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ORIGINAL RESEARCH

Clinical and Economic Burden of Managing Patients with Sickle Cell Disease Receiving Frequent Red Blood Cell Transfusions in the United States

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Purpose: Standard of care for patients with sickle cell disease (SCD) includes red blood cell transfusions (RBCTs). Data on clinical and economic outcomes of patients with SCD receiving frequent RBCTs are limited.

Materials and Methods: This longitudinal, retrospective, claims-based analysis used the Merative™ MarketScan® Commercial, Medicare, and Multi-State Medicaid databases. Patients with SCD (identified using ICD-9/10 codes) receiving frequent RBCTs (≥6 RBCTs during any 12-month period) between January 1, 2015, and March 1, 2019, were included. The index date was the date of the sixth RBCT. Eligible patients were required to have ≥12 months of continuous enrollment pre- and post-index. Patients were followed from index to end of enrollment, death, or end of the study period (February 29, 2020), whichever came first. Clinical complications, all-cause healthcare resource utilization (HCRU), and healthcare costs were descriptively summarized during follow-up.

Results: A total of 919 patients with SCD receiving frequent RBCTs met the eligibility criteria for inclusion. Patients experienced a mean of 4.0 vaso-occlusive crises (VOCs) per patient per year (PPPY) and received a mean of 8.3 RBCTs PPPY during follow-up. The most common clinical complications were iron overload (77%), infections (66%), and cerebrovascular disease (48%). Patients had a mean of 2.3 inpatient admissions, 83.5 outpatient visits, and 37.4 outpatient prescriptions PPPY during follow-up. Mean total annual healthcare costs were $106,123 PPPY, including mean inpatient, outpatient medical, and outpatient pharmacy costs of $48,463, $28,307, and $29,353, respectively. Compared to those with <2 baseline VOCs, patients with ≥2 baseline VOCs had more HCRU and higher annual healthcare costs.

Conclusion: Despite utilizing available care with frequent RBCTs, patients with SCD experienced a variety of disease and transfusion-related complications, including frequent VOCs and iron overload, which led to substantial HCRU and costs. These findings highlight the need for novel therapies for this patient group.

Keywords: complication, cost, healthcare resource utilization, vaso-occlusive crises, treatment

Introduction

Sickle cell disease (SCD) is an inherited disorder affecting approximately 120,000 people in the United States (US).[1] SCD is characterized by mutations in the beta globin gene that lead to the production of abnormal sickle hemoglobin.[2] Polymerization of sickle hemoglobin leads to red blood cell (RBC) distortion, resulting in impaired RBC function, blood vessel obstruction, and painful vaso-occlusive crises (VOCs).[2,3] Standard of care for patients with SCD includes hydroxyurea and RBC transfusions (RBCTs), the latter of which decreases the proportion of circulating sickled RBCs, thus improving blood flow.[2,4]

Previous studies have noted that approximately 90% of adults with SCD will have received at least one RBCT in their lifetime.[5,6] Patients with SCD may receive simple or exchange transfusions for the management of acute symptoms and

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complications (eg, acute clinical stroke, transient ischemic attacks, acute chest syndrome, acute multiorgan failure, etc).[7] In addition, patients with SCD can receive chronic simple or exchange transfusions for primary and secondary stroke prevention and to reduce the frequency of recurrent VOCs.[7] Previously, published literature has found that stroke recurs in approximately 60% of patients without chronic RBCT therapy and in approximately 20% with chronic RBCT therapy despite maintenance of a sickled hemoglobin percentage of less than 30%.[5,8–10]

While RBCTs can alleviate or prevent morbidity in some patients with SCD with acute and chronic complications,[5] there can be a variety of issues with the therapy. Frequent RBCTs can lead to complications including bloodborne infection, iron overload, and other transfusion-related complications.[5,6,11] In addition, there can be issues with availability of blood due to existing alloimmunization and given the clinical recommendations for prophylactic red cell antigen matching to lower the risk of alloimmunization.[5,6,12] There are limited data on the clinical complications, treatment utilization, healthcare resource utilization (HCRU), and healthcare costs in patients with SCD who are receiving frequent RBCTs in the US. This longitudinal, retrospective, claims-based analysis aimed to describe the clinical and economic burden in patients with SCD receiving frequent RBCTs (defined as ≥6 RBCTs during any 12-month period) in the US.

