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Original Article

Neutrophil-to-lymphocyte and Platelet-to-lymphocyte Ratios in Pediatric Sickle Cell Disease: Association with Vaso-occlusive Crises and Treatment Modalities

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ABSTRACT

Platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) are emerging markers for inflammation. In sickle cell disease (SCD), inflammation is a central feature of vaso-occlusive crises (VOC). This study evaluated NLR and PLR dynamics in pediatric SCD patients during VOC and it examined the impacts of treatments such as hydroxyurea and chronic transfusion therapy on these markers. This cross-sectional study included 100 SCD patients aged 2-27 years presenting for VOC. Paired t-tests and ANOVA were used to compare VOC and steady-state values with $p<0.05$ considered statistically significant. Total white blood cell count, absolute neutrophil count, and NLR were significantly elevated during VOC. Platelet counts were significantly higher during steady state in untreated patients, but no significant differences were observed in PLR. In treated patients, platelet counts remained elevated both at steady state and during VOC. No significant differences in NLR or PLR were found between the treatment groups. These findings support NLR as a sensitive marker of inflammation during VOC in pediatric SCD patients. However, treatment modalities such as hydroxyurea and chronic transfusions may not significantly impact NLR and PLR levels. Larger, prospective studies are needed to further define their roles in disease monitoring.

Keywords: Platelet-lymphocyte ratio, neutrophil-lymphocyte ratio, sickle cell disease, vaso-occlusive crisis

Introduction

Sickle cell disease (SCD) is an autosomal recessive disorder caused by a point mutation in the beta-globin gene (on chromosome 11) which substitutes glutamic acid for valine at position 6 of the β-globin chain. This mutation promotes hemoglobin polymerization, leading to red cell deformation, hemolysis and vaso-occlusion. Vaso-occlusion is a well-known sequalae of SCD often manifesting as painful episodes, particularly in the bones.

Hydroxyurea is a pharmacological agent which increases fetal hemoglobin in red blood cells (RBCs) by inhibiting ribonucleotide reductase. It has been shown to reduce the frequency of pain crises and hospitalizations in patients with SCD (1). While chronic transfusions therapy is primarily

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used for stroke prevention, it has also been suggested to prevent acute pain episodes (2).

Vaso-occlusion triggers inflammation through various mechanisms including endothelial activation, tissue ischemia and re-perfusion injury. In response, various components of the immune system become activated promoting investigation into their role during vaso-occlusive crises (VOC) (3). Studies have demonstrated increased platelet activation and changes in platelet counts as well as higher absolute neutrophil count (ANC) and neutrophil activation during VOCs (4,5). In recent years, systemic inflammatory markers such as platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) have emerged as potential markers of inflammation during VOC. These ratios have demonstrated utility in a variety of inflammatory conditions, such as osteoarthritis, coronary microcirculatory disease, Chron's disease, and rheumatoid arthritis (6-9).

This study aimed to evaluate PLR and NLR as markers of inflammation in pediatric patients with SCD during VOC and to assess further their potential prognostic value in disease monitoring. In addition, we examined the effects of therapeutic interventions such as the use of hydroxyurea and chronic transfusions on these inflammatory biomarkers.

Materials and Methods

This retrospective cross-sectional study included 100 patients with SCD aged 2-27 who presented to the St. Christopher's Hospital Emergency Department for VOC. VOC was defined as acute pain in the extremities, back, or chest in known SCD patients without an alternative identifiable cause. Steady state was collected during outpatient follow-up. NLR, PLR were calculated using absolute values on CBC. Patients were grouped based on treatment status: untreated, hydroxyurea-treated, or on chronic transfusions. Statistical analysis included paired t-testing and ANOVA with a significance threshold of $p<0.05$.

