Usefulness of Semisupervised Machine-Learning-Based Phenogrouping to Improve Risk Assessment for Patients Undergoing Transcatheter Aortic Valve Implantation

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Semisupervised machine-learning methods are able to learn from fewer labeled patient data. We illustrate the potential use of a semisupervised automated machine-learning (AutoML) pipeline for phenotyping patients who underwent transcatheter aortic valve implantation and identifying patient groups with similar clinical outcome. Using the Transcatheter Valve Therapy registry data, we divided 344 patients into 2 sequential cohorts (cohort 1, n = 211, cohort 2, n = 143). We investigated patient similarity analysis to identify unique phenogroups of patients in the first cohort. We subsequently applied the semisupervised AutoML to the second cohort for developing automatic phenogroup labels. The patient similarity network identified 5 patient phenogroups with substantial variations in clinical comorbidities and in-hospital and 30-day outcomes. Cumulative assessment of patients from both cohorts revealed lowest rates of procedural complications in Group 1. In comparison, Group 5 was associated with higher rates of in-hospital cardiovascular mortality (odds ratio [OR] 35, 95% confidence interval [CI] 4 to 309, p = 0.001), in-hospital all-cause mortality (OR 9, 95% CI 2 to 33, p = 0.002), 30-day cardiovascular mortality (OR 18, 95% CI 3 to 94, p <0.001), and 30-day all-cause mortality (OR 3, 95% CI 1.2 to 9, p = 0.02) . For 30-day cardiovascular mortality, using phenogroup data in conjunction with the Society of Thoracic Surgeon score improved the overall prediction of mortality versus using the Society of Thoracic Surgeon scores alone (AUC 0.96 vs AUC 0.8, p = 0.02). In conclusion, we illustrate that semisupervised AutoML platforms identifies unique patient phenogroups who have similar clinical characteristics and overall risk of adverse events post-transcatheter aortic valve implantation. **(Am J Cardiol 2020;136:122−130)**

Transcatheter aortic valve implantation (TAVI) has become the standard of care for patients with severe aortic stenosis and a high or prohibitive surgical risk.[1,2] Although several risk scores to predict operative mortality have been applied,[3−5] there are no specific methods for disease groupings for aortic stenosis patients who underwent TAVI. Contemporary use of novel bioinformatics techniques, such as automated machine learning (AutoML), are capable of ingesting vast sets of data and developing improved risk stratification models. We have recently explored the use of unsupervised machine-learning technique for mapping cardiac dysfunction.[6] In the current study, we extend this approach to investigate the development and validation of a semisupervised AutoML algorithm that utilizes these 2 layers of analytical techniques: first, we use unsupervised machine-learning framework that identifies unique patient phenogroups, and second, we train a supervised learning using an automated platform to label an unknown patient to a specific phenogroup. We subsequently compared the validity of the semisupervised AutoML pipeline for identifying meaningful patient phenogroups by comparing the clinical characteristics and outcomes for each group.

Methods

The West Virginia University Institutional Review Board approved this study. An author (PPS) acted as the honest data broker to ensure PHI (Protected Health Information) and HIPAA (Health Insurance Portability and Accountability Act) adherence during the data management, analytics, and ML. Data scientists and research scientists in the project used a single institution deidentified database from the patients submitted to the Society of Thoracic Surgeon/ACC (American College of Cardiology). Transcatheter Valve Therapy registry (TVT) registry. All analyses were performed using the deidentified data.

We included all patients who underwent TAVI at West Virginia University Hospital from April 2014 to May 2019. To account for the changing risk profile and improvement in

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Declaration of Helsinki: Our study complies with the tenets of the Declaration of Helsinki. In addition, the locally appointed ethics committee has approved the research protocol used in this study, and informed consent has been obtained from the subjects (or their legally authorized representative).

See page 129 for disclosure information.

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TAVI procedural technique and devices over time, the patients were divided into 2 cohorts: April 2014 to June 2018 (cohort 1) and July 2018 to May 2019 (cohort 2). First, we used routinely clinical features in cohort 1 for identifying unique patient groups (phenogroups) with aortic stenosis. Next, to identify these phenogroups in cohort 2, we developed a supervised machine-learning classifier, which when provided with the clinical features, would provide phenogroup labels for new individuals. Phenogroup validation was then performed in 2 steps: (1) Comparison of clinical features between the phenogroups; (2) Outcome Validation: The phenogroups were compared for their association with TAVI outcomes (not used in development of the model). This method used here is consistent with previous work where authors have sought validation outside the derivation cohort using a historical validation cohort.[7] The severity of aortic stenosis was determined following the recommendations of the European Association of Cardiovascular Imaging and the American Society of Echocardiography.[8]

The outcomes were selected according to the Valve Academic Research Consortium Criteria-2.[9] Our clinical end points included all-cause mortality and cardiovascular mortality both of which were expressed as in-hospital and within 30 days. The other end points included atrial fibrillation, stroke, transient ischemic attack, myocardial infarction, major bleeding, acute kidney injury, stages I, II, III and/or dialysis and major vascular complications, all were reported within 30 days. We have used the latest versions of online STS calculator available online through the whole course of the study (http://riskcalc.sts.org/stswebriskcalc/calculate).