Materials and Methods

Study Design and Data Source

Data from the Merative™ MarketScan® Commercial, Medicare, and Multi-State Medicaid Databases (Merative™, Ann Arbor, MI) were included in this retrospective analysis. The MarketScan® Databases contain de-identified inpatient medical, outpatient medical, and outpatient prescription data for approximately 198.9 million commercially insured individuals and their dependents between 1995 and 2020, approximately 14.4 million individuals with Medicare supplemental insurance between 1995 and 2020, and approximately 52 million enrollees with Medicaid between 1999 and 2020. Relevant information was obtained from patients with SCD receiving frequent RBCTs between January 1, 2015, and February 29, 2020.

Study Population

Patients with ≥1 inpatient or ≥2 outpatient claims with an international Classification of Diseases, 9th and 10th Revision (ICD-9/10) diagnosis code of SCD between January 1, 2015, and March 1, 2019,[13] ≥6 RBCT claims (at least 3 days apart) during any 12-month period after the earliest qualifying SCD diagnosis (index date: the date of the 6th RBCT), and ≥12 months of continuous enrollment before and after the index date were eligible for inclusion. Patients were excluded if they had ≥2 non-diagnostic claims for sickle cell trait or if they had any evidence of hematopoietic stem cell transplant at any point in the study period.

The follow-up period for all patients was ≥12 months, beginning on the index date and ending on the earliest date of end of continuous enrollment, end of the study period (February 29, 2020), or death.

Study Outcomes and Statistical Analysis

Demographics, clinical outcomes, treatment utilization, HCRU, and healthcare costs of patients with SCD receiving frequent RBCTs were characterized using descriptive analyses. Continuous variables were reported as means (standard deviation [SD]) and as n (%) for categorical variables. Demographics including age, sex, and payer type were assessed at the index date.

Annualized rates (per patient per year [PPPY]) of all-cause HCRU included inpatient admissions, outpatient visits (including emergency department, office, laboratory, and other outpatient visits), and outpatient prescriptions; annualized rates of VOCs and RBCTs were characterized separately. Annualized healthcare costs (comprised of inpatient, outpatient medical, and outpatient prescription costs) were based on the paid amounts of adjudicated claims, including payer and health plan payments, as well as patient cost-sharing in the form of co-payment, deductible, and co-insurance. Costs were inflated to 2022 US Dollars using the Medical Care Component of the Consumer Price Index.

Prevalence (%) of clinical complications was summarized descriptively during the variable-length follow-up. The proportion of individuals with treatments of interest in the variable-length follow-up period, as well as the number of claims for each treatment PPPY, were captured using medical or pharmacy claims.

Subgroup analyses were conducted based on the number of VOCs during the 12-month baseline period (<2 VOCs at baseline vs ≥2 VOCs at baseline) and payer type (commercial vs Medicaid). Patients who had ≥6 RBCTs during each year of the follow-up period were also analyzed separately.

Results

Demographics

Of 27,448 patients with SCD in the databases, 919 patients met the eligibility criteria and were included in the study (Figure 1). The mean (SD) age of patients with SCD with frequent RBCTs was 19.5 years (13.3), and 466 patients (50.7%) were female (Table 1). A total of 721 patients (78.5%) were captured in the Medicaid database and 195 (21.2%) were covered by commercial insurance (Table 1).

Clinical Complications

Patients with SCD receiving frequent RBCTs experienced a mean (SD) of 4.0 (8.2) VOCs PPPY during the variable-length follow-up period (Table 2). The most common complications in patients with SCD receiving frequent RBCTs during the variable-length follow-up were iron overload (77.1%), infections (65.6%), cerebrovascular disease (48.0%), chronic lung disease (42.8%), and mental health complications (ie, anxiety or depression; 30.7%; Table 2). The most common cerebrovascular disease complications were stroke (28.9%) and moyamoya disease (15.5%).

