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ORIGINAL PAPER

Haemoglobinopathies

Burden of vaso-occlusive crisis, its management and impact on quality of life of Indian sickle cell disease patients

Tulika Seth[1] | Shashank Udupi[2] | Suman Jain[3] | Seema Bhatwadekar[4] | Nandakumar Menon[5] | Rabindra Kumar Jena[6] | Ravindra Kumar[7] | Shomik Ray[8] | Bharat Parmar[9] | Anil Kumar Goel[10] | Ashvin Vasava[11] | Anupam Dutta[12] | Priyanka Samal[13] | Riya Ballikar[14] | Deepa Bhat[15] | Tuphan Kanti Dolai[16] | Jina Bhattacharyya[17] | Disha Shetty[2] | Manish Mistry[2] | Dipty Jain[18]

Correspondence
Dipty Jain, Arihant Multispecialty Hospital, Nagpur, Maharashtra 440026, India.
Email: diptyjain57@gmail.com

Funding information
Novartis Healthcare Private Limited

Summary
Sickle cell disease (SCD) with vaso-occlusive pain crisis (VOC) significantly impacts patient well-being and often results in extensive healthcare resource utilization. This study assessed the VOC burden, its management and its impact on patients' quality of life (QoL). A cross-sectional observational study was conducted between November 2021 and June 2022, including 1000 SCD patients from high-prevalence states in India. Data on demographics, clinical characteristics, VOC severity, management and QoL were collected. The study revealed that 33.5% of patients reported at least one VOC episode during the study period. In the year prior to their enrolment, 836 (83.60%) patients reported at least one VOC episode, with an equal proportion of 407/487 (83.6%) adults and 429/513 (83.6%) paediatric patients, reducing their QoL across all domains compared to patients without VOC. Of these, 469/1000 patients (46.9%) experienced ≥3 VOC episodes. Additionally, 764/1000 (76.40%) patients managed their VOCs at healthcare facilities, with 501/1000 (50.1%) requiring inpatient admissions. Further, 71.80% of patients received Hydroxyurea (HU) therapy. The study depicts the severity of the Arab–Indian haplotype in Indian SCD patients visiting healthcare settings based on high VOC burden. This highlights the urgent need for better management strategies and resource allocation for these patients.

KEYWORDS
healthcare utilization, quality of life, sickle cell disease, vaso-occlusive crisis

INTRODUCTION

Sickle cell disease (SCD), characterized by beta-globin chain point mutation,[1] has seen 41.40% increase in global prevalence, from 5.46 million to 7.74 million between 2000 and 2021.[2] India's contribution to global SCD burden is 16%,[3] primarily driven by central belt (Gujarat to Odisha) and pockets in Assam, West Bengal, Tamil Nadu, Kerala and Karnataka.[4] The Indian SCD phenotype, characterized by Arab–Indian haplotype, is believed to be milder than in the African population.[5,6] However, a central Indian study showed high complication rates and mortality in newborns,[7] indicating clinical and geographical variations in Indian phenotype, necessitating further investigation.

For affiliations refer to page 307.

Vaso-occlusive pain crisis (VOC) is a hallmark manifestation of SCD,[8] with limited nationwide epidemiological studies. Understanding its burden is vital due to its impact on mortality, complications, quality of life (QoL) and healthcare resource utilization. Single-centre studies in India have reported 30–80% VOC frequency and hospitalization rates of 35–70%.[7,9–14] Hydroxyurea (HU) is the standard of care and primary disease-modifying therapy for SCD and VOC.[15–17] However, the impact of VOC on QoL, its economic burden, its overall management pattern and challenges in Indian SCD patients remain unexplored.

Available studies from India are inadequate for accurately reflecting the epidemiology of VOC in various healthcare settings and different access to resources. Also, they employed varied methodologies and sampling designs. It is challenging to estimate the VOC burden and its impact at the national level. A multicentre, nationwide study (B-VOCAL SCD) was planned as an initial study to bring various regional centres together and collect data. The B-VOCAL study primarily aimed to estimate the VOC prevalence among SCD patients visiting healthcare facilities. Secondarily, the study included the assessment of the burden of complicated and uncomplicated VOCs determined by organ involvement; frequency of severe VOCs assessed by specific tools; burden of home- and healthcare-managed VOCs in the year prior to enrolment; pattern of HU use and SCD management; impact of VOC on QoL, estimate its economic burden and enhance clinical care and healthcare resource allocation among SCD patients visiting healthcare facilities. The current article focuses on the assessment of VOC burden, management and pattern of HU use and impact of VOCs on QoL of Indian SCD patients.

METHODS

Study design

This multicentric, cross-sectional observational study conducted in India was registered in the Clinical Trials Registry of India (https://ctri.nic.in/Clinicaltrials/login.php; #CTRI/2021/10/037430). To address generalizability, a consecutive sampling strategy for patient recruitment and purposive sampling for centre selection were employed (Figure S1). Based on the geographical disease burden, purposive sampling was used to select 14 centres from SCD-prevalent Indian states and Union Territories (Figure S2).

The feasibility of the study assessed, overall SCD care and burden at centres in India, which revealed limited centres with dedicated SCD clinics. SCD patients are treated along with patients with other disease conditions in various healthcare settings, including government tertiary hospitals ($n = 6$), private tertiary hospitals ($n = 4$), Non-Governmental Organization-operated hospitals ($n = 2$), healthcare setups (HCS) funded by the government ($n = 1$), and HCS subsidized by the government ($n = 1$). Based on feasibility parameters and ethics committee timelines, we chose consecutive sampling to enroll 1000 patients and obtained consent quickly.

The study design was adopted to include all healthcare visits by SCD patients from the first patient's index visit to 1000th patient's index visit, from November 24th, 2021, to June 28th, 2022 (7-month – study period). The cross-sectional study design was consciously chosen, to capture a 'snapshot' of all the VOC episodes in the 14 healthcare facilities in the defined study period. At index visits, the data of all study variables were captured, and at subsequent visits, the available hospitalization- and VOC-related data were captured (Figure 1).

Additionally, we retrospectively collected data on the VOC burden from the year prior to each patient's enrolment which allowed us to include historical data on healthcare resource utilization and home management of VOC in a defined time period for all the patients. This strategy ensured a comprehensive view of VOC occurrences within the study cohort. The study was conducted in accordance with the ethical principles of Declaration of Helsinki[18] and International Council for Harmonization Good Clinical Practice guidelines.[19]

Participants

Adult and paediatric patients with an established SCD diagnosis at least 12 months before the index visit of the patient with any genotype ($N = 1000$) at various healthcare centres in high SCD-prevalent states across India were included. Patients receiving crizanlizumab or any other investigational product for managing VOC during the previous 12 months from the day of study enrolment were excluded. Written informed consent was obtained from all study participants.

Objectives and endpoints

We evaluated two primary endpoints in the study period: the proportion of SCD patients with at least one VOC episode out of the total study sample and the total number of VOC episodes leading to healthcare visits, to the total number of healthcare visits by all the patients. The secondary endpoints include the severity of VOCs (using the Numeric Pain Rating Scale for individuals ≥7 years of age and the Faces Pain Scale for children aged 3–7 years) and the proportion of patients with complicated and uncomplicated VOCs. The study also evaluated the proportion of patients with at least one VOC episode and the total number of VOCs leading to healthcare visits (healthcare utilization) and managed at home in the year prior to enrolment. Other secondary endpoints included the treatment strategies of VOCs and SCD including the pattern of HU use. This study also evaluates the impact of VOC and SCD on quality of life.

