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Outcomes of Transcutaneous Aortic Valve Replacement among high risk WV sample population.

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Outcomes of transcutaneous aortic valve replacement among high risk WV population

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Abstract

Introduction

Transcatheter aortic valve replacement (TAVR) is a relatively new strategy for replacing the aortic valve. We elected to review our early experience to see if we could identify clinical characteristics at baseline or immediately following the procedure that would predict death within one year.

Methods

Charts for all patients assigned to receive TAVR procedure at St Mary's Medical Center, Huntington, West Virginia between April 2013 and November 2016 were identified and reviewed. A total of seventy-two cases were included.

Results

All-cause mortality rate at index hospitalization, 30 days, and 12 months was 5.6%(N=4), 6.9%(N=5), 19.4%(N=14) respectively. Stroke rate at index hospitalization, 30 days, and 12 months was 2.8%(N=2), 2.8%(N=2), 8.3%(N=6) respectively. Major predictors of death were post procedure GFR, contrast volume, and number of antiplatelet agents therapy (AUC= 0.638, 0.632, 0.637 respectively).

Conclusion

We found that post procedure GFR, less number of antiplatelet agents post procedure, and contrast volume may predict mortality within first 12 months post TAVR. Further studies focused on the above factors may be warranted.

Keywords

transcathether, aortic valve, percutaneous, mortality, hypertension, blood pressure, correlation, machine learning

Introduction

Transcatheter aortic valve replacement (TAVR) is a relatively new strategy for replacing the aortic valve in patients with severe aortic stenosis (AS) who are felt to be at significant or prohibitive risk for conventional surgical approach.[1] The positive results from various randomized controlled trials (RCTs) led to rapid evolution of the procedure.[2-4] Both balloon-expandable and self-expandable valves showed comparable results as compared to surgical aortic valve replacement (SAVR).[2, 3] Recently the procedure was approved to include intermediate surgical risk patients based on PARTNER 2 cohort.[4] Although the very definition of the high risk population predicts a high mortality rate, we elected to review our early experience after performing more than 50 TAVR procedures to see if we could identify clinical characteristics at baseline or immediately following the procedure that would predict early death (death within one

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year) in our high risk population. To facilitate such identification, we chose to employ various machine learning methods effective in predicting categorical outcomes.[5]

Methods

Charts of all patients assigned to receive TAVR procedure at St Mary's Medical Center, Huntington, West Virginia between April 2013 and November 2016 were identified and reviewed. A total of 72 high-risk cases were included. One of these patients died prior to undergoing the procedure. Pre-procedural, procedural, and post-procedural data were obtained and analyzed. The baseline characteristics of these patients are shown in Table 1. Primary outcomes were identified as all cause mortalities and strokes at index hospitalization, 30 days, and 12 months. Secondary outcomes data were identified as access site complications, heart failure symptoms, renal failure, length of stay, and post-procedural valvular hemodynamics.

Table 1: Baseline patient characteristics

Characteristic	TAVR (N=72)
Age-yr	80.4 ± 8.7
Male sex—no. (%)	38 (53)
STS score	10.4 ± 6.2
NYHA Class III or IV no. (%)	69(95.8)
KCCQ 12	29.6±11.6
Coronary artery disease—no. (%)	
- One vessel	19(26.3)
- Two vessels	10(13.8)
- Three vessels	8(11.1)
Previous CABG—no. (%)	20(27.7)
Previous PCI—no. (%)	20(27.7)
PCI within 30 days prior procedure—no. (%)	5(6.9)
Cerebrovascular disease--no. (%)	22(30.5)
Peripheral vascular disease--no. (%)	35(48.6)
Diabetes Mellitus --no. (%)	28(38.8)
Hypertension—no. (%)	71(98.6)
COPD—no. (%)	53(73.6)
Oxygen dependent —no. (%)	20(27.7)
Pre procedure GFR	56.3±23.0
Atrial fibrillation —no. (%)	16(22.2)
1st Degree AVB —no. (%)	15(20.8)
RBBB—no. (%)	13(18)
PPM/AICD —no. (%)	13(18)
Aortic Valve Area – CM^2	0.72±0.18
Mean Gradient —mmHg	51.1±12.2
Left Ventricular Ejection Fraction — (%)	48.4±12.4
Moderate or Severe mitral regurgitation — no. (%)	16(22.2)
Mitral stenosis —no. (%)	15(20.8)

Statistical analysis

All analysis was performed using the open source program R. The data was cleaned by excluding variables with large numbers of missing values. Variables with more moderate amounts of missing values that had numeric data had the average value placed into missing value categories. Analysis of 72 subjects was then possible. Machine learning was performed on a dataset without missing values. Parameters used for subsequent analysis are shown in Table 1. Before deciding to analyze the dataset without missing values, multiple methods of imputation for both missing

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categorical and continuous data were employed and yielded results similar to analysis on the cleansed data.

