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ORIGINAL RESEARCH

Elevated Composite Inflammatory Markers are Associated with Clinical Severity and Long-term Amputation Risk in Patients with Critical Limb Ischemia after Percutaneous Transluminal Angioplasty

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ABSTRACT

Background: Chronic limb-threatening ischemia (CLTI) represents the advanced stages of peripheral arterial disease (PAD) and is caused by atherosclerotic damage in the lower limbs, having a greater risk of major amputation. **Aim:** The aim of this study was to analyze the impact of systemic immune index (SII), systemic inflammation response index (SIRI), and the aggregate index of systemic inflammation (AISI) on the clinical severity and long-term risk of amputation among patients with CLTI after percutaneous transluminal angioplasty (PTA). **Material and Methods:** This is a retrospective observational study involving 104 patients diagnosed with CLTI and treated with PTA. Based on clinical severity, the cohort was divided into two groups: stage III Leriche-Fontaine and stage IV Leriche-Fontaine. **Results:** We observed higher levels of SII ($p = 0.027$), SIRI ($p = 0.0008$), and AISI ($p = 0.0024$) in patients with trophic lesions. Kaplan–Meier analysis showed that patients with values of SII ($p = 0.008$), SIRI ($p = 0.022$), and AISI ($p = 0.006$) above the median at the time of admission are at a higher risk of major amputation in the long term following PTA. At the multivariate regression analysis, high baseline values of SIRI (odds ratio (OR) = 2.28; $p = 0.017$) and AISI (OR = 2.32; $p = 0.043$) were associated with stage IV Leriche-Fontaine, but not SII (OR = 1.71; $p = 0.055$). Additionally, in the Cox regression analysis, we found that SII (hazard ratio (HR) = 1.56; $p = 0.010$), SIRI (HR = 1.63; $p = 0.009$), and AISI (HR = 1.55; $p = 0.016$) are predictive factors for long-term risk of major amputation after endovascular treatment. **Conclusions:** Elevated levels of SIRI and AISI have been found to be linked with the severity of clinical symptoms and an increased risk of long-term major amputation in patients with CLTI following PTA. Additionally, higher baseline values for SII were associated with a greater risk of major amputation, but not with clinical severity in the same group of patients.

Keywords: critical limb ischemia, percutaneous transluminal angioplasty, vascular surgery, inflammatory biomarkers

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INTRODUCTION

Chronic limb-threatening ischemia (CLTI) represents the advanced stages of peripheral arterial disease (PAD) and is caused by atherosclerotic damage in the lower limbs.[1,2] According to the Leriche-Fontaine classification,[3] patients with CLTI present the following stages: stage III with rest pain and stage IV with trophic lesions.[1–3] Patients with CLTI typically present with advanced age, a higher incidence of comorbidities and risk factors, as well as a greater risk of major amputation.[1,2,4]

Patients with CLTI exhibit a higher level of systemic inflammatory status than healthy controls[5] and those in the initial stages of PAD.[6,7] Recently, intensive research in vascular surgery has been conducted on inflammatory biomarkers derived from blood counts, such as the neutrophil-to-lymphocyte ratio (NLR), the monocyte-to-lymphocyte ratio (MLR), and the platelet-to-lymphocyte ratio (PLR).[5–14] Currently, none of the biomarkers mentioned above are used in medical practice. As a result, composite biomarkers have been developed, such as the systemic immune index (SII), the systemic inflammation response index (SIRI), and the aggregate index of systemic inflammation (AISI).[9] However, few articles have been published on the prognostic role of SII, SIRI, and AISI in vascular surgery, especially in patients with PAD, and to our knowledge, they have not been analyzed in patients with CLTI treated with endovascular interventions.

The aim of this study was to analyze the impact of SII, SIRI, and AISI on the clinical severity and long-term risk of major amputation in patients with CLTI after percutaneous transluminal angioplasty (PTA).

