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The role of prognostic nutritional index in patients with non-ST segment elevation acute coronary syndrome

Objective — The importance of nutritional status in non-ST segment elevated acute coronary syndrome (NSTE-ACS) is not clear. In this study, the importance of prognostic nutritional index (PNI) in terms of in-hospital mortality in patients with NSTE-ACS and its relationship with the Global Record of Acute Coronary Events (GRACE) risk score were investigated.

Material and methods — A total of 498 consecutive NSTE-ACS patients were recorded retrospectively. PNI for nutritional status assessment of patients with NSTE-ACS. PNI was calculated as 10 × serum albumin (g/dL) + 0.005 × total lymphocyte count (per mm^3). The association between PNI and GRACE risk score was assessed.

Results — Patients were classified as low-risk group (≤108 points, n=222), medium-risk group (109–140 points, n=161) and high-risk group (>140 points, n=115) according to the GRACE score. The mean PNI value was found to be the lowest in the high-risk group compared to other risk groups. There was a significant negative correlation between GRACE risk score and PNI (p<0.001). In multivariate analysis, PNI resulted as a predictor of in-hospital mortality independent of GRACE risk score (OR=0.909; 95% CI: 0.842–0.981; p=0.01). PNI value in the high risk group for in-hospital mortality was determined to have significant predictive ability (AUC=0.710; 95% CI: 0.61–0.80; p<0001).

Conclusions — PNI evaluation is a useful and easy method to evaluate the nutritional status of patients with NSTE-ACS. Our study suggests that the PNI is significantly associated with in-hospital mortality, and GRACE risk score in patients with NSTE-ACS. This study is the basis for new studies to investigate whether PNI contributes additional prognostic to the GRACE risk score.

Keywords — Prognostic nutritional index; non-ST segment elevated acute coronary syndrome (NSTE-ACS); in-hospital mortality

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Introduction

Non-ST-segment elevation acute coronary syndrome (NSTE-ACS) is one of the leading causes of morbidity, hospitalization and death worldwide [1, 2]. It has been reported that the annual incidence of NSTE-ACS is higher than ST-segment elevation myocardial infarction (STEMI) [3]. The NSTE-ACS prognosis determines both the initial clinical risk and the use of proven treatments. Appropriate treatment according to the risk classification in these patients has the potential to improve clinical outcomes [3, 4]. The Global Record of Acute Coronary Events (GRACE) risk score, both in the entire ACS spectrum and in NSTE-ACS, provides an excellent ability to assess patients' risk of in-hospital and long-term death. Heart rate, systolic blood pressure, electrocardiographic changes, cardiac ischemia biomarkers, Killip degree, and pre-hospital cardiac arrest are independent variables of the GRACE risk score [5].

It has been reported that malnutrition causes many complications to develop in hospitalized patients and the adverse outcomes after discharge [6]. For example, it has been reported that wound healing is delayed, response to infection decreases [7], length of hospital stay increases [8], and mortality and morbidity increase [9]. Malnutrition is an important problem among patients with cardiovascular diseases. Similarly, the prevalence of malnutrition among older STEMI patients is estimated to be around 55% [10]. Malnutrition is generally thought to cause pathophysiological effects such as decreased protein reserves, calorie collapse, hypoalbuminemia, impaired vascular permeability, and impaired immunity or changes in heart function [11]. Various score indexes reflecting malnutrition have been associated with a hospital stay, cardiovascular events and mortality [12]. One of these risk scores is prognostic nutritional index (PNI). The PNI is a combined nutritional-inflammatory score that

reflects nutritional status based on serum albümin (SA) levels and lymphocyte count [13]. It was first reported by Onodera et al that low PNI is a risk factor associated with short- and long-term adverse outcomes in patients with gastrointestinal malignancies [14]. It is stated that PNI, which is extremely easy to calculate, can be used as a predictive nutritional marker in various cardiovascular diseases such as acute heart failure and STEMI [12, 15]. However, PNI has not been evaluated in patients with NSTE-ACS, and the relationship of PNI with the GRACE risk score has not been fully investigated in these patients. In this study we aimed to investigate the relationship between PNI and GRACE risk score and in-hospital mortality in patients with NSTE-ACS.

