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Cardiac Rehabilitation

Hospital-Acquired Functional Decline and Clinical Outcomes in Older Patients Undergoing Transcatheter Aortic Valve Implantation

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Background: This study aimed to assess the relationship between hospital-acquired functional decline and the risk of mid-term all-cause death in older patients undergoing transcatheter aortic valve implantation (TAVI).

Methods and Results: In total, 463 patients (mean age 85 years, interquartile range [IQR]: 82, 88) undergoing elective TAVI at Sakakibara Heart Institute between 2010 and 2018, who were followed up for 3 years, were enrolled in the study. Hospital-acquired functional decline after TAVI, which was defined by at least a 1-point decrease on the Short Physical Performance Battery before discharge compared to the preoperative score, was assessed. A total of 113 patients (24.4%) showed hospital-acquired functional decline after TAVI, and 50 (11.3%) patients died over a mean follow-up period of 1.9±0.8 years. Kaplan-Meier survival curves indicated that hospital-acquired functional decline was significantly associated with all-cause mortality (log-rank test, P=0.001). On multivariate Cox regression analysis, hospital-acquired functional decline was associated with a higher risk of all-cause mortality (OR 2.108, 95% CI 1.119–3.968, P=0.021) independent of sex, body mass index, advanced chronic kidney disease, and preoperative frailty, as assessed by the modified essential frail toolkit.

Conclusions: Hospital-acquired functional decline is associated with mid-term all-cause mortality in older patients following TAVI. Trajectory of functional status is a vital sign, and it is useful for risk stratification in older patients following TAVI.

Key Words: All-cause death; Frailty; Hospital-acquired functional decline; Mid-term outcome; Transcatheter aortic valve implantation

Transcatheter aortic valve implantation (TAVI) has become the standard treatment for older patients with severe aortic stenosis.[1] The primary goals after TAVI are to minimize morbidity and mortality; however, healthy life expectancy and successful ageing with minimal disability are also essential targets of treatment in older patients after TAVI. Although accurate prognosis is essential for optimizing clinical management and treatment decision-making, functional status as a consequence of biological heterogeneity are not typically included in standard cardiovascular risk scores.[2,3]

The functional status recovery trajectory during hospitalization was recently recognized as an essential outcome in the older population. Hospital-acquired functional decline, which refers to either a new or worsened functional decline during hospitalization that was not present before hospitalization, develops in at least 30% of hospitalized older patients.[4] Moreover, hospital-acquired functional decline is a powerful predictor of future disability or mortality after hospitalization in the older population.[5,6] However, there is little evidence for the relationship between hospital-acquired functional decline and mortality in older patients following TAVI.

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The aims of this study were to evaluate the relationship between hospital-acquired functional decline and mid-term mortality in older patients undergoing TAVI. The study also aimed to assess the prognostic value of hospital-acquired functional decline when added to standard cardiovascular risk scores.

Methods

Participants

The study population comprised 463 patients with aortic stenosis who underwent TAVI at the Sakakibara Heart

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Table 1. Clinical Characteristics of Patients

