Journal of Cardiology 74 (2019) 34–39

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

Evaluation of objective nutritional indexes as predictors of one-year outcomes after transcatheter aortic valve implantation

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ARTICLE INFO

Article history:
Received 21 December 2018
Received in revised form 4 February 2019
Accepted 28 February 2019
Available online 28 March 2019

Keywords:
Transcatheter aortic valve implantation
Aortic valve stenosis
Objective nutritional index
Nutritional status
Frailty

ABSTRACT

Background: Objective nutritional indexes have been shown to predict prognoses in some clinical settings. We aimed to investigate the prognostic values of these indexes in patients undergoing transcatheter aortic valve implantation (TAVI).
Methods: We retrospectively analyzed 95 consecutive patients who underwent TAVI at our institution from December 2013 to February 2017. As objective nutritional indexes, a controlling nutritional status (CONUT) score, prognostic nutritional index (PNI), and geriatric nutritional risk index (GNRI) were calculated at baseline. The optimal cut-off values were determined using receiver operating characteristic curve analysis. According to the cut-off values, we investigated the association of these indexes with 1-year clinical outcomes including all-cause mortality and re-hospitalization due to heart failure.
Results: In the Kaplan–Meier analysis, patients with a higher CONUT score and lower PNI had significantly higher incidence rates of 1-year mortality (26.9% vs. 2.9%; $p < 0.001$, 17.4% vs. 2.0%; $p = 0.011$, respectively) and composite outcome of mortality and re-hospitalization due to heart failure (38.5% vs. 13.0%; $p = 0.006$, 39.3% vs. 11.9%; $p = 0.002$, respectively). On Cox hazard analysis, CONUT score and PNI were significantly associated with 1-year mortality [hazard ratio (HR): 1.91; 95% confidence interval (CI): 1.27–2.88; $p = 0.002$, HR: 0.86; 95% CI: 0.75–0.99; $p = 0.031$, respectively] and the composite outcome (HR: 1.49; 95% CI: 1.11–2.00; $p = 0.007$, HR: 0.88; 95% CI: 0.80–0.97; $p = 0.011$, respectively).
Conclusions: The CONUT score and PNI are associated with 1-year clinical outcomes especially with 1-year all-cause mortality in patients undergoing TAVI. Moreover, the CONUT score and PNI might have better predictive values than GNRI.

Introduction

Transcatheter aortic valve implantation (TAVI) has rapidly evolved as a definitive treatment option with improved clinical outcomes in surgical high-risk patients with severe aortic valve stenosis (AS). However, it is also known that some patients still have a poor prognosis even after this treatment due to their intrinsic clinical risks [1]. Therefore, preoperative recognition of patients at risk of early mortality or re-hospitalization is critical for risk stratification and appropriate therapeutic intervention in patients who are candidates for TAVI. For this reason, many prognostic factors have been identified in this population previously [2–9].

Nutritional status is reported to be an important prognostic indicator in various diseases [10–12]. Although malnutrition is

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https://doi.org/10.1016/j.jjcc.2019.02.017
0914-5087/

assumed to be common in elderly and surgical high-risk patients undergoing TAVI, the clinical significance of a nutritional risk assessment in these patients has not been well studied. Moreover, standard methodology for nutritional assessment of AS patients has not been established.

Some objective nutritional indexes such as the controlling nutritional status (CONUT), prognostic nutritional index (PNI), and geriatric nutritional index (GNRI) have been reported to be useful for assessing malnutrition and predicting clinical outcomes in patients with cardiovascular diseases including heart failure, coronary artery disease, and peripheral artery disease [13–19]. Therefore, we aimed to investigate the nutritional status assessed by these established indexes and their prognostic values in patients undergoing TAVI.

Methods

The present study retrospectively enrolled a total of 95 consecutive patients who underwent TAVI between December 2013 and February 2017 at our hospital. The multidisciplinary heart team discussed all cases, and a consensus was achieved regarding the therapeutic strategy for each case. TAVI was performed in a hybrid operating room under general anesthesia using balloon-expandable or self-expandable transcatheter aortic valves. All patients provided written informed consent prior to study enrollment and the identities of these patients have been protected.

