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Original Article

Comparison of atherogenic indices and systemic inflammation in peripheral artery disease based on localization

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Abstract

Aim: Peripheral artery disease (PAD) is a heterogeneous atherosclerotic process shaped by segment-specific lipid and inflammatory mechanisms. This study aimed to evaluate the diagnostic and predictive value of these parameters in distinguishing disease localization by comparing atherogenic (AIP, CRI-I/II) and systemic inflammatory (SIRI, AISI, NLR, SII) biomarker profiles between proximal and distal PAD.

Material and Methods: This single-center retrospective cohort study (2020–2025) screened 782 patients with PAD confirmed by angiography. After propensity score matching for key covariates, 150 proximal and 150 distal cases were analyzed. Laboratory data from ±14 days of the imaging date were used to calculate the lipid (AIP, CRI-I, CRI-II) and hematological-inflammatory indices (NLR, SII, SIRI, AISI). Comparative, regression, and ROC analyses were performed.

Results: In distal PAD, AIP, SIRI, AISI, and CRP values were significantly higher, whereas in proximal PAD, CRI-I/II and NLR values were higher. In multivariate analysis, SIRI remained the strongest independent predictor of distal disease. ROC analysis identified SIRI as the most sensitive predictor of distal PAD and CRI-II as the most specific predictor of proximal PAD. Clinically, distal PAD is associated with a high prevalence of diabetes mellitus (DM) and chronic kidney disease (CKD).

Conclusion: This study highlights that readily accessible hematological and lipid-derived indices can distinguish between proximal and distal PAD phenotypes, reflecting different pathophysiological mechanisms. This study aimed to integrate these inexpensive biomarkers into clinical assessment to improve early risk classification, guide phenotype-specific treatment, support personalized treatment strategies, and ultimately improve clinical decision-making in patients with PAD.

Keywords: Peripheral artery disease, atherogenic index of plasma, castelli risk index, systemic inflammation response index, aggregate index of systemic inflammation

INTRODUCTION

Peripheral artery disease (PAD) is a biologically heterogeneous syndrome that ranges from intermittent claudication to chronic limb-threatening ischemia [1]. It affects more than 200 million people worldwide [2]. The pathophysiology of the disease cannot be explained solely by lipid accumulation; it is a complex process involving lipid metabolism disorders, chronic low-grade inflammation, and endothelial dysfunction [3]. The disease exhibits different phenotypes based on its anatomical distribution, which is important for risk classification and the personalization of treatment strategies. Although current guidelines and classification schemes such as the Global Vascular Guidelines [4-7] and GLASS [8] aim to incorporate the heterogeneity of the disease into clinical 2 decision-making processes, the role of phenotype-specific biomarkers in clinical practice remains unclear [4].

Anatomical distribution significantly influences disease phenotype: proximal arterial lesions (aortoiliac and femoropopliteal

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segments) are generally associated with LDL-mediated classical macroatherosclerosis and hypercholesterolemia, whereas distal (infrapopliteal) disease is more closely related to metabolic disorders such as microvascular dysfunction, chronic inflammation, insulin resistance, and prothrombotic tendency [9]. Distal PAD frequently occurs in the presence of diabetes mellitus (DM) and chronic kidney disease (CKD), presents with widespread and multilevel stenosis, and carries a higher risk of amputation [10]. This biological dichotomy suggests that disease phenotypes develop through different lipid and inflammatory mechanisms.

Atherogenic indices are accessible biomarkers that reflect different aspects of lipid metabolism. The atherogenic index of plasma (AIP) indirectly indicates the presence of low-density lipoprotein cholesterol (LDL-C) by jointly evaluating triglyceride (TG) load and high-density lipoprotein cholesterol (HDL-C) levels, which are associated with microvascular atherothrombotic processes [11,12]. In contrast, the Castelli Risk Indices (CRI-I and CRI-II) are more closely related to macrovascular atherosclerotic plaque accumulation [12,13]. Similarly, systemic inflammatory indices, such as The Systemic Immune-Inflammation Index (SII), Systemic Inflammation Response Index (SIRI), and Aggregate Index of Systemic Inflammation (AISI), provide a comprehensive indicator of the vascular inflammatory burden by integrating neutrophil, monocyte, and platelet components [14]. Although studies showing the relationship between these lipid and inflammatory markers and PAD severity and prognosis are increasing, comparative analyses based on anatomical phenotypes are limited [15].

This study tested the hypothesis that anatomical phenotypes of PAD are associated with distinct biochemical and inflammatory profiles. Therapeutic patterns between proximal and distal PAD phenotypes, along with the differing profiles of systemic inflammatory and atherogenic indices, and their diagnostic and predictive values were examined in detail. In this respect, this study overcomes the limitation of considering PAD as a single entity and contributes to the literature by examining both lipid and inflammation axes in a localization-based (proximal vs. distal) holistic framework in a propensity score matching (PSM)-balanced cohort. This study aimed to reveal phenotypic differences using simple, noninvasive blood tests. Thus, it offers an innovative and applicable approach that could directly contribute to clinical practice in terms of early diagnosis, risk classification, and personalized treatment strategies.

MATERIAL AND METHODS

Study Design, Patient Selection, Data Sources, and Ethical Approval

This single-center, retrospective, observational study was analytically designed using the PSM method. The study included patients diagnosed with PAD who were followed up or treated at a tertiary referral cardiovascular surgery center between January 2020 and January 2025. This study was conducted in accordance with the principles of the Helsinki Declaration. Ethical approval for the study was obtained from the Ethics Committee No. 1 of Ankara Bilkent City Hospital (Approval No: 1-25-1442; 2 July 2025) and reported in accordance with the STROBE guidelines [16]. Owing to the retrospective design of the study, no additional informed consent was obtained, and all data were anonymized.

The study population consisted of patients diagnosed with PAD who were followed-up or treated at the clinic during the specified period. All clinical, laboratory, and imaging data were obtained from the hospital's electronic medical record system at the tertiary referral cardiovascular surgery center. Diagnosis was determined based on diagnostic codes, clinical data, and imaging results from the hospital information management system (HIMS). The initial patient pool was identified through automated electronic screening without manual intervention using the codes (n=1062), "Peripheral Arterial Disease" (ICD-10 code: I70.2), and related imaging or surgical procedure codes. No manual filtering was applied at this stage to minimize selection bias. Surgical and endovascular procedure records, ICD-10 codes, surgical notes, anesthesia records, and intervention reports were used as the primary data sources during data collection. The inclusion criteria were as follows: age ≥ 18 years; symptomatic PAD with ≥50% lesion detected in the lower extremities, confirmed by Doppler ultrasound, CT angiography, or DSA; fasting lipid profile and complete blood count within 3 months prior to imaging; and a stable antilipidemic treatment regimen for the last ≥90 days or not having used it at all. The exclusion criteria included non-atherosclerotic arterial pathology, active infection or inflammatory disease, malignancy, immunosuppressive therapy, dialysis dependence, and changes in lipid-lowering agents within the last 90 days.

