Journal of the American Heart Association

ORIGINAL RESEARCH

Association Between the Malnutrition Status and All-Cause Mortality in Patients With Moderate and Severe Aortic Stenosis: A Prospective Cohort Study

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BACKGROUND: Malnutrition status is an important predictor of prognosis in patients after aortic valve replacement. However, the prognostic value of malnutrition status in patients with moderate-to-severe aortic stenosis is unclear. This study aimed to evaluate the effect of malnutrition on all-cause mortality in patients with moderate-to-severe aortic stenosis using the Patient Controlled Nutritional Status (CONUT) score, nutritional risk index, and prognostic nutritional index.

METHODS AND RESULTS: A total of 536 patients with moderate-to-severe aortic stenosis were selected in the ARISTOTLE (Aortic Valve Diseases Risk Factor Assessment and Prognosis Model Construction) study conducted between January 2013 and December 2022 in 3 academic institutions. Patients were grouped according to different nutritional status assessment methods. CONUT, nutritional risk index, and prognostic nutritional index were calculated at baseline. The primary study outcome was all-cause mortality. Cox regression was used to assess the association between nutritional status and all-cause mortality. During a median 34.2-month follow-up period, a total of 120 (22.4%) patients died. All-cause mortality was significantly higher in lower prognostic nutritional index, lower nutritional risk index, and higher CONUT groups. Compared with normal nutrition, malnutrition was associated with an increased risk for all-cause death (adjusted hazard ratio for mild and moderate–severe malnutrition, respectively: 2.82 [95% CI, 1.69–4.71; *P*<0.001] and 3.31 [95% CI, 1.74–6.32; *P*<0.001] for the CONUT).

CONCLUSIONS: In patients with moderate or severe aortic stenosis, we found that high CONUT scores, low nutritional risk index scores, and low prognostic nutritional index scores were associated with all-cause death. The poorer the nutritional status, the greater the risk of malnutrition-related all-cause mortality.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT06069232.

Key Words: all-cause mortality ■ aortic valve stenosis ■ CONUT ■ malnutrition status ■ NRI ■ PNI ■ prognosis

Aortic stenosis (AS) was the third most frequent cardiovascular disease after coronary artery disease and systemic arterial hypertension in developed country.[1,2] Currently, aortic valve replacement (AVR) remains the only effective treatment for severe AS.[3] Some patients have a poor prognosis even with AVR. Thus, more risk assessment and interventions for patients with AS are needed.

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This article was sent to Amgad Mentias, MD, Associate Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.124.037086

For Sources of Funding and Disclosures, see page 12.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Malnutrition is common in patients with aortic stenosis, and worsening malnutrition is associated with higher all-cause mortality regardless of the malnutrition index used in patients with moderate-to-severe aortic stenosis.

What Are the Clinical Implications?

- There are few interventions for patients with aortic stenosis, and nutritional status may be a potential target for intervention in this group of people.

Nonstandard Abbreviations and Acronyms

ARISTOTLE	Aortic Valve Diseases Risk Factor Assessment and Prognosis Model Construction
AS	aortic stenosis
AVR	aortic valve replacement
CONUT	controlling nutritional status
NRI	nutritional risk index
PNI	prognostic nutritional index

Recent evidence has shown a high prevalence of malnutrition in patients with AS and are associated with an increased risk of all-cause mortality, readmission, and prolonged hospital stay after AVR.[4–6] Previous studies have shown that malnutrition is an important adverse prognostic factor for cardiovascular diseases such as heart failure, acute coronary syndrome, and peripheral artery disease.[6–8] Thus, aside from the well-known risk factors, such as advanced age, multiple comorbidities, or cardiac-related factors, malnutrition may be a modifiable prognostic intervention for patients with AS.[9] In recent years, numerous studies have been conducted on malnutrition in AVR surgical populations, and all of these studies have consistently demonstrated that malnutrition is independently associated with increased mortality, complications, readmission rates, and resource use.[10–12] However, the prognostic value of malnutrition status in patients with moderate-to-severe AS was unclear.

Several objective nutritional measures, such as the Patient Controlled Nutritional Status (CONUT) score,[13] Prognostic nutritional index (PNI)[14] and nutritional risk index (NRI)[15] have been reported to assess malnutrition and predict clinical outcomes in patients with cardiovascular disease. CONUT was developed by Ulibarri et al. in 2005 as a screening tool for the nutritional status of hospitalized patients. CONUT calculated from serum albumin concentration, total peripheral lymphocyte count, and total cholesterol concentration, is a tool used to screen for malnutrition status. It has been used to evaluate the prognosis of hypertension,[16] heart failure,[17] and patients after percutaneous coronary intervention.[18] NRI, which was proposed by Buzby et al., is a simple tool to assess nutritional status calculated from albumin, height, and weight. Previous studies have suggested that NRI has a good prognostic value in certain cardiovascular disease populations, such as patients with heart failure[19] and those who had percutaneous coronary intervention[20] and transcatheter AVR[21]. PNI is also a frequently used screening and nutritional status assessment tool. It is also used to screen nutritional status in patients after left ventricular assist devices[22] or transcatheter AVR.[23] Compared with traditional nutrition indicators, the scoring can be calculated by integrating multiple laboratory data or body measurement data. They are simple, convenient and have been shown to be one of the determinants of mortality and morbidity in patients with cardiovascular disease, such as hypertension, heart failure, and prognosis of percutaneous coronary intervention.[16,18,19]

Accordingly, we aim to report the prevalence, clinical associations, and prognostic consequences of malnutrition in a contemporary cohort of patients with AS using 3 different scoring systems.

METHODS

Study Design and Participants

In the ARISTOTLE (Aortic Valve Diseases Risk Factor Assessment and Prognosis Model Construction) study, which is an ongoing multicenter cohort study, patients diagnosed with moderate-to-severe AS at 3 academic institutions (the First Affiliated Hospital of Sun Yat-Sen University, the Affiliated Hospital of Guangdong Medical University and the Second Affiliated Hospital of Shantou Medical University) were enrolled between January 2013 and December 2022. The data that support the findings of this study are available from the corresponding author upon reasonable request. Case inclusion criteria for the study were as follows: (1) >18 years old; (2) diagnosis of moderate-to-severe AS by echocardiography based on guidelines. Moderate-to-severe AS was defined as aortic valve area ≤1.5 cm^2 or peak aortic jet velocity ≥3 m/s, mean aortic pressure gradient ≥20 mm Hg.[24] For this analysis, patients with nutritional variables were selected, and patients with missing other variables (N=41) and lost to follow-up (N=33) were excluded. Finally, 536 patients with moderate-to-severe AS were included for analysis. The study design and screening process are described in detail in Figure S1. The study protocol has received approval from the institutional review board for clinical research and animal testing at the First Affiliated Hospital of Sun Yat-sen University and registered at Clinical Trials.gov (Number: NCT06069232). The procedures followed were in accordance with institutional guidelines, and the subjects gave informed consent.

