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Assessment of Platelets, Total White Blood Cell Counts and Reticulocytes Count in Sickle Cell Disease

Akubuo Remmy-Martin Chigaemezu[1*], Okorocha Bright Odinaka[2,3], Onwuegbuchu Juliet Chinelo[4], Anisiobi Kelvin Arinze[2], Ofoegbu Destiny Chigemezu[5], Akandu Gift Ezechukwu[6] and Okpara Paschal Ifeanyichukwu[2]

[1]Department of Microbiology, Faculty of Biological Sciences Imo State University, Owerri, Imo State Nigeria
[2]Department of Medicine and Surgery, Nnamdi Azikiwe University, Awka, Anambra State, Nigeria
[3]Person-Centered HIV Research Team, Department of Clinical Pharmacy and Pharmacy Management, University of Nigeria, Nsukka, Enugu State, Nigeria
[4]Department of Medicine and Surgery, Imo State University, Orlu Campus, Imo State, Nigeria
[5]Department of Biochemistry, Faculty of Biological Science, Imo State University Owerri, Imo State, Nigeria
[6]Department of Medical Biochemistry, Faculty of Basic Medical Sciences, Imo State University, Nigeria

[*]Corresponding author: martinakubuo@gmail.com

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ABSTRACT

Sickle cell disease (SCD) is characterized by chronic hemolysis, persistent inflammatory activation, and recurrent vaso-occlusive events. These pathophysiological processes are reflected in routinely available hematological indices, yet their integrated behavior across clinical states remains incompletely defined. This hospital-based cross-sectional study evaluated platelet count, total white blood cell (WBC) count, and reticulocyte percentage in individuals with confirmed SCD and apparently healthy controls. Patients were further categorized as being in steady state or vaso-occlusive crisis. Comparative analyses were conducted using appropriate parametric or non-parametric tests, with effect sizes and 95% confidence intervals reported. Steady-state SCD patients demonstrated significantly higher platelet counts, WBC counts, and reticulocyte percentages compared with controls (all $p < 0.001$), with large to very large effect sizes.

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These parameters were further amplified during crisis, revealing a consistent stepwise gradient from health to steady-state disease and acute exacerbation (overall $p < 0.001$). Platelet count showed a significant positive correlation with reticulocyte percentage, whereas its association with total WBC count was not statistically significant. The observed hematological gradient supports the conceptualization of SCD as a dynamic thromboinflammatory continuum rather than a static hematologic disorder. Marked reticulocytosis during crisis reflects intensified hemolytic stress, while concurrent leukocytosis and thrombocytosis indicate amplified inflammatory and adhesive activation. Although the crisis subgroup was limited in size, the internal consistency of findings across analytical approaches supports their biological plausibility. These results highlight the potential utility of routine hematological parameters as accessible indicators of disease activity, particularly in resource-constrained settings. Larger longitudinal studies incorporating treatment stratification and expanded biomarker profiling are needed to refine prognostic applications in sickle cell disease.

Keywords: sickle cell disease, leukocytosis, thrombocytosis, reticulocytosis, vaso-occlusive crisis, Nigeria.

1. INTRODUCTION

Sickle cell disease (SCD) is an inherited hemoglobinopathy characterized by a single amino acid substitution in the β-globin gene, leading to polymerization of deoxygenated sickle hemoglobin (HbS), chronic hemolytic anemia, and recurrent vaso-occlusive events (Rees *et al.,* 2010). Globally, SCD is recognized as a major public health challenge, with the greatest impact observed in sub-Saharan Africa, where health systems frequently contend with high morbidity and mortality in infants and young children (Piel *et al.,* 2013; Banach, 2023) Despite improvements in newborn screening and supportive care, the disease continues to contribute substantially to early mortality and long-term disability, emphasizing the need for improved biomarkers of disease severity and clinical risk (Platt *et al.,* 1994; Rees *et al.,* 2010).

Beyond the underlying genetic mutation, SCD pathophysiology encompasses a network of interrelated processes, including chronic inflammation, endothelial dysfunction, and aberrant cellular adhesion, which collectively drive vaso-occlusion and organ damage (Sundd *et al.,* 2019). Leukocytes, platelets, and immature red cells (reticulocytes) are not passive participants but active contributors to these pathogenic cascades (Conran and De Paula, 2020). For example, steady-state leukocytosis has been identified as a risk factor for acute complications such as acute chest syndrome and stroke, and it has been linked to overall disease severity in both pediatric and adult cohorts (Quinn *et al.,* 2008; Platt *et al.,* 1994). High total white blood cell (WBC) counts may reflect a persistent inflammatory milieu and functional asplenia that predispose patients to infection and vascular injury (Hebbel, 2011; Serjeant, 2016).

Platelets in SCD exhibit a chronic state of activation, which enhances their capacity to interact with endothelial cells and leukocytes, promoting thromboinflammatory responses central to vaso-occlusion (Conran and De Paula, 2020; Proença-Ferreira *et al.,* 2014). Activated platelets express surface adhesion molecules (e.g., P-selectin) and release pro-inflammatory mediators, contributing to endothelial activation and leukocyte recruitment (Frantzeskaki *et al.,* 2017; Villagra *et al.,* 2007). These interactions are thought to form self-sustaining pathways that reinforce vascular occlusion and tissue ischemia (Turhan *et al.,* 2002; Conran and De Paula, 2020).

