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Nutritional risk index predicts survival in patients undergoing transcatheter aortic valve replacement

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ABSTRACT

Background: Among patients undergoing transcatheter aortic valve replacement (TAVR), prognosis is impacted by nutritional status, but the influence of the nutritional risk index (NRI) is unknown. Here we calculated the NRI to determine the prevalence and prognostic impact in terms of mortality of malnutrition in TAVR patients.
Methods and results: This retrospective multicenter study included 941 patients who underwent TAVR between 2008 and 2016 (mean age, 80.7 ± 6.5 years; 57% female). The NRI was calculated as 1.519 × albumin (g/L) + 41.7 × (real weight [kg] / ideal weight [kg]). The mean NRI was 98.1 ± 7.0%. The patients were stratified into the following groups based on malnutrition risk: severe (NRI < 83.5; $n = 83$; 8.82%), moderate (83.5 ≥ NRI < 97.5; $n = 370$; 39.32%), mild (97.5 ≥ NRI < 100; $n = 102$; 10.84%), and no risk (NRI ≥ 100; $n = 386$; 41.02%). During the follow-up period (2.1 ± 1.1 years), 186 patients died, representing 19.8% of the total cohort. Cox regression models were used to analyze the relationship between NRI and mortality during follow-up. Compared to patients with no or mild nutritional risk, those with moderate or severe nutritional risk had a 45% greater risk of mortality during follow-up (adjusted HR, 1.45; 95% CI, 1.05–1.99; $P = 0.021$).
Conclusion: Malnutrition is common among TAVR patients. Our present data indicated that the NRI was independently associated with increased risk of death during long-term follow-up after TAVR. Based on its potential to improve risk prediction, NRI appears to be a promising tool for the clinical assessment of patients who are candidates for TAVR.

1. Introduction

Transcatheter aortic valve replacement (TAVR) is a well-established treatment for severe aortic stenosis (AS) in patients who are inoperable or have a high surgical risk [1,2]. The results of the recent PARTNER 2 and SURTAVI studies suggest that TAVR may also be a suitable alternative for patients with intermediate surgical risk [1–4]. However, some patients do not exhibit the expected benefits after TAVR [5–10], and the presently used surgical risk scores are insufficient for predicting futility following TAVR. For better risk estimation in these patients, there is a need to develop ad-hoc scores involving assessment of the degree of frailty, functional status, and comorbidity [1,2].

In the geriatric population, factors such as frailty, cognitive impairment, functional limitation, and malnutrition predict greater risk [11–14]. Undernutrition is common in patients with cardiovascular disease (e.g., heart failure) [15,16], hospitalized patients, and older patients [17], and is an independent risk factor for poor clinical outcome in each of these contexts. Nutritional status is a marker of frailty, and is associated with higher mortality and morbidity among patients with severe AS who undergo TAVR [11–14] or aortic valve replacement surgery (AoVS) [18,19].

Studies have evaluated body mass index (BMI) and hypoalbuminemia as markers of nutritional status, and assessed their prognostic relevance in heart diseases [20–22]. However, these parameters do not accurately assess nutritional status individually [23]. The geriatric

Abbreviations: AS, aortic stenosis; AoVS, aortic valve surgery; BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; HF, heart failure; NRI, nutritional risk index; PCI, percutaneous coronary intervention; TAVR, transcatheter aortic valve replacement.

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nutritional risk index (NRI) is a simple tool that enables identification of patients at risk of undernutrition [17,24]. The NRI is calculated based on serum albumin levels and body weight, and has been validated in various surgical and clinical contexts [25–29].

In the present study, we aimed to use the NRI to determine the prevalence of malnutrition among patients with severe AS who undergo TAVR, and to analyze the prognostic value of the NRI with regard to long-term mortality.

