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ORIGINAL PAPER

Prognostic impact of nutritional status assessed by the Controlling Nutritional Status score in patients with stable coronary artery disease undergoing percutaneous coronary intervention

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Abstract

Background Recently, malnutrition has been shown to be related to worse clinical outcomes in patients with heart failure. However, the association between nutritional status and clinical outcomes in patients with coronary artery disease (CAD) remains unclear. We investigated the prognostic value of malnutrition assessed by the Controlling Nutritional Status (CONUT; range 0–12, higher = worse, consisting of serum albumin, cholesterol and lymphocytes) score in patients with CAD.

Methods The CONUT score was measured on admission in a total of 1987 patients with stable CAD who underwent elective percutaneous coronary intervention (PCI) between 2000 and 2011. Patients were divided into two groups according to their CONUT score (0–1 vs. ≥2). The incidence of major adverse cardiac events (MACE), including all-cause death and non-fatal myocardial infarction, was evaluated.

Results The median CONUT score was 1 (interquartile range 0–2). During the median follow-up of 7.4 years, 342 MACE occurred (17.2%). Kaplan–Meier curves revealed that patients with high CONUT scores had higher rates of MACE (log-rank $p < 0.0001$). High CONUT scores showed a significant increase in the incidence of MACE compared with low CONUT scores, even after adjusting for confounding factors (hazard ratio: 1.64, 95% confidence interval 1.30–2.07, $p < 0.0001$). Adding CONUT scores to a baseline model with established risk factors improved the C-index ($p = 0.02$), net reclassification improvement ($p = 0.004$) and integrated discrimination improvement ($p = 0.0003$).

Conclusions Nutritional status assessed by the CONUT score was significantly associated with long-term clinical outcomes in patients with CAD. Pre-PCI assessment of the CONUT score may provide useful prognostic information.

Keywords Malnutrition · Coronary artery disease · Percutaneous coronary intervention · Controlling Nutritional Status score

Introduction

Malnutrition is a crucial issue for aged and hospitalized patients because of its high morbidity and mortality [1]. Several studies have shown that malnutrition is related to worse clinical outcomes in patients with end-stage renal failure, cancer, clinical limb ischemia or heart failure [2–6]. Nutritional assessment could be a useful predictor for patients with these diseases; however, there are several elements of malnutrition and nutritional status is difficult to assess. Nutritional assessment should be practical, easy to perform, noninvasive and not require the use of any devices. The Controlling Nutritional Status (CONUT) score is an efficient tool and helps evaluate protein reserves, calorie depletion and immune defenses [7]. Although previous studies showed that the CONUT score was associated with adverse clinical events among patients with heart failure [8, 9], the prognostic impact of CONUT scores in

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stable coronary artery disease (CAD) patients was not fully investigated. Therefore, the present study aimed to evaluate the prognostic value of malnutrition assessed by the CONUT score among CAD patients who underwent elective percutaneous coronary intervention (PCI).

Methods

Study population and data collection

The present investigation was a single-center, observational, retrospective cohort study. Among consecutive patients with CAD who underwent 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 was available were included.

Baseline CONUT score was calculated from serum albumin levels, total cholesterol levels and total lymphocyte counts as previously reported (Table 1) [7]. Data of these components were collected in the morning of the day of PCI. CONUT scores range from 0 to 12. A person with normal nutritional status would have a CONUT score of 0, and the higher the score, the worse the nutritional status. We used the continuous variable CONUT score as the test variable and all-cause death and non-fatal myocardial infarction (MI) as the state variables. An investigation using the receiver operating characteristics curve showed the most appropriate cutoff value for the CONUT score to be 2 (area under the curve: 0.591; the sensitivity was 0.549 and the specificity was 0.593). Therefore, we set 2 as the cutoff value and divided patients into a low CONUT score (0–1) group and a high CONUT score ($\geq$2) group.

