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Original Research Article

Association of vaso-occlusive crisis frequency with hepatic fibrosis in patients with sickle cell disease: a hospital-based observational study

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ABSTRACT

Background: Sickle cell disease (SCD) is characterized by recurrent vaso-occlusive crises (VOC) and progressive multi-organ damage, including hepatic fibrosis. While iron overload is a known contributor to liver injury, the role of crisis frequency in hepatic fibrosis remains underexplored. This study aimed to evaluate the association between vaso-occlusive crisis frequency and hepatic fibrosis in patients with sickle cell disease.
Methods: This hospital-based cross-sectional observational study included 50 patients with confirmed sickle cell disease attending a tertiary care hospital in Dibrugarh, Assam. Liver stiffness measurement (LSM) was assessed using shear wave elastography as a surrogate marker of hepatic fibrosis. Crisis frequency, transfusion history, and iron profile parameters were recorded. The association between crisis frequency and liver stiffness was analysed using one-way analysis of variance (ANOVA).
Results: The mean LSM was 6.62±1.35 kPa. Fibrosis staging revealed 22% of patients in F0-F1, 62% in F2, and 16% in F3. Patients with higher crisis frequency had significantly increased liver stiffness compared to those with fewer crises (p=0.004). A statistically significant positive association was observed between crisis frequency and hepatic fibrosis.
Conclusions: Increased vaso-occlusive crisis frequency is associated with higher liver stiffness and may serve as a clinical predictor of hepatic fibrosis in SCD. Early identification of high-risk patients may facilitate timely monitoring and intervention.

Keywords: Hepatic fibrosis, Shear wave elastography, Sickle cell disease, Vaso-occlusive crisis

INTRODUCTION

Sickle cell disease (SCD) is an inherited hemoglobinopathy characterized by chronic hemolysis, recurrent vaso-occlusive crises (VOC), and progressive organ damage. With improved survival, chronic complications such as hepatic involvement have emerged as significant contributors to morbidity.[1,2]

Hepatic involvement in sickle cell disease is multifactorial, resulting from the combined effects of recurrent vaso-occlusive episodes, chronic hemolysis, and transfusion-related iron overload. Repeated vaso-occlusive crises lead to obstruction of the hepatic sinusoids, causing localized ischaemia and subsequent ischaemia-reperfusion injury. This process promotes oxidative stress, endothelial dysfunction, and inflammatory activation, ultimately resulting in hepatocellular damage and progressive fibrosis.[3]

In addition to ischaemic injury, iron overload plays a significant role in hepatic damage in patients receiving repeated blood transfusions. Excess iron accumulates in hepatocytes and Kupffer cells, generating reactive oxygen species and triggering lipid peroxidation and fibrogenic pathways. Over time, this leads to activation of hepatic

stellate cells and deposition of extracellular matrix, contributing to liver fibrosis.[4]

While iron overload has been extensively studied as a determinant of hepatic fibrosis, the independent contribution of vaso-occlusive crisis frequency remains less clearly defined.[5] Given that recurrent crises represent repeated episodes of microvascular injury, it is plausible that higher crisis frequency may accelerate hepatic fibrosis even in the absence of severe iron overload.[6]

Therefore, evaluating the relationship between vaso-occlusive crisis frequency and hepatic fibrosis is essential to better understand disease progression and identify simple clinical predictors for early detection of liver involvement in patients with sickle cell disease. The aim of this study was to determine the association between vaso-occlusive crisis frequency and hepatic fibrosis, using liver stiffness measurement (LSM) as a non-invasive surrogate marker.

METHODS

This was a hospital-based cross-sectional observational study conducted at Assam Medical College and Hospital, Dibrugarh over a period of one year (October 2024 to September 2025). A total of 50 patients with confirmed sickle cell disease were enrolled.

The study was approved by the Institutional Ethics Committee (IEC), Assam Medical College and Hospital, Dibrugarh (Ref. No.:AMC/EC/2026/98). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrolment. For participants below 18 years of age, assent from the participant along with written informed consent from the parent or legal guardian was obtained.