2. Methods

2.1. Study population

This retrospective observational multicenter study included patients who underwent TAVR due to AS between October 2008 and August 2016 at three hospitals in Spain: Hospital Clínico Universitario de Santiago de Compostela, Hospital Virgen de la Victoria de Málaga, and Hospital Central de Asturias. A total of 1073 consecutive patients were initially enrolled. However, 132 were excluded due to a lack of the necessary data for NRI calculation, including information regarding the presence of hypo/hypernatremia, severe liver disease, and severe renal insufficiency to ensure that albuminemia changes were related to malnutrition. Thus, the final cohort comprised 941 patients. No patients were excluded due to a lack of data regarding the other variables used in the regression analysis.

All study participants were evaluated by a “Heart Team” that was responsible for selecting patients for percutaneous treatment of valvular disease. Demographic, clinical, interventional, and follow-up data were retrospectively collected from electronic medical records and from medical examinations at the participating hospitals. The study was carried out in accordance with the principles of the Declaration of Helsinki.

2.2. Nutritional risk index

The nutritional risk index was calculated as 1.519 × serum albumin (g/L) + 41.7 × (actual body weight [kg] / ideal body weight [kg]), using the formula modified for use in an elderly population by Bouillanne et al. [17], based on the original by Buzby et al. [24] Ideal body weight was determined using the Lorentz formula: [17] height (cm) − 100 − ([height (cm) − 150] / 4) for males, or height (cm) − 100 − ([height (cm) − 150]/2.5) for females. If the ratio of actual body weight (kg) to ideal body weight (kg) was ≥1, the assigned value was 1, as previously published [17,24–29]. This method prevents the underdiagnosis of malnourished and obese patients. The NRI was calculated using the actual body weight of the patient on the day of the TAVR procedure, and the albumin value from the control analysis performed the day before TAVR.

Based on NRI values, we classified the patients into four groups: no nutritional risk (NRI > 100), mild nutritional risk (97.5 ≤ NRI <100), moderate nutritional risk (83.5 ≤ NRI < 97.4), and severe nutritional risk (NRI < 83.5) [24,25,28]. To facilitate our analysis, we combined the groups to form two categories: no and mild nutritional risk, and moderate and severe nutritional risk. These two categories were analyzed in terms of baseline characteristics, incidence of adverse events during the procedure, and survival following TAVR.

2.3. TAVR procedure

The TAVR procedure was most often performed under conscious sedation. General anesthesia was used in only 8% ($n = 76$) of procedures, in the context of non-femoral arterial access and in first implants. In most cases, valve implantation was performed via femoral arterial access, while the remaining TAVR procedures were performed using axillary access. All procedures were performed using the implant technique previously described in the literature [30,31].

The Medtronic CoreValve™ percutaneous bioprosthesis (Medtronic Inc., Minneapolis, MN, USA) was implanted in all patients. Prior to implantation, echocardiography, coronary catheterization, and CT were performed to determine the anatomy of the aortic root and the vascular access. Complications resulting from the procedure were recorded according to the provisions of the Valve Academic Research Consortium-2 (VARC-2) consensus document [32].

2.4. Statistical analysis

We compared baseline clinical characteristics according to no/mild nutritional risk versus moderate/severe nutritional risk using Student's *t*-tests for continuous variables, and chi-square tests for categorical variables. To assess the association between NRI and all-cause mortality, we performed stepwise Cox multivariable regression analysis including variables that showed a P value of <0.05 in univariate mortality analysis. The multivariate analysis included the following variables: age (continuous variable), peripheral artery disease, prior heart failure, COPD, chronic kidney disease, hemoglobin (continuous variable), STS (continuous variable), femoral approach, post-TAVI aortic regurgitation grade III–IV, in-hospital major bleeding, need of pacemaker, and NRI (continuous variable). From the adjusted Cox regression model, predicted death rates were estimated, and their correlations with NRI were examined using a quadratic regression with a 95% confidence interval. Survival curves were constructed for time-to-event variables using Kaplan-Meier estimates, and compared with the log-rank test. All analyses were two-tailed, and differences were considered significant if the P value was <0.05. Statistical analyses were performed using SPSS version 22.0 and Stata 14.0.

