

Socioeconomic health and impact of sickle cell disease and vaso-occlusive crises in India: results from B-VOCAL study

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ABSTRACT

Background Sickle cell disease (SCD) with vaso-occlusive pain crisis (VOC) has a major impact on healthcare resource utilisation and poses a significant financial burden for the patients. This study examines the economic implications of managing VOC in individuals with SCD in India, from the perspectives of patients, healthcare system and society.

Methods This cross-sectional, observational study included 1000 patients with SCD across 14 centres enrolled from November 2021 to June 2022. Data were collected systematically using a structured electronic case record form. Employing a cost-of-illness approach, the study assessed the economic impact of SCD and VOC management, including assessing patient/caregiver costs, healthcare provider costs and societal burdens extrapolated to the larger SCD population in India.

Findings Patients incurred substantial out-of-pocket expenses, with a median (IQR) annual expenditure of INR 22 080/US\$267 (IQR: INR 36 990/US\$447.7), representing 14.65% (26.53) of their annual household income. Overall, catastrophic healthcare expenditure (CHE) for total annual average SCD care with VOC management was experienced by 624 patients (62.40%). Moreover, 334 patients (33.4%) experienced CHE of >25% of the annual household income. Patients with SCD with VOC had significantly higher median annual healthcare expenditures and used a higher median percentage of their yearly household income on healthcare compared with those without VOC (19.82% vs 6.08%; $p<0.001$). Cost incurred by healthcare providers for VOC management in different healthcare facilities (outpatient department/emergency department/intensive care unit) was similar across different reimbursed facilities (government tertiary care hospitals, non-governmental organisation-operated healthcare centres and government-subsidised healthcare setups). The estimated societal burden for VOC management in 1 year for 1000 patients visiting different healthcare facilities was around INR 35 119 074 (~US\$0.42 million).

Interpretation These findings highlight the considerable economic strain on both patients and healthcare providers in SCD and VOC management, which is similar to the other

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ India accounts for the second highest global burden of sickle cell disease (SCD). It mainly affects the patients belonging to tribal and non-tribal communities from the lower socioeconomic strata.

WHAT THIS STUDY ADDS

- ⇒ Our study is the largest study evaluating the economic impact of SCD and vaso-occlusive crisis (VOC) on patient and the healthcare system at a national level.
- ⇒ The analysis from our study not only provides valuable insights into the direct and indirect costs of average SCD and VOC management, but also demonstrated a substantial proportion (64%) of patients and families facing healthcare expenditure in a catastrophic range.
- ⇒ Overall, the study reported a substantial societal burden (US\$0.42 million) for VOC management in 1 year for 1000 patients visiting different healthcare facilities.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ The study highlights the importance of focused interventions such as universal healthcare coverage, expanding access to care and evaluating the role of newer treatment modalities to improve socioeconomic health in SCD among Indian patients.
- ⇒ Overall, the study provides critical information that can be used for developing policies in the field of research for deriving optimal patient outcomes and efficient resource utilisation.

non-communicable diseases emphasising the urgent need for targeted interventions to improve financial hardships among patients.

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INTRODUCTION

Sickle cell disease (SCD) is a heritable, autosomal haemoglobinopathy¹ identified by the WHO as an imminent global health issue.² From 2000 to 2021, its worldwide prevalence has increased by 41.4%.³ India contributes to 16% of the global SCD prevalence.^{4,5}

Vaso-occlusive crisis (VOC) is a hallmark clinical manifestation of SCD, affecting patients' morbidity, mortality⁶ and quality of life.⁷ VOC episodes lead to frequent healthcare visits and hospitalisations. VOCs result in maximum healthcare resource utilisation (HCRU), contributing to 78% of emergency department (ED) visits and 95% of inpatient department (IPD) admissions.^{8,9} This has a considerable economic impact on patients including direct and indirect costs, and the healthcare system which caters to the SCD care.¹⁰ Direct costs refer to hospital stays, treatment, medical expenses and transportation charges; indirect costs encompass loss in wages and loss of productivity due to disease.¹¹ Considering the higher hospitalisation rate with VOCs, a higher VOC burden is accompanied by increased financial costs, which emphasises how critical it is for all stakeholders to comprehend the financial ramifications.¹² However, there are limited data on the economic impact of managing VOC and SCD along with VOC in the Indian population.

India's high out-of-pocket expenses (OOPEs) on healthcare imposes a significant financial burden, leading to catastrophic healthcare expenditure (CHE) for patients and their families.^{13,14} Moreover, costs incurred by government-sponsored healthcare providers have also gained paramount importance in every cost-of-illness study. Although patients are responsible for managing their health, government-sponsored healthcare providers face the financial burden of delivering care to these patients.¹⁵ Therefore, it is essential to record the cost incurred for the patient and the government-funded healthcare provider for a disease like SCD that has a huge impact.

There are limited studies in India that estimate the economic burden of treating SCD and related VOCs. A structured economic assessment is needed to make an effective National Action Plan for SCD management. Therefore, this study was planned with an aim to assess the economic impact of VOC and SCD on patients, healthcare centres catering to patient care and society. In addition to providing valuable insight into the economic burden of VOCs, the information uncovered by this study could play a crucial role in resource allocation.

METHODS

Study design

B-VOCAL, a multicentre, cross-sectional observational study (CTRI No. CTRI/2021/10/037430), used a prevalence-based cost of illness¹⁶ methodology to assess the economic burden of SCD and VOC management. Patient recruitment followed a consecutive sampling methodology, whereas centre selection was done through

a purposive sampling strategy (section 1.1 of methods and online supplemental figures S1–S3). The study design has been detailed in the online supplemental appendix. The schematic diagram of economic impact evaluation provides further clarity on methodology and the parameters assessed (figure 1).

Participants

Adult and paediatric patients (aged ≥ 2 years) with an established diagnosis of SCD at least 12 months prior to index visit of any genotype ($n=1000$) from various healthcare centres in high SCD-prevalent states across India were included after obtaining informed consent. Patients receiving crizanlizumab or any other investigational product for managing VOC during and the previous 12 months from the day of study enrolment were excluded (section 1.2 of the online supplemental appendix). All patients provided written informed consent for the study participation, and the protocol received approval from the respective institutional review boards or independent ethics committees.

Objective and endpoints

The study objective was to estimate the economic burden for SCD and VOC management on patients and healthcare providers. The respective endpoints and variables assessed for evaluation of the overall cost (direct and indirect) incurred by a patient/caregiver, healthcare centres, societal burden and subgroup analysis of the cost incurred by the patient and the healthcare system for SCD and VOC management are summarised in section 1.4 of the online supplemental appendix.

Data collection

The study used primary data and reinforced secondary data from patient records as the predominant methodology for data collection. All patient data, including HCRUs, were collected using a structured electronic case report form on the index visit (section 1.4). We have summarised the data collection process and the elements included for the current analysis in section 1.3 of methods in the online supplemental appendix. The conversion rates for INR to US\$ were INR 82.63=US\$1 (as of 2 November 2023). Sample size estimation is given in online supplemental appendix 1.6.

