Five-Meter Walk Test as a Predictor of Prolonged Index Hospitalization After Transcatheter Aortic Valve Implantation

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There are no studies evaluating comprehensive predictors of transcatheter aortic valve implantation (TAVI) outcomes encompassing frailty assessments in a South-East Asian cohort. In this longitudinal single-center cohort, all patients who underwent TAVI in a tertiary cardiac center and comprehensively assessed for frailty at baseline were included in a registry. The primary outcome was to investigate frailty indices predictive of prolonged index hospitalization after TAVI. Seventy-six patients with a mean age of 77.6 ± 8.5 years were included. Mean Society of Thoracic Society Predicted Risk of Mortality score was 5.2 ± 3.0, with 11 (14.5%) patients classified as high-risk (Society of Thoracic Society Predicted Risk of Mortality >8). Mean and median index hospitalization duration were 9.2 ± 5.6 and 7 [4.5 to 9.5] days, respectively. Univariate analysis demonstrated that lower hemoglobin (Hb) ($p < 0.01$), longer 5-meter walk test (5MWT) ($p < 0.01$), lower dominant hand grip strength ($p < 0.01$), the use of transaortic access ($p = 0.01$), new atrial fibrillation post-TAVI ($p < 0.01$), and lower postprocedural Hb ($p < 0.01$) were associated with longer index hospitalization duration. Multivariate linear regression demonstrated preoperative Hb, preoperative atrial fibrillation and 5MWT were independent baseline predictors of index hospitalization duration ($p < 0.05$). Additionally, a 5MWT cutoff of 11 seconds (0.45 m/s) had a high specificity (88.6%) in predicting prolonged index hospitalization duration. In conclusion, this is the first comprehensive frailty assessment in a South-East Asian cohort demonstrating 5MWT to be a significant predictor of prolonged index hospitalization. This simple and effective frailty assessment index may be considered to optimize patient selection for TAVI. **(Am J Cardiol 2020;132:100−105)**

Traditional risk assessment tools used to prognosticate patients undergoing transcatheter aortic valve implantation (TAVI) were based on the Society of Thoracic Surgeons − Postoperative Risk of Mortality (STS-PROM) score. Although these have been extensively validated for surgical aortic valve replacements (SAVR), it was neither intended nor formally validated in large patient cohorts for TAVI. Patient factors like frailty are not taken into consideration by surgical risk scores and a more holistic assessment is required to better prognosticate patients who underwent TAVI for optimal patient selection.[1,2] Although several studies have tried to incorporate a small component of frailty assessments to evaluate for predictors of outcomes post-TAVI,[3−15] there are no studies evaluating comprehensive predictors of TAVI outcomes encompassing frailty assessments in a South-East Asian (SEA) cohort. Singapore, being a multiracial nation in this region, serves as a good representation.[16] Accordingly, the aim of this study is to evaluate the utility of frailty assessments as a predictor of outcomes post-TAVI, in particular, the length of index hospitalization for TAVI procedure.

Methods

Since April 2016, all patients who underwent TAVI in a tertiary cardiac center were assessed comprehensively for frailty at baseline. These patients were included in a TAVI frailty registry (Centralised Institutional Review Board Reference 2014/2165). Patients assessed for baseline frailty between April 2016 and April 2018 were included in this prospective single-center cohort study.

All patients were assessed by our local heart valve team comprising cardiothoracic surgeons and cardiologists. Patients were assessed for suitability of SAVR, TAVI, balloon valvuloplasty or optimal medical therapy.