MATERIAL AND METHODS

STUDY DESIGN

This is a retrospective observational study involving all patients diagnosed with CLTI, treated endovascularly, and admitted to the Vascular Surgery Clinic of the County Emergency Clinical Hospital of Târgu Mureș from January 2020 to December 2022. Patients with severe atherosclerotic lesions above the inguinal level (more than 70% stenosis of the common or external iliac artery) and those with oncological, hematological, or autoimmune conditions were excluded. Moreover, patients who tested positive for COVID-19 or had any infection confirmed within 3 months before admission were also excluded owing to the increased risk of complications associated with COVID-19[15–23] and the increase in systemic inflammation.[15–17] After applying these exclusion criteria, 104 patients with CLTI were enrolled in the study. Based on the clinical severity of the disease, the cohort was divided into a group with stage III Leriche-Fontaine and a group with stage IV Leriche-Fontaine.

DATA COLLECTION

Demographic information, comorbidities, and laboratory data from the day of admission, as well as characteristics of atherosclerotic lesions from computed tomography angiography (CTA) were collected from the hospital's electronic database. The comorbidities that were followed included cardiovascular pathologies such as hypertension, atrial fibrillation, ischemic heart disease, and chronic heart failure, along with diabetes, varicose veins, and composite comorbidities. In addition, cardiovascular events (history of myocardial infarction or angina pectoris) and cerebrovascular events (stroke or transient ischemic attack), as well as active smoking, obesity, and dyslipidemia were noted. The preoperative CTA results showed the presence of atherosclerotic lesions in the superficial femoral artery, popliteal artery, anterior tibial artery, posterior tibial artery, and peroneal artery. The severity of the lesions was measured as follows: severe stenosis (stenosis of 70–90%), subocclusive stenosis (stenosis of 90–99%), and occlusion along the entire length of the artery.

COMPOSITE INFLAMMATORY BIOMARKERS

Using the preoperative neutrophil, monocyte, platelet, and lymphocyte counts, composite inflammatory biomarkers were calculated as follows:

- SII = neutrophil count × platelet count / lymphocyte count
- SIRI = neutrophil count × monocyte count / lymphocyte count
- AISI = neutrophil count × platelet count × monocyte count / lymphocyte count

STUDY ENDPOINTS

In the short term, we assessed clinical severity, and in the long term, we monitored the risk of major amputation (above the ankle level) by contacting patients by phone.

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS for Mac OS version 29.0.2.0 (IBM Corp). The average age, laboratory

