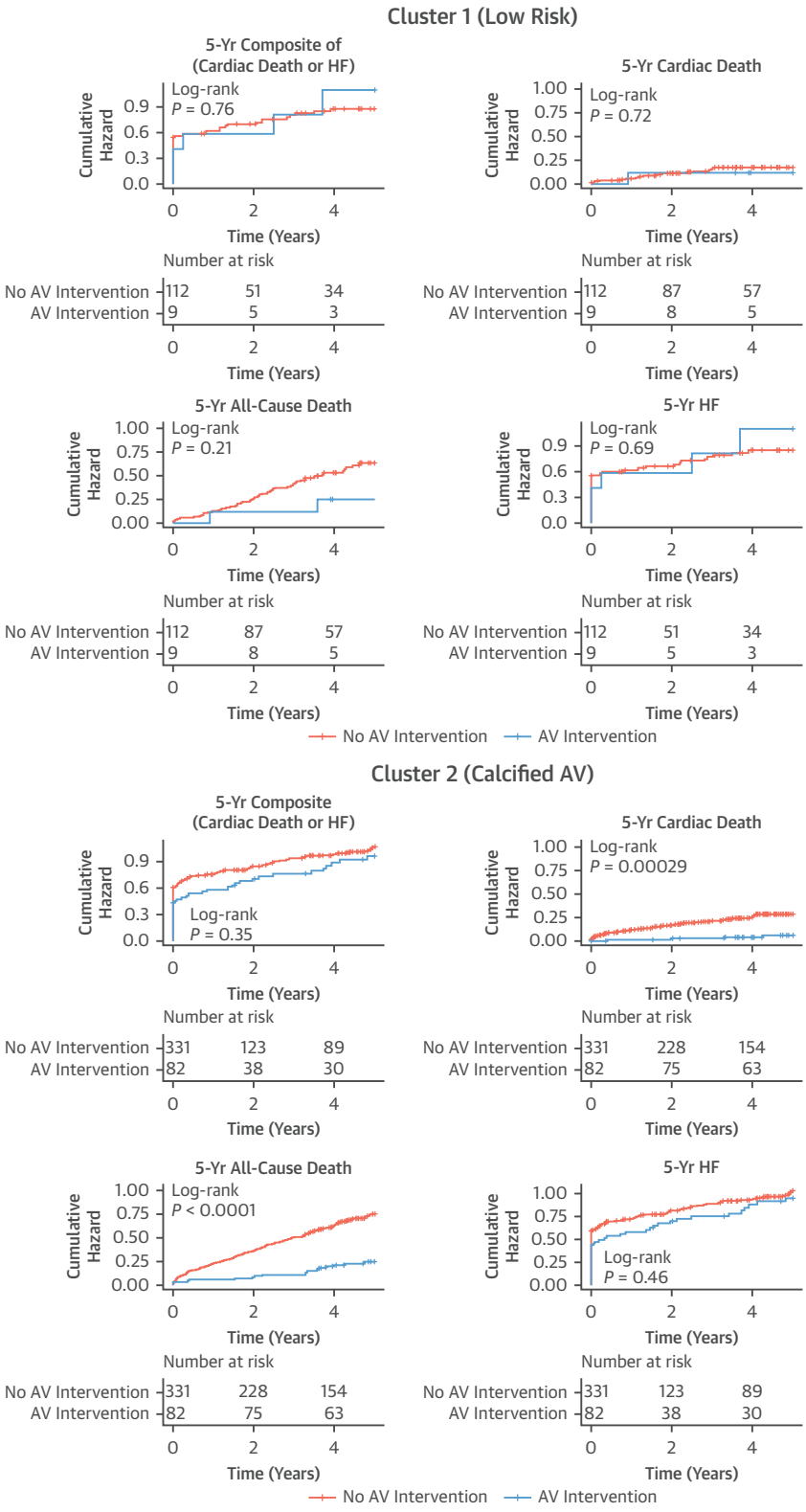
This work builds on previous reports that identified the moderate AS group as having a risk of adverse cardiovascular outcomes similar to that of the severe AS group when compared with no AS, thus leading to calls for more timely AV intervention in moderate AS.[9,35,36] In particular, previous studies reported that patients with moderate AS with HF with reduced ejection fraction had an increased risk of HF hospitalization or mortality compared with no AS and improved survival with AV intervention.[36,37] Our study used both unsupervised and supervised machine learning algorithms and data-driven approaches to identify clinically distinct phenotypes of patients with moderate AS, beyond using echocardiographic parameters. The key findings included the following: the 4 distinct clusters had clinically different phenotypes, associated with differential risks of mortality, HF, and the need for AV intervention. Cluster #1 comprised a low-risk group; cluster #2 was most likely to have a calcified AV; cluster #3 had a low-flow phenotype; and cluster #4 was a CV-comorbid group, which had the highest risk of adverse outcomes. AV intervention may modify the association between the clinical outcomes and cluster groups and appeared to have greatest benefit in reducing cardiac death in the calcified AV cluster (#2) and the CV-comorbid cluster (#4), but it had no significant effect in the low-risk cluster (#1) and the low-flow cluster (#3) (**Central Illustration**). These results were consistent after adjustment for Parsonnet score in the calcified AV cluster (#2). However, this finding was limited by the low rate of AV interventions and unbalanced groups. Furthermore, this study also developed a supervised machine learning model to identify the distinct clusters and validated these cluster groups and outcomes with a geographically separate data set. We observed that moderate AS is not homogeneous, and subtypes should have different management approaches.