	Hospital-acquired functional decline			P-value
	All (n=463)	Present (n=113)	Absent (n=350)	
Age, years	85 (82, 88)	85 (82, 88)	84 (81, 88)	0.886
Gender, female, n (%)	331 (71)	82 (73)	249 (71)	0.801
BMI, kg/m^2	22.2 (20.0, 24.9)	22.2 (19.5, 24.9)	22.5 (20.1, 25.0)	0.407
NYHA class III or IV, n (%)	115 (25)	31 (27)	84 (24)	0.534
LVEF, %	62 (57, 66)	63 (58, 66)	62 (59, 66)	0.797
AVA, cm^2	0.67 (0.55, 0.76)	0.66 (0.56, 0.75)	0.68 (0.57, 0.78)	0.143
Mean PG, mmHg	54 (43, 66)	54 (42, 65)	53 (43, 64)	0.870
STS-PROM score, points	5.58 (3.77, 7.58)	5.95 (3.96, 8.10)	5.00 (3.59, 7.16)	0.063
Comorbidity				
Diabetes mellitus, n (%)	109 (24)	28 (25)	81 (23)	0.785
Hypertension, n (%)	334 (72)	85 (75)	249 (71)	0.446
Dyslipidemia, n (%)	224 (48)	45 (40)	179 (51)	0.065
Myocardial infarction, n (%)	42 (9)	10 (9)	32 (9)	1.000
History of heart failure, n (%)	64 (18)	24 (21)	60 (17)	0.212
Hemoglobin, n (%)	11.7 (10.6, 12.7)	11.3 (10.3, 12.7)	11.7 (10.6, 12.8)	0.746
Albumin, g/dL	3.9 (3.6, 4.1)	3.9 (3.5, 4.1)	3.9 (3.7, 4.1)	0.746
Creatinine, g/dL	0.88 (0.72, 1.10)	0.86 (0.72, 1.11)	0.90 (0.74, 1.08)	0.313
eGFR, mL/min/1.73 m^2	50.4 (40.5, 62.1)	48.3 (39.6, 61.7)	50.9 (38.6, 62.1)	0.655
CKD category				0.433
Non-CKD	103 (29)	36 (32)	67 (28)	
Moderate CKD	226 (64)	70 (63)	156 (64)	
Advanced CKD	27 (7)	6 (5)	21 (8)	
Handgrip strength, kg	16 (12, 22)	16 (10, 21)	16 (12, 22)	0.129
Usual gait speed, m/s	0.81 (0.61, 0.99)	0.78 (0.61, 0.93)	0.83 (0.63, 1.00)	0.078
SPPB score at admission, points	10 (7, 12)	10 (8, 12)	10 (7, 12)	0.390
SPPB score at discharge, points	10 (6, 12)	7 (5, 10)	11 (8, 12)	<0.001
HDSR, points	25 (22, 28)	25 (22, 28)	25 (22, 28)	0.687
mEFT score, points	1 (0, 2)	1 (0, 2)	1 (1, 2)	0.818
Pre-operative frailty, n (%)	65 (14)	19 (17)	46 (13)	0.331
Early ambulation, days	5 (3, 10)	6 (3, 10)	5 (4, 9)	0.591
Return to home, n (%)	444 (96)	101 (89)	343 (98)	<0.001

Values are presented as median (interquartile range) or n (%). AVA, aortic valve area; BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration ratio; HDSR, Hasegawa's dementia scale-revised; LVEF, left ventricular ejection fraction; mEFT, modified Essential Frailty Toolset; NYHA, New York Heart Association; PG, peak gradient; SPPB, short physical performance battery; STS-PROM, Society of Thoracic Surgery predictive risk of mortality.

Institute, Tokyo, Japan, between October 2013 and December 2018. To facilitate comparisons with previous studies, this analysis only included patients who were discharged alive after TAVI. All information was retrospectively obtained from medical records or from telephone interviews. This study complied with the principles of the Declaration of Helsinki regarding investigations in humans, and was approved by the local institutional board at the Sakakibara Heart Institute (ID: 18-039). We applied the opt-out form to obtaining informed consent by posting the document at the hospital or on their website.

Clinical Outcomes

The primary endpoint of this study was all-cause mortality following TAVI. The secondary endpoint was early outcomes after TAVI, including death at 30 days, stroke, life-threatening bleeding, acute kidney injury (AKI), major vascular complication, and permanent pacemaker implantation. Events were collected using medical records or the hospital database.

Definition of Hospital-Acquired Functional Decline

Hospital-acquired functional decline was defined by a decrease in at least 1 point on the short physical performance battery (SPPB) before discharge compared to the score obtained on 1 day before the TAVI. The SPPB is a highly standardized geriatric physical functioning test that consists of tests for balance, gait, strength, and endurance.[7] A change in SPPB score of 1.0 point was considered a meaningful change.[8] The balance test evaluated the ability to stand with both feet together side-by-side in a semi-tandem and tandem position. The gait test assessed the time to walk 4 m, performed at the patient's usual pace. The 5-time chair-standing test measured the time to rise from a chair 5 times consecutively with arms folded across the chest as quickly as possible. The total SPPB scores ranged from 0 to 12 points, and higher scores indicated better physical functioning status.

