

ORIGINAL RESEARCH

# Neutrophil-to-Lymphocyte Ratio and Systemic Inflammation Index as Predictors of Poor Outcome in Patients with Critical Limb Ischemia Treated with Remote Endarterectomy

Anca Alexandra Derșidan<sup>1</sup>, Claudiu Constantin Ciucanu<sup>1</sup>, Agatha Maria Ilioniu<sup>1</sup>, Ionela Georgiana Bodiui<sup>1</sup>, Carina Diana Covalcic<sup>1</sup>, Ludovic Alexandru Szanto<sup>1</sup>, Adrian Vasile Mureșan<sup>1,2</sup>

<sup>1</sup> Clinic of Vascular Surgery, Emergency County Hospital, Târgu Mureș, Romania

<sup>2</sup> Department of Vascular Surgery, "George Emil Palade" University of Medicine, Pharmacy, Science and Technology, Târgu Mureș, Romania

## ABSTRACT

**Introduction:** Severe ischemia occurring in the lower limbs represents the advanced stage of peripheral artery disease (PAD). Atherosclerosis and inflammatory markers have been intensively studied to identify prognostic tools with a role in the evolution of patients with PAD. The aim of this study is to demonstrate the predictive value of systemic inflammatory markers such as the neutrophil-to-lymphocyte ratio (NLR) and the systemic inflammation index (SII) in the prognosis of patients diagnosed with critical leg ischemia (CLI) undergoing infringuinal surgical revascularization with remote endarterectomy. **Materials and methods:** This retrospective study included all patients admitted to the Vascular Surgery Clinic of the County Emergency Clinical Hospital of Târgu Mureș, Romania between January 2018 and December 2021, who had critical limb ischemia Leriche-Fontaine stage III and were treated with endarterectomy. Patients were divided into two groups based on the presence or absence of patency in the lower limbs at 12 months. **Results:** There was a higher baseline value of neutrophil count ( $p < 0.0001$ ), platelet count ( $p = 0.006$ ), NLR and SII value ( $p < 0.0001$ ), as well as a lower value of lymphocyte count ( $p = 0.001$ ) in the group without patency at 12 months. The ROC curve analysis showed that the NLR and SII were associated with the risk of major amputation and primary patency failure at 12 months, while multivariate analysis has shown that arterial hypertension (OR 3.63,  $p = 0.04$ ), history of myocardial infarction (OR 2.93,  $p = 0.009$ ), diabetes mellitus (OR 2.20;  $p = 0.04$ ) and smoking (OR 3.48,  $p < 0.0001$ ) were also predictors of primary patency failure. **Conclusions:** The results of this study demonstrated the predictive role of NLR and SII regarding poor outcomes among patients with CLI Leriche-Fontaine stage III undergoing infringuinal surgical revascularization with remote endarterectomy.

**Keywords:** neutrophil-to-lymphocyte ratio, systemic inflammation index, critical limb ischemia, remote endarterectomy, biomarkers

## ARTICLE HISTORY

Received: December 5, 2022

Accepted: December 15, 2022

## CORRESPONDENCE

**Claudiu Constantin Ciucanu**

Str. Gheorghe Marinescu nr. 50

540136 Târgu Mureș, Romania

Tel: +40 734 134 044

Email: claudiu.ciucanu@gmail.com

Anca Alexandra Derșidan: Str. Gheorghe Marinescu nr. 50, 540136 Târgu Mureș, Romania. Tel: +40 799 902 727, Email: dersidan.anca@yahoo.com

Agatha Maria Ilioniu: Str. Gheorghe Marinescu nr. 50, 540136 Târgu Mureș, Romania. Tel: +40 757 695 453, Email: 7agathi@gmail.com

Ionela Georgiana Bodiui: Str. Gheorghe Marinescu nr. 50, 540136 Târgu Mureș, Romania. Tel: +40 755 284 310, Email: bodiu\_ionela@yahoo.com

Carina Diana Covalcic: Str. Gheorghe Marinescu nr. 50, 540136 Târgu Mureș, Romania. Tel: +40 740 083 856, Email: covalcic.carina@yahoo.com