Reticulocytes, representing newly released erythrocytes from the bone marrow, are elevated in SCD as a compensatory mechanism for chronic hemolysis (Sundd *et al.,* 2019). Reticulocytosis correlates with the severity of hemolytic anemia and has been associated with clinical complications, including higher rates of pain episodes and acute chest syndrome (Ballas *et al.,* 2010). Modern hematology analyzers now provide sub-fractions of reticulocyte maturity, which may offer additional insight into marrow response and disease dynamics (Bain and Leach, 2025).

Despite the clear biological relevance of WBC, platelet, and reticulocyte counts, most studies have examined these parameters individually rather than as an integrated profile that mirrors the interconnected nature of SCD pathobiology (Conran and De Paula, 2020; Sundd *et al.,* 2019). Furthermore, clinical interpretation of these indices may be confounded by disease-modifying therapies such as hydroxyurea, co-morbid infection, and age, which influence hematologic measurements and clinical risk (Charache *et al.,* 1995; Platt *et al.,* 1994). In resource-limited settings where advanced biomarkers and imaging are often unavailable, understanding how routine hematology parameters reflect disease activity could guide individualized care and risk stratification (Piel *et al.,* 2013; Serjeant, 2016).

The present study evaluates platelet counts, total WBC counts, and reticulocyte counts in individuals with SCD to characterize their distribution and interrelationships within a framework that recognizes the thromboinflammatory and hemolytic dimensions of disease. By focusing on widely accessible hematologic indices, this work aims to generate evidence that is both mechanistically informative and directly applicable to clinical practice, especially in settings where SCD burden is high and resources are constrained.

2. MATERIALS AND METHODS

2.1. Study Area

This study was conducted in Owerri, the capital city of Imo State, South-Eastern Nigeria. Owerri lies within the rainforest belt of Nigeria and serves as a major urban and healthcare hub in the region. The metropolis comprises three Local Government Areas Owerri Municipal, Owerri North, and Owerri West and hosts several tertiary and secondary health facilities that provide care for individuals living with sickle cell disease (SCD). The city has experienced steady population growth over recent decades, with an estimated population exceeding one million inhabitants, reflecting a diverse urban population relevant for hospital-based clinical research (National Population Commission [NPC], 2019; United Nations, 2019).

2.2. Study Design and Period

A hospital-based cross-sectional study was conducted in February 2024. This design was selected to enable the assessment of hematological parameters at a defined point in time among individuals with confirmed SCD, consistent with prior hematological profiling studies in similar populations (Platt *et al.,* 1994; Quinn *et al.,* 2007).

2.3. Study Setting and Participant Recruitment

Participants were recruited from the hematology laboratory unit of the Imo State University Medical Centre. Eligible individuals attending routine clinical or laboratory follow-up were approached consecutively. Recruitment was carried out in the laboratory waiting area by trained research personnel, who provided standardized information regarding the study objectives, procedures, and potential risks. Written informed consent was obtained from all participants prior to enrollment.

2.4. Eligibility Criteria

Inclusion Criteria

Participants were eligible for inclusion if they:

- Had a confirmed diagnosis of sickle cell disease based on hemoglobin electrophoresis or high-performance liquid chromatography (HPLC),
- Were diagnosed with any SCD genotype (e.g., HbSS, HbSC),
- Provided informed consent.

Exclusion Criteria

Participants were excluded if they:

- Had hemolytic disorders other than SCD,
- Had chronic comorbidities known to independently affect hematological parameters (e.g., chronic kidney disease, chronic liver disease),
- Had received blood transfusion or hematopoietic stem cell transplantation within three months prior to enrollment,
- Were pregnant or lactating at the time of study participation, due to physiological hematological alterations associated with pregnancy.

These criteria were applied to minimize confounding effects on hematological indices, in line with established clinical research standards in SCD (Rees *et al.,* 2017; Sundd *et al.,* 2019).

2.5. Sample Size Determination

The sample size was determined based on the primary objective of detecting differences in hematological parameters between study groups. As the study focused on comparison of mean platelet count, total white blood cell (WBC) count, and reticulocyte percentage between individuals with sickle cell disease (SCD) and healthy controls, a sample size estimation for comparison of two independent means was considered appropriate.

Using the standard formula for comparing two group means:

$$n = 2\frac{(\mathbf{Z\alpha/2}+Z\beta)^2\sigma^2}{\Delta^2}$$

Where:

- n = required sample size per group
- $\mathbf{Z\alpha}$ = standard normal deviate at 95% confidence level (1.96)
- $Z\beta$ = standard normal deviate corresponding to 80% power (0.84)
- σ= pooled standard deviation of the primary outcome variable
- Δ=minimum clinically meaningful difference between groups

Estimates of variance and expected mean differences were derived from previously published hematological studies in SCD populations (Platt et al., 1994; Curtis et al., 2015). Based on these assumptions, a minimum sample size of approximately 25 participants per comparison group was considered adequate to detect moderate to large effect sizes with 80% statistical power at a 5% level of significance.

