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Effect of the Prognostic Nutrition Index on Long-Term Outcomes in Unprotected Left Main Coronary Artery Revascularization

Objective	The prognostic nutritional index (PNI) is a practical, applicable, prognostic scoring system. However, its clinical significance in unprotected left main coronary artery (ULMCA) patients undergoing percutaneous coronary intervention (PCI) has not yet been clarified. This study aimed to examine the relationship between malnutrition as assessed by PNI and major adverse cardiac events (MACE) in ULMCA patients undergoing PCI.
Material and methods	185 patients who were hospitalized in our clinic underwent coronary angiography, had a critical LMCA lesion, and underwent angiography-guided PCI were included. The study population was divided into tertiles based on the PNI values. A high PNI (n=142) was defined as a value in the third tertile (≥ 34.0), and a low PNI (n=43) was defined as a value in the lower 2 tertiles (< 34.0). The primary endpoint was MACE.
Results	MACE and mortality rates in the low PNI group were significantly higher compared to the high PNI group (51% vs. 30%, p=0.009; 44% vs. 20%, p=0.002, respectively). High PNI (HR:1.902; 95% CI:1.112–3.254; p=0.019), previous stroke (HR:3.025; 95% CI:1.038–8.810; p=0.042) and SYNTAX score (HR:1.028; 95% CI:1.004–1.057, p=0.023) were independent predictors of MACE in the multivariable cox regression analyzes.
Conclusions	In patients undergoing ULMCA PCI, nutritional status can be considered an indicator of MACE rates by evaluating the PNI score. This index can be used for risk classification.

Keywords	Prognostic nutritional index; unprotected left main coronary; MACE, mortality
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Introduction

The left main coronary artery (LMCA) perfuses more than 75% of the myocardium in most patients. Therefore, revascularization of this region is complex and risky [1]. In addition, 4% of the patients who underwent coronary angiography were found to have left main coronary artery disease [2]. The efficacy and safety of percutaneous coronary intervention (PCI) for LMCA disease has been evaluated in several clinical trials and in observational registry analyses. In recent years, PCI has been accepted as an alternative treatment modality to coronary artery bypass grafting (CABG) in patients with unprotected LMCA disease (ULMCA) and low-intermediate risk coronary artery disease (CAD) [3]. One reason for this is that PCI strategies have improved, become more effective, and operator experience has increased. Large-scale studies

comparing the long-term outcomes of CABG and PCI treatment strategies have been performed previously [4–6]. However, potential risk factors affecting the long-term outcome in patients undergoing ULMCA PCI have not been adequately studied.

Malnutrition has been reported to be associated with worse clinical outcomes in patients with malignancy, renal failure, and heart failure [7]. However, assessing nutritional status is not easy since there are various elements of malnutrition [8]. Albumin is a plasma protein that is mainly responsible for plasma oncotic pressure, and it is a good indicator of nutritional status. In addition, albumin has anti-inflammatory and anti-oxidative properties, such as binding to various toxic agents and scavenging free radicals [9].

Lymphocytes are one of the components of the white blood cell population and play a fundamental role during inflammation. The prognostic nutritional index (PNI), calculated from the serum albumin concentration and the total lymphocyte count, has been used to estimate the risk of complications after gastrointestinal surgery [10]. PNI is easy to calculate, and it is a good predictor for patients with malignant diseases [10]. In addition, in recent years, some studies of the prognostic significance of PNI after CABG have been conducted. These studies revealed that PNI has a predictive value on mortality and the incidence of adverse events [9, 11, 12]. The PNI score is a practical, applicable, and prognostic scoring system. However, its clinical significance in patients who have undergone ULMCA PCI has not yet been clarified. The aim in this study was to examine the relationship between malnutrition as assessed by the PNI score and long-term prognosis of ULMCA patients undergoing PCI.

Material and methods

Study Design

This research included 185 patients who applied to Dicle University Faculty of Medicine, Department of Cardiology, between 01-01-2012 and 01-01-2017. These patients underwent coronary angiography, had a critical LMCA lesion, and underwent angiography-guided LMCA PCI.

Inclusion criteria for the study: patients who presented with a) stable coronary artery disease, b) unstable coronary artery disease, or c) acute coronary syndrome and who underwent single or double stent implantation. Intravascular ultrasound imaging (IVUS) was not used in any of the patients.