The sample size was calculated using the formula for estimating a population proportion: $n=Z^2 \times P(1-P)/d^2$, where n is the required sample size, Z is the Z-statistic for a 95% confidence level (Z=1.96), P is the expected prevalence of the outcome of interest based on prior literature, and d is the allowable margin of error (precision), taken as 0.05.[7] Using an estimated prevalence of significant liver stiffness in sickle cell disease of approximately 13.6% from prior studies and accounting for a non-response rate of approximately 10%, a final sample of 50 patients was enrolled.[8]

Patients were included if they had a confirmed diagnosis of sickle cell disease based on haemoglobin electrophoresis or high-performance liquid chromatography (HPLC), were aged more than 13 years, were attending the outpatient or inpatient Departments of General Medicine, and were willing to provide informed consent to participate in the study. Patients were excluded if they had a known diagnosis of cirrhosis, hepatocellular carcinoma, or decompensated liver failure. Those with significant comorbidities affecting liver function or iron metabolism, including chronic hepatitis B or C infection, significant alcohol use disorder, or metabolic dysfunction-associated steatotic liver disease, were also excluded. Pregnant or lactating females were excluded due to potential confounding effects on liver stiffness and serum ferritin levels. Patients unable to undergo shear wave elastography due to technical limitations such as a body mass index greater than 40, ascites, or other conditions precluding reliable measurements, and those unwilling to give consent, were similarly excluded.

Vaso-occlusive crisis (VOC) frequency was determined from patient interviews and hospital records. A vaso-occlusive crisis was defined as an episode of acute pain requiring medical attention consistent with sickle cell-related pain crisis. The number of episodes over the preceding 12 months was recorded and used to categorize patients for analysis. Liver stiffness measurement (LSM) was performed using shear wave elastography by an experienced radiologist. Patients fasted overnight and were examined in the supine position; a region of interest was placed in the right hepatic lobe (three to five cm below the capsule). The median of multiple readings was recorded in kilopascals (kPa) and used to categorize fibrosis stage (F0-F4) using standard cut-offs.

Statistical analysis was carried out using the Statistical Package for Social Sciences (SPSS) for Windows, version 20.0 (SPSS Inc., Chicago, USA) along with Microsoft Excel 2010. Continuous variables were summarized as mean with standard deviation (mean±SD), whereas categorical variables were described in terms of frequency and percentage. Group comparisons of continuous variables across three or more independent categories were performed using one-way analysis of variance (ANOVA). A p value of less than 0.05 was considered to indicate statistical significance.

RESULTS

A total of 50 patients with confirmed sickle cell disease were included in this study.

Age distribution

Patients ranged from childhood to middle age, with a strong predominance in the ≤20 years group (40; 80%). Smaller proportions were seen in the 20-29 years (six; 12%), 30-39 years (three; 6%), and 40-49 years (one; 2%) age groups, with no patients aged ≥50 years. The mean age was 18.20±6.24 years (Figure 1).

Gender distribution

In the present study, out of a total of 50 patients, 27 patients (54.0%) were male and 23 patients (46.0%) were female. The male-to-female ratio was 1.17:1, indicating a slight male predominance in the study population (Figure 2).

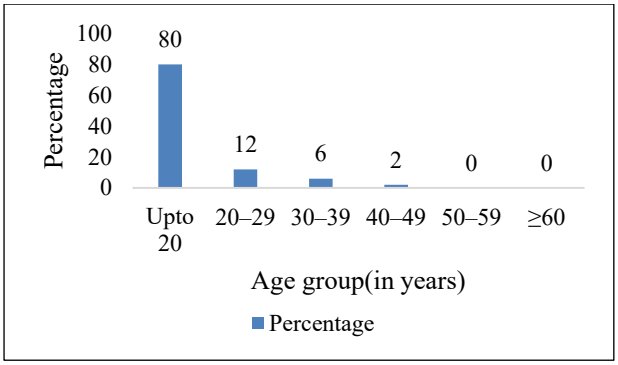

Figure 1: Age distribution of study participants.

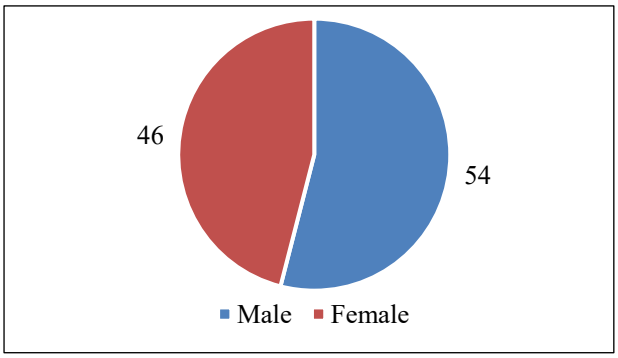

Figure 2: Gender distribution of study participants.

Distribution based on sickle cell genotype

Out of the total 50 patients, the most common genotype was HbSS, seen in 18 patients (36%), making it the predominant genotype in the study population. This was followed by HbS/HbE, present in 12 patients (24%), and HbAS, found in 11 patients (22%). The least common genotype was HbS/β-thalassemia, observed in nine patients (18%) (Figure 3).

