Research Article

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Economic burden of sickle cell disease in the United States: a retrospective analysis of a commercial insurance database

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Aim: To evaluate healthcare resource utilization (HCRU) and costs for US commercially insured adult and pediatric patients with sickle cell disease (SCD) and matched non-SCD cohorts. **Materials & methods:** Patients with ≥3 SCD diagnosis codes (D57.0–D57.219; D57.4–D57.819) from July 2016 to December 2020 were identified from the IBM® MarketScan® Commercial database. The earliest SCD diagnosis was defined as the index date. Non-SCD control patients were matched 1:1 on age, gender and region. Continuous 6-month baseline and ≥12-month follow-up coverage was required. Follow-up HCRU and costs (2020 USD) were calculated per patient per year. Pediatric (<18 years) and adult (≥18 years) patients were analyzed separately. **Results:** For 1299 pediatric patients with SCD and matched controls, mean (SD) age was 10.0 (4.8) years and 51% were female; mean (SD) follow-up was 34.3 (14.4) months. In the first 12 months, pediatric patients with SCD had higher HCRU (hospitalizations: 0.6 vs 0.01; hospital length of stay: 2.4 vs 0.05 days; outpatient visits: 13.4 vs 6.0; office visits: 6.9 vs 4.7; prescriptions: 12.8 vs 3.8) and mean total costs ($31,445 vs $2844), mainly due to hospitalizations ($15,195 vs $477) and outpatient visits ($12,746 vs $1758), versus controls (all $p < 0.0001$). For 2792 adults with SCD and matched controls, mean (SD) age was 38.0 (13.2) years and 62% were female; mean (SD) follow-up was 31.8 (13.7) months. Adults with SCD had higher per-patient per-year HCRU (hospitalizations: 0.8 vs 0.06; hospital length of stay: 4.3 vs 0.2 days; outpatient visits: 20.9 vs 9.3; office visits: 10.4 vs 6.9; prescriptions: 20.5 vs 11.7) and mean total costs ($42,550 vs $7522), also due to hospitalizations ($20,056 vs $1326) and outpatient visits ($17,508 vs $4301), versus controls (all $p < 0.0001$). **Conclusion:** The economic burden of SCD among pediatric and adult patients is substantial with increased HCRU and costs compared with matched controls. Better treatments for SCD could reduce the economic burden for patients, as well as payers.

Plain language summary

What was the aim of this research? The aim of this study was to compare the healthcare usage and costs of commercially insured people with and without sickle cell disease (SCD).

How was the research carried out? Using commercial insurance claims data from July 2016 to December 2020, patients with SCD were each matched to someone without SCD who was the same age, gender, and living in the same region. Healthcare resource usage and costs from the first SCD diagnosis between July 2016 and December 2019, or from a random date during the same period for those without SCD, were calculated per patient per year. Pediatric (<18 years) and adult (≥18 years) patients were analyzed separately.

What were the results? Pediatric patients with SCD had significantly more healthcare usage compared with those without SCD. In the first 12 months of follow-up, patients with SCD had more hospitalizations (39.3-fold), ER visits (6.3-fold), outpatient visits (2.2-fold), and prescriptions (3.4-fold). Healthcare costs were also higher for patients with versus without SCD ($31,445 vs $2844), primarily due to hospitalizations ($15,195 vs $477) and outpatient visits ($12,746 vs $1758). Adult patients with SCD also had higher healthcare usage compared with those without SCD, with more hospitalizations (14.4-fold), ER visits (7.2-fold), and twice as many outpatient visits and prescriptions during follow-up. Their higher healthcare costs ($42,550 vs $7522) were also due to hospitalizations ($20,056 vs $1326) and outpatient visits ($17,508 vs $4301).

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What do the results of the study mean? Commercially insured pediatric and adult patients with SCD in the US have substantially higher healthcare resource utilization and costs compared with matched controls. Better treatments for SCD could reduce the economic burden for both patients and payers.

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Keywords: commercial insurance • costs • healthcare resource utilization • retrospective • sickle cell disease

Background

Sickle cell disease (SCD) is the most common inherited hemoglobinopathy in the US [1]. Based on records from universal newborn SCD screening programs that have been implemented across the US since 2006, the crude birth prevalence for SCD between 2016 and 2020 has been estimated to be one in every 2070 live births [2,3]. Among the estimated 100,000 individuals in the US affected by SCD, approximately 60% are adults ≥18 years of age [1,4]. Mutations to the β-globin gene and the ensuing formation of sickle hemoglobin (HbS) result in the sickling of erythrocytes that is characteristic of SCD. Through hemolysis, vaso-occlusive crisis (VOC) or other property changes in the red blood cell, the complications of this lifelong illness affect multiple organ systems, leading to substantial morbidity and increased mortality [5–7].

In the US, the medical costs of patients with SCD are substantial due to the healthcare services required for the management of SCD and its complications, with inpatient care accounting for a significant portion of the costs [8]. Among pediatric patients with SCD, inpatient hospitalizations have been reported to cost up to $900 million per year [9]. Moreover, the lifetime medical costs associated with SCD have been estimated to be $1.7 million per patient [10]. While the healthcare resource utilization (HCRU) and costs of SCD have been assessed in a number of published studies, most of these analyses were conducted among patients with noncommercial insurance provided by Medicaid and Medicare, government-funded insurance plans that provide healthcare coverage for low-income individuals and those ≥65 years of age or <65 years with certain disabilities or conditions, respectively [11]. Although a handful of studies have described the HCRU and costs of commercially insured SCD patients with healthcare coverage purchased from private companies, their focus was largely on patients with severe SCD as evidenced by VOCs and/or other SCD-related complications [12–14]. Three studies investigated the burden of SCD among commercially insured patients with and without SCD [10,15,16]. The first study evaluated the burden of SCD among patients who had recurrent VOCs [16]. While the second study evaluated HCRU stratified by service category (e.g., inpatient, outpatient and office visits, etc.), the SCD and control cohorts were constructed using two different data sources and estimates of SCD-attributable costs were limited to the total medical costs paid by insurers and out-of-pocket (OOP) costs paid by patients, which could include copays, deductibles, coinsurance and any medical care or supplies not covered by insurers; the corresponding healthcare service costs were not reported [10]. The third study was a continuation of a prior study that provided a granular description of the HCRU and costs of pediatric patients with SCD [12]. However, the follow-up study only evaluated the economic burden of pediatric SCD [15]. Furthermore, this study was conducted using data for healthcare services received nearly two decades ago, as did several of the other studies of commercially insured populations [10,12,13].

There is limited information available regarding the contemporary real-world clinical and financial burden of patients with SCD in the US who have commercial healthcare coverage. In particular, the medical costs of specific healthcare service categories as well as the OOP costs of patients with SCD are largely unknown. The aim of this study was to evaluate the all-cause HCRU and healthcare costs of commercially insured pediatric and adult patients with SCD in the US versus matched control patients without SCD in a more contemporary dataset.

Materials & methods

Study design & data source

This study was a retrospective cohort study using data from the IBM® MarketScan® Commercial database from 1 January 2016 through 31 December 2020. The database contains individual-level, de-identified, structured healthcare claims information from employers, health plans and hospitals that reflects real-world treatment patterns and costs by tracking millions of patients, offering detailed information about all aspects of healthcare. Data about individual patients are integrated from all providers of care, maintaining healthcare utilization and cost record

connections at the patient level. Used primarily for research, these databases are fully compliant with US privacy laws and regulations such as the Health Insurance Portability and Accountability Act (HIPAA).

Study population

Patients diagnosed with SCD during the index identification period, 1 July 2016 to 31 December 2019, were identified based on the presence of ≥3 inpatient or outpatient International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10) diagnosis codes for SCD (D57.0–D57.219 or D57.4–D57.819) on different dates. The date of the earliest SCD diagnosis to occur during the index identification period was defined as the index date. Those who received a hematopoietic stem cell transplant (HSCT) or bone marrow transplant prior to the index date were excluded from the study.