We calculated CONUT scores, PNI, and GNRI, all of which are established objective nutritional indexes in other populations, based on the data at the time of hospital admission. The CONUT score consists of three variables: serum albumin, total cholesterol, and total lymphocyte count (Table 1) [20]. The PNI is calculated as follows: PNI = 10 × serum albumin (g/dL) + 0.005 × total lymphocyte (count per mm^3) [21]. The GNRI is calculated as follows: GNRI = 14.89 × serum albumin (g/dL) + 41.7 × body weight/ideal body weight. Ideal body weight is calculated as follows: body height − 100 − [(body height − 150)/4] for males, and body height − 100 − [(body height − 150)/2.5] for females [22].

Medical records were retrospectively reviewed with regard to patient characteristics including medical history, comorbidities, laboratory data, echocardiographic data, and procedural data. All measurements except for procedural data were obtained at the time of hospital admission. The occurrence of clinical events was also recorded from medical records or by telephone interview and 1-year follow-up data were obtained from all 95 patients.

We evaluated both 1-year all-cause mortality and re-hospitalization due to worsening heart failure as clinical outcomes. The composite outcome including both events was also evaluated. For the composite outcome in patients who had multiple events during the period, the time until the first event was used in our calculations.

Categorical data are represented as frequencies and percentages and the differences between groups were evaluated with a Chi-square test. Continuous variables were tested for normal distribution using the Kolmogorov–Smirnov test. Non-normally distributed variables are expressed as median values and interquartile ranges (IQR) and compared between groups using Mann–Whitney *U* test. Normally distributed variables are expressed as mean values ± standard deviation (SD) and compared between groups using Student's *t*-test.

Receiver operating characteristic (ROC) curves were generated to investigate the prognostic accuracy of CONUT score, PNI, and GNRI for 1-year mortality, re-hospitalization due to worsening heart failure, and the composite outcome. Event-free survival curves were constructed using the Kaplan–Meier method and compared using the log-rank test. A univariate and multivariate Cox proportional hazards model was used to calculate hazard ratios (HRs) and 95% confidence intervals (95% CI) for clinical endpoints. Throughout the present study, a *p*-value of <0.05 was considered significant. Statistical analyses were performed using EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

Table 1
CONUT score calculation.

Score	0	2	4	6
Serum albumin (g/mL)	≥3.5	3.0–3.49	2.50–2.99	<2.50
Score	0	1	2	3
Total cholesterol (mg/dL)	≥180	140–179	100–139	<100
Lymphocytes (counts/mL)	≥1600	1200–1599	800–1199	<800

CONUT, controlling nutritional status.

Results

The baseline characteristics of the 95 patients enrolled in the study are summarized in Table 2. The median age of the patients was 84 years and 70.5% of patients were female. New York Heart Association functional class III or IV were observed in 37.9% of patients. The median of the Society of Thoracic Surgeons score and the Logistic Euro score were 5.18 (IQR: 3.96–7.12) and 10.74 (IQR: 7.48–17.22), respectively. More than 80% of patients were treated with the trans-femoral approach and balloon-expandable valves (SAPIEN XT or SAPIEN 3, Edwards Lifesciences, Irvine, CA, USA). As for the objective nutritional indexes, the median CONUT score was 2 (IQR: 2–4) and the mean PNI and GNRI were 46.4 ± 4.89 and 100.6 ± 10.8, respectively.

Of 95 patients, 9 patients (9.5%) died, 12 patients (12.6%) experienced re-hospitalization due to worsening heart failure, and 19 patients (20.0%) had the composite outcome within 1 year after TAVI. The mortality group had significantly lower hemoglobin level and total cholesterol level than non-mortality group. Otherwise, there were no significant differences in baseline characteristics between the two groups. As for the objective nutritional indexes, the mortality group had a significantly lower CONUT score or PNI than the non-mortality group; however, there was no significant difference between the two groups in GNRI.