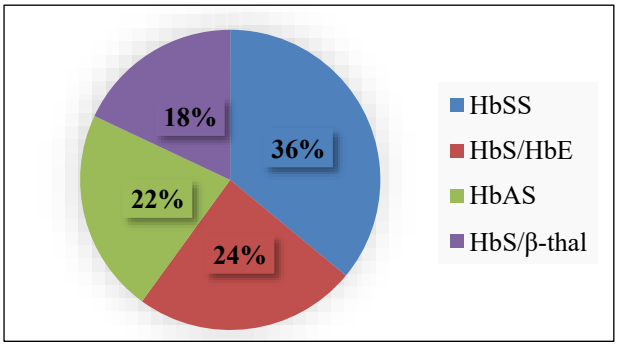

Figure 3: Distribution of patients by sickle cell genotype.

Distribution of patients based on transfusion history

Regarding blood transfusion history, the majority of the patients had received blood transfusions, accounting for 46 patients (92.0%), while four patients (8.0%) had no history of blood transfusion (Figure 4).

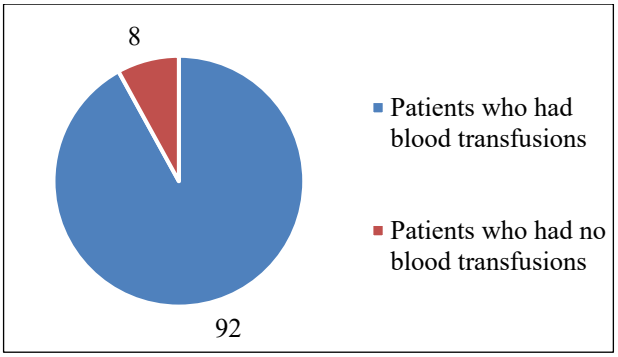

Figure 4: Distribution of patients based on transfusion history.

Distribution of patients according to number of blood transfusions per year

With respect to the number of blood transfusions per year, 26 patients (52.0%) received fewer than five transfusions, 18 patients (36.0%) received five to ten transfusions, and six patients (12.0%) received more than ten transfusions per year (Figure 5).

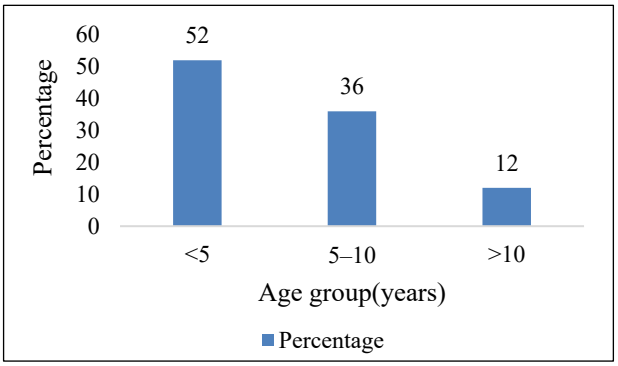

Figure 5: Distribution of patients by number of blood transfusions per year.

Distribution of patients according to fibrosis grading based on liver stiffness measurement

Fibrosis grading based on liver stiffness measurement (LSM) revealed that 11 patients (22.0%) were in the F0-F1 stage, 31 patients (62.0%) were in the F2 stage, and eight patients (16.0%) were in the F3 stage. No patients were observed in the F4 stage. The mean LSM of the study population was 6.62±1.35 kPa (Figure 6).

Vaso-occlusive crisis frequency distribution

Among the study participants, 72% (n=36) had no vaso-occlusive crises, 18% (n=9) experienced one crisis per year, and 10% (n=5) had two crises per year, while none reported more than two crises annually. Overall, the majority of patients had absent or low crisis frequency (Figure 7).

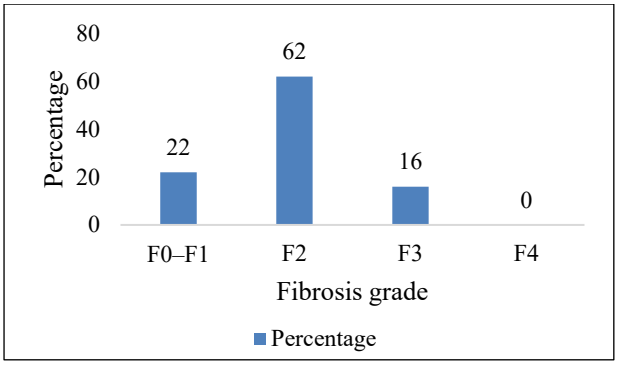

Figure 6: Distribution of patients by hepatic fibrosis stage based on liver stiffness measurement.