Data collection and study assessment

The study used primary data and reinforced secondary data from patient records as the predominant methodology for data collection. A structured electronic case record form was

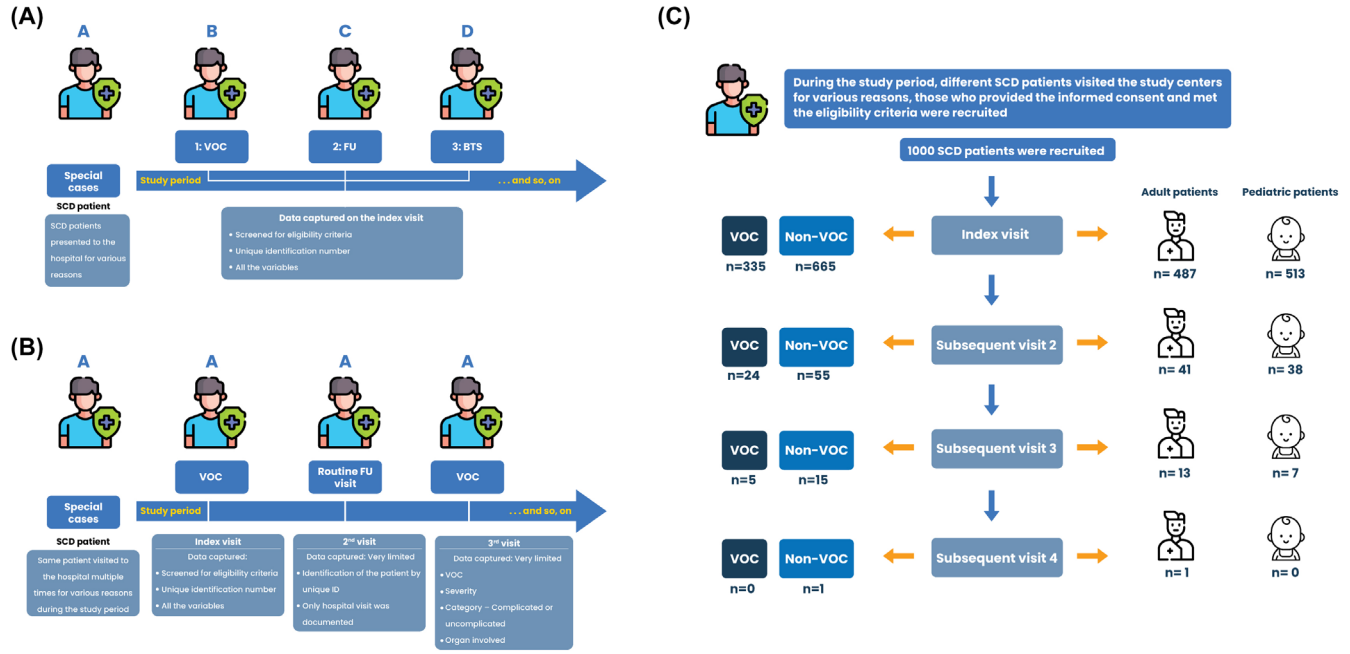

FIGURE 1 Patient recruitment strategy. (A) Shows one out of three patients with VOC. During the study period, different SCD patients 1 (A), 2 (B), and 3 (C) up to 1000 visited the hospital for various reasons like VOC, routine follow-up and blood transfusion. All the patients visiting the hospital who provided the informed consent were screened for eligibility criteria and assigned a unique identification number. All variables pertaining to the study were captured on the first (index) visit. (B) Shows one patient with VOC at the index visit* who experienced another VOC at the third hospital visit. During the study period between the index visit of the 1st patient and the index visit of the 1000th patient, the same patient (e.g. patient A in the figure) might have visited the hospital multiple times for various reasons (i.e. VOC, follow-up, blood transfusion). For such patients, on the index visit, a unique identification number was assigned post-screening for eligibility, and all the variables pertaining to the study were captured. During the patient's subsequent visits to the hospital, limited data pertaining to the reason for a hospital visit, such as VOC, its severity, category (complicated/uncomplicated) and organ involved, were documented during the study period. (C) Flow diagram for the disposition of 1000 patients with SCD for the study period between the 1st patient's index visit: Nov 24, 2021, and the 1000th patient index visit: June 28, 2022.*Index Visit: The patient's visit to the study site where the patient provides informed consent and all the data about the study are captured for the first time.

used for data collection for study variables. Validated questionnaires were used to assess pain severity (numerical pain rating scale for all patients aged >7 years and FACES pain scale for patients aged 3–7 years with pain scores of 0–10[20]) and QoL domains (ASCQ-Me questionnaire for adult patients,[21] SCD-specific QoL questionnaire developed by Patel and Pathan for paediatric patients[22] and EQ-5D-5L questionnaire[23,24]). Also, VOC-associated pain in SCD patients was classified into two categories: complicated, if it involved organ damage, and uncomplicated if it occurred without organ involvement and was not attributed to any other medical condition.

Statistical analysis

This was a descriptive study, with the primary endpoint being the proportion of SCD patients with at least one VOC. The data were screened for normality of distribution using the Shapiro–Wilk test.[25] Normally distributed variables were summarized using mean ± standard deviation (SD), non-normally distributed variables were presented as median (IQR) and categorical variables were presented as frequency (%). The comparison of subgroups among adult and paediatric SCD patients with and without VOCs used inferential statistics at a 5% significance level. All data analyses were performed using RStudio Version 1.4.1106 (USA).

RESULTS

Demographics and clinical characteristics

The study included 1000 SCD patients, with 487 (48.70%) adults (≥18 years), and 513 (51.30%) paediatric patients (2–17 years). The demographic and clinical characteristics, laboratory investigations and organ complications among the study population are detailed in Table 1 and Tables S1 and S2.

Prevalence and severity of VOC among SCD patients

During the study period (November 2021–June 2022), 335/1000 (33.50%) patients reported at least one episode of VOC which comprised the primary endpoint of this study. Additionally, 364 out of 1100 healthcare visits (33.09%) by the patients were due to VOCs, which was the co-primary endpoint of this study. At index visits, 297/1000 (29.7%)

TABLE 1 Demographic and clinical characteristics of patients with SCD.

