Heart Surgery Forum 2023; 26(3): E225–E233
doi: 10.1532/hsf.5303

Article

Systemic Immune-Inflammation Index Predicts Restenosis after Interventions for Lower Extremity Arteriosclerosis Obliterans

Shao-Yong Tian[1,*]

[1]Department of Intervention, Harrison International Peace Hospital, 053000 Hengshui, Hebei, China
*Correspondence: jrktsy@outlook.com (Shao-Yong Tian)

Submitted: 13 November 2022 Revised: 5 December 2022 Accepted: 27 February 2023 Published: 31 May 2023

Abstract

Background: To investigate the association between the pretreatment systemic immune-inflammation index (SII) and restenosis after interventions for lower extremity arteriosclerosis obliterans (ASO). **Methods**: We retrospectively evaluated 309 patients with ASO who underwent endovascular interventions between January 2018 and December 2021. Pretreatment inflammatory markers, including the SII, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic inflammation response index (SIRI), aggregate index of systemic inflammation (AISI), and C-reactive protein (CRP) were collected. The logistic regression model was used to determine the associations between these inflammatory markers and restenosis. Clinical manifestations, ankle-brachial index (ABI), and quality of life after intervention also were compared. **Results**: The pretreatment SII ($p < 0.001$), NLR ($p < 0.001$), PLR ($p < 0.001$), SIRI ($p = 0.002$), AISI ($p < 0.001$), and CRP ($p = 0.036$) were significantly higher in patients with restenosis than in those without restenosis. Among the four markers, SII had the highest area under the curve (AUC) in predicting restenosis (SII *vs.* NLR *vs.* PLR *vs.* SIRI *vs.* AISI *vs.* CRP: 0.715 *vs.* 0.689 *vs.* 0.695 *vs.* 0.643 *vs.* 0.691 *vs.* 0.596). Multivariate analysis revealed that the pretreatment SII was the only independent factor for restenosis (hazard ratio [HR]: 4.102; 95% confidence interval [CI]: 1.155–14.567; $p = 0.029$). Moreover, a lower SII was associated with significantly better improvements in clinical manifestations (Rutherford classification 1–2: 67.5% *vs.* 52.9%, $p = 0.038$) and ABI (median: 0.29 *vs.* 0.22; $p = 0.029$), together with better quality of life ($p < 0.05$ for physical functioning, social functioning, pain, and mental health). **Conclusions**: The pretreatment SII is an independent predictor of restenosis after interventions in patients with lower extremity ASO, providing more accurate prognosis prediction than other inflammatory markers.

Keywords

arteriosclerosis obliterans; systemic immune-inflammation index; restenosis; quality of life

Introduction

Peripheral artery disease (PAD) is a major cardiovascular disease with an increasing prevalence worldwide that affected over 236 million people in 2015 [1,2]. Lower extremity arteriosclerosis obliterans (ASO) is the most common type of PAD, which is caused by arteriosclerosis of the arteries supplying the legs and is characterized by a number of symptoms, including intermittent claudication, rest pain, and tissue loss. In recent years, endovascular interventions have emerged as the primary revascularization strategy for ASO [3–5]. Despite the rapid development of intervention techniques, a high incidence of restenosis remains a continual challenge [6–9]. Factors affecting the risk of restenosis after endovascular intervention have widely been explored.

Systemic inflammation plays a pivotal role in the pathological process of atherosclerosis [10]. Several inflammatory markers based on circulating blood cell counts, such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII) have been related to the severity and prognosis of coronary artery disease (CAD) [11–14]. Likewise, both NLR and PLR were positively associated with the severity and prognosis of lower extremity ASO in a retrospective study of 211 patients [15]. However, the prognostic value of SII or its relative utility when compared with other inflammatory markers remains unclear. As a composite score integrating neutrophil, lymphocyte, and platelet counts, the SII was hypothesized to be more effective than either NLR or PLR. Thus, we aimed to investigate the role of SII in restenosis after endovascular interventions for patients with lower extremity ASO.

Materials and Methods

Study population: This study retrospectively reviewed patients with lower extremity ASO who underwent endovascular interventions at our institution between January 2018 and December 2021. Eligible patients were included, if they met the diagnostic criteria of lower extremity ASO, according to the American College of Cardiology/American Heart Association (ACC/AHA) Guidelines

