ORIGINAL ARTICLE

Combined effect of nutritional status on long-term outcomes in patients with coronary artery disease undergoing percutaneous coronary intervention

Hideki Wada[1] · Tomotaka Dohi[1] · Katsumi Miyauchi[1] · Hirohisa Endo[1] · Shuta Tsuboi[2] · Manabu Ogita[2] · Takatoshi Kasai[1] · Shinya Okazaki[1] · Kikuo Isoda[1] · Satoru Suwa[2] · Hiroyuki Daida[1]

Abstract

Previous studies have reported the prognostic value of objective nutritional indices such as the Controlling Nutritional Status (CONUT) score, Geriatric Nutritional Risk Index (GNRI) and Prognostic Nutritional Index (PNI). However, the effects of these indices in patients with coronary artery disease (CAD) who have undergone percutaneous coronary intervention (PCI) remain unclear. Furthermore, there are insufficient data to combine these indices. A total of 1984 patients who underwent elective PCI were enrolled. The Combined Objective Nutritional Score was determined by assigning 1 point each for high CONUT score (3–12), low GNRI (< 98) or low PNI (< 45). Patients were grouped into normal nutritional status (0 points), mild-to-moderate malnutrition (1–2 points) and severe malnutrition (3 points). Incidences of all-cause death and cardiac death were evaluated. Among the 1984 patients, 514 (25.9%) and 244 (12.3%) had mild-to-moderate and severe malnutrition, respectively. During follow-up (median 7.4 years), 293 all-cause deaths were identified, including 92 cardiac deaths. Kaplan–Meier curves showed ongoing divergence in rates of death among nutritional statuses determined by the novel score (log rank test, $p < 0.0001$). Multivariate Cox hazard analysis showed that patients with a Combined Objective Nutritional Score of 3 showed 2.91-fold (95% confidence interval (CI) 2.10–4.00; $p < 0.0001$) and 2.16-fold (95% CI 1.15–3.92; $p = 0.02$) increases in risk of mortality and cardiac mortality compared with patients with a Combined Objective Nutritional Score of 0. In conclusion, malnutrition as evaluated by the Combined Objective Nutritional Score was significantly associated with worse long-term cardiovascular outcomes among CAD patients who underwent PCI.

Keywords Malnutrition · Coronary artery disease · Percutaneous coronary intervention · Asian population

Introduction

Malnutrition has been recognized as an independent risk factor for unfavorable events in patients with heart failure [1, 2]. Weight loss with development of cardiac cachexia is commonly associated with declines in physical function and worse prognosis. Evaluation of nutritional status is, therefore, recommended in guidelines for heart failure [3,

4] and early nutritional intervention can reduce the risk of adverse cardiac events in these patients [5]. Some objective nutritional indices such as the Controlling Nutritional Status (CONUT) score [6], Geriatric Nutritional Risk Index (GNRI) [7] and Prognostic Nutritional Index (PNI) [8, 9], have been reported as useful clinical predictors of mortality or morbidity in patients with heart failure [10–14].

Some recent studies have evaluated nutritional status using these objective nutritional indices and have demonstrated associations between clinical outcomes and malnutrition in patients with coronary artery disease (CAD) [15–17]. Although CONUT score, GNRI and PNI might offer useful predictive markers, these indices were calculated using different methods that show various advantages and disadvantages. The aim of our study was to evaluate the prognostic values of these three objective nutritional indices among CAD patients who have undergone elective percutaneous

✉ Tomotaka Dohi
tdohi@juntendo.ac.jp

1 Department of Cardiovascular Medicine, Juntendo University Graduate School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

2 Department of Cardiology, Juntendo University Shizuoka Hospital, Izunokuni, Shizuoka, Japan

coronary intervention (PCI). Furthermore, we combined data from these indices and evaluated the effects of a novel combined score (Combined Objective Nutritional Score) on long-term outcomes.

Materials and methods

Study population and data collection

The present study was a single-center, observational, retrospective cohort study. Among consecutive patients with CAD who underwent elective PCI for the first time at Juntendo University Hospital, Tokyo, Japan, between January 2000 and December 2011, only patients for whom pre-procedural CONUT score, GNRI and PNI were available were investigated. Patients with known malignancy or active inflammatory disease were excluded from the study.