Since ideal cut-off values for each index are not well studied in this population, the cut-off values of each nutritional index for each clinical outcome were determined using ROC curve analyses. Each ROC curve and the cut-off values are summarized in Fig. 1. Area under the ROC curve (AUC) for 1-year mortality was 0.819 (95% CI: 0.690–0.948) for the CONUT score, 0.745 (95% CI: 0.614–0.876) for the PNI, and 0.606 (95% CI: 0.396–0.816) for the GNRI. The AUC for re-hospitalization due to worsening heart failure was 0.622 (95% CI: 0.473–0.772) for the CONUT score, 0.618 (95% CI: 0.441–0.795) for the PNI, and 0.519 (95% CI: 0.328–0.710) for the GNRI. The AUC for the composite outcome was 0.711 (95% CI: 0.590–0.832) for the CONUT score, 0.699 (95% CI: 0.567–0.832) for the PNI, and 0.608 (95% CI: 0.460–0.756) for the GNRI. For each outcome, the largest AUC was obtained for the CONUT score, followed in order by the PNI, and the GNRI (Fig. 1).

One-year Kaplan–Meier curves of all-cause mortality, re-hospitalization due to worsening heart failure, and the composite outcome according to each objective nutritional index cut-off value are summarized in Fig. 2. Patients with a higher CONUT score or lower PNI had significantly higher incidence of 1-year mortality (26.9% vs. 2.9%; $p < 0.001$, 17.4% vs. 2.0%; $p = 0.011$, respectively). Although patients with a lower GNRI also had a higher incidence of 1-year mortality, the difference was not statistically significant (12.2% vs. 7.4%; $p = 0.405$). As for re-hospitalization due to worsening heart failure, although patients with a higher CONUT score, lower PNI, or lower GNRI had higher incidence rates, the

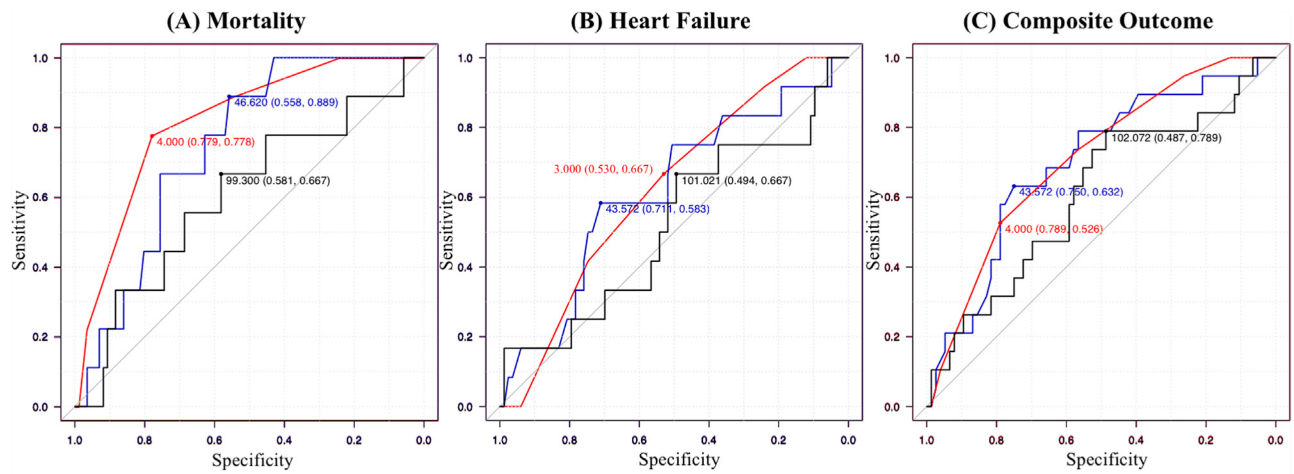
Table 2
Comparison of Baseline characteristics of study patients with and without one-year all-cause mortality.

