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Original Research Article

Evaluation of the Potential of Inflammatory and Coagulation Biomarkers as Predictors of Vaso-Occlusive Episodes in Children with Sickle Cell Disease: A Prospective Cohort Study

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Abstract

Background: The primary cause of morbidity among children with sickle cell disease are vaso-occlusive episodes (VOEs). Pathophysiology of VOEs are greatly influenced by systemic inflammation and hypercoagulability. This study evaluated the potential of certain inflammatory markers (CRP, IL-6) and coagulation (D-dimer, fibrinogen) biomarkers as potential early predictors of VOEs in children with Sickle cell disease.

Methodology: A 12-month study was conducted on 18 pediatric patients with SCD, aged between the years of 2–18 at a tertiary hematology clinic. Standardized laboratory assays were employed to evaluate the baseline and follow-up blood samples for CRP, IL-6, D-dimer, and fibrinogen levels. All patients were followed up at every three months and also during VOEs. Paired tests, regression models, and ROC curve analysis were used to establish the associations between the biomarker levels, VOE occurrence, severity, and pain scores in children.

Results: During the follow-up periods almost half of the patients developed had VOEs. In contrast to baseline levels, the mean biomarker levels during VOEs rose significantly ($p<0.001$). Compared to patients who were stable, those patients who developed VOEs later showed elevated baseline biomarker levels. Fibrinogen and D-dimer displayed the highest predictive accuracy (AUC≈1.0). followed by CRP and IL-6. Biomarker levels correlated positively with pain score ($r>0.96$, $p<0.01$), thereby, establishing the link between biochemical variations and clinical severity.

Conclusion: In pediatric SCD the VOE occurrence and severity can be predicted by the elevated baseline and crisis-state levels of CRP, IL-6, D-dimer, and fibrinogen. These biomarkers show potential for early risk assessment and clinical monitoring. To establish clinical cut off values and confirm clinical applicability, larger multicenter studies are needed.

Keywords: Coagulation bioarkers, Inflammatory biomarkers, Sickle Cell Disease, Vaso-occlusive Episodes.

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Introduction

Sickle cell disease (SCD) is one the most common inherited hemoglobinopathies, brought on by abnormal hemoglobin S polymerization in hypoxic conditions, that results in sickled shaped red blood cells.[1] These aberrantly formed erythrocytes causes vaso-occlusion, hemolysis, and ischemia. Recurrent vaso-occlusive episodes (VOEs) are hallmark of this disease and the primary cause of morbidity in children.[2] Pediatric patients are especially more at risk, since VOEs occurs more frequently in childhood and lead to several long-term complications such as stroke, acute chest syndrome, and impaired growth.[3] The pathophysiology of VOE Is significantly influnced by systemic inflammation and hypercoagulability. During acute painful crises, elevated levels of coagulation markers like D-dimer and fibrinogen, as well as inflammatory biomarkers such as C-reactive protein (CRP) and interleukin-6 (IL-6) were frequently reported, suggesting their potential utility in predicting the onset of VOE.[4] Hospitalizations, further complications, and even medical expenses may be reduced by the early detection of changes in the biomarkers levels that could allow timely for interventions. However, very few studies have explicitly evaluated the prognostic significance of these biomarkers in pediatric SCD patients. Therefore, the purpose of this study was to ascertain whether the inflammatory (CRP, IL-6) and coagulation (D-

dimer, fibrinogen) biomarkers could effectively predict the onset of VOEs in pediatric SCD patients. Determining the correlations between these biomarker levels and the severity of VOE, assessing the feasibility of biomarker monitoring in routine clinical practices, and investigating its associations with clinical outcomes including length of hospitalization and pain scores, were the secondary objectives.