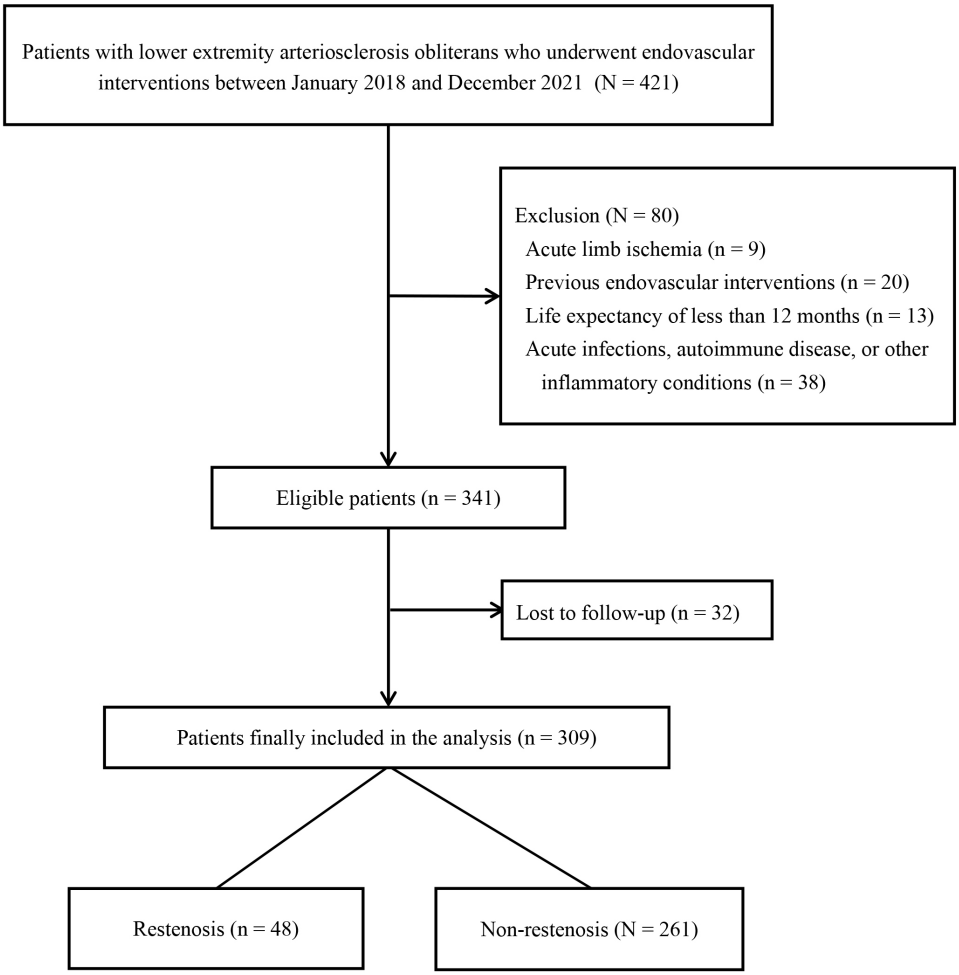

Fig. 1. Diagram of study population.

[4] and received elective percutaneous transluminal angioplasty (PTA) with or without stent placement. The following patients were excluded: (1) acute limb ischemia; (2) previous endovascular interventions of the lower extremities; (3) contraindications for endovascular interventions; (4) life expectancy of less than 12 months; (5) acute infections, autoimmune disease, or other inflammatory conditions; and (6) loss to follow up. Finally, a total of 309 patients were included (Fig. 1). This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the institutional review board of our institution. Informed consent was obtained from all study patients.

Treatments: After sufficient assessments, all patients received standard PTA. A 4-F or 6-F vascular sheath was introduced into the artery. After systemic heparinization, diagnostic angiography was performed. The affected artery was first treated with balloon dilatation. If residual stenosis $\geq$50% or flow-limiting dissection was observed after repeated balloon inflations, a self-expanding nitinol stent was implanted. All procedures were performed by surgeons with at least 150 cases of endovascular interventions.

Postintervention medical therapy included antiplatelet therapy for at least 1 year. Other therapies consisted of statin agents, cilostazol, blood pressure control, glycemic control, smoking cessation, and exercise therapy. Patients were followed by clinical manifestations, physical examination, and ABI at 1 month, 6 months, and 12 months. Computed tomographic angiography (CTA) routinely was performed to determine restenosis after 6 months of intervention.

Study outcomes and definitions: The primary efficacy outcome was the restenosis rate, defined as the proportion of patients who experienced significant vascular stenosis ($\geq$50%) in the treated segment [16]. Other efficacy outcomes included the clinical effective rate, ankle-brachial index (ABI), and quality of life. Clinical effectiveness was defined as the alleviation of clinical manifestations after 6 months of intervention. For patients with a pretreatment Rutherford classification of 5–6 or 3–4, a postintervention Rutherford classification of $\leq$4 or $\leq$2, respectively, was considered clinically effective. The ABI was calculated as the ratio of the highest systolic pressure of the anterior or posterior tibial artery to the highest systolic pressure of the