We first performed topological data analysis (TDA), which uses unsupervised machine learning to aggregate patient groups with similar clinical characteristics and studied in-hospital and 30-day adverse outcomes to delineate the incumbent risk. TDA is based on topology, a mathematical discipline which measures and represents shape, to create compact visual representations of high-dimensional datasets.[10–12] This is performed automatically within the software, by deploying an ensemble machine-learning algorithm that iterates through overlapping subject bins of different sizes that resample the metric space (with replacement), thereby using a combination of the metric location and similarity of subjects in the network topology. The algorithm returns the most stable, consensus vote for the resulting "golden network" (Reeb graph), representing the multidimensional data shape. The application of this method to our dataset creates clusters of patients that appear as nodes (points), and relations among clusters are represented by edges or lines as interconnections between the

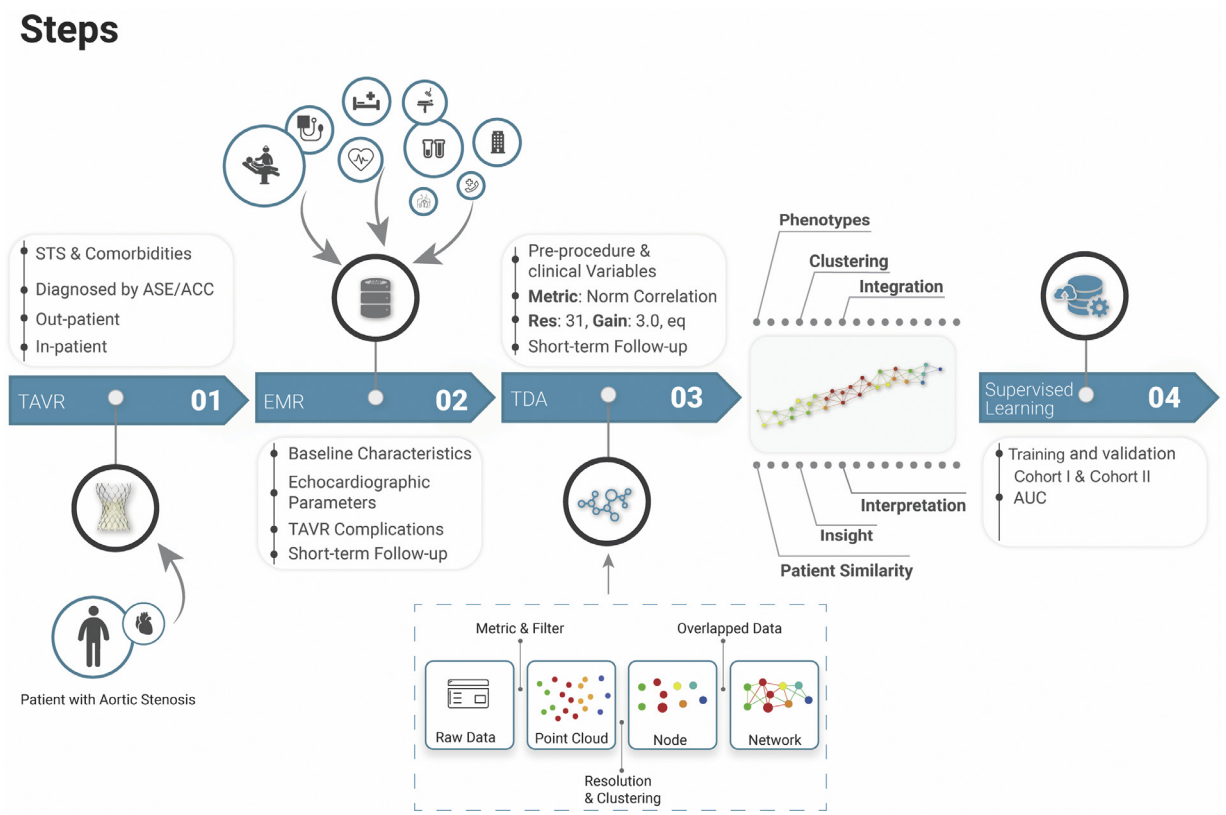

Figure 1. Study flow diagram.

This figure illustrates the flow chart of the steps from the start to the end of the study. Step 1 is the search for the patients who underwent transcatheter aortic valve implantation (TAVI) for severe aortic stenosis (AS) by looking at the institution's STS/ACC/TVT registry. The second step was to collect all the baseline, clinical, and echocardiographic variables from the electronic medical records followed by data extraction and organization in the Microsoft Excel sheets. The unsupervised machine learning was then used to generate patient similarity networks with subsequent formation of 5 distinct phenogroups which resemble each other based on their resemblance in baseline and outcomes variables. These groups were randomly split in 70:30 fashion using supervised machine-learning algorithm, OptiML leading to formation of multiple models. Finally, the best fit models were then applied on a second cohort of patients serving as validation cohort to predict the outcomes in this cohort that patients might have experienced.

nodes (Figure 1). TDA has been extensively validated and successfully implemented in various diseases, such as aortic stenosis, infectious diseases, genetic profiling of cancers and spinal cord injury.[12–15]

To extend the ability of the unsupervised TDA network to develop phenogroups for clinical features of the second cohort, we used a cloud-based supervised AutoML platform (OptiML, BigML.com, Corvallis, Oregon, http://bigml.com). We first randomly split the first cohort to generate 70% training set and 20% as a validation set. We used recursive feature elimination to identify 23 best features and then we evaluated multiple supervised machine-learning algorithms, using automated Optimized Model (OptiML). OptiML is an optimization process for model selection and parametrization that automatically finds the best supervised models to solve classification problems. Using Bayesian parameter through using an optimization technique called sequential model-based algorithm configuration optimization, OptiML creates and evaluates hundreds of supervised models (decision trees, ensembles, logistic regressions, and deep nets) and returns a list of the best models for the data. Eliminating the need for manual and trial-and-error-based exploration of algorithms and parameters, OptiML saves significant time and provides improved performance for AutoML practitioners of all levels. This process was performed with Monte-Carlo cross-validation in the training set. Finally, we identified 10 best models based upon their area under the curve (AUC) scores, which included 9 models with L1 regularization and one with L2 regularization. Subsequently we created an ensemble model (fusion model), which were evaluated in the hold-out validation set. Such techniques of making fusion models help combining diverse and independent models for reducing the generalization error.

