ORIGINAL ARTICLE

Valvular Heart Disease

Impact of Frailty Markers for Unplanned Hospital Readmission Following Transcatheter Aortic Valve Implantation

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Background: Various frailty markers have been developed to guide better patient selection for transcatheter aortic valve implantation (TAVI). This study aimed to investigate the frequency and specific causes of unplanned hospital readmission after TAVI, and to investigate which frailty markers better predicted outcomes.

Methods and Results: We retrospectively reviewed 155 patients for whom we calculated their Short Physical-Performance Battery (SPPB), Placement of AoRTic TraNscathetER Valve (PARTNER) frailty scale, frailty index, clinical frailty scale, modified Fried scale, and gait speed. The primary endpoint was unplanned readmission following TAVI. The clinical model was established using variables that were identified as independent predictors in multivariate analysis. Incremental values were assessed after adding each frailty marker to the clinical model, and were compared between frailty markers. Although unplanned readmission <30 days was 1.9%, 23% of patients had an unplanned readmission following TAVI mainly because of heart failure and pneumonia within 1 year. Frailty markers other than the modified Fried scale were independently associated with unplanned readmission. The SPPB and the PARTNER frailty scale significantly increased discriminatory performance for predicting unplanned readmission.

Conclusions: Unplanned readmissions following TAVI in the present study were fewer than previously reported. There seems to be a difference between frailty markers in their predictive performance. Precise frailty assessment may result in reducing unplanned admissions after TAVI and therefore better quality of life.

Key Words: Clinical frailty scale; Gait speed; Modified Fried scale; Transcatheter aortic valve replacement (TAVR)

railty has become a major theme in cardiovascular diseases because of the aging population and the increasingly complex nature of patients.¹ Over the last decades, transcatheter aortic valve implantation (TAVI) has emerged as a less invasive alternative to surgical valve replacement. Although there is a tremendous survival advantage and symptom benefit for many patients undergoing TAVI compared with medical therapy, some patients have died soon after the procedure.²-3 Recently, various frailty markers have been developed to guide better patient selection for TAVI.4-12

Reducing readmission has been targeted as a top strategic priority in an effort to improve patient care and decrease costs, and the additional costs associated with such a high readmission rate may lead some to question the procedural cost-effectiveness.¹³ The association between frailty and unplanned readmission has been recently reported in surgical patients.¹⁴ However, no studies have compared their utility for predicting unplanned readmission following TAVI,

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and data for the Japanese population are scarce.

The purpose of this study was to investigate the frequency, and specific causes of unplanned hospital readmission after the initial hospitalization for TAVI, and to investigate which frailty markers better predict unplanned readmission.

Methods

Study Population

The study population comprised 172 patients with severe aortic stenosis who underwent TAVI at the Sakakibara Heart Institute between November 2013 and July 2016; 155 of them (90%) had sufficient data to allow for comprehensive frailty assessment. The treatment was initially determined according to the following: (1) presence of

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| Table 1. Baseline Patients' Characteristics | | | | |
|---|--------------------|--|--|--|
| Characteristic | Overall (n=155) | | | |
| Age, years | 85 (82, 88) | | | |
| Women, % | 99 (65) | | | |
| Body mass index (kg/m²) | 21.0 (18.4, 24.2) | | | |
| NYHA classification III/IV, % | 81 (53) | | | |
| STS score, % | 6.0 (4.7, 8.2) | | | |
| Frailty markers | | | | |
| SPPB (0-12) | 10 (6, 12) | | | |
| PARTNER frailty scale (0–12) | 7 (5, 9) | | | |
| Frailty index (Japan) (0-15) | 4 (2, 5) | | | |
| Clinical frailty scale (1-9) | 4 (3, 5) | | | |
| Modified Fried Scale (0-4) | 2 (2, 3) | | | |
| Gait speed, m/s | 0.7 (0.5, 0.9) | | | |
| Diabetes mellitus, % | 38 (25) | | | |
| Hypertension, % | 124 (82) | | | |
| Dyslipidemia, % | 91 (60) | | | |
| Previous myocardial infarction, % | 12 (7.9) | | | |
| Previous bypass surgery, % | 20 (13) | | | |
| Peripheral artery disease, % | 36 (23) | | | |
| Previous stroke, % | 16 (10) | | | |
| Previous pacemaker implantation, % | 7 (4.6) | | | |
| Atrial fibrillation, % | 36 (23) | | | |
| COPD (moderate/severe), % | 12 (7.9) | | | |
| Hemoglobin level, g/dL | 11.2 (10.4, 12.3) | | | |
| eGFR, mL/min/1.73 m ² | 51±15 | | | |
| Albumin level, g/dL | 3.8 (3.4, 4.0) | | | |
| Ejection fraction, % | 62 (56, 65) | | | |
| Aortic valve area, cm ² | 0.64±0.14 | | | |
| Mean gradient, mmHg | 54±16 | | | |
| MR (moderate/severe) | 6 (3.8) | | | |
| Pulmonary artery pressure, mmHg | 26 (21, 31) | | | |

