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Inflammatory and Coagulation Biomarkers in Sickle Cell Disease by Vaso-Occlusive Crisis and Pain Status: A Cross-Sectional Study

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Abstract

Background: Inflammation and coagulation activation contribute to sickle cell disease, but routine biomarkers have inconsistent associations with vaso-occlusive crisis and pain.

Methods: This hospital-based cross-sectional analytical study included 54 patients with confirmed sickle cell disease. C-reactive protein, D-dimer, prothrombin time, and activated partial thromboplastin time were compared between the recorded vaso-occlusive crisis and steady-state groups. Serum 25-hydroxyvitamin D was compared between participants with and without pain or crisis at sampling. Two-sided Mann-Whitney U tests were used, with Holm correction across the five planned comparisons. Exploratory Kruskal-Wallis analyses assessed nine laboratory variables across three recorded clinical categories.

Results: The dataset contained 17 steady-state participants, 23 with vaso-occlusive crisis, and 14 with chronic complications. D-dimer was higher during vaso-occlusive crisis than during steady state (median 1.62 vs. 0.96 micrograms of fibrinogen-equivalent units per milliliter; Holm-adjusted p=0.021; rank-biserial correlation=0.535). The 25-hydroxyvitamin D concentration was lower when pain or crisis was present (median 15.75 vs. 21.25 ng/mL; adjusted p=0.028; rank-biserial correlation=-0.436). C-reactive protein showed an unadjusted difference but did not remain significant after correction (adjusted p=0.083). Prothrombin time and activated partial thromboplastin time did not differ. Reticulocyte count showed the strongest exploratory difference across the three clinical categories (adjusted p<0.001).

Conclusions: In this small cross-sectional cohort, D-dimer was higher in the vaso-occlusive crisis group, and 25-hydroxyvitamin D was lower among participants with pain or crisis at sampling after correction for five comparisons. The results do not establish diagnostic thresholds or causality. Larger prospective studies with clinically verified group assignment and adjustment for treatment and other confounders are required.

Categories: Hematology, Pathology
Keywords: coagulation biomarkers, c-reactive protein (crp), d-dimer, inflammatory biomarkers, sickle cell disease (scd), vitamin d

Introduction

Sickle cell disease is an inherited hemoglobin disorder characterized by hemolysis, vaso-occlusion, inflammation, endothelial activation, and progressive organ injury. The Global Burden of Disease 2021 analysis estimated that 7.74 million people were living with sickle cell disease and that 515,000 affected infants were born in 2021 [1]. Clinical expression ranges from stable periods to acute vaso-occlusive crises and chronic organ complications.

Hemolysis and vascular injury amplify inflammatory and hemostatic pathways [2]. C-reactive protein has been associated with pain-related hospitalization and vaso-occlusive crisis in several cohorts [3-5]. D-dimer and other markers of coagulation activation can be elevated in sickle cell disease and have been linked to acute crisis, hemolysis, and selected clinical complications [6-9]. Routine screening tests such as prothrombin time and activated partial thromboplastin time may remain unchanged despite coagulation activation [10,11]. Vitamin D deficiency is also common, and lower 25-hydroxyvitamin D concentrations have been reported in patients with crisis, although age, nutrition, sunlight exposure, genotype, treatment, and comorbidity may influence this association [12,13].

Evidence from Indian clinical populations remains limited. The primary objectives of this study were to compare C-reactive protein, D-dimer, prothrombin time, and activated partial thromboplastin time between participants recorded as having vaso-occlusive crisis and those recorded as being in steady state and to compare serum 25-hydroxyvitamin D between participants with and without pain or crisis at the time of sampling. The secondary exploratory objective was to compare nine laboratory variables across the three recorded clinical categories: steady state, vaso-occlusive crisis, and chronic complications.

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Materials And Methods

Study design and setting

This hospital-based cross-sectional analytical study was conducted in the Department of Pathology at Gandhi Medical College and associated Hamidia Hospital in Bhopal, India. The Institutional Ethics Committee of Gandhi Medical College approved the study (approval number: 16303/MC/IEC/2024; IEC protocol number: 191/IEC/2024; review date: March 27, 2024). The study was conducted from May 2024 to November 2025. Participant recruitment and data collection occurred from May 6, 2024, through March 26, 2025, within the one-year ethics approval period. From March 27, 2025, through November 5, 2025, study activities were limited to data cleaning, statistical analysis, interpretation of the results, and manuscript preparation. No additional participant recruitment, participant contact, specimen collection, or clinical data collection occurred after March 26, 2025.

