Mortality and Clinical Complications Among Patients With Sickle Cell Disease With Recurrent Vaso-Occlusive Crises in France

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INTRODUCTION

- Sickle cell disease (SCD) is a genetic disorder characterized by expression of abnormal sickle hemoglobin, which leads to a variety of acute and chronic complications[1-3]
- 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[1,2,4,5]
- There are limited contemporary data on the clinical burden and mortality in patients with SCD with recurrent VOCs in France[4]

OBJECTIVE

- To describe mortality and clinical complications among patients with SCD with recurrent VOCs in France

METHODS

Study Design and Database

- A longitudinal, retrospective cohort study design utilized the French National Health Data System database, Système National des Données de Santé (SNDS), to identify patients with SCD with recurrent VOCs
- The SNDS is a national claims database that captures pseudonymized, longitudinal data for ~99% of the French population, inclusive of overseas territories and reports claims data for 65 million insurees[6]
  - The SNDS contains details of all primary care, hospital, and pharmacy records reimbursed in France
- The study was conducted from January 1, 2012, to March 1, 2020, and included a 7-year eligibility period (from January 1, 2012, to March 1, 2019) and a minimum follow-up of 1 year after inclusion

Patient Identification

- Patients were included in the analysis if they met the following inclusion criteria:
  - At least 1 inpatient claim or registration in the long-term disease (LTD) database with a diagnosis of SCD between January 1, 2012, and March 1, 2019
  - At least 2 VOCs/year in any 2 consecutive years after the first qualifying SCD diagnosis record between January 1, 2012, and March 1, 2019
  - A VOC was defined as an inpatient claim with a relevant diagnosis of SCD with crisis, priapism, or acute chest syndrome
  - At least 12 months of follow-up data after and including the index date
- Patients were excluded if they met the following exclusion criterion:
  - Evidence of hereditary persistence of fetal hemoglobin or hematopoietic stem cell transplant at any time in their medical records
- The index date was the date of the second VOC record in the second year of 2 consecutive years
- All patients were followed for at least 12 months from the index date until death or the end of the study period (March 1, 2020)

Study Measures and Analysis

- Descriptive analyses were conducted for demographics, rate of VOCs, mortality, and clinical complications (acute and chronic) for patients with SCD with recurrent VOCs
  - Mean (standard deviation [SD]) values were reported for continuous variables and frequencies/proportions (n [%]) for categorical variables
  - In all cases where data were available for <10 patients, values were masked to protect patient confidentiality
- Demographics, including age, sex, and area of residence, were assessed at the index date
- Mortality rates (deaths per 100 person-years), mortality proportion (% of total population), and mean age of death were calculated during the variable follow-up period
  - To avoid immortal time bias in mortality rate estimates, person-years were measured starting from 1 year after the index date
- The proportions of patients with acute and/or chronic complications (% of total population) were calculated during the variable follow-up period
  - The patient-level rates of acute complications (per patient per year [PPPY]) were calculated during the variable follow-up period and reported as the mean number of events PPPY

Subgroup Analyses

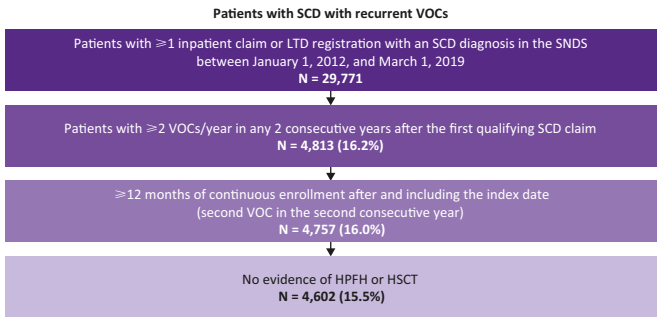
- Descriptive analyses for clinical complications and mortality were conducted among 2 subgroups of patients:
  - VOC frequency during follow-up (<2 and ⩾2 VOCs PPPY)
  - Age (years) at the index date (0–11, 12–35, and ⩾36)

RESULTS

Patient Demographics

- A total of 4,602 patients with SCD with recurrent VOCs were identified in the SNDS database (**Figure 1**)

Figure 1. Patient Attrition[a]



HPFH, hereditary persistence of fetal hemoglobin; HSCT, hematopoietic stem cell transplant; LTD, long-term disease; SCD, sickle cell disease; SNDS, Système National des Données de Santé; VOC, vaso-occlusive crisis.
[a]Values presented in parentheses represent the proportion of total number of patients with ⩾1 inpatient claim or LTD database registration during the study period.

