Healthcare Resource Utilization Among Patients with Sickle Cell Disease and Recurrent Vaso-Occlusive Crises in the Netherlands

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BACKGROUND

- Sickle cell disease (SCD) is a rare genetic disorder characterized by expression of abnormal sickle hemoglobin, which leads to a variety of acute and chronic complications and shortened lifespan.[1]
- Vaso-occlusive crisis (VOC), a hallmark clinical feature in patients with SCD, causes debilitating pain often requiring emergency department visit or hospitalization.[2]
- In the Netherlands, the prevalence of SCD is currently estimated to be between 1,500 and 2,000 patients.[3]
- There is limited information from the Netherlands on the healthcare resource utilization (HCRU) of patients with SCD and recurrent VOCs.

OBJECTIVE

- To describe the HCRU of patients with SCD and recurrent VOCs in the Netherlands.

METHODS

Study Design & Database

- This longitudinal, retrospective cohort study utilized healthcare data from the PHARMO Data Network.
- The PHARMO Data Network is a population-based data source with combined anonymous electronic healthcare data from different primary and secondary healthcare settings in the Netherlands.
  - The different data sources, including data from general practitioners, inpatient/outpatient pharmacies, clinical laboratories, hospitals, the Netherlands cancer registry, pathology registry and perinatal registry, are linked on a patient level through validated algorithms.
- The PHARMO Data Network covers 20%-25% of 17 million active persons in the Netherlands.[4]
- The study was conducted from January 1, 2013 to December 31, 2021 and included a 6-year SCD patient selection period (January 1, 2014 to December 31, 2020), and a minimum of 1 year of data availability before and after patient inclusion in the study.

Patient Identification

- Patients were included in the analysis if they met the following inclusion criteria:
  1. At least one diagnosis of SCD between January 1, 2014 to December 31, 2020
  2. At least two VOCs per year in at least two consecutive years in the selection period
     - VOCs were defined as SCD with crisis, priapism, acute splenic sequestration, or acute chest syndrome
  3. At least 12 months of data availability before and after the index date (date of the second VOC in the second consecutive year)
- Patients were excluded if they met the following exclusion criteria:
  - Evidence of hematopoietic stem cell transplant (HSCT), hereditary persistence of fetal hemoglobin, diagnosis of sickle-cell trait, or diagnosis of alpha-thalassemia during baseline, index, or follow-up
- All patients were followed for at least 12 months from the index date to death, loss to follow-up, or the end of the study period (December 31, 2021).

Study Measures and Analysis

- Descriptive analyses were conducted for demographics and HCRU for patients with SCD and recurrent VOCs.
  - Mean (standard deviation [SD]) values were reported for continuous variables and frequencies/proportions (n,%) for categorical variables. Median (Q1-Q3) was also reported for age.
  - All values with a count of less than 5 patients were suppressed according to data protection requirements.
- Demographics were assessed at the index date, including sex, age, and socioeconomic status.
- Rate of HCRU (per patient per year [PPPY]) was calculated over the variable-length follow-up period.
- Rate of VOCs (PPPY) was calculated over the variable-length follow-up period.

Subgroup Analyses

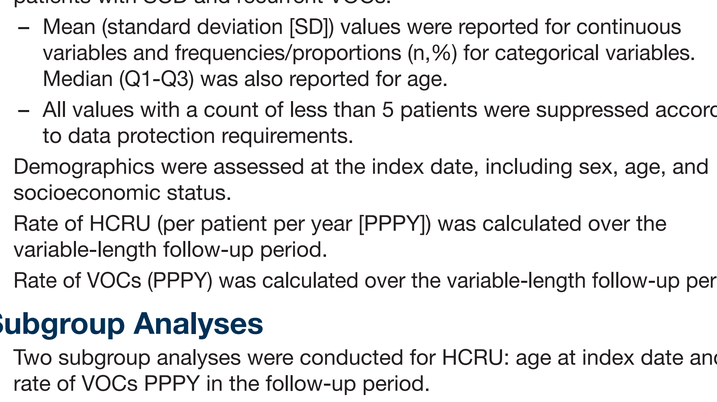
- Two subgroup analyses were conducted for HCRU: age at index date and rate of VOCs PPPY in the follow-up period.
  - Age at Index date: 0 – 11 years, 12 – 35 years , and ≥ 36 years
  - Rate of VOCs in the follow-up period: < 2 PPPY and ≥ 2 PPPY