Participants

Patients older than one year with a diagnosis of sickle cell disease confirmed by high-performance liquid chromatography (HPLC) who attended the outpatient department or were admitted during the recruitment period were recruited consecutively. Patients who declined participation, had received a blood transfusion within the preceding three months, had an acute concurrent infection or another acute or chronic inflammatory disease unrelated to sickle cell disease, or had undergone recent surgery were excluded. Of 75 patients assessed for eligibility, 21 met one or more exclusion criteria, and 54 eligible participants were included in the final analysis. Complete values were available for all analyzed laboratory variables.

Clinical categories

Clinical presentation was classified at recruitment using three mutually exclusive categories: steady state, vaso-occlusive crisis, and chronic complications. Vaso-occlusive crisis was defined as an acute onset of nociceptive pain requiring analgesic treatment, with no other medically identifiable cause. Steady state was defined as a period free from acute pain, infection, hospitalization, or blood transfusion for a minimum of three weeks before sampling. Chronic complications were defined as documented long-term organ damage attributable to sickle cell disease, including avascular necrosis, sickle nephropathy, or retinopathy, present at the time of recruitment.

A separate binary field recorded whether pain or crisis was present at sampling. The recorded clinical category was used for the C-reactive protein, D-dimer, prothrombin time, and activated partial thromboplastin time analyses because these comparisons evaluated participants recorded as having vaso-occlusive crisis against those recorded as being in steady state. The pain-or-crisis-at-sampling field was used for the 25-hydroxyvitamin D analysis because this comparison examined vitamin D concentration in relation to contemporaneous pain or crisis, irrespective of the recorded clinical category. The recorded categories were retained without post hoc reclassification.

Variables

The grouping variable was the recorded clinical category. The five prespecified biomarkers were C-reactive protein, 25-hydroxyvitamin D, D-dimer, prothrombin time, and activated partial thromboplastin time. Hemoglobin, reticulocyte count, lactate dehydrogenase, and aspartate aminotransferase were examined as additional exploratory variables. The recorded category was used without reclassification from the free-text presentation fields. The available data did not permit adjustment for age, sex, genotype, treatment, comorbidity, season, or sampling time relative to symptoms; residual confounding and potential category misclassification were therefore considered when interpreting the results.

Laboratory measurements

Venous blood was collected using standard aseptic technique. C-reactive protein was measured by an immunoturbidimetric assay on the BA200 clinical chemistry analyzer (BioSystems S.A., Barcelona, Spain), with a local laboratory reference interval of less than 5 mg/L. Serum 25-hydroxyvitamin D was measured by chemiluminescent immunoassay on the UniCel DxI 800 Access immunoassay system (Beckman Coulter, Inc., Brea, California, United States), with a local reference interval of 30-100 ng/mL.

D-dimer was measured in citrated plasma using a particle-enhanced immunoturbidimetric assay on the Sysmex CA-1500 automated coagulation analyzer (Sysmex Corporation, Kobe, Japan), with a local reference interval of less than 0.5 µg FEU/mL. Prothrombin time and activated partial thromboplastin time were determined on the same analyzer using photo-optical clot detection. The corresponding local reference intervals were 11-15 seconds for prothrombin time and 25-35 seconds for activated partial thromboplastin time. Instrument calibration was performed according to institutional laboratory procedures, and internal quality control was conducted using two levels of standard control material representing normal and abnormal values.

Study size

The study has 54 participants and 12 variables. Participant identifiers were unique, there were no duplicate rows, and no values were missing from the nine laboratory variables. All laboratory values were numeric and positive. A conventional 1.5-interquartile-range screen identified potential extremes in hemoglobin, lactate dehydrogenase, aspartate aminotransferase, and prothrombin time. The workbook summary statistics and hypothesis tests were independently reproduced. No prospective sample-size calculation was documented, and all eligible records were analyzed.

Statistical analysis

Continuous variables are summarized as medians and interquartile ranges because several distributions were skewed. The planned comparisons used two-sided Mann-Whitney U tests with tie-corrected normal approximation and no continuity correction. C-reactive protein, D-dimer, prothrombin time, and activated partial thromboplastin time were compared between the vaso-occlusive crisis group and the steady-state group. The 25-hydroxyvitamin D concentration was compared between participants with and without pain or crisis at sampling. Holm correction was applied across these five comparisons. Rank-biserial correlation was calculated as an effect-size estimate, with positive values indicating higher values in the first listed group. Hodges-Lehmann median differences were calculated from all pairwise differences.

