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Predicting the severity of sickle cell disease using hematological, biochemical, and cellular parameters

Viren Laljbhai Vaghasiya [1]*, Divya D Bambhaniya [1], Jitendra Gordhanbhai Nasit [1], Bhoomika H Rupavatiya [1]

1. Medical College Baroda, the Maharaja Sayajirao University of Baroda, Vadodara, Gujarat, India
* Correspondence: Viren Laljbhai Vaghasiya. Medical College Baroda, the Maharaja Sayajirao University of Baroda, Vadodara, Gujarat, India.
Tel: +918980008830; Email: viren.vaghasiya-path@msubaroda.ac.in

Abstract

Background: Sickle cell disease is a hemoglobinopathy caused by a point mutation and has a heterogeneous clinical course. The level of Hb F within erythrocytes is believed to be the most important parameter determining disease severity. The aim of this study was to investigate whether Hb F level, F-cell count, and sickle cell percentage after in vitro induction of sickling can predict the severity of the disease.

Methods: All necessary data were collected from clinical history, biochemistry, and pathology laboratory tests. This was a cross-sectional study with 31 participants. Statistical analyses were performed using the correlation coefficient and chi-square test to identify significant differences between variables. Statistical analysis was performed using MedCalc software.

Results: The majority of patients fell into the mild severity score category, with a lack of severe disease phenotypes. The number of painful episodes, hospitalizations, and cumulative disease severity scores were associated with high levels of LDH and indirect bilirubin. However, none of the clinical disease severity parameters or the overall cumulative disease severity score was associated with Hb F level, F-cell count, or the percentage of sickled cells after in vitro induction of sickling. A high percentage of F-cells was associated with high MCV, MCH, and MCHC and low RDW, LDH, and indirect bilirubin levels.

Conclusion: Sickle cell disease severity is related to the susceptibility of RBCs to hemolysis, as indicated by serum LDH and indirect bilirubin levels. However, the extent of hemolysis may depend on multiple factors rather than F-cell count or Hb F level alone.

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Introduction

Sickle cell disease is a chronic and debilitating genetic condition resulting from a single point mutation in the β-globin gene of hemoglobin. This point mutation makes erythrocytes prone to acquiring a sickle shape under hypoxic conditions and to premature hemolysis.

In India, sickle cell disease is one of the most frequently encountered hemoglobinopathies, particularly in the central, southern, and north-eastern parts of the country. In Gujarat, the sickle cell gene has an overall prevalence of about 6.5%, rising to nearly 11% in tribal populations (1).

Sickled erythrocytes are less flexible and sticky. While travelling through the peripheral circulation, they cause vessel obstruction, stasis, and hyperviscosity, which lead to hemorrhages, infarctions, and ischemic necrosis of tissues and organs throughout the body, resulting in complications such as vaso-occlusive crisis and associated stroke, splenic sequestration crisis, jaundice, leg ulcers, priapism, and painful episodes.

Despite the uniform underlying point mutation, clinical severity varies markedly among patients from different geographical areas and communities. Sickle cell disease generally has a mild phenotype in the Indian population; however, there is wide variation in disease severity among individual patients (2).

The Hb F and Hb S content within erythrocytes is thought to be the most important factor determining disease severity by influencing polymerization and sickling. However, the relationship between Hb F percentage and clinical severity of sickle cell disease is variable. It has been postulated that a heterogeneous distribution of Hb F within erythrocytes could be the reason, and that Hb F content in individual erythrocytes could be a critical determinant of the Hb F effect (3,4).

Hb F as a percentage of total hemoglobin can be detected by HPLC or capillary electrophoresis, which provides the percentage of Hb F in a hemolysate but not in individual erythrocytes. There are also immunological and chemical methods that estimate the percentage of erythrocytes containing increased amounts of Hb F compared to normal adult erythrocytes, termed F-cells (3). It is not possible to reliably estimate Hb F in individual erythrocytes, although Nicolas Hebert et al. have attempted this in their study (5). If this parameter can be obtained, it is theoretically considered the most ideal parameter to demonstrate the protective effect of Hb F on disease severity.