Data Collection and Echocardiography

The baseline characteristics were evaluated at the time of initial diagnosis of moderate-to-severe AS on echocardiography or as close as possible to the date of diagnosis. The clinical data, including patients' age, sex, smoking and drinking history, disease history as well as medication records, were collected through self-reports upon admission and subsequently confirmed by health care professionals against inpatient data. Hypertension was defined as systolic blood pressure ≥140 mm Hg and diastolic blood pressure ≥90 mm Hg, or use of antihypertensive medication, or previous physician diagnosis of hypertension. Diabetes was defined as fasting blood glucose ≥126 mg/dL, or hemoglobin A1c ≥6.5%, or nonfasting blood glucose ≥200 mg/dL.[25,26] Diabetes was also defined as use of antidiabetic medicines, or previous physician diagnosis. Coronary heart disease, chronic kidney disease, chronic obstructive lung disease, atrial fibrillation, and stroke were defined as previous physician diagnosis. Systolic blood pressure and diastolic blood pressure were measured by medical staff with a sphygmomanometer in the morning after the patients rested for 5 minutes, while heart rate was recorded. Body mass index (BMI) was calculated by dividing weight (kg) by the square of height (m^2). The laboratory parameters assessed in this study included total cholesterol, low-density lipoprotein cholesterol, serum albumin, and total lymphocyte count. All measurements were conducted using standardized methods. Glomerular filtration rate was estimated using the Chronic Kidney Disease Epidemiology Collaboration equation with serum creatinine.[24]

The comprehensive transthoracic echocardiography was performed using a commercially available ultrasound device in accordance with the guidelines by the American Society of Echocardiography. The maximum ejection velocity of the aortic valve was estimated by continuous wave Doppler recordings from apical 3- or 5-chamber views and mean transvalvular pressure gradient was calculated using the modified Bernoulli equation,[27] and aortic valve area was determined through application of the continuity equation. The left ventricular ejection fraction be calculated using the Simpson method.

Definitions

The CONUT index was derived from laboratory data, including measurements of albumin concentration, lymphocyte count, and cholesterol levels. A score of 0 to 1 is classified as normal, and scores of 2 to 4, 5 to 8, and 9 to 12 reflect mild, moderate, and severe malnutrition, respectively.[13] Buzby et al. originally defined the NRI using the formula 1.519×serum albumin (g/L)+41.7×(current body weight [kg]/usual body weight [kg]). Ideal body weight was used instead of average body weight, calculated using the Lorenz formula, that is, height (cm)-100-([height (cm)-150]/4) for men and height (cm)-100-([height (cm)-150]/2.5) for women. According to the results of calculation, the patients were divided into 4 groups: severe nutritional risk (NRI <83.5), moderate nutritional risk (83.5–97.5), mild nutritional risk (97.5–100) and no nutritional risk (NRI >100).[28] The PNI was calculated according to the following formula: 10×serum albumin (g/dL)+0.005×total lymphocyte count (mm^3). A score of >38 was defined as normal, and a score of 35 to 38 and <35 reflected moderate and severe malnutrition, respectively. Note that there is no "mild" category for the PNI.[14] PNI tools is a kind of malnutrition screening and assessment tool. This study mainly used it as screening tool for malnutrition. Based on the recommendations of the Nutritional Epidemiology and Dietary Assessment Study, the Strengthening the Reporting of Observational Studies in Epidemiology nutritional reporting[29] guidelines were used.

Outcome

The primary end point of this study was all-cause mortality, information on the occurrence of all-cause mortality and AVR was identified by reviewing hospital records, examining the death certificates or telephone follow-up. All patients were followed up by telephone or outpatient service at least once a year. Follow-up time was calculated as the period between the date of AS diagnosis and the date of death or last follow-up.

Statistical Analysis

Continuous variables were expressed as mean±SD when following a normal distribution, and categorical variables were expressed as frequencies and percentages. The patients were grouped according to different nutritional status indicators. One-way ANOVA or Kruskal–Wallis test was used to compare normally and nonnormally distributed continuous variables, respectively. Categorical variables were compared using the Pearson chi-square test. Cox regression was conducted to evaluate hazard ratios (HR) and 95% CI for the association between the malnourished state with all-cause mortality in different malnutrition states. Three multivariable models were built and used to adjust for potential confounders of all-cause mortality. In Model 1, we adjusted for only age and sex. In Model 2, we adjusted for personal

Table 1. Baseline Clinical Characteristics of Patients With Moderate-to-Severe AS of CONUT Scores