Values are mean±SD, n (%) or median (interquartile range). COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; MR, mitral regurgitation; NYHA, New York Heart Association; PARTNER, Placement of AoRTic TraNsathetER; SPPB, Short Physical-Performance Battery; STS, Society of Thoracic Surgeons.

symptoms; (2) degenerative aortic stenosis with New York Heart Association (NYHA) classification ≥II; (3); a mean gradient >40 mmHg or jet velocity >4.0 m/s; or (4) aortic valve area <1 cm² (0.6 cm²/m²). All cases were reviewed by a multidisciplinary team consisting of cardiac surgeons, interventional cardiologists, and imaging specialists, and patients were deemed to be high-risk or inoperable. Exclusion criteria were: (1) bicuspid or non-calcified aortic valve; (2) failed surgical bioprosthesis implantation; (3) severe aortic regurgitation; or (4) patient on dialysis. The Society of Thoracic Surgeons (STS) risk score for predicted risk of death was calculated for each patient. The institutional review board approved the study. All information was retrospectively obtained from patients' medical records or by telephone interview, so there was follow-up and accounting of all patients.

Frailty Assessment

Participants were instructed to walk at a comfortable pace in a well-lit, unobstructed hallway for a distance of 5 m. Patients were permitted to use assist devices such as walkers and canes. Gait speed was calculated by dividing 5 m by the time needed to walk this distance in seconds. Patients repeated the walk 3 times, if possible, and their mean speed was calculated. Patients unable to walk the distance because of shortness of breath or desaturation at rest were recorded as having a gait speed of 0 m/s.⁴

The Short Physical-Performance Battery (SPPB) was derived from a 4-m walking velocity, time to rise from a seated position 5 times, and standing balance. 15 Walking velocity was measured with a 4-m walk performed at the patient's 'usual' pace. Participants were allowed to use canes or walkers. Participants sat in a straight-backed chair with arms folded across their chest and stood up 5 times consecutively as quickly as possible. Time to complete 5 chair rises was measured. Participants were asked to hold 3 increasingly difficult standing positions for 10s each: the side-by-side stand, semi-tandem stand (standing with feet parallel and the heel of 1 foot touching the base of the 1st toe of the opposite foot), and the full-tandem stand (standing with 1 foot directly in front of the other). Individuals received a 0 score for each task they are unable to complete. Scores from 0 to 4 were assigned for remaining tasks, according to established methods. Scores were summed to obtain the SPPB, ranging from 0 to 12, with higher scores reflecting better physical function. A SPPB score ≤5 indicates that the patient is frail.

The modified Fried frailty scale was defined from 4 domains as previously reported, ranging from 0 to 4 with higher scores reflecting greater frailty. Weakness and slow gait speed were respectively defined using the best handgrip strength valve and the best-timed walk over 5-m at the patient's usual pace, stratified by sex and body size. Low physical activity was defined using the Katz index of activities in daily living. In our study, unintentional weight loss was defined as a self-reported unintentional weight loss >3 kg over the preceding 6 months.

Placement of the AoRTic TraNscathetER Valve (PARTNER) frailty scale was defined from 4 domains as previously reported, ranging from 0 to 12, with higher scores reflecting greater frailty.⁴

The clinical frailty scale was completed based on the patient's functional status as previously described, ranging from 1 to 9 with higher scores reflecting greater frailty.⁷

The frailty index, called the Kaigo-Yobo Checklist, is known as a marker of frailty and is widely used particularly in Japan. It comprises 15 easy-to-answer questions, ranging from 0 to 15 with higher scores reflecting greater frailty (**Table S1**).¹⁶

Endpoint and Other Criteria

The primary endpoint was all-cause (cardiac and non-cardiac) unplanned hospital readmission following TAVI. Echocardiographic findings were analyzed by full-time academic echocardiographers using ACC/AHA guidelines. Procedural complications were defined according to the Valve Academic Research Consortium-2 Criteria.¹⁷ Device success was defined as the absence of procedural death, correct positioning of a single prosthetic valve, and intended performance of the prosthetic valve. The complications at 30 days included all-cause death, all stroke, life-threatening bleeding, acute kidney injury (AKIN, stage 2 or 3), coronary obstruction requiring intervention, major vascular complications, and valve-related dysfunction requiring a repeat procedure. TAVI was performed as previously described.²

