Clinical and Economic Burden in Pediatric Patients With Sickle Cell Disease With Recurrent Vaso-Occlusive Crises in the United States

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BACKGROUND

- Sickle cell disease (SCD), a rare genetic disorder due to a variant in the β-globin gene, affects ~120,000 people in the United States. SCD is characterized by the expression of abnormal sickle-shaped hemoglobin leading to multi-organ acute and chronic complications, including vaso-occlusive crises (VOCs)[1-4]
- Recurrent VOCs are a hallmark clinical feature of SCD; they can begin in childhood, causing debilitating pain, frequent hospitalizations, and leading to end-organ damage and accelerated mortality over time[2,3,5]
- Even in childhood, disease burden is substantial. Disease progression is associated with increased healthcare resource utilization (HCRU) and economic burden[6,7]
- For pediatric patients experiencing recurrent VOCs, there are limited data on clinical complications, HCRU, and costs, as previously published studies focused on broader populations[8-12]

OBJECTIVE

- To describe the clinical and economic burden of disease among pediatric patients with SCD with recurrent VOCs in the United States

METHODS

Study Design and Database

- The Merative™ MarketScan® Commercial, Medicare, and Multi-State Medicaid Databases contain de-identified inpatient medical, outpatient medical, and outpatient prescription drug data
- A retrospective cohort study design was used to identify patients with SCD in the MarketScan Databases between January 1, 2014, and December 31, 2024

SCD Patient Identification

- Patients were included if they met the following inclusion criteria:
  - At least 1 inpatient claim with a principal diagnosis of SCD or ≥2 non-diagnostic outpatient claims for SCD within 365 days of each other between January 1, 2014, and December 31, 2024
  - At least 2 VOCs per year in any 2 consecutive years after the first qualifying SCD diagnosis claim; the index date was the date of the second VOC claim in the second year of the 2 consecutive years[a]
  - At least 24 months of continuous enrollment with medical and pharmacy benefits before the index date
  - At least 12 months of continuous enrollment with medical and pharmacy benefits after and including the index date, and ending on the earliest date of either inpatient death, end of continuous enrollment, or end of the study period (December 31, 2024)
  - **Primary cohort:** Patients were required to be 5 to 11 years old at index
  - **Secondary cohorts:** Patients were required to be 5 to 11 or ≥12 years old at index and had experienced ≥2 VOCs per patient per year (PPPY) throughout the entire follow-up period
    - These secondary cohorts were compared to the primary cohort to evaluate the clinical and economic burden associated with SCD patients with continued recurrent VOCs across different age groups
- Patients were excluded if they met the following exclusion criteria:
  - At least 2 claims with a diagnosis code for sickle cell trait during the baseline or follow-up period
  - Evidence of hematopoietic stem cell transplantation (HSCT) during the baseline or follow-up period

Matched Control Identification

- Individuals in the MarketScan Databases without a claim with a diagnosis code for SCD, β-thalassemia, any other blood disorder, or HSCT at any time during their MarketScan enrollment were included in the general population
- Matched controls were compared with the primary cohort to contextualize the clinical and economic burden of patients with SCD aged 5 to 11 years
- Five controls were matched on age, sex, region, payer type, and duration of follow-up data to each patient with SCD
- Index dates for controls were assigned based on the distribution of index dates among patients with SCD
- Consistent with SCD cases, matched controls were required to have ≥24 months of continuous enrollment with medical and pharmacy benefits before the index date and ≥12 months of continuous enrollment including and after the index date

[a]A VOC was defined as an inpatient or emergency room (ER) medical claim with a diagnosis code for acute chest syndrome, priapism, SCD with crisis, or splenic sequestration associated with SCD, and an accompanying Current Procedural Terminology code for physician evaluation and management. At least 3 days between the service dates of VOCs were required to be considered discrete events.