Ludovic Alexandru Szanto: Str. Gheorghe Marinescu nr. 50, 540136 Târgu Mureș, Romania. Tel: +40 737 801 160, Email: szanto.ludovic@gmail.com

Adrian Vasile Mureșan: Str. Gheorghe Marinescu nr. 50, 540136 Târgu Mureș, Romania. Tel: +40 744 894 319, Email: adrian.muresan@umfst.ro

## INTRODUCTION

Severe ischemia that occurs in the lower limbs represents the advanced stage of peripheral artery disease, manifesting with ischemic rest pain or tissue necrosis and corresponding to stages III–IV of the Leriche-Fontaine classification.<sup>1–3</sup> Untreated, the evolution of patients diagnosed with critical limb ischemia (CLI) is unfavorable, with a high risk of amputation and mortality. In one meta-analysis, in which 1,527 patients diagnosed with CLI without surgical or endovascular treatment were analyzed over a period of 12 months, the authors found a rate of approximately 20% for both amputation risk and mortality.<sup>4</sup>

The atherosclerotic process has been intensively studied to identify prognostic tools with a role in the evolution of patients with peripheral arterial disease (PAD). As atherogenesis is a local and systemic inflammatory process, the analysis of certain markers of systemic inflammation is mandatory.<sup>5–7</sup> Moreover, increased interest has been exhibited towards inflammatory markers derived from the total number of neutrophils, lymphocytes, and thrombocytes such as the neutrophil-lymphocyte ratio (NLR) or the systemic inflammatory index (SII), high values of these markers being associated with poor outcome in atherosclerotic diseases.<sup>5,8</sup> Furthermore, several studies have demonstrated their predictive value in patients with chronic kidney disease,<sup>9,10</sup> cardiovascular emergencies,<sup>11–13</sup> abdominal trauma,<sup>14</sup> and more recently, in patients with COVID-19.<sup>15–19</sup>

The purpose of this study is to demonstrate the predictive value of systemic inflammatory markers (NLR and SII) in the poor prognosis of patients diagnosed with CLI undergoing infrainguinal surgical revascularization with remote endarterectomy.

## MATERIAL AND METHODS

### STUDY DESIGN

We carried out a retrospective study that included all patients admitted to the Vascular Surgery Clinic of the County Emergency Clinical Hospital of Târgu Mureș, Romania between January 2018 and December 2021, who were diagnosed with CLI, Leriche-Fontaine stage III, and treated with remote endarterectomy. Exclusion criteria were patients in Leriche-Fontaine stage I, II, and IV, patients with a systemic inflammatory illness, recently diagnosed tumor, hematological illness, and autoimmune disorders. Furthermore, based on a recently published

paper regarding the relationship between inflammatory markers and the negative evolution of patients with COVID-19, patients with a history of COVID-19 infection were also excluded. Patients included in the study were divided into two groups according to the presence of patency at 12 months.

### DATA COLLECTION

We retrieved demographic information about the patients from the hospital's computerized database. From the medical records, we collected information about the main comorbidities: arterial hypertension, heart failure, history of myocardial infarction, ischemic heart disease, diabetes mellitus, and chronic kidney disease, as well as risk factors: smoking and obesity.

### PREOPERATIVE EXAMINATION AND REVASCULARIZATION METHOD

A physical examination and a blood test (glucose, hemoglobin, hematocrit, lymphocyte count, neutrophil count, platelet count) were part of the preoperative examination. The NLR and the SII were calculated using the following formulas:

$$\text{NLR} = \text{neutrophils/lymphocytes}$$

$$\text{SII} = (\text{neutrophils} \times \text{platelets})/\text{lymphocytes}$$

### STUDY OUTCOMES

The main outcomes were primary patency and amputation incidence at 12 months. Primary patency was established by the presence of arterial flow at Doppler ultrasound. In terms of amputation, we quantified all amputations above the ankle.

### ETHICAL APPROVAL

The study was carried out in compliance with the Helsinki Declaration and was authorized by the Ethics Committee of Târgu Mureș Emergency County Hospital (protocol code: 4875, March 4, 2022). All participants provided written informed consent to be included in the study.