| Table 2. Procedural Outcomes | |
|--|--------------------|
| Outcome | Overall (n=155) |
| Transfemoral approach, % | 115 (74) |
| Device | |
| SAPIEN XT 20 mm, % | 4 (2.5) |
| SAPIEN XT 23 mm, % | 84 (54) |
| SAPIEN XT 26 mm, % | 39 (25) |
| SAPIEN XT 29 mm, % | 3 (1.9) |
| SAPIEN 3 23 mm, % | 8 (5.1) |
| SAPIEN 3 26 mm, % | 4 (2.5) |
| CoreValve 26 mm, % | 6 (3.8) |
| CoreValve 29 mm, % | 7 (4.5) |
| Procedure time, min | 103 (75, 130) |
| Radiation time, min | 20 (16, 26) |
| Contrast media, mL | 97 (80, 126) |
| Length of stay after TAVI, days | 11 (9, 17) |
| Device success, % | 143 (92) |
| Early safety at 30 days, % | 139 (90) |
| Death, % | 2 (1.2) |
| All stroke, % | 4 (2.5) |
| Life-threatening bleeding, % | 5 (3.2) |
| Acute kidney injury (AKIN stage 2 or 3), % | 3 (1.9) |
| Coronary obstruction requiring intervention, % | 0 (0) |
| Major vascular complication, % | 17 (11) |

Values are mean±SD, n (%) or median (interquartile range). TAVI, transcatheter aortic valve implantation.

Readmission was defined as admission to a hospital ward or an intensive care unit following discharge after the index hospitalization for TAVI. The primary diagnosis on the discharge report was used to determine the main cause of readmission. Planned readmission was defined as either readmission for a few specific conditions or elective procedure categories (percutaneous coronary intervention, endovascular treatment, orthopedic surgery, and gastrointestinal surgery) or readmission for which the principal diagnosis was not an acute condition or a complication of care. Readmission not meeting either criterion was categorized as unplanned. Causes of readmission were grouped as being of cardiac or noncardiac origin. Cardiac causes included heart failure, arrhythmia, acute coronary syndrome, prosthesis related (endocarditis and valve thrombosis) and aortic dissection. Noncardiac causes included infection (respiratory, urinary tract, gastrointestinal, and other), trauma, anemia, ischemic stroke, bleeding, acute renal failure, and other conditions (e.g., dehydration, hyperkalemia, anaphylactic shock).¹³

Statistical Analysis

Continuous variables are expressed as the mean±standard deviation or median with interquartile range, and categorical variables as the number and percentage. Normality of distribution for continuous variables was tested using the Shapiro-Wilk test. A 2-sided P-value <0.05 was considered statistically significant. To determine the influence on the relationship between outcomes, variables (shown in **Table 1**) with P-values <0.25 in the univariate analysis were entered into the multivariate Cox regression analysis. In the sensitivity analysis, post-procedural variables (device

| Table 3. Causes of Unplanned Readmission | on |
|--|-------------------------------|
| Follow-up, days | Overall (n=155) 479±319 |
| All-cause unplanned readmission | 64 (41) |
| Unplanned readmission <30 days | 3 (1.9) |
| Cardiac causes | 27 |
| Heart failure | 16/27 (59) |
| Arrhythmia | 5/27 (18) |
| Tachycardia | 3 |
| Bradycardia | 2 |
| Angina pectoris | 1/27 (3.7) |
| Endocarditis | 3/27 (11) |
| Left ventricular thrombus | 1/27 (3.7) |
| Aortic dissection | 1/27 (3.7) |
| Noncardiac causes | 37 |
| Infection | 21/37 (56) |
| Pneumonia | 11 |
| Urinary tract infection | 2 |
| Gastrointestinal infection | 3 |
| Upper respiratory infection | 3 |
| Other infection | 2 |
| Trauma | 5/37 (13) |
| Fall | 1 |
| Fracture | 4 |
| Anemia | 3/27 (8.1) |
| Cerebrovascular event | 2/37 (5.4) |
| Access site bleeding complication | 1/37 (2.7) |
| Renal failure | 2/37 (5.4) |
| Other (dehydration, hyperkalemia, anaphylaxis shock) | 3/37 (8.1) |

Values are n (%).

success and early safety), which can affect the primary endpoint, were included in the multivariate analysis. Receiver-operating characteristic (ROC) analysis was performed using unplanned readmission at 1 year and allcause death at 1 year (n=133), and the area under the curve was compared using the Delong method. In the analysis for the primary endpoint (unplanned readmission), we established a clinical model consisting of variables that were identified as independent predictors in multivariate analysis: NYHA classification, STS score, atrial fibrillation, chronic obstructive pulmonary disease (COPD), and hemoglobin and albumin levels. Incremental values were assessed after adding each frailty marker to the clinical model, and compared between frailty markers. On the other hand, because there was a small number of patients who died during this study, discriminatory performance for all-cause death was adjusted using 2 important variables (age and sex). Incremental values were assessed after adding each frailty marker to this model, and compared between frailty markers. All analyses were performed using SPSS version 22.0 (IBM, Armonk, NY, USA) and R version 2.13 (R Foundation for Statistical Computing).

