



## Original article

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



Taishi Okuno (MD)<sup>a</sup>, Keita Koseki (MD)<sup>a</sup>, Toru Nakanishi (MD)<sup>a</sup>, Kei Sato (MD)<sup>a</sup>, Kai Ninomiya (MD)<sup>a</sup>, Daijiro Tomii (MD)<sup>a</sup>, Tetsu Tanaka (MD)<sup>a</sup>, Yu Sato (MD)<sup>a</sup>, Yu Horiuchi (MD)<sup>a</sup>, Hideki Koike (MD)<sup>a</sup>, Kazuyuki Yahagi (MD)<sup>a</sup>, Kota Komiyama (MD, PhD)<sup>a</sup>, Jun Tanaka (MD)<sup>a</sup>, Jiro Aoki (MD, PhD)<sup>a</sup>, Motoi Yokozuka (MD)<sup>b</sup>, Sumio Miura (MD)<sup>c</sup>, Kengo Tanabe (MD, PhD)<sup>a,\*</sup>

<sup>a</sup> Division of Cardiology, Mitsui Memorial Hospital, Tokyo, Japan

<sup>b</sup> Division of Anesthesia, Mitsui Memorial Hospital, Tokyo, Japan

<sup>c</sup> Division of Cardiovascular Surgery, Mitsui Memorial Hospital, Tokyo, Japan

## 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.

© 2019 Published by Elsevier Ltd on behalf of Japanese College of Cardiology.

## 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

\* Corresponding author at: Director of Division of Cardiology, Mitsui Memorial Hospital, Kanda-Izumicho 1, Chiyoda-ku, Tokyo 101-8643, Japan.  
E-mail address: [kengo-t@zd5.so-net.ne.jp](mailto:kengo-t@zd5.so-net.ne.jp) (K. Tanabe).

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:  $PNI = 10 \times \text{serum albumin (g/dL)} + 0.005 \times \text{total lymphocyte (count per mm}^3\text{)}$  [21]. The GNRI is calculated as follows:  $GNRI = 14.89 \times \text{serum albumin (g/dL)} + 41.7 \times \text{body weight/ideal body weight}$ . Ideal body weight is calculated as follows:  $\text{body height} - 100 - [(body height - 150)/4]$  for males, and  $\text{body height} - 100 - [(body height - 150)/2.5]$  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  $\pm$  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).

## 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  $46.4 \pm 4.89$  and  $100.6 \pm 10.8$ , 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 1**  
CONUT score calculation.

| Score                                  | 0           | 2         | 4         | 6        |
|----------------------------------------|-------------|-----------|-----------|----------|
| Serum albumin (g/mL)                   | $\geq 3.5$  | 3.0–3.49  | 2.50–2.99 | $< 2.50$ |
| Score                                  | 0           | 1         | 2         | 3        |
| Total cholesterol (mg/dL)              | $\geq 180$  | 140–179   | 100–139   | $< 100$  |
| Lymphocytes (counts/mL)                | $\geq 1600$ | 1200–1599 | 800–1199  | $< 800$  |
| CONUT, controlling nutritional status. |             |           |           |          |

