An elevated neutrophil-lymphocyte ratio independently predicts mortality in chronic critical limb ischemia

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Background: **Atherogenesis represents an active inflammatory process with leucocytes playing a major role. An elevated white blood cell count has been shown to be predictive of death in coronary artery disease patients. The aim of this study was to examine the predictive ability of neutrophil count and neutrophil/lymphocyte ratio for predicting survival in patients with critical lower limb ischemia (CLI).**

Methods: **All patients admitted to a single vascular unit with CCLI were identified prospectively over a 2-year period starting from January 2005. Patient demographics, clinical history, comorbidity, and risk factors for peripheral vascular disease were documented. The white blood count and differential cell count at admission was recorded. Overall, patient mortality was studied as the primary outcome.**

Results: **One hundred forty-nine patients were identified, with a median age of 72 years (Interquartile range [IQR], 65.7-81). A neutrophil-lymphocyte ratio (NLR) of ≥5.25 was taken as the cutoff, based upon the receiver-operating-characteristic.The median follow up was 8.7 months (IQR, 3.1-16). During the follow-up period, there have been 62 deaths (43.4%). An elevated neutrophil/lymphocyte ratio and a high troponin level (>0.1) were found to be the only two factors independently associated with shorter survival on multivariate analysis using the Cox proportional hazards model.**

Conclusions: **This study suggests that an elevated NLR can identify a poor-risk subset of patients among those being treated for critical limb ischemia. This simple, inexpensive test may, therefore, add to risk stratification of these high-risk patients. (J Vasc Surg 2010;52:632-6.)**

Adverse cardiovascular events are a significant cause of major morbidity and mortality in the perioperative period. Patients with chronic critical limb ischemia (CLI) have a high incidence of coronary heart disease (CHD), with autopsy studies showing that >90% of patients have advanced coronary atherosclerosis.[1-3] The 1-year mortality rate has been reported to be 26% and as high as 75% at 10 years.[4] Risk stratification for patients who present with CLI has become increasingly important in order to improve clinical decision making and to determine the most appropriate therapy for individual patients, by identifying not only high-risk patients but also determining which patients would benefit most from newer, less-invasive, or potentially less-durable therapies. Identifying patients at risk before an operation is also useful if used to modify the perioperative management and reduce complication rates.

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In recent years, it has been noted that atherosclerosis represents an active inflammatory process in which leucocytes play a major role. The white blood cell (WBC) count and its subtypes have been found to correlate with outcome in stable and unstable coronary syndromes, including ST-elevation myocardial infarction (MI) and non–ST-elevation MI.[5-8] The neutrophil/lymphocyte ratio (NLR) has emerged as a prognostic marker and with a proinflammatory state being associated with worse outcomes in cardiac disease as well as in oncologic surgery.[9-11]

This study was conducted to investigate the role of admission NLR in predicting all-cause mortality in patients with CLI who underwent therapeutic intervention.

PATIENTS AND METHODS

All patients admitted with CLI at a single university teaching hospital were entered into this prospective study over a 2-year period. CLI was defined using the following criteria for diagnosis: more than 2 weeks of recurrent foot pain at rest that requires regular use of opiate analgesics and is associated with an ankle systolic pressure of 50 mm Hg or less, or a toe systolic pressure of 30 mm Hg or less, or a nonhealing wound or gangrene of the foot or toes (Rutherford categories 4 and 5). The protocol was approved by the institutional review board.

Demographic characteristics, medical histories, laboratory studies (including WBC counts and automated peripheral differential counts), and outcomes data were collected by the research team using a standardized database. Any subsequent surgical or radiological intervention was also documented as follows: primary surgery (limb salvage), primary surgery (amputation), radiological, or a combined procedure. Patients with evidence of acute limb ischemia, infected ischemic ulcers, or current symptomatic or unstable coronary disease (n = 3) were excluded from outcome analysis. All-cause mortality following admission was the primary outcome variable.