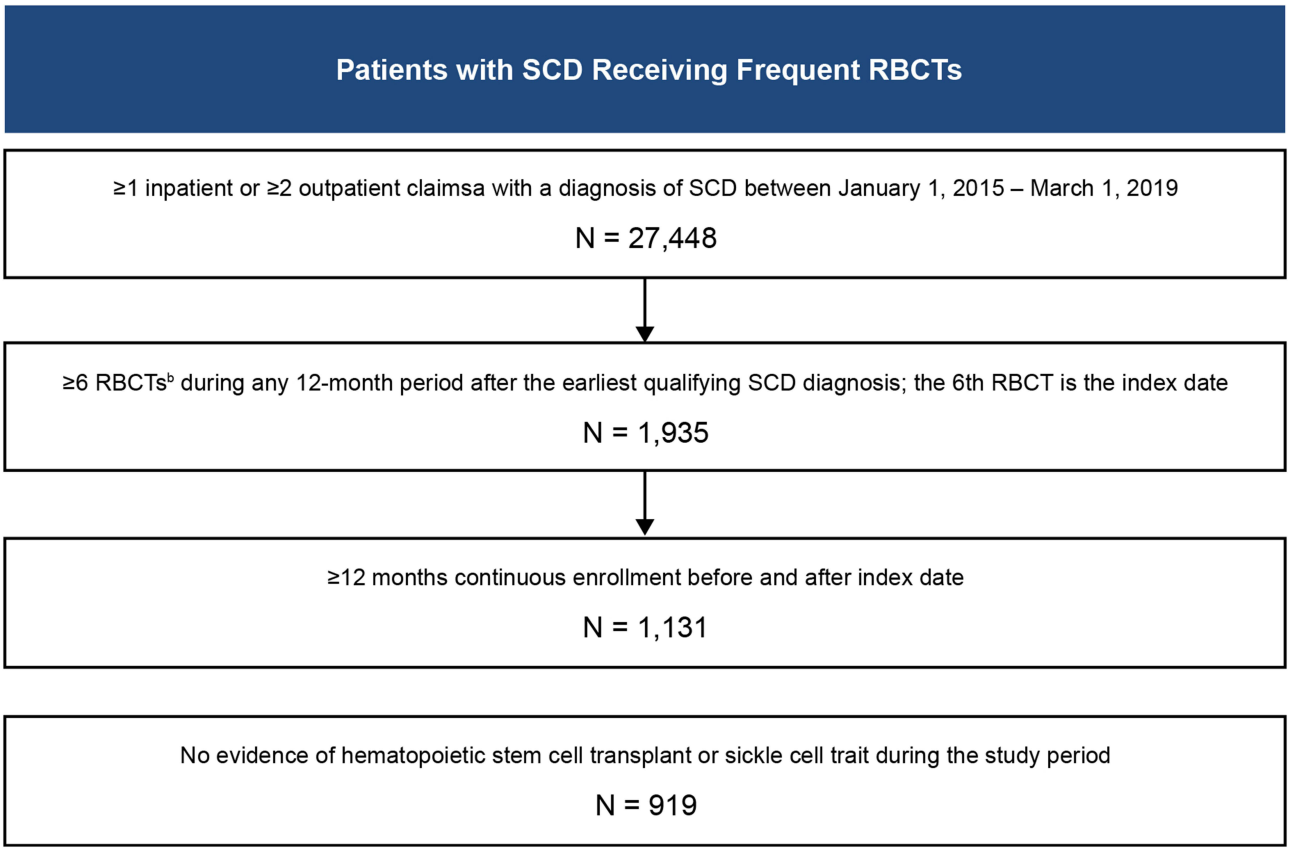

Figure 1 Selection of Patients with SCD Receiving Frequent RBCTs.
Notes: [a]Within 365 days of each other; [b]Claims for RBCTs must be at least 3 days apart to be considered separate events.
Abbreviations: RBCT, red blood cell transfusion; SCD, sickle cell disease.

Table 1 Patient Demographics

	Patients with SCD with Frequent RBCTs (n = 919)
Age, mean (SD, min-max), years	19.5 (13.3, 0–73)
Sex, n (%)	
Female	466 (50.7)
Male	453 (49.3)
Payer type, n (%)	
Commercial	195 (21.2)
Medicaid	721 (78.5)
Medicaid fee for service	370 (40.3)
Medicare supplemental	3 (0.3)
Years of follow-up, mean (SD)	3.1 (1.2)

Abbreviations: RBCT, red blood cell transfusion; SCD, sickle cell disease; SD, standard deviation.

Table 2 Clinical Complications During Follow-up

	Patients with SCD with Frequent RBCTs (n = 919)[a]
Rate of VOCs PPPY, mean (SD)	4.0 (8.2)
Clinical complication, n (%)	
Iron overload/hemochromatosis	709 (77.1)
Infections	603 (65.6)
Cerebrovascular disease	441 (48.0)
Chronic lung disease	393 (42.8)
Mental health complications (ie, anxiety or depression)	282 (30.7)
Cardiopulmonary complications	218 (23.7)
Chronic pain	185 (20.1)
Renal complications	183 (19.9)
Bone and joint problems	154 (16.8)
Hypercoagulable state	141 (15.3)

Notes: [a]Number (%) of patients with VOC in follow-up period: 679 (73.9%).
Abbreviations: PPPY, per patient per year; RBCT, red blood cell transfusion; SCD, sickle cell disease; SD, standard deviation; VOCs, vaso-occlusive crises.

