

Clinical utility of neutrophil to lymphocyte ratio in sickle cell disease with vaso-occlusive crisis

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BRIEF COMMUNICATION

Clinical Utility of Neutrophil to Lymphocyte Ratio in Sickle Cell Disease With Vaso-Occlusive Crisis

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Abstract

Background and objectives: The neutrophil-to-lymphocyte ratio represents a universally accessible value that correlates with inflammation and prognosis in several disease states; however, the role of this biomarker in sickle cell disease remains poorly explored. Hence, the objective of the present study was to determine its potential clinical utility in patients with sickle cell disease.

Patients: Herein, we retrospectively reviewed 143 patients with sickle cell disease who presented to the emergency department with fever and painful vaso-occlusive crisis.

Results: The examined cohort had a prevalence of 11% confirmed bacterial infection, with approximately two-thirds reporting the use of hydroxyurea. The neutrophil-to-lymphocyte ratio was lowest in the vaso-occlusive crisis-only group when compared with all other groups; this ratio was the highest in those with a confirmed bacterial infection. Patients with confirmed bacterial infection experienced the longest mean length of in-hospital stay, approximately 2 weeks, whereas patients with viral infections and vaso-occlusive crisis had the shortest stay (4–5 days). An elevated neutrophil-to-lymphocyte ratio on presentation correlated with confirmed bacterial infection (area under the curve 0.76); maximum specificity (76%) and sensitivity (69%) for confirmed bacterial infection were achieved using a neutrophil-to-lymphocyte ratio threshold ≥ 4.6 . However, the neutrophil-to-lymphocyte ratio did not predict acute chest syndrome in this patient cohort.

Conclusion: The neutrophil-to-lymphocyte ratio is a promising biomarker in sickle cell disease with diagnostic and prognostic utility.

Keywords: Sickle cell disease, Vaso-occlusive crisis, Fever, Infection, Hydroxyurea

1. Introduction

Patients with sickle cell disease (SCD) are at increased risk of developing serious infections due to functional asplenia and altered humoral immunity. The signs and symptoms of sepsis, such as fever, malaise, tachycardia, pleurisy, and arthralgia, are common in SCD but can be notoriously non-specific. The clinical presentation of sepsis overlaps with several SCD-related conditions, including vaso-occlusive crises (VOC), and are not consistent signs of true infection.

The neutrophil-to-lymphocyte ratio (NLR), calculated as the absolute neutrophil count divided by the absolute lymphocyte count, represents a universally accessible value that correlates with inflammation and prognosis in several conditions.

Few studies have evaluated NLR as a biomarker in sickle cell disease, and its utility in differentiating infection from VOC in SCD remains unknown.

2. Materials and methods

We retrospectively reviewed 143 patients with SCD who presented to the emergency department with fever and painful crises. Inclusion criteria for both groups were patients with SCD, 17 years and older, and complete blood count with differential at presentation. Patients who had received antibiotics prior to presentation were excluded. Data collected on presentation included genotype, age, gender, complete blood count, and hydroxyurea use. The patients were divided into categories based on discharge diagnoses: patients with VOC only ($n = 88$), viral infection ($n = 10$), confirmed bacterial

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infection ($n = 16$), confirmed and suspected bacterial infection (SBI) ($n = 41$), and cases diagnosed as acute chest syndrome (ACS) on discharge were ($n = 18$) for exploratory analysis. Four cases could not be categorized into VOC or infectious groups: three pulmonary emboli and one new diagnosis of malignancy.

Chronic bacterial infection (CBI) was defined as a positive clinical source with bacterial culture (blood, body fluid, urine, respiratory or cerebrospinal fluid) or *Clostridium difficile* toxin assay. Sources included colitis, pyelonephritis, cellulitis, osteomyelitis, pneumonia, and tonsillitis. Viral infections were defined as a negative bacterial culture in the presence of a virus detected on polymerase chain reaction using a nasopharyngeal swab. Data were analyzed between groups using descriptive statistics (Table 1); receiver-operating characteristic (ROC) curves were generated with the area under the curve (AUC) calculation using 95% confidence intervals (Fig. 1). Clopper-Pearson and Hanley-McNeil statistical methods were used.

3. Results

Characteristics of the cohort are presented in Table 1. Genotype HbSS (73%) was most prevalent, followed by HbSC (23%) and HbSβ (4%). The sample included two-thirds of young adult males, with 61% reporting adherence to hydroxyurea. Overall, two patient deaths were recorded, one from CBI and the other from SBI. The mean hemoglobin (Hb) was

approximately 8 g/dL. As expected, the VOC group had a lower mean white blood cell count than patients with a bacterial infection. Further examination revealed that the mean NLR was lowest in the VOC group when compared with all others, and this value was the highest in the CBI group. The patients with CBI had the longest mean length of hospital stay, approximately 2 weeks, with the shortest stay documented for viral infections and VOC (4–5 days).