Demographic data and information about coronary risk factors, medications, revascularization procedure-related factors, and co-morbidities were prospectively collected and analyzed. Blood samples were collected in the early morning after overnight fasting, and blood pressure (BP) was measured on admission. Patients with BP > 140/90 mmHg or those receiving antihypertensive drugs were regarded as hypertensive. Dyslipidemia was defined as low-density lipoprotein cholesterol (LDL-C) ≥ 140 mg/dl, high-density lipoprotein cholesterol (HDL-C) ≤ 40 mg/dl, triglycerides ≥ 150 mg/dl, or current treatment with statins and/or lipid-lowering agents [18]. Diabetes mellitus was defined as either hemoglobin A1c ≥ 6.5% or medication with insulin or oral hypoglycemic drugs. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate < 60 ml/min/1.73 m^2 as calculated using the Modification of Diet in Renal Disease equation modified with a Japanese coefficient using baseline serum creatinine [19]. A current smoker was defined as a person who was smoking at the time of PCI or who had stopped smoking within 1 year before PCI. Left ventricular ejection fraction (LVEF) was assessed using left ventricular angiography or echocardiography before PCI. All patients had symptoms of effort angina, documented myocardial ischemia, or both.

Written, informed consent was obtained from all patients before undergoing PCI. This study was performed in accordance with the Declaration of Helsinki and with the approval of our institutional review board.

Primary endpoints

Both all-cause death and cardiac death during the follow-up period were evaluated. Cardiac death was defined as death from CAD, cardiogenic shock, or sudden death. Clinical follow-up comprised analyses of clinical charts and responses to questionnaires sent to patients or their families, and telephone contact. Mortality data were collected from the medical records of patients who died or who were treated at our institution, and details and causes of death were obtained from other hospitals to which patients had been admitted.

Evaluation of nutritional indices

Baseline CONUT score was calculated from serum albumin levels, total cholesterol levels and total lymphocyte counts as follows: serum albumin ≥ 3.5 g/dl, 0 points; 3.0–3.4 g/dl, 2 points; 2.5–2.9 g/dl, 4 points; and < 2.5 g/dl, 6 points; total cholesterol ≥ 180 mg/dl, 0 points; 140–179 mg/dl, 1 point; 100–139 mg/dl, 2 points; and < 100 mg/dl, 3 points; and total lymphocyte count ≥ 1600/ml, 0 points; 1200–1599/ml, 1 point; 800–1199/ml, 2 points; and < 800/ml, 3 points [6]. CONUT scores range from 0 to 12. An individual with normal nutritional status would have a CONUT score of 0, with higher scores indicating worse nutritional status.

GNRI was calculated from serum albumin and body weight and height obtained on hospital admission, as previously described: GNRI = 14.89 × serum albumin (g/dl) + 41.7 × (actual body weight/ideal body weight). Actual body weight/ideal body weight was set to 1 when the body weight of the patient exceeded the ideal body weight. Ideal body weight in the present study was calculated using a body mass index (BMI) of 22 kg/m^2, because of its validity [20], instead of the value calculated using the Lorentz formula in the original GNRI equation [7].

Baseline PNI was calculated as 10 × serum albumin (g/dl) + 0.005 × total lymphocyte count (per mm^3) [9]. Data for these components were collected in the morning on the day of PCI.

Risk of malnutrition was defined as present when the patient showed CONUT score ≥ 3, GNRI < 98 or PNI < 45 [7, 9, 21]. We gave these patients 1 point for each criterion met, and this total was considered the Combined Objective Nutritional Score (e.g., a patient with a CONUT score of 2, a GNRI of 97 and a PNI of 43 would have a Combined Objective Nutritional Score of 2 points). Patients were divided into three groups according to this combined assessment score as: Group 1, normal nutritional status (0 points); Group 2, mild-to-moderate malnutrition (1–2 points); and Group 3, severe malnutrition (3 points).