Logistic Regression and Support Vector Machine

We used a generalized linear (logistic regression) model as our default [6] using only baseline variables for the prediction of composite endpoint outcomes. In addition, we examined the utility of a support vector machine (SVM) which involves the multi-dimensional sorting of data based on the development of a hyperplane which best segregates the two classes.[8] Using the CARET package, we employed two tuning parameters to control the performance of the SVM: kernel and C. We used the radial kernel option from the CARET package. When radial kernel is applied, Sigma needs to be specified to avoid over-fitting. The second tuning parameter used was C which specifies the penalty for misclassification. The best combination of C and Sigma values are determined using cross-validation. Sigma and C values were optimized within the CARET package, and values of 1e-4 and 32 were used thereafter.

Random Forest

The third method we applied is the random forest which employs decision trees to construct a predictive model using a set of binary rules applied to calculate a target value. We used two tuning parameters for random forest: the number of trees (ntree) averaged (1000) and the number of variables (mtry=9) randomly sampled as candidates at each split in each tree. The mtry parameter was varied and optimized using the ROC on the training set.[7.8]

Neural Network

We also tried a feed-forward neural network. Different feed forward neural network architectures were explored using the nnet and neuralnet packages.[9] We found optimal performance with one hidden layer containing 9 hidden neurons with a decay value 0.24 after initial exploration.

Model Comparisons

The CARET package was used for comparison of the mature models employing 10 folds and 3 repeats.[10] Other packages within R were used for different specific tasks (e.g., nnet for construction of the neural network, random forest (randomForest) for constructing random forests).[9,11-15] All numeric data were centered and scaled prior to analysis with all of the above methods. The R code used for these analyses is shown in appendix 1.

Training and Test Sets

In the first phase, we varied tuning parameters on a training subset with the CARET package. For the support vector machine, the sigma and c values were varied from 0.1 to 1. Once these parameters were optimized for the different methods, we used different seed values to split the training and testing sets (50% training:50% testing). We then employed the strategy of 3 repeats of the 10 folds with CARET on the different training subsets achieved varying the seed to initiate randomization to divide the set into training and testing subsets.

Results

A total of 72 patients underwent TAVR. One patient died before getting the assigned procedure. Transfemoral access was 88.9%(N=64), Transapical access was 11.1%(N=8). The characteristics of the patients at baseline are shown in Table 1. Valve types used are shown in Table 2.

Table 2: Valve types

Valve Type	Number
Sapien	38
Sapien XT	20
CoreValve	10
Sapein 3	4

Death and Stroke

Death rate from any cause at 12 months was 19.4%(N=14) of which 4(5.6%) died during index hospitalization and one (1.3%) at 30 days. Stroke incidence at 12 months was 8.3%(N=6) of which two patients (2.8%) had stroke during index hospitalization, no new cerebrovascular events at 30 days.
Major multivariate predictors of death from any cause at 12 months are presented in Table 3 and Figure 1. Comparison of those with and without early death (< 12 months) is shown in Table 4.

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Table 3: Mean and Standard Error of Mean (SEM) of Receiver Operator Curve (ROC) values utilizing different techniques. Top five predictor variables of death at 12 months.

Model AUC mean+/SEM	**RForest** 0.64+/0.02	**SVM** 0.57+/0.01	**Nnet** 0.59+/0.01	**Rpart** 0.51+/0.02	**GLM** 0.61+/0.03
Variables	Post.procedure. GFR [#]	Contrast. Vol [$]	Antiplatelet	Age	Pre. AVA [!!]
	Antiplatelet	Antiplatelet	Contrast. Vol [$]	Groin.Hematoma	Post-LBBB
	Contrast. Vol [$]	Post.pro.EF [%]	Hgb.pre **	Duration of hospitalization	Pre-LBBB
	Pre.Procedure. GFR[#]	Duration of hospitalization	Oxygen	Bl.transfusion	Contrast.Vol[$]
	Duration of hospitalization	NYHA.post[&&]	Anticoagulation	Hgb. Post **	PAD