Material and methods

Study design

This was a monocentric, retrospective observational study. Adhering to the study principles of the Helsinki Declaration, and the study protocol was approved by the local ethics committee of our hospital.

Study population

The records of 565 NSTE-ACS patients identified as 61 unstable angina pectoris and 437 NSTE-myocardial infarction (MI) that were hospitalized in the coronary care unit between December 2015 and May 2019 were retrospectively evulated. NSTEMI was defined as patients with no ST-segment elevation criteria on electrocardiography (ECG) and typical ischemic chest pain with an increase in troponin level (troponin-I >0.06 ng/mL). Unstable angina pectoris was defined as patients with no ST-segment elevation criteria on ECG and typical ischemic chest pain with troponin levels within normal limits (troponin-I <0.06 ng/mL) [16]. The treatment of patients was organized in line with the guidelines of the European Society of Cardiology and an antiplatelet was started. All patients were started on angiotensin converting enzyme inhibitors, beta blockers and statins without contraindications within the first 24 hours after hospitalization. All Patients underwent coronary angiography and were referred to percutaneous coronary intervention or coronary bypass surgery within the indication.

Exclusion criteria: 1) acute STEMI, 2) patients under 18 years of age, 3) PNI scores cannot be calculated due to lack of SA or lymphocyte values, 4) patients with malignancy, cirrhosis, hematological proliferative disease, active infection, active or chronic inflammatory or autoimmune disease, recently receiving blood transfusions. 67 patients were not included in the final analysis, 52 SA data were not available, 12 patients had active infection and 3 patients received a blood transfusion. Consequently, data of 498 patients diagnosed with NSTE-ACS were analyzed for the study.

Laboratory tests included complete blood count, fasting glucose level, lipid profile, NT-proBNP, SA, troponin level, liver and kidney tests. The weight and height of the participants were measured and the body mass index (BMI) (kg/m^2) was calculated using the formula: BMI = weight/(height) 2.

For the GRACE risk score, patients' age, heart rate, systolic blood pressure (SBP), creatinine value, Killip degree, pre-hospital cardiac arrest, ST-segment deviation in ECG, and increase in troponin I were recorded. The GRACE risk scores were classified as low-risk group (<108 points), medium-risk group (108–140 points), and high-risk groups (>140 points) [5]. We evaluated in-hospital mortality and GRACE risk score for each patient.

The baseline PNI was calculated as 10×SA (g/dL) + 0.005 × total lymphocyte count (per mm^3) [14].

Patients with SBP ≥140 and diastolic BP (DBP) ≥90 mmHg or patients taking antihypertensive drugs were considered hypertensive. Diabetes mellitus was defined as patients with fasting blood glucose level ≥126 mg/dl or above 200 mg/dl in any measurement or using insulin or oral hypoglycemic medication, or hemoglobin A1c ≥6.5%.

Standard echocardiographic measurements were made to the patients included in the study according to the American Echocardiography Association/European Echocardiography Association guidelines [17]. Ejection fraction (EF) was calculated using the modified Simpson's method and left ventricular EF (LVEF) was considered <50% decreased and LVEF ≥50% was considered normal.

During the hospital stay all clinical data of patients were examined and all-cause mortality before hospital discharge was accepted as in-hospital mortality.