Exploratory Kruskal-Wallis tests with tie correction compared hemoglobin, reticulocyte count, lactate dehydrogenase, aspartate aminotransferase, D-dimer, C-reactive protein, prothrombin time, activated partial thromboplastin time, and 25-hydroxyvitamin D across the three recorded clinical categories. Holm correction was applied across the nine omnibus tests. For variables that remained significant, Dunn pairwise comparisons were performed with Holm correction across the three pairs. No multivariable or stratified adjustment was performed because information on age, sex, sickle cell genotype, hydroxyurea therapy, transfusion history outside the three-month exclusion window, comorbidities, season, and sampling time relative to symptom onset was not available in the de-identified dataset. The reported group comparisons are therefore unadjusted, apart from multiplicity adjustment of the p-values, and residual confounding was considered when interpreting the findings. Statistical significance was defined as a two-sided adjusted p-value below 0.05. Analyses were independently verified using Python 3.12 (Python Software Foundation, Wilmington, Delaware, United States).

Results

Participant distribution

The analysis included 17 participants recorded as being in steady state, 23 recorded as having vaso-occlusive crisis, and 14 recorded as having chronic complications. Pain or crisis at sampling was recorded as present for 32 participants and absent for 22. All vaso-occlusive crisis records were marked as having pain or crisis. Seven chronic-complication records and two steady-state records were also marked as having pain or crisis, demonstrating that the two grouping fields were not interchangeable (Table *1*).

Field	Recorded value	Number	Percentage
Clinical category	Steady state	17	31.5
	Vaso-occlusive crisis	23	42.6
	Chronic complications	14	25.9
Pain or crisis at sampling	Present	32	59.3
	Absent	22	40.7

TABLE 1: Clinical category distribution

Biomarker distributions

D-dimer was higher in the vaso-occlusive crisis group than in the steady-state group, with a Hodges-Lehmann median difference of 0.57 micrograms of fibrinogen-equivalent units per milliliter. The difference remained significant after Holm correction. The 25-hydroxyvitamin D concentration was lower when pain or crisis was present, with a Hodges-Lehmann median difference of -4.45 ng/mL, and this comparison also remained significant. C-reactive protein was higher in the vaso-occlusive crisis group in the unadjusted analysis, but the comparison did not remain significant after Holm correction. Prothrombin time and activated partial thromboplastin time did not differ between the vaso-occlusive crisis and steady-state groups (Table *2* and Figure *1*).

Biomarker	Comparison	Group 1 median (IQR)	Group 2 median (IQR)	Raw p	Holm p	Rank-biserial r
C-reactive protein (mg/L)	Vaso-occlusive crisis vs. steady state	109.20 (63.85-148.30)	56.00 (24.40-92.60)	0.028	0.083	0.412
D-dimer (µg FEU/mL)	Vaso-occlusive crisis vs. steady state	1.62 (1.19-2.23)	0.96 (0.82-1.28)	0.004	0.021	0.535
25-Hydroxyvitamin D (ng/mL)	Pain or crisis present vs. absent	15.75 (10.90-19.65)	21.25 (16.20-23.40)	0.007	0.028	-0.436
Prothrombin time (s)	Vaso-occlusive crisis vs. steady state	16.10 (13.65-18.70)	15.40 (13.60-16.70)	0.286	0.572	0.199
Activated partial thromboplastin time (s)	Vaso-occlusive crisis vs. steady state	42.30 (39.35-45.35)	43.30 (34.60-47.70)	0.870	0.870	0.031

TABLE 2: Overall inflammatory and coagulation biomarker distributions

Values are medians with interquartile ranges. Group 1 is the first group named in the Comparison column; a positive rank-biserial correlation indicates higher values in Group 1. Raw p-values are from two-sided Mann-Whitney U tests, and Holm p-values are adjusted across the five primary comparisons. The C-reactive protein, D-dimer, prothrombin time, and activated partial thromboplastin time comparisons included 23 participants with vaso-occlusive crisis and 17 in steady state. The 25-hydroxyvitamin D comparison included 32 participants with pain or crisis and 22 without.