Table 2. TAVI Procedures and Early Outcomes After TAVI

	Hospital-acquired functional decline			P-value
	All (n=463)	Present (n=113)	Absent (n=350)	
Transfemoral approach, n (%)	412 (89)	97 (86)	315 (90)	0.220
Procedure time, min	74 (60, 95)	75 (60, 108)	71 (60, 90)	0.168
Stay in intensive care unit, days	0 (0, 1)	0 (0, 1)	0 (0, 0)	0.106
Postoperative hospital stay, days	8 (6, 12)	10 (7, 15)	8 (5, 11)	<0.001
Death at 30 days, n (%)	0 (0)	0 (0)	0 (0)	–
Stroke, n (%)	4 (0.9)	2 (1.5)	2 (0.7)	0.525
Life-threatening bleeding, n (%)	4 (0.9)	2 (1.5)	2 (0.7)	0.525
AKI, AKIN stage 2 or 3, n (%)	2 (0.4)	0 (0)	2 (0.7)	0.568
Major vascular complication, n (%)	12 (2.6)	6 (4.5)	6 (2.0)	0.536
Permanent pacemaker implantation, n (%)	54 (11.7)	16 (14.2)	39 (11.1)	0.389

Values are presented as median (interquartile range) or n (%). AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; TAVI, transcatheter aortic valve implantation.

Pre-operative Frailty Assessment

The essential frailty toolkit (EFT) is a brief 4-item test including the chair rise test, hemoglobin levels, albumin levels, and the Mini Mental State Examination (MMSE) score, and it is recommended that the EFT scale is applied as a frailty screening tool, and for prediction of morbidity and mortality after TAVI.[9] In our study, we used Hasegawa's dementia scale-revised (HDS-R), which is widely used as a cognition screening tool in Japan.[10] We refer to this modified methodology for the EFT as the modified Essential Frailty Toolset (mEFT). The mEFT comprises the following: (1) 5-time chair standing test without arms: 0 points for ≤15 s, 1 point for ≥15 s, and 2 points if unable to complete; (2) hemoglobin level: 0 points if ≥13 g/dL in men or ≥12 g/dL in women, 1 point if <13 g/dL in men or <12 g/dL in women; (3) serum albumin: 0 points if ≥3.5 g/dL, 1 point if <3.5 g/dL; and (4) cognition: 0 points if HDS-R score ≥20 points, 1 point if HDS-R score <20 points. Higher scores reflected a greater risk of frailty. Summing up the mEFT subscales, we calculated a total mEFT score; a cut off of ≥3 was used to identify pre-operative frailty.

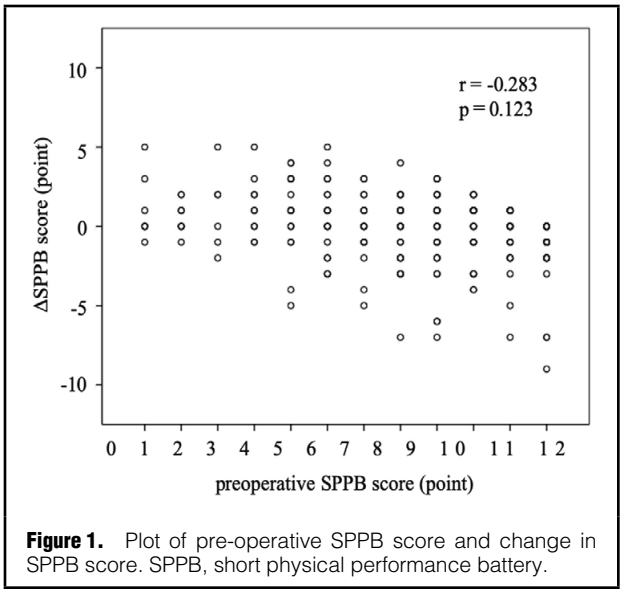

Figure 1. Plot of pre-operative SPPB score and change in SPPB score. SPPB, short physical performance battery.