3. Results

3.1. Baseline characteristics

This study included a total of 941 patients with severe AS who underwent TAVR. According to the NRI, 41.02% ($n = 386$) presented no nutritional risk, 10.84% ($n = 102$) mild nutritional risk, 39.32% ($n = 370$) moderate nutritional risk, and 8.82% ($n = 83$) severe nutritional risk. When grouped into two categories, 51.9% ($n = 488$) presented no/mild risk and 48.1% ($n = 453$) presented moderate/severe risk (Fig. 1).

Table 1 presents the patients' baseline characteristics, procedure characteristics, and the adverse events after implantation. Analyses were performed to compare patients with no/mild nutritional risk versus those with moderate/severe nutritional risk. Compared to the moderate/severe nutritional risk group, the no/mild nutritional risk group included a greater proportion of women (60.0% vs 53.4%, $P = 0.041$), showed a higher percentage of dyslipidemia (57.8% vs 51.4%, $P = 0.050$), and exhibited a significantly higher BMI (29.1 ± 4.9 vs 28.0 ± 5.0, $P = 0.001$). Compared to the no/mild nutritional risk group, the moderate/severe nutritional risk group had a significantly lower glomerular filtration rate (GFR) based on MDRD-4 (53.0 ± 22.6 vs 57.9 ± 23.8 mL/min/1.73 m^2, $P = 0.001$), significantly lower hemoglobin levels (11.3 ± 2.4 vs 11.6 ± 1.7 g/dL, $P = 0.016$), and a poorer risk profile as estimated by STS score (6.3 ± 4.1 vs 5.4 ± 3.6%, $P = 0.001$).

The majority of patients in both groups received implants via femoral access. The two groups did not differ with regards to complications after the procedure, except that the moderate/severe NRI group more frequently experienced major bleeding events (39.3% vs 28.7%, $P = 0.049$). During the follow-up period (2.1 ± 1.1 years; median, 2.8 years), total mortality was 19.8% ($n = 186$). The mortality rate was 6.7 (95% CI 5.3–8.4) per 100 persons/year in patients without or with mild malnutrition, vs 11.5 (95% CI 9.5–13.9) per 100 persons/year in patients with moderate or severe malnutrition, $P < 0.001$. With respect to the cause of death, there was differences between both groups driven by the difference in mortality from non-cardiovascular causes: 6.8% in patients with no/mild malnutrition vs. 12.8% in patients with moderate/severe malnutrition, $P < 0.001$. No differences were found in cardiovascular mortality between the two groups (8.8% in patients with no/mild malnutrition vs. 9.9% in patients with moderate/severe malnutrition, $P = 0.555$).

3.2. Relationship between NRI and mortality

After classifying patients into two groups according to NRI (no/mild nutritional risk, and moderate/severe nutritional risk), we analyzed the effect of NRI on mortality from any cause during follow-up. Supplementary Table 1 shows the results of univariate analysis, indicating which variables were significantly associated with mortality during follow-up.

We next performed multivariate analysis, accounting for the possible presence of interacting and confounding factors (Supplementary Table 2). The results revealed that the following factors were independent predictors of adverse prognosis: previous admission for heart failure (HF) (HR, 1.18; 95% CI, 1.04–1.33; $P = 0.010$), COPD (HR, 1.48; 95% CI, 1.05–2.09; $P = 0.025$), CKD (HR, 1.46; 95% CI, 1.03–2.06; $P = 0.032$), STS score (HR, 1.04; 95% CI, 1.01–1.08; $P = 0.041$), and major in-hospital bleeding (HR, 2.10; 95% CI, 1.32–3.36; $P = 0.002$). NRI as a continuous variable was inversely associated with mortality during follow-up (HR, 0.98; 95% CI, 0.96–0.99; $P = 0.019$), with each additional point on the NRI (indicating lower nutritional risk) associated with a 2% lower

