Kocatepe Tıp Dergisi
Kocatepe Medical Journal
26:28-32/Ocak 2025 Sayısı

ARAŞTIRMA YAZISI / RESEARCH ARTICLE

PERİFERİK ARTER HASTALIĞI OLAN HASTALARDA SİSTEMİK İMMÜN-ENFLAMASYON İNDEKSİNİN MORTALİTE ÜZERİNE ETKİSİ

EFFECT OF SYSTEMIC IMMUNE-INFLAMMATION INDEX ON MORTALITY IN PATIENTS WITH PERIPHERAL ARTERY DISEASE

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ÖZET

AMAÇ: Aterosklerotik hastalıklar arasında koroner arter hastalığı ve serebrovasküler hastalıktan sonra üçüncü sıradaki mortalite ve morbidite nedeni olan periferik arter hastalığı, dünya genelinde önemli bir sağlık sorunudur. Çalışmamız, inflamasyon ve agregasyonun birleşik bir belirteci olan sistemik immün-inflamasyon indeksi ile periferik arter hastalığı olan hastalarda sağkalım arasındaki ilişkiyi araştırmayı amaçlamaktadır.

GEREÇ VE YÖNTEM: Bu retrospektif kohort çalışmasında, 2010-2020 yılları arasında periferik arter hastalığı tanısı konmuş 432 bireyin hasta kayıtları incelenmiştir. Hastaların hemogram testlerindeki trombosit-lenfosit oranlarından yola çıkarak sistemik immün-inflamasyon indeksi hesaplanmış ve bu indeks ile mortalite arasındaki ilişki Kaplan Meier analizi ile değerlendirilmiştir.

BULGULAR: Çalışma bulgularımız, sistemik immün-inflamasyon indeksinin periferik arter hastalığında mortalitenin bağımsız bir belirleyicisi olduğunu ortaya koymuştur. İstatistiksel analizler, yüksek sistemik immün-inflamasyon indeksi değerlerinin (> 854), periferik arter hastalığı ve tip 2 diyabet mellituslu bireylerde artmış mortalite ile ilişkili olduğunu göstermiştir (OR: 1.02, %95 GA: 0.98-1.04, p<0.001).

SONUÇ: Sonuç olarak, sistemik immün-inflamasyon indeksi, periferik arter hastalığı olan hastalarda sağkalımı öngördüren önemli bir faktördür. Bu bulgular, periferik arter hastalığı yönetiminde inflamasyon ve immün yanıtın rolünü daha iyi anlamamıza yardımcı olabilir ve potansiyel tedavi stratejilerinin geliştirilmesine katkı sağlayabilir.

ANAHTAR KELİMELER: Periferik arter hastalığı, Sistemik immün-inflamasyon indeks, Ölüm oranı, Tip 2 diabetes mellitus, Epidemiyoloji.

ABSTRACT

OBJECTIVE: Peripheral artery disease ranks as the third leading cause of death and illness following coronary artery disease and cerebrovascular disease among atherosclerotic conditions, representing a significant health concern worldwide. Our study aims to explore the association between the systemic immune-inflammation index a combined marker of inflammation and aggregation and survival in patients with peripheral artery disease.

MATERIAL AND METHODS: In this retrospective cohort study, we examined the medical records of 432 individuals diagnosed with peripheral artery disease between the years 2010 and 2020. The systemic immune-inflammation index was calculated based on platelet to lymphocyte ratios from the patients' complete blood count tests, and the relationship between this index and mortality was assessed using the Kaplan-Meier survival analysis.

RESULTS: Our findings demonstrate that the systemic immune-inflammation index is an independent predictor of mortality in peripheral artery disease. Statistical analyses have shown that higher values of the systemic immune-inflammation index (> 854), correlate with increased mortality in individuals with peripheral artery disease and type two diabetes mellitus (OR: 1.02, %95 GA: 0.98-1.04, p<0.001).

