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Case Report

Neutrophil-to-Lymphocyte Ratio in Pediatric Sickle Cell Anemia: A Case-Control Study from Gezira State, Sudan

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Abstract

Background: Sickle Cell Anemia (SCA) is a common hereditary hemoglobinopathy marked by chronic intravascular hemolysis, recurrent microvascular occlusion, and sustained systemic inflammation.

Objective: This study evaluated the clinical utility of the Neutrophil-to-Lymphocyte Ratio (NLR) as an accessible inflammatory biomarker among pediatric SCA patients in Sudan and examined its relationships with disease manifestations, clinical crisis phenotypes, and therapeutic regimens.

Methods: A hospital-based case-control investigation was conducted at Wad Medani Pediatric Teaching Hospital in Gezira State, Sudan, enrolling 130 pediatric participants (80 confirmed SCA cases and 50 healthy controls). A formal sample size calculation was performed to ensure statistical power (>80%). Automated complete blood counts were performed using a Sysmex XP-300 hematology analyzer to calculate absolute NLR values. Statistical comparisons, ROC diagnostic evaluations, and stratified subgroup analyses were performed using SPSS version 22.

Results: Pediatric SCA patients exhibited significantly elevated mean NLR compared with healthy controls (3.89 ± 2.60 vs. 1.56 ± 0.29, $p < 0.001$). Receiver Operating Characteristic (ROC) analysis revealed robust diagnostic discrimination (AUC = 0.79, 95% CI: 0.71–0.87), yielding 63.8% sensitivity and 98.0% specificity at an optimal cutoff of >2.2. NLR levels varied markedly by clinical crisis category ($p = 0.001$), peaking during hand-foot syndrome (6.84 ± 1.66) and acute infection (5.00 ± 3.06). However, subgroup comparisons involving rare complications (such as acute chest syndrome, n=2, and cerebrovascular accident, n=2) require cautious interpretation due to limited subgroup sample sizes. Hydroxyurea therapy was associated with a substantial reduction in mean NLR (1.48 ± 0.33 vs. 4.44 ± 2.57 in non-treated cases, $p = 0.001$). Conversely, NLR exhibited no significant correlation with patient age, sex, underlying anemia severity, or routine folic acid supplementation.

Conclusion: NLR represents a cost-effective, readily available leukocytic biomarker that effectively reflects systemic inflammatory activity during acute vaso-occlusive crises and demonstrates favorable pharmacological response to hydroxyurea in pediatric SCA. While limited subgroup sizes warrant larger prospective validation, serial NLR monitoring offers clinical utility in resource-constrained settings.

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Introduction

Sickle cell anemia (SCA) represents one of the most prevalent monogenic red blood cell disorders globally, imposing a heavy clinical burden characterized by acute pain episodes, progressive end-organ injury, and premature mortality [1,2]. The underlying molecular pathogenesis stems from a single nucleotide substitution (GAG to GTG) within the β-globin gene (HBB), yielding abnormal hemoglobin S (HbS). Under deoxygenated conditions, HbS polymerizes into rigid intracellular fibers that distort erythrocyte morphology, precipitate microvascular occlusion, and accelerate intravascular hemolysis [2]. Sub-Saharan Africa bears the highest burden of the disease, accounting for an estimated 230,000 newborns affected annually (representing approximately 0.74% of live births across the region) [3].

In Sudan, the estimated prevalence of SCA ranges between 2.0% and 30.4%, with the highest disease frequencies documented among populations in Western Sudan. Gene flow and historical migration patterns—particularly among West African tribes such as the Hausa, Fulani, and Bargo—have contributed significantly to the local distribution of the sickle cell gene [4]. Specific regional subgroups, such as the Albagara (Misseria), demonstrate prevalence rates reaching 30%, alongside a 16% prevalence documented among immigrant communities from Blue Nile Province [5]. Clinical manifestations among affected individuals encompass severe acute crises—including painful vaso-occlusive crisis (VOC), acute chest syndrome (ACS), cerebrovascular accident (CVA), splenic sequestration, and severe infectious complications [6].