After applying these criteria, 782 patients were eligible for analysis. Patients were divided into two groups based on the distribution of suprapopliteal and infrapopliteal disease according to the anatomical location of the most distal significant lesion detected by angiography.

- **Suprapopliteal group (n=375):** ≥50% stenosis at the aorto-iliac or femoropopliteal level but no significant lesion at the below-knee level.
- **Infrapopliteal group (n=407):** ≥50% stenosis at the tibial-peroneal or pedal level but no significant lesion in the proximal segments.

Coding was performed blindly by two researchers based on Doppler ultrasound, CT angiography, or DSA reports, and disagreements were resolved by a third researcher. PSM was applied to reduce selection bias, and variables, such as age, sex, BMI, hypertension (HT), diabetes, and smoking, were included in the model. Matching was performed using the 1:1 nearest-

neighbor method and a caliper 4 width of 0.2 standard deviation (SD). A total of 150 patients were selected from each group, forming the original cohort of 300 patients. Intergroup balance was verified using the standardized mean difference (SMD) criterion of <0.1. PSM achieved adequate intergroup balance across all baseline variables (standardized mean difference<0.1) (Supplementary Table S1). The study design, sample flow, and selection criteria are presented in Figure 1.

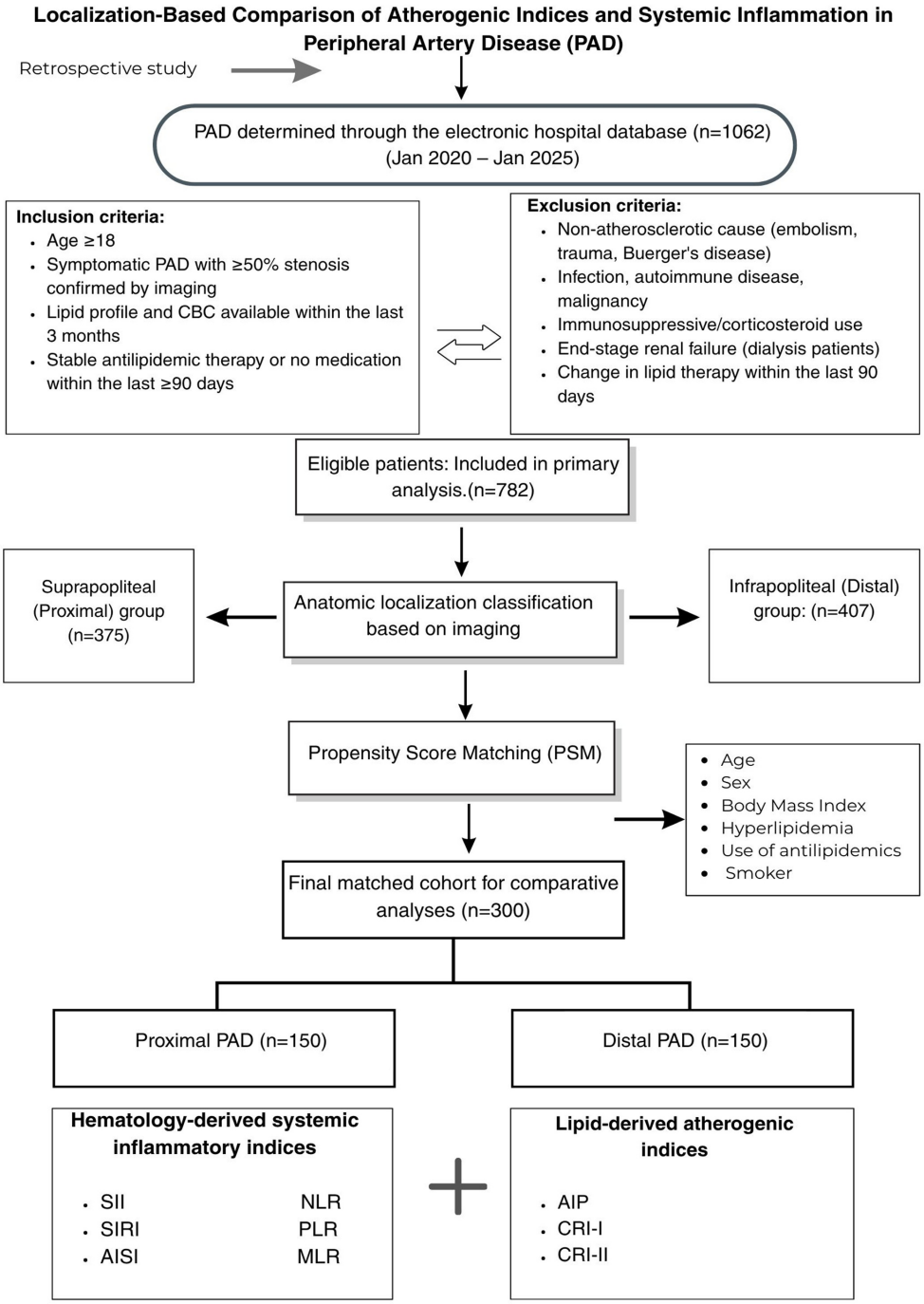

Figure 1. Flowchart of patient selection and study design for localization-based comparisons of atherogenic and inflammatory indices in PAD
Abbreviations: PAD: Peripheral Artery Disease; SII: Systemic Immune-Inflammation Index; SIRI: Systemic Inflammation Response Index; AISI: Aggregate Index of Systemic Inflammation; NLR: Neutrophil-to-Lymphocyte Ratio; PLR: Platelet-to-Lymphocyte Ratio; MLR: Monocyte-to-Lymphocyte Ratio; AIP: Atherogenic Index of Plasma; CRI-I: Castelli Risk Index I; CRI-II: Castelli Risk Index II

Table 1. Baseline demographic and clinical characteristics of patients with proximal and distal peripheral artery disease

Patient Characteristics	Proximal PAD (n=150)		Distal PAD (n=150)		p
	Mean±SD	Median	Mean±SD	Median	
Age	56.8±14.5	59.5	57.8±14.4	60.0	0.533
Sex					
Male	98	65.33%	110	73.33%	0.133
Female	52	34.67%	40	26.67%	0.156
Weight	79.3±11.4	77.6	79.2±11.4	78.0	0.981
BMI	28.0±4.8	27.1	28.2±5.2	26.9	0.749
HT	41	27.33%	33	22.00%	0.382
DM	19	12.67%	33	22.00%	0.033
HL	42	28.00%	36	24.00%	0.278
CAD	21	14.00%	11	7.33%	0.061
CKD	9	6.00%	16	10.67%	0.144
COPD	12	8.00%	10	6.67%	0.658
Smoker	37	24.67%	32	21.33%	0.493

PAD: Peripheral artery disease; SD: Standard deviation; BMI: Body mass index; HT: Hypertension; DM: Diabetes mellitus; CAD: Coronary artery disease; COPD: Chronic obstructive pulmonary disease; CKD: Chronic kidney disease

Laboratory Analyses and Index Calculations

The index date was defined as the day on which biochemical sampling was performed, and laboratory and imaging data were analyzed within a ±14-day time window. Only postoperative measurements ≥30 days were considered for patients who underwent revascularization. All biochemical data were obtained using standard analysis methods in the hospital's central laboratory as part of the routine clinical practice.

