 ● Koşuyolu Heart J 2022;25(3):262-269 • DOI: 10.51645/khj.2022.m316

Association Between Systemic Immune-Inflammation Index and Long-Term Mortality in Patients with Critical Limb-Threatening Ischemia Undergoing Endovascular Therapy Below the Knee

Yalçın Avcı[1](İD), Mustafa Duran[2](İD), Ali Rıza Demir[1](İD), Gökhan Demirci[1](İD), Ömer Taşbulak[1](İD), Arda Güler[1](İD), Ahmet Arif Yalçın[1](İD), Sezgin Atmaca[1](İD), Mehmet Ertürk[1](İD)

[1] Clinic of Cardiology, Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital, İstanbul, Türkiye
[2] Clinic of Cardiology, Konya City Hospital, Konya, Türkiye

ABSTRACT

Introduction: Endovascular interventions have been increasingly used for the treatment of patients suffering from below-the-knee (BTK) ischemic lesions. Yet, there is a paucity of data regarding long-term adverse events in patients with critical limb ischemia (CLI) undergoing endovascular revascularization for BTK lesions. Recently introduced systemic immune-inflammation index (SII) is a reliable indicator of poor outcomes in various cardiovascular conditions. Herein, we aimed to investigate the prognostic role of the SII on mortality in patients with CLI undergoing endovascular revascularization for BTK lesions.

Patients and Methods: The records of 112 patients with symptomatic CLI undergoing endovascular revascularization for BTK lesions between January 2015 and December 2019 were analyzed. Patients were divided into groups with low and high SII values based on an SII cut-off value derived from a ROC analysis. For each group, procedural details and follow-up outcomes were analyzed.

Results: The mean follow-up time was 40.3 ± 19.9 months. According to our data, patients with high SII values had higher rates of mortality compared to patients with low SII values (65.2% vs 30.3%, p< 0.001). To determine the SII cut-off value for predicting mortality, the ROC curve was drawn, and the best cut-off value was determined as 966 by using the Youden index, (AUC= 0.658, 95% CI= 0.556-0.760, p= 0.004). Cox multivariate regression analysis also identified the SII score as an independent predictor of mortality.

Conclusion: SII is an independent predictor of mortality, especially among patients with CLI who underwent endovascular revascularization for BTK lesions.

Key Words: Endovascular procedures; inflammation; peripheral arterial disease

Diz Altı Endovasküler Tedavi Uygulanan Kritik Bacak İskemisi Olan Hastalarda Sistemik İmmun-İnflamasyon İndeksi ile Uzun Dönem Mortalite Arasındaki İlişki

ÖZET

Giriş: Diz altı iskemik lezyonları olan hastaların tedavisinde endovasküler müdahaleler giderek daha fazla kullanılmaktadır. Yine de, diz altı lezyonları için endovasküler revaskülarizasyon uygulanan kritik bacak iskemisi olan hastalardaki uzun vadeli advers olaylarla ilgili çok az veri bulunmaktadır. Son zamanlarda kullanılan sistemik immün-inflamasyon indeksi (SII), çeşitli kardiyovasküler koşullarda kötü sonuçların güvenilir bir göstergesidir. Burada, diz altı lezyonları için endovasküler revaskülarizasyon uygulanan kritik bacak iskemisi olan hastalarda SII' nin mortalite üzerindeki prognostik rolünü araştırmayı amaçladık.

Hastalar ve Yöntem: Ocak 2015 ile Aralık 2019 tarihleri arasında diz altı lezyonları için endovasküler revaskülarizasyon uygulanan semptomatik kritik bacak iskemisi olan 112 hastanın kayıtları analiz edildi. Hastalar, ROC analizinden elde edilen SII eşik değerine göre düşük ve yüksek SII değerlerine sahip gruplara ayrıldı. Her grup için prosedür detayları ve takip sonuçları analiz edildi.

Bulgular: Ortalama takip süresi 40.3 ± 19.9 aydı. Verilerimize göre SII değeri yüksek olan hastalarda mortalite oranı düşük olan hastalara göre daha yüksekti (%65.2'ye karşı %30.3, p< 0.001). Mortaliteyi tahmin etmek amacıyla SII cut-off değerini belirlemek için ROC eğrisi çizildi ve Youden indeksi kullanılarak en iyi cut-off değeri 966 olarak belirlendi (AUC= 0.658, 95% CI= 0.556-0.760, p= 0.004). Ayrıca, Cox çok değişkenli regresyon analizi SII skorunu mortalitenin bağımsız bir öngörücüsü olarak tanımladı.

Sonuç: SII, özellikle diz altı lezyonları için endovasküler revaskülarizasyon uygulanan kritik bacak iskemisi olan hastalarda bağımsız bir mortalite öngördürücüsüdür.