Patient Demographics (Continued)

- The mean age of patients with SCD with recurrent VOCs was 19.8 years (SD: 13.5; range: 1–76), and 51.8% of patients were female (**Table 1**)
- Most patients (85.6%) lived in metropolitan France, approximately half of whom (53%) lived in the broad Paris area (Île-de-France) and 13.5% of whom lived in Overseas France (**Table 1**)

Table 1. Baseline Demographics

	Patients With SCD With Recurrent VOCs (N = 4,602)
Age, years, mean (SD; range)	19.8 (13.5; 1–76)
Age categories (years), n (%)	
0–11	1,561 (33.9)
12–35	2,464 (53.5)
⩾36	577 (12.5)
Female, n (%)	2,384 (51.8)
Broad area of residence, n (%)	
Metropolitan France	3,940 (85.6)
Overseas France	621 (13.5)
Unknown	41 (0.9)
LTD registration, n (%)[a]	4,202 (91.3)
With SCD code	4,089 (88.9)
Follow-up time, years, mean (SD; range)	4.4 (1.8; 1.0–7.2)

LTD, long-term disease; SCD, sickle cell disease; VOC, vaso-occlusive crisis.
[a]Patients were registered to this database with the corresponding ICD-10 code for the disease that required long-term and/or expensive treatment due to its severity and/or chronic nature.

Mortality

- The overall mortality rate for patients with SCD with recurrent VOCs was 0.64 deaths per 100 person-years
- During the variable follow-up period, 101 (2.2%) patients with SCD with recurrent VOCs died (**Table 2**)
  - The mean age of death was 39.3 years (SD: 17.5), which is >40 years lower than the life expectancy of the French general population (males and females: 82.3 years; females: 85.5 years; males: 79.3 years[7])

Table 2. Mortality

	Patients With SCD With Recurrent VOCs (N = 4,602)
Overall mortality rate, deaths per 100 person-years	0.64
Deaths, n (%)	101 (2.2)
Age at death, years, mean (SD)	39.3 (17.5)

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

Clinical Complications

- The most common chronic complications were anemia/leukocytosis (44.1%), chronic pain (26.6%), and gallbladder disease (17.8%) (**Table 3**)

Table 3. Chronic Clinical Complications

Chronic Complication, n (%)	Patients With SCD With Recurrent VOCs (N = 4,602)
Anemia/leukocytosis	2,029 (44.1)
Chronic pain	1,222 (26.6)
Early menopause	567 (23.8)
Gallbladder disease/cholelithiasis	817 (17.8)
Hepatobiliary complications	773 (16.8)
Pregnancy complications	375 (15.7)
Mental health complications	709 (15.4)
Anxiety	521 (11.3)
Depression	349 (7.6)
Cerebrovascular disease	552 (12.0)
Cardiopulmonary complications	510 (11.1)
Heart failure	270 (5.9)
Cardiomegaly	212 (4.6)
Pulmonary hypertension	183 (4.0)
Bone and joint problems	476 (10.3)
Avascular necrosis	450 (9.8)
Osteoneocrosis	38 (0.8)
Asthma	441 (9.6)
Renal complications	333 (7.2)
Liver complications	316 (6.9)
Neurocognitive impairment	137 (3.0)
Malignancy	37 (0.8)

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

- All patients (100%) experienced VOCs during the variable follow-up period, averaging 3.8 VOCs PPPY (**Table 4**)
- In addition to VOCs, the most prevalent acute complications were infections (42.0%), multiorgan failure (38.2%), and gallstones (16.8%) (**Table 4**)

Table 4. Acute Clinical Complications

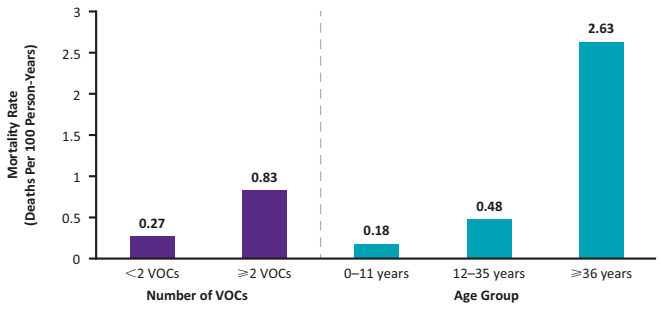
Acute Complication	Patients With SCD With Recurrent VOCs (N = 4,602)	
	Mean Rate PPPY (SD)	Proportion, n (%)[a]
VOCs	3.82 (3.57)	4,602 (100)
Infections[b]	0.23 (0.57)	1,931 (42.0)
Multiorgan failure[c]	0.25 (0.67)	1,758 (38.2)
Gallstones	0.07 (0.24)	773 (16.8)
Acute renal failure	0.03 (0.18)	212 (4.6)
Strokes	0.04 (0.43)	184 (4.0)
Leg ulcer	0.05 (0.58)	156 (3.4)

PPPY, per patient per year; SCD, sickle cell disease; SD, standard deviation; VOC, vaso-occlusive crisis.
[a]Proportion of patients with any incidence of an acute complication that occurred during the variable follow-up period; [b]Inclusive of bacteremia, osteomyelitis, septicemia, and viral infections; [c]Inclusive of cardiac, hepatic, kidney, ovarian, cerebrovascular, polyglandular, and respiratory failures.