A greater proportion of patients with ≥2 baseline VOCs versus <2 baseline VOCs experienced chronic pain (≥2 baseline VOCs: 42.7% vs <2 baseline VOCs: 3.6%), cardiopulmonary complications (36.2% vs 14.5%), and mental health complications (43.4% vs 21.3%) during the variable-length follow-up period (Table 3). Compared with patients with commercial insurance, patients covered by Medicaid had a higher mean (SD) rate PPPY of VOCs (Medicaid: 4.53 [8.89] vs commercial: 2.18 [4.48]; Supplementary Table S1). In addition, a greater proportion of patients covered by Medicaid versus commercial insurance experienced mental health complications (Medicaid: 34.3% vs commercial: 17.9%), chronic lung disease (46.5% vs 29.7%), cerebrovascular disease (51.2% vs 35.4%), and infections (70.0% vs 49.2%) in the variable-length follow-up period (Supplementary Table S1). Compared with the overall patient cohort (patients with SCD receiving frequent RBCTs at baseline), patients with ≥6 RBCTs during each year of follow-up had a lower mean (SD) rate PPPY of VOCs (≥6 RBCTs during each year of follow-up: 2.4 [5.6] vs overall: 4.0 [8.2]; Table 2 and Supplementary Table S1).

Table 3 Clinical Complications by Number of Baseline Vaso-Occlusive Crises

	Patients with <2 VOCs During Baseline (n = 530)[a]	Patients with ≥2 VOCs During Baseline (n = 389)[a]	Number of RBCTs During Each Year of Follow-up, ≥6 RBCTs[a] (n = 491)
Rate of VOCs PPPY, mean (SD)	0.79 (1.27)	8.43 (11.09)	2.39 (5.64)
Clinical complication, n (%)			
Iron overload/hemochromatosis	443 (83.6)	266 (68.4)	395 (80.4)
Infections	297 (56.0)	306 (78.7)	284 (57.8)
Cerebrovascular disease	302 (57.0)	139 (35.7)	268 (54.6)
Chronic lung disease	200 (37.7)	193 (49.6)	203 (41.3)
Mental health complications (ie anxiety or depression)	113 (21.3)	169 (43.4)	135 (27.5)
Cardiopulmonary complications	77 (14.5)	141 (36.2)	99 (20.2)
Chronic pain	19 (3.6)	166 (42.7)	65 (13.2)
Renal complications	99 (18.7)	84 (21.6)	94 (19.1)
Bone and joint problems	34 (6.4)	120 (30.8)	63 (12.8)
Hypercoagulable state	44 (8.3)	97 (24.9)	63 (12.8)

Notes: [a]Mean (SD) years of follow-up: <2 VOCs during baseline (n = 530): 3.3 (1.2) and ≥2 VOCs during baseline: 2.8 (1.1); ≥6 RBCTs during each year of follow-up: 2.9 (1.2).
Abbreviations: PPPY, per patient per year; SD, standard deviation; VOCs, vaso-occlusive crises.

Treatment Utilization

Patients with SCD receiving frequent RBCTs had a mean (SD) of 8.3 (4.0) RBCTs PPPY during the follow-up period (Table 4). Approximately 47% of patients had at least one prescription for hydroxyurea during the follow-up period. The mean (SD) number of claims PPPY was 13.5 (20.8) for iron chelation therapy, 8.9 (15.6) for opioids, and 1.8 (2.9) for hydroxyurea (Table 4).

Compared with patients with <2 baseline VOCs, those with ≥2 baseline VOCs had a lower rate of RBCTs per year during follow-up (≥2 baseline VOCs: 7.0 [4.1] vs <2 baseline VOCs: 9.3 [3.7]), and a higher mean (SD) number of claims PPPY for opioids (17.0 [20.2] vs 2.9 [6.2]; Supplementary Table S2). The number of RBCTs PPPY during the follow-up period was similar across payer types (Supplementary Table S3). Compared with the overall patient cohort, patients with ≥6 RBCTs during each year of follow-up had a higher mean (SD) rate of RBCTs of 11.2 (2.5) PPPY (vs 8.3

