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ORIGINAL PAPER

Nutritional status and risk of all-cause mortality in patients undergoing transcatheter aortic valve replacement assessment using the geriatric nutritional risk index and the controlling nutritional status score

Kyusup Lee[1] · Jung-Min Ahn[2] · Do-Yoon Kang[2] · Euihong Ko[2] · Osung Kwon[2] · Pil Hyung Lee[2] · Seung-Whan Lee[2] · Dae-Hee Kim[2] · Ho Jin Kim[3] · Joon Bum Kim[3] · Suk Jung Choo[3] · Duk-Woo Park[2] · Seung-Jung Park[2]

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Abstract

Background Nutritional status, a key marker of patient frailty, is an important prognostic factor after transcatheter aortic valve replacement (TAVR). Few investigations have evaluated the clinical usefulness of nutritional assessment tools for predicting the risk of mortality following TAVR.

Methods A total of 412 patients with symptomatic severe AS who underwent TAVR between March 2010 and August 2017 were stratified into subgroups by their Geriatric Nutritional Risk Index [GNRI, low ≤ 98 vs. high > 98 (better nutritional status)] and Controlling Nutritional Status (CONUT) score [low ≤ 3 vs. high ≥ 4; (poorer nutritional status)]. The primary study outcome was all-cause mortality at 1 year.

Results Patients with low GNRI score showed a significantly higher 1-year mortality rate as compared to those with high GNRI score (13.0% vs. 3.2%, respectively; $P = 0.001$). Similarly, patients with high CONUT score had a significantly higher rate of 1-year mortality than those with low CONUT score (15.7% vs. 6.2%, respectively; $P = 0.005$). However, in multivariable Cox proportional-hazards models, low GNRI was the only independent predictor of mortality (adjusted hazard ratio, 3.77; 95% confidence interval 1.54–9.20; $P = 0.004$). Overall, integration of GNRI into conventional risk models of STS score or logistic EuroSCORE resulted in improved predictive value for mortality measured by the net reclassification improvement and the integrated discrimination improvement.

Conclusions In patients undergoing TAVR, low GNRI (but not high CONUT score) was independently associated with a higher risk of 1-year mortality. Further research is required to determine whether nutritional screening and management can improve clinical outcomes in patients undergoing TAVR.

Kyusup Lee and Jung-Min Ahn contributed equally to this article.

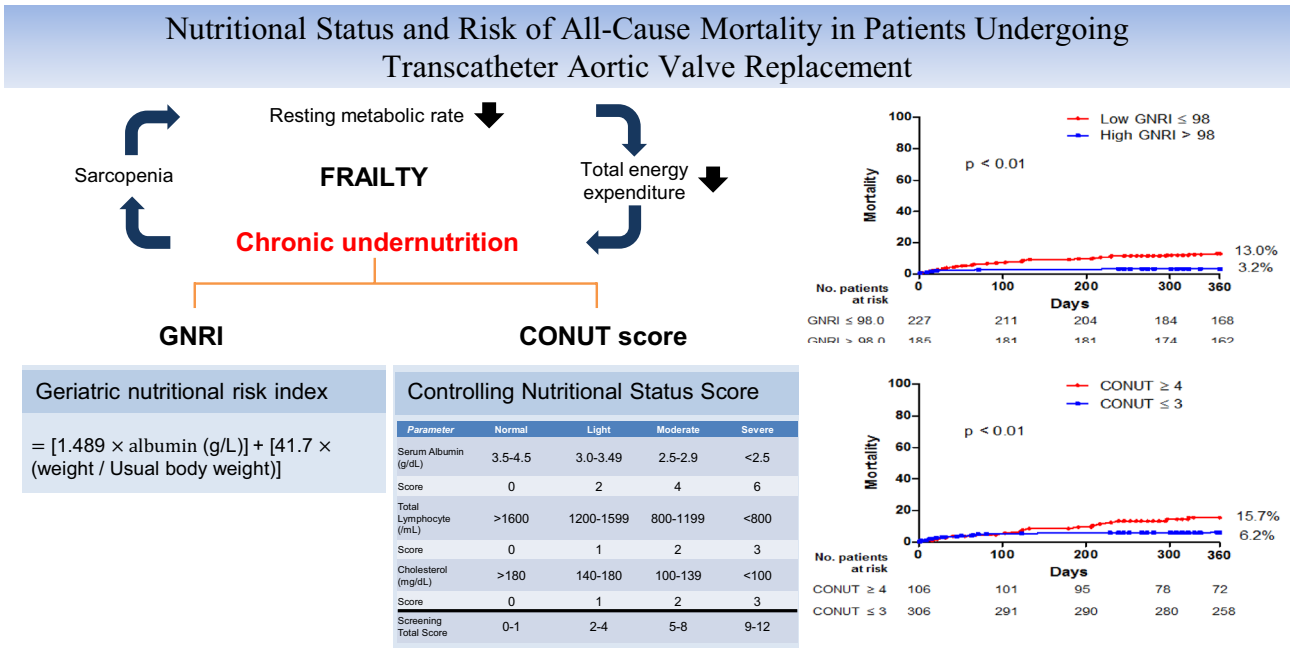
✉ Duk-Woo Park
dwpark@amc.seoul.kr

[1] Department of Cardiology, Daejeon St Mary's Hospital, The Catholic University of Korea, Daejeon, South Korea