A specialised questionnaire aimed at examining the cost-related variables for SCD was devised through a comprehensive approach by a health economics expert, followed by meticulous review by a study steering committee consisting of senior clinicians and epidemiologists. The validation phase encompassed pilot testing at various study centres, incorporating feedback to ensure a comprehensive scope covering cost-related variables pertinent to VOC and SCD treatment.

Cost analysis assessment

Patient or caregiver cost burden

In step 1, patients' monthly OOPEs for average SCD management, excluding VOC management and other

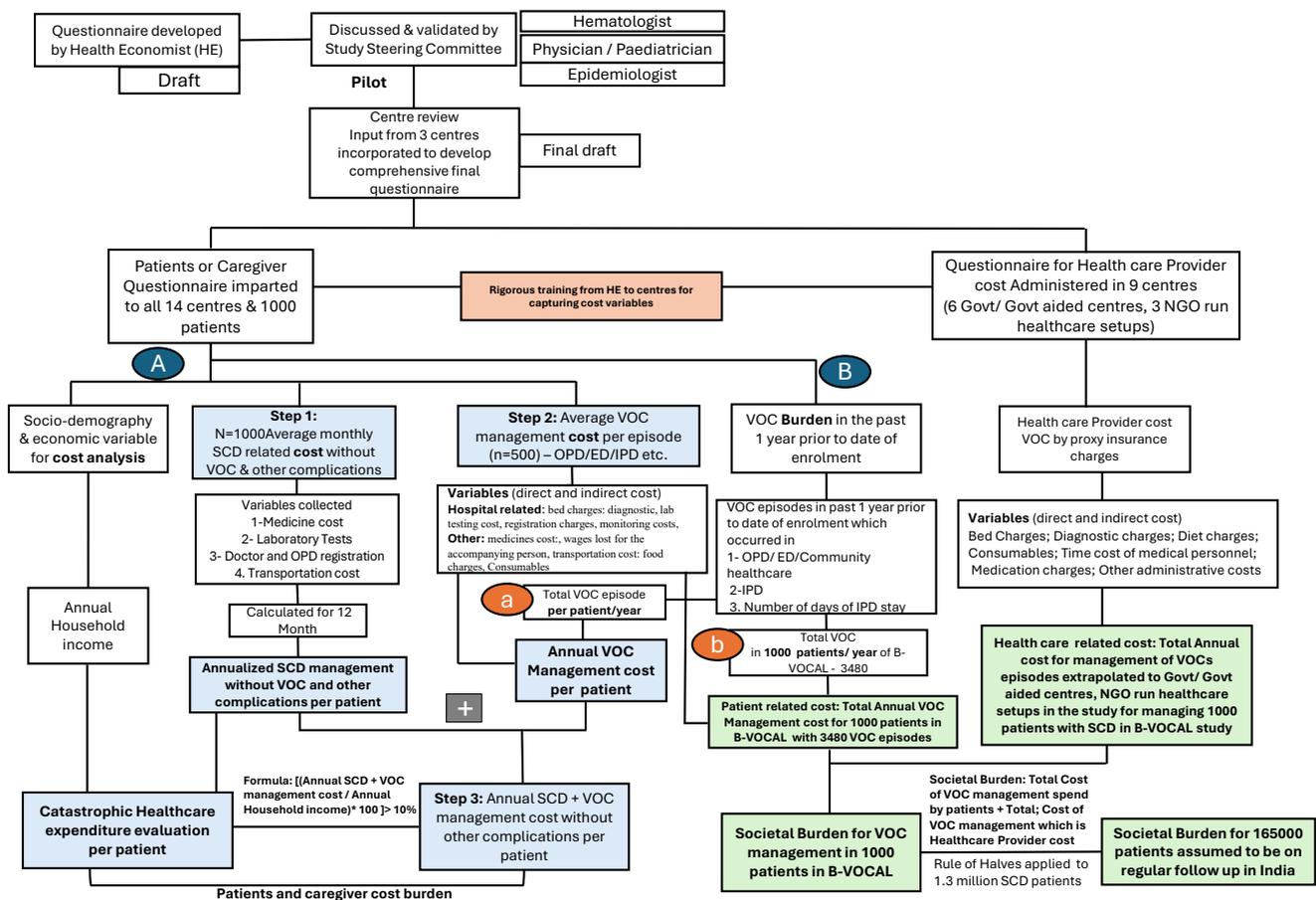


Figure 1 Schematic diagram of the study for the cost analysis assessment. A—Sociodemographic variables and average cost calculation for 1. SCD management and 2. VOC management. B—Burden of VOC measurement. a. Per patient, b. total for 1000 patients. Step a, Average VOC management cost per episode; for multiple variables evaluated total VOC episode/patient/year; step b: VOC burden in 1 year which evaluated total VOC in 1000 patients/year of the study. ED, emergency department; IPD, inpatient department; NGO, non-governmental organisation; OPD, outpatient department; SCD, sickle cell disease; VOC, vaso-occlusive crisis.

complications, were assessed. This cost was calculated for 12 months as the annualised cost of SCD management, excluding VOC management and other complications (n=1000). In step 2, the direct and indirect costs of managing VOC in different settings (outpatient department (OPD)/IPD/ED, etc) for current and previous episodes within a 3-month period (to minimise the recall bias) were calculated (n=500, had VOC episode during the index visit or in past 3 months from enrolment date). The average cost from these episodes was applied for the total number of VOC episodes (OPD/IPD/ED, etc) that occurred in the past 1 year prior to the study enrolment to calculate the total annual cost for VOC management per patient (n=1000). In step 3, the total annual cost of SCD care with VOC and without other complications was estimated by adding the individual patients' annualised cost of the management of SCD without VOC and other complications (step-1) with annual cost for managing VOC (step-2). The study assesses the economic impact of the above three parameters on patients and family using the CHE (>10%) methodology. WHO criteria were used for defining CHE, which states catastrophic expenditure

as household expenditures on health greater than 10% or 25% of total household expenditure or income, based on sustainable development goals indicator 3.8.2.¹⁷

The costs incurred by patients for SCD and VOC management were further analysed and categorised into subgroups, as outlined in section 1.5 of the methods in the online supplemental appendix.

Healthcare provider cost for VOC management

The cost incurred by healthcare providers for VOC management was evaluated for different healthcare setups, such as government tertiary care hospitals, non-governmental organisation (NGO)-operated healthcare centres and government-subsidised healthcare setups. In such healthcare setups, the VOC management is either free-of-cost to patients or has provisions for government reimbursement. Therefore, the cost incurred by healthcare providers for VOC management across different healthcare setups was determined based on proxy insurance charges for various cost components. The variables captured to assess the healthcare provider cost for VOC

management in patients are detailed in section 1.4 of methods in the online supplemental appendix.