Although definitive diagnosis relies on hemoglobin electrophoresis, high-performance liquid chromatography (HPLC), or molecular DNA analysis, these diagnostic techniques are costly and frequently inaccessible in resource-constrained sub-Saharan healthcare settings [7]. Contemporary pathophysiology recognizes SCA not merely as a structural red cell disorder, but as a state of chronic systemic inflammation. Intravascular hemolysis releases free catalytic heme, which activates vascular endothelial cells and recruits innate immune subsets—including neutrophils, monocytes, and platelets [8,9]. White blood cell count parameters serve as widespread inflammatory metrics; however, isolated leukocyte indices can be confounded by physiological stress. In contrast, the neutrophil-to-lymphocyte ratio (NLR)—calculated by dividing absolute neutrophil count by absolute lymphocyte count—provides a novel, stable inflammatory index that balances active innate immunity against adaptive immune responses [10,11]. While NLR has gained diagnostic interest in cardiovascular and infectious pathologies [12-14], empirical data regarding its clinical utility in pediatric SCA within Sudan remain limited.

Furthermore, while disease-modifying therapies such as hydroxyurea (HU) and supportive regimens like folic acid supplementation are routinely administered, their differential impacts on cellular inflammatory kinetics like NLR remain insufficiently characterized in local pediatric populations. This investigation evaluated NLR dynamics in pediatric SCA patients in Gezira State, Sudan, assessing its diagnostic accuracy, its associations with specific acute clinical crisis phenotypes, and its response to hydroxyurea and folic acid therapies.

Methodology

Study design and setting

A hospital-based case-control study was conducted at Wad Medani Pediatric Teaching Hospital in Gezira State, Sudan, covering the period from September 2022 to June 2024. The tertiary facility serves as a primary pediatric referral center for hematological disorders across Gezira State and neighboring agricultural regions.

Study population and eligibility criteria

The study enrolled 130 pediatric participants aged 1 to 18 years, comprising 80 confirmed SCA cases and 50 age- and sex-matched healthy controls. SCA diagnosis was verified through qualitative hemoglobin electrophoresis (HbSS genotype). Case participants were enrolled during acute clinical presentation or inpatient admission, capturing real-time hematological parameters during acute events. Healthy controls consisted of age-matched pediatric individuals without underlying hematological abnormalities, chronic inflammatory states, or active acute infections.

Inclusion criteria encompassed pediatric patients aged <18 years with documented HbSS disease whose parents or legal guardians provided written informed consent (with patient assent obtained when appropriate). Exclusion criteria comprised: (1) concomitant hemoglobinopathies or thalassemia traits; (2) co-existing chronic metabolic or systemic conditions (such as diabetes mellitus); (3) systemic antibiotic therapy initiated prior to blood sampling (to prevent confounding leukocyte profiles); and (4) hemolyzed, clotted, or insufficient blood specimens.

Sample size estimation

To ensure adequate statistical power for evaluating differences in mean NLR between pediatric SCA cases and healthy controls, a sample size calculation was conducted prior to study execution using two-sample mean comparison formulas (G*Power version 3.1.9.7). Based on preliminary pilot data and published literature on pediatric hemoglobinopathies [18,19], assuming an expected mean difference in NLR of 1.5 units between groups (SD ± 2.5), a two-sided significance level (α) of 0.05, and a statistical power (1 - β) of 80% (0.80), the minimum total sample size required was determined to be 112 participants (70 cases and 42 controls). To account for potential specimen loss or technical non-evaluability, the target sample size was expanded to 130 participants (80 confirmed SCA cases and 50 healthy controls). This final sample size provided a statistical power exceeding 85% to detect primary differences in NLR between cases and controls.

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Laboratory analysis

Venous blood samples (3.0 mL) were collected aseptically into standard ethylenediaminetetraacetic acid (EDTA) tubes. Complete blood count (CBC) determinations were performed within 2 hours of collection using a calibrated Sysmex XP-300 automated hematology analyzer (Sysmex Corporation, Kobe, Japan). Absolute neutrophil count (ANC) and absolute lymphocyte count (ALC) were extracted to compute the NLR (ANC/ALC) [13,14].