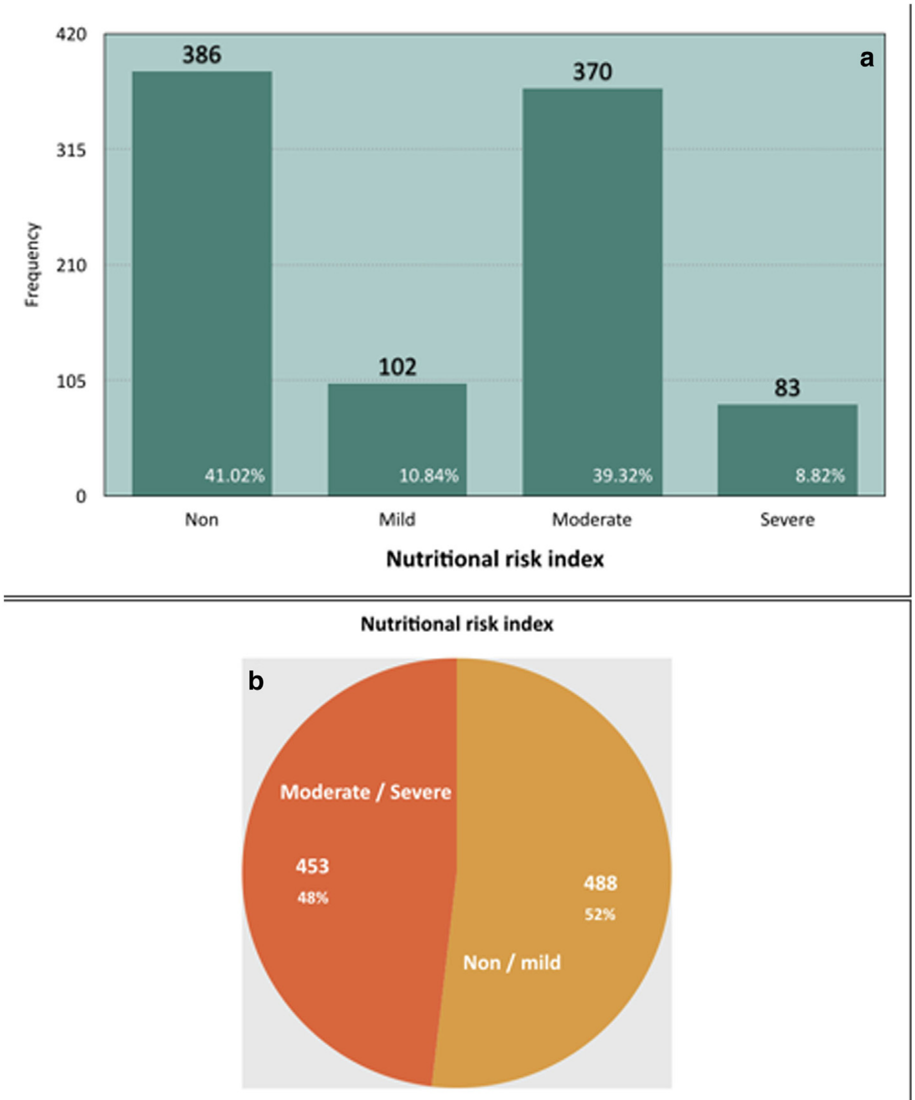

Fig. 1. Patient distribution by NRI (a) and after classification into two groups (b). The largest patient groups were the no nutritional risk group (41.02%) and the moderate nutritional risk group (39.32%). After reclassification, patients were almost evenly distributed between the non/mild nutritional risk ($n = 488$) and moderate/severe nutritional risk ($n = 453$) groups. NRI, nutritional risk index.

risk of mortality. Fig. 2 shows the relationship between various nutritional risk values (expressed as a continuous variable) and the total mortality across follow-up after TAVR. Mortality incidence was lower among patients with higher NRI values; i.e., in patients with no or mild nutritional risk compared to in patients with moderate or severe risk.

After classifying patients according to NRI, we observed that a moderate/severe malnutrition risk was associated with total mortality during follow-up (HR, 1.70; 95% CI, 1.26–2.30; $P = 0.001$). After adjustment for confounding variables (Supplementary Table 2), patients with moderate/severe nutritional risk showed a 45% higher risk of mortality from any cause during follow-up (HR, 1.45; 95% CI, 1.05–1.99; $P = 0.021$). Fig. 3 presents the Kaplan-Meier survival curves for the two nutritional risk categories of patients with AS who underwent TAVR.