For the categorical variables, the comparisons between the groups of interest and the remaining subjects were performed using Pearson's chi-square test or Fisher's exact test, whereas we used the nonparametric Kolmogorov-Smirnov test for continuous variables. A p value of <0.05 was considered statistically significant. TDA was performed using the Ayasdi cloud-based platform (version 7.13, Ayasdi, Inc., Menlo Park, California). The OptiML was performed using the BigML cloud-based platform (BigML, https://bigml.com). To assess the performance of our model, we used several common performance measures, namely specificity, sensitivity (recall), false-negative rate (miss rate), and area under the receiver operating characteristics (ROC) curve. To test the similarity of phenogroups performance for prediction of the outcomes, the 2 groups were combined together, and a multivariable logistic regression was performed with the phenogroups and cohorts incorporated as independent variables to predict the adverse outcomes. We also used sequential logistic regression models with incorporation of STS risk score over underlying phenogroups information from both cohorts for predicting adverse outcomes. The improvement in discrimination with the addition of variables was assessed by the change in the c-statistic and the DeLong.[16] All statistical analyses were performed using MedCalc Statistical Software version 14.8.1 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2020) and maintained at a significance level of 0.05 ($p \leq 0.05$).

Results

We included 354 patients with severe aortic stenosis (AS), divided into 2 cohorts. First, cohort 1 of 211 patients (median age 80 [74 to 86 age range], 45% males) and cohort 2 of 143 patients (median age 79 [75 to 84], 49.7% males). The baseline clinical and echocardiographic parameters of the groups are shown in (Tables 1 and 2). We first created a topological map of the cohort 1 patients who underwent TAVI at our institution using preprocedural clinical and echocardiographic parameters. The flow chart of the study is shown in (Figure 1).

We delineated 5 patient phenogroups. Group 1 ($n = 38$) had patients with a classic high gradient, normal Left ventricular ejection fraction (LVEF), severe AS with aortic valve area of 0.56 cm^2 [0.50, 0.70] ($p < 0.001$), LVEF of 63% [56, 65%] ($p < 0.001$), and mean pressure gradient of 55.0 [46.0 to 61.0] ($p < 0.001$) mmHg. The STS risk score classified this group as intermediate with a median risk score of 4.70 [3.55, 5.44] and $p < 0.001$. Group 2 ($n = 41$) is comprised of classic high gradient as well as low gradient, normal LVEF, severe AS patients**.** These patients had higher predominance of single vessel CAD (33%, $p = 0.01$). The STS median risk was 6.00 [3.60, 7.40] which classified this group as intermediate risk. Group 3 ($n = 61$) is the largest cohort with similar echocardiographic parameters to Group 2. Group 4 ($n = 41$) had a mix of patients with high and low gradients, normal and reduced LVEF, severe AS patients. Patients in this group had hostile chest anatomy (14.6%, $p < 0.001$). The median STS risk was (8.10 [5.20,11.33], $p < 0.003$). Group 5 ($n = 30$) had higher number of pacemakers and ICDs (23%, $p = 0.016$), pre-TAVI cardiac procedures (43%, $p = 0.04$) and heart failure exacerbations before TAVI The details of the baseline characteristics and echocardiographic parameters are shown in (Tables 1 and 2).

To study the applicability of the phenogroups developed in cohort 1, we developed a supervised classifier that could predict new patient's phenogroups. The performance of the model was first verified. The fusion model was highly accurate for predicting the presence of 5 phenogroups identified using TDA with best prediction seen in Group 1 (AUC: 0.94, accuracy: 0.90) and Group 5 (AUC: 0.93, accuracy: 0.88). The performance of the algorithm was lower for Group 3 (AUC: 0.74, accuracy: 0.73) followed by intermediate performance for Group 2 (AUC: 0.82, accuracy: 0.83) and Group 4 (AUC: 0.82, accuracy: 0.81; Online Supplemental figures).

On applying the supervised fusion classifier to cohort 2 with more heterogenous population of patients with low-, intermediate-, and high-risk STS risk scores, interestingly, the model continued to predict in-hospital events of all-cause mortality and cardiovascular mortality for Group 1 (0 for both) and Group 5 (2, 11.1%, $p = 0.007$), which was similar to validation with outcomes seen in cohort 1 (see Table 3). Also, major bleeding was closely predicted for Group 5 (2, 11.1% vs 3, 10%; Table 3) between cohorts 1 and 2, respectively. The model performed well for predicting all-cause mortality for Group 3 and in-hospital outcomes for Group 5.

Overall on combining both cohorts, Group 1 was associated with the lowest rates of procedural complications post-

Table 1
Baseline clinical and echocardiographic characteristics (cohort 1)