FEU: fibrinogen-equivalent units; IQR: interquartile range

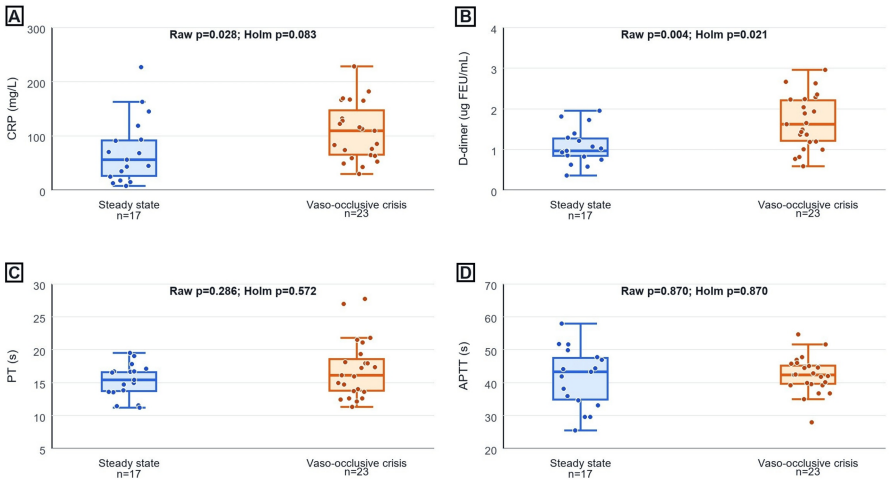


FIGURE 1: Biomarkers in vaso-occlusive crisis and steady state

Panels show C-reactive protein (A), D-dimer (B), prothrombin time (C), and activated partial thromboplastin time (D). Boxes show the interquartile range and median; whiskers extend to the most extreme value within 1.5 times the interquartile range; points represent individual participants. Raw p-values are from two-sided Mann-Whitney U tests. Holm p-values are adjusted across the five primary comparisons.

APTT: activated partial thromboplastin time; CRP: C-reactive protein; FEU: fibrinogen-equivalent units; PT: prothrombin time

The 25-hydroxyvitamin D distribution according to pain or crisis status at sampling is shown in Figure 2.

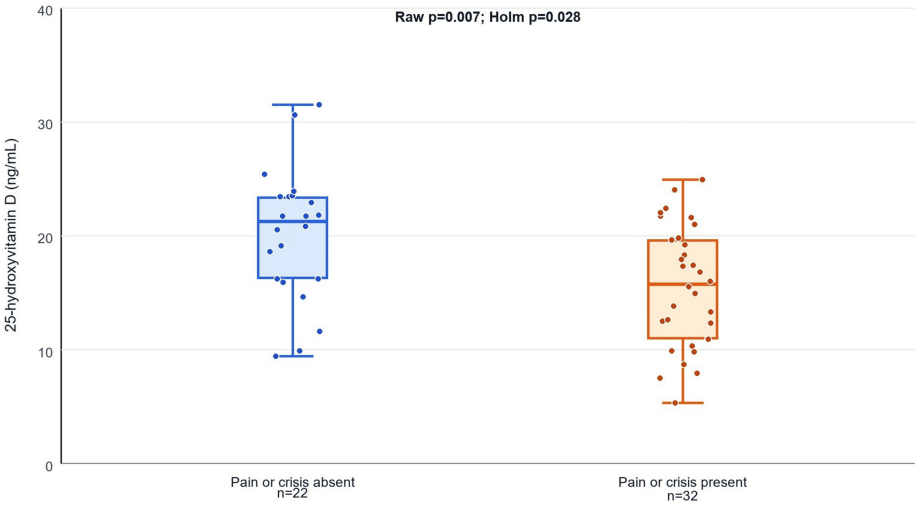


FIGURE 2: Vitamin D according to pain or crisis status

Boxes show the interquartile range and median; whiskers extend to the most extreme value within 1.5 times the interquartile range; points represent individual participants. The raw p-value is from a two-sided Mann-Whitney U test. The Holm p-value is adjusted across the five primary comparisons.