Characteristics	CONUT groups				*P* value
	Risk of malnutrition (N=536)	Absent (N=226)	Mild (N=233)	Moderate and severe (N=77)	
Demographic and anthropomorphic data					
Age, y	66.41±12.39	65.10±11.78	66.84±13.33	68.95±10.74	0.049
Sex, men	324 (60.4)	121 (53.5)	149 (63.9)	54 (70.1)	0.013
Body mass index, kg/m^2	22.74±3.70	23.38±3.57	22.22±3.85	22.41±3.30	0.002
Systolic blood pressure, mm Hg	129.06±22.00	131.04±21.81	128.25±21.84	125.73±22.79	0.160
Diastolic blood pressure, mm Hg	71.31±12.67	73.07±12.44	70.10±12.66	69.82±12.90	0.034
Heart rate, bpm	78.05±15.20	76.02±13.94	78.45±14.16	82.79±20.08	0.003
Personal history					
Smoking	156 (29.1)	60 (26.5)	70 (30)	26 (33.8)	0.444
Drinking	75 (14)	34 (15)	26 (11.2)	15 (19.5)	0.158
Commodities					
Hypertension	238 (44.4)	94 (41.6)	104 (44.6)	40 (51.9)	0.286
Diabetes	98 (18.3)	37 (16.4)	39 (16.7)	22 (28.6)	0.041
Coronary heart disease	137 (25.6)	42 (18.6)	76 (32.6)	19 (24.7)	0.003
Stroke	44 (8.2)	16 (7.1)	13 (5.6)	15 (19.5)	<0.001
Atrial fibrillation	90 (16.8)	35 (15.5)	43 (18.5)	12 (15.6)	0.665
Chronic kidney disease	42 (7.8)	8 (3.5)	17 (7.3)	17 (22.1)	<0.001
Chronic obstructive pulmonary disease	26 (4.9)	6 (2.7)	13 (5.6)	7 (9.1)	0.060
Laboratory data					
Triglyceride, mmol/L	1.25±0.72	1.45±0.83	1.08±0.53	1.15±0.72	<0.001
Low-density lipoprotein cholesterol, mmol/L	2.87±1.02	3.35±0.75	2.55±0.92	2.44±1.37	<0.001
High-density lipoprotein cholesterol, mmol/L	1.15±0.34	1.24±0.31	1.12±0.33	0.97±0.38	<0.001
Albumin, g/dL	3.78±0.50	4.04±0.32	3.77±0.39	3.06±0.51	<0.001
Lymphocyte count, mm^3	1654±671	2019±588	1474±596	1130±539	<0.001
Total cholesterol, mg/mL	175.15±52.11	201.89±38.08	158.24±47.88	147.84±63.76	<0.001
Estimated glomerular filtration rate, mL/min per 1.73 m^2	71.73±23.40	76.63±20.45	70.88±23.02	59.94±27.96	<0.001
Echocardiographic parameters					
Aortic valve insufficiency	498 (92.9)	203 (89.8)	220 (94.4)	75 (97.4)	0.040
Mitral valve insufficiency	396 (73.9)	156 (69)	181 (77.7)	59 (76.6)	0.090
Mitral valve stenosis	133 (24.8)	57 (25.2)	58 (24.9)	18 (23.4)	0.948
Pulmonary arterial hypertension	224 (41.8)	75 (33.2)	111 (47.6)	38 (49.4)	0.003
Left ventricular ejection fraction, %	61.60±12.65	63.02±12.48	60.60±12.26	60.44±13.96	0.068
Peak jet velocity, m/s	4.17±0.96	4.12±0.90	4.22±1.03	4.15±0.93	0.684
Mean gradient, mm Hg	42.57±19.77	41.85±19.19	43.02±20.05	43.36±20.76	0.828
Aortic valve area, cm^2	0.92±0.32	0.92±0.31	0.92±0.32	0.95±0.33	0.544
Therapy					
Antiplatelets	218 (40.7)	88 (38.9)	99 (42.5)	31 (40.3)	0.739
Stains	231 (43.1)	99 (43.8)	98 (42.1)	34 (44.2)	0.912
Antihypertension medication	363 (67.7)	154 (68.1)	156 (67)	53 (68.8)	0.940
Hypoglycemic medications	113 (21.1)	47 (20.8)	40 (17.2)	26 (33.8)	0.008
Oral anticoagulant	205 (38.2)	94 (41.6)	86 (36.9)	25 (32.5)	0.311
Diuretic	354 (66)	140 (61.9)	156 (67)	58 (75.3)	0.094
Aortic valve replacement	275 (51.3)	117 (51.8)	119 (51.1)	39 (50.6)	0.981

Data are shown as mean±SD or n (%). Baseline characteristics of the 536 patients from the Multiple Research Centre, stratified by the optimal cut of CONUT index. Groups were grouped according to the scores: Absent (0–1), Mild (2–4), Moderate and Severe (5–12). AS indicates aortic stenosis; and CONUT, Controlling Nutritional Status score.

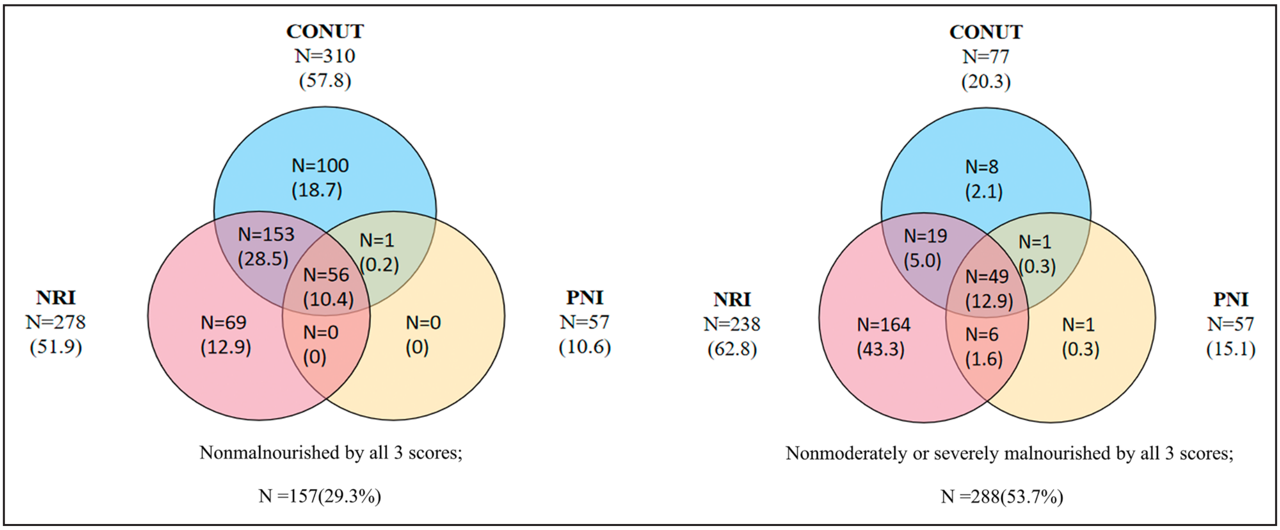

Figure 1. Prevalence of malnutrition according to 3 different scoring systems.
Venn diagram. The numbers reported outside each circle indicate the cumulative frequency of malnutrition (any degree [left] vs moderate–severe [right]) according to each malnutrition score. The overlap area of the circles reflects the frequency of overlap of each malnutrition diagnosis. CONUT indicates Controlling Nutritional Status score; NRI, nutritional risk index; and PNI, prognostic nutritional index.

history, comorbidities, and echocardiographic data on top of Model 1. In Model 3, demographic data, anthropomorphic, personal history, commodities, laboratory, echocardiographic parameters, and therapy data were included as covariates. The receiver operating characteristic curve was used to evaluate the discrimination of the 3 nutritional indicators. All analyses were conducted in SPSS version 25, Stata 17.0 and R software (R version 4.2.2). A 2-sided *P* value <0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

Among the patients, 60.4% were male, and the median age was 66.4 years. The baseline clinical characteristics and laboratory findings of the patients, stratified according to low or high CONUT, NRI, and PNI score, are shown in Table 1. On an average, patients in the high CONUT group (i.e., poor nutritional status) were older and more likely to be male, be smokers and drinkers, and have a lower BMI and estimated glomerular filtration rate compared with their nourished counterparts. There were no significant differences in BMI at each level of malnutrition. There were high proportions of patients with diabetes, stroke, chronic kidney disease, and chronic obstructive lung disease in high CONUT group, and no differences were found in other comorbidities between groups. It stands to reason that they also showed different nutritive features (lower lipids, albumin and lymphocyte count). There were similar features in NRI and PNI (Tables S1 and S2).