CONCLUSIONS: In conclusion, the systemic immune-inflammation index is a significant determinant of survival in patients with peripheral artery disease. These results can enhance our understanding of the role of inflammation and immune response in the management of peripheral artery disease and may contribute to developing potential therapeutic strategies.

KEYWORDS: Peripheral Artery Disease, Systemic immune-inflammation index, Mortality, Type 2 diabetes mellitus, Epidemiology.

Geliş Tarihi / Received: 25.02.2024
Kabul Tarihi / Accepted: 07.08.2024
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INTRODUCTION

Peripheral Artery Disease (PAD) is a chronic inflammatory atherosclerotic process that affects blood flow to the extremities, especially the legs, due to atherosclerosis of arteries other than the coronary and cerebral arteries. Perıpheral Artery Dısease (PAH) is a major health problem with high mortality and morbidity rates, affecting approximately 200 million people worldwide (1,2). PAD is the third most common cause of cardiovascular mortality (3). Diabetes Mellitus (DM), Hypertension (HT), Hyperlipidemia (HL), male gender, age, smoking, cardiovascular diseases, metabolic events and inflammatory causes are risk factors (1).

Chronic inflammation plays a role in atherosclerosis of peripheral artery endothelium, and this process involves both the cellular and humoral immune systems (1). In vascular inflammation, lipid accumulation and leukocyte accumulation in the subendothelial region of the vascular wall are characteristic of atherosclerosis (4). Studies in the literature have shown that increased leukocyte count, especially monocytes and neutrophils, are independent predictors of cardiovascular events (5). Changes in the amount of leukocytes in the blood and/or impairment in chemokine-chemokine receptor interactions may affect the further progression of atherosclerosis by changing the number of monocytes and neutrophils. Thus, it is considered that the role of leukocytes in atherosclerosis is important and research on this subject is necessary (5).

In this context, neutrophil, platelet and lymphocyte counts in peripheral blood are used to calculate many indices, including the systemic immune inflammation index (SII) (6). In addition, the prognostic values of many biomarkers such as albumin, C-reactive protein and fibrinogen are used in the Neutrophil-Lymphocyte Ratio (NLR) in PAD. Platelet-Lymphocyte Ratio (PLR) and Monocyte-Lymphocyte Ratio (MLR) are available in the literature (7). Previous studies have shown that SII increases in PAD, but the prognostic value of SII in PAD and its relationship with mortality have not been adequately investigated so far (6). This study was planned to retrospectively evaluate the prognostic value of SII in PAD and its relationship with mortality.

MATERIAL AND METHODS

The Departments of Cardiology at Afyonkarahisar Health Sciences University conducted a retrospective cohort study approved by the Institutional Local Ethics Committee. The study included 528 patients diagnosed with peripheral arterial disease between January 2010 and January 2020 at our clinic. However, 84 patients were excluded due to lack of data or not meeting the inclusion criteria. The study involved the assignment of patients into two groups: deceased (all-cause mortality) (group 1, n:174) and living (group 2, n:258). All patients included in the study were selected from individuals aged over 18 years who presented to the adult cardiology outpatient clinic and underwent conventional peripheral angiography. Demographic data and laboratory findings were extracted from the medical records of all patients. Additionally, neutrophil (N), lymphocyte (L), and platelet (P) levels were obtained from the patients' hemogram records. The SII was calculated as N x P/L (6). The dates of initial diagnosis and death for all deceased patients were obtained from the national death notification system. Patients who were pregnant, had cancer, or had active infections were excluded due to the potential alterations in their blood test results compared to normal conditions. We did not include cases of carotid artery and upper extremity artery disease in our study for the following reasons:

1- Upper extremity artery disease is an infrequent condition in our clinical practice.
2- Carotid artery angiography is not routinely performed during peripheral artery angiography procedures.