Results

The demographic characteristics of the study participants are summarized in Table I. A total of one hundred patients with SCD who presented to the St. Christopher's Hospital Emergency Department for VOC over a 3.5-year period were included. The mean age of the cohort was 14.6 (range: 2-26) years. Of the participants, 52% were male and 48% were female. Genotypes included were hemoglobin SS, SC, Sb^+ thalassemia and Sb^0 thalassemia. Of the patients, 41 were not receiving disease modifying therapies, 48 had been on hydroxyurea for at least one year, and 11 were receiving chronic transfusions therapy.

There was a significantly elevated total white blood cell count (WBC), ANC and NLR in the SCD patients in the VOC state ($p<0.0001$). Platelet count was significantly higher during the steady state when compared to VOC ($p<0.05$). There was no significant difference in lymphocyte count or PLR (Table II).

The patients were grouped based on their treatment status into treated (hydroxyurea or chronic transfusions), not treated, and further subdivided by specific therapy. Across all groups, except for the transfusion only group, there was a significant increase in ANC and NLR ratio in the SCD patients in the VOC state ($p<0.001$) (Figures 1 and 2). Moreover, the relative increase in NLR during VOC was greater than ANC alone, suggesting that NLR may serve as a more sensitive indicator during acute episodes.

When comparing treated patients (hydroxyurea or chronic transfusions) to untreated patients, WBC, platelets and lymphocytes were significantly higher in the treated groups during both the steady state and VOC. However, no significant differences were observed between the treatment groups for ANC, NLR or PLR (Table III).

Table I. Demographic characteristics of the study participants

Variable	Average/ Number	Range/ Percentage
Age (years)	14.6	2-26
Gender		
Male	53	53%
Female	47	47%
Ethnicity		
Black or African American	78	78%
Hispanic or Latino	19	19%
Other	3	3%
Genotype		
SS	67	67%
SC	25	25%
Sb^+ thalassemia	4	4%
Sb^0 thalassemia	4	4%
Therapy		
None	41	41%
Hydroxyurea	48	48%
Chronic transfusions	11	11%

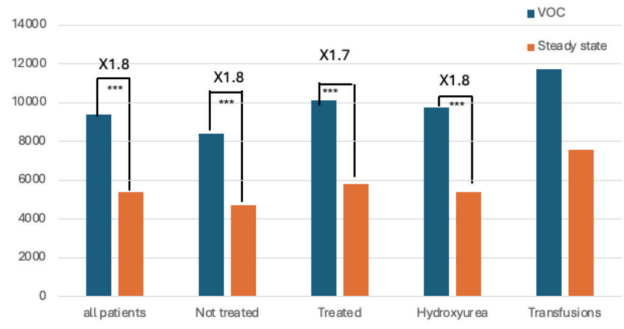

Figure 1. Neutrophil count during steady vs. VOC state grouped by treatment status. ***p<0.001 and X represents the VOC/steady state value

VOC: Vaso-occlusive crises

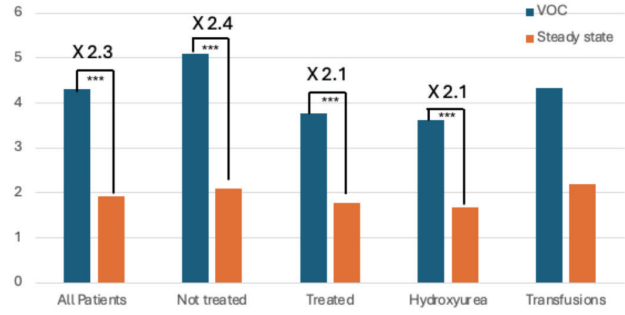

Figure 2. NLR during steady state vs. VOC state grouped by treatment status. ***p<0.001 and X represents the VOC/steady state value

NLR: Neutrophil-to-lymphocyte ratio, VOC: Vaso-occlusive crises

Table II. Cell line counts, NLR, and PLR in SCD patients during steady and VOC state