Exclusion criteria were: a) patients who underwent CABG after coronary angiography or were followed up with medical therapy only, b) moderate to severe heart valve disease, c) mechanical complications of myocardial ischemia, d) malignancy, e) life expectancy <1 yr, f) active infection, g) end-stage kidney or liver diseases, h) thrombolytic therapy in the last 24 hr, i) hematological disease, j) systemic inflammatory disease, k) age <18 years and >90 yrs.

The study was conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by the local ethics committee.

Definitions

A detailed medical history was taken from all patients at the time of admission. Hypertension (HT) was defined as systolic blood pressure (SBP) ≥140 mmHg, diastolic blood pressure (DBP) ≥90 mmHg, or using antihypertensive medication. Diabetes mellitus (DM) was defined as fasting glucose of 126 mg/dl or use of antidiabetic agents or HbA1c>7%. Dyslipidemia was defined as total cholesterol >200 mg/dl or low-density lipoprotein (LDL) >130 mg/dl. Smoking was defined as currently smoking. Coronary artery disease (CAD) was defined as >50% narrowing in at least one coronary artery. Peripheral arterial disease (PAD) was defined as >50% stenosis in peripheral arteries. Ischemic stroke was defined an episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction, according to the 2013 American Heart Association/American Stroke Association (AHA/ASA) guidelines [13].

Blood Samples

Hematological and biochemical tests were performed on venous blood samples taken from each patient just before routine coronary angiography. The numbers and types of shaped elements in the blood was measured with an automated hematological analyzer (Abbott Cell-Dyn 3700; Abbott Laboratory, Abbott Park, IL, USA). Biochemical measurements were made using standard methods.

Coronary Angiographic Evaluation

Coronary angiography was performed in each patient with a 6F or 7F guiding catheter via femoral or radial artery access. Intravenous heparin was administered to all patients according to the latest guidelines. Predilation, postdilation, kissing balloon dilatation, and proximal optimization were performed with appropriate coronary balloons in accordance with the coronary artery diameter and lesion status as indicated for each patient. Patients with stable angina pectoris, in addition to acetylsalicylic acid, received dual antiplatelet therapy with clopidogrel, prasugrel, or ticagrelor for post-procedure 6–12 mos. Patients with acute coronary syndrome received this medication for at least 12 mos. Three independent and experienced cardiologists evaluated the coronary angiographic images separately to calculate Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX Score: SS) and SYNTAX score-II (SS-II) [14, 15]. Anatomically based SS was calculated using coronary

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Table 1. Demographic, clinical, and angiographic characteristics of patients

Variable	High PNI (n=142)	Low PNI (n=43)	p value
Age (yrs)	63.9±11.7	68.8±12.3	0.020
Female gender	36 (25)	14 (33)	0.351
DM	32 (23)	17 (40)	0.027
Hypertension	65 (46)	16 (37)	0.321
Previous CAD	102 (72)	37 (86)	0.059
Chronic kidney disease	7 (5)	8 (19)	0.004
Dysplidemia	71 (50)	16 (37)	0.141
Smoking	106 (75)	35 (81)	0.363
Previous stroke	5 (4)	0 (0)	0.212
Peripheral artery disease	12 (8)	4 (9)	0.862
Anemia	18 (13)	16 (37)	< 0.001
LVEF (%)	54.9 ± 8.7	51.6±10.1	0.035
SYNTAX score	29.8±10.7	36.6±10.2	< 0.001
Diagnosis at admission	–	–	0.005
STEMI	4 (3)	4 (9)	–
USAP/NSTEMI	48 (34)	23 (54)	–
SAP	90 (63)	16 (37)	
Lesion features	–	–	0.826
Osteal/mid	34 (24)	11 (26)	–
Distal	108 (76)	32 (74)	–
Revascularization strategy	–	–	0.258
Provisional	111 (78)	37 (86)	–
Bifurcation	31 (22)	6 (14)	–
T-stent	8 (26)	2 (33)	–
Crush	10 (32)	2 (33)	–
Cullotte	13 (42)	2 (33)	–
Predilatation	107 (75)	23 (54)	0.006
Postdilatation	130 (92)	40 (93)	0.756
Final Kissing	32 (23)	5 (12)	0.117
Additional vessel	–	–	0.942
One vessel	59 (42)	16 (37)	–
Two vessel	42 (30)	15 (35)	–
Three vessel	14 (10)	4 (9)	–
Outcomes			–
MACE	42 (30)	22 (51)	0.009
Mortality	29 (20)	19 (44)	0.002
Repeat revascularization	18 (13)	7 (16)	0.545
Myocardial reinfarction	16 (11)	6 (14)	0.634