In addition, a control cohort was built. For inclusion in this cohort, patients could not have received an SCD diagnosis during the study period. These control patients were assigned a random index date from within the index identification period, and exact matched 1:1 to SCD patients based on age, gender and US geographic region [17]. All study patients were also required to have continuous medical and pharmacy insurance enrollment during the 6-month pre-index baseline period and for ≥12 months during the post-index follow-up period. The follow-up period was censored at the end of either continuous medical and pharmacy coverage or the study (31 December 2020), whichever occurred earlier. SCD patients and their matched controls were stratified by age into pediatric (age <18 years) and adult (age ≥ 18 years) populations which were assessed in separate analyses.

Patient demographics

The demographic characteristics of SCD and control patients were evaluated on the index date and consisted of age, gender, US geographic census region and health plan type. The duration of the follow-up period was also reported.

SCD-related treatments & complications

SCD-related treatments during the overall follow-up period were only evaluated among SCD patients. SCD-related treatments consisted of medications and procedures used in the management of SCD. SCD-related medications were identified by National Drug Codes and included hydroxyurea, pain medication (opioids such as codeine, morphine, meperidine, hydromorphone, butorphanol, levorphanol, methadone, oxymorphone, fentanyl, oxycodone and hydrocodone; ketorolac; and nonsteroidal anti-inflammatory drugs [NSAIDs]), iron chelators (deferasirox, deferoxamine, desferrioxamine), erythropoiesis-stimulating agents (erythropoietin, darbepoetin alfa, methoxy polyethylene glycol-epoetin beta) and antibiotics (penicillin, erythromycin, amoxicillin). Although l-glutamine was approved for the treatment of SCD in patients ≥5 years in July 2017, therapeutic uptake has been low and its usage was not evaluated in this study [18,19]. Given the limited follow-up available from US FDA approval in late 2019 to the end of the study, crizanlizumab and voxelotor treatment were not evaluated since their true utilization would not be captured. In addition, voxelotor was withdrawn from markets worldwide in September 2024. SCD-related treatment procedures were identified by the presence of Current Procedural Terminology, fourth edition (CPT-4) and ICD-10 diagnosis and procedure codes and included vaccination, blood transfusion, transcranial doppler ultrasound (TCD) screening, HSCT and bone marrow transplantation. Although HSCT typically includes the transplantation of cells sourced from bone marrow, peripheral blood and umbilical cord blood, there are specific procedure codes in the US that are designated for bone marrow transplants. Therefore, bone marrow transplants were evaluated as a separate procedure. SCD-related complications during both the first 12 months and the overall follow-up period were evaluated among both SCD and control patients. The prevalence of SCD-related complications was identified by the presence of CPT-4 and ICD-10 diagnosis and procedure codes for each complication as appropriate.

Healthcare resource utilization

All-cause inpatient, outpatient and pharmacy HCRU were evaluated among both SCD and control patients and included all healthcare claims. Outpatient claims included office visits, laboratory and diagnostic tests, biopsies, imaging, urgent care and ER visits. In addition to the overall outpatient HCRU, office visits and ER visits were further explored. Pharmacy usage consisted of all outpatient prescription drug claims. The frequency of hospitalizations, outpatient visits, office visits, ER visits and pharmacy usage during both the first 12 months and the overall follow-up period were reported. The number of hospitalizations, hospital length of stay (LOS),

outpatient visits, office visits, ER visits and pharmacy claims were evaluated per patient per year (PPPY) during the first 12 months as well as the overall follow-up period. In addition, inpatient- and ER-related HCRU were evaluated among patients with at least one hospitalization or ER visit, respectively, during the first 12 months of follow-up and the overall follow-up period.

Healthcare costs

All-cause inpatient, outpatient and pharmacy healthcare costs were evaluated among both SCD and control patients and consisted of the total gross payments from health plans, patients and/or other third-party payers for the services reported in all healthcare claims. Hospitalization, outpatient visit, office visit, ER visit and pharmacy usage costs were evaluated during both the first 12 months and the overall follow-up period. In addition, both total healthcare costs and OOP costs were reported. Total healthcare costs were calculated as the combined inpatient, outpatient visits and outpatient pharmacy costs. OOP costs were calculated by subtracting the payment received by the health plan from the total gross payment. Inpatient- and ER-related healthcare costs were also evaluated among patients with at least one hospitalization or ER visit, respectively, during the first 12 months of follow-up as well as the overall follow-up period. All costs were inflation adjusted to 2020 cost levels using the Medical Care component of the Consumer Price Index and reported PPPY.

Statistical analysis

Bivariate statistics were used to describe patient demographics, SCD-related treatment, SCD-related complication rates, HCRU and costs. Counts and percentages were reported for categorical variables. Continuous variables were summarized using means, standard deviations (SD) and medians. Patients who were missing any of the data necessary to assess an outcome or covariate variable were not included in the analysis of said variable. The impact of SCD was assessed by determining the fold difference in the all-cause HCRU and costs of SCD cohort patients and their exact matched control counterparts. Chi-squared test and Student's *t*-test were used for the cohort comparisons of categorical and continuous variables, respectively. Statistical analyses were conducted using SAS® 9.4 (SAS Institute, NC, USA).

Results

Patient demographics

Between 1 July 2016 and 31 December 2019, 1299 patients under 18 years old were included in the pediatric population and 2792 patients were included in the adult population. The same exact number of matched control patients were added to each population, 1299 and 2792, respectively. While the proportions of pediatric patients with each type of health plan were relatively similar between the cohorts, a slightly higher proportion of pediatric patients with SCD had health maintenance organization (HMO) coverage (18.6 vs 12.7%) while fewer patients with SCD had preferred provider organization (PPO) coverage (48.2 vs 52.6%) (Table 1). In general, HMOs are more affordable due to lower premiums and deductibles but are more restrictive, limiting patients to a set network of providers and requiring referrals for specialist care. PPOs have higher premiums, but provide more flexibility, allowing patients to see in- and out-of-network specialists without referral. The mean (SD) follow-up was 35.1 (14.3) and 33.5 (14.4) months for pediatric patients with SCD and their matched controls, respectively.

Similar to the pediatric population, a slightly higher proportion of adults with SCD had HMO coverage (17.8 vs 10.8%) while fewer adults with SCD had PPO coverage (45.8 vs 50.1%) (Table 1). The mean (SD) follow-up was 32.6 (13.8) months for the SCD cohort and 31.0 (13.5) months for controls.

SCD-related treatment & complications

During the overall follow-up period, 34.9% of pediatric patients with SCD received hydroxyurea (Table 2). A significant proportion of pediatric patients required pain medication during the follow-up period; 61.3% received $\geq$1 prescription for an opioid pain medication, 31.8% were prescribed ketorolac and 35.0% received an NSAID. Nearly a quarter of pediatric patients with SCD received at least one blood transfusion procedure with a mean (SD) of 2.6 (9.7) transfusions during the overall follow-up period. Approximately 43% of pediatric patients with SCD received TCD screening and less than 2% of received an HSCT or bone marrow transplant.

During the first 12 months of the follow-up period, the frequency of SCD-related complications was fivefold higher among pediatric patients with SCD (72.4 vs 14.3%, $p < 0.0001$). The most common acute complications were VOCs (51.9%), dactylitis (44.2%) and acute chest syndrome (13.2%) (Table 3). The most com-

Table 1. Patient demographic characteristics.