Materials and Methodology

Study Design and Population: This prospective cohort study was meticulously planned and carried out over a period of 24 months. It included 12 months of patient recruitment period followed by a and 12 months of follow-up and analytic period. The study was conducted at the Pediatric Hematology Clinic of SSMCH, a referral center for children diagnosed with sickle cell disease. Children and adolescents with a confirmed diagnosis of SCD, between the ages of 2 to 18 years, who had the genotypes HbSS, HbSC, and HbS/β-thalassemia made up the study population. All patients were recruited from the outpatient registry of the Pediatric Hematology Clinic. 18 patients who fulfilled the eligibility criteria were enrolled into the study. Criteria for inclusion were: Children between the ages of 2–18 years diagnosed with SCD (HbSS, HbSC, or HbS/β-thalassemia) who were under regular follow-up at the clinic. For children under 7 years of age written informed consent was obtained from parents or legal guardians and when appropriate, consent was taken directly from children of seven years and above. Patients with concurrent acute infections or any inflammatory conditions unrelated to SCD, children who had received a blood transfusion within the past 4 weeks, and those with autoimmune or coagulation disorders were excluded from the study. Additionally, children participating in other interventional studies were not eligible.

Baseline Assessment: At the time of enrollment, comprehensive demographic and clinical data were recorded for all patients, including age, sex, genotype of SCD, family history, history of VOEs, current medications, and comorbidities. Baseline blood samples were procured for analysis of the investigative biomarkers, which comprises of CRP, IL-6, D-dimer, and fibrinogen.

Follow-Up and Monitoring: All patients were monitored and clinically documented for over a period of 12 months. Clinical evaluations/ follow-up visits were scheduled at every 3 months. All unscheduled visits or hospitalizations were also documented when patients came in with acute symptoms of VOEs. VOEs were clinically defined as sudden episodes of pain that necessitates medical intervention, which was always confirmed by a hematologist. During each episode, the severity of pain was assessed using validated pain scales. FACES scale was employed for younger children and for older children Numeric Rating Scale with values ranging from 0-10 was used. Detailed history of every hospitalization, duration and intensity of pain, and any details of other accompanying comorbidities during the study period were also documented

Sample Collection and Laboratory Analysis: Venous blood samples (5 mL) were collected at baseline, during each scheduled follow up visit, and within the 24 hours following the onset of VOE. Immediately after sample collection, all the specimens were processed and then stored at a temperature of 80°C until the time of analysis. The following standardized laboratory assays were used for each biomarker:

- CRP levels were measured using the Turbidimetric method.
- IL-6 levels were quantified using the Enzyme-Linked Immunosorbent Assay (ELISA).
- D-dimer values were determined by the Latex Agglutination test.
- Fibrinogen levels were assessed through the Clauss method.

10% of the randomly selected samples were analyzed twice for quality control. To gaurentee accuracy all laboratory assays were calibrated using a standard control. Electronic case report forms (eCRFs) were used to enter all clinical and laboratory data. Data consisted of biomarker values, frequency and severity of VOEs, duration of hospitalization, and the occurrence of any complications. In order to minimize errors, all the entered data were cross-checked by two independent investigators.

Outcome Measures: Evaluating the efficacy of inflammatory biomarkers (CRP, IL-6) and coagulation markers (D-dimer, fibrinogen) early predictors of VOEs within 72 hours of its onset was regarded as the primary outcome. Sensitivity, specificity, and predictive accuracy of each biomarker were also assessed.

Secondary outcomes comprised of any correlations between biomarker levels and the severity of VOEs, including pain scores, the duration of each hospitalization, as well as associations with other comorbidities like acute chest syndrome. Additionally, the feasibility of incorporating this method of biomarker monitoring into standard clinical practices was also checked.

Statistical Analysis: Analysis of the data collected was performed using the SPSS version 22. Categorical variables were presented as frequencies and percentages, while continuous variables were summarized as Mean and Standard Deviation.

Logistic regression was used to analyze the predictive ability of biomarkers with ROC curves. AUC values were utilized to determine the optimal cut-offs values for each biomarker. The comparison between VOE and non-VOE states were done using Wilcoxon Signed-Rank Tests and paired t-tests. Pearson or Spearman coefficients were used to determine the the correlation between the biomarker levels and VOE severity. A p value <0.05 was considered to be statistically significant.