**Table 2**

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

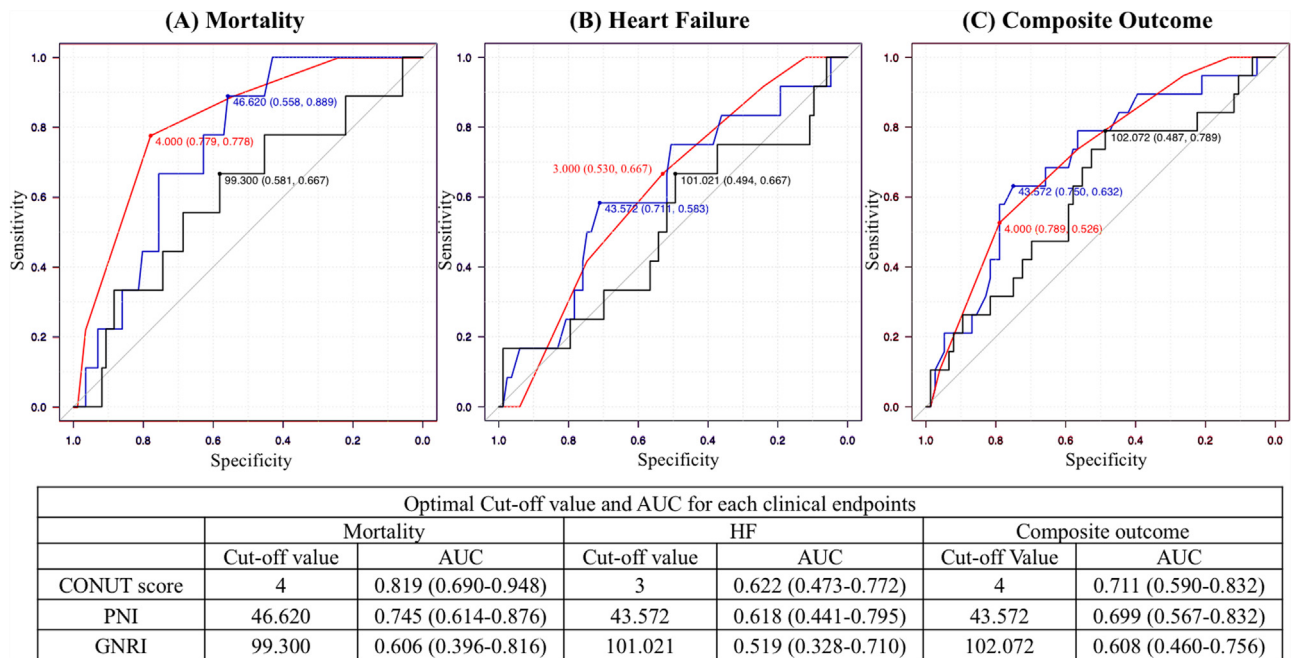
|                                                       | All patients (n=95) | Mortality + (n=9)   | Mortality – (n=86)  | p-Value |
|-------------------------------------------------------|---------------------|---------------------|---------------------|---------|
| Age (years)                                           | 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 <sup>2</sup> )                  | 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 <sup>2</sup> )       | 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 <sup>2</sup> )       | 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).