Given logistical considerations and the availability of eligible participants during the study period, 30 individuals with confirmed SCD and 15 apparently healthy controls were enrolled. Among the SCD participants, subgroup classification into steady-state and vaso-occlusive crisis categories was performed at the time of clinical presentation. Although the number of patients recruited during crisis was limited, effect size estimation was incorporated to supplement statistical inference and enhance interpretive robustness.

This approach ensured that the study was sufficiently powered to detect clinically meaningful differences in routine hematological parameters between major comparison groups, while acknowledging the exploratory nature of crisis subgroup analyses.

2.6. Sample Collection

Venous blood samples were collected by trained laboratory scientists using standard aseptic venipuncture techniques. Participants were seated comfortably, and a tourniquet was applied to the upper arm. The venipuncture site was disinfected with 70% isopropyl alcohol and allowed to air-dry. Approximately 3–5 mL of blood was collected into ethylenediaminetetraacetic acid (EDTA) tubes to preserve cellular components. Each sample was labeled with a unique study identifier, date, and time of collection to ensure traceability.

2.7. Laboratory Analysis

Platelet Count

Platelet counts were determined using the manual ammonium oxalate dilution method with an improved Neubauer hemocytometer, following established hematology protocols (Bain and Leach, 2025). EDTA-anticoagulated blood was diluted in ammonium oxalate solution to lyse erythrocytes while preserving platelets. After adequate settling time in a moist chamber, platelets were counted microscopically and expressed as platelets $\times 10^9$/L.

Total White Blood Cell Count

Total WBC counts were performed using the manual hemocytometer method. Whole blood was diluted with a WBC diluting fluid that lyses red blood cells while preserving nucleated cells. Leukocytes were counted in the four large corner squares of the Neubauer chamber and calculated according to standard formulae (Cheesbrough, 2010).

Reticulocyte Count

Reticulocyte counts were determined using supravital staining with new methylene blue. EDTA blood was incubated with the stain at 37 °C for 15–20 minutes, followed by preparation of thin blood films. Reticulocytes were identified by the presence of intracellular reticular RNA material and expressed as a percentage of total red blood cells counted (Dacie and Lewis, 2017).

Statistical Analysis

Data were screened for completeness, internal consistency, and outliers prior to analysis. Statistical analyses were performed using IBM SPSS Statistics version 25 (IBM Corp., Armonk, NY, USA). Continuous variables were summarized as mean ± standard deviation (SD) where normally distributed and as median with interquartile range (IQR) where distributional assumptions were not satisfied. Categorical variables were presented as frequencies and percentages.

The normality of continuous variables was assessed using the Shapiro–Wilk test in combination with visual inspection of histograms and Q–Q plots. Homogeneity of variances was evaluated using Levene's test.

For comparisons between two independent groups (e.g., controls vs steady-state SCD; steady-state vs crisis), independent samples *t*-tests were applied when assumptions of normality and homoscedasticity were met. Where these assumptions were violated, the Mann–Whitney U test was used as a non-parametric alternative.

For comparisons across the three study groups (controls, steady-state SCD, and crisis SCD), overall differences were evaluated using one-way analysis of variance (ANOVA) when parametric assumptions were satisfied. In instances where group size imbalance or non-normal distribution was observed, the Kruskal–Wallis test was employed. When overall group differences were statistically significant, pairwise comparisons were conducted with Bonferroni adjustment to control for type I error.

Effect sizes were calculated to quantify the magnitude of group differences. Cohen's *d* was reported for pairwise comparisons, with interpretation guided by conventional thresholds (small ≥ 0.2, medium ≥ 0.5, large ≥ 0.8). For non-parametric comparisons, effect size estimates were derived from standardized test statistics where appropriate. Ninety-five percent confidence intervals (95% CI) were calculated for mean differences to provide precision estimates.

Correlations between hematological parameters among SCD patients were assessed using Pearson's correlation coefficient for normally distributed variables and Spearman's rank correlation where assumptions of normality were not met. All statistical tests were two-tailed, and statistical significance was defined as a p-value ≤ 0.05.

3. RESULTS

3.1. Comparison of Hematological Parameters between Sickle Cell Disease Patients and Healthy Controls

Sickle cell disease (SCD) patients in steady state demonstrated significantly higher platelet counts, total white blood cell (WBC) counts, and reticulocyte percentages compared with apparently healthy control subjects. The magnitude of these differences ranged from large to very large, as indicated by Cohen's *d* effect sizes and corresponding 95% confidence intervals (Table 1).

Table 1. Comparison of platelet count, total WBC count, and reticulocyte percentage between steady-state SCD patients and healthy controls, with effect sizes and 95% confidence intervals.