TABLE 1. Patient characteristics by clinical severity

Variables	All patients *n* = 104	Stage III Leriche-Fontaine *n* = 44	Stage IV Leriche-Fontaine *n* = 60	p value
Age, years, mean ± s.d.	70.59 ± 9.13	68.86 ± 7.62	71.86 ± 9.96	0.081
Male, n (%)	81 (77.88%)	33 (75.00%)	48 (80.00%)	0.794
Comorbidities and risk factors, n (%)				
Hypertension	90 (86.53%)	38 (86.36%)	52 (86.67%)	0.133
Ischemic heart disease	61 (58.65%)	21 (47.72%)	40 (66.67%)	0.305
Chronic heart failure	42 (40.38%)	14 (31.81%)	28 (46.66%)	0.127
Atrial fibrillation	12 (11.54%)	3 (6.81%)	9 (15.0%)	0.197
Cardiovascular events	13 (12.50%)	4 (9.09%)	9 (15.0%)	0.368
Cerebrovascular events	14 (13.46%)	4 (9.09%)	10 (16.67%)	0.263
Diabetes mellitus	63 (60.57%)	23 (52.27%)	40 (66.67%)	0.529
Varicose veins	11 (10.57%)	4 (9.09%)	7 (11.67%)	0.673
Obesity	26 (25.0%)	9 (20.45%)	17 (28.33%)	0.359
Active smoking	50 (48.07%)	21 (47.72%)	29 (48.33%)	0.951
Dyslipidemia	49 (47.11%)	18 (40.91%)	31 (51.67%)	0.278
Laboratory data, mean ± s.d.				
Hemoglobin, g/dl	12.62 ± 1.86	13.07 ± 1.75	12.28 ± 1.89	0.030*
Hematocrit, %	38.16 ± 5.22	98.29 ± 4.53	37.33 ± 5.56	0.098
Leukocytes, × 10^3/µl	9.44 ± 3.09	8.45 ± 2.69	10.17 ± 3.19	0.005*
BUN, mg/dl	45.05 ± 24.97	38.61 ± 12.73	49.39 ± 29.91	0.163
Creatinine, mg/dl	1.31 ± 1.52	0.98 ± 0.29	1.55 ± 1.96	0.829
eGFR, ml/min/1.73 m^2	82.20 ± 31.91	83.16 ± 24.87	81.48 ± 36.52	0.813
Glucose, mg/dl	132.33 ± 58.99	128.83 ± 50.75	134.91 ± 64.72	0.840
AST, U/L	19.83 ± 8.41	20.56 ± 9.10	19.30 ± 7.92	0.580
ALT, U/L	19.74 ± 11.60	20.28 ± 10.84	19.34 ± 12.21	0.439
Neutrophils, × 10^3/µl	6.67 ± 2.79	5.70 ± 2.16	7.38 ± 3.01	0.002*
Lymphocytes, × 10^3/µl	2.04 ± 1.48	1.93 ± 0.69	2.12 ± 1.86	0.840
Monocytes, × 10^3/µl	0.73 ± 0.31	0.62 ± 0.29	0.79 ± 0.29	<0.001*
PLT, × 10^3/µl	271.60 ± 105.54	258.35 ± 75.25	281.37 ± 122.96	0.671
INR	1.18 ± 0.35	1.19 ± 0.37	1.17 ± 0.33	0.461
aPTT	28.83 ± 11.36	28.50 ± 12.84	29.12 ± 10.04	0.465
Major amputation, n (%)	16 (15.38%)	6 (13.63%)	10 (16.67%)	0.672
Mortality, n (%)	13 (12.50%)	3 (6.81%)	9 (15.0%)	0.134
Follow-up period, years, mean ± s.d.	1.26 ± 0.81	1.32 ± 0.84	1.22 ± 0.79	0.785
Length of stay, days, mean ± s.d.	6.17 ± 4.13	6.02 ± 4.08	6.28 ± 4.20	0.782

*Statistically significant

data, follow-up period, and length of stay were presented as mean ± s.d. We used Student's t-test and the Mann–Whitney test to assess differences between continuous variables, and the chi-squared test to compare characteristics between groups for dichotomous variables. We used receiver operating characteristics (ROC) curve analysis to determine the cut-off values of SII, SIRI, and AISI. Additionally, multivariate Cox proportional hazard analyses were used to identify independent predictors of clinical severity and major amputation risk in patients with PAD. We used Kaplan–Meier curves to model the crude association between SII, SIRI, and AISI and major amputation risk, and the log rank test to compare the curves. All tests were two-tailed, and a p value of ≤0.05 was considered statistically significant.

RESULTS

The study included 104 patients with CLTI, with an average age of 70.59 ± 9.13 years. Of these patients, 81 (71.88%) were male. In terms of clinical presentation, 44 patients (42.30%) had stage III Leriche-Fontaine, and 60 patients (57.70%) had stage IV Leriche-Fontaine (Table 1). There were no statistically significant differences between the

TABLE 2. Characteristics of atherosclerotic lesions of the infrainguinal arteries at preoperative CTA

