EE528

Healthcare Resource Utilization Among Patients With Sickle Cell Disease With Recurrent Vaso-Occlusive Crises in England

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INTRODUCTION

- Sickle cell disease (SCD) is a rare genetic disorder characterized by the expression of abnormal sickle hemoglobin, which leads to a variety of acute and chronic complications[1-4]
- Vaso-occlusive crises (VOCs), a hallmark clinical feature in patients with SCD, cause debilitating pain and can lead to additional organ complications and increased mortality[2,3,5]
- There are varying definitions of VOC in academic literature, with some more recent clinical trials defining VOC as SCD with acute pain crisis, acute chest syndrome, priapism, or splenic sequestration[6-7]
- There are limited data on healthcare resource utilization (HCRU) in a population experiencing recurrent VOCs (defined as experiencing ⩾2 VOCs per year for 2 consecutive years) in England

OBJECTIVE

- To describe the HCRU of patients with SCD with recurrent VOCs (defined as experiencing ⩾2 VOCs [SCD with acute pain crisis, acute chest syndrome, or priapism] per year for 2 consecutive years) in England

METHODS

Study Design and Database

- A longitudinal, retrospective cohort study design was used to identify patients with SCD in the Clinical Practice Research Datalink (CPRD) linked with the Hospital Episode Statistics (HES) database
  - CPRD Aurum is a large, anonymized, longitudinal source of electronic medical records containing ~13 million registered patients from over 1,375 UK primary care centers
  - HES is a data warehouse containing details of all admissions to National Health Services (NHS) hospitals in England (~168 acute NHS trusts)
    - The HES database contains details of all inpatient admissions, accident and emergency attendances, and outpatient appointments at NHS hospitals in England
- Overall, the study included data from July 1, 2008, to June 30, 2019, and included a 10-year eligibility period (July 1, 2008, to June 30, 2018), as well as a minimal follow-up of 1 year after inclusion (i.e., until June 30, 2019, for patients with an index date at the end of June 2018)

Patient Identification

- Patients were included in the analysis if they met the following inclusion criteria:
  - Primary or secondary diagnosis of SCD between July 1, 2008, to June 30, 2018
  - At least 2 VOCs per year in any 2 consecutive years after the first qualifying SCD diagnosis record
    - A VOC was defined as SCD with acute pain crisis, acute chest syndrome, or priapism
  - Registered within the CPRD and eligible for an HES linkage
  - At least 12 months of follow-up data after and including the index date (see definition below)
- Patients were excluded if they met the following exclusion criteria:
  - Evidence of hematopoietic stem cell transplant or hereditary persistence of fetal hemoglobin at any time in their medical records
  - Genotype recorded as HbSC in their more recent medical history
- The index date was the date of the second VOC record in the second year of 2 consecutive years
- All patients were followed for ⩾12 months from index to a censoring event or the end of the study period (June 30, 2019)

Matched Controls

- Each patient with SCD with recurrent VOCs was exact matched to 5 controls without SCD from the general population without replacement
- Matching was based on the following criteria: age (in years) at index (±5 years), sex, geographic region of general practice, and ethnicity
- Matched controls were assigned the same index date as their matched patients
- Matched controls had to be registered within the CPRD at index, to be eligible for an HES linkage, and to have ⩾1 year of follow-up data from the index date
- Matched controls were followed for ⩾12 months from index to a censoring event or the end of the study period (June 30, 2019)

Study Measures and Analysis

- Descriptive analyses were conducted for patient demographics and HCRU for patients with SCD with recurrent VOCs and matched controls
  - Mean (standard deviation [SD]) values were reported for continuous variables, and frequencies/ proportions (n [%]) were reported for categorical variables
  - In all reporting, patient numbers <5 were masked (i.e., reported as "–") to protect patient confidentiality, and secondary masking was applied where required to avoid back-calculation

Study Measures and Analysis (Continued)

- Demographics, including age, sex, ethnicity, and socio-economic status, were assessed at index; the presence of baseline transfusions was assessed in the 2-year baseline period prior to index
  - Socio-economic status was calculated using the Index of Multiple Deprivation (IMD) (composite measure of material deprivation including income, employment, education and skills, health, housing, crime, access to services, and living environment) for patients with SCD with recurrent VOCs and matched controls
- The rate of HCRU (per patient per year [PPPY]) was calculated during follow-up
- Comparative analyses were conducted for HCRU between patients and matched controls; a Z-test was used for significance testing ($P<0.05$)