4. Discussion

Here we report the first analysis of the association between NRI and mortality from any cause during long-term follow-up in a cohort of patients with severe AS who underwent TAVR. Our results revealed an inverse association, with lower NRI values (indicating greater nutritional risk) associated with higher mortality during follow-up. Compared to patients with no/low nutritional risk, those with moderate/severe nutritional risk (NRI < 97.5) showed a 45% higher risk of death from any cause. Moreover, we found that malnutrition was a common condition, affecting 48.1% of our sample. These results may suggest that pre- and post-TAVR interventions aimed at improving nutritional status could alter these patients' prognosis, and that NRI assessment as an instrument for the detection of malnutrition should be included in the process of selecting candidate patients for TAVR.

TAVR has been a revolutionary innovation in AS treatment, enabling valve replacement for many patients who previously would have been ineligible for surgery. Before the Heart Team makes a treatment decision for patients with severe AS, there must be a comprehensive cardiological assessment, as well as a careful assessment of any comorbidities and a geriatric assessment, particularly regarding frailty status [1,2]. Such evaluation is conducted with the aims of identifying patients for whom TAVR would be futile, and of better stratifying surgical patients for whom risks are underestimated due to the presence of geriatric comorbidities or frailty status not included in classic scores.

Frailty is a geriatric syndrome characterized by reduced ability to recover from stress factors due to subclinical deficiencies, particularly

Table 1
Baseline characteristics of the population in two groups based on nutritional risk index (NRI).

Variables	Nutritional risk index		
	No/low nutritional risk (n = 488)	Moderate/severe nutritional risk (n = 453)	*P* value
Baseline characteristics			
Age, years	80.4 ± 6.5	81.0 ± 6.5	0.121
Female sex, %	60.0	53.4	0.041
BMI, kg/m^2	29.1 ± 4.9	28.0 ± 5.0	0.001
Diabetes, %	32.8	35.1	0.454
Hypertension, %	84.0	83.0	0.675
Dyslipidemia, %	57.8	51.4	0.050
Peripheral artery disease, %	14.5	15.1	0.820
Coronary artery disease, %	41.6	47.2	0.082
Prior heart failure, %	67.4	71.7	0.191
NYHA III–IV, %	42.6	45.7	0.343
Prior stroke, %	13.3	12.6	0.728
Atrial fibrillation, %	26.6	35.8	0.079
Bundle branch block, %	28.2	28.8	0.908
COPD, %	24.8	29.4	0.115
GFR, mL/min/1.73 m^2	57.9 ± 23.8	53.0 ± 22.6	0.001
Hemoglobin, g/dL	11.6 ± 1.7	11.3 ± 2.4	0.016
LEVF<50%, %	23.5	18.6	0.539
PA (mm Hg)	47.4 ± 18.2	47.4 ± 15.7	0.986
STS score, %	5.4 ± 3.6	6.3 ± 4.1	0.001
TAVR procedure and in-hospital outcomes			
PCI prior TAVR, %	23.0	25.0	0.673
Femoral approach, %	93.5	93.4	0.950
Aortic regurgitation III/IV, %	4.4	3.8	0.136
Need of pacemaker, %	26.4	30.2	0.335
Vascular complications, %	7.6	9.1	0.592
In-hospital major bleeding, %	28.7	39.3	0.049
In-hospital myocardial infarction, %	2.2	2.11	0.890
In-hospital stroke, %	2.7	2.6	0.968
In-hospital mortality, %	5.5	4.6	0.531

Values are presented as mean ± SD or %.
BMI, body mass index; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate (MDRD-4); LVEF, left ventricular ejection fraction; NYHA, New York Heart Association functional classification; PAP, pulmonary artery pressure; PCI, percutaneous coronary intervention; STS score, risk score of the Society of Thoracic Surgeons.

cardiovascular, nutritional, and musculoskeletal deficiencies. Frailty is associated with higher mortality in the general population [33], and with adverse events among patients with ischemic heart disease [34] and after stressful clinical situations, such as cardiac surgery or TAVR [11–14,18,35]. Frailty can be estimated using a composite of indices that assess a patient's functional, cognitive, and nutritional status.