Nine different atherogenic and systemic inflammatory indices were calculated for patients in the matched cohort using lipid profiles [total cholesterol (TC), HDL-C, LDL-C, and TG] and complete blood count (CBC) parameters [neutrophils, lymphocytes, monocytes, and platelets] obtained from fasting blood samples via HIMS. The calculated indices were used for localization-based comparative analyses between the PAD groups. These indices and their formulas are shown in Figure 2.

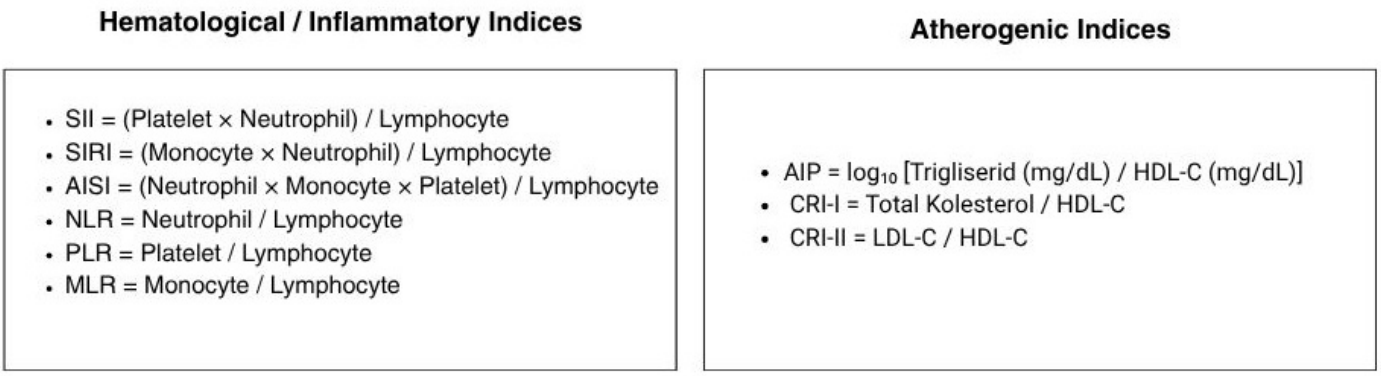

Figure 2. Formulas of hematology-derived systemic inflammatory indices and lipid-derived atherogenic indices used in this study.
Abbreviations: SII: Systemic Immune-Inflammation Index; SIRI: Systemic Inflammation Response Index; AISI: Aggregate Index of Systemic Inflammation; NLR: Neutrophil-to-Lymphocyte Ratio; PLR: Platelet- 11 to-Lymphocyte Ratio; MLR: Monocyte-to-Lymphocyte Ratio; AIP: Atherogenic Index of Plasma; CRI-I: Castelli Risk Index I; CRI-II: Castelli Risk Index II

Treatment Strategies (Descriptive) and Study Outcomes

Treatment types were classified into two main groups: medical and surgical. The revascularization strategy was evaluated under three subheadings: endovascular intervention alone, surgical revascularization alone, and surgical plus endovascular (hybrid/staged) approaches. Since all patients received standard medical treatment according to current guidelines, the analysis was based on the presence and type of revascularization; no duplicate categories such as "medical + surgical" were created.

The primary endpoint of the study was to determine the relationship between disease localization and biomarker profiles (AIP, CRI-I/II, NLR, PLR, SII, SIRI, AISI, and CRP) and evaluate the performance of these markers in distinguishing anatomical phenotypes. The secondary endpoints included the type and frequency of revascularization and the need for reintervention.

Statistical Analysis

In this study, the normality of continuous variables was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. The Independent Samples t-test was used for normally distributed variables, and the Mann-Whitney U test was used for non-normally distributed variables. Categorical variables were expressed as numbers and percentages (%) and were compared using the chi-square test or Fisher's exact test. Multivariate logistic regression analysis was performed to identify independent predictors of the distal (infrapopliteal) phenotype, and model calibration was evaluated using the Hosmer–Lemeshow goodness-of-fit test. Receiver Operating Characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of each index in distinguishing infrapopliteal from suprapopliteal PAD. The area under the curve (AUC) and 95% confidence interval (CI) were calculated for each. The optimal cutoff value for each significant index was determined using the Youden index (J=sensitivity + specificity–1). In all analyses, a two-tailed p-value of <0.05 was considered statistically significant.

SPSS the Statistical Package for the Social Sciences (SPSS) version 27.0 (IBM Corp., Armonk, NY, USA). Microsoft® Excel® Microsoft 365 (Version 2503 Build 16.0.18623.20116) was used for tables, Microsoft Visio Professional 2019 was used for graphs and images, and Canva Pro was used for the flowcharts.

RESULTS

After matching, the PAD cases included in the study were divided into two groups based on lesion location: proximal (suprapopliteal) (n=150) and distal (infrapopliteal) (n=150) and compared in terms of basic demographic and clinical characteristics. The basic demographic and clinical characteristics of the groups are shown in Table 1. The age, body weight, and BMI distributions were similar. Although the male ratio was higher in both groups in terms of sex distribution, this difference did not reach statistical significance between the groups (p=0.133). The most common comorbid condition was HT, which was observed at a similar frequency in both groups ($p>0.05$). In contrast, the prevalence of DM was significantly higher in the distal PAH group than in the proximal group (p=0.033). The groups showed similar characteristics in terms of other comorbidities (all $p>0.05$).