Prevalence and Clinical Associations of Malnutrition

The percentage of patients with malnutrition varied from 57.8% with the CONUT, to 51.9% with the NRI, and to 10.6% with the PNI. Using the CONUT and NRI, 233 (43.5%) and 40 (7.5%) patients had mild malnutrition, respectively. By CONUT, NRI, and PNI calculations, 77 (14.4%), 238 (44.4%), and 57 (10.6%) patients had moderate-to-severe malnutrition, respectively (Figure 1). According to each malnutrition score, only 29.3% were classified as nonmalnourished in any degree of malnutrition by all 3 scores, and only 53.7% were nonmoderately or severely malnourished by all 3 scores.

Clinical Outcomes

During a median 34.17 months follow-up period, a total of 120 (22.4%) patients died. All-cause mortality were significantly higher in lower PNI, lower NRI, and higher CONUT groups (the log-rank values for 3 groups <0.01; Figure 2). Table 2 summarizes the results of Cox proportional hazards analysis of all-cause mortality. As a continuous variable, malnutrition was an independent predictor of all-cause mortality risk, regardless of the indicator of malnutrition used for CONUT (1.208 [95% CI, 1.102–1.325; *P*<0.001]), NRI (0.961 [95% CI, 0.937–0.985; *P*=0.002]) and PNI (0.949 [95% CI, 0.921–0.978; *P*=0.001]). Compared with normal nutrition, malnutrition risk was associated with an increased risk for all-cause death (adjusted HR for mild and moderate–severe malnutrition, respectively) for the CONUT (2.820 [95% CI, 1.688–4.709; *P*<0.001] and

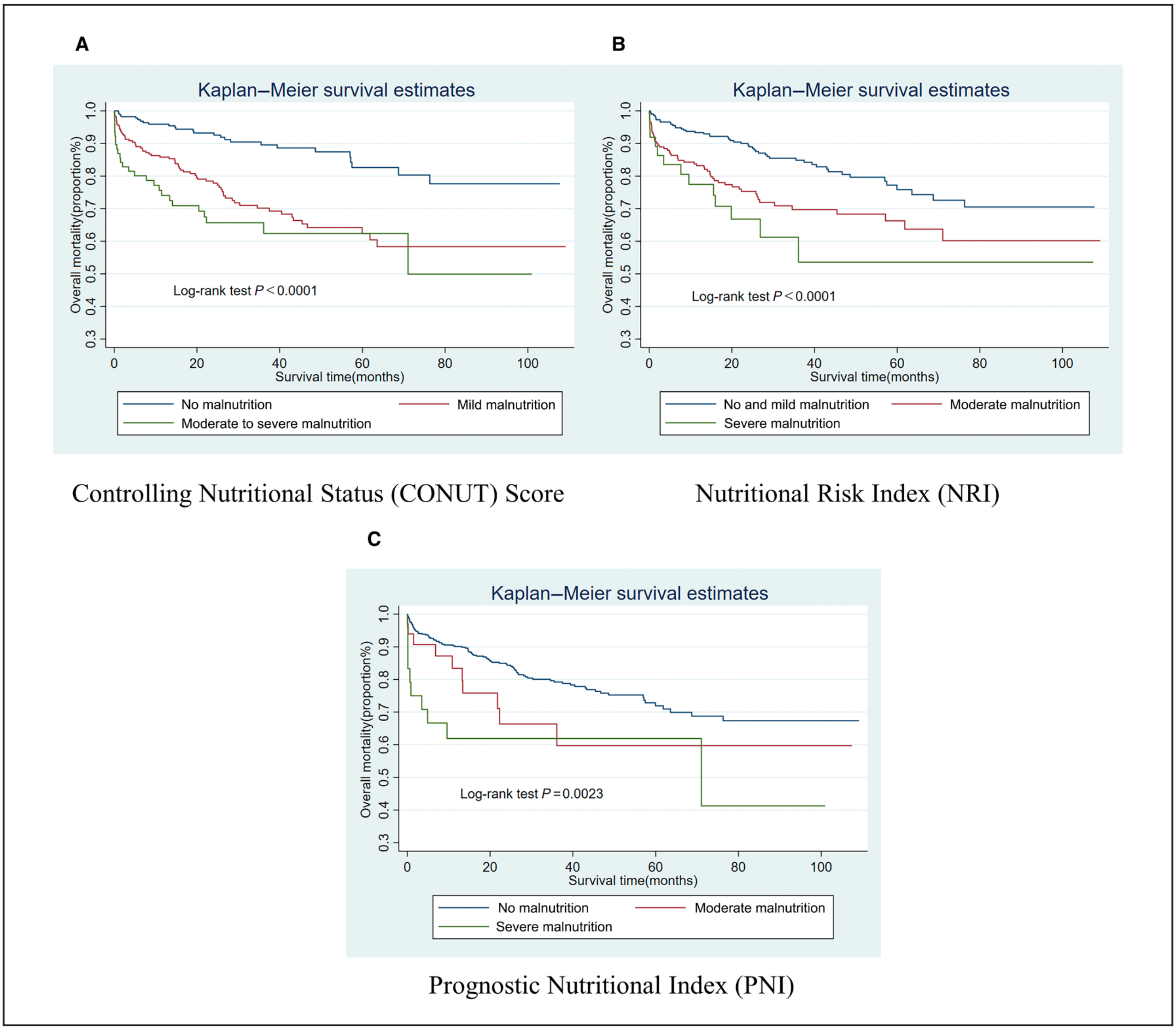

Figure 2. Survival curve of patients with moderate and severe aortic stenosis.
Survival curve of patients with moderate and severe aortic stenosis for all-cause mortality by the CONUT score (A), NRI (B), and PNI (C). CONUT indicates Controlling Nutritional Status score; NRI, nutritional risk index; and PNI, prognostic nutritional index.