Data are number (percentage) or mean±SD. CAD, coronary artery disease; DM, diabetes mellitus; LVEF, left ventricular ejection fraction; SYNTAX, percutaneous coronary intervention with TAXus and cardiac surgery; MACE, major adverse cardiac events.

arteries with ≥50% luminal stenosis and ≥1.5 mm diameter. The coronary arteries were divided into 16 segments. Other predictive factors such as calcification and lesion length were evaluated. Clinical variables such as age, gender, creatinine clearance, left ventricular ejection fraction, peripheral artery disease, chronic obstructive pulmonary disease were recorded and used to calculate SS- II [15].

PNI Definition

PNI was calculated as suggested by Onodera et al using the following formula:

$$10 \times \text{plasma albumin value (g/dl)} + 0.005 \times \text{total lymphocyte count in peripheral blood (per mm}^3\text{)}$$ [16].

he study population was divided into tertiles based on the PNI values. A high PNI (n=142) was defined as a value in the third tertile (≥34.0), and a low PNI (n=43) was defined as a value in the lower 2 tertiles (<34.0).

MACE and Follow-Up

The primary endpoint was major adverse cardiac events (MACE), including all-cause death, repeat revascularization, and myocardial reinfarction. The follow-up period was defined as the time from admission for angiography until death from any cause or the last clinic visit (an average of 5 years of follow-up). Follow-up data, including hospital epicrisis, were collected from the national data recording system, and from patients' families or their doctors by in-person or telephone interviews.

Statistical Analysis

Data were analyzed using SPSS for Windows version 25.0 (Armonk, NY: IBM Corp.). The distribution of the data was analyzed using Kolmogorov-Smirnov tests. Categorical variables were expressed as percentages and were compared with Chi-square tests. Continuous variables with normal distribution were expressed as mean±standard deviation (SD) and were compared using Student's t tests. Continuous variables with non-normal distribution were expressed as median (25^{th}-75^{th} percentile) and were compared using Mann-Whitney U tests. Univariate analysis and multivariate analysis were used to identify predictors of MACE. The optimum PNI score cut-off values for the prediction of mortality were determined using receiver operating characteristic (ROC) curve analysis. The DeLong test was used to compare the area under the curve (AUC) with each of these parameters (MACE and PNI) [17]. Moreover, the increased discriminative value of the PNI was also estimated using net reclassification improvement (NRI) and integrated discrimination improvement [18]. Survival analysis and MACE was performed using Kaplan–Meier analysis. A p value of <.05 was considered significant.

Results

There were 142 patients in the high PNI group and 43 patients in the low PNI group. The demographic, clinical, and angiographic findings of the patients are listed in Table 1. Age,

Table 2. Laboratory values of the patients

Variable	High PNI (n=142)	Low PNI (n=43)	p value
Lymphocyte (×10³/μl)	2.4±1.0	1.9±0.9	0.010
Albumin (mg/dl)	3.9±0.3	3.1± 0.3	< 0.001
WBC (×10³/μl)	10.1±5.0	10.4±4.7	0.705
Hemoglobin (mg/dl)	14.3±2.5	12.0±2.0	< 0.001
Total cholesterol (mg/dl)	187.4±49.9	153.7±48.7	< 0.001
Glucose (mg/dl)	148.5±79.3	165.4±79.4	0.221
eGFR (ml/min per 1.73 m²)	84.6±22.3	75.3±32.8	0.036

Data are mean ±SD. WBC, white blood cell; eGFR, estimated glomerular filtration rate.