Significant differences were observed between the groups in terms of treatment and pharmacological profiles (Table 2). The revascularization rates (especially surgical revascularization) were significantly higher in the proximal PAD group than in the distal group (48.7% and 16.7%, respectively; $p<0.001$), whereas medical treatment alone (80.7%) was more common in patients with distal PAD. Looking at the revascularization subtypes, surgical intervention was 26.0% in the proximal group and 3.3% of the proximal and distal groups, respectively ($p<0.001$). The endovascular and hybrid rates were lower, and the differences between the phenotypes were limited. Endovascular interventions were performed in 16.7% and 12.0% of patients, whereas hybrid approaches were used in 6.0% and 1.3% of patients. The need for reintervention was significantly higher in the proximal phenotype group (12.7% vs. 4.0%; p=0.007). Antilipidemic drug use was similar between the groups (p=0.450), and no significant difference was found in the distribution of antilipidemic drug types (P=0.881). Anticoagulation for PAD indication (10.7% vs. 3.3%; p=0.033) and cilostazol use for symptom control were significantly higher in the distal phenotype group (24.7% vs. 10.7%; p=0.001).

Comparative analyses of the hematological, inflammatory, and atherogenic profiles revealed significant differences between the proximal and distal PAD phenotypes (Table 3). Hematologically, lymphocyte counts were lower in patients with distal PAD ($p<0.001$), whereas platelet counts were slightly higher in patients with proximal PAD (p=0.017). Furthermore, in the distal PAD group, the systemic inflammation markers SIRI, AISI, NLR, and monocyte-to-lymphocyte ratio (MLR) were significantly higher than those in the proximal PAD group (all $p<0.05$). The SII tended to increase in the distal group but did not reach statistical significance (p=0.069). Among the lipid-derived atherogenic indices, the AIP was significantly higher in the distal PAD group (p=0.016), whereas the CRI-I and CRIII were higher in the proximal PAD group ($p<0.001$ and p=0.043, respectively). The levels of biochemical markers, including CRP, creatinine, and lactate dehydrogenase (LDH), were also significantly higher in the distal PAD group.

In the multivariate logistic regression model comparing proximal and distal PAD phenotypes, inflammatory indices, particularly SIRI, emerged as the strongest independent predictors of distal PAD (Table 4). In the univariate analysis, both NLR and SIRI were significantly associated with the distal phenotype, whereas AISI and SII showed weaker correlations.

Among lipid-derived markers, CRI-II showed an inverse relationship with distal localization, consistent with its strong association with proximal PAD; however, AIP demonstrated limited discriminatory power. After adjusting for clinical covariates (age, sex, BMI, diabetes, HT, CAD, and CRI), the SIRI remained the only statistically significant independent predictor. The overall multivariate model showed good calibration according to the Hosmer–Lemeshow goodness-of-fit test (χ^2=13.381, df=8, p=0.09), indicating adequate agreement between the predicted and observed outcomes.

Table 2. Baseline demographic and clinical characteristics of patients with proximal and distal peripheral artery disease

Therapeutic Profiles	Proximal PAD (n=150)		Distal PAD (n=150)		p
	n	%	n	%	
Type of treatment					
Not receiving treatment	6	4.0%	4	2.7%	< 0.001
Medical treatment	71	47.3%	121	80.7%	
Revascularization	73	48.7%	25	16.7%	
Type of revascularization				0.0%	
Surgical	39	26.0%	5	3.3%	< 0.001
Endovascular	25	16.7%	18	12.0%	
Hybrid	9	6.0%	2	1.3%	
Need for reintervention	19	12.7%	6	4.0%	0.007
Use of antilipidemics	48	32.0%	42	28.0%	0.450
Antilipidemic drug type				0.0%	
Atorvastatin	23	15.3%	16	10.7%	
Rosuvastatin	4	2.7%	7	4.7%	
Pitavastatin	4	2.7%	2	1.3%	
Statin + Ezetimibe	7	4.7%	5	3.3%	0.881
Gemfibrozil	3	2.0%	3	2.0%	
Fenofibrate	1	0.7%	2	1.3%	
Statin + Fenofibrate	3	2.0%	4	2.7%	
Statin + Gemfibrozil	3	2.0%	3	2.0%	
Use of antiplatelet agents				0.0%	
ASA	111	74.0%	97	64.7%	0.215
Clopidogrel	18	12.0%	27	18.0%	
Dual antiplatelet	15	10.0%	22	14.7%	
Reason for anticoagulant use				0.0%	
Due to PAD	5	3.3%	16	10.7%	0.033
Non-PAD use	11	7.3%	7	4.7%	
Anticoagulant type				0.0%	
NOAC	10	6.7%	12	8.0%	0.139
Warfarin	2	1.3%	9	6.0%	
LMWH	4	2.7%	2	1.3%	
Cilostazol use	16	10.7%	37	24.7%	0.001

PAD: peripheral artery disease; ASA: acetylsalicylic acid; NOAC: non–vitamin K oral anticoagulant. LMWH: low molecular weight heparin; Dual antiplatelet: combined use of ASA and clopidogrel. Revascularization=surgical or endovascular restoration of blood flow. Hybrid: combined surgical and endovascular approach. Cilostazol: phosphodiesterase-3 (PDE-3) inhibitor used for intermittent claudication

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Table 3. Comparison of hematological, inflammatory, and atherogenic profiles between proximal and distal peripheral artery disease (PAD) phenotypes

Basic and derived blood parameters	Proximal PAD (n=150)		Distal PAD (n=150)		p
	Mean±SD	Median	Mean±SD	Median	
Basic hematological parameters					
WBC	7.74±2.12	7.30	7.73±1.90	7.58	0.670
HGB	12.57±2.47	12.90	12.29±2.38	12.75	0.240
HCT	38.29±7.83	39.70	38.11±7.69	39.30	0.820
PLT	251.53±85.88	226.00	238.73±91.25	208.00	0.017
Neutrophil	5.17±1.94	4.40	5.35±1.53	5.58	0.108
Lymphocyte	1.66±0.22	1.63	1.49±0.18	1.48	0.000
Monocyte	0.79±0.16	0.81	0.81±0.15	0.83	0.205
Hematology-derived systemic inflammatory indices					
AISI	629.80±363.84	539.81	703.60±372.21	618.76	0.033
SII	782.67±374.00	686.10	862.91±403.85	786.31	0.069
SIRI	2.56±1.31	2.29	3.00±1.25	2.78	0.000
NLR	3.18±1.26	2.83	3.66±1.19	3.53	0.000
PLR	153.02±51.53	143.17	162.04±62.65	142.23	0.419
MLR	0.49±0.13	0.47	0.56±0.14	0.55	0.000
Lipid-derived atherogenic indices					
AIP	0.33±0.21	0.27	0.35±0.21	0.33	0.016
CRI-I	5.87±0.73	5.85	5.69±1.71	5.37	0.000
CRI-II	4.19±1.79	3.81	3.79±1.77	3.45	0.043
Biochemical parameters					
Urea	37.94±17.33	35.75	40.83±18.04	38.10	0.160
Creatinine	1.04±0.27	1.03	1.12±0.34	1.06	0.017
Sodium	139.69±2.93	140.00	139.56±3.04	140.00	0.702
Potassium	4.56±0.79	4.50	4.53±0.78	4.47	0.799
LDH	216.71±84.23	191.50	268.80±100.01	263.00	0.000
AST	28.43±12.69	27.00	30.06±11.81	29.00	0.077
ALT	34.45±18.86	34.00	38.44±27.54	34.20	0.436
CRP	5.24±11.24	1.86	10.98±24.24	3.30	0.001

