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# Neutrophil-lymphocyte ratio predicts disease severity and outcome after lower extremity procedures

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## Abstract

**Objective:** Neutrophil-Lymphocyte Ratio (NLR) has been associated with inferior outcomes after lower extremity (LE) interventions. NLR has been associated with systemic inflammation and atherosclerotic burden. We examined NLR, severity of peripheral arterial disease (PAD) and outcomes following endovascular or open surgical procedures.

**Methods:** Inpatients undergoing lower extremity procedures (2008 to 2016) were selected from Cerner HealthFacts® database using ICD-9 procedure codes. Disease severity was grouped into claudication, rest pain and tissue loss. Outcomes were identified using ICD-9 codes. NLR was calculated pre-and postoperatively. Chi-square analysis and multivariable logistic regression were performed. A receiver-operating curve (ROC) analysis was used to determine the cutoff for preoperative (Low < 3.65; High ≥ 3.65) and postoperative (Low < 5.96; High ≥ 5.96) NLR values.

**Results:** 3,687 patients were evaluated; 2,183 (59%) underwent endovascular procedures and 1,504 (41%) had open procedures. Compared with black patients, claudication was more frequent in white patients (81.7% vs. 72.7%; $P < .0001$), and tissue loss was less common (12.9% vs. 20.9%; $P < .0001$). NLR values were higher for patients with tissue loss than rest pain or claudication (4.89, 4.33 and 3.11, respectively; $P < .0001$). Open procedures were associated with higher postoperative NLR values than endovascular procedures (6.8 vs. 5.2; $P < .0001$). Mean pre- and postoperative NLR were greater in patients with more severe PAD. Multivariable analysis demonstrated that preoperative high NLR was strongly associated with in-hospital death (OR 5.4, 95% CI 1.68–17.07), cardiac complications (OR 2.9, 95% CI 1.57–5.40), amputation (OR 2.5, 95% CI 1.65–3.87), renal failure (OR 1.9, 95% CI 1.18–2.93), respiratory complications (OR 1.7, 95% CI 1.09–2.76) and prolonged length of stay (OR 1.9, 95% CI 1.89–3.71).

**Conclusions:** Pre- and post-operative NLR significantly increases with disease severity for PAD, providing further evidence of NLR as a biomarker of a patient's systemic inflammatory state. After adjusting for confounders, NLR still remained strongly associated with death and other adverse outcomes following intervention for PAD. Further study of the clinical association of NLR with other vascular disorders, such as symptomatic carotid stenosis and symptomatic and ruptured

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aortic aneurysmal disease, is planned to guide individualized treatment to prevent stroke or aneurysm rupture.

## INTRODUCTION

Peripheral arterial disease (PAD) is a disorder that ranges from asymptomatic through intermittent claudication to rest pain and tissue loss; it affects between 8 and 12 million patients in the United States.[1] Arterial territory affected is highly variable, and can range from single anatomic level involvement, such as the femoropopliteal segment, presenting most commonly with intermittent claudication, to multilevel atherosclerosis that often leads to rest pain and tissue loss. The mechanisms behind the spectrum of disease severity and anatomic level of disease are unclear, although female sex, low HDL-cholesterol and absence of diabetes has been associated with larger vessel, early-onset aortoiliac occlusive disease.[2] Similarly, diabetes and renal insufficiency have been associated with a more distal, or small vessel pattern of disease; tibial atherosclerosis.[3] Although intermittent claudication can be a very stable chronic symptom, progression to rest pain and tissue loss—critical limb ischemia—often leads to major amputation.[4]

The neutrophil-lymphocyte ratio (NLR) is a simple ratio calculated by dividing the absolute neutrophil count by the lymphocyte count in a differential sample of the complete blood count.[5] The ratio could be an indicator of the degree of systemic inflammation,[6] which has been linked with risk factors for atherosclerosis such as diabetes mellitus, hypertension, hyperlipidemia and endothelial dysfunction.[7, 8] The link between systemic inflammation and cardiovascular disease has been demonstrated in numerous reports,[9–12] and the anti-inflammatory effects of statin medications have been postulated to be an important factor in cardiovascular risk reduction in addition to their lipid-lowering properties.[13–15]

NLR has been proposed as an inexpensive biomarker of the inflammatory balance of a patient and has been linked to poor outcome in oncologic disciplines[16–18] and cardiology with respect to post-myocardial infarction[19, 20] and coronary intervention.[21, 22] Despite the clear association of NLR with atherosclerosis, few reports have evaluated the value of NLR in vascular disorders,[23–26] although NLR has been described as a marker for mortality in patients with critical limb ischemia undergoing infrapopliteal percutaneous interventions[27] and for outcomes following lower extremity amputation.[23] We hypothesized that due to the increased atherosclerotic and inflammatory burden, NLR would be associated with the severity of symptoms for patients with PAD, with higher NLR for tissue loss than rest pain and claudication. Furthermore, concordant with other studies of NLR and vascular disorders, we hypothesized that a higher NLR would be associated with poor outcomes following lower extremity procedures.

## METHODS

### Data source

The International Classification of Disease, Ninth Edition, Clinical Modification (ICD-9-CM) diagnosis and procedure codes were used to identify patients who underwent endovascular or open surgery for PAD between 2008 and 2015 from the Cerner Health

Facts® database. Health Facts is a proprietary database comprised of electronic medical records from hospitals and hospital systems that use Cerner Corporation's electronic health record and that choose to contribute data. Cerner de-identifies and standardizes the data before including them in Health Facts using statistical methods that are compliant with the Health Insurance Portability and Accountability Act (HIPAA). Informed patient consent was not needed as the Health Facts database is completely de-identified. The study was exempted by the Institutional Review Board at the University of Missouri.