	All patients (n = 95)	Mortality + (n = 9)	Mortality − (n = 86)	p-Value
Age (years)	84 [81–88]	83 [76–89]	84 [81–87]	0.774
Female	67 (70.5)	5 (55.6)	62 (72.1)	0.442
Body mass index (kg/m^2)	21.9 ± 4.1	22.3 ± 3.7	21.9 ± 4.1	0.758
Objective nutritional index				
CONUT score	2 [2–4]	2 [2–3]	4 [4–4]	0.001
PNI	46.4 ± 4.89	43.0 ± 3.3	46.8 ± 4.9	0.027
GNRI	100.6 ± 10.8	97.8 ± 10.4	100.9 ± 10.8	0.420
Logistic Euro SCORE (%)	10.74 [7.48–17.22]	9.92 [6.54–14.37]	10.74 [7.56–17.32]	0.596
STS score: mortality (%)	5.18 [3.96–7.12]	5.34 [4.35–10.87]	5.08 [3.96–6.96]	0.496
NYHA functional class III/IV	36 (37.9)	3 (33.3)	33 (38.4)	1.000
Concomitant diseases				
Hypertension	66 (69.5)	5 (55.6)	61 (70.9)	0.448
Diabetes	22 (23.2)	1 (11.1)	21 (24.4)	0.680
Dyslipidemia	55 (57.9)	3 (33.3)	52 (60.5)	0.160
Chronic kidney disease (eGFR < 60)	33 (34.7)	5 (55.6)	28 (32.6)	0.268
COPD	10 (10.5)	1 (11.1)	9 (10.5)	1.000
Atrial fibrillation	26 (27.4)	5 (55.6)	21 (24.4)	0.108
Previous history				
Previous MI	2 (2.1)	0 (0.0)	2 (2.3)	1.000
Prior stroke	13 (13.7)	3 (33.3)	10 (11.6)	0.104
Previous PAD	2 (2.1)	0 (0.0)	2 (2.3)	1.000
Blood cell counts and laboratory data (pre-procedure)				
Hemoglobin (g/dL)	10.9 [9.7–12.3]	9.2 [9.2–10.9]	10.9 [9.9–12.4]	0.027
WBC	4700 [4100–6550]	4900 [3800–5600]	4700 [4120–6570]	0.580
Lymphocytes	1117 [866–1613]	846 [836–1460]	1169 [926–1660]	0.132
Platelet Counts	18.6 [14.4–21.4]	17.9 [16.3–18.2]	18.7 [14.1–21.4]	0.703
eGFR	54.6 [38.5–64.4]	40.5 [30.2–65.7]	54.6 [39.6–64.4]	0.315
ALB (g/dL)	4.1 [3.7–4.4]	3.8 [3.4–3.9]	4.1 [3.7–4.4]	0.096
T-CHO	176.0 [151.5–195.0]	138.0 [130.0–158.0]	177.5 [158.0–195.8]	0.003
Na	139 [137–142]	138 [135–140]	140 [137–142]	0.206
K	4.4 [4.0–4.8]	4.4 [4.3–4.7]	4.4 [4.0–4.8]	0.433
BNP	178.5 [115.3–438.8]	284.2 [162.5–383.5]	171.0 [111.2–441.3]	0.250
Echocardiographic data (pre-procedure)				
LVEF ≤35%	5 (5.3)	1 (11.1)	4 (4.7)	0.399
LV end-diastolic diameter (mm)	42.7 ± 6.7	46.1 ± 9.3	42.4 ± 6.3	0.111
LV end-systolic diameter (mm)	27.3 ± 7.5	30.8 ± 10.2	26.9 ± 7.1	0.141
Calculated Aortic valve area (cm^2)	0.66 ± 0.18	0.68 ± 0.22	0.65 ± 0.18	0.676
Mean aortic gradient (mmHg)	58.5 ± 18.7	48.2 ± 13.5	59.5 ± 18.9	0.085
Peak jet velocity (m/s)	4.77 ± 0.78	4.32 ± 0.57	4.81 ± 0.79	0.074
Moderate or severe AR	10 (10.5)	0 (0)	10 (13.0)	0.588
Moderate or severe MR	24 (25.3)	2 (22.2)	22 (28.2)	1.000
Moderate or severe TR	16 (16.8)	2 (22.2)	14 (17.7)	0.665
Medications (pre-procedure)				
RAS inhibitors	59 (62.1)	4 (44.4)	55 (64.0)	0.292
Beta-blockers	24 (25.2)	3 (33.3)	21 (24.4)	0.688
Statins	48 (50.5)	4 (44.4)	44 (51.8)	0.737
Oral anticoagulation	16 (16.8)	2 (22.2)	14 (16.3)	0.645
Procedural data				
Trans-femoral approach	82 (86.3)	9 (100.0)	73 (84.9)	0.636
Balloon-expandable valves (XT/S3)	81 (85.3)	8 (88.9)	73 (84.9)	1.000
Echocardiographic data (post-procedure)				
Calculated aortic valve area (cm^2)	1.62 ± 0.43	1.59 ± 0.34	1.63 ± 0.44	0.804
Mean aortic gradient (mmHg)	11.7 ± 5.3	10.3 ± 2.5	11.8 ± 5.5	0.420
Peak jet velocity (m/s)	2.15 ± 0.43	2.07 ± 0.30	2.16 ± 0.44	0.517
Aortic regurgitation ≥ moderate	4 (5.8)	1 (16.7)	3 (4.8)	0.333