3.314 [95% CI, 1.737–6.324; $P<0.001$]), NRI (2.161 [95% CI, 1.232–3.791; $P=0.007$] and 2.872 [95% CI, 1.270–6.497; $P=0.011$]), and PNI (1.107 [95% CI, 0.529–2.318; $P=0.787$] and 1.722 [95% CI, 0.818–3.623; $P=0.152$]). The restricted spline curve of CONUT, NRI, and PNI of patients with moderate and severe AS were also consistent with these results (Figure 3).

In addition, we divided patients according to age of 60 and 75 years, sex, BMI of 24 kg/m^2, presence or absence of underlying diseases and AVR, and so on. The risk of malnutrition-related all-cause mortality was relatively higher among individuals who were older, nonsmokers, nondrinkers, free from hypertension and coronary heart disease, exhibited good renal function, did not receive AVR, and had better left ventricular ejection fraction and more severe maximum ejection velocity of the aortic valve. However, none of the interactions suggested statistical significance based on CONUT ($P>0.05$ for all interactions, Figure 4).

Receiver Operating Characteristics Curve Analysis

Receiver operating characteristic curve for each nutritional status index are shown in Figure 5. Area under the receiver operating characteristic curve for all-cause mortality was 0.6471 for the CONUT score, 0.5992 for the NRI, and 0.6673 for the PNI (Figure 5).

Table 2. Association Between the State of Malnutrition and All-Cause Mortality in the Patients With Moderate-to-Severe AS

			Model 1		Model 2		Model 3	
	Events	Populations	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P* value
CONUT, continuous								
Per 1-point increment	120	536	1.260 (1.166–1.361)	<0.001	1.220 (1.121–1.327)	<0.001	1.208 (1.102–1.325)	<0.001
CONUT, categorical				<0.001		<0.001		<0.001
(normal nutrition as reference)	27	226						
Mild risk	67	233	2.812 (1.791–4.415)	<0.001	2.519 (1.580–4.015)	<0.001	2.820 (1.688–4.709)	<0.001
Moderate and severe risk	26	77	3.973 (2.295–6.881)	<0.001	2.924 (1.645–5.198)	<0.001	3.314 (1.737–6.324)	<0.001
NRI, continuous								
Per 1-point increment	120	536	0.968 (0.951–0.986)	0.001	0.972 (0.953–0.990)	0.003	0.961 (0.937–0.985)	0.002
NRI, categorical				0.001		0.011		0.034
(normal nutrition as reference)	43	258						
Mild risk	8	40	1.177 (0.549–2.523)	0.675	1.153 (0.531–2.503)	0.719	1.645 (0.702–3.857)	0.252
Moderate risk	56	201	1.873 (1.252–2.801)	0.002	1.694 (1.108–2.591)	0.015	2.161 (1.232–3.791)	0.007
Severe risk	13	37	2.938 (1.558–5.540)	0.001	2.727 (1.420–5.237)	0.003	2.872 (1.270–6.497)	0.011
PNI, continuous								
Per 1-point increment	120		0.929 (0.904–0.954)	<0.001	0.937 (0.909–0.966)	<0.001	0.949 (0.921–0.978)	0.001
PNI, categorical				0.003		0.060		0.356
(normal nutrition as reference)	100	479						
Moderate risk	10	33	1.679 (0.876–3.220)	0.119	1.299 (0.665–2.539)	0.445	1.107 (0.529–2.318)	0.787
Severe risk	10	24	2.868 (1.484–5.539)	0.002	2.283 (1.134–4.598)	0.021	1.722 (0.818–3.623)	0.152

Cox regressions were used. Model 1 adjusted by sex, age. Model 2 adjusted by model 1 + smoking status, drinking status, hypertension, diabetes, coronary heart disease, stroke, chronic obstructive pulmonary disease, atrial fibrillation, chronic kidney disease, aortic insufficiency, mitral stenosis, mitral insufficiency, pulmonary arterial hypertension. Model 3 Adjusted by model 2 + body mass index, systolic blood pressure, heart rate, estimated glomerular filtration rate, low-density lipoprotein cholesterol, left ventricular ejection fraction, The maximum velocity of the aortic valve orifice, antiplatelets, stains use, antihypertension medication, oral anticoagulant, hypoglycemic drugs, diuretic, and aortic valve replacement. AS indicates aortic stenosis; CONUT, Controlling Nutritional Status score; HR indicates hazard ratio; NRI, nutritional risk index; and PNI, prognostic nutritional index.

DISCUSSION

In this multicenter, Chinese aortic stenosis cohort, we evaluated the prognostic value of malnutrition risk in predicting mortality in patients with moderate-to-severe AS. The main findings of this study were as follows: 1) malnutrition was prevalent in AS patients; 2) Worsening malnutrition was associated with higher all-cause mortality regardless of the malnutrition index used.

The first issue that should be highlighted is the prevalence of malnutrition. Malnutrition is common in many cardiovascular disease populations. A study including more than 5062 patients with acute coronary syndrome found the percentage of patients with malnutrition varied from 8.9% with the PNI, to 49.8% with the CONUT score, and to 59.5% with the NRI in the cohort.[12] Malnutrition is also common in patients with chronic heart failure, with a prevalence of about 45%.[30] In patients undergoing AVR, Sara Emami et al. observed a prevalence of 5% for malnutrition,[31] whereas Kenichi Ishizu et al.[12]observed a prevalence of 16.6%, 60.5%, and 13.8% patients for moderate or severe malnutrition according to the CONUT, GNRI (geriatric nutritional risk index) and PNI. There have been no prior studies specifically assessing the prevalence of malnutrition in general populations with moderate-to-severe AS.