Study Measures and Analyses

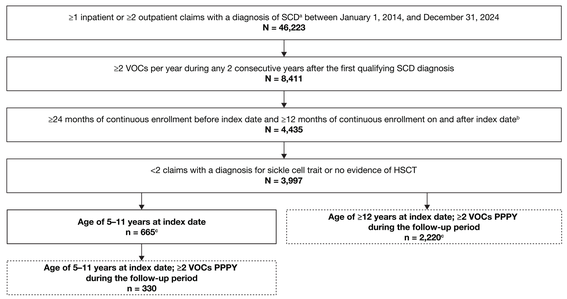
- Demographics, including age, sex, payer type, and duration of follow-up were reported at the index date
- The annualized rates of VOCs (PPPY) were characterized
- The proportion of individuals with clinical complications was reported through the presence of non-diagnostic claims during the follow-up period
- The proportion of individuals with treatments of interest in the follow-up period was captured
- Annualized rates of all-cause HCRU included inpatient admissions, ER visits, outpatient visits, and pharmacy prescriptions
- The proportion of patients with ≥1 inpatient admission and outpatient visit was also reported
- Annualized inpatient, outpatient, and prescription costs (PPPY) were based on the paid amounts of adjudicated claims, including insurer and health plan payments, as well as patient cost-sharing in the form of co-payment, deductibles, and co-insurance
  - Costs for commercially and Medicaid fee-for-service (FFS) insured patients were reported separately
- Costs were inflated to 2024 US dollars using the Medical Care Component of the Consumer Price Index
- All study measures were summarized using descriptive statistics
  - Mean (standard deviation [SD]) values were reported for continuous variables, and frequencies (n)/proportions (%) were reported for categorical variables
- Comparative analyses were conducted between patients with SCD and matched controls for HCRU and annual costs
  - Chi-square tests were used to evaluate differences in categorical variables, and *t* tests were used for continuous variables
  - *P*<0.05 was considered statistically significant

RESULTS

Patient Demographics

- Six hundred and sixty-five patients aged 5 to 11 years were identified as having SCD with recurrent VOCs and met the other inclusion/exclusion criteria (**Figure 1**) and were matched to 3,324 individuals from the general population (**Table 1**)
- Demographics are provided for 4 cohorts: patients with SCD aged 5 to 11 years, controls aged 5 to 11 years, and patients with SCD aged 5 to 11 or ≥12 years with ≥2 VOCs PPPY during the follow-up (**Table 1**)

Figure 1. SCD Attrition Table



HSCT, hematopoietic stem cell transplantation; ICD, International Classification of Diseases; PPPY, per patient per year; SCD, sickle cell disease; VOC, vaso-occlusive crisis.
[a]ICD-9 codes (282.41, 282.42, 282.61, and 282.62) and ICD-10 codes (D5700–D5703, D5709, D571, D5740, D5741, D5742, D5743, D57431–D57433, D57438, D57439, D5744, D5745, D57451–D57453, D57458, D57459).
[b]Follow-up begins on the index date and ends with the earliest of death, end of continuous enrollment, or end of the study period (December 31, 2024).
[c]285 patients were aged 0 to 4 years at the index date and were not included in the analyses; 3,047 patients were aged ≥12 years at the index date.

Table 1. Patient Demographics by Age Group

Patient Demographics	Primary Cohort	Matched Controls	Secondary Cohorts	
	Patients With SCD With Recurrent VOCs Aged 5–11 Years (n = 665)	Controls Aged 5–11 Years (n = 3,324)	Patients Aged 5–11 Years With ≥2 VOCs PPPY (n = 330)	Patients Aged ≥12 Years With ≥2 VOCs PPPY (n = 2,220)
Age at index date (years)				
Mean (SD)	8.1 (2.0)	8.1 (2.0)	8.3 (2.0)	26.3 (10.8)
Min–Max	5–11	5–11	5–11	12–73
Sex, n (%)				
Male	352 (52.9)	1,760 (52.9)	177 (53.6)	979 (44.1)
Female	313 (47.1)	1,564 (47.1)	153 (46.4)	1,241 (55.9)
Payer, n (%)				
Medicaid	597 (89.8)	2,984 (89.8)	293 (88.8)	1,771 (79.8)
Medicaid FFS	272 (40.9)	1,359 (40.9)	131 (39.7)	1,027 (46.3)
Commercial	68 (10.2)	340 (10.2)	37 (11.2)	447 (20.1)
Medicare	0 (0)	0 (0)	0 (0)	2 (0.1)
Duration of follow-up (years)				
Mean (SD)	4.3 (2.3)	4.3 (2.3)	4.1 (2.3)	3.9 (2.3)

FFS, fee-for-service; PPPY, per patient per year; SCD, sickle cell disease; SD, standard deviation; VOC, vaso-occlusive crisis.