Statistical analysis

Statistical evaluation was done using Statistical Package for Social Sciences (SPSS) for Windows 20 (IBM SPSS Inc., Chicago, IL). The normal distribution of the data was evaluated with the Kolmogorov-Smirnov test. Numerical variables with normal distribution were presented as mean±standard deviation and numerical variables without normal distribution were shown as median (minimum and maximum). ANOVA test (posthoc: Bonferroni correction) was used for comparison of numerical variables that showed normal distribution between groups according to GRACE scores classes and PNI classes, and Kruskal Wallis H test (posthoc: Dun's correction) was used to compare numerical variables that did not show normal distribution. Chi-Square and Fisher's exact Chi-Square test was used to compare categorical data. The relationship between GRACE scores, PNI, and numerical variables was

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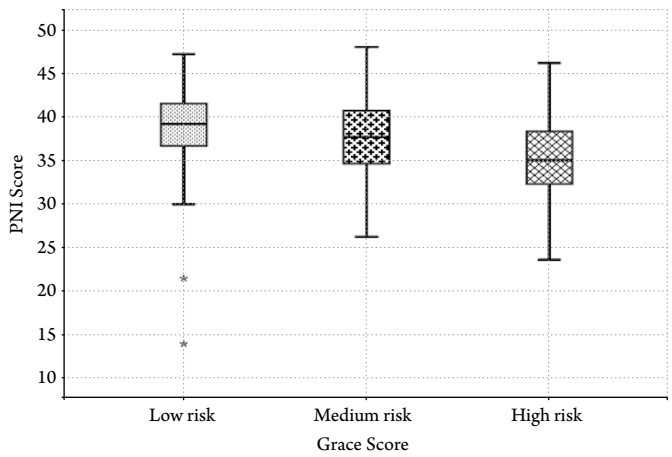
Table 1. Demographic and Biochemical Characteristics of Patients in GRACE Risk Score Groups

Variables	GRACE Risk Score			p, value
	≤108, low-risk group (n=222)	109–140, medium-risk group (n=161)	>140, high-risk group (n=115)	
Gender				
Men, n (%)	163 (73.4)	108 (67.1)	74 (64.3)	0.169
Women, n (%)	59 (26.6)	53 (32.9)	41 (35.7)	
Age (years)	54.2±10.2	65.6±9.7	74.7±8.5	<0.001
BMI (kg/m²)	28.4±4.9	27.5±4.5	28.1±4.7	0.320
HT, n (%)	102 (45.9)	108 (67.1)	71 (61.7)	<0.001
DM, n (%)	62 (27.9)	81 (50.3)	47 (40.9)	<0.001
Smokers, n (%)	117 (52.7)	52 (32.3)	27 (23.5)	<0.001
Previous CAD, n (%)	93 (41.9)	83 (51.6)	62 (53.9)	0.087
SBP (mmHG)	146.6±28.2	131.3±27.3	124.9±26.2	<0.001
DBP (mmHG)	82.6±18	75.9±15.4	72.4±14.9	<0.001
HR (beats/min)	75.8±15.5	79.6±17	84.1±17.9	<0.001
EF	53.5±9.4	50.8±9.9	47.2±11.6	<0.001
PNI	38.8±4.6	37.3±4.4	35.2±5.3	<0.001
Glucose (mg/dL)	109 (68-–430)	130 (56–597)	122 (75–741)	0,001
Creatinine (mg/dL)	0.9 (0.6–13)	1.1 (0.6–8.9)	1.1 (0.6–8.6)	<0,001
Troponin hospitalization (ng/mL)	1.3 (0–27302)	1.2 (0–11090) 1.8	8.3 (0–25145)	<0,001
Lymphocyte (109/L)	2.0 (0.5–7.0)	(0.2–7.9)	1.8 (0.2–7.0)	<0,001
Albumin (g/dL)	3.9±0.5	3.7±0.4	3.5±0.5	<0.001
Leukocyte (109/L)	9.6±3.1	9.8±3.5	10.2±3.9	0.333
Hb (g/dL)	14.2±2.2	13.7±2.1	12.8±2.3	<0.001
Total cholesterol (mg/dL)	184.8±48.4	172.5±37	180.2±53.8	0.324

BMI: body mass index, HT: hypertension, DM: diabetes mellitus, CAD: coronary artery disease, SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate, EF: ejection fraction, GRACE: Global Registry of Acute Coronary Events, PNI: Prognostic nutritional index, Hb: hemoglobin, $p < 0.05$ value was considered significant.