CONUT, controlling nutritional status; PNI, prognostic nutritional index; GNRI, geriatric nutritional index; STS, society of thoracic surgeons; NYHA, New York Heart Association; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; PAD, peripheral artery disease; WBC, white blood cell count; eGFR, estimated glomerular filtration rate; ALB, albumin; T-CHO, total cholesterol; Na, sodium; K, potassium; BNP, brain natriuretic peptide; LVEF, left ventricular ejection fraction; LV, left ventricular; AR, aortic regurgitation; MR, mitral regurgitation; TR, tricuspid regurgitation; RAS, renin-angiotensin-aldosterone; XT, SAPIEN XT (Edwards Lifesciences, Irvine, CA, USA); S3, SAPIEN 3 (Edwards Lifesciences).

statistical significance was only observed in PNI (17.3% vs. 8.5%; p = 0.162, 23.4% vs. 8.0%; p = 0.031, 15.0% vs. 10.9%; p = 0.524, respectively). As for the composite outcome, a higher CONUT score and lower PNI were associated with significantly higher incidence rates (38.5% vs. 13.0%; p = 0.006, 39.3% vs. 11.9%; p = 0.002, respectively). Patients with lower GNRI also had a higher incidence of the composite outcome; the difference was not statistically significant (26.4% vs. 11.9%; p = 0.070).

We also performed univariate and multivariate Cox-proportional hazard analyses to examine the effects of each objective nutritional index on clinical outcomes and the results are summarized in Table 3. The univariate Cox-proportional hazard analysis demonstrated that the CONUT score and PNI were significantly associated with 1-year mortality (HR: 1.91; 95% CI: 1.27–2.88; p = 0.002, HR: 0.86; 95% CI: 0.75–0.99; p = 0.031, respectively) and the composite outcome (HR: 1.49; 95% CI: 1.11–2.00; p = 0.007, HR: 0.88; 95% CI: 0.80–0.97; p = 0.011, respectively). Even after adjusting for age, the CONUT score and PNI were significantly associated with the composite outcome (HR: 1.49; 95% CI: 1.12–2.00; p = 0.007, HR: 0.88; 95% CI: 0.80–0.97; p = 0.011, respectively).