	Overall $N = 1000$	Adult patients $n = 487$	Paediatric patients $n = 513$
Age (years, median [IQR])	17 (17)	27 (14)	10 (6)
Age-wise categorization[a]; *n* (%)			
Early childhood and preschoolers (2–5 years)	80 (8)	-	-
School-age children (6–11 years)	218 (21.8)	-	-
Adolescents (12–17 years)	215 (21.5)	-	-
Young-age adults (18–30 years)	292 (29.2)	-	-
Middle-aged adults (31–45 years)	145 (14.5)	-	-
Old-age adults (46–64 years)	48 (4.8)	-	-
Elderly (≥65 years)	2 (0.2)	-	-
Gender; *n* (%)			
Male	567 (56.7)	251 (51.54)	316 (61.6)
Female	433 (43.3)	236 (48.46)	197 (38.4)
Body weight; kg			
Median (IQR)	39.95 (27)	50 (11.1)	24 (14.2)
Domicile; *n* (%)			
Rural	680 (68)	322 (66.12)	358 (69.79)
Urban	260 (26)	134 (27.52)	126 (24.56)
Suburban	60 (6)	31 (6.37)	29 (5.65)
Annual household income; INR[b]			
Mean ± SD	186 915.92 ± 213 532.41	160 229.92 ± 121 993.54	200 481.64 ± 246 391.42
Median (IQR)	135 500 (110 000)	120 000 (11 600)	144 000 (110 000)
Mode of payment; *n* (%)			
Insurance	310 (31)	64 (19.1)	246 (36.99)
Self-pay	424 (42.40)	126 (37.61)	298 (44.81)
BPL (availing free/subsidized healthcare services under Rashtriya Swasthya Bima Yojana)	266 (26.60)	145 (43.28)	121 (18.20)
Type of healthcare facility; *n* (%)			
Government tertiary	362 (36.20)	175 (35.93)	187 (36.45)
Private tertiary	223 (22.30)	161 (33.06)	62 (12.09)
NGO operated	153 (15.30)	71 (14.58)	82 (15.98)
Healthcare facilities funded by the government	115 (11.50)	26 (5.34)	89 (17.35)
Healthcare facilities subsidized by the government	147 (14.7)	54 (11.09)	93 (18.13)
Type of visit to healthcare setting; *n* (%)			
OPD	805 (80.50)	403 (82.75)	402 (78.36)
IPD	181 (18.10)	77 (15.81)	104 (20.27)
ED	14 (1.40)	7 (1.44)	7 (1.36)
Genotype documented in total SCD patients; *n* (%)	854 (85.40)	397 (81.52)	457 (89.08)
Genotypes			
HbSS	767 (89.81)	352 (88.66)	415 (90.81)
HbS ß-thalassemia	76 (8.90)	42 (10.58)	34 (7.44)
HbSC	3 (0.35)	1 (0.25)	2 (0.44)
Other genotypes[c]	8 (0.94)	2 (0.50)	6 (1.31)
Age at the time of SCD diagnosis			
Median (IQR)	5 (10)	11 (15)	3 (4.92)
Age range; *n* (%)			
<1 year	106 (10.60)	17 (3.49)	89 (17.35)
1–2 years	188 (18.80)	54 (11.09)	134 (26.12)
3–5 years	218 (21.80)	75 (15.40)	143 (27.88)
6–10 years	212 (21.20)	95 (19.51)	117 (22.81)
>10 years	276 (27.60)	246 (50.51)	30 (5.85)

(Continues)

TABLE 1 (Continued)

	Overall $N=1000$	Adult patients $n=487$	Paediatric patients $n=513$
Duration of disease, median (IQR)	8 (12)	16 (14.1)	5 (6.4)
Disease duration, range, *n* (%)			
<1 year	0 (0)	0 (0)	0 (0)
1–2 years	167 (16.70)	35 (7.19)	132 (25.73)
3–5 years	200 (20)	51 (10.47)	149 (29.04)
6–10 years	240 (24)	85 (17.45)	155 (30.21)
>10 years	393 (39.30)	316 (64.89)	77 (15.01)
Patients family members affected with SCD; *n* (%)	359 (35.90)	171 (35.11)	188 (36.65)

Abbreviations: BPL, below poverty line; ED, emergency department; Hb, haemoglobin; HbA, haemoglobin A; HbA2, haemoglobin A2, HbF, foetal haemoglobin; HbS, sickle haemoglobin; HPLC, high-performance liquid chromatography; IQR, interquartile range; INR, Indian Rupee; IPD, inpatient department; IQR, interquartile range; NGO, non-governmental organization; OPD, outpatient department; SCD, sickle cell disease; SD, standard deviation; VOC, vaso-occlusive crisis.

[a]Age-wise categorization was done based on data from UNICEF India, WHO India, and the International Institute for Population Sciences (IIPS). (-), NA (not applicable).

[b]1 USD conversion taken as INR 83.26 [as of November 2, 2023].

[c]HbSD, Compound Heterozygous sickle cell (Punjab) phenotype, Hb sickle delta thalassemia.

patients experienced uncomplicated VOCs. Out of these, acute pain was reported in 249/297 (83.84%) patients, and acute chronic pain was reported in 48/297 (16.2%) patients (Table 2).

Among 487 adult patients, 158 (32.44%) reported at least one VOC episode resulting in a healthcare visit with a median pain score of 7 (IQR: 3), while 133/158 (84.17%) reported moderate to severe VOC episodes. Among 513 paediatric patients, 173 (33.72%) reported VOCs, resulting in healthcare visits. The intensity of pain due to VOC in adults and paediatric patients is summarized in Table 3.

Healthcare resource utilization and home-managed VOCs

In the year prior to enrolment, of all SCD patients ($N=1000$), 836 (83.60%) reported 5428 VOCs, including those managed at home and those managed at a healthcare facility; 633/1000 (63.3%) patients had ≥3 VOCs. In the same time period, 764/1000 (76.40%) patients required 3480 healthcare visits due to VOCs out of a total of 5752 healthcare visits (60.5%). Patients with ≥3 and >5 VOCs that required healthcare visits were 46.9% (469/1000) and 22.5% (225/1000), respectively. Additionally, 501/1000 (50.10%) patients were admitted to the inpatient department for 5610 inpatient admission days, with a median (IQR) of 8 days (IQR: 11). The details of the healthcare resource utilization in adult and paediatric cohorts are highlighted in Table 4 and Table S9. In the same time period, 512/1000 (51.20%) of patients surveyed managed 1948 VOCs at home, with 228/1000 (22.8%) experiencing ≥3 VOCs (Table S3). Among 512 SCD patients, 83.20% cited less severe pain and 15.43% cited transportation challenges due to distance from healthcare centres as the primary reasons for managing VOCs at home. Detailed strategies and reasons for home management of VOCs across adult and paediatric cohorts are summarized in Table S4. Regional distribution of VOCs for the past year in SCD patients is depicted in Figure 2A.

TABLE 2 Prevalence of complicated and uncomplicated vaso-occlusive crises.

Complicated and uncomplicated VOCs with clinical manifestations	Overall ($N=1000$) *n* (%)	Adult ($N=487$) *n* (%)	Paediatric ($N=513$) *n* (%)
Total	335 (33.5)	158 (32.4)	177 (34.5)
Patients with uncomplicated VOC; *n* (%)	297 (29.7)	139 (28.5)	158 (30.8)
Acute pain	249 (83.8)	111 (79.9)	138 (87.3)
Acute on chronic pain	48 (16.2)	28 (20.1)	20 (12.7)
Patients with complicated VOC; *n* (%)	38 (3.8)	19 (3.9)	19 (3.7)
Acute chest syndrome	23 (60.5)	14 (73.7)	9 (47.4)
Hepatic sequestration	10 (26.3)	2 (10.5)	8 (42.1)
Splenic sequestration	4 (10.5)	2 (10.5)	2 (10.5)
Ischemic stroke/ transient ischemic attack	1 (2.6)	1 (5.3)	0 (0)

Note: Acute pain is a new severe pain with sudden onset; Acute on chronic pain is a sudden severe pain added to existing chronic pain.

