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The Preoperative Neutrophil-to-Lymphocyte Ratio as a Predictor of Infectious Complications after Lower Limb Amputation in Diabetic Patients in Tropical Environments

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Abstract

Background: Infections of the lower limb in diabetics patients are challenging injuries to treat. Amputation often leads to treatment major. However, the risk of complications remains high after amputation. The aim of this study was to elucidate the correlations of the preoperative neutrophil/lymphocyte ratio (NLR) with wound complications after amputation. **Methods**: This study included patients who underwent lower extremity amputations due to diabetes from January 2023 to June 2024 at University Teaching Hospital Cocody, Ivory Coast. Factors associated with postoperative infection after amputation were assessed by univariate and multivariate analysis. **Results**: We undertook one hundred and twenty amputations (n = 120) of lower limbs over the period of study. Here are 63 (52.5%) men. The mean age was 62.34 ± 11.36 (37 - 91) years. Of 120 patients, 95 (79.2%) patients had a high NLR preoperatively. The majority of 88 (73.3%), underwent below-knee amputation. The postoperative infection rate as 71 (59.2%). In univariate analysis, a higher neutrophil and lymphocyte count preoperatively was associated with postoperative infection ($p = 0.001$). Preoperatively, a higher NLR was also associated with postoperative infection ($p = 0.0001$). Logistic regression analysis showed that age and high preoperative NLR ($p < 0.05$) were risk factors for infection after lower limb amputation in diabetic patients. **Conclusion:** Preoperative NLR identifies diabetic patients at increased risk of infection after major limb amputation. This simple index may facilitate targeted preventive measures for high-

risk patients.

Keywords

Amputation, Diabetic Foot, Infection, Lower Limb, Neutrophil-to-Lymphocyte Ratio, NLR

1. Introduction

Peripheral vascular disease and diabetes remain the leading factors of nontraumatic major extremity amputation in the world [1]. Several predictors of early failure of amputation, including closed amputation in the presence of sepsis, emergency amputation, and tobacco use, have been described in the literature [2]. The rate of re-amputation, however, (reported to be as high as 40%) has remained unchanged despite advances in noninvasive diagnostic tools, endovascular interventions, and medical management [2]. Numerous screening tools, markers, and scoring systems have been evaluated for the diagnosis, risk prediction, and outcome assessment of sepsis; however, they possess certain limitations. For instance, the white blood cell count, erythrocyte sedimentation rate, and C-reactive protein exhibit poor sensitivity and specificity. Procalcitonin, D-dimer, and CD14 are expensive and impractical options, while microbiological cultures are time-consuming and prone to high false-negative rates [3]. Therefore, the search for an ideal marker that is quick, readily available, and applicable across various settings such as wards, emergency departments, and ICUs for the diagnosis and prognostication of sepsis continues [3]. The neutrophil-to-lymphocyte ratio (NLR) is an inflammatory biomarker that reflects the dynamic balance of the immune system [3]. The neutrophil-to-lymphocyte ratio (NLR) has emerged as an important indicator of inflammation and has been shown to have prognostic value for systemic inflammation in patients with chronic conditions [4]. The NLR is based on two markers: neutrophils (the initial line of defense) and lymphocytes (the regulatory component of inflammation) [5]. Because of its consistency and minimal influence from physiological and pathological factors, the NLR is superior to other leukocyte parameters [6]. The NLR is also a relatively cheaper and more accessible tool for evaluating inflammatory conditions. Hence, the NLR may be a prospective indicator of vascular complications and a predictor of poor outcomes in cases of diabetes mellitus [7]. Despite mounting evidence describing elevated NLR as a predictor of poor outcomes in these disease processes, the mechanism of action resulting in those observations remains unknown [8]. However, there are limited studies on the role of NLR in managing diabetic patients. In this study, we analyze the neutrophil-to-lymphocyte ratio as a predictor of infectious complications following infectious complications after lower limb amputation in patients with diabetes. We hypothesized that a higher NLR would be associated with poor outcomes following amputation. Some studies have shown that the NLR is a predictor

of diabetic foot ulcers during treatment, and an elevated NLR was associated with bad outcomes in patients with diabetic foot ulcers [9]. However, no studies have focused on the association between the peroperative NLR and diabetic foot wound outcomes following amputation.

2. Methods

This was a retrospective cohort study carried out over the period from January 2023 to June 2024 in the orthopedic surgery and traumatology department of the University Hospital Center of Cocody in Ivory Coast. The inclusion criteria were the following: 1) patients diabetic; 2) with tibial or femoral amputation for gangrene of the lower limb; 3) age ≥ 18 years; 4) a follow-up of patients within six months postoperative. Patients were excluded according to the following criteria: 1) non-diabetic patients, 2) patients who lacked laboratory or follow-up data, 3) patients with severe systemic infections or blood diseases that affect neutrophils and lymphocytes, and 4) patients with complications including serious dysfunctions of the heart, lung, kidney, brain, and other organs. Data on age, sex, history of smoking, and alcohol abuse were collected from individual medical records. The parameters such as type of diabetes, disease duration, type of gangrene, amputation level, wound complications, the need for reamputation, pre- and postoperative hemoglobin concentration, blood cell count, platelet count, lymphocyte count, and neutrophil count were also collected. Neutrophil-to-Lymphocyte Ratio (NLR) was calculated immediately. The criteria used to diagnose postoperative infection are defined [10]. These infections involve soft tissues deep into the subcutaneous tissue, including muscles and fascial planes and bone. This diagnosis requires 1 of the following criteria [10]:

- Presence of purulent discharge from the surgical site.
- Wound dehiscence.
- Deliberate re-opening of a deep incision by the surgeon due to suspicion of infection or wound spontaneously dehisces, and a positive wound culture and at least one infectious symptom is present (e.g., fever, localized pain, or tenderness)

Forget *et al.* identified that normal NLR values in an adult, non-geriatric, population in good health are between 0.78 and 3.53 [11]. An NLR of >3.53 was considered high, and an NLR of <3.53 was considered normal [11].

3. Statistical Analysis

The data were analyzed using IBM SPSS software version 25 (IBM Corp., Armonk, NY, USA). Descriptive statistics were performed for quantitative variables (mean, standard deviation, minimum, maximum) and qualitative variables (frequency). The Kolmogorov-Smirnov test was used to test the normality of the data, and a non-parametric test was used if normality was rejected. Qualitative variables were evaluated by the chi-square test. A multiple logistic regression model was employed to determine the risk factors of infection after lower limb amputation. Independ-

ent variables were age (years), gender, type of gangrene, haemoglobin rate, neutrophil count, lymphocyte count, preoperative NLR, and site of amputation. A p-value < 0.05 was considered statistically significant.

4. Results

We undertook one hundred and twenty amputations (n = 120) of lower limbs over the period of study. There are 63 (52.5%) men nd 57 (47.5%) women with a mean age of 62.34 ± 11.36 (37 - 91) years. The average duration of diabetes was 75.84 ± 67.39 (1 - 360) months. Wet gangrene predominated in 88 (73.3%) cases. Before amputation, the mean neutrophil count was 76.09 ± 13.30, and the lymphocyte count was 15.02 ± 10.12. The mean Neutrophil/Lymphocyte Ratio (NLR) was 8.67 ± 7.74, and 95 (79.2%) patients had a high NLR preoperatively. The majority of patients, 88 (73.3%), underwent below-knee amputation compared to above-knee amputation, 32 (26.7%). The post-operative infection rate as 71 (59.2%). The patient characteristics are shown in **Table 1.** After amputation, the mean neutrophil count was 73.57 ± 12.46, and the lymphocyte count was 18.02 ± 10.45. The neutrophil-to-lymphocyte ratio (NLR) was 6.08 ± 4.86. The gender, age group, and type of gangrene were not significantly associated with postoperative infection (p > 0.05) (**Table 2**). In univariate analysis (**Table 2**), a higher neutrophil and lymphocytes count preoperatively was associated with postoperative infection (p = 0.001). Preoperatively, a higher NLR was also associated with postoperative infection (p = 0.0001). Multivariate logistic regression analysis showed that age ≥ 60 years (odds ration (OR): 0.922, 95% confidence interval (CI): 0.872 - 0.975, p = 0.005), preoperative neutrophil count (OR: 1.205, 95% CI: 1.019 - 1.426; p = 0.0001), lymphocyte count (OR: 1.774, 95% CI: 1.321 - 2.372; p = 0.03), and NLR preoperative (OR: 0.792, 95% CI: 0.715 - 0.877; p = 0.0001) were independent risk factors for infection after lower limb amputation in diabetic patients (**Table 3**).

5. Discussion

The aim of this study was to investigate the influence of high preoperative NLR on the occurrence of an infection of the amputation stump in diabetic subjects. The current study outcomes have shown an association between high NLR preoperative ratio and the occurrence of postoperative stump infection after amputation (p < 0.05). These findings serve as more evidence of the use of NLR as a marker of the inflammatory balance of a patient. It may be useful when discussing and trying to mitigate individual risks of complications after lower limb amputation in diabetic patients. The results also further validate the use of this simple blood test as a clinical indicator of disease severity. Complete healing of diabetic foot wounds is difficult due to infection, peripheral artery disease, diabetic neuropathy, and other reasons [12]. The measurement of NLR is a simple and low-cost method that can be performed even in resource-limited areas to predict infection after lower limb amputation in diabetic patients. NLR is a biomarker that is easily accessible and simple to calculate. The NLR is also a marker used to de-