Among the patients with AS in this study, comparing the clinical characteristics of 3 nutritional indexes in 536 patients, the prevalence of malnutrition risk depended on the nutritional index used, ranging from 57.8% with the CONUT, to 51.9% with the NRI score, and to 10.6% with the PNI (Table 3). It can be found that PNI detected far fewer patients who were malnourished compared with the other indicators. Because PNI identifies patients only as moderately or severely malnourished, it may underestimate the overall incidence of malnutrition. In fact, PNI (15.1%) and CONUT score (20.3%) were more consistent in terms of the prevalence of moderate-to-severe malnutrition, which may reflect the similarity of variables on which the two indicators are

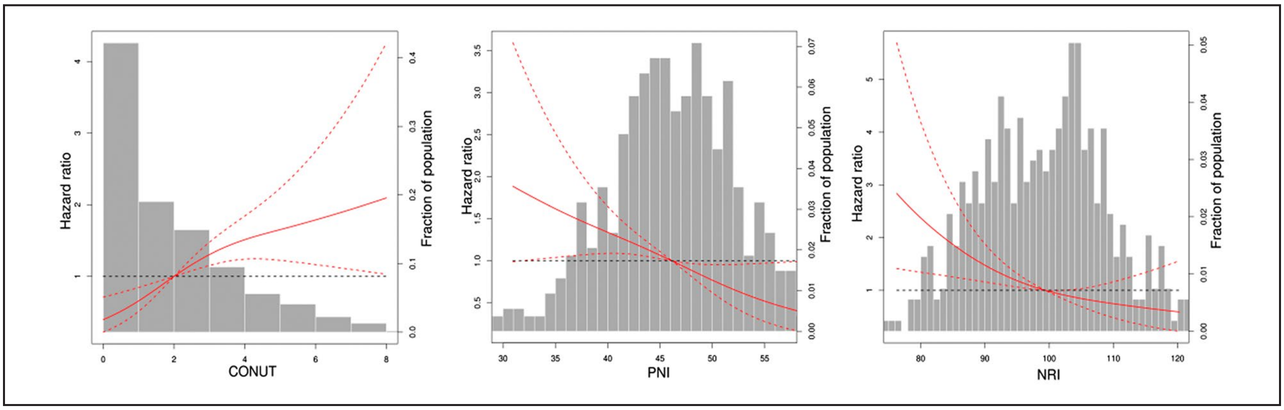

Figure 3. Restricted cubic spline showing the relationship between continuous baseline CONUT, NRI, PNI, and all-cause death in 536 patients on dialysis with moderate or severe aortic stenosis.
Dashed lines depict the 95% CIs. Outcomes were adjusted for sex, age, smoking status, drinking status, hypertension, diabetes, coronary heart disease, stroke, chronic obstructive pulmonary disease, atrial fibrillation, chronic kidney disease, aortic insufficiency, mitral stenosis, mitral insufficiency, pulmonary arterial hypertension, body mass index, systolic blood pressure, heart rate, estimated glomerular filtration rate, low-density lipoprotein cholesterol, left ventricular ejection fraction, The maximum velocity of the aortic valve orifice, antiplatelets, statin use, antihypertension medication, oral anticoagulant, hypoglycemic drugs, diuretic, and aortic valve replacement. CONUT indicates Controlling Nutritional Status score; NRI, nutritional risk index; and PNI, prognostic nutritional index.

based. On the other hand, NRI considering anthropometric factors found a higher prevalence of moderate-to-severe malnutrition (62.8%).

The use of nutritional parameters has gained increasing popularity in recent years, as numerous studies have shown that they were effective in the prognosis of cardiovascular diseases. Poor nutritional status has been shown to be risk factor for mortality in older adults with cardiovascular diseases, such as acute coronary syndrome, ischemic heart disease, AS, and heart failure were considered.[32] Similarly, other studies have demonstrated that incorporating the nutritional evaluation provided by the CONUT score into existing prediction models significantly increased the predictive with some cardiovascular diseases ability for death.[20] The findings of studies on AS disease have yielded similar outcomes. Several previous studies have confirmed that nutritional status is independently associated with the risk of all-cause mortality in patients undergoing AVR with AS.[23,31,33] The predictive impact of malnutrition measures on mortality was further validated even after adjusting for clinical variables recognized to have a poor prognosis, including the Clinical Frailty Scale, American Society for Thoracic Surgery Predictive Mortality Risk score, and renal function.[34]

The prevalence of AS in the general population is 0.4%, and 1.7% in the population >65 years old in developed countries. Currently, AVR remains the only effective treatment for severe AS.[2] Medical treatment options are limited. Therefore, the identification of patients at risk of early mortality is crucial for risk stratification and appropriate therapeutic intervention in individuals with a high prevalence and limited treatment options in AS. Similarly, it is important to explore additional risk factors for intervention to improve outcomes in patients who may not undergo surgery due to various reasons such as physical condition, underlying disease, or financial limitations. Our study used 3 malnutrition screening measures and directly compared three nutrition scales. After adjustment for covariates related to all-cause death and cardiovascular disease, the multivariate COX regression analysis revealed that moderate or severe malnutrition, regardless of the malnutrition index used by the patient, was independently associated with an increased risk of all-cause mortality compared with normal nutrition status. In CONUT and NRI classification, nutrition status and the risk for all-cause mortality in a certain dose–response associations were observed. The more severe the malnutrition status, the greater the impact of malnutrition on the risk of all-cause mortality in individuals with AS. This may suggest that malnutrition may be a risk stratification and intervention factor. Although this relationship is not apparent in the PNI classification, this might be attributed to the fact that PNI's definition of malnutrition status is more rigorous and the data distribution is skewed.

Currently, a diverse range of established screening instruments are used in clinical settings to detect malnutrition, including CONUT, NRI, PNI, the Malnutrition Universal Screening Tool, Nutrition Risk Screening 2002,[35] Mini Nutritional Assessment and its Short Form[36] and so on. The measures selected in our study are supported by robust evidence, possess relative simplicity, and can be readily applied in clinical settings. The CONUT index accurately reflects the nutritional status and immune function of the body.[13] Multivariable analysis confirmed CONUT