Statistical analysis

Statistical processing was conducted using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). Quantitative variables were expressed as mean ± standard deviation (SD), and categorical metrics as frequencies and percentages. Parametric two-sample comparisons utilized the independent-samples t-test, whereas multi-group comparisons were evaluated via one-way analysis of variance (ANOVA). Where exact p-values were calculated as < 0.001 by SPSS, they were reported explicitly as $p < 0.001$ rather than $p = 0.000$ to adhere to standard statistical reporting guidelines. Receiver operating characteristic (ROC) curve analysis evaluated the diagnostic capacity of NLR in distinguishing SCA cases from controls, determining the area under the curve (AUC), optimal cutoff, sensitivity, and specificity. Stratified subgroup analyses were performed across crisis types, age brackets, gender, and treatment status. Subgroup categories with limited sample sizes (such as acute chest syndrome, cerebrovascular accident, and GIT infection) were evaluated descriptively and interpreted with suitable statistical caution due to restricted power in low-frequency clinical subsets. Statistical significance was established at $p < 0.05$.

Ethical considerations

Ethical approval was granted by the Ethics Committee of the Gezira State Ministry of Health, Sudan. Formal written informed consent was secured from parents/guardians prior to enrollment. Participant data were anonymized to maintain confidentiality.

Results

The study evaluated 130 participants (80 SCA cases and 50 healthy controls). Among cases, males represented 60.0% (n = 48) and females 40.0% (n = 32). The predominant age bracket was 1–5 years (36.3%, n = 29), followed by 6–10 years (32.5%, n = 26), 11–15 years (26.2%, n = 21), and > 15 years (5.0%, n = 4). A positive family history of SCA was documented in 82.5% (n = 66) of cases. Baseline disease severity stratified by hemoglobin concentration indicated severe anemia (Hb < 7 g/dL) in 48.7% (n = 39) of cases. Hydroxyurea therapy was reported in 18.8% (n = 15) of cases, whereas 90.0% (n = 72) received routine folic acid supplementation (Table 1).

Vaso-occlusive crisis (VOC) constituted the primary acute crisis event (60.0%, n = 48), followed by hemolytic crisis (12.5%, n = 10), hand-foot syndrome/dactylitis (8.8%, n = 7), acute infection (5.0%, n = 4), acute chest syndrome (2.5%, n = 2), cerebrovascular accident (2.5%, n = 2), and gastrointestinal infection (1.3%, n = 1) (Table 2). At hospital presentation, the predominant chief complaints were bone pain (42.5%, n = 34) and fever (40.0%, n = 32), followed by abdominal disturbance (10.0%, n = 8) and other symptoms (7.5%, n = 6) (Figure 1).

Table 1: Demographic and clinical characteristics of study population (cases) (n = 80).

Variable	Category	Frequency (n) [%]
Gender	Boys	48 (60.0%)
	Girls	32 (40.0%)
Age groups	1 – 5 years	29 (36.3%)
	6 – 10 years	26 (32.5%)
	11 – 15 years	21 (26.2%)
	> 15 years*	4 (5.0%)
Family history	Yes	66 (82.5%)
	No	14 (17.5%)
Anemia severity	Mild (Hb > 10 g/dL)	11 (13.8%)
	Moderate (Hb 7–10 g/dL)	30 (37.5%)
	Severe (Hb < 7 g/dL)	39 (48.7%)
Folic acid administration	Yes	72 (90.0%)
	No	8 (10.0%)
Hydroxyurea administration	Yes	15 (18.8%)
	No	65 (81.2%)

***Note:** Standardized age classification label (> 15 years) corrected from original typo for textual and cross-table consistency.

Table 2: Distribution of the study population according to Crises of SCA (n = 80).

Crises Type	Frequency (n)	Percentage (%)
Vaso-Occlusive Crisis (VOC)	48	60.00%
Hemolytic Crisis	10	12.50%
Hand-Foot Syndrome (Dactylitis)	7	8.80%
Infection (Systemic/Respiratory)	4	5.00%
Acute Chest Syndrome (ACS)*	2	2.50%
Cerebrovascular Accident (CVA)*	2	2.50%
Gastrointestinal (GIT) Infection*	1	1.30%
Unknown / Unspecified	6	7.50%
Total	80	100.00%

***Note:** Subgroup numbers for rare clinical complications (ACS, CVA, GIT infection) reflect real-time acute admissions during the study timeframe; findings in these small subsets should be interpreted with caution.