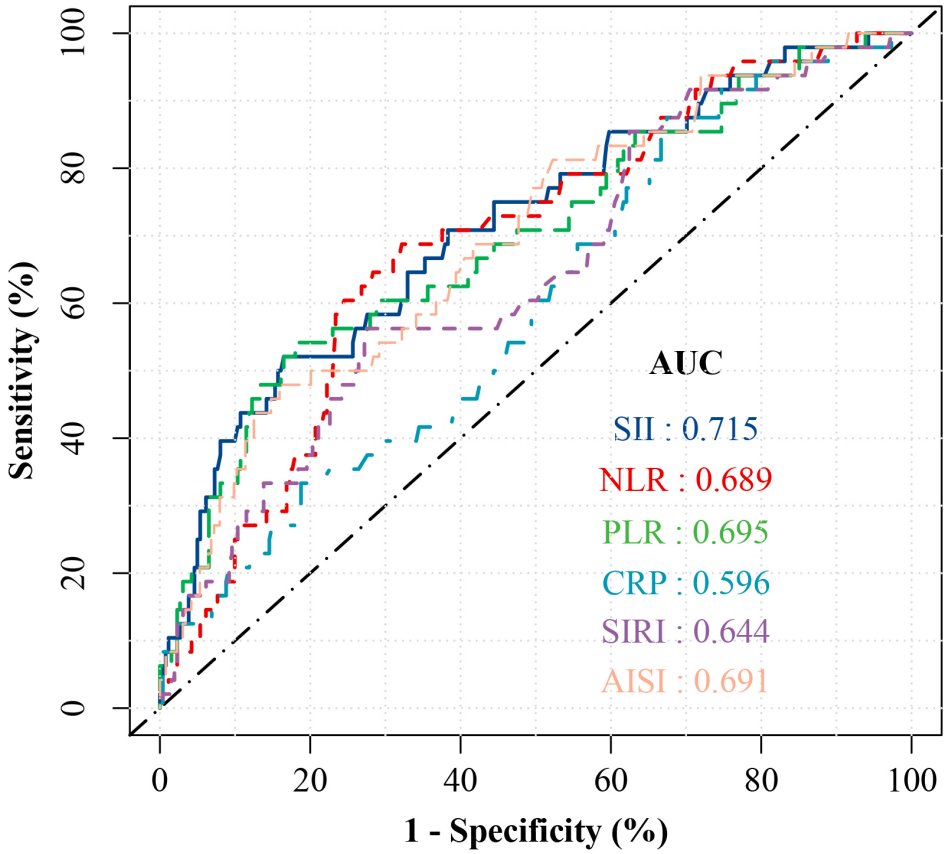

Fig. 2. Areas under the receiver operating characteristic curves for restenosis.

bilateral brachial arteries. Quality of life was assessed using the Short Form Six Dimensions (SF-6D) before and after intervention. The scale consisted of six items: physical functioning, role limitations, social functioning, pain, mental health, and vitality [17]. A lower score indicates a better quality of life.

Routine blood tests were carried out one week before intervention, including neutrophil count, lymphocyte count, platelet count, and C-reactive protein (CRP). As previously reported, NLR was calculated by dividing neutrophil count by lymphocyte count, PLR was calculated by dividing platelet count by lymphocyte count, and SII was calculated as platelet count × neutrophil count/lymphocyte count. Moreover, the systemic inflammation response index (SIRI) was calculated as monocyte count × neutrophil count/lymphocyte count, and the aggregate index of systemic inflammation (AISI) was calculated as platelet count × monocyte count × neutrophil count/lymphocyte count [18].

Statistical analysis: Statistical analyses were performed using SPSS (version 21.0, IBM Corp., Armonk, NY, USA). Categorical variables are presented as frequencies (percentages), and continuous variables are presented as the mean (standard deviation [SD]) or median (interquartile range [IQR]). Differences between groups were assessed using the χ^2 test, t test, or Wilcoxon rank sum test, as appropriate. Logistic regression was used for univariate and multivariate analyses of clinical factors associated with restenosis. Variables with a value of $p < 0.1$ in the univariate analysis was included in the multivariate analysis. Receiver operating characteristic (ROC) curves were generated to evaluate the predictive value by calculating the area under the curve (AUC). All tests were two-sided with a significance level of $p < 0.05$.

Results

Baseline characteristics: A total of 309 patients with lower extremity ASO were included in the present study. Of these, 228 patients (73.8%) were male, and the mean age was 70.9 years (SD: 5.5). All patients had ABI <0.90 and Rutherford classification 3–6 disease. After six months of intervention, restenosis was identified in 15.5% of patients (n = 48). Compared with patients without restenosis, patients with restenosis had significantly lower ABI (median: 0.51 *vs.* 0.55; $p = 0.013$), higher NLR (median: 3.2 *vs.* 2.5; $p < 0.001$), higher PLR (median: 185 *vs.* 133; $p < 0.001$), higher SII (median: 527 *vs.* 340; $p < 0.001$), higher SIRI (median: 1.34 *vs.* 0.95; $p = 0.002$), higher AISI (median:

Figure 3

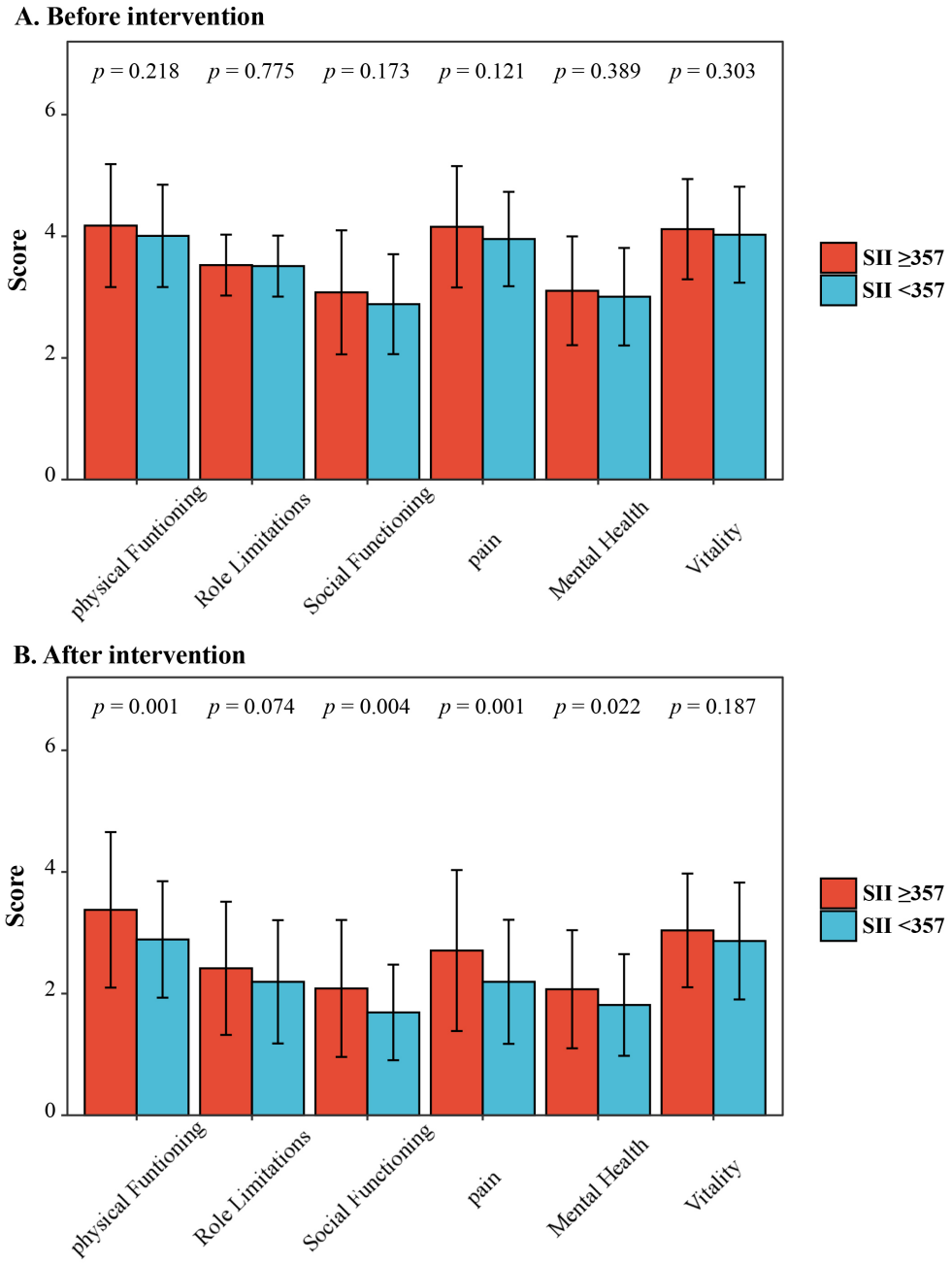

Fig. 3. Short Form Six Dimensions scores, according to the pretreatment systemic immune-inflammation index (SII) at baseline (A) and after 6 months of intervention (B).

240 *vs.* 120; $p < 0.001$), and higher CRP (median: 7.6 *vs.* 6.7 mg/L; $p = 0.036$) levels at baseline (Table 1).

Prognostic value of SII: Among the four inflammatory markers, the AUC value was highest for SII (0.715; 95% confidence interval [CI]: 0.633–0.797) and was higher than that for NLR (0.688; 95% CI: 0.609–0.767), PLR (0.695; 95% CI: 0.609–0.781), SIRI (0.643; 95% CI: 0.557–0.728), AISI (0.691; 95% CI: 0.608–0.773), or CRP (0.596; 95% CI: 0.511–0.680) (Fig. 2). The cut-off values for SII, NLR, PLR, SIRI, AISI, and CRP were set as their medians. In the univariate analysis, pretreatment ABI, NLR, PLR, AISI, and SII were significantly associated with postintervention restenosis (all $p < 0.05$). Multivariate analysis revealed that only pretreatment SII was an independent risk factor for restenosis (hazard ratio [HR]: 4.102; 95% CI: 1.155–14.567; $p = 0.029$) (Table 2).

Associations between baseline characteristics and SII: The associations between clinical factors and SII were shown in Table 3. Patients with a higher SII (≥ median [357]) were more likely to be older (mean: 68.5 *vs.* 67.2

Table 1. Baseline characteristics according to presence or absence of restenosis.

Characteristic	Overall (n = 309)	Restenosis (n = 48)	Non-restenosis (n = 261)	*p* value
Age, years	67.9 (5.5)	68.4 (5.6)	67.8 (5.5)	0.491
<70	180 (58.3%)	26 (54.2%)	154 (59.0%)	0.532
≥70	129 (41.7%)	22 (45.8%)	107 (41.0%)	
Gender, male	228 (73.8%)	35 (72.9%)	193 (73.9%)	0.882
Body weight, kg	68.7 (7.7)	68.6 (6.8)	68.8 (7.9)	0.875
Body mass index, kg/m^2	23.0 (2.0)	22.9 (1.8)	23.0 (2.0)	0.778
Cardiovascular risk factors and coexisting conditions				
Hypertension	184 (59.5%)	30 (62.5%)	154 (59.0%)	0.650
Diabetes	115 (37.2%)	23 (47.9%)	92 (35.2%)	0.095
Hyperlipidemia	102 (33.0%)	18 (37.5%)	84 (32.2%)	0.472
Coronary heart disease	95 (30.7%)	16 (33.3%)	79 (30.3%)	0.672
Chronic kidney disease	49 (15.9%)	9 (18.8%)	40 (15.3%)	0.551
Smoking	158 (51.1%)	28 (58.3%)	130 (49.8%)	0.278
Alcohol drinking	145 (46.9%)	25 (52.1%)	123 (47.1%)	0.528
ASO characteristics				
Rutherford classification				0.280
3–4	255 (82.5%)	37 (77.1%)	218 (83.5%)	
5–6	54 (17.5%)	11 (22.9%)	43 (16.5%)	
ABI	0.54 (0.37–0.78)	0.51 (0.26–0.66)	0.55 (0.39–0.78)	0.013
Laboratory findings				
NLR	2.6 (2.1–3.3)	3.2 (2.5–4.3)	2.5 (2.0–3.1)	<0.001
PLR	137 (107–186)	185 (119–267)	133 (103–177)	<0.001
SII	357 (228–638)	527 (339–1016)	340 (223–558)	<0.001
SIRI	0.97 (0.68–1.51)	1.34 (0.81–2.40)	0.95 (0.64–1.38)	0.002
AISI	130 (83–264)	240 (121–480)	120 (76–232)	<0.001
CRP, mg/L	7.0 (2.6–18.6)	7.6 (4.6–27.8)	6.7 (2.4–17.3)	0.036