Societal burden

Total patient-related cost and healthcare-related cost for VOC management of 1000 patients in 1 year was calculated by multiplying average cost from these episodes derived from the patient or caregiver cost and healthcare provider cost to the total number of VOC episodes (OPD/IPD/ED, etc) that occurred in the past 1 year prior to the study enrolment (3480 episodes). The societal burden of VOC management for 1000 patients for 1 year was calculated by adding the patient-related cost and healthcare provider-related cost. An estimated 1.3 million SCD cases reside in India.¹⁸ To evaluate the societal burden, we applied the rule of halves framework used for the non-communicable disease to estimated 1.3 million patients with SCD, of which 625 000 (50%) will be diagnosed, of those 325 000 (25%) will have access to healthcare, of which 162 500 (12.5%) will visit healthcare regularly.¹⁹

Statistical analysis

Data were screened for normality and summarised using mean±SD, median (IQR) or frequency (%). For the cost data, extreme outliers were treated with imputation values. For variables with higher zero values, mean values were presented instead of median to avoid zero median values. Both mean±SD and median (IQR) values are represented in tables. Based on the normality, while median (IQR) is ideal, both mean±SD and median (IQR) are shown to provide additional clarity to the readers. Difference between the groups was analysed using non-parametric tests (Mann-Whitney U for two groups, Kruskal-Wallis for >2) considering the non-normal cost data. Significant Kruskal-Wallis results led to post-hoc Dunn's pairwise tests. Significance was at $p<0.05$, adjusted by Bonferroni correction (p_{adj}) to prevent errors. The details of statistical analysis are described in the online supplemental appendix section 1.6 and 1.7. The data analysis was conducted using RStudio V.1.4.1106.

RESULTS

Sociodemographic characteristics

The study enrolled 1000 patients with SCD, with 567 men (56.70%) and mean age, 19.71 years (SD: 12.49). The cohort included 513 paediatric (51.30%) and 487 adult patients (48.70%; online supplemental table S1) included with a significant difference in the median (IQR) annual household income in adults (INR/US\$: 150 000/1815 (145 500/1761)) vs paediatrics (INR/US\$: 120 000/1452 (95 000/1150)), $U=108545$, $p<0.001$; Mann-Whitney U test (table 1). A significant difference was observed in the median annual household income of patients with SCD who visited different healthcare facilities ($\chi^2=170.64$, $df=4$, $p<0.001$; Kruskal-Wallis test (online supplemental table S2). A significant difference in the median (IQR) annual household income was also observed for patients visiting government tertiary facility compared with

private tertiary (INR/US\$: 110 000/1331 (78 000/944) vs 200 000/2420 (300 000/3631)), respectively, $Z=-9.42$, $p_{adj}<0.001$; Dunn test with Bonferroni correction. Furthermore, the detailed sociodemographic details, stratification and comparison of sociodemographic parameters across age groups (2–5, 6–11, 12–17, 18–30, 31–40 and >40 years), episodes of VOC and geographical zones are summarised in online supplemental tables S1–S6.

Patient or caregiver cost burden

The annualised cost of SCD management, excluding VOC management and other complications, annual VOC Management cost per patient in the last 1 year and total annual cost of SCD with VOC management without other complications among adult and paediatric patients and across different healthcare facilities are detailed in table 2. The direct and indirect costs of managing VOC in different settings (OPD/IPD/ED, etc) for current and previous episodes (<3 months) have been shown in figure 2A and B.

A detailed analysis of the overall population along with subgroups on the median annual cost, median percentage of annual healthcare expenditure of annual household income and proportion of patients with CHE for annualised cost of SCD management is given in figure 3 (A–A': excluding VOC management and other complications; B–B': total annual cost for VOC management; C–C': total annual cost of SCD care with VOC and without other complications). Additionally, results for the subgroup analysis are summarised in the online supplemental appendix (tables S7–S9).

Healthcare provider cost for the management of VOC

Cost incurred by the healthcare providers for VOC management

The cost incurred by the healthcare providers for VOC management at different healthcare settings (OPD, IPD, intensive care unit (ICU), ED and daycare) of different healthcare facilities (government, NGO-operated hospital and healthcare set up subsidised by government) is depicted in table 1.

Societal burden

Total cost for the management of VOC incurred by patients (direct and indirect cost) and healthcare providers
The total cost incurred by the patients/caregivers and healthcare provider for the management of all the VOC episodes for 1 year in different settings is summarised in figure 4A,B. Healthcare visits due to VOC in the past 1 year into different healthcare facilities and the costs incurred by patients and healthcare providers for the management of per episode of VOC at OPD/CP/daycare/ED, IPD/ward and ICU settings are summarised in online supplemental tables S10–S12). The summation of the total patients and healthcare providers cost revealed the total cost incurred for VOC management in the past 1 year for 1000 patients as INR 35 119 074/US\$425 016 (figure 4C and online supplemental table S13). The extrapolation of this cost to estimated patients with SCD

Table 1 Cost SCD and VOC management

	Overall	Paediatric	Adult	Government tertiary	Private tertiary	NGO operated	Healthcare setup funded by the government	Healthcare setup subsidised by the government
<i>Step 1: Annualised cost of SCD management, excluding VOC management and other complications</i>								
Number of patients	1000	513	487	362	223	153	115	147
<i>Direct and indirect costs of SCD management without VOC and other complications (INR)</i>								
Medicine cost	731.07±860.06	509.14±690.06	962.44±954.46	711.38±594.16	1634.08±1002.04	0±0	230.87±151.83	316.67±564.46
Diagnostic cost	274.84±477.8	231.96±512.41	319.54±434.9	273.64±470.23	544.48±540.33	0±0	93.48±213.01	328.33±672.23
Doctors' fees	151.26±288.9	111.16±250.08	193.06±319.43	85.91±203.15	421.52±398.99	0.33±4.04	47.83±92.1	124.17±198.19
OPD registration fees	40.97±98.67	37.19±87.09	44.91±109.41	27.26±88.17	65.7±138.75	21.7±36.92	74.26±96.25	16.38±40.16
Transportation expenses	615.9±871.46	586.84±855.38	646.25±887.88	654.06±799.27	715.83±928.81	834.27±1235.54	240.43±155.58	197.94±105.01
<i>Total monthly SCD management expenses without VOC and other complications (INR)</i>								
Mean±SD	1728.74±1679.56	1420.65±1533.83	2053.28±1764.74	1750.87±1348.94	3380.72±1943.68	854.67±1226.63	686.87±426.48	892.99±906.31
Median (IQR)*	1150 (1900)	810 (1130)*	1500 (2530)*	1410 (1500)†	3500 (1500)†	500 (1500)†	600 (1500)†	700 (1500)†
<i>Annualised SCD management expenses without VOC and other complications (derived) (INR)</i>								
Mean±SD	20 744.86±20154.69	17 047.74±18405.92	24 639.35±21 176.93	21 010.41±16 187.32	40 568.61±23 324.11	10 256±14 719.52	8242.43±5117.78	10 715.92±10 875.7
Median (IQR)*	13 800 (22 800)*	9720 (13 740)*	18 000 (30 600)	16 920 (16 440)†	42 000 (33 240)†	6000 (6000)†	7200 (4080)†	8400 (7200)†
<i>Step 2: Annual VOC management cost per patient in the last 1 year</i>								
<i>Cost for VOC management in the last 1 year patients; INR</i>								
Number of patients	764	388	376	348	142	78	94	102
OPD/CP/daycare	2527.23±9436.75	2295.62±3308.42	2766.22±3552.92	2180.17±2900.04	5097.89±5147.06	1592.31±1899.40	829.79±577.69	2411.76±2696.06
ED	357.33±1251.4	286.6±817.37	430.32±1576.81	289.66±924.25	669.01±2253.76	215.38±546.79	153.19±362.10	450.98±1113.62
IPD	9997.62±14536.62	11 734.9±14953.97	8204.91±13886.32	12 153.10±14 995.18	13 770.08±0878.98	3956.44±4436.86	3906.38±6144.42	7625.00±7814.40
<i>Total cost for VOC management in the last 1 year patients; INR</i>								
Mean±SD	12 882.18±15 239.99	14 317.11±14856.07	11 401.45±15507.16	14 622.93±14528.69	19 536.99±22 921	5764.13±5163.22	4889.36±6001.13	10 487.75±8084.84
Median (IQR)*	7110 (13 280)	7920 (15 403.5)*	6120 (9460)*	8640 (12 960)†	17 458.5 (19 358.5)†	4906 (7006)†	4320 (4320)†	7575 (9150)†
<i>Step 3: Annual SCD+VOC management cost without other complications per patient (INR)</i>								
Number of patients	1000	513	487	362	223	153	115	147
Mean±SD	30 586.84±27 002.01	27 876.28 ± 24 506.73	33 442.11±29 156.29	35 067.81±21 533.95	53 009.2±34 283.04	13 194.58±14 990.34	12 238.96±8915.99	17 993.13±14 128.73
Median (IQR)*	22080 (36 990)	18 000 (37 942.5)*	25 620 (36 000)*	30 120 (33 930)†	52 458.5 (43 200)†	8400 (11 889)†	9720 (9000)†	13 975 (15 725)†