	Steady state	VOC	p value
WBC (x10³/mL)	10.32	14.38	<0.0001**
Neutrophils (x10³/mL)	5.367	9.372	<0.0001**
Lymphocytes (x10³/mL)	3.469	3.418	0.817
Platelets (x10³/mL)	391	356	<0.05*
Neutrophil-to-lymphocyte ratio	1.93	4.30	<0.0001**
Platelet-to-lymphocyte ratio	0.128	0.142	0.181

NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, SCD: Sickle cell disease, VOC: Vaso-occlusive crises, WBC: White blood cell count

Table III. Cell line counts, NLR and PLR in SCD patients treated (with either chronic transfusions or hydroxyurea) compared to untreated patients in both steady state and VOC state

	Treated	Untreated	p value
WBC (x10³/mL)			
Steady	11.5	8.59	<0.01*
VOC	15.8	12.3	<0.01*
Neutrophils (x10³/mL)			
Steady	5,791	4,712	0.146
VOC	10,090	8,379	0.085
Platelets (x10³/mL)			
Steady	433.65	328.1	<0.01*
VOC	393.85	299.2	<0.01*
Lymphocytes (x10³/mL)			
Steady	3,984	2,747.8	<0.001**
VOC	3,950	2,674	<0.01*
NLR			
Steady	1.77	2.1	0.366
VOC	3.765	5.1	0.228
PLR			
Steady	0.127	0.128	0.922
VOC	0.132	0.156	0.324

*p<0.01, **p<0.001
NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, SCD: Sickle cell disease, VOC: Vaso-occlusive crises, WBC: White blood cell count

Discussion

It is well known that VOC increases inflammation and is associated with leukocytosis. As the most predominant leukocytes in the blood stream, the elevation in neutrophil number during VOC state has been studied extensively. Elevated neutrophil counts have been associated with disease severity in SCD, including higher rates of VOC and complications (10). For instance, the use of GM-CSF or G-CSF increasing the number neutrophils leads to more severe VOC with worse outcomes and it is contraindicated in SCD (11). Conversely, one case study showed that congenital neutropenia was associated with better outcomes (12).

Numerous studies have investigated the role of neutrophil in the pathophysiology of VOC. Sickled RBCs lead to hemolysis and tissue ischemia, which in turn cause injury to the endothelium and trigger an inflammatory response which includes margination of neutrophils. Neutrophils are recruited to post-capillary venules by P- and E-selectins. In murine models, the absence of these selectins reduces neutrophil recruitment and protects against VOC (13). The binding of neutrophils to E-selectins then activates Mac-1 (CD11b/CD18). This enhances adhesion of neutrophil to endothelium and facilitates interaction with RBC. These adherent neutrophils, when bound to sickled RBC are believed to exacerbate VOC by slowing

blood flow and increasing the likelihood of polymerization in the microvasculature. The inactivation of Mac-1 or the use of antibodies against it have been shown to diminish neutrophil-RBC interactions and improve circulation in mice during VOC (14). Furthermore, Mac-1 expression is upregulated in SCD, and SS-RBC adhere to PMN more than normal erythrocytes (14,15). These findings underscore the complex and critical role of neutrophils in the development of VOC. As expected, neutrophil counts were significantly elevated during VOC when compared to the steady state for our cohort.

NLR has been found to be useful as a marker of inflammation in various other chronic diseases (16). In line with prior studies in adults, NLR was found to be higher in VOC groups when compared to steadystate groups. Prior adult studies have also found a higher NLR in SCA patients than HbA controls (5). NLR was significantly increased during the VOC state in this pediatric study and correlated positively with WBC and ANC. While the elevation of NLR could be partially attributed to elevated neutrophil counts, the magnitude of the change in NLR exceeded that of neutrophils alone suggesting that NLR may serve as a more stable marker of inflammation in the setting of VOC.