termine the prognosis of and mortality associated with certain diseases [13]. Yüce *et al.* reported that a high preoperative NLR was significantly associated with increased 1-year mortality in patients who underwent amputation due to diabetic foot complications [14]. Elevated NLR values have been reported to be associated with more severe infections and poorer wound healing outcomes, which could be explained by the role of neutrophils in both combating infection as well as causing collateral tissue damage through the release of proteolytic enzymes and oxidative agents [15] [16]. A high NLR in patients with type II diabetes mellitus is associated with a high risk of coronary artery disease [17]. A high NLR is also correlated with a poor prognosis in patients with hip fractures and bone metastasis [13] [17]. An NLR is a novel immune-inflammatory response marker that can be used to assess the suppressive and excitatory activities of the immune system [18]. Chen *et al.* [19] showed that higher NLR may be a reliable predictive biomarker of mortality in patients with diabetic foot ulcer-related amputations. Demirdal *et al.* [20] found that the NLR was higher in amputated versus non-amputated patients and that the NLR could be used to predict the diabetic foot ulcer-related amputation risk. The significance of the NLR lies in its ability to reflect the dynamic interplay between these cellular components of the immune system. A high NLR indicates an imbalance skewed toward increased neutrophilic activity, correlating with elevated endothelial damage and dysfunction [21]. Consequently, high NLRs serve as a prognostic indicator for adverse outcomes in various pathological contexts. The neutrophil-to-lymphocyte ratio (NLR) is derived from the quotient of the neutrophil count to the lymphocyte count obtained through a standard differential blood cell ount test [9]. This metric presents a cost-effective and readily accessible means of gauging immune system activity [9]. NLR is less influenced by physiological processes like dehydration or physical exercise and is expected to better characterize the pathological change [22] [23]. We found a strong association between preoperative NLR and postoperative infection after amputation. The association 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. The present study highlights the association between overall risk of infectious 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. This is the study aimed at predicting the prognosis of infection after amputation of a diabetic using the preoperative NLR. There were limitations inherent to the use of NLR as a biomarker of systemic inflammation. Further investigations, such as exploring additional biomarkers of inflammation or conducting randomized controlled trials, are necessary to validate the observed associations. This study had limitations. Indeed, we did not consider other risk factors in our NLR comparison. Furthermore, NLR was the only biomarker of systemic inflammation used. Further research, such as exploring additional biomarkers of inflammation or conducting randomized controlled trials, is needed

to validate the observed associations.

Table 1. Characteristics of patients.

Variables	n (%)
Gender	
Male	63 (52.5)
Female	57 (47.5)
Age (years)	
Mean ± SD (range)	62.34 ± 11.36 (37 - 91)
Age < 60 years	47 (39.2)
Age ≥ 60 years	73 (60.8)
Duration of diabetes (month)	75.84 ± 67.39
Type of gangrene	
Wet gangrene	88 (73.3)
Dry gangrene	32 (26.7)
Data preoperative	
Neutrophil count	76.09 ± 13.30
Lymphocyte count	15.02 ± 10.12
NLR preoperative	8.67 ± 7.74
Site of amputation	
Below-knee	88 (73.3)
Above-knee	32 (26.7)
Infection	
Yes	71 (59.2)
No	49 (40.8)
Data postoperative	
Neutrophil count	73.57 ± 12.46
Lymphocyte count	18.02 ± 10.45
NLR postoperative	6.08 ± 4.86

SD: Standard Deviation; NLR: Neutrophil-to-Lymphocyte Ratio.

Table 2. Results of univariate analysis.

Variables	Postoperative infection		p-value
	Yes	**No**	
Gender			0.919
Male	37	26	
Female	34	23	

Continued

Age (years)			0.225
Age < 60 years	31	16	
Age ≥ 60 years	40	33	
Type of gangrene			0.695
Wet gangrene	53	35	
Dry gangrene	18	14	
Hemoglobin rate			0.545
<10 g/dL	47	35	
≥10 g/dL	24	14	
Neutrophil count preoperative			0.0001
High	43	45	
Normal	28	4	
Lymphocyte count preoperative			0.001
High	71	42	
Normal	0	7	
Preoperative NLR			0.0001
NLR High	46	49	
NLR normal	25	0	
Site of amputation			0.978
Below-knee	52	36	
Above-knee	19	13	

Table 3. Results of multiple logistic regression to identify risk factors of infection after lower limb amputation.

Independent variables	Coefficient ± SE	OR [LCI-UCI]	p-value
Age (years)	−0.081 ± 0.029	0.922 [0.872 - 0.975]	0.005
Preoperative Neutrophil Count	0.187 ± 0.086	1.205 [1.019 - 1.426]	0.03
Preoperative Lymphocyte Count	0.573 ± 0.148	1.774 [1.321 - 2.372]	0.0001
NLR Preoperative	−0.234 ± 0.052	0.792 [0.715 - 0.877]	0.0001

SE, standard error; OR, odds ratio; LCI, 5% lower confidence interval; UCI, 95% upper confidence interval.

6. Conclusion

This retrospective study demonstrated that diabetic patients undergoing major lower limb amputation and with a higher baseline neutrophil-to-lymphocyte ratio tended to be at risk of postoperative infection. This is the first study to demonstrate that NLR could be a predictive factor for limb amputation outcomes in diabetic patients. NLR counting is particularly useful because it is a simple, routinely

available, and inexpensive hematological test. The preoperative high NLR can be used as prognostic marker when predicting the risk of infection complications after lower limb amputation.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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