Continued

Table 1 Continued

Overall	Paediatric	Adult	Government tertiary	Private tertiary	NGO operated	Healthcare setup funded by the government	Healthcare setup subsidised by the government
Total monthly SCD management expenses without VOC and other complications: $\chi^2=95626$ ($p<0.001$); Among different hospital setting†† $\chi^2=358.66$, $df=4$ ($p<0.001$) Annualised SCD management expenses without VOC and other complications: * $U=95626$ ($p<0.001$); Among different hospital setting† $\chi^2=358.66$, $df=4$ ($p<0.001$); Total cost for VOC management in the last one-year prior to date of enrolment patients: * $U=65285$ ($p<0.012$); Among different hospital setting† $\chi^2=101.83$, $df=4$, ($p<0.001$) Annual SCD+VOC management with VOC and other complications: * $U=108\ 421.5$ ($p<0.001$); Among different hospital setting† $\chi^2=352.94$, $df=4$ ($p<0.001$). Median annual household healthcare expenditure out of annual household income. †Mann-Whitney U test statistic. ††Kruskal-Wallis χ^2 test statistic. ED, emergency department; IPD, inpatient department; NGO, non-governmental organisation; OPD, outpatient department; SCD, sickle cell disease; VOC, vaso-occlusive crisis.							

(162 500) assumed to be on regular follow-up was INR 5 706 849 525/US\$68.55 million. We extrapolated the societal burden in 1000 patients from the current study to an estimated 162 500 (12.5%) patients with SCD assumed to be on regular follow-up to derive the societal burden of VOC management in India (figure 4D).

DISCUSSION

The burden of SCD has been reported mostly in the disadvantaged populations, including African Americans, people in sub-Saharan Africa, and tribal and non-tribal groups belonging to lower socioeconomic strata in India.^{20–22} In India, SCD distribution is heterogeneous with high prevalence in the state of Gujarat, Maharashtra, Madhya Pradesh, Chhattisgarh, Jharkhand, Odisha, Assam, Andhra Pradesh and Telangana.^{5 19 23 24}

There are small pockets of SCD prevalence among tribal predominant districts in the southern region of Karnataka, northern Tamil Nadu, Kerala and West Bengal.^{5 23–25} Hence, the impact of the disease is non-uniform across the country, specifically affecting high burden districts and states of India.

The B-VOCAL study examined 1000 patients with SCD from 14 centres in 11 states in India. This is the first study in India evaluating the economic impact of the disease and VOC on the patients and healthcare system. The methodology and rigorous training programme for accurate data collection established a solid foundation for investigating the economic issues related to SCD and VOC management among socioeconomically vulnerable populations residing in high prevalence states of India.

The study’s baseline characteristics indicate that the patients’ mean age was 19.71±12.49 years (adults: 29.82±10.14; paediatric: 10.12±4.17) and most patients were from rural domicile (680 of 1000 (68%)), while 73.2% of the general Indian population are from rural domicile. These findings align with the distribution and demographic profiles of patients with SCD in India that have been reported in other studies.^{23 25} Our data indicated that patients with SCD exhibit unemployment rates and annual household incomes comparable to those found in the general population, as documented in reports. The median (IQR) annual household income of our patient population was INR 135 500 (110 000 (US\$1627.43)), which is similar to the average annual household income of the general population (INR 125 000–500 000 (US\$1513–6051)) in India.²⁶ The annual household income of the Indian SCD cohort was substantially lower than that in developed countries like the USA (US\$28 678±1143)²⁷ and higher than the Nigerian cohort (US\$333 in 2014).²⁸ Regarding payment methods, 424 patients (42.40%) paid out-of-pocket, which is comparable to the high OOPE rate of 47.1% observed in the general population as per the National Health Accounts report for 2019–2020.¹³ Among reimbursed segments, 26.60% patients were below poverty line (BPL) card holders (free of cost treatment in network healthcare

Table 2 Cost (direct and indirect) of VOC incurred by the healthcare providers for different healthcare facilities across different healthcare settings

	Overall	Government tertiary	NGO operated	Healthcare setup subsidised by the government
Number of centres	9	5	3	1
<i>Daycare</i>				
Direct and indirect costs (INR)				
Bed charges	372.5±322.16	204±227.41	730±325.27	500±0
Medication charges	1163.75±1120.69	850±782.62	2030±2078.89	1000±0
Diagnostic charges	713.75±586.98	686±610.72	1050±636.4	180±0
Diet charges	292.5±222.37	370±243.93	95±7.07	300±0
Consumables	348.75±192.39	390±201.25	320±254.56	200±0
Time cost of medical personnel	1750±2642.37	2250±3307.19	375±176.78	2000±0
Other administrative costs	475±533.85	500±644.2	250±353.55	800±0
Total costs for daycare (INR)				
Mean±SD	5116.25±4280.76	5250±5520.4	4850±2474.87	4980±0
Median (IQR)*	4407.5 (2610)	3835 (3180)	4850 (1750)	4980 (0)
<i>Intensive care unit (ICU)</i>				
Direct and indirect costs (INR)				
Bed charges	2383.33±1923.97	2460±2140.79	–	2000±0
Medication charges	3583.33±2437.55	3200±2514.96	–	5500±0
Diagnostic charges	1750±1129.16	1600±1193.73	–	2500±0
Diet charges	358.33±220.04	370±243.93	–	300±0
Consumables	1025±794.83	830±710.28	–	2000±0
Time cost of medical personnel	3583.33±3168.86	2900±3008.32	–	7000±0
Other administrative costs	1033.33±1059.56	840±1059.72	–	2000±0
Total costs for ICU (INR)				
Mean±SD	13 716.67±7443.77	12 200±7211.8	–	21 300±0
Median (IQR)†	14 000 (13 175)	9700 (11 700)	–	21 300 (0)
<i>Inpatient department (IPD)/WARD</i>				
Direct and indirect costs (INR)				
Bed charges	350.71±347.29	199±231.88	960±0	500±0
Medication charges	830±652.41	850±782.62	560±0	1000±0
Diagnostic charges	657.14±472.08	700±570.09	600±0	500±0
Diet charges	320±225.02	370±243.93	90±0	300±0
Consumables	420±175.5	460±151.66	140±0	500±0
Time cost of medical personnel	2214.29±2852	2450±3318.51	250±0	3000±0
Other administrative costs	885.71±915.48	740±939.68	500±0	2000±0
Total costs for WARD (INR)				
Mean±SD	5677.86±4826.59	5769±5669.77	3100±0	7800±0
Median (IQR)*	3835 (5462.5)	3835 (6225)	3100 (0)	7800 (0)
<i>Outpatient department (OPD)</i>				
Direct and indirect costs (INR)				
Bed charges	–	–	–	–
Medication charges	737.5±1162.74	340±417.43	1850±2333.45	500±0
Diagnostic charges	843.75±681.09	810±770.06	850±919.24	1000±0
Diet charges	–	–	–	–