This exclusion criterion was established to ensure the homogeneity and reliability of the study results, focusing on conditions more commonly encountered and routinely treated in our clinic. HT is defined as a blood pressure reading of 140/90 mmHg or higher, and/or the receipt of antihypertensive treatment. HL is defined as having total plasma cholesterol levels exceeding 200 mg/dL, plasma LDL cholesterol levels of 130 mg/dL or higher, triglyceride levels of 150 mg/dL or higher, or HDL cholesterol levels in men of 40 mg/dL or lower and in women of 50

mg/dL or lower. Additionally, individuals may be classified as having HL if they are receiving lipid-lowering treatment. DM is defined as having a fasting plasma glucose level of 126 mg/dL (6.94 mmol/L) or higher and/or receiving glucose-lowering treatment. Individuals who reported smoking a minimum of five cigarettes per day were classified as smokers. Cerebrovascular events were classified as either ischemic or hemorrhagic. Patients with atherosclerotic heart disease were included in the study if they exhibited angiographically detected coronary artery stenosis, underwent percutaneous transluminal coronary angioplasty or stenting, or had undergone coronary artery bypass surgery.

Ethical Committee

The study received ethics committee approval from Afyonkarahisar Health Sciences University Medical Ethics Committee on 01/04/2022, with the reference number 2022/4. We conducted the study following the principles of the Declaration of Helsinki and the good clinical practices protocol.

Statistical Analysis

The statistical analysis was conducted using SPSS software version 20.0. Normality of the variables was assessed using both visual and analytical methods. Descriptive statistics were reported using standard deviation and mean or interquartile ranges and median. The Chi-square test was used to compare categorical and nominal variables, such as hypertension, gender, hyperlipidemia, and diabetes. The Mann-Whitney U test was used to compare nonparametric data, while parametric data were compared using t-tests. Kaplan-Meier analysis was used to evaluate the time to death events in the two groups. Hazard ratios and their corresponding 95% confidence intervals were obtained from stratified Cox proportional-hazards models. The risk of mortality in PAD patients was assessed using the Cox regression model (CRM). Multivariate analysis was performed, and 95% confidence intervals (CI) and odds ratios (OR) were calculated. A p-value of 0.05 or lower was considered statistically significant.

RESULTS

In our study, 432 patients were enrolled. The mean age (SD) was 76.2 ± 10.2 years, with 129 men (74.1%) and 45 women (25.9%) in group 1 (dead). The mean age (SD) was 66.6 ± 8.94 years, with 231 men (89.5%) and 27 women (10.5%) in group 2 (alive). Baseline characteristics, blood, and anthropometric measurements of the study population are provided in **Table 1**.

Table 1: Baseline demographic and clinical characteristics of study groups

Variables	Group 1 (Dead) (n:174)	Group 2 (Alive) (n:258)	P value
Gender, n Male / Female, n (%)	129/45 (74.1%/25.9%)	231/27 (89.5%/10.5%)	<0.001*
Age	76.2 ± 10.2	66.6 ± 8.94	0.007#
DM, n (%)	103 (59.2%)	95 (36.8%)	<0.001*
HT, n (%)	96 (55.2%)	105 (40.7%)	0.003*
Smoking, n (%)	88 (50.6%)	117 (45.3%)	0.287*
HL, n (%)	34 (19.3%)	46 (17.8%)	0.654*
CAD, n (%)	97 (55.7%)	141 (54.7%)	0.822*
HF, n (Ejection Fraction <40%)	50 (28.7%)	33 (12.8%)	0.081*
CRF, n (%)	29 (16.7%)	18 (7%)	0.002*
Stroke, n (%)	19 (10.9%)	23 (8.9%)	0.177*
Atrial Fibrilation n (%)	44 (25.3%)	32 (12.4%)	0.001*
Amputation, n (%)	39 (22.4%)	30(11%)	0.004*
Fasting glucose (mg/dl)**	139(98-198)	112(92-164)	0.005**
CRP (mg/dl)**	2.6(1.5-7.8)	1.3(0.8-2.5)	<0.001**
Hgb (g/dl)	11.2 ± 0.45	12.7 ± 0.51	<0.001#
Creatinine (mg/dl)	1(0.8-1.5)	0.9 (0.78-1.13)	<0.001**
Total cholesterol (mg/dl)	164(145-190)	163 (142-198)	0.954**
Triglyceride (mg/dl)	152 (106-189)	146 (107-178)	0.250**
LDL (mg/dl)	125(93-146)	114 (90-140)	0.104**
HDL (mg/dl)	39.3 ± 2.1	10.1 ± 2.17	0.017#
WBC ($x10^3$/uL)	11.1 ± 1.4	9.9± 1.5	0.104#
Mean platelet volume	14.9 ± 1.6	9.5 ± 1.2	0.116#
Neutrophil count ($x10^3$/uL)	8.3 ± 0.9	6.71 ± 0.8	0.008#
Lymphocyte count ($x10^3$/uL)	1.95 ± 0.26	2.11 ± 0.7	<0.001#
Monocyte count ($x10^3$/uL)	0.86 ± 0.72	1.22 ± 0.64	0.462#
Platelet count ($x10^3$/uL)	286.8 ± 18.7	264.6 ± 17.7	0.372#
PAI	0.60±0.02	0.55±0.02	0.031#
SII	1062(581-2496)	740(485-1288)	<0.001**