Our study attempted to explore the relationship between disease severity in pediatric patients on hydroxyurea therapy and Hb F percentage measured by HPLC, as well as flow-cytometric assessment of F-cell count as a percentage of the total erythrocyte count. F-cells, being cells with higher Hb F levels, are presumed to be protective against sickling. In line with this hypothesis, we further investigated the association between the percentage of sickled cells following induction in a laboratory setting and the clinical severity of the disease.

Additionally, we evaluated various hematological and biochemical parameters, such as LDH and bilirubin levels, to identify the parameter that best correlates with the severity of sickle cell disease in patients receiving hydroxyurea therapy.

Methods

A one-year, time-bound cross-sectional study was conducted in the western part of India. A total of 31 outpatient pediatric patients (Less than 13 years of age) with sickle cell disease were included in the study after obtaining consent from the parent or guardian. Patients who had received a blood transfusion in the last 3 months were excluded from the study, as recent transfusion may affect some of the variables under investigation. Blood samples were obtained for various laboratory tests, including F-cell count.

Demographic, clinical, and laboratory data were collected from the Pediatrics, Pathology, and Biochemistry departments. F-cell count data were obtained from a private laboratory, as the samples were outsourced.

Structured questionnaires were employed to obtain the current clinical profile and past medical history, including details on the age at initial diagnosis. Information was obtained regarding the degree of splenic and hepatic enlargement, frequency of complications in the past 12 months, and lifetime incidence of complications for each patient. Past medical records were reviewed in cases of ambiguity in the information.

Scoring of sickle cell disease severity was performed identical to that described by Adegoke et al. (6). Six parameters were used to assess the patient's present state, clinical status during the past 12 months, and the severity of lifetime complications. Each item was scored based on its frequency and/or severity using a scale from 1 to 5. The total score (0 - 30) was computed for each child, after which disease severity was categorized as mild (< 5), moderate (6 - 17), or severe (> 17). Complete blood count, serum lactate dehydrogenase, and bilirubin levels were assessed using standard laboratory procedures during the outpatient department visit.

A 5-part automated cell counter (HORIBA Pentra XLR) was used to perform the complete blood count. Serum LDH was measured using a fully automated ERBA XL-640 analyzer. Bilirubin was measured using a semi-automated Microlab ARX 50-V analyzer. Blood samples were then further subjected to high-performance liquid chromatography (HPLC) on a Bio-Rad VARIANT II HPLC device. F-cell count was performed at a private laboratory using a DeFLEX flow cytometer with FITC-conjugated mouse monoclonal antibody against fetal hemoglobin.

In vitro induction of red cell sickling was performed using a method similar to that described by Oyenike MA et al. (7). A solution of 20 µL of 2% sodium metabisulfite was added to 20 µL of washed erythrocytes, mixed well, and sealed with liquid paraffin to exclude air and maintain hypoxia. Results were documented after 24 hours. Counts of sickled and total erythrocytes (Normal and abnormal) were obtained from five randomly selected fields across the slide. Results were expressed as the percentage of sickled erythrocytes.

Statistical analysis was performed using correlation coefficients to examine relationships between variables and chi-square tests to assess the significance of differences between groups. MedCalc software was used to conduct all statistical analyses.

Results

The study population consisted of 31 pediatric patients, with 5 (16%) aged ≤ 5 years, 15 (48%) aged 6 - 10 years, and 11 (36%) aged 11 - 13 years. The average age was 9 years. The study population included 22 (71%) male children and 9 (29%) female children. The mean age at first presentation of the patients was 4.7 years.

A large proportion of the study population comprised follow-up cases of sickle cell disease, and the majority reported no current symptoms. Others presented with pallor, pain in the limbs or abdomen, fever, cough, and hematuria.