Continued

Table 2 Continued

	Overall	Government tertiary	NGO operated	Healthcare setup subsidised by the government
Consumables	188.75±217.48	190±213.31	280±311.13	0±0
Time cost of medical personnel	488.75±646.32	532±845.2	375±176.78	500±0
Other administrative costs	187.5±210.02	160±207.36	250±353.55	200±0
Total costs for OPD (INR)				
Mean±SD	2446.25±2304.67	2032±2350.77	3605±3387.04	2200±0
Median (IQR)*	1750 (2152.5)	1300 (1840)	3605 (2395)	2200 (0)
<i>Emergency department (ED)</i>				
Direct and indirect costs (INR)				
Bed charges	568.12±664.74	517±854	730±325.27	500±0
Medication charges	1038.75±1194.88	650±858.78	2030±2078.89	1000±0
Diagnostic charges	731.25±696.39	650±821.58	1050±636.4	500±0
Diet charges	292.5±308.49	370±373.5	95±7.07	300±0
Consumables	436.25±309.28	470±376.83	320±254.56	500±0
Time cost of medical personnel	987.5±1167.03	1030±1389.06	375±176.78	2000±0
Other administrative costs	385.62±433.27	317±433.38	250±353.55	1000±0
Total costs for emergency department (ED) (INR)				
Mean±SD	4440±3760.6	4004±4736.38	4850±2474.87	5800±0
Median (IQR)*	4450 (4445)	1750 (4830)	4850 (1750)	5800 (0)

Total costs for Day care (INR)* $\chi^2 = 0.388$, $df=2$, $(p=0.824)$; Total costs for ICU (INR)† $U = 0.500$, $(p=0.373)$; Total costs for WARD (INR)* $\chi^2 = 0.720$, $df=2$ $(p=0.698)$; Total costs for OPD (INR)* $\chi^2 = 0.576^*$, $df=2$, $(p=0.750)$; Total costs for Emergency Department (ED) (INR)* $\chi^2 = 0.810$, $df=2$ $(p=0.667)$.
 *Kruskal-Wallis test statistic value (χ^2).
 †Mann-Whitney U test statistic value.
 NGO, non-governmental organisation; VOC, vaso-occlusive crisis.

facilities), 12.6% had Ayushman Bharat which is a health insurance scheme sponsored by the government of India and 184 (18.4%) had other insurance coverages for the treatment of SCD. However, only 36.5% of the general Indian population are covered under different health

insurance schemes in 2021.²⁹ India follows a decentralised approach towards healthcare, which means that health insurance is not mandatory. Every citizen is entitled to free healthcare at government-run facilities, and each state is responsible for managing these services.

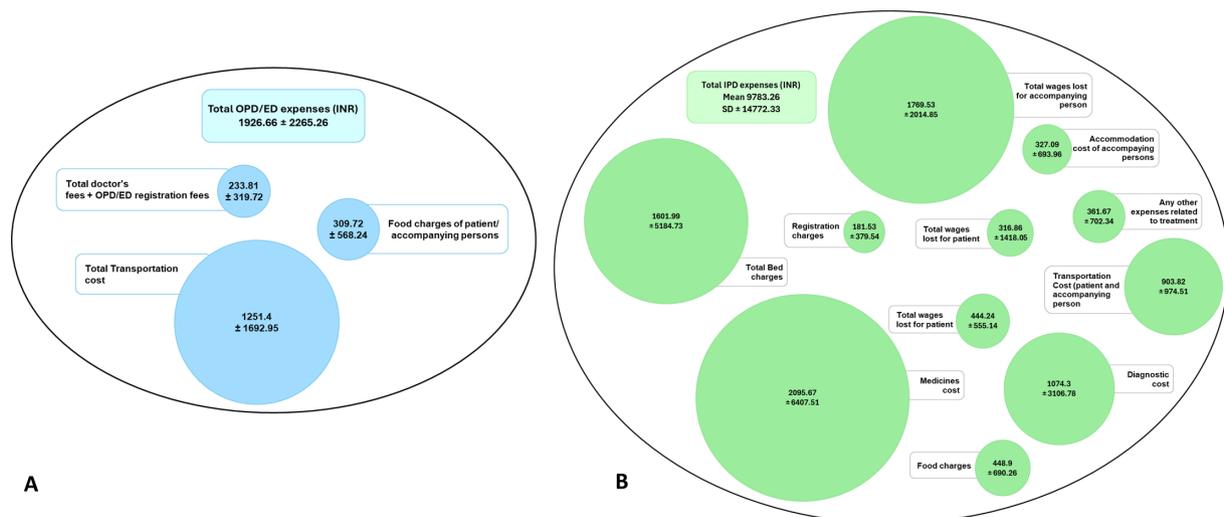


Figure 2 Direct and indirect costs of managing VOC in different settings (A: OPD or ED setting and B. IPD setting) (n=500). ED, emergency department; IPD, inpatient department; OPD, outpatient department; VOC, vaso-occlusive crisis.