Patients were followed up in outpatient clinics following discharge. For patients who died while an in-patient, hospital records and autopsy results were retrieved and reviewed. Mortality was recorded from the hospital Patient Administration System. For patients who died in the community, general practitioners were approached to ascertain the cause of death. A secondary endpoint of cardiac-specific mortality was also recorded from the death certificate (MI, arrhythmias, congestive cardiac failure) and by reviewing the hospital notes.

Statistical analysis. The effect of NLR on outcome was studied by constructing a receiver operating characteristic (ROC) curve with all-cause mortality as the primary variable. (Fig 1). Analysis was performed using SPSS version 11.0.0 (SPSS Inc, Chicago, IL). The chi-square test was used to perform univariate analysis for categorical variables and Mann-Whitney *U* test for continuous variables. Results are presented as median with interquartile range unless otherwise specified. Survival analysis was conducted using Kaplan-Meier survival curves, and differences were compared using the log-rank test. Cox regression analysis of all variables was conducted in a stepwise fashion. A *P* value ≤ .05 was considered statistically significant.

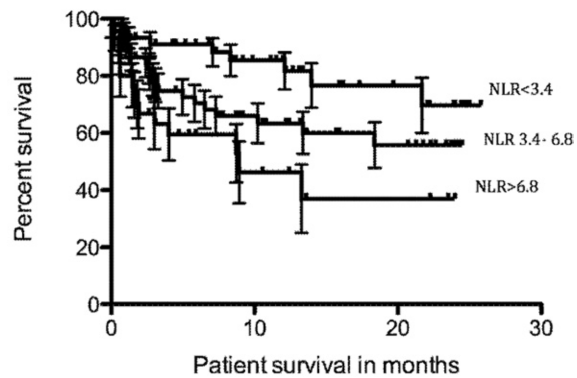
RESULTS

One hundred fifty-one patients met the inclusion criteria for analysis during the study period. Two patients were excluded because of insufficient data at admission. The median age was 72 years (interquartile range [IQR], 65.7-81 years) and median follow-up was 8.7 months (IQR, 3.1-16 months).

Selection of a cutoff for the NLR. An analysis of the NLR with respect to mortality was conducted using tertiles of existing data (ie, using cutoffs of NLR <3.4, NLR between 3.4 and 6.8, and an NLR >6.8). This calculation provided fairly good discriminant value ($P = .022$; Fig 1A).

While NLR appeared to affect the outcome in a continuous fashion, we chose to use a single cutoff point to better inform clinical practice. An ROC was constructed to study the effect of NLR with all-cause mortality as the primary variable (Fig 1B). The ROC characteristic had a c-statistic of 0.69, and a value of NLR ≥5.25 was selected as a cutoff, to maximize sensitivity and specificity. A sensitivity of 69% and a specificity of 71% were obtained for the final model. Sixty-five (43.9%) patients had a neutrophil lymphocyte ratio ≥5.25 at admission.

The univariate analysis of the two groups based on factors studied is shown in Table I. Tissue loss at presentation was comparable between groups. Older patients were significantly more likely to have an elevated NLR, with the mean age in the high NLR group versus low NLR group being 76.1 ± 10.1 years versus 70.6 ± 10.7 years, respectively ($P = .03$). The incidence of diabetes and hypertension were significantly higher in the low NLR group, while elevated troponin levels (>0.1) were more commonly found in the high NLR group. Statin use differed between groups (32.5% in the low NLR group vs 18.8% in the high NLR group; $P = .06$). No trends could be demonstrated for the other variables on univariate analysis (Table I). The absolute neutrophil and lymphocyte counts for the low and high NLR groups were significantly different (neutrophil counts 5.9 ± 2.1 vs 10.3 ± 4.5, $P < .001$; lymphocyte counts 2.3 ± 2.4 vs 1.1 ± 0.5, $P < .001$).



