Diagnostic Impact of Immunonutritional Indices in Peripheral Arterial Disease Severity and Complexity

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Abstract

Purpose

We aimed to evaluate the relationships between the severity of peripheral arterial disease (PAD) and immune-nutritional status, as quantified by the prognostic nutritional index (PNI), controlling nutritional status score (CONUT), and modified Glasgow prognostic score (mGPS).

Methods and results

One hundred forty-eight patients with severe lower extremity PAD diagnosed by angiography constituted the study population. All patients had at least one severe superficial femoral arterial disease (SFA). According to the presence of a chronic total occlusion in SFA (SFA CTO), the study population was divided into two groups. Patients with SFA CTO (n: 84) had a significantly lower PNI (43.4 ± 4.8 vs. 49.1 ± 4.7 , $p < 0.001$), worse mGPS and CONUT scores than those without SFA CTO (n: 64). A comparison of the three groups, those classified according to PNI tertiles ($PNI \geq 48$, n: 49; $43.8 < PNI < 48$, n: 49; $PNI < 43.8$, n: 50), revealed that a lower PNI was associated with the presence of a TASC C-D lesion in the femoropopliteal segment, SFA CTO, long lesion, and long CTO. Furthermore, PNI was found to be an independent predictor of SFA CTO in the logistic regression analysis. Diagnostic performance of PNI was better than mGPS and CONUT scores in ROC curve comparison.

Conclusion

This is the first study demonstrating the relationship between PNI and PAD severity. Our results and the prognostic value of PNI should be validated in a larger prospective cohort.

Introduction

Lower extremity peripheral artery disease (PAD) is a manifestation of atherosclerotic vascular disease. Its severity and complexity is significantly associated with poor prognosis (1). Despite the omission of The Trans-Atlantic Inter-Society Consensus-II (TASC-II) classification in recent guidelines regarding various PAD types, it was used to assess PAD according to anatomic distribution and to reflect the severity and complexity of lesions (stenosis and occlusions) for many years (2). Clinical studies have revealed that the TASC-II classification has a prognostic impact in PAD and gives useful information when choosing a revascularization strategy (endovascular or surgical) (3–4). The use of easily available diagnostic tools that can reflect the severity of PAD in clinical practice can allow patients to be detected and treated early and, consequently, improve their prognosis.

The increased prevalence of PAD in recent years, in addition to classical risk factors, hypertension, dyslipidemia, smoking, is believed to be mainly attributable to aging populations and the growing

prevalence of risk factors, especially diabetes mellitus (5). However, traditional risk factors do not entirely describe the excess risk of PAD. The link between atherosclerosis and malnutrition increases the risk of cardiovascular mortality in elderly patients with poor nutritional status, as stated in previous studies (6). Although it has been estimated to range from 20–50% in hospitalized patients (7–8), malnutrition is commonly overlooked in clinical practice. Various methods and indices for nutritional evaluation have been advocated and used to predict unfavorable prognoses in some clinical settings (9–11). The modified Glasgow prognostic score (mGPS), prognostic nutritional index (PNI), controlling nutritional status (CONUT) score, and geriatric nutritional risk index (GNRI) are not only objective markers of malnutrition but also of immunological status (12). Since PAD is both an inflammatory disease and postulated to be more common in malnourished subjects, we hypothesized that these markers could be associated with PAD's complexity and severity as assessed by peripheral angiogram.

Methods

Study population

A consecutive 190 patients with PAD who underwent peripheral angiography at Gebze Fatih State Hospital between June 2019 and March 2020 were retrospectively screened. Exclusion criteria were active infections, a recent major surgical procedure, trauma, neoplastic disease, and previously diagnosed with systemic inflammatory disease, vasculitis, and malignancy. We also excluded patients with digital ulcers and with acute thromboembolic occlusions causing acute limb ischemia. The remaining 148 patients with significant PAD diagnosed via an angiogram constituted the study population. Demographic, clinical, laboratory, and procedural variables were obtained from reviewing our institution's electronic medical records.