	Pediatric		Adult	
	SCD (n = 1299)	Control (n = 1299)	SCD (n = 2792)	Control (n = 2792)
Gender, n (%)				
Female	658 (50.7%)	658 (50.7%)	1722 (61.7%)	1722 (61.7%)
Male	641 (49.4%)	641 (49.4%)	1070 (38.3%)	1070 (38.3%)
Age, years				
Mean (SD)	9.9 (4.8)	9.9 (4.8)	38.0 (13.2)	38.0 (13.2)
Median	10	10	38	38
Age group				
≤ 3 years	173 (13.3%)	173 (13.3%)	–	–
4–11 years	568 (43.7%)	568 (43.7%)	–	–
12–17 years	558 (43.0%)	558 (43.0%)	–	–
18–30 years	–	–	968 (34.7%)	968 (34.7%)
31–44 years	–	–	872 (31.2%)	872 (31.2%)
45–54 years	–	–	564 (20.2%)	564 (20.2%)
55–64 years	–	–	388 (13.9%)	388 (13.9%)
Geographic region, n (%)				
North Central	195 (15.0%)	195 (15.0%)	344 (12.3%)	344 (12.3%)
Northeast	276 (21.3%)	276 (21.3%)	593 (21.2%)	593 (21.2%)
South	775 (59.7%)	775 (59.7%)	1703 (61.0%)	1703 (61.0%)
West	45 (3.5%)	45 (3.5%)	140 (5.0%)	140 (5.0%)
Missing/unknown	8 (0.6%)	8 (0.6%)	12 (0.4%)	12 (0.4%)
Health plan type, n (%)				
Comprehensive	37 (2.9%)	21 (1.6%)	109 (3.9%)	85 (3.0%)
EPO	8 (0.6%)	7 (0.5%)	24 (0.9%)	14 (0.5%)
HMO	241 (18.6%)	165 (12.7%)	496 (17.8%)	301 (10.8%)
POS	127 (9.8%)	115 (8.9%)	281 (10.1%)	304 (10.9%)
PPO	626 (48.2%)	683 (52.6%)	1278 (45.8%)	1399 (50.1%)
Other	235 (18.1%)	287 (22.1%)	541 (19.4%)	635 (22.7%)
Missing/unknown	25 (1.9%)	21 (1.6%)	63 (2.3%)	54 (1.9%)
Follow-up duration, months				
Mean (SD)	35.1 (14.3)	33.5 (14.4)	32.6 (13.8)	31.0 (13.5)
Median	34	32	29	28

EPO: Exclusive provider organization; HMO: Health maintenance organization; POS: Point-of-service; PPO: Preferred provider organization; SCD: Sickle cell disease; SD: Standard deviation.

mon chronic complications during this period were retinopathy (3.6%), avascular necrosis (2.9%) and scleral icterus (2.3%). The corresponding SCD-related complications data for the overall follow-up period is reported in Table 4.

Among adults with SCD, 25.6% received hydroxyurea during the overall follow-up period (Table 2). The majority of adults required pain medication during the follow-up period with 77.9% prescribed an opioid, 38.9% prescribed ketorolac and 50.9% prescribed an NSAID. More than a quarter of adults with SCD received at least one blood transfusion procedure with a mean (SD) of 2.1 (7.0) transfusions during the overall follow-up period. TCD screening (1.7%), HSCT (0.4%) and bone marrow transplants (0.1%) were rare among adults with SCD.

Approximately 86% of adults with SCD had an SCD-related complication during the first 12 months of the follow-up period, a 4.4-fold higher frequency of complications compared with their matched controls (Table 3). The most common acute complications during this period were VOCs (57.1%), dactylitis (52.4%) and acute kidney injury (13.4%). The most common chronic complications were retinopathy (11.7%), avascular necrosis (9.7%), scleral icterus (3.6%) and chronic kidney disease (3.6%). The corresponding SCD-related complications data for the overall follow-up period is reported in Table 4.

Table 2. Sickle cell disease-related treatment during the follow-up period.

	Pediatric (n = 1299)	Adult (n = 2792)
Hydroxyurea, n (%)	453 (34.9%)	716 (25.6%)
HSCT, n (%)	19 (1.5%)	10 (0.4%)
Bone marrow transplant, n (%)	17 (1.3%)	2 (0.1%)
Pain medication, n (%)	895 (68.9%)	2390 (85.6%)
Opioids	796 (61.3%)	2174 (77.9%)
Ketorolac	413 (31.8%)	1086 (38.9%)
NSAID	454 (35.0%)	1422 (50.9%)
Iron chelation agents, n (%)	73 (5.6%)	158 (5.7%)
Erythropoiesis-stimulating agent, n (%)	2 (0.2%)	73 (2.6%)
Antibiotics, n (%)	753 (58.0%)	1236 (44.3%)
Vaccination, n (%)	1127 (86.8%)	1564 (56.0%)
Pneumococcal conjugate vaccine	435 (33.5%)	657 (23.5%)
Influenza vaccine	979 (75.4%)	1323 (47.4%)
Hepatitis vaccine	192 (14.8%)	149 (5.3%)
Meningococcal vaccine	693 (53.4%)	244 (8.7%)
Blood transfusion, n (%)	299 (23.0%)	761 (27.3%)
Transfusions during follow-up		
Mean (SD)	2.6 (9.7)	2.1 (7.0)
Median	0	0
Transfusions per year		
Mean (SD)	0.82 (2.86)	0.76 (2.39)
TCD, n (%)	555 (42.7%)	46 (1.7%)
TCD screenings during follow-up, n		
Mean (SD)	0.98 (1.48)	0.02 (0.27)
Median	0	0
TCD screenings per year, n		
Mean (SD)	0.33 (0.48)	0.01 (0.11)

HSCT: Hematopoietic stem cell transplant; NSAID: Non-steroidal anti-inflammatory drugs; SCD: Sickle cell disease; SD: Standard deviation; TCD: Transcranial doppler ultrasound.

Healthcare resource utilization

In the first 12 months of the follow-up period, pediatric patients with SCD had significantly higher HCRU than their control counterparts for all resource categories, with hospitalizations (32.6 vs 1.1%, $p < 0.0001$) and ER visits (49.7 vs 14.2%, $p < 0.0001$) showing the largest differences between the cohorts (Figure 1A). In addition, the mean number of services received by the SCD cohort during the first 12 months of the follow-up period were higher than that of their matched control cohort, with the largest fold differences occurring for hospitalizations and ER visits (Table 5). Furthermore, hospital LOS among pediatric patients with SCD was significantly higher than that of pediatric patients without SCD. Among pediatric patients who were hospitalized during the first 12 months of the follow-up period, mean LOS tended to be longer for the SCD cohort compared with the control cohort (7.3 vs 4.8 days, $p = 0.41$) (Table 7). Among pediatric patients who had ≥1 ER visit, the mean number of visits was higher for patients with SCD versus controls during the first 12 months of follow-up (2.4 vs 1.3 visits, $p < 0.0001$) (Table 8). HCRU among the pediatric population during the overall follow-up period is reported in Figure 2A & Tables 6, 9 & 10.

Similar to the pediatric population, adults with SCD had significantly higher HCRU than their control counterparts across all resource categories. The largest differences in the frequency of resource utilization were among hospitalizations (7.5-fold, $p < 0.0001$) and ER visits (3.6-fold, $p < 0.0001$) during the first 12 months of follow-up (Figure 1B). Hospitalizations and ER visits also accounted for the most substantial fold differences in the number of services received by the adult SCD and control cohorts during the first 12 months of follow-up (Table 5). In addition, hospital LOS among adults with SCD was 23.9-fold longer than that of their control counterparts; among adults with ≥1 hospitalization, the difference remained significantly higher for those with SCD, with a mean LOS

Table 3. Sickle cell disease-related complications during the first 12 months of follow-up.

