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Original article

Prognostic value of objective nutritional status after transcatheter aortic valve replacement

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ABSTRACT

Background: This study aimed to elucidate the prognostic value of objective nutritional status after transcatheter aortic valve replacement (TAVR).
Methods: This study enrolled 150 consecutive patients who underwent TAVR between February 2014 and March 2017. Nutritional status was assessed using the Controlling Nutritional Status (CONUT) score before TAVR. Patients were divided into a high CONUT score (malnutrition status >4 points, $n = 30$) or low CONUT score (normal nutritional status 1–4 points, $n = 120$) group. The primary endpoint was mortality within 1-year post-TAVR.
Results: Patients in the high CONUT group were characterized by low body mass index (kg/m^2) (20.3 ± 2.4 vs. 22.8 ± 3.5, $p < 0.001$), a higher prevalence of atrial fibrillation (43% vs. 23%, $p = 0.03$), and more common frailty [median (interquartile range) Clinical Frailty Scale (CFS) score, 4.5 (3.75–6) vs. 4 (3–5), $p < 0.001$]. Mortality rate within 1-year post-TAVR was significantly higher in the high CONUT group (43.6% vs. 6.7%, $p < 0.001$). High CONUT score was independently associated with poor prognosis post-TAVR [adjusted hazard ratio, 8.20; 95% confidence interval (CI), 3.10–22.6; $p < 0.001$]. On integrated discrimination improvement (IDI) analysis, malnutrition status improved CFS for predicting mortality post-TAVR (IDI, 0.15; 95% CI, 0.07–0.23; $p < 0.001$).
Conclusions: Objective malnutrition status was predictive of mortality post-TAVR and provided complementary prognostic information to the CFS. Thus, objective nutritional status may refine the clinical risk stratification of patients who undergo TAVR.

Introduction

The incidence of elderly patients with severe aortic stenosis (AS) has been increasing in recent decades. Transcatheter aortic valve replacement (TAVR) is associated with similar clinical outcomes compared to surgical aortic valve replacement among patients with severe symptomatic AS and a high surgical risk [1]. TAVR also had good cost effectiveness especially for inoperable patients [2]. TAVR is recommended for patients with a life expectancy >1 year who are expected to experience an improved quality of life after the procedure [3]. To identify optimal candidates for TAVR, adequate pre-screening or risk stratification are required. Frailty is common among elderly patients undergoing TAVR and has been associated with poor procedural outcomes [4–7]. As a tool reflecting frailty degree, the Clinical Frailty Scale (CFS), an outcome of the Canadian Study of Health and Aging, is a useful marker for predicting post-TAVR mortality [8]. The CFS was a simple, objective, and useful scoring tool but only evaluated with “eye-ball.” Indeed, factors that could not be evaluated with “eye-ball” and did not necessarily disturb one's ability to move were also reportedly associated with a poor outcome after TAVR [9–11].

The objective nutritional status of patients is noted in a broad spectrum of fatal diseases. The Controlling Nutritional Status

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(CONUT) score evaluates protein reserve depletion, caloric depletion, and impaired immune defenses, which are reportedly associated with poor outcome in patients with chronic heart failure and peripheral artery disease [12,13]. Patients who underwent TAVR are at a high surgical risk so that nutritional status can play a key role in prognosis, but the prognostic value of nutritional status after TAVR has not been fully elucidated. We believe that the availability of an objective nutritional status would evaluate patients' frailty from a different viewpoint from the CFS. Thus, an objective nutritional status could potentially be used to refine the prognostic risk stratification determined by the CFS. The aim of the present study was to assess the prognostic value of objective nutritional status after TAVR evaluated by the CONUT score.

Method

Study population

This retrospective and observational study enrolled 150 consecutive patients who underwent TAVR between February 2014 and March 2017. The inclusion criteria were the presence of symptomatic degenerative AS, mean gradient >40 mmHg/jet velocity >4.0 m/s, and aortic valve area <1.0 cm^2 (or effective orifice area index <0.6 cm^2/m^2). We selected patients for whom TAVR was considered the best treatment option based on clinical consensus by a multidisciplinary heart team comprising cardiac surgeons, interventional cardiologists, anesthetists, and imaging specialists. The primary exclusion criteria were the presence of a failed surgical bioprosthesis and the introduction of hemodialysis due to lack of reimbursement in Japan. The medical ethics committees at all hospitals approved this study protocol and written informed consent was obtained from all patients prior to TAVR.