### STATISTICAL ANALYSIS

SPSS for Mac OS version 28.0.1.0 was used for the statistical analysis (SPSS, Inc., Chicago, IL). Chi-square tests were employed to investigate the correlations between

hematological ratios and category factors. To assess differences in continuous variables, Student's t test or the Mann-Whitney tests were applied. The ROC curve analysis was performed to calculate the cut-off values of hematological ratios and to assess their predictive potential. The Youden index was used to obtain the proper NLR and SII cut-off values (Youden Index = sensitivity + specificity - 1, ranging from 0 to 1). To identify independent risk factors, a multivariate logistic regression analysis with variables with  $p < 0.1$  was done.

## RESULTS

We enrolled 119 patients, with a mean age of 69.48 years (range 50-93), from whom 86 were male. Depending on primary patency at 12 months, the patients were divided into two groups: Group 1 with the presence of patency, and Group 2 with the absence of patency. In terms of comorbidities and risk factors, there was a higher incidence

of arterial hypertension ( $p = 0.04$ ), history of myocardial infarction ( $p = 0.04$ ), diabetes mellitus ( $p = 0.03$ ), and smoking ( $p = 0.009$ ) in Group 2.

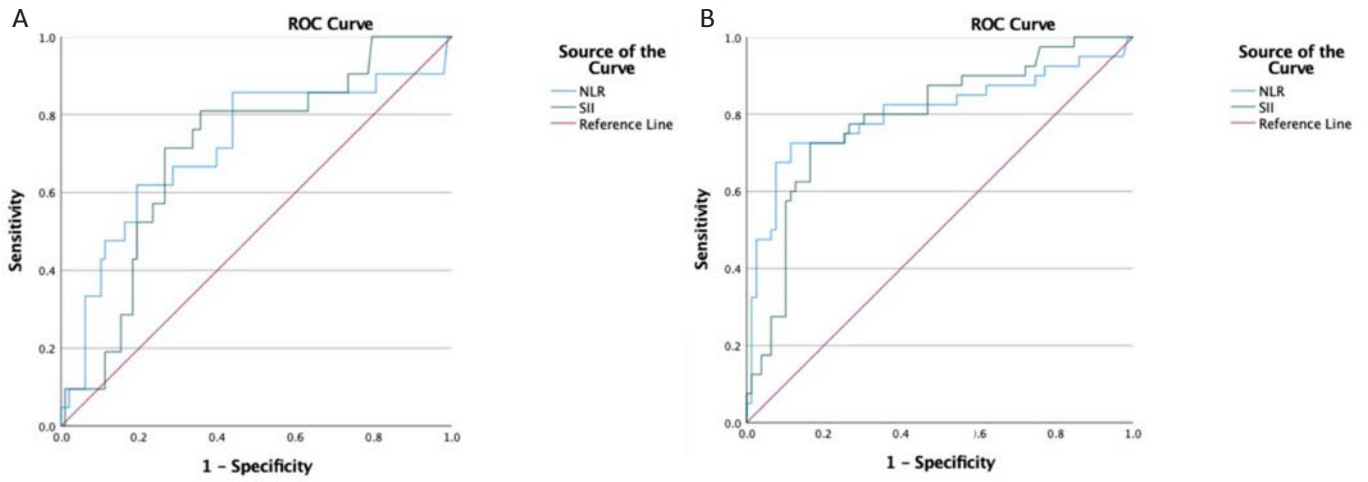
Regarding laboratory data, there was a higher baseline value of neutrophil count ( $p < 0.0001$ ), platelet count ( $p = 0.006$ ), NLR and SII value ( $p < 0.0001$ ), as well as a lower value of lymphocyte count ( $p = 0.001$ ) in Group 2. Also, there was a higher rate of amputation in Group 2 ( $p < 0.0001$ ). The rest of the analyzed variables are presented in Table 1.

At the ROC curve analysis, the NLR and the SII were associated with the risk of major amputation and primary patency failure at 12 months, as presented in Figure 1. The area under the curve (AUC), the optimal cut-off value, and the sensitivity and specificity of NLR and of the platelet-to-lymphocyte ratio (PLR) are presented in Table 2.

