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Scientific letter

Clinical clustering of TAVI patients: multivariate profiling and outcome associations using two-step cluster analysis

Clasificación clínica de pacientes con TAVI: análisis multivariante y correlación con resultados mediante agrupamiento en dos fases

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To the Editor,

Transcatheter aortic valve implantation (TAVI) has revolutionized the management of severe aortic stenosis (AS).[1] Despite increasing TAVI experience and procedural improvement, outcomes remain hard to foresee.[1] Several clinical and anatomical risk factors have been well established as independent predictors of adverse events.[2] Nonetheless, the macro-level interactions between them are complex and challenging to quantify with traditional models, particularly given the dynamic clinical trajectory of AS.

Although standardized risk scores, such as the Society of Thoracic Surgeons (STS) score and the EuroSCORE II offer estimates of procedural risk[3] they miss the broader clinical profile and interactions. Advanced statistical techniques, such as multivariate cluster analysis, can identify subgroups, potentially uncovering patterns overlooked by conventional risk stratification. This study aimed to stratify TAVI patients using a 2-step cluster analysis based on clinical and risk factor variables and evaluate the association between these clusters and procedural timing and clinical outcomes.

We conducted a retrospective, single-center study with 300 patients undergoing TAVI from 2020 through 2023, without immediate cardiac surgery back-up. Data were retrospectively analyzed. Procedural and outcome definitions followed the Valve Academic Research Consortium-3 criteria.[4] A 2-step cluster analysis was performed, incorporating variables such as age, sex, New York Heart Association (NYHA) functional class, significant mitral regurgitation, pulmonary hypertension, and relevant comorbidities, including chronic kidney disease and atrial fibrillation.

Clusters were compared regarding baseline characteristics, procedural variables, and outcomes. The primary composite endpoint was 30-day mortality, stroke, and 1-year hospital readmission. Secondary endpoints included 1-year mortality, stroke, hospital readmission, permanent pacemaker implantation, and vascular complications. Statistical analyses were performed using IBM SPSS Statistics, Version 30.0 (IBM Corp., Armonk, NY, USA).

Two clusters were identified: Cluster 1 (n = 182) and Cluster 2 (n = 32) (silhouette coefficient, 0.69). The remaining patients had incomplete data for clustering variables. Baseline demographic and comorbidity profiles were similar between clusters. Mean age (82 ± 5 vs 83 ± 5 years; $P = .6$), female sex (54% vs 50%; $P = .7$), and comorbidities did not differ significantly (table 1). Additionally, echocardiographic and computed tomography parameters were similar between the 2 clusters (table 1).

Differences emerged in clinical presentation and procedural timing. Cluster 1 had a higher proportion of NYHA III/IV patients (52% vs 25%; $P = .005$), previous hospitalization for AS (28% vs 3%; $P = .03$), significant mitral regurgitation (30% vs 12%; $P = .05$), and pulmonary hypertension (64% vs 43%; $P = .03$) at baseline initial assessment. Notably, these patients had a significantly shorter median TAVI waiting time (48 [24-72] vs 93 [47-139] days; $P = .03$), suggesting a prioritization based on symptomatic burden and perceived procedural urgency.

Despite patients from Cluster 1 being more symptomatic, their outcomes were better vs those from Cluster 2. The primary composite endpoint of death, stroke, and hospital readmission occurred in 12% of Cluster 1 patients vs 100% of Cluster 2 patients (risk ratio [RR], 8.3; 95% confidence interval [95%CI], 5.2-13.3; $P < .001$). The 30-day all-cause mortality rate was 1% in Cluster 1 vs 6% in Cluster 2 (RR ,5.7; 95%CI, 0.8-38.9; $P = .05$). The 1-year mortality rate remained significantly lower in Cluster 1 at 7% vs 29% in Cluster 2 (RR, 4.1; 95%CI, 1.9-8.6; $P < .001$). Similarly, stroke occurred in only 0.5% of patients from Cluster 1 while 16% of the patients from Cluster 2 experienced this complication (RR, 33.3; 95%CI, 4.5-247.7; $P < .001$). The 1-year rate of hospital readmissions was also less common in Cluster 1, occurring in 13% of patients vs 88% in Cluster 2 (RR, 6.77; 95%CI, 3.7-12.5; $P < .01$). Rates of vascular complications and permanent pacemaker implantation were similar between the clusters (5.5% vs 9.4%, RR, 1.7; 95%CI, 0.5-5.7; $P = .4$ and 21% vs 23%, RR, 1.10; 95%CI, 0.6-2.2; $P = .9$, respectively).

This study demonstrates that multivariate clustering can identify distinct clinical profiles within a TAVI cohort, revealing paradoxical but clinically meaningful outcome patterns. Patients with advanced symptoms (NYHA III/IV) and prior AS-related hospitalizations, typically considered higher risk, achieved better survival and lower complication rates vs less symptomatic patients.