Subgroup	Events	No.	HR (95%CI)	P	P for interaction
Overall	120	536	1.208 (1.102–1.325)	<0.001	
Age, yrs					0.613
≤ 60	22	155	1.174 (0.830–1.659)	0.365	
60–75	44	245	1.193 (1.015–1.403)	0.033	
≥75	54	136	1.357 (1.104–1.668)	0.004	
Gender					0.819
Men	68	324	1.176 (1.043–1.326)	0.008	
Women	52	212	1.248 (1.028–1.516)	0.025	
BMI, kg/m²					0.339
≤24	78	337	1.174 (1.039–1.326)	0.010	
>24	42	199	1.277 (1.040–1.568)	0.130	
Smoking					0.371
Yes	33	156	1.194 (0.980–1.456)	0.001	
No	87	380	1.243 (1.099–1.406)	0.079	
Drinking					0.687
Yes	16	75	1.475 (0.778–2.794)	0.233	
No	104	461	1.236 (1.114–1.371)	<0.001	
Hypertension					0.073
Yes	67	238	1.143 (0.994–1.314)	0.061	
No	53	298	1.453 (1.245–1.695)	<0.001	
Diabetes					0.75
Yes	34	98	1.357 (1.044–1.764)	0.022	
No	86	438	1.193 (1.070–1.330)	0.002	
CHD					0.269
Yes	36	137	1.065 (0.832–1.365)	0.617	
No	84	399	1.250 (1.123–1.391)	<0.001	
GFR , ml/min/1.73m²					0.761
≤60	54	150	1.126 (0.980–1.294)	0.094	
>60	66	386	1.348 (1.151–1.579)	<0.001	
LVEF, %					0.696
≤50	25	97	0.952 (0.556–1.630)	0.858	
>50	95	439	1.220 (1.103–1.349)	<0.001	
Vmax, m/s					0.645
≤4	63	241	1.140 (0.978–1.330)	0.093	
>4	57	295	1.423 (1.215–1.666)	<0.001	
AVR					0.653
Yes	24	275	1.221 (0.972–1.532)	0.086	
No	96	261	1.223 (1.096–1.366)	<0.001	

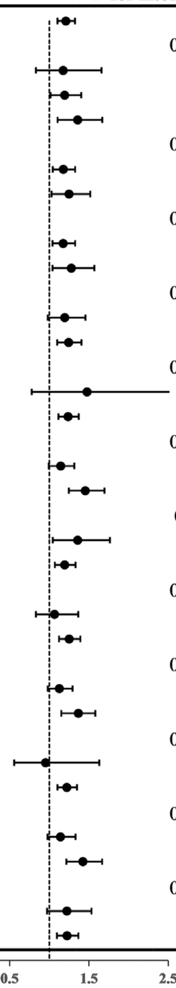

Figure 4. Subgroup analysis of association between the state of malnutrition and all-cause mortality in the patients with moderate-to-severe AS based on CONUT.
Adjusted by sex, age, smoking status, drinking status, hypertension, diabetes, CHD, stroke, chronic obstructive pulmonary disease, atrial fibrillation, chronic kidney disease, aortic insufficiency, mitral stenosis, mitral insufficiency, pulmonary arterial hypertension, body mass index, systolic blood pressure, heart rate, estimated glomerular filtration rate, low-density lipoprotein cholesterol, left ventricular ejection fraction, The maximum velocity of the aortic valve orifice, antiplatelets, stains use, antihypertension medication, oral anticoagulant, hypoglycemic drugs, diuretic, and aortic valve replacement. AS indicates aortic stenosis; AVR, aortic valve replacement; BMI, body mass index; CHD, coronary heart disease; GFR, glomerular filtration rate; HR, hazard ratio; LVEF, left ventricular ejection fraction; and V_{max}, maximum ejection velocity of the aortic valve.

as an independent risk factor for increased all-cause mortality with moderate–severe AS, and it was associated with a 20.8% increase in risk compared with a lower CONUT score. In receiver operating characteristic curve analysis, CONUT and PNI scores exhibited the strongest correlation with adverse outcomes and outperformed NRI. The three measures employed in our study shared the commonality of serum albumin. The Valve Academic Research Consortium criteria defined low serum albumin as one of the factors reflecting malnutrition.[37] Serum albumin level is often reduced in patients with malnutrition and AS. The association between hypoalbuminemia and post-AVR mortality with patients with AS has been established in previous studies.[38,39] The measurement indicators of CONUT also encompass plasma total cholesterol. This suggests that the use of statins may potentially affect the CONUT score. However, our analysis revealed no significant difference in statins usage between the CONUT groups (P=0.912).