Results

Overall Outcomes After TAVI

Patients' demographic and clinical characteristics at baseline

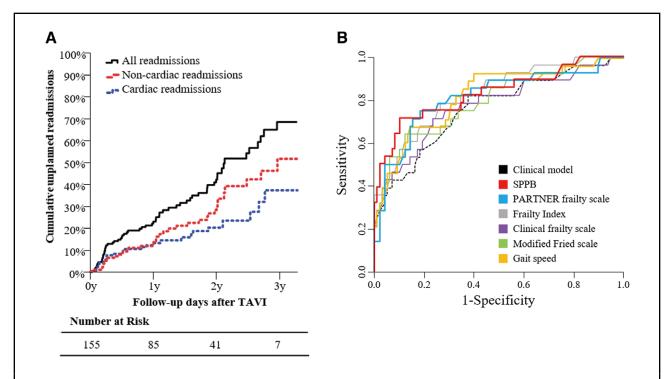


Figure. (A) Kaplan-Meier curves for unplanned readmissions, which were 23±3% at 1 year, 43±4% at 2 years, and 69±6% at 3 years (solid black line). (B) Receiver-operating characteristic (ROC) analysis for unplanned readmission. Each frailty scale was added to the clinical model. The ROC curve demonstrates that the Short Physical-Performance Battery (SPPB) and the Placement of AoRTic TraNscathetER Valve (PARTNER) frailty scale had significantly increased discriminatory performance for predicting unplanned readmission.

are shown in **Table 1**. Mean age was 84±5.8 years (median, 85 years). Death at 30 days after TAVI was 1.2% (same patient is described as a death in the early-safety section in **Table 2**) with a mean STS score of 7.3±5.1% (median, 6.0%). Length of stay after TAVI was 14±10 days (median, 11 days), and 144 of 155 patients (92%) were discharged to home. Other procedural outcomes are shown in **Table 2**.

Table 3 demonstrates the causes of unplanned admission following TAVI. With 479±319 days observation period, 64 (41%) patients had an unplanned readmission following TAVI. Only 3 patients (1.9%) had an unplanned readmission less than 30 days after TAVI. Of 64 admissions, 27 were for cardiac causes, and 37 were noncardiac causes. Of the 27 admissions with a cardiac cause, 16 (59%) were heart failure, while of the 37 admissions with a noncardiac cause, 21 (56%) were infections. Of the 22 planned readmissions, 7 were for percutaneous coronary intervention, 2 for endovascular treatment, 7 for orthopedic surgery, for treatment for malignancy (1 multiple myeloma, 1 renal cell carcinoma, 1 pancreatic cancer, and 2 lung cancer) and 1 for cataract surgery. Note that of the 64 patients, 11 (17.1%) had more than 2 unplanned readmissions.

Figure A demonstrates the unplanned readmission rate following TAVI for cardiac and noncardiac causes in a Kaplan-Meier analysis. Total unplanned readmission rates were 23±3% at 1 year, 43±4% at 2 years, and 69±6% at 3 years.

Association Between Primary Endpoint and Clinical Characteristics

By univariate analysis of the baseline variables (shown in

Table 1), NYHA classification, STS score, dyslipidemia, previous bypass surgery, peripheral artery disease, atrial fibrillation, COPD, hemoglobin level, estimated glomerular filtration rate, albumin level, ejection fraction, and mitral regurgitation were significantly associated with unplanned readmission (Table 4). These variables were entered into the multivariate Cox regression analysis, whereas all the frailty markers were significantly associated with unplanned readmission in the univariate analysis and were entered into the multivariate model one by one. The analysis found that the SPPB, the PARTNER frailty scale, the frailty index, the clinical frailty scale and the gait speed were independently associated with unplanned readmission even after adjustment in the multivariate analysis. The modified Fried scale had a trend towards an association with unplanned readmission (Table 5). Other associated variables are shown in **Table 4**.

In the sensitivity analysis, post-procedural variables, device success (hazard ratio 1.29, 95% confidence interval 0.46–3.59, P=0.616) and early safety (hazard ratio 0.91, 95% confidence interval 0.48–1.71, P=0.770) were entered into multivariate model with variables with P<0.25 (**Table 3**). The result did not differ in the analysis.

ROC Analysis

The SPPB and the PARTNER frailty scale significantly increased the discriminatory performance for predicting unplanned readmission if they were entered in the clinical model (**Table 6**, **Figure B**). Furthermore, if each frailty marker was added to the model consisting of age and sex for predicting all-cause death, the SPPB, the PARTNER