Subgroup Analyses

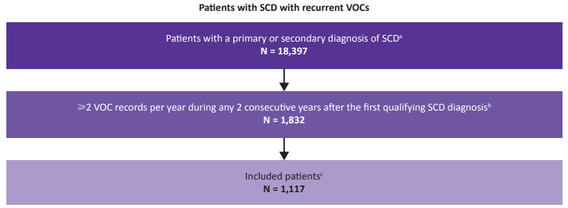
- Three subgroup analyses were conducted for HCRU: age at index (0–11 years, 12–35 years, or ⩾36 years), number of VOCs PPPY in the follow-up period (<2 VOCs PPPY or ⩾2 VOCs PPPY), and transfusion received at baseline (yes or no)
  - Patients with ⩾2 VOCs PPPY were further categorized into the following subgroups: 2–4, >4–6, >6–8, >8–10, or >10 VOCs PPPY

RESULTS

Patient Demographics

- A total of 1,117 patients with SCD with recurrent VOCs were identified in the CPRD-HES linked database and matched to 5,585 controls (**Figure 1**)
- The mean age of patients with SCD with recurrent VOCs was 24.96 years (SD: 14.23; range: 1–86), and 51.4% of patients were female (**Table 1**)
- Demographics between patients with SCD with recurrent VOCs and matched controls were broadly similar (**Table 1**)

Figure 1. Patient Attrition



SCD, sickle cell disease; VOC, vaso-occlusive crisis.

[a]The number of total patients with SCD was likely overestimated due to potential misclassification; this number likely includes patients with a sickle cell trait who were miscoded as having SCD; [b]A VOC was defined as SCD with acute pain crisis, acute chest syndrome, or priapism; [c]Additional exclusion criteria included the following: registration within the CPRD at index, eligibility for HES data linkage, 1 year of follow-up data, evidence of hematopoietic stem cell transplant or hereditary persistence of fetal hemoglobin at any time in the patients' medical records, and a genotype recorded as HbSC in the patients' more recent medical history.

Table 1. Baseline Demographics

	Patients With SCD With Recurrent VOCs (N = 1,117)	Matched Controls (N = 5,585)
Age (years), mean (SD; range)	24.96 (14.23; 1–86)	25.07 (15.49; 0–88)
Age categories (years), n (%)		
0–11	219 (19.6)	1,297 (23.2)
12–17	110 (9.85)	549 (9.8)
18–35	539 (48.3)	2,303 (41.2)
⩾36	249 (22.3)	1,436 (25.7)
Sex, n (%)		
Female	574 (51.4)	2,870 (51.4)
Male	543 (48.6)	2,715 (48.6)
Ethnicity, n (%)		
Black	1,023 (91.6)	5,115 (91.6)
Other	29 (2.6)	145 (2.6)
Mixed	25 (2.2)	125 (2.2)
South Asian	24 (2.2)	120 (2.2)
White	16 (1.4)	80 (1.4)
Socio-economic status (IMD), n (%)[a]		
Q1 (lower IMD score)	38 (3.4)	218 (3.9)
Q2	81 (7.3)	379 (6.8)
Q3	190 (17.0)	883 (15.8)
Q4	395 (35.4)	2,019 (36.2)
Q5 (higher IMD score)	413 (37.0)	2,080 (37.2)
Follow-up time (years), mean (SD)	4.69 (2.9)	4.24 (2.7)

IMD, Index of Multiple Deprivation; Q, quintile; SCD, sickle cell disease; SD, standard deviation; VOC, vaso-occlusive crisis.

[a]IMD is a composite measure of material deprivation such as income, employment, education and skills, health, housing, crime, access to services, and living environment. Lower IMD score equates to less deprived; higher IMD score equates to more deprived.

