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An analysis of inpatient pediatric sickle cell disease: Incidence, costs, and outcomes

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Abstract

Objective: To identify characteristics of pediatric sickle cell disease (SCD) hospitalizations and to examine admission demographics and medical expenditures.

Methods: Admissions with SCD were identified from the 2009 and 2012 releases of the Healthcare and Cost Utilization Project's Kids Inpatient Database. Disease-specific secondary diagnoses including acute chest syndrome (ACS), vaso-occlusive pain crisis (VOC), splenic sequestration, and stroke/transient ischemic attack were analyzed for patient and hospital demographics. Analytical endpoints included total healthcare expenditures and mortality.

Results: We reviewed 75,234 inpatient hospitalizations with a diagnosis of SCD. Over $900,000,000 was spent annually in associated healthcare expenditure. The median length of hospitalization stay (LOS) for all admissions was 3 days (interquartile range [IQR] 2–5 days). VOC was the most frequent secondary diagnosis, recording 48,698 total hospitalizations and a median LOS of 3 days (IQR 2–6 days). Of the 8,490 hospitalizations with ACS, the infant population had a significantly higher mortality rate compared to other age groups (2% vs. 0.3%, $P < 0.001$). Cerebral vascular accidents incurred the second highest median hospitalization cost ($18,956), behind ACS ($22,631). A high proportion of Caucasian patients died during hospitalization for VOC (0.4% vs. 0.1%, $P = 0.014$) and ACS (4% vs. 0.2%, $P < 0.001$) when compared to non-Caucasians.

Conclusion: Inpatient hospitalizations for secondary manifestations of pediatric SCD were associated with significant healthcare expenditures. Patients with an increased statistical risk for death during hospitalization included Caucasians with SCD complications of ACS and VOC, and patients <1-year-old with ACS. Further research is needed to substantiate the associated clinical significance of these findings.

KEYWORDS

acute chest syndrome, cerebrovascular accident, hospitalization costs, kids inpatient database, sickle cell disease, splenic sequestration, vaso-occlusive crisis

1 | INTRODUCTION

Sickle cell disease (SCD) is an autosomal recessive genetic defect in hemoglobin,[1] with approximate incidences as high as one in 365 persons in the Black U.S. population.[2] Disease manifestations can include pain crisis, splenic sequestration, acute chest syndrome (ACS), and cerebrovascular accident (CVA). These conditions are largely the result of a mechanistically similar vaso-occlusive phenomena,[1,3] yet the morbidity, mortality, and healthcare expenditure associated with each presentation differs greatly. The National Institutes of Health has dedicated over one quarter of a billion dollars in recent years (2007–2013) to basic science and clinical research efforts targeting treatment and prevention modalities within this disorder.[4]

In 2010, Brousseau and colleagues reported sickle cell vaso-occlusive pain crisis (VOC) was the leading cause of hospital utilization for SCD patients.[5] They found demographic and socioeconomic factors including age and insurance payer type to modify one's frequency of hospitalization and incidence of 30-day rehospitalization.

Abbreviations: ACS, acute chest syndrome; CVA, cerebrovascular accident; ED, Emergency Department; KID, Kids Inpatient Database; LOS, length of hospitalization stay; SCD, sickle cell disease; TCD, transcranial doppler; VOC, vaso-occlusive pain crisis