Patients selected for TAVI predominantly had severe AS, as defined according to American Heart Association/American

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College of Cardiology[17] and European Society of Cardiology[18] guidelines with transthoracic echocardiogram findings of aortic maximum velocity (Vmax) ≥4 m/s or mean pressure gradient ≥40 mm Hg. Patients with low-flow/low-gradient AS were also included with AVA ≤1.0 cm^2 with resting aortic Vmax <4 m/s or mean pressure gradient <40 mm Hg when found to have true AS after dobutamine stress echocardiogram or CT aortic valve calcium score.[17] Severity of symptoms were stratified using New York Heart Association.[19]

Frailty was objectively defined through various frailty indices. Cutoffs were based on the original intent of the indices and interpretations adopted or adapted from previous studies. For Body Mass Index (BMI), a cutoff of <18.5 kg/m^2, which classifies a patient as underweight, was considered frail.[20] For clinician based assessment of frailty, the Canadian Study of Health and Aging-Clinical Frailty Scale was used; a score of >4 was considered frail, as defined by the authors of the study and as adopted in other studies as well.[21,22] For Physical Self-Maintenance Scales, frailty was defined based on previous studies as a Lawton-Brody Instrumental Activities of Daily Living Scale of <7[15] and a Katz score of <6.[6,10,15] In terms of cognitive tests, a Mini-Mental State Examination score of <24, which is the cutoff for cognitive impairment[23], and the inability to complete a cognition clock test,[24] was defined as frail. For general frailty assessments, the use of mobility aids[25] and any falls within last 6 months[26] were also classified as frail. In terms of motor function, 5-meter walk test (5MWT) (seconds, s) and dominant hand grip strength (kilograms, kg) were evaluated as continuous variables, with increasing time for 5MWT and lower dominant hand grip strength defined as being frail.

The primary outcome was index hospitalization duration. Thirty-day mortality was not used as a study end point as there no mortality within thirty days for the study cohort.

Normally distributed continuous variables were expressed as mean ± standard deviation (SD). Non-normally distributed variables were expressed as median and interquartile range. Binomial data were analyzed using chi-square-tests, whereas continuous data were analyzed using independent *t* test. Multivariate linear regression was applied to study the association between the log transformation of index hospitalization duration and baseline characteristics that had p <0.10. Before statistical analyses were undertaken, the study protocol was fully developed. Cutoffs for frailty indices deemed significant were obtained using the Receiver Operating Characteristic curve based on Youden index. All statistical analyses were performed using IBM's Statistical Package for the Social Sciences Statistics Version 23.

Results

In total, 76 patients with a mean age of 77.6 ± 8.5 years were included. Figure 1 demonstrates the distribution of index hospitalization duration with most patients discharged within 7 days (59.2%). Of note, no patient in our cohort died within 30 days.

Table 1 shows the baseline characteristics of patients who underwent TAVI divided into 2 groups based on index hospitalization duration (≤7 days vs >7 days).

For all 76 patients who underwent TAVI, there were relatively equal numbers between genders (51.3% men).