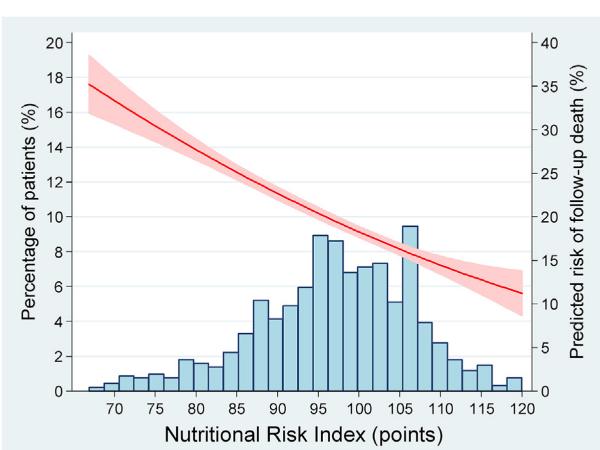

Fig. 2. Patient distribution according to nutritional risk index, and association with total mortality during follow-up. For each point lower on the nutritional risk index (indicating greater nutritional risk) the mortality rate during follow-up is higher.

In the present study, we used the NRI to assess malnutrition risk in a cohort of patients undergoing TAVR. Previous studies have evaluated the prognostic relevance of two classic nutritional status markers: BMI and hypoalbuminemia [20–23]. However, neither of these parameters can accurately assess nutritional status independently. The NRI is a validated tool for estimating the risk of undernutrition in various populations, including both hospitalized patients and outpatients. The NRI shows strong prognostic value for mortality, adverse events, and deterioration of functional capacity, which is superior to that achieved using BMI and albumin separately [24–29].

The Mini Nutritional Assessment (MNA) has previously been used to assess the prevalence of malnutrition and prognosis as part of geriatric assessment in patients undergoing TAVR. Such investigations also reveal a high prevalence of malnutrition as a component of frailty status and geriatric syndrome. The MNA, the frailty index, and the geriatric assessment each have prognostic value regarding functional deterioration, mortality, and MACCE following TAVR [12,14]. In studies applying the MNA to predict events after TAVR [12–14], malnutrition is identified using an MNA cut-off point of <12. However, this assumption has not been validated in previous studies, showing an MNA cut-off point of 17 for undernutrition [36,37].

Both the MNA and NRI show acceptable correlations regarding the identification of undernutrition risk. However, the two methods lead to different patient classification, with the MNA having lower specificity and thus a greater tendency to classify patients as undernourished. Both the MNA and NRI show significant correlations with albumin, total protein, transferrin, and anthropometric parameters (e.g., BMI, weight loss, and arm circumference). Notably, the MNA can be difficult to apply in elderly patients, such as those undergoing TAVR, since this test requires an accurate and reliable self-assessment of nutrition and diet parameters. In contrast, the NRI is easier to calculate and to implement as a standard routine in clinical practice, since the necessary parameters are available from routine examination of the patient, without requiring specific anthropometric measurements, subjective questionnaires, or uncommon laboratory data.

Assessment of malnutrition risk is part of the geriatric assessment of patients who undergo TAVR, and plays a role in determining frailty status. Our present findings and the potential use of the NRI for early identification of patients at malnutrition risk who are going to undergo TAVR could be highly relevant in daily clinical practice. Such patients could potentially benefit from interventions to improve or maintain their nutritional status prior to implantation of the percutaneous prosthesis. Notably, in patients with heart failure, such intervention is beneficial in terms of clinical improvement and quality of life [38]. Moreover, NRI calculation as part of geriatric assessment could help identify patients with decreased physiological reserve in various systems, and in whom percutaneous intervention on the aortic valve would entail a high risk of functional deterioration and mortality. With regard to the prediction of mortality after TAVR, it has been demonstrated that geriatric assessment scores add value to classic surgical scores [12].