[2] Department of Cardiology, Asan Medical Center, University of Ulsan College of Medicine, 88, Olympic-ro 43-gil, Songpa-gu, Seoul 05505, South Korea

[3] Department of Thoracic and Cardiovascular Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea

Graphic abstract



Keywords Aortic stenosis · Mortality · Nutritional status · Transaortic valve replacement

Abbreviations

AS	Aortic stenosis
BMI	Body-mass index
CONUT	Controlling nutritional status
CT	Computed tomography
EuroSCORE	Logistic European System for cardiac operative risk evaluation
GNRI	Geriatric nutritional risk index
STS	Society of thoracic surgeons
TAVR	Transcatheter aortic valve replacement
VARC	The valve academic research consortium

Introduction

In patients with severe symptomatic aortic stenosis (AS), procedural results and short- and long-term clinical outcomes of transcatheter aortic valve replacement (TAVR) have markedly improved with the availability of newer devices, simplified procedures, and greater procedural expertise [1, 2]. Nevertheless, mortality after TAVR remains still high, particularly in elderly, fragile patients and in those who are considered inoperable or a high surgical risk [3–7]. Thus, in patients who are undergoing TAVR procedures, enhanced risk assessment would be of great clinical value to accurately identify those at increased risk of post-TAVR mortality, allowing patients to be targeted for preventive or therapeutic measures.

In elderly patients, frailty is considered to be an important factor when defining a patient's general health status and is known to be a significant predictor of worse clinical outcomes in patients undergoing TAVR [8, 9]. Among several important components reflecting the degree of frailty, chronic undernutrition or malnutrition is a key determinant of disability and death. Simple risk scoring algorithms, such as the Geriatric Nutritional Risk Index (GNRI) and the Controlling nutritional status (CONUT) score, have been proposed as useful screening tools for the assessment of nutritional status [10–12]. Several studies have shown the clinical value of these tools in diverse patient populations [12–17]. However, there are limited data regarding the prognostic value and clinical utility of these nutritional assessment tools in elderly patients undergoing TAVR. We, therefore, investigated the clinical impact of baseline GNRI and CONUT scores on mortality and determine the incremental usefulness of these scores beyond conventional risk stratification models in 'real-world' patients undergoing TAVR.

Materials and methods

Study population and TAVR procedures

Consecutive patients with symptomatic, severe AS undergoing TAVR between March 2010 and August 2017 from three heart centers in East Asia were considered eligible for this study. Inclusion criteria include patients with symptomatic severe aortic stenosis who are not candidates for surgical aortic valve replacement because of coexisting illnesses. We did not exclude any of patients who received TAVR to lessen the selection bias. For the current study, patients who have valid information on each component of the GNRI and CONUT score at baseline were included in this analysis. At screening, all patients underwent clinical evaluation, including medical history, physical examination, electrocardiography, chest radiography, echocardiography, computed tomography (CT), and laboratory testing (complete blood count, liver function test, blood urea nitrogen, serum creatinine, serum electrolyte, and brain natriuretic peptide). Traditional surgical risk score models were considered according to the Society of Thoracic Surgeons (STS) score and the Logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE).

The decision to proceed with TAVR was made by the local multidisciplinary heart team following consideration of the patient's age, comorbidities, and surgical risk. TAVR was performed according to standard methods [18] and the valve type (balloon- or self-expandable) was determined by the heart team. The size of the aortic annulus was analyzed using 3-dimensional, multi-detector computed tomography and echocardiography to determine the device size. The transfemoral route was preferred; if this was not possible, other approaches (such as via the apical, subclavian, or direct aortic routes) were considered.

This study protocol was approved by the institutional review board of each participating center, and all patients provided written informed consent.

Nutritional assessment

The nutritional status of each patient was evaluated using two composite indexes: the GNRI and CONUT score. The GNRI, which includes two nutritional indicators (serum albumin and the patient's body weight compared with usual body weight), was developed by modifying the nutritional risk index for elderly patients: $\text{GNRI} = 1.489 \times \text{albumin (g/L)} + 41.7 \times \text{body weight (kg)/usual body weight (kg)}$, with higher values reflecting a better nutritional status [10, 19]. Patients were stratified into two groups according to the GNRI score: $\text{GNRI} \leq 98$ (low GNRI, indicating poor nutritional status) and > 98 (high GNRI, indicating normal nutritional status) [10, 13, 20, 21]. The CONUT score was calculated using serum albumin, total lymphocyte count, and total cholesterol values, with higher scores indicating a worse nutritional status [11]. Patients were grouped according to their CONUT score [low, ≤ 3 (< 75th percentile] and high, ≥ 4 [≥ 75th percentile)] [14, 22]. All laboratory data for the calculation of GNRI and CONUT score were obtained at baseline prior to TAVR.

