

REVIEW

Neutrophil-to-Lymphocyte Ratio – Risk of Amputation and Mortality in Patients with Limb-Threatening Ischemia – a Systematic Review

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ABSTRACT

Acute limb ischemia (ALI) and chronic limb-threatening ischemia (CLTI) are severe vascular conditions that can be lethal. The inflammatory response in these diseases, characterized by increased levels of neutrophils and platelets, highlights the importance of prompt management. The neutrophil-to-lymphocyte ratio (NLR) has emerged as a useful biomarker during the COVID-19 pandemic and high NLR levels were found to be associated with an increased risk of ALI and other thromboembolic events. The aim of this systematic review was to analyze the prognostic role of the NLR regarding the risk of amputation and mortality in patients diagnosed with ALI and CLTI. We included 12 studies (five for ALI, with 1,145 patients, and seven for CLTI, with 1,838 patients), following the PRISMA guidelines. Treatment results were evaluated, including amputation and mortality. We found that high NLR values were consistently associated with an increased risk of amputation and/or mortality, with pooled odds ratios ranging from 1.28 to 11.09 in patients with ALI and from 1.97 to 5.6 in patients with CLTI. The results suggest that NLR may represent an important tool for informed decision-making in the management of these patients.

Keywords: acute limb ischemia, chronic limb-threatening ischemia, inflammatory biomarkers, mortality, outcome

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INTRODUCTION

Acute limb ischemia (ALI) and chronic limb-threatening ischemia (CLTI) are severe vascular conditions that can lead to amputation and even death if left untreated.^{1,2} ALI is characterized by a sudden blockage of arterial blood flow, which can cause pain, loss of function, and skin pallor.¹ CLTI is the final stage of peripheral arterial disease and is characterized by symptoms such as persistent pain, trophic disorders, and impaired mobility.²

The inflammatory state that dominates ALI increases the number of neutrophils, which are the primary responders to the site of injury, and platelets that adhere to the activated endothelium.³ Additionally, numerous articles have demonstrated that neutrophils have an essential role in the acute phase of certain thromboembolic events, such as myocardial infarction,^{4–6} both in patient cohorts⁴ and in experimental models.^{5,6} Furthermore, the crucial role of lymphocytes in both the inflammatory and repair phase following an acute event is well established.^{7,8}

The neutrophil-to-lymphocyte ratio (NLR) biomarker has gained significant attention due to its ability to indicate poor outcomes in patients with various diseases. It is derived from the total number of neutrophils and lymphocytes and is a prognostic factor in end-stage kidney disease,^{9–11} atherosclerotic diseases,^{12,13} COVID-19,^{14–16} and other pathologies.^{17,18} Additionally, it was demonstrated that the COVID-19 pandemic led to an increase in the incidence of patients with ALI¹⁹ as well as thromboembolic events,^{20–26} and recently, Arbănași *et al.*¹⁶ demonstrated that high NLR values are associated with the risk of developing ALI in a cohort of 510 patients with COVID-19.

The aim of this systematic review was to analyze the prognostic role of the NLR regarding the risk of amputation and mortality in patients diagnosed with ALI and CLTI.

METHODS

We carried out a systematic review of the literature according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, using articles from the PubMed database and the search terms ‘acute limb ischemia’ or ‘chronic limb-threatening ischemia’ and ‘NLR’.

Two independent reviewers (B.L. and E.R.) conducted the literature search. We included all articles with relevant titles published from January 1, 2010 to January 1, 2023. Only articles published in English were considered. Studies written in languages other than English, studies unrelated to this topic or with insufficient data, as well as non-confirmatory cases and duplicate articles were excluded.

We found 2,301 articles that met the search criteria and added eight articles from the reference lists of these articles. We excluded 835 duplicates and 1,449 articles that did not meet the inclusion criteria. From the remaining 25 articles we excluded seven with unclear methodology, four diagnostic-type studies, and two articles that involved patients with COVID-19. The PRISMA flow chart of the investigation plan is shown in Figure 1.