TABLE 1 Database characteristics

	Admissions (%)	ACS (%)	Vaso-occlusive (%)	Splenic (%)	Stroke (%)
No.	75,234	8,490	48,698	1,881	3,669
Ages					
<1	4,022 (5.3)	137 (1.6)	830 (1.7)	237 (12.9)	–
1–5	15,957 (21.2)	1,978 (23.3)	7,312 (15.0)	1,089 (59.5)	197 (4.6)
6–10	12,321 (16.4)	2,165 (25.5)	7,595 (15.6)	265 (14.5)	534 (14.5)
11–15	13,925 (18.5)	1,698 (20.2)	9,684 (19.9)	139 (7.6)	898 (24.5)
16–20	28,897 (38.4)	2,505 (29.5)	23,193 (47.6)	98 (5.3)	2060 (56.1)
O/NR	112 (0.1)	–	84 (0.2)	–	–
Sex					
Male	37,661 (50.1)	4,754 (56.0)	24,033 (49.4)	996 (54.4)	1813 (49.4)
Female	37,452 (49.8)	3,729 (43.9)	24,585 (50.5)	839 (45.6)	1856 (50.6)
Race					
Caucasian	1,124 (1.6)	107 (1.3)	664 (1.4)	36 (2.0)	31 (0.9)
Black	61,366 (81.6)	6,843 (80.6)	40,614 (83.4)	1,370 (74.8)	3012 (82.1)
Hispanic	3,428 (4.6)	400 (4.7)	2,091 (4.3)	150 (8.2)	181 (4.9)
Asian	177 (0.2)	32 (0.4)	103 (0.2)	11 (0.6)	10 (0.3)
O/NR	9,038 (12.0)	1,108 (13.1)	5,225 (10.7)	263 (14.4)	434 (11.8)
LOS (IQR)	3 (2–5)	4 (3–7)	3 (2–6)	3 (2–4)	3 (2–6)
Charges ($)	14,337	22,631	15,566	14,858	18,956
(IQR)	(8,314–25,620)	(13,314–41,190)	(9,139–27,726)	(9,065–27,098)	(10,785–35,100)
Death	91 (0.1)	25 (0.3)	47 (0.1)	–	20 (0.5)

ACS, acute chest syndrome; Splenic, splenic sequestration; stroke, stroke/transient ischemic attack; O/NR, other/not recorded during hospitalization; LOS, length of hospitalization stay (days); IQR, interquartile range; –, too few patients to report national incidence estimation, LOS and charges reported as median with IQR.

Two related publications reported similar trends in hospitalization and incidence.[6,7] Despite significant scientific inquiry into SCD incidence and associated healthcare expenditures, there remains a lack of population-based investigation into factors contributing to one's length of hospitalization stay (LOS), and outcome analysis, including death.

The population-based database approach we have employed affords statistical power in analyzing SCD hospitalizations in low incidence groups, as well as providing better aggregate perspectives to already well-studied populations. In the United States, progressive social advancements and generations of immigration have created a vibrant, melting-pot population. With this comes a variety of genetic diseases that are being seen in a more diverse group of patients. In Europe, immigration en masse is a more recent phenomenon than in the United States and its effects are already being seen in hemoglobinopathies and SCD epidemiology.[8,9] As a result, reporting on traditionally understudied groups has added utility in the modern world. Although not often reported in the United States, A New York newborn screening program estimates Caucasian (non-Hispanic) SCD incidences as low as 1: 40,000 births.[10] Large patient sample sizes possible through large databases are required for adequate power to analyze these hospitalizations.

Our analysis aimed to identify populations with high-risk complications and the expenditures associated with those complications. Furthermore, our analysis of admissions with SCD stands to not only direct therapy in communities with heavy disease burden, such as Black and Hispanic American communities, but also shed light on populations with lower incidences of SCD that are not typically studied.

2 | METHODS

We reviewed inpatient records from 2009 and 2012 of the Kids Inpatient Database (KID).[11] The KID is maintained by the Agency for Healthcare Research and Quality's Healthcare Cost and Utilization Project, and contains information about patient and hospital characteristics for roughly 80% of hospitalizations for children (<21 years) in the United States. The database includes admissions from approximately 4,100 U.S. hospitals in 44 of the 50 states. Historically, new releases of the KID have occurred every 3 years, with versions of the KID prior to 2016 used ICD-9 coding, while subsequent versions used ICD-10. Our study, utilizing the 2009 and 2012 databases, represents a comprehensive analysis with one coding scheme (ICD-9). Several recent publications have used the KID in a similar manner to characterize other pediatric conditions.[12–14]

Admissions with SCD were identified within the KID by queries of ICD-9 diagnosis codes 282.62 (Hb-SS disease with crisis), 282.61 (Hb-SS disease without crisis), and 282.60 (Sickle cell anemia not otherwise specified (NOS)). Admissions with potential disease-specific SCD diagnoses (ACS, VOC, CVA, splenic sequestration) were identified by