Additionally, a multivariate analysis was performed to identify the predictors of patency failure at 12 months. As seen in Table 3, arterial hypertension (OR 3.63,  $p = 0.04$ ), history of myocardial infarction (OR 2.93,  $p = 0.009$ ), dia-

**TABLE 1.** Demographic, comorbidities, risk factor, and laboratory data for all patients

Variables	All patients n = 119	Group 1 n = 79	Group 2 n = 40	p value
Age, mean $\pm$ SD (min-max)	69.48 $\pm$ 7.38 (50-93)	69.58 $\pm$ 6.99 (50-93)	69.3 $\pm$ 8.17 (50-88)	0.85
Male gender no. (%)	86 (72.27%)	60 (75.95%)	26 (65%)	0.83
<b>Comorbidities and risk factors, no. (%)</b>				
Arterial hypertension	98 (82.35%)	61 (77.22%)	37 (92.5%)	0.04
Heart failure	72 (60.5%)	43 (54.43%)	29 (72.5%)	0.059
History of myocardial infarction	42 (35.29%)	23 (29.11%)	19 (47.5%)	0.04
Ischemic heart disease	95 (79.83%)	61 (77.22%)	34 (85%)	0.32
Diabetes mellitus	56 (47.06%)	32 (40.51%)	24 (60%)	0.03
Chronic kidney disease	25 (21.01%)	15 (18.99%)	10 (25%)	0.44
Smoking	63 (52.94%)	35 (44.3%)	28 (70%)	0.009
Obesity	41 (34.45%)	24 (30.38%)	17 (42.5%)	0.19
<b>Laboratory data, median [Q1-Q3]</b>				
Hemoglobin, g/dL	11.94 [10.54-13.37]	11.94 [10.49-13.22]	11.91 [10.56-13.53]	0.45
Hematocrit, %	36.55 [32.12-40.77]	36.41 [32.13-40.87]	37.1 [32.13-40.59]	0.44
Glucose, mg/dL	107 [93-135.4]	108 [94-135.4]	106 [92-137.25]	0.4
Neutrophils $\times 10^3$ /uL	6.23 [4.89-7.86]	5.23 [4-6.59]	7.87 [6.44-9.62]	<0.0001
Lymphocytes $\times 10^3$ /uL	2.07 [1.53-2.63]	2.33 [1.79-2.94]	1.62 [1.31-2.15]	0.001
Monocytes $\times 10^3$ /uL	0.65 [0.52-0.79]	0.61 [0.47-0.72]	0.74 [0.6-0.99]	0.27
Platelets $\times 10^3$ /uL	254.3 [206.3-309]	225.15 [193.8-281.3]	283 [227.9-340.95]	0.006
NLR	2.8 [2.12-4.12]	2.4 [2.03-3.07]	4.6 [3.05-6.47]	<0.0001
SII	678.9 [514.3-1332.12]	579.97 [465.71-819.8]	1358.72 [797.18-1658.81]	<0.0001
<b>Outcomes</b>				
Major amputation, no. (%)	22 (18.49%)	4 (5.06%)	18 (45%)	<0.0001



**FIGURE 1.** The ROC curve of NLR and SII regarding the risk of major amputation (A) and primary patency failure at 12 months (B)

betes mellitus (OR 2.20;  $p = 0.04$ ), and smoking (OR 3.48,  $p < 0.0001$ ) were predictive of patency failure at 12 months. Moreover, the elevated baseline value of NLR and SII were strong independent predictors of patency failure at 12 months ( $p < 0.0001$  for both) (Table 3).

The Kaplan-Meier graphs for primary patency failure at 12 months and amputation risk evaluation in relation to the optimum NLR and SII cut-off values are shown in Figure 2.

## DISCUSSION

The main result of this study is the demonstration of the negative predictive role of inflammatory markers derived from peripheral blood count (NLR and SII) for the evolution of patients with CLI, without tissue necrosis (Leriche-Fontaine stage III), following endarterectomy of the femoral-popliteal axis, in terms of amputation risk and failure of vascular patency. Moreover, the presence of car-

diovascular comorbidities, such as arterial hypertension and myocardial infarction, were significant predictors for the negative evolution of the studied patients. Likewise, the presence of diabetes and smoking were associated with a high rate of patency failure at 12 months and a higher amputation risk.