Nutritional status

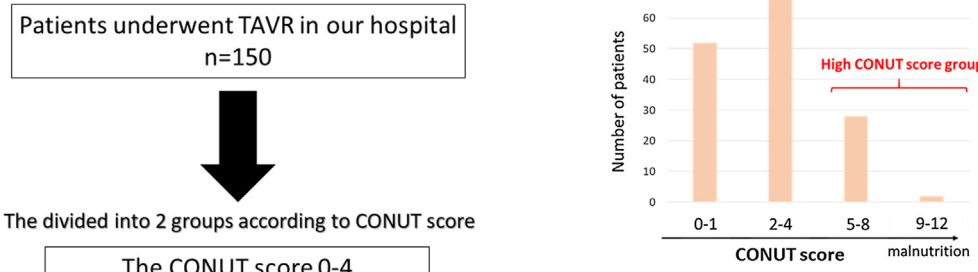
In this study, CONUT score was used to evaluate the objective nutritional status. This system, developed for hospitalized patients, evaluated the following three parameters: serum albumin level, total cholesterol level, and total lymphocyte count [14]. Serum albumin level indicates protein reserves, serum total cholesterol level indicates caloric depletion, and total lymphocyte count indicates immune system impairment due to malnutrition (Fig. 1). Patients with CONUT scores of 0–1 have a normal nutritional status; those with a score of 2–4 are at mild risk; those with a score of 5–8 are at moderate risk; and those with a score of 9–12 are at severe risk of malnutrition. In this study, the CONUT score was categorized into two groups as follows: high CONUT group (CONUT score ≥5) (malnutrition status) and low CONUT group (CONUT score 0–4) (normal nutritional status) [15].

CFS scores

The CFS scores were determined by a trained medical professional according to Canadian Study of Health and Aging grading criteria [16,17]. All CFS stages were calculated by face to face assessments with patients and families to determine the baseline frailty status before TAVR. The CFS score range was 1 (very fit) to 9 (terminally ill).

Statistical analysis

Continuous variables are expressed as mean ± standard deviation or median and interquartile range (IQR; 25–75%) as appropriate. Categorical variables are expressed as numbers and percentages. Continuous variables were compared using the unpaired Student's *t*-test or Wilcoxon rank sum test according to variable distribution. The chi-square test or Fisher's exact test was used to compare categorical variables. A Cox regression analysis was performed to obtain the hazard ratio (HR) for mortality. Thereafter, a multivariate analysis was performed using the variables with *p*-values < 0.05 on univariate analysis and known prognostic factors to examine their independent associations with mortality. The mortality rate within 1 year after TAVR was evaluated using Kaplan–Meier analysis. The log-rank test was performed to compare mortality rates. Model performance was evaluated by calculating C-statistics. Improvement in predictive accuracy following the addition of the CONUT score to the CFS was evaluated as follows: (1) C-statistics was compared with the method of Delong et al. [18] and (2) the net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were calculated as described by Pencina et al. [19]. All statistical analyses were performed using a standard program package (JMP



Assessment of the CONUT score

Parameters				
Serum albumin	3.5	3.00-3.49	2.50-2.99	<2.50
Albumin score	0	2	4	6
Total lymphocyte count	≧1600	1200-1599	800-1199	<800
Lymphocyte score	0	1	2	3
Total cholesterol score	≧180	140-179	100-139	<100
Cholesterol score	0	1	2	3
Interpretation				
Total score	0-1	2-4	5-8	9-12
Risk of Malnutrition	normal nutrition status	mild risk	moderate risk	severe risk

Fig. 1. Study design.
TAVR, transcatheter aortic valve replacement; CONUT, Controlling Nutritional Status.

Table 1
Patient characteristics.