Data are No. (%), mean (standard deviation [SD]), or median (inter quartile range [IQR]). ABI, ankle-brachial index; ASO, arteriosclerosis obliterans; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; AISI, aggregate index of systemic inflammation; CRP, C-reactive protein.

years; $p = 0.038$), male (78.7% *vs.* 68.8%; $p = 0.048$), have Rutherford classification 5–6 disease (23.2% *vs.* 11.7%; $p = 0.008$), have a lower ABI (median: 0.53 *vs.* 0.55; $p = 0.023$), have a higher NLR (median: 3.2 *vs.* 2.1; $p < 0.001$), have a higher PLR (median: 185 *vs.* 107; $p < 0.001$), have a higher SIRI (median: 1.37 *vs.* 0.75; $p < 0.001$), have a higher AISI (median: 259 *vs.* 85; $p < 0.001$), and have a higher CRP (median: 8.9 *vs.* 4.8 mg/L; $p < 0.001$) than those with a lower SII (<357).

Associations between patient outcomes and SII: Table 4 shows the patient outcomes after six months of intervention, according to the pretreatment SII (Table 4). In addition to a significantly lower restenosis rate (7.8% *vs.* 23.2%; $p = 0.010$), a lower SII also was associated with a significant improvement in clinical manifestations (Rutherford classification 1–2: 67.5% *vs.* 52.9, $p = 0.038$; clinical effective rate: 73.3% *vs.* 62.6%, $p = 0.042$). Moreover, a higher postintervention ABI (median: 0.80 *vs.* 0.74; $p = 0.001$) and greater improvement in ABI (median: 0.29 *vs.* 0.22; $p = 0.029$) were observed in patients with a lower SII than in those with a higher SII.

Quality of life: All patients completed the SF-6D questionnaire at baseline and after six months of intervention. The baseline scores for each indicator were comparable between patients with a higher SII and those with a lower SII (all $p > 0.05$, Fig. 3A) (Fig. 3). After intervention, a lower SII was significantly associated with better physical functioning ($p = 0.001$), social functioning ($p = 0.004$), pain ($p = 0.001$), and mental health ($p = 0.022$) (Fig. 3B).

Discussion

In the present study, we demonstrated a significant association between the pretreatment SII and restenosis after endovascular interventions of lower extremity ASO with patients with a higher SII more likely to experience restenosis. Compared with the NLR, PLR, SIRI, AISI, and CRP, the SII showed superiority for predicting restenosis. In addition, patients with a lower SII achieved significantly better improvements in clinical manifestations and ABI, together with better quality of life.

Table 2. Univariate and multivariate analyses for restenosis.

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age (per 1 year)	1.020 (0.964–1.079)	0.490		
Gender (female *vs.* male)	1.054 (0.527–2.110)	0.882		
Body mass index (per 1 kg/m^2)	0.978 (0.838–1.141)	0.777		
Hypertension (yes *vs.* no)	1.158 (0.614–2.184)	0.650		
Diabetes (yes *vs.* no)	1.690 (0.909–3.144)	0.097	1.895 (0.987–3.640)	0.055
Hyperlipidemia (yes *vs.* no)	1.264 (0.667–2.396)	0.472		
Coronary heart disease (yes *vs.* no)	1.152 (0.598–2.219)	0.672		
Chronic kidney disease (yes *vs.* no)	1.275 (0.573–2.835)	0.551		
Smoking (yes *vs.* no)	1.411 (0.757–2.630)	0.279		
Alcohol drinking (yes *vs.* no)	1.220 (0.659–2.258)	0.528		
Rutherford classification (5–6 *vs.* 3–4)	1.412 (0.737–2.706)	0.298		
ABI (per 0.1)	0.792 (0.662–0.948)	0.011	0.833 (0.693–1.001)	0.051
NLR (≥2.6 *vs.* <2.6)	3.163 (1.600–6.254)	0.001	1.716 (0.680–4.328)	0.253
PLR (≥137 *vs.* <137)	2.015 (1.063–3.819)	0.032	0.710 (0.268–1.885)	0.492
SII (≥357 *vs.* <357)	3.636 (1.810–7.302)	<0.001	4.102 (1.155–14.567)	0.029
SIRI (≥0.97 *vs.* <0.97)	1.635 (0.873–3.062)	0.124		
AISI (≥130 *vs.* <130)	2.507 (1.299–4.835)	0.006	0.757 (0.272–2.102)	0.593
CRP, mg/L (≥7.0 *vs.* <7.0)	1.209 (0.652–2.242)	0.546		

The cut-off values of the 4 inflammatory markers were set as the medians. HR, hazard ratio; CI, confidence interval; ABI, ankle-brachial index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; AISI, aggregate index of systemic inflammation; CRP, C-reactive protein.