The involvement of neutrophils and lymphocytes in the systemic inflammatory response, as well as their influence on the atherosclerotic process, is well understood.<sup>20,21</sup> Zhang *et al.* investigated the relationship between SII and the occurrence of PAD in 6,576 patients and demonstrated with multivariable logistic regression that a higher SII level was a risk factor for the diagnosis of PAD (OR 1.51,  $p = 0.001$ ).<sup>22</sup> Additionally, Paquissi *et al.*<sup>23</sup> recently published a literature review in which they analyzed the predictive value of NLR as a biomarker in coronary artery disease,<sup>24-33</sup> cerebrovascular disease,<sup>34-38</sup> and PAD,<sup>39-48</sup> and demonstrated that NLR was an inflammatory marker with a predictive role in atherosclerosis.

**TABLE 2.** The ideal cut-off value, AUC, specificity, and sensitivity of NLR and SII regarding the risk of major amputation and primary patency failure at 12 months

Variables	Cut-off	AUC	Std. error	95% CI	Sensitivity	Specificity	p value
<b>Major amputation</b>							
NLR	4.01	0.716	0.069	0.580-0.851	61.9%	80.6%	0.002
SII	1008.07	0.707	0.059	0.590-0.823	71.4%	73.5%	0.003
<b>12-month patency</b>							
NLR	3.81	0.803	0.049	0.706-0.900	72.5%	88.6%	<0.0001
SII	956.65	0.792	0.045	0.704-0.880	72.5%	83.5%	<0.0001

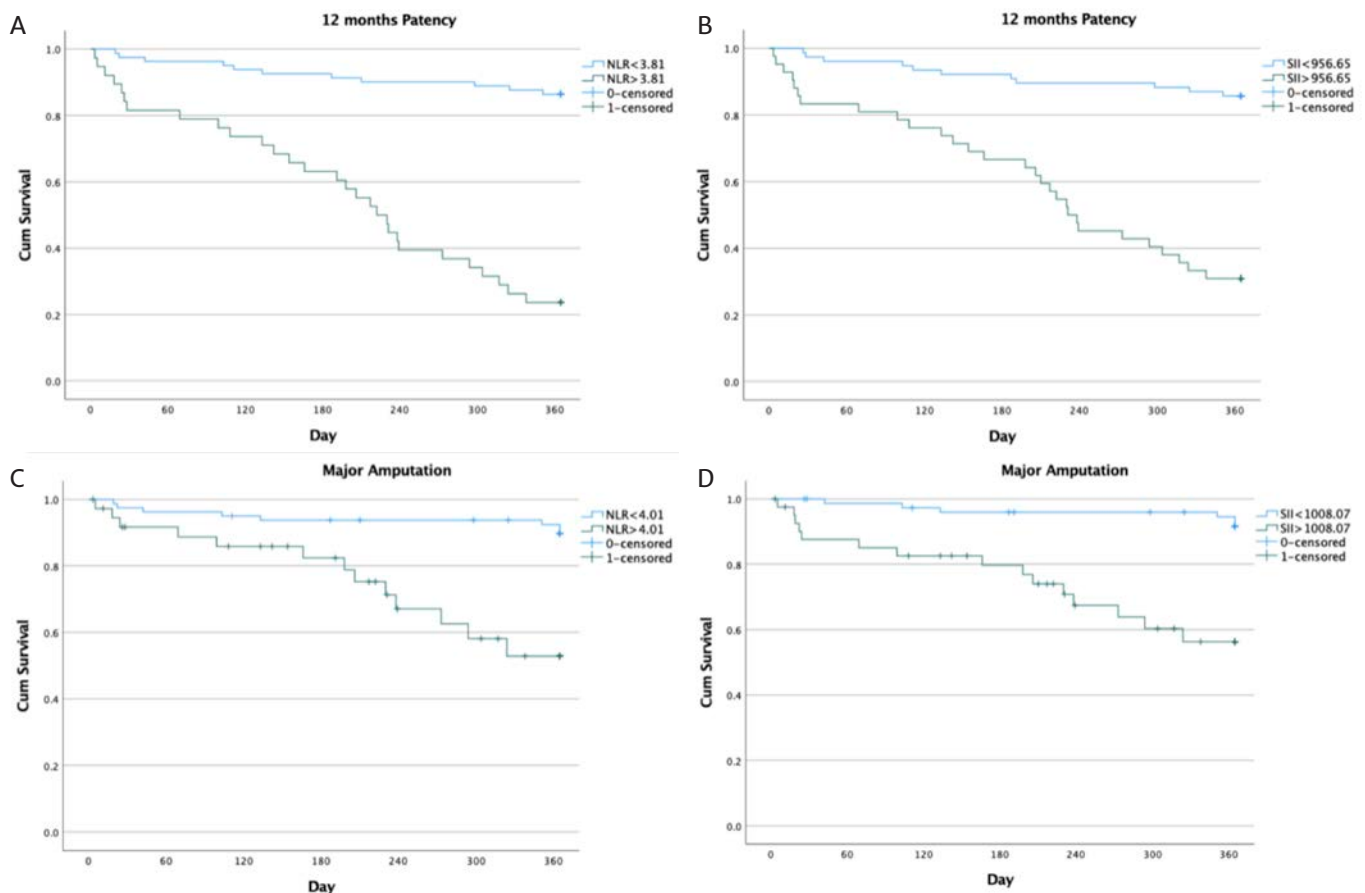
**TABLE 3.** Multivariate analysis of underlying risk factors and inflammatory markers, and primary patency failure at 12 months following remote endarterectomy