ICD-9 codes, with patient demographic and hospitalization characteristics characterized. Admission sample weights provided by the KID were used to adjust the roughly 80% cohort of American hospitalizations into a validated nationwide estimation. Endpoints included patient age, race, gender, billable charges excluding physician fees, death, and LOS. Charges from 2009 were adjusted for inflation by utilizing US Department of Commerce Bureau of Economic Analysis website coefficients to match 2012 costs. Our study qualified as nonidentifiable human subject research employing the use of publicly available data, and thus was exempted from institutional review board (IRB) approval.

2.1 | Statistical analysis

Data were grouped for analysis using SPSS statistical software version 23 (IBM Corp., Armonk, NY) and Microsoft Excel (Seattle, WA). Median and interquartile range (IQR) were used to describe the distribution of data for LOS and charges per admission. A multivariate binary logistic regression analysis was conducted to explore independent predictors contributing to mortality (mortality vs. no mortality) during SCD hospitalization. Analysis of variance analyses were run to compare continuous samples where applicable, with a threshold for statistical significance set at $P < 0.05$.

3 | RESULTS

A total of 75,234 hospitalizations reporting a diagnosis of SCD were collectively reported in 2009 and 2012 (Table 1). Of these hospitalizations, 70.1% and 87.3% were from urban teaching hospitals in 2009 and 2012, respectively, with approximately only 3.5% from rural hospitals during each of the 2 years. Annual healthcare expenditure for SCD admissions totaled over $900,000,000, with a median hospitalization cost of $14,337 per stay. Black patients accounted for a majority of admissions (81.6%) with Hispanics (4.6%) and Caucasians (1.6%) totaling substantially smaller cohorts. Individuals between 16 and 20 years old accounted for 38.4% of hospitalizations for SCD.

The overall mortality associated with any inpatient hospitalization was 0.1%. Multivariate analysis (Table 2) demonstrated that a diagnosis of congenital heart disease ($P < 0.001$), sepsis ($P < 0.001$), stroke ($P < 0.001$), and ACS ($P < 0.001$) all carried statistical predilection for increased risk of patient death during these pediatric hospitalizations.

3.1 | Acute chest syndrome

Overall, there were 8,490 hospitalizations recording a diagnosis of ACS (Table 1). The median length of hospitalization in this cohort was 4 days (IQR range 3–7 days), with median hospitalization charges $22,631 per admission. Figures 1a and 1b depict incidence and length of stay by age grouping, respectively. Twenty-five patients (0.3%) admitted with ACS died during their hospitalization. Table 3 details rates of mortality in ACS; as displayed, patients <1-year-old had a statistically significant higher risk of death ($P < 0.001$). Also, a statistically significant greater proportion of Caucasian patients (3.8%) died during hospitalization when compared to mortality from SCD in other racial and ethnic groups ($P < 0.001$). Collectively, hospitalizations for ACS averaged $162,797,570 in annual expenditures.

TABLE 2 Multivariate analysis: mortality by diagnosis/characteristic regression outputs

	Odds ratio	95% CI for odds ratio	*P*-value
SCD related			
Sepsis	44.6	28.8–69.2	<0.001
CVA	3.7	2.2–6.3	<0.001
ACS	3.4	2.1–5.7	<0.001
Splenic sequestration	1.1	0.2–6.2	0.916
Vaso-occlusive pain	0.4	0.3–0.7	<0.001
Non-SCD related			
CHD	15.5	4.1–58.5	<0.001
Obesity	1.9	0.5–7.1	0.327
OSA	1.3	0.4–4.8	0.678
Asthma	0.7	0.4–1.2	0.225
Dehydration	0.3	0.1–1.3	0.100
DM	0.0	0.0–0.0	0.994
Other characteristics			
Gender	1.2	0.8–1.8	0.380
Teaching hospital	1.1	0.6–1.8	0.744
Non-Black	0.8	0.4–1.4	0.440
Age <5	0.4	0.2–0.8	0.006
Constant			<0.001

Odds ratio reflects death incidence in conjunction with comorbid diagnosis, and gender represents male sex.
CVA, cerebral vascular accident; ACS, acute chest syndrome; CHD, congenital heart disease; OSA, obstructive sleep apnea; DM, diabetes mellitus.