Variable	Overall	Phenogroup (1)	Phenogroup (2)	Phenogroup (3)	Phenogroup (4)	Phenogroup (5)	P Value
n-number of patients	211	38	41	61	41	30	
Age (years)	80.00 [73.50, 86.00]	82.00 [73.25, 86.75]	79.00 [74.00, 83.00]	78.00 [74.00, 84.00]	80.00 [70.00,86.00]	82.00 [73.25, 87.00]	0.77
Male	95 (45%)	9 (24%)*	18 (44%)	30 (49%)	23 (56%)	15 (50%)	0.04
Prior pacemaker	21 (10%)	0	0	6 (10%)	8 (20%)*	7 (23%)*	0.001
Prior ICD	11 (5%)	0	0	1 (2%)	3 (7%)	7 (23%)	<0.001
Prior PCI	75 (36%)	4 (11%)*	14 (34%)	26 (43%)	22 (54%)*	9 (30%)	0.001
Prior CABG	54 (26%)	2 (5%)*	4 (10%)*	20 (33%)	17 (42%)*	11 (37%)	<0.001
Prior aortic valve	21 (10%)	0	2 (5%)	5 (8%)	6 (15%)	8 (27%)*	0.003
Prior stroke	45 (21%)	6 (16%)	9 (22%)	19 (31%)*	6 (15%)	5 (17%)	0.22
Prior TIA	25 (12%)	5 (13%)	7 (17%)	4 (7%)	4 (10%)	5 (17%)	0.44
Prior PAD	61 (29%)	4 (11%)*	16 (39%)	21 (34%)	14 (35%)	6 (20%)	0.02
Smoker	32 (15%)	4 (11%)	6 (15%)	12 (20%)	8 (20%)	2 (7%)	0.42
Hypertension	196 (93%)	38 (100%)*	38 (93%)	58 (95%)	37 (90%)	25 (86%)	0.19
Diabetes	95 (45%)	11 (29%)*	23 (56%)	27 (44%)	25 (61%)*	9 (31%)	0.01
ESRD on dialysis	11(5%)	0	2 (5%)	2 (3%)	6 (15%)*	1(3%)	0.03
Pre-TAVI Hb, median (range)	11.70 [10.00,13.15]	11.95 [10.72,13.00]	11.90 [9.90,13.30]	11.50 [9.90,13.60]	11.40 [9.30,12.70]	12.20 [11.05, 13.00]	0.60
Pre-TAVI Cr, median (range)	1.05 [0.83, 1.46]	0.99 [0.79,1.18]	1.00 [0.81,1.49]	1.06 [0.82,1.51]	1.23 [0.87,1.89]	1.02 [0.85, 1.36]	0.14
Chronic lung disease							0.26
0 – not present	115 (55%)	24 (63%)	21 (51%)	30 (49%)	19 (48%)	21 (72%)	
1- mild	49 (23%)	10 (26%)	8 (20%)	15 (25%)	12 (30%)	4 (14%)	
2 - moderate	24 (12%)	1 (3%)	6 (15%)	11 (18%)*	3 (8%)	3 (10%)	
3- severe	21 (10%)	3 (8%)	6 (15%)	5 (8%)	6 (15%)	1 (3%)	
Home O_2	45 (21%)	7 (18%)	10 (24%)	13 (21%)	10 (24%)	5 (17%)	0.92
Hostile chest	10 (5%)	0	0	3 (5%)	6 (15%)*	1 (3%)	0.01
Prior MI	87 (41%)	8 (21%)*	14 (34%)	28 (46%)	23 (56%)*	14 (47%)	0.01
Prior CHF	106 (51%)	11 (29%)*	23 (56%)	27 (44%)	23 (58%)	22 (73%)*	0.004
NYHA							0.43
1	20 (10%)	7 (19%)	3 (7%)	5 (8%)	3 (8%)	2 (7%)	
2	31 (15%)	7 (19%)	7 (17%)	7 (12%)	5 (13%)	5 (17%)	
3	101 (49%)	12 (33%)	19 (46%)	30 (50%)	26 (65%)	14 (47%)	
4	55 (27%)	10 (28%)	12 (29%)	18 (30%)	6 (15%)	9 (30%)	
Cardiogenic shock	2 (1%)	0	0	0	0	2 (7%)*	0.01
Pre-TAVI cardiac procedures	59 (29%)	6 (16%)	11(27%)*	16 (27%)	14 (34%)*	12 (43%)*	0.17
Porcelain aorta	10 (5%)	0	0	4 (7%)	3 (7%)	3 (10%)	0.14
Atrial fibrillation	81 (38%)	16 (42%)	13 (32%)	22 (36%)	15 (37%)	15 (50%)	0.57
Prior conduction defect	69 (33%)	13 (34%)	9 (23%)	23 (38%)	14 (34%)	10 (35%)	0.61
Number of coronary arteries narrowed:							0.01
0	54 (26%)	17 (46%)	13 (32%)	11 (18%)	6 (15%)	7 (23%)	
1	45 (22%)	9 (24%)*	14 (34%)	11 (18%)	7 (18%)	4 (13%)	
2	31 (15%)	4 (11%)	4 (10%)	11 (18%)	6 (15%)	6 (20%)	
3	79 (38%)	7 (19%)	10 (24%)	28 (46%)*	21 (53%)*	13 (43%)	
Left main	15 (7%)	0	0	5 (8%)	8 (21%)*	2 (7%)	0.002
Proximal LAD	41 (20%)	4 (11%)	3 (7%)	12 (20%)	14 (36%)*	8 (27%)	0.012
STS risk score	5.65 [4.00, 8.73]	4.70 [3.55, 5.44]*	6.00 [3.60, 7.40]	6.20 [4.20, 10.00]	8.10 [5.20, 11.33]*	5.21 [4.20, 10.00]	0.004
KCCQ12_Overall	35.59 [19.40, 58.73]	42.45 [18.10, 74.74]	34.38 [20.83, 47.92]	34.12 [15.23, 63.67]	37.50 [27.1, 45.83]	37.24 [17.71, 57.03]	0.67
Echocardiographic characteristics							
LVEF (%)	55.00 [45.00, 63.00]	63.00 [55.50, 65.00]*	59.00 [55.00, 65.00]*	55.00 [46.00, 63.00]	55.00 [35.00,63.00]	35.00 [20.00,55.00]*	<0.001
RVSP (mmHg)	42.00 [32.00, 55.00]	41.00 [32.50, 45.00]	39.00 [29.25, 54.25]	44.00 [31.25, 55.00]	39.00 [33.00,55.00]	48.00 [39.50, 57.00]	0.36
AV Peak Velocity (cm/s)	4.00 [3.52, 4.47]	4.40 [4.25, 4.95]*	4.05 [3.62, 4.57]	4.00 [3.50, 4.30]	3.85 [3.40, 4.22]*	3.70 [3.18, 4.10]*	<0.001
							0.87