FIGURE 3 Comparing Outcomes at 5 Years Using Cumulative Hazard Plots With an External Validation Data Set



HF = heart failure; other abbreviation as in Figure 2.

FIGURE 4 **Comparing Cardiac Death for Each Cluster Over 5 Years With or Without AV Intervention Using a Validation Data Set**



Abbreviations as in Figures 1 to 3.

Continued on the next page

FIGURE 4 Continued

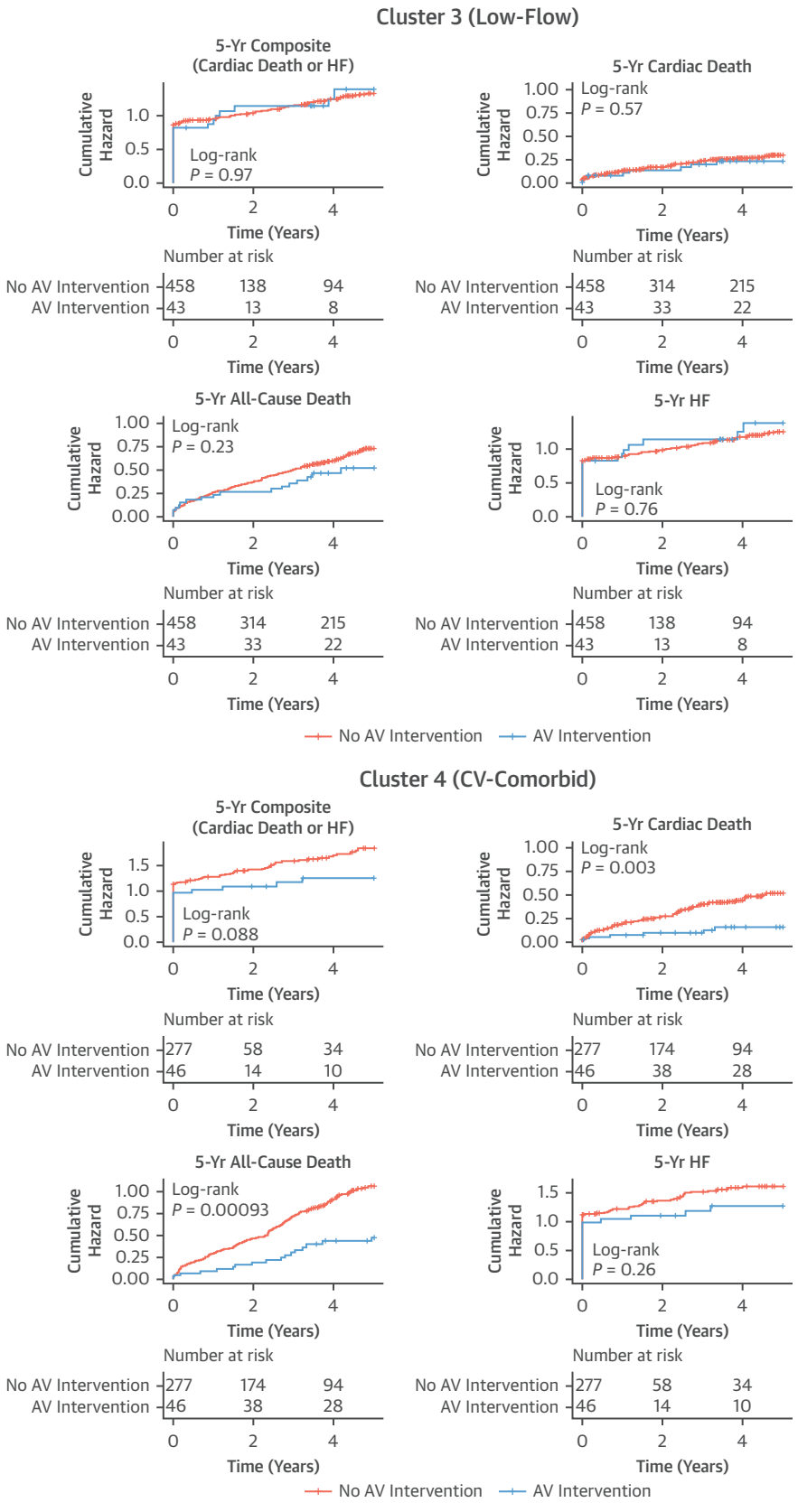


TABLE 4 Effect of 1-Year AV Intervention on Outcomes at 5 Years in Each Cluster

Cluster	Univariate or Multivariate[a]	Composite (Cardiac Death, HF)	Cardiac Death (Death as Competing Risk)	HF Hospitalization (death as Competing Risk)
Training set				
1. Low-risk	Univariate	0.93 (0.63-1.38); $P = 0.70$	0.00 (0.00-0.00); NA	1.00 (0.69-1.46); $P > 0.90$
	Multivariate	1.55 (0.73-3.31); $P = 0.30$	0.00 (0.00-0.00); NA	1.17 (0.80-1.71); $P = 0.40$
2. Calcified AV	Univariate	0.61 (0.45-0.83); $P = 0.002$	0.27 (0.12-0.63); $P = 0.002$	0.68 (0.51-0.92); $P = 0.011$
	Multivariate	1.0 (0.53-1.88); $P > 0.90$	0.35 (0.15-0.82); $P = 0.015$	0.78 (0.58-1.06); $P = 0.11$
3. Low-flow	Univariate	0.67 (0.38-1.20); $P = 0.20$	0.15 (0.02-1.10); $P = 0.062$	0.77 (0.44-1.34); $P = 0.40$