Results

Table 1: Baseline Demographic and Clinical Characteristics of the Study Cohort (N=18)

Characteristic	Value
Age (years)	
Mean (SD)	11.39 (3.24)
Median [Min, Max]	11.50 [6, 17]
Sex, n (%)	
Male	9 (50.0%)
Female	9 (50.0%)
Genotype, n (%)	
HbSS	11 (61.1%)
HbSC	5 (27.8%)
HbSβ-thal	2 (11.1%)
VOE Occurrence, n (%)	
Yes	9 (50.0%)
No	9 (50.0%)

Table 2: Descriptive Statistics of Biomarker Levels at Baseline and During Vaso-Occlusive Episodes (VOE)

Biomarker	State	N	Mean	SD	Median	Minimum	Maximum
CRP (mg/L)	Baseline	18	7.69	3.02	7.50	2.80	13.2
	During VOE	18	30.09	23.93	23.55	4.70	70.3
IL-6 (pg/mL)	Baseline	18	8.81	3.32	8.25	3.50	14.3
	During VOE	18	52.73	44.91	44.65	6.10	118.2
D-dimer (ng/mL)	Baseline	18	508.89	178.82	510.00	240	780
	During VOE	18	1280.00	933.85	1070.00	280	2800
Fibrinogen (mg/dL)	Baseline	18	303.89	53.68	300.00	210	390
	During VOE	18	381.67	111.05	375.00	240	550
Pain Score	During VOE	18	4.61	3.55	4.50	0	10

Table 3: Comparison of Biomarker Levels by Sickle Cell Genotype (One-Way ANOVA)

Biomarker	Genotype	N	Mean	SD	p-value
Baseline CRP (mg/L)	HbSC	5	5.84	1.27	0.279
	HbSS	11	8.36	3.28	
	HbSβ-thal	2	8.65	4.17	
Baseline IL-6 (pg/mL)	HbSC	5	7.42	1.80	0.404
	HbSS	11	9.43	3.98	
	HbSβ-thal	2	8.90	1.27	
Baseline D-dimer (ng/mL)	HbSC	5	448.00	131.42	0.671
	HbSS	11	532.73	206.06	
	HbSβ-thal	2	530.00	155.56	
Baseline Fibrinogen (mg/dL)	HbSC	5	286.00	30.50	0.631
	HbSS	11	307.27	60.97	
	HbSβ-thal	2	330.00	70.71	

Table 4: Comparison of Baseline Biomarkers Between Patients Who Later Developed a VOE and Those Who Did Not (Independent Samples T-Test)

Biomarker	VOE Group	Mean	SD	p-value
Baseline CRP (mg/L)	Yes	9.67	2.43	0.002
	No	5.72	2.18	
Baseline IL-6 (pg/mL)	Yes	10.99	2.82	0.002
	No	6.63	2.17	
Baseline D-dimer (ng/mL)	Yes	628.89	130.90	0.002
	No	388.89	135.69	
Baseline Fibrinogen (mg/dL)	Yes	347.22	29.27	<0.001
	No	260.56	32.25	

Table 5: Biomarker Levels During VOE Event and Pain Scores, Stratified by VOE Occurrence Group

Measurement	VOE Group	Mean	SD	p-value
CRP during VOE (mg/L)	Yes	51.98	11.60	<0.001
	No*	8.21	2.15	
IL-6 during VOE (pg/mL)	Yes	95.27	14.41	<0.001
	No*	10.19	2.51	
D-dimer during VOE (ng/mL)	Yes	2152.22	365.44	<0.001
	No*	407.78	88.85	
Fibrinogen during VOE (mg/dL)	Yes	484.44	39.09	<0.001
	No*	278.89	30.18	
Pain Score	Yes	7.89	1.27	<0.001
	No	1.33	1.00	

Group: "Yes" = Patients who had a VOE during follow-up (n=9). "No" = Patients who did not have a VOE (n=9).