Variables		All patients n = 104	Stage III Leriche-Fontaine n = 44	Stage IV Leriche-Fontaine n = 60	p value
Superficial femoral artery	70–90%	10 (9.61%)	4 (9.09%)	6 (10.0%)	0.877
	90–99%	14 (13.46%)	7 (15.91%)	7 (11.66%)	0.531
	Occlusion	17 (16.34%)	10 (22.72%)	7 (11.66%)	0.132
Popliteal artery	70–90%	6 (5.76%)	2 (4.54%)	4 (6.67%)	0.647
	90–99%	12 (11.53%)	7 (15.91%)	5 (8.33%)	0.232
	Occlusion	13 (12.5%)	2 (4.54%)	11 (18.33%)	0.036*
Anterior tibial artery	70–90%	3 (2.88%)	-	3 (5.0%)	0.132
	90–99%	10 (9.61%)	1 (2.27%)	9 (15.0%)	0.007*
	Occlusion	28 (26.92%)	10 (22.72%)	18 (30.0%)	0.409
Posterior tibial artery	70–90%	2 (1.92%)	-	2 (3.33%)	0.221
	90–99%	8 (7.69%)	1 (2.27%)	7 (11.66%)	0.076
	Occlusion	34 (32.69%)	10 (22.72%)	24 (40.0%)	0.064
Peroneal artery	70–90%	3 (2.88%)	1 (2.27%)	2 (3.33%)	0.221
	90–99%	15 (14.42%)	4 (9.09%)	11 (18.33%)	0.185
	Occlusion	7 (6.73%)	1 (2.27%)	6 (10.0%)	0.031*

*Statistically significant

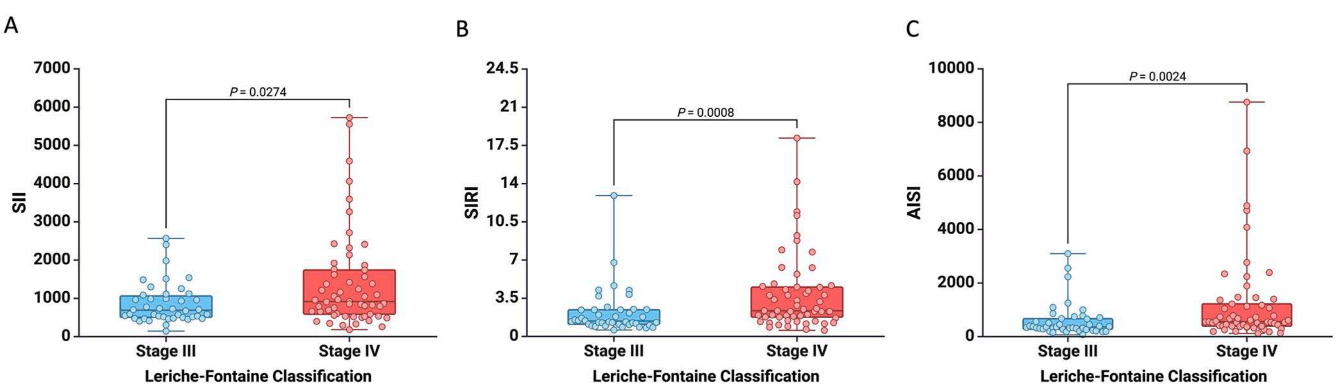

FIGURE 1. Graphical representation of the differences in SII (**A**), SIRI (**B**), and AISI (**C**) inflammatory biomarker values between patients with stage III and stage IV according to the Leriche-Fontaine classification