	Multivariate	4.33 (1.34-14.0); $P = 0.015$	0.27 (0.04-2.03); $P = 0.20$	0.97 (0.55-1.69); $P > 0.90$
4. CV-comorbid	Univariate	0.78 (0.50-1.22); $P = 0.30$	0.35 (0.11-1.10); $P = 0.072$	0.90 (0.61-1.34); $P = 0.60$
	Multivariate	0.46 (0.11-1.85); $P = 0.30$	0.43 (0.13-1.39); $P = 0.20$	1.04 (0.69-1.55); $P = 0.90$
External validation				
1. Low-risk	Univariate	1.07 (0.46-2.48); $P = 0.90$	0.78 (0.10-5.94); $P = 0.80$	1.20 (0.64-2.22); $P = 0.60$
	Multivariate	1.43 (0.43-4.69); $P = 0.60$	0.77 (0.09-6.46); $P = 0.80$	1.04 (0.57-1.89); $P > 0.90$
2. Calcified AV	Univariate	0.84 (0.62-1.15); $P = 0.30$	0.21 (0.08-0.57); $P = 0.002$	0.93 (0.72-1.20); $P = 0.60$
	Multivariate	0.95 (0.59-1.51); $P = 0.80$	0.28 (0.10-0.77); $P = 0.013$	1.09 (0.83-1.41); $P = 0.50$
3. Low-flow	Univariate	0.98 (0.68-1.41); $P > 0.90$	0.84 (0.41-1.73); $P = 0.60$	1.08 (0.83-1.39); $P = 0.60$
	Multivariate	1.01 (0.68-1.49); $P > 0.90$	0.93 (0.45-1.92); $P = 0.90$	1.12 (0.87-1.44); $P = 0.40$
4. CV-comorbid	Univariate	0.77 (0.54-1.11); $P = 0.20$	0.34 (0.15-0.78); $P = 0.011$	0.89 (0.69-1.15); $P = 0.40$
	Multivariate	1.65 (1.06-2.56); $P = 0.026$	0.36 (0.15-0.87); $P = 0.022$	1.00 (0.80;-1.25); $P > 0.90$