Table 3. Medical treatments received by the patients

Variable	High PNI (n=142)	Low PNI (n=43)	p value
Acetylsalicylic acid Adenosine diphosphate (ADP) receptor inhibitors	140 (98.6)	42 (97.7)	0.677
Clopidogrel	92 (64.8)	18 (41.9)	0.023
Ticagrelor	44 (31.0)	23 (53.5)	
Prasugrel	6 (4.2)	2 (4.7)	
Vitamin K antagonist	1 (0.7)	1 (2.3)	0.412
Non-Vitamin K antagonist	4 (2.8)	1 (2.3)	0.670
Statin	137 (96.5)	40 (93.0)	0.329
Variable	High PNI (n=142)	Low PNI (n=43)	p value
Acetylsalicylic acid Adenosine diphosphate (ADP) receptor inhibitors	140 (98.6)	42 (97.7)	0.677
Clopidogrel	92 (64.8)	18 (41.9)	0.023
Ticagrelor	44 (31.0)	23 (53.5)	
Prasugrel	6 (4.2)	2 (4.7)	
Vitamin K antagonist	1 (0.7)	1 (2.3)	0.412
Non-Vitamin K antagonist	4 (2.8)	1 (2.3)	0.670
Statin	137 (96.5)	40 (93.0)	0.329

Data are number (percentage).

chronic kidney disease, SYNTAX score were significantly greater in the low PNI group. DM, anemia, LVEF, and the primary endpoints of the study, MACE and mortality rates, were significantly greater in the high PNI group. There was no significant difference between the two groups in terms of revascularization and myocardial infarction during follow-up. Other variables are compared in Table 1.

Laboratory findings are listed in Table 2. Lymphocyte, albumin, hemoglobin, total cholesterol, and estimated glomerular filtration rate (eGFR) were significantly greater in the high PNI group. Other variables are compared in Table 2. The medical treatments received by the patients are listed in Table 3.

In the multivariable cox regression analyzes, high PNI, previous stroke, and Syntax score were found to be significant, independent predictors of MACE (Table 4). The Kaplan-Meier analysis examined the relationship between PNI score and MACE and all-cause mortality during a mean follow-up period of 5 yrs. This test detected a significant increase in MACE and all-cause mortality rates during the follow-up period in the low PNI group (Figures 1 and 2).

NRI and integrated discrimination improvement (IDI) values were applied to compare the abilities of parameters predictive MACE. PNI in the multivariable model and PNI, stroke and SYNTAX score in the multivariable model plus model were included. The multivariable model and the multivariable model plus PNI (including stroke and SYNTAX score) had a similar accuracy for predicting MACE (multivariable model vs multivariable model plus PNI; AUC: 0.693 vs 0.680, z=0.738, p=0.460, Figure 3). Addition of CAD to the multivariable model resulted in a NRI of 35.5% (z=7.113, p=0.0215), and an IDI of 0.021 (p < 0.05).

Discussion

In this study, we investigated predictive value of malnutrition as assessed by the PNI score for MACE in ULMCA patients undergoing PCI. In conclusion, we found

Table 4. Univariate and multivariate analyses of MACE predictors

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
High PNI	1.385 (1.301–1.474)	<0.001	1.902 (1.112–3.254)	0.019
eGFR	0.988 (0.979–0.997)	0.011	–	–
Age	1.022 (1.000–1.045)	0.054	–	–
Previous stroke	3.251 (1.174–9.000)	0.023	3.025 (1.038–8.810)	0.042
Syntax score	1.038 (1.015–1.062)	0.001	1.028 (1.004–1.057)	0.023
Peripheral artery disease	1.493 (0.736-3.027)	0.267	–	–
Glucose	1.003 (1.001-1.005)	0.026	–	–

HR, hazards ratio; SYNTAX, percutaneous coronary intervention with TAXus and cardiac surgery; eGFR, estimated glomerular filtration rate; PNI:, prognostic nutritional index.

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that the prevalence of all-cause mortality and stroke was higher in malnourished patients, and reflected in their PNI as compared to patients with normal nutrition.

Because the LMCA perfuses such a large area of the myocardium, treatment of ULMCA represents one of the greatest challenges in interventional cardiology. CABG was accepted as the preferred treatment modality for ULMCA lesions, due to the high risk of myocardial infarction. There have been significant improvements in the outcome of percutaneous interventions for ULMCA lesions as a result of improvements in percutaneous techniques and stenting devices, as well as more effective combined anti-platelet and anti-ischemic agents. Studies have confirmed that PCI treatment of ULMCA lesions can be an effective and alternative treatment option compared to CABG [5, 6, 19]. We showed that, together with the preferred treatment strategy for these lesions, malnutrition can have an impact on long-term MACE rates.