3.2 | Vaso-occlusive crisis

VOC accounted for 48,698 hospitalizations, the highest subtotal over the 2-year period of study (Table 1), with nearly half (47.6%) of the hospitalizations in patients aged 16–20 years (Fig. 1c). Caucasian admissions contributed to only 1.4% of the VOC cohort; however, these patients carried a statistically significant increased risk of death during their hospitalization (0.4%, $P = 0.020$) (Table 3). In all, 47 patients (0.1%) with a diagnosed VOC died during their inpatient stay. Collectively, hospitalizations for vaso-occlusive crises averaged $588,632,958 in annual expenditures.

3.3 | Splenic sequestration

Splenic Sequestration was most commonly identified in admissions of patients <5 years in age (72.4%) (Table 1) (Fig. 2a). Length of stay trended toward longer hospitalizations as age increased (Fig. 2b). Death was an uncommon occurrence and witnessed in <0.1% of hospitalizations for splenic sequestration. Collectively, hospitalizations for splenic sequestration averaged $21,287,099 in annual expenditures.

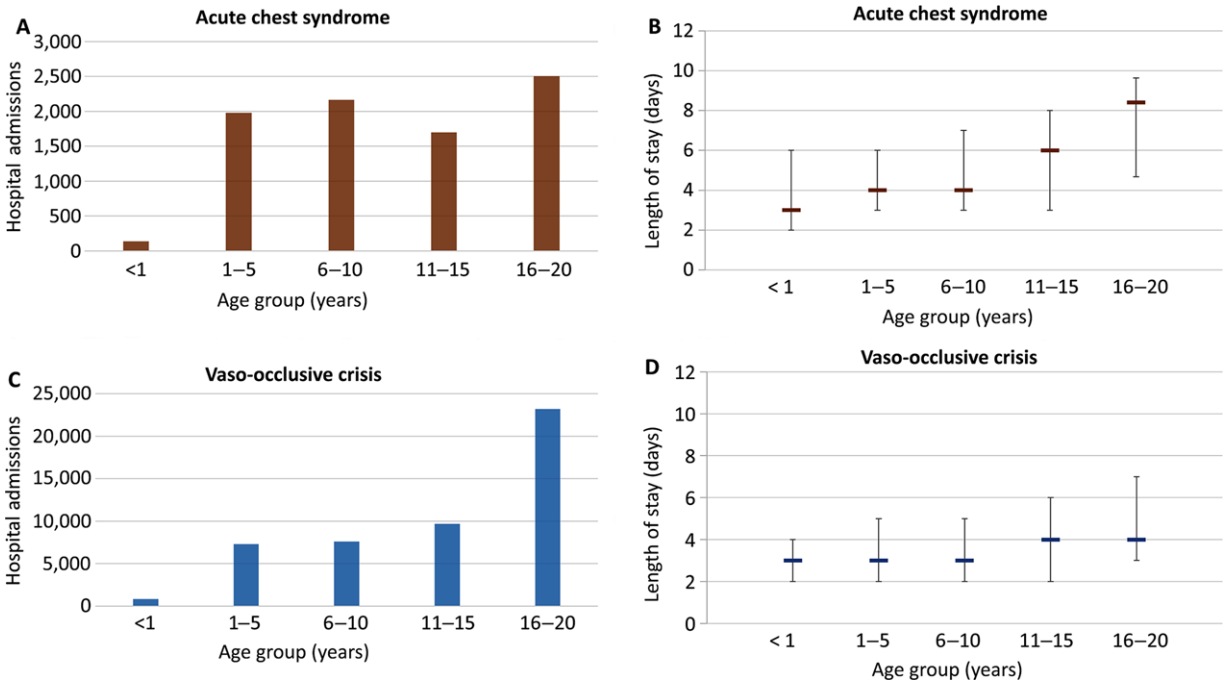

FIGURE 1 Acute chest syndrome (ACS) (A and B) and vaso-occlusive crisis (C and D). Total number of hospitalizations stratified by age group (A and C) and median length of hospitalization stay (LOS) (B and D) by age group