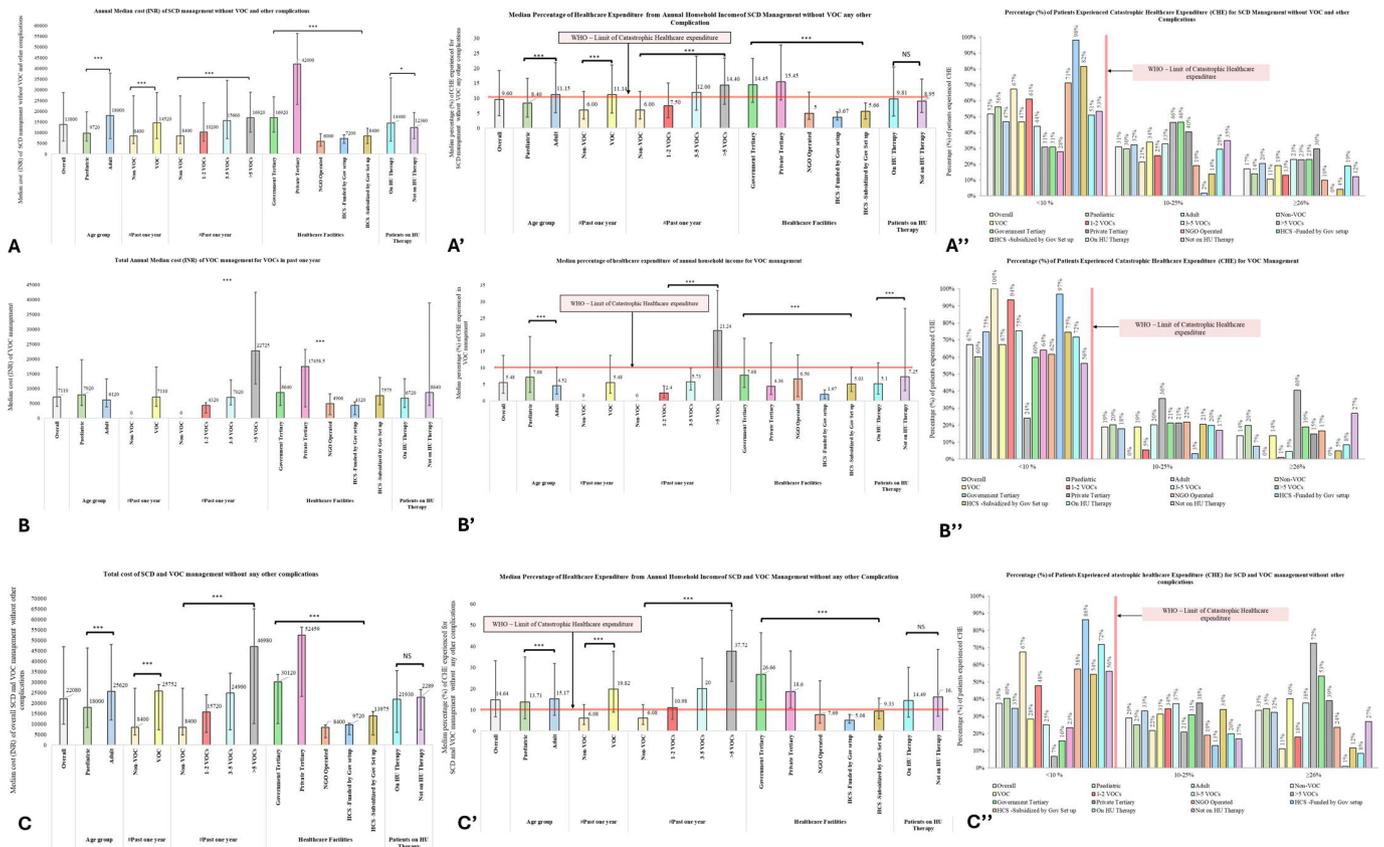


Figure 3 Patient/caregiver cost burden. (A) Annual median cost for overall SCD management without VOC and other complications and within different subgroups. The annual median cost for the overall SCD management and among the major subgroups is depicted with the IQR as the error bar. (A') Median percentage of healthcare expenditure of annual household income for overall SCD management without VOC and other complications and within different subgroups. The median percentage of CHE for overall SCD management and among the major subgroups is depicted with the IQR as the error bar. (A'') Percentages of patients who experienced CHE for overall SCD management without VOC and other complications and within different subgroups. The percentages of patients that experienced CHE for overall SCD management and among the major subgroups are depicted with the IQR as the error bar. (B) Annual median cost of overall VOC management and within different subgroups for the VOCs reported in the past 1 year. The annual median cost of overall VOC management and among the major subgroups is depicted with the IQR as the error bar. (B') Median percentage of healthcare expenditure of annual household income for overall VOC management and within different subgroups for the VOCs reported in the past 1 year. The median percentage of CHE for overall VOC management and among the major subgroups is depicted with the IQR as the error bar. (B'') Percentages of patients who experienced CHE for overall VOC management and within different subgroups for the VOCs reported in the past 1 year. The percentages of patients that experienced CHE for overall VOC management and among the major subgroups are depicted with the IQR as the error bar. (C) Annual median cost of overall SCD and VOC without other complications and within different subgroups. The annual median cost of overall SCD and VOC management without other complications and among the major subgroups is depicted with the IQR as the error bar. (C') Median percentage of CHE for overall SCD and VOC management without other complications and within different subgroups. The median percentage of CHE for overall SCD and VOC management without other complications and among the major subgroups is depicted with the IQR as the error bar. (C'') Percentages of patients who experienced CHE for overall SCD and VOC management without other complications and within different subgroups. The percentages of patients that experienced CHE for overall SCD and VOC management without other complications and among the major subgroups are depicted with the IQR as the error bar. Significance level, * $p < 0.05$, ** 0.01 , *** 0.001 , NS, not significant. Note: #Past 1 year represents prior to date of enrolment; The conversion rates for INR to US\$ were INR 82.63=US\$1 (as of 2 November 2023). CHE, catastrophic healthcare expenditure; ED, emergency department; HU, hydroxyurea; HCS, healthcare setup; IPD, inpatient department; NGO, non-governmental organisation; OPD, outpatient department; SCD, sickle cell disease; VOC, vaso-occlusive crisis.

However, a significant number of patients prefer seeking medical care from private providers.³⁰

The general Indian population experienced an overall CHE of 16.51% for various health-related expenses.¹⁴ In a recent study, CHE was evaluated for non-communicable diseases such as cardiovascular diseases, cancer and

chronic respiratory diseases. The findings indicated that the overall CHE >10% and >25% of annual household income were 63.61% and 39.6%, respectively.³¹ Our study results revealed comparable CHE levels, with 62.4% and 33.4% of study participants experiencing CHE of >10% and 25% of annual household income,