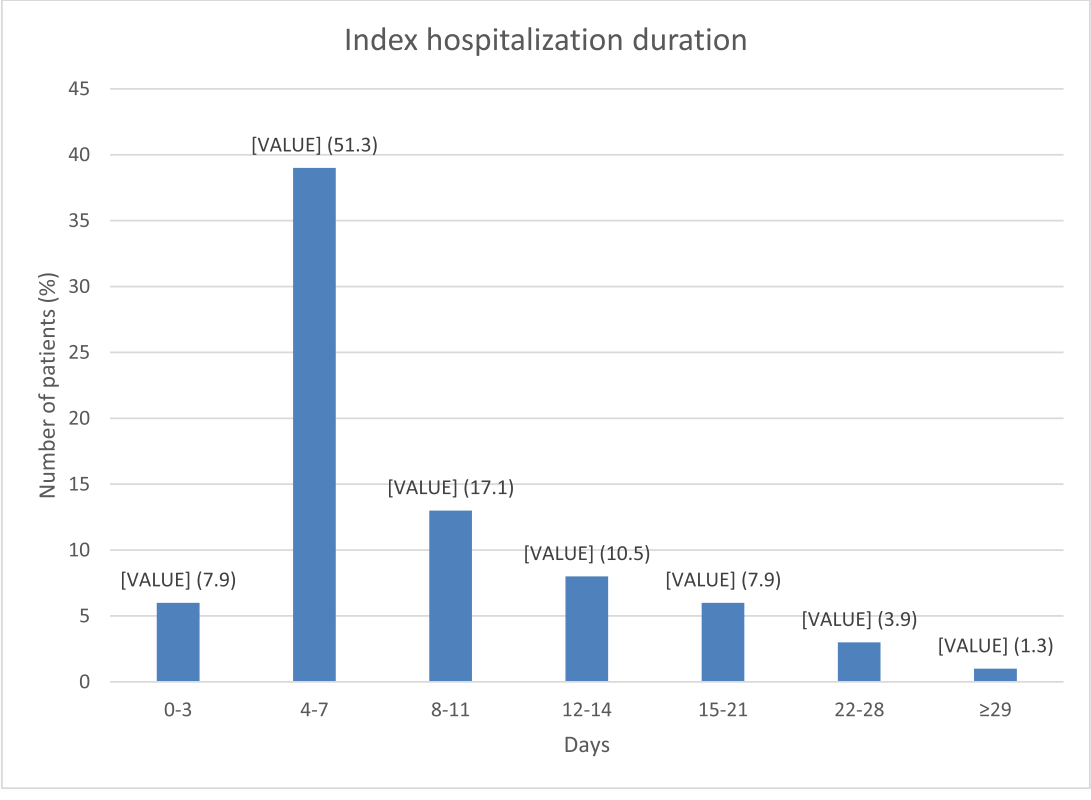

Figure 1. Distribution of index hospitalization duration of patients post-TAVI.

Table 1
Baseline characteristics of patients based on index hospitalization duration

Variable	Overall (N = 76)	Index hospitalization duration		p value
		≤7 days (N = 45)	>7 days (N = 31)	
Age (years), mean ± SD	77.6±8.5	78.0±9.1	77.0±7.6	0.59
Age >80years	33 (43.4%)	22 (48.9%)	11 (35.5%)	0.25
Men	39 (51.3%)	24 (53.3%)	15 (48.4%)	0.67
Hypertension	64 (84.2%)	40 (88.9%)	24 (77.4%)	0.18
Hyperlipidemia	61 (80.3%)	38 (84.4%)	23 (74.2%)	0.27
Coronary artery disease	45 (59.2%)	27 (60.0%)	19 (61.3%)	0.91
Stroke	9 (11.8%)	5 (11.1%)	4 (12.9%)	0.81
Hemoglobin (g/dL), mean ± SD	11.4±1.4	11.8±1.3	10.8±1.5	<0.01
Estimated mean ± SD glomerular filtration rate (mL/min/1.73m^2),	46.4±28.7	51.3±28.2	39.4±28.4	0.08
Obstructive pulmonary disease (asthma and chronic obstructive pulmonary disease)	7 (9.2%)	5 (11.1%)	2 (6.5%)	0.49
Atrial fibrillation	16 (21.1%)	6 (13.3%)	10 (32.3%)	0.05
Surgical of Thoracic Surgeons Predicted Risk of Mortality score, mean ± SD	5.2±3.0	5.3±3.4	5.1±2.3	0.75
Low <4%	34 (44.7%)	21 (46.7%)	13 (41.9%)	0.44
Intermediate 4-<8%	31 (40.8%)	16 (35.6%)	15 (48.4%)	
High >8%	11 (14.5%)	8 (17.8%)	3 (9.7%)	
New York Heart Association	0.35			
I/II, n (%)	51 (67.1%)	32 (71.1%)	19 (61.3%)	
III, n (%)	18 (23.7%)	11 (24.4%)	7 (22.6%)	
IV, n (%)	7 (9.2%)	2 (4.4%)	5 (16.1%)	
Frailty indices				
Body Mass Index (kg/m^2), mean ± SD	24.3±5.3	25.0±5.4	23.3±5.1	0.17
Body Mass Index <18.5 kg/m^2	11 (14.5%)	7 (15.6%)	4 (12.9%)	0.10
Clinical Frailty Score >4	21 (27.6%)	12 (26.7%)	9 (29.0%)	0.82
Lawton-Brody Scale <7	28 (36.8%)	14 (31.1%)	14 (45.2%)	0.21
Katz <6	10 (13.1%)	5 (11.1%)	5 (16.1%)	0.53
Mobility aids	30 (39.5%)	17 (37.8%)	13 (41.9%)	0.72
5-meter walk test (s)	8.5±5.7	6.9±3.7	11.0±7.3	<0.01
Dominant hand grip (kg), mean ± SD	18.3±6.5	20.0±6.1	15.8±6.4	<0.01
Cognition clock test (if unable to complete)	34 (44.7%)	22 (50.0%)	12 (38.7%)	0.33
Mini mental state examination <24	25 (32.9%)	13 (30.2%)	12 (38.7%)	0.45
Echocardiographic parameters				
Aortic mean pressure gradient (mm Hg), mean ± SD	48.4±12.9	48.7±11.3	48.0±15.1	0.81
Aortic mean pressure gradient >50 mm Hg	29 (38.2%)	19 (42.2%)	10 (32.3%)	0.38
Aortic valve area (cm^2), mean ± SD	0.7±0.2	0.7±0.2	0.7±0.1	0.80
Left ventricle ejection fraction (%), mean ± SD	54.1±13.2	53.6±13.4	54.7±13.2	0.73
LVEF <50%	26 (34.2%)	16 (35.6%)	10 (32.3%)	0.77
Pulmonary artery systolic pressure (mm Hg), mean ± SD	36.7±14.1	34.8±11.2	39.3±17.1	0.20
Pulmonary artery systolic pressure >40 mm Hg	22 (28.9%)	11 (28.2%)	11 (39.3%)	0.34
Mod-severe aortic regurgitation	24 (31.6%)	15 (33.3%)	9 (29.0%)	0.69
Mod-severe mitral regurgitation	16 (21.1%)	9 (20.0%)	7 (22.6%)	0.79