Statistical analysis

Quantitative data are presented as mean ± standard deviation or median and interquartile range (IQR). Categorical variables are presented as frequencies. Continuous variables across groups were compared using one-way analysis of variance or the Kruskal–Wallis test. Categorical variables (presented as frequencies) were compared using the Chi-squared

test. Unadjusted cumulative event rates were estimated using Kaplan–Meier curves and compared across groups. Cox proportional hazards models were used to assess uni- and multivariate covariates. Hazard ratios (HRs) and confidence intervals (CIs) were calculated for each factor by Cox proportional hazards analysis. Three Cox multivariate models were used: Model 1, unadjusted; Model 2, adjusted for age and sex; and Model 3, adjusted for the variables in Model 2 plus CKD, current smoker status, diabetes mellitus, family history of CAD, hypertension, LVEF and statin use. Differences were considered significant at the level of $p < 0.05$. Statistical analyses were performed using JMP version 12.0 software (SAS Institute, Cary, NC, USA).

Results

Prevalence of malnutrition in patients with stable CAD

Of the 2092 patients who underwent elective PCI, pre-procedural CONUT score, GNRI and PNI data were available for 1984 patients (94.8%). For these patients, median CONUT score was 1 (IQR 0, 2), median GNRI was 101.3 (IQR 96.8, 105.7) and median PNI was 48.9 (IQR 45.4, 48.9). Figure 1a, c, e shows the distribution of each Objective Nutritional Index. Using these indices as a screening tool for malnutrition, 21–28% of patients were at risk of malnutrition [CONUT score ≥ 3, 421 patients (21.2%); GNRI < 98, 562 patients (28.3%); and PNI < 45, 459 patients (23.1%)]. Using these data, the Combined Objective Nutritional Score was calculated and patients were divided into 3 groups: Group 1, 1226 patients (61.8%); Group 2, 514 patients (25.9%); and Group 3, 244 patients (12.3%) (Table 1).

Baseline and procedural characteristics

Clinical and procedural characteristics of the patients are shown in Table 2. Patients with worse nutritional status were significantly older and showed a higher prevalence of diabetes mellitus, multivessel coronary disease and CKD, as well as lower LDL-C, HDL-C, triglycerides and LVEF. Patients in this group were also less likely to be current smokers or to have been receiving treatment using statins on admission.