PAD: Peripheral Artery Disease; WBC: White Blood Cell; HGB: Hemoglobin; HCT: Hematocrit; PLT: Platelet; AISI: Aggregate Index of Systemic Inflammation; SII: Systemic Immune-Inflammation Index; SIRI: Systemic Inflammation Response Index; NLR: Neutrophil-to-Lymphocyte Ratio; MLR: Monocyte-to-Lymphocyte Ratio; PLR: Platelet-to-Lymphocyte Ratio; AIP: Atherogenic Index of Plasma; CRI-I: Castelli Risk Index-I; CRI-II: Castelli Risk Index-II

Table 4. Results of univariate and multivariate logistic regression analysis: biomarkers predicting PAD

Variables	Proximal PAD (n=150)				Distal PAD (n=150)			
	OR	95%	C.I	p	OR	95%	C.I	p
Demographic characteristics								
Age	1.005	0.989	1.021	0.493				
Sex	1.459	0.890	2.391	0.134				
BMI	1.010	0.965	1.057	0.672				
DM	0.514	0.277	0.953	0.035	0.552	0.293	1.038	0.065
HT	1.334	0.787	2.260	0.285				
CRI	0.468	0.203	1.078	0.075	0.478	0.202	1.129	0.092
Smoke	1.207	0.704	2.070	0.493				
Hematology-derived systemic inflammatory indices								
AISI	1.001	1.000	1.001	0.085				
SII	1.001	1.000	1.001	0.077				
SIRI	1.315	1.091	1.585	0.004	1.282	1.058	1.554	0.011
NLR	1.391	1.145	1.689	0.001				
MLR	44.795	7.401	271.124	0.000				
Lipid-derived atherogenic indices								
AIP	1.384	0.471	4.071	0.555				
CRI-I	0.887	0.727	1.084	0.242				
CRI-II	0.879	0.772	1.002	0.053	0.892	0.781	1.019	0.093

BMI: Body mass index; HT: Hypertension; DM: Diabetes mellitus; CKD: Chronic kidney disease; AISI: Aggregate Index of Systemic Inflammation; SII: Systemic Immune-Inflammation Index; SIRI: Systemic Inflammation Response Index; NLR: Neutrophil-to-Lymphocyte Ratio; MLR: Monocyte-to-Lymphocyte Ratio; AIP: Atherogenic Index of Plasma; CRI-I: Castelli Risk Index-I; CRI-II: Castelli Risk Index-II. Note. Model calibration was acceptable (Hosmer–Lemeshow test: p=0.63)

Table 5. Diagnostic performance of selected biomarkers based on ROC analysis for predicting the distal (infrapopliteal) peripheral artery disease phenotype

Variables	AUC	p	95%	CI	Cut-off	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
AISI	0.571	0.033	0.51	0.64	422.24	79.33%	36.67%	55.61%	63.95%
SIRI	0.619	0.000	0.555	0.683	1.93	80.67%	44.00%	59.02%	69.47%
NLR	0.633	0.000	0.570	0.697	2.630	81.33%	89.33%	93.85%	70.53%
AIP	0.581	0.016	0.515	0.646	0.335	51.05%	69.59%	61.86%	59.54%
CRI-1^{-1}	0.568	0.033	0.503	0.632	3.420	50.67%	34.67%	43.68%	41.27%
CRI-2^{-1}	0.675	0.000	0.613	0.737	5.595	15.33%	82.67%	46.94%	49.40%

NLR: Neutrophil-to-Lymphocyte Ratio; SII: Systemic Immune-Inflammation Index; SIRI: Systemic Inflammation Response Index; AISI: Aggregate Index of Systemic Inflammation; AIP: Atherogenic Index of Plasma; CRI-1^{-1}: Castelli Risk Index-I (reciprocal transformation); CRI-II: Castelli Risk Index-II (reciprocal transformation). Note: The positive condition is coded as the distal (infrapopliteal) phenotype. To ensure directional consistency, the CRI-I and CRI-II were used reciprocally (HDL-C/TC, HDL-C/LDL-C) in the ROC analysis; the reciprocal transformation was uniform and did not affect discriminative power. Therefore, the discrimination criterion mathematically satisfies the equation AUC(CRI) + AUC(CRI^{-1})=1

Receiver operating characteristic (ROC) curve analysis was performed to evaluate the discriminatory performance of the hematological, inflammatory, and atherogenic indices in predicting the distal PAD phenotype (Table 5). SIRI (AUC=0.619, p<0.001, cut-off=1.93) demonstrated a strong "exclusion" capacity for distal disease, with high sensitivity (80.7%) and low specificity (44.0%). NLR showed a balanced sensitivity-specificity profile (81.33% and 89.33%, respectively), demonstrating a similar and slightly higher discriminatory capacity (AUC=0.633) than that of PLR. In contrast, lipid derived indices showed a more selective but complementary diagnostic pattern to that of hematology derived indices. As distal PAD was defined as an event in the ROC analysis, indices showing a negative correlation with this phenotype (e.g., CRI-I and CRI-II) were directionally calculated as AUC<0.5. This finding reflects the biological orientation of CRI-I and CRI-II toward proximal LDL-induced macrovascular atherosclerosis rather than a lack of discriminatory ability. Therefore, reciprocal transformation (CRI-I^{-1}=HDL-C/TC; CRI-II^{-1}=HDL-C/LDL-C) was applied to methodologically correct the statistical values and make them interpretable. After transformation, CRI-II had the highest AUC value among the atherogenic parameters in favor of proximal PAD (AUC=0.675). CRI-I also showed weak performance in favor of the proximal phenotype (AUC=0.568). The ROC curves illustrating the discriminatory performance of the hematology-derived inflammatory indices and lipid-derived atherogenic indices for distal PAD are presented in Figure 3A and 3B, respectively.