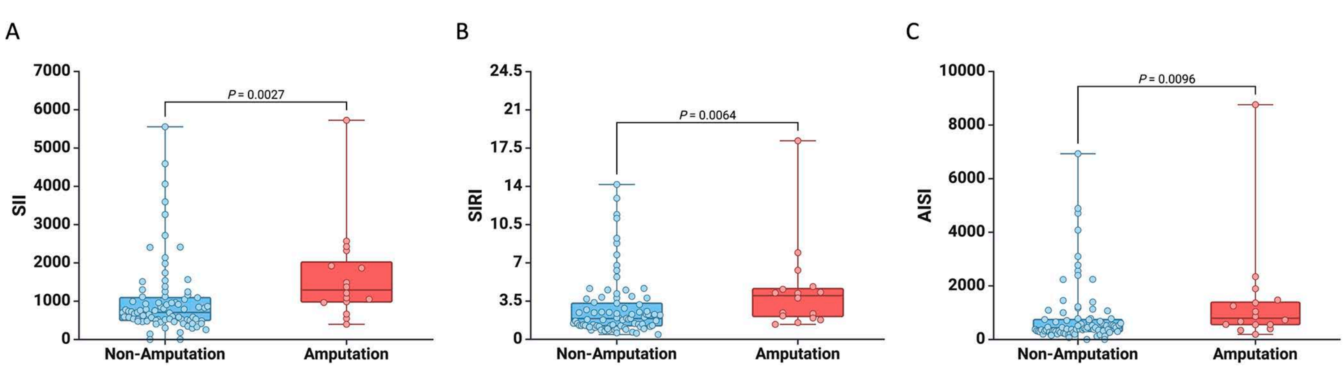

FIGURE 2. Graphical representation of the differences in SII (**A**), SIRI (**B**), and AISI (**C**) inflammatory biomarker values between patients with and without major amputation during follow-up

TABLE 3. ROC analysis for predicting clinical severity and major amputation

Variables	Cut-off	AUC	Std. error	95% CI	Sensitivity	Specificity	p value
Stage IV Leriche-Fontaine							
SII	–	0.633	0.057	0.492–0.715	–	–	0.052
SIRI	1.68	0.698	0.053	0.594–0.803	77.2%	52.4%	<0.001*
AISI	362.25	0.680	0.055	0.572–0.787	80.7%	50.0%	0.001*
Major amputation							
SII	961.68	0.731	0.067	0.600–0.862	81.3%	69.9%	0.001*
SIRI	1.49	0.712	0.060	0.595–0.829	93.8%	42.2%	<0.001*
AISI	395.68	0.698	0.067	0.568–0.829	87.5%	47.0%	0.003*

*Statistically significant

two groups in terms of demographic data, comorbidities, and risk factors (Table 1). However, patients in stage IV had increased levels of leukocytes (p = 0.005), neutrophils (p = 0.002), and monocytes (p < 0.001), as well as lower levels of hemoglobin (p = 0.030) (Table 1). There was also no significant difference in the risk of major amputation and length of stay between the two groups (Table 1).

Additionally, we analyzed the severity of atherosclerotic lesions in the superficial femoral artery, popliteal artery, and infra-popliteal artery. Patients with stage IV Leriche-Fontaine had a higher incidence of PA occlusion (p = 0.036), subocclusive ATA stenoses (p = 0.007), and peroneal artery occlusion (p = 0.031) (Table 2).

We observed higher levels of three inflammatory biomarkers, the SII (p = 0.027), SIRI (p = 0.0008), and AISI (p = 0.0024) in patients with trophic lesions (Figure 1). Furthermore, the levels of these biomarkers were also higher in patients who underwent major amputation during the follow-up (Figure 2).

We performed a ROC analysis to determine the correlation between SII, SIRI, and AISI values at baseline and the two endpoints. Our findings indicate that SIRI (AUC, 0.698; p < 0.001 and AUC, 0.712; p < 0.001) and AISI (AUC, 0.680; p = 0.001 and AUC, 0.698; p = 0.003) are useful predictors of clinical severity and the risk of major amputation in the long term. On the other hand, although the findings suggest that SII is a useful prognostic factor of major amputation (AUC, 0.731; p = 0.001), it may not be a reliable predictor of clinical severity (p = 0.052) (Table 3).

According to the Kaplan–Meier graph presented in Figure 3, patients with values of SII (p = 0.008), SIRI (p = 0.022), and AISI (p = 0.006) above the median at the time

TABLE 4. Factors predicting clinical severity and long-term risk of major amputation following PTA