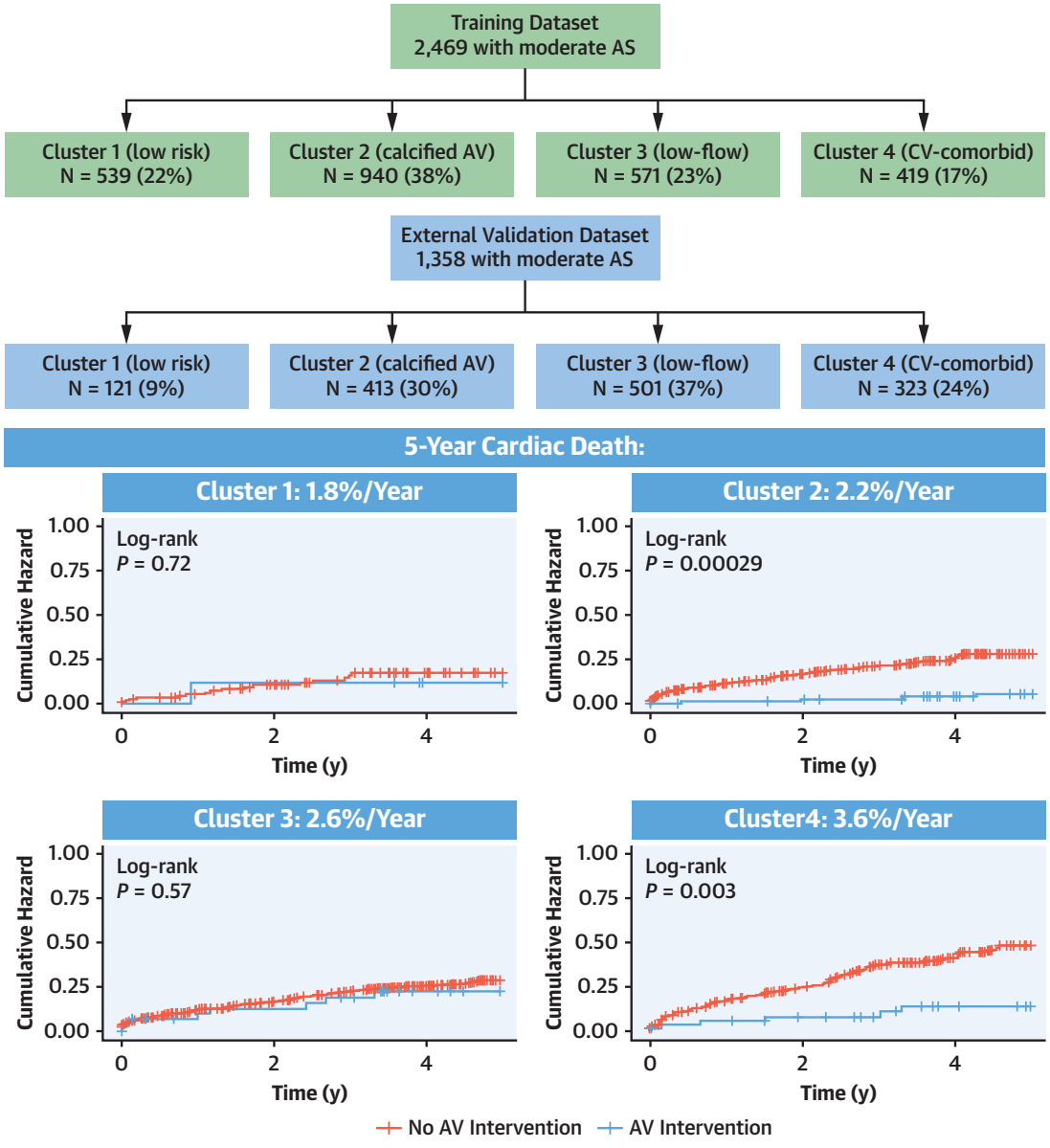
Values are HR (95% CI), unless otherwise noted. [a]Multivariate: adjusted for Parsonnet score: good (0-4), fair (5-9), poor (10-14), high (15-19), and extremely high (20+).[32]
NA = not applicable; other abbreviations as in Table 1.