* Chi-square test p<0.05 statistical significance, # Independent simple T-test, ** Mann Whitney U test, ±: standard deviation, ( ):Interquartile ranges, n: Individual number. CAD: Coronary artery disease, CRF: Chronic renal failure, CRP: C-reactive protein, DM: Diabetes Mellitus, HDL: High-Density Lipoprotein, HF: Heart failure, Hgb: Hemoglobin, HL: Hyperlipidemia, HT: Hypertension, LDL: Low-Density Lipoprotein, PAD: Peripheral artery disease, PAI: Plasma atherogenic index, SII: Systemic immune-inflammation index, WBC: White blood cell

Multivariate regression analysis was performed on the variables found to be significantly higher in Group 1. Female gender, age, presence of DM, creatinine levels, and SII were identified as predictors of mortality. The multivariate regression analysis of independent predictors of mortality is presented in **Table 2**.

Table 2: Multivariate regression analyse of independent predictor of mortality

Variables	Multivariate	P value
	OR, (95 % CI)	
GENDER(MALE)	0.45(0.31-0.66)	<0.001
AGE	1.04(1.02-1.05)	<0.001
DM	1.70(1.24-2.34)	0.001*
HDL	1.00(0.99-1.01)	0.532
CAD	1.16(0.80-1.62)	0.349
CREATİNİN	1.16(1.04-1.30)	0.009
AF	1.11(0.77-1.60)	0.5173
CRP	1.02(0.99-1.06)	0.060
HEMOGLOBİNE	0.99(0.97-1.01)	0.614
PAI	1.61(0.79-3.27)	0.185
SII	1.02(0.98-1.04)	<0.001

AF: Atrial fibrillation, CAD: Coronary artery disease, CI: Confidence interval, DM: Diabetes mellitus, HDL: High-Density Lipoprotein, HL: Hyperlipidemia, OR: Odds ratio, PAI: Plasma atherogenic index, p<0.05: Statistical significance, SII: Systemic immune-inflammation index

Kaplan Meier analysis was applied to determine survival rates according to SII in the study patients. The patients were divided into two groups based on the SII median value, which was determined to be 854, and evaluated accordingly. The results of the Kaplan-Meier analysis were all significantly different ($p < 0.001$), and these findings are presented in **Figure 1**.