Exploratory clinical category analyses

Reticulocyte count showed the strongest exploratory difference across the three recorded clinical categories and remained significant after correction across nine laboratory variables. Median reticulocyte counts were 2.10%, 2.90%, and 4.30% in the steady-state, vaso-occlusive crisis, and chronic-complication groups, respectively. Dunn comparisons showed higher reticulocyte counts in the chronic-complication group than in the steady-state and vaso-occlusive crisis groups (both adjusted $p<0.001$); the steady-state and vaso-occlusive crisis groups did not differ after pairwise adjustment (adjusted $p=0.070$). The 25-hydroxyvitamin D concentration also differed across clinical categories after correction; the steady-state group had higher values than the vaso-occlusive crisis group (adjusted $p=0.001$), while the other pairwise comparisons were not significant (Table *3*).

Laboratory variable	Steady state median (IQR)	Vaso-occlusive crisis median (IQR)	Chronic complications median (IQR)	H	Raw p	Holm p	Epsilon-squared
Hemoglobin (g/dL)	8.70 (6.50-9.40)	8.20 (7.65-8.60)	8.00 (7.05-9.18)	0.041	0.980	1.000	0.000
Reticulocyte count (%)	2.10 (1.80-2.70)	2.90 (2.05-3.45)	4.30 (3.67-4.88)	26.152	<0.001	<0.001	0.474
Lactate dehydrogenase (U/L)	331.91 (253.96-488.15)	410.14 (263.51-652.50)	463.30 (332.90-767.40)	2.596	0.273	1.000	0.012
Aspartate aminotransferase (U/L)	53.90 (35.30-121.10)	70.20 (51.05-114.45)	62.80 (44.02-81.43)	1.103	0.576	1.000	0.000
D-dimer (µg FEU/mL)	0.96 (0.82-1.28)	1.62 (1.19-2.23)	1.16 (0.81-1.67)	8.401	0.015	0.105	0.126
C-reactive protein (mg/L)	56.00 (24.40-92.60)	109.20 (63.85-148.30)	50.25 (32.35-67.68)	6.895	0.032	0.191	0.096
Prothrombin time (s)	15.40 (13.60-16.70)	16.10 (13.65-18.70)	16.80 (14.30-18.32)	1.582	0.453	1.000	0.000
Activated partial thromboplastin time (s)	43.30 (34.60-47.70)	42.30 (39.35-45.35)	42.20 (37.60-43.53)	0.316	0.854	1.000	0.000
25-Hydroxyvitamin D (ng/mL)	21.70 (16.20-23.90)	13.80 (10.60-18.55)	19.40 (13.10-21.77)	12.470	0.002	0.016	0.205

TABLE 3: Exploratory laboratory comparisons across clinical categories

Values are medians with interquartile ranges. The category sample sizes were 17 for steady state, 23 for vaso-occlusive crisis, and 14 for chronic complications. H is the tie-corrected Kruskal-Wallis statistic; epsilon-squared is the omnibus effect-size estimate. Raw p-values are unadjusted, and Holm p-values are adjusted across all nine exploratory tests.

APTT: activated partial thromboplastin time; AST: aspartate aminotransferase; CRP: C-reactive protein; FEU: fibrinogen-equivalent units; IQR: interquartile range; LDH: lactate dehydrogenase; PT: prothrombin time

Discussion

Across five planned comparisons, D-dimer remained higher in the vaso-occlusive crisis group than in the steady-state group, and 25-hydroxyvitamin D remained lower among participants with pain or crisis at sampling. The C-reactive protein difference was nominal and did not remain significant after correction. Prothrombin time and activated partial thromboplastin time did not differ. These findings support associations with the recorded clinical states but do not establish diagnostic thresholds, independent predictors, or causal effects.

The D-dimer result is consistent with earlier work showing coagulation and fibrinolytic activation during vaso-occlusive crisis [6,7,11]. D-dimer also correlates with hemolysis and selected complications in other sickle cell disease cohorts [8,9]. In this study, the median difference was 0.57 micrograms of fibrinogen-equivalent units per milliliter, and the rank-biserial correlation indicated a moderate-to-large separation between the recorded groups. The cross-sectional design and absence of detailed information about symptom onset, thrombosis, transfusion history outside the three-month exclusion window, anticoagulation, and treatment prevent use of this result as a diagnostic or prognostic cutoff.

C-reactive protein was higher in the vaso-occlusive crisis group before multiplicity correction, which is directionally consistent with studies associating C-reactive protein with crisis, pain-related hospitalization, or disease outcome [3-5]. However, the adjusted p-value was 0.083, and values overlapped widely between groups. This result should therefore be treated as inconclusive rather than evidence that C-reactive protein independently distinguishes vaso-occlusive crisis in this cohort.