	Pediatric			Adult		
	SCD (n = 1299)	Control (n = 1299)	p-value	SCD (n = 2792)	Control (n = 2792)	p-value
Acute complications, n (%)						
Vaso-occlusive crisis	674 (51.9%)	0 (0.0%)	–	1593 (57.1%)	0 (0.0%)	–
Dactylitis	574 (44.2%)	0 (0.0%)	–	1463 (52.4%)	0 (0.0%)	–
Priapism	11 (0.9%)	0 (0.0%)	–	50 (1.8%)	0 (0.0%)	–
Acute chest syndrome	171 (13.2%)	0 (0.0%)	–	290 (10.4%)	0 (0.0%)	–
Sepsis	19 (1.5%)	0 (0.0%)	–	168 (6.0%)	7 (0.3%)	<0.0001
Stroke	34 (2.6%)	0 (0.0%)	–	100 (3.6%)	7 (0.3%)	<0.0001
Acute kidney injury	57 (4.4%)	7 (0.5%)	<0.0001	375 (13.4%)	54 (1.9%)	<0.0001
Albuminuria	31 (2.4%)	2 (0.2%)	<0.0001	122 (4.4%)	10 (0.4%)	<0.0001
Gallstones	54 (4.2%)	1 (0.1%)	<0.0001	170 (6.1%)	21 (0.8%)	<0.0001
Infection	119 (9.2%)	80 (6.2%)	0.0040	99 (3.6%)	60 (2.2%)	0.0017
Chronic complications, n (%)						
Scleral icterus	30 (2.3%)	0 (0.0%)	–	99 (3.6%)	3 (0.1%)	<0.0001
Pulmonary hypertension	5 (0.4%)	0 (0.0%)	–	55 (2.0%)	5 (0.2%)	<0.0001
Chronic kidney disease	34 (2.6%)	0 (0.0%)	–	100 (3.6%)	7 (0.3%)	<0.0001
End stage renal disease	4 (0.3%)	0 (0.0%)	–	35 (1.3%)	4 (0.1%)	<0.0001
Avascular necrosis	38 (2.9%)	0 (0.0%)	–	272 (9.7%)	2 (0.1%)	<0.0001
Leg ulcers	0 (0.0%)	0 (0.0%)	–	76 (2.7%)	4 (0.1%)	<0.0001
Retinopathy	47 (3.6%)	0 (0.0%)	–	326 (11.7%)	7 (0.3%)	<0.0001
Joint replacement	1 (0.1%)	0 (0.0%)	–	31 (1.1%)	8 (0.3%)	0.0002

SCD: Sickle cell disease.

Table 4. Sickle cell disease-related complications during the overall follow-up period.

	Pediatric			Adult		
	SCD (n = 1299)	Control (n = 1299)	p-value	SCD (n = 2792)	Control (n = 2792)	p-value
Acute complications, n (%)						
Vaso-occlusive crisis	920 (70.8%)	0 (0.0%)	–	1912 (68.5%)	0 (0.0%)	–
Dactylitis	812 (62.5%)	0 (0.0%)	–	1802 (64.5%)	0 (0.0%)	–
Priapism	19 (1.5%)	0 (0.0%)	–	64 (2.3%)	0 (0.0%)	–
Acute chest syndrome	339 (26.1%)	0 (0.0%)	–	533 (19.1%)	0 (0.0%)	–
Sepsis	48 (3.7%)	0 (0.0%)	–	361 (12.9%)	23 (0.8%)	<0.0001
Stroke	56 (4.3%)	1 (0.1%)	<0.0001	179 (6.4%)	18 (0.6%)	<0.0001
Acute kidney injury	120 (9.2%)	16 (1.2%)	<0.0001	617 (22.1%)	108 (3.9%)	<0.0001
Albuminuria	63 (4.9%)	6 (0.5%)	<0.0001	212 (7.6%)	21 (0.8%)	<0.0001
Gallstones	115 (8.9%)	2 (0.2%)	<0.0001	311 (11.1%)	51 (1.8%)	<0.0001
Infection	293 (22.6%)	192 (14.8%)	<0.0001	250 (9.0%)	161 (5.8%)	<0.0001
Chronic complications, n (%)						
Scleral icterus	65 (5.0%)	2 (0.2%)	<0.0001	193 (6.9%)	8 (0.3%)	<0.0001
Pulmonary hypertension	24 (1.9%)	1 (0.1%)	<0.0001	206 (7.4%)	11 (0.4%)	<0.0001
Chronic kidney disease	54 (4.2%)	9 (0.7%)	<0.0001	396 (14.2%)	86 (3.1%)	<0.0001
End stage renal disease	2 (0.2%)	2 (0.2%)	1.0000	66 (2.4%)	4 (0.1%)	<0.0001
Avascular necrosis	80 (6.2%)	1 (0.1%)	<0.0001	455 (16.3%)	2 (0.1%)	<0.0001
Leg ulcers	0 (0.0%)	0 (0.0%)	–	115 (4.1%)	7 (0.3%)	<0.0001
Retinopathy	84 (6.5%)	0 (0.0%)	–	493 (17.7%)	20 (0.7%)	<0.0001
Joint replacement	4 (0.3%)	0 (0.0%)	–	70 (2.5%)	28 (1.0%)	<0.0001

SCD: Sickle cell disease.

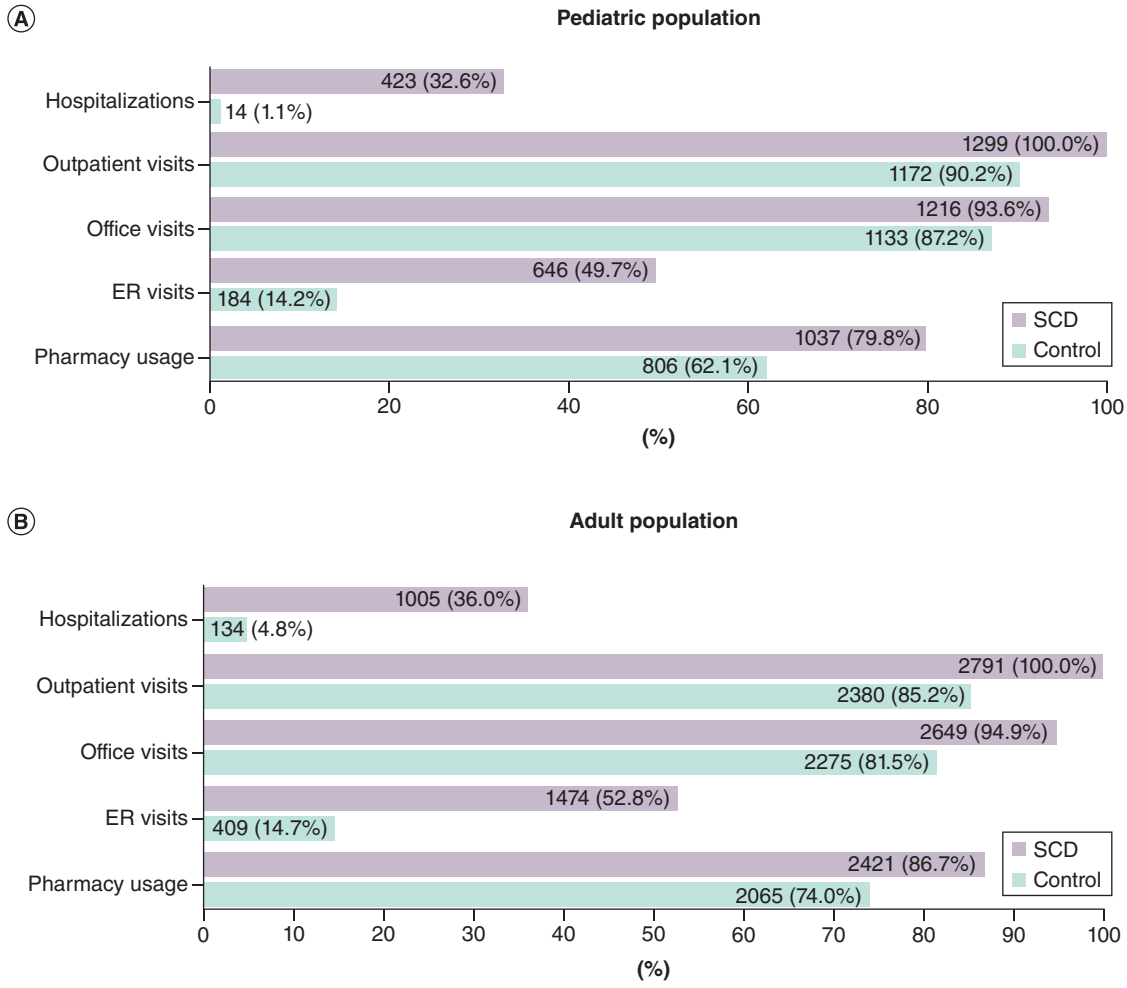

Figure 1. Healthcare resource utilization during the first 12 months of follow-up. (A) Comparison of the pediatric SCD and control cohorts. **(B)** Comparison of the adult SCD and control cohorts. For each resource category, the number and percentage of patients in each cohort who received these healthcare services during the first 12 months of the follow-up period are displayed.
$p < 0.0001$ for all comparisons.
ER: Emergency room; SCD: Sickle cell disease.