HCRU

- Patients with SCD with recurrent VOCs averaged 5.84 VOCs PPPY during follow-up
  - Of the 5.84 VOCs PPPY, 5.18 were SCD with acute pain crisis, 0.52 were acute chest syndrome, and 0.13 were priapism
- Patients with SCD with recurrent VOCs averaged 7.59 inpatient hospital visits, 9.60 outpatient visits, and 31.06 outpatient prescriptions (all PPPY) (**Table 2**)
  - Of the 7.59 inpatient hospital visits PPPY, 4.61 occurred for <1 day and 2.98 occurred for ⩾1 day
- Patients with SCD with recurrent VOCs had significantly higher HCRU than matched controls (**Table 2**)

Table 2. HCRU

HCRU, Mean Rate PPPY (SD)	Patients With SCD With Recurrent VOCs (N = 1,117)	Matched Controls (N = 5,585)
Hospital visits (any)*	22.17 (26.62)	2.63 (5.99)
Accident and emergency*	4.97 (10.59)	0.53 (1.62)
Inpatient*	7.59 (14.50)	0.32 (2.71)
<1 day*	4.61 (13.10)	0.21 (2.62)
⩾1 day*	2.98 (3.64)	0.11 (0.34)
Outpatient*	9.60 (10.69)	1.78 (4.18)
Primary care visits[a,b]	6.98	4.12
General practitioner*	4.94 (5.37)	2.93 (3.50)
Nurse*	2.04 (3.20)	1.19 (2.28)
Outpatient prescriptions*	31.06 (60.62)	7.58 (27.77)

HCRU, healthcare resource utilization; PPPY, per patient per year; SCD, sickle cell disease; SD, standard deviation; VOC, vaso-occlusive crisis.

[a]Statistical testing not conducted for primary care visits; [b]SD not available.

**P<0.001 between patients with SCD and matched controls (Z-test).*

Subgroup Analysis: HCRU

- HCRU increased as patient age increased
  - Patients in the oldest age cohort (⩾36 years) had the highest rates (PPPY) of primary care visits (10.06), outpatient prescriptions (60.66), and hospital visits (29.95) (**Table 3**)
- Patients with a higher number of VOCs (⩾2 VOC PPPY in the follow-up period) had higher HCRU than those with a lower number of VOCs (<2 VOCs PPPY in the follow-up period)
  - As the number of VOCs PPPY in the follow-up period increased, the mean rate of hospital visits PPPY increased as well (**Figure 2**)
- Patients who received a transfusion in the 2-year baseline period had higher HCRU than those who did not receive one (**Table 3**)

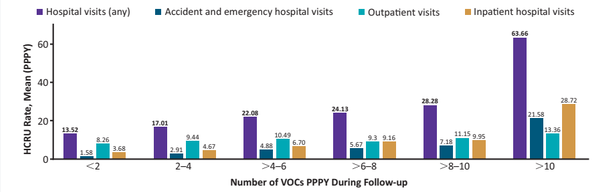
Table 3. HCRU by Subgroup

HCRU, Mean Rate PPPY (SD)	Age Subgroups			VOC Subgroups		Transfusion Subgroups	
	0–11 Years (n = 219)	12–35 Years (n = 649)	⩾36 Years (n = 249)	<2 VOCs (n = 421)	⩾2 VOCs (n = 696)	Baseline Transfusion (n = 303)	No Baseline Transfusion (n = 814)
Hospital visits (any)	14.70 (9.11)	21.70 (24.80)	29.95 (37.40)	13.52 (12.34)	27.40 (31.20)	29.80 (32.10)	19.33 (23.67)
Accident and emergency	2.36 (2.17)	5.60 (11.87)	5.65 (11.16)	1.58 (1.54)	7.02 (12.94)	5.98 (12.31)	4.60 (9.86)
Inpatient	4.32 (4.23)	7.39 (13.52)	11.00 (20.76)	3.68 (7.41)	9.96 (17.01)	11.68 (17.45)	6.07 (12.91)
<1 day	2.46 (3.93)	4.11 (11.88)	7.80 (19.38)	2.63 (7.26)	5.81 (15.49)	8.25 (15.85)	3.26 (11.64)
⩾1 day	1.86 (1.38)	3.28 (3.77)	3.20 (4.40)	1.05 (0.71)	4.16 (4.16)	3.43 (4.32)	2.82 (3.34)
Outpatient	8.02 (5.55)	8.71 (9.42)	13.31 (15.42)	8.26 (7.46)	10.41 (12.18)	12.13 (13.38)	8.66 (9.34)
Primary care visits[a]	5.09	6.44	10.06	6.15	7.49	7.12	6.93
General practitioner	3.37 (2.77)	4.53 (5.12)	7.39 (6.78)	4.14 (4.27)	5.43 (5.89)	5.14 (5.38)	4.87 (5.38)
Nurse	1.72 (4.32)	1.91 (2.89)	2.67 (2.68)	2.01 (2.41)	2.06 (3.59)	1.98 (2.29)	2.06 (3.48)
Outpatient prescriptions	28.14 (23.46)	20.69 (38.10)	60.66 (105.32)	27.57 (53.90)	33.17 (64.29)	40.21 (76.58)	27.65 (53.13)