Table 4 Treatment Utilization

	Patients with SCD with Frequent RBCTs (n = 919)[a]	
	n (%)	Number of claims PPPY, mean (SD)
RBCTs	919 (100)	8.3 (4.0)
Pain medication	816 (88.8)	11.6 (18.1)
Opioids	739 (80.4)	8.9 (15.6)
NSAIDs	664 (72.3)	2.4 (4.1)
Gabapentin	133 (14.5)	0.4 (1.5)
Iron chelation therapy	615 (66.9)	13.5 (20.8)
Folic acid	555 (60.4)	2.4 (3.2)
Hydroxyurea	436 (47.4)	1.8 (2.9)
Penicillin	225 (24.5)	1.2 (3.5)

Notes: [a]Median number of Claims PPPY are: RBCTs: 8.8; pain medications: 3.8; Opioids: 1.7; NSAIDs: 0.9; Gabapentin: 0.0; Iron chelation therapy: 6.0; Folic acid: 0.9; Hydroxyurea: 0.0; Penicillin: 0.0.
Abbreviations: NSAID, nonsteroidal anti-inflammatory drug; PPPY, per patient per year; RBCT, red blood cell transfusion; SCD, sickle cell disease; SD, standard deviation.

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Table 5 Annual Healthcare Resource Utilization

	Patients with SCD with Frequent RBCTs (n = 919)[a]
Inpatient, mean (SD)	
Number of inpatient admissions PPPY	2.3 (3.7)
Total days of hospitalization PPPY	12.6 (23.5)
Outpatient, mean (SD)	
Number of outpatient visits PPPY	83.5 (71.4)
Number of emergency room visits PPPY	4.4 (14.1)
Number of office visits PPPY	15.9 (10.9)
Number of laboratory visits PPPY	21.3 (13.3)
Number of other outpatient visits PPPY	41.9 (59.7)
Outpatient pharmacy, mean (SD)	
Number of prescriptions PPPY	37.4 (33.4)

Notes: [a]Median HCRU PPPY are: Number of inpatient admissions: 0.9; Total days of hospitalization: 3.0; number of outpatient visits: 64.3; Number of emergency room visits: 1.4; Number of office visits: 14.3; Number of laboratory visits: 18.7; Number of other outpatient visits: 25.3; Number of prescriptions: 28.4.
Abbreviations: PPPY, per patient per year; RBCT, red blood cell transfusion; SCD, sickle cell disease; SD, standard deviation.

(4.0) for overall cohort) and a lower mean (SD) rate of opioid utilization (7.0 [12.7] vs 8.9 [15.6]) during the follow-up period (Table 4 and Supplementary Table S4).

Healthcare Resource Utilization and Costs

Patients with SCD receiving frequent RBCTs had a mean (SD) of 2.3 (3.7) inpatient admissions, 83.5 (71.4) total outpatient visits, 4.4 (14.1) emergency department visits, and 37.4 (33.4) outpatient prescriptions PPPY during follow-up (Table 5). Mean (SD) total healthcare costs PPPY for patients with SCD receiving frequent RBCTs were $106,123 ($130,534; Figure 2). Mean (SD) inpatient, outpatient pharmacy, and outpatient medical costs were $48,463 ($116,732), $29,353 ($41,670), and $28,307 ($37,670), respectively, during the follow-up period (Figure 2).

Compared with patients with <2 baseline VOCs, patients with ≥2 baseline VOCs had higher mean (SD) total healthcare costs (≥2 baseline VOCs: $140,679 [$171,581] vs <2 baseline VOCs: 80,760 [$80,331]; Figure 3). The primary driver of the cost difference between the groups was inpatient costs, whereby mean (SD) inpatient costs in patients with ≥2 baseline VOCs was >5-times higher ($90,936 [$161,635]) than in patients with <2 baseline VOCs ($17,290 [$46,736]; Figure 3). Compared with patients with commercial coverage, patients with Medicaid fee-for-service