Hydroxyurea has been shown to reduce the frequency and severity of episodes in patients with SCD (13). While its primary mechanism is to increase levels of HbF, it also reduces neutrophil counts and suppresses inflammatory activation (14). Several studies have explored the effect of hydroxyurea on neutrophil function, including expression of integrins and adhesion markers which are known to be associated with increased neutrophil activation (13,14,17). However, in our study, we observed no significant difference in neutrophil count or NLR between those patients on hydroxyurea and those untreated. This may be explained by a lack of adherence to the medication or by worsened disease severity at baseline for those patients on medication.

While hydroxyurea therapy has been shown to decrease leukocytosis and supress increased neutrophil activation, the impact of transfusions on neutrophils is less clear. One pediatric study of patients with SCD aged 2-18 on an exchange transfusion (ET) program found no significant change in neutrophil, monocyte, or platelet counts between baseline (before the ET program was started) and during the ET program (18). Another study in SCD children observed persistent neutrophilic leukocytosis and unchanged expression of neutrophil activation markers in those patients receiving monthly exchange transfusions (17). In our study, no significant changes in neutrophil count or NLR were seen in the transfusion group, though the small sample size (n=11) limited our ability to detect meaningful differences. Larger studies are needed in order to better determine the immunologic impact of chronic transfusions in SCD.

In our cohort, the platelet counts were significantly higher during the steady state than the presentation with VOC, consistent with previous observations that platelet counts decline in the acute phases and rise during recovery. Following VOC, rebound thrombocytosis is believed to occur due to the structural similarity between erythropoietin and thrombopoietin which increases due to hemolysis. Prior studies in adults with SCD have demonstrated similar trends: elevated platelet counts during asymptomatic periods, a moderate decrease in platelet count during crises, followed by marked thrombocytosis in recovery (15). Furthermore, declining platelet counts during VOC have been associated with complications such as acute chest syndrome (19).

Interestingly, when stratified by treatment groups, a significant drop in the platelet count during VOC was only observed in the non-treated cohort. In contrast, patients receiving hydroxyurea or chronic transfusions maintained higher platelet counts at both steady state and during VOC. This may suggest that treatments such as hydroxyurea and chronic transfusions either attenuate the drop in platelets during the initial phase of VOC, accelerate recovery or help maintain platelet counts consistently. However, despite this difference in the platelet dynamic, no significant changes in PLR were observed, suggesting that PLR may be a less sensitive marker in this context.

Conclusion

In this study of pediatric patients with SCD, NLR significantly increased during VOC compared to the steady state, supporting its utility as sensitive inflammatory marker. While neutrophil counts contributed to this rise, the proportionally greater increase in NLR suggests that it may offer added value beyond absolute counts. PLR did not show significant changes across disease states or treatment groups. Additionally, neither hydroxyurea nor chronic packed RBC transfusions significantly affected NLR or PLR levels in this cohort. This study had several limitations which may impact the interpretation of its results. The cross-sectional design does not account for intra-patient variability over time. The sample size, particularly in the chronic transfusion group, was small and may limit its statistical power. Treatment adherence to hydroxyurea

was not objectively measured, potentially confounding comparisons between the treated and untreated groups. Additionally, only single timepoints were used for VOC and steady-state measurements, which may not fully capture the dynamic nature of inflammatory markers in SCD. Future prospective studies with longitudinal sampling and better adherence tracking are needed in order to validate these findings.

Ethics

Ethics Committee Approval: Ethical committee approval for this study was obtained from Drexel University Office of Research and Innovation (approval number: HRP-200, protocol number: 240901773, date: 02.01.2020).

Informed Consent: A waiver of consent and HIPAA authorization was granted due to the retrospective nature of the study (data collected during routine clinical care and poses minimal risk or affect).

Footnotes

Authorship Contributions

Concept: J.Z., N.A., Design: J.Z., N.A., Data Collection or Processing: J.Z., J.H., Analysis or Interpretation: M.Z., Literature Search: J.Z., Writing: J.Z., N.A.

Conflict of Interest: All authors declare that they have no conflict of interest.

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