Pattern of HU use and VOCs

Of 1000 patients, 718 (71.80%) were using HU therapy at various doses for a median duration of 36 (Range: 12.58–72 months, IQR: 59.42) months. However, the median current dose of HU at 14.70 mg/kg/day (Range: 10.14–19.25, IQR: 9.1) was given for a median duration of 15.50 (Range: 6–48 months, IQR: 42) months. Of 718 patients on HU treatment, 545 (75.91%) reported at least one VOC episode, and 321 (44.71%) reported ≥3 VOC episodes (Figure 2B, Table 5).

In this study 11.70% received opiates and 29.10% received NSAIDs to manage SCD and VOC episodes. Depending on

TABLE 3 Severity of vaso-occlusive crisis based on pain scores.

	Adult patients[a] *n* (%)	Paediatric patients (aged 8–18 years)[a] *n* (%)	Paediatric patients (aged 3–7 years)[b] *n* (%)
Total number of patients; *n* (%)	158 (32.44)	127 (73.41)	46 (26.59)
Pain score; median (IQR)	7 (3)	5 (5)	4 (4)
Severity of VOCs, *n* (%)			
Mild	25 (15.82)	50 (39.37)	20 (43.48)
Moderate	49 (31.01)	34 (26.77)	20 (43.48)
Severe	84 (53.16)	43 (33.86)	6 (13.04)

Abbreviations: IQR, interquartile range; VOC, vaso-occlusive crisis.

[a]Numerical Pain Rating Scale (NPRS) was used for adults and paediatric patients from 8 to 18 years of age.

[b]FACES pain scale was used for paediatric patients between 3 and 7 years of age.

TABLE 4 Burden of VOCs in the year prior to enrolment.

Categories	Home and healthcare facility-managed VOCs	VOCs managed at home	VOCs managed at healthcare facilities
Overall (*N* = 1000)			
Patients reported at least one VOC, *n* (%)	836 (83.60)	512 (51.2)	764 (76.4)
Occurrence of 1 VOC, Rates /100 PY	83.6	51.2	76.4
Total VOCs resulting in 1000 patients per year	5428	1948	3480
Mean ± SD of patients who reported VOCs	6.49 ± 5.85	3.80 ± 4.43	4.55 ± 3.81
Median (IQR) of patients who reported VOCs	5 (6)	2 (3)	3 (4)
Number of VOC episodes	**Patients managed VOCs at home and healthcare facilities**	**Patients managed VOCs at home**	**Patients managed VOCs at healthcare facilities**
1–2 VOCs, *n* (%)	203 (24.28)	284 (55.47)	295 (38.61)
1–2 VOCs/100 PY	20.3	28.4	29.5
3–5, *n* (%)	265 (31.70)	147 (28.71)	244 (31.94)
3–5/100 PY	26.5	14.7	24.4
>5, *n* (%)	368 (44.02)	81 (15.82)	225 (29.45)
>5/100 PY	36.8	8.1	22.5

Abbreviation: PY, person years.

haemoglobin levels, 31.99% of patients received simple blood transfusions to manage SCD and VOCs. Details of the pattern of HU use and other management measures are shown in Table 4 and Tables S5–S7.

Impact of VOC on QoL of adult and paediatric SCD patients

EQ-5D-5L: Of 1000 patients, 286 (28.60%) reported problems with mobility, 262 (26.20%) in self-care, and 306 (30.60%) in performing usual daily activities. Additionally, 422 (42.20%) and 279 (27.90%) patients experienced pain and anxiety/depression, respectively. On average, patients reported an overall health utility score of 0.893 ± 0.182, while adults and paediatric patients reported 0.879 ± 0.196 and 0.906 ± 0.166, respectively (Table S8). In the year prior to enrolment, SCD patients with VOCs (*n* = 764) showed lower mean health utility scores (0.865 ± 0.198) than patients with no VOC episodes (*n* = 236; 0.983 ± 0.058; Figure 3A).

ASCQ-Me: Overall mean scores of 486 adult patients were estimated for emotional impact (56.70 ± 9.38), pain impact (55.86 ± 10.54), sleep impact (57.78 ± 8.47), social functioning impact (59.57 ± 10.84), stiffness impact (58.25 ± 10.15) and pain episodes (50.00 ± 9.99). In the year prior to enrolment, the mean ASCQ-Me scores were significantly lower ($p < 0.001$) in pain episodes and higher in all other domains in adults without VOC, confirming a healthier QoL than adult patients with VOCs (Figure 3B).

In addition, this SCD-specific QoL tool assessed the QoL of 513 paediatric SCD patients across 20 domains. Among these patients, poor QoL domains indicated by 374 (72.90%)

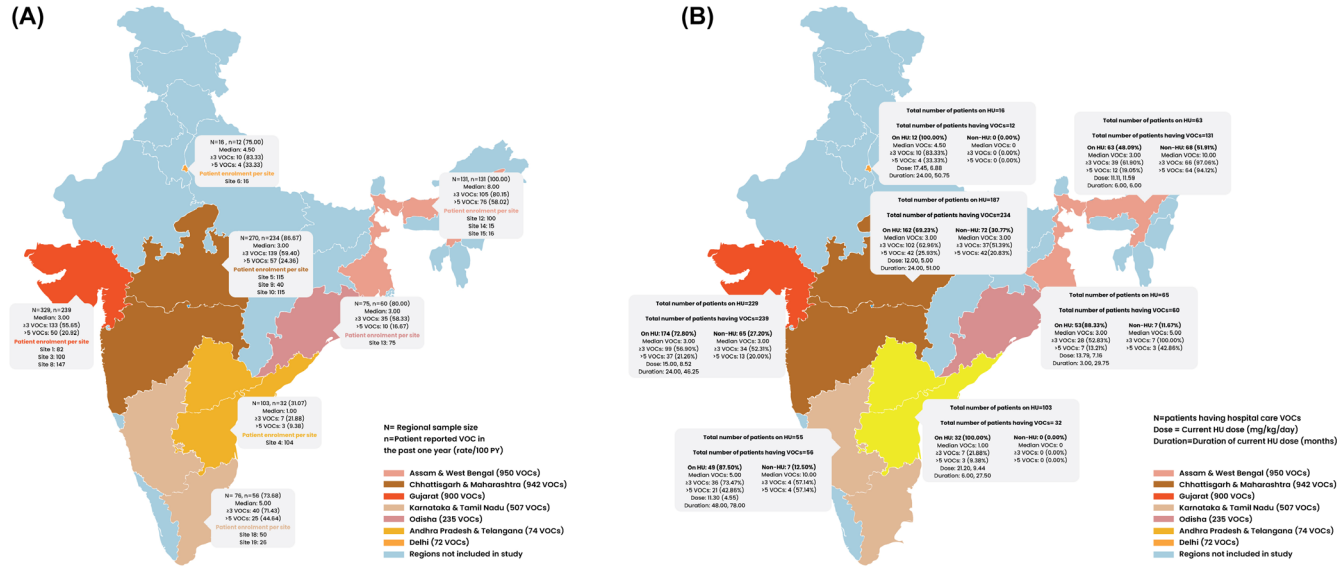

FIGURE 2 Regional VOC distributions. (A) Regional distribution of VOC in India, (B) Regional distribution of VOC episodes across India based on HU therapy. *N* represents the total number of patients from the region. *n*, represents the number of patients who experienced at least one VOC in the year prior to enrolment. Data represented as *n* (%).