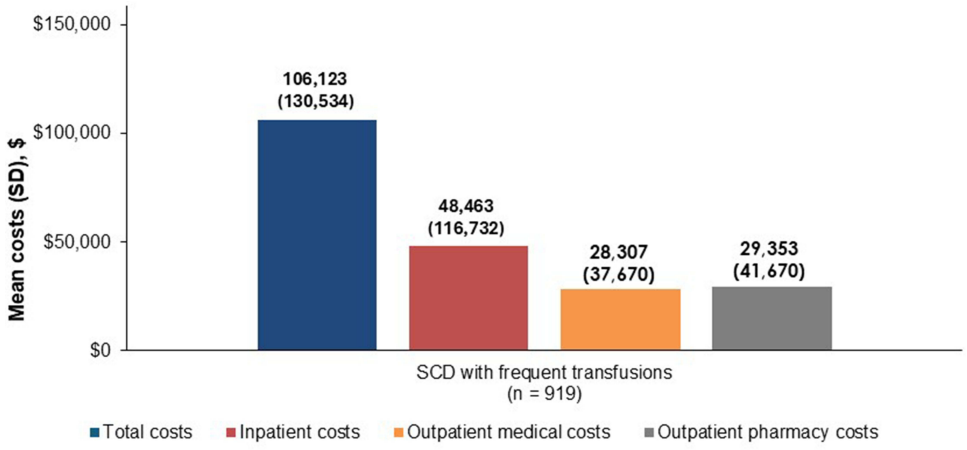

Figure 2 Mean Annual Costs for Patients with SCD Receiving Frequent RBCTs.
Abbreviations: SCD, sickle cell disease; SD, standard deviation.

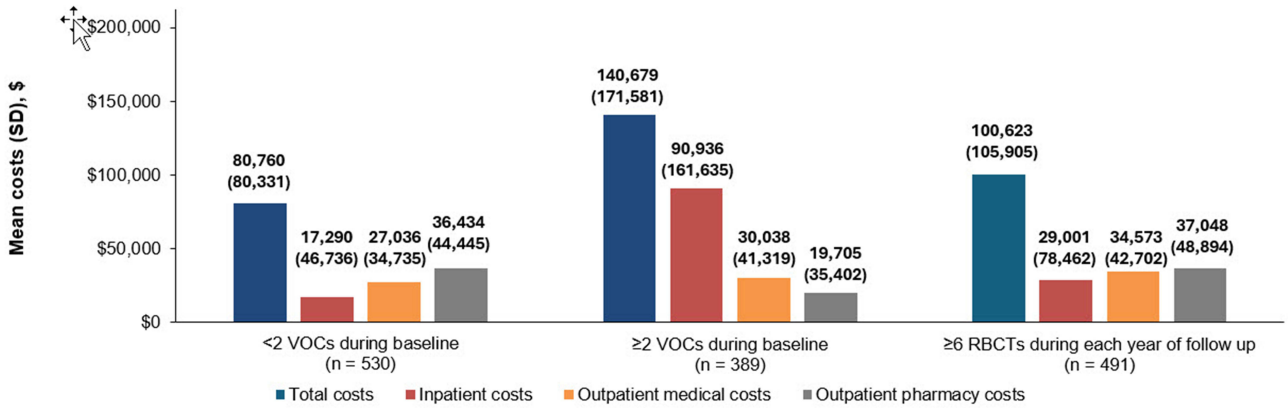

Figure 3 Mean Annual Costs by Number of Baseline Vaso-Occlusive Crises and Number of RBCTs during Each Year of Follow-up.
Abbreviations: SD, standard deviation; VOCs, vaso-occlusive crises.

(FFS) coverage had higher mean (SD) HCRU for inpatient admissions: (Medicaid FFS: 2.9 [4.0] vs commercial: 1.3 [1.9]), emergency department visits (5.4 [18.1] vs 2.8 [6.3]), and outpatient prescriptions: (41.2 [33.4] vs 26.2 [24.2]; Supplementary Table S5). Mean (SD) total costs were similar between those covered by Medicaid FFS and commercial insurance (Medicaid FFS: $136,624 [$157,584] vs commercial: $134,169 [$103,628]; Supplementary Figure S1). Compared with the overall patient cohort, patients with ≥6 RBCTs during each year of follow-up had similar total healthcare costs (≥6 RBCTs during each year of follow-up: $100,623 [SD, $105,905] vs overall: $106,123 [$130,534]). This was driven by lower inpatient costs (≥6 RBCTs during each year of follow-up: $29,001 [SD, $78,462]), but higher outpatient medical ($34,573 [SD, $42,702]) and outpatient pharmacy costs ($37,048 [SD, $48,894]) in patients with ≥6 RBCTs during each follow-up year than the overall population.

Discussion

In this longitudinal, retrospective, claims-based analysis, patients with SCD who received frequent RBCTs had frequent VOCs, as well as substantial clinical complications, HCRU, and costs. In addition, patients with more baseline VOCs had increased utilization of healthcare resources and had higher costs than those with fewer baseline VOCs.

