Prevalence of Splenomegaly and Splenic Complications in Adults with Sickle Cell Disease and Its Relation to Fetal Hemoglobin

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ABSTRACT

Background: Spleen has been found to be the earliest organ involved in sickle cell disease (SCD) patients with variable manifestations in different geographical regions. It usually undergoes autosplenectomy by adolescence but in countries like India, the course of the disease and splenic manifestations are different. And here we aim to study these differences and the relationship between spleen size and fetal hemoglobin (HbF) and various splenic complications in our patients with sickle cell disease.

Materials and Methods: This is an observational study of 62 adult patients with sickle cell disease admitted in our prestigious institute in the northwestern part of India, mostly hailing from the tribal population. The clinical and ultrasonographic methods have been used to identify splenomegaly and spleen size and prevalence have been calculated. The correlation coefficient has been calculated between fetal hemoglobin, sickle hemoglobin, and spleen size.

Results: The analysis done revealed that 77.4% of patients had abnormal spleen with high average HbF(14.9±5.0) values compared to those who had normal spleen(12.12±4.1). Only 2 patients were found to have no spleen and 3.3% had splenic infarct. All patients with splenomegaly had anemia, 51.6% of patients were in sickle cell crisis and 22.5% were having infections. We also found a weak but positive correlation between spleen size and HbF.

Conclusion: This study revealed the persistence of the spleen, the high prevalence of splenomegaly in the Indian adult population with sickle cell disease, and higher levels of fetal hemoglobin, the exact reason for which is still a subject of speculation that needs research. But this paper provides clear evidence of different natural courses of SCD in India.

Keywords: Sickle cell disease; Spleen; Splenomegaly; Fetal hemoglobin

INTRODUCTION

Sickle cell disease is one of the sickle cell disorders, which is an inherited group of blood disorders. It is a single-gene disorder causing a systemic syndrome characterized by anemia, acute painful episodes, organ ischemia, and chronic organ damage affecting life expectancy. Sickle cell disease (SCD) results from homozygous inheritance of beta-globin subunit of hemoglobin molecule mutation and is the most severe form of sickle cell disorders¹. Sickle cell disease (SCD) term includes the homozygous state of the presence of hemoglobin S without normal adult
hemoglobin (HbA) and the symptomatic compound heterozygous states\textsuperscript{2}. In SCD, variable amounts of fetal hemoglobin (HbF) are present, and its presence is associated with a milder form of the disease\textsuperscript{3}. SCD can affect any organ of the body, putting treating physicians in a diagnostic dilemma, but the spleen is the most common and one of the early involved organs\textsuperscript{4}. Splenomegaly is found during the first decade of life, but later it undergoes atrophy progressively due to repeated vaso-occlusive attacks, ultimately leading to autosplenectomy\textsuperscript{4,5}. In the world literature on SCD, splenic enlargement in adults is considered rare, and it signifies a less severe disease \textsuperscript{6,7}. In a study published by Ahmed et al., (2016) on spleen in SCD, 28 of 67 paediatric patients below 10.5 years had splenomegaly, while in the age group of 11 - 20 years, two and only one had splenomegaly in the age range of 21 to 30 years\textsuperscript{5}. Splenomegaly in SCD is a territorial-linked sickle manifestation.