Table 1 summarizes the clinical characteristics of the patients with sickle cell disease in the present study. Thirty-two percent of the patients had one painful episode in one year, with only 19% of subjects having more than three painful episodes in one year. Fifty-two percent of the patients required no blood transfusion in one year. Only 13% of subjects required two or three blood transfusions in one year. Fifty-two percent of the patients required one-time hospitalization in one year, with only one subject requiring hospitalization more than three times in the last year. Ninety-four percent of patients had liver enlargement of less than 2 cm, with only one subject having 2 - 5 cm liver enlargement and one subject having more than 5 cm liver enlargement. Eighty-four percent of patients had spleen enlargement of less than 5 cm, with only one subject having 5 - 10 cm spleen enlargement. Only one subject had a past history of cerebrovascular events, and one subject had a chronic leg ulcer. Around 19 (62%) patients had moderate anemia (7 to 10 g Hb/dL), 8 (25%) subjects were in the mild anemia category, and 4 (13%) subjects were in the severe anemia category. On HPLC testing, the mean Hb F and Hb S levels were 19.5% ± 5.4 and 72.3% ± 5.8, respectively.

Table 2 shows the results of correlations between laboratory parameters and clinical parameters. Hb F showed no significant correlation with any clinical parameter. There was no significant correlation between in vitro sickle cell percentage and any clinical parameter.

Painful episodes were significantly correlated with MCHC, LDH, total bilirubin, and indirect bilirubin. Painful episodes and MCHC had an inverse relationship, while painful episodes showed a direct relationship with LDH, total bilirubin, and indirect bilirubin.

Table 1. Clinical characteristics and disease severity score of the study population

Severity score	Number of patients					
	Painful episodes in the last year (%)	Transfusion in last year (%)	Hospitalization in the last year (%)	Liver enlargement (%)	Spleen enlargement (%)	Specific complication (%)
0	7 (23)	16 (52)	10 (32)	29 (94)	26 (84)	29 (94)
1	10 (32)	11 (35)	16 (52)	1 (3)	5 (16)	1 (3)
2	8 (26)	4 (13)	4 (13)	1 (3)	0	0
3	6 (19)	0	1(3)	-	-	0
4	-	-	-	-	-	0
5	-	-	-	-	-	1 (3)

Table 2. Correlation of various clinical severity parameters with laboratory parameters

Laboratory parameters	Clinical parameter of severity			
	Painful episodes (P-Value)	**Hospitalization (P-Value)**	**Transfusion requirement (P-Value)**	**Severity score (P-Value)**
Hemoglobin	0.264	0.266	**0.033**	0.161
HCT	0.434	0.268	**0.030**	0.192
Erythrocyte count	0.977	0.791	0.153	0.828
MCV	0.196	0.173	0.404	0.092
MCH	0.110	0.183	0.317	0.095
MCHC	**0.041**	0.529	0.293	0.256
RDW	0.364	0.765	0.958	0.413
Total WBC count	0.780	0.385	0.944	0.429
Platelet count	0.405	0.694	0.821	0.367
HB A2	0.064	0.676	0.907	0.725
HB F	0.887	0.832	0.487	0.940
HB S	0.499	0.811	0.602	0.565
F-cell count	0.188	0.908	0.973	0.645
LDH	**0.001**	**0.001**	**0.0002**	**< 0.0001**
Total bilirubin	**0.000**	**0.002**	0.096	**0.000**
Direct bilirubin	0.651	0.470	0.380	0.479
Indirect bilirubin	**0.005**	**0.004**	0.151	**0.001**
Percentage of sickled cells after induction of *in vitro* sickling	0.715	0.712	0.610	0.889

The number of hospitalizations was significantly correlated with LDH, total bilirubin, and indirect bilirubin. The number of blood transfusions was significantly correlated with hemoglobin, hematocrit, and LDH. Finally, the laboratory parameters that significantly correlated with disease severity scores were LDH, total bilirubin, and indirect bilirubin. A notable negative finding was that F-cell count, in vitro sickling percentage, and Hb F level did not correlate with any of the clinical severity parameters. Serum LDH and indirect bilirubin levels were found to correlate with disease severity when considering most of the clinical severity parameters.

Table 3 shows the correlation of disease severity scores with various laboratory parameters. Severity scoring was performed for 31 subjects, of whom 25 (80%) had mild disease and 6 (20%) had moderate disease. No subjects were found in the severe category.