Cardiac Rehabilitation

We examined early mobilization or exercise after the TAVI procedure, including getting out of bed, standing at the bed side, and walking along a corridor according to the Japanese Circulation Society (JCS) cardiac rehabilitation guidelines.[11] Moreover, we investigated the postoperative duration until patients could complete a 100-m corridor walk without assistance at a comfortable pace as early ambulation, which is one of the important indicators of postoperative recovery of physical activity.

Statistical Analysis

Continuous variables were expressed as the median (interquartile range [IQR]), and category variables as number and percentage. The 2 groups were compared using the chi-squared test for categorical covariates, or the Mann-Whitney U-test. A 2-sided P value less than 0.05 was considered statistically significant. A univariate logistic regression analysis was performed to obtain the odds ratio for hospital-acquired functional decline after TAVI. To determine the influence of the relationship between the outcomes, variables with P-values <0.10 in the univariate analysis were entered into a multivariate Cox regression analysis. To avoid collinearity in the present study, the Society of Thoracic Surgeons predicted risk of mortality (STS-PROM) score was excluded from the multivariate analysis because some of their components were inserted into the model. In contrast, the increase in predictive accuracy obtained by adding hospital-acquired functional decline to the subcategory of STS-PROM score was assessed with a Cox regression analysis instead. To assess the potential effects modification had on the relationship between hospital-acquired functional decline and mid-term mortality, subgroup analyses of hospital-acquired functional decline were performed in a 3-subgroup reclassification of STS-PROM scores (Low risk: <5%, Middle risk: ≥5% to <10%, and High risk: ≥10%). All analyses were performed using SPSS version 23.0 for Windows (IBM Corp., Armonk, NY, USA).

Results

Study Population

Baseline demographic and characteristic data are shown in

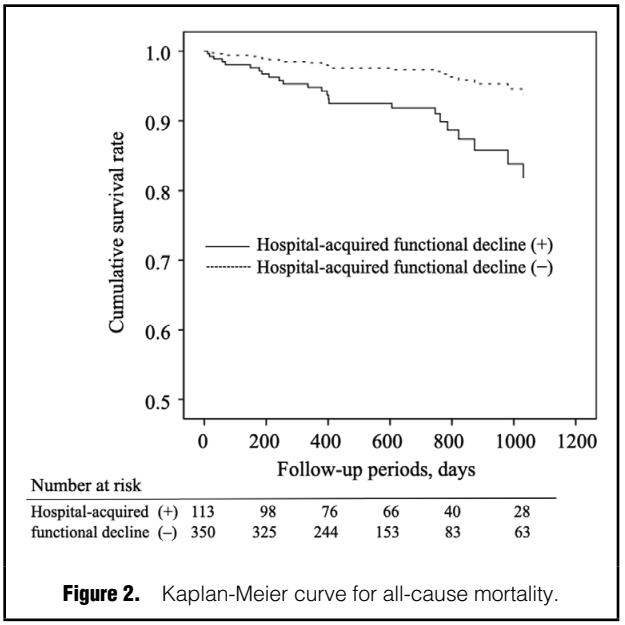

Figure 2. Kaplan-Meier curve for all-cause mortality.

Tables 1 and **2**. By definition, 113 of 463 patients (24.4%) had hospital-acquired functional decline after TAVI. There was no significant difference between the 2 groups in terms of STS-PROM score, TAVI procedure, early outcomes following TAVI including all-cause death at 30 days, stroke, life-threatening bleeding, moderate to severe AKI, major vascular complications, or permanent pacemaker implantation. Patients with hospital-acquired functional decline had significantly longer postoperative hospital stays and had a lower discharge to home rate than those without hospital-acquired functional decline. **Figure 1** demonstrates the plot of pre-operative SPPB scores and change in the SPPB score. There was no significant correlation between pre-operative SPPB score and change in the SPPB score (r=−0.283, P=0.123). In addition, pre-operative SPPB score, usual gait speed, handgrip strength, implementation of early ambulation, mEFT score, and pre-operative frailty were not significantly associated with hospital-acquired functional decline.