Groups at risk			
NLR <3.4	25	11	0
NLR 3.4-6.8	25	12	0
NLR>6.8	7	4	0

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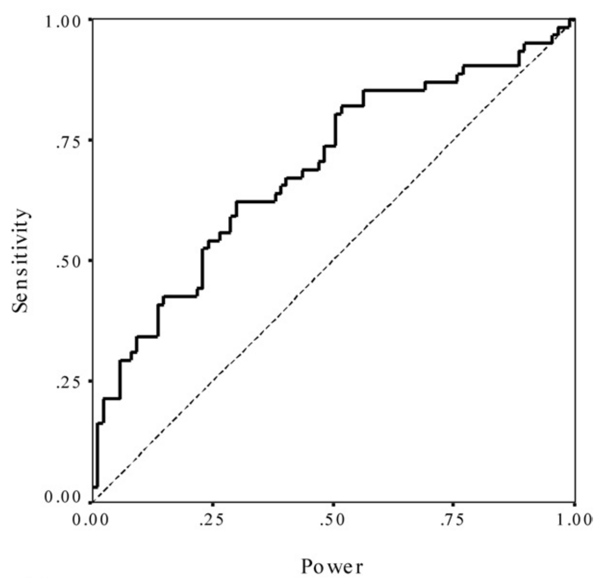


B C statistic : 0.69

Fig 1. **(A)** Kaplan-Meier curves for neutrophil/lymphocyte ratio (*NLR*) using tertiles ($P = .002$). **(B)** A receiver operating characteristic (ROC) for neutrophil-lymphocyte ratio versus mortality.

Table I. Univariate analysis of risk factors for patients with critical ischemia

Variable	*NLR <5.25 (n = 83)*	*NLR ≥5.25 (n = 66)*	P *value*
Age >70 years (86)	41 (49.3%)	45 (68.1%)	.03
Diabetes (44)	36 (43.4%)	8 (12.1%)	<.001
Hypertension (83)	53 (63.8%)	30 (45.5%)	.04
Previous myocardial infarction (14)	11 (13.2%)	3 (4.5%)	.5
Previous cerebrovascular accident (15)	11 (13.2%)	4 (6.1%)	.18
Renal failure (8)	3 (3.6%)	5 (7.6%)	1
Smokers (103)	63 (75.9%)	40 (60.6%)	.14
Troponin >0.1 (50)	19 (22.9%)	31 (41.9%)	.003
Tissue loss at admission	16 (19.2%)	11 (16.7%)	.8
Statin use	27 (32.5%)	12 (18.8%)	.06

NLR, Neutrophil/lymphocyte ratio.
Figures are presented as n and percentage.
Renal failure, patients who were on dialysis at the time of assessment.

Table II. Analysis of procedures for elevated neutrophil/lymphocyte ratio

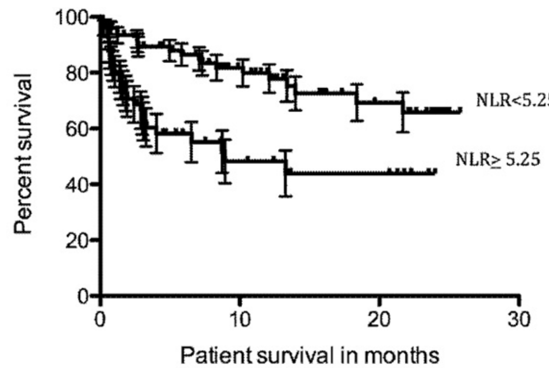
	NLR <5.25 (n = 83)	*NLR ≥5.25 (n = 66)*	P *value*
Surgery (non amputation)	21 (25.3%)	6 (9.1%)	.5
Angioplasty/stenting	21 (25.3%)	12 (18.2%)	1
Combined procedure	11 (13.2%)	5 (7.6%)	1
Major amputation	11 (13.2%)	12 (18.2%)	.5
Minor amputation	6 (7.2%)	3 (4.5%)	
Conservative/palliative	23 (27.7%)	27 (40.9%)	.6

NLR, Neutrophil/lymphocyte ratio.