Table 3 presents a comparison of various hemogram parameters across different categories of disease severity. LDH, total bilirubin, and indirect bilirubin showed statistically significant differences (P = 0.004, 0.007, and 0.018, respectively), while MCV was close to significance (P = 0.056).

Figure 1 illustrates the correlation between F-cell count and various laboratory parameters. MCV, MCH, MCHC, RDW, LDH, and direct bilirubin demonstrated significant correlations with F-cell count. F-cell count was directly related to MCV, MCH, and MCHC and inversely related to RDW, LDH, and total bilirubin.

Table 3. Comparison of various hematological parameters based on disease severity score

Laboratory parameters (Unit)	Mild severity	Moderate severity	P-Value
Hb (g/dL)	8.8 ± 1.7	8.0 ± 2.2	0.311
Erythrocyte (10^6/µL)	3.7 ± 0.8	3.7 ± 0.9	0.312
PCV (%)	28.2 ± 5.0	25.8 ± 6.3	0.97
MCV (fL)	77.3 ± 10.1	68.9 ± 4.3	0.056
MCH (pg)	24.4 ± 3.9	21.3 ± 2.3	0.082
MCHC(g/dL)	31.4 ± 1.6	30.9 ± 1.8	0.574
RDW-CV (%)	18.7 ± 2.96	19.4 ± 3.49	0.586
Total WBC (/µL)	9296 ± 5115	5583 ± 2102	0.095
Platelet (10^3/µL)	327 ± 1.3	284 ± 1.3	0.476
Sickling *in vitro* (%)	81.4 ± 17.9	79.5 ± 18.8	0.818
HBF (%)	19.85 ± 6.04	18.25 ± 2.63	0.535
HBS (%)	72.35 ± 6.34	72.52 ± 4.49	0.951
LDH (IU/L)	778.32 ± 335.29	1299.83 ± 519.54	0.004
Total bilirubin (mg/dl)	1.548 ± 0.95	2.73 ± 0.67	0.007
Direct bilirubin (mg/dl)	0.88 ± 1.51	0.93 ± 0.28	0.943
Indirect bilirubin (mg/dl)	0.95 ± 0.76	1.80 ± 0.65	0.018
F-cell count (%)	55.8 ± 27.0	59.7 ± 21.3	0.749