of 12.0 versus 3.8 days for hospitalizations during the first 12 months of follow-up ($p < 0.0001$) (Table 7). Among adults who had ≥1 ER visit, the mean number of visits was higher among those with SCD (3.2 vs 1.5 visits, $p < 0.0001$) during the first 12 months of follow-up (Table 8). HCRU among the adult population during the overall follow-up period is reported in Figure 2B & Tables 6, 9 & 10 and is generally similar to the finding from the 12 months of follow-up.

Healthcare costs

Pediatric patients with SCD versus the control cohort had significantly higher costs overall, with 11-fold higher mean total costs during the first 12 months of follow-up ($31,445 vs $2844, $p < 0.0001$) (Table 5). The difference in overall costs was mostly accounted for by hospitalizations and outpatient visits. Among pediatric patients with ≥1 hospitalization, inpatient costs were comparable between the SCD and control cohorts during the first 12 months (Table 7). ER visits accounted for the greatest difference in outpatient costs between the pediatric SCD and control cohorts. The mean cost of ER visits among pediatric patients who had ≥1 ER visit was significantly higher for those with SCD ($3435 vs $1572, $p < 0.0001$) during the first 12 months of the follow-up (Table 8). Furthermore, the pediatric SCD cohort also incurred higher OOP costs across all resource categories than the control cohort

Table 5. Healthcare resource utilization and costs during the first 12 months of follow-up.

	Pediatric			Adult		
	SCD (n = 1299)	Control (n = 1299)	Fold difference	SCD (n = 2792)	Control (n = 2792)	Fold difference
Resource utilization, mean (SD)						
Hospitalizations	0.6 (1.1)	0.01 (0.18)	39.3×	0.8 (1.8)	0.05 (0.25)	15.7×
Length of stay (days)	2.4 (7.3)	0.05 (0.65)	45.8×	4.3 (12.3)	0.2 (1.2)	23.9×
Outpatient visits	13.4 (14.9)	6.0 (10.1)	2.2×	21.1 (25.1)	8.8 (14.3)	2.4×
Office visits	6.9 (7.8)	4.7 (6.9)	1.5×	10.7 (10.8)	6.6 (9.5)	1.6×
ER visits	1.2 (2.3)	0.2 (0.6)	6.3×	1.7 (4.0)	0.2 (0.8)	7.6×
Pharmacy usage	12.8 (14.1)	3.8 (7.4)	3.4×	20.3 (23.0)	11.5 (19.1)	1.8×
Costs, USD, mean (SD)						
Overall costs	31,445 (72,213)	2844 (13,411)	11.1×	41,205 (72,885)	6650 (19,011)	6.2×
Hospitalizations	15,195 (54,222)	477 (8397)	31.9×	19,071 (48,377)	1153 (6847)	16.5×
Outpatient visits	12,746 (24,187)	1758 (4176)	7.3×	17,327 (35,582)	3786 (12,151)	4.6×
Office visits	1564 (2105)	745 (1006)	2.1×	2358 (4878)	1387 (6891)	1.7×
ER visits	1708 (4264)	223 (964)	7.7×	2362 (6447)	299 (1313)	7.9×
Pharmacy usage	3504 (18,546)	610 (4389)	5.7×	4807 (19,178)	1711 (8412)	2.8×
Out-of-pocket costs, USD, mean (SD)						
Overall costs	2071 (2487)	489 (861)	4.2×	2496 (2832)	971 (1574)	2.6×
Hospitalization	504 (1292)	19 (283)	26.0×	643 (1446)	78 (496)	8.2×
Outpatient visits	1397 (1910)	393 (711)	3.6×	1614 (2220)	703 (1224)	2.3×
Office visits	250 (391)	190 (321)	1.3×	392 (544)	329 (585)	1.2×
ER visits	237 (538)	57 (256)	4.1×	303 (723)	67 (299)	4.5×
Pharmacy usage	171 (416)	77 (293)	2.2×	240 (460)	190 (608)	1.3×

ER: Emergency room; SCD: Sickle cell disease; SD: Standard deviation; USD: 2020 US dollars.

Table 6. Per patient per year healthcare resource utilization and costs during the overall follow-up period.

	Pediatric			Adult		
	SCD (n = 1299)	Control (n = 1299)	Fold difference	SCD (n = 2792)	Control (n = 2792)	Fold difference
Resource utilization, n (%)						
Hospitalizations	0.6 (1.0)	0.01 (0.13)	38.8×	0.8 (1.6)	0.06 (0.21)	14.4×
Length of stay (days)	2.4 (6.1)	0.06 (0.56)	41.7×	4.3 (11.3)	0.2 (1.4)	20.2×
Outpatient visits	13.1 (15.9)	6.2 (10.3)	2.1×	20.9 (25.1)	9.3 (14.0)	2.2×
Office visits	6.6 (8.5)	4.9 (7.2)	1.3×	10.4 (9.9)	6.9 (8.9)	1.5×
ER visits	1.1 (2.0)	0.2 (0.4)	6.1×	1.6 (3.8)	0.2 (0.6)	7.2×
Pharmacy usage	12.6 (13.7)	3.8 (7.2)	3.3×	20.5 (22.6)	11.7 (18.5)	1.8×
Costs, USD, mean (SD)						
Overall costs	32,409 (63,331)	2939 (11,965)	11.0×	42,550 (75,922)	7522 (20,363)	5.7×
Hospitalizations	15,541 (41,912)	441 (6546)	35.2×	20,056 (49,502)	1326 (6173)	15.1×
Outpatient visits	12,525 (24,062)	1842 (4132)	6.8×	17,508 (37,609)	4301 (12,424)	4.1×
Office visits	1482 (2450)	808 (2174)	1.8×	2363 (4893)	1473 (6361)	1.6×
ER visits	1573 (3503)	221 (770)	7.1×	2270 (5952)	314 (1277)	7.2×
Pharmacy usage	4343 (20,849)	656 (4517)	6.6×	4985 (17,151)	1895 (9255)	2.6×
Out-of-pocket costs, USD, mean (SD)						
Overall costs	1837 (1854)	494 (742)	3.7×	2282 (2243)	994 (1353)	2.3×
Hospitalization	445 (915)	20 (215)	22.7×	594 (1187)	83 (369)	7.2×
Outpatient visits	1222 (1326)	402 (614)	3.0×	1445 (1569)	723 (1022)	2.0×
Office visits	223 (300)	189 (289)	1.2×	367 (478)	327 (496)	1.1×
ER visits	214 (415)	61 (204)	3.5×	264 (567)	72 (260)	3.7×
Pharmacy usage	170 (355)	73 (251)	2.3×	243 (451)	188 (550)	1.3×

ER: Emergency room; SCD: Sickle cell disease; SD: Standard deviation; USD: 2020 US dollars.

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Table 7. Healthcare resource utilization and costs among patients with ≥1 hospitalization during the first 12 months of follow-up.