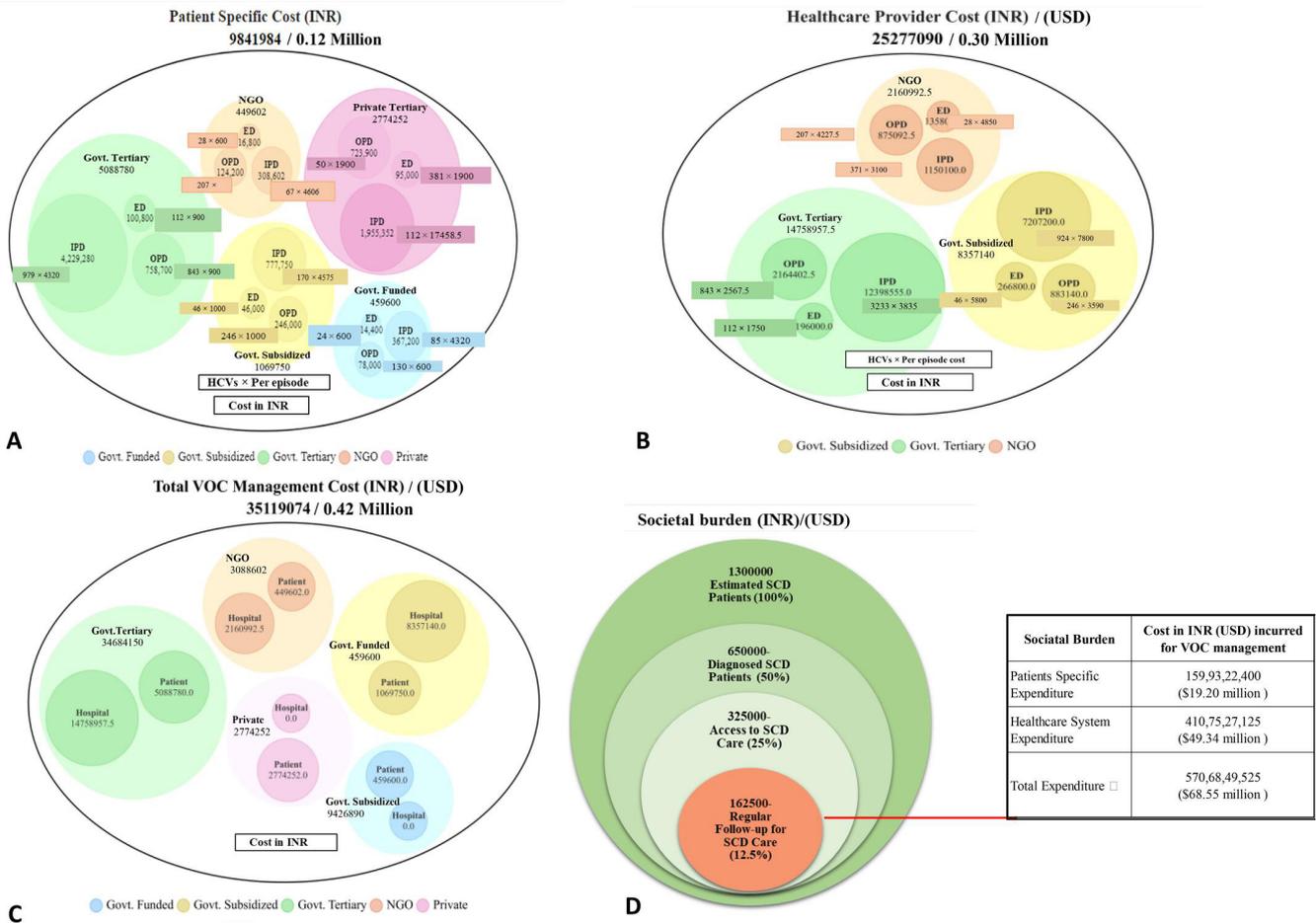


Figure 4 Societal burden for the overall disease management, including the cost incurred by the patients and the healthcare providers. (A) Total patient-related cost for VOC management for different healthcare facilities. The total cost for VOC management incurred by the patients was calculated by multiplying the per episode VOC cost with the number of healthcare visits by the patients in the past 1 year to different healthcare facilities for VOC management. (B) Total healthcare-related cost for VOC management for different healthcare facilities. The total cost for VOC management incurred by the healthcare providers was calculated by multiplying the per episode VOC cost with the number of healthcare visits by the patients in the past 1 year to different healthcare facilities for VOC management, for IPD, per episode of VOC/day in IPD cost. (C) Total cost for VOC management for different healthcare facilities. The total cost for VOC management was calculated by summing up the total cost incurred by the patients for VOC management for different healthcare facilities with the total cost incurred by the healthcare providers for VOC management for different healthcare facilities. (D) Societal burden. The societal burden for overall SCD and VOC management incurred by the patients and the healthcare providers in 1000 patients was extrapolated to 162 500 patients with SCD. Note: The conversion rates for INR to US\$ were INR 82.63=US\$1 (as of 2 November 2023). ED, emergency department; IPD, inpatient department; NGO, non-governmental organisation; OPD, outpatient department; SCD, sickle cell disease; VOC, vaso-occlusive crisis.

respectively. Our study estimate for the cost of managing SCD employs a conservative approach, excluding additional acute and chronic complications (such as aplastic crisis, chronic kidney disease, etc) and ICU admissions.³² These findings indicate that the economic impact of SCD and VOC on patients and their families is substantially greater compared with the general population, and comparable to non-communicable diseases like cardiovascular diseases, cancer and chronic respiratory diseases. Therefore, an effective national action plan to reduce the financial burden on patients and their families is needed.

The CHE was derived by the median annual OOPE for the management of SCD and VOC without other complications, which cost US\$265.19 per patient. In the OPD/

ED setting, transportation was the major cost driver, while in the IPD setting, medication expenses, bed charges and lost wages were the primary factors. A previous study based on secondary research of National Sample Survey data for the Indian population reported medicine and travel as the largest contributors to OOPE, highlighting the importance of access to free medicine and decentralisation, and strengthening of peripheral care in India.³³ Inpatient admission was the major contributor to the overall median cost for VOC management in India, which is similar to that in the Nigerian, US and European cohorts. The total costs were found to be comparatively lower than previous cost studies conducted in other developing countries like Nigeria (yearly cost per patient

is US\$4063.20) and developed countries like the USA (US\$16 668) and the Netherlands (US\$42 339.5).^{32 34 35} However, the total cost burden of SCD and VOC management without other complications was 14.64% of the study patient's annual household income. The median percentage of the annual OOPE for the management of SCD was 3% to 5% of the annual household income of African-Americans in the USA,³⁶ which is considerably lower than our study.

The present study reported that adult patients had higher median (IQR) annual expenditures on SCD with VOC management than paediatric patients and a higher percentage of healthcare expenditure out of their annual household income (15.17% vs 13.71%; $p < 0.001$). This could be due to the gradual development of SCD complications over time, which become more apparent and common in older patients, resulting in frequent healthcare visits and hospitalisations.³⁷ A similar trend was reported by Kauf *et al*, who observed an increase in total healthcare costs among patients with SCD with age, from US\$892 to US\$2562 per patient-month in the groups aged 0–9 years and 50–64 years, respectively.³⁴ However, our study did not explore the predictors of increased healthcare expenses among the adult population.

In our study, patients with SCD who experienced VOC in the past year had significantly higher median (IQR) annual total healthcare expenditures (INR/US\$22 080/267 (36 990)/448) vs 1150/13.9 (1900/23); $p < 0.001$) and a higher median percentage of healthcare expenditure out of their annual household income compared with those who did not report VOC (19.82% vs 6.08%; $p < 0.001$). This is because VOCs require urgent interventions, such as hospital admissions and emergency care visits, which can lead to higher healthcare expenditure.³⁸ The proportion of patients experiencing CHE (>10% of annual household income) also increased with the frequency of VOCs. Therefore, effective clinical measures are needed to reduce VOC incidence among patients with SCD.

The median annual cost of the management of SCD and VOC was higher in the private tertiary facilities compared with the rest of the facilities.³⁹ The median percentage of annual healthcare expenditure of annual household income and CHE was higher in the government tertiary facilities compared with the rest. The reason behind this interesting finding was that the median (IQR) annual household income of patients with SCD who visited government tertiary facilities was lower than that of patients who visited private tertiary facilities (INR 110 000 (78 000), (US\$1321.16) vs INR 200 000 (300 000), (US\$2412.11)), which drove their higher percentage of CHE compared with patients that visited other healthcare facilities.⁴⁰

Moreover, the median (IQR) healthcare expenditure out of annual household income on the management of SCD with VOC was found to be significantly greater among patients from the suburban rural community (17.59 (28.65%)) as compared with patients from the

urban community (8 (17.48)) ($p < 0.001$). These findings are in concurrence with the observations of a study that reported OOPE as a share of total household expenditure was higher in the rural areas of India.⁴¹ Moreover, 69.5% of patient belonging to rural suburban domicile and 56.7% who were BPL experienced catastrophic expenditure on SCD with VOC management (online supplemental tables 11–13).