The break-up of interventional procedures is shown in Table II. There was a nonsignificantly higher incidence of major amputations in the elevated NLR group (18.1% vs 13.2%; $P = .5$). A higher number of patients with lower NLR underwent vascular reconstructive surgery (25.1% vs 9.2%; $P = .5$). There was no difference in the failure rates of surgical revascularization in both groups (n = 2 and n = 3; $P = .32$). There was no significant difference in the rates of nonsurgical or conservative management between the groups.

There were 62 deaths during the course of the study. Thirty-eight of these occurred within the elevated NLR group, while 24 mortalities occurred in the low NLR group (58.4% vs 28.6%; $P < .001$). Of the 20 deaths which were specifically attributed to cardiac causes, seven (8.4% of the cohort mortality) occurred in the low NLR group, while 13 (19.5% of the cohort mortality) occurred in the high NLR group ($P = .055$). Median survival for the low NLR group was not reached, while the median survival for the elevated NLR group was 8.6 months ($P = .006$ on log-rank survival analysis; Fig 2).

Risk factors for mortality, including age >70 years, elevated troponin, history of stroke or previous MI, statin use, renal failure, elevated NLR, and smoking history (at any time), were included in a Cox regression model and analyzed in a stepwise fashion. An elevated troponin, NLR ≥ 5.25, and statin use pre-admission were independent predictive factors of all-cause mortality (hazard ratios [95% confidence interval], 3.1 [1.6-5.6] and 2.3 [1.2-4.2], 0.2 [0.06-0.7]; $P < .001$, .007, and .13, respectively; Table III).



Patients at risk

NLR < 5.25	43	20	0
NLR ≥ 5.25	14	6	0

Fig 2. Kaplan-Meier survival curve for neutrophil/lymphocyte ratio (*NLR*), with a cutoff of 5.25.

Table III. Multivariate analysis of factors affecting mortality in patients with critical limb ischemia

	Hazard ratio (95% confidence interval)	P *value*
Elevated troponin	3.1 (1.6-5.6)	<.001
Neutrophil/lymphocyte ratio >5.25	2.3 (1.2-4.2)	.007
Diabetes mellitus	0.5 (0.2-1.1)	.1
Hypertension	1.4 (0.7-2.6)	.4
Previous myocardial infarction	1.2 (0.4-3.8)	.8
Renal failure	0.3 (0.05-3.7)	.3
Statin use	0.2 (0.06-0.7)	.013

DISCUSSION

This study demonstrates that an elevated NLR is associated with higher mortality in patients with peripheral arterial disease who present with CLI.

Patients suffering from peripheral artery disease bear a considerable risk of MI, stroke, or cardiovascular death that is directly related to the severity of disease.[12] A mortality rate of 43% is seen over a median follow-up time of 8.7 months, indicating a high risk of poor outcome, and this underscores the need for additional parameters for risk stratification.

Leukocytes of the monocyte-macrophage lineage have a crucial pathophysiologic role in the development of atherosclerotic plaque and deposition of lipids therein. The role of granulocytes, which accounts for 50% to 70% of the total WBC count in the atherothrombotic process, seems less clear. However, in most of the prospective cohort studies that have provided information on differential WBC count, the number of neutrophils correlated primarily and consistently in a positive manner with the atherosclerotic load and ischemic conditions.[5,13-16]

NLR has been found to be an independent predictor of short-term mortality in patients with acute coronary disease. Neutrophils mediate inflammatory response by numerous biochemical mechanisms, such as release of arachidonic acid metabolites and platelet-aggravating factors, cytotoxic oxygen-derived free radicals, and hydrolytic enzymes such as myeloperoxidase, elastase, various hydrolytic enzymes, and acid phosphatases. The neutrophil-lymphocyte ratio therefore reflects both the neutrophilia of inflammation and the relative lymphopenia of cortisol-induced stress response.[17]