Anahtar Kelimeler: Endovasküler prosedürler; enflamasyon; periferal arteriyel hastalık

Cite this article as: *Avcı Y, Duran M, Demir AR, Demirci G, Taşbulak Ö, Güler A, et al. Association between systemic immune-inflammation index and long-term mortality in patients with critical limb-threatening ischemia undergoing endovascular therapy below the knee. Koşuyolu Heart J 2022;25(3):262-269.*

Correspondence

Yalçın Avcı

E-mail: dryalcinavci@hotmail.com
Submitted: 19.09.2022
Accepted: 07.11.2022
Available Online Date: 01.12.2022

INTRODUCTION

Critical limb ischemia (CLI) is a coronary artery disease risk equivalent and strongly associated with an increased risk of cardiovascular morbidity and mortality[1,2]. Although bypass surgery is still the gold standard for below-the-knee (BTK) cases, most patients with significant BTK lesions are deemed ineligible for surgical revascularization due to extensive comorbidities and frailty[3]. Therefore, endovascular revascularization has emerged as an alternative treatment option for patients at high or prohibitive surgical risk[4]. However, there is a paucity of data regarding long-term adverse events in patients with CLI undergoing endovascular revascularization for BTK lesions[5].

Recently, a novel inflammatory marker has been defined for the evaluation of patients' inflammatory and immune status: the systemic immune-inflammation index (SII), defined as platelet count x neutrophil/lymphocyte ratio[6]. This index was an independent predictor of adverse events in cancer patients and associated with adverse events in several types of cardiovascular conditions[7-10]. However, the predictive ability of SII for mortality has not been reported in patients with CLI undergoing endovascular revascularization for BTK lesions. The current study aimed to investigate the prognostic role of the SII on mortality in patients with CLI undergoing endovascular revascularization.

PATIENTS and METHODS

Study Population

We screened 142 consecutive patients who underwent below-the-knee endovascular treatment for critical limb ischemia between January 2015 and December 2019. The study population's demographic and clinical risk factors and the indication for the endovascular procedures were retrospectively analyzed. Exclusion criteria were the presence of active infection, malignancy, chronic inflammatory disease, hepatic failure, and planned major amputation before the endovascular intervention. Patients in whom technical success was not achieved were also excluded from the study. After applying the exclusion criteria, 112 patients were enrolled. Informed consent was obtained from all patients following the ethical guidelines of the 1975 Declaration of Helsinki protocol and the study was approved by a research ethics committee.

Data Collection

The demographics, comorbidities, medications, laboratory parameters, and lesion characteristics were collected from patient records and the hospital database. A comprehensive metabolic panel was conducted to measure complete blood cell counts, liver and kidney functions, and serum lipid levels. Blood samples were collected from the antecubital vein after a 12-h fast before undergoing the endovascular procedure. Complete blood count parameters, including platelets, neutrophils, and lymphocytes were evaluated with an automated analyzer. An automatic hematology analyzer (Sysmex, XT-2000i) was used for whole blood counts. The SII was calculated with the formula, SII= Total peripheral platelets count x neutrophil/lymphocyte ratio[6]. Based on the ROC analysis, patients were divided into groups with low (SII< 966) and high (SII> 966) SII values.

Endovascular Procedure

Before the endovascular intervention, a multidisciplinary vascular team assessed the patient's eligibility for endovascular revascularization, considering the patient's functional status, comorbid conditions, and technical feasibility. All procedures were performed under systemic heparinization to maintain an activated clotting time of approximately 300 s. Antegrade access with the use of 6F sheaths is the preferred access site for the majority of the patients. In case of access failure, a retrograde approach was used. The equipment, intervention approach, and procedural technique were left at the operator's discretion. Technical success was described as restoring direct flow in the target vessel and residual stenosis of <30%. After the intervention, the vascular access site closure was achieved via ProGlide (Abbott, USA) vascular closure device or, if necessary, via manual compression. All patients were treated with 81 or 100 mg of acetylsalicylic acid and clopidogrel (75 mg). Acetylsalicylic acid therapy was continued indefinitely, and clopidogrel was continued for six months. Other medications, including antihypertensive, cilostazol, and lipid-lowering drugs, were prescribed according to evidence-based guidelines.

After the index procedure, patients were followed in accordance with a prespecified protocol. During the scheduled follow-up visits routine physical examination, ankle-brachial index (ABI) measurement, and serial duplex ultrasound imaging were performed. The need for reintervention, development of adverse clinical events, and health status were also evaluated. Patients had follow-up visits at one, six, and 12 months and every year after that.

The primary endpoint of the study was long-term mortality, which is a composite of cardiovascular and non-cardiovascular deaths occurring after the index procedure. The secondary endpoint of the study was major amputation, which is defined as the amputation above the ankle. Primary and secondary endpoints of the study population were reviewed and confirmed by a multidisciplinary vascular team blinded to patients' clinical and laboratory data.