On examining the diagnostic performance of NLR in differentiating from VOC (Fig. 1), the best performance was noted for discriminating CBI, with an AUC value of 0.76. Maximum specificity (76%) and sensitivity (69%) for CBI were achieved using an NLR threshold ≥ 4.6 . When SBIs with non-diagnostic evaluation were included with CBI, the NLR performance decreased to AUC = 0.68. Regarding viral infection, NLR could discriminate from VOC but afforded only a modest performance, with AUC = 0.70. Finally, the mean NLR on admission was higher in cases diagnosed with ACS on discharge (Table 1); however, there was no significant predictive ability on ROC analysis (Fig. 1).

4. Discussion

Historically, sepsis has been an important cause of mortality in SCD [1–3]. In the last two decades, increased newborn screening, vaccination against encapsulated organisms, and prophylactic penicillin have successfully decreased deaths due to bacterial sepsis in resource-rich countries [4]. Nevertheless,

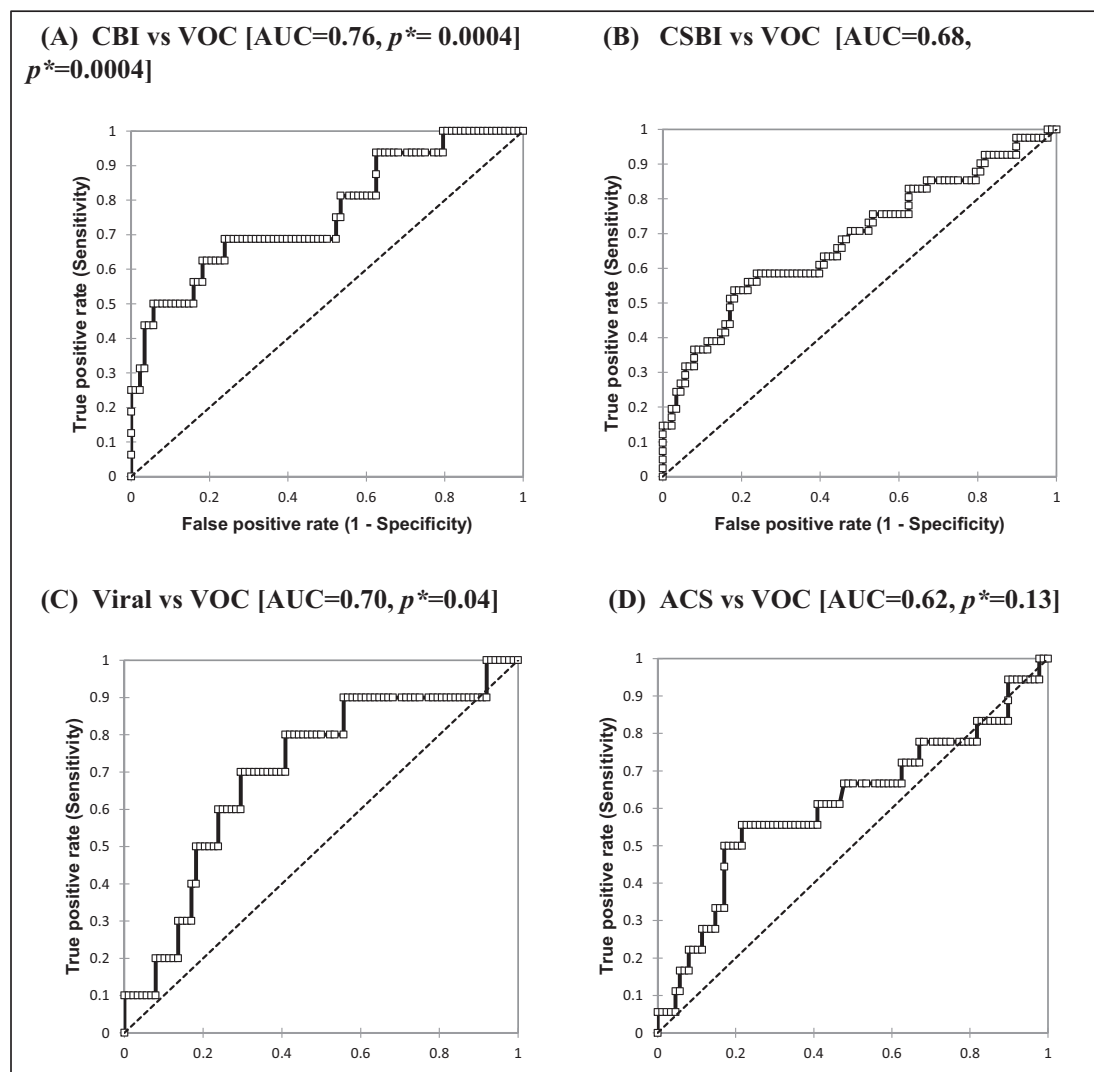
Table 1. Characteristics of the cohort.