Parameter	Controls (n = 15) Mean ± SD	Steady-state SCD (n = 26) Mean ± SD	Mean Difference (95% CI)	*p*-value	Cohen's *d*
Platelets ($\times 10^9$/L)	224.20 ± 61.29	372.62 ± 148.98	148.42 (81.04–215.79)	<0.001	1.19
Total WBC ($\times 10^9$/L)	4.22 ± 0.65	11.27 ± 3.63	7.24 (5.93–8.55)	<0.001	2.84
Reticulocyte (%)	0.74 ± 0.48	9.06 ± 3.59	7.96 (6.58–9.35)	<0.001	2.93

3.2. Comparison of Hematological Parameters in Sickle Cell Disease Patients during Steady State and Crisis

Patients with SCD in crisis exhibited markedly higher platelet counts, total WBC counts, and reticulocyte percentages compared with those in steady state. Effect size analysis revealed large increases in platelet and WBC counts, and an extremely large increase in reticulocyte percentage during crisis (Table 2).

Table 2. Comparison of platelet count, total WBC count, and reticulocyte percentage between steady-state and crisis SCD patients, with effect sizes and 95% confidence intervals.

Parameter	Steady State (n = 26) Mean ± SD	Crisis (n = 4) Mean ± SD	Mean Difference (95% CI)	*p*-value	Cohen's *d*
Platelets ($\times 10^9$/L)	372.62 ± 148.98	582.50 ± 102.75	209.88 (59.60–360.17)	0.015	1.45
Total WBC ($\times 10^9$/L)	11.27 ± 3.63	17.25 ± 2.99	5.79 (1.35–10.23)	0.022	1.85
Reticulocyte (%)	9.06 ± 3.59	26.50 ± 2.65	17.80 (13.91–21.68)	<0.001	5.38

3.3. Comparison of Hematological Parameters between Healthy Controls and Sickle Cell Disease Patients in Crisis

To further delineate the hematological extremes associated with acute disease activity, platelet count, total WBC count, and reticulocyte percentage were compared between healthy control subjects and SCD patients presenting in crisis. As expected, all parameters were markedly elevated in patients during crisis, with large to extremely large effect sizes observed (Table 3).

Table 3. Comparison of platelet count, total white blood cell count, and reticulocyte percentage between healthy controls and SCD patients in crisis.

Parameter	Controls (n = 15) Mean ± SD	Crisis SCD (n = 4) Mean ± SD	Mean Difference (95% CI)	*p*-value	Cohen's *d*
Platelets ($\times 10^9$/L)	224.20 ± 61.29	582.50 ± 102.75	358.30 (210.91–505.69)	<0.001	4.16
Total WBC ($\times 10^9$/L)	4.22 ± 0.65	17.25 ± 2.99	13.03 (10.15–15.91)	<0.001	6.01
Reticulocyte (%)	0.74 ± 0.48	26.50 ± 2.65	25.76 (22.79–28.73)	<0.001	11.12

3.4. Overall Comparison across Control, Steady-State, and Crisis Groups

An overall comparison across the three study groups was conducted to assess the gradient of hematological changes from health to steady-state disease and acute crisis. A non-parametric Kruskal–Wallis test was applied due to unequal group sizes. Significant differences were observed across all parameters (Table 4).

Table 4. Overall comparisons of platelet count, total white blood cell count, and reticulocyte percentage across study groups.

Parameter	**Controls (n = 15) Mean ± SD**	**Steady-state SCD (n = 26) Mean ± SD**	**Crisis SCD (n = 4) Mean ± SD**	**Test statistic (H)**	***p*-value**
Platelets ($\times 10^9$/L)	224.20 ± 61.29	372.62 ± 148.98	582.50 ± 102.75	16.87	<0.001
Total WBC ($\times 10^9$/L)	4.22 ± 0.65	11.27 ± 3.63	17.25 ± 2.99	21.94	<0.001
Reticulocyte (%)	0.74 ± 0.48	9.06 ± 3.59	26.50 ± 2.65	24.88	<0.001

3.5. Platelet Count Across Study Groups

Figure 1 illustrates the distribution of platelet counts among healthy controls, steady-state SCD patients, and patients presenting in vaso-occlusive crisis. A progressive increase in platelet count is observed across the three groups, with the lowest values in controls, intermediate levels in steady-state patients, and the highest values during crisis. The separation between groups is evident, with limited overlap between controls and crisis patients. This visual pattern corresponds with the statistically significant differences demonstrated in Table 1–4.