Statistical Analysis

The data analysis was performed using SPSS Statistics for Windows, version 16.0 (IBM Corp., Armonk, USA). In this study, data are expressed as mean ± standard deviation (SD) for normal distribution and as median (25^{th}-75^{th} percentiles) for abnormal distribution. The Kolmogorov-Smirnov and Shapiro-Wilk test was utilized to check continuously distributed variables. The Chi-square and Fisher's exact test were utilized to evaluate qualitative variables. The Student's t-test was utilized for normally distributed variables and the variables were shown as mean ± SD. The Mann-Whitney U test was utilized to compare continuously non-normally distributed variables. In all analyses, $p< 0.05$ was considered statistically significant. The receiver-operating characteristic (ROC) curve analysis was utilized to assess the optimal cut-off point of SII to predict mortality following the endovascular intervention. The impact of several variables on mortality was assessed by univariate regression analysis. In these analyses, any variable with unadjusted $p< 0.05$ was identified as a confounding factor and was included in multivariate regression analyses to identify the independent predictor of mortality. Cumulative survival rates were also illustrated using the Kaplan-Meier method.

RESULTS

Among the 112 patients with CLI who underwent endovascular revascularization for BTK lesions, 76.8% were male with a mean age of 64.4 ± 11.0 years. High SII values were detected in 46 patients, and 66 had low SII values. Baseline demographic characteristics, detailed medical history, and laboratory findings of the study population are summarized in Table 1. Both groups had similar demographic and clinical characteristics ($p> 0.05$). All patients underwent endovascular revascularization with plain balloon angioplasty. Of the whole cohort, the anterior tibial artery was found to be the most intervened artery (54.5%), followed by the posterior tibial artery (40.2%) and the popliteal artery (27.7%). Twenty-five patients (22.3%) also underwent concomitant above-the-knee interventions during the index procedure.

Patients with high SII values had significantly lower levels of serum hemoglobin (11.0 ± 2.2 g/dL vs 12.9 ± 2.1 g/dL), lymphocyte count (1.60 ± 0.61 10^9/L vs 2.46 ± 0.82 10^9/L), and estimated glomerular filtration rate (eGFR), [72 (28-92) mL/min/ 1.73 m^2 vs 89 (62-96) mL/min/1.73 m^2)] than patients with low SII values, ($p< 0.05$ respectively). On the other hand, serum C-reactive protein (CRP) level [37 (10-92) mg/L vs 12 (6-29) mg/L], white blood cell counts (WBC), [10.6 (9.1-12.8) 10^6/L vs 9.1 (7.5-10.2) 10^6/L], neutrophil counts (8.69 ± 3.24 10^9/L vs 5.47 ± 1.58 10^9/L), and platelet counts (354 ± 120 10^3/mm^3 vs 259 ± 78 10^3/mm^3) were significantly higher in patients with high SII values compared to patients with low SII values ($p< 0.05$ respectively). In terms of medications, both groups had similar properties ($p> 0.05$).

Of the whole cohort, the mean follow-up time was 40.3 ± 19.9 months. A total of 50 (44.6%) patients died during long-term follow-up. According to our data, patients with high SII values had higher mortality rates than those with low SII values (65.2% vs. 30.3%, $p< 0.001$). With respect to the secondary endpoint of the study, both groups had similar rates of major amputation (23.9% vs. 18.2%, $p> 0.05$) (Figure 1).

To identify the prognostic mortality indicators, several variables, including age, history of chronic kidney disease (CKD), smoking history, serum hemoglobin, CRP levels, the use of statins, and SII values were included in the univariate Cox regression analysis. After excluding variables that showed no impact on mortality in the univariate analysis, Cox multivariate regression analysis was performed, which identified CKD, the use of statins, and the SII score as independent predictors of mortality (Table 2). According to our data, SII was the best predictor of mortality among the aforementioned parameters ($p< 0.001$). The ROC curve was drawn to determine the SII cut-off value for predicting mortality and the best cut-off value was determined as 966 by using the Youden index (AUC= 0.658, 95% CI= 0.556-0.760, p= 0.004), (Figure 2). Above this cut-off value, CSF could be detected with a sensitivity of 60.0% and a specificity of 74.2%. The Kaplan-Meier curve demonstrating the follow-up survival in both groups was also illustrated (Figure 3).

DISCUSSION

In this study, we evaluated the prognostic role of the SII on mortality in patients with CLI undergoing endovascular revascularization for BTK lesions and we found that the SII score was a strong predictor of mortality. To the best of our knowledge, this is the first study evaluating the relationship between SII and mortality in patients with CLI undergoing endovascular revascularization.

Since the Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II) updated guidelines, endovascular interventions have been increasingly used to treat patients suffering from BTK ischemic lesions[11]. Although multiple trials have demonstrated the safety and effectiveness of these endovascular approaches in treating BTK ischemic lesions, it is challenging to determine the optimal strategy to manage these lesions[12]. According to currently available data, plain balloon angioplasty is the gold standard endovascular approach in the treatment of BTK ischemic lesions, accompanied by bare-metal stents as a bailout option[13,14].