Demographic data, coronary risk factors and medication use were collected from our institutional database. 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) $\geq$140 mg/dl, high-density lipoprotein cholesterol (HDL-C) $\leq$40 mg/dl, triglycerides $\geq$150 mg/dl or current treatment with statins and/or lipid-lowering agents [10]. Diabetes mellitus was defined as either hemoglobin A1c $\geq$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 the diet in renal disease equation modified with a Japanese coefficient using baseline serum creatinine [11]. A current smoker was defined as a person who smoked at the time of PCI or who had quit smoking within 1 year before PCI. All patients had symptoms of effort angina, documented myocardial ischemia or both.

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

Primary endpoints

The primary outcome was major adverse cardiac events (MACE), defined as a composite of all-cause death and non-fatal MI. Clinical follow-up included a review of medical charts, telephone contact and questionnaires sent to patients or their families. 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. Cardiac death was defined as death from CAD, cardiogenic shock or sudden death. Non-cardiac death was defined as death from other causes. MI was defined as evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia.

Statistical analysis

Quantitative data are presented as mean ± standard deviation (SD) or medians (interquartile range, IQR). Categorical variables are presented as frequencies. Continuous variables were compared using an unpaired t test or the Mann–Whitney *U* test. Categorical variables (presented as frequencies) were compared using the Chi-squared test or Fisher's exact probability test. Unadjusted cumulative

Table 1 Evaluation of CONUT scores

Parameter	Score			
Serum albumin, g/dl	$\geq$3.5	3.0–3.4	2.5–2.9	<2.5
Albumin score	0	2	4	6
Total cholesterol, mg/dl	$\geq$180	140–179	100–139	<100
Cholesterol score	0	1	2	3
Total lymphocytes, count/ml	$\geq$1600	1200–1599	800–1199	<800
Lymphocyte score	0	1	2	3

CONUT Controlling Nutritional Status

event rates between the two groups were compared using Kaplan–Meier curves and the log-rank test. Patients were also stratified by with or without CKD and age using 65 years as the cutoff in the Kaplan–Meier analysis. Effects of the CONUT score on clinical outcomes after PCI were determined using multivariate Cox proportional hazard regression analysis. Model 1 was adjusted for age and sex. Model 2 was adjusted for the variables in model 1 plus body mass index (BMI) and CKD. Model 3 was adjusted for the variables in model 2 plus established risk factors such as current smoking, diabetes, dyslipidemia, hypertension, left ventricular ejection fraction (LVEF), multivessel disease and statin use on admission. CONUT score levels were included in the multivariate modeling, and hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated.

To assess whether the accuracy of predicting adverse cardiac events would improve after adding CONUT scores into a baseline model with established risk factors (i.e., age, CKD, current smoking, diabetes, dyslipidemia, hypertension, LVEF, multivessel disease and use of statins), the C-index, net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were calculated. Differences were considered significant at $p < 0.05$. Statistical analyses were carried out using JMP version 12.0 (SAS Institute, Cary, NC, USA) and R version 3.2.3 (http://www.R-project.org/; R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline and procedural characteristics

Of the 2092 patients who underwent elective PCI, preprocedural CONUT data were available for 1987 patients (95.0%). For these patients, the median CONUT scores were 1 (IQR: 0, 2). Figure 1 shows the distribution of CONUT scores. Clinical and procedural characteristics of the patients are shown in Table 2. Patients in the high CONUT score group were significantly older and had a higher prevalence of hypertension, multivessel disease and CKD, as well as lower BMI, LDL-C, HDL-C, triglycerides and hemoglobin A1c levels on admission. Patients in this group were also less likely to be current smokers, have dyslipidemia and have lower LVEF.

Clinical outcomes

The median follow-up period was 7.4 years (IQR: 4.6–10.1 years). In total, 342 (frequency: 16.3%) cases of MACE were identified during follow-up, including 293 (14.0%) deaths and 49 (2.3%) non-fatal MIs. Among 293 all-cause deaths, 92 cardiac deaths [low CONUT group: 43 (3.8%), high CONUT group: 49 (5.7%)] and 201 non-cardiac deaths [low CONUT group: 86 (7.6%), high CONUT group: 115 (13.4%)] were occurred. Figure 2 shows the Kaplan–Meier curves for MACE for the two groups. The cumulative incidences of MACE were clearly higher in the high CONUT score group (log-rank $p < 0.0001$). Furthermore, Kaplan–Meier curves for MACE showed significant differences in the incidence of events between the two groups, even stratified by CKD and age of 65 years (Fig. 3).