It has been long known that myocardial injury (acute MI) is followed by neutrophilia. Acute MI was excluded in our primary analysis, but neutrophilia also could mark an augmented, more chronic adaptive response to ischemia. Neutrophilia may also indicate maladaptive processes: circulating leukocyte-platelet aggregates appear in acute coronary syndromes and may facilitate vascular plugging and infarct extension.[18,19] Additionally, a decrease in CD4+ count and the CD4+/CD+8 ratio has been observed in patients with acute MI. Lymphocyte subsets such as CD4+ are decreased after acute MI and are correlated with a low ejection fraction and small infarct size. A decrease in the number and suppressive function of naturally occurring CD4+CD25+ regulatory T cells occurs in acute phases of acute coronary syndromes, potentially due to oxidized low-density lipoprotein.

NLR correlated well with other markers of a proinflammatory state; recent studies of long-term outcome in cardiac disease as well as oncologic resections have shown associations of high C-reactive protein and elevated NLR with poor long-term outcome.[17,20] While the detrimental effect of NLR on outcome is continuous, we chose to select a single cutoff for clinical relevance. The overall accuracy of an NLR cutoff of >5.25 in this dataset was 66.4%. This cutoff correlated favorably to oncological and cardiac data.[10,17]

This study was prospective in patient enrollment and follow-up but was observational in nature and subject to limitations, including selection bias. Most patients were on antiplatelet therapy at the time of admission; however, just 39 (26.3%) were on statin therapy. Additionally, we could not compare NLR with other inflammatory markers, such as C-reactive protein, fibrinogen, or myeloperoxidase, because they were not routinely obtained in our study population. Most of our patients had fairly aggressive correction of anemia to maintain a hemoglobin of more than 80 g/L in patients with no cardiac history, or 100 g/L in patients with angina or proven cardiac disease, and this variable could therefore not be analyzed in this study.

On multivariate analysis, an elevated troponin, no statin use, and a high NLR were found to independently predict mortality in this patient subgroup. The impact of an elevated troponin on survival in patients with noncardiac disease has been reported in hemodialysis patients[21] and CLI by several groups, including our own.[22-24] Statins have an important protective role for mortality and major cardiovascular events (stroke, MI) in patients with peripheral arterial disease; no specific protective effect has been demonstrated in amputation-free survival in recent literature.[25-29] The impact of an elevated NLR and its relation to mortality has not been reported before in this patient set.

Risk-stratification models utilizing existing clinical data exist and provide reasonable discrimination between good and poor risk candidates for surgical intervention. Additional information provided on the patient's proinflammatory state by biomarkers may improve the discriminant value of such scores.[30,31] The NLR is an inexpensive and readily available test. Patients undergoing vascular surgery all undergo preoperative full blood counts. NLR is a readily available biomarker that conveys important information about the patient's inflammatory activity. NLR can be easily calculated from the differential WBC count, which is routinely performed on admission and is universally available. Unlike many other inflammatory markers and bioassays, NLR is an inexpensive and readily available marker that provides an additional level of risk stratification beyond that provided by conventional risk scores in predicting in-hospital and long-term mortality. Moreover, it is available preoperatively and may be of use in counseling patients with regard to treatment options and possible outcome. It may be a useful prognostic indicator in CLI that does not require any additional resources for routine use.

AUTHOR CONTRIBUTIONS

Conception and design: IS
Analysis and interpretation: IS, SA
Data collection: JS, NB, PC
Writing the article: IS, SA, JS, NB, PC
Critical revision of the article: IS, SA
Final approval of the article: IS, SA, JS, NB, PC
Statistical analysis: IS, SA, JS, NB, PC
Obtained funding: N/A
Overall responsibility: IS

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