Table 3. Baseline characteristics according to the systemic immune-inflammation index (SII).

Characteristic	High SII (n = 155)	Low SII (n = 154)	*p* value
Age, years	68.5 (5.4)	67.2 (5.5)	0.038
Gender, male	122 (78.7%)	106 (68.8%)	0.048
Body mass index, kg/m^2	23.0 (2.0)	23.0 (2.0)	0.932
Hypertension	98 (63.2%)	86 (55.8%)	0.186
Diabetes	62 (40.0%)	53 (34.4%)	0.310
Hyperlipidemia	57 (36.8%)	45 (29.2%)	0.158
Coronary heart disease	52 (33.5%)	43 (27.9%)	0.284
Chronic kidney disease	31 (20.0%)	18 (11.7%)	0.046
Smoking	87 (56.1%)	71 (46.1%)	0.078
Alcohol drinking	78 (50.3%)	70 (45.5%)	0.392
Rutherford classification			0.008
3–4	119 (76.8%)	136 (88.3%)	
5–6	36 (23.2%)	18 (11.7%)	
ABI	0.53 (0.33–0.71)	0.55 (0.42–0.78)	0.023
NLR	3.2 (2.8–4.3)	2.1 (1.8–2.5)	<0.001
PLR	185 (155–244)	107 (92–123)	<0.001
SIRI	1.37 (0.93–2.37)	0.75 (0.54–1.01)	<0.001
AISI	259 (169–423)	85 (57–107)	<0.001
CRP, mg/L	8.9 (4.8–23.7)	4.8 (2.2–12.3)	<0.001

Data are No. (%), mean (standard deviation [SD]), or median (inter quartile range [IQR]). ABI, ankle-brachial index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SIRI, systemic inflammation response index; AISI, aggregate index of systemic inflammation; CRP, C-reactive protein.

There is growing evidence that inflammation and the immune system play an important role in the initiation and progression of atherosclerosis [19]. Over the past decades, several ratios based on circulating neutrophil, lym-

Table 4. Patient outcomes after 6 months of intervention according to the systemic immune-inflammation index (SII).

Characteristic	High SII (n = 155)	Low SII (n = 154)	*p* value
Restenosis	36 (23.2%)	12 (7.8%)	0.010
Rutherford classification			0.038
0–2	82 (52.9%)	104 (67.5%)	
3–4	58 (37.4%)	45 (29.2%)	
5–6	15 (9.7%)	5 (3.2%)	
Clinical effective	97 (62.6%)	113 (73.3%)	0.042
ABI	0.74 (0.54–0.93)	0.80 (0.63–1.02)	0.001
Improvement in ABI	0.22 (0.06–0.41)	0.29 (0.10–0.44)	0.029

Data are No. (%) or median (inter quartile range [IQR]). ABI, ankle-brachial index.

phocyte, and platelet counts (e.g., NLR, PLR, and SII) have been developed to reflect systematic and local inflammatory status. Neutrophils secrete inflammatory mediators and activate other immune cells, which promotes endothelial dysfunction and atheroma generation [20,21]. Platelets promote atherosclerosis by secreting proinflammatory cytokines, chemokines, and platelet-derived growth factors [22]. Conversely, lymphocytes regulate the inflammatory response and inhibit the development of atherosclerosis [23,24]. A high SII may be associated with a high inflammatory status and thereby reflect atherosclerotic burden. A recent study by Liu *et al*. [25] showed that the SII is an independent risk factor for the occurrence and severity of CAD. Our study also revealed that patients with a higher SII had significantly poorer clinical manifestations and a lower ABI.

Previous studies have demonstrated the associations of both NLR and PLR with the risk of cardiovascular events [26–30]. In a retrospective study involving 148 PAD patients with advanced chronic kidney disease, Chen *et al*. [31] revealed that the NLR was an important prognostic predictor of mortality and major amputation after PTA. In a recent study, Ye *et al*. [15] reported that higher NLR and PLR were both associated with a significantly higher 1-year readmission rate. Likewise, our data also showed that a higher SII was significantly associated with poorer outcomes, including a higher rate of restenosis. Although the mechanisms of restenosis have not been well studied, a growing body of evidence has suggested that the intervention-induced inflammatory response plays an important role in promoting intimal hyperplasia [32]. Thus, we speculate that patients with a high SII are more likely to have an excessive immune response caused by endovascular interventions and thereby experience a high risk of postintervention restenosis. Some therapies targeting systemic and local inflammation may provide more benefits in these high-risk patients [33,34].

Our results also showed that SII had a higher predictive value than NLR, PLR, SIRI, AISI, and CRP. In addition, SII was the only independent factor for restenosis among the four inflammatory markers. A feasible explanation is that the SII is a composite score and may not be easily affected by outside interference in comparison with CRP. Moreover, the SII developed by three blood cell counts may provide a more comprehensive reflection of inflammatory status than NLR and PLR, which were both developed by two blood cell counts. The SII also exhibited a higher predictive value than both SIRI and AISI, which can be explained by the non-significant association between the monocyte count (as continuous variables) and restenosis (HR: 3.511; 95% CI: 0.688–17.924; $p = 0.131$).