Clinical outcomes

Median duration of follow-up was 7.4 years (IQR 4.6–10.1 years). In total, 293 (frequency, 14.8%) all-cause deaths were identified during follow-up, including 92 (4.6%) cases of cardiac death. All-cause deaths among patients stratified by nutritional status using CONUT score, GNRI and PNI are presented in Fig. 1b, d, f. Kaplan–Meier curves
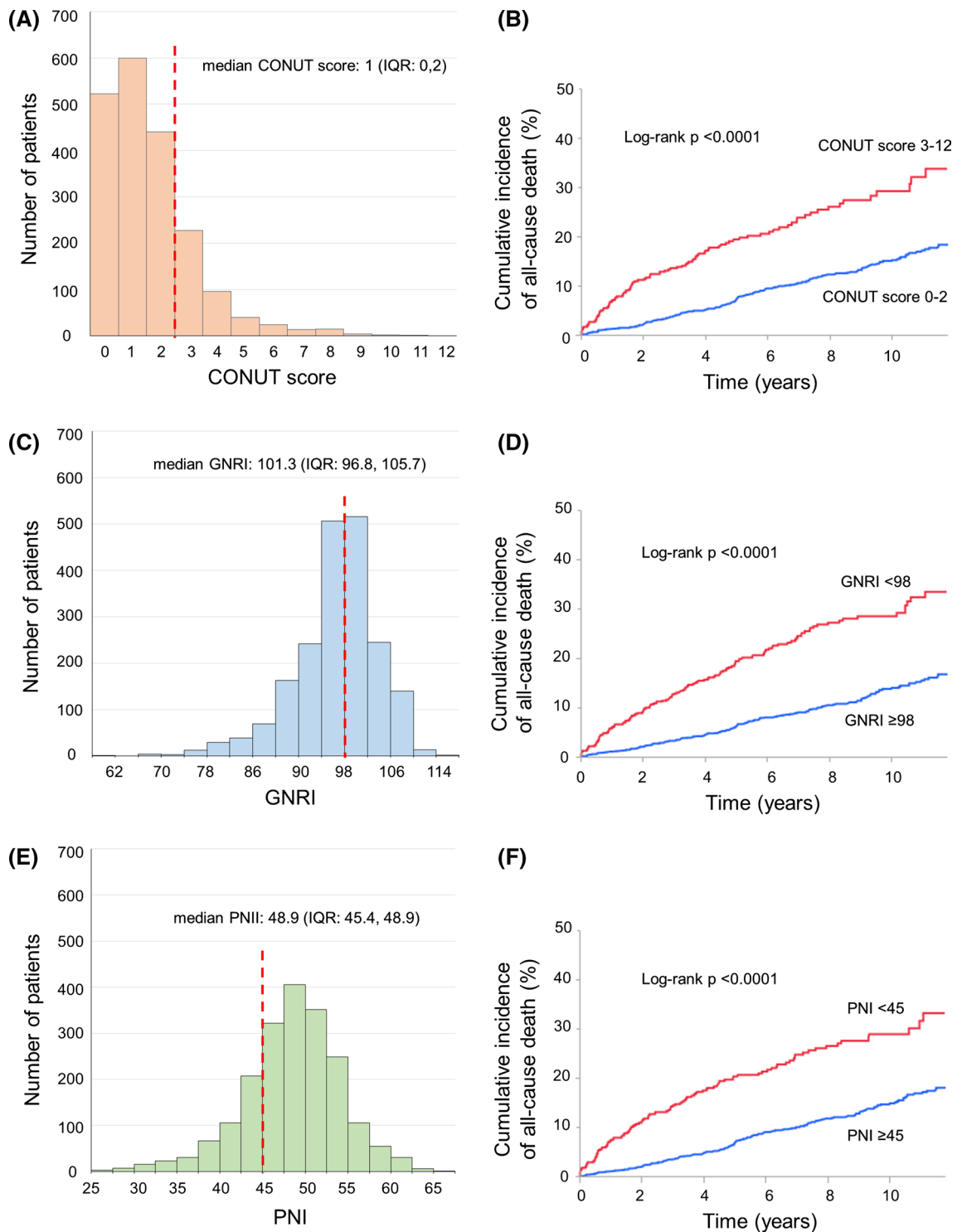
showed that the incidence of death was significantly higher in malnourished patients assessed using each Objective Nutritional Index than in those who were not (log rank test, $p < 0.0001$ each). Furthermore, Kaplan–Meier analysis also showed that cumulative incidences of all-cause death and cardiac death increased clearly and significantly with worse nutritional status among patients stratified by Combined Objective Nutritional Score (log rank test, both $p < 0.0001$; Fig. 2).

Table 3 shows Cox proportional hazard analyses for all-cause death and cardiac death. In unadjusted Cox modeling (Model 1), rate of all-cause death and cardiac death rose progressively with groups of worse nutritional status (both $p < 0.0001$ for trend). After adjustment for age and sex, Model 2 yielded similar results. Patients in Group 2 and Group 3 were significantly associated with all-cause death and cardiac death compared with patients in Group 1. Even after adjusting for age, sex and other risk factors (Model 3), patients with a Combined Objective Nutritional Score of 3 (Group 3) displayed a 2.91-fold (95% CI 2.10–4.00; $p < 0.0001$) and 2.16-fold (95% 1.15–3.92; $p = 0.02$) increase in risk of mortality and cardiac mortality compared with those with a Combined Objective Nutritional Score of 0 (Group 1).

Discussion

The major findings of the present study were as follows: (1) patients with worse nutritional status tended to show worse clinical characteristics, such as advanced age or higher prevalences of diabetes mellitus or CKD; (2) malnourished patients assessed by each Objective Nutritional Index (CONUT score, GNRI and PNI) displayed higher mortality than those without malnutrition; (3) the Combined Objective Nutritional Score effectively stratified CAD patients, and patients with worse malnutrition had significantly higher risks of all-cause death and cardiac death than those without malnutrition, even after adjusting for other risk factors.