Study outcomes and follow-up

The primary study outcome was all-cause mortality at 1 year. Secondary outcome included procedural complications and cardiovascular death, stroke (any or disabling), and bleeding events (any or major/life-threatening) at 1 year. All study outcomes were defined according to the criteria of the Valve Academic Research Consortium-2 (VARC-2) [23]. All events were independently reviewed and adjudicated by an independent group of clinicians blinded to the study purpose.

Clinical, procedural, and outcome data were collected using a dedicated electronic case report form, which included baseline clinical, laboratory, echocardiographic, and computed tomographic data as well as procedural and clinical follow-up data. Clinical follow-up after TAVR was performed via clinic visits and/or telephone interview at 1, 6, and 12 months and every 6 months thereafter. Referring cardiologists, general practitioners, and patients were contacted as necessary to obtain further information. At each follow-up contact, data pertaining to patients' clinical status and occurrence of any adverse clinical events were collected.

Statistical analysis

Baseline characteristics of the study population, including patient demographics, risk factors or comorbidities, clinical presentation, cardiac status, and anatomic/procedural features, were examined using proportions for categorical variables and means ± standard deviation (SD) according to the groups stratified by predefined criteria of the GNRI and CONUT score. Continuous variables are presented as mean ± SD and compared using Student's *t* test (for parametric variables) or Mann–Whitney *U* test (for non-parametric variables). Categorical variables are presented as counts or percentages and compared using the Chi square or Fisher exact test, as appropriate.

Cumulative incidence was estimated by the Kaplan–Meier method and differences were assessed using the log-rank test. The entire follow-up dataset was used to analyze time-to-event outcomes and patients were censored at the time of death, outcomes of interest or last available follow-up, whichever came first. A Cox proportional hazards model

was used to identify independent predictors of primary outcome of all-cause mortality. Covariates with a P value < 0.1 by univariate analysis and clinically relevant variables were included in the multivariable, stepwise Cox regression models.

The GNRI and CONUT scores were included into conventional risk models of STS score and logistic EuroSCORE to determine whether they improved the discrimination of the model. The ability to classify risk was assessed with the use of the C statistic in each Cox regression model [24]. In addition, the continuous net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were calculated to assess the predictive improvement of GNRI or CONUT score beyond the conventional risk model [25, 26]. All statistical analysis was performed using SPSS version 21.0 (IBM Corp. Armonk, NY) and R version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria). All P values were two-sided and values less than 0·05 were judged statistically significant.

Results

Study population and baseline characteristics

Between March 2010 and August 2017, a total of 412 patients with severe symptomatic AS who underwent TAVR and had valid measurement of the GNRI and CONUT scores were included in this analysis. The median GNRI was 97.0 (IQR, 90.9–103.2; minimum, 64.0; maximum, 127.2) and the median CONUT score was 2 (IQR, 1–4; minimum, 1; maximum, 4). The baseline clinical characteristics and laboratory findings of the patients, stratified according to low or high GNRI and CONUT score, are shown in Table 1. Patients in the low GNRI group (i.e., poor nutritional status) were older, had a lower mean body-mass index, had a higher mean STS score and logistic EuroSCORE, and had a higher proportion of prior stroke and renal insufficiency than the high GNRI group (i.e., better nutritional status). Similarly, patients with a high CONUT score (i.e., poor nutritional status) were older, had a lower body-mass index, had a higher mean STS and logistic EuroSCORE, and had a higher proportion of prior myocardial infarction, stroke and renal insufficiency than the low CONUT score group (i.e., better nutritional status).

Baseline echocardiographic, CT, and procedural characteristics are shown in Table 2. Patients with a poor nutritional status (low GNRI or high CONUT score) had a larger indexed aortic valve area (AVA), higher maximal velocity of transtricuspid valve regurgitation, and a higher prevalence of moderate to severe ascending aortic arch calcification. However, there were no significant differences in procedural characteristics. Periprocedural complications, according to low or high of GNRI and CONUT score, are shown in supplementary Table 1. Overall, there were no significant differences between the groups, with the exception of the rate of bleeding, which was significantly higher in the high CONUT score group, and the rate of in-hospital death, which was higher in the low GNRI group.

Clinical outcomes

The median duration of follow-up was 499.5 days (interquartile range 289.5–1059.3 days). The primary outcome of all-cause mortality at 1 year was significantly higher in patients with low GNRI than in those with high GNRI (13.0% vs. 3.2%, respectively; Table 3 and Fig. 1). The 1-year cardiovascular death rate was also significantly higher in the low GNRI group, but there were no significant differences in the rate of stroke and bleeding events between the low- and high GNRI groups. The 1-year rate of all-cause mortality was also significantly higher in patients with high CONUT scores than in those with low scores (15.7% vs. 6.2%, respectively; Table 3 and Fig. 2). The rate of any stroke and the rate of any bleeding was also significantly higher in the high CONUT score group than in the low score group.