Optimal Cut-off value and AUC for each clinical endpoints						
	Mortality		HF		Composite outcome	
	Cut-off value	AUC	Cut-off value	AUC	Cut-off Value	AUC
CONUT score	4	0.819 (0.690-0.948)	3	0.622 (0.473-0.772)	4	0.711 (0.590-0.832)
PNI	46.620	0.745 (0.614-0.876)	43.572	0.618 (0.441-0.795)	43.572	0.699 (0.567-0.832)
GNRI	99.300	0.606 (0.396-0.816)	101.021	0.519 (0.328-0.710)	102.072	0.608 (0.460-0.756)

Fig. 1. Receiver operating characteristic (ROC) curves for all-cause mortality (A), re-hospitalization due to heart failure (B), and the composite outcome (C). Red line indicates CONUT score, blue line indicates PNI, and black line indicates GNRI. Each number on the ROC curves is cut-off value which maximizes the sum of sensitivity and specificity. AUC, area under the curve; CONUT, controlling nutritional status; PNI, prognostic nutritional index; GNRI, geriatric nutritional index; HF, heart failure.

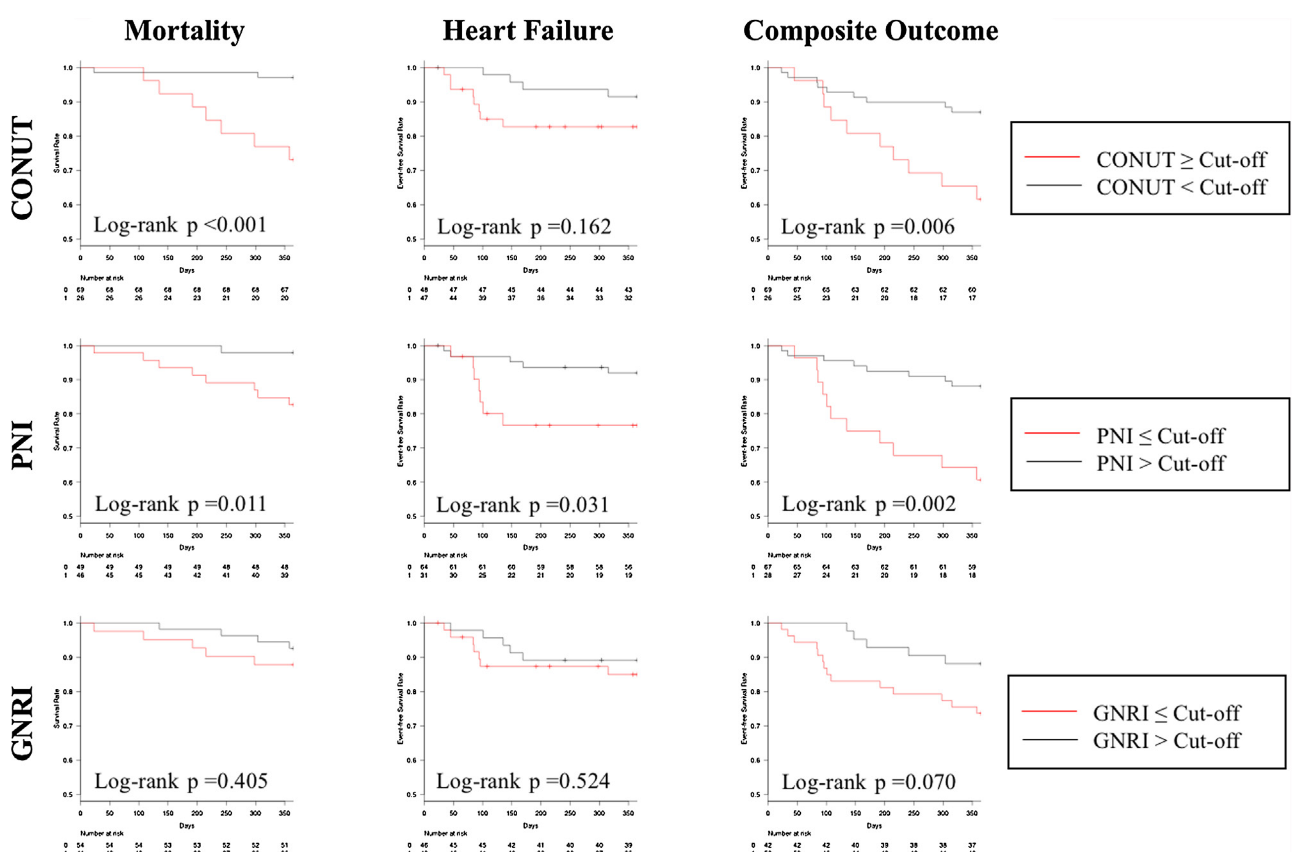


Fig. 2. Kaplan–Meier Analysis for all-cause mortality, re-hospitalization due to heart failure, and the composite outcome according to the cut-off values of CONUT score, PNI, and GNRI.
CONUT, controlling nutritional status; PNI, prognostic nutritional index; GNRI, geriatric nutritional index.

Table 3
Univariate and multivariate cox proportional hazard analysis for one-year clinical outcomes.

	Univariate		Age-adjusted	
	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Mortality				
CONUT score	1.91 (1.27–2.88)	0.002		
PNI	0.86 (0.75–0.99)	0.031		
GNRI	0.98 (0.92–1.04)	0.413		
Re-hospitalization due to heart failure				
CONUT score	1.30 (0.89–1.89)	0.182		
PNI	0.92 (0.82–1.04)	0.166		
GNRI	0.98 (0.93–1.04)	0.565		
Composite outcome				
CONUT score	1.49 (1.11–2.00)	0.007	1.49 (1.12–2.00)	0.007
PNI	0.88 (0.80–0.97)	0.011	0.88 (0.80–0.97)	0.011
GNRI	0.97 (0.93–1.01)	0.127		