| Parameters | HR | 95% CI | P value | Adjusted HR | 95% CI | P value |
|--|------|-----------|---------|----------------|-----------|---------|
| Age (every 10-year increase) | 0.90 | 0.59-1.37 | 0.640 | | | |
| Women | 0.83 | 0.49-1.40 | 0.501 | | | |
| Body mass index (<20 kg/m² decrease) | 1.05 | 0.74-1.48 | 0.766 | | | |
| NYHA classification (every degree increase) | 2.28 | 1.54-3.37 | < 0.001 | 1.62 | 1.08-2.44 | 0.019 |
| STS score (every 4% increase) | 1.72 | 1.35-2.19 | < 0.001 | 1.59 | 1.18-2.13 | 0.002 |
| Diabetes mellitus | 1.33 | 0.96-2.33 | 0.317 | | | |
| Hypertension | 1.19 | 0.63-2.24 | 0.577 | | | |
| Dyslipidemia | 0.64 | 0.38-1.06 | 0.080 | | | |
| Previous myocardial infarction | 0.79 | 0.24-2.56 | 0.706 | | | |
| Previous bypass surgery | 0.46 | 0.18-1.16 | 0.103 | | | |
| Peripheral artery disease | 1.39 | 0.79-2.45 | 0.248 | | | |
| Previous stroke | 0.84 | 0.36-1.97 | 0.700 | | | |
| Previous pacemaker implantation | 0.79 | 0.19-3.26 | 0.752 | | | |
| Atrial fibrillation | 1.87 | 1.10-3.18 | 0.019 | 2.49 | 1.41-4.40 | 0.002 |
| COPD (moderate/severe) | 4.79 | 2.39-9.59 | < 0.001 | 7.71 | 3.50-16.9 | < 0.001 |
| Hemoglobin level (<11 g/dL) | 1.98 | 1.19-3.31 | 0.009 | 1.93 | 1.14-3.28 | 0.014 |
| eGFR (every 15 mL/min/1.73 m² decrease) | 1.33 | 0.99-1.79 | 0.057 | | | |
| Albumin level (<3.5 g/dL) | 2.32 | 1.40-3.84 | 0.001 | 2.03 | 1.17-3.55 | 0.012 |
| Ejection fraction (every 10% decrease) | 1.25 | 0.96-1.65 | 0.095 | | | |
| Aortic valve area (every 0.1 cm ² increase) | 1.07 | 0.98-1.47 | 0.648 | | | |
| Mean pressure gradient (every 10-mmHg decrease) | 0.97 | 0.82-1.15 | 0.781 | | | |
| MR (every degree increase) | 1.47 | 1.02-2.12 | 0.038 | | | |
| Pulmonary artery pressure (>40 mmHg) | 1.33 | 0.63-2.80 | 0.446 | | | |
| Transfemoral approach | 1.26 | 0.69-2.30 | 0.445 | | | |
| SAPIEN XT vs. CoreValve vs. SAPIEN 3 | 0.95 | 0.63-1.44 | 0.822 | | | |

 $\mbox{CI},$ confidence interval; HR, hazard ratio. Other abbreviations as in Table 1.

| Table 5. Adjusted HR of Each Frailty Marker | | | |
|---|----------------|-----------|---------|
| Frailty marker | Adjusted HR | 95% CI | P value |
| SPPB (every 1 point decrease) | 1.10 | 1.03-1.18 | 0.005 |
| PARTNER frailty scale (every 1 point increase) | 1.20 | 1.08-1.34 | 0.001 |
| Frailty index (every 1 point increase) | 1.28 | 1.15-1.43 | < 0.001 |
| Gait speed (every 0.1 m/s decrease) | 1.18 | 1.20-1.30 | 0.001 |
| Modified Fried scale (every 1 point increase) | - | - | 0.067 |
| Clinical frailty scale (every 1 point increase) | 1.68 | 1.13–2.50 | 0.010 |

Abbreviations as in Tables 1,4.

| Table 6. Incremental AUC of Frailty Markers for Unplanned Readmission | | | | |
|---|------|-----------|--------------|---------|
| Frailty parameter | AUC | 95% CI | Δ AUC | P value |
| Clinical model | 0.76 | 0.65-0.87 | - | _ |
| +SPPB (every 1 point decrease) | 0.83 | 0.73-0.92 | +0.07 | 0.021 |
| +PARTNER frailty scale (every 1 point increase) | 0.81 | 0.71-0.97 | +0.05 | 0.050 |
| +Frailty index (every 1 point increase) | 0.82 | 0.73-0.91 | +0.06 | 0.058 |
| +Clinical frailty scale (every 1 point increase) | 0.77 | 0.66-0.88 | +0.01 | 0.354 |
| +Modified Fried scale (every 1 point increase) | 0.79 | 0.69-0.89 | +0.03 | 0.293 |
| +Gait speed (every 0.1 m/s decrease) | 0.82 | 0.73-0.91 | +0.06 | 0.075 |

AUC, area under the curve. Other abbreviations as in Tables 1,4.