Laboratory analysis

Before the peripheral angiography, blood samples were collected after twelve hours of fasting and analyzed in our institution's laboratory. Laboratory variables, including hemoglobin level, lymphocyte count, blood glucose, creatinine, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, and albumin evaluated. White blood cell, hematocrit, and platelet counts were measured as part of the automated complete blood count using a Coulter LH 780 Hematology Analyzer (Beckman Coulter Ireland, Inc, Galway, Ireland). The albumin levels were measured using a Roche Diagnostics Cobas 8000 c502 Analyzer (Indianapolis, USA). Definition and calculation of PNI (13), CONUT score (14), and mGPS (15) are presented in Table 1.

Angiographic analysis

PAD was evaluated on the peripheral angiogram, contralateral to the site of retrograde access, or ipsilateral to the site of antegrade access, in the lower extremities. Stenosis ≥ 70 % in diameter was defined as a severe disease. The disease level was classified as suprapopliteal (iliac, femoral, and popliteal arteries), infrapopliteal (anterior tibial, peroneal, and posterior tibial arteries) arteries. Lesion

characteristics were defined regarding the angiographic findings according to the TASC-II classification (3). A superficial femoral artery (SFA) lesion greater than 25 cm was described as a long lesion (16). Chronic total occlusion (CTO) is a lesion that was at least three months old. If the participant had never received imaging, a clinical definition is used, which included the presence of an occluded SFA without filling defects in the body of the occlusion to indicate a more acute or subacute occlusion as well as having no clinical history of acute onset symptoms or other signs of acute limb ischemia (17).

Statistical analysis

SPSS version 17.0 (SPSS Inc, Chicago, USA) was used to perform the statistical analysis. To assess the normal distribution of continuous variables, a Kolmogorov-Smirnov test was performed. Continuous variables with and without a normal distribution were expressed as a mean $\pm$ standard deviation and median, interquartile range. Categorical variables were expressed as percentages, and the chi-square test was used to compare the variables. Continuous and non-continuous variables between the two groups were compared using the student t-test and Mann–Whitney U test. Multivariable logistic regression analysis was used to determine independent predictors of the superficial femoral artery (SFA CTO). The predictive performance of PNI for diagnosing SFA CTO lesions was assessed using receiver-operating characteristic (ROC) curve analyses. The predictive validities of PNI, albumin, and lymphocyte count were quantified as the area under the ROC curves (c statistics). Comparing the c statistics were performed by the DeLong's test. A two-sided p-value of < 0.05 was considered significant.

Results

The cohort composed 148 patients (69 ± 10 years, 4.1% female) with severe PAD. All patients had a severe SFA lesion and participants were separated into two groups: patients with chronic total occlusion of SFA (n: 84) and patients without it (n: 64), as determined by peripheral angiography. The baseline characteristics and laboratory findings of the patients were given in Table 2. Although 95.9% (n: 142) of study participants were male, female sex was more prevalent in patients with SFA CTO ($p=0.029$). The frequency of hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease and smoking was comparable among patients with and without SFA CTO lesions. Ankle brachial indices of patients with SFA CTO were lower than without SFA CTO (0.629 ± 0.081 vs. 0.685 ± 0.076 , $p < 0.001$). Walking distance was shorter in patients with SFA CTO compared to those without SFA CTO [150 (120-185) vs. 190 meters (150-220), $p < 0.001$]. Comparison of laboratory parameters revealed that, subjects with SFA CTO had lower serum albumin levels compared to those without SFA CTO. Despite patients with SFA CTO had a lower leucocyte count, especially the lymphocyte subgroup, they had a higher neutrophil count and neutrophil to lymphocyte ratio in comparison to those without SFA CTO.