“Turf wars” described by Tubman et al. can be related to malaria endemicity\textsuperscript{8}. Clinicians in certain parts of the world do consider this diagnosis of SCD of SS genotype in adult patients having splenomegaly\textsuperscript{5}. Splenomegaly in SCD is linked with malaria-endemicity, a less severe disease, the persistence of high fetal hemoglobin level (HbF), and concomitant presence of alpha-thalassemia\textsuperscript{6,8,9}. Sequestration crisis is frequently seen in sickle cell disease, and trapped RBCs lead to splenic enlargement and dysfunction. It may cause hypersplenism, and a patient may present with pancytopenia. Acute splenic sequestration crisis, hypersplenism, massive splenic infarctions, and splenic abscess are the various complications that make splenectomy necessary because these complications are associated with increased morbidity and mortality\textsuperscript{10}. In some parts of the world, hyposplenism or asplenia is reported at the ninth month in three-fourths of pediatric patients having homozygous sickle cell disorder which will be present in the majority (up to 90%) at 12-15 months of age\textsuperscript{9,11}. Patients in Europe exhibit transient splenomegaly followed by splenic dysfunction and atrophy by the age of 6 years\textsuperscript{9,12}. Howell—Jolly bodies, a symbol of splenectomy and asplenia, were demonstrated in peripheral smears of children having SCD. The presence of Howell Jolly bodies is considered an indicator of hypofunction of the spleen despite splenomegaly, a contradicting feature\textsuperscript{12}. Hypofunction of the spleen leading to pneumonia and acute splenic sequestration resulted in decreased two-year survival in Jamaican children with homozygous sickle cell (SS) disease, which was 87%, compared to 99% in normal controls\textsuperscript{13}. In a study of Nigerian adults with SCD, 4% had splenomegaly at the mean age of 23 years\textsuperscript{14}. Splenomegaly has similarly been described in SCD cohorts in malarious regions of India and the Saudi Middle East\textsuperscript{15,16}. The natural history and course of sickle cell disease are different in India. Moreover, the difference is seen in the persistence of splenomegaly and various splenic complications compared to the western population, which can be linked to malaria\textsuperscript{16}. This study aimed to find the prevalence of splenomegaly in adult patients with sickle cell disease (HbSS). Moreover, it attempts to study the profile of various splenic complications in these patients. The reason for conducting this study was to find the correlation between fetal hemoglobin and the persistence of the spleen in this subset of the population and highlight the different courses of disease in Indian tribal populations.

MATERIALS AND METHODS

This is an observational study conducted at SBKS Medical Institute and Research Centre affiliated to Sumandeep Vidyapeeth, Pipariya, Dist Vadodara, India. Primary objective of the study was to find out the prevalence of splenomegaly as well as splenic complications in adult patients of sickle cell disease. This study was approved by institutional Ethics Committee on 21\textsuperscript{st} November 2016, and the study period was three and a half years (Dec, 2016 to June 2020). This study included adult patients more than 18 years old with sickle cell disease. Written informed consent was obtained from all study participants. Patients with sickle cell disease who were suspected to have splenic complications were admitted to the emergency department and medical wards. Splenomegaly, functional asplenia, hypersplenism, splenic sequestration, and others were considered as splenic complications which
were identified on clinical basis and/or on investigations. Abdominal ultrasonography was done in all patients. Exclusion criteria included: (i) patients in whom abdominal ultrasonography could not be performed (ii) splenic complications from causes other than sickle cell disorder. Splenic complications were determined based on clinical history, examination findings, haematological findings, imaging, and biochemical investigations. The presence of leukopenia/leukocytosis, thrombocytopenia, malaria parasite, Howell-Jolly bodies on peripheral smear (suggestive of functional asplenia), splenic sequestration, and/or hypersplenism was detected in patients included in the study. All patients (newly diagnosed and known cases) were treated with hydroxyurea and multivitamins. According to the requirement and severity of the disease, patients were given supplemental oxygen and blood products.

Sixty-two patients were enrolled in this study. Documentation of clinical and family history and detailed examination findings were recorded in a structured case record form (CRF). A thorough general physical and systemic examination was carried out, especially for fever, jaundice, anemia, and other relevant clinical indicators to look for the “tell-tale signs” of SCD and its complications. Abdominal examination was performed for organomegaly and obtaining information regarding the liver, gall bladder, spleen, and other viscera. Patients were examined for spleen size and spleen-related complications. Palpation of the spleen was done with the standard method, and also with modified methods. Splenic enlargement was also detected by percussion technique, dull note of percussion in Traube’s space replacing normal gastric tympany. Splenic Percussion Sign (Castell’s Sign) was also elicited by percussioning inferior costal space on the left anterior axillary line (Castell’s Point). A change in percussion note from tympany to dullness on inspiration suggested splenic enlargement.