CLUSTER DEFINITION. Recognizing the potential divergence between the silhouette and Davies-Bouldin indices in determining the optimal cluster count, we emphasized the imperative role of clinical interpretation in guiding this clustering decision-making process. Thus, in our analysis, we departed from the conventional use of the silhouette and Davies-Bouldin indices as the primary determinants of selecting clustering groups. Instead, we adopted a "clinical metric" as the pivotal criterion for cluster selection. By systematically evaluating clustering outcomes across varying numbers of groups, ranging from 2 to 5 (eg, Supplemental Table 9 describes the characteristics of the 3 clusters from the PAM algorithm), we discerned that using 4 clusters held the greatest clinical significance. This study adds an unsupervised method to cluster patients other than using echocardiographic parameters, but it includes comorbidity and is also different from cardiac damage staging and showed incremental value.

EVENTS IN MODERATE AS. The appropriate responses to the risk of moderate AS are currently a topic of huge interest. There is little question that moderate AS carries a risk of adverse outcomes that is comparable (albeit likely rather lower) to that of severe AS and greater than that of no or mild AS. In a recent meta-analysis of 25 studies of patients with moderate AS (12,143 patients followed up for 3.7 years),[38] all-cause death occurred in 9.0 (95% CI: 6.9-11.7) per 100 person-years, compared with cardiac death in 4.9 (95% CI: 3.1-7.5), HF in 3.9 (95% CI: 1.9-8.2), sudden death in 1.1 (95% CI: 0.8-1.5), and AVR in 7.2 (95% CI: 4.3-12.2). A higher risk of mortality was associated with symptoms, LV dysfunction, diabetes mellitus, and coronary artery disease. These findings are concordant with our observations, in that the CV-comorbid cluster had the highest risk. These patients are also unlikely to have this risk reduced by AVR.