Figure 1. PNI values according to GRACE risk groups: The mean PNI value in the high-risk group was low compared to other risk groups (p<0.001)



evaluated by Pearson and Spearman correlation analysis. Logistic regression analysis was used to test the importance of data on mortality. PNI, age, GRACE risk score, and hemoglobin levels were selected for multivariable logistic regression analyses. The adjusted odd ratios (OR) and 95% confidence intervals (CI) are presented. The prediction value of PNI was evaluated with the receiver operating characteristic (ROC) curve analysis Youden index method. In statistical analysis, p<0.05 value was considered significant.

Results

The study population consisted of 498 NSTE-ACS patients. In total, the age range of patients was 31–91 years, an average of 62.6±12.7 years, and 69.3% of men (n=345). A total of 281 patients (56.3%) were hypertensive, 190 patients (38.1%) were diabetic, 196 patients (39.3%) were smoking, 181 patients (36.3%) were LVEF <50% and 235 patients (47.1%) had coronary artery disease (CAD) before.

The distribution of demographic findings according to the GRACE risk groups is shown in Table 1. There was a significant decrease in mean LVEF levels according to the increased risk classes (Table 1). The mean PNI level was found lower in the high-risk group compared to other risk groups (Figure 1). The median creatinine level was found to be lower in low-risk patients, and the median creatinine level did not differ significantly in moderate and high-risk patients. The median troponin I level was found to be higher in high-risk patients compared to other risk groups. The mean SA level was found to be the lowest in the high-risk group. The median glucose level was lower in low-risk patients compared to medium and high-risk patients. Other laboratory parameters did not differ significantly between groups (Table 1).

In the correlation analysis PNI showed a significant positive correlation with the following: hemoglobin, total

cholesterol, LVEF, BMI, a significant negative correlation – with age, creatinine, troponin I, glucose, total leukocyte count (Table 2). In addition, there was a significant negative correlation between GRACE risk score and PNI (p<0.001) (Figure 2).

In the hospital period 30 (6%) patients died. Demographic and biochemical characteristics of patients with and without in-hospital mortality are shown in Table 3. For in-hospital mortality, PNI, GRACE risk score, age, hemoglobin were analyzed using a multivariate logistic regression model. The PNI was the independent predictor of in-hospital mortality (Table 4).

PNI predictive values were determined according to the GRACE risk group; low risk group (PNI1 >37.0), medium risk group (PNI2=35.9–37.0) and high risk group (PNI3 <35.9). In the study of receiver operating characteristic (ROC) curve for in-hospital mortality; PNI1 (Areas under the curve (AUC) =0.294; 95% CI=0.206–0.383; p<0.001), PNI2 (AUC=0.496; 95% CI=0.390–0.602; p=0.9), PNI3 (AUC=0.710; 95% CI=0.615–0.804, p<0.001) and PNI3 was found to significantly predict in-hospital mortality (Figure 3).

Table 2. PNI correlation factors

Variables	PNI	
	r	p
GRACE risk score	–0,323	<0,001
Age	–0,407	<0,001
BMI	0,159	0,006
EF	0,182	<0,001
Creatinine	–0,212	<0,001
Troponin I	–0,149	0,001
Leukocyte	–0,227	0,005
Hb	0,275	<0,001
Total cholesterol	0,303	<0,001
Glucose	–0,116	0,01

GRACE: Global Registry of Acute Coronary Events, PNI: Prognostic nutritional index, BMI: body mass index, EF: ejection fraction, Hb: hemoglobin.