+ As stratified by PARTNER trial as outlined in supplementary table 1 and 2.

Comparing the 2 groups in Table 1 based on index hospitalization duration, most of the variables were similar and showed no significant difference. Of those with significant difference, lower hemoglobin (Hb) ($p < 0.01$), longer 5MWT ($p < 0.01$), lower dominant hand grip strength ($p < 0.01$) were associated with long index hospitalization duration. In particular, various frailty indices, including mean BMI, stratified Clinical Frailty Scale, Lawton-Brody Instrumental Activities of Daily Living Scale, Katz, use of mobility aids, cognition clock test, and a Mini-Mental State Examination did not show significant difference.

Table 2 shows intraprocedural and postprocedural characteristics of patients who underwent TAVI also divided based on index hospitalization duration (≤7 days vs >7 days).

Overall, a minority of patients required transaortic access (6.6%). In terms of valve type, Corevalves (65.8%) and Sapien valves (26.3%) form the majority. Comparing the 2 groups in Table 2 based on index hospitalization duration, the use of transaortic access ($p = 0.01$), new atrial fibrillation (AF) post-TAVI ($p < 0.01$) and lower postprocedural Hb ($p < 0.01$) were associated with long index hospitalization duration. Of note, there were no significant difference in length of stay based on valve types used.

As seen in Table 3, multivariate linear regression was applied to study the association between the log of index hospitalization duration and baseline characteristics with $p < 0.10$ which included preoperative Hb, preoperative estimated glomerular filtration rate, preoperative AF, BMI, 5MWT, and dominant hand grip strength. We also included the STS-PROM score in our analysis to confirm if this

Table 2
Procedural and postprocedural characteristics of patients based on index hospitalization duration