Two previous studies have reported unsupervised clustering methods to phenotype AS, albeit in different groups and with different goals. Kwak et al[39] identified 3 distinct groups with moderate or severe AS from 398 patients in South Korea, with a median of 2.4 years follow-up, and with significant differences in risks of mortality: 1) cardiac dysfunction; 2) older adults with comorbidities, especially, end-stage renal disease; and 3) no cardiac dysfunction or comorbidities and validated with a separate historical cohort of 262 patients. Furthermore, Lachmann et al[40] identified 4 distinct groups with severe AS among 366 patients who underwent TAVR and found differences in 2-year mortality without validation: 1) a reference group with an intermediate symptomatic burden and preserved cardiac function; 2) postcapillary pulmonary hypertension; 3) mostly severely impaired cardiac function; and 4) dilation of all cardiac chambers and impairment of left and right ventricular function. There were differences in disease severity or entities compared with our current study, which focused on

CENTRAL ILLUSTRATION **Identification of 4 Clusters in the Training and Validation Data Sets**



Sen J, et al. JACC Cardiovasc Imaging. 2024;■(■):■-■.

The comparison of cardiac death between patients with or without aortic valve intervention is shown in the validation data. AS = aortic stenosis; AV = aortic valve; CV = cardiovascular.

the moderate AS group of patients who did not undergo TAVR or surgical AVR at baseline. In addition, our current study has a larger sample size and longer follow-up, with a median of 9 years, and it validated the generalizability of clustering with a geographically separate cohort during the same time period.

There have also been previous attempts to define phenotypes of moderate AS. The most similar paper was a smaller (n = 1,245) study of moderate AS,[41] in which patients were categorized into 5 groups according to the extent of extra-aortic valvular cardiac abnormalities detected at diagnosis (no abnormalities

to the involvement of various cardiac structures). Over a median follow-up of 4.3 years, 564 patients (45.3%) died. A notable trend emerged, showing higher mortality rates correlating with an increased extent of extra-aortic valvular cardiac abnormalities. This trend persisted after adjusting for AV intervention as a time-dependent factor in all groups with other cardiac disturbances, thus emphasizing the prognostic relevance of these findings. However, in contrast to this current study, the groups were defined on the basis of the extent of extra-aortic valvular cardiac abnormalities, the study investigators did not use unsupervised algorithms, and they lacked an external validation group.

In patients with moderate AS, cardiovascular deaths primarily stem from myocardial-related issues such as congestive HF or sudden death.[42] Interestingly, despite this finding, the proportion of HF was either similar or higher in the intervention group compared with the medical group. Notably, within the cluster #2 calcified AV group, the intervention group had lower cardiac mortality, yet it did not exhibit any significant impact on HF hospitalizations. An essential aspect affecting the analysis is the substantial proportion of patients with pre-existing HF at baseline, accounting for 20% in the internal group and a higher 53% in the external group. As a result, interpreting the effects of AV intervention is better informed by observing survival curves of incident HF over time. This study demonstrated that over time, the AV intervention group generally had a lower risk of HF, with significance evident, particularly in patients with calcified AV.

In our study, cardiovascular risk factors and cardiac comorbidities had the highest impact on cluster #4 assignment, associated with the highest risk of all-cause mortality, cardiac mortality, and HF hospitalization. Cluster #4 had the largest proportion of patients with LVEF lower than 50% (35%) and the largest proportion of patients with HF with reduced ejection fraction (14.3%). Although these findings support the hypothesis that moderate AS increases afterload and induces cardiac remodeling in patients with low LVEF,[37] they also reflect the multimorbid status of these patients. AV intervention was also associated with improved survival in this group. Many of these patients with moderate AS at baseline progressed to severe AS and required AV intervention during the follow-up period. However, in the training set, there was no difference in other outcomes, cardiac death, HF hospitalization, or the composite outcome.

The calcified AV cluster (#2) appeared to derive a significant benefit from AV intervention. This study also suggested that the low-flow cluster (#3) had the least benefit from AV intervention and, after adjustment with the Parsonnet score, AV intervention appear to have a 4 times higher risk of composite of cardiac death or HF, which may be driven by the higher proportion of HF in patients with AV intervention in the training set. However, a larger sample size with balanced groups is needed to confirm the effect of AV intervention.