Table 3. Demographic and Biochemical Characteristics of Patients with and without In-Hospital Mortality

Variables	Patients with in-hospital mortality (n=30)	Patients without in-hospital mortality (n=468)	p, value
Age, years	72.4±11.2	61.9±12.5	<0.001
Men, n (%)	18 (60)	327 (69)	0.3
BMI, kg/m²	27.1±5.2	28.0±4.7	0.4
HT, n (%)	21 (70)	260 (56)	0.1
DM, n (%)	17 (56)	173 (37)	0.05
Smoker, n (%)	8 (26)	188 (40)	0.1
Previous CAD, n (%)	15 (51)	220 (47)	0.7
EF (%)	47.7±9.4	51.4±10.4	0.05
Leukocyte (109/L)	10.4±3.3	9.7±3.4	0.3
Hb (g/dL)	12.5±2.2	13.7±2.2	0.005
Glucose (mg/dL)	155.9±82.0	146±81.6	0.5
Total cholesterol (mg/dL)	166.2±30.1	180.8±47.3	0.2
NT-proBNP	5651.7 ±8977.7	3814.0±7578.3	0.2
Troponin hospitalization (ng/mL)	217.6 (0–6528)	251.0 (0–11724)	0.2
GRACE risk score	138.2±35.8	113.8±31.9	<0.001
PNI	33.7±4.2	37.6±4.8	<0.001

BMI: body mass index, HT: hypertension, DM: diabetes mellitus, CAD: coronary artery disease, EF: ejection fraction, Hb: hemoglobin, GRACE: Global Registry of Acute Coronary Events. PNI: Prognostic nutritional index.

Table 4. Multivariate Logistic Regression Analyses In-Hospital Mortality

Variables	OR	95% CI	p
PNI	0.909	0.842–0.981	0,01
GRACE risk score	1.007	0.992–1.023	0.3
Hb	0,940	0.788–1.120	0,4
Age	1.044	0.996–1.095	0.07

OR: Odds ratio; CI: Confidence interval, PNI: Prognostic nutritional index, GRACE: Global Registry of Acute Coronary Events, Hb: hemoglobin.

Discussion

In this study, it was investigated whether PNI was associated with GRACE risk score and in-hospital mortality in patients with NSTE-ACS patients whose nutritional status was evaluated with PNI. It is also the first study to correlate

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Figure 2. Correlation between GRACE risk score and PNI

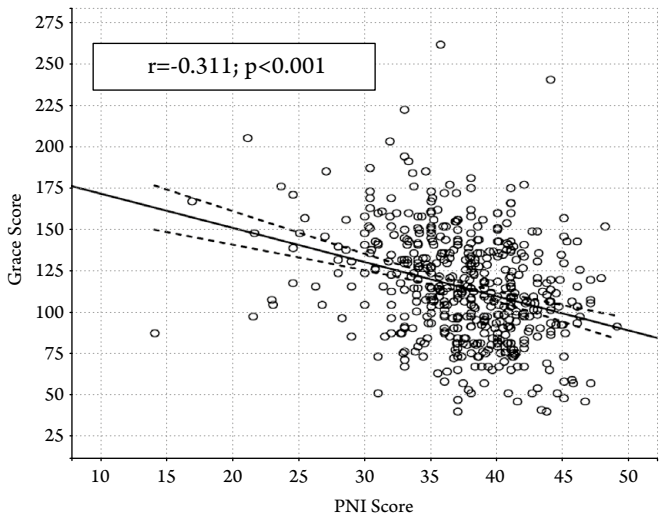
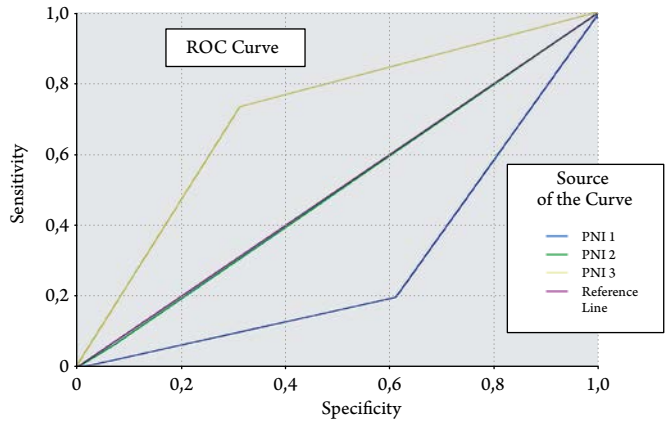