Nutritional indices and angiographic characteristics of all patients and comparison of two groups are listed in Table 3. Patients allocated in SFA CTO group not only had severe disease according to TASC classification, but also they had severe bilateral femoropopliteal disease, longer lesion and more prevalent long CTO and infrapopliteal disease compared to patients without SFA CTO. Among nutritional

indices, PNI were significantly lower in patients with SFA CTO compared to those without SFA CTO (43.4 ± 4.8 vs. 49.1 ± 4.7 , $p < 0.001$). Similarly, patients with SFA CTO had an increased mGPS and CONUT scores (Table 2). Furthermore, study population divided into three tertiles according to increased PNI values ($\text{PNI} \geq 48$, $n:49$; $43.8 < \text{PNI} < 48$, $n:49$; $\text{PNI} < 43.8$, $n: 50$). Patients in the lower PNI tertile tended to have SFA CTO more frequently when compared to those in the higher PNI tertile (80 vs. 69.4 vs. 20.4 %, $p < 0.001$, respectively). Patients with PNI less than 43.8 had worse femoropopliteal TASC-II grades compared to those with higher PNI values. Also, subjects in the lower tertile had more bilateral femoropopliteal TASC-II C-D lesions in comparison to those with higher PNI (8.2 vs. 36.7 vs. 34%, $p = 0.005$). Lesions longer than 25 cm, long CTOs and aortailiac disease were seen more frequently in patients with lower PNI when compared to those with higher PNI ($p < 0.001$). However, the frequency of infrapopliteal diseases was comparable among PNI groups (Table 4).

Multivariable logistic regression analysis were performed to examine the effect of confounding factors which chosen among comorbidities and laboratory parameters on the basis of our results and their clinical importance, on the performance of PNI in the diagnosis of SFA CTO. After adjusting clinically and statistically relevant confounding factors(female gender, ABI, walking distance, albumin, white blood cell and lymphocyte count), 1 (one) point decrease in PNI value was found to be associated with 23.0% increase in the diagnosis of SFA CTO in our study population(OR: 0.77; 95% CI: 0.69–0.85; $p < 0.001$).

ROC curve analysis showed that $\text{PNI} \leq 45.9$ predicted the presence of SFA CTO with a sensitivity and specificity of 81.2% and 76.2% (Area under the curve (AUC): 0.807; 95% CI: 0.734–0.867 ($p < 0.001$)). Furthermore, ROC curve comparison revealed that PNI had better diagnostic performance than lymphocyte count, NLR, CONUT and mGPS scores ($p < 0.001$ for each comparison) but not albumin ($p=0,504$); in predicting presence of SFA CTO (Figure 1). Result of ROC curve analysis of above-mentioned parameters were listed in Table 5.

Discussion

The present study revealed that PNI is significantly associated with PAD severity and is an independent predictor for severe and complex femoropopliteal PAD as determined by the TASC-II classification in subjects diagnosed with peripheral angiography. Furthermore, PNI predicted occluded SFA more accurately than lymphocyte count, NLR, CONUT and mGPS scores.

Since systemic inflammation and malnutrition are related to cardiovascular events, the appraisal of immune-nutritional status in patients with cardiovascular diseases has gained popularity in recent years. PNI is feasible to efficiently and economically assess the inflammation-based nutritional situation and subsequent outcomes of patients with PAD. It requires simple and widely present objective markers like serum albumin levels and total lymphocyte counts. Many studies are demonstrating the prognostic significance of PNI for various medical conditions (18). Also, PNI is associated with poor prognosis in stable coronary artery disease (CAD) and heart failure. To our knowledge, no study has investigated the

possible relationship between PNI and PAD severity. Our study demonstrated that decreased PNI was significantly associated with severe and complex femoropopliteal arterial disease.