The potential impact of early intervention in patients with moderate AS and high-risk features requires further investigation. Delving deeper into the impact of interventions, especially at an earlier stage in these high-risk cohorts, stands as a pertinent area for future research endeavors, by aiming to refine and optimize clinical management and improve patient outcomes.

STUDY STRENGTHS. Thousands of consecutive patients with moderate AS with more than 7 years of follow-up were included in this study. The data set included validated echocardiographic data for clustering and validation. The physicians treating the patients were blinded to the results of cluster assignments. The validation cohort was an entirely independent cohort from a different state. The confirmation of the findings occurred despite differences in the groups, especially in HF hospitalization rates between the training and external validation cohorts (48% vs 69%). The latter reflects differences in demographic compositions; the validation group was older, was socially disadvantaged, and had a greater proportion of cardiovascular risk factors such as atherosclerosis, hypertension, and diabetes.

STUDY LIMITATIONS. The limitations included missing values for echocardiographic parameters and blood pressure measurements that required imputation, as well as the possibility that some comorbidities or risk factors may have been missed if they were not coded in medical records. In addition, the selection of a cohort leaned toward “mildly” moderate AS because moderate AS was defined on the basis of a combination of AVA, V_{max}, and DSI. The average AVA measured 1.4 cm^2 (the upper limit of the cutoff for defining moderate AS). Fourth, this study’s design cannot effectively address the impact of AV intervention across different clusters, this inquiry. Moreover, the study encountered an imbalance between the numbers of patients with and without AV intervention, thus hindering a comprehensive assessment of the benefits associated with AV intervention. This study performed adjustment for Parsonnet score to reduce the confounding bias from risk factors for cardiac surgical procedures between the groups with

and without AV intervention. The Parsonnet score was used instead of The Society of Thoracic Surgeons Adult Cardiac Surgery Database Operative Risk Score or the European System for Cardiac Operative Risk Evaluation II given a lack of data for certain variables required to calculate the respective scores. The timing of AV intervention varied notably, spanning from 0 to 15 years, with an average duration of 7.6 years, and this further complicated the evaluation of intervention effects. Therefore, the analysis was limited to evaluating the effect of AV intervention within 1 year. Finally, the primary indications for AV intervention in this specific cohort—whether driven by AS or by coronary artery bypass grafting—remain uncertain because of insufficient data.

CONCLUSIONS

Multiple comorbidities are key drivers of adverse cardiovascular events among patients with moderate AS. In our exploratory analysis, patients who did not have calcific AV disease did not seem to benefit from AV intervention, but we require a balanced, prospective trial to investigate this further. By subphenotyping patients with moderate AS, a tailored management strategy for selecting the appropriate timing of AV intervention and/or adjunctive treatments could be applied in these patients. Clinical and demographic factors, in addition to echocardiographic parameters, are needed to improve phenotyping of moderate AS to identify patients who are most likely and least likely to benefit from intervention.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Moderate AS is associated with increased risk but comprises a heterogeneous group. Careful phenotyping may identify groups of patients (eg, with calcified valves) who may benefit from valvular intervention, but other groups (eg, with low-risk and low-flow clusters) may not benefit but require a larger sample size with balanced groups to confirm its effect.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Multiple comorbidities and cardiovascular risk factors, including ischemic heart disease, acute coronary syndrome, atherosclerosis, diabetes, hypertension, and hyperlipidemia, predict poor cardiovascular outcomes in patients with moderate AS and require careful attention before intervention is recommended.

TRANSLATIONAL OUTLOOK: Additional research on a tailored management strategy for selecting appropriate timing of aortic valvular intervention and/or adjunctive treatments could be assessed for different clinical, demographic, and echocardiographic phenotypes in moderate AS.

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KEY WORDS aortic stenosis, cluster analysis, comorbidity, moderate

APPENDIX For an expanded Methods section as well as supplemental figures, tables, and references, please see the online version of this paper.