RESULTS

We included 12 studies in this systematic review, of which five were related to ALI, with a total of 1,145 patients, and seven were related to CLTI, with a total of 1,838 patients.

In terms of demographic data, the average age of patients with ALI was 73.06 years (range 66–79), with 717 (62.62%) of these patients being male. The average age of patients with CLTI was 71.96 years (range 64–81), with

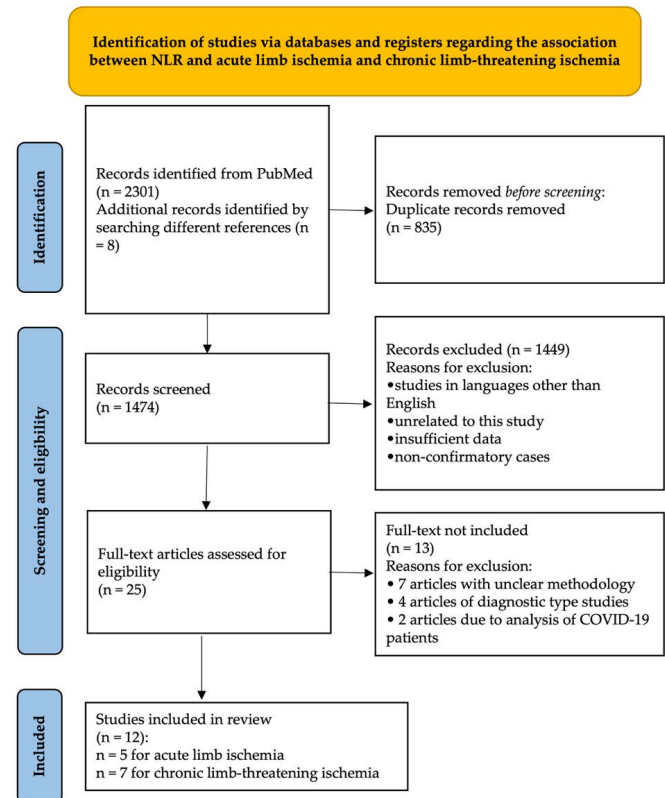


FIGURE 1. PRISMA flow chart of studies included in the systematic review

1,282 (69.75%) being male. In terms of comorbidities, 869 patients with ALI (75.9%) had hypertension, 387 (33.8%) had diabetes, 371 (32.4%) had ischemic heart disease, and 458 (40%) were active smokers. Of the patients with CLTI, 1,151 (62.62%) had hypertension, 844 (45.92%) had diabetes, 643 (34.98%) had ischemic heart disease, and 992 (53.97%) were active smokers (Table 1).

The disease etiology, treatment, and outcomes of the 1,145 patients with ALI are presented in Table 2. The disease had an embolic etiology in 521 patients (45.5%) and a thrombotic etiology in 434 patients (37.9%). As far as localization is concerned, 588 patients (51.35%) presented a thrombosis located at the femoral-popliteal axis, 123 (10.74%) at the aorto-iliac axis, and 35 (3.06%) below the knee artery. Treatment included embolectomy in 62.62% (n = 717), bypass in 9% (n = 103), and hybrid techniques or other treatments in 9.61% (n = 110) of patients. Regarding the outcomes, 19.04% (n = 218) had to undergo major amputation after surgery, and 15.55% (n = 178) did not survive.

The results of the receiver operating characteristic (ROC) analysis specific to each study are presented in Table 3. In patients with ALI, the average optimal cut-off value of NLR was 5.49 (range 4.23–6.66), with an average area under the curve (AUC) of 0.730 (range 0.639–0.860), an