Patient Characteristics	All Patients (n = 143)	Viral Infection (n = 10)	Confirmed Bacterial Infection (n = 16)	Acute Chest Syndrome (n = 18)	Confirmed/Suspected Bacterial Infection (n = 41)	VOC only (n = 88)
Genotype						
SS (%)	73	70	69	89	78	70
SC (%)	23	30	25	6	17	26
SThal (%)	4	0	6	5	5	4
Mean age (years)	34	33	37	27	32	35
Female (%)	34	20	56	33	41	33
Hydroxyurea use (%)	61	50	63	50	49	68
Mean length of stay (days)	6.4	4.0	14.8	6.9	10.0	4.8
Mean Hb (g/dL)	8.3	7.7	7.8	7.5	7.8	8.5
Mean WBC ($\times 10^9/L$)	14.9	14.3	20.1	16.2	18.0	13.6
(range)	(2.5–44.2)	(2.5–29.2)	(9.5–44.2)	(5.6–26.1)	(5.6–44.2)	(2.8–27.7)
Mean NLR	6.2	6.8	15.3	7.8	10.0	3.9
Optimal diagnostic NLR ^b	n/a	4.2	4.6	4.9	5.0	n/a
AUC for NLR (95% CI) ^a	n/a	0.70 (0.51–0.89)	0.76 (0.62–0.90)	0.62 (0.47–0.76)	0.68 (0.58–0.79)	n/a

AUC, area under the curve; CI, confidence interval; Hb, hemoglobin; NLR, neutrophil-to-lymphocyte ratio; WBC, white blood cell; VOC, vaso-occlusive crises.

^a When used to differentiate the event from VOC.

^b Defined as NLR value achieving maximum combined sensitivity and specificity.



* p -value for difference between the AUC and 0.5 with $\alpha=0.05$ for significance

**CBI=Confirmed bacterial infection; CSBI=confirmed and suspected bacterial infection; VOC=vaso-occlusive crisis only; ACS=acute chest syndrome

Fig. 1. Receiver-operating characteristic (ROC) curves for neutrophil-to-lymphocyte ratio (NLR) performance.

while mortality is decreasing in the United States, bacterial infection remains a major contributor to mortality [5] and the two deaths in our study were attributed to CBI and confirmed/SBI (CSBI), respectively.

Several pathogens identified in patients with SCD are not covered by immunization, including those represented in this cohort, *Escherichia coli*, *C. difficile*, *Staphylococcus aureus*, and *Enterobacter* and *Pseudomonas* spp. It should be noted that SCD is a global disease, and in many countries, such as Africa, bacterial infection is often fatal [6]. Fever in SCD is a common diagnostic dilemma, given that fever is frequently the first sign of severe bacterial infection but can also indicate SCD-related comorbidities such as VOC or ACS.

As all patients with SCD who present with fever are likely to undergo complete blood count testing, the NLR represents a potential biomarker that, if validated, would be quick and easily accessible. To date, few studies have investigated NLR in SCD. One study has compared NLR in 30 patients with VOC with the same number during the steady state, as well as healthy controls. The authors found that NLR was elevated in SCD when compared with healthy controls. In addition, NLR was increased in VOC when compared with steady state [7]. Two studies have reported that hydroxyurea use can alter NLR [8,9]. To the best of our knowledge, NLR has not been examined as a diagnostic tool for bacterial infection in a modern-day cohort of patients with SCD.

Our finding that NLR is elevated in VOC is consistent with the results of previous reports, and approximately two-thirds of this group reported hydroxyurea use. An 11% prevalence of CBI was documented in the examined cohort, and elevated NLR correlated with CBI, affording a modest performance as a diagnostic test. The sensitivity at an optimal threshold of $\text{NLR} \geq 4.6$ was 69%; therefore, the test should not be used alone in decision-making. To increase sensitivity to $>90\%$, the NLR threshold would have to decrease to 2.25, resulting in poorer specificity (40%).

5. Conclusion

An elevated NLR on presentation in SCD correlates with confirmed bacterial infection versus VOC only. NLR on presentation also significantly correlated with viral infection but failed to predict ACS, exhibiting a simple correlation with the length of hospital stay. Given the widespread availability and cost-effectiveness of NLR testing, the findings of the present study should be explored in large-scale studies to validate the optimal cutoff for sensitivity/specificity.

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Permission to reproduce material from other sources

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Data availability statement

Not applicable.

Clinical trial registration

Not applicable.

Declaration of Competing Interest

The authors report there are no competing interests to declare.

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