	High CONUT (n = 30)	Low CONUT (n = 120)	p-value
Baseline characteristic			
Age	87 ± 5	86 ± 5	0.72
BMI (kg/m^2)	20.2 ± 2.4	22.8 ±2.5	<**0.001**
Low BMI (<20)	6 (20%)	12 (10%)	0.15
the Clinical Frailty Scale	4.5 [3.75–6]	4 [3–5]	<**0.001**
Hypertension (n, %)	23 (77%)	96 (80%)	0.69
Dyslipidemia (n, %)	5 (17%)	30 (25%)	0.48
Statin use (n, %)	7 (23%)	28 (23%)	0.62
Diabetes mellitus (n, %)	9 (30%)	38 (32%)	0.86
Chronic kidney disease (n, %)	23 (77%)	76 (63%)	0.16
Proteinuria (n, %)	2 (7%)	11 (9%)	0.65
Liver disease (n, %)	2 (7%)	4 (3%)	0.13
Atrial fibrillation (n, %)	13 (43%)	28 (23%)	0.03
Prior history of PCI (n, %)	12 (40%)	46 (38%)	0.87
Prior history of CABG (n, %)	1 (3%)	10 (8%)	0.31
Peripheral artery disease (n, %)	2 (7%)	11 (9%)	0.65
Logistic Euro Score	16.9 ±10.0	13.7 ± 9.6	0.12
Echocardiographic and CT parameters			
AVA-index	0.45 [0.37–0.55]	0.42 [0.34–0.49]	0.11
Stroke volume (mL)	46 [34–59]	50 [41–62]	0.08
LVEF (%)	63 [49–68]	62 [57–67]	0.85
Annulus area (mm^2)	396 [366–456]	392 [350–449]	0.48

CONUT, Controlling Nutritional Status; BMI, body mass index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; CT, computed tomography; AVA, aortic valve area; LVEF, left ventricular ejection fraction.

version 13; SAS Institute Inc., Cary, NC, USA; and R 3.2.4. with additional packages, including R cmdr, Epi, pROC, and PredictABEL). A p-value of <0.05 was considered statistically significant.

Results

Baseline characteristics

Patients were divided into two groups according to the CONUT score: high CONUT group (≥5 points, n = 30) and low CONUT group (normal nutritional status; 1–4 points, n = 120) (Fig. 1). Fig. 1 also shows the distribution of the CONUT score in this study population. Baseline characteristics are shown in Table 1. Mean body mass index (BMI) (kg/m^2) was lower in the high CONUT group than in the low CONUT group (20.3 ± 2.4 vs. 22.8 ± 3.5, $p < 0.001$), but the percentage of patients whose BMI was <20 was similar between the two groups (20% vs. 10%, p = 0.15) [20]. The prevalence of atrial fibrillation and CFS was higher in the high CONUT group than in the low CONUT group (43% vs. 23%, p = 0.03) [median (IQR), 4.5 (3.75–6) vs. 4 (3–5), $p < 0.001$]. Parameters concerning echocardiography and computed tomography were similar between the two groups.

Procedural characteristics

Procedural characteristics are shown in Table 2; there was no intergroup difference. The transfemoral approach was the most common access site (70–80% of cases). Balloon expandable valves were frequently implanted in this cohort, while the variation of valve size was also similar between the two groups. Contrast volume (102 ± 32 mL vs. 119 ± 59 mL, p = 0.14), fluoroscopy time (22 ± 8 min vs. 23 ± 11 min, p = 0.76), and procedure time (95 ± 37 min vs. 92 ± 40 min, p = 0.68) were also similar between the two groups (high CONUT group vs. low CONUT group).

In-hospital outcomes

In-hospital outcomes are shown in Table 3. The incidence of in-hospital death (7% vs. 2%, p = 0.17), life-threatening or disabling bleeding (10% vs. 8%, p = 0.78), acute kidney injury (16% vs. 8%, p = 0.20), and major (0% vs. 4%, p = 0.13) and minor vascular complications (7% vs. 6%, p = 0.87) were similar between the high and low CONUT groups. The hospitalization period was significantly longer in the high CONUT group than in the low CONUT group [median (IQR), 12 (9–26) days vs. 11 (8–17) days, p = 0.0002].

Table 2
Procedure characteristics.