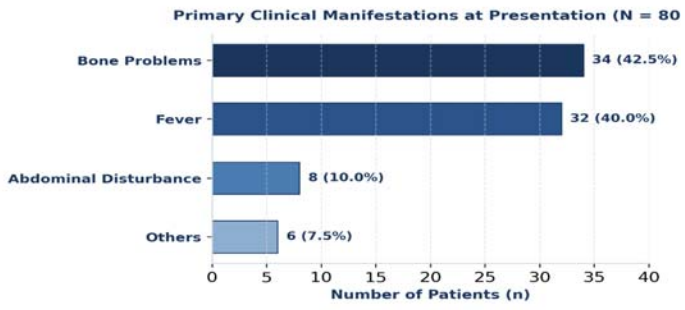

Figure 1: Primary clinical manifestations among pediatric SCA patients (N = 80): Bone Problems 34 (42.5%), Fever 32 (40.0%), Abdominal Disturbance 8 (10.0%), Others 6 (7.5%).

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Mean NLR values were evaluated across demographic and clinical subgroups. Comparative analyses revealed that NLR did not differ significantly by sex (p = 0.616; Table 3), age group (p = 0.851; Table 4), chief presenting clinical manifestation (p = 0.121; Table 5), or underlying hemoglobin severity grading (p = 0.841; Table 7). In contrast, mean NLR differed significantly across clinical crisis categories (p = 0.001; Table 6). Patients presenting with hand-foot syndrome (dactylitis) exhibited the highest mean NLR (6.84 ± 1.66), followed by those presenting with acute infection (5.00 ± 3.06) and acute VOC (4.08 ± 2.50). Subgroup metrics for low-frequency crisis presentations (e.g., ACS, CVA, GIT infection) are listed in Table 6; however, as noted, these small subset numbers limit statistical power and necessitate cautious interpretation.

Evaluating therapeutic interventions revealed distinct biological response profiles between folic acid supplementation and hydroxyurea (HU) therapy. Folic acid administration significantly improved core red blood cells parameters—including RBC count (2.84 ± 0.74 vs. 2.05 ± 1.11 × 10^12/L, p = 0.008), Hb concentration (8.51 ± 2.23 vs. 6.20 ± 3.41 g/dL, p = 0.010), and HCT percentage (25.53 ± 6.77 vs. 18.66 ± 9.90 %, p = 0.011)—but had no statistically significant impact on mean NLR (3.70 ± 2.41 vs. 5.57 ± 3.71, p = 0.204; Table 8).

In contrast, hydroxyurea therapy was associated with a marked, statistically significant reduction in mean NLR (1.48 ± 0.33 vs. 4.44 ± 2.57 in non-treated cases, p = 0.001). Hydroxyurea also significantly improved RBC count (3.12 ± 0.70 vs. 2.68 ± 0.82 × 10^12/L, p = 0.044), Hb concentration (9.44 ± 1.96 vs. 8.01 ± 2.48 g/dL, p = 0.023), and HCT percentage (28.08 ± 5.80 vs. 24.10 ± 7.52 %, p = 0.033) (Table 9).

Pediatric SCA patients exhibited a significantly higher mean NLR compared to healthy controls (3.89 ± 2.60 vs. 1.56 ± 0.29, p < 0.001; Table 10).

Receiver operating characteristic (ROC) curve analysis evaluated the diagnostic capability of NLR to discriminate pediatric SCA patients from healthy controls. The analysis demonstrated robust diagnostic accuracy with an area under the curve (AUC) of 0.79 (95% CI: 0.71–0.87). At an optimal cut-off value of > 2.2, NLR yielded a sensitivity of 63.8% and a specificity of 98.0% (Figure 2).

Table 3: Comparison of Mean NLR Between Males and Females.

Gender	N	Mean NLR	Std. Deviation	p-value
Male	48	3.78	2.45	0.616
Female	32	4.07	2.83	

Table 4: Comparison of Mean NLR Across Age Groups.

Age Group	N	Mean NLR	Std. Deviation	p-value
1–5 years	29	3.6	2.59	0.851
6–10 years	26	4.21	2.97	
11–15 years	21	3.84	2.18	
> 15 years*	4	4.16	2.78	

Table 5: Comparison of Mean NLR Across Clinical Manifestations.

Clinical Manifestations	N	Mean NLR	Std. Deviation	p-value
Fever	32	3.6	2.67	0.121
Abdominal disturbance	8	4.39	3	
Bone problem	34	3.85	2.31	
Others	6	6.09	2.57	

Table 6: Comparison of Mean NLR Across Types of SCA Crises.