TABLE 1. The general characteristics of the studies included in the review

Study	Year	Country	No. of patients	Mean age (years)	Male sex, n (%)	Hypertension, n (%)	Ischemic heart disease, n (%)	Diabetes, n (%)	Active smoking, n (%)
ALI									
Taşoğlu et al. ²⁷	2013	Turkey	245	66.04	152 (62%)	144 (59%)	–	60 (24%)	170 (70%)
Coelho et al. ²⁸	2021	Portugal	345	73	188 (54.5%)	277 (83.5%)	157 (45.5%)	92 (27.5%)	136 (39.4%)
Taurino et al. ²⁹	2021	Italy	177	78.9	115 (65%)	145 (81.9%)	–	70 (39.5%)	–
Pasqui et al. ³⁰	2021	Italy	168	77.8	109 (64.9%)	128 (76.1%)	45 (26.7%)	54 (32.1%)	18 (10.7%)
Arbănași et al. ³¹	2022	Romania	210	69.56	153 (72.86%)	175 (83.33%)	169 (80.48%)	111 (52.86%)	134 (63.81%)
CLTI									
Spark et al. ³²	2010	UK	149	72	–	83 (55.7%)	–	44 (29.53%)	103 (69.12%)
Chan et al. ³³	2014	Australia	97	81	50 (64.9%)	42 (54.6%)	49 (63.6%)	46 (59.7%)	–
Gonzalez-Fajardo et al. ³⁴	2014	Spain	561	74	465 (83%)	354 (63.10%)	131 (23.35%)	258 (45.98%)	362 (64.52%)
Erturk et al. ³⁵	2014	Turkey	508	64	413 (81.3%)	311 (61.22%)	207 (40.74%)	213 (41.92%)	266 (52.36%)
Taşoğlu et al. ³⁶	2014	Turkey	104	69	86 (82.7%)	46 (44.2%)	–	39 (37.5%)	74 (71.2%)
Su et al. ³⁷	2021	Taiwan	195	74	102 (52.3%)	129 (66.15%)	75 (38.46%)	134 (68.71%)	46 (23.58%)
Russu et al. ³⁸	2022	Romania	224	69.72	166 (74.11%)	186 (83.04%)	181 (80.8%)	110 (49.11%)	141 (62.95%)

average sensitivity of 70.10%, and a specificity of 68.11 %. In patients with CLTI, the average optimal cut-off value of NLR was 4.8 (range 3.2–8), with an average AUC of 0.715 (range 0.640–0.821), an average sensitivity of 61.4%, and a specificity of 82.62%.

DISCUSSION

In this systematic review, we examined the role of NLR in the post-revascularization progression of patients with ALI and CLTI. We found that high NLR values are

TABLE 2. Disease etiology, treatment, and outcomes of patients with ALI

Study	Study group value	Control group value	Cut-off value	AUC/ROC analysis	Sensitivity (%)	Specificity (%)	Outcome
ALI							
Taşoğlu et al. ²⁷	9.7	6.1	5.2	0.7	63%	63%	Amputation
Coelho et al. ²⁸	8.8	3.6	5.4	0.860	90.5%	73.6%	Death or major amputation at 30 days
Taurino et al. ²⁹	–	–	5	0.823	–	–	Amputation at 30 days
	–	–	5	0.776	–	–	Mortality at 30 days
Pasqui et al. ³⁰	8.9	6.5	6.66	0.712	77.8%	65.3%	Amputation at 26.9 ± 22.1 months
	8.08	5.6	5.57	0.639	62.3%	56.04%	Mortality at 26.9 ± 22.1 months
Arbănași et al. ³¹	5.78	2.61	4.23	0.829	70.2%	83%	Major amputation at 30 days
CLTI							
Spark et al. ³²	–	–	5.25	0.690	60%	71%	Mortality at 8.7 months (3.1–16 months)
Chan et al. ³³	–	–	5.25	–	–	–	Mortality at 12 months
Gonzalez-Fajardo et al. ³⁴	–	–	5	0.64	32%	87.5%	Amputation-free survival at 31 months
Erturk et al. ³⁵	–	–	3	–	–	–	Cardiovascular death at 20 months (12–27 months)
Taşoğlu et al. ³⁶	3.8	2.4	3.2	0.71	–	–	Major amputation at 46 months
Su et al. ³⁷	–	–	8	–	62%	82.1%	Mortality at 12 months
Russu et al. ³⁸	6.40	2.21	3.95	0.821	82.6%	89.9%	Primary patency at 12 months