VOCs and Clinical Complications

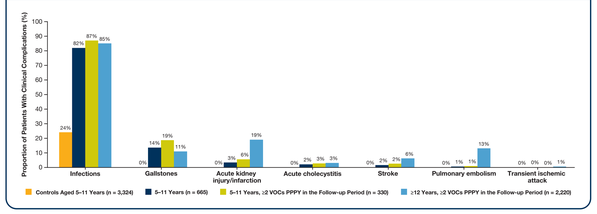
- Complications are pronounced from childhood
  - Patients in the primary cohort aged 5 to 11 years with recurrent VOCs experienced a mean of 2.6 VOCs PPPY during the follow-up; among those with ≥2 VOCs PPPY, patients aged 5 to 11 years or ≥12 years had a mean of 4.0 or 8.5 VOCs PPPY, respectively (**Table 2**)
  - Patients in the primary cohort aged 5 to 11 years with recurrent VOCs experienced a significantly higher mean number of total complications compared with controls (4.1 versus 0.2), driven by both acute (3.4 versus 0.1) and chronic complications (0.7 versus 0.1)
  - Among the primary cohort of patients aged 5 to 11 years with recurrent VOCs, 82% experienced infections, the most common acute complication, compared with 24% of the matched control cohort (**Figure 2**)
  - In patients with ≥2 VOCs PPPY, the prevalence of complications was generally higher in the ≥12 years than the 5 to 11 years cohort, although some complications were more common in patients aged 5 to 11 years than in those aged ≥12 years (**Figure 2**; **Figure 3**)
  - In patients with ≥2 VOCs PPPY, stroke was reported in 2% of patients aged 5 to 11 years compared with 6% of those aged ≥12, and pulmonary embolism was reported in 1% of patients aged 5 to 11 years versus 13% of those aged ≥12 years (**Figure 2**)

Table 2. VOCs by Age Group

VOCs	Primary Cohort	Matched Controls		Secondary Cohorts	
	Patients With SCD With Recurrent VOCs Aged 5–11 Years (n = 665)	Controls Aged 5–11 Years (n = 3,324)	*P* Value	Patients Aged 5–11 Years With ≥2 VOCs PPPY (n = 330)	Patients Aged ≥12 Years With ≥2 VOCs PPPY (n = 2,220)
Total number of VOC events,[a] mean (SD)	2.6 (2.4)	0 (0)	<0.001	4.0 (2.7)	8.5 (8.0)
Acute chest syndrome, n (%)	388 (58.3)	0 (0)	<0.001	220 (66.7)	1,359 (61.2)
Priapism, n (%)	13 (2.0)	0 (0)	<0.001	10 (3.0)	80 (3.6)
SCD with crisis, n (%)	658 (98.9)	0 (0)	<0.001	330 (100.0)	2,220 (100.0)
Splenic sequestration, n (%)	72 (10.8)	0 (0)	<0.001	39 (11.8)	125 (5.6)
Patients with an inpatient VOC, n (%)	576 (86.6)	0 (0)	<0.001	314 (95.2)	2,128 (95.9)
Average duration of inpatient VOC events (days), mean (SD)	3.8 (2.2)	-	-	3.9 (2.2)	5.3 (3.5)

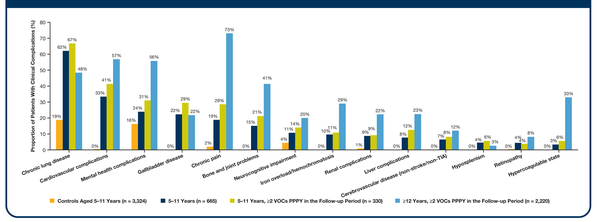
PPPY, per patient per year; SCD, sickle cell disease; SD, standard deviation; VOC, vaso-occlusive crisis.
[a]With a VOC diagnosis; must be at least 3 days apart to qualify as separate VOC events.