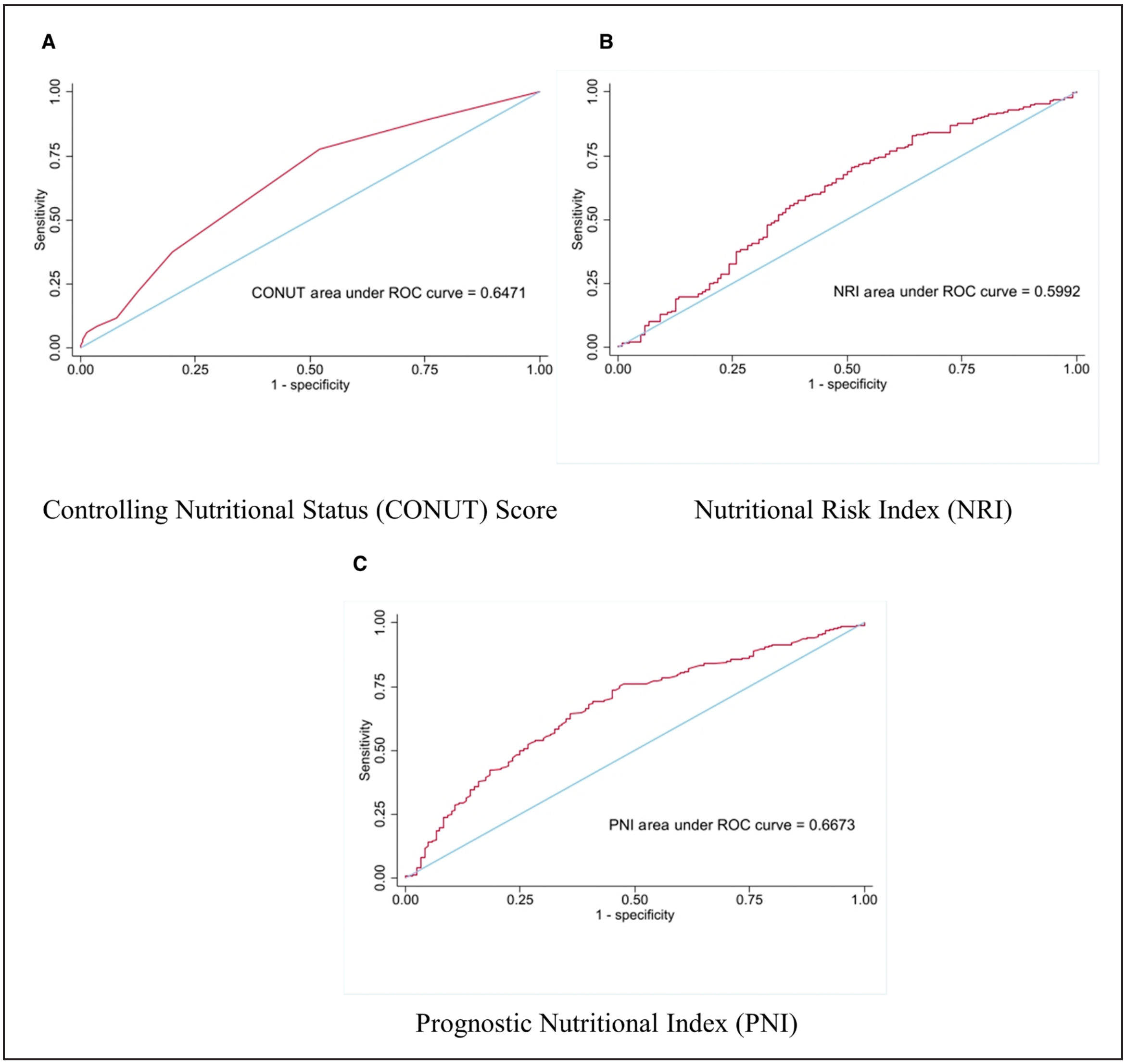

Figure 5. ROC curves of CONUT, NRI, and PNI of patients with moderate and severe aortic stenosis.
Receiver operating characteristic curve for nutrition risk index and all-cause mortality; area under the curve: (**A**) Controlling Nutritional Status Score: 0.65; (**B**) nutritional risk index: 0.60; (**C**) prognostic nutritional index: 0.67. CONUT indicates Controlling Nutritional Status score; NRI, nutritional risk index; PNI, prognostic nutritional index; and ROC, receiver operating characteristic.

The potential explanation for the association between malnutrition and poor prognosis in patients with AS lies in the possibility that nutritional status may serve as systemic inflammation and immune function surrogate markers.[40] It is well documented that this chronic progressive disease is accompanied by a long-term inflammatory process that may lead to decreased mobility, muscle mass, appetite, and poor nutritional status in patients.[41] Simultaneously, systemic inflammation has the potential to trigger atherosclerosis, thereby potentially contributing to elevated cardiovascular mortality rates observed in individuals with suboptimal nutritional status.[42]

A lower BMI is typically indicative of malnutrition. However, our study found that patients with severe malnutrition had a higher average weight compared with those with moderate malnutrition based on CONUT and PNI criteria. A high prevalence of malnutrition in patients with overweight or obesity has also been reported in previous investigations of acute coronary syndromes, which emphasizes that malnutrition does not equal underweight.[7] Furthermore, subgroup analyses did not show any significant interaction between malnutrition and BMI. Therefore, we should screen malnutrition using objective indicators that are not influenced by anthropometric and visual factors.

In people with AS, malnutrition, as a factor that can be interfered with, is associated with higher all-cause mortality. Intervention of nutritional status may be a potential intervention target for patients with AS. Health

Table 3. Procedures for the Evaluation of Each Nutritional Index

Nutritional indices		Risk of malnutrition			
		Absent	Mild	Moderate	Severe
Controlling Nutritional Status score, points		0–1	2–4	5–8	9–12
Formula	Albumin, g/dL (score)	≥3.5 (0)	3.0–3.5 (2)	2.5–3.0 (4)	<2.5 (6)
	Total cholesterol, mmol/L (score)	≥180 (0)	140–180 (1)	100–140 (2)	<100 (3)
	Lymphocyte count, $\times 10^9$/L (score)	≥1.60 (0)	1.20–1.59 (1)	0.80–1.19 (2)	<0.80 (3)
Study population, n (%)		226 (42.2)	233 (43.5)	71 (13.2)	6 (1.1)
Nutritional risk index, points		≥100	97.50–99.99	83.50–97.49	<83.50
Formula	1.489×serum albumin (g/L)+41.7×(weight in kilograms/ideal weight)				
Study population, n (%)		258 (48.1)	40 (7.5)	201 (37.5)	37 (6.9)
		≥38	…	35–38	<35
Prognostic nutritional index score, points					
Formula	10×serum albumin (g/dL)+0.005×total lymphocyte count (mm^3)				
Study population, n (%)		479 (89.4)	…	33 (6.2)	24 (4.5)

care providers may consider incorporating nutritional status screening into existing assessment systems for patients with AS, integrating more disciplines for individual assessment and management of patients, or focusing on monitoring patients' nutritional status, which may bring more benefits to this group of patients.

Limitations

The study has several important limitations. First, the lack of consensus on the definition of malnutrition and the absence of a comparison between these 3 scoring tools and other complex comprehensive nutritional screening tools may underestimate the true magnitude of the undernourished population. Second, there was no information on educational attainment, marital status, or socioeconomic characteristics, which may have influenced our perception of malnutrition. Third, a limitation of this study is the changes in nutritional status during follow-up were unknown. The study used 1-time evaluation methods as predicting factors and did not account for dietary or nutritional changes during the follow-up period, patients may alter their diet and nutritional status due to changes in disease severity or comorbidities. Posthospitalization nutritional interventions might also influence the accuracy of this malnutrition screening. In addition, the scope of our study was limited to an Asian population, thus a more extensive and comprehensive follow-up investigation of the results in other racial or ethnic groups is warranted.

CONCLUSIONS

The study revealed that malnutrition was an independent risk factor associated with increased all-cause mortality in patients diagnosed with moderate-to-severe AS, regardless of the malnutrition index used.

ARTICLE INFORMATION

Received June 16, 2024; accepted November 7, 2024.

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Acknowledgments

Li Bingzhen, Zhang Shaozhao, Xu Chaoguang, Li Jilin, and Chen Jianying designed research; Li Bingzhen, Zhang Shaozhao, Xu Chaoguang, Xiong Zhenyu, Hui Ziwen, and Huang Mengting conducted research; Li Bingzhen and Xu Chaoguang analyzed data; and Li Bingzhen and Zhang Shaozhao wrote the paper. Liao Xinxue and Zhuang Xiaodong had primary responsibility for final content. All authors read and approved the final article.

Sources of Funding

This study was supported by the National Natural Science Foundation of China (82070384, 82370358 to X. Liao), Guangdong Basic and Applied Basic Research Foundation (2021A1515110266 to Z. Xiong).

Disclosures

None.

Supplemental Material

Tables S1–S2
Figure S1

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