(*continued*)

Table 1 (***Continued***)

Variable	Overall	Phenogroup (1)	Phenogroup (2)	Phenogroup (3)	Phenogroup (4)	Phenogroup (5)	P Value
AV Annulus Size (cm)	24.00 [23.00, 26.00]	24.00 [23.00, 26.00]	24.00 [23.00, 26.00]	24.00 [23.00, 27.00]	26.00 [23.0, 26.00]	24.50 [23.0, 26.00]	
AVA (cm^2)	0.66 [0.54, 0.79]	0.56 [0.50, 0.70]*	0.70 [0.58, 0.80]	0.69 [0.60, 0.80]	0.61 [0.57, 0.73]	0.68 [0.60, 0.79]	0.03
AV MPG (mmHg)	42.00 [33.00, 53.50]	55.00 [46.00, 61.00]*	42.00 [35.00, 54.25]	42.00 [32.00, 50.00]	37.0 [29.0,49.25]*	38.0 [28.0, 45.00]*	<0.001
AV Peak Gradient (mmHg)	66.0 [52.00, 80.75]	81.50 [74.00, 98.25]*	70.0 [56.00, 87.00]	65.0 [51.00, 78.00]	58.0 [48.0,73.00]*	55.0 [41.0,66.00]*	<0.001
Post-TAVI LVEF (%)	58.00 [50.00, 63.00]	62.5 [55.75, 65.00]	63.00 [58.00, 65.00]	59.0 [55.00, 63.00]	53.0 [40.0,62.50]	41.00 [23.0, 56.50]	<0.001
Post-TAVI MPG (mmHg)	10.0 [8.00, 14.00]	10.0 [7.00, 13.00]	10.0 [8.00, 13.50]*	11.0 [8.50, 15.00]	10.0 [8.50,14.00]*	9.0 [8.00,13.50]*	0.88
Post-TAVI KCCQ12_Overall	78.13 [64.06, 92.71]	76.3 [59.68, 94.27]	81.25 [61.11, 90.10]	76.04 [56.25, 87.50]	89.58* [66.67,96.62]	78.13 [64.85, 95.05]	0.23

ICD = implantable cardioverter defibrillator; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft; PAD = peripheral arterial disease; TIA = transient ischemic attack; ESRD = end stage renal disease; MI = myocardial infarction; CHF = congestive heart failure; TAVI = transcatheter aortic valve implantation; LAD = left anterior descending artery; STS = short-term risk score; KCCQ = Kansas city cardiomyopathy questionnaire; CAD = coronary artery disease; LVEF = left ventricular ejection fraction; RVSP = right ventricular systolic pressure; AV = aortic valve; AVA = aortic valve area; MPG = mean pressure gradient.

* p value − significant.

Table 2
Baseline clinical and echocardiographic characteristics (cohort 2)

Variable	Overall	Phenogroup (1)	Phenogroup (2)	Phenogroup (3)	Phenogroup (4)	Phenogroup (5)	P Value
N = number of patients	143	27	37	44	17	18	
Age (years)	79.39 [75.07, 84.36]	79.30 [73.89, 83.09]	79.95 [75.18, 84.89]	80.48 [75.22, 84.40]	75.10 [72.35, 79.66]*	83.50 [79.95, 88.50]*	0.04
Male	71 (50%)	10 (37%)	12 (32%)*	27 (61%)	11 (65%)	11 (61%)	0.02
Prior pacemaker	18 (13%)	3 (11%)	2 (5%)	5 (11%)	4 (24%)	4 (22%)	0.23
Prior ICD	4 (3%)	1 (4%)	0	1 (2%)	2 (12%)	0	0.16
Prior PCI	40 (28%)	3 (11%)*	8 (22%)	18 (41%)*	7 (41%)	4 (22%)	0.03
Prior CABG	32 (22%)	1 (4%)*	0	16 (36%)*	10 (59%)*	5 (28%)	<0.001
Prior aortic valve	29 (20%)	6 (22%)	8 (22%)	6 (14%)	6 (35%)	3 (17%)	0.43
Prior stroke	22 (15%)	2 (7%)	7 (19%)	7 (16%)	2 (12%)	4 (22%)	0.64
Prior TIA	16 (11%)	2 (7%)	4 (11%)	5 (11%)	2 (12%)	3 (17%)	0.91
PAD	28 (20%)	3 (11%)	10 (27%)	10 (23%)	5 (29%)	0	0.05
Smoker	17 (12%)	1 (4%)	7 (19%)	6 (14%)	1 (6%)	2 (11%)	0.43
Hypertension	132 (92%)	25 (93%)	36 (97%)	40 (91%)	17 (100%)	14 (78%)*	0.10
Diabetes	61 (43%)	5 (19%)*	19 (51%)	16 (36%)	15 (88%)*	6 (33%)	<0.001
ESRD on dialysis	9 (6%)	1 (4%)	0	0	7 (41%)*	1 (6%)	<0.001
Pre-TAVI Hb, median (range)	11.85 [9.90, 13.30]	12.20 [11.12, 13.60]	11.00 [9.10, 13.30]	12.20 [10.70, 12.93]	9.90 [9.20, 11.80]	13.15 [12.08, 14.55]	0.004
Pre-TAVI Cr, median (range)	1.13 [0.84, 1.42]	0.98 [0.82, 1.16]	1.03 [0.81, 1.42]	1.10 [0.87, 1.32]	2.12 [1.72, 4.10]	1.18 [0.88, 1.38]	<0.001
Chronic lung disease							NS
0 − not present	89 (62%)	24 (89%)	22 (60%)	23 (52%)	8 (47%)	12 (67%)	
1- Mild	31 (22%)	0	10 (27%)	12 (27%)	4 (24%)	5 (28%)	
2- Moderate	12 (8%)	1 (4%)	3 (8%)	5 (11%)	3 (18%)	0	
3- Severe	11 (8%)	2 (7%)	2 (5%)	4 (9%)	2 (12%)	1 (6%)	
Home O_2	28 (20%)	1 (4%)*	9 (24%)	11 (25%)	6 (35%)	1 (6%)	0.02
Hostile chest	6 (4%)	0	3 (8%)	1 (2%)	1 (6%)	1 (6%)	0.46
Prior MI	41 (29%)	0	11 (30%)	18 (41%)*	9 (53%)*	3 (17%)	<0.001
Prior CHF	82 (57%)	10 (37%)*	23 (62%)	20 (46%)	16 (94%)*	13 (72%)	0.001
NYHA							NS
1	12 (8%)	3 (11%)	3 (8%)	3 (7%)	0	3 (17%)	
2	50 (35%)	12 (44%)	12 (32%)	14 (32%)	6 (35%)	6 (33%)	