Table 6: Logistic Regression Analysis for Prediction of VOE Occurrence using Baseline Biomarkers

Variables in the Equation					
Predictor	**B**	**S.E.**	**Wald**	**p-value**	**Exp(B)**
Baseline CRP	-16.193	3635.0	0.000	0.996	0.000
Baseline IL-6	40.061	5405.0	0.000	0.994	2.502E17
Baseline D-dimer	-0.176	49.927	0.000	0.997	0.839
Baseline Fibrinogen	-3.560	429.367	0.000	0.993	0.028
Constant	963.145	114700.0	0.000	0.993	-

Table 7: Correlation of Biomarker Levels and Pain Score During Vaso-Occlusive Episodes (VOE)Pearson Correlation (Parametric)

	CRP during VOE	IL-6 during VOE	D-dimer during VOE	Fibrinogen during VOE	Pain Score
CRP during VOE	1	.988**	.989**	.974**	.968**
IL-6 during VOE	.988**	1	.989**	.984**	.980**
D-dimer during VOE	.989**	.989**	1	.979**	.975**
Fibrinogen during VOE	.974**	.984**	.979**	1	.992**
Pain Score	.968**	.980**	.975**	.992**	1

*** Correlation is significant at the 0.01 level (2-tailed).*

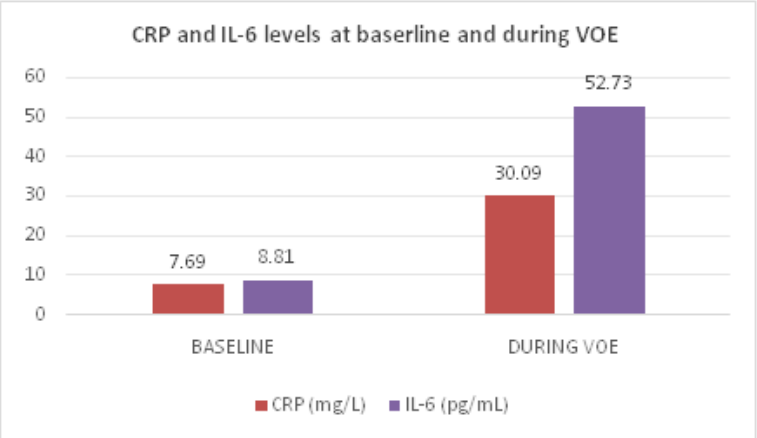

Figure 1: Descriptive Statistics of CRP and IL-6 Levels at Baseline and During Vaso-Occlusive Episodes

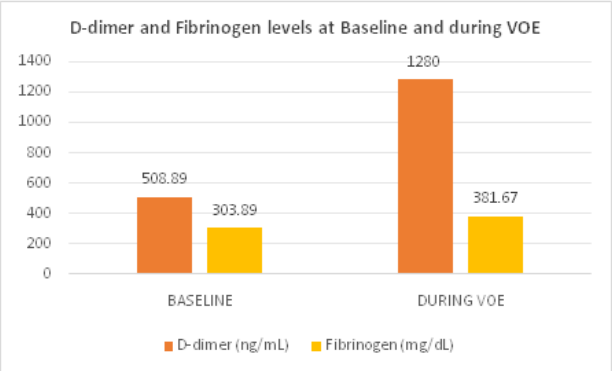

Figure 2: Descriptive Statistics of D-dimer and Fibrinogen Levels at Baseline and During Vaso-Occlusive Episodes