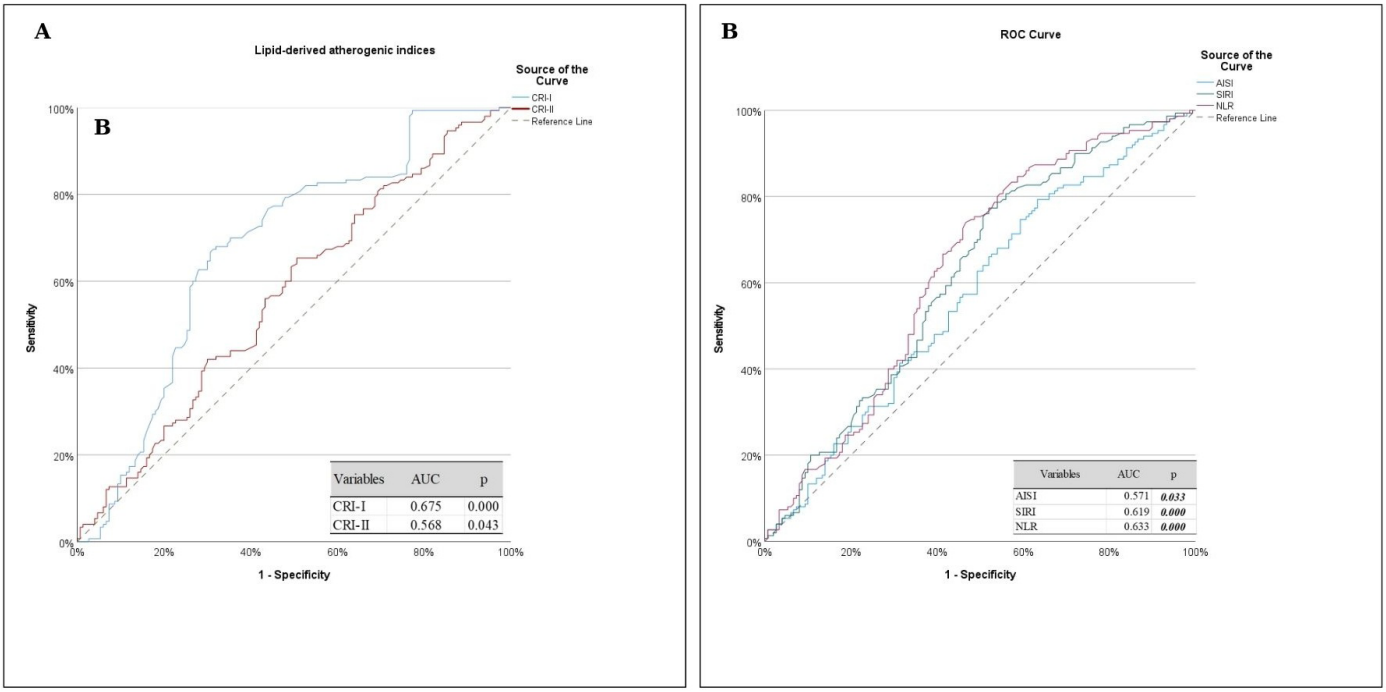

Figure 3A–B. Receiver operating characteristic (ROC) curves of hematology- and lipid-derived indices for predicting the distal (infrapopliteal) phenotype.
(A) Hematology-derived systemic inflammatory indices were evaluated for discriminatory ability. (B) Lipid-derived atherogenic indices CRI-I and CRI-II were evaluated. Abbreviations: AISI: Aggregate Index of Systemic Inflammation; SIRI: Systemic Inflammation Response Index; NLR: Neutrophil-to-Lymphocyte Ratio; CRI-I: Castelli Risk Index I; CRI-II : Castelli Risk Index II; AUC: Area Under the Curve Note: In ROC analysis, the positive condition was defined as the distal (infrapopliteal) phenotype. As CRI-I (TC/HDL-C) and CRI-II (LDL-C/HDL-C) values increase with proximal atherosclerotic disease, the original scales produced AUC values<0.5, distinguishing distal involvement. This reversal reflects the orientation of the indices rather than a decrease in discriminatory power. Reciprocal forms were analyzed to ensure directional consistency and comparability. (CRI-I^{-1}=HDL-C/TC; CRI-II^{-1}=HDL-C/LDLC). This transformation preserves the ranking and does not alter discriminatory performance

DISCUSSION

The findings of this study indicated that lipid profiles in PAD follow a segment-specific pattern. The marked elevation of AIP in the distal phenotype supports the triglyceride/HDL imbalance [17] and the contribution of dysfunctional HDL particles to endothelial damage and tissue hypoperfusion at the microvascular level [18] in the context of DM and CKD. This indicates a microvascular metabolic disorder characterized by insulin resistance and small dense LDL particles. In the proximal phenotype, elevated CRI-I and CRI-II reflect the macrovascular atherosclerotic process based on LDL accumulation. [19]. The

lack of significance of HDL levels in this group indicates that the LDL-dominant lipid load was predominant. Consequently, proximal disease is associated with cholesterol-rich apoB-lipoproteins and plaque-related inflammation, whereas distal disease is characterized by TG and inflammation-focused metabolic dysfunction at the microvascular level [20]. From a clinical perspective, the inverse ROC orientation of CRI-I and CRI-II further supports their association with proximal LDL-driven macrovascular atherosclerosis. The need for reciprocal transformation in ROC analysis does not indicate statistical weakness; rather, it highlights the opposing biological behavior of lipid-derived indices compared with inflammation-based markers in PAD phenotyping.

Our study demonstrated that distal PAD reflects a more complex pathophysiological process along the inflammatory axis. Significant increases in SIRI, AISI, NLR, CRP, and LDH levels indicate that metabolic and inflammatory stress are predominant in the distal phenotype. This suggests that distal disease cannot be explained by a simple inflammatory response alone; rather, it represents a thromboinflammatory process involving endothelial damage, monocyte-mediated atherogenesis and platelet activation. In particular, the marked elevation of SIRI (monocyte component) and AISI (monocyte + platelet component) levels was the strongest indicator of thrombo-inflammatory activity in this phenotype. In contrast, the fact that SII only showed a tendency to increase without reaching significance indicates that the platelet/lymphocyte ratio alone does not have sufficient discriminatory power and that the monocyte component (SIRI/AISI) makes a critical contribution to defining the inflammatory process. **Consistent with this observation, previous studies have shown that inflammation-derived ratios such as the neutrophil-to-lymphocyte ratio can predict endovascular treatment outcomes in patients with peripheral artery disease, further supporting the clinical relevance of hematology-derived indices in vascular phenotyping [21].