TABLE 5 Pattern of HU usage in SCD patients.

Pattern of HU use	Overall (*N* = 1000) *n* (%)	Adult (*N* = 487) *n* (%)	Paediatric (*N* = 513) *n* (%)
Currently on HU	718 (71.80)	368 (75.6)	350 (68.3)
Currently not on HU	282 (28.20)	119 (24.4)	163 (31.8)
Current HU dose[a]	716	366	350
Current HU dose; median (IQR) mg/kg/day [range Q1 – Q3]	14.70 (9.1) [10.14–19.25]	12.34 (8) [10–18]	15 (7.5) [12.5–20]
≤15	439 (61.3)	244 (66.7)	195 (55.7)
>15	277 (38.7)	122 (33.3)	155 (44.3)
Duration of current HU dose[a]	716	366	350
Median (IQR) duration of current hydroxyurea dose (months) [Range Q1–Q3]	15.50 (42) [6 - 48]	24 (54) [6–60]	12 (27) [3–30]
<3 months	119 (16.6)	47 (12.8)	72 (20.6)
3–6 months	108 (15.1)	59 (16.1)	49 (14)
7–12 months	109 (15.2)	50 (13.7)	59 (16.9)
>1–5 years	259 (36.2)	119 (32.5)	140 (40)
6–10 years	88 (12.3)	60 (16.4)	28 (8)
>10 years	33 (4.6)	31 (8.5)	2 (0.6)
If currently not on hydroxyurea but receiving it in the past			
Never given HU in the past	241 (85.5)	99 (83.2)	142 (87.1)
Received but discontinued	41 (14.5)	20 (16.8)	21 (12.9)
Reason for discontinuation			
Non-adherent/non-compliant	15 (36.6)	6 (30)	9 (42.9)
Stopped HU after low blood counts	10 (24.4)	7 (35)	3 (14.3)
Challenge with HU access	7 (17.1)	1 (5)	6 (28.6)
Inadequate HU response	4 (9.8)	3 (15)	1 (4.8)
Intolerance	3 (7.3)	1 (5)	2 (9.5)
Others (SCD associated complications)	2 (4.9)	2 (10)	0 (0)

Abbreviations: HU, hydroxyurea; IQR, interquartile range; SCD, sickle cell disease; VOC, vaso-occlusive crisis.

[a]Data for two patients were not available.

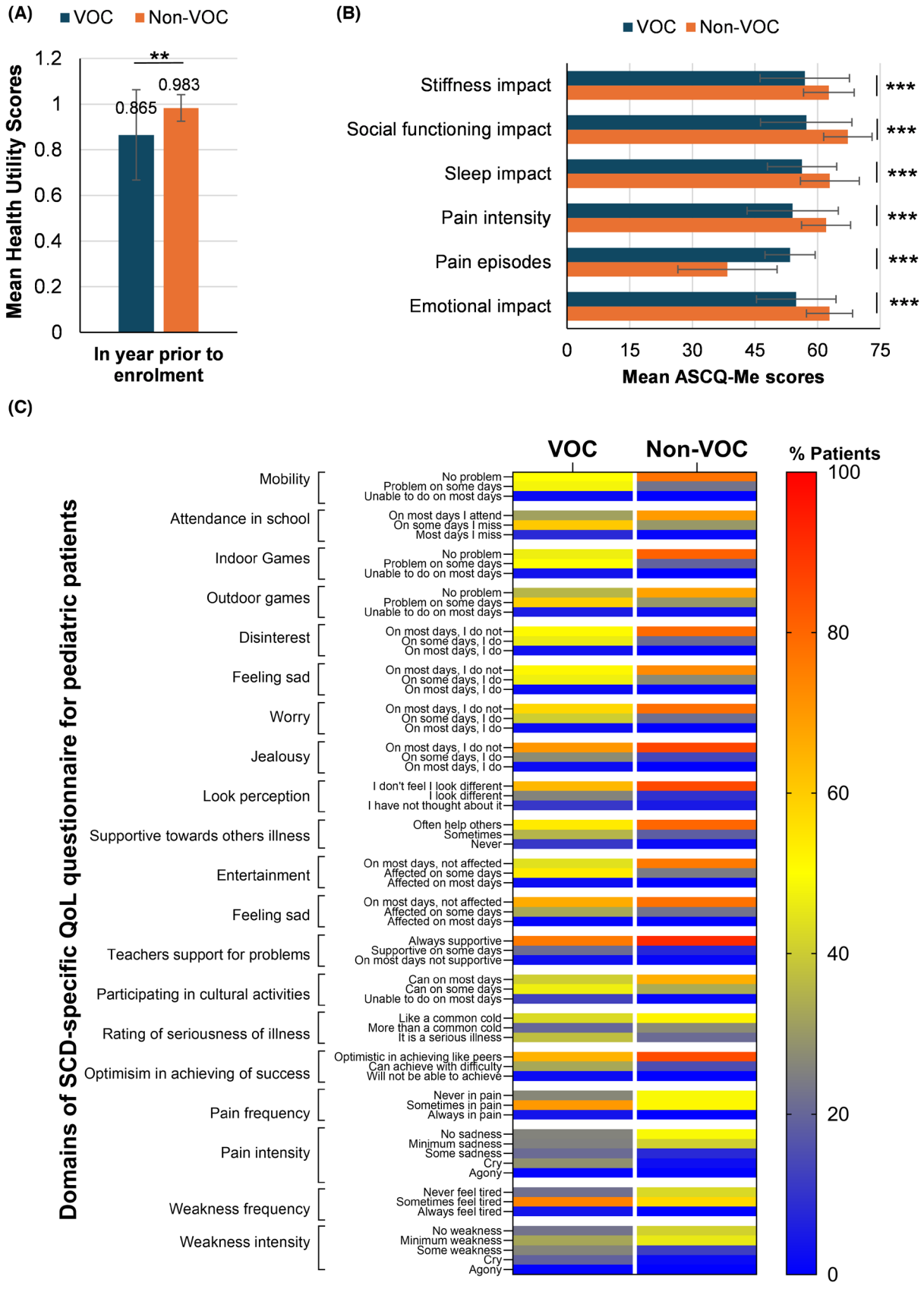

FIGURE 3 Analysis of the quality of life of SCD patients reporting VOC episodes versus those reporting no VOC in the year prior to enrolment. (A) Mean health utility scores from EQ-5D-5L questionnaire ($N = 1000$). (B) Mean ASCQ-Me scores from 487 adult SCD patients. (C) Heat map of the proportion of SCD paediatric patients' responses to the paediatric-specific SCD questionnaire. *n* represents the number of patients in each group. Data represented as Mean ± Standard deviation of health utility scores. (Independent sample *t*-test $^{**}p < 0.01$, $^{***}p < 0.001$).

were weakness frequency, 373 (72.71%) weakness intensity, 352 (68.61%) pain intensity and 350 (68.23%) pain frequency domains. Additionally, paediatric patients with VOCs in the year prior to treatment showed a greater impact on QoL across all domains compared to those without VOCs (Figure 3C).

The relationship of VOC and HU use with laboratory parameters is depicted in Table 6. Our results demonstrated significant differences in various haematological and biochemical markers among those experiencing VOC versus no VOC, those with or without HU therapy and among HU users with or without VOC as detailed in Table 6.