Association Between Hospital-Acquired Functional Decline and Mortality

A total of 50 (11.3%) patients died over a mean follow-up period of 1.9±0.8 years. Kaplan-Meier survival curves indicated that hospital-acquired functional decline was significantly associated with all-cause mortality (log-rank test, P=0.001) (**Figure 2**). After performing univariate analysis, age, sex, body mass index (BMI), left ventricular ejection fraction, diabetes mellitus, chronic kidney disease (CKD) category, serum albumin, N-Terminal pro Brain Natriuretic Peptide, postoperative hospital stay, pre-operative frailty, and hospital-acquired functional decline were entered into the multivariate Cox regression analysis (**Table 3**). Male sex (OR 3.363, 95% CI 1.409–8.027, P=0.006), BMI (OR 0.809, 95% CI 0.718–0.911, P<0.001), advanced CKD (OR 4.042, 95% CI 1.26312.934, P=0.019), pre-operative frailty (OR 5.392, 95% CI 1.974–14.726, P=0.001), and hospital-acquired functional decline (OR 2.670, 95% CI 1.200–5.942, P=0.016) were independently associated with all-cause mortality.

Figure 3 shows the reclassification of 3-year all-cause mortality risk when hospital-acquired functional decline was added to the three subgroups of STS-PROM scores.

Table 3. Predictors of All-Cause Mortality in Univariate and Multivariate Cox Regression Analysis

	Univariate analysis				Multivariate analysis			
	HR	95% CI		P value	HR	95% CI		P value
Age (every 1-year increase)	1.053	0.990	1.120	0.098				
Male (reference female)	2.845	1.623	4.987	<0.001	3.363	1.409	8.027	0.006
BMI (every 1 kg/m^2 increase)	0.865	0.793	0.943	0.001	0.809	0.718	0.911	<0.001
NYHA class ≥III (every degree increase)	1.286	0.845	1.959	0.241				
LVEF (every 1% increase)	0.974	0.945	1.004	0.093				
AVA (every 1 cm^2 increase)	0.758	0.103	5.589	0.786				
Mean PG (every 1 mmHg increase)	0.994	0.977	1.012	0.529				
Hypertension	0.613	0.334	1.125	0.114				
Diabetes mellitus	1.761	0.944	3.285	0.075				
Hemoglobin (every 1 g/dL increase)	0.907	0.756	1.088	0.293				
CKD category								
Non-CKD	1				1			
Moderate CKD	0.604	0.309	1.179	0.139	0.552	0.226	1.349	0.193
Advanced CKD	3.053	1.334	6.984	0.008	4.042	1.263	12.934	0.019
Serum albumin (every 1 g/dL increase)	0.190	0.094	0.381	<0.001				
CRP	1.058	0.946	1.183	0.324				
NT-pro BNP	1.000	1.000	1.000	0.001				
Postoperative hospital stay	1.005	1.000	1.010	0.051				
Pre-operative frailty	6.988	3.966	12.311	<0.001	5.392	1.974	14.726	0.001
SPPB score (every 1 point increase)	0.912	0.834	0.996	0.040				
Hospital-acquired functional decline	4.022	2.264	7.146	<0.001	2.670	1.200	5.942	0.016

CRP, C-reactive protein; HR, hazard ratio; NT-pro BNP, N-terminal B-type natriuretic peptide. Other abbreviations as in Table 1.