3.4 | Cerebrovascular accident

In total, 3,669 cerebrovascular events occurred during SCD hospitalizations (Table 1). Incidence increased with age (Fig. 2c). A graph identifying median length of stay by age group revealed longer hospitalizations for older patients as well (Fig. 2d). No age cohort carried a statistically significant predilection for death following a cerebrovascular event (Table 3). Overall, 20 patients (0.5%) died during an admission associated with a CVA or transient ischemic attack. Collectively, hospitalizations for CVA in pediatric SCD totaled $64,724,078 in annual expenditures.

TABLE 3 2009 and 2012 inpatient mortality

	ACS	Vaso-occlusive	Stroke/transient ischemic attack
N	25	47	20
Ages			
<1	2.0%$^{P<0.001}$	0.0%$^{P=0.233}$	0.0%$^{P=0.907}$
1–5	0.0%	<0.1%	0.9%
6–10	0.4%	0.1%	0.3%
11–15	0.1%	0.1%	0.7%
16–20	0.5%	0.1%	0.5%
Sex			
Male	0.2%$^{P=0.638}$	0.1%$^{P=0.831}$	0.6%$^{P=0.778}$
Female	0.4%	0.1%	0.5%
Race			
Caucasian	3.8%$^{P<0.001}$	0.4%$^{P=0.020}$	0.0%$^{P=0.361}$
Black	0.2%	0.1%	0.7%
Hispanic	0.0%	0.2%	0.0%
Asian	0.0%	0.0%	0.0%
O/NR	0.4%	<0.1%	0.0%

ACS, acute chest syndrome; O/NR, other/not recorded during hospitalization; statistical analysis exponents compare death rates by cohort, that is, % of males versus females that died during hospitalization, percentages represent proportions for a given cohort.

4 | DISCUSSION

Investigation of the cost, length of stay, and mortality of SCD hospitalizations and its complications can provide useful context to clinical presentation. As with other database studies, our results rely on the accuracy of medical chart reporting of demographics, an important caveat that is discussed further in the limitations. Despite that our study encompasses one of the largest current collections of SCD patients and enables adequate power for analysis of understudied patient populations. We found that Caucasian patients had increased rates of mortality during hospitalizations for ACS or VOC. Despite widespread newborn screening in the United States,[15] SCD may be underrecognized in the non-Black population, especially if patients have immigrated to the United States after the newborn period. From a practical standpoint, the absolute mortality (n = 4) in the Caucasian SCD demographic limited any definitive clinical conclusions. Finally, we must consider that the KID may have inaccurately categorized patients by racial or ethnic group, especially in situations involving biracial children. Further study of SCD-related mortality in non-Black populations may help substantiate these findings.

With regard to ACS, the significantly higher mortality we report in infant admissions may be due to the relatively non-specific criteria for