Variable	Overall (N = 76)	Index hospitalization duration		p value
		≤7 days (N = 45)	>7 days (N = 31)	
Intraprocedural characteristics				
Transaortic access	5 (6.6%)	0 (0.0%)	5 (16.1%)	0.01
Valve type	0.50			
Corevalve Evolut/Evolut R/Evolut Pro	50 (65.8%)	29 (64.4%)	21 (67.7%)	
SAPIEN XT or 3	20 (26.3%)	12 (26.7%)	8 (25.8%)	
LOTUS	1 (1.3%)	0 (0.0%)	1 (3.2%)	
PORTICO	5 (6.6%)	4 (8.9%)	1 (3.2%)	
Postprocedural characteristics				
New atrial fibrillation	5 (8.3%)	0 (0.0%)	5 (16.1%)	<0.01
Heart block requiring permanent pacemaker	5 (6.6%)	3 (6.7%)	2 (6.5%)	0.97
Hemoglobin (g/dL), mean ± SD	10.1±1.8	10.5±1.8	9.4±1.5	<0.01
Blood transfusion	5 (6.6%)	2 (4.4%)	3 (9.7%)	0.37
Acute kidney injury*	9 (11.8%)	7 (15.6%)	2 (6.5%)	0.23
Stroke	3 (3.9%)	1 (2.2%)	2 (6.5%)	0.35
Infection	2 (2.6%)	1 (2.2%)	1 (3.2%)	0.79
Delirium	2 (2.6%)	0 (0.0%)	2 (6.5%)	0.08

* AKI as defined by KDIGO criteria.

Table 3
Linear regression of baseline variables on index hospitalization duration

	Univariate		Multivariate	
	Beta	p value	Beta	p value
Hemoglobin	−0.33	<0.01	−0.34	<0.01
Estimated glomerular filtration rate	−0.22	0.06		
Atrial fibrillation	0.23	0.04	0.24	0.03
Body mass index	−0.27	0.02		
5 meter walk test	0.34	<0.01	0.29	0.02
Dominant hand grip strength	0.24	0.04		
Society of Thoracic Surgeons − Predicted Risk of Mortality score	0.06	0.60		

prognostic score was a significant predictor. Multivariate analysis showed that preoperative Hb, preoperative AF, and 5MWT were independent predictors of index hospitalization duration ($p < 0.05$). Notably, STS-PROM score was not significant.

The mean gait speed in our cohort was 1.70 ± 1.14 ms^{-1}. A 5MWT cutoff of 11 seconds (0.45 ms^{-1}) had a Youden index of 0.279, with a sensitivity of 39.3% and a specificity of 88.6% for predicting prolonged index hospitalization stay defined as more than 7 days. With a prevalence of 38.9% in our cohort defined as frail, the positive predictive value was 68.8% and the negative predictive value was 69.6%.

Discussion

Our single-center prospective cohort study demonstrated that among a comprehensive battery of frailty assessments, longer 5MWT significantly predicted prolonged index TAVI hospitalization duration. Multivariate linear regression analysis confirmed 5MWT to independently identify patients with prolonged index TAVI hospitalization when additional baseline characteristics and frailty indices were considered. A cutoff of 11 seconds had higher specificity in predicting for prolonged hospitalization duration. This is a simple and unbiased objective test that can be utilized to assess a patient's frailty and index hospitalization post-TAVI.

Comparing our cohort to other salient studies, the mean and median index hospitalization duration were 9.2 ± 5.6 and 7 [4.5 to 9.5] days respectively in our patients was similar to other studies.[27–29] Among limited studies evaluating index hospitalization post-TAVI, van Mourik et al[27] demonstrated in their single-center study that lower Metabolic Equivalent Score and lower diastolic blood pressure were associated with prolonged index hospitalization duration. In a larger multi-center study, Arbel et al[28] showed that older age and atrial fibrillation (AF) were associated with longer index hospitalization duration, whereas lower New York Heart Association class, higher left ventricle ejection fraction and higher mean aortic gradients were associated with shorter index hospitalization duration. Although our patient cohort also had pre-existing AF as an independent predictor of long index hospitalization stay, the other variables did not show significant difference in index hospitalization duration. Notably, these studies did not include any markers of frailty in their analysis. This suggests that a frailty index like 5MWT could be a more precise predictor.