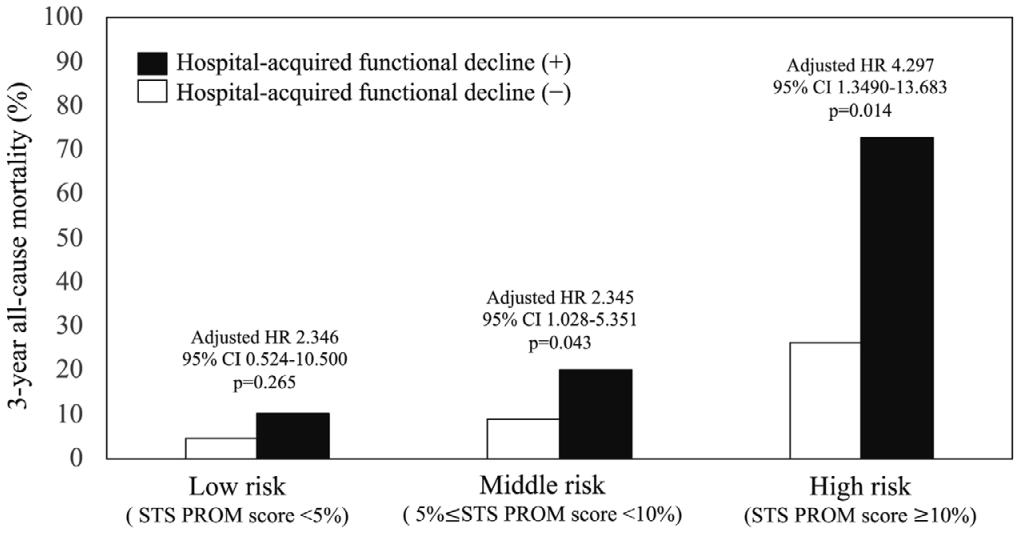

Figure 3. Distribution of the all-cause mortality rate in each STS-PROM score. Reclassification of all-cause mortality risk when hospital-acquired functional decline was added to the STS-PROM score subgroup. Adjusted model: adjusted for gender, body mass index, CKD category, and preoperative frailty. CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; STS-PROM, Society of Thoracic Surgery predicted risk of mortality.

In patients at high risk (STS-PROM score ≥10%), the addition of hospital-acquired functional decline presented a 2.76-fold increase in 3-year all-cause mortality risk (HR 4.297, 95% CI 1.3490–13.683, P=0.014). In addition, in the middle-risk group (≥5% to <10% STS-PROM score) and the low-risk group (<5% STS-PROM score), the addition of hospital-acquired functional decline presented a 2.27-fold (HR 2.345, 95% CI 1.028–5.351, P=0.043) and a 2.23-fold (HR 2.346, 95% CI 0.524–10.500, P=0.265) increase in 3-year all-cause mortality risk, respectively. In addition, when the patients were divided into 2 subgroups according to pre-operative SPPB score, hospital-acquired functional decline was significantly associated with all-cause mortality in both the impaired function status group (SPPB score <9 points; adjusted HR: 5.815; 95% CI: 2.243–15.072; P<0.001) and the robust functional status group (adjusted HR: 4.335; 95% CI: 1.188–15.819; P=0.026).

Discussion

The present study had several strengths. To the best of our knowledge, this is the first study to confirm that hospital-acquired functional decline occurs in a significant proportion of patients despite the standard acute phase of cardiac rehabilitation that follows TAVI. Moreover, hospital-acquired functional decline was independently associated with worse clinical outcomes. Our findings suggest that trajectory of functional status is a vital sign, and it is useful for risk stratification in older patients following TAVI.

TAVI focuses on morbidity or mortality in older patients with severe aortic valve stenosis, and healthy life expectancy with minimal disability is also a significant target. Previous reports have shown that impaired functional status can predict future disability and mortality in geriatric populations.[12,13] Therefore, recovery of functional status during hospitalization is also one of the essential outcomes for older patients who undergo TAVI. To understand any apparent contradictions regarding age, biological age is more important for detection of worse outcomes than chronological age in older patients. In the present study, there is no significant correlation between hospital-acquired functional decline and pre-operative functional status or frailty. These results indicate that hospital-acquired functional decline is independent of functional status and pre-operative frailty, and might be explained by a susceptibility to hospital-induced various stresses. The potential mechanism underlying the relationship between hospital-acquired functional decline and prognosis in older patients with TAVI remains unclear. However, previous studies have shown that functional decline during hospitalization is a key trigger that acts as one of the contributors to future disability or mortality.[14,15]