HR, hazard ratio; CI, confidence interval; CONUT, Controlling Nutritional Status; PNI, Prognostic Nutritional Index; GNRI, Geriatric Nutritional Index.

Table 4
Nutritional status and cause of death in nine patients.

Patient No.	Age	Sex	CONUT score	PNI	GNRI	Cause of death	Days after TAVI
Case 1	75	F	4	48.0	109	Pneumonia	241
Case 2	89	F	4	43.2	117	Heart Failure	135
Case 3	74	F	4	41.3	88	Septic shock	215
Case 4	81	M	4	38.2	87	Pneumonia	298
Case 5	90	F	5	39.8	87	Subarachnoid hemorrhage	108
Case 6	88	M	5	40.8	99	Sudden death, cause unknown	358
Case 7	83	M	2	45.9	94	Pneumonia	23
Case 8	76	M	4	43.2	96	Gastric cancer	192
Case 9	91	F	3	46.6	102	Pyogenic spondylitis	304

CONUT, controlling nutritional status; PNI, prognostic nutritional index; GNRI, geriatric nutritional index; TAVI, transcatheter aortic valve implantation.

Discussion

In the present study, the CONUT score and PNI were significantly associated with 1-year clinical outcomes especially with 1-year all-cause mortality in patients undergoing TAVI. Moreover, the CONUT score and PNI had better predictive values than GNRI. Malnutrition, which was evaluated by the CONUT score, PNI, or GNRI, is known to be well associated with frailty, and its correlation with prognosis in various diseases has been shown in previous reports [2–11]. Shibata et al. have reported that GNRI is an important surrogate marker for predicting worse clinical outcomes even in patients undergoing TAVI [23]. More recently, Honda et al. have shown that CONUT score was strongly associated with 1-year mortality after TAVI in an analysis of 150 consecutive patients [24]. To the best of our knowledge, this study is the first to compare CONUT scores, PNI, and GNRI in patients undergoing TAVI, as well as to suggest that CONUT scores and PNI were superior to GNRI in predicting mortality after TAVI.