**Study population.—**The study included patients undergoing elective endovascular or open procedures for PAD. Patients were excluded from the study if they were less than 21 years old at admission; had admissions during which both endovascular and open procedures were performed; had no laboratory data available, had no known codes for PAD severity, or had admissions flagged as emergent or urgent.

**Covariates.—**Patients' demographics (age, sex, and race), and acute and chronic problems at the index admission (e.g., chronic heart disease, diabetes, hypertension) were examined. The Agency for Healthcare Research and Quality's (AHRQ) Clinical Classifications Software was used to group diagnosis codes into clinically relevant groups. We used ICD-9 CM codes for the encounter to calculate the Charlson Comorbidity Index.[28] We separated the overall cohort into claudication, rest pain and tissue loss groups by selecting the most severe diagnosis code.

**Statistical analysis.—**All analyses were performed in SAS for Windows version 9.4 (SAS Institute, Cary, NC). We calculated NLR by dividing the absolute neutrophil count by the absolute lymphocyte count. Pre-operative NLR was divided into low (< 3.65) and high (≥ 3.65) and post-operative NLR into low (< 5.96) and high (≥ 5.96) values based on the results of a receiver operating characteristic (ROC) analysis that examined length of hospital stay, using mean values for pre- and postoperative periods (see Figure 1). A chi-square statistic was used to evaluate the relationship of NLR with patient characteristics, infections, acute and chronic problems, length of stay, and complications. In addition, multivariable logistic regression was used to examine the association between NLR and any infection, length of stay > 10 days, renal failure, respiratory and cardiac complications, amputation, and in-hospital mortality after adjusting for patient characteristics. We calculated odds ratios (OR) and 95% CIs and assessed model discrimination with the c-statistic (or area under the curve), where 0.5 is no better than a coin toss and 1.0 indicates a perfect fit. Model calibration over the range of risk was assessed with the Hosmer-Lemeshow goodness-of-fit chi-square test, with p-values >.05 indicating adequate fit.

# RESULTS

## Demographics

A total of 3,687 patients were identified. Endovascular procedures were performed in 2,183 patients (59%) and open procedures in 1,504 patients (41%). Mean age was 68.5 and the majority of patients were male (60%) or of white race (77%). Patients were analyzed in two groups; those with preoperative NLR values and those with postoperative values and were only included if they had complete data. Outcomes refer to those occurring during the initial hospital stay.

Table 1 describes the patient sample by PAD severity. Unadjusted analysis of the groups revealed that patients with tissue loss were older than those with rest pain (71.2 vs. 68.1; $P < .0001$), who were in turn older than those with claudication (68.1 vs. 67; $P = .02$). When examining the differences in clinical presentations by race, black patients more often presented with tissue loss than with claudication (21% vs. 13%; $P < .0001$), whereas a greater proportion of white patients presented with claudication than tissue loss (81.7% vs. 72.7%; $P < .0001$).

Figure 2 demonstrates that preoperative NLR was higher in patients with rest pain than claudication (4.33 vs. 3.11; $P < .0001$) and higher still for those with tissue loss (4.89 vs. 3.11; $P < .0001$). Evaluating the trend between preoperative and postoperative NLR by procedure type and by PAD severity (Figure 3), a clear increase in NLR value is seen with increasing PAD severity ($P < .0001$). Open procedures were associated with higher baseline NLR values both preoperatively (4.53 vs. 3.56; $P < .0001$) and postoperatively (6.81 vs. 5.19; $P < .0001$) than endovascular procedures (Figure 3).

Table 2 details the patient characteristics for 1,455 patients with preoperative NLR levels. Unadjusted analyses demonstrate that patients with high NLR are older (70 vs. 67; $p < .0001$), have a higher Charlson Index (3.27 vs. 2.46; $P < .0001$), and more often have tissue loss (56.5% vs. 27.3%; $P < .0001$) compared to patients with low preoperative NLR. A higher percentage of patients with chronic kidney disease (30.6% vs. 13.7%; $P < .0001$) and diabetes (50.5% vs. 44.3%; $P = .02$) had a higher NLR. Similar findings to the preoperative NLR data were seen for the 2701 patients with postoperative NLR data (Table 3).

## Outcomes

**Unadjusted analysis—**Length of stay was longer for patients with tissue loss than rest pain or claudication (6.4 vs. 4.1 vs. 2.3 days; all $P < .0001$). In the patients with preoperative NLR values, a high NLR was associated with the following complications (Table 2): renal failure (11.6% vs. 4.1%; $P < .0001$), cardiac complications/myocardial infarction (6.6% vs. 1.9%; $P < .0001$), respiratory problems (8.8 vs. 4.5%; $P = .0008$), infection (25.7% vs. 11.8%; $P < .0001$), amputation (18.2% vs. 4.3%; $P < .0001$), in-hospital death (2.8% vs. 0.4%; $P = .0001$), and increased length of stay (9.2 days vs. 6.6 days; $P < .0001$).

Similarly, for patients with postoperative NLR data, a high NLR was also associated with the following complications (Table 3): renal failure (6.41% vs. 2.3%; $P < .0001$), respiratory problems (6.3 vs. 2.6%; $P = .0008$), infection (14.0% vs. 7.0%; $P < .0001$), amputation (8.5% vs. 2.8%; $P < .0001$) and increased length of stay (13.1 days vs. 3.7 days; $P < .0001$).