(*continued*)

Table 2 (***Continued***)

Variable	Overall	Phenogroup (1)	Phenogroup (2)	Phenogroup (3)	Phenogroup (4)	Phenogroup (5)	P Value
3	64 (45%)	12 (44%)	18 (49%)	20 (46%)	8 (47%)	6 (33%)	
4	17 (12%)	0	4 (11%)	7 (16%)	3 (18%)	3 (17%)	
Cardiogenic shock	3 (2%)	0	0	1 (2%)	0	2 (11%)*	0.11
Pre-TAVI cardiac procedures	10 (7%)	2 (8%)	4 (11%)	1 (2%)	3 (18%)	0	0.14
Porcelain aorta	4 (3%)	0	1 (3%)	1 (2%)	2 (12%)	0	0.22
Atrial fibrillation	59 (41%)	9 (33%)	9 (24%)*	21 (48%)	9 (53%)	11 (61%)	0.04
Prior conduction defect	8 (6%)	2 (7%)	1 (3%)	1 (2%)	3 (18%)	1 (6%)	0.16
Number of coronary arteries narrowed:		*	*	*			NS
0	55 (39%)	16 (62%)	25 (68%)	4 (10%)	3 (18%)	7 (39%)	
1	17 (12%)	3 (12%)	4 (11%)	5 (11%)	2 (12%)	3 (17%)	
2	21 (15%)	6 (23%)	4 (11%)	8 (18%)	2 (12%)	1 (6%)	
3	49 (35%)	1 (4%)	4 (11%)	27 (61%)	10 (59%)	7 (39%)	
Left main	15 (11%)	1 (4%)	0	7 (16%)	5 (29%)*	2 (11%)	0.005
Proximal LAD	33 (23%)	2 (8%)*	7 (19%)	14 (32%)	6 (35%)	4 (22%)	0.11
STS risk score	4.84	3.07	4.30	4.94	11.34	5.08	<0.001
	[3.30, 7.53]	[2.05, 5.32]*	[3.34, 5.76]	[3.56, 6.91]	[9.31, 12.51]*	[4.24, 6.88]	
KCCQ12_Overall	33.33	40.63	32.29	34.38	16.67	43.23	0.12
	[17.19, 58.85]	[23.44, 66.84]	[16.67, 54.69]	[26.04, 56.77]	[11.46, 29.69]*	[9.38, 66.67]	
Echocardiographic characteristics							
LVEF (%)	55.00	65.00	60.00	53.00	45.00	27.50	<0.001
	[40.00, 63.00]	[59.00, 68.00]*	[55.00, 63.00]*	[39.50, 61.50]	[35.00, 55.00]*	[25.00, 46.75]*	
RVSP (mmHg)	47.00	51.00	41.00	50.00	47.50	49.00	0.33
	[35.00, 58.00]	[39.25, 56.25]	[34.38, 50.00]*	[41.00, 61.00]	[35.50, 55.95]	[36.00, 62.00]	
AV peak velocity (cm/s)	4.00	4.70	4.10	3.85	3.40	3.30	<0.001
	[3.50, 4.30]	[4.32, 5.00]*	[3.82, 4.30]	[3.52, 4.18]	[3.00, 3.90]*	[2.73, 3.95]*	
Annulus size (cm)	25.00	23.50	24.00	26.00	26.00	25.00	0.04
	[23.00, 27.00]	[22.00, 26.75]	[22.00, 25.00]*	[24.00, 27.00]*	[23.00, 26.00]	[24.00, 27.00]	
AVA (cm^2)	0.70	0.60	0.78	0.70	0.70	0.80	0.04
	[0.60, 0.90]	[0.50, 0.79]*	[0.65, 1.00]	[0.67, 0.83]	[0.60, 0.70]	[0.67, 1.00]	
AV MPG (mmHg)	40.00	54.00	43.00	38.50	29.00	27.50	<0.001
	[30.00, 50.00]	[47.00, 64.50]*	[38.00, 50.00]*	[29.75, 44.00]	[24.00, 38.00]*	[18.50, 38.00]*	
AV peak gradient (mmHg)	64.50	88.00	70.00	58.00	49.00	50.50	<0.001
	[50.00, 78.00]	[73.00,100.00]*	[64.00, 77.00]*	[46.00, 69.00]*	[38.50, 60.75]*	[33.75, 55.50]*	
Post-TAVI LVEF (%)	57.00	63.00	59.00	55.00	53.00	40.00	<0.001
	[49.50, 63.00]	[56.50, 68.00]*	[55.00, 67.25]*	[49.00, 60.00]	[45.50, 57.50]	[29.00, 54.50]*	
Post-TAVI MPG (mmHg)	11.50	14.00	12.00	11.00	10.50	8.00	0.005
	[9.00, 15.00]	[10.00, 18.00]	[10.00, 15.00]	[9.00, 13.00]	[10.00, 17.25]	[7.25, 11.00]	
Post-TAVI KCCQ12_Overall	80.21	83.33	78.13	80.38	71.35	84.72	0.91
	[57.63, 88.89]	[59.38, 90.63]	[57.03, 86.98]	[60.59, 88.28]	[50.00, 86.85]	[56.51, 90.28]	