	High CONUT (n = 30)	Low CONUT (n = 120)	p-value
Trans femoral approach (n, %)	22 (73%)	93 (82%)	0.33
Pre dilatation (n, %)	26 (87%)	101 (84%)	0.73
Balloon expandable valve (n, %)	29 (97%)	119 (99%)	0.34
Valve size (n, %)			
20	0 (0%)	5 (4%)	
23	20 (67%)	77 (64%)	0.51
26	9 (30%)	35 (29%)	
29	1 (3%)	3 (3%)	
Contrast volume (mL)	102 ± 32	119 ± 59	0.14
Fluoroscopy time (min)	22 ± 8	23 ± 11	0.76
Procedure time (min)	95 ± 37	92 ± 40	0.68
Transfusion (n, %)	20 (67%)	75 (63%)	0.67

CONUT, Controlling Nutritional Status.

Table 3
In-hospital outcomes.

	High CONUT (n = 30)	Low CONUT (n = 120)	p-value
All-cause death (n, %)	2 (7%)	2 (2%)	0.17
Life-threatening or disabling bleeding (n, %)	3 (10%)	10 (8%)	0.78
Acute kidney injury (n, %)	5 (16%)	10 (8%)	0.20
Major vascular complication (n, %)	0 (0%)	5 (4%)	0.13
Minor vascular complication (n, %)	2 (7%)	7 (6%)	0.87
Hospitalization period (days)	12 [9–26]	11 [8–17]	0.002

CONUT, Controlling Nutritional Status.

Assessment of mortality

The overall mortality rate at 1 year was 14.3% (Fig. 2). Causes of death in this study cohort are shown in Fig. 2. The most common cause of death was infection/sepsis, which accounted for almost one-third of all deaths (34%), followed by cardiac causes of death (14%). The incidence of non-cardiac death was higher in high CONUT group than low CONUT group (43.3% vs. 9.2%, $p < 0.001$) but the incidence of cardiac death was similar between the two groups (3.3% vs. 2.5%, $p = 0.28$). The mortality rate of the high CONUT group was significantly higher than that of the low CONUT group (43.6% vs. 6.7%, log-rank test; $p < 0.001$) (Fig. 3).

The assessment of predictors for mortality after TAVR are shown in Table 4. On univariate analysis, CFS (per 1-point increase) [HR, 1.62; 95% confidence interval (95% CI), 1.22–2.19; $p = 0.006$], high CONUT score (compared with low CONUT score; HR, 10.3; 95% CI, 4.04–26.1; $p < 0.001$), and BMI <20 (HR, 3.36; 95% CI, 1.70–9.67; $p = 0.02$) were associated with mortality after TAVR. After the multivariate analysis, the CFS (per 1-point increase) (HR, 1.44; 95% CI, 1.04–1.99, $p = 0.02$) and high CONUT score (compared with low CONUT score) (HR, 8.82; 95% CI, 1.27–61.3; $p < 0.001$) were the independent predictors of mortality after TAVR.

Clinical implication of combination of nutritional status and frailty for predicting mortality after TAVR

The predictive performance of the CFS reflected by C-statistics was 0.69 (95% CI, 0.59–0.80; $p < 0.001$). Upon the addition of malnutrition status to the CFS, C-statistics significantly increased to 0.82 (95% CI, 0.73–0.90; $p < 0.001$) compared with CFS alone ($p = 0.009$) (Table 5).

The NRI analysis showed significantly improved reclassification when high CONUT score was added to the CFS for mortality (NRI, 0.91; 95% CI, 0.53–1.30, $p < 0.001$). Similarly, the IDI analysis also demonstrated high CONUT score improved the CFS for predicting mortality (IDI, 0.15; 95% CI, 0.07–0.23; $p < 0.001$).

Discussion

In the present study, we demonstrated that objective nutritional status is strongly associated with increasing mortality after TAVR. Importantly, the addition of nutritional status resulted in an improved predictive performance for mortality beyond the CFS, a well-known and widely used scaling tool.

We showed that malnutrition status was associated with 1-year mortality after TAVR. Previously, little was discussed about the clinical impact of objective nutritional status of patients who underwent TAVR. A past study reported that malnutrition assessed with CONUT score was significantly and negatively related with hemoglobin and estimated glomerular filtration rate (eGFR) values [21]. A decrease in hemoglobin and eGFR was associated with poor outcome after TAVR [9,10]. We considered CONUT score a potentially comprehensive score to represent patient frailty so that objective nutritional status was strongly associated with mortality. As far as we know, how to consider statin use when calculating CONUT score was not defined previously. In this study, statin use was not associated with lower cholesterol level and CONUT score (Supplementary Material 1). The relationship between statin use and malnutrition is under discussion in elderly patients with cardiovascular disease [22] and further studies are needed to reveal the beneficial role of statins on the nutritional status.