**Multivariable analysis—**We separately modeled preoperative and postoperative NLR to determine whether the association of NLR with outcome persisted through the perioperative period. Table 4 demonstrates five separate multivariable models (in-hospital death, renal failure, cardiac/MI, infection, and length of stays > 10 days) each adjusted for clinically relevant variables (age, sex, race, disease severity and pre-existing conditions) based on the non-adjusted results noted in tables 3 and 4. Preoperative high NLR was associated with in-hospital death (OR 5.4, 95% CI 1.7–17), prolonged length of stay (OR 2.6, 95% CI 1.9–3.7), cardiac complications and myocardial infarction (OR 2.9, 95% CI 1.6–5.4), and renal failure (OR 1.9, 95% CI 1.2–2.9). In the postoperative period, high NLR was associated with prolonged length of stay (OR 2.9, 95% CI 1.9–4.3), infection (OR 1.6, 95% CI 1.2–2.2), and renal failure (OR 2.0, 95% CI 1.3–3.3) (Table 4). Other model covariates that were significantly associated with the outcomes under study (in-hospital death, renal failure, cardiac/MI complications, infection and prolonged length of stay) are also detailed in Table 4.

## Discussion

In this study, we found an association between increasingly severe symptoms of PAD and NLR values in a graded response from claudication to tissue loss. We also describe a strong independent association between the NLR values pre- and post-operatively and complications following lower extremity procedures. These findings serve as more evidence of the use of NLR as a marker of the inflammatory balance of a patient and may be useful when discussing and trying to mitigate individual risks of complications associated with endovascular and open procedures for PAD. The results also further validate the use of this simple blood test as a clinical indicator of disease severity.

NLR has been described as an indicator for poor outcome in oncologic and cardiovascular disorders. Adverse outcomes are linked to higher NLR, which is thought to be associated with a shift towards a systemic proinflammatory balance. Inflammation has been linked with atherosclerosis, and furthermore, the degree of inflammation correlates with the severity and outcome of disease.[29] With this in mind, peripheral arterial disease provides an ideal opportunity to study the graded effect of systemic inflammation, given ranked severity of symptoms from mild claudication to rest pain and tissue loss.

Teperman *et al.* (2017) describe a similar study evaluating the relationship between NLR and severity of lower extremity PAD by evaluating angiographic images. NLR was divided into tertiles across the range of values and the level of anatomic obstruction classified as ‘severe’ if a >70% diameter stenosis by visual estimate was seen on peripheral angiography. The authors concluded that elevated NLR was independently associated with severe multi-level PAD.[30] The association of NLR and atherosclerosis severity has been previously described in the cardiology literature and provides more evidence of a ‘dose effect’ between atherosclerotic burden, inflammation and symptoms.[31]

In the present study we also demonstrated a difference in NLR value between patients undergoing endovascular procedures and those undergoing open procedures who had similar symptoms (e.g. both had rest pain). Open surgical procedures are known to activate inflammatory cascades and the stress response, leading to hypothalamic-pituitary axis (HPA) stimulation of cortisol production and other metabolically-active hormones such as corticotrophin (ACTH) and growth hormone (GH).[32] Endovascular procedures are generally thought to incite a lower level of overall stress response than open procedures, although the data are not definitive.[33, 34] Based on these findings and those of the previously-described studies, we propose that NLR accurately reflects the balance towards a proinflammatory state, with higher values serving as a clinical measure of the severity of atherosclerotic disease burden. While this seems self-evident in that claudication patients are clinically less symptomatic than rest pain patients, it opens the discussion for wider applications for NLR in vascular disorders.

The role of NLR and disease severity in other vascular diseases, such as carotid artery stenosis, has yet to be evaluated. The clinical challenge for practitioners who manage these disorders has always been to balance the risks of the intervention with the risks of non-operative management. Park *et al.* (2016) describe the natural history of asymptomatic moderate carotid artery stenosis is the era of medical therapy.[35] The authors followed 124 patients with carotid artery stenosis in the range 50–69% over a 5-year period with duplex ultrasound. The authors describe a progression to severe stenosis (>70%) over this timeframe in 31.8% of the cohort, with carotid intervention in 18.6% of patients. Symptom development occurred in 3% of the moderate grade carotid artery stenosis cohort over the follow-up period. Despite more sophisticated imaging techniques[36, 37] and better medical management there is still no reliable method to detect which patients will progress to severe stenosis or even which patients are at risk for symptom development. NLR offers a promising and inexpensive biomarker that correlates with inflammatory and atherosclerotic burden and may allow identification of patients at high-risk for carotid stenosis progression or symptom development and lead to enhanced surveillance and possible earlier intervention.

Similarly, aortic aneurysmal disease is a vascular disorder that exhibits a relatively binary management strategy. Broadly speaking, infrarenal aortic aneurysms less than 5.5 cm are typically managed non-operatively, whereas those > 5.5 cm are considered for treatment when the operative risk is not greater than the estimated annual rupture risk.[38] There are patients, however, that develop symptomatic, ruptured and rapidly enlarging aneurysms despite a standardized surveillance schedule.[39] Equally as concerning are those patients who lose eligibility for endovascular repair due to aneurysmal dilation of the infrarenal neck of the aneurysm during the period of surveillance.[40] NLR has previously been associated with poor outcomes in the postoperative period following both elective and ruptured abdominal aortic aneurysm (AAA) repair.[24, 26] Aurelian *et al.* (2019) describe their findings from a comparative study of ruptured to non-ruptured infrarenal abdominal aortic aneurysm repair.[41] The authors report that an NLR value > 5 was associated with higher 30-day mortality following open surgical repair and a 5 times greater possibility of AAA rupture. Higher overall NLR values were seen in patients with ruptured than non-ruptured AAA. These important findings may pave the way to more sophisticated risk prediction tools; integrating biomarkers such as NLR with traditional size-based criteria to create a more accurate individualized risk of rupture. This may, in turn, lead to early intervention in those patients deemed at highest risk of rupture who may not necessarily be at 5.5 cm or greater.