Figure 2. Acute Complications by Age Group



PPPY, per patient per year; vaso-occlusive crisis.

Figure 3. Chronic Complications by Age Group[a]



PPPY, per patient per year; TIA, transient ischemic attack; VOC, vaso-occlusive crisis.
[a]All chronic complications ≥5% in at least 1 cohort shown.

Annual HCRU, Treatments, and Costs

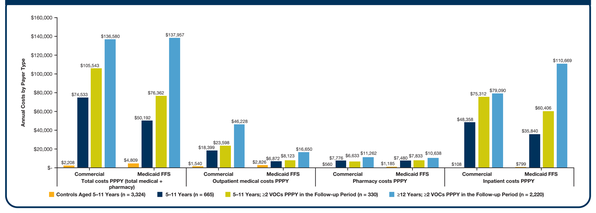
- Compared to matched controls, patients with SCD with recurrent VOCs aged 5 to 11 years had significantly higher HCRU and a greater proportion received pain medications, including opioids (**Table 3**)
  - Inpatient admissions PPPY: 1.5 versus 0.02
  - ER visits PPPY: 2.5 versus 0.4
  - Pain medications (%): 98.3% versus 28.6%
  - Opioids (%): 97.7% versus 13.2%
- In the ≥2 VOCs PPPY cohorts, HCRU and treatment use were higher in the ≥12 years cohort than the 5 to 11 years cohort (**Table 3**):
  - Inpatient admissions PPPY: 4.3 versus 2.4
  - ER visits PPPY: 8.6 versus 3.4
  - Iron chelation therapy (%): 19.5% versus 9.1%
  - Blood transfusion (%): 64.5% versus 53.6%
- Patients with SCD with recurrent VOCs aged 5 to 11 years had annual costs significantly higher than their matched controls (**Figure 4**)
  - Differences in costs were driven by inpatient and outpatient medical costs, with VOC-related costs accounting for a substantial proportion of total annual costs (**Figure 4**; **Table 4**)
- Cost burden was evident from childhood; in the ≥2 VOCs PPPY cohorts, annual total costs PPPY were higher in the ≥12 years cohort than the 5 to 11 years cohort across payer types (**Figure 4**)

Table 3. Annual HCRU and Treatment Regimens by Age Group

Annual HCRU and Treatment Regimens	Primary Cohort	Matched Controls		Secondary Cohorts	
	Patients With SCD With Recurrent VOCs Aged 5–11 Years (n = 665)	Controls Aged 5–11 Years (n = 3,324)	*P* Value	Patients Aged 5–11 Years With ≥2 VOCs PPPY (n = 330)	Patients Aged ≥12 Years With ≥2 VOCs PPPY (n = 2,220)
Inpatient					
Patients with an admission in entire follow-up, n (%)	590 (88.7)	169 (5.1)	<0.001	317 (96.1)	2,154 (97.0)
Inpatient admissions PPPY, mean (SD)	1.5 (1.6)	0.02 (0.1)	<0.001	2.4 (1.9)	4.3 (4.0)
Outpatient, mean (SD)					
Outpatient visits PPPY[a]	35.4 (27.8)	15.3 (29.6)	<0.001	41.4 (26.8)	66.7 (65.8)
ER visits PPPY	2.5 (2.4)	0.4 (0.6)	<0.001	3.4 (3.0)	8.6 (14.0)
Office visits PPPY[b]	10.3 (7.8)	3.0 (3.3)	<0.001	11.7 (8.4)	13.1 (12.9)
Laboratory visits PPPY[c]	7.2 (5.8)	1.0 (1.3)	<0.001	8.3 (6.5)	12.6 (12.8)
Other outpatient visits PPPY[d]	15.4 (19.9)	11.0 (28.0)	<0.001	18.0 (17.3)	32.5 (47.7)
Pharmacy, n (%)					
Pain medications	654 (98.3)	950 (28.6)	<0.001	328 (99.4)	2,215 (99.8)
Opioids	650 (97.7)	438 (13.2)	<0.001	328 (99.4)	2,211 (99.6)
NSAIDs	620 (93.2)	763 (23.0)	<0.001	318 (96.4)	2,018 (90.9)
Gabapentin	67 (10.1)	28 (0.8)	<0.001	54 (16.4)	727 (32.7)
Hydroxyurea	442 (66.5)	0 (0)	<0.001	234 (70.9)	1,635 (73.6)
Iron chelation therapy	52 (7.8)	0 (0)	<0.001	30 (9.1)	432 (19.5)
Blood transfusion	304 (45.7)	0 (0)	<0.001	177 (53.6)	1,432 (64.5)