PNI was first used by Buzby et al. in 1980 as an objective nutritional screening tool [20]. It was subsequently used by Onodera et al. to assess surgical risk in patients with gastrointestinal malignancies [16]. The PNI has been used as a predictive nutritional marker in patients with various diseases, such as malignancy and acute heart failure [21, 22]. In addition, nutrition, as reflected by the PNI, has been reported to effect long-term mortality and MACE rates in patients with stable CAD and carotid artery stent implantation [8, 23].

Various nutritional scores have been defined to date, including the Mini-Nutritional Assessment (MNA), the Subjective Global Assessment (SGA), the Geriatric Nutritional Risk Index (GNRI), and the Controlling Nutritional Status (CONUT) score. SGA and MNA include the evaluator's subjective impressions. Both subjective knowledge and objective knowledge are important, but collecting subjective assessments in routine clinical practice can be difficult. GNRI and CONUT scores are objective nutritional assessment indexes. GNRI is usually calculated from plasma albumin and body mass index (BMI). However, in patients with normal or higher BMIs, malnutrition is likely to be underestimated. The CONUT score requires total cholesterol values to assess nutritional status. However, it is recommended that patients with CAD be treated with statin therapy to lower their total cholesterol. Therefore, total cholesterol may not be an appropriate nutritional index for CAD patients.

PNI can be easily calculated from plasma albumin concentration and total lymphocyte count. Atherosclerotic plaque rupture is a lymphocyte-mediated inflammatory process [24]. In the acute phase of CAD, lymphocytopenia is a common finding during the stress response and is secondary to increased corticosteroid. Lymphocytes are an

Figure 1. Kaplan–Meier Analysis between PNI Score and MACE during the 5-yr follow-up period

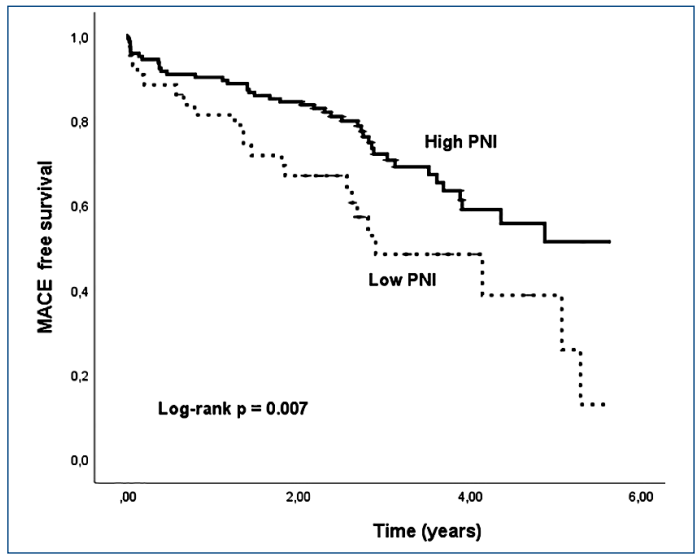


Figure 2. Kaplan-Meier analysis between PNI Score and All-cause mortality during the 5-yr follow-up period