We also found a strong association between preoperative and postoperative NLR and poor outcome. The associations of preoperative NLR with adverse outcome is of prime interest, as this raises an interesting question about the ability to predict which patients will be at higher risk for complications based on NLR level. Traditional vascular surgery risk calculators have focused primarily on adverse cardiac risk. The most commonly used and well-validated online risk calculators include the National Surgical Quality Improvement Program (NSQIP), a nationally validated, risk-adjusted, outcomes-based program to measure and improve the quality of surgical care;[42] the Revised Cardiac Risk Index (RCRI), a validated tool for estimating a patient's risk of perioperative cardiac complications using patient-specific comorbidities;[43] and the Vascular Study Group of New England Cardiac Risk Index (VSG-CRI), a similar risk prediction tool based upon specific comorbidities in the vascular population.[44] The present study highlights the association between overall risk of complications and the preoperative NLR value for individual patients. This information, known ahead of any proposed operative treatment, might allow for a more informed discussion with the patient regarding the expected risks and complications, depending on the baseline preoperative NLR value.

NLR has been reported in a variety of different ways; ranging from arbitrary cutoffs,[24, 45] tertiles or quartiles,[46] and more sophisticated thresholds determined by receiver operating characteristics.[47, 48] There has not been an established method for reporting NLR, making comparison across the body of literature challenging. NLR values are highly sensitive to illness and stress and represent the pro- or anti-inflammatory state of an individual. Therefore, establishing a true baseline NLR can be challenging due to the inability to control the environment and circumstances in which the NLR value was obtained.

## Conclusion

The neutrophil-lymphocyte ratio exhibits an association with the PAD severity and rises in a graded fashion following endovascular or open surgery in a manner consistent with the invasive nature of the procedure. We suggest that the NLR provides a robust tool for assessing the underlying proinflammatory state of an individual. Further, an elevated NLR in the perioperative period is associated with adverse outcomes. Given the evidence underlying inflammation in the development of atherosclerosis and overall adverse outcomes, we recommend further evaluation of the NLR as a biomarker for adverse outcomes in vascular disorders and also plan to incorporate the NLR into a multimodal risk prediction array including other biomarkers of outcome such as HbA1c, albumin, ESR and CRP, for example. We propose to next study the clinical association of NLR with symptomatic carotid stenosis and symptomatic and ruptured aortic aneurysmal disease with the hope to integrate NLR with traditional risk factors to guide individualized treatment prior to stroke or aneurysm rupture.

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## ARTICLE HIGHLIGHTS

**Type of Research:**

Retrospective analysis of prospectively collected data from the Cerner HealthFacts database

**Key Findings:**

In a cohort of 3,687 patients undergoing endovascular or open procedures for peripheral arterial disease (PAD), the neutrophil-to-lymphocyte ratio (NLR) positively correlated with the degree of disease severity. The NLR value was also positively correlated with the degree of surgical stress, with open procedures exhibiting higher NLR values than endovascular procedures. Most importantly, an elevated NLR value in the perioperative period was associated with all adverse outcomes, including death, following procedures for PAD.

**Take home Message:**

The NLR value could be used to identify patients with a proinflammatory state, who are at risk for progression of atherosclerosis and adverse outcome. Further study of the clinical use of NLR in predicting sentinel events in vascular disorders such as stroke or ruptured aortic aneurysm should be the next step for this promising biomarker.