RESULTS

Patient Demographics

- A total of 383 patients with SCD and recurrent VOCs were identified in PHARMO Data Network. (**Figure 1**)
  - Treatment data was available for a subset of 64 patients
- The mean age of patients with SCD and recurrent VOCs was 26.9 years (SD: 14.4) and 53.3% of patients were female. (**Table 1**)
- Data on socio-economic status was reported in a small proportion of patients (83 patients, 21.7%); among these patients, 65.1% were of low socio-economic status. (**Table 1**)
- The mean duration of follow-up was 3.1 years (SD: 1.6). (**Table 1**)

Figure 1. Attrition Table



sCD, sickle cell disease; **VOCs,** vaso-occlusive crises; **HSCT,** hematopoietic stem cell transplant; **HPFH,** hereditary persistence of fetal hemoglobin
[1] VOCs defined as having ICD-10 diagnosis codes for any of the following conditions: SCD with crisis, priapism, acute splenic sequestration, or acute chest syndrome.
[2] Additional exclusion criteria include <12 months data availability before index date, diagnosis of sickle-cell trait, diagnosis of alpha-thalassemia during baseline, index, and follow-up.

Table 1. Baseline Demographics

Patient characteristics	SCD and recurrent VOCs, N=383
Sex, n (%)	
Male	168 (43.9%)
Female	204 (53.3%)
Missing	11 (2.9%)
Age at index date	
Mean (SD)	26.9 (14.4)
Median (Q1-Q3)	24.0 (18.0-35.0)
Min-Max	1.0 - 72.0
Missing	11 (3%)
Socio-economic status, n (%)[1]	83 (21.7%)
Low	54 (65.1%)
Middle	13 (15.7%)
High	16 (19.2%)
Years of follow-up, mean (SD)	3.1 (1.6)

Q, quartile; **SD,** standard deviation; **SCD,** sickle cell disease; **VOCs,** vaso-occlusive crises
[1] Socio-economic status is a relative measure based on scores of the Netherlands Institute for Social Research, which aggregates mean household income, percentages of households with a low income, inhabitants without a paid job, and households with a low mean education. Based on social-economic status data, patients in the PHARMO database are categorized as low, middle, and high. Furthermore, percentage of patients with low, middle, and high in Table 1 were calculated among patients with available data on social-economic status.

Table 2. HCRU

Healthcare Resource Utilization	Prevalence, n (%)	Rate (PPPY), Mean (SD), (95% CI)
Outpatient specialist visits	357 (93.2%)	7.0 (5.9), (6.4 - 7.6)
VOC related	306 (79.9%)	3.4 (4.0), (3.0 - 3.8)
Not VOC related	320 (83.6%)	3.6 (4.1), (3.2 - 4.0)
Inpatient hospitalizations	307 (80.2%)	2.5 (3.4), (2.2 - 2.8)
VOC related	278 (72.6%)	1.7 (2.7), (1.4 - 2.0)
Not VOC related	190 (49.6%)	0.8 (1.8), (0.6 - 1.0)
Total number of hospital days	NA	13.9 (20.3), (11.6 - 16.2)
Inpatient hospitalizations with < 1 day	163 (42.6%)	1.0 (2.2), (0.7 - 1.2)
VOC related	110 (28.7%)	0.6 (1.5), (0.4 - 0.7)
Not VOC related	107 (27.9%)	0.6 (1.8), (0.4 - 0.8)
Inpatient hospitalizations with ≥ 1 day	288 (75.2%)	1.9 (2.4), (1.6 - 2.2)
VOC related	254 (66.3%)	1.6 (2.2), (1.3 - 1.8)
Not VOC related	152 (39.7%)	0.4 (0.5), (0.3 - 0.4)
Any treatment (N=64)[1,2]	61 (95.3%)	20.7 (49.5); (8.3 - 33.1)