Larger studies are needed to validate the NRI within a geriatric and frailty score, in combination with other predictive scores of events after TAVR. Such investigations would probably result in better risk stratification of these patients, and enable the ascertainment of whether changes of the NRI are related to clinical and/or prognostic differences.

4.1. Study limitations

The retrospective design of the present investigation implies a series of limitations inherent to this type of study. This study was also observational, and thus the results provide associative evidence without allowing establishment of causality.

In this study, we evaluated NRI based on albumin and patient weight at the time of intervention, and did not monitor changes of these parameters throughout the follow-up. A total of 132 patients were excluded

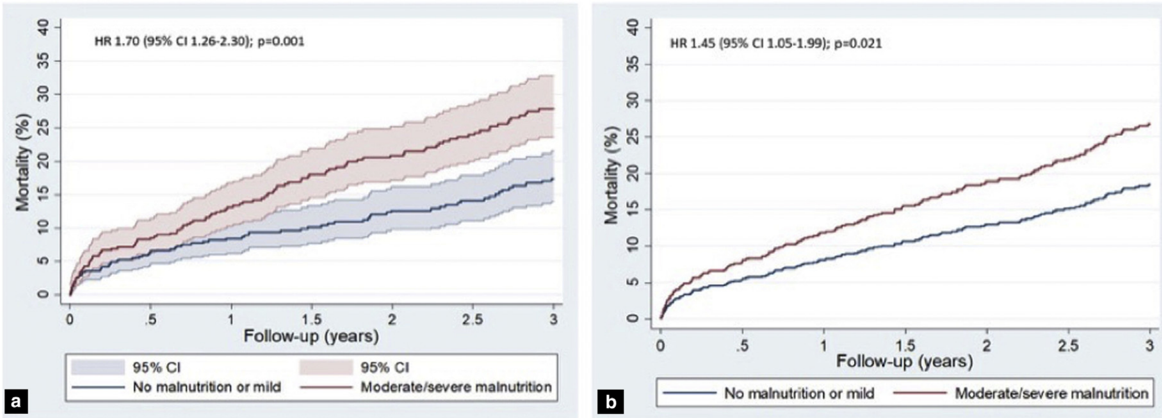

Fig. 3. Kaplan-Meier survival curves after reclassifying patients into no/mild nutritional risk and moderate/severe nutritional risk groups according to their NRI, without adjustment (3a) and after adjustment for confounding factors (3b). Multivariable analyses was performed after adjustment for age, peripheral artery disease, prior heart failure, COPD, chronic kidney disease, hemoglobin, STS score, general anesthesia, femoral approach, post-TAVI aortic regurgitation grade III-IV, in-hospital major bleeding, and need of pacemaker. 95% CI, 95% confidence interval; HR, hazard ratio.

due to a lack of data necessary for the NRI calculation, which may influence the generalizability of the study. Moreover, the population analyzed in the present study was referred for TAVR because they had a high surgical risk as assessed by STS score. Thus, the present results are only applicable to this population. Younger patients and those with low/intermediate surgical risk are typically referred for surgery, while some elderly patients with prohibitive surgical risk are referred for medical management. Further studies are needed to evaluate the NRI and its prognostic value specifically in these two populations.

No follow-up data were available regarding hospitalization due to heart failure or functional status after TAVR procedure, which are important outcomes in elderly patients who undergo transcatheter aortic valve replacement, and who would offer more value to the study.

5. Conclusions

In the present study, NRI calculation revealed a frequent risk of undernutrition among patients with AS who undergo TAVR. Our results further demonstrated that the NRI as an indicator of malnutrition is a promising predictor of mortality from any cause during long-term follow-up after TAVR. Since malnutrition is a potentially modifiable state, the present findings may have important clinical implications regarding the outcome of patients undergoing TAVR. Larger studies are needed to examine NRI use in daily clinical practice, and its value within a broader frailty score.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.11.097.

Conflict of interest

Juan H. Alonso-Briales, José M. Hernández-García, César Morís, and Ramiro Trillo Nouche are proctors for Medtronic.

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