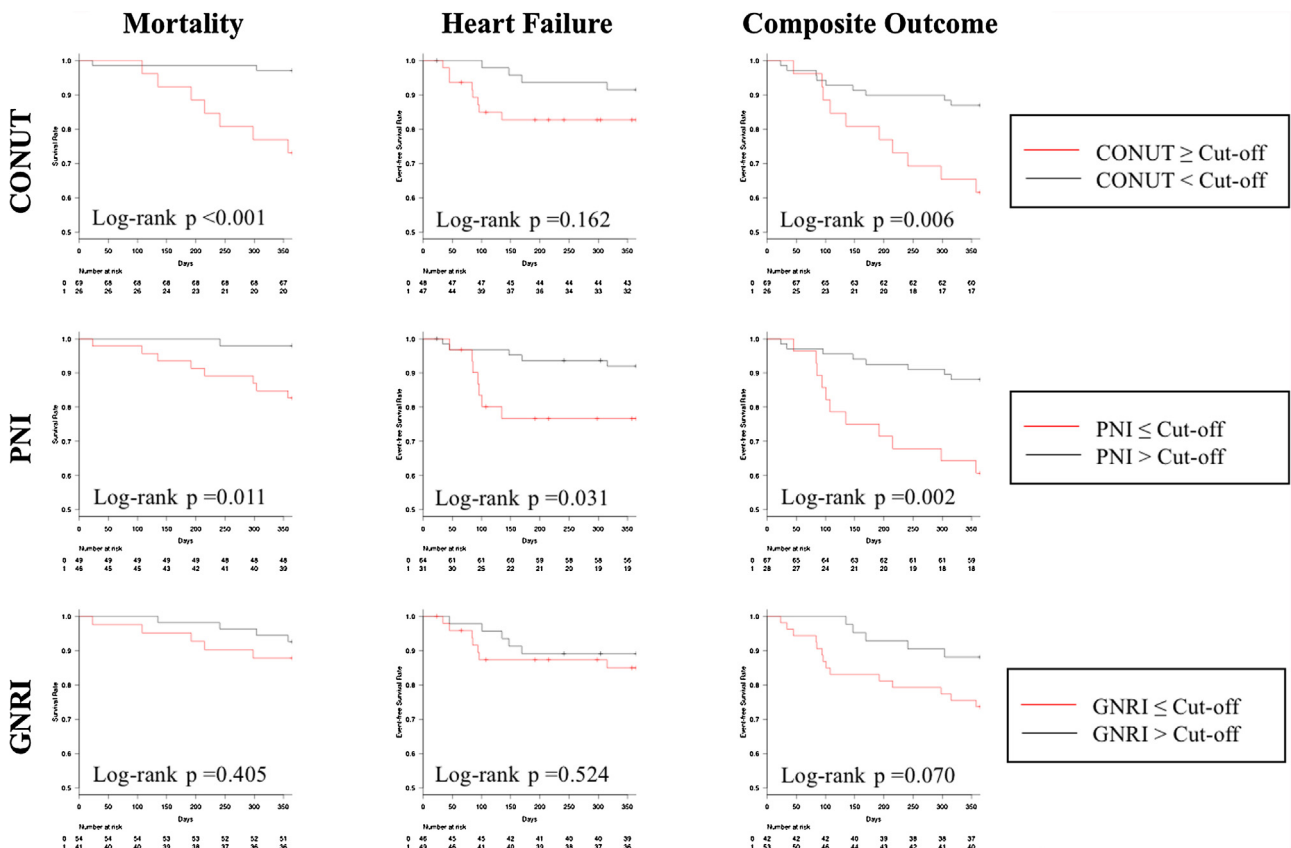
statistical significance was only observed in PNI (17.3% vs. 8.5%;  $p = 0.162$ , 23.4% vs. 8.0%;  $p = 0.031$ , 15.0% vs. 10.9%;  $p = 0.524$ , respectively). As for the composite outcome, a higher CONUT score and lower PNI were associated with significantly higher incidence rates (38.5% vs. 13.0%;  $p = 0.006$ , 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).