Our observation could be explained by the effects of malnutrition and inflammation on serum albumin and lymphocyte. Malnutrition reduces albumin concentration by decreasing its synthesis rate. It leads to a reduced response to acute disease, exacerbates chronic diseases, and decreases long-term survival. Malnutrition is associated with atherosclerosis development and increased cardiovascular mortality in older patients (19, 20). It appears to be an independent predictor of poorer outcomes in PAD patients (21–27). In a cohort of patients treated with endovascular therapy for PAD, preprocedural malnutrition was a significant predictor of adverse outcomes (28). In agreement with the studies mentioned above, we observed that a decreased albumin level is related to the severity and complexity of the femoropopliteal disease. Also, malnutrition leads to a deficiency of essential vitamins and amino acids. The lack of these vital nutrients can depress cell-mediated immunity or humoral immunity. The number and function of both B and T cells would be significantly diminished, leading to a lower lymphocyte count (29).

Inflammation plays an important role both in the initiation and progression of PAD. The inflammatory mediators participating in this process are similar to those contributing to the development of CAD (30–34). Furthermore, inflammatory markers, particularly CRP, are useful in predicting future cardiovascular events for CAD patients. Although it did not have statistical significance, we observed that the SFA CTO group has numerically higher CRP values compared to patients without SFA CTO. The inflammatory activity can have a significant impact on the serum albumin levels. Some cytokines, such as IL-2 and IL-6, inhibit albumin's hepatic synthesis (35–37). Systemic inflammation makes a patient susceptible to malnutrition, and malnutrition exacerbates inflammation, which leads to a vicious cycle. Furthermore, the lymphocyte count is affected in inflammatory situations due to an increased breakdown and a common finding in response to increased corticosteroids in stress conditions. Hypo-responsiveness of albumin and lymphocytes to disease states indicates an impaired immunonutritional status.

Although many sophisticated imaging tools are used to determine PAD and ABI's diagnosis and prognosis and are easily obtainable and reproducible, ABI remains valid. The test's validity in clinical settings has been proven in previous studies (38–40). In agreement with the literature, we found ABI to be an independent predictor of femoropopliteal disease severity.

There was no prognostic data because of the observational nature of our study. Also, being a retrospective and single-center design makes the study prone to bias. Despite the statistical significance being high, our relatively small sample size is another drawback. PNIs were evaluated only once; their changes with time during the follow-up period were not assessed. Although diagnostic performance of PNI seemed to be independent from albumin in multivariable logistic regression analysis, there was no statistically significant difference between their AUC values in ROC curve comparison. Further studies with larger population is needed to validate if PNI has better diagnostic performance than albumin. Neither sophisticated tools more clearly revealing malnutrition nor a high sensitive CRP showing baseline chronic inflammation were used.

Conclusion

The PNI should be considered a clinical tool and marker of disease severity and complexity in PAD. It can be utilized to determine high-risk patients who may benefit from more aggressive therapy and close follow-up. As we explained in detail, a novel predictive parameter, PNI, was introduced to patients with PAD, which includes both albumin and lymphocyte counts. PNI brings these two essential measurements together and presents a unique prognostic value.

Declarations

Ethics

Because of the retrospective design of the present study, informed consent was not taken from the participants. Ethic Board of Kocaeli Derince Research And Education Hospital approved the study protocol with file number 2020/47. The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Conflict of Interest

The authors have no conflicts of interest to declare.

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Author Contributions

All authors contributed to the conception of the work and drafted the manuscript. All authors critically revised the manuscript. All gave final approval and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Tables

Table 1

Definition immunonutritional indices

Nutritional indices	Degree of malnutrition			
	Normal	Mild	Moderate	Severe
Prognostic nutritional index (13)				
10 x serum albumin (g/dL) + 0.005 x total lymphocyte count (mm ³)	>38	-	35–38	<35
Controlling nutritional status score (14)				
Albumin (g/L) (score)	≥35 (0)	30–34 (2)	25–29 (4)	<25 (6)
Cholesterol (mmol/L) (score)	>4.65 (0)	3.62– 4.65 (1)	2.59– 3.61 (2)	<2.59 (3)
Total lymphocyte count, x10 ⁹ /L (score)	≥1.60 (0)	1.20– 1.59 (1)	0.80– 1.19 (2)	<0.80 (3)
Overall score	0–1	2–4	5–8	9–12
Modified Glasgow prognostic score (15)				
CRP ≤1 (g/dL) and albumin ≥3.5 (g/dL) (0 point)	0	1	1	2
CRP >1 (g/dL) (regardless of albumin level) (1 point)				
CRP >1 (g/dL) and albumin <3.5 (g/dL) (2 point)				
CRP, C-reactive protein.				