Table 1. Comparison of demographic and clinical characteristics of patients according to SII level

Variables	All patients (n= 112)	Low SII (n= 66)	High SII (n= 46)	p
Age, years	64.4 ± 11.0	63.3 ± 11.9	65.9 ± 9.4	0.211
Male gender, n (%)	86 (76.8)	48 (72.7)	38 (82.6)	0.223
Hypertension, n (%)	63 (56.3)	35 (53.0)	28 (60.9)	0.411
Diabetes mellitus, n (%)	95 (84.8)	54 (81.8)	41 (89.1)	0.289
Hyperlipidemia, n (%)	35 (31.3)	19 (28.8)	16 (34.8)	0.501
Current smoking, n (%)	63 (56.3)	38 (57.6)	25 (54.3)	0.735
Prior CAD, n (%)	66 (58.9)	40 (60.6)	26 (56.5)	0.666
CHF, n (%)	13 (11.6)	6 (9.1)	7 (5.3)	0.319
History of stroke, n (%)	12 (10.7)	4 (6.1)	8 (17.4)	0.068
CKD, n (%)	33 (29.5)	15 (22.7)	18 (39.1)	0.061
Atrial fibrillation, n (%)	16 (14.3)	10 (15.2)	6 (13.0)	0.754
Previous contralateral major amputation, n (%)	6 (5.4)	3 (4.5)	3 (6.5)	0.688
Previous ipsilateral minor amputation, n (%)	10 (8.9)	7 (10.6)	3 (6.5)	0.522
Fontaine classification, n (%)				
Stage III	41 (36.6)	28 (42.4)	13 (28.3)	0.126
Stage IV	71 (63.4)	38 (57.6)	33 (71.7)	0.126
Rutherford classification, n (%)				
Stage IV	44 (39.3)	30 (45.5)	14 (30.4)	0.109
Stage V	43 (38.4)	24 (36.4)	19 (41.3)	0.597
Stage VI	25 (22.3)	12 (18.2)	13 (28.3)	0.208
Lesion localization, n (%)				
Popliteal artery	31 (27.7)	17 (25.8)	14 (30.4)	0.586
Anterior tibial artery	61 (54.5)	35 (53.0)	26 (56.5)	0.715
Tibioperoneal truncus	8 (7.1)	3 (4.5)	5 (10.9)	0.270
Posterior tibial artery	45 (40.2)	25 (37.9)	20 (43.5)	0.552
Peroneal artery	28 (25.0)	16 (24.2)	12 (26.1)	0.824
Concomitant PTA above the knee	25 (22.3)	11 (16.7)	14 (30.4)	0.085
Laboratory parameters				
Hemoglobin, g/dL	12.1 ± 2.3	12.9 ± 2.1	11.0 ± 2.2	<0.001
WBC, 10^6/L	9.6 (8.1-11.1)	9.1 (7.5-10.2)	10.6 (9.1-12.8)	<0.001
eGFR, mL/min/1.73 m^2	81 (56-95)	89 (62-96)	72 (28-92)	0.007
Total cholesterol, mg/dL	174 ± 46	169 ± 44	180 ± 47	0.225
HDL-c, mg/dL	36 ± 9	37 ± 9	36 ± 9	0.518
LDL-c, mg/dL	104 ± 37	99 ± 37	112 ± 37	0.066
Triglyceride, mg/dL	145 (104-209)	145 (99-213)	146 (105-205)	0.845
CRP, mg/L	14 (7-43)	12 (6-29)	37 (10-92)	<0.001
Albumin, g/dL	3.73 ± 0.48	3.78 ± 0.45	3.66 ± 0.51	0.198
Neutrophils, 10^9/L	6.79 ± 2.87	5.47 ± 1.58	8.69 ± 3.24	<0.001
Lymphocyte, 10^9/L	2.11 ± 0.85	2.46 ± 0.82	1.60 ± 0.61	<0.001
Platelets x 10^3/mm^3	298 ± 108	259 ± 78	354 ± 120	<0.001

Table 1. Comparison of demographic and clinical characteristics of patients according to SII level (continued)

Variables	All patients (n= 112)	Low SII (n= 66)	High SII (n= 46)	p
Medication, n (%)				
Aspirin	85 (75.9)	51 (77.3)	34 (73.9)	0.683
Clopidogrel	14 (12.5)	9 (13.6)	5 (10.9)	0.663
Cilastozol	9 (8.0)	6 (9.1)	3 (6.5)	0.735
Statin	51 (45.5)	31 (47.0)	20 (43.5)	0.715
ACEi/ARB	25 (22.3)	18 (27.3)	7 (15.2)	0.132
B-blocker	53 (47.3)	33 (50.0)	20 (43.5)	0.496
Calcium channel blocker	31 (27.7)	19 (28.8)	12 (26.1)	0.753

SII: Systemic immune-inflammation index, CAD: Coronary artery disease, CHF: Congestive heart failure, CKD: Chronic kidney disease, WBC: White blood cell, eGFR: Estimated glomerular filtration rate, HDL-c: High density lipoprotein cholesterol, LDL-c: Low-density lipoprotein cholesterol, CRP: C-reactive protein, ACEi/ARB: Angiotensin-converting enzyme inhibitor/ angiotensin receptor blocker.