Table 4 summarizes the results of Cox proportional hazards analysis of all-cause mortality. In the univariate analysis, a low GNRI and a high CONUT score was associated with an increased risk of all-cause mortality. However, in the multivariate Cox regression analysis, we observed an independent association between malnutrition according to the GNRI but not with the CONUT score and mortality at 1 year.

Incremental value of GNRI and CONUT score over conventional risk model

The improvement in risk discrimination of conventional risk models for all-cause mortality by the addition of the GNRI and CONUT score is shown in Table 5. The addition of the GNRI to the STS score and logistic EuroSCORE resulted in a non-significant increase in the ability to classify risk, as measured by the C-statistic. In addition, the integration of the GNRI into STS score or logistic EuroSCORE resulted in a significant improvement in the predictive value for mortality, as measured by the NRI and the IDI, suggesting the addictive prognostic value of the GNRI score for risk stratification of mortality. However, the addition of CONUT score resulted in no change of C-statistics and model discrimination measured by the NRI and the IDI.

Table 1 Baseline patient characteristics

Variable	All patients ($n=412$)	GNRI ≤ 98 ($n=227$)	GNRI > 98 ($n=185$)	*P*	CONUT ≥ 4 ($n=106$)	CONUT ≤ 3 ($n=306$)	*P*
Age, years	78.7 ± 5.2	79.7 ± 5.2	77.4 ± 4.8	< 0.001	79.9 ± 5.1	78.3 ± 5.2	0.006
Male	198 (48.1)	117 (51.5)	81 (43.8)	0.12	56 (52.8)	142 (46.4)	0.25
Body-mass index, kg/m^2	23.9 ± 3.4	22.0 ± 2.4	26.3 ± 2.8	< 0.001	22.8 ± 3.4	24.3 ± 3.2	< 0.001
Body-surface area, m^2	1.6 ± 0.2	1.5 ± 0.2	1.7 ± 0.1	< 0.001	1.6 ± 0.1	1.6 ± 0.1	0.05
Logistic Euro-SCORE, %	12.1 (7.7, 20.8)	12.5 (7.9, 22.0)	11.9 (7.5, 19.8)	0.15	14.4 (8.4, 21.7)	11.6 (7.5, 20.4)	0.023
STS score, %	3.2 (2.3, 5.1)	3.9 (2.7, 5.6)	2.6 (1.9, 3.8)	< 0.001	4.2 (2.7, 6.2)	2.9 (2.1, 4.6)	< 0.001
Hypertension	350 (85.0)	186 (81.9)	164 (88.6)	0.06	90 (84.9)	260 (85.0)	0.99
Diabetes mellitus	131 (31.8)	67 (29.5)	64 (34.6)	0.27	37 (34.9)	94 (30.7)	0.43
Hyperlipidemia	270 (65.5)	138 (60.8)	132 (71.4)	0.03	66 (62.3)	204 (66.7)	0.41
Current smoker	45 (10.9)	25 (11.0)	20 (10.8)	0.95	11 (10.4)	34 (11.1)	0.84
Atrial fibrillation	58 (14.1)	35 (15.4)	23 (12.4)	0.39	20 (18.9)	38 (12.4)	0.10
History of MI	22 (5.3)	16 (7.0)	6 (3.2)	0.09	11 (10.4)	11 (3.6)	0.007
Prior PCI	117 (28.4)	63 (27.8)	54 (29.2)	0.75	34 (32.1)	83 (27.1)	0.33
Prior CABG	24 (5.8)	12 (5.3)	12 (6.5)	0.61	9 (8.5)	15 (4.9)	0.17
Prior AVR	9 (2.2)	4 (1.8)	5 (2.7)	0.52	4 (3.8)	5 (1.6)	0.24
History of CHF	81 (19.7)	51 (22.5)	30 (16.2)	0.11	24 (22.6)	57 (18.6)	0.37
NYHA class, III or IV	202 (49.0)	113 (49.8)	89 (48.1)	0.74	58 (54.7)	144 (47.1)	0.17
History of CAD	165 (40.0)	89 (39.2)	76 (41.1)	0.70	44 (41.5)	121 (39.5)	0.72
History of CVA	41 (10.0)	29 (12.8)	12 (6.5)	0.03	19 (17.9)	22 (7.2)	0.001
History of PAD	24 (5.8)	14 (6.2)	10 (5.4)	0.74	10 (9.4)	14 (4.6)	0.07
Renal insufficiency	127 (30.8)	81 (35.7)	46 (24.9)	0.02	52 (49.1)	75 (24.5)	< 0.001
eGFR, mL/min/1.73 m^2	72.2 (53.8, 84.8)	68.0 (49.0, 84.0)	74.7 (58.2, 86.0)	0.032	60.3 (40.6, 79.2)	74.1 (59.8, 87.0)	< 0.001
Chronic lung disease	32 (7.8)	16 (7.0)	16 (8.6)	0.55	11 (10.4)	21 (6.9)	0.24
Chronic liver disease	15 (3.6)	9 (4.0)	6 (3.2)	0.70	7 (6.6)	8 (2.6)	0.06
Laboratory data							
Albumin, g/dL	3.6 (3.3, 3.8)	3.3 (3.1, 3.6)	3.8 (3.6, 4.0)	< 0.001	3.2 (2.9, 3.4)	3.7 (3.5, 3.8)	< 0.001
Hemoglobin, g/dL	11.6 (10.6, 12.8)	11.3 (10.3, 12.3)	12.2 (11.2, 13.3)	< 0.001	10.8 (10.0, 12.0)	12.0 (10.8, 13.0)	< 0.001
Creatinine, mg/dL	0.9 (0.7, 1.2)	1.0 (0.8, 1.2)	0.9 (0.7, 1.1)	0.008	1.1 (0.8, 1.5)	0.9 (0.7, 1.1)	< 0.001
Total cholesterol, mg/dL	148 (124, 176)	143 (118, 169)	154 (130, 180)	0.002	125 (108, 142)	157 (135, 182)	< 0.001
Total lymphocyte count (/μL)	1680 (1327, 2154)	1555 (1229, 1944)	1857 (1421, 2298)	< 0.001	1214 (979, 1660)	1797 (1461, 2235)	< 0.001
BNP, pg/mL	196 (83, 479)	281 (102, 616)	144 (57, 350)	< 0.001	334 (133, 780)	72 (72, 419)	< 0.001