Procedural timing and patient surveillance intensity might contribute to the different outcomes reported. More symptomatic

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Table 1. Baseline characteristics, procedural data, and clinical outcomes according to cluster analysis in patients undergoing TAVI

Variable	Total (n = 300)	Cluster 1 (n = 182)	Cluster 2 (n = 32)	*P*-value
Baseline				
Age				
Mean, SD	82 ± 5	82 ± 6	83 ± 5	.6
Median, IQR	82 [78-86]	82 [78-86]	84 [79-87]	
Female, (%)	54%	54%	50%	.7
Katz score > 4 (%)	96%	97%	94%	.6
STS score				
Mean, SD	5.2 ± 4.5	4.9 ± 4.2	5.8 ± 4.3	.3
Median, IQR	3.8 [2.8-6.9]	3.7 [2.7-6.6]	4.0 [2.8-7.8]	
STS score high risk (> 8)	17%	13%	22%	.2
EuroSCORE	2.32-2.4	2.2-2	2.6-2	.5
Hospital admission due to AS	22%	28%	3%	.03
NYHA > 2	51%	52%	25%	.005
Comorbidities				
HTN	86%	85%	88%	.7
DM	35%	36%	41%	.6
CAD	21%	16%	25%	.2
COPD/OSA	11%	10%	16%	.3
GFR < 30 mL/kg/m^2	11%	11%	16%	.5
Atrial fibrillation	22%	24%	19%	.5
MI	9%	9%	13%	.5
PCI	14%	12%	22%	.1
Stroke	8%	8%	18%	.07
ECG				
1st AV block	12%	11%	13%	.8
LBBB	9%	8%	7%	.8
RBBB	7%	6%	16%	.05
TTE				
Mean gradient (mmHg)	48 ± 14	49 ± 13	46 ± 15	.2
AVA (cm^2)	0.7 ± 0.2	0.7 ± 0.2	0.8 ± 0.2	.08
LVEF (%)	56 ± 11	55 ± 10	57 ± 10	.7
LVEF < 40%	13%	10%	10%	.9
SPAP > 40mmHg	54%	64%	43%	.03
Significant MR	30%	30%	12%	.05
CT				
Aortic calcium score	721 ± 88			.3
Min femoral diameter (mm)	7.3-1.8	7.0-1.9	7.3-1.6	.3
Laboratory findings				
Hemoglobin	12.2 ± 1.9	12.3 ± 1.8	12.1 ± 2.2	.8
Serum creatinine	1.2, 0.6	1.0, 0.6	1.0, 0.8	.9
NT-proBNP	526 ± 284	510 ± 269	657 ± 291	.09
TAVI waiting time (days)	60-101	48-98	93-92	.03
Outcomes				
Death, stroke and hospital readmission	25%	12%	100%	< .001
30-day mortality rate	3.7%	1%	6%	.05
1-year mortality rate	12%	7%	29%	< .001
Stroke	2.8%	0.5%	16%	< .001
Hospital admission	17%	13%	88%	< .01
Pacemaker implantation	20%	21%	23%	.9
Vascular complication	7.8%	5.5%	9.4%	.4

AS, aortic stenosis; AV, atrioventricular; AVA, aortic valve area; CAD, coronary artery disease; CT, computed tomography; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; ECG, electrocardiogram; GFR, glomerular filtration rate; HTN, hypertension; IQR, interquartile range; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MR, mitral regurgitation; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OSA, obstructive sleep apnea; PCI, percutaneous coronary intervention; RBBB, right bundle branch block; SD, standard deviation; SPAP, systolic pulmonary artery pressure; STS, Society of Thoracic Surgeons; TAVI, transcatheter aortic valve implantation; TTE, transthoracic echocardiogram.
Data are expressed as no. (%), mean ± standard deviation or median [interquartile range].

patients tend to undergo closer clinical follow-up and prioritized TAVI scheduling, as reflected by the significantly shorter waiting times observed in Cluster 1. Conversely, patients with less severe symptoms are often deprioritized, experiencing procedural delays during which subclinical deterioration or decline in functional status can be significant. AS is a progressive condition, with substantial mortality on the waiting list. Moreover, a history of unplanned hospital admission for AS should be considered a significant warning sign to anticipate intervention, given its association with increased risk of subsequent events. Former studies have shown that delayed intervention is associated with higher rates of adverse outcomes,[5] thus supporting the notion that waiting time is a critical modifiable risk factor. Moreover, current risk prediction models inadequately account for dynamic clinical evolution and complex factor interactions. STS and EuroSCORE II values were comparable between clusters, yet outcomes differed substantially. The higher outcome rate from Cluster 2 raises concerns about unrecognized vulnerability and cumulative procedural risk aggravated by disease progression during the waiting period. These findings suggest that, beyond baseline comorbidities, procedural timing and dynamic clinical follow-up should be part of risk stratification and procedural prioritization strategies in TAVI programs.

This study has several limitations. Its retrospective single-center design may limit external validity. Small sample size, especially in Cluster 2, limits power. Unmeasured factors, such as frailty may have influenced outcomes. The 2-step cluster model, while robust, is sensitive to the included variables and missing data, potentially

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affecting cluster assignment and interpretation. Additionally, our conclusions may not be applicable to centers with short waiting lists.

This clustering method allows a macroscopic view and the identification of potential interactions between multiple clinical variables by organizing patients into groups. However, further studies with larger sample sizes are needed to validate this risk assessment approach. These findings highlight the importance of minimizing waiting times and ensuring close follow-up in managing AS. Multidimensional clinical profiling and dynamic procedural scheduling should be considered when optimizing TAVI care pathways to improve patient outcomes.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request

FUNDING

None declared.

ETHICAL CONSIDERATIONS

This study was conducted in full compliance with the Declaration of Helsinki and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines on clinical research. As a retrospective analysis of anonymized data, formal ethical approval and informed consent were waived. This study was conducted in full compliance with the SAGER (Sex and Gender Equity in Research) guidelines. Sex and gender considerations were addressed appropriately, and any potential sex- or gender-related differences were assessed and reported where relevant.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

No artificial intelligence tools were used in the preparation of this manuscript.

AUTHORS' CONTRIBUTIONS

A. Rocha de Almeida: conceptualization, methodology, data curation, formal analysis, investigation, writing – original draft, writing – review and editing. R. Viana: writing – original draft, writing – review and editing. R. Fernandes: writing – review and editing. A. Bento: writing – review and editing. L. Patrício: conceptualization, supervision, writing – review and editing, validation.

CONFLICTS OF INTEREST

None declared.

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