| Table 7. Incremental AUC of Frailty Markers for All-Cause Death | | | | |
|---|------|-----------|--------------|---------|
| Frailty parameter | AUC | 95% CI | Δ AUC | P value |
| Age+Sex | 0.66 | 0.49-0.83 | _ | _ |
| Age+Sex+SPPB (every 1 point decrease) | 0.90 | 0.83-0.98 | +0.24 | 0.012 |
| Age+Sex+PARTNER frailty scale (every 1 point increase) | 0.87 | 0.80-0.94 | +0.21 | 0.025 |
| Age+Sex+Frailty index (every 1 point increase) | 0.90 | 0.82-0.97 | +0.24 | 0.003 |
| Age+Sex+Clinical frailty scale (every 1 point increase) | 0.85 | 0.74-0.95 | +0.19 | 0.051 |
| Age+Sex+Modified Fried scale (every 1 point increase) | 0.84 | 0.68-0.99 | +0.18 | 0.051 |
| Age+Sex+Gait speed (every 0.1 m/s decrease) | 0.83 | 0.70-0.95 | +0.17 | 0.053 |

Abbreviations as in Tables 1,4,6.

frailty scale and the Frailty Index significantly increased discriminatory performance (**Table 7**).

Discussion

The purpose of this study was to investigate the frequency, and specific causes of unplanned hospital readmission after initial hospitalization for TAVI, and to investigate which frailty markers could better predict unplanned readmission. Although the number of unplanned readmissions < 30 days was quite low in this study, one-quarter of patients had an unplanned readmission within 1 year following TAVI mainly for heart failure or pneumonia. We found that the SPPB, the PARTNER frailty scale, the frailty index, the clinical frailty scale and the gait speed were independently associated with unplanned readmission. The modified Fried scale had a trend towards an association with unplanned readmission. The SPPB and the PARTNER frailty scale significantly increased discriminatory performance for predicting unplanned readmission, while the SPPB, the PARTNER frailty scale and the Frailty Index significantly increased discriminatory performance for predicting allcause death in the ROC analysis.

Predictive Factors of Unplanned Readmission

The SPPB, the PARTNER frailty scale, the frailty index, the clinical frailty scale and the gait speed were independently associated with unplanned readmission, while the modified Fried scale had a trend towards an association with unplanned readmission. Frailty is an important parameter for predicting poor outcomes following intervention.^{14,18,19} The modified Fried scale is reported to be associated with length of stay, but not with readmission, which is consistent with the present study's results.6 Nonetheless, this is the first study to compare commonly used frailty markers for predicting unplanned readmission in TAVI patients. Many patients undergoing TAVI usually have cardiac and extracardiac comorbidities both of which are strongly associated with frailty. Not only the comorbidities themselves but also frailty, which leads to vulnerability to stressors, are important in any assessment to avoid unexpected deterioration of the patient's general condition. They still require attention following TAVI, even if the procedure is performed without complications.

Variables associated with unplanned readmission, such as COPD or atrial fibrillation in the multivariate model (**Table 4**), were consistent with a previous study.¹³ In our sensitivity analysis, device success and early safety at 30 days did not predict unplanned readmission after TAVI, suggesting most patients in Japan with procedural compli-

cations had adequate additional hospitalization to manage them following TAVI. Albumin level may also be used as a frailty marker for unplanned readmission.^{1,3,4,7}

Low body mass index, a concept similar to frailty, has already been reported as a predictive factor for poor outcomes in patients with severe aortic stenosis, ²⁰ but was not associated with unplanned readmission in the present study, probably because recent changes in body weight (or body mass index) are more important for frailty, and also because body mass index varies widely between races independent of frailty. ²¹

Discriminatory Performance of Each Frailty Assessment

The SPPB and the PARTNER frailty scale significantly increased discriminatory performance for predicting unplanned readmission, and the SPPB, the PARTNER frailty scale and the Frailty Index significantly increased discriminatory performance for predicting all-cause death in the ROC analysis.

More than 20 frailty markers have been developed but because of a lack of consensus, there is variability among studies and confusion about which marker to use. Most markers focus on more than 1 core domain, and multidimensional frailty assessment has been performed for predicting outcomes, but single-domain markers are more likely to be adopted clinically because of ease of implementation. Because the present study population was smaller than that previously reported regarding clinical frailty scale in a Japanese population, information is limited in the present analysis. However, the strength of this study was the complete dataset of frailty scores. In the present analysis, there was a difference between the frailty markers for predictive performance, even after adjustment.