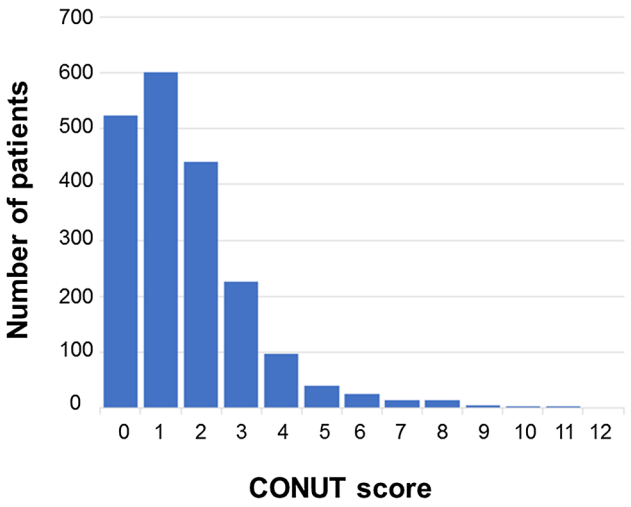

Fig. 1 Distribution of CONUT scores. The median CONUT score was 1 (IQR: 0, 2). *CONUT* Controlling Nutritional Status, *IQR* interquartile range

Table 3 shows the results of Cox proportional hazard regression analysis for MACE. The high CONUT score group was significantly associated with MACE compared with the low CONUT score group (HR: 1.64, 95% CI 1.30–2.07; $p < 0.0001$), even after adjustment for other risk factors (age, sex, BMI, CKD, current smoking, diabetes, dyslipidemia, hypertension, LVEF, multivessel disease and statin use). Continuous variables of the CONUT score were also related to the incidence of adverse cardiac events in all models (HR: 1.23 per 1 CONUT score increase, 95% CI 1.16–1.32; $p < 0.0001$).

Discrimination and reclassification of the CONUT score

Adding the CONUT score to a baseline model with established risk factors improved the prediction of MACE as shown by the significant increase in the C-index (Table 4). Furthermore, the addition of the CONUT score significantly improved the reclassification of patients beyond the baseline model with established risk factors (NRI: 0.17, 95% CI 0.05–0.29; $p = 0.004$). IDI also