The Valve Academic Research Consortium (VARC-2) criteria defined low serum albumin as one of the frailty factors reflecting malnutrition [25]. Furthermore, previous reports have shown that low serum albumin is associated with all-cause mortality after TAVI [26–28]. The other components of each nutritional index such as body weight, lymphocyte count, and total cholesterol have been reported as prognostic indicators in patients with cardiovascular diseases [29–31]. Therefore, adding these components to serum albumin could make it possible to evaluate a patient's frailty and nutritional status more accurately. In fact, in our data, AUC for 1-year mortality and the composite outcome were 0.669 (95% CI 0.501–0.836) and 0.632 (95% CI 0.488–0.776) for serum albumin, respectively, both of which were lower than those for the CONUT score and PNI. Since the CONUT score includes total cholesterol, the score might be influenced by statin use. Unfortunately, it has not been well studied how to consider the effect of statins when calculating the CONUT score. However, in our analysis, statin use was not associated with a significant difference in the CONUT score ($p = 0.266$) (Supplementary Material). Moreover, the CONUT score was significantly associated with the composite outcome after adjusting for statin use (HR: 1.48; 95% CI: 1.11–1.96; $p = 0.007$).

In our data, GNRI did not have strong predictive value compared with the CONUT score and PNI. One possible reason is that GNRI could not directly reflect nutritional status in this population. Previously, Horiuchi et al. reported that GNRI, which includes body weight in the calculation, could be affected by fluid retention due to heart failure [19]. Since patients with severe AS are developing congestive heart failure at a certain rate, the CONUT score and PNI, which do not include body weight in the calculation, might have better predictive values than GNRI.

TAVI has evolved into an alternative and cost-effective therapeutic option with significantly improved clinical outcomes for surgical high-risk patients deemed unsuitable for aortic valve replacement [32–34]. This medical advancement, however, led to new clinical concerns that some of these high-risk patients may die early due to non-cardiac causes or repeat re-hospitalization due to heart failure and other medical problems even after TAVI [1,35]. In fact, in the present study, most of the early mortality after TAVI was due to non-cardiac causes (Table 4). This is considered to be due to a patient's diminished physiological reserve, which is expressed as frailty. Previously, many frailty factors such as body mass index, subcutaneous fat area, gait speed, and multidimensional geriatric assessments have been reported to be useful for risk stratification of these high-risk patients [4–9]. Our results showed that objective nutritional indexes such as the CONUT score and PNI might also be useful to assess a patient's frailty and for risk stratification.

Our study has several limitations worth noting. First, this was a single-center retrospective observational study with a small sample size. Although the differences in baseline characteristics could significantly affect outcomes, the total number of outcomes was small and not sufficient for multivariate analysis for adjusting confounders. Second, the clinical events were not adjudicated by an independent clinical event committee. Third, the cut-off values of each index used in the present study were originally developed by using ROC curves. Therefore, our results should be interpreted cautiously until verified in further studies.

In spite of these limitations, we believe this study has important clinical implications. Objective nutritional indexes such as the CONUT score, PNI, and GNRI are still infrequently used for risk stratification of patients undergoing TAVI. These are objective indexes that can be easily calculated from simple and widely available markers such as serum albumin, total lymphocyte counts, total serum cholesterol, and body weight. Therefore, these indexes can be generally and widely used without any inter-observer variability, which is an important feature for risk stratification tools. Further studies utilizing a larger cohort will be required to validate our findings and to also determine the optimal cut-off values in this population.

Conclusions

With the study's limitations in mind, we conclude that CONUT scores and PNI are associated with 1-year clinical outcomes especially with 1-year all-cause mortality in patients undergoing TAVI. Moreover, CONUT scores and PNI might have better predictive values than GNRI.

Conflicts of interest

Dr. Tanabe receives honoraria from Edwards Lifesciences and Medtronic. Dr. Yokozuka receives honoraria from Edwards Lifesciences. Other authors report no conflicts of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jjcc.2019.02.017.

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