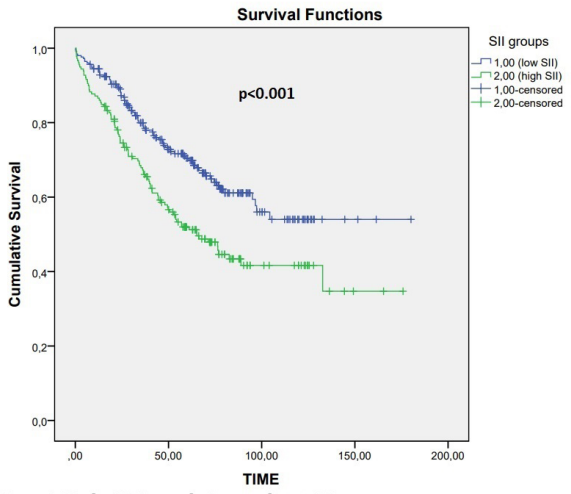

Figure 1: Kaplan Meier analysis according to SII

DISCUSSION

The article presents a retrospective study that investigates the prognostic value of SII in 432 patients with PAD. This is the first comprehensive academic study to investigate the potential relationship between SII and survival in PAD patients alone. The results indicate that SII ≥854 was independently associated with significantly shorter survival in the PAD group. A strong correlation was found between SII and mortality, and it was determined that SII is an independent predictor of mortality ($p < 0.001$). PAD risk factors include advanced age, male gender, smoking, cardiovascular disease, diabetes mellitus, hypertension, hypercholesterolemia, and metabolic and inflammatory biomarkers, many of which also affect mortality (8, 9). Studies have reported that the development of PAD also increases mortality in diabetes mellitus and chronic renal failure (10, 11). This study corroborates the findings of prior studies on the association between DM, creatinine levels, and mortality.

Although classical atherosclerotic risk factors can be corrected with lifestyle changes and drugs, mortality rates for PAD do not decrease sufficiently. For this reason, the need to investigate other risk factors that affect mortality and to identify different predictors has arisen (12). Particularly, the biomarkers of inflammation, which is an important etiology of the disease, were the subject of interest of researchers in previous studies (7).

N, L, and P counts are strong markers for demonstrating systemic inflammatory processes. Studies have shown that neutrophils and lymphocytes indicate the sensitivity of atherosclerotic plaque (4). NLRs have been the subject of studies showing cellular and humoral immune activity, while PLR ratios have been studied to show the relationship between immune activation and aggregation (13). These ratios have been used to predict mortality in cardiovascular diseases such as PAD, heart failure, cancer, and systemic inflammatory diseases (7, 14, 15). Previous studies have only assessed the possible role of SII, a composite of PLR and NLR, in PAD, which also incorporates three parameters (N, T, L) (16).

Studies have shown that SII is an important index predicting mortality in morbid conditions such as heart failure, various malignancies, atrial fibrillation, coronary artery disease, carotid artery disease, and aortic stenosis (17, 18). Yang et al. (18) found a correlation between SII and major adverse cardiovascular events in coronary artery disease. Similarly, Aydın et al. (19) demonstrated that SII was a significant predictor of cerebrovascular events in carotid artery disease. Studies showing that SII is helpful in de-

termining the risk of contrast-induced nephropathy before interventional procedures and in the diagnosis of acute coronary syndrome have also attracted attention in the literature (20, 21).

In PAD, both NLR and PLR are associated with disease severity. Even higher amputation rates were found at high PLR and NLR values (22). Few studies have examined SII, a composite of both, in PAD. Our study corroborates the finding of Zhang et al. (6) that SII is an independent risk factor for PAD. We also demonstrated that SII was an independent predictor of mortality in PAD patients. This suggests that PAD patients with high SII should be monitored more closely. The study's main limitations are its retrospective design, which prevents full determination of causality, and the use of only one hemogram test value. To avoid the impact of acute diseases and the lifespan of blood cells, serial tests would be preferable. SII is an independent risk factor associated with mortality in PAD, and calculating SII can be a useful index for predicting prognosis.

REFERENCES

1. Criqui MH, Aboyans V. Epidemiology of Peripheral Artery Disease. Circ Res. 2015;116(9):1509–26.

2. Fowkes FGR, Rudan D, Rudan I, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. The Lancet. 2013;382(9901):1329–40.

3. Klein AJ, Ross CB. Endovascular treatment of lower extremity peripheral arterial disease. Trends Cardiovasc Med. 2016;26(6):495–512.