[#] GFR; Glomerular Filtration rate
[$] Contrast. Vol; Contrast volume in ML
[%] Post.Pro.EF; Post procedure Ejection Fraction
[!!] AVA; Aortic Valve Area in CM^2
[&&] NYHA.Post; New York Heart Association Class
** Hgb Pre/Post; Hemoglobin Pre and Post procedure

Figure 1: Receiver operator curves (ROC) in one of the techniques showing sensitivity against specificity for generalized linear model (GLM)
– red color, area under curve (AUC) = 0.56, support vector machine (SVM)
– green color, AUC=0.63, neural network (NNet)
– orange color, AUC= 0.63, random forest (RFor)
– purple color, AUC= 0.63

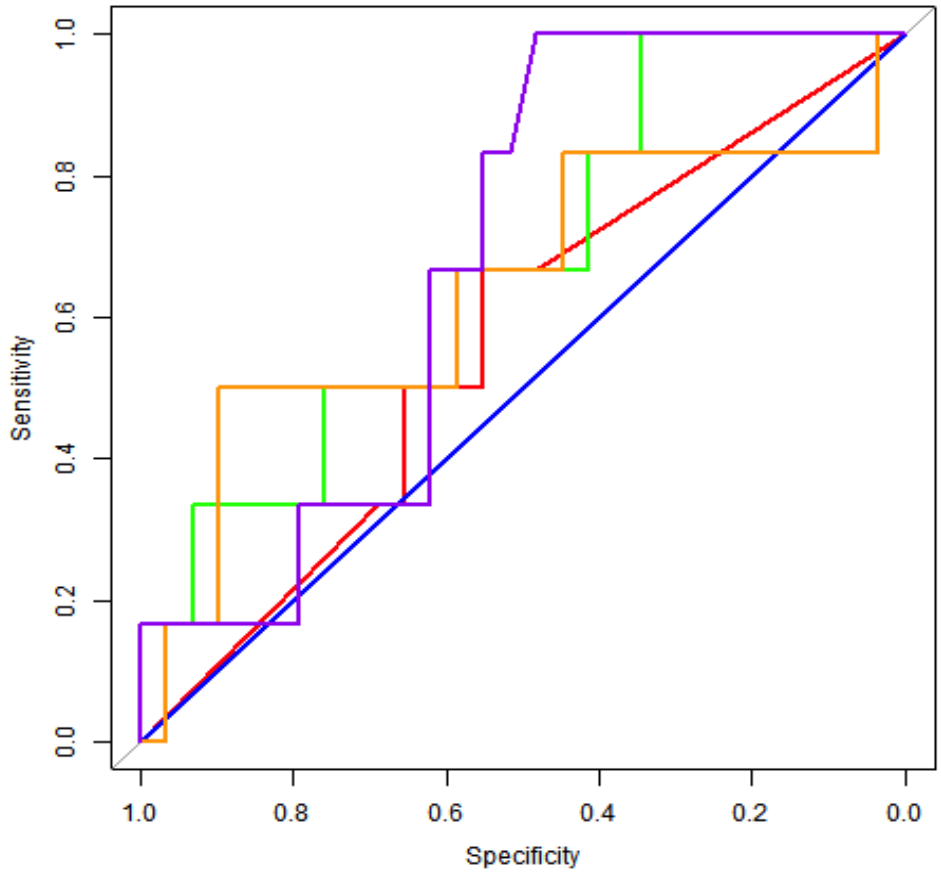

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Table 4: Comparison of those with and without early death (< 12 months)

Variable	**Death < 12 months (N=14)**	**Alive > 12 months (N=58)**	**P-value**
Age	81.9+/-8.2	80.2+/-8.9	NS
Gender	7M/7F	31M/27F	NS
DM	5	23	NS
HTN	14	57	NS
STS Score	0.11+/-0.10	0.10+/-0.05	NS
Coronary Arteries with Narrowing	0.93+/-1.27	0.86+/-0.98	NS
Prior PCI	2	18	NS
Prior CABG	3	17	NS
Coronary Intervention within 30 days prior	0	5	P<0.05
PAD	7	28	NS
Carotid Artery Stenosis	4	18	NS
Pre. PPM. AICD	4	9	NS
AVB 1st degree	3	12	NS
Pre-procedure. LBBB	0	4	NS
Post-procedure. LBBB	5	19	NS
New. PPM	2	3	NS
Pre-RBBB	4	9	NS
Pre-Atrial Fibrillation	2	14	NS
Post-Atrial Fibrillation	3	16	NS
Post procedure Aortic regurgitation grade	1.1+/-0.9	1.1+/-0.9	NS
COPD/Lung disease	8	45	NS
Oxygen treatment	6	14	NS
Pre-procedure GFR	47+/-26	59+/-22	NS
Post-procedure GFR	47+/-21	58+/-21	NS