	SCD	Control	Fold difference	p-value
Pediatric population, mean (SD)	**n = 423**	**n = 14**		
Hospitalizations, n	1.8 (1.2)	1.35 (1.1)	1.3×	0.2229
Length of stay (days)	7.3 (11.3)	4.8 (4.2)	1.5×	0.4090
Total costs	$46,663 (87,012)	$44,258 (70,380)	1.1×	0.9186
Out-of-pocket costs	$1547 (1875)	$1797 (2133)	0.9×	0.6250
Adult population, mean (SD)	**n = 1005**	**n = 134**		
Hospitalizations, n	2.3 (2.3)	1.1 (0.4)	2.1×	<0.0001
Length of stay (days)	12.0 (18.1)	3.8 (4.0)	3.2×	<0.0001
Total costs	$52,981 (68,611)	$24,027 (20,740)	2.2×	<0.0001
Out-of-pocket costs	$1787 (1940)	$1626 (1622)	1.1×	0.3593

SCD: Sickle cell disease; SD: Standard deviation.

Table 8. Healthcare resource utilization and costs among patients with ≥1 emergency room visit during the first 12 months of follow-up.

	SCD	Control	Fold difference	p-value
Pediatric population, mean (SD)	**n = 646**	**n = 184**		
ER visits, n	2.4 (2.8)	1.3 (0.8)	1.8×	<0.0001
Total costs	$3435 (5536)	$1572 (2110)	2.2×	<0.0001
Out-of-pocket costs	$476 (685)	$404.68 (569)	1.2×	0.1946
Adult population, mean (SD)	**n = 1474**	**n = 409**		
ER visits, n	3.2 (5.0)	1.5 (1.4)	2.1×	<0.0001
Total costs	$4475 (8325)	$2044 (2868)	2.2×	<0.0001
Out-of-pocket costs	$573 (914)	$457 (659)	1.3×	0.0161

ER: Emergency room; SCD: Sickle cell disease; SD: Standard deviation.

(Table 5). The corresponding PPPY healthcare costs during the overall follow-up period among the pediatric population are reported in Tables 6, 9 & 10.

The healthcare costs of adults with and without SCD followed the same trends as that of the pediatric population with significantly higher PPPY costs overall, as well as for each resource category during the first 12 months of follow-up (Table 5). The difference in overall costs was primarily driven by costs for hospitalizations and outpatient visits. Among adults with ≥1 hospitalization, inpatient costs were significantly higher for patients in the SCD cohorts during the first 12 months of follow-up ($52,981 vs $24,027, $p < 0.0001$) (Table 7). ER visits accounted for the greatest difference in outpatient costs between the adult SCD and control cohorts as well. The mean cost of ER visits among adults with ≥1 ER visit was significantly higher for those with SCD ($4475 vs $2044, $p < 0.0001$) during the first 12 months of the follow-up (Table 8). OOP costs were higher among adults with SCD compared with their control counterparts across all resource categories (Table 5). The corresponding PPPY healthcare costs during the overall follow-up period among the adult population are reported in Tables 6, 9 & 10.

Discussion

In this retrospective cohort study of pediatric and adult patients with SCD and commercial healthcare coverage in the US, both HCRU and costs were substantially higher among patients with SCD compared with their matched non-SCD counterparts. The overall costs for the SCD cohort were 11-fold and 6-fold that of their matched controls for pediatric and adult patients, respectively. Hospitalizations accounted for the largest proportion of the total healthcare costs for both pediatric and adult patients with SCD. Compared with patients without SCD, the hospitalization costs of those with SCD were 32- to 35-fold higher for pediatric patients and 15- to 17-fold higher for adult patients. ER visits accounted for the next highest fold difference with seven- to eightfold higher costs for both pediatric and adult patients with SCD. Correspondingly, hospitalizations and ER visits accounted the most differences in HCRU compared with the non-SCD patients.

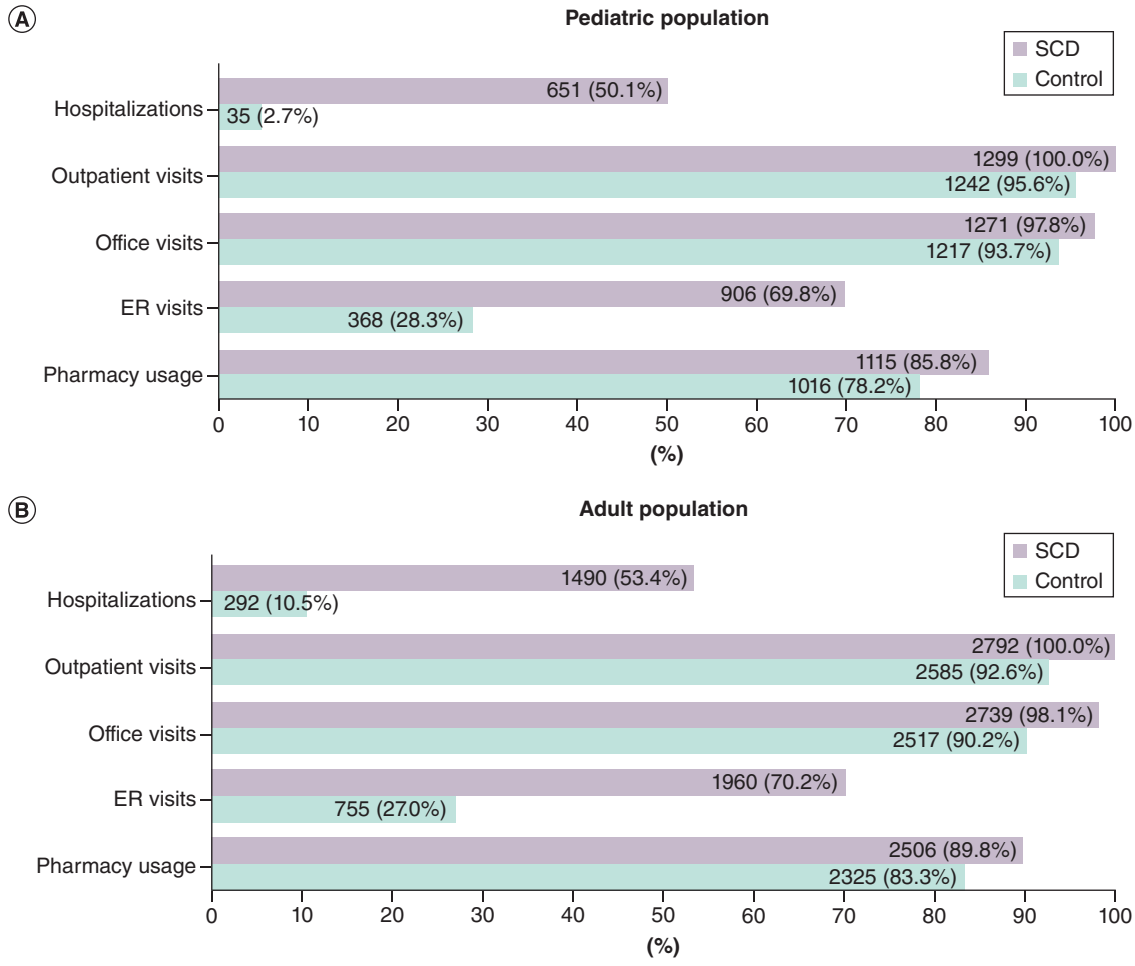

Figure 2. Healthcare resource utilization during the overall follow-up period. (A) Comparison of the pediatric SCD and control cohorts. **(B)** Comparison of the adult SCD and control cohorts. For each resource category, the number and percentage of patients in each cohort who received these healthcare services during the overall follow-up period are displayed.
$p < 0.0001$ for all comparisons.
ER: Emergency room; SCD: Sickle cell disease.

Table 9. Per patient per year healthcare resource utilization and costs among patients with ≥1 hospitalization during the overall follow-up period.