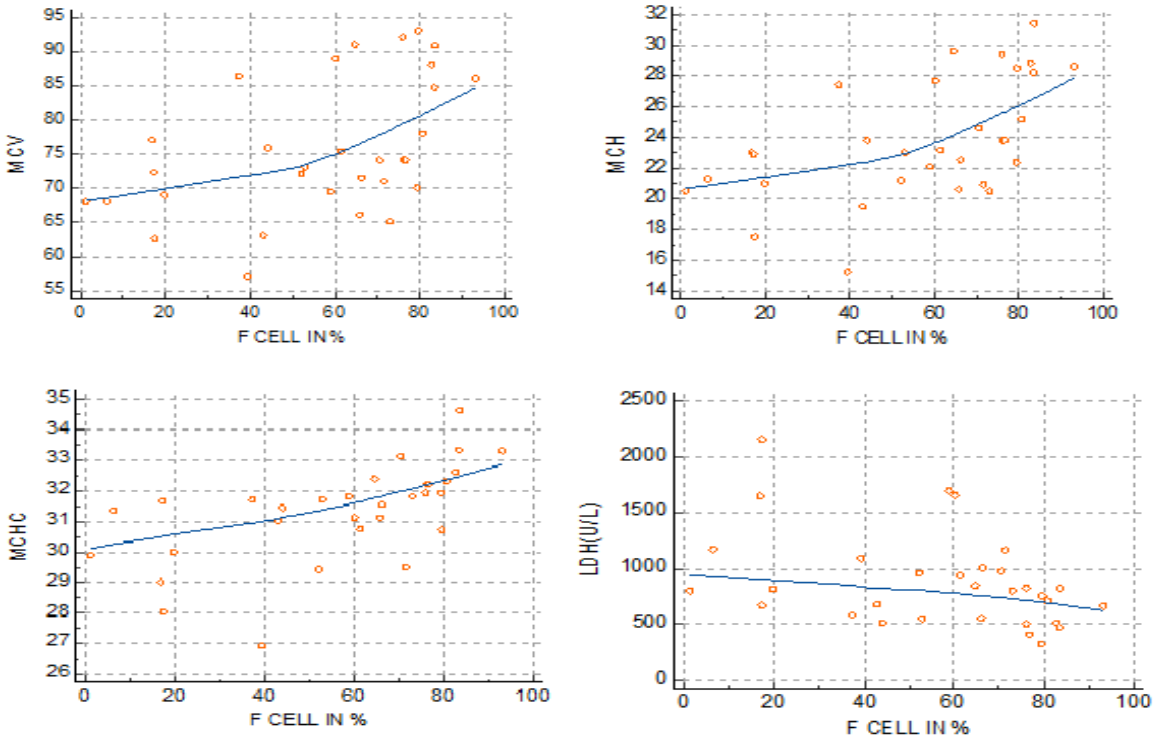

Figure 1. Relation of F-cell count to other laboratory parameters in sickle cell disease

Discussion

Our findings indicate that certain parameters demonstrated significant correlations with disease severity, while others conventionally regarded as severity markers in sickle cell disease did not correlate with severity among patients undergoing hydroxyurea therapy. In this study, the majority of patients were asymptomatic or exhibited only mild symptoms, likely because they were follow-up cases who were clinically stable and managed on an outpatient basis.

The majority of patients were in the mild severity score category, and none of the patients fell into the severe category according to the disease severity score. On average, patients had moderate anemia. There were relatively fewer painful episodes overall among all patients, and painful episodes were associated with a decrease in MCHC and an increase in LDH, total bilirubin, and indirect bilirubin levels.

The present study showed that the number of hospitalizations was associated with high levels of LDH, total bilirubin, and indirect bilirubin. Only a few patients had significant (Score 2/3) liver or spleen enlargement. There were no patients with acute chest syndrome, pneumococcal meningitis, avascular necrosis, gallstones, osteomyelitis, or priapism in the present study.

The overall cumulative disease severity score was directly associated with LDH, total bilirubin, and indirect bilirubin, with higher scores associated with higher levels of these parameters. This observation can be attributed to the heightened vulnerability of RBCs to splenic destruction in more severe disease, given that serum LDH and bilirubin levels serve as indicators of the degree of hemolysis.

However, none of the clinical disease severity parameters or the overall cumulative disease severity score was associated with hematological parameters such as Hb F level measured by HPLC, which is commonly used to monitor patients on hydroxyurea therapy. Other tested parameters, such as F-cell count and the percentage of sickled cells following in vitro induction, also failed to demonstrate a significant correlation. These findings indicate that Hb F levels or F-cell counts are not related to disease severity in patients with sickle cell anemia. However, as shown in Figure 1, higher F-cell counts were positively associated with increased MCV, MCH, and MCHC, while demonstrating an inverse relationship with LDH levels. No significant correlations were observed with other hematological parameters. Okocha E et al. found a significant positive correlation between disease severity and MCHC, MCV, and WBC, and a negative correlation between disease severity and Hb and PCV (8). Powar DR et al. observed no correlation between the severity of sickle cell disease and Hb F levels or RBC indices (9).

The results of the present study do not agree with the general opinion that a high level of Hb F has a beneficial effect on the severity of sickle cell anemia, or at least suggest that there is no effect in mild and moderate severity cases. Similar results were reported by Powar DR et al. (9), Ozsoylu et al. (10), and Serjeant et al. (11), although these studies had lower mean Hb F values than our study mean (19.5%). The strongest evidence supporting the beneficial effect of elevated Hb F levels on the severity of sickle cell disease comes from studies of Arabian patients with sickle cell anemia (12-16). In the study by Perrine et al. (16), Arabian SS cases demonstrated marked differences in their clinical presentation, with 75% of patients exhibiting mild manifestations. In our study, patients also had relatively mild symptoms, but this was observed after hydroxyurea therapy.