In addition, many previous studies have already reported a relationship between frailty markers and death in this patient population. 4,5,7–10,12,18,22 In this era of newer technology providing safer procedures, we can recognize that the risk following TAVI is getting lower, and so our questions have shifted to not only the causes of deaths but also the quality of life following TAVI.23 In this analysis, multifaceted rather than simple one-sided, objective rather than subjective, and multi-grade rather than simple few-grade evaluation seemed superior for reflecting frailty and therefore predicting the outcomes following TAVI, because essentially frailty is complex and multifactorial. 1,4,6,7,19,22 Furthermore, a physical performance test might capture information, such as underlying diseases, that cannot be captured using self-reported measurements.¹⁵ A recent publication showing that the Essential Frailty Toolset consisting of chair rise test, part of the SPPB, cognitive

impairment, and hemoglobin and serum albumin levels had greatest predictive performance is consistent with the present study's results. The difference in the performance of the various frailty tools may be caused by slight differences in the population (including having surgical patients in the study). ¹⁸ One of the advantages in precisely assessing frailty is that special care can be given, such as an outpatient rehabilitation program, early follow-up or visiting nursing after TAVI, if the patient is considered frail enough to be concerned about readmission. Precise frailty assessment may result in reducing unplanned admissions after TAVI and therefore better quality of life. Of note, the PARTNER frailty scale may not be generalized as a predictor of outcomes in other populations, because it has been validated particularly in the TAVI population. ⁴

Overall Outcomes After TAVI

The number of unplanned readmissions <30 days was quite low in this study, but one-quarter of all patients had an unplanned readmission within 1 year following TAVI mainly for heart failure and pneumonia, which is consistent with previous research.¹³ Unplanned readmissions for noncardiac causes greater than for cardiac causes, which is consistent with patients who are at high surgical risk because of various extracardiac comorbidities.2 Also, TAVI was performed in index admissions and patients were likely to be in a more stable condition from the perspective of cardiovascular disease. Patients' characteristics and the outcomes in the present study are comparable to those reported in other Japanese studies.7,11,24,25 On the other hand, despite similar mean STS scores, the mortality and readmission rates in the present study were lower than those of a US registry, probably because of our learning curve.26 This present data did not include our initial experience with patients who were in the Japanese trial that began in 2010. Although the length of stay in this study was significantly longer than that of the US registry because of differences in the healthcare systems, it can be justified by the much lower unplanned readmission rate <30 days and the higher discharge to home rate.

Study Limitations

This study has a number of important limitations to note. First, this study was limited by its retrospective nature and was performed at a single center. Second, it included a relatively small number of patients. Therefore broad generalization of the findings cannot be supported. We have presented the study in terms of preliminary results that suggest that the findings may apply to a broader TAVI population. Third, frailty markers at follow-up were not obtained, which potentially could assess if individual physical performance excluding cardiopulmonary function was deteriorated by severe aortic stenosis.

Conclusions

Our study offers some important conclusions. We demonstrated a quite low unplanned readmission <30 days, and one-quarter of patients had an unplanned readmission within 1 year following TAVI. Most frailty markers were independent predictors of unplanned readmission following TAVI, and there seems to be a difference between those frailty markers in their predictive performance. Multifaceted, objective, and multi-grade evaluation seems superior to reflect frailty. Precise frailty assessment may result in

reducing unplanned admissions after TAVI and therefore better quality of life.

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Conflict of Interest

T.T. is a proctor for Edwards Lifesciences and Medtronic.