The present study is the first in India to determine the cost incurred by the healthcare providers for the VOC management based on proxy insurance charges. The average cost of managing VOC per patient per day in IPD, ICU, OPD and daycare settings has been found to be similar across reimbursement facilities. However, the burden of patients with SCD in India visiting government tertiary hospitals is substantially higher than in hospitals operated by NGOs or in healthcare setups subsidised by the government, resulting in higher HCRU with substantial financial ramifications for the government.

Despite lower healthcare costs than in some countries, SCD management still accounts for a significant financial burden on patients and healthcare providers. In our study, the total cost (by patient and healthcare providers) incurred for VOC management in 1 year for 1000 patients visiting different healthcare facilities was around INR 35 119 074 (~US\$0.42 million). The societal burden applied for 12.5% of the estimated SCD population visiting the hospitals regularly based on the rule of halves framework, including the expenses of patients (~INR 160 Cr/US\$19 million) and the healthcare providers (~INR 410 Cr/US\$49 million), was around INR ~570 crores (~US\$68.54 million). These results highlight the importance of policy interventions for addressing not only the direct costs related to SCD and VOC management but also the indirect costs such as travel, loss of income and productivity causing additional burden on the financial resources of low-income households in India. It is also important to consider strategies making primary care more accessible to patients with SCD. Enhancing the optimal usage of drugs and employing intensive treatment strategies may help limit the overall burden on patients and the healthcare system in India.

Additionally, our study highlighted that outliers who had high CHE (>Q3) belonged to rural domicile with higher disease duration, higher number of healthcare visits due to VOC and lower annual household income compared with overall study population. The number of patients undergoing hydroxyurea therapy was substantially lower compared with the overall study population. This analysis highlights a unique patient subgroup with distinct payment implications for health policy and health insurance amendments (online supplemental table 13).

Although this study offers valuable insights into the burden of VOCs and the management of SCD in India, it is important to acknowledge its limitations. The results of this hospital-based observational study might not apply to patients with SCD living in community settings. The cost estimate may differ based on the lack of cost estimate

analysis for severe/acute/chronic complications of SCD; hence, it is a conservative estimate of average SCD and total non-complicated VOC cost.

In summary, to the best of our knowledge, this is the first study from India that shows a significant part of healthcare costs in SCD care is paid as OOOPE. It appears that CHE (>10%) in SCD with VOC management without other complications was similar to other chronic non-communicable diseases like cardiovascular diseases, cancer and chronic respiratory diseases. Lower- and middle-income countries, such as India, need to strengthen the holistic approach to attain universal healthcare coverage, update disability standards and ensure access to decentralised care for improved socio-economic health in SCD.

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Contributors All authors have made substantial contributions to all of the following. DJ, TS, SU, SJ, SB, NKM, RKJ, RK, SR, DS and MM contributed to the conceptualisation. DJ, TS, SU, SJ, SB, NKM, RKJ, RK, SR and MM contributed to the methodology. DJ, TS, SJ, SB, NKM, BP, AKG, AV, AD, PS, RB, DB, TKD and JB contributed to the investigation. DJ, TS, SU, SR, DS and MM contributed to the project administration. DJ, TS, SU, SJ, SB, NM, SR, BP, AG, AV, AD, PS, RB, DB, TKD, JB, DS and MM contributed to the resources. DJ, TS, SU, SJ, SB, NM, RJ, RK, SR and MM contributed to the formal analysis. DJ, TS, SU, SJ, SB, NM, RJ, RK, SR, DS and MM contributed to the validation. DJ, TS, SU and SR contributed to writing original draft. DJ, TS, SU, SJ, SB, NM, RJ, RK, SR, BP, AKG, AV, AD, PS, RB, DB, TKD, JB, DS and MM contributed to writing, reviewing and editing. DJ, TS and SR contributed to the supervision. All the authors have reviewed the manuscript and have agreed to publication. SR is responsible for the overall content as guarantor.

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Competing interests All the authors declare no direct or indirect conflict of interest and competing financial interests for this article. SU and DS are full-time employees of Novartis Healthcare Private Limited. MM was a full-time employee of Novartis Healthcare Private Limited at the time the study was completed and is currently employed at Eli Lilly.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved. The B VOCAL study has been approved by the ethics committee/institutional review board(s) of all the sites. The ethics approval reference number for each site has been provided as follows and also included in the supplementary material (table 14): Institute ethics committee, All India Institute of Medical Sciences (AIIMS), Raipur: ECR/714/Inst/CT/2015/RR-21; Institute ethics committee, Assam Medical College, Dibrugarh, Assam: ECR/636/Inst/AS/2014; Human Research Ethics Committee, Government Medical College, Majura Gate, Surat, Gujarat: ECR/42/Inst/GJ/2013/RR-19; IEC, Zydus Hospitals and Healthcare Research Pvt Ltd, Anand, Gujarat: ECR/560/Inst/GJ/2014/RR-20; Institutional Ethics Committee JSS Medical College, Sri Shivarathreeswara Nagar, Mysore, Karnataka: ECR/387/Inst/KA/2013/RR-19; Institutional Ethics Committee MEBEH, Mahatme Eye Bank Eye Hospital, Somalwada Nagpur, Maharashtra: ECR/638/Inst/MH/2014/RR-20; Institutional Ethics Committee, Gauhati Medical College and Hospital, Guwahati, Assam: ECR/1470/Inst/AS/2020; RIPON Independent Ethics Committee, Chinmaya Nagar, Chennai: ECR/299/IndT/TN/2018; IEC IMS and SUM Hospital, Bhubaneswar Khordha, Orissa: ECR/627/Inst/OR/2014/RR-20; Kingsway Hospitals Ethics Committee, Kingsway Hospitals, Nagpur, Maharashtra: ECR/1269/Inst/MH/2019; Anand Institutional Ethics Committee, Anand Multispecialty Hospital, Vadodara Gujarat: ECR/725/Inst/GJ/2015/RR-21 Institutional Ethical Committee of Kamala Hospital and Research Centre for Thalassaemia and Sickle Cell Patients, Kamala Hospital and Research Centre, Ranga Reddy, Telangana: EC/NEW/INST/2021/1581; Institute ethics committee, All India Institute of Medical Sciences (AIIMS), New Delhi: ECR/538/Inst/DL/2014/RR-20; Ethics Committee, N.R.S. Medical College, NRS Medical College and Hospital, Kolkata, West Bengal: ECR/609/Inst/WB/2014/RR-20. Participants gave informed consent to participate in the study before taking part. The study was conducted in accordance with the ethics principles of the Declaration of Helsinki and the Good Clinical Practice guidelines defined by the International Council for Harmonisation (ICH-GCP).

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Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. All data generated or analysed during this study are included in this article and its appendix. The additional raw data files will be available from the corresponding author upon request through email.

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