Contrast (ml)	92+/-84	111+/-44	NS
Hemoglobin (Pre, gm/dl)	11.5+/-2.0	11.5+/-1.6	NS
Hemoglobin (Discharge, gm/dl)	9.9+/-0.6	10.5+/-1.2	NS
Platelets (Pre, x10^3/ul)	192+/-52	199+/-114	NS
Platelets (Discharge, x10^3/ul)	164+/-74	158+/-76	NS
Blood transfusion	7	17	NS
Sheath access	11	52	NS
Baseline EF (%)	49+/-15	48+/-11	NS
Post-procedure EF	55+/-14	52+/9	NS
Pre Aortic Valve Area (cm^2)	0.71+/-0.15	0.76+/-0.19	NS
Post Aortic Valve Area (cm^2)	2.12+/-0.45	2.55+/-2.29	NS
LVID Pre (mm)	45.1+/-8.4	46..8+/-7.3	NS
IVSD (mm)	13.3+/-2.1	12.4+/-2.8	NS
LVOT diameter (mm)	21.4+/-1.9	20.7+/-1.9	NS
LVOT area (mm^2)	35.8+/-6.6	33.6+/-6.1	NS
Mean gradient (pre, mmHg)	55.57143	50.0+/-11.6	NS
Mean gradient (post, mmHg)	14.2+/-8.7	9.9+/-4.1	NS
Mitral regurgitation (degree 0-4+)	1.64+/-1.21	1.60+/-1.05	NS
Mitral stenosis (N)	1	19	NS (p=0.054)
NYHA class (pre)	3.1+/-0.4	3.3+/-0.6	NS
NYHA class (post)	2.0+/-1.1	1.4+/-0.8	NS
Anticoagulation (N)	1	18	NS (p=0.068)
Antiplatelet (number of drugs)	1.2+/-0.9	1.6+/-0.6	P<0.05
Access site complication (N)	0	4	NS

Groin hematoma (N)	0	3	NS
Duration of hospitalization (days)	7.6+/-5.5	4.1+/-2.4	

Procedure outcomes

The procedure was aborted in one patient due to inability to pass the valve through transfemoral approach. Patient died before getting transapical approach. None of the patients required conversion to open surgical approach. A total of 5 (6.9%) patients required PCI at or within 30 days prior to the procedure. All transfemoral (88.9%, N=64) approach patients performed utilizing arterial cut down for sheath access. Combined access site complications rate was 5.6%(N=4). Major and minor access site hematoma rate was 4.2%(N=3). 33.3%(N=24) patients required at least 1 unit of red blood cell transfusion. Mean contrast volume was 108 milliliters.

Other clinical outcomes

There was a significant reduction in symptoms to New York Heart Association (NYHA) class I or II at follow up visits. There was a significant increase in Kansas City Cardiomyopathy Questionnaire (KCCQ) points at 30 days (P< 0. 02) and 12 months (P=<0.02) follow up. Mean KCCQ before TAVR was 29, which increased to 54 and 53 at 30 days and 1 year respectively. Mean post procedure GFR (55.9±23.2). Rate of new onset left bundle branch block (LBBB) was 27.7%(N=20). Five patients (6.9%)required new permanent pacemaker (PPM) placement. A total of 4(5.5%) patients developed new onset atrial fibrillation.

Echocardiographic data

Aortic Valve Area (AVA) showed a significant increase as compared to baseline (P= 0.000000001662, t=-6.9), with a mean post procedure AVA of (2.4 CM^2 ±2.0). There was a significant reduction in the mean gradient across aortic valve (P=< 0.022), average post procedure mean gradient (10.6 mmHg ± 5.3). Mean post procedure aortic regurgitation including paravalvular and valvular jets was mild. Ejection fraction showed improvement post intervention with mean value of 52% as compared to 48% pre-intervention relation to outcome are shown in Table 4.