This study had several limitations. First, as a retrospective study, selection bias was inevitable. Second, this study is limited by a small sample size and a short follow-up time. However, the sample size of 309 and 6-month follow-up period are sufficient to achieve our study outcomes and to inform future research. Third, the postintervention SII was not investigated in the present study because these values were difficult to obtain from each patient. Further research is still needed.

Conclusions

In conclusion, the SII, but not NLR, PLR, SIRI, AISI, or CRP, was a strong predictor of restenosis in patients with lower extremity ASO who underwent endovascular interventions. Patients with a lower SII were more likely to achieve better clinical outcomes. This low-cost, easily obtained marker may serve as a novel adjuvant tool in decision-making processes.

Availability of Data and Materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

SYT conceived of the study and designed the study, analyzed the data and wrote the manuscript. The author

contributed to editorial changes in the manuscript. The author read and approved the final manuscript. The author have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the ethics committee of the Harrison International Peace Hospital (approval number: 2022Y0808). Informed consent was obtained from all study patients.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The author declares no conflict of interest.

References

[1] Song P, Rudan D, Zhu Y, Fowkes FJI, Rahimi K, Fowkes FGR, *et al*. Global, regional, and national prevalence and risk factors for peripheral artery disease in 2015: an updated systematic review and analysis. The Lancet Global Health. 2019; 7: e1020–e1030.

[2] Goodall R, Salciccioli JD, Davies AH, Marshall D, Shalhoub J. Trends in peripheral arterial disease incidence and mortality in EU15+ countries 1990-2017. European Journal of Preventive Cardiology. 2021; 28: 1201–1213.

[3] Layden J, Michaels J, Bermingham S, Higgins B, Guideline Development Group. Diagnosis and management of lower limb peripheral arterial disease: summary of NICE guidance. British Medical Journal. 2012; 345: e4947.

[4] Gerhard-Herman MD, Gornik HL, Barrett C, Barshes NR, Corriere MA, Drachman DE, *et al*. 2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Journal of the American College of Cardiology. 2017; 69: e71–e126.

[5] Aboyans V, Ricco JB, Bartelink MLEL, Björck M, Brodmann M, Cohnert T, *et al*. Editor's Choice - 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS). European Journal of Vascular and Endovascular Surgery. 2018; 55: 305–368.

[6] Schillinger M, Sabeti S, Loewe C, Dick P, Amighi J, Mlekusch W, *et al*. Balloon angioplasty versus implantation of nitinol stents in the superficial femoral artery. The New England Journal of Medicine. 2006; 354: 1879–1888.

[7] Laird JR, Katzen BT, Scheinert D, Lammer J, Carpenter J, Buchbinder M, *et al*. Nitinol stent implantation versus balloon angioplasty for lesions in the superficial femoral artery and proximal popliteal artery: twelve-month results from the RESILIENT randomized trial. Circulation. Cardiovascular Interventions. 2010; 3: 267–276.

[8] Tepe G, Laird J, Schneider P, Brodmann M, Krishnan P, Micari A, *et al*. Drug-coated balloon versus standard percutaneous transluminal angioplasty for the treatment of superficial femoral and popliteal peripheral artery disease: 12-month results from the IN.PACT SFA randomized trial. Circulation. 2015; 131: 495–502.

[9] Ouriel K, Adelman MA, Rosenfield K, Scheinert D, Brodmann M, Peña C, *et al*. Safety of Paclitaxel-Coated Balloon Angioplasty for Femoropopliteal Peripheral Artery Disease. JACC: Cardiovascular Interventions. 2019; 12: 2515–2524.

[10] Brevetti G, Giugliano G, Brevetti L, Hiatt WR. Inflammation in peripheral artery disease. Circulation. 2010; 122: 1862–1875.

[11] Serrano CV, Jr, de Mattos FR, Pitta FG, Nomura CH, de Lemos J, Ramires JAF, *et al*. Association between Neutrophil-Lymphocyte and Platelet-Lymphocyte Ratios and Coronary Artery Calcification Score among Asymptomatic Patients: Data from a Cross-Sectional Study. Mediators of Inflammation. 2019; 2019: 6513847.

[12] Angkananard T, Inthanoo T, Sricholwattana S, Rattanajaruskul N, Wongsoasu A, Roongsangmanoon W. The Predictive role of Neutrophil-to-Lymphocyte Ratio (NLR) and Mean Platelet Volume-to-Lymphocyte Ratio (MPVLR) for Cardiovascular Events in Adult Patients with Acute Heart Failure. Mediators of Inflammation. 2021; 2021: 6889733.

[13] Ye Z, Hu T, Wang J, Xiao R, Liao X, Liu M, *et al*. Systemic immune-inflammation index as a potential biomarker of cardiovascular diseases: A systematic review and meta-analysis. Frontiers in Cardiovascular Medicine. 2022; 9: 933913.

[14] He L, Xie X, Xue J, Xie H, Zhang Y. Association of the systemic immune-inflammation index with all-cause mortality in patients with arteriosclerotic cardiovascular disease. Frontiers in Cardiovascular Medicine. 2022; 9: 952953.