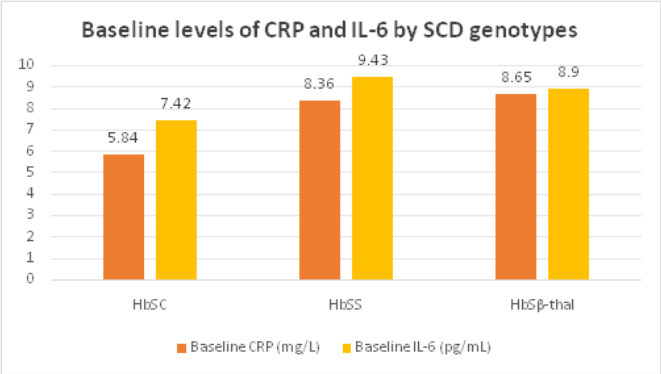

Figure 3: Comparison of Baseline levels of CRP and IL-6 by SCD genotypes

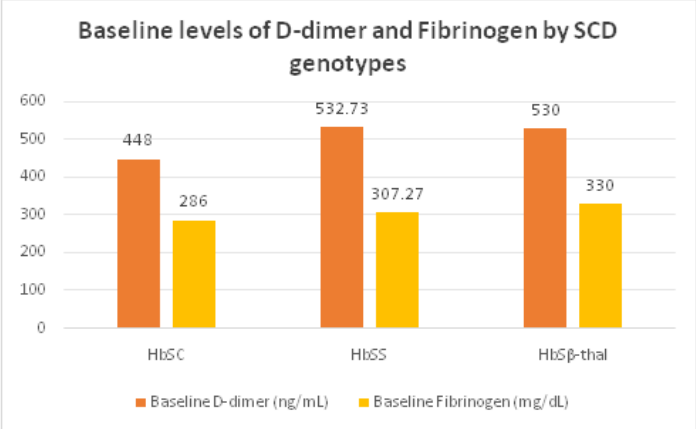

Figure 4: Comparison of Baseline levels of D-dimer and Fibrinogen by SCD genotypes

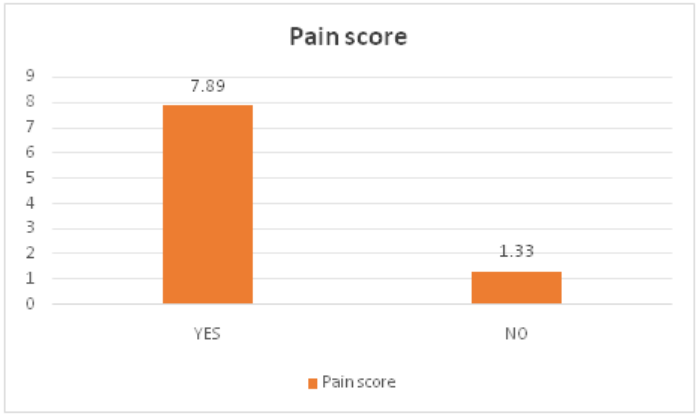

Figure 5: Pain Scores reported during VOE

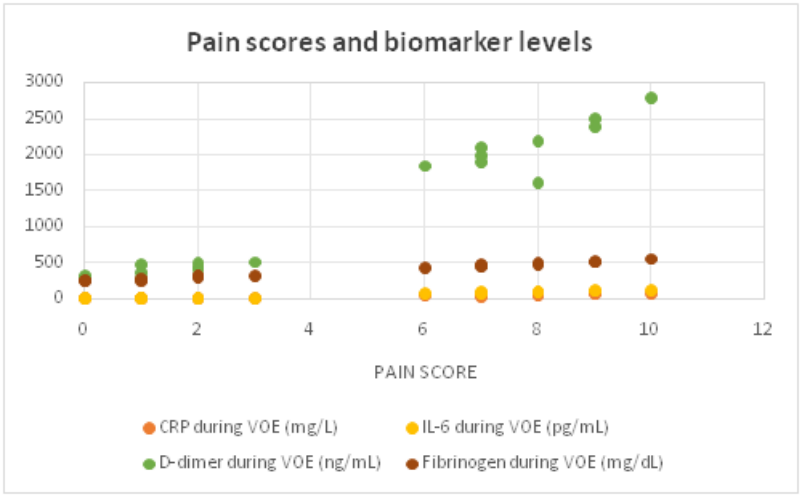

Figure 6: Correlation of Biomarker Levels and Pain Score During Vaso-Occlusive Episodes