The concept of frailty has been defined as a biological syndrome with reduced functional reserve and resilience to stressors, resulting from cumulative deficits across multiple physiological systems, which leads to a high risk of adverse clinical outcomes. Most studies have confirmed that frailty is a prognostic tool for later clinical outcomes including mortality, morbidity, and quality of life after TAVI.[16] The present study also revealed a similar trend regarding frailty (defined by the mEFT) in that pre-operative frailty was associated with all-cause mortality following TAVI. The original EFT was proposed by Afilalo et al and reports suggest that it outperforms other frailty scales in identifying patients at high risk of mortality following TAVI.[9] The advantage of FET is that it is easy to perform in a short period of time and it has a low cost, and each component is reversible or modifiable by intervention.

In addition, we observed that BMI was associated with clinical outcomes in patients with TAVI.[17,18] Our results are in line with some previous reports, which found a beneficial effect of being overweight or obese on mortality

outcomes after TAVI, otherwise known as the obesity paradox.[19] The mechanism behind the obesity paradox remains unconfirmed. There are several possible factors that could explain the paradoxical effect of BMI on clinical outcomes. Overweight or obese patients may have a protective buffer from the negative effects of increasing inflammation following the acute phase of medical and interventional treatment. Moreover, muscle mass loss and malnutrition may reflect a lower BMI and have been associated with increasing mortality in patients undergoing TAVI.[20,21] Lower BMI may reflect muscle mass loss, and malnutrition might be associated with the vulnerability of multiple physiological systems, which results in increased risk of adverse outcomes following TAVI.

Moreover, we demonstrated that advanced CKD led to increased risk of mid-term all-cause mortality. More recently, several studies have shown that advanced CKD was associated with a decrease in functional status and increase in all-cause mortality through an accelerated progression of coronary artery disease, and that CKD leads to an increase in exacerbation of congestive heart failure, which results in an increased risk of adverse outcomes following TAVI.[22,23]

Hospital-acquired functional decline is believed to be a result of physical inactivity during hospitalization,[24] and therefore, early ambulation or stepwise increased physical activity play a crucial role in the prevention of functional decline and/or recovery of the pre-admission functional status. However, in the current study, early ambulation was not associated with hospital-acquired functional decline after TAVI. Developing effective therapeutic strategies to restore the functional status of elderly TAVI patients during hospitalization still remains a challenge. There is a very limited number of studies that have tried to implement an acute phase of rehabilitation comprising resistance exercises that are particularly effective at targeting functional decline in older populations.[25] Functional decline is affected by not only muscle wasting, but also by reduced muscle strength, neuromuscular dysfunction, and impaired muscle contractility. Resistance training has been shown to improve neuromuscular function and muscle contractility, which leads to improved muscle power, and neuromuscular function and muscle contractility are more closely related to improvements in physical performance than muscle strength. Based on this observation, comprehensive intervention, including early ambulation and/or stepwise increase of physical activity, and resistance training are increasingly important for the prevention of hospital-acquired functional decline in older patients undergoing TAVI. Further research is needed to determine whether promotion of an integrated acute phase of cardiac rehabilitation can help older patients who undergo TAVI to recover functional performance.

Study Limitations

There were some limitations to this study. This was a single-center, retrospective cohort study, and the number of adverse events was low. Patients with severe aortic valve stenosis and unstable hemodynamics at baseline could not complete the pre-operative functional assessment so were not enrolled, and this may have led to selection bias. Moreover, the cognitive impairment domain of the EFT was assessed by the HDS-R instead of the MMSE, which is also widely used in Japan to screen cognitive impairment with a cut-off value of less than 20 points. However, HDS-R scores can independently predict mid-term outcomes following TAVI.[26]

Conclusions

Hospital-acquired functional decline was associated with all-cause mortality in older patients following TAVI. Thus, trajectory of functional status is a vital sign, and it is useful for risk stratification in older patients following TAVI.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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