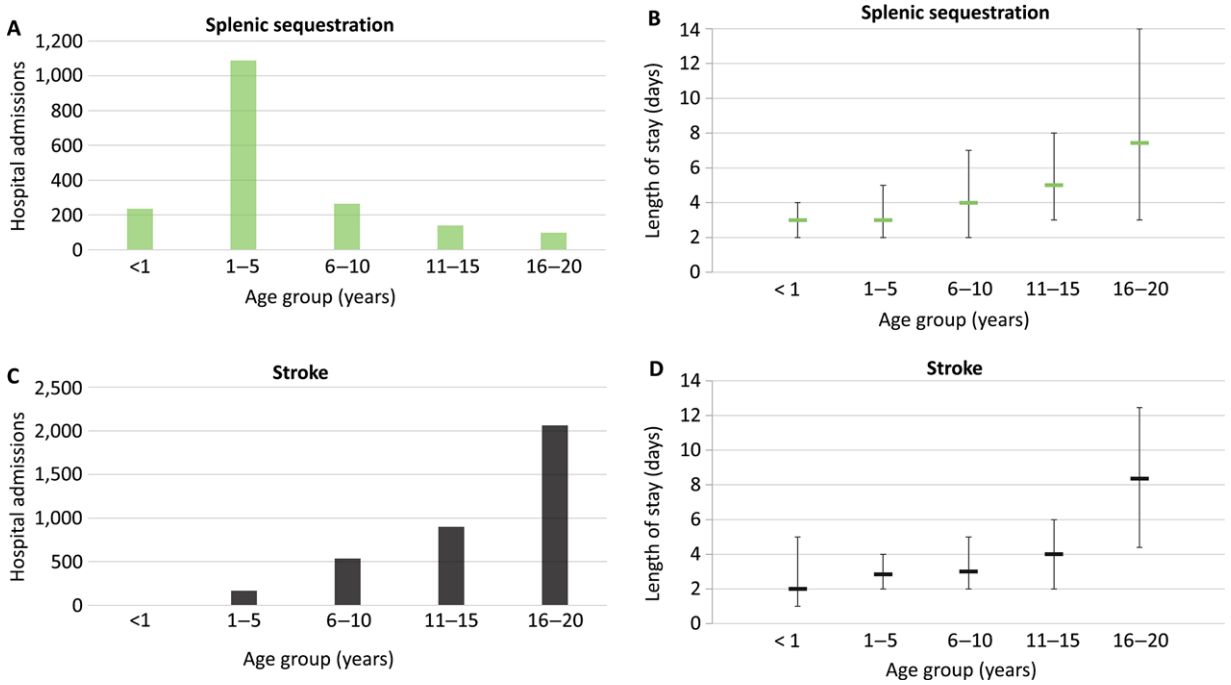

FIGURE 2 Splenic sequestration (splenic) (A and B) and stroke (C and D). Total number of hospitalizations stratified by age group (A and C) and median length of hospitalization stay (LOS) (B and D) by age group

ACS (fever, increased work of breathing, new infiltrate on chest X-ray, decline of respiratory status, etc.). This may lead to underrecognition, and misdiagnosis of ACS for less severe clinical entities such as pneumonia or bronchiolitis. A recent report proposes that monitoring the *rate* of respiratory decline can help ensure a more accurate diagnosis of ACS.[16] Heightened vigilance and the refinement of ACS diagnostic criteria may curtail mortality in this high-risk age group.

VOC hospitalizations accounted for over half of the total hospitalizations and were more common in older pediatric age groups. These findings support a similar analysis of KID data from 1997 where LOS also increased with age.[7] This highlights an ever-present clinical scenario suggesting that age may be a reliable predictor of a patient's LOS or episodic severity. We suspect that recognition of this clinical trend may allow for streamlining measures to decrease hospital expenditure and patient suffering by encouraging early and adequate pain management strategies. However, it seems that the unfortunate incorporeal nature of an individual's pain, in combination with recent initiatives to decrease opioid medication use may still leave practitioners hesitant to adequately manage a patient's VOC pain crisis. Emergency department (ED) providers may have a bias toward pain medication addiction when it comes to sickle cell related pain.[17] African Americans with SCD have been shown to have 25% longer ED wait times compared to other patient populations, suggesting that racial disparities may impact time to medical care.[18] Nonetheless, this hesitancy toward swift care and analgesia in the ED might allow pain crises to advance to levels more difficult to manage, further increasing LOS and costs.

In line with prior literature, we found that patients admitted for splenic sequestration most commonly were within the youngest population of patients analyzed (0–5 years). In a cohort of 190 patients with SCD diagnosed at birth, the median age of the first episode of acute splenic sequestration crisis occurred at 1.4 years.[19] Moreover, these same patients experienced 437 episodes of splenic sequestration collectively with 67% of these patients experiencing more than one episode.[19] In our analysis, the incidence of splenic sequestration hospitalizations also decreased as patients grew older. This is likely explained by the notion that the probability of sequestration decreases as the amount of functional splenic tissue decreases in older patients through repeated tissue infarctions. Up to 90% of SCD patients aged 5 years old have functional or anatomical asplenia.[20] Also noteworthy, patient mortality from splenic sequestration was low (<0.1%) in our sample. However, older reports from a sickle cell cohort study with 216 patients from 1981 had mortality rates as high as 12% within the first episode.[21] The decline we see in mortality rates between our data and older reports over the last 35 years may be due to implementation of more widespread newborn screening, patient education, transfusion programs, and prophylactic splenectomies.[22]