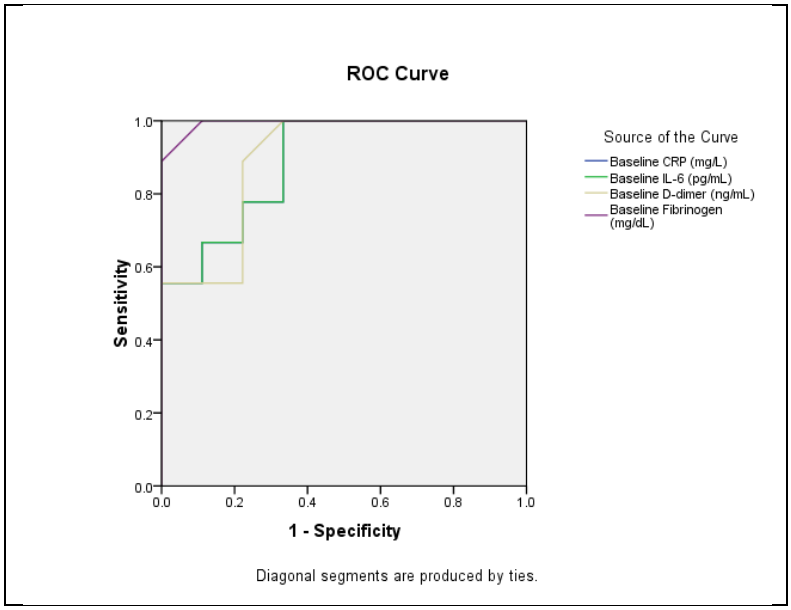

Figure 7: Predictive Accuracy of Baseline Biomarkers for VOE (ROC Curve Analysis)

18 pediatric patients with sickle cell disease, with a mean age of 11.39 years were enrolled for this prospective study. All patients were evenly divided between males and females. Based on the genotypic distribution of SCD, HbSS was the predominant variant, followed by HbSC and HbSβ-thalassemia. During the 12-month follow-up period, nearly half of the patients experienced at least one

vaso-occlusive episode, while the other remaining stayed clinically stable throughout the study. This distribution of the episodes enabled the comparison between patients with and without VOEs. Table 1 shows the baseline demographic and clinical characteristics.

Biomarker levels at Baseline and during VOE: Significant differences in the biomarker levels were observed between the baseline and VOE stages. At baseline values of CRP, IL-6, D-dimer, and fibrinogen levels were suggestive of clinical stability of the disease. In contrast, during VOEs, all four biomarkers showed significant elevations, reflecting heightened systemic inflammation and hypercoagulability that are triggered by acute episodes. The consistent biochemical variations that were observed across the VOE group, underscore their potential as sensitive indicators of clinical deterioration. Moreover, a strong positive association was observed between the increase in biomarker levels and the severity of pain scores. The comparative findings are shown in Table 2 and illustrated in Graph 1 & 2.

Association between biomarkers levels and Sickle cell Genotype: When biomarker values were compared across the different genotypes of SCD, children with HbSS genotype showed higher mean levels of CRP, IL-6, D-dimer, and fibrinogen than those with HbSC and HbSβ-thalassemia. However, these differences were not statistically significant, suggesting that the baseline biomarker concentrations may not be determined solely by genotype. This implies that, although HbSS patients usually experience a more severe clinical course, factors such as the variations in individual host responses or environmental factors can also influence biomarker levels. The results are shown in Table 3 and illustrated in Graph 3 & 4.

Baseline biomarkers levels and the risk of developing VOE: At baseline all four biomarkers were markedly elevated in patients who developed VOEs compared to those who remained clinically stable throughout follow-up. Hence, it implies that inflammatory and coagulation activity can be elevated even in the absence of clinical symptoms. This may signify an underlying condition with a vascular susceptibility that put patients at a risk of developing to acute episodes. These results support the hypothesis that baseline biomarker assessment can aid in the stratification of patients into higher and lower risk groups for developing VOEs. (Table 4 and Figure 2).