ICD = implantable cardioverter defibrillator; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft; PAD = peripheral arterial disease; TIA = transient ischemic attack; ESRD = end stage renal disease; MI = myocardial infarction; CHF = congestive heart failure; TAVI = transcatheter aortic valve implantation; LAD =left anterior descending artery; STS = short-term risk score; KCCQ = Kansas city cardiomyopathy questionnaire; CAD = coronary artery disease; LVEF = left ventricular ejection fraction; RVSP = right ventricular systolic pressure; AV = aortic valve; AVA = aortic valve area; MPG = mean pressure gradient.

* - p value – significant, NS – nonsignificant.

TAVI (odds ratio [OR] 0.25, 95% confidence interval [CI] 0.09 to 0.7, p = 0.009). In the contrary, Group 5 was associated with higher rates of in-hospital cardiovascular mortality (OR 35, 95% CI 4 to 309, p = 0.001), in-hospital all-cause mortality (OR 9, 95% CI 2 to 33, p = 0.002), 30-day cardiovascular mortality (OR 18, 95% CI 3 to 94, p <0.001), and 30-day all-cause mortality (OR 3, 95% CI 1.2 to 9, p = 0.02; Figure 3). For 30-day cardiovascular mortality, using phenogroups in conjunction with the STS score improved the overall prediction versus using the STS scores alone (AUC 0.96 vs AUC 0.8, p = 0.02; Figure 2). For 30-day all-cause mortality there was no difference between phenogroups in conjunction with STS score compared with STS score alone (AUC 0.8 vs 0.77, respectively, p = 0.6).

Discussion

In the current study, we investigated the use of semisupervised AutoML algorithms using patient similarity analysis to characterize AS patient into subgroups to understand the similarities in clinical presentations and outcomes related to TAVI. Despite the small sample size, we illustrate the advantages of using a semisupervised pipeline that improved performance and prediction of the outcomes in

Table 3
Post-TAVI complications (cohort 1 and 2)

Outcomes	Phenogroup (1)		Phenogroup (2)		Phenogroup (3)		Phenogroup (4)		Phenogroup (5)		P Value	
N = number of events (%)	Cohort 1	Cohort 2	Cohort 1	Cohort 2	Cohort 1	Cohort 2	Cohort 1	Cohort 2	Cohort 1	Cohort 2	Cohort 1	Cohort 2
All-cause mortality (In-hospital)	0	0	0	0	4 (7%)	0	0	0	3 (10%)	2 (11%)	0.03	0.007
All-cause mortality (30 days)	0	1 (4%)	2 (5%)	1 (3%)	6(10%)	1 (3%)	1 (2%)	1 (6%)	3 (10%)	3 (17%)	0.18	0.16
Cardiovascular death (In-hospital)	0	0	0	0	1 (2%)	0	0	0	3 (10%)	2 (11%)	0.01	0.007
Cardiovascular death (30 days)	0	0	0	0	1 (2%)	1 (2%)	0	0	3 (10%)	2 (11%)	0.01	0.06
Atrial fibrillation	2 (5%)	1 (4%)	2 (5%)	3 (8%)	6(10%)	0	2 (5%)	0	0	2 (11%)	0.42	0.18
Stroke	1 (3%)	2 (7%)	2 (5%)	1 (3%)	2 (3%)	2 (5%)	1 (2%)	1 (6%)	0	0	0.81	0.76
TIA	0	0	0	0	0	1 (2%)	1 (2%)	0	0	0	0.38	0.68
MI	0	0	0	0	0	1 (2%)	1 (2%)	1 (6%)	0	1 (6%)	0.38	0.39
Major bleeding	1 (3%)	1 (4%)	1 (2%)	0	3 (5%)	1 (2%)	3 (7%)	0	3 (10%)	0	0.57	0.38
Acute kidney injury 1	0	1 (4%)	1 (2%)	1 (3%)	2 (3%)	1 (2%)	2 (5%)	1 (6%)	2 (7%)	0	0.88	0.88
Acute kidney injury 2	0	0	1 (2%)	0	3 (5%)	0	1 (2%)	1 (6%)	2 (7%)	0	0.54	0.11
Acute kidney injury 3	0	0	0	0	1 (2%)	0	0	0	1 (3%)	0	0.49	NS
Acute kidney injury 3 or dialysis	0	0	1 (2%)	1 (3%)	4 (7%)	0	1 (2%)	1 (6%)	2 (7%)	0	0.42	0.38
Major vascular complications	0	1 (4%)	0	0	2 (3%)	1 (2%)	1 (2%)	0	0	0	0.49	0.68

Cohort 1 = 211 patients, Cohort 2 = 143 patients, TIA = transient ischemic attack; MI = myocardial infarction, * - p value – significant, NS = nonsignificant.

Figure 2. Receiver operating characteristics (ROC) with area under the curve AUC) for comparison of phenogroups with STS versus STS for cardiovascular mortality.
For 30-day cardiovascular mortality, using phenogroups in conjunction with the STS score improved the overall prediction versus using the STS scores alone (AUC 0.96 vs AUC 0.8, p = 0.02).

different patient groups compared with the traditional surgical risk score calculator.