**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](https://doi.org/10.1016/j.jjcc.2019.02.017).

## References

- [1] Holmes Jr DR, Brennan JM, Rumsfeld JS, Dai D, O'Brien SM, Vemulapalli S, et al. Clinical outcomes at 1 year following transcatheter aortic valve replacement. *JAMA* 2015;313:1019–28.
- [2] Ando T, Takagi H, Briassoulis A, Umemoto T. Does diabetes mellitus impact prognosis after transcatheter aortic valve implantation? Insights from a meta-analysis. *J Cardiol* 2017;70:484–90.
- [3] Asami M, Windecker S, Praz F, Lanz J, Hunziker L, Rothenbuehler M, et al. Transcatheter aortic valve replacement in patients with concomitant mitral stenosis. *Eur Heart J* 2018. [http://dx.doi.org/10.1093/eurheartj/ehy834](https://doi.org/10.1093/eurheartj/ehy834). December 28 [Epub ahead of print].
- [4] Gonzalez-Ferreiro R, Munoz-Garcia AJ, Lopez-Otero D, Avanzas P, Pascual I, Alonso-Briales JH, et al. Prognostic value of body mass index in transcatheter aortic valve implantation: a "J"-shaped curve. *Int J Cardiol* 2017;232:342–7.
- [5] Sannino A, Schiattarella GG, Toscano E, Gargiulo G, Giugliano G, Galderisi M, et al. Meta-analysis of effect of body mass index on outcomes after transcatheter aortic valve implantation. *Am J Cardiol* 2017;119:308–16.
- [6] Castillo-Moreno JA, Garcia-Escribano IA, Martinez-Pascual-de-Riquelme M, Jaulent-Huertas L, Dau-Villarreal DF, Rubio-Paton R, et al. Prognostic usefulness of the 6-minute walk test in patients with severe aortic stenosis. *Am J Cardiol* 2016;118:1239–43.
- [7] Stortecky S, Schoenenberger AW, Moser A, Kalesan B, Juni 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;5:489–96.
- [8] Okuno T, Koseki K, Nakanishi T, Ninomiya K, Tomii D, Tanaka T, et al. Prognostic impact of computed tomography-derived abdominal fat area on transcatheter aortic valve implantation. *Circ J* 2018;82:3082–9.
- [9] Kano S, Yamamoto M, Shimura T, Kagase A, Tsuchi M, Kodama A, et al. Gait speed can predict advanced clinical outcomes in patients who undergo transcatheter aortic valve replacement: insights from a Japanese multicenter registry. *Circ Cardiovasc Interv* 2017;10. pii: e005088.
- [10] Sun X, Luo L, Zhao X, Ye P. Controlling Nutritional Status (CONUT) score as a predictor of all-cause mortality in elderly hypertensive patients: a prospective follow-up study. *BMJ open* 2017;7:e015649.
- [11] Iseki Y, Shibutani M, Maeda K, Nagahara H, Ohtani H, Sugano K, et al. Impact of the preoperative Controlling Nutritional Status (CONUT) Score on the survival after curative surgery for colorectal cancer. *PLoS ONE* 2015;10:e0132488.
- [12] Matsumura T, Mitani Y, Oki Y, Fujimoto Y, Ohira M, Kaneko H, et al. Comparison of Geriatric Nutritional Risk Index scores on physical performance among elderly patients with chronic obstructive pulmonary disease. *Heart Lung* 2015;44:534–8.
- [13] Narumi T, Arimoto T, Funayama A, Kadowaki S, Otaki Y, Nishiyama S, et al. Prognostic importance of objective nutritional indexes in patients with chronic heart failure. *J Cardiol* 2013;62:307–13.
- [14] Honda Y, Nagai T, Iwakami N, Sugano Y, Honda S, Okada A, et al. Usefulness of Geriatric Nutritional Risk Index for assessing nutritional status and its prognostic impact in patients aged  $\geq 65$  years with acute heart failure. *Am J Cardiol* 2016;118:550–5.
- [15] Cheng YL, Sung SH, Cheng HM, Hsu PF, Guo CY, Yu WC, et al. Prognostic Nutritional Index and the risk of mortality in patients with acute heart failure. *J Am Heart Assoc* 2017;6. pii: e004876.
- [16] Kunimura A, Ishii H, Uetani T, Aoki T, Harada K, Hirayama K, et al. Impact of nutritional assessment and body mass index on cardiovascular outcomes in patients with stable coronary artery disease. *Int J Cardiol* 2017;230:653–8.