Despite receiving frequent RBCTs, patients experienced substantial clinical burden, with an average of approximately 4 VOCs PPPY. RBCTs can be utilized in patients with SCD to manage acute complications including VOCs, and can also be used chronically to reduce the frequency of VOCs in individuals with recurrent VOCs.[14,15] As we are not able to definitively differentiate whether patients were receiving transfusions as acute treatments for VOCs or as chronic transfusion therapy, it is difficult to assess the effectiveness of frequent transfusions in this patient population. For this reason, we conducted a subgroup analysis of patients who received ≥6 RBCTs each year of the follow-up period as an approximation to patients receiving chronic transfusion therapy. In these patients, we observed a lower rate of VOCs than in the overall patient cohort, which supports previous literature demonstrating fewer VOCs in patients who received more frequent RBCT.[14,16,17]

Patients with SCD receiving frequent RBCTs had a high prevalence of clinical complications including cerebrovascular conditions, cardiopulmonary complications, infections, and anxiety or depression, consistent with other published literature.[6,18,19] The overall prevalence of cerebrovascular complications (eg, stroke, moyamoya disease) was higher in the current study than in previously published reports.[20,21] This difference is likely driven by the eligibility criteria for the current study (ie, patients with SCD receiving frequent RBCTs), which favors selection of patients with a history of or high risk for cerebrovascular disease. In a recent review of the global burden of transfusion in SCD, Inusa et al noted that "the indications for chronic transfusions with the most evidence-based support are primary and silent stroke prevention".[6] Given that chronic transfusions are recommended for primary and secondary stroke prevention in patients with SCD,[22] it is understandable that there was a high prevalence of patients with stroke and cerebrovascular complications in the group receiving frequent RBCTs.

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The finding that patients with increased VOCs at baseline had increased clinical burden is consistent with previously published literature demonstrating that patients with more frequent VOCs have an increased prevalence of complications.[18,19,23] Of note, there was a higher prevalence of cerebrovascular disease in patients with <2 VOCs than in those with ≥2 baseline VOCs in the current study, likely due to the VOC-reduction effect of chronic transfusions and the higher likelihood of patients who had experienced a previous stroke to be on a chronic transfusion regimen. It should be noted that statistical testing was not conducted comparing subgroups and thus differences noted above are descriptive. Additional research that incorporates formal statistical testing or matches groups on demographics would bolster the analyses performed here and provide additional information on the differences in the outcomes based on the baseline number of VOCs and other subgroups analyzed in this study.

This study included only patients who received at least 6 RBCTs during any 12-month period, more than half of whom (53.4%) received at least 6 RBCTs each year during follow-up. Given the high frequency of RBCTs in this population, it is inevitable that the majority of patients also had claims for iron chelation therapy, as these therapies are indicated for iron overload, which often occurs following chronic use of RBCTs.[4] Further supporting this hypothesis, iron overload was the most common complication in this study. In addition, we found opioids to be the most commonly prescribed pain medication in patients with SCD with frequent RBCTs. In the subgroup analysis, patients with more VOCs at baseline had greater claims for opioids, indicating increased pain burden. These findings are consistent with other published reports.[19,20,24] It is also not surprising that patients with ≥6 RBCTs during each year of follow-up have an even lower number of opioid claims given that this subgroup of patients has fewer VOCs. In the current study, approximately half of the patients had a claim for hydroxyurea in the follow-up period, and the mean frequency of claims was approximately 2 PPPY; this low utilization of hydroxyurea is consistent with previously published literature in patients with SCD.[19]

Our finding that patients receiving frequent RBCTs utilized substantial healthcare resources and incurred significant healthcare costs which increased with more VOCs was consistent with previous studies.[23,25] Mean total costs in this study were higher than previously published costs in patients with SCD.[25–27] This finding is likely a result of the stringent eligibility criteria in the current study, which focused on patients with more severe disease (ie, those requiring frequent RBCTs). Patients on frequent RBCTs are more likely to be on this treatment due to recurrent VOCs and/or cerebrovascular complications for whom RBCTs are part of standard clinical practice. Also, previous studies in patients with SCD have demonstrated higher costs in patients with cerebrovascular complications.[28]

Patients covered by Medicaid had a greater prevalence of clinical complications, more HCRU, and greater utilization of opioids than those covered by commercial insurance, the latter of which is consistent with previous studies.[29] Although HCRU was higher in the Medicaid FFS cohorts, the total annual costs in this subgroup were similar to commercial patients PPPY. Given the higher HCRU, we would have expected costs to also be higher for individuals covered by Medicaid, but the equivalent costs likely indicate the lower reimbursement rates for Medicaid compared with commercial insurance, something that is well reported in the literature. Due to the increase in capitation-based payments associated with Medicaid in recent years (a common issue for cost analyses given the trajectory of healthcare from FFS to value-based care), the payer subgroup cost analysis focused on patients with Medicaid FFS plans. Cost results from all patients with Medicaid are included in the overall results and should be interpreted with the caveat that they likely underestimate total healthcare costs. As reported in previous studies, patients with SCD are at higher risk for being adversely affected by social determinants of health (eg, race, income), potentially leading to the increased health disparities between payer types observed in this study.[30,31]