Comparing our cut-off 5MWT to other studies, our cohort had a significantly higher mean gait speed of 1.70 ms^{-1} as compared to the mean gait speed of 1.05 ms^{-1} in Wilson et

al.[25] However, the cutoff for frailty was significantly lower than the gait speed of 0.8 ms^{-1} proposed by the International Academy on Nutrition and Aging task force through a systematic review as a predictor of adverse outcomes in the elderly.[30] These differences suggest that the SEA cohort of patients with severe symptomatic aortic stenosis represent a unique cohort from the archetypal predominantly Caucasian group, and typical cutoffs for frailty indices, like gait speed, cannot be applied sweepingly.

Even more limited are studies that include frailty assessments as part of their evaluation. In a study by Frei et al[29] who set out to identify baseline and periprocedural variables affecting hospital index hospitalization duration, they demonstrated that gait speed and serum C-reactive protein were independent predictors of index hospitalization duration post-TAVI. Nonetheless, this study limited their frailty indices to gait speed only. As a secondary end point, Chauhan et al[11] demonstrated in their composite frailty index score of 15-ft walk test, Katz index, preoperative serum albumin, and dominant handgrip strength that patients classified as frail had increased index hospitalization duration. This study differs from ours, as our data demonstrated 5MWT to be an independent predictor of index hospitalization duration without the need to incorporate other markers of frailty.

Various other studies have sought to utilize different components of a frailty assessments in identifying predictors of 1-year mortality. Among the larger studies, Green et al demonstrated in a composite frailty score of serum albumin, grip strength, gait speed, and Katz index associated with 1-year all-cause mortality.[7] Similarly, Shimura et al[9] also identified albumin, gait speed (15 feet), and grip strength as markers of frailty predictive of 1-year mortality. Due to no 30-day mortality and low 1-year mortality rate in our center, our data have not been powered to evaluate mortality as a meaningful end point; this would be an end point that we hope to evaluate in future. Our study also suggests that STS-PROM score may not necessarily be useful in predicting outcomes, especially index hospitalization duration, post-TAVI. TAVI-specific mortality scoring systems have been created but not validated in large patient cohorts.[3,4,31] However, these scores rarely incorporate frailty indices, with none incorporating the 5MWT as part of the assessment. For a more holistic assessment, it might be useful to consider including the 5MWT in the evaluation of patients as part of the pre-TAVI assessment.

Limitations inherent in our nonrandomized noncontrolled prospective observational single-center study are the lack of a comparison patient cohort undergoing SAVR, balloon valvuloplasty or optimal medical therapy. Additionally, it appears that the dominant hand grip strength criteria used by the PARTNER trial may not necessarily be applicable in the SEA cohort to determine frailty, which suggests more trials may need to be done to determine the best method for better delineation. Further, systematic selection and allocation bias cannot be excluded. Nevertheless, given the comprehensive and timely collection of follow-up data, the results are still robust for this prospective study. These results are also highly relevant and representative for a SEA cohort not investigated before. With the inclusion of more extensive parameters and higher patient numbers, we also aim to explore a proposed risk score with external validation as an extension to this study.

In conclusion, this is the first comprehensive frailty assessment in a SEA cohort demonstrating 5MWT to be a significant predictor of prolonged index hospitalization.

CRediT author statement

Ji Quan Samuel Koh: conceptualization, methodology, formal analysis, investigation, writing - original draft, writing - review & editing, visualization, project administration. **Nadiah Bte Mohamed Rahim**: methodology, investigation. **E Lynn Sng**: methodology, investigation. **Liang Zhong**: methodology, formal analysis. **Nishanth Thiagarajan**: writing - review & editing. **Soo Teik Lim**: writing - review & editing, **See Hooi Ewe**: writing - review & editing, **Victor Chao**: writing - review & editing, **Kay Woon Ho**: conceptualization, methodology, formal analysis, writing - review & editing, visualization, project administration

Impact on daily practice

5MWT is a simple yet effective frailty assessment index that may be considered to optimize patient selection for TAVI.

Disclosures

Dr Kay Woon Ho - Proctor for Medtronic.

The rest of authors have no conflicts of interest to declare.

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