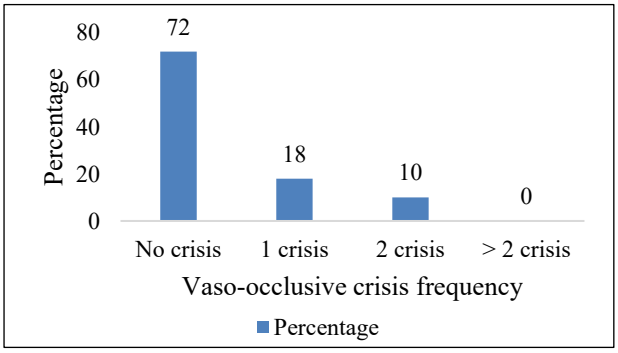

Figure 7: Distribution of patients by vaso-occlusive crisis frequency.

Association of liver stiffness with crisis frequency

In this study, it was found that patients with no crisis episodes (n=36) had a mean LSM of 6.27±1.08 kPa, while those with one crisis episode (n=9) had a mean LSM of 7.23±1.82 kPa. Patients with two crisis episodes (n=5) demonstrated a mean LSM of 8.08±0.91 kPa. The overall mean LSM of the study population was 6.62±1.35 kPa. The difference in LSM across the crisis groups was found to be statistically significant (p=0.004, one-way ANOVA) (Table 1).

Table 1: Association of liver stiffness with vaso-occlusive crisis frequency.

Crisis frequency (episodes/year)	Number	Mean LSM (kPa)	Standard deviation (±SD)
0	36	6.27	1.08
1	9	7.23	1.82
2	5	8.08	0.91
Total	50	6.62	1.35

*p value = 0.004 (one-way ANOVA); statistically significant at p<0.05

DISCUSSION

The present study evaluated the association between vaso-occlusive crisis (VOC) frequency and hepatic fibrosis in patients with sickle cell disease (SCD), using liver stiffness measurement (LSM) as a non-invasive surrogate marker.

The study population was predominantly young, with most patients belonging to the ≤20 years age group, reflecting the natural history of SCD where chronic complications are increasingly recognised in adolescents and young adults.[9] A slight male predominance was observed. The majority of patients had a history of blood transfusion, and repeated transfusions are a recognised contributor to iron accumulation and hepatic fibrosis in SCD.

In the present study, a significant proportion of patients demonstrated hepatic fibrosis, with the majority in the F2 stage. This suggests that moderate fibrosis develops early and remains clinically silent for a prolonged period. These findings are consistent with the pathophysiological mechanisms described in SCD, where chronic haemolysis, sinusoidal obstruction, and repeated ischaemia-reperfusion injury lead to progressive hepatic damage.[10,11] The absence of advanced fibrosis (F4) may be attributed to the younger age group and exclusion of patients with overt liver disease. Shear wave elastography served as a practical and reproducible non-invasive tool for LSM, particularly relevant in resource-limited settings where MRI-based liver iron quantification is unavailable.

A key finding of this study was the significant association between VOC frequency and liver stiffness. Patients with increasing crisis frequency showed progressively higher LSM values, and this association was statistically significant (p=0.004). This observation can be explained by the underlying pathophysiology of SCD. Recurrent vaso-occlusive episodes result in sinusoidal blockage within the liver, leading to ischaemia reperfusion injury, oxidative stress, and inflammatory activation. Over time, these repeated insults stimulate hepatic stellate cells and promote fibrogenesis.[12] Thus, VOC frequency may serve not only as a marker of disease severity but also as an independent contributor to hepatic fibrosis.

This study has several limitations. It was conducted at a single centre, which limits the generalizability of findings. The cross-sectional design precluded assessment of longitudinal changes in liver stiffness. Clinical outcomes such as complications and mortality were not captured. Confounding factors including hydration status, comorbidities, and concurrent therapy were not adjusted for. Furthermore, iron profile parameters and confirmatory investigations were not systematically performed, limiting mechanistic interpretation.

CONCLUSION

This study demonstrates a significant association between vaso-occlusive crisis frequency and hepatic fibrosis in patients with sickle cell disease. Patients with higher crisis frequency showed greater liver stiffness, suggesting that recurrent vaso-occlusive episodes contribute to

progressive hepatic injury. Vaso-occlusive crisis frequency may serve as a simple and clinically useful marker for identifying patients at higher risk of hepatic fibrosis, enabling early monitoring and intervention. Future multicenter, prospective studies with outcome correlation are warranted to validate these findings.

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