Types of Crises	N	Mean NLR	Std. Deviation	p-value
Unknown / Unspecified	6	1.57	0.5	0.001
Acute Chest Syndrome (ACS)*	2	2.9	1.84	
Cerebrovascular Accident (CVA)*	2	2.35	1.34	
Hand-Foot Syndrome (Dactylitis)	7	6.84	1.66	
Hemolytic Crisis	10	2.24	2.22	
Infection (Systemic/Respiratory)	5	5	3.06	
Vaso-Occlusive Crisis (VOC)	48	4.08	2.5	
Total / Overall Cases	80	3.89	2.6	

***Note:** Standardized table formatting and subgroup numbers. Infection category includes 4 systemic/respiratory infections and 1 GIT infection (n=5 total). Statistical comparisons across small subsets (ACS, CVA) should be interpreted with appropriate caution.

Table 7: Comparison of Mean NLR According to Hemoglobin Grading.

Hb Grading	N	Mean NLR	Std. Deviation	p-value
Mild (Hb > 10 g/dL)	11	3.85	3.39	0.841
Moderate (Hb 7–10 g/dL)	30	3.89	2.94	
Severe (Hb < 7 g/dL)	39	4.22	2.43	

Table 8: Effects of Folic Acid Administration on RBC Parameters and NLR.

Parameter	Folic Acid	N	Mean	Std. Deviation	p-value
NLR	Yes	72	3.7	2.41	0.204
	No	8	5.57	3.71	
RBC count (x10^12/L)	Yes	72	2.84	0.74	0.008
	No	8	2.05	1.11	
Hemoglobin (g/dL)	Yes	72	8.51	2.23	0.01
	No	8	6.2	3.41	
Hematocrit (%)	Yes	72	25.53	6.77	0.011
	No	8	18.66	9.9	

Table 9: Effects of Hydroxyurea (HU) Therapy on RBC Parameters and NLR.

Parameter	Hydroxyurea	N	Mean	Std. Deviation	p-value
NLR	Yes	15	1.48	0.33	0.001
	No	65	4.44	2.57	
RBC Count (x10^12/L)	Yes	15	3.12	0.7	0.044
	No	65	2.68	0.82	
Hemoglobin (g/dL)	Yes	15	9.44	1.96	0.023
	No	65	8.01	2.48	
Hematocrit (%)	Yes	15	28.08	5.8	0.033
	No	65	24.1	7.52	

Table 10: Comparison of Mean NLR Between Pediatric SCA Patients and Healthy Controls.

Group	N	Mean NLR	Std. Deviation	p-value
SCA Cases	80	3.89	2.6	**< 0.001***
Healthy Controls	50	1.56	0.29	

***Note:** Standardized p-value reporting (< 0.001) in accordance with scientific reporting guidelines.

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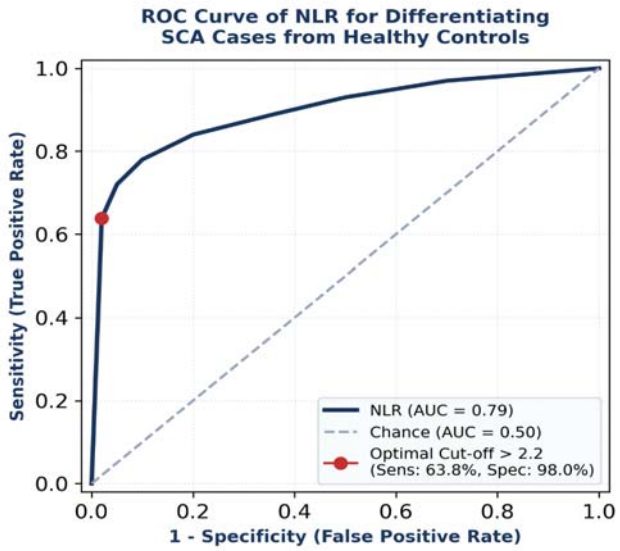

Figure 2: Receiver operating characteristic (ROC) curve of NLR for differentiating pediatric SCA patients from healthy controls (AUC = 0.79, Cutoff > 2.2, Sensitivity 63.8%, Specificity 98.0%).