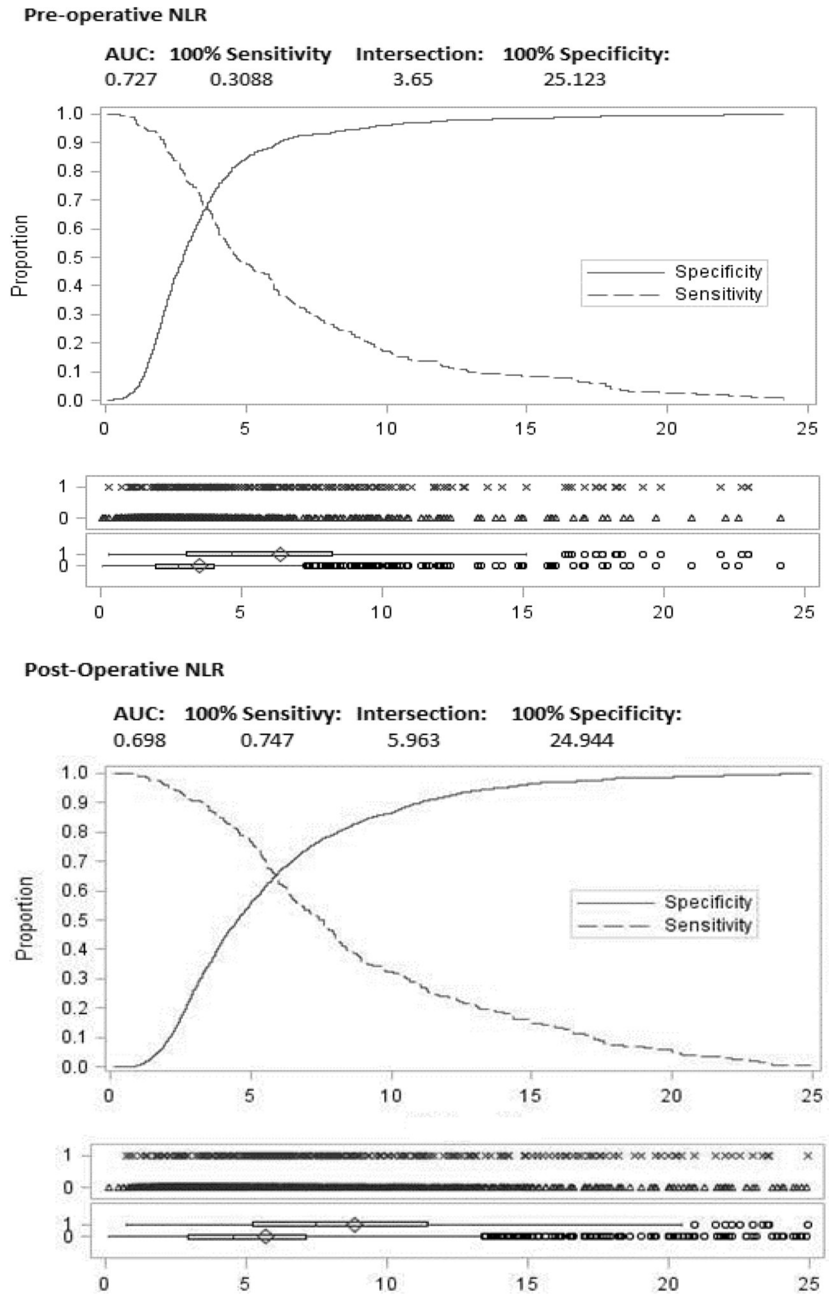


**Figure 1.**

Receiver-operating curve characteristics

AUC = area under the curve; NLR = neutrophil-lymphocyte ratio

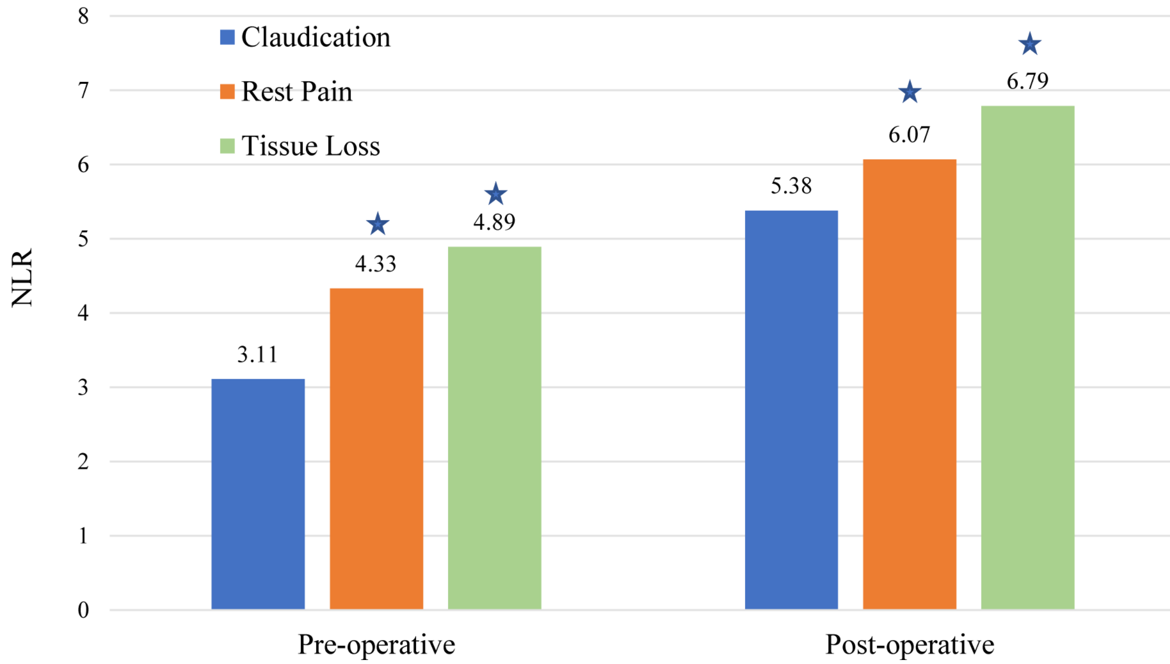


**Figure 2.**

Pre- and post-operative NLR by PAD severity

★ Denotes significant difference compared with claudication within each time period.

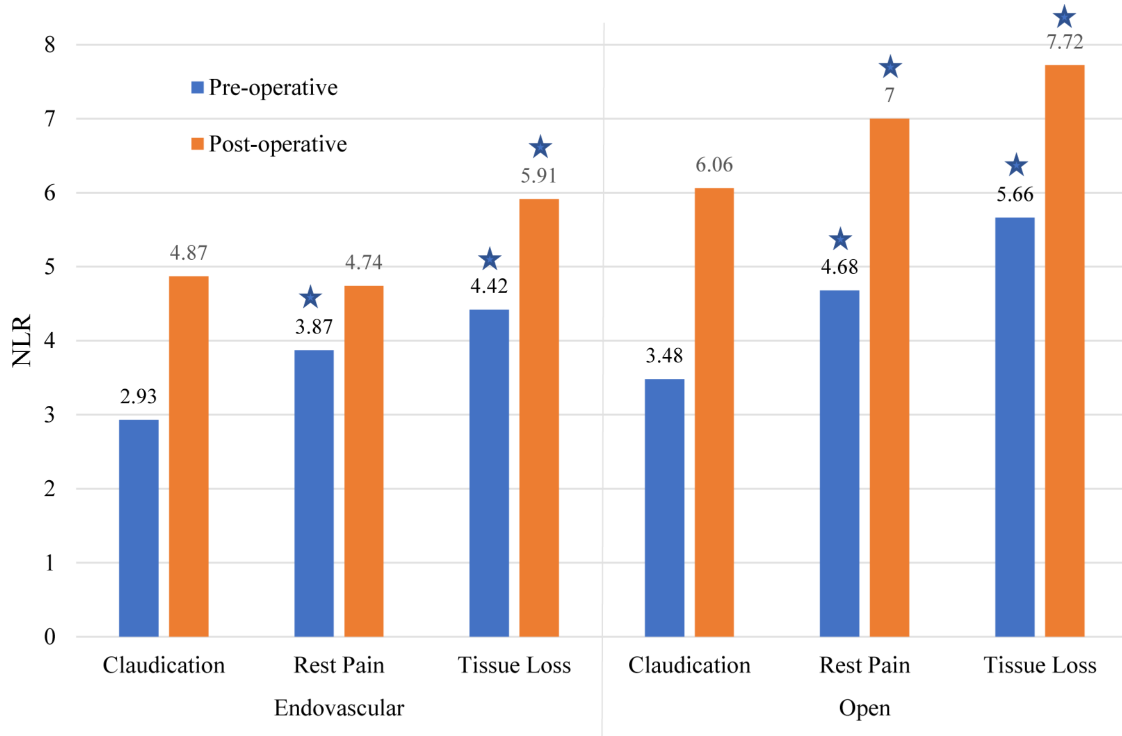


**Figure 3.**

Pre- and post-operative NLR by procedure type and PAD severity.