Recent interest in using AutoML in healthcare has received enthusiastic endorsements for cancer phenotyping,[17] cardiac imaging,[18,19] and risk prediction.[20,21] Similarly, AutoML aims at "learning" from data compared with well-known and established statistical approaches.[20] In the statistical approach, a probabilistic model is usually built, which is based on the assumption that the provided data are a subset of a larger population that can be described by a model. In contrast, machine-learning emphasizes predictions, and thus its efficiency is evaluated via prediction performance. Moreover, the unbiased view of the available data by the machine-learning algorithms can lead to the discovery of previously unseen relationships among data, whereas the classic approaches may overlook these relationships due to model restrictions.[20]

A previous study used administrative database of TAVI patients to develop a supervised machine-learning model to predict mortality.[22] The approach introduced in the present study is applicable to more contemporary TAVI population and utilizes state-of-the-art methods that can be applied to extract meaningful information from smaller sample sizes with sparse clinical outcome. Firstly, we used TDA as an initial step to understand the structure of the data. Topology is a mathematical discipline that studies shape,[23] whereas TDA refers to the adaptation of this discipline to analyzing highly complex data.[23] It draws on the philosophy that all data have an underlying shape and that shape has meaning. The platform draws together a broad range of ML, statistical, and geometric algorithms to create a summary or compressed representation of all the data points in a large dataset and thus to rapidly uncover critical patterns and relationships in that dataset. TDA augments supervised learning algorithms (semisupervised learning) by effectively constructing a collection or ensemble of models rather than making global assumptions regarding all the

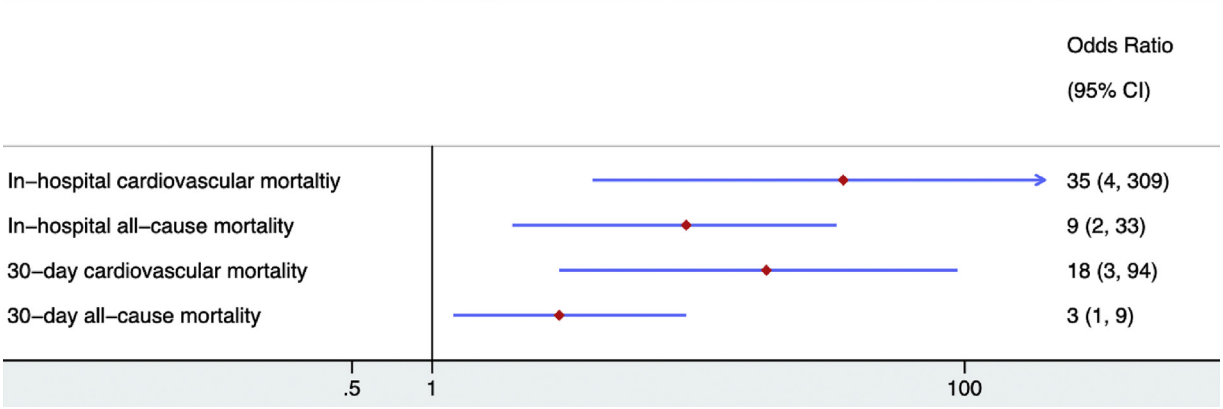

Figure 3. Forest plot of combined cohorts comparing Group 5.

underlying data. This eliminates the need to create a single model that works well on all of the data, which is a difficult if not impossible mission. This "collection of models" method generates more accurate results and can incorporate any supervised algorithm.[20,23]

A close look at the data from the cohort 1 demonstrated intermediate risk assigned to all 5 groups as per STS risk calculator. However, we did witness higher in-hospital and 30-day mortality in Group 5. Additionally, although, the patients in Group 4 were deemed high risk with a median STS score of 8, this group was not associated with higher rates of all-cause and cardiovascular mortality. This is quite interesting that machine-learning models may improve risk stratification in ways to mitigate immediate postprocedural complications and work as an adjunct to complement STS risk calculators. Although the steps of machine-learning appear complicated, the final outcome can be an app-based or cloud-based online model that can function automatically like the common risk prediction tools. The main advantage of the AutoML approach is its inherent ability to ingest large sets of variables to develop patient-specific predictions.

Our study has several limitations. First, this study explored the potential of applying AutoML approaches using data from a single center with a relatively small number of patients. Second, newer algorithms that use optimized deep learning models or reinforcement learning would need to be evaluated in the future. Third, the comparator in in the current study was the STS score which was originally designed to predict 30 days surgical outcomes rather than in-hospital outcomes after TAVI. Fourth, the current dataset included mostly patients with intermediate STS risk scores, and the applicability of the model on patients with low-risk STS scores needs to be tested in a larger cohort. Fifth, we evaluated the in hospital and 30 days outcomes, and the value of the AutoML model to predict long-term functional recovery and adverse events needs to be addressed. Finally, as the data was derived from the TVT registry and hence we were not able to include other important variables like calcium scoring and computed tomography data as these are not captured by the registry data.

In the current study, we investigated the use of a semisupervised AutoML algorithm to predict in-hospital and 30-day outcomes in patients with severe AS treated with TAVI. Our findings revealed improved performance and prediction of the outcomes in different patient groups by using a novel AutoML model compared with the traditional surgical risk score calculator.

Credit Author Statement

Yasir Abdul Ghaffar, Partho P. Sengupta: conceptualization, investigation, methodology, writing-original draft and writing-review and editing.

Mohammed Osman: methodology, analysis, writing-review and editing.

Sirish Shrestha: data curation, visualization, methodology.

Faizan Shaukat; data curation.

Mohamad Alkhouli, Bryan Raybuck & Vinay Badhwar; supervision.

Disclosures

Partho P. Sengupta is a consultant for Heart Sciences, Ultromics. Yasir Abdul Ghaffar, Mohammed Osman, Sirish Shrestha, Faizan Shaukat, Nobuyuki Kagiyama, Mohammed Alkhouli, Bryan Raybuck, and Vinay Badhwar have nothing 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.2020.08.048.

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