Biomarker responses during VOE: During VOEs, levels of all the measured biomarkers rose significantly, thus help clearly distinguish between the patients with VOE and those patients who remained stable. Patients experiencing VOEs also reported significantly higher pain scores, which corresponded closely to the biochemical variations. (Graph 5) The concurrent surges in CRP, IL-6, D-dimer, and fibrinogen reflect both inflammatory and coagulation processes and the clinical severity of each episode. This reinforces the value of these biomarkers as real-time markers of disease activity.(Table 5)

Predictive value of baseline biomarker levels: Results of regression analysis reveals that the initial biomarker levels were strong predictors of the occurrence of VOEs. The integrated biomarker model effectively categorized all patients into VOE and non-VOE groups, resulting in a 100% prediction accuracy. These results highlight the biomarker's considerable potential as predictors for disease activity. However, given the limited sample size, these findings should be interpreted with caution, since the predictive power may be overestimated. (Table 6)

Receiver Operating Characteristic (ROC) Curve Analysis: ROC curve analysis supported the discriminative ability of biomarkers in classifying patients by predicting VOEs. Best predictive performance was demonstrated by fibrinogen (AUC approaching 1.0), followed by D-dimer, CRP, and IL-6. All four biomarkers showed remarkable accuracy in distinguishing between VOE and non-VOE states, thus highlighting their potential clinical applicability for risk stratification. ROC values are illustrated in the Figure 1.

Correlation between the biomarkers levels and pain score: Correlation analysis has found a significant positive association between biomarker levels and clinical pain scores during VOEs. Among the four biomarkers that was tested, fibrinogen showed the strongest connection with pain severity, followed by D-dimer, IL-6, and CRP. These findings suggest that increased biomarker levels not only help predict VOEs but also reflect the severity of the clinical symptoms, effectively linking laboratory values to patient-reported outcomes. (Table 7 and Graph 6)

Discussion

The current research looked into the role of inflammatory and coagulation biomarkers like CRP, IL-6, D-dimer, and fibrinogen in predicting the occurrence of vaso-occlusive episodes in pediatric patients with SCD. The data revealed that all four biomarkers' values were marked higher during VOEs. This suggests that regular monitoring of these biomarker levels can be effective tool for predicting disease activity, allowing for early intervention and potentially improving the clinical results.

In the current study, fibrinogen and D-dimer displayed the highest predictive accuracy for VOE occurrence, which was followed by CRP and IL-6.

The robust link observed between elevated fibrinogen and D-dimer levels and VOE supports the idea that hypercoagulability plays a key role in the pathogenesis of sickle cell disease. In line with these findings, is the results of the study by Mohamed EA on Sudanese SCD patients who found that fibrinogen and D-dimer levels were greater in majority of patients experiencing vaso-occlusive crisis than those who were stable (67% and 71% respectively). The increase in D-dimer was statistically significant ($p = 0.006$).5 Similar findings were also reported by Ataga and Key, who discovered that plasma fibrinogen and D-dimer levels were significantly raised during acute pain episodes than during steady states, indicating an enhanced coagulation activation during VOEs.[6]

Research by Ataga et al., found a strong correlation between the D-dimer levels and hemolysis markers in patients with history of stroke. This confirmed the link between coagulation markers and acute and chronic clinical severity in SCD patients.[7] Furthermore, Francis et al. also found substantial evidence of strong association between higher levels of D-dimer and clinical severity of vaso-occlusive pain, thereby supporting their role as indicators of thromboinflammatory activity.[8]

The Inflammatory biomarkers CRP and IL-6 found in this research increased concurrently during VOEs, showing that systemic inflammation often occurs alongside episodes of vascular occlusion. These findings are comparable with study by Pathare et al., who reported elevated levels of IL-6 and CRP during acute pain episodes compared to clinically stable SCD patients in Oman, emphasizing their role as indicators of acute inflammatory burden.[9] Similarly, Krishnan et al.reported that persistently elevated levels of CRP were associated with frequent VOE occurrence and longer hospitalizations, highlighting their prognostic relevance.[10] The positive correlation between IL-6 and pain severity found in this study gives credibility to the role of inflammatory cytokines in nociceptive signaling and vascular responses during SCD crises.