The mortality rate for CVA was the highest of the four diagnoses, while median costs ranked second highest. This result illustrates the clinical and economic impact that a stroke diagnosis carries in patients with SCD. For such reasons, primary stroke prevention strategies have been becoming more popular. A recent systematic review and cost-effectiveness analysis concluded that use of transcranial doppler (TCD) ultrasonography for identifying children with high risk for stroke and prophylactic blood transfusions appeared to be both clinically effective and cost-effective when compared to screening with TCD ultrasonography alone.[23] Other studies have shown that hydroxyurea therapy is another cost-effective option for secondary stroke prevention in children with SCD, especially in resource constrained countries.[24] Newer investigations from the TWiTCH trial have shown that hydroxyurea therapy can decrease TCD velocities,

which may be an indicator of reduced stroke risk in pediatric SCD patients.[25]

Such innovative prevention strategies are starting to change the age distribution of stroke diagnosis in patients with SCD. When looking at a pediatric subset (ages 0–20) from a prospective, multicenter study that enrolled 4,082 patients from the years 1978 to 1988, there was a peak incidence of stroke between ages of 2 and 9.[26] However, our data show that SCD hospitalization with stroke was far more common in the 10–20 age range, with a peak in the 19-year-old age group. We hypothesize that such a shift in age preference during the last few decades could largely be a result of prevention strategies and close monitoring earlier in a patient's life. However, as a patient ages, the financial burden and time commitment required to manage SCD becomes sizeable. These patients may be lost to follow up, rendering prevention strategies difficult to implement, effectively delaying CVA incidence rather than reducing it. The time-intensive nature of SCD in children is highlighted by reports that claim these students miss up to 10% of the average school year.[27] Thus, there may be a necessity to implement programs to help alleviate the inconveniences that are associated with frequent sickle cell care (e.g., driving long distances to hospitals with sickle cell programs). While some effective programs already exist,[28] more focus on this matter may help recapture patients lost to follow up for these reasons.

Although our study encompasses one of the largest cohorts of pediatric SCD hospitalizations available and identifies key demographical discrepancies of care, the resources incorporated into our analysis carry a few important limitations worthy of remark. Primarily, KID data use hospital discharge paperwork and rely on the accuracy of reported admission characteristics. Specifically, patient race is a difficult analysis to validate from hospital level discharge as patient demographics may not be self-reported.[29,30] Yet, the more often a patient presents to a healthcare system (e.g., hospitalizations), there is greater agreement between patient self-reported race/ethnicity data and administrative recording of race/ethnicity (e.g., medical chart data).[29] In other words, there are more opportunities to record accurate demographic data. From this we can reasonably surmise that the SCD admission demographics from the KID database are more likely to be accurate since SCD patients frequently visit healthcare systems (e.g., emergency department visits, hospitalizations, etc.).[31] Second, databases such as the KID contain only admission-level data and frequently do not provide information about treatment modalities or patient history for context. Therefore, this impacts the applicability of some of our findings. Finally, without patient identifiers to examine one's severity of disease it becomes difficult to identify whether a small subset of patient's greatly impacts expenditure and resource utilization in SCD. However, by including over 70,000 hospitalizations, from over 4,000 hospitals nationwide, the quantity of data analyzed provides an aggregate hospitalization depiction that still provides utility from an epidemiological perspective. Typically, large database studies such as this offer a broad complement to more clinically focused intrainstitutional studies where case-specific data are more robust, but likely underpowered.

In conclusion, the data presented here highlight pediatric SCD mortality and related patient demographics. Additionally, SCD and its common complications are associated with considerable aggregate and admission-level expenditures. Hospitalizations with ACS and VOC in Caucasian populations are associated with statistically significant higher mortality rates, as are infants with ACS. Further studies may more closely characterize these discrepancies.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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