	SCD	Control	Fold difference	p-value
Pediatric population, mean (SD)	**n = 651**	**n = 35**		
Hospitalizations, n	1.1 (1.2)	0.53 (0.57)	2.1×	0.0053
Length of stay (days)	4.8 (8.0)	2.1 (2.7)	2.2×	0.0508
Total costs	$31,011 (55,022)	$16,379 (36,974)	1.9×	0.1207
Out-of-pocket costs	$888 (1130)	$728.04 (1112)	1.2×	0.4149
Adult population, mean (SD)	**n = 1490**	**n = 292**		
Hospitalizations, n	1.5 (2.0)	0.5 (0.4)	2.8×	<0.0001
Length of stay (days)	8.1 (14.5)	2.0 (3.9)	3.9×	<0.0001
Total costs	$37,582 (62,722)	$12,681 (14,868)	3.0×	<0.0001
Out-of-pocket costs	$1113 (1436)	$794 (862)	1.4×	0.0002

SCD: Sickle cell disease; SD: Standard deviation.

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Table 10. Per patient per year healthcare resource utilization and costs among patients with ≥1 ER visit during the overall follow-up period.

	SCD	Control	Fold difference	p-value
Pediatric population, mean (SD)	**n = 906**	**n = 368**		
ER visits, n	1.5 (2.2)	0.6 (0.6)	2.5×	<0.0001
Total costs	$2255 (4007)	$781 (1289)	2.9×	<0.0001
Out-of-pocket costs	$306 (467)	$213.81 (337)	1.4×	0.0006
Adult population, mean (SD)	**n = 1960**	**n = 755**		
ER visits, n	2.2 (4.4)	0.8 (1.0)	2.8×	<0.0001
Total costs	$3234 (6881)	$1162 (2246)	2.8×	<0.0001
Out-of-pocket costs	$376 (645)	$265 (446)	1.4×	<0.0001

ER: Emergency room; SCD: Sickle cell disease; SD: Standard deviation.

These findings are consistent with the few previously published analyses of commercially insured patients with SCD. HCRU and healthcare costs were evaluated among 621 commercially insured pediatric patients (aged 1–17 years) with SCD in 2005 [12]. In comparison to our study, similar proportions of pediatric patients with SCD were hospitalized (38 vs 33%, mean of 0.8 vs 0.6 admissions per patient), had ER visits (45 vs 50%, mean of 0.9 vs 1.2 visits per patient), and outpatient pharmacy utilization (82 vs 80%, mean of 10.8 vs 12.8 pharmacy claims per patient). However, the pediatric SCD patients with at least one hospitalization from the previous study had a shorter mean total hospital LOS than those in our study (3.9 vs 7.3 days). In comparison to pediatric patients with SCD, the mean total annual healthcare costs of the 2,550,959 pediatric patients without SCD were 11-fold lower ($14,722 vs $1293) [12,15]. When stratified by resource category, pediatric patients with SCD had 34-fold higher inpatient costs, eightfold higher outpatient costs, and twofold higher pharmacy costs compared with pediatric patients without SCD [15]. After taking into account inflation rate adjustment from 2005 to 2020, the costs in our study are higher than those of the previous study. In part, this may be due to study duration, where our study includes healthcare services incurred between 2016 and 2020 while the other study covers a single year, 2005. A longitudinal study covering 5-year periods between 2010 and 2018 reported annual inpatient and ER admission rates that varied by 19.8 and 15.8%, respectively [13]. In part, the higher costs of our study may also be due to pediatric patients who received an HSCT or bone marrow transplant in the follow-up period. While the costs of transplantation were not evaluated in this study, the total costs of allogeneic HSCT at 1 year have been reported to range from $69,218 to $637,193 [20]. Among the pediatric patients with SCD in our study, total costs at the 97.5th percentile were $182,106, potentially representing transplant-related costs. However, while mean costs may have been skewed by the high costs of HSCT, the median total costs of patients with SCD were still substantially higher than that of their matched non-SCD counterparts ($9042 vs $817, 11.1× fold difference). In addition, one of the largest discrepancies was the proportion of the total costs due to pharmacy usage; pharmacy usage accounted for a greater proportion of the total costs in our study (11.1 vs 3.6%). The higher costs could potentially be due to the increased use of hydroxyurea (35 vs 11%), pain medication (69 vs 45%) and iron chelation agents (5.6 vs 0.2%) in our study [12].

In a prior study by Johnson *et al.* [10] where 20,891 patients were followed from 2007 to 2018, the lifetime burden of total SCD-related medical costs among non-elderly patients with commercial insurance was estimated to be $1.7 million (2020 USD) with $44,000 in OOP costs. Compared with their matched non-SCD counterparts, the mean number of hospitalizations (0.57 vs 0.04), ER visits (1.3 vs 0.14), office visits (4.6 vs 2.4) and prescription fills (8.0 vs 1.6) per year were higher among the pediatric patients (aged ≤18 years). Patients 19–30 and 31–64 years of age demonstrated the same trend, with higher utilization among those with SCD (age 19–30: 0.69 vs 0.07 hospitalizations, 1.9 vs 0.2 ER visits, 4.5 vs 2.4 office visits and 9.8 vs 2.4 prescription fills; age 31–64: 0.46 vs 0.07 hospitalizations, 1.12 vs 0.18 ER visits, 6.5 vs 3.7 office visits and 15.9 vs 8.5 prescription fills). Similar to our study, total medical costs, OOP costs and the utilization of corresponding resource categories were higher among patients with SCD and increased with age.

A longitudinal analysis of the economic burden of severe SCD assessed all-cause HCRU and costs over a 5-year period among patients with commercial and Medicare coverage from 2010 to 2018 [13]. Among the overall population, 48.4–68.2% of patients were hospitalized each year, with a mean (SD) of 1.2 (2.2) to 1.7 (2.3) admissions per year; the mean (SD) LOS per admission was 4.1 (3.7) days. Annually, 57.6–73.4% of patients had

an ER visit, with a mean (SD) of 2.1 (5.3) to 2.6 (4.4) visits per year. In our study, the proportions of patients who were hospitalized (50.1–53.4%) and had an ER visit (69.8–70.2%) were also comparable to that of the longitudinal study, as were the mean number of hospitalizations PPPY during the overall follow-up period (1.1–1.5) among patients who were hospitalized. However, hospital LOS was longer (4.8–8.1 days) and there were fewer ER visits (1.5–2.2 visits per year). When stratified by age, the pediatric patients (<18 years of age) in the longitudinal study had mean annual costs (2018 USD) of approximately $29,250 for hospitalizations, $2210 for ER visits, $1380 for office visits and $4000 for outpatient pharmacy usage, resulting in total costs of $52,210. Compared with these pediatric patients, costs were generally higher among patients 18–30 years of age while patients ≥31 years had intermediate costs. Apart from office visits, all other resource categories reported in the longitudinal study had higher utilization and costs compared with our study. In part, this may be due to differences in the composition of the study populations. Patients in the longitudinal study were required to have at least one VOC within the first 2 years of follow-up and thus might have been selected as higher-risk patients than those in our study. Yet the two studies showed many comparable results and in our study population, 71% of the pediatric patients and 69% of the adult patients had at least one VOC during the entire follow-up period (median of 34 and 29 months, respectively).

This finding of higher costs among patients with VOCs is supported by two studies that evaluated the impact of VOCs on the healthcare costs of patients with SCD [14,16]. In one study of 16,092 commercially insured patients ≥16 years of age from 2001 to 2017 who had 0, 1 or ≥2 VOC episodes within a 1-year follow-up period, mean annual total all-cause healthcare costs increased with the number of VOCs from $15,747 (2018 USD, no VOCs) to $27,194 (1 VOC) and to $64,555 (≥2 VOCs) [14]. While inpatient costs increased threefold for patients with 0–1 VOC and 2.9-fold for those with 1 to ≥2 VOCs, the corresponding increases for outpatient costs were lower at 1.2- and 1.5-fold; ER costs increased by 1.9- and 2.6-fold. Another study found that recurrent VOCs, defined as ≥2 VOCs per year for 2 consecutive years, resulted in even higher costs [16].