Table 2 Baseline clinical, angiographic and procedural characteristics

	Overall ($n = 1987$)	Low CONUT score group 0–1 ($n = 1126$)	High CONUT score group ≥2 ($n = 861$)	p
CONUT score (IQR)	1 (0, 2)	1 (0, 1)	2 (2, 3)	<0.0001
Serum albumin, g/dl	4.0 ± 0.4	4.1 ± 0.3	3.8 ± 0.5	<0.0001
Albumin score				
0, *n* (%)	1789 (90.0)	1126 (100)	663 (77.0)	
2, *n* (%)	143 (7.2)	0 (0)	143 (16.6)	
4 or 6, *n* (%)	55 (2.8)	0 (0)	55 (6.4)	
Total cholesterol, mg/dl	182.0 ± 36.0	196.3 ± 31.6	163 ± 32.7	<0.0001
Cholesterol score				
0, *n* (%)	1006 (50.6)	794 (70.5)	212 (24.6)	
1, *n* (%)	757 (38.1)	332 (29.5)	425 (49.5)	
2 or 3, *n* (%)	224 (11.3)	0 (0)	224 (25.9)	
Total lymphocytes, count/ml (IQR)	1607 [1293, 1988]	1850 [1610, 2191]	1278 [1047, 1510]	<0.0001
Lymphocyte score				
0, *n* (%)	1002 (50.4)	856 (76.0)	146 (17.0)	
1, *n* (%)	616 (31.0)	270 (24.0)	346 (40.2)	
2 or 3, *n* (%)	369 (18.6)	0 (0)	369 (42.8)	
Baseline characteristics				
Age, years	66.4 ± 9.5	65.0 ± 9.3	68.2 ± 9.6	<0.0001
Male, *n* (%)	1646 (82.8)	933 (82.9)	713 (82.8)	0.98
Hypertension, *n* (%)	1454 (73.2)	795 (70.6)	659 (76.5)	0.003
Diabetes, *n* (%)	952 (47.9)	518 (46.0)	434 (50.4)	0.05
Dyslipidemia, *n* (%)	1452 (73.1)	856 (76.0)	596 (69.3)	0.0008
Current smoker, *n* (%)	469 (23.7)	306 (27.3)	163 (18.9)	<0.0001
Family history of CAD, *n* (%)	567 (28.7)	341 (30.4)	226 (26.4)	0.05
Multivessel disease, *n* (%)	1203 (60.5)	637 (56.6)	566 (65.7)	<0.0001
BMI, kg/m^2	24.2 ± 3.4	24.6 ± 3.1	23.7 ± 3.6	<0.0001
LDL-C, mg/dl	109.8 ± 30.8	120.2 ± 28.5	96.2 ± 28.4	<0.0001
HDL-C, mg/dl	44.6 ± 13.5	45.6 ± 13.9	43.3 ± 12.8	0.0002
TG, mg/dl	136.5 ± 72.0	152.1 ± 78.9	116.1 ± 55.7	<0.0001
FBG, mg/dl	109.2 ± 33.2	109.5 ± 31.3	108.8 ± 35.5	0.65
HbA1c, %	6.4 ± 1.2	6.5 ± 1.3	6.3 ± 1.2	0.01
hs-CRP, mg/dl	0.10 [0.04, 0.21]	0.10 [0.04, 0.21]	0.10 [0.04, 0.22]	0.29
eGFR, ml/min/1.73 m^2	65.3 ± 22.1	69.2 ± 18.8	60.3 ± 24.9	<0.0001
CKD, *n* (%)	681 (34.3)	317 (28.2)	364 (42.3)	<0.0001
HD, *n* (%)	126 (6.3)	31 (2.8)	95 (11.0)	<0.0001
LVEF, %	62.8 ± 12.1	63.9 ± 11.1	61.3 ± 13.1	<0.0001
Medication				
Aspirin, *n* (%)	1858 (94.8)	1053 (95.0)	805 (94.6)	0.66
ACE-I/ARB, *n* (%)	943 (48.1)	518 (46.8)	425 (49.9)	0.16
β-Blocker, *n* (%)	987 (50.4)	545 (49.2)	442 (51.9)	0.23
OHA, *n* (%)	612 (31.3)	341 (30.8)	271 (31.9)	0.60
Insulin, *n* (%)	253 (12.7)	129 (11.5)	124 (14.4)	0.05
Statin, *n* (%)	1122 (57.3)	641 (57.9)	481 (56.6)	0.57
Lesion and procedure characteristics				
LAD culprit coronary artery, *n* (%)	886 (44.6)	512 (45.5)	374 (43.4)	0.37
Reference lumen diameter, mm	2.9 ± 0.5	2.9 ± 0.5	2.9 ± 0.5	0.21
Stent size, mm	3.0 [2.75, 3.5]	3.0 [2.5, 3.5]	3.0 [2.75, 3.5]	0.68

ACE-I angiotensin-converting enzyme inhibitors, *ARB* angiotensin receptor blockers, *BMI* body mass index, *CAD* coronary artery disease, *CKD* chronic kidney disease, *CONUT* Controlling Nutritional Status, *eGFR* estimated glomerular filtration rate, *FBG* fasting blood glucose, *HbA1c* hemoglobin A1c, *HD* hemodialysis, *HDL-C* high-density lipoprotein cholesterol, *hs-CRP* high-sensitivity C-reactive protein, *IQR* interquartile range, *LAD* left anterior descending artery, *LDL-C* low-density lipoprotein cholesterol, *LVEF* left ventricular ejection fraction, *OHA* oral hypoglycemic agents, *TG* triglycerides