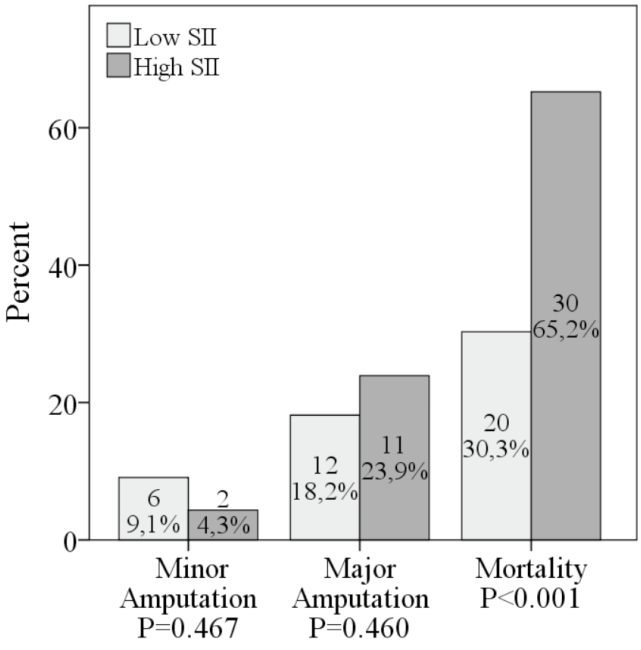

Figure 1. Comparison of endpoints according to SII level.
SII: Systemic immune-inflammation index.

On the other hand, drug-coated balloons (DCB) and drug-eluting stents (DES) have shown improved outcomes in the treatment of BTK ischemic lesions[15-18]. However, not only is the evidence on the effectiveness and safety of DCB and DES in long diffuse BTK lesions very scarce, but these novel local drug delivery technologies also have higher procedural costs[17,18]. Besides, the data regarding the impact of each endovascular treatment modality on procedural outcomes and long-term mortality are sparse. Previous reports revealed that age, body mass index, heart failure, bedridden state, renal failure, lesion severity, previous peripheral revascularization, and technical success were significant predictors of mortality following endovascular revascularization for BTK ischemic lesions[5,19,20].

In our study, significant predictors of mortality following endovascular revascularization were CKD, the use of statins, and higher SII scores. Among these parameters, a higher SII score was the strongest independent predictor of death (p< 0.001). Previous reports revealed a strong association between hematological indices, including neutrophils, plate-

Table 2. Univariable and multivariable Cox regression analysis to detect independent risk factors that may affect the mortality

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	p	HR (95% CI)	p
Age	1.033 (1.006-1.062)	0.018	1.021 (0.991-1.052)	0.167
CKD	2.480 (1.421-4.330)	0.001	2.448 (1.356-4.419)	0.003
History of stroke	2.160 (1.047-4.457)	0.037	1.484 (0.666-3.310)	0.335
Statin	0.579 (0.326-1.027)	0.061	0.453 (0.248-0.827)	0.010
Hemoglobin	0.895 (0.795-1.009)	0.070	1.110 (0.954-1.292)	0.177
CRP	1.005 (1.001-1.009)	0.029	1.002 (0.996-1.008)	0.530
High SII	3.933 (2.160-7.164)	<0.001	4.573 (2.216-9.436)	<0.001

HR: Hazard ratio, CI: Confidence interval, CKD: Chronic kidney disease, CRP: C-reactive protein, SII: Systemic immune-inflammation index.

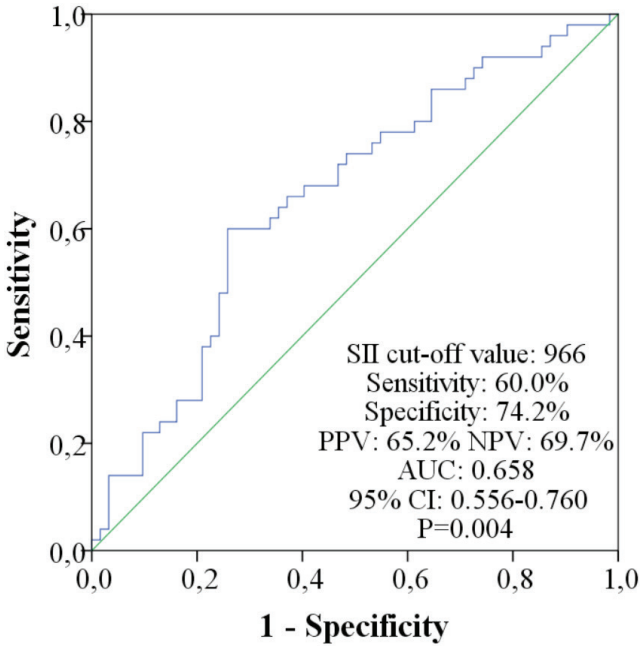

Figure 2. ROC curve analysis of SII value for predicting total mortality.
SII: Systemic immune-inflammation index, PPV: Positive predictive value, NPV: Negative predictive value, AUC: Area under the curve, CI: Confidence interval.