Interestingly, the incidence of in-hospital death was not related with nutritional status. This discrepancy may be influenced by the limited data set but could indicate that predictors of short- and mid-term mortality were not necessarily in accord. A past study reported diabetes mellitus was associated with similar periopera-

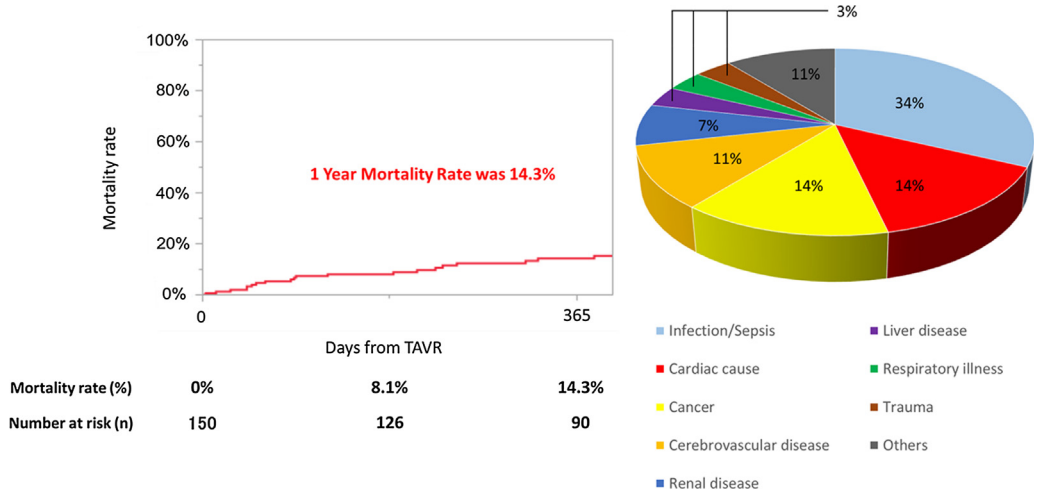
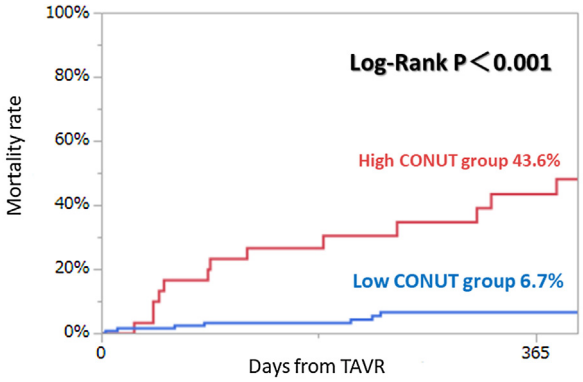


Fig. 2. Kaplan–Meier analysis for mortality rate in overall patients and causes of death in this study cohort.
TAVR, transcatheter aortic valve replacement.



High CONUT	Mortality rate (%)	0%	26.7%	43.6%
	Number at risk (n)	30	24	13
Low CONUT	Mortality rate (%)	0%	3.4%	6.7%
	Number at risk (n)	120	102	77

Fig. 3. Kaplan–Meier analysis of mortality rate comparing the high and low CONUT groups.
TAVR, transcatheter aortic valve replacement; CONUT, Controlling Nutritional Status.

Table 4
Assessment of predictors of mortality after transcatheter aortic valve replacement.

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
AF	1.93	0.78–4.81	0.16			
The CFS per 1-point increase	1.62	1.22–2.19	0.006	**1.44**	**1.04–1.99**	**0.02**
High CONUT vs Low CONUT	10.3	4.04–26.1	<0.001	**8.82**	**1.27–61.3**	**<0.001**
BMI < 20	3.36	1.70–9.67	0.02	2.49	0.69–8.94	0.16
DM	0.85	0.34–2.10	0.73			
CKD	1.69	0.67–4.30	0.27			
PAD	2.09	0.60–7.36	0.25			

AF, atrial fibrillation; CFS, Clinical Frailty Scale; BMI, body mass index; DM, diabetes mellitus; CKD, chronic kidney disease; PAD, peripheral artery disease; CONUT, Controlling Nutritional Status.