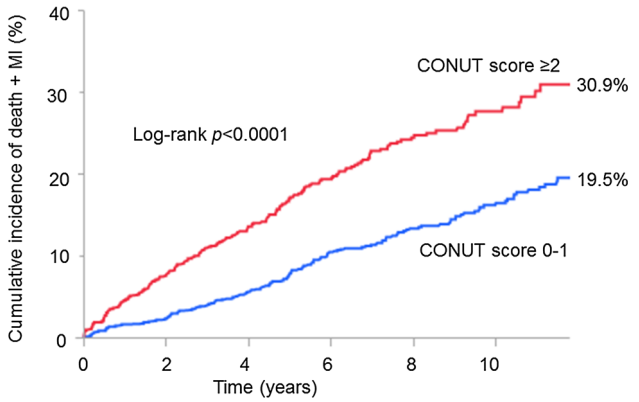

Fig. 2 Kaplan–Meier curves for MACE. The cumulative incidence of MACE was clearly higher in the high CONUT group (log-rank $p < 0.0001$). *CONUT* Controlling Nutritional Status, *MACE* major adverse cardiac events, *MI* myocardial infarction

improved significantly compared to the baseline model after adding the CONUT score.

Discussion

The major findings of the present study are as follows: (1) Patients with high CONUT scores showed a significantly higher incidence of cardiac events than patients with low CONUT scores; (2) even after adjusting for important risk factors, an increase in CONUT score was associated with worse long-term outcomes in patients following PCI; and (3) the addition of the CONUT score to a conventional prediction model significantly improved risk prediction for major cardiac events.

The CONUT score was first reported by Ignacio de Ulíbarri et al. as an objective screening tool for identifying undernutrition in a hospital population [7]. Previous studies have reported the prognostic value of the CONUT score for several chronic diseases [12–14]. Nochioka et al. demonstrated that poor nutritional status assessed by the CONUT score was associated with an increased risk of adverse cardiac events for patients with chronic heart failure [9]. Malnutrition assessed by the CONUT score has also been reported to be an independent determinant of long-term outcomes in patients with acute heart failure [8, 15]. Recently, the CONUT score has been shown to be associated with clinical outcomes for patients with ischemic heart disease. Basta et al. evaluated 945 patients with ST-elevation MI for 2 years and showed that nutritional status evaluated by the CONUT score affected prognosis in elderly patients [16]. Kunikura et al. followed 1004 patients with stable CAD for 4.9 years and found a combined effect of the CONUT score and BMI for predicting adverse cardiac events [17]. In the present study, we assessed the usefulness of the CONUT score as a single predictor of long-term clinical outcomes among patients with stable CAD. Several studies have assessed the impact of malnutrition for elderly or CKD patients with heart