Values are presented as *n* (%) or mean ± standard deviation, or median (interquartile range), depending on variable distribution

GNRI Geriatric Nutritional Risk index, *CONUT* Controlling Nutritional Status, *AVR* aortic valve replacement, *BNP* brain natriuretic peptide, *CABG* coronary artery bypass grafting, *CAD* coronary artery disease, *CHF* congestive heart failure, *CVA* cerebrovascular accident, *eGFR* estimated glomerular filtration rate, *MI* myocardial infarction, *NYHA class* New York Heart Association Functional classification, *PAD* peripheral artery disease, *PCI* percutaneous coronary intervention, *STS score* the Society of Thoracic Surgery risk score

Table 2 Baseline echocardiographic and CT data and procedural characteristics

Variable	All patients ($n=412$)	GNRI ≤ 98 ($n=227$)	GNRI > 98 ($n=185$)	*P*	CONUT ≥ 4 ($n=106$)	CONUT ≤ 3 ($n=306$)	*P*
Echocardiographic parameters							
Peak jet velocity, m/s	4.9 (4.3, 5.5)	4.9 (4.3, 5.3)	5.0 (4.4, 5.6)	0.15	4.7 (4.2, 5.3)	5.0 (4.4, 5.5)	0.013
Peak gradient, mm Hg	97 (76, 119)	95 (74, 113)	99 (76, 126)	0.12	87 (69, 114)	99 (77, 121)	0.017
Mean gradient, mm Hg	57 (44, 74)	56 (43, 70)	58 (46, 75)	0.16	53 (41, 68)	58 (46, 74)	0.026
Aortic valve area, cm^2	0.60 (0.49, 0.72)	0.60 (0.50, 0.70)	0.60 (0.48, 0.74)	0.92	0.64 (0.52, 0.73)	0.59 (0.49, 0.71)	0.06
Indexed AVA, cm^2/m^2	0.39 ± 0.11	0.40 ± 0.11	0.37 ± 0.10	0.005	0.41 ± 0.11	0.38 ± 0.10	0.03
TR Vmax, m/s	2.6 (2.4, 3.0)	2.7 (2.4, 3.1)	2.6 (2.3, 2.9)	0.024	2.7 (2.4, 3.2)	2.6 (2.3, 2.9)	0.021
LV ejection fraction, %	62 (57, 65)	62 (57, 66)	62 (57, 65)	0.53	62 (56, 65)	62 (57, 65)	0.63
AR ≥ grade 2	57 (13.8)	35 (15.4)	22 (11.9)	0.30	17 (16.0)	40 (13.1)	0.45
MR ≥ grade 2	43 (10.4)	26 (11.5)	17 (9.2)	0.46	11 (10.4)	32 (10.5)	0.98
CT parameters							
Aortic annulus							
Maximal diameter, mm	26.5 ± 2.8	26.5 ± 2.7	26.4 ± 3.0	0.64	26.9 ± 2.9	26.3 ± 2.8	0.10
Minimal diameter, mm	21.0 ± 2.4	20.8 ± 2.2	21.2 ± 2.6	0.16	21.1 ± 2.3	20.9 ± 2.4	0.61
Area, mm^2	435.0 ± 84.5	83.4 ± 5.5	86.1 ± 6.4	0.88	87.0 ± 8.4	83.5 ± 4.8	0.13
Perimeter, mm	75.3 ± 7.3	75.3 ± 7.1	75.2 ± 7.5	0.97	76.1 ± 7.3	75.0 ± 7.2	0.15
Total calcium amount, mm^3	575.3 ± 7.3	355.5 ± 300.6	354.9 ± 273.5	0.99	333.1 ± 272.5	362.9 ± 294.0	0.37
Moderate to severe calcification of the ascending aortic arch	114 (27.7)	76 (33.5)	38 (20.5)	0.003	41 (38.7)	73 (23.9)	0.003
Procedural characteristics							
Approach route							
TF approach	393 (95.4)	214 (94.3)	179 (96.8)	0.24	99 (93.4)	294 (96.1)	0.14
Non-TF approach	19 (4.6)	13 (5.7)	6 (3.2)		7 (6.6)	12 (3.9)	
Transapical approach	14 (3.4)	8 (3.5)	6 (3.2)		4 (3.8)	10 (3.3)	
Transaortic approach	4 (1.0)	4 (1.8)	0 (0)		3 (2.8)	1 (0.3)	
Trans-subclavian approach, *n*	1 (0.2)	1 (0.4)	0 (0)		0 (0)	1 (0.3)	
Valve type							
Balloon expandable	270 (65.5)	144 (63.4)	126 (68.1)	0.32	66 (62.3)	204 (66.7)	0.41
Self-expandable	142 (34.5)	83 (36.6)	59 (31.9)		40 (37.7)	102 (33.3)	
Anesthesia							
MAC	203 (49.3)	120 (52.9)	83 (44.9)	0.11	55 (51.9)	148 (48.4)	0.53
General anesthesia	209 (50.7)	107 (47.1)	102 (55.1)		51 (48.1)	158 (51.6)	
Balloon post-dilatation	121 (29.4)	68 (30.0)	53 (28.6)	0.77	38 (35.8)	83 (27.1)	0.09