Malnutrition is not rare, but represents a crucial issue for aged or hospitalized patients. Malnutrition has been reported to be related to worse clinical outcomes in patients with end-stage renal failure, cancer, heart failure and myocardial infarction (MI) [14, 22–24]. To date, several nutritional markers have been reported, including lymphocyte count, serum albumin levels, total cholesterol, the Mini-Nutritional Assessment (MNA) [25], the Subjective Global Assessment (SGA) [26], CONUT score, GNRI or PNI. Underweight status has also been reported as related to worse nutritional status and a greater risk of cardiovascular events [27]. The MNA or SGA require subjective assessment, which might be affected by medical staff and their experience. In addition, obtaining these data is not

Fig. 1 Distribution of objective nutritional indices and Kaplan–Meier curves for all-cause death. **a** Distribution of CONUT score. **b** Kaplan–Meier curves stratified by CONUT score (0–2 vs. 3–12). **c** Distribution of GNRI. **d** Kaplan–Meier curves stratified by GNRI levels (≥ 98 vs. < 98). **e** Distribution of PNI. **f** Kaplan–Meier curves for all-cause death stratified by PNI levels (≥ 45 vs. < 45). Median CONUT score, GNRI and PNI were 1 (IQR 0, 2), 101.3 (IQR 96.8, 105.7) and 48.9 (IQR 45.5, 48.9), respectively. Kaplan–Meier curves showed that the incidence of death was significantly higher in malnourished patients assessed using each Objective Nutritional Index than in those who were not (log rank test, all $p < 0.0001$). *CONUT* controlling nutritional status, *GNRI* Geriatric Nutritional Risk Index, *PNI* Prognostic Nutritional Index

Table 1 Patients evaluated as malnourished and combined objective nutritional score

Parameter	Score	Number of patients (%)
CONUT score	3–12	421 (21.2)
GNRI	<98	562 (28.3)
PNI	<45	459 (23.1)
Combined objective nutritional score	0	1226 (61.8)
	1–2	514 (25.9)
	3	244 (12.3)

CONUT (controlling nutritional status) score is calculated from serum albumin, total cholesterol levels and total lymphocyte count. CONUT scores range from 0–12, with higher scores representing worse status

GNRI (Geriatric Nutritional Index) = $14.89 \times$ serum albumin levels (g/dl) + $41.7 \times$ [actual body weight/ideal body weight]

PNI (Prognostic Nutritional Index) = $10 \times$ serum albumin (g/dl) + $0.005 \times$ total lymphocyte count (mm^3)

easy in daily clinical situations. Single blood parameters or bodyweight are easy to use and assess, but assessments using only one indicator may be affected by various factors. CONUT score, GNRI and PNI each use two or three objective parameters to evaluate different aspects of nutritional conditions. Calculating these indices using inexpensive markers is simple and easy. However, these indices are calculated using different methods and components, and each has specific advantages and disadvantages. First, GNRI is usually calculated by serum albumin and BMI, but may underestimate malnutrition in patients with a normal or larger BMI. PNI is calculated by serum albumin and lymphocyte count. Basta et al. assessed the prognostic value of CONUT score and PNI in patients with ST-elevation MI, but PNI was not associated with increased risk of cardiovascular events [22]. CONUT score is calculated from three blood parameters (serum albumin, total cholesterol and lymphocyte count), offering an advantage over other objective indices using two parameters. However, patients with CAD are recommended to be treated with statin therapy, so total cholesterol level may not be an appropriate nutritional marker for CAD patients. The present study assessed nutritional status using these three objective nutritional indices, finding that those patients assessed as showing poor nutrition experienced a higher incidence of all-cause death. Furthermore, patients with worse nutritional status evaluated using the Combined Objective Nutritional Score were at significantly higher risk of not only all-cause death, but also cardiac death. To the best of our knowledge, this is first study to evaluate the association between malnutrition and long-term cardiac mortality. Our findings indicate that nutritional assessment using this novel combined score should be taken into consideration in patients who have undergone PCI.