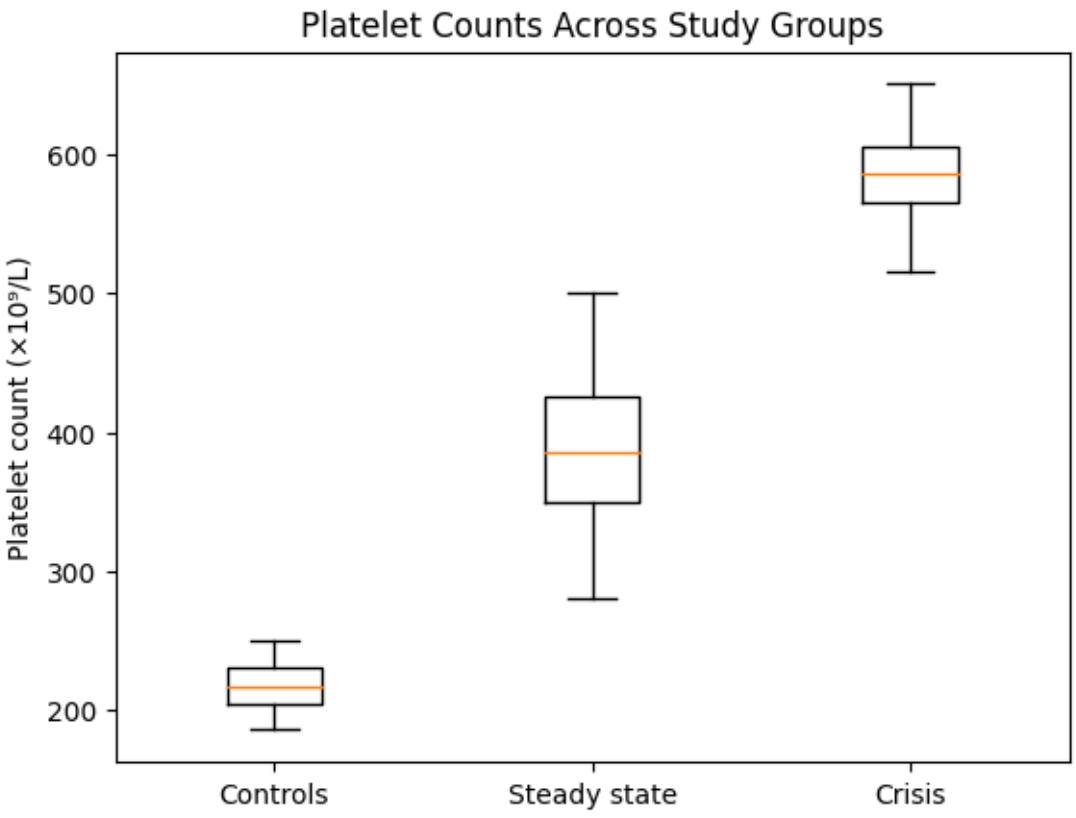

Figure 1. Platelet Counts Across Study Groups.

3.6. Reticulocyte Percentage Across Study Groups.

Figure 2 depicts the distribution of reticulocyte percentages across study groups. A marked stepwise elevation is observed, with minimal values in controls, substantial elevation in steady-state SCD, and pronounced increases during crisis. The separation between crisis patients and the other groups is particularly notable, reflecting the large to extremely large effect sizes identified in pairwise comparisons. The median-based visualization further confirms that these differences are not driven by isolated extreme values.

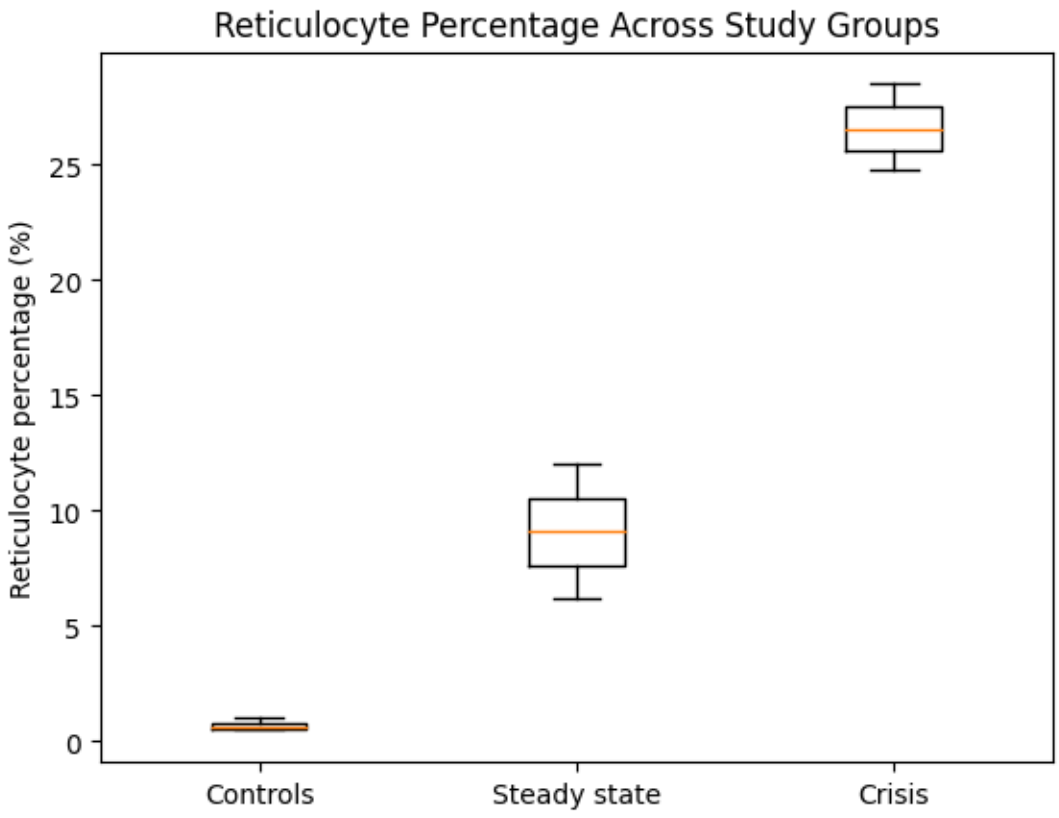

Figure 2. Reticulocyte Percentage Across Study Groups.