ER, emergency room; FFS, fee-for-service; HCRU, healthcare resource utilization; NSAID, nonsteroidal anti-inflammatory drug; PPPY, per patient per year; SCD, sickle cell disease; SD, standard deviation; VOC, vaso-occlusive crisis.
[a]Outpatient visit claims were grouped by patient, provider type (e.g., primary care provider), and date to identify a single visit. ER, outpatient office visits, laboratory visits, and other outpatient visits were included in this total.
[b]Outpatient office visit claims were grouped by patient, provider type, and date to identify a single visit in an office setting.
[c]Laboratory visits claims were grouped by patient, provider type, and date to identify a single visit in a laboratory setting.
[d]Other outpatient visit claims were grouped by patient, provider type, and date to identify a single visit in a non-office setting (e.g., visits for screening, X-rays, transfusions, intravenous iron chelation administration, etc).

Figure 4. Annual Costs by Payer Type and Age



FFS, fee-for-service; PPPY, per patient per year; VOC, vaso-occlusive crisis.

Table 4. VOC and Transfusion Costs by Payer Type and Age

Annual VOC and Transfusion Costs	Primary Cohort		Secondary Cohorts			
	Patients With SCD With Recurrent VOCs Aged 5–11 Years		Patients Aged 5–11 Years With ≥2 VOCs PPPY		Patients Aged ≥12 Years With ≥2 VOCs PPPY	
	Commercial (n = 68)	Medicaid FFS (n = 272)	Commercial (n = 37)	Medicaid FFS (n = 131)	Commercial (n = 449)	Medicaid FFS (n = 1,027)
VOC costs PPPY[a], mean (SD)	$44,805 ($65,256)	$34,428 ($66,170)	$69,700 ($79,567)	$58,139 ($87,390)	$79,611 ($83,465)	$108,880 ($205,522)
Average cost per VOC	$16,458 ($19,674)	$11,873 ($16,365)	$19,965 ($24,806)	$13,460 ($18,035)	$16,043 ($16,069)	$14,634 ($33,253)
Transfusion costs PPPY[a], mean (SD)	$9,780 ($26,652)	$8,888 ($22,428)	$13,682 ($33,834)	$13,082 ($28,892)	$16,104 ($27,261)	$32,564 ($71,017)

FFS, fee-for-service; PPPY, per patient per year; SCD, sickle cell disease; SD, standard deviation; VOC, vaso-occlusive crisis.
[a]VOC and transfusion costs were included in the costs for the inpatient and outpatient settings where they occurred.

Limitations

- This study used administrative claims data collected for reimbursement purposes and is therefore subject to potential misclassification bias; only direct costs are included in this analysis, which likely underestimate the burden of disease associated with SCD
- Given the minimum 12-month post-index period for patients with SCD, those who died, went on long-term disability, or were not continuously enrolled for ≥12 months were excluded from the analysis and might have systematically different outcomes than patients who met enrollment criteria

CONCLUSIONS

- **Pediatric patients aged 5 to 11 years with SCD with recurrent VOCs experience a substantial burden of SCD-related complications despite availability and utilization of chronic treatments**
- **Beginning in childhood, SCD with recurrent VOCs is associated with considerable HCRU and substantial costs, which are significantly higher than those of the matched controls from the general population**
- **From childhood, SCD with recurrent VOCs imposes significant clinical and economic burden, highlighting the need for potentially curative therapies early in the disease course**

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Disclosures

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