Laboratory investigations included CBC, Blood Indices and RDW, Sickle Solubility Screening Test (SSST), and other radiological, biochemical and microbiological tests which were needed for adequate clinical care. “NESTROFT” (Naked Eye Single Tube Red Cell Osmotic Fragility Test) as a screening test was applied to identify suspected patients based on haematological parameters. Peripheral smear was examined with Giemsa and also with Field stain. Haemoglobin analysis was done by HPLC.

Abdominal sonography was performed to confirm the presence of spleen, its morphology, size, and splenic complications. Spleen size more than 11 cm was considered splenomegaly in this study which was based on the study done by Hosey RG et al., reporting splenic length on USG in young college students of 10.65x5.16 cm in length and width. It was further categorized into mild, (spleen size 11-12cm), moderate (12-18 cm), and huge (>18 cm) splenomegaly for our study group patients. Absence of spleen, splenic size and morphology of spleen was recorded. Other imaging modalities were used, when USG did not delineate splenic complications properly.

Anaemia was considered to be present, if Hb in males was less than 13g/dl and in female less than 12 g/dl. It was further classified in mild, moderate, and severe by the level of haemoglobin concentration in blood. Severe anaemia was considered if Hb was less than 8 g/dl, moderate if it was between 8–10.9, and mild anaemia if haemoglobin was between 11–11.9 in females and 11-12.9 in males.

For statistical analysis of the data collected, we have used Mann-Whitney test for a comparison between normal and abnormal spleen. Moreover, correlation coefficient has been calculated between Hb fractionation and spleen size.

RESULTS
This study included 62 patients with sickle cell disease. The mean age of sickle cell disease patients in our study was 26.56±6.13 years. There were 4 patients in the age group of 18-20 years, 39 out of 62 belonged to the age group of 21-30 years, 17 patients belonged to age group of 31-40 years, and there was only 1 patient between age group of 41-50 years. None of the patients were above the age of 50 years. Of 62 patients, 39 (62.9%) were male and 23(37.1%) were female. All the patients with SCD presented with fatigue and body ache, making them...
the most common presenting symptoms. 32 (51.61%), 33 (53.23%), and 26 (41.94%) out of 62 patients had fever, jaundice and abdominal pain, respectively. Pallor was present in 98.39% patients, and organomegaly was found (hepatomegaly and/or splenomegaly) in 64.52% of patients.

**Spleen and splenic complications**

It was found that 40 (64.52%) out of 62 patients had clinically palpable spleen. USG abnormalities were studied, and we found that 48 (77.4%) out of 62 had abnormal spleen (Figures 2-3). Normal-sized spleen was found in 14 (22.6%) patients. Two patients had asplenia, two had splenic infarcts with splenomegaly, and one was found to have gamma Gandy bodies with mild splenomegaly (Figures 4-5). In a study conducted to investigate the prevalence of gender-related splenomegaly, we found that 28 (45%) patients were male and 20 (32%) were female out of 62 study patients, implying that 45% of patients who had splenomegaly were male, so higher prevalence was observed in males. The graph below describes the number of patients with SCD with different grades of splenomegaly (Figure 1). The average spleen size was found to be 12.42±3.62 cm.

![Bar graph to show number of patients (X axis) having asplenia, normal size spleen, mild, moderate and massive splenomegaly on abdominal ultrasonography](image-url)

![Splenic Infarct](image-url)
Figure 3. Splenomegaly

Figure 4: Siderotic Nodules – Gamma Gandy Bodies

Figure 5: Splenomegaly with Gamma Gandy Bodies
Splenomegaly and Hb electrophoresis