DISCUSSION

This large Indian study, which included 1000 patients from 14 centres across 11 states and union territories, provided novel insights into the overall VOC burden, clinical characteristics, healthcare utilization and economic implications for SCD patients in India. Its robust methodology ensures comprehensive representation and generalizability to the SCD population seeking healthcare support.

Previous studies documented milder clinical phenotypes for Indian patients due to Arab–Indian haplotype.[5,6] There are regional differences in the severity of disease, prevalence of anaemia and complications, with a median VOC rate of 60%.[26–28] Our study is the first nationwide multicentre hospital-based study that included patients with SCD from different regions of India and revealed that 83.60% of patients reported 5428 VOC episodes in the year prior to enrolment. Notably, the current study observed 76.4% of SCD patients required healthcare visits to manage VOC, which aligns with the global SWAY survey, which reported 76% of SCD patients required healthcare visits to manage VOC in lower-and-middle-income countries (LMICs).[29] The present study observed the prevalence of ≥3 VOCs in a year was 46.9% (469/1000), which aligns with the maximum prevalence of ≥3 VOCs (67%), as reported by Zaidi et al.[30] and more than 40% of patients who reported a median of 3 VOCs reported in the SWAY survey for LMICs.[29] These data suggest a potentially higher disease severity among Indian patients visiting healthcare facilities, which has not been reported in published studies thus far.

A prospective single-centre study revealed higher incidence rates of VOC in an Indian newborn cohort (85.2/100PY) than the Cooperative Study of Sickle Cell Disease cohort (32.4/100-PY).[7,31] In our study, the centres did not start at the same time, so we used the last patient index visit as the study closure. As a result, we did not apply the 100-person-year calculation for VOC episodes. We represented the event rates per 100 person-years for VOC episodes in the year prior to enrolment for comparison with global cohorts.[32,33] The VOC event rate calculated in our study revealed that 76.40/100-PY of SCD patients experienced VOCs in 1 year. A retrospective analysis of the Bethesda Sickle Cell Cohort Study (2001–2007) showed the rate of occurrence of one severe VOC episode (60/100 PY vs. 76.40/100 PY) and >5 VOC episodes in the year prior to enrolment (22/100 PY vs. 22.5/100 PY) in patients compared to our Indian cohort.[34] Considering these results and the VOC burden obtained in this study, we surmise that Indian SCD patients with the Arab–Indian haplotype do not have a milder phenotype compared to US SCD patients. Meanwhile, in SCD patients with the Arab–Indian haplotype living in the Middle East, similar rates of VOCs (48.23% vs. 76.40%) have been reported.[35] Similar blood transfusion rates were reported in SCD patients in the Middle Eastern and Indian cohorts,[36] suggesting comparable management strategies for patients from different regions. The widespread presence of Arab–Indian haplotype in the region accounts for the similarity in disease characteristics.[37]

In contrast, sub-Saharan Africa exhibits significantly higher VOC incidence and severe SCD-related complications than the Indian cohort, which is attributed to the prevalence of the more severe Benin haplotype in that region.[38–41]

The clinical presentation of SCD in India is generally less severe compared to the African population due to the high prevalence of the Asian haplotype and elevated levels of foetal haemoglobin (HbF), which requires lower HU dosage for better patient prognosis.[7] HU therapy effectively manages SCD, reducing VOC frequency and severity worldwide, including in India.[8] Unlike the SWAY survey, with 31% HU usage,[29] our study showed high HU usage [718 (71.80%)]. The median duration of HU therapy across all doses was 36 (IQR: 59.42) months. Additionally, the median duration of HU therapy at the current dose of 14.70 mg/kg/day was 15.50 (IQR: 42) months, aligning with the Indian clinical practice of administering a fixed low dose.[42] Our study showed substantially higher HU usage than the European (27%), North American (41%), South American (62%), Middle-Eastern (37%) and Asian (57%) cohorts.[29] However, this study included patients from healthcare settings with higher HU usage, which may not be relevant to community-dwelling SCD patients. In our study, we noticed that patients with SCD were given a consistently low dose of HU in line with Indian clinical norms. However, 58.90% of these patients on HU therapy were found to have ≥3 VOC episodes in the year prior to enrolment. Our findings aligned with another observation from a subset of the Indian tribal paediatric SCD population, where 116/160 (72.50%) patients reported recurrent VOC episodes within a year. This underscores the challenges in effectively managing VOC occurrences in SCD patients, even with established therapeutic interventions such as HU.[43] The results from this study highlight the need to optimize HU use, improve strategies for identifying HU failure and develop newer therapies and treatment modalities, including bone marrow transplants and gene therapy.

We also stratified our analysis of laboratory parameters among SCD patients based on the occurrence of VOCs and the use of HU therapy, revealing significant differences among these subgroups (Table 6). Patients experiencing VOCs in the year prior to enrolment, exhibited

TABLE 6 Details of laboratory investigations in patients segregated by the occurrence of VOC episodes and HU therapy.