Figure 3. Receiver operating characteristic (ROC) curve analysis



PNI values according to risk groups (PNI1, PNI2, PNI3) predicting mortality; PNI1 (AUC:0.294, p<0.001), PNI2 (AUC: 0.496, p=0.9), PNI3 (AUC: 0.710, p<0.001)

the levels of PNI with the GRACE risk score (p<0,001). Also we found that PNI is an independent predictor for in-hospital mortality (OR = 0.909; 95% CI: 0.842–0.981; p=0.01). PNI value in the high risk group for in-hospital mortality was determined to have significant predictive ability (AUC = 0.710; 95% CI:0.615–0.804; p<0001).

NSTE-ACS is reported to be associated with an in-hospital mortality rate of approximately 5% [18], and long-term mortality rates were higher in NSTE-ACS patients than in patients with STE-ACS [19]. NSTE-ACS is generally slightly different compared to STEMI pathophysiology; rather than coronary obstruction, there is a decrease in coronary blood flow causing partial or temporary coronary obstruction [20]. The pathophysiological difference between NSTE-ACS and STEMI is critical when determining treatment strategies for NSTE-ACS [3]. In current guidelines, it is recommended to identify the risk groups of NSTE-ACS and consider early invasive treatment for patients with a high risk NSTE-ACS accordingly. Therefore, early risk classification is very important at the time of admission to determine treatment strategy and to assess the risk of mortality in hospitalized patients with NSTE-ACS. For the risk classification of NSTE-ACS it is recommended to calculate the GRACE risk score in international guidelines [4, 5]. Moreover, it is stated that the GRACE risk score has superior distinguishing performance compared to other ACS risk scores [21]. Our study is the first one to examine the relationship between GRACE risk score and PNI in patients with NSTE-ACS. A negative correlation was found between the GRACE risk score and PNI (p<0.001). PNI value in the high risk group for in-hospital mortality was determined to have significant predictive ability (AUC 0.71). The PNI assessment can be a useful and easy method to evaluate the nutritional status of NSTE-ACS and may provide additional prognostic value in these patients.

Previous studies have found that PNI is a useful and good indicator of prognosis and clinical outcomes in acute STEMI patients [15, 22]. Yoo S.H. et al, in their study, defined malnutrition as an independent factor affecting complications after acute MI and all-cause mortality [23]. In this study, nutritional deficiencies have been shown to increase complications after MI such as cardiogenic shock, recurrent stroke, major bleeding, newly detected atrial fibrillation or ventricular tachycardia, new heart failure, acute kidney failure, sepsis, and multiorgan failure. Complications after AMI were thought to cause an increase in in-hospital mortality. Another study found nutritional status evaluated by PNI as an independent predictor of long-term cardiovascular outcomes in patients with stable CAD after elective percutaneous coronary intervention. In this study, patients with low PNI have a higher frequency of not only all-cause mortality but also cardiac mortality [11]. There is a lack of information about the effect of nutritional status on clinical outcomes, especially in patients affected by acute cardiovascular events such as NSTE-ACS. We think that nutritional evaluation is important in NSTE-ACS patients, known to have high mortality and morbidity rates.