Malnutrition is a complex state comprising reductions in protein reserves, caloric collapse, and weakening of the immune defenses. In patients with chronic diseases such as heart failure, malnutrition affects the natural evolution of the disease and the disease in turn affects the nutritional status. This relationship in heart failure has been explained as part of the "vicious circle" of chronic heart failure [10]. A previous study reported that malnutrition was significantly associated with higher concentrations of inflammatory markers and carotid atherosclerosis in patients with chronic heart failure [28]. A relationship between malnutrition and atherosclerosis was also reported in CAD patients. Ko et al. showed that relative muscle mass was negatively associated with prevalence of coronary calcification [29]. Furthermore, serum albumin is one of the components of CONUT score, GNRI and PNI. Although serum albumin is usually used as a nutritional marker, albumin levels are influenced by factors such as synthesis, clearance, and dilution. Under inflammatory conditions, serum albumin concentration is affected by decreased hepatic synthesis, increased leakage into the interstitial space, and catabolism [30]. In addition to the inflammatory factor, antioxidant properties of serum albumin have been reported [31]. Increased oxidative stress represents an important pathogenic factor in cardiovascular disease. These mechanisms might influence the association between malnutrition and cardiovascular outcomes in the present study. CONUT score, GNRI and PNI are calculated by serum albumin level as one of the components. Thus, the combined score might be mainly influenced by serum albumin level. However, other components such as total lymphocyte counts, total cholesterol level and BMI, also affected clinical outcomes among patients in the present study. Univariate Cox hazard analysis for mortality showed that each component was associated with clinical outcomes (not shown in the result).

Our results suggest that evaluation of nutritional status might be useful for risk stratification of stable CAD patients. However, few nutritional intervention studies have investigated CAD patients with poor nutritional status. A future task is thus to clarify what medical treatments or nutritional interventions can improve the prognosis of such patients.

This study has several limitations. First, as a single-center, observational study of a small patient cohort, unknown confounding factors might have affected the