Discussion

Sickle cell anemia (SCA) is increasingly recognized as a chronic, low-grade inflammatory state punctuated by acute, severe inflammatory surges during painful vaso-occlusive crises and infectious episodes [8,9]. In this hospital-based study from Gezira State, Sudan, pediatric patients with SCA exhibited significantly elevated mean NLR compared with healthy controls (3.89 ± 2.60 vs. 1.56 ± 0.29, $p < 0.001$). Furthermore, ROC curve analysis yielded an AUC of 0.79 with a specificity of 98.0% at an optimal threshold of > 2.2, supporting the clinical utility of NLR as a rapid surrogate inflammatory indicator in low-resource settings.

Pathophysiological mechanisms and cellular kinetics

The physiological mechanisms driving elevated NLR involve neutrophil priming and intravascular activation. In SCA, intravascular hemolysis releases cell-free hemoglobin and toxic heme, which stimulate endothelial adhesion molecules (P-selectin, VCAM-1) and recruit activated neutrophils. Activated neutrophils adhere to the vascular wall and directly catch rigid sickled red cells, promoting microvascular occlusion [8,18]. Neutrophils also secrete reactive oxygen species (ROS), myeloperoxidase, and inflammatory cytokines (IL-1β, IL-6, TNF-α) that amplify vascular stress. Simultaneously, stress-induced apoptosis, impaired thymic output, or splenic sequestration during acute events can induce relative lymphopenia, accelerating the rise in NLR [19]. Thus, NLR functions as a dual parameter, balancing active innate effector responses against adaptive immune status [10-12].

Comparison with regional and international literature

Our findings align closely with findings reported across sub-Saharan Africa and global cohorts. Efobi et al. in Nigeria reported significantly elevated leukocyte ratios among pediatric SCA cases during steady-state and acute crisis, identifying NLR as a robust marker of clinical disease severity [18]. Similarly, Emokpae et al. observed marked NLR elevations in patients with sickle cell nephropathy, correlating ratio magnitude with proteinuria and vascular end-organ injury [19]. In Saudi Arabia and North America, studies by Maharaj & Chang and Al-Khatti et al. confirmed that NLR spikes during acute vaso-occlusive episodes, serving as a predictor of inpatient hospital length of stay and requirement for parenteral opioid therapy [12]. Furthermore, Marchesani et al. detailed how pediatric immune cell subsets undergo dynamic shifts during acute crises, supporting our observation that NLR reflects systemic inflammatory surges [8]. In the Middle Eastern context, Zahran et al. reported parallel leukocyte dynamics in Egyptian pediatric cohorts, further substantiating NLR's regional validity [21].

Crisis phenotypes and rationale for stratified analyses

A major finding of this study is the significant variation in mean NLR across acute clinical crisis categories ($p = 0.001$). Patients presenting with hand-foot syndrome (dactylitis) exhibited the highest mean NLR (6.84 ± 1.66), followed by those presenting with acute infection (5.00 ± 3.06) and acute VOC (4.08 ± 2.50). The rationale for stratifying NLR across distinct clinical crisis phenotypes stems from the differing localized and systemic inflammatory intensities characteristic of each event. Microvascular infarction within the bone marrow beds of infant hands and feet during dactylitis triggers intense localized osteonecrosis and rapid, dense neutrophil recruitment, generating extreme systemic leukocytic elevations [18,20]. In systemic infection, pathogen-driven innate immune activation drives profound neutrophil expansion. Conversely, steady-state baseline or unspecified non-acute presentation demonstrated much lower NLR levels (1.57 ± 0.50).

However, it is vital to emphasize that certain subgroup sample sizes in our study—specifically acute chest syndrome ($n = 2$), cerebrovascular accident ($n = 2$), and GIT infection ($n = 1$)—were small, reflecting the single-center acute admission frequency during the study period. While these subsets demonstrate elevated or fluctuating ratios, these specific subgroup numbers are insufficient for definitive statistical inferences. Therefore, subgroup-specific findings must be interpreted with caution, and future multi-center studies with larger subgroup cohorts are warranted.

Rationale for demographic and disease severity stratifications

To isolate whether NLR is driven primarily by acute inflammatory states rather than baseline demographic or hematological characteristics, we performed stratified analyses across age brackets, gender, and anemia severity. The absence of significant correlations between NLR and age ($p = 0.851$), sex ($p = 0.616$), or underlying hemoglobin grading ($p = 0.841$) confirms that NLR acts as a dynamic metric reflective of acute inflammatory activation rather than chronic baseline anemia or non-specific demographic differences [15-17]. This stability across age and sex brackets enhances its clinical utility in pediatric triage.