HCRU, healthcare resource utilization; PPPY, per patient per year; SCD, sickle cell disease; SD, standard deviation; VOC, vaso-occlusive crisis.

[a]SD not available.

Figure 2. HCRU by Number of VOCs PPPY



HCRU, healthcare resource utilization; PPPY per patient per year; VOC, vaso-occlusive crisis.

LIMITATIONS

- This study used ICD-10 codes (HES) and Medcodes (CPRD) to identify patients with SCD and thus is subject to misclassification bias due to inaccurate coding
  - The number of patients with SCD was likely overestimated due to patients with a sickle cell trait being coded as having SCD
  - HCRU was likely underestimated because any drugs prescribed in secondary care (i.e., hydroxycarbamide, iron chelation therapies, etc.) could not be identified through the HES database
- There is no standard definition for SCD with recurrent VOCs and thus it is difficult to conduct direct comparisons between this study and other published literature. Although most VOCs in the follow-up period were due to acute pain crises, the study definition of VOC (i.e., SCD with acute pain crisis, acute chest syndrome, or priapism) also makes comparability difficult with previous publications that did not use a similar definition for VOC
  - Splenic sequestration had no ICD-10 code and therefore could not be included in the VOC definition
- Given the minimum 12-month post-index period for patients with SCD with recurrent VOCs, individuals who died or were not continuously enrolled for ⩾12 months post-index were excluded, which could have led to an underestimation of HCRU

CONCLUSIONS

- Patients with SCD with recurrent VOCs had significantly higher HCRU than matched controls from the general population in England
- Older age, a higher number of VOCs, and receiving a transfusion in the 2-year baseline period were associated with higher HCRU
- Elevated HCRU in patients with SCD with recurrent VOCs highlights the need for innovative therapies that can reduce the number of VOCs and associated HCRU

ACKNOWLEDGMENTS

The study was supported by Vertex Pharmaceuticals Incorporated. Editorial coordination and support were provided by Nathan Blow, PhD, under the guidance of the authors. Editorial support was provided by Iona Linford, MEng, and Nicholas Strange of Complete HealthVizion, Inc., IPG Health Medical Communications, Inc., Chicago, IL, USA, funded by Vertex Pharmaceuticals Incorporated.

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AUTHOR DISCLOSURES

This study was based in part on data from the Clinical Practice Research Datalink obtained under license from the UK Medicines and Healthcare products Regulatory Agency. The data were provided by patients and collected by the NHS as part of their care and support. The interpretation and conclusions contained in this study are those of the authors alone. This study was sponsored by Vertex Pharmaceuticals Incorporated and CRISPR Therapeutics. CU, SC, JH, and NL are employees of Vertex Pharmaceuticals Incorporated and may hold stock or stock options in the company. NFL, FCI, and SF are employees of IQVIA and may hold stock or stock options in the company. FS has received research grants from IQVIA, Novartis Pharma AG, and Vertex Pharmaceuticals Incorporated; received honoraria from Biologix FZ co, Bristol Myers Squibb, Chiesi Ltd, and Novartis Pharma AG; served as an advisory board or committee member for Agios, bluebird bio, Bristol Myers Squibb, Silence Therapeutics Plc, and Vertex Pharmaceuticals Incorporated; and acted as Chair for the UK Forum on Haemoglobin Disorders.

Presented at The Professional Society for Health Economics and Outcomes Research (ISPOR) Annual Scientific Meeting, May 7–10, 2023, Boston, MA, USA