The differences in biomarkers between proximal and distal PAD were strongly correlated with the clinical patterns reported in this study and the literature. The increased prevalence of DM and CKD in the distal phenotype, accompanied by high AIP, SIRI, AISI, and NLR levels and an increased amputation rate, is biologically consistent [21,22]. Current clinical guidelines primarily guide therapeutic decision making in peripheral artery disease based on anatomical distribution, symptom severity, and established clinical risk factors [5-7]. However, this approach may not fully reflect the biological heterogeneity observed among patients within the same anatomical categories. Biomarker-based phenotyping offers an additional layer of risk stratification by distinguishing lipid-dominant and thrombo-inflammatory profiles beyond anatomy. In this context, high thromboinflammatory indices, such as SIRI and AISI, in distal PAD may support intensified strategies targeting inflammation, thrombosis, and metabolic dysfunction, in addition to standard medical therapy, while the predominance of LDL-focused indices, such as CRI-I and CRI-II, in proximal PAD provides a biological rationale for more aggressive lipid-lowering approaches. These findings suggest that phenotype specific biomarkers can complement, rather than replace, guideline-driven treatment by increasing biological sensitivity. Furthermore, the marked elevation of CRP in the distal region supports an inflammatory background that is consistent with microvascular tissue damage and ulcer burden [23]. The study's finding of a significant association between DM and distal PAD supports the notion that diabetes-related microvascular damage accelerates atherosclerosis in the peripheral vascular beds. Furthermore, diabetes-related microcirculatory dysfunction, medial calcification, and ulcer tendency reinforce the inflammatory basis for distal disease [24]. However, the similar prevalence of CKD in both groups in our study may be due to the similar cardiometabolic risk profile of the population or the balanced distribution of CKD stages in the two groups. Furthermore, while proximal PAD reflects macrovascular atherosclerosis focused on LDL and total cholesterol, higher revascularization and reintervention rates are associated with the suitability of these segments for surgical and endovascular interventions [25,26]. This "cross-pattern" AIP↑ distally / CRI↑ proximally; SIRI/AISI↑ distally / NLR↑ proximally has been demonstrated based on localization within the same cohort, suggesting a biological basis for phenotype-specific risk stratification and personalized treatment approaches.

Treatment distribution also reflects these biomarker differences: the prominence of surgical and hybrid revascularization in proximal PAD demonstrates a guideline-compliant macrovascular approach [5-7], while the management of distal PAD predominantly with medical therapy is related to the technical difficulties and limited long-term success of infrapopliteal lesions [5,7]. The more frequent use of cilostazol and anticoagulants in the distal phenotype [27] reflects the clinical manifestations of an increased thromboinflammatory burden. These treatment differences emphasize the translational relevance of the observed biomarker profiles, suggesting that pharmacological modulation of inflammation and platelet activity by agents such as cilostazol and anticoagulants may be particularly beneficial in the distal thromboinflammatory phenotype of PAD. In this context, adjuvant strategies targeting triglyceride/HDL balance and inflammatory activity (e.g., fibrates, omega-3 ethyl esters, and colchicine) in distal PAH and LDL-focused intensive lipid-lowering therapies (statins, ezetimibe, PCSK9 inhibitors) in proximal PAH are emerging as rational approaches. Furthermore, tailoring follow-up protocols according to phenotype may be advisable; close monitoring for restenosis/reocclusion in proximal patients and limb salvage strategies focusing on wound care, WIfI scoring, and pedal arch integrity in distal patients may increase clinical benefits.

In summary, this study identified proximal and distal peripheral artery disease as biologically distinct phenotypes characterized by divergent lipid-derived and inflammation-derived index profiles. Within a propensity score–matched cohort, readily available biomarkers such as AIP, CRI-I/II, SIRI, AISI, and NLR capture this heterogeneity beyond anatomical localization alone. Clinically, these indices are not substitutes for guideline-based classification but may serve as practical adjuncts to refine biological risk stratification and inform phenotype-oriented discussions of treatment priorities, including LDLfocused strategies in proximal PAD and thrombo-inflammatory or metabolic targeting in distal diseases.

Limitations

This study had some limitations. Although the PSM method was used to reduce potential bias, the design of the retrospective and single-center study makes it unlikely that the residual effects of unmeasured or unrecorded confounding variables can be completely eliminated. However, the lack of data on drugs such as statins and antidiabetics has created a potential limitation, particularly in the interpretation of inflammatory indices. Statins are known to exert pleiotropic anti-inflammatory effects independent of lipid lowering [28], whereas antidiabetic therapies may modulate systemic inflammation through improved glycemic control and insulin sensitivity [29]. Therefore, the absence of detailed treatment-related data may have influenced the absolute levels of inflammation-derived indices, such as SIRI, AISI, and NLR. Nevertheless, as treatment patterns were relatively balanced between groups after propensity score matching, this limitation is more likely to affect the magnitude rather than the direction of the observed interphenotypic differences. The cross-sectional nature of the study does not allow for the examination of the long-term prognostic effects (e.g., mortality and risk of major amputation) of the evaluated biomarkers. In addition, the retrospective design did not permit standardized pre- and post-treatment assessments of the evaluated indices. Laboratory measurements were obtained within a predefined time window around imaging rather than at serial time points after medical, endovascular, or surgical interventions. Consequently, although these biomarkers appear useful for phenotypic characterization, their potential role as follow-up parameters or indicators of treatment response cannot be determined from the present study. Furthermore, the absence of advanced lipid parameters such as ApoB, Lp(a), and residual cholesterol, or detailed distal anatomy indicators (e.g., runoff score, ankle-brachial index), limited the full reflection of lipidomic and morphological heterogeneity in the study. The inclusion of such markers could have allowed for a more refined characterization of atherogenic burden and distal anatomical complexity, potentially strengthening phenotype discrimination. However, the primary aim of this study was to evaluate readily available and low-cost biomarkers applicable to routine clinical practice; thus, the main conclusions regarding localization-based biological patterns remain valid despite the absence of these advanced measurements.

CONCLUSION

This study demonstrates that peripheral artery disease is characterized by distinct localization based biological phenotypes that can be distinguished using simple, readily available hematological and lipid-derived indices. These findings deepen our understanding of the pathophysiological heterogeneity of PAD while reinforcing the potential use and clinical importance of systemic inflammatory and atherogenic indices. Our findings highlight the potential clinical value of integrating low-cost biomarker panels into routine assessments to support early phenotypic risk stratification and individualized management strategies for PAD. Importantly, these markers can complement angiographic assessment by providing a biological context that anatomy alone cannot capture. To validate these observations, investigate their prognostic impact, and determine whether biomarker guided, phenotype-specific therapeutic approaches can improve limb-related and cardiovascular outcomes in PAD patients, prospective, multicenter studies are needed in the future.