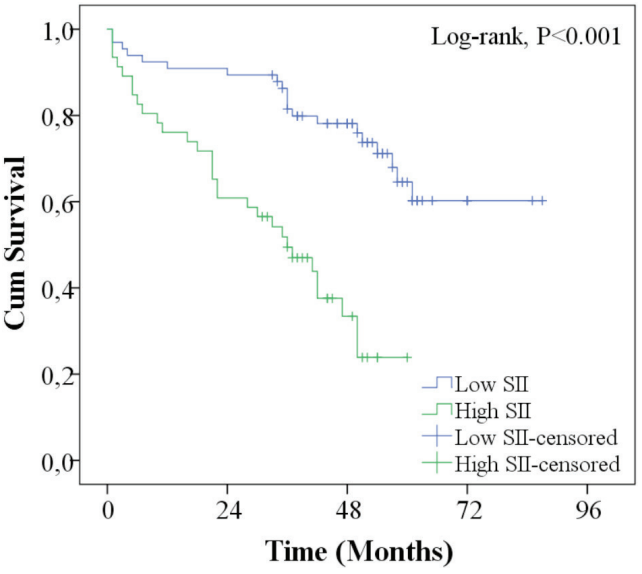

Figure 3. Kaplan-Meier curves for total mortality.
SII: Systemic immune-inflammation index.

lets, lymphocytes, and atherosclerotic burden. They also revealed the negative impacts of these hematological indices on several cardiovascular conditions[21,22]. Additionally, they combined these hematological indices, such as the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR), and used them as novel risk scores for predicting adverse events in patients with a history of cardiovascular diseases[23,24]. Apart from these biomarkers, a novel SII index has been introduced to clinical practice. This index is a simple and effective biomarker that combines these hematological indices and has a better predictive ability in determining the patient's inflammatory status. Findings from previous reports proved the prognostic value of SII for major adverse clinical events and mortality in various cardiac conditions such as chronic heart failure, coronary artery disease, and severe aortic stenosis[25,26]. In our study, patients with higher SII scores had higher neutrophil and lower lymphocyte values, which reflect more severe inflammation. In the immune-inflammatory response setting, higher neutrophil counts provoke plaque disruption, direct endothelial cell damage, and microvascular plugging, whereas lower lymphocyte counts lead to adverse physiological stress with a hypercoagulable state. Therefore, patients with higher NLR and PLR were more prone to severe atherosclerosis and major adverse events[27-29].

The immune-inflammatory process is also involved in the pathophysiology of peripheral artery disease severity. According to previous reports, there is an increased risk of progression to CLI in patients with peripheral artery disease having higher NLR or PLR values[30,31]. In addition, these hematological indices are associated with poor response to medical treatment, amputation requirement, cardiovascular complications, and worse survival[32-35]. Likewise, a higher SII score has been shown as an independent risk factor for peripheral artery disease severity and associated complications[36]. Considering the complex interaction between peripheral artery disease severity and inflammation, our results confirmed the outcomes of previous reports. In addition, the higher mortality rates in patients with higher SII scores compared with lower SII scores confirmed the proven role of these indices not only in the severity of inflammation but also in predicting future adverse events.

Study Limitations

There are several limitations of our study. First, this study has a limited number of patients and was conducted at a single center. Second, although there have been several studies investigating the prognostic ability of SII in terms of predicting major adverse cardiovascular events (MACE) in various conditions, we did not follow our patients regarding those parameters. Third, in our study, we included only the patients in whom technical success was achieved which might lead to an underestimation of long-term mortality following the procedure. Fourth, due to common practice, in our study, all patients underwent endovascular revascularization by using plain balloon angioplasty, accompanied by bare-metal stents as

a bailout option. Therefore, the results of our study cannot be extrapolated to patients undergoing endovascular revascularization by using DCB or DES.

CONCLUSION

SII is an independent predictor of mortality, especially among patients with CLI who underwent endovascular revascularization for BTK lesions. Considering the strong association between peripheral artery disease severity and systemic inflammation this simple and easily calculable index can be utilized in daily practice.

Ethics Committee Approval: The approval for this study was obtained from İstanbul Mehmet Akif Ersoy Thoraric and Cardiovascular Surgery Training and Research Hospital Clinical Research Ethics Committee (Decision no: 2022.06.40, Date: 02.08.2022).