	Patency failure at 12 months		
	OR	95% CI	p value
Arterial hypertension	3.63	1.03–13.2	0.04
Heart failure	2.20	0.96–5.02	0.06
Myocardial infarction	2.93	1.30–6.58	0.009
Diabetes mellitus	2.20	1.01–4.78	0.04
Smoking	4.48	1.13–7.16	<0.001
NLR	20.56	7.68–54.71	<0.001
SII	11.84	4.81–29.15	<0.001

In the study published by Urbanowicz *et al.*, carried out on 538 patients with off-pump coronary artery bypass surgery, the authors demonstrated that a value greater than  $4.3 \times 10^9/L$  for the number of neutrophils (HR 13.44,  $p = 0.037$ ) and a value of NLR above 3.5 (HR 2.21,  $p < 0.001$ ) were predictive factors of long-term mortality.<sup>49</sup> Moreover, in a group of 95 patients with CLI undergoing in-

frainguinal angioplasty and stenting, Lee *et al.* found that a NLR greater than 2.75 (81.3% sensitivity and 50.8% specificity) was a predictor for restenosis.<sup>50</sup>

Russu *et al.* demonstrated in a study on 224 patients with femoropopliteal disease undergoing infrainguinal surgical revascularization that a baseline higher value of NLR ( $>3.95$ ) was a predictive factor for primary patency

**FIGURE 2.** Kaplan-Meier graphs for primary patency failure at 12 months, based on the ideal cut-off values for NLR (A) and SII (B) ( $p < 0.001$  for both markers; log-rank  $p$ ) and risk of amputation, based on the ideal cut-off values for NLR (C) and SII (D) ( $p < 0.001$ ; log-rank  $p$ ).

failure, amputation risk, and mortality during a 12-month follow-up period.<sup>8</sup> Additionally, Teperman *et al.* demonstrated that high NLR values were associated with PAD severity in a group of 733 patients.<sup>51</sup>

Despite the impressive results and the medium-term follow-up (12 months), this study has several limitations. Firstly, it was a retrospective, single-center research, with a relatively small group of patients. In the years to come, we suggest multicenter trials with long-term follow-ups and complication tracking. Secondly, the patients enrolled in this study were diagnosed with CLI Leriche-Fontaine stage III; thus, the results cannot be generalized to patients with trophic disorders (Leriche-Fontaine stage IV).

## CONCLUSIONS

The results of this study demonstrated the predictive role of NLR and SII regarding poor outcomes in patients with CLI Leriche-Fontaine stage III, undergoing infrainguinal surgical revascularization with remote endarterectomy. The presence of cardiovascular disease, diabetes mellitus, and risk factors such as active smoking were predictors for all outcomes registered.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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