Advanced age is one of the strongest risk factors for CAD and has been reported to be an independent predictor for poor outcomes following ACS [24]. In large studies to date, approximately 32–43% of patients over the age of 75 years represent NSTE-ACS applicants [25]. In our patient population, the group with high GRACE risk score is older (average age 74.7±8.5 years). In our study a significant negative correlation was found between PNI and age. In addition, LVEF determined by echocardiography has been reported to be a strong predictor of mortality in NSTEMI patients, although it is not included in GRACE risk scoring and similar early risk classification algorithms [26]. Previous studies have found an independent association with PNI-based nutritional status, both short and long-term cardiovascular mortality in patients with acute heart failure [13]. In our study LVEF was <50% in 36.3% of patients

and LVEF was significantly lower in the group with high GRACE risk score compared to other risk groups. In our study, a significant correlation was found between PNI and EF. In addition, various biomarkers play a role in defining the severity of malnutrition. It has been reported that values such as SA, BMI, hemoglobin and total cholesterol may be lower in patients with malnutrition [27]. In our study, a positive correlation was found between PNI and hemoglobin, BMI and total cholesterol.

PNI provides information on both nutritional and immunological status, as PNI is calculated based on the two-component SA level and the total number of lymphocytes in peripheral blood. Various mechanisms may be responsible for low PNI associated with mortality. First, increased inflammatory activity in the NSTE-ACS may be responsible for a decrease in SA level. SA has many important functions in the body, such as regulation of vascular oncotic pressure, regulation of various metabolic functions, antioxidant activity [28], and the reduction in SA level is often used as an indicator of nutritional status in clinical practice. It has been reported that decreased SA is associated with an increased risk of cardiovascular mortality and all-cause mortality [29]. Another may be associated with a low number of lymphocytes. Lymphocytopenia is a finding that can be seen secondary to increased corticosteroid levels as a result of increased stress response in acute coronary events [30]. In previous studies, lymphocytopenia was independently associated with the occurrence of complications and death after acute MI [31].

One of the features of this study is that PNI is lower than reported in other studies. As noted above, malnutrition affects several factors, and NSTE-ACS patients often have more comorbidities than STEMI patients. For example, Chen et al found in patients hospitalized for STEMI the PNI score <45 was significantly associated with the clinical outcome in STEMI [15]. In our study the mean PNI was 37.4 and the prognostic value of PNI was confirmed in this study, but PNI values were much lower than in other studies. In our study, unlike the study done by Chen et al, the patients are older, have higher rates of arterial hypertension and diabetes mellitus, and also have a lower ejection fraction, all these factors may have caused a lower detection of PNI in our patienst groups.

Study limitations

This study has several limitations. This is a single-center and retrospective study and the patient population is relatively small. There is no patient data after patients are discharged from the hospital, and therefore long-term mortality rates are unknown. Besides, when calculating PNI, basal albumin levels, and basal lymphocyte counts were used, and calculations were not made by serial measurements of PNI components.

Conclusions

The GRACE risk score is routinely used for stratification of patients with ACS. PNI evalution for the risk classification of patients with NSTE-ACS may be beneficial and contribute to the GRACE risk score during the hospitalization period. Our study showed that PNI may provide additional prognostic value in patients with NSTE-ACS. In addition, this study showed that decreased PNI resulted as a predictor of in-hospital mortality independent of GRACE risk score. This result suggests that the risk of malnutrition assessed by PNI in these patients can be used as an easy, simple and inexpensive method without spending too much time. We think that these important findings of our analysis can guide clinical practical applications in order to guide the treatment. Future studies are needed to clarify whether correction of nutritional status in patients with NSTE-ACS will improve prognosis and to investigate whether PNI provides additional prognostic contribution to the GRACE risk score.

Abbreviations

PNI: Prognostic nutritional index. ACS: Acute coronary syndrome. MI: Myocardial infarction. NSTE-ACS: Non-ST segment elevated acute coronary syndrome. NSTEMI: Non-ST segment elevated myocardial infarction. STEMI: ST-segment elevated myocardial infarction. CAD: Coronary artery disease. GRACE: The Global Registry of Acute Coronary Events. EF: Ejection fraction. SA: Serum albümin. ECG: Electrocardiography. BMI: Body mass index

No conflict of interest is reported.

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