★ Denotes significant difference compared with claudication within each time period.

**Table 1.**

Patient and encounter characteristics, by PAD severity

| | PAD Severity | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Claudication | | Rest Pain | | Tissue Loss[a] | | | | |
| | N | % | N | % | N | % | *P*-value[b] | *P*-value[c] | *P*-value[d] |
| All | 1970 | 100.00 | 534 | 100.00 | 1183 | 100.00 | -- | -- | -- |
| Age, mean (SD) | 67.0 | (10.2) | 68.1 | (10.8) | 71.2 | (11.7) | <.0001 | <.0001 | .02 |
| 21–59 | 471 | 23.91 | 119 | 22.28 | 210 | 17.75 | | | |
| 60–69 | 672 | 34.11 | 178 | 33.33 | 311 | 26.29 | | | |
| 70–79 | 599 | 30.41 | 149 | 27.90 | 330 | 27.90 | | | |
| 80 or older | 228 | 11.57 | 88 | 16.48 | 332 | 28.06 | | | |
| Race | | | | | | | .72 | <.0001 | .0002 |
| White | 1609 | 81.68 | 393 | 73.60 | 860 | 72.70 | | | |
| Black | 256 | 12.99 | 104 | 19.48 | 248 | 20.96 | | | |
| Other/unknown | 105 | 5.33 | 37 | 6.93 | 75 | 6.34 | | | |
| Gender | | | | | | | .21 | .004 | .0005 |
| Female | 729 | 37.01 | 242 | 45.32 | 498 | 42.10 | | | |
| Male | 1241 | 62.99 | 292 | 54.68 | 685 | 57.90 | | | |
| Marital status | | | | | | | .09 | <.0001 | .08 |
| Married, life partner | 915 | 46.45 | 224 | 41.95 | 516 | 43.62 | | | |
| Divorced, separated | 240 | 12.18 | 73 | 13.67 | 117 | 9.89 | | | |
| Single, widowed | 594 | 30.15 | 186 | 34.83 | 448 | 37.87 | | | |
| Unknown | 221 | 11.22 | 51 | 9.55 | 102 | 8.62 | | | |
| Hospital bed size | | | | | | | .002 | .10 | .06 |
| <200 | 528 | 26.80 | 157 | 29.40 | 290 | 24.51 | | | |
| 200–299 | 335 | 17.01 | 67 | 12.55 | 205 | 17.33 | | | |
| 300–499 | 397 | 20.15 | 102 | 19.10 | 279 | 23.58 | | | |
| 500 or more | 710 | 36.04 | 208 | 38.95 | 409 | 34.57 | | | |
| Procedure type | | | | | | | <.0001 | <.0001 | <.0001 |
| Endovascular | 1272 | 64.57 | 232 | 43.45 | 679 | 57.40 | | | |
| Open | 698 | 35.43 | 302 | 56.55 | 504 | 42.60 | | | |
| Length of stay, mean (SD) | 2.27 | (4.09) | 4.10 | (4.68) | 6.39 | (7.63) | <.0001 | <.0001 | <.0001 |
| < 10 days | 1927 | 97.82 | 499 | 93.45 | 940 | 79.46 | | | |
| > 10 days | 43 | 2.18 | 35 | 6.55 | 243 | 20.54 | | | |

SD = Standard deviation.

[a]Tissue loss = gangrene or ulcer

[b]*P*-value based on chi-square (or t-test for continuous) comparison between PAD tissue loss (gangrene/ulcer) and rest pain.

[c]*P*-value based on chi-square (or t-test for continuous) comparison between PAD tissue loss (gangrene/ulcer) and claudication.

[d]*P*-value based on chi-square (or t-test for continuous) comparison between PAD rest pain and claudication..