[15] Ye M, Qian X, Guo X, Wang H, Ni Q, Zhao Y, *et al*. Neutrophil-Lymphocyte Ratio and Platelet-Lymphocyte Ratio Predict Severity and Prognosis of Lower Limb Arteriosclerosis Obliterans. Annals of Vascular Surgery. 2020; 64: 221–227.

[16] Cai Z, Guo L, Qi L, Cui S, Tong Z, Guo J, *et al*. Midterm Outcome of Directional Atherectomy Combined with Drug-Coated Balloon Angioplasty Versus Drug-Coated Balloon Angioplasty Alone for Femoropopliteal Arteriosclerosis Obliterans. Annals of Vascular Surgery. 2020; 64: 181–187.

[17] Petersohn S, Ramaekers BLT, Olie RH, Ten Cate-Hoek AJ, Daemen JWHC, Ten Cate H, *et al*. Comparison of three generic quality-of-life metrics in peripheral arterial disease patients undergoing conservative and invasive treatments. Quality of Life Research. 2019; 28: 2257–2279.

[18] Campesi I, Montella A, Sotgiu G, Dore S, Carru C, Zinellu A, *et al*. Combined oral contraceptives modify the effect of smoking on inflammatory cellular indexes and endothelial function in healthy subjects. European Journal of Pharmacology. 2021; 891: 173762.

[19] Libby P, Loscalzo J, Ridker PM, Farkouh ME, Hsue PY, Fuster V, *et al*. Inflammation, Immunity, and Infection in Atherothrombosis: JACC Review Topic of the Week. Journal of the American College of Cardiology. 2018; 72: 2071–2081.

[20] Drechsler M, Megens RTA, van Zandvoort M, Weber C, Soehnlein O. Hyperlipidemia-triggered neutrophilia promotes early atherosclerosis. Circulation. 2010; 122: 1837–1845.

[21] Drechsler M, Döring Y, Megens RTA, Soehnlein O. Neutrophilic granulocytes - promiscuous accelerators of atherosclerosis. Thrombosis and Haemostasis. 2011; 106: 839–848.
[22] Kyaw T, Peter K, Li Y, Tipping P, Toh BH, Bobik A. Cytotoxic lymphocytes and atherosclerosis: significance, mechanisms and therapeutic challenges. British Journal of Pharmacology. 2017; 174: 3956–3972.
[23] Núñez J, Miñana G, Bodí V, Núñez E, Sanchis J, Husser O, *et al*. Low lymphocyte count and cardiovascular diseases. Current Medicinal Chemistry. 2011; 18: 3226–3233.
[24] Tsiantoulas D, Sage AP, Mallat Z, Binder CJ. Targeting B cells in atherosclerosis: closing the gap from bench to bedside. Arteriosclerosis, Thrombosis, and Vascular Biology. 2015; 35: 296–302.
[25] Liu Y, Ye T, Chen L, Jin T, Sheng Y, Wu G, *et al*. Systemic immune-inflammation index predicts the severity of coronary stenosis in patients with coronary heart disease. Coronary Artery Disease. 2021; 32: 715–720.
[26] 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: 456–460.
[27] 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: e67688.
[28] Larmann J, Handke J, Scholz AS, Dehne S, Arens C, Gillmann HJ, *et al*. Preoperative neutrophil to lymphocyte ratio and platelet to lymphocyte ratio are associated with major adverse cardiovascular and cerebrovascular events in coronary heart disease patients undergoing non-cardiac surgery. BMC Cardiovascular Disorders. 2020; 20: 230.
[29] Li H, Zhou Y, Ma Y, Han S, Zhou L. The prognostic value of the platelet-to-lymphocyte ratio in acute coronary syndrome: a systematic review and meta-analysis. Kardiologia Polska. 2017; 75: 666–673.
[30] Zhao WM, Tao SM, Liu GL. Neutrophil-to-lymphocyte ratio in relation to the risk of all-cause mortality and cardiovascular events in patients with chronic kidney disease: a systematic review and meta-analysis. Renal Failure. 2020; 42: 1059–1066.
[31] Chen IC, Yu CC, Wu YH, Chao TH. Elevated Neutrophil-to-Lymphocyte Ratio Predicts Intermediate-Term Outcomes in Patients Who Have Advanced Chronic Kidney Disease with Peripheral Artery Disease Receiving Percutaneous Transluminal Angioplasty. Acta Cardiologica Sinica. 2016; 32: 532–541.
[32] Gallo G, Pierelli G, Forte M, Coluccia R, Volpe M, Rubattu S. Role of oxidative stress in the process of vascular remodeling following coronary revascularization. International Journal of Cardiology. 2018; 268: 27–33.
[33] Jiang Y, Fan J, Li Y, Wu G, Wang Y, Yang J, *et al*. Rapid reduction in plaque inflammation by sonodynamic therapy inpatients with symptomatic femoropopliteal peripheral artery disease: A randomized controlled trial. International Journal of Cardiology. 2021; 325: 132–139.
[34] Yuan S, Bruzelius M, Damrauer SM, Håkansson N, Wolk A, Åkesson A, *et al*. Anti-inflammatory diet and incident peripheral artery disease: Two prospective cohort studies. Clinical Nutrition. 2022; 41: 1191–1196.