		Patients visiting healthcare centres		Patients currently on HU treatment		If yes, the segregation of laboratory parameters	
Parameter	**Overall**	**Patients reporting VOCs in the year prior to enrolment**	**Patients reporting no VOCs in the year prior to enrolment**	**No**	**Yes**	**Patients on HU reporting VOCs in the past 1 year**	**Patients on HU reporting no VOCs in the past 1 year**
No. of patients	1000	764	236	282	718	545	174
Complete blood count							
Haemoglobin (g/dL)	8.97 ± 1.80	8.84 ± 1.81***	9.4 ± 1.69	8.58 ± 1.81	9.11 ± 1.77***	9.02 ± 1.79*	9.37 ± 1.71
Red blood cells (millions/mm^3)	3.46 ± 0.98	3.4 ± 1.02*	3.61 ± 0.85	3.52 ± 1.09	3.44 ± 0.95	3.42 ± 1.02	3.47 ± 0.75
White blood cell (per μL)	10.47 ± 5.67	10.86 ± 6.01**	9.42 ± 4.48	11.51 ± 6.31	10.2 ± 5.47*	10.5 ± 5.71*	9.43 ± 4.7
Neutrophils (%)	56.69 ± 15.9	58.35 ± 16.36***	51.74 ± 13.3	60.56 ± 15.23	55.43 ± 15.92***	57.14 ± 16.45***	50.86 ± 13.44
Eosinophils (%)	2.82 ± 2.92	2.76 ± 2.87	3 ± 3.05	2.86 ± 2.71	2.81 ± 2.99	2.75 ± 2.88	2.96 ± 3.26
Basophils (%)	0.33 ± 0.87	0.3 ± 0.96	0.42 ± 0.54	0.13 ± 0.25	0.4 ± 0.99***	0.36 ± 1.11	0.5 ± 0.56
Monocytes (%)	5.98 ± 3.72	5.89 ± 3.99	6.24 ± 2.8	5.89 ± 3.75	6.01 ± 3.71	5.95 ± 4.05	6.18 ± 2.65
Lymphocytes (%)	33.58 ± 14.28	32.14 ± 14.63***	37.91 ± 12.26	30.59 ± 14.06	34.55 ± 14.23***	33.07 ± 14.63***	38.6 ± 12.23
Platelet count (per mm^3)	284.65 ± 171.29	274.63 ± 168.24**	314.87 ± 177.24	274.89 ± 171.84	287.76 ± 171.15	280.11 ± 167.32	309.12 ± 180.25
Mean platelet volume (fL)	15.11 ± 19.83	17.24 ± 21.85	13.34 ± 17.92	20.37 ± 26.03	14.62 ± 19.19	16.55 ± 20.98	13.07 ± 17.58
Red cell distribution width (CV) (%)	18.55 ± 5.45	18.6 ± 4.9	18.42 ± 6.77	18.57 ± 3.58	18.55 ± 5.77	18.58 ± 5.18	18.48 ± 7.01
Red cell distribution width (SD) (g/L)	45.79 ± 18.38	46.94 ± 19.01	42.63 ± 18.82	-	45.79 ± 18.38	46.94 ± 19.01	42.63 ± 18.82
Platelet distribution width (%)	15.65 ± 3.48	15.63 ± 2.94	15.66 ± 3.84	16.46 ± 6.95	15.58 ± 3.09	15.74 ± 2.84	15.47 ± 3.27
Foetal haemoglobin during the study (n = 87) (%)	18.42 ± 7.6	18.05 ± 7.5	22.11 ± 8.1	18.75 ± 4.56	18.36 ± 8.04	17.91 ± 7.98	22.11 ± 8.1
Foetal haemoglobin at diagnosis (n = 676; %)	18.24 ± 8.08	17.99 ± 8.18	19.09 ± 7.68	16.61 ± 6.99	18.79 ± 8.35**	18.47 ± 8.55	19.72 ± 7.68
HbS (Haemoglobin S; %)	67.98 ± 14.61	68.31 ± 13.95	61.98 ± 24.16	66.86 ± 13.49	68.28 ± 14.93	68.73 ± 14.11	61.98 ± 24.16
Mean corpuscular volume (fL)	81.22 ± 15.48	81.34 ± 15.62	80.88 ± 15.12	78.14 ± 13.34	82.17 ± 15.98**	82.05 ± 16.15	82.48 ± 15.57
Mean corpuscular haemoglobin (pg)	27.54 ± 6.79	27.7 ± 7.37	27.07 ± 4.7	26.08 ± 4.94	28.01 ± 7.23**	28.13 ± 7.99	27.66 ± 4.65
Mean corpuscular haemoglobin concentration (g/dL)	33.13 ± 4.46	33.2 ± 5.07	32.95 ± 1.57	32.85 ± 2.34	33.22 ± 4.93	33.31 ± 5.69	32.99 ± 1.53
Iron profile							
Serum iron (μg/dL)	90.69 ± 55.26	91.05 ± 56.43	82.5 ± 9.19	67.09 ± 43.8	95.41 ± 56.55	96.09 ± 57.96	82.5 ± 9.19
Total iron-binding capacity (μg/dL)	332.78 ± 186.07	335.92 ± 190.33	270 ± 0	550.6 ± 342.18	296.48 ± 131.11*	298.04 ± 134.97	270 ± 0
Ferritin (ng/mL)	869.99 ± 1407.18	877.13 ± 1278.46	860.09 ± 1576.82	806.85 ± 1073.94	878.21 ± 1447.3	894.51 ± 1329.02	860.09 ± 1576.82
Transferrin saturation (%)	22.78 ± 10.99	22.78 ± 10.99	-	-	22.78 ± 10.99	22.78 ± 10.99	-
Liver function tests							
Lactate dehydrogenase (U/L)	559.85 ± 353.89	585.24 ± 360.08	336.4 ± 198.9	736.82 ± 519.73	508.63 ± 278.32	517.39 ± 283.64	406.33 ± 219.89
Alanine transaminase (U/L)	43.44 ± 97.65	46.06 ± 111.14	35.39 ± 29.09	52.48 ± 118.42	40.16 ± 88.9	42.92 ± 101.51	32.13 ± 29.64

(Continues)

TABLE 6 (Continued)

Parameter	Overall	Patients visiting healthcare centres		Patients currently on HU treatment		If yes, the segregation of laboratory parameters	
		Patients reporting VOCs in the year prior to enrolment	Patients reporting no VOCs in the year prior to enrolment	No	Yes	Patients on HU reporting VOCs in the past 1 year	Patients on HU reporting no VOCs in the past 1 year
Aspartate transaminase (U/L)	50.77 ± 122.97	55.89 ± 142.39	36.3 ± 18.29	54 ± 121.01	49.44 ± 123.92	53.91 ± 146.23	38.39 ± 18.66
Alkaline phosphatase (U/L)	160.27 ± 105.45	163.13 ± 108.48	151.8 ± 95.91	179.29 ± 121.6	154.88 ± 99.97	159.3 ± 103.13	144.52 ± 91.8
Indirect bilirubin (mg/dL)	2.12 ± 2.15	1.96 ± 2.09*	2.47 ± 2.23	1.64 ± 1.89	2.26 ± 2.2**	2.02 ± 2.1	2.82 ± 2.35
Bilirubin-direct (mg/dL)	1.03 ± 2.4	1.11 ± 2.59	0.82 ± 1.82	1.37 ± 4	0.91 ± 1.47	1.01 ± 1.72	0.68 ± 0.35
Total Bilirubin (mg/dL)	2.98 ± 2.83	2.93 ± 3.05	3.11 ± 2.18	2.56 ± 2.92	3.13 ± 2.79*	3 ± 2.96	3.47 ± 2.3
Total albumin (g/dL)	4.04 ± 0.77	3.97 ± 0.87*	4.2 ± 0.48	3.55 ± 1.11	4.16 ± 0.61***	4.13 ± 0.71	4.21 ± 0.42
Total protein (g/dL)	7.31 ± 1.02	7.34 ± 0.98	7.21 ± 1.13	7.22 ± 0.99	7.33 ± 1.02	7.4 ± 0.96	7.18 ± 1.14
Renal function tests							
Serum urea (mg/dL)	21.68 ± 15.11	22.04 ± 15.97	19.31 ± 7.16	21.59 ± 14.55	21.73 ± 15.46	22.15 ± 16.12	17.69 ± 4.96
Serum creatinine (mg/dL)	0.6 ± 0.45	0.63 ± 0.49**	0.49 ± 0.22	0.6 ± 0.54	0.6 ± 0.41	0.63 ± 0.45**	0.5 ± 0.23
Serum uric acid (mg/dL)	5.08 ± 3.79	5.08 ± 3.88	5.12 ± 0.53	5.12 ± 3.88	5.07 ± 3.77	5.05 ± 3.88	5.26 ± 0.44
Blood urea nitrogen (mg/dL)	10.17 ± 8.61	10.19 ± 9.03	10 ± 0	8.77 ± 2.64	10.45 ± 9.45	10.5 ± 10.02	10 ± 0

*p-value < 0.05. **p-value < 0.01. ***p-value < 0.001.

significantly lower haemoglobin levels (8.84 g/dL), red blood cells (3.4 million/mm^3), lymphocytes (32.14%) and platelet counts (274.63/mm^3), while having significantly higher values for white blood cells (10.86/μL), neutrophils (58.35%) and serum creatinine (0.63 mg/dL) compared to patients without VOC. Similarly, iron-binding capacity (296.48 μg/dL), neutrophils (55.43%) and white blood cells (10.2/μL) were significantly lower, and haemoglobin (9.11 g/dL), lymphocytes (34.55%), basophils (0.4%) and HbF at diagnosis (18.79%) were significantly higher in HU users. Within the HU users, haemoglobin (9.02 g/dL) and lymphocytes (33.07%) were significantly lower, and white blood cells (10.5/μL), neutrophils (57.14%) and serum creatinine (0.63 mg/dL) were significantly higher in patients with VOCs episodes. These results show the variations in haematological and biochemical parameters between patients who do and do not experience VOCs, those with and without HU treatment, and among HU users, those with and without VOCs. Further studies are needed to identify predictors of treatment outcomes and to develop tailored management strategies for this population.