**Table 2.**

Preoperative sample characteristics by NLR level

| | Overall | | Low NLR[a] | | High NLR[a] | | |
|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | *P*-value |
| Overall | 1455 | 100.00 | 922 | 63.4 | 533 | 36.6 | -- |
| Age, mean (SD) | 68.3 | (11.2) | 67.3 | (10.9) | 70.0 | (11.3) | <.0001 |
| Gender | | | | | | | .26 |
| Female | 557 | 38.28 | 363 | 39.37 | 194 | 36.40 | |
| Male | 898 | 61.72 | 559 | 60.63 | 339 | 63.60 | |
| Race | | | | | | | .72 |
| White | 1129 | 77.59 | 719 | 77.98 | 410 | 76.92 | |
| Black | 248 | 17.04 | 152 | 16.49 | 96 | 18.01 | |
| Other race | 78 | 5.36 | 51 | 5.53 | 27 | 5.07 | |
| Charlson Index, mean (SD) | 2.76 | (1.78) | 2.46 | (1.59) | 3.27 | (1.96) | <.0001 |
| Procedure type | | | | | | | .002 |
| Endovascular | 874 | 60.07 | 581 | 63.02 | 293 | 54.97 | |
| Open | 581 | 39.93 | 341 | 36.98 | 240 | 45.03 | |
| PAD Severity | | | | | | | <.0001 |
| Claudication | 712 | 48.93 | 552 | 59.87 | 160 | 30.02 | |
| Rest pain | 190 | 13.06 | 118 | 12.80 | 72 | 13.51 | |
| Tissue loss | 553 | 38.01 | 252 | 27.33 | 301 | 56.47 | |
| NLR, mean (SD) | 3.97 | (3.41) | -- | -- | -- | -- | -- |
| Pre-existing conditions | | | | | | | |
| Chronic heart disease | 680 | 46.74 | 423 | 45.88 | 257 | 48.22 | .38 |
| Chronic kidney disease | 289 | 19.86 | 126 | 13.67 | 163 | 30.58 | <.0001 |
| Diabetes | 677 | 46.53 | 408 | 44.25 | 269 | 50.47 | .02 |
| Outcomes | | | | | | | |
| Renal failure | 100 | 6.87 | 38 | 4.12 | 62 | 11.63 | <.0001 |
| Cardiac/MI | 53 | 3.64 | 18 | 1.95 | 35 | 6.57 | <.0001 |
| Respiratory problems | 88 | 6.05 | 41 | 4.45 | 47 | 8.82 | .0008 |
| Infection | 246 | 16.91 | 109 | 11.82 | 137 | 25.70 | <.0001 |
| Amputation | 137 | 9.42 | 40 | 4.34 | 97 | 18.20 | <.0001 |
| In-hospital death | 19 | 1.31 | 4 | 0.43 | 15 | 2.81 | .0001 |
| Length of stay, mean (SD) | 5.12 | (7.9) | 3.57 | (6.56) | 7.81 | (9.18) | <.0001 |
| Length of stay > 10 days | 223 | 15.33 | 74 | 8.03 | 149 | 27.95 | <.0001 |

[a]Pre-operative NLR Low (< 3.65), High (≥ 3.65).

PAD = peripheral arterial disease; SD = standard deviation; MI = myocardial infarction; NLR = neutrophil to lymphocyte ratio

**Table 3.**

Postoperative sample characteristics by NLR level

| | Overall | | Low NLR[a] | | High NLR[a] | | |
|---|---|---|---|---|---|---|---|
| | **N** | **%** | **N** | **%** | **N** | **%** | ***P*-value** |
| Overall | 2701 | 100.0 | 939 | 34.7 | 1762 | 65.2 | -- |
| Age, mean (SD) | 68.6 | 10.9 | 67.2 | 11.2 | 69.3 | 10.7 | <.0001 |
| Gender | | | | | | | <.0001 |
| Female | 1070 | 39.61 | 421 | 44.83 | 649 | 36.83 | |
| Male | 1631 | 60.39 | 518 | 55.17 | 1113 | 63.17 | |
| Race | | | | | | | <.0001 |
| Caucasian | 2054 | 76.05 | 668 | 71.14 | 1386 | 78.66 | |
| African American | 484 | 17.92 | 199 | 21.19 | 285 | 16.17 | |
| Other race | 163 | 6.03 | 72 | 7.67 | 91 | 5.16 | |
| Charlson Index, mean (SD) | 2.50 | 1.62 | 2.24 | 1.47 | 2.64 | 1.67 | <.0001 |
| Procedure type | | | | | | | <.0001 |
| Endovascular | 1395 | 51.65 | 594 | 63.26 | 801 | 45.46 | |
| Open | 1306 | 48.35 | 345 | 36.74 | 961 | 54.54 | |
| PAD Severity | | | | | | | <.0001 |
| Claudication | 1384 | 51.24 | 569 | 60.60 | 815 | 46.25 | |
| Rest pain | 408 | 15.11 | 133 | 14.16 | 275 | 15.61 | |
| Tissue loss | 909 | 33.65 | 237 | 25.24 | 672 | 38.14 | |
| NLR, mean (SD) | 6.00 | 4.22 | -- | -- | -- | -- | -- |
| Pre-Existing Conditions | | | | | | | |
| Chronic heart disease | 1343 | 49.72 | 447 | 47.60 | 896 | 50.85 | .10 |
| Chronic kidney disease | 443 | 16.40 | 100 | 10.65 | 343 | 19.47 | <.0001 |
| Diabetes | 1120 | 41.47 | 372 | 39.62 | 748 | 42.45 | .15 |
| Outcomes | | | | | | | |
| Renal failure | 135 | 5.00 | 22 | 2.34 | 113 | 6.41 | <.0001 |
| Cardiac/MI | 103 | 3.81 | 29 | 3.09 | 74 | 4.20 | .15 |
| Respiratory problems | 135 | 5.00 | 24 | 2.56 | 111 | 6.30 | <.0001 |
| Infection | 313 | 11.59 | 66 | 7.03 | 247 | 14.02 | <.0001 |
| Amputation | 175 | 6.48 | 26 | 2.77 | 149 | 8.46 | <.0001 |
| In-hospital death | 20 | 0.74 | 3 | 0.32 | 17 | 0.96 | .06 |
| Length of stay, mean (sd) | 4.25 | 5.42 | 2.70 | 3.34 | 5.08 | 6.09 | <.0001 |
| Length of stay > 10 days | 266 | 9.85 | 35 | 3.73 | 231 | 13.11 | <.0001 |

[a]Post-operative NLR Low (< 5.96), High (≥ 5.96).