Table 5
Clinical implication of combination of nutritional status and frailty for predicting mortality after TAVR.

	C-statistics (95% CI)	*p*-value	NRI (95% CI)	*p*-value	IDI (95% CI)	*p*-value
Mortality after TAVR						
Clinical Frailty Scale	0.69 (0.59–0.80)	<0.001				
+malnutrition status (High CONUT score)	0.82 (0.73–0.90)	<0.001	0.91 (0.53–1.30)	<0.001	0.15 (0.07–0.23)	<0.001

CONUT, Controlling Nutritional Status; NRI, net reclassification improvement; IDI, integrated discrimination improvement; TAVR, transcatheter aortic valve replacement.

tive complications but was associated with increased mid-term all-cause mortality after TAVR [23]. According to a previous report, the cause of death after TAVR differed among time periods (<48 h, procedural complications; and >48 h, predominantly noncardiac) [24]. In fact, our study also showed that one-third of all deaths were caused by infection/sepsis, whereas cardiac death accounted for only 14% of all causes. The CONUT score included lymphocyte count and total cholesterol level, which reflect immune system function and caloric depletion. Moreover, malnutrition was associated with systemic inflammation represented by the upregulation of monocyte tumor necrosis factor-α production and reportedly promotes atherosclerosis [21,25]. For these reasons, malnutrition status would be related with mid-term rather than short-term outcomes due to the higher incidence of noncardiac death during mid-term after TAVR.

Functional status is a strong predictor of morbidity and mortality, and Rodés-Cabau et al. identified frailty as an independent predictor of 2-year mortality in patients treated with TAVR [26]. The CFS is a widely known tool that is used to assess risk after TAVR procedure and is reported to well-stratify patient risk of mortality after TAVR [8]. This study also shows that CFS (per 1-point increase) was an independent predictor of mortality after TAVR in accordance with previous studies. The CFS is an objective and useful scaling tool, but its limitation was that this scale is only evaluated with “eye-ball.” Assessment with “eye-ball” was simple and objective but insufficient to fully evaluate patient frailty.

We believe that an objective nutritional status, “not eye-ball” method, has the potential to compensate for deficiencies of the CFS, “eye-ball” method for prediction of mortality after TAVR. Here we also showed that the addition of an evaluation of objective nutritional status to the CFS improved the predictive ability of the CFS alone in terms of C-statistics, IDI, and NRI. This fact provides a perspective that enables us to more strictly stratify the risk of patients for selecting appropriate candidates for TAVR. Another important point was that both scaling tools were simple and objective. It is also valuable to state this fact in consecutive and

unselected patients with the elderly, who have a higher prevalence of comorbidities and frailty in real-world clinical practice for TAVR.

The combination of these “eye-ball” and “not eye-ball” scaling tools were innovative for stratifying patient risk of TAVR, but the method to improve the prognosis of patients who underwent TAVR was not clarified. Our concern was that improvements in functional or nutritional status before TAVR also improve patient prognosis after TAVR. A past study reported that a 12-week intervention with oral nutritional supplementation plus physical exercise improves the functional and nutritional status of frail older adults [27]. Improvements in nutritional status reduce the clinical impact of infections in older adults [28]. Thus, such interventions prior to TAVR could improve the prognosis of patients after TAVR, but this point must be evaluated in further studies.

Limitations

The present study has several limitations. To maximize the elimination of any unmeasured confounders and selection bias, we consecutively assessed all patients who underwent TAVR in our hospital; however, this was a single-center observational study. The small sample size could have led to a bias in the results and was thought to be powerless for assessing prognosis. We evaluated only 1-year mortality in this study. The relationship between objective nutritional status and long-term mortality should be assessed in the future. Further studies are needed to elucidate the method for improving patient outcomes after TAVR.

Conclusion

Objective nutritional status evaluated using CONUT score was strongly associated with 1-year morality after TAVR. The CONUT score provided complementary prognostic information to the CFS for predicting mortality. The combination of these “eye-ball” and “not eye-ball” simple scaling tools suggested that it may be useful for redefining clinical risk stratification in patients who underwent TAVR.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jjcc.2018.11.013.

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