Limitations

This study used administrative claims data collected for reimbursement purposes and is therefore subject to potential misclassification bias. Identification of SCD was based solely on ICD-9 and ICD-10 codes (1 inpatient or 2 outpatient claims), which is consistent with previously published literature[13,19,32,33] in SCD; utilization of alternative registry-based datasets (eg, Registry and Surveillance System for Hemoglobinopathies)[34] would likely lead to reduced risk of misclassification. Administrative claims databases capture insurer-paid amounts and associated patient cost-sharing, which might underestimate the full cost of care to the healthcare system. In addition, HCRU such as outpatient visits

were based on unique visits to a particular healthcare provider and thus could occur on the same day. In this analysis, only direct healthcare costs are included in this analysis, which likely underestimates the overall costs. Patients covered by managed Medicaid are subject to capitation payment models, leading to fixed costs per member per month. As the overall cohort includes managed Medicaid in addition to commercial and Medicaid FFS, costs in the overall cohort are likely underestimated. In addition, administrative claims databases do not capture the number of units per transfusion event; thus, the overall transfusion volume was not assessed in this analysis. Patients who went on long-term disability, died within 12-months of follow-up, or otherwise did not meet enrollment criteria may have systematically different outcomes than patients who met the enrollment criteria. The proportion of patients with clinical complications was unadjusted and based on each patient's variable-length follow-up period. Patients covered by Medicaid had a longer follow-up than those covered by commercial insurance and thus, comparisons based on unadjusted proportions should be interpreted with caution. In addition, certain clinical complications could be underestimated given that they were identified utilizing ICD-10 codes and there are sometimes non-specific codes for certain complications (eg, alloimmunization); utilization of a different data source with more clinically focused data (eg, registry or electronic health record) could potentially reduce the risk of underestimation of complications.

Conclusions

Despite receiving frequent RBCTs, patients with SCD still experienced significant disease and transfusion-related clinical complications and had substantial healthcare costs. Patients with SCD who received frequent RBCTs with more VOCs at baseline experienced greater HCRU and higher total costs during follow-up. This highlights the need for novel therapies that can reduce VOCs, other SCD complications, and the associated economic burden of the disease.

Data Sharing Statement

The Merative™ MarketScan® Research Databases used for this study are available from Merative. Restrictions apply to the availability of these data, which were used under license for this study. All database records are de-identified and fully compliant with United States patient confidentiality requirements, including the Health Insurance Portability and Accountability Act (HIPAA) of 1996. The databases have been evaluated and certified by an independent third party to be in compliance with the HIPAA statistical de-identification standard. The databases were certified to satisfy the conditions set forth in Sections 164.514 (a)-(b)1ii of the HIPAA privacy rule regarding the determination and documentation of statistically de-identified data. Because this study uses only de-identified patient records and does not involve the collection, use, or transmittal of individually identifiable data, the data does not involve human subjects (per the definition of human subjects in the Code of Federal Regulations (CFR) Title 45 Part 46.102(e)). Thus, this study was exempted from Institutional Review Board (IRB) approval.

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Disclosure

CU, NL, and SJ are employees of Vertex Pharmaceuticals Incorporated and may hold stock or stock options in the company. SJ reports personal fees from Vertex Pharmaceuticals and Alnylam Pharmaceuticals, outside the submitted work. MJ and KE are employees of Merative and may hold stock or stock options in the company. BA has received research funding from Accordant, Afimmune, Agios, Bluebird Bio, Editas, Fulcrum, Genzyme, Global Blood Therapeutics, Hemanext, NovoNordisk, Pfizer, Roche, Sanius Health, Sanofi, and Vertex Pharmaceuticals

Incorporated; and has served as an advisory board member or consultant for Agios, Aruvant, Bluebird Bio, CRISPR Therapeutics AG, CVS/Accordant, Cyclerion, Emmaus, Forma Therapeutics, GBT, Hemanext, Novartis, NovoNordisk, Roche, Terumo, and Vertex Pharmaceuticals Incorporated. The authors report no other conflicts of interest in this work.

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