The independent t-test was used for comparing mean Hb electrophoresis values in patients with splenomegaly and normal-sized spleen. Mann-Whitney test was used for significant difference between the two groups (abnormal and normal-sized spleen in SCD patients) in relation to median HbS, HbF, and HbA2 level. Forty-eight patients out of 62 had abnormal spleen, 46 patients had splenomegaly of different grades, and 2 had asplenia. The average HbF level in patients with splenomegaly was 14.90±5.08, HbS 71.51±6.93, and average HbA2 was found to be 2.63±0.93. Whereas, 14 out of 62 patients had normal-sized spleen and the average HbF level in these patients was 12.12±4.12, average HbS was 64.04±14.28, and average HbA2 was 2.69±0.37. Patients (n=2) with asplenia had HbS – 78.40/78.20, HbF – 16.60/14.60, HbA2 - 2.30/3, respectively. As shown below in Table 1, the mean HbF, HbS and HbA2 values were compared between patients with splenomegaly and with normal spleen. We observed that the average HbF values in patients who had splenomegaly were higher than those with normal spleen but was not found statistically significant (p-value: 0.067). Whereas, comparing HbS values between patients with splenomegaly and those with normal-sized spleen revealed that mean HbS values were higher in patients with splenomegaly with statistical significance (P-value :0.009).

Table 1: comparison between Hb Electrophoresis average values with patients with splenomegaly and normal spleen

<table>
<thead>
<tr>
<th>Hb Electrophoresis( Mean values)</th>
<th>Splenomegaly(N = 46)</th>
<th>Normal Spleen (N = 14)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbS</td>
<td>71.51±6.93</td>
<td>64.04±14.28</td>
<td>0.009</td>
</tr>
<tr>
<td>HbF</td>
<td>14.90±5.08</td>
<td>12.12±4.12</td>
<td>0.067</td>
</tr>
<tr>
<td>HbA2</td>
<td>2.63±0.93</td>
<td>2.69±0.37</td>
<td>0.8153</td>
</tr>
</tbody>
</table>

A non-parametric test (Mann Whitney test) was used to compare the two groups of patients with abnormal (including splenomegaly and asplenia) and normal-sized spleen. According to the results of this comparison, z-value and p-value for HbS, HbF, HbA2 were found to be 1.875 (p-value: 0.061), 2.567( p-value : 0.010) and 0.806( p value: 0.420) respectively, as shown below in the Table 2. Our value is 2.5 standard deviation below the mean value which is statistically significant.

Table 2: Showing results of Mann Whitney test for comparison between normal and abnormal spleen

<table>
<thead>
<tr>
<th>Spleen Size</th>
<th>N</th>
<th>Mean Rank</th>
<th>Sum of Ranks</th>
<th>z-value</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal Spleen</td>
<td>48</td>
<td>33.81</td>
<td>1623.00</td>
<td>-1.875</td>
<td>0.061</td>
</tr>
<tr>
<td>Normal Spleen</td>
<td>14</td>
<td>23.57</td>
<td>330.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>62</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal Spleen</td>
<td>48</td>
<td>34.66</td>
<td>1663.50</td>
<td>-2.567</td>
<td>0.010</td>
</tr>
<tr>
<td>Normal Spleen</td>
<td>14</td>
<td>20.68</td>
<td>289.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>62</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal Spleen</td>
<td>48</td>
<td>30.51</td>
<td>1464.50</td>
<td>-0.806</td>
<td>0.420</td>
</tr>
<tr>
<td>Normal Spleen</td>
<td>14</td>
<td>34.89</td>
<td>488.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>62</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The correlation coefficient between spleen size and HbS and HbF has been calculated using non-parametric correlation method. The correlation coefficient between HbF and spleen size is found to be 0.243, suggesting 24% (weak) correlation between them with p-value of 0.057, indicating a statistically significant result. The coefficient between HbS and spleen size was 0.587, suggesting 58.7%, good correlation between HbS and spleen size, with p-value of <0.001, indicating a statistically significant result. (Table 3)

<table>
<thead>
<tr>
<th></th>
<th>HbF</th>
<th>Spleen Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbS</td>
<td>Correlation Coefficient (P)</td>
<td>0.407 (0.001)</td>
</tr>
<tr>
<td>HbF</td>
<td>Correlation Coefficient (P)</td>
<td>0.243 (0.057)</td>
</tr>
</tbody>
</table>