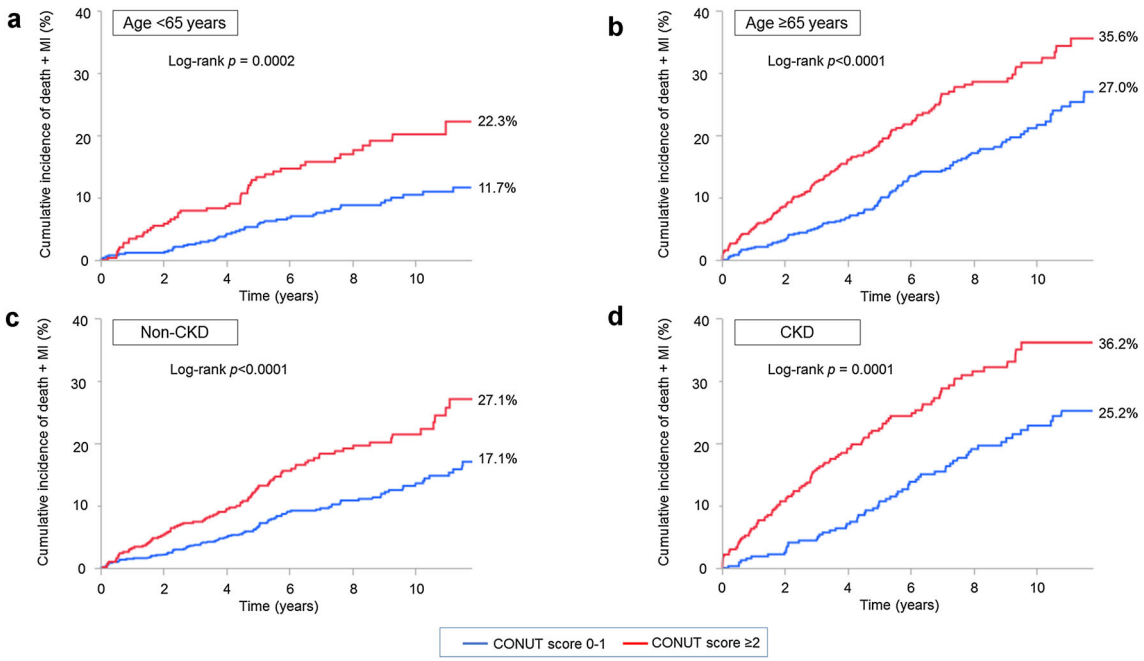

Fig. 3 Kaplan–Meier curves for MACE among patients aged <65 years (**a**); aged ≥65 years (**b**); without CKD (**c**); and with CKD (**d**). Kaplan–Meier curves for MACE show significant differences in the incidence of events between the two groups, even stratified by CKD or age of 65 years (log-rank test, all $p < 0.001$). *CKD* chronic kidney disease, *CONUT* Controlling Nutritional Status, *MACE* major adverse cardiac events, *MI* myocardial infarction

Table 3 Cox proportional hazard model for MACE

	HR	95% CI	*p*
CONUT score as the categorical variable (Ref.: low CONUT score group)			
Crude	1.95	1.57–2.41	<0.0001
Model 1	1.76	1.42–2.19	<0.0001
Model 2	1.63	1.31–2.04	<0.0001
Model 3	1.64	1.30–2.07	<0.0001
CONUT score as the continuous variable (HR for 1 CONUT score point increase)			
Crude	1.33	1.26–1.41	<0.0001
Model 1	1.29	1.21–1.37	<0.0001
Model 2	1.25	1.17–1.32	<0.0001
Model 3	1.23	1.16–1.32	<0.0001

Model 1: adjusted for age and sex

Model 2: adjusted for age, sex, body mass index (BMI) and chronic kidney disease (CKD)

Model 3: adjusted for age, sex, BMI, CKD, current smoker, diabetes, dyslipidemia, hypertension, left ventricular ejection fraction, multivessel disease and statin use

95% CI 95% confidential interval, *CONUT* Controlling Nutritional Status, *HR* hazard ratio, *MACE* major adverse cardiac events

failure, CAD or other chronic disease [2, 9, 16, 18]; however, in our study, patients in the high CONUT score group had a higher incidence of MACE, including the non-elderly and those without CKD. Our findings indicate that nutritional assessment using the CONUT score should be taken into consideration for stable CAD patients.

To date, several nutrition indicators have been reported, such as serum albumin, total cholesterol levels, the Mini-Nutritional Assessment (MNA) [19], the Subjective Global Assessment (SGA) [20] and the Geriatric Nutritional Risk Index (GNRI) [21]. The MNA and SGA require subjective data evaluated by medical staff. In addition, assessments using only one indicator of malnutrition may be affected by various factors and not provide adequate information. The CONUT score is appropriate for evaluating different aspects of various components of malnutrition. Malnutrition is a complex state involving depletion of the protein reserve, caloric consumption and decreasing immune defenses. Furthermore, it is simple to evaluate the CONUT score using inexpensive objective markers. The GNRI is also an objective nutrition assessment tool, using serum albumin, body weight and height. Further study is needed to assess which nutritional index is better for evaluating nutritional status and predicting clinical outcomes of CAD patients.