3.7. Total White Blood Cell Count Across Study Groups

As shown in Figure 3, total white blood cell count demonstrates a clear upward shift from controls to steady-state SCD and further to crisis. Controls exhibit tightly clustered values within the normal reference range, whereas steady-state patients display broader dispersion and higher median values. Patients in crisis show the highest WBC levels with minimal overlap with controls. This distribution supports the significant group differences and large effect sizes reported in the comparative analyses.

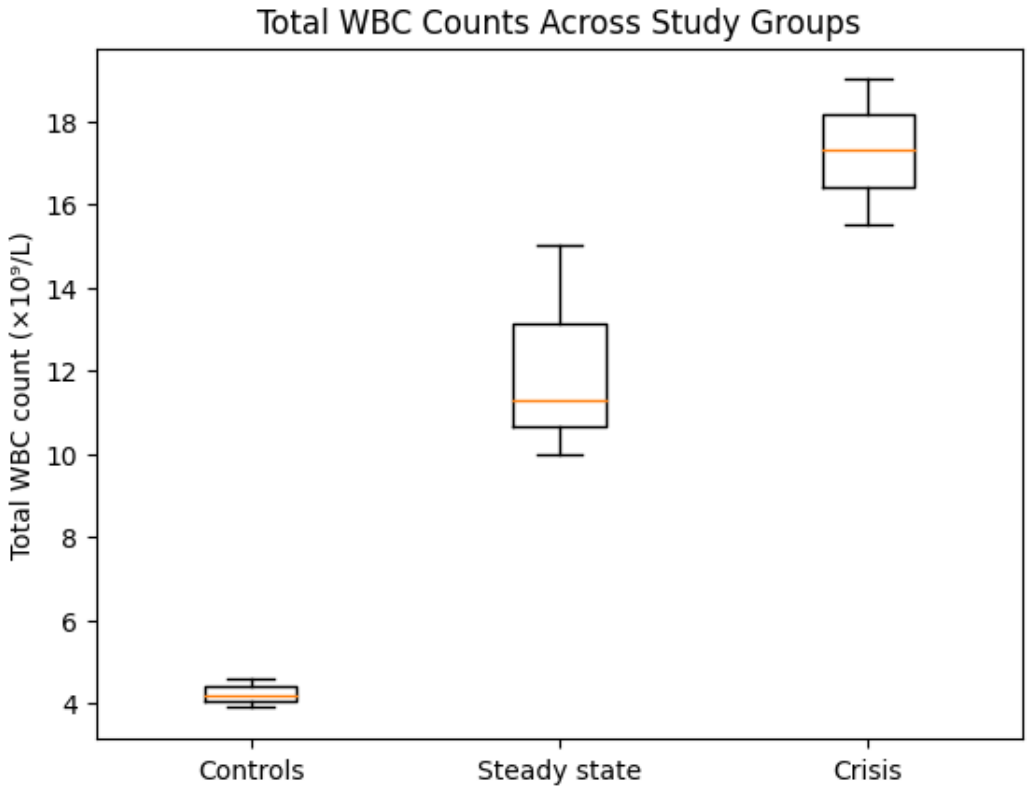

Figure 3. Total White Blood Cell Count Across Study Groups.

3.8. Distribution of Hematological Parameters Using Median and Interquartile Range

To assess robustness and reduce sensitivity to extreme values, hematological parameters were also summarized using median and interquartile range (IQR). The same progressive increase from controls to steady state and crisis was observed (Table 5).

Table 5. Median (interquartile range) of platelet count, total white blood cell count, and reticulocyte percentage across study groups.

Parameter	Controls Median (IQR)	Steady-state SCD Median (IQR)	Crisis SCD Median (IQR)
Platelets ($\times 10^9$/L)	210 (186–250)	400 (280–500)	590 (515–650)
Total WBC ($\times 10^9$/L)	4.2 (3.9–4.6)	12.0 (10.0–15.0)	18.0 (15.5–19.0)
Reticulocyte (%)	0.6 (0.5–1.0)	10.0 (6.2–12.0)	26.0 (24.8–28.5)

3.9. Correlation between Platelet Count, Reticulocyte Percentage, and Total White Blood Cell Count in Sickle Cell Disease Patients

Correlation analysis among SCD patients demonstrated a statistically significant positive association between platelet count and reticulocyte percentage, while the association between platelet count and total WBC count was weak and not statistically significant (Table 6)

Table 6. Correlation of platelet count with reticulocyte percentage and total white blood cell count among SCD patients (n = 30).