The lower 25-hydroxyvitamin D concentration among participants with pain or crisis is also consistent with previous cross-sectional reports [12,13]. This comparison used the pain or crisis field across all three clinical categories, whereas the other four primary comparisons used the recorded clinical category. Vitamin D status can be influenced by season, nutrition, sun exposure, age, renal and hepatic function, supplementation, genotype, hydroxyurea, and other treatments. These variables were unavailable, so residual confounding is likely. The result does not show that vitamin D deficiency caused pain or that supplementation would improve sickle cell outcomes; randomized evidence remains limited [14].

Prothrombin time and activated partial thromboplastin time showed no evidence of differences between vaso-occlusive crisis and steady state. These screening tests assess limited portions of the coagulation cascade and may not reflect thrombin generation, fibrinolysis, endothelial activation, or platelet activation. Prior studies have similarly reported increased D-dimer with normal or inconsistently altered routine coagulation times, although prolonged values can occur in selected patients [10,11].

Reticulocyte count had the largest exploratory effect across the three recorded clinical categories, with the chronic-complication group showing higher values than both other groups. Reticulocyte count may reflect erythropoietic response and hemolytic activity, but it also varies with anemia severity, transfusion, marrow function, genotype, and treatment. The analysis was exploratory, and these covariates were unavailable, so the finding should be considered hypothesis-generating.

Strengths and limitations

The analysis used all 54 records, independently reproduced the workbook summary, retained all observations, reported effect sizes, and controlled multiplicity for both the planned and exploratory test families. The main limitations are the small sample, single-center design, cross-sectional measurement, lack of a prospective sample-size calculation, and use of recorded group labels without source-level clinical adjudication. This reliance on recorded free-text classifications may limit reproducibility across centers that use different clinical definitions or classification practices. The primary analyses also used two different grouping variables: four comparisons used clinical category, while the vitamin D comparison used pain or crisis status. Two records labeled as steady state were marked as having pain or crisis at sampling, which raises the possibility of timing differences, data-entry inconsistency, or category misclassification.

Consecutive recruitment reduced but did not eliminate the possibility of selection bias. Because participants were recruited from the outpatient and inpatient services of a single hospital, individuals who sought hospital-based care and met the eligibility criteria may differ systematically from community-based populations with sickle cell disease or patients managed in other institutions. The exclusion of patients with recent blood transfusion, acute concurrent infection, or recent surgery further limits applicability to these clinical contexts. Consequently, the findings may not be generalizable to other institutions, geographic regions, or populations with different genotypes and treatment patterns. The comparisons of nine laboratory variables across the three recorded clinical categories were exploratory. Although Holm correction was applied to control multiplicity, the small category-specific samples, absence of a prospective power calculation, and lack of covariate adjustment limit the precision and conclusiveness of these results. The exploratory findings should therefore be regarded as hypothesis-generating.

Potentially influential laboratory observations were retained. These limitations reduce precision and preclude causal, diagnostic, prognostic, or risk-stratification claims. The results require confirmation in a prospectively characterized cohort with standardized definitions and verified data capture.

Conclusions

In this cross-sectional cohort, D-dimer was higher in the recorded vaso-occlusive crisis group than in the steady-state group, and 25-hydroxyvitamin D was lower among participants with pain or crisis at sampling after Holm correction across five comparisons. C-reactive protein showed an unadjusted difference but did not remain significant after correction, while prothrombin time and activated partial thromboplastin time did not differ.

Given the small sample, cross-sectional design, and inability to adjust for important confounders, the observed associations do not establish causal relationships, diagnostic or prognostic utility, or independent clinical prediction. Reticulocyte count showed a strong exploratory difference across the recorded clinical categories, but this result also requires confirmation. Larger prospective studies should use clinically adjudicated group assignment, standardized sampling times, recorded treatments and confounders, and longitudinal measurements before these biomarkers are used for clinical decision-making.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Mansi Sharma, Maneesh Sulya

Acquisition, analysis, or interpretation of data: Mansi Sharma, Ashish Koshti, Rita Saxena

Drafting of the manuscript: Mansi Sharma, Ashish Koshti

Critical review of the manuscript for important intellectual content: Mansi Sharma, Ashish Koshti,

Maneesh Sulya, Rita Saxena

Supervision: Ashish Koshti, Maneesh Sulya

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. Institutional Ethics Committee of Gandhi Medical College issued approval 16303/MC/IEC/2024. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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