Variables	Stage IV Leriche-Fontaine			Major amputation		
	OR	95% CI	p value	HR	95% CI	p value
Male	1.33	0.52–3.38	0.545	1.34	0.38–4.70	0.649
Age	1.41	0.94–2.12	0.100	0.98	0.61–1.59	0.928
Ischemic heart disease	1.52	0.68–3.39	0.306	1.31	0.89–1.93	0.159
Diabetes mellitus	1.45	0.66–3.17	0.351	2.59	0.86–7.74	0.089
Obesity	1.54	0.61–3.87	0.361	0.82	0.26–2.55	0.729
Active smoking	1.03	0.47–2.23	0.951	1.75	0.59–4.96	0.262
Dyslipidemia	1.55	0.71–3.38	0.279	1.24	0.46–3.34	0.672
Leriche-Fontaine III	–	–	–	0.77	0.28–2.12	0.612
Leriche-Fontaine IV	–	–	–	1.30	0.47–3.57	
SII	1.71#	1.04–3.46	0.055	1.56#	1.11–2.19	0.010*
SIRI	2.28#	1.16–4.49	0.017	1.63#	1.13–2.36	0.009*
AISI	2.32#	1.03–5.26	0.043	1.55#	1.08–2.22	0.016*

#HR expressed per 1 s.d. increase in baseline
*Statistically significant

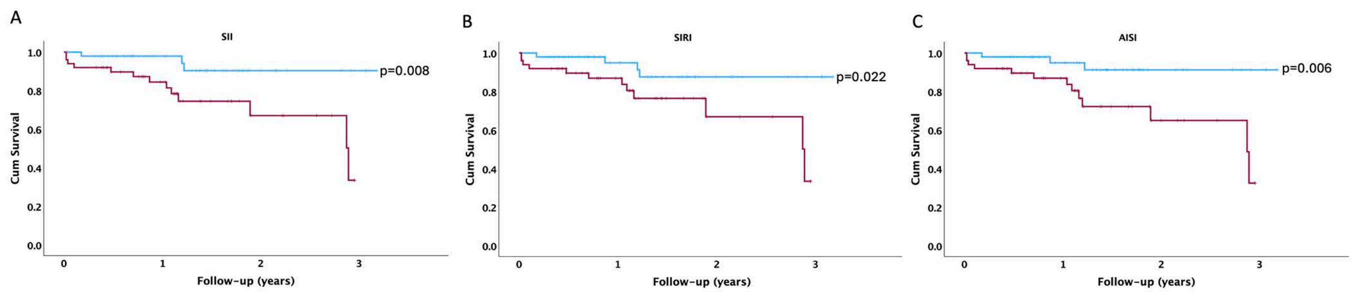

FIGURE 3. Kaplan–Meier graph showing the incidence of major amputation during follow-up, categorized by the median values of SII (**A**), SIRI (**B**), and AISI (**C**)

of admission are at a higher risk of major amputation in the long term, following PTA.

We also performed a multivariate regression analysis to identify risk factors that can predict clinical severity. Our findings suggest that high baseline values of SIRI (OR = 2.28; p = 0.017) and AISI (OR = 2.32; p = 0.043), but not SII (OR = 1.71, p = 0.055), are associated with stage IV Leriche-Fontaine (Table 4). Additionally, the results of the Cox regression analysis suggest that SII (HR = 1.56; p = 0.010), SIRI (HR = 1.63; p = 0.009), and AISI (HR = 1.55; p = 0.016) are predictive factors for long-term risk of major amputation after following PTA (Table 4).

DISCUSSION

The main findings of our study present for the first time, to our knowledge, that composite inflammatory biomarkers SII, SIRI, and AISI can predict the clinical severity and the risk of major amputation in the long term after endovascular treatment for CLTI.

The development of atherosclerotic plaques is influenced by several factors,[9,12,24–34] including cardiovascular risk factors,[9,12,24,25] changes in local hemodynamics and biomechanics,[26–30] and high levels of inflammation.[31–34] Patients with CLTI have a poor prognosis,[1,2] and studies have shown that those with high levels of inflammatory markers are at a greater risk of amputation and long-term mortality.[35,36] There is also evidence that patients with PAD have a more pro-inflammatory genetic profile than healthy individuals, and that this is further potentiated by the severity of the disease.[37] Furthermore, Gremmels *et al.*[36] have found that interleukin 6 (HR = 1.35; p = 0.01) and interferon gamma-inducible protein 10 (HR = 1.49; p = 0.006) can predict major events in patients with severe limb ischemia.