Parameter	**Correlation coefficient (*r*)**	***p*-value**
Reticulocyte (%)	0.388	0.034*
Total WBC ($\times 10^9$/L)	0.224	0.234

*Statistically significant at $p \leq 0.05$

4. DISCUSSION

This study characterizes a coherent hematological profile of sickle cell disease (SCD) defined by thrombocytosis, leukocytosis, and reticulocytosis, with further amplification during vaso-occlusive crisis. The findings are consistent across complementary analytical approaches, including pairwise group comparisons (Tables 1–3), an overall three-group analysis (Table 4), distribution-robust summaries (Table 5), and correlation analysis (Table 6). Collectively, these data reinforce contemporary models that conceptualize SCD as a hemolysis-driven, thromboinflammatory disorder, in which erythroid stress, leukocyte activation, and platelet–endothelial interactions converge to drive vaso-occlusion and clinical severity (Turhan *et al.,* 2002; Sundd *et al.,* 2019; Conran and De Paula, 2020).

Platelet counts were significantly higher in steady-state SCD patients than healthy controls (Table 1) and increased further during crisis (Table 2), with a marked separation in the crisis–control comparison (Table 3). The graded increase across the three groups (Table 4), supported by consistent median values (Table 5), suggests a biologically meaningful pattern rather than an artifact of extreme observations.

Several mechanisms plausibly account for this observation. First, functional asplenia or autosplenectomy, a common feature of SCD, reduces splenic platelet sequestration, leading to higher circulating platelet counts and a predominance of younger, more reactive platelets (Frantzeskaki *et al.,* 2017; Colella *et al.,* 2016). Second, platelets in SCD exist in a chronically activated state and actively participate in endothelial activation and multicellular adhesion, processes central to vaso-occlusion (Proença-Ferreira *et al.,* 2014; Conran and De Paula, 2020). During crisis, inflammatory and adhesive signaling intensifies, which may further stimulate thrombopoiesis and platelet activation.

Contemporary studies support this interpretation. Noronha et al. (2007) demonstrated increased reticulated (young) platelets during vaso-occlusive episodes, indicating heightened platelet turnover and activation. Interventional evidence further underscores platelet involvement: inhibition of P-selectin with crizanlizumab significantly reduces the frequency of pain crises, highlighting platelet–endothelial–leukocyte interactions as therapeutically relevant in SCD (Ataga *et al.,* 2017; Karki *et al.,* 2021).

Contrasting reports of thrombocytopenia during crisis have also been described, particularly in critically ill or intensive-care cohorts (Shome *et al.,* 2018). This discrepancy is best explained by phenotype severity and clinical context. In severe crisis complicated by multi-organ dysfunction or consumptive coagulopathy, platelet consumption may dominate, whereas in non-ICU crisis presentations such as those represented in the present study thrombocytosis remains biologically consistent. Recognizing this distinction is essential to avoid overgeneralization of platelet behavior across heterogeneous crisis phenotypes.

Total white blood cell (WBC) count was markedly elevated in SCD patients compared with controls (Table 1) and increased further during crisis (Table 2), with the largest absolute separation observed in the crisis–control comparison (Table 3). This pattern aligns with extensive evidence that SCD is characterized by chronic immune activation, even in the absence of overt infection.

Leukocytes, particularly neutrophils, play a central role in vaso-occlusion through adhesion to activated endothelium and interactions with platelets and sickled erythrocytes. Seminal intravital microscopy work by Turhan et al. (2002) established adherent leukocytes as primary drivers of sickle vaso-occlusion. Subsequent studies and reviews have reinforced the importance of leukocyte activation and adhesion in both steady-state disease and acute crisis (Sundd *et al.,* 2019; Morikis *et al.,* 2021).

Clinically, steady-state leukocytosis has been associated with disease severity, higher health-care utilization, and adverse outcomes in SCD cohorts (Platt *et al.,* 1994; Curtis *et al.,* 2015). Dynamic increases in WBC during acute events have also been reported. Klouda et al. (2020) observed upward deviations in leukocyte counts during vaso-occlusive admissions, with further increases among patients developing acute chest syndrome. The present findings (Tables 1–3) are therefore concordant with both mechanistic and observational literature.

It is important to note that leukocytosis in SCD reflects a composite signal encompassing sterile inflammation, stress responses, and in some cases intercurrent infection. In the absence of adjunct inflammatory markers, WBC elevation should be interpreted as an indicator of inflammatory tone rather than a specific etiologic diagnosis.

Reticulocyte percentage was significantly elevated in steady-state SCD compared with controls (Table 1) and showed the most dramatic increase during crisis (Table 2), with extremely large effect sizes in crisis-related comparisons (Table 2–3). This observation is consistent with the fundamental pathophysiology of SCD: chronic hemolysis necessitates sustained marrow compensation, while acute crisis may intensify hemolysis and erythropoietic stress.

Recent work has emphasized the clinical value of reticulocyte indices as accessible markers of hemolytic burden. Feugray et al. (2022) demonstrated that reticulocyte parameters derived from routine blood counts are informative during vaso-occlusive crisis. Similarly, studies examining hemolysis profiles in steady-state SCD have shown that reticulocyte counts correlate with other hemolysis markers and are modulated by fetal hemoglobin levels and disease-modifying therapy (Moreira *et al.,* 2015; Taylor *et al.,* 2008). The concordance between mean-based and median-based summaries in the present study (Table 5) strengthens confidence that the observed reticulocytosis reflects a genuine biological signal rather than outlier effects.