Informed Consent: This is retrospective study, we could not obtain written informed consent from the participants.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept/Design - YA, MD; Analysis/Interpretation - YA, ÖT; Data Collection - YA, SA, GD; Writing - YA, AG; Critical Revision - AY, ME; Final Approval - ME; Statistical Analysis - AD; Overall Responsibility - YA.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declare that this study has received no financial support.

REFERENCES

1. Davies MG. Criticial limb ischemia: Epidemiology. Methodist Debakey Cardiovasc J 2012;8(4):10-4. [Crossref]
2. Uccioli L, Meloni M, Izzo V, Giurato L, Merolla S, Gandini R. Critical limb ischemia: Current challenges and future prospects. Vasc Health Risk Manag 2018;14:63-74. [Crossref]
3. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FGR. Intersociety consensus for the management of peripheral arterial disease (TASC II). J Vasc Surg 2007;45:5-67. [Crossref]
4. Agarwal S, Sud K, Shishehbor MH. Nationwide trends of hospital admission and outcomes among critical limb ischemia patients: From 2003-2011. J Am Coll Cardiol 2016;67(16):1901-13. [Crossref]
5. Zeller T, Micari A, Scheinert D, Baumgartner I, Bosiers M, Vermassen FEG, et al. The IN.PACT DEEP clinical drug-coated balloon trial: 5-year outcomes. JACC Cardiovasc Interv 2020;13(4):431-43. [Crossref]
6. Hu B, Yang XR, Xu Y, Sun YF, Sun C, Guo W, et al. Systemic immune-inflammation index predicts prognosis of patients after curative resection for hepatocellular carcinoma. Clin Cancer Res 2014;20(23):6212-22. [Crossref]
7. Yang R, Chang Q, Meng X, Gao N, Wang W. Prognostic value of systemic immune-inflammation index in cancer: A meta-analysis. J Cancer 2018;9(18):3295-302. [Crossref]
8. Huang J, Zhang Q, Wang R, Ji H, Chen Y, Quan X, et al. Systemic immune-inflammatory index predicts clinical outcomes for elderly patients with acute myocardial infarction receiving percutaneous coronary intervention. Med Sci Monit 2019;25:9690-701. [Crossref]
9. Seo M, Yamada T, Morita T, Frukawa Y, Tamaki S, Iwasaki Y, et al. Prognostic value of systemic immune-inflammation index in patients with chronic heart failure. Eur Heart J 2018;39(1):ehy564.P589. [Crossref]
10. Yang YL, Wu CH, Hsu PF, Chen SC, Huang SS, Chan WL, et al. Systemic immune inflammation index (SII) predicted clinical outcome in patients with coronary artery disease. Eur J Clin Invest 2020;50(5):13230. [Crossref]
11. Jaff MR, White CJ, Hiatt WR, Fowkes GR, Dormandy J, Razavi M, et al. An update on methods for revascularization and expansion of the TASC lesion classification to include below-theknee arteries: A supplement to the Inter-Society consensus for the management of peripheral arterial disease (TASC II). Vasc Med 2015;20(5):465-78. [Crossref]
12. Rathakrishnan B, Secemsky EA. Turning the tide: Evolution of below-the-knee endovascular intervention. Vasc Med 2021;26(1):26-7. [Crossref]
13. Peregrin JH, Koznar B, Kovác J, Lastovicková J, Novotný J, Vedlich D, et al. PTA of infrapopliteal arteries: Long-term clinical follow-up and analysis of factors influencing clinical outcome. Cardiovasc Intervent Radiol 2010;33(4):720-5. [Crossref]
14. Odink H, van den Berg A, Winkens B. Technical and clinical long-term results of infrapopliteal percutaneous transluminal angioplasty for critical limb ischemia. J Vasc Interv Radiol 2012;23(4):461-7. [Crossref]
15. Schmidt A, Piorkowski M, Werner M, Ulrich M, Bausback Y, Bräunlich S, et al. First experience with drug-eluting balloons in infrapopliteal arteries: Restenosis rate and clinical outcome. J Am Coll Cardiol 2011;58(11):1105-9. [Crossref]
16. Liistro F, Porto I, Angioli P, Grotti S, Ricci L, Ducci K, et al. Drug-eluting balloon in peripheral intervention for below the knee angioplasty evaluation (DEBATE-BTK): A randomized trial in diabetic patients with critical limb ischemia. Circulation 2013;128(6):615-21. [Crossref]
17. Karnabatidis D, Spiliopoulos S, Diamantopoulos A, Katsanos K, Kagadis GC, Kakkos S, et al. Primary everolimus- eluting stenting versus balloon angioplasty with bailout bare metal stenting of long infrapopliteal lesions for treatment of critical limb ischemia. J Endovasc Ther 2011;18(1):1-12. [Crossref]
18. Katsanos K, Karnabatidis D, Diamantopoulos A, Spiliopoulos S, Siablis D. Cost-effectiveness analysis of infrapopliteal drug-eluting stents. Cardiovasc Intervent Radiol 2013;36(1):90-7. [Crossref]
19. Söderström MI, Arvela EM, Korhonen M, Halmesmäki KH, Albäck AN, Biancari F, et al. Infrapopliteal percutaneous transluminal angioplasty versus bypass surgery as first-line strategies in critical leg ischemia: A propensity score analysis. Ann Surg 2010;252(5):765-73. [Crossref]
20. Alexandrescu VA, Hubermont G, Philips Y, Guillaumie B, Ngongang C, Vandenbossche P, et al. Selective primary angioplasty following an angiosome model of reperfusion in the treatment of Wagner 1-4 diabetic foot lesions: Practice in a multidisciplinary diabetic limb service. J Endovasc Ther 2008;15(5):580-93. [Crossref]
21. Afari ME, Bhat T. Neutrophil to lymphocyte ratio (NLR) and cardiovascular diseases: An update. Expert Rev Cardiovasc Ther 2016;14(5):573-7. [Crossref]
22. Balta S, Ozturk C. The platelet-lymphocyte ratio: A simple, inexpensive and rapid prognostic marker for cardiovascular events. Platelets 2015;26(7):680-1. [Crossref]
23. Arbel Y, Finkelstein A, Halkin A, Birati EY, Revivo M, Zuzut M, et al. Neutrophil/lymphocyte ratio is related to the severity of coronary artery disease and clinical outcome in patients undergoing angiography. Atherosclerosis 2012;225(2):456-60. [Crossref]
24. Kurtul A, Murat SN, Yarlioglues M, Duran M, Ergun G, Acikgöz SK, et al. Association of platelet-to-lymphocyte ratio with severity and complexity of coronary artery disease in patients with acute coronary syndromes. Am J Cardiol 2014;114(7):972-8. [Crossref]
25. Candemir M, Kiziltunc E, Nurkoç S, Sahinarslan A. Relationship between systemic immune-inflammation index (SII) and the severity of stable coronary artery disease. Angiology 2021;72(6):575-81. [Crossref]
26. Tosu AR, Kalyoncuoglu M, Biter HB, Cakal S, Selcuk M, Çinar T, et al. Prognostic value of systemic immune-inflammation index for major adverse cardiac events and mortality in severe aortic stenosis patients after TAVI. Medicina (Kaunas) 2021;57(6):588. [Crossref]