Table 2

Baseline demographic and laboratory characteristics of patients with lower extremity peripheral arterial disease

	All patients (n:148)	Patients without SFA CTO (n:64)	Patients with SFA CTO (n:84)	p value
Age, years	69±10	69±10	68±9	0.256
Female gender, n(%)	6 (4.1)	0 (0.0)	6 (7.1)	0.029
Hypertension, n(%)	112 (75.7)	35 (79.5)	60 (73.4)	0.168
Diabetes mellitus, n(%)	47 (31.8)	18 (28.1)	29 (34.5)	0.407
Hyperlipidemia, n(%)	53 (35.8)	26 (40.6)	27 (32.1)	0.286
CAD, n(%)	117(79.1)	51 (79.7)	66 (78.6)	0.869
Smoking, n(%)	86 (58.1)	39 (60.9)	47 (56)	0.543
ABI	0.653±0.084	0.685±0.076	0.629±0.081	<0.001
Walking distance (m)	150 (130-200)	190 (150-220)	150 (120-185)	<0.001
Fasting blood glucose, mg/dl	109 (95-151)	109 (93-155)	114 (97-150)	0.455
Creatinine, mg/dl	0.96 (0.82- 1.17)	0.95 (0.78-1.16)	0.94 (0.83-1.17)	0.320
Total Cholesterol, mg/dl	175±42	173±38	177±45	0.742
LDL cholesterol, mg/dl	106±31	105±30	107±31	0.710
HDL cholesterol, mg/dl	39±11	40±13	39±10	0.932
Triglyceride, mg/dl	125 (90-165)	130 (89-198)	120 (91-165)	0.763
CRP, mg/dl	0.80 (0.44- 1.43)	0.72(0.44-1.3)	0.85 (0.45-2)	0.151
Albumin, g/dl	3.7±0.3	3.9±0.3	3.6±0.3	<0.001
White blood cell count, 10 ³ /μL	8.0±3.1	8.4±2	7.7±3.9	<0.001
Haemoglobin, g/dl	14.2±2.4	14.3±2	14.1±2.6	0.667
Neutrophil count, 10 ³ /μL	5.5±3.2	5.5±2	5.5±3.8	0.027

Lymphocyte count, 10 ³ /μL	1.7±0.8	2±0.7	1.5±0.7	<0.001
Platelet count, 10 ³ / μL	237±78	226±57	246±90	0.549
NLR	2.8(1.9-4.3)	2.7(1.9-3.3)	2.9(1.9-6.0)	0.046
SFA; Superficial femoral artery, CTO; Chronic total occlusion, ABI; Ankle-brachial index, CAD; coronary artery disease, CRP; C-Reactive protein, LDL; low density lipoprotein, HDL; high density lipoprotein				

Table 3

Comparison of nutritional indices and angiographic characteristics of patients with SFA CTO and those without SFA CTO.