CI, confidence interval; **NA,** Not applicable, **PPPY,** per patient per year; **SCD,** sickle cell disease; **SD,** standard deviation; **VOCs,** vaso-occlusive crises
[1] Treatment was defined as at least one dispensation of drug from outpatient pharmacy data
[2] Any treatment includes any drug dispensed, including those specifically investigated (e.g., hydroxycarbamide, penicillin, folic acid, iron chelation therapies, and pain medication)

HCRU

- Patients with SCD and recurrent VOCs on average experienced 7.0 (SD: 6.9) VOCs PPPY in the follow-up period.
- Patients had a mean of 2.5 (SD: 3.4) inpatient hospitalizations, 13.9 (SD: 20.3) days spent in the hospital, and 7.0 (SD: 5.9) outpatient specialist visits (all PPPY). (**Table 2**)
- 42.6% of patients had inpatient hospitalizations with < 1 day of stay, with a mean of 1.0 hospitalization PPPY (SD: 2.2). (**Table 2**)
- 75.2% of patients had inpatient hospitalizations with ≥ 1 day of stay, with a mean of 1.9 hospitalizations PPPY (SD: 2.4). (**Table 2**)
- Among a subset of patients with outpatient pharmacy data available (N=64), patients had a mean of 20.7 (SD: 49.5) prescriptions dispensed PPPY during follow-up. (**Table 2**)

Subgroup Analysis: HCRU by Age and VOC Subgroups

- Rate of HCRU generally increased with increasing age. (**Table 3**)
- Patients with ≥ 2 VOCs PPPY in the follow-up period had higher rates of HCRU than those with <2 VOCs PPPY in the follow-up period. (**Table 3**)
  - Mean rate of overall outpatient specialist visits was higher among patients with SCD with ≥ 2 VOCs (8.5 visits PPPY) compared to patients experiencing < 2 VOCs per year (3.2 visits PPPY).
  - Mean rate of inpatient hospitalizations was higher among patients with SCD with ≥ 2 VOC (3.1 hospitalizations PPPY) compared to patients experiencing < 2 VOCs per year (0.8 hospitalizations PPPY).