Discussion

We evaluated the high-risk population who underwent TAVR at our institution at the very beginning of our TAVR program. Variable baseline risk factors and elevated pre-procedure Society of Thoracic Surgery (STS) risk score predict increased mortality.[16] Interestingly, in our study the three major predictors of mortality within twelve months were procedural related factors, however no statistical significance was noted possibly due to small sample size. Not surprisingly, two out of three elements were renal related. Acute Kidney Injury (AKI) is a frequently encountered complication post TAVR.[17, 18] Several predictors of AKI have been studied.[19] Pre existing chronic kidney disease, respiratory failure, blood transfusion, previous stroke, frequent intraprocedural valve reposition, periprocedural embolization, hemodynamic

instability associated with rapid pacing, and use of contrast medium were strong predictors for acute kidney injury.[18, 20]

In our study contrast media volume was a predictor for increased 12 months mortality. Nevertheless, limiting contrast use is a priority during TAVR; complexity of cases, however, may mandate the opposite. Interestingly, a meta-analysis of four cohort studies which included 891 TAVR patients did not show a significant association between contrast media volume and risk of AKI, [21] however the small number of the included studies is a limitation of the analysis. Thus further studies may be warranted to evaluate whether contrast media volume alone without AKI is a potential independent surrogate for increase mortality post TAVR. New onset AKI demonstrated worse short and long prognostic impacts among TAVR population. According to a meta-analysis of 5, 971 patients, post procedure AKI was associated with increased all cause and cardiovascular mortality early and at 12 months.[22] RenalGuard system utilizing furosemide induced diuresis with matched isotonic saline may be an effective tool in reducing incidence of post TAVR AKI.[23, 24]

Valve designs and procedural techniques have evolved significantly over the recent period. Lower valve profile has enhanced valve deliverability and reduced complications. Sheath size has decreased significantly from 24 French (Fr) to 14-16 Fr thus reducing the need for arterial cut down and access site complications. Moreover, addition of an external skirt to the balloon expandable valves (Sapien XT, Sapien 3) reduced paravalvular regurgitation.[25] In our sample only four patients demonstrated access site complications, however majority of the valves were early generation with higher profile and required arterial cut down in nearly all of the transfemoral cases. Despite using early generation valves in the majority of cases, the mean degree of paravalvular regurgitation was mild.

Thirty days and 12 months stokes rates were 2.8%(N=2), and 8.3%(N=6) respectively. Our 30 days rate is lower than results reported in large prospective cohorts (2.8% vs. 5% in the PARTNER trial), while our 12 months results are comparable (8.3 vs. 7.8).[3, 4] Neurological events post TAVR are classified as early within first 24-48 hours (procedural related), delayed between 2-30 days, and late after 30 days (patient and disease related factors).[26] Small aortic valve area, balloon post dilatation, and atrial fibrillation are associated with increased incidence of early cerebrovascular accidents (CVAs). Chronic atrial fibrillation, prior cerebrovascular disease, and transapical approach are some predictors of late CVAs.[27] Currently there is controversy about the benefit of embolic protection devices, however recent meta-analysis of randomized control trials demonstrated promising role in stroke reduction; future large studies may answer this question.[28]

Sedation technique during the procedure has evolved since the advent of TAVR. Initially the procedure was only done under general anesthesia, as is the case in our early sample. However, currently most of the TAVR in our institution are performed under conscious sedation. Hence ICU hours and cost of care have significantly reduced by using conscious sedation.[29] Finally, we have noticed that mono-antiplatelet therapy (MAPT) in our population was a strong predictor of increased 12 months mortality. The current consensus is utilizing heparin during the procedure and dual antiplatelet therapy (DAPT) for 6 months following the implantation of the valve.[30] Interestingly, a large meta-analysis showed conflicting results regarding dual versus single

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antiplatelet therapy.[31, 32] Analysis of nine studies, which included 7991 patients, demonstrated a significant reduction in mortality and a slight benefit in stroke prevention without increase in major bleeding, as compared to MAPT alone.[31] Addition of oral anticoagulation to MAPT did not show any benefit when it compared to DAPT in the same meta-analysis. However, another meta-analysis of six studies which included 840 patients showed increased bleeding risk with DAPT, with no reduction in mortality, stroke, or myocardial infarction.[32] Hence, despite its increasing use, the optimal antiplatelet management of patients undergoing TAVR remains uncertain. Given our small sample size, further multicenter studies are warranted to delineate the association between MAPT and mortality risk among TAVR population.

In conclusion, we found that post procedure GFR, less number of antiplatelet agents post procedure, and contrast volume may predict mortality within first 12 months post TAVR. Further studies focused on the above factors may be warranted.

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