Table 2 Baseline characteristic of patients

|	Overall ($n=1984$)	Group 1 ($n=1226$)	Group 2 ($n=514$)	Group 3 ($n=244$)	p value
CONUT score	1 [0, 2]	1 [0, 1]	2 [1, 3]	4 [3, 5]	< 0.0001
CONUT score ≥ 3, n (%)	421 (21.2)	0 (0)	177 (34.4)	244 (100)	< 0.0001
GNRI	101.3 [96.8, 105.7]	104.4 [101.3, 107.2]	96.8 [94.7, 99.8]	89.3 [83.9, 92.3]	< 0.0001
GNRI < 98, n (%)	562 (28.3)	0 (0)	318 (61.9)	244 (100)	< 0.0001
PNI	48.9 [45.4, 52.1]	51.0 [48.8]	45.6 [43.9, 47.9]	39.4 [36.3, 41.5]	< 0.0001
PNI < 45, n (%)	459 (23.1)	0 (0)	215 (41.8)	244 (100)	
Serum albumin (g/dl)	4.0 ± 0.4	4.2 ± 0.3	3.8 ± 0.3	3.2 ± 0.4	< 0.0001
Total cholesterol (mg/dl)	182.0 ± 36.0	189.3 ± 34.1	174.9 ± 35.7	160.1 ± 34.2	< 0.0001
Total lymphocytes (count/ml)	1680 ± 585	1843 ± 545	1514 ± 568	1210 ± 447	< 0.0001
Body mass index (kg/m^2)	24.2 ± 3.4	24.9 ± 3.1	23.4 ± 3.4	22.7 ± 3.6	< 0.0001
Baseline characteristics					
Age (years)	66.4 ± 9,5	64.9 ± 9.2	68.0 ± 9.1	70.4 ± 10.2	< 0.0001
Male, n (%)	1643 (82.8)	1034 (84.3)	409 (79.6)	200 (82.0)	0.06
Hypertension, n (%)	1451 (73.1)	883 (72.0)	378 (73.5)	190 (77.9)	0.16
Diabetes mellitus, n (%)	950 (47.9)	562 (45.8)	246 (47.9)	142 (58.2)	0.002
Dyslipidemia, n (%)	1450 (73.1)	947 (77.2)	354 (69.0)	149 (61.1)	< 0.0001
Current smoker, n (%)	469 (23.7)	317 (25.9)	100 (19.5)	52 (21.3)	0.009
Family history of CAD, n (%)	566 (28.6)	357 (29.3)	152 (29.7)	57 (23.4)	0.14
Multivessel coronary disease, n (%)	1201 (60.5)	713 (58.2)	319 (62.1)	169 (69.3)	0.003
LDL-C (mg/dl)	109.8 ± 30.8	114.3 ± 30.0	105.7 ± 31.4	95.9 ± 28.5	< 0.0001
HDL-C (mg/dl)	44.6 ± 13.5	45.1 ± 13.4	44.6 ± 13.0	42.0 ± 15.0	0.005
Triglycerides (mg/dl)	136.6 ± 72.1	149.9 ± 78.3	119.5 ± 52.8	105.6 ± 55.6	< 0.0001
HbA1c (%)	6.4 ± 1.2	6.4 ± 1.2	6.4 ± 1.2	6.5 ± 1.4	0.55
High-sensitivity C-reactive protein, mg/dl	0.10 [0.04, 0.21]	0.10 [0.04, 0.20]	0.10 [0.04, 0.23]	0.16 [0.05, 0.33]	< 0.0001
eGFR (ml/min/1.73 m^2)	65.3 ± 22.1	69.3 ± 17.6	62.8 ± 23.7	50.3 ± 30.2	< 0.0001
Chronic kidney disease, n (%)	680 (34.3)	333 (27.2)	204 (39.7)	143 (58.6)	< 0.0001
Left ventricular ejection fraction (%)	62.8 ± 12.1	64.3 ± 10.9	61.7 ± 12.3	57.3 ± 15.3	< 0.0001
Medication					
ACE-I/ARB, n (%)	941 (48.1)	563 (46.6)	243 (47.9)	135 (55.8)	0.03
β Blocker, n (%)	987 (50.4)	614 (50.8)	249 (49.1)	124 (51.2)	0.78
Oral hypoglycemic agents, n (%)	611 (31.2)	361 (29.9)	164 (32.4)	86 (35.5)	0.19
Statin, n (%)	1120 (57.3)	735 (60.9)	266 (52.5)	119 (49.2)	0.0001
Lesion and procedure characteristics					
LAD culprit coronary artery, n (%)	883 (44.5)	549 (44.8)	222 (43.2)	112 (45.9)	0.74
Reference lumen diameter (mm)	2.87 ± 0.51	2.87 ± 0.52	2.87 ± 0.48	2.86 ± 0.52	0.98
Stent size (mm)	3.0 [2.75, 3.5]	3.0 [2.5, 3.5]	3.0 [2.75, 3.5]	3.0 [2.75, 3.5]	0.09

ACE-I angiotensin-converting enzyme inhibitors, *ARB* angiotensin receptor blockers, *CAD* coronary artery disease, *CONUT* controlling nutritional status, *eGFR* estimated glomerular filtration rate, *GNRI* Geriatric Nutritional Risk Index, *HbA1c* hemoglobin A1c, *HDL-C* high-density lipoprotein cholesterol, *LAD* left anterior descending artery, *LDL-C* low-density lipoprotein cholesterol, *PNI* Prognostic Nutritional Index

outcomes, regardless of analytical adjustments. Second, the nutritional status of patients was evaluated only once in the present study; changes over time during the follow-up period were not assessed.