Table 3. HCRU by Age and VOC Frequency Subgroups

Healthcare Resource Utilization	Age Groups			VOC Frequency	
	0-11 Years (N=47)	12-35 Years (N=237)	≥ 36 Years (N=88)	< 2 VOCs (N=107)	≥ 2 VOCs (N=276)
	Rate (PPPY) Mean (SD), (95% CI)	Rate (PPPY) Mean (SD), (95% CI)	Rate (PPPY) Mean (SD), (95% CI)	Rate (PPPY) Mean (SD), (95% CI)	Rate (PPPY) Mean (SD), (95% CI)
Outpatient specialist visits	5.5 (4.2), (4.2 - 6.7)	7.2 (5.8), (6.5 - 7.9)	8.2 (6.4), (6.8 - 9.6)	3.2 (3.9), (2.5 - 4.0)	8.5 (5.9), (7.8 - 9.2)
VOC related	2.4 (2.1), (1.7 - 3.0)	3.4 (3.6), (3.0 - 3.9)	4.4 (5.5), (3.2 - 5.5)	0.6 (0.7),(0.5 - 0.8)	4.5 (4.2), (4.0 - 5.0)
Not VOC related	3.1 (4.3), (1.8 - 4.4)	3.8 (4.2), (3.2 - 4.3)	3.8 (3.8), (3.0 - 4.6)	2.6 (4.0), (1.8 - 3.4)	4.0 (4.1), (3.5 - 4.5)
Inpatient hospitalizations	1.2 (2.1), (0.6 - 1.8)	2.8 (3.2), (2.4 - 3.2)	2.5 (4.3), (1.6 - 3.4)	0.8 (1.0), (0.7 - 1.0)	3.1 (3.8), (2.7 - 3.6)
VOC related	0.7 (0.9), (0.5 - 1.0)	2.0 (2.7), (1.7 - 2.4)	1.5 (3.3), (0.9 - 2.2)	0.6 (0.5), (0.5 - 0.7)	2.1 (3.0), (1.8 - 2.5)
Not VOC related	0.5 (1.6), (0.0 - 1.0)	0.8 (1.6), (0.6 - 1.0)	1.0 (2.2), (0.5 - 1.4)	0.3 (0.7), (0.2 - 0.4)	1.0 (2.0), (0.8 - 1.2)
Total number of hospital days	8.9 (13.0), (3.9 - 13.9)	14.8 (19.1), (12.2 - 17.5)	15.2 (26.5), (8.6 - 21.8)	6.2 (8.7), (4.3 - 8.2)	16.6 (22.4), (13.7 - 19.5)
Inpatient hospitalizations with < 1 day	0.4 (1.5), (0.0 - 0.8)	1.1 (2.3), (0.8 - 1.4)	1.0 (2.4), (0.5 - 1.5)	0.2 (0.5), (0.1 - 0.3)	1.2 (2.5), (0.9 - 1.5)
VOC related	0.1 (0.2), (0.0 - 0.1)	0.6 (1.6), (0.4 - 0.8)	0.3 (0.9), (0.1 - 0.5)	0.1 (0.2), (0.0 - 0.1)	0.6 (1.6), (0.4 - 0.8)
Not VOC related	0.3 (1.4), (0.1 - 0.7)	0.5 (1.5), (0.3 - 0.7)	0.7 (2.0), (0.3 - 1.1)	0.1 (0.4), (0.1 - 0.2)	0.6 (1.8), (0.4 - 0.9)
Inpatient hospitalizations with ≥ 1 day	1.3 (1.0), (0.9 - 1.7)	2.0 (2.0), (1.8 - 2.3)	2.1 (3.7), (1.2 - 3.0)	0.8 (0.7), (0.7 - 1.0)	2.3 (2.6), (1.9 - 2.6)
VOC related	1.0 (0.9), (0.7 - 1.3)	1.7 (1.9), (1.4 - 1.9)	1.7 (3.5), (0.8 - 2.5)	0.7 (0.5), (0.5 - 0.8)	1.9 (2.5), (1.5 - 2.2)
Not VOC related	0.3 (0.5), (0.1, 0.5)	0.4 (0.5), (0.3 - 0.5)	0.4 (0.6), (0.3 - 0.5)	0.2 (0.4), (0.1 - 0.3)	0.4 (0.6), (0.3 - 0.5)
Any treatment[1,2]	3.8 (4.2), (0.0 - 7.8)	19.8 (45.7), (5.7 - 33.8)	31.9 (69.6), (0.0 - 72.1)	23.1 (64.1), (0.0 - 54.0)	19.7 (42.8), (6.8 - 32.5)

SD, standard deviation; **CI,** confidence interval; **PPPY,** per patient per year; **SCD,** sickle cell disease; **VOCs,** vaso-occlusive crises
[1] Treatment was defined as at least one dispensation of drug from outpatient pharmacy data
[2] Any treatment includes any drug dispensed, including those not specifically investigated (e.g., hydroxycarbamide, penicillin, folic acid, iron chelation therapies, and pain medication)

Limitations

- The data collected in this study are based on administrative medical records. Therefore, measurement errors and possible inaccuracy of diagnostic and procedural codes could happen.
- Given the minimum 12-month post-index period for patients with SCD, individuals who were not continuously enrolled for at least 12 months post-index date were excluded, which potentially could lead to underestimation of HCRU.
- Treatment use and socio-economic status results should be interpreted with caution due to the limited number of patients who had socio-economic status reported.
- Prevalence of HCRU should be interpreted with caution due to the variable length of the follow-up period.

CONCLUSIONS

- **Patients with SCD and recurrent VOCs in the Netherlands continue to have substantial HCRU.**
- **Older age and higher number of VOCs were generally associated with increased HCRU.**
- **These findings among patients with SCD and recurrent VOCs highlight the need for novel therapies that can reduce the number of VOCs and the associated HCRU.**

References

1. Azar, S. and T.E. Wong, Sickle Cell Disease: A Brief Update. *Med Clin North Am*, 2017. 101(2): p. 375-393.
2. Ware, R.E., et al., Sickle cell disease. *Lancet,* 2017. 390(10091): p. 311-323.
3. Lobitz, S., et al., Newborn screening for sickle cell disease in Europe: recommendations from a Pan-European Consensus Conference. *Br J Haematol,* 2018. 183(4): p. 648-66.
4. Kuiper J, et al. Existing Data Sources for Clinical Epidemiology: The PHARMO Database Network *Clinical Epidemiology*. 2020; 12: 415-422.

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