As we can see in this spearman’s Rho correlation presented in the form of a scatter diagram – graph 1, it shows positive and good correlation with increasing spleen size and HbS value, whereas there is a positive but weaker correlation between spleen size and HbF. (Graph 2)
Anemia and other manifestations
It was found that all the patients had severe or moderate anemia, 40.32% patients had severe anemia and 59.67% had moderate anemia (Table 4). The mean Hb values were found to be 7.95±1.87, ranging from 3.40 gm% to 11 gm%, and mean reticulocyte count was found to be 1.51±0.55%. Blood indices were also studied, and the average level of hematocrit in SCD patients was 28.94±4.56. The average level of MCV was 73.07±6.80, MCH was 27.40±2.53, and RDW was 19.83±2.67. We found one patient who had aplastic crisis with corrected reticulocyte count of 0.26%, pancytopenia and moderate splenomegaly with splenic infarct.

<table>
<thead>
<tr>
<th>Severity of Anaemia</th>
<th>SCD</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe Anaemia</td>
<td>25</td>
<td>40.32%</td>
</tr>
<tr>
<td>Moderate Anaemia</td>
<td>37</td>
<td>59.67%</td>
</tr>
<tr>
<td>Mild Anaemia</td>
<td>0</td>
<td>0.00%</td>
</tr>
<tr>
<td>Normal</td>
<td>0</td>
<td>0.00%</td>
</tr>
<tr>
<td>Total</td>
<td>62</td>
<td>100.00%</td>
</tr>
</tbody>
</table>

The Table 5 below shows that 46 patients with sickle cell disease and splenomegaly had anemia, 14 patients with splenomegaly had infections (7 had Urinary tract infection, 4 had malaria, 3 had acute gastroenteritis), 32 patients were in sickle cell crisis, six patients had cholelithiasis, and six had hyperbilirubinemia.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SCD (N)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaemia</td>
<td>48</td>
<td>77.4%</td>
</tr>
<tr>
<td>Infections</td>
<td>14</td>
<td>22.5%</td>
</tr>
<tr>
<td>Crisis</td>
<td>32</td>
<td>51.6%</td>
</tr>
<tr>
<td>Gall Bladder complications</td>
<td>6</td>
<td>9.67%</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>6</td>
<td>9.67%</td>
</tr>
<tr>
<td>AKI</td>
<td>1</td>
<td>1.61%</td>
</tr>
</tbody>
</table>
DISCUSSION

The sickle-cell gene in India was first described 68 years ago among the tribal groups in South India. This disease gene has also been described from other parts, but it is prevalent mostly among tribal population of India\(^\text{23,24}\). The Sickle gene is also linked with G6PD deficiency in these tribal populations \(^\text{23}\). Sickle cell disease in India is considered different from other parts of the world and is an Arab-Indian haplotype, which has increased HbF levels and was less severe in the type\(^\text{23,25}\). Researchers have also identified other differences in the forms of frequent alpha-thalassemia, low MCV, lower HbA\(_2\) levels, prolonged survival time, and better splenic functions\(^\text{25,26,27}\).

One of the important aspects of the pathogenesis of this disease is its splenic manifestation\(^\text{11}\). The spleen is one the most common and early organs affected by sickle cell hemoglobinopathy. Hence, it is crucial to understand the various splenic manifestations, including splenomegaly, splenic infarct, sequestration syndrome and asplenia. Although studies from India described the difference between Indian sickle cell disease and spleen manifestations from patients elsewhere in the world, especially in the pediatric age group, this type of study in the adult population is lacking. As India has the largest tribal population globally, and the prevalence of sickle cell carriers varies from 1 to 40 percent in many SCD patients who survived into late adulthood, we attempted to conduct this study on our patients. It is essential to state that our institute provides services to the rural tribal population hailing from Gujarat and Madhya Pradesh\(^\text{23}\) and runs various health programs for sickle cell disorder patients. In addition, the screening of antenatal patients is a usual practice\(^\text{28}\). Like studies in other parts of the world which documented the absence of the spleen in children and adults, in this study, as one of the main objectives, we attempted to record the presence of spleen and splenomegaly. We had only two cases of asplenia, and two others had splenic infarct with splenomegaly.