In conclusion, nutritional status evaluated by three objective nutritional indices; CONUT score, GNRI and PNI, was associated with long-term outcomes in stable CAD patients treated with PCI. In addition, the Combined Objective Nutritional Score effectively stratified these populations and patients evaluated as showing a poorer nutritional condition exhibited a higher risk of cardiovascular events.
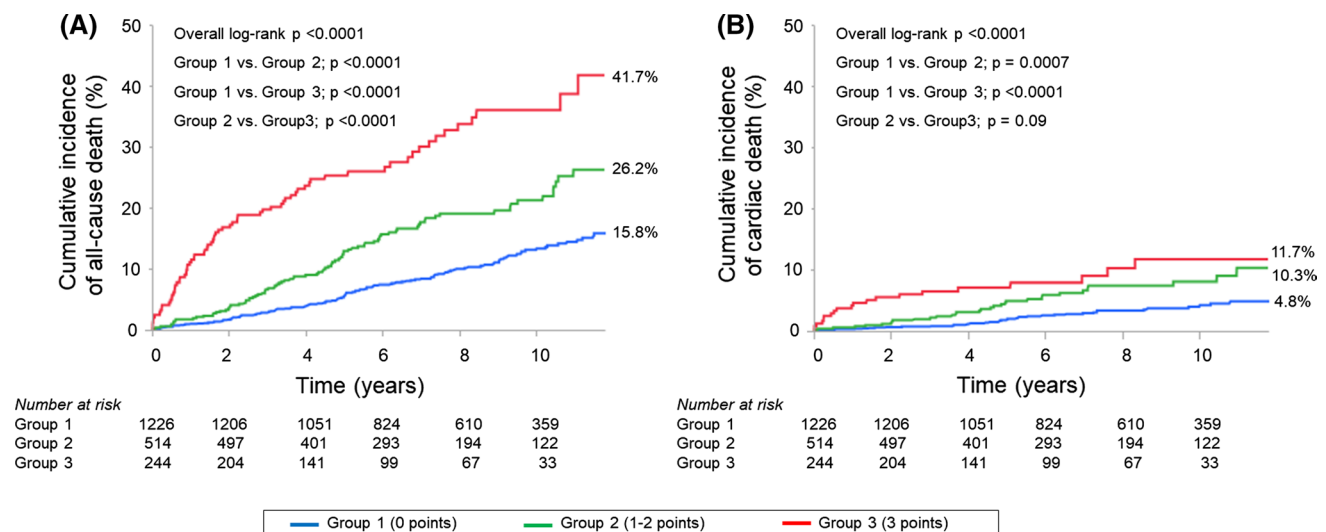
Fig. 2 Kaplan–Meier curves for cardiovascular events stratified using the Combined Objective Nutritional Index. **a** Kaplan–Meier curves for all-cause death. **b** Kaplan–Meier curves for cardiac death. Kaplan–Meier analysis showed that cumulative incidences of all-cause death and cardiac death increased clearly and significantly with worse nutritional status among patients stratified by Combined Objective Nutritional Score (log-rank test, both $p < 0.0001$)

Table 3 Cox proportional hazard model for all-cause death and cardiac death

	All-cause death				Cardiac death			
	HR	95% CI	*p* value	*p* for trend	HR	95% CI	*p* value	*p* for trend
Model 1				<0.0001				<0.0001
Group 2 vs. Group 1	1.97	1.51–2.58	<0.0001		2.28	1.43–3.62	0.0007	
Group 3 vs. Group 1	4.16	3.10–5.54	<0.0001		3.71	2.11–6.29	<0.0001	
Model 2				<0.0001				<0.0001
Group 2 vs. Group 1	1.75	1.33–2.29	<0.0001		2.09	1.30–3.34	0.003	
Group 3 vs. Group 1	3.31	2.44–4.45	<0.0001		3.14	1.77–5.41	0.0002	
Model 3				<0.0001				0.03
Group 2 vs. Group 1	1.54	1.15–2.05	0.004		1.64	0.99–2.72	0.06	
Group 3 vs. Group 1	2.91	2.10–4.00	<0.0001		2.16	1.15–3.92	0.02	

Model 1 crude, *Model 2* adjusted for age and sex, *Model 3* adjusted for age, sex, chronic kidney disease, current smoker, diabetes mellitus, family history of coronary artery disease, hypertension, left ventricular ejection fraction and statin use, *95% CI* 95% confidence interval, *HR* hazard ratio

Compliance with ethical standards

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

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