	All patients (n:148)	Patients without SFA CTO (n:64)	Patients with SFA CTO (n:84)	p value
PNI	45.9 ± 5.5	49.1 ± 4.7	43.4 ± 4.8	< 0.001
CONUT score				0.004
Normal(0–1)	52(35.1)	31(48.4)	21(25.0)	
Mild (2–4)	91(61.5)	33(51.6)	58(69.0)	
Moderate and severe(> 4)	5(3.4)	0(0.0)	5(6.0)	
mGPS				0.035
Normal	92(62.2)	45(70.3)	47(56.0)	
Mild-moderate	41(27.7)	17(27.6)	24(28.6)	
Severe	15(10.1)	2(3.1)	13(15.5)	
Femoropopliteal TASC-II Class (%)				
A	22 (14.9)	20 (31.3)	2 (2.4)	< 0.001
B	21 (14.2)	15 (23.4)	6 (7.1)	
C	73 (49.3)	27 (42.2)	46 (54.8)	
D	32 (21.6)	2 (3.1)	30 (35.7)	
Bilateral femoropopliteal TASC-II C-D, (%)	39 (26.9)	6 (9.4)	33 (39.3)	< 0.001
Lesion length > 25 cm (%)	75 (50.7)	21 (32.8)	54 (64.3)	0.001
Long CTO (%)	28 (32.2)	0.0 (0)	28 (65.1)	< 0.001
Aortoiliac disease (%)	79 (53.4)	29(45.3)	50 (59.5)	0.086
Infrapopliteal disease (%)	38 (25.7)	4 (6.3)	34 (40.5)	< 0.001
SFA; Superficial femoral artery, CTO; Chronic total occlusion, PNI; Prognostic nutritional index, CONUT; controlling nutritional status, mGPS; Modified Glasgow Prognostic Score, TASC-II; Trans Atlantic Inter-Society Consensus-II				

Table 4
Extremity lesion properties according to PNI tertiles

		PNI $\geq$ 48; n:49	43.8 < PNI < 48; n:49	PNI < 43.8; n:50	p value
SFACTO n (%)		10 (20.4)	34(69.4)	40(80.0)	< 0.001
Fem-pop TASC n (%)	A	10(20.4)	6(12.2)	6(12.0)	
	B	15(30.6)	4(8.2)	2(4.0)	< 0.001
	C	20(40.8)	23(46.9)	30(60.0)	
	D	4(8.2)	16(32.7)	12(24.0)	
Bilateral fem-pop TASC II C or D n (%)		4(8.2)	18(36.7)	17(34)	0.005
Lesion length $\geq$ 25cm n (%)		14(28.6)	27(55.1)	34(68)	< 0.001
Long CTO n (%)		4(8.2)	20(40.8)	30(60)	< 0.001
Aortoiliac Disease n (%)		32(65.3)	17(34.7)	30(60)	0.005
Infrapopliteal Disease n (%)		12(24.5)	10(20.4)	16(32)	0.407
PNI; Prognostic nutritional index, SFACTO; Superficial femoral artery chronic total occlusion, TASC-II; TransAtlantic Inter-Society Consensus-II, CTO; Chronic total occlusion					

Table 5
ROC curve analysis of PNI, albumin, lymphocyte count, NLR, mGPS and CONUT scores

	AUC	95% CI	p value	Cutoff*	Sensitivity	Specificty
PNI	0,807	0,734 to 0,867	< 0,001	≤ 45.9	83,3	75,0
Albumin	0,782	0,707 to 0,846	< 0,001	< 3,8	76,2	75,0
Lymphocyte	0,726	0,647 to 0,796	< 0,001	≤ 1,7	73,8	67,2
mGPS	0,588	0,504 to 0,668	0,067	> 0	44,1	70,3
CONUT	0,64	0,557 to 0,717	0,004	> 1	75,0	48,4
NLR	0,592	0,508 to 0,672	0,189	< 2,3	52,4	71,9
PNI; Prognostic nutritional index, NLR; neutrophil to lymphocyte ratio, CONUT; controlling nutritional status, mGPS; Modified Glasgow Prognostic Score, TASC-II.						

Figures

Figure 1

ROC curve comparison of PNI, CONUT, mGPS, NLR in prediction of SFA CTO.

Figure 2

Total occlusion of right external iliac, common and superficial femoral arteries

Figure 3

Total occlusion of previously stented distal and stent-free native proximal, mid left superficial femoral artery