Values are presented as *n* (%) or mean ± SD, or median (interquartile range), depending on variable distribution

GNRI geriatric nutritional risk index, *CONUT* controlling nutritional status, *AVA* aortic valve area, *CT* computed tomography, *LV* left ventricle, *MAC* monitored anesthetic care, *MR* mitral regurgitation, *TF* transfemoral, *TR Vmax* tricuspid regurgitation peak velocity

Discussion

This observational study evaluated the prognostic relevance and clinical usefulness of two different nutritional assessment tools (the GNRI and the CONUT score) in patients with severe AS undergoing TAVR for predicting all-cause mortality. In the univariate analyses, poor nutritional status, defined by low GNRI or high CONUT score,

Table 3 Clinical outcomes at 12 months

Outcomes	All patients ($n=412$)	GNRI ≤ 98 ($n=227$)	GNRI > 98 ($n=185$)	P	CONUT ≥ 4 ($n=106$)	CONUT ≤ 3 ($n=306$)	P
Primary outcome							
Death from any causes	35 (8.5)	29 (13.0)	6 (3.2)	0.001	16 (15.7)	19 (6.2)	0.005
Secondary outcomes							
Death from cardiovascular causes	19 (4.6)	15 (6.8)	4 (2.2)	0.03	8 (8.2)	11 (3.6)	0.09
Stroke							
Any	25 (6.1)	17 (7.9)	8 (4.6)	0.16	11 (11.4)	14 (4.8)	0.02
Disabling	10 (2.4)	4 (2.8)	6 (2.2)	0.73	5 (5.1)	5 (1.7)	0.07
Bleeding							
Any bleeding	176 (42.7)	100 (44.4)	76 (41.1)	0.44	55 (52.7)	121 (39.6)	0.02
Major or life threatening	136 (33.0)	74 (32.7)	62 (33.5)	0.92	40 (38.0)	96 (31.4)	0.23

Event rates (percentages) were derived from the Kaplan–Meier method

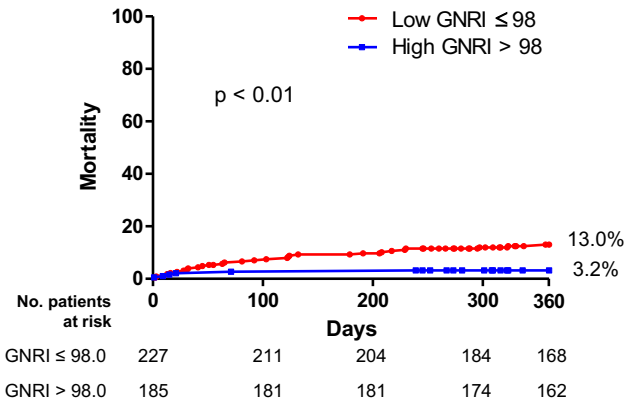


Fig. 1 Kaplan–Meier curves for 1-year all-cause mortality stratified by geriatric nutritional risk index (GNRI)