References

- Afilalo J, Alexander KP, Mack MJ, Maurer MS, Green P, Allen LA, et al. Frailty assessment in the cardiovascular care of older adults. J Am Coll Cardiol 2014; 638: 747–762.
- Makkar RR, Fontana GP, Jilaihawi H, Kapadia S, Pichard AD, Douglas PS, et al. Transcatheter aortic-valve replacement for inoperable severe aortic stenosis. N Engl J Med 2012; 366: 1696– 1704
- Lindman BR, Alexander KP, O'Gara PT, Afilalo J. Futility, benefit, and transcatheter aortic valve replacement. *JACC Cardiovasc Interv* 2014; 7: 707–716.
- Green P, Woglom AE, Genereux P, Daneault B, Paradis JM, Schnell S, et al. The impact of frailty status on survival after transcatheter aortic valve replacement in older adults with severe aortic stenosis: A single-center experience. *JACC Cardiovasc Interv* 2012; 5: 974–981.
- Stortecky S, Schoenenberger AW, Moser A, Kalesan B, Jüni P, Carrel T, et al. Evaluation of multidimensional geriatric assessment as a predictor of mortality and cardiovascular events after transcatheter aortic valve implantation. *JACC Cardiovasc Interv* 2012: 5: 489–496.
- Huded CP, Huded JM, Friedman JL, Benck LR, Lindquist LA, Holly TA, et al. Frailty status and outcomes after transcatheter aortic valve implantation. *Am J Cardiol* 2016; 117: 1966–1971.
- Shimura T, Yamamoto M, Kano S, Kagase A, Kodama A, Koyama Y, et al. Impact of the clinical frailty scale on outcomes after transcatheter aortic valve replacement. *Circulation* 2017; 135: 2013–2024.
- 8. Okoh AK, Chauhan D, Kang N, Haik N, Merlo A, Cohen M, et al. The impact of frailty status on clinical and functional outcomes after transcatheter aortic valve replacement in nonagenarians with severe aortic stenosis. *Catheter Cardiovasc Interv* 2017; **90:** 1000–1006.
- Kleczynski P, Dziewierz A, Bagienski M, Rzeszutko L, Sorysz D, Trebacz J, et al. Impact of frailty on mortality after transcatheter aortic valve implantation. *Am Heart J* 2017; 185: 52–58.
- Kleczynski P, Dziewierz A, Bagienski M, Rzeszutko L, Sorysz D, Trebacz J, et al. Long-term mortality and quality of life after transcatheter aortic valve insertion in very elderly patients. J Invasive Cardiol 2016; 28: 492–496.
- Shimura T, Yamamoto M, Kano S, Kagase A, Kodama A, Koyama Y, et al. Impact of frailty markers on outcomes after transcatheter aortic valve replacement: Insights from a Japanese multicenter registry. *Ann Cardiothorac Surg* 2017; 6: 532–537.
- Chauhan D, Haik N, Merlo A, Haik BJ, Chen C, Cohen M, et al. Quantitative increase in frailty is associated with diminished survival after transcatheter aortic valve replacement. *Am Heart* J 2016; 182: 146–154.
- Nombela-Franco L, del Trigo M, Morrison-Polo G, Veiga G, Jimenez-Quevedo P, Abdul-Jawad Altisent O, et al. Incidence, causes, and predictors of early (≤30 days) and late unplanned hospital readmissions after transcatheter aortic valve replacement. JACC Cardiovasc Interv 2015; 8: 1748–1757.
- Wahl TS, Graham LA, Hawn MT, Richman J, Hollis RH, Jones CE, et al. Association of the modified frailty index with 30-day surgical readmission. *JAMA Surg* 2017; 152: 749-757.
- Guralnik JM, Ferrucci L, Simonsick EM, Salive ME, Wallace RB. Lower-extremity function in persons over the age of 70 years as a predictor of subsequent disability. N Engl J Med 1995; 332: 556–561.
- Shinkai S, Watanabe N, Yoshida H, Fujiwara Y, Nishi M, Fukaya T, et al. Validity of the "Kaigo-Yobo Check-List" as a frailty index. Nihon Koshu Eisei Zasshi 2013; 60: 262–274.

- Kappetein AP, Head SJ, Généreux P, Piazza N, van Mieghem NM, Blackstone EH, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: The Valve Academic Research Consortium-2 consensus document. *J Am Coll Cardiol* 2012; 60: 1438–1454.
 Afilalo J, Lauck S, Kim DH, Lefèvre T, Piazza N, Lachapelle K,
- Afilalo J, Lauck S, Kim DH, Lefèvre T, Piazza N, Lachapelle K, et al. Frailty in older adults undergoing aortic valve replacement: The FRAILTY-AVR Study. J Am Coll Cardiol 2017; 70: 689–700.
- Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: Evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001; 56: M146–M156.
- Yamamoto M, Mouillet G, Oguri A, Gilard M, Laskar M, Eltchaninoff H, et al. Effect of body mass index on 30- and 365day complication and survival rates of transcatheter aortic valve implantation (from the FRench Aortic National CoreValve and Edwards 2 [FRANCE 2] registry). Am J Cardiol 2013; 112: 1932–1937.
- Fukui S, Kawakami M, Otaka Y, Ishikawa A, Mizuno K, Tsuji T, et al. Physical frailty in older people with severe aortic stenosis. Aging Clin Exp Res 2016; 28: 1081–1087.
- Alfredsson J, Stebbins A, Brennan JM, Matsouaka R, Afilalo J, Peterson ED, et al. Gait speed predicts 30-day mortality after transcatheter aortic valve replacement: Results from the Society of Thoracic Surgeons/American College of Cardiology trans-

- catheter valve therapy registry. Circulation 2016; 133: 1351–1359.
- Wendler O, Schymik G, Treede H, Baumgartner H, Dumonteil N, Neumann FJ, et al. SOURCE 3: 1-year outcomes post-transcatheter aortic valve implantation using the latest generation of the balloon-expandable transcatheter heart valve. *Eur Heart J* 2017; 38: 2717–2726.
- Takimoto S, Saito N, Minakata K, Shirai S, Isotani A, Arai Y, et al. Favorable clinical outcomes of transcatheter aortic valve implantation in Japanese patients: First report from the Post-Approval K-TAVI Registry. Circ J 2016; 81: 103–109.
- Hioki H, Watanabe Y, Kozuma K, Nara Y, Kawashima H, Kataoka A, et al. Pre-procedural dual antiplatelet therapy in patients undergoing transcatheter aortic valve implantation increases risk of bleeding. *Heart* 2017; 103: 361–367.
- Mack MJ, Brennan JM, Brindis R, Carroll J, Edwards F, Grover F, et al. Outcomes following transcatheter aortic valve replacement in the United States. *JAMA* 2013; 310: 2069–2077.

Supplementary Files

Supplementary File 1

Table S1. Frailty index

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