4. Rymer JA, Swaminathan RV, Aday AW, et al. The Current Evidence for Lipid Management in Patients with Lower Extremity Peripheral Artery Disease: What Is the Therapeutic Target? Curr Cardiol Rep. 2021;23(3):13.

5. Taleb S. Inflammation in atherosclerosis. Arch Cardiovasc Dis. 2016;109(12):708–15.

6. Zhang Z, Chen Z. Higher Systemic Immune-Inflammation Index is Associated With Higher Likelihood of Peripheral Arterial Disease. Ann Vasc Surg. 2022;84:322–6.

7. Onofrei V, Crișan A, Adam CA, et al. The Role Played by Novel Inflammatory Markers in Assessment of Peripheral Artery Disease. Medicina (B Aires). 2023;59(9):1557.

8. Rahman MS, Woollard K. Atherosclerosis. In 2017. 2017:1003:121-144.

9. Agnelli G, Belch JJF, Baumgartner I, Giovas P, Hoffmann U. Morbidity and mortality associated with atherosclerotic peripheral artery disease: A systematic review. Atherosclerosis. 2020;293:94–100.

10. Vrsalovic M, Vucur K, Vrsalovic Presecki A, et al. Impact of diabetes on mortality in peripheral artery disease: a meta-analysis. Clin Cardiol. 2017;40(5):287–91.

11. Özgür Y. Relationship between Vitamin D Deficiency, Albuminuria, Peripheral Artery Disease and 5-year Mortality in Chronic Kidney Disease. J Coll Physicians Surg Pak. 2021;31(6):644-650.

12. Kou M, Ding N, Ballew SH, Salameh MJ, Martin SS, et al. Conventional and Novel Lipid Measures and Risk of Peripheral Artery Disease. Arterioscler Thromb Vasc Biol. 2021;41(3):1229–38.

13. Yalım Z, Aldemir M, Emren SV. Association of Inflammatory Markers with Multisite Artery Disease in Patients with Peripheral Arterial Disease. Clínica e Investigación en Arteriosclerosis. 2021;33(2):55–61.

14. Emir S, Aydin M, Can G, et al. Comparison of colorectal neoplastic polyps and adenocarcinoma with regard to NLR and PLR. 2015;19(19):3613-8.

15. Zahorec R. Neutrophil-to-lymphocyte ratio, past, present and future perspectives. Bratislava Medical Journal. 2021;122(07):474–88.

16. Kelesoglu S, Yilmaz Y, Elcık D, Kalay N. Systemic immune inflammation index: a novel predictor for coronary collateral circulation. Perfusion. 2022;37(6):605–12.

17. Wang Y, Zhuang Y, Lin C, et al. The neutrophil-to-lymphocyte ratio is associated with coronary heart disease risk in adults: A population-based study. PLoS One. 2024;19(2):e0296838.

18. Yang Y, Wu C, Hsu P, et al. Systemic immune-inflammation index (SII) predicted clinical outcome in patients with coronary artery disease. Eur J Clin Invest. 2020;50(5): e13230.

19. Aydin C, Alpsoy Ş, Akyüz A, et al. Could the systemic immune-inflammation index be a predictor to estimate cerebrovascular events in hypertensive patients? Blood Press Monit. 2022;27(1):33–8.

20. Ketenciler S, Ada S. Systemic immune inflammation index: is it a new marker for contrast-induced nephropathy? Anatolian Current Medical Journal. 2022;4(3):311–6.

21. Ozturk S, Erdoğan M, Turan Y. Systemic immune-inflammation index and high-sensitivity cardiac troponin T in acute coronary syndromes. Acta Medica Alanya. 2021;5(3):218–25.

22. Chen W, Chen K, Xu Z, et al. Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio Predict Mortality in Patients with Diabetic Foot Ulcers Undergoing Amputations. Diabetes Metab Syndr Obes. 2021;14:821-829**.**