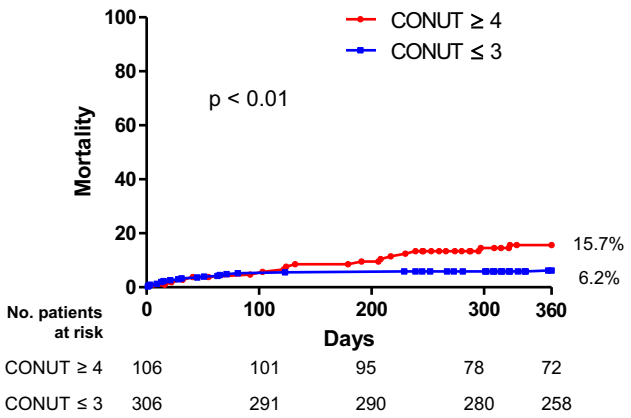


Fig. 2 Kaplan–Meier curves for 1-year all-cause mortality stratified by controlling nutritional status (CONUT) score

was associated with an increased risk of all-cause mortality at 1 year. In the multivariable analyses, lower GNRI was independently associated with 1-year all-cause mortality, but not with the CONUT score. For the assessment of mortality risk-prediction, integration of GNRI into traditional tools (STS score or logistic EuroSCORE) resulted in an improved risk stratification.

Patient risk stratification is crucial for identifying appropriate candidates for TAVR procedures and predicting major cardiovascular events and mortality. The logistic EuroSCORE and STS score are the most widely used tools for the prediction of mortality in patients undergoing TAVR. However, both models were developed and validated in a standard surgical risk population and their predictive power is, therefore, suboptimal in patients with severe AS receiving TAVR. It has been suggested that the predictive power of these models could be improved by the addition of specific clinical and anatomical variables that affect mortality [27], including frailty and nutritional status, which are known to be important factors and are not included in either risk model [28]. Several studies have suggested the association and clinical usefulness of an additive nutritional or frailty assessment index for predicting mortality following TAVR [8, 29–34]. In the current study, we evaluated two nutritional assessment tools, the GNRI and CONUT score, for predicting mortality following TAVR. Conventional frailty assessment is based on physical performance measures or cognitive assessments and could not be easily assessed in patients with a high comorbidity burden or in extremely frail patients [13, 35].The GNRI and CONUT score can be useful in overcoming the limitations of frailty assessments, being readily determined from available laboratory data and records of body weight/height.

Table 4 Univariate and multivariate predictors of all-cause mortality at 12 months

Variables	Univariate		Multivariate	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
GNRI ≤ 98	4.13 (1.72–9.96)	0.002	3.77 (1.54–9.20)	0.004
CONUT ≥ 4	2.51 (1.29–4.88)	0.007	‡	‡
Age	1.05 (0.98–1.12)	0.19	‡	‡
Male gender	1.89 (0.95–3.76)	0.07	‡	‡
Body-mass index, kg/m^2	0.93 (0.84–1.03)	0.15	*	*
Logistic EuroSCORE	1.04 (1.03–1.06)	< 0.001	*	*
STS score	1.07 (1.04–1.10)	< 0.001	1.05 (1.02–1.08)	0.001
Diabetes mellitus	2.64 (1.36–5.13)	0.004	*	*
Previous MI	3.07 (1.19–7.91)	0.020	*	*
Previous PCI	1.94 (0.99–3.79)	0.052	*	*
PAD	3.41 (1.41–8.21)	0.006	*	*
Renal insufficiency[a]	3.16 (1.62–6.17)	0.001	*	*
Dialysis	5.77 (2.52–13.22)	< 0.001	*	*
RBBB	2.72 (1.23–6.02)	0.013	2.56 (1.10–5.98)	0.029
Albumin	0.85 (0.79-0.91)	< 0.001	*	*
Hemoglobin	0.80 (0.68–0.96)	0.013	‡	‡
Transfemoral approach	0.36 (0.13–1.02)	0.06	‡	‡
Transaortic valve Vmax	0.63 (0.41–0.95)	0.027	‡	‡
MR ≥ grade 2	1.69 (0.84–3.39)	0.14	*	*
TR Vmax ≥ 3.4 m/s	2.32 (1.01–5.31)	0.047	*	*
LV EF, %	0.97 (0.94–0.99)	0.005	‡	‡

CONUT Controlling Nutritional Status, *GNRI* Geriatric Nutritional Risk Index, *HR* hazard ratio, *LVEF* left ventricular ejection fraction, *MI* myocardial infarction, *MR* mitral regurgitation, *PAD* peripheral artery disease, *PCI* percutaneous coronary intervention, *RBBB* right bundle branch block, *STS score* The Society of Thoracic Surgery risk score, *TR Vmax* tricuspid regurgitation peak velocity

*Not used for multivariate analysis because of collinearity problems

[a]Renal insufficiency was defined as eGFR < 60 mL/min/1.73 m^2

‡Not retained as an independent predictor in the multivariate analysis

Table 5 Discrimination and reclassification performance of geriatric nutritional risk index to predict primary outcome of all-cause mortality at 12 months