27. Angkananard T, Anothaisintawee T, McEvoy M, Attia J, Thakkinstian A. Neutrophil lymphocyte ratio and cardiovascular disease risk: A systematic review and meta-analysis. Biomed Res Int 2018;2018:2703518. [Crossref]

28. Dale MA, Ruhlman MK, Baxter BT. Inflammatory cell phenotypes in AAAs; Their role and potential as targets for therapy. Arterioscler Thromb Vasc Biol 2015;35(8):1746-55. [Crossref]

29. Simpson E, Cantor H. Regulation of the immune response by subclasses of T lymphocytes II. The effect of adult thymectomy upon humoral and cellular responses in mice. Eur J Inmunol 1975;5(5):337-43. [Crossref]

30. Belaj K, Pichler M, Hackl G, Rief P, Eller P, Hafner F, et al. Association of the derived neutrophil-lymphocyte ratio with critical limb ischemia. Angiology 2016;67(4):350-4. [Crossref]

31. Gary T, Pichler M, Belaj K, Hafner F, Gerger A, Froehlich H, et al. Platelet-to-lymphocyte ratio: A novel marker for critical limb ischemia in peripheral arterial occlusive disease patients. PLoS One 2013;8(7):67688. [Crossref]

32. Luo H, Yuan D, Yang H, Yukui M, Huang B, Yang Y, et al. Post-treatment neutrophil-lymphocyte ratio independently predicts amputation in critical limb ischemia without operation. Clinics 2015;70(4):273-7. [Crossref]

33. Gonza'lez-Fajardo JA, Brizuela-Sanz JA, Aguirre-Gerva's B, Merino-Díaz B, Del Río-Solá L, Martín-Pedrosa M, et al. Prognostic significance of an elevated neutrophil-lymphocyte ratio in the amputation-free survival of patients with chronic critical limb ischemia. Ann Vasc Surg 2014;28(4):999-1004. [Crossref]

34. Pourafkari L, Choi C, Garajehdaghi R, Tajlil A, Dosluoglu HH, Nader ND. Neutrophil-lymphocyte ratio is a marker of survival and cardiac complications rather than patency following revascularization of lower extremities. Vasc Med 2018;23(5):437-44. [Crossref]

35. Erdoğan SB, Selçuk ÜN, Baştopçu M, Arslanhan G, Çakmak AY, Kuplay H, et al. Critical limb ischemia patients clinically improving with medical treatment have lower neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios. Vascular 2021;29(6):920-6. [Crossref]

36. 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. [Crossref]