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Pharmacological responses: hydroxyurea vs. folic acid

The therapeutic response profiles observed in this study provide important biological insights. Folic acid administration significantly improved core erythroid parameters (RBC count, hemoglobin, hematocrit) by supporting DNA synthesis during compensatory erythropoiesis, but had no significant effect on NLR ($p = 0.204$) [21]. Conversely, hydroxyurea therapy was associated with a dramatic reduction in mean NLR (1.48 ± 0.33 vs. 4.44 ± 2.57 in non-treated cases, $p = 0.001$). Hydroxyurea exerts potent myelosuppressive and anti-inflammatory actions by suppressing neutrophil precursor lineage proliferation, downregulating endothelial adhesion molecules (P-selectin, ICAM-1), reducing circulating reticulocytes, and elevating anti-sickling fetal hemoglobin (HbF) levels [2,21]. The near-normalization of NLR in hydroxyurea-treated pediatric cases highlights its potential utility as an accessible, cost-effective surrogate biomarker for monitoring anti-inflammatory treatment adherence and pharmacological response in resource-constrained clinics.

Clinical applicability and operational constraints

From a clinical standpoint, NLR offers substantial operational advantages in sub-Saharan African healthcare settings like Sudan. Because NLR is calculated directly from routine complete blood count (CBC) differential channels, it requires no specialized laboratory equipment or added financial costs. At a threshold of > 2.2, NLR demonstrated high specificity (98.0%), making it an effective rule-in tool to identify patients experiencing acute inflammatory spikes requiring intensified anti-inflammatory, analgesic, or antimicrobial management.

However, clinical implementation must account for important constraints. Although highly specific, the moderate sensitivity (63.8%) indicates that normal NLR levels do not entirely rule out mild or localized vaso-occlusive events. Furthermore, NLR is a non-specific inflammatory marker; concurrent subclinical bacterial/viral infections, physiological stress, corticosteroid administration, or recent blood transfusions can alter neutrophil and lymphocyte counts. Therefore, NLR should be utilized as a complementary triage and monitoring parameter alongside clinical assessment rather than a standalone diagnostic metric.

Study strengths and comprehensive limitations

A key strength of this study is providing first-hand empirical data on leukocytic inflammatory ratios among pediatric SCA patients in Sudan, detailing variations across acute crisis types and disease-modifying therapies. However, several important limitations must be acknowledged:

1. **Single-Center Hospital Design and Sampling Bias:** Conducting the study exclusively at Wad Medani Pediatric Teaching Hospital introduces potential sampling bias toward patients with more severe or acute clinical manifestations seeking tertiary hospital care, potentially overrepresenting elevated NLR levels compared to outpatient community steady-state populations.
2. **Restricted Subgroup Sample Sizes:** Subgroup sample sizes for specific acute complications (ACS n=2, CVA n=2, GIT infection n=1) were limited, restricting statistical power for robust subgroup comparisons.
3. **Lack of Concomitant Inflammatory Biomarkers:** Due to resource constraints in Gezira State, concurrent secondary acute-phase reactants—such as C-reactive protein (CRP), high-sensitivity CRP, ferritin, or pro-inflammatory cytokines (IL-6, TNF-α)—were not measured to correlate directly with NLR dynamics.
4. **Cross-Sectional Design:** The cross-sectional nature of sample collection during acute hospital presentation precludes longitudinal tracking of individual patient NLR trajectories from steady-state through acute crisis resolution.

Conclusion and recommendations

The neutrophil-to-lymphocyte ratio (NLR) serves as a practical, low-cost inflammatory biomarker in pediatric sickle cell anemia. Because NLR is calculated directly from routine complete blood counts, it incurs no additional financial or laboratory burden. NLR effectively reflects systemic inflammatory intensity during acute vaso-occlusive episodes—particularly dactylitis and acute infection—and demonstrates a favorable pharmacological response to hydroxyurea therapy. Integrating serial NLR measurements into pediatric clinical workflows may assist clinicians in low-resource settings in evaluating acute disease activity and monitoring therapeutic response. Future prospective multi-center studies with larger subgroup cohorts and serial biomarker measurements are recommended to establish standard age-adjusted NLR reference thresholds and validate its prognostic utility in pediatric SCA management.

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