- [17] Wada H, Dohi T, Miyauchi K, Doi S, Konishi H, Naito R, et al. Prognostic impact of nutritional status assessed by the Controlling Nutritional Status score in patients with stable coronary artery disease undergoing percutaneous coronary intervention. *Clin Res Cardiol* 2017;106:875–83.
- [18] Yokoyama M, Watanabe T, Otaki Y, Watanabe K, Toshima T, Sugai T, et al. Impact of objective malnutrition status on the clinical outcomes in patients with peripheral artery disease following endovascular therapy. *Circ J* 2018;82:847–56.
- [19] Horiuchi Y, Tanimoto S, Okuno T, Aoki J, Yahagi K, Sato Y, et al. Hemodynamic correlates of nutritional indexes in heart failure. *J Cardiol* 2018;71:557–63.
- [20] Ignacio de Ulibarri J, Gonzalez-Madrone A, de Villar NG, Gonzalez P, Gonzalez B, Mancha A, et al. CONUT: a tool for controlling nutritional status. First validation in a hospital population. *Nutr Hosp* 2005;20:38–45.
- [21] Onodera T, Goseki N, Kosaki G. Prognostic nutritional index in gastrointestinal surgery of malnourished cancer patients. *Nihon Geka Gakkai Zasshi* 1984;85:1001–5.
- [22] Cereda E, Pedrollo C. The Geriatric Nutritional Risk Index. *Curr Opin Clin Nutr Metab Care* 2009;12:1–7.
- [23] Shibata K, Yamamoto M, Kano S, Koyama Y, Shimura T, Kagase A, et al. Importance of Geriatric Nutritional Risk Index assessment in patients undergoing transcatheter aortic valve replacement. *Am Heart J* 2018;202:68–75.
- [24] Honda Y, Yamawaki M, Shigemitsu S, Kenji M, Tokuda T, Tsutsumi M, et al. Prognostic value of objective nutritional status after transcatheter aortic valve replacement. *J Cardiol* 2018. [http://dx.doi.org/10.1016/j.jjcc.2018.11.013](https://doi.org/10.1016/j.jjcc.2018.11.013). pii: S0914-5087(18)30341-1 [Epub ahead of print].
- [25] Kappetein AP, Head SJ, Genereux 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 (VARC-2). *Eur J Cardiothorac Surg* 2012;42:S45–60.
- [26] Koifman E, Magalhaes MA, Ben-Dor I, Kiramijyan S, Escarrega RO, Fang C, et al. Impact of pre-procedural serum albumin levels on outcome of patients undergoing transcatheter aortic valve replacement. *Am J Cardiol* 2015;115:1260–4.
- [27] Bogdan A, Barbash IM, Segev A, Fefer P, Bogdan SN, Asher E, et al. Albumin correlates with all-cause mortality in elderly patients undergoing transcatheter aortic valve implantation. *EuroIntervention* 2016;12:e1057–64.
- [28] Yamamoto M, Shimura T, Kano S, Kagase A, Kodama A, Sago M, et al. Prognostic value of hypoalbuminemia after transcatheter aortic valve implantation (from the Japanese Multicenter OCEAN-TAVI Registry). *Am J Cardiol* 2017;119:770–7.
- [29] Clark AL, Fonarow GC, Horwich TB. Obesity and the obesity paradox in heart failure. *Prog Cardiovasc Dis* 2014;56:409–14.
- [30] Marculi M, de Souza Buto MF, Madaloso BA, Nunes RA, Cuoco MA, de Paula RS, et al. Lymphocyte count and prognosis in patients with heart failure. *Int J Cardiol* 2015;188:60–2.
- [31] Greene SJ, Vaduganathan M, Lupi L, Ambrosio AP, Mentz RJ, Konstam MA, et al. Prognostic significance of serum total cholesterol and triglyceride levels in patients hospitalized for heart failure with reduced ejection fraction (from the EVEREST Trial). *Am J Cardiol* 2013;111:574–81.
- [32] Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med* 2011;364:2187–98.
- [33] Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med* 2010;363:1597–607.
- [34] Koder S, Kiyosue A, Ando J, Komuro I. Cost effectiveness of transcatheter aortic valve implantation in patients with aortic stenosis in Japan. *J Cardiol* 2018;71:223–9.
- [35] Van Mieghem NM, van der Boon RM, Nuis RJ, Schultz C, van Geuns RJ, Serruys PW, et al. Cause of death after transcatheter aortic valve implantation. *Catheter Cardiovasc Interv* 2014;83:E277–82.