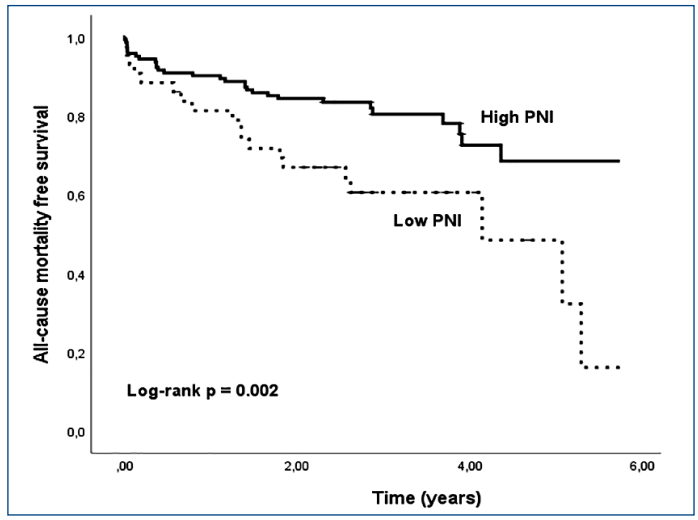
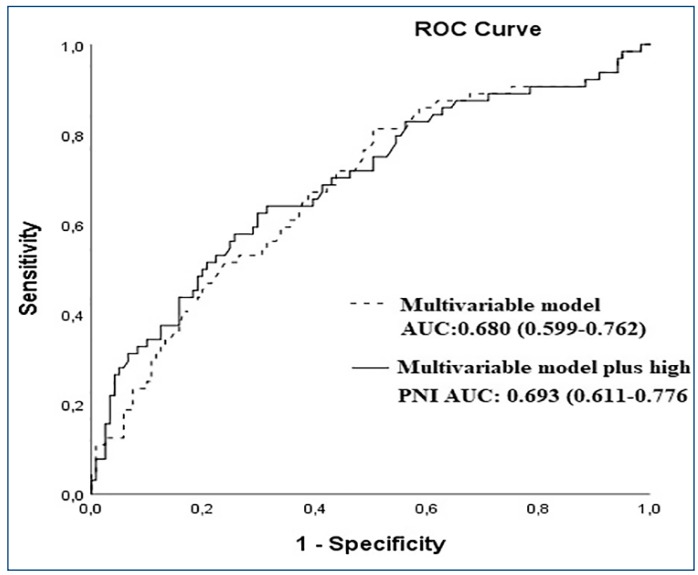


Figure 3. The cut-off value of the PNI score associated with MACE in the ROC curve analysis



important part of the immune system and the prognostic role of lymphocyte count has been previously investigated in coronary artery disease, myocardial infarction and cardiovascular diseases [25]. Plasma albumin is an important platelet aggregation inhibitor that plays a role in anti-aggregation and increases the production of prostaglandin D2 (PGD2) [26]. In addition to its oncotic properties, albumin also has antioxidant and anti-inflammatory properties by scavenging reactive oxygen radicals and limiting their production [27]. It makes up the majority of total plasma protein. In addition, hypoalbuminemia increases blood viscosity and impairs endothelial function. Malnutrition leads low intake of calories, decreased protein reserves, and weakening of the immune system. These conditions are especially common in patients with CAD. The 2021 American Society of Cardiology guidelines further emphasized the impact of cognitive behavioral therapy and lifestyle changes on improving cardiac outcomes in patients undergoing coronary revascularization [28]. Basta et al. studied the relationship between nutritional status and clinical outcomes in elderly patients with ST-elevation myocardial infarction [29]. They found that approximately 55% of these patients were in a state of malnutrition. Nakagomi et al. showed that in patients with chronic heart failure, malnutrition is associated with higher concentrations of inflammatory markers and carotid atherosclerosis [30].

Age and comorbid conditions affect nutritional status. In this study, patient age and the prevalence of comorbidity were greater in the low PNI group. This may have affected mortality and MACE rates. However, in multivariate analysis, it can be thought that PNI value may have a predictive value on MACE compared to other variables.

Study Limitations

Our study has some limitations. It was a single-center retrospective study and had a relatively small sample size. PNI scores were not evaluated after hospital discharge. Therefore, the effect of changes in PNI scores on clinical outcomes during the post-discharge follow-up period could not be evaluated. Malnutrition was assessed using only the PNI score. Other nutritional indicators such as CONUT, MNA, SGA and GNRI were not used. The high rate of age in the low PNI group may also have affected the MACE rates relatively. In addition, PNI may be affected by hormonal changes such as plasma catecholamine and cortisol, but we could not measure these hormones in our study.

Conclusion

In patients undergoing ULMCA PCI, nutritional status can be considered as an indicator of MACE rates by evaluating the PNI score. Thus, the PNI score may be useful for risk stratification of patients undergoing ULMCA PCI. However, larger studies are needed to generalize the findings of our study and translate them into clinical results.

Informed Consent

Written informed consent was obtained from all participants who participated in this study.

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No conflict of interest is reported.

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