PAD = peripheral arterial disease; SD = standard deviation; MI = myocardial infarction; NLR = neutrophil-lymphocyte ratio

**Table 4.**

Multivariable logistic regression model results

| | *Preoperative NLR Model* | | | | *Postoperative NLR Model* | | | |
|---|---|---|---|---|---|---|---|---|
| | | 95% CI | | | | 95% CI | | |
| | **OR** | **Low** | **High** | ***P*-value** | **OR** | **Low** | **High** | ***P*-value** |
| *In-hospital death* | | | | | | | | |
| Chronic heart disease | 0.771 | 0.293 | 2.031 | .59 | 0.761 | 0.306 | 1.896 | .55 |
| Chronic kidney disease | 2.835 | 1.030 | 7.798 | .04 | 2.069 | 0.764 | 5.599 | .15 |
| Diabetes | 0.617 | 0.222 | 1.720 | .35 | 1.281 | 0.501 | 3.277 | .60 |
| Procedure type (open v. endo) | 1.460 | 0.556 | 3.834 | .44 | 0.673 | 0.265 | 1.711 | .40 |
| NLR (high vs. low) | 5.359 | 1.682 | 17.074 | .004 | 2.663 | 0.758 | 9.356 | .12 |
| PAD severity (rest pain v. claud.) | 2.059 | 0.551 | 7.688 | .28 | 1.394 | 0.351 | 5.538 | .63 |
| PAD severity (tissue loss v. claud.) | 0.949 | 0.277 | 3.259 | .93 | 1.439 | 0.503 | 4.121 | .49 |
| *Renal failure* | | | | | | | | |
| Chronic heart disease | 1.276 | 0.815 | 1.999 | .28 | 1.213 | 0.834 | 1.765 | .31 |
| Chronic kidney disease | 4.797 | 3.006 | 7.655 | <.0001 | 4.495 | 3.063 | 6.598 | <.0001 |
| Diabetes | 1.652 | 1.007 | 2.708 | .04 | 2.089 | 1.400 | 3.117 | .0003 |
| Procedure type (open v. endo) | 1.537 | 0.983 | 2.403 | .05 | 1.471 | 1.010 | 2.143 | .04 |
| NLR (high vs. low) | 1.857 | 1.177 | 2.930 | .007 | 2.042 | 1.259 | 3.310 | .003 |
| PAD severity (rest pain v. claud.) | 1.361 | 0.616 | 3.008 | .44 | 1.576 | 0.870 | 2.857 | .13 |
| PAD severity (tissue loss v. claud.) | 2.252 | 1.266 | 4.006 | .005 | 2.072 | 1.324 | 3.243 | .001 |
| *Cardiac/MI* | | | | | | | | |
| Chronic heart disease | 1.684 | 0.931 | 3.044 | .08 | 1.543 | 1.017 | 2.340 | .04 |
| Chronic kidney disease | 2.540 | 1.363 | 4.733 | .003 | 1.877 | 1.172 | 3.004 | .008 |
| Diabetes | 1.545 | 0.827 | 2.885 | .17 | 1.230 | 0.807 | 1.876 | .33 |
| Procedure type (open v. endo) | 1.520 | 0.854 | 2.705 | .15 | 1.472 | 0.972 | 2.229 | .06 |
| NLR (high vs. low) | 2.907 | 1.565 | 5.400 | .0007 | 1.057 | 0.672 | 1.664 | .80 |
| PAD severity (rest pain v. claud.) | 0.968 | 0.382 | 2.452 | .94 | 1.346 | 0.737 | 2.459 | .33 |
| PAD severity (tissue loss v. claud.) | 0.989 | 0.494 | 1.979 | .97 | 1.643 | 1.028 | 2.626 | .03 |
| *Infection* | | | | | | | | |
| Chronic heart disease | 0.827 | 0.602 | 1.136 | .24 | 0.889 | 0.684 | 1.156 | .38 |
| Chronic kidney disease | 1.636 | 1.154 | 2.318 | .005 | 1.793 | 1.340 | 2.401 | <.0001 |
| Diabetes | 1.202 | 0.859 | 1.682 | .28 | 1.387 | 1.059 | 1.818 | .01 |
| Procedure type (open v. endo) | 1.219 | 0.885 | 1.678 | .22 | 1.060 | 0.815 | 1.381 | .66 |
| NLR (high vs. low) | 1.324 | 0.965 | 1.816 | .08 | 1.605 | 1.178 | 2.185 | .002 |
| PAD severity (rest pain v. claud.) | 2.779 | 1.448 | 5.335 | .002 | 2.401 | 1.480 | 3.896 | .000 |
| PAD severity (tissue loss v. claud.) | 14.06 | 8.720 | 22.685 | <.0001 | 8.972 | 6.284 | 12.81 | <.0001 |
| *LOS > 10 days* | | | | | | | | |
| Chronic heart disease | 1.034 | 0.738 | 1.449 | .84 | 0.883 | 0.665 | 1.171 | .38 |
| Chronic kidney disease | 2.230 | 1.549 | 3.209 | <.0001 | 2.205 | 1.618 | 3.005 | <.0001 |

| | *Preoperative NLR Model* | | | | *Postoperative NLR Model* | | | |
|---|---|---|---|---|---|---|---|---|
| | | 95% CI | | | | 95% CI | | |
| | **OR** | **Low** | **High** | ***P*-value** | **OR** | **Low** | **High** | ***P*-value** |
| Diabetes | 0.877 | 0.615 | 1.252 | .47 | 0.981 | 0.733 | 1.314 | .89 |
| Procedure type (open v. endo) | 2.700 | 1.919 | 3.799 | <.0001 | 1.613 | 1.209 | 2.154 | .001 |
| NLR (high v. low) | 2.645 | 1.886 | 3.709 | <.0001 | 2.896 | 1.971 | 4.255 | <.0001 |
| PAD severity (rest pain v. claud.) | 1.986 | 1.073 | 3.674 | .02 | 2.309 | 1.393 | 3.826 | .001 |
| PAD severity (tissue loss v. claud.) | 7.808 | 4.923 | 12.38 | <.0001 | 7.634 | 5.206 | 11.19 | <.0001 |

OR=odds ratio, CI=confidence interval, NLR=neutrophil to lymphocyte ratio, PAD=peripheral artery disease, MI=myocardial infarction

Patient demographics (age, race, gender) were also included in each model, but not these covariates were not included in the table.