TABLE 3. Clinical cases and surgical procedures for ALI

Study	Cause		Location			Treatment			Complication	
	Embolic, n (%)	Thrombotic, n (%)	Aortoiliac, n (%)	Femoral-popliteal axis, n (%)	Below the knee artery, n (%)	Embolectomy, n (%)	Bypass, n (%)	Other, n (%)	Amputation, n (%)	Mortality, n (%)
Taşoğlu et al. ²⁷	224 (92%)	21 (8%)	44 (18%)	189 (78%)	–	224 (92%)	21 (8%)	–	36 (14.69%)	25 (10%)
Coelho et al. ²⁸	157 (45.5%)	188 (54.5%)	60 (17.4%)	261 (75.7%)	24 (7%)	280 (81.2%)	35 (10.1%)	30 (8.7%)	84 (24.34%)	–
Taurino et al. ²⁹	73 (41.3%)	104 (58.7%)	–	–	–	95 (53.7%)	9 (5.1%)	73 (41.2%)	23 (12.9%)	29 (16.4%)
Pasqui et al. ³⁰	67 (39.9%)	121 (60.1%)	19 (11.3%)	138 (82.1%)	11 (6.5%)	–	–	–	18 (10.7%)	77 (45.8%)
Arbănași et al. ³¹	–	–	–	–	–	118 (72.39%)	38 (23.31%)	7 (4.29%)	57 (27.14%)	47 (22.38%)

associated with an increased risk of amputation and/or mortality, with pooled odds ratios ranging from 1.28 to 11.09 in patients with ALI, and from 1.97 to 5.6 in patients with CLTI. Additionally, the ROC analysis identified optimal cut-off values for NLR, with a narrow distribution. The average cut-off value was 5.49 (range 4.23–6.66) for patients with ALI and 4.8 (range 3.2–8) for patients with CLTI.

This biomarker has already been proven to be useful in the prediction of poor outcomes in the context of other vascular diseases such as stroke, acute pulmonary embolism, abdominal aortic aneurysm, and numerous cardiac pathologies. In a study involving 448 patients with acute ischemic stroke,³⁹ Chen *et al.* analyzed the relationship between NLR and outcomes, and demonstrated that high NLR values are associated with poor functional outcomes 3 months after the index events, identifying an optimal cut-off value of 3.51 (78.1% sensitivity and 83.2% specificity). Similarly, in a study involving 116 patients with stroke, Brooks *et al.*⁴⁰ demonstrated that high NLR values at admission are associated with poor recovery and mortality following endovascular therapy. More recently, Xu *et al.*⁴¹ identified in a cohort of 341 of patients diagnosed with stroke that a baseline value of NLR higher than the optimal cut-off value of 4.21 (52.7% sensitivity and 72% specificity) is associated with the risk of stroke progression in the first week after admission.

Another vascular pathology in which the prognostic role of NLR has been demonstrated is abdominal aortic aneurysm (AAA).^{42–44} Kardzadeh *et al.*⁴² have shown in a cohort of 80 patients with ruptured AAA that high preoperative values of NLR (OR 4.28, $p = 0.02$) are associated with the risk of morbidity 30 days post operation. Similarly, Aure-

lian *et al.*⁴³ have shown that NLR values above the cut-off value of 5 are associated with a five times higher risk of AAA rupture. In a cohort of 350 patients, Appleton *et al.* demonstrated that preoperative NLR values greater than 5 are associated with 30-day mortality ($p = 0.0007$) and 10-year mortality ($p = 0.043$) after AAA repair.

Regarding cardiac pathology, numerous studies have examined the local and systemic inflammatory response in the remodeling of cardiac function and poor outcomes of patients with acute coronary syndrome.^{6,45–50} However, the cost of identifying these biomarkers is high and their availability in current practice is very limited; hence, NLR has recently been intensively analyzed and studied.^{51–56}

CONCLUSIONS

This systematic review emphasizes the importance of NLR in the prognosis of both ALI and CLTI. Elevated NLR levels were consistently associated with an increased risk of amputation and death. This indicates that NLR may serve as a useful tool for decision-making in the management of these patients.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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