Albumin, which is a component of the CONUT score, is the major protein in human plasma and the most abundant protein in the extracellular component [22]. Albumin synthesis is regulated by stimuli including nutrient intake, insulin levels and oncotic pressure. Hypoalbuminemia is therefore thought to result from malnutrition, inflammation or cachexia [23]. Inflammation has been reported to play a major role in the initiation and progression of atherosclerosis and the triggering of cardiovascular disease events [24, 25]. In addition to nutritional and inflammatory factors, albumin has been reported to have several physiological functions related to atherothrombogenesis [26–28]. Low lymphocyte counts have also been associated with worse outcomes in patients with CAD [29, 30]. Lymphocytopenia is considered to be related to physiological stress due to corticosteroid release and reflect a poorly regulated immune response [31]. Although hypercholesterolemia is a well-known risk factor for cardiovascular disease in the general population, an association between low serum cholesterol and poor outcomes has been reported for patients with chronic heart failure and end-stage renal failure as well as the elderly [32–34]. This reverse epidemiology finding might occur in patients in which CAD has already been detected and treated. For these reasons, low serum albumin, total cholesterol and total lymphocyte count values could affect worse clinical outcomes after PCI.

Malnutrition is not a rare condition for patients with CAD. Of course, its rate among CAD patients is generally lower compared to those with heart failure or hospitalized patients. In our study, 49 and 24% of the patients were at a mild (CONUT score: 1–2) and moderate–severe risk (CONUT score: >3) [7] of malnutrition, respectively. Malnutrition is often present in cachexia, which is a complex metabolic syndrome characterized by anorexia, weight loss, insulin resistance and increased muscle protein breakdown [23]. These conditions carry a poor prognosis and are often found in patients with chronic heart disease. The association between malnutrition, inflammation and atherosclerosis has been reported in patients with end-stage renal disease [35]. Nakagomi et al. showed that a high

Table 4 Evaluation of predictive models for MACE

	C-index (95% CI)	*p*	NRI (95% CI)	*p*	IDI (95% CI)	*p*
MACE						
Established risk factors	0.665 (0.632–0.698)	Ref.		Ref.		Ref.
Established risk factors + CONUT score	0.681 (0.648–0.714)	0.02	0.17 (0.05–0.29)	0.004	0.013 (0.006–0.021)	0.0003

Established risk factors included age, chronic kidney disease, current smoking, diabetes, dyslipidemia, hypertension, left ventricular ejection fraction, multivessel disease and use of statins

95% CI 95% confidence interval, *CONUT* Controlling Nutritional Status, *IDI* integrated discrimination improvement, *MACE* major adverse cardiac events, *NRI* net reclassification improvement

CONUT score was significantly associated with inflammation and carotid atherosclerosis identified by carotid intima-media thickness in patients with chronic heart failure [36]. Thus, this malnutrition, inflammation and atherosclerosis (MIA) syndrome might be an important issue for not only CKD patients, but also patients with heart failure or CAD.

Some studies have shown that nutritional intake, such as supplementation, may be beneficial for patients with chronic heart failure [37, 38]. It may be possible that nutritional intervention is useful for CAD patients with undernutrition. Further investigations are required to evaluate whether nutritional interventions improve clinical outcomes in this population. In addition, previous studies demonstrated the association between frailty or physical activity and cardiovascular disease [39, 40]. Thus, it might be more useful to add or combine some information of this status such as frailty screening tools, cardiac pulmonary testing or muscle volume of patients, to the nutritional status assessed by the CONUT score in CAD patients.

We must acknowledge some limitations. First, as a single-center, observational study of a small patient cohort, unknown confounding factors might have affected the outcomes regardless of analytical adjustments. Second, the present study evaluated the CONUT score only once and did not assess changes over time. Third, a propensity-matched analysis would be a better way to assess the impact of CONUT score in clinical outcomes. However, sample size and clinical events of the present study were relatively small and the Cox hazard analysis or the discrimination analysis showed the usefulness of the CONUT score. Finally, the information about the compliance of cardiovascular drugs was not available. Poor compliance might affect the adverse outcomes.

Conclusions

In this study, nutritional status evaluated by the CONUT score was associated with long-term outcomes in patients with stable CAD after undergoing elective PCI. Pre-PCI assessment of the CONUT score may provide useful prognostic information in clinical practice.

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Compliance with ethical standards

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