Similar to our study, these previously published studies utilized data from the MarketScan Commercial database for their analyses, allowing for a crude assessment of SCD-related HCRU and costs over time. Unlike the life expectancy of patients with SCD, which has trended higher from 38 to 42 years in 2005 to 54 years in 2019, the economic burden of SCD has not improved significantly over the same time period [7,21]. The substantial HCRU and costs of patients with SCD continue to be primarily due to a greater need for inpatient and ER admissions to manage complications such as VOCs and other SCD-related chronic complications. This is likely due to the limited treatment options available for the management of SCD-related complications. Prior to 2017, hydroxyurea was the only FDA-approved pharmacological intervention available for the treatment of SCD. Studies have demonstrated that hydroxyurea treatment is associated with decreased VOC events, fewer hospitalizations and ER admissions, and lower healthcare costs [22–24]. However, as demonstrated in our study, hydroxyurea treatment remains underutilized [25]. So, there remains a gap to improve healthcare treatments for SCD patients. In addition, previous studies reported that approximately 45% of commercially insured patients with SCD were prescribed pain medication [12,14]. Among patients with recurrent VOCs or other complications indicative of severe SCD, the proportion of patients prescribed an opioid increased to over 90% [13,16]. In our study, 69% of the pediatric and 86% of the adult populations required pain medication during the overall follow-up period; 61 and 78% of the pediatric and adult patients, respectively, were prescribed an opioid. This widespread use of pain medication further demonstrates that there is an unmet need for treatments to improve the management of SCD and its complications and reduce the associated economic burden.

In our study, 58 and 56% of the pediatric and adult patients with SCD, respectively, had PPO or point-of-service coverage. PPO and point-of-service healthcare plans enhance access to the specialist care needed for the treatment of SCD by permitting the use of out-of-network healthcare providers, although this comes with increased OOP costs for patients. However, nearly 20% of patients had HMO or exclusive provider organization healthcare plans, which do not offer coverage for out-of-network providers. As a result, patients may not seek required medical care if it cannot be obtained through in-network providers. Moreover, care obtained through out-of-network providers may not be reliably captured in the database, resulting in possible underestimation of the HCRU and costs of these patients. Further research into the potential impact of different levels of commercial insurance coverage on the management of SCD and its complications is warranted. In addition, it has been demonstrated that SCD healthcare disparities are considerable compared with other orphan diseases, resulting in poorer outcomes [26]. Countries with a higher prevalence of SCD, such as countries in sub-Saharan Africa and India, have implemented comprehensive programs to improve the management of SCD and reduce disease burden; these programs include early screening,

public education to increase disease awareness and increased healthcare access [27]. Such programs may be effective in reducing the clinical and economic burden of SCD [28]. However, additional research is required to evaluate the benefit of such preventive programs on the economic burden of SCD among commercially insured patients with SCD.

Limitations

The findings of this study should be interpreted in the context of certain limitations. The administrative claims included in this database are collected for billing purposes. As a result, these records lack clinical detail and may be subject to miscoding or coding errors. Since the MarketScan Commercial database does not report race, patients could not be matched on that characteristic. Furthermore, the Commercial database is not representative of all privately insured patients but only those covered by certain employer-sponsored health plans. In addition, the clinical manifestation of SCD varies based on the inherited hemoglobin variants; hemoglobin SC (HbSC) and hemoglobin SS (HbSS) result in clinically milder and more severe forms of SCD, respectively. In our study, no distinction was made between patients with SCD genotypes that would require different levels of care, such as HbSC and HbSS, since genotype information may not be captured for all individuals in the database. However, the adult SCD population may have lower disease severity since they were able to maintain employment. Accordingly, SCD-related HCRU and costs may be underestimated. Moreover, healthcare during 2020 may have been underutilized by both the patients with SCD and their matched non-SCD counterparts due to the COVID-19 pandemic. Although the database is a very large convenience sample, our study findings may not generalize to the entire US or regions not well represented in the data source, as well as to patients who are uninsured or have other types of healthcare coverage. Finally, this study excluded individuals without commercial insurance, who may have a greater economic burden.

Conclusion

This retrospective cohort analysis highlights the substantial economic burden of SCD among patients enrolled in US commercial insurance plans. Both the pediatric and adult populations had substantially higher HCRU compared with their matched controls. Furthermore, costs for payers as well as OOP costs for patients were higher across all resource categories. These findings align with previous studies reflecting the burden of illness associated with SCD. They also suggest that more optimal SCD treatments may have the potential to reduce the economic burden for patients with SCD, as well as payers.

Author contributions

All authors were responsible for study conception and design, acquisition of data, data analysis and interpretation, and drafting and revision of the manuscript.

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Competing interests disclosure

GT Barcelos is a current employee and stockholder of Pfizer AG; T Peixoto was an employee of Pfizer Portugal at the time the study was conducted; CL Baker is a current employee and stockholder of Pfizer Inc.; J Alvir was an employee of Pfizer Inc. at the time the study was conducted; J Lin is a current employee of Novosys Health LLC, which received research funding from Pfizer Inc. The authors have no other competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript apart from those disclosed.

Writing disclosure

Medical writing assistance was provided by G Lin of Novosys Health, and was funded by Pfizer, Inc.

Ethical conduct of research

This study utilized de-identified, HIPAA-compliant patient data from the IBM MarketScan Commercial Database; institutional review board approval was not required.

Data sharing statement

This study used data available from IBM's MarketScan Commercial Database. Restrictions apply to the availability of these data, which were used under a licensing agreement.

Summary points

- Sickle cell disease (SCD) is the most common inherited blood disorder in the US.
- There is limited information available regarding the contemporary real-world clinical and financial burden of patients with SCD in the US who have commercial healthcare coverage.
- This retrospective cohort study used 2016–2020 administrative claims data from the MarketScan Commercial database.
- Between 1 July 2016 and 31 December 2019, 1299 pediatric patients and 2792 adults with SCD were identified by the presence of $\geq$3 SCD diagnoses on different days. Patients with SCD were matched 1:1 to patients with no SCD diagnoses on age, gender and region.
- The economic burden of SCD among pediatric and adult commercially insured US patients is substantial with increased healthcare resource utilization and costs compared with matched controls. During the first 12 months of follow-up, pediatric patients had 39.3-fold more hospitalizations, 2.2-fold more outpatient visits, 6.3-fold more emergency room (ER) visits and 3.4-fold more pharmacy usage. Adult patients had 15.7-fold more hospitalizations, 2.4-fold more outpatient visits, 7.6-fold more ER visits and 1.8-fold more pharmacy usage.
- Among both pediatric and adult patients with SCD, hospitalizations and ER visits accounted the most substantial increases in healthcare resource utilization compared with the non-SCD patients. During the first 12 months of follow-up, patients with SCD were hospitalized (pediatric: 32.6 vs 1.1%; adult: 36.0 vs 4.8%, $p < 0.0001$) or visited the ER (pediatric: 49.7 vs 14.2%; adult: 52.8 vs 14.7%, $p < 0.0001$) with greater frequency than non-SCD patients.
- Compared with non-SCD patients, pediatric patients with SCD had significantly higher mean total costs of $31,445 versus $2844 during the first 12 months of follow-up. Total mean costs were $41,205 versus $6650 for adult patients with versus without SCD.
- Hospitalizations and outpatient visits accounted for largest proportions of the total healthcare costs. Among pediatric patients, hospitalization ($15,195 vs $477) and outpatient ($12,746 vs $1758) costs were significantly higher among those with SCD. The cost of hospitalizations ($19,071 vs $1153) and outpatient visits ($17,327 vs $3786) were also significantly higher among adult patients with SCD.
- In addition to expanding the therapeutic options available, more innovative treatments for SCD can potentially reduce the economic burden for patients with the disease, as well as payers.

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