Sickle cell disease has variability in presentation, comorbidities, HbF levels, risk factors and splenic function, and spleen size based on different geographical locations\(^\text{28,29}\). We selectively studied the patients with sickle cell disease (homozygous) and not those with sickle cell trait or sicklethalassemia disorders.

In our study, the clinically palpable spleen was recorded in Case record forms (CRF); however, clinical palpation of the spleen is considered less sensitive. The ultrasonographic finding of splenic size was determined in all patients. Of 62 patients with sickle cell disease (SS), the clinically palpable spleen was present in 64.52% of patients, and the prevalence of splenomegaly in adults with SCD was found to be 77.4%. Meanwhile, 32% were female and 45% were male. In a study conducted by Parmar D et al., 50 out of 95 cases (52.63%) diagnosed with sickle cell disease had splenomegaly\(^\text{30}\). Splenomegaly in adulthood can cause hypersplenism, and hematological parameters can improve after splenectomy\(^\text{31}\).

The splenic enlargement in adult patients is thought to be due to the persistence of fetal hemoglobin\(^\text{16,27}\). Although the exact mechanism of high HbF in the Indian population is still not understood, it has been well documented that HbF is a very powerful modulator of the clinical and the haematologic features of sickle cell anemia. It has been found that the Saudi-Indian and Senegal haplotypes of HBB-like gene cluster have exceptionally higher HbF levels, hence associated with milder disease and lesser episodes of crisis\(^\text{32}\). In our study, we found that there was a higher level of an average of HbF in patients with splenomegaly (~14.90±5.08) compared to those with a normal spleen (~12.12±4.12). Although the presence of splenomegaly was not significantly associated with higher levels of HbF, a positive but weaker correlation was found in our study. Despite higher HbS, splenic sequestration crisis, and infarcts in patients leading to autosplenectomy, we observed a higher prevalence of splenomegaly, implying the presence of some other protective factors. Probably higher HbF levels protect the spleen from undergoing infarction and have better spleen function. In the African population, various studies were in line with our findings. In a Nigerian study published in 2019, lower mean HbF values were found in children with autosplenectomy and mean HbF was higher (9.6%±5.9%), but no significant...
correlation between F levels and spleen size was found. Of 62 patients included in this study, 3.3% had asplenia, 3.3% had splenomegaly with infarct, and 6.7% had cholelithiasis. The gall bladder involvement was in the form of gallstones due to hemolysis. Similarly, higher bilirubin levels suggest an ongoing hemolytic process in our study groups. The mean total bilirubin was found to be 3.57±3.28 in our study. 77.4% of patients had anemia, and 22.5% of patients had infections. Four out of 62 patients had malaria. In a study conducted by Balci et al., abdominal ultrasonography revealed hepatomegaly, gallbladder disease, and renal parenchymal disease as common manifestations in patients with sickle cell. Splenomegaly was the most common finding in our study, though 6.7% of patients had gallstones. Another important finding was microcytic hypochromic anemia in our patients, which can be attributed to the high prevalence of iron deficiency anemia in this subset of the population. In a study conducted by Lakhani JD et al. on patients with sickle cell hemoglobinopathy (n=537) in our hospital, microcytic hypochromic anemia and calculated Mentzer and Srivastava’s index were found higher, indicating the prevalence of iron deficiency anemia in these patients as well. This finding can also be due to sickle-alpha thalassemia in these patients. This study revealed the persistence of spleen and high prevalence of splenomegaly in western India comprising tribal belt of Gujarat and Madhya Pradesh. The study included patients with concomitant malaria (n=4) and higher levels of fetal hemoglobin. The exact reason of splenomegaly remained unknown and requires further investigation. But this paper provides clear evidence of different natural courses of SCD in India.

LIMITATION
The study population included patients admitted to the hospital, producing a biased sample.

CONCLUSION
This study revealed the persistence of spleen and splenomegaly in adult patients, different courses of disease in the Indian population, and higher levels of HbF in the study groups.

CONFLICT OF INTEREST
The authors declare that there is no conflict of interest.

REFERENCES