In a recent study by Ferreira *et al.*,[38] it was observed that patients with CLTI had a smaller skeletal muscle area (p = 0.013) and higher levels of inflammatory biomarkers, such as C-reactive protein (p < 0.001), fibrinogen (p < 0.001), serum albumin (p = 0.001), and total cholesterol (p = 0.013), than those with claudication. The same authors conducted another study, which showed that in patients with CLTI, more CD45+ leukocyte inflammatory cells were found in muscle biopsies at the level of the sartorius muscle (p = 0.034).[39] These changes can have an irreversible effect on the muscles of the lower limb, increasing the risk of major amputation in the long term. Ferreira *et al.*[40] conducted a study to examine changes in inflammatory biomarkers at admission, at 3 months, and at 6 months in patients who underwent successful revascularization treatment. The results showed that there was an increase in C-reactive protein and fibrinogen levels and a decrease in serum albumin and total cholesterol levels at 3 months after revascularization, but no significant changes were observed at 6 months.[40] The study concluded that prompt revascularization can partially reverse the inflammatory status of patients.

Recently, various inflammatory biomarkers have been proposed for cardiovascular disease, including SII, SIRI, and AISI, derived from blood cell counts. In this study, we have demonstrated the predictive role of these biomarkers regarding the clinical severity of PAD and the risk of major amputation in patients with CLTI, following PTA treatment. Studies by Candemir *et al.*[41] and Mangalesh *et al.*[42] have shown that high baseline SII values predict the severity of atherosclerotic lesions in patients with stable[41] or acute coronary syndrome.[42] On the other hand, Yang *et al.*[43] have found that SII has a prognostic role superior to the usual risk factors in nonfatal myocardial infarctions, nonfatal stroke, and cardiac death in a cohort of 5,602 patients with coronary artery disease. Similarly to our results, Oflar *et al.*[44] found a positive correlation between SII values and the severity of PAD (r = 0.363; p < 0.001). Additionally, Aktemur *et al.*[45] demonstrated that SII can predict long-term mortality after PTA in patients with iliac artery disease (OR = 3.346; p < 0.001).

There are a few studies on the prognostic value of SIRI in cardiovascular disease.[46–51] Wang *et al.*[46] found that high SIRI values are associated with the presence of cardiovascular disease and metabolic disorders. Xia *et al.*[47] demonstrated that elevated SII and SIRI are associated with cardiovascular mortality and all-cause mortality. In addition, Dziedzic *et al.*,[48] Li *et al.*,[49] Liu *et al.*,[50] and Han *et al.*[51] found that high SIRI values are associated with the severity of coronary disease and with the evolution of patients with myocardial infarction after percutaneous coronary intervention. Although AISI has not yet been analyzed in patients with PAD or CLTI, our study marks the first analysis of this biomarker, and we have demonstrated its predictive role in clinical severity and major amputation risk following PTA treatment.

There are some limitations to this study that need to be mentioned. First, it is an observational retrospective study that included patients from a single center. In the future, we need prospective studies that involve multiple centers to validate our findings and establish biomarker threshold values. Second, the study only involved patients with stage III–IV Leriche-Fontaine, therefore our results cannot be extrapolated to patients with stage I–II Leriche-Fontaine. Last, we could not obtain accurate data on the degree of restenosis after PTA because we relied on patients' self-reporting of major amputations.

CONCLUSIONS

This study found elevated levels of SIRI and AISI to be linked with the severity of clinical symptoms and an increased risk of major amputation in the long term in patients with CLTI following PTA. Additionally, higher baseline values for SII were associated with a greater risk of major amputation, but not with clinical severity in the same group of patients. In the future, composite biomarkers derived from blood cell counts could be used to better identify patients at risk and personalize their therapeutic strategies. These biomarkers are highly accessible and cost-effective, making them a promising tool for healthcare professionals.

CONFLICT OF INTEREST

Nothing to declare.

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