Baseline (%) HbF modifies VOC severity and is regulated by genetic variations.[44] In our study, HbF levels at the time of diagnosis were 18.24% ($n = 676$) and during the study, it was 18.42% ($n = 87$). HbF values did not differ among adults and paediatrics, patients with and without VOCs, with the number of VOC episodes and among patients using HU therapy except HbF at the time of diagnosis (Table 2 and Figure S3). This could be due to the limited availability of real-world baseline data, especially for HbF levels, as it is not monitored in routine clinical practice in India. Despite high HbF levels, adult SCD patients with Arab–Indian haplotype are not benign because their HbF levels decrease with age,[45] and their F-cells have heterocellular and variable HbF distribution.[46] Genetic variations, sub-optimal dosing, non-adherence, limited access and delayed treatment onset collectively resist improved outcomes of HU therapy.[15,17,42] Therefore, a comprehensive approach is required to optimize the dosage of HU for VOC management in Indian SCD patients and monitor for the frequent clinical observation of thrombocytopenia.

Our study showed that VOC has a significant negative impact on the QoL of Indian SCD patients in various domains, including physical health, emotional well-being, social functioning and daily activities. Complications related to VOC can lead to exclusion from normal activities, resulting in isolation, stigma and reduced social support for Indian SCD patients. Interventions and care strategies are needed to address their physical and psycho-social challenges.

This hospital-based study on SCD may lack generalizability to community settings. While it effectively captures epidemiological data, recall bias from annual healthcare utilization data is possible. It omits SCD complications and VOC-related ICU admissions, affecting disease severity assessment in India. The semi-validated

paediatric QoL questionnaire provides insight but limits global comparison.

Our study revealed unique perspectives on the SCD landscape, VOC burden, management strategies and the impact of VOC on QoL in India.

AUTHOR CONTRIBUTIONS

Conceptualization and Validation: TS, SU, SJ, SB, NKM, RKJ, RK, SR, DS, MM and DJ. Methodology and Formal Analysis: TS, SU, SJ, SB, NKM, RKJ, RK, SR, MM and DJ. Project Administration: TS, SU, SR, DS, MM and DJ. Writing-Original draft: TS, SU, SR and DJ. Writing-Reviewing and Editing: TS, SU, SJ, SB, NKM, RKJ, RK, SR, BP, AG, AV, AD, PS, RB, DB, TKD, JB, DS, MM and DJ. All the authors have reviewed the manuscript and have agreed to publication.

AFFILIATIONS

[1]Department of Hematology, All-India Institute of Medical Sciences, New Delhi, Delhi, India
[2]Department of Oncology Medical Affairs, Novartis Healthcare Private Limited, Mumbai, Maharashtra, India
[3]Thalassemia and Sickle Cell Society, Hyderabad, Telangana, India
[4]Haemato Oncology Care Centre, Vadodara, Gujarat, India
[5]ASHWINI Gudalur Adivasi Hospital, Gudalur, Tamil Nadu, India
[6]Srirama Chandra Bhanj Medical College & Hospital, Cuttack, Odisha, India
[7]ICMR-National Institute of Research in Tribal Health, Jabalpur, Madhya Pradesh, India
[8]Public Health Foundation of India, New Delhi, Delhi, India
[9]Zydus Medical College and Hospital Civil Hospital, Dahod, Gujarat, India
[10]All India Institute of Medical Sciences, Raipur, Chhattisgarh, India
[11]Government Medical College and New Civil Hospital, Surat, Gujarat, India
[12]Assam Medical College and Hospital, Dibrugarh, Assam, India
[13]Institute of Medical Sciences and sum Hospital, Bhubaneshwar, Odisha, India
[14]KIMS-Kingsway Hospital, Unit of SPANV Medisearch Life Sciences Pvt. Ltd., Nagpur, Maharashtra, India
[15]JSS Medical College and Hospital, Mysuru, Karnataka, India
[16]Nil Ratan Sircar Medical College and Hospital, Kolkata, West Bengal, India
[17]Gauhati Medical College and Hospital, Guwahati, Assam, India
[18]Arihant Multispecialty Hospital, Nagpur, Maharashtra, India

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Novartis Healthcare Private Limited funded this study. Novartis participated in its design and conduct, including data collection, management, analysis and interpretation; preparation, review and approval of the manuscript.

CONFLICT OF INTEREST STATEMENT

No conflicts of interest declared.

DATA AVAILABILITY STATEMENT

All data generated or analysed during this study are included in this article and its appendix. The redacted study protocol and the statistical analysis plan are separately uploaded with the submission. The additional raw data files can be obtained from the corresponding author upon reasonable request through email. For original data, please contact diptyjain57@gmail.com. Datasets analysed during the current study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The study approval was obtained from the Institute Ethics committees of respective sites prior to patient enrolment: Nilratan Sircar Medical College and Hospital, Kolkata (NRSMS/IEC/79/2021); AIIMS, New Delhi (IEC-845/03.12.2021, RP-25/2021); Kamala Hospital and Research Centre, Hyderabad (IEC/ECKHRTS2103/2021); Kingsway Hospitals, Nagpur (KH/EC/25/2021); Institute of Medical Sciences and Sum Hospital, Bhubaneshwar (Ref.No/IEC/IMS.SH/SOA/2021/280); Ripon Independent Ethics Committee, Chennai (ECR/299/Indt/TN/2018/RR-21); Gauhati Medical College and Hospital, Guwahati (No. MC/128/2020/44); Mahatme Eye Bank Eye Hospital, Nagpur (Reg.No.ECR/638/Inst/MH/2014/RR-20); JSS Medical College, Mysuru (JSSMC/IEC/17112021/09/CT Final Approval/2021-22); Zydus Medical College and Hospital, Dahod (ECR/1464/Inst/GJ/2020/0592021 Paediatrics no. 01/2021); Government Medical College, Surat (GMCS/STU/ETHICS/Approval/25567/21); Assam Medical College, Dibrugarh (No. AMC/EC/1716); AIIMS, Raipur (Letter no.: 1999/IEC-AIIMSRPR/2021) and Anand Multispecialty Hospital, Vadodara (CSEG101AIN01).

PATIENT CONSENT STATEMENT

Informed consent was obtained from all participants enrolled in the study.

CLINICAL TRIAL REGISTRATION

This multicentric, cross-sectional observational study conducted in India was registered in the Clinical Trials Registry of India (https://ctri.nic.in/Clinicaltrials/login.php), with trial number CTRI/2021/10/037430.

ORCID

Suman Jain https://orcid.org/0000-0001-6237-1913
Ravindra Kumar https://orcid.org/0000-0001-9469-8080
Shomik Ray https://orcid.org/0000-0001-9345-8982
Dipty Jain https://orcid.org/0000-0002-8628-4977

TWITTER

Tulika Seth drtulikahemat

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