Our study demonstrated limited variability in disease severity, with most patients falling into the mild score category. In contrast, Alabid T et al. reported wider variability in severity patterns among Sudanese patients with sickle cell disease using a scoring system based on simple clinicopathological parameters. In their study, most patients were in the moderate and severe score categories, and only 21% of patients were in the mild score category, which is opposite to our findings (17). This further supports the notion that disease severity is influenced by multiple genetic factors that vary across geographical regions, as well as by environmental, socio-economic, and treatment-related differences. The present study supports the belief that Indian patients with sickle cell disease respond well to hydroxyurea therapy and tend to have relatively mild disease. Adegoke SA et al. reported that sickle cell disease in children exhibits wide clinical variability in severity. In their study, 33.9% of patients had mild disease, 55.7% had moderate disease, and 10.4% had severe disease based on their severity scoring system. They found that hematological parameters were higher in severe disease, while Hb F levels were lower (6). However, different studies use different disease severity scoring systems, which can be a potential source of variability in results.

There was no correlation between in vitro sickling and any of the severity scores or laboratory parameters, except that a high percentage of sickled erythrocytes was associated with a high F-cell percentage. This finding could be explained by the fact that higher levels of fetal hemoglobin help prevent polymerization of erythrocytes; however, this association was not linked to disease severity.

F-cell count did not correlate with any of the clinical parameters or the cumulative clinical severity score. Hb F is believed to have a protective effect against sickling, which forms the basis for the association of higher Hb F levels with milder disease. However, in patients on hydroxyurea therapy, Hb F levels and F-cell counts did not correlate with disease severity. This suggests that other factors and mechanisms of action of hydroxyurea therapy may be more important than increased Hb F levels within erythrocytes. Studies with larger sample sizes and greater variability in clinical severity are needed. Another possible explanation is that F-cell count may not truly reflect the number of erythrocytes protected from sickling, as the quantity of Hb F within individual erythrocytes and the number of F-cells containing protective levels of Hb F may be more relevant. Therefore, Hb F levels and F-cell counts may not be necessary for assessing disease severity in patients with sickle cell anemia receiving hydroxyurea therapy, based on our study results.

This study is limited by its reliance on information recalled by patients or their caregivers, which may introduce recall bias. Additionally, the small sample size - partly due to restrictions during the COVID-19 pandemic - may have reduced the statistical power to detect significant associations. All patients were receiving hydroxyurea therapy, which may have altered the relationship between disease severity and various parameters. Furthermore, there was no representation of patients with severe disease severity scores.

Conclusion

Hb F percentage, F-cell count, and the percentage of sickled cells after in vitro induction are not related to disease severity in patients receiving hydroxyurea therapy. Therefore, these tests are not necessary for assessing disease severity in hydroxyurea-treated sickle cell anemia patients. In hydroxyurea-treated sickle cell disease patients, serum LDH, total bilirubin, and indirect bilirubin were the only parameters associated with disease severity, indicating that severity reflects increased RBC vulnerability to hemolysis. Nonetheless, hemolysis appears to depend on several factors and not solely on F-cell count or Hb F levels. The study needs to be repeated with a larger sample size to determine whether the results are applicable to the broader population.

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Ethical Statement

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Conflicts of Interest

The authors declare that they have no conflict of interest.

Author Contributions

Viren L. Vaghasiya: Writing-Review and Editing, Writing-Original draft, Visualization, Validation, Supervision, Resources, Project

administration, Methodology, Investigation, Formal analysis, Data curation, and Conceptualization; Divya D. Bambhaniya: Writing-Review and Editing, Writing-Original draft, Validation, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, and Conceptualization; Jitendra G. Nasit: Writing-Review and Editing, Writing-Original draft, Project administration, Validation, Supervision, Formal analysis; Bhoomika Rupavatiya: Writing-Review and Editing, Writing-Original draft, Project administration, Validation, Data curation, and Formal analysis.

Data Availability Statement

Additional data supporting the study findings are available from the corresponding author on request.

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