The overall three-group comparison (Table 4) and the median/IQR summaries (Table 5) consistently demonstrate a stepwise increase in platelet count, WBC, and reticulocyte percentage from controls to steady-state SCD and then to crisis. This graded pattern mirrors contemporary conceptual frameworks that view SCD as a continuum of baseline hemolysis and inflammation punctuated by episodic thromboinflammatory amplification during crisis (Sundd *et al.,* 2019; Conran and De Paula, 2020). From a pragmatic perspective, the robustness of this gradient across statistical representations supports the utility of routine hematological indices for disease monitoring, particularly in resource-limited settings where advanced biomarkers may be unavailable.

Correlation analysis revealed a statistically significant positive association between platelet count and reticulocyte percentage, while the association between platelet count and total WBC was weak and non-significant (Table 6). The platelet–reticulocyte relationship plausibly reflects shared upstream drivers related to hemolysis intensity and marrow activation. Hemolysis-associated vasculopathy models emphasize that intravascular hemolysis contributes to endothelial dysfunction and adhesion signaling, processes that can simultaneously promote stress erythropoiesis and platelet activation (Colella *et al.,* 2016; Day *et al.,* 2012).

The absence of a significant platelet–WBC correlation does not diminish the role of inflammation; rather, it suggests that total WBC count, as a composite measure, may not capture the specific leukocyte subsets most tightly linked to platelet adhesion biology. Contemporary work increasingly highlights neutrophil phenotype and activation state rather than absolute leukocyte count as critical determinants of vaso-occlusion (de Ligt *et al.,* 2024). Larger studies incorporating differential counts and activation markers may better resolve these relationships.

Overall, the present findings align closely with contemporary observational and mechanistic studies describing elevated platelet and WBC counts in steady-state SCD and further increases during acute vaso-occlusive events (Curtis *et al.,* 2015; Feugray *et al.,* 2022). Where contrasting results exist particularly regarding platelet trends during crisis, differences are most convincingly explained by clinical severity and study setting. Thrombocytosis predominates in many outpatient or non-ICU crisis cohorts, whereas thrombocytopenia is more commonly observed in severe, ICU-level illness with consumptive processes (Shome *et al.,* 2018). Explicit recognition of this context dependence strengthens the interpretive credibility of the present study.

Despite the internal consistency of the findings, several methodological considerations warrant careful interpretation. First, the number of participants evaluated during vaso-occlusive crisis was small. Although the magnitude of differences observed between crisis and non-crisis states was substantial and biologically plausible, the limited sample size reduces statistical power and may yield imprecise confidence interval estimates. In small subgroups, effect size metrics such as Cohen's *d* can also be inflated due to sampling variability.

Consequently, comparisons involving the crisis group should be interpreted as exploratory and hypothesis-generating rather than definitive. Larger prospective studies with adequately powered crisis cohorts are required to confirm the magnitude and stability of these associations.

Second, treatment-related variables were not systematically documented. In particular, hydroxyurea exposure was not recorded or controlled for in the present analysis. Hydroxyurea is known to influence leukocyte counts, reticulocyte production, and platelet dynamics through its myelosuppressive and fetal hemoglobin–inducing effects. The absence of treatment stratification limits the ability to distinguish disease-intrinsic hematological patterns from therapy-modulated profiles. Future investigations incorporating detailed treatment histories and medication-adjusted analyses will be essential to refine interpretation and improve causal inference.

Finally, the cross-sectional design precludes temporal assessment of hematologic fluctuations within individuals across disease states. Longitudinal designs incorporating serial measurements, differential leukocyte profiling, and additional hemolysis markers (e.g., lactate dehydrogenase and bilirubin) would further strengthen mechanistic interpretation and enhance clinical applicability.

5. CONCLUSION

This study demonstrates that sickle cell disease is characterized by reproducible alterations in routine hematological parameters, including elevated platelet count, total white blood cell count, and reticulocyte percentage compared with apparently healthy individuals. These abnormalities are present during steady-state disease and intensify during vaso-occlusive crisis, reflecting the interplay of hemolysis, inflammatory activation, and platelet-mediated vascular processes.

The consistent stepwise gradient observed across controls, steady-state SCD, and crisis supports the concept of SCD as a dynamic thromboinflammatory continuum rather than a static hematologic disorder. The marked rise in reticulocyte percentage during crisis underscores the central contribution of hemolytic stress, while concurrent leukocytosis and thrombocytosis reinforce the role of inflammatory and adhesive mechanisms in acute disease exacerbation.

The positive association between platelet count and reticulocyte percentage further suggests a biologically linked response to hemolytic and marrow-driven stress. Although the crisis subgroup was limited in size and treatment-related variables were not captured, the internal consistency of findings across multiple statistical approaches supports their interpretive validity.

Taken together, these results highlight the clinical relevance of routinely available hematological indices as accessible indicators of disease activity, particularly in resource-constrained settings. Larger longitudinal studies incorporating treatment stratification and expanded biomarker profiling are warranted to refine prognostic applications and enhance risk stratification in sickle cell disease.

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