Models	C-statistics		NRI		IDI	
	C-index (95% CI)	*P* value	Index (95% CI)	*P* value	Index (95% CI)	*P* value
Logistic EuroSCORE	0.680 (0.584–0.776)	Reference	Reference	Reference	Reference	Reference
Plus GNRI[a]	0.732 (0.636–0.828)	0.16	0.321 (0.040–0.424)	0.02	0.027 (0.004–0.065)	0.01
Plus CONUT[a]	0.696 (0.600–0.792)	0.58	0.241 (-0.031-0.433)	0.09	0.014 (-0.001–0.068)	0.09
STS score	0.709 (0.613–0.805)	Reference	Reference	Reference	Reference	Reference
Plus GNRI[a]	0.735 (0.639–0.831)	0.37	0.293 (0.152–0.432)	0.02	0.026 (0.006–0.060)	0.007
Plus CONUT[a]	0.707 (0.611–0.803)	0.94	0.212 (-0.044–0.410)	0.11	0.013 (0.000–0.069)	0.04

The Society of Thoracic Surgeons (STS) score measures patient risk at the time of cardiovascular surgery on a scale of 0–100%, with higher numbers indicating greater risk. The logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE), which measures patient risk at the time of cardiovascular surgery, is calculated using a logistic-regression equation, with scores ranging from 0 100%, with higher scores indicating greater risk

CONUT controlling nutritional status, *GNRI* geriatric nutritional risk index, *CI* confidence interval, *NRI* net reclassification index, *IDI* integrated discrimination improvement

[a]Categorized variables (low vs. high GNRI and low vs. high CONUT score)

Several studies have reported that serum albumin levels are associated with a greater risk of all-cause mortality in patients undergoing TAVR [31, 36, 37]. The VARC-2 criteria also defined serum albumin < 3.5 g/dL as one of the frailty factors reflecting a nutritional parameter [23]. In the current study, we found that the GNRI and CONUT score, which incorporate albumin values, reflected mortality risk. However, in the multivariable analyses, after adjustment for other risk covariates, lower GNRI (≤ 98) only remained as the independent predictor of all-cause death at 1 year. This association was similar to that seen in a recent report of data from a Japanese multicenter registry [13]. By contrast, the CONUT score, which incorporates three laboratory findings (i.e., albumin, lymphocyte count, and cholesterol levels), was not independently associated with all-cause death at 1 year. Previous studies have, however, demonstrated the usefulness of the CONUT score as a tool for assessing nutritional status in patients with heart failure or stable coronary artery disease [38, 39]. The exact reasons for the discrepancy seen between the CONUT score and the GNRI in the current study is unclear, but may in part be explained by a lack of information on baseline body characteristics in the CONUT score and differences in combined comorbidities, practice pattern of TAVR procedures, or racial and ethnic differences between our study population and those enrolled in previous studies. Also, it might be possible that the sample size of study population was not high enough to show independence of the CONUT score for predicting of mortality and that cholesterol level might be affected in patients receiving statin therapy. From a practical standpoint, GNRI may be a more sensitive marker of nutritional status than CONUT score when considering the nutritional status of patients prior to TAVR.

Models for risk prediction are widely used in clinical practice to stratify patients and assign treatment strategies. Traditionally, risk models have been evaluated using the area under the receiver-operating characteristic curve (i.e., C-statistics) [24], but this method has been criticized as lacking sensitivity when comparing models and for having little direct clinical relevance [40]. To overcome these limitations, methods based on risk stratification have been proposed to compare predictive models (e.g., the reclassification calibration statistic, the NRI, and the IDI) [26]. In the current study, while there were no statistically significant changes in the C-statistic, the integration of the GNRI into the STS score or logistic EuroSCORE resulted in a significant improvement for mortality prediction, measured by the NRI and the IDI. By contrast, the addition of the CONUT score did not significantly improve the model discrimination beyond the STS or logistic EuroSCORE. These reclassification measures may be useful in demonstrating the ability of new models and markers to change risk strata and alter treatment decisions.

The current study has potential limitations. First, this was a retrospective, nonrandomized, observational study and hence suffers from potential selection and ascertainment bias. Therefore, the overall findings should be considered to be hypothesis-generating. Second, owing to the limited number of patients and events, our study was underpowered to detect clinically meaningful differences in hard clinical outcomes. Thus, further investigation in larger studies with a longer follow-up period is warranted. Third, although potential confounding factors were included in the multivariate model, additional confounding or unmeasured factors were not fully evaluated. Fourth, we did not simultaneously measure the frailty index, and comparison of the nutritional status and frailty status was, therefore, not feasible. Finally, our study involved an Asian population and extrapolation of these data to other ethnic groups may be limited.

Conclusion

In patients with severe symptomatic aortic stenosis undergoing TAVR, poor nutritional status measure by the GNRI and the CONUT score was associated with an increased risk of all-cause mortality at 1 year. However, in the multivariable analysis with adjustment of relevant clinical covariates, only low GNRI was independently associated with 1-year all-cause mortality. Baseline assessment of GNRI substantially augmented the prediction of mortality beyond traditional risk models, suggesting that this simple nutritional marker could be useful for the identification of the patients with a worse prognosis after TAVR.

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Compliance with ethical standards

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

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