Even during the steady state, patients who experienced VOEs had a significant rise in baseline biomarker values implying that subclinical inflammation or coagulation activation may contribute to the occurrence of future episodes. Hibbert et al., who observed comparable findings where SCD patients in steady state had higher levels of baseline inflammatory markers when compared to healthy controls. These higher levels were capable of predicting subsequent crises.[11] This finding emphasizes the potential value of serial biomarker monitoring in identifying high-risk patients who may benefit from targeted preventive therapy.

According to the results of ROC analysis, fibrinogen displayed excellent discriminative performance (AUC 0.994), indicating its potential as a sensitive biomarker for VOE prediction. This finding is congruent with the findings of Connes et al., who identified fibrinogen as the major contributor in the incidence of increased blood viscosity and vascular occlusion in patient with SCD.4 Famodu also reported that serum fibrinogen levels in steady state SCD patients were considerably higher than in the healthy controls, implying that fibrinogen may not only function as a biomarker of vascular risk but also as a potential predictor of crisis severity.[12]

Furthermore, the substantial correlation between fibrinogen and pain scores observed in this study is consistent with that discovered by Qari et al., who found that biomarkers of coagulation activation were closely associated with pain intensity and clinical severity during VOEs.[13] Together, these findings imply that employing inflammatory and coagulation biomarkers into clinical monitoring methods could improve the individualized disease monitoring and management of SCD.

Results from the study revealed that some patients with elevated baseline biomarkers developed VOEs, while others had mild reactions or more muted responses, suggesting individual variability in host response and healing capability. This heterogeneity is also documented in studies of coagulation profiles in children with SCD. The study by Noubouossie et al. demonstrated that while many children had elevated endogenous thrombin potential (ETP) and D-dimer in steady state, the amplitude of increase during crisis varied considerably among individuals.[14] Furthermore, Setty et al. In his study correlated D-dimer and soluble thrombomodulin with hemolysis markers and found that these associations varied depending on individual hemolytic burden, again indicating variability.[15]

Finally, our results support the translational potential of risk stratification in pediatric SCD based on biomarkers. According to Colombatti et al., the endothelial activation and markers of coagulation such as D-dimer in children are often elevated even before the clinical manifestations of microvascular disease. This suggests that early changes in biomarker level can be detected and potentially treated even before the occurrence of any major events.[16]

Regardless of these promising results, it is imperative that we acknowledge the various limitations of this study. The results cannot be generalized owing to the relatively small sample size, and the single-center design may induce demographic bias. The brief follow-up period restricted any long-term assessment of variations in

biomarker levels across multiple crises. Furthermore, variables such as hydroxyurea therapy or baseline nutritional status were not considered, since these could have an impact on the biomarker levels. Larger population and longitudinal sampling are required in the future so as to validate these findings and establish a optimal clinical cutoff value for the biomarker levels.

Conclusion

The study shows that demonstrates that in pediatric sickle cell disease the inflammatory and coagulation biomarkers levels, specifically CRP, IL-6, fibrinogen and D-dimer, can be utilized as reliable predictors of vaso-occlusive episodes and indicator of disease activity. Fibrinogen and D-dimer exhibit the highest predictive accuracy, while elevated baseline and crisis-state levels of biomarkers indicate persistent inflammation and hypercoagulability. The results also indicate promise for integrating assessment of biomarkers into routine clinical care, so as to facilitate early risk detection and timely. Intervention. However, more thorough multicenter studies are required to validate these findings and determine the clinical cut-off values.

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