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REFERENCES

1. Campia U, Gerhard-Herman M, Piazza G, Goldhaber SZ. Peripheral artery disease: Past, present, and future. Am J Med. 2019;132:1133-41.
2. Horváth L, Németh N, Fehér G, Kívés Z, Endrei D, Boncz I. Epidemiology of peripheral artery disease: Narrative review. Life (Basel). 2022;12:1041.
3. Theofilis P, Sagris M, Oikonomou E, Antonopoulos AS, Siasos G, Tsioufis C, et al. Inflammatory mechanisms contributing to endothelial dysfunction. Biomedicines. 2021;9:781.
4. Conte MS, Bradbury AW, Kolh P, White JV, Dick F, Fitridge R, et al. Global vascular guidelines on the management of chronic limb-threatening ischemia. Eur J Vasc Endovasc Surg. 2019;58:S1-109.e133.

5. Aboyans V, Ricco JB, Bartelink MEL, Björck M, Brodmann M, Cohnert T, et al. 2017 ESC guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the European Society for Vascular Surgery (ESVS). Eur Heart J. 2018;39:763-816.
6. Chakfé N, Diener H, Lejay A, Assadian O, Berard X, Caillon J, et al. Editor's choice – European Society for Vascular Surgery (ESVS) 2020 clinical practice guidelines on the management of vascular graft and endograft infections. Eur J Vasc Endovasc Surg. 2020;59:339-84.
7. Gornik HL, Aronow HD, Goodney PP, Arya S, Brewster LP, Byrd L, et al. 2024 ACC/AHA guideline for the management of lower extremity peripheral artery disease. Circulation. 2024;149:e1313-410.
8. Wijnand JGJ, Zarkowsky D, Wu B, van Haelst STW, Vonken E-JPA, Sorrentino TA, et al. The global limb anatomic staging system (GLASS) for CLTI: Improving inter-observer agreement. J Clin Med. 2021;10:3454.
9. Alghanimi IA, Al-Sharydah AM, Alqutub AA, Zeidan N, Bukhamseen F, Alradhi A, et al. Anatomical distribution patterns of peripheral arterial disease according to patient characteristics: A unicentral cohort study. Vasc Health Risk Manag. 2023;19:447-57.
10. Poledniczek M, Neumayer C, Kopp CW, Schlager O, Gremmel T, Jozkowicz A, et al. Micro- and macrovascular effects of inflammation in peripheral artery disease: Pathophysiology and translational therapeutic approaches. Biomedicines. 2023;11:2284.
11. Płaczkowska S, Sołkiewicz K, Bednarz-Misa I, Kratz EM. Atherogenic plasma index or non-high-density lipoproteins as markers best reflecting age-related high concentrations of small dense low-density lipoproteins. Int J Mol Sci. 2022;23:—.
12. Kim SH, Cho YK, Kim YJ, Jung CH, Lee WJ, Park JY, et al. Association of the atherogenic index of plasma with cardiovascular risk beyond traditional risk factors: A nationwide population-based cohort study. Cardiovasc Diabetol. 2022;21:81.
13. Raaj I, Thalamati M, Gowda MNV, Rao A. The role of the atherogenic index of plasma and Castelli risk indices I and II in cardiovascular disease. Cureus. 2024;16:e74644.
14. Xia Y, Xia C, Wu L, Li Z, Li H, Zhang J. Systemic immune inflammation index (SII), systemic inflammation response index (SIRI) and risk of all-cause mortality and cardiovascular mortality: A 20-year follow-up cohort study. J Clin Med. 2023;12:1128.
15. Anand PK. Lipids, inflammasomes, metabolism and disease. Immunol Rev. 2020;297:108-22.
16. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: Guidelines for reporting observational studies. J Clin Epidemiol. 2008;61:344-49.
17. Hu Y, Liang Y, Li J, Li X, Yu M, Cui W. Correlation between atherogenic index of plasma and cardiovascular disease risk across cardiovascular-kidney-metabolic syndrome stages 0-3: A nationwide prospective cohort study. Cardiovasc Diabetol. 2025;24:40.
18. Chiesa ST, Charakida M, McLoughlin E, Nguyen HC, Georgiopoulos G, Motran L, et al. Elevated high-density lipoprotein in adolescents with type 1 diabetes is associated with endothelial dysfunction in the presence of systemic inflammation. Eur Heart J. 2019;40:3559-66.
19. Aday AW, Lawler PR, Cook NR, Ridker PM, Mora S, Pradhan AD. Lipoprotein particle profiles, standard lipids, and peripheral artery disease incidence. Circulation. 2018;138:2330-41.
20. Galimberti F, Casula M, Olmastroni E. Apolipoprotein B compared with low-density lipoprotein cholesterol in the atherosclerotic cardiovascular diseases risk assessment. Pharmacol Res. 2023;195:106873.
21. Uzeyir Y, Mehmet Fatih K, Yusuf T, Mustafa Mert O. Prognostic significance of neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios in endovascular treatment success and recurrence in peripheral arterial disease. Turk J Vasc Surg. 2025;34:147-54.
22. Sun Y, Li F, Zhou Y, Liu A, Lin X, Zou Z, et al. Nonlinear association between atherogenic index of plasma and type 2 diabetes mellitus in overweight and obesity patients: Evidence from Chinese medical examination data. Cardiovasc Diabetol. 2024;23:226.
23. Di Stolfo G, Mastroianno M, Pacilli MA, De Luca G, Coli CR, Bevere EML, et al. Role of C-reactive protein as a predictor of early revascularization and mortality in advanced peripheral arterial disease. J Clin Med. 2025;14:815.
24. Alnima T, Meijer RI, Spronk HMH, Warlé M, Cate HT. Diabetes-versus smoking-related thrombo-inflammation in peripheral artery disease. Cardiovasc Diabetol. 2023;22:257.
25. Balling M, Nordestgaard BG, Langsted A, Varbo A, Kamstrup PR, Afzal S. The association between small dense low-density lipoprotein cholesterol and peripheral artery disease: A large-scale cohort study and meta-analysis. Eur J Prev Cardiol. 2025;—.
26. Heffron SP, Ruuth MK, Xia Y, Hernandez G, Äikäs L, Rodriguez C, et al. Low-density lipoprotein aggregation predicts adverse cardiovascular events in peripheral artery disease. Atherosclerosis. 2021;316:53-57.
27. Sohn M, Lim S. The role of cilostazol, a phosphodiesterase-3 inhibitor, in the development of atherosclerosis and vascular biology: A review with meta-analysis. Int J Mol Sci. 2024;25:—.
28. Oesterle A, Laufs U, Liao JK. Pleiotropic effects of statins on the cardiovascular system. Circ Res. 2017;120:229-43.
29. Li D, Zhong J, Zhang Q, Zhang J. Effects of anti-inflammatory therapies on glycemic control in type 2 diabetes mellitus. Front Immunol. 2023;14:1125116.