Subgroup Analyses: Mortality

- Patients with a greater number of VOCs had higher mortality rates (<2 VOCs: 0.27; ⩾2 VOCs: 0.83) (**Figure 2**)
- Increased age was associated with higher mortality rates (0–11 years: 0.18; 12–35 years: 0.48; ⩾36 years: 2.63) (**Figure 2**)

Figure 2. Subgroup Analyses: Mortality Rates by Number of VOCs and Age[a,b]



VOC, vaso-occlusive crisis.
[a]Deaths during follow-up (n [%]) by number of VOCs: <2 VOCs (14 [0.9]); ⩾2 VOCs (87 [2.9]); [b]Deaths during follow-up (n [%]) by age: 1–11 years (blinded); 12–35 years (43 [1.8]); ⩾36 years: (49 [8.5]).

Subgroup Analyses: Clinical Complications

- Patients with a higher number of VOCs (⩾2 VOCs PPPY during follow-up) had a higher prevalence of chronic clinical complications than those with a lower number of VOCs (<2 VOCs PPPY during follow-up) (**Table 5**)

Subgroup Analyses: Clinical Complications (Continued)

- Older patients (aged ⩾36 years) had a higher prevalence of chronic clinical complications than younger patients (aged 0–11 and 12–35 years), including renal (aged ⩾36 years: 24.6%; aged 0–11 years: 1.6%; aged 12–35 years: 6.7%) and cardiopulmonary (aged ⩾36 years: 27.4%; aged 0–11 years: 3.7%; aged 12–35 years: 11.9%) (**Table 5**)

Table 5. Subgroup Analyses: Chronic Clinical Complications by Number of VOCs and Age

Chronic Complication, n (%)[a]	VOCs PPPY		Age Group		
	<2 VOCs (n = 1,638)	⩾2 VOCs (n = 2,964)	0–11 Years (n = 1,561)	12–35 Years (n = 2,464)	⩾36 Years (n = 577)
Anemia/leukocytosis	504 (30.8)	1,525 (51.5)	553 (35.4)	1,168 (47.4)	308 (53.4)
Chronic pain	228 (13.9)	994 (33.5)	291 (18.6)	797 (32.4)	134 (23.2)
Early menopause	175 (20.4)	392 (25.7)	113 (15.3)	386 (29.9)	68 (19.1)
Mental health complications	100 (6.1)	609 (20.6)	103 (6.6)	495 (20.1)	111 (19.2)
Gallbladder disease/cholelithiasis	235 (14.4)	582 (19.6)	350 (22.4)	394 (16.0)	73 (12.7)
Hepatobiliary complications	225 (13.7)	548 (18.5)	339 (21.7)	365 (14.8)	69 (12.0)
Pregnancy complications	123 (14.3)	252 (16.5)	0	347 (26.9)	28 (7.9)
Cerebrovascular disease	103 (6.3)	449 (15.2)	197 (12.6)	277 (11.2)	78 (13.5)
Cardiopulmonary complications	93 (5.7)	417 (14.1)	58 (3.7)	294 (11.9)	158 (27.4)
Heart failure	50 (3.1)	220 (7.4)	-	136 (5.5)	131 (22.7)
Cardiomegaly	36 (2.2)	176 (5.9)	51 (3.3)	137 (5.6)	24 (4.2)
Pulmonary hypertension	26 (1.6)	157 (5.3)	-	96 (3.9)	81 (14.0)
Bone and joint problems	92 (5.6)	384 (13.0)	61 (3.9)	327 (13.3)	88 (15.3)
Avascular necrosis	86 (5.2)	364 (12.3)	57 (3.7)	316 (12.8)	77 (13.3)
Osteoneocrosis	-	30 (1.0)	-	17 (0.7)	14 (2.4)
Asthma	98 (6.0)	343 (11.6)	184 (11.8)	230 (9.3)	27 (4.7)
Renal complications	66 (4.0)	267 (9.0)	25 (1.6)	166 (6.7)	142 (24.6)
Liver complications	66 (4.0)	250 (8.4)	21 (1.4)	192 (7.8)	103 (17.9)
Neurocognitive impairment	23 (1.4)	114 (3.9)	19 (1.2)	83 (3.4)	35 (6.1)
Malignancy	-	31 (1.1)	0	18 (0.7)	19 (3.3)
Delayed puberty	11 (0.7)	28 (0.9)	14 (0.9)	25 (1.0)	0 (0.0)

PPPY, per patient per year; VOC, vaso-occlusive crisis.
[a]Values with patient numbers <10 were masked (i.e., "-") to protect patient confidentiality.

- Older age and a higher number of VOCs were positively associated with higher rates of acute complications in patients with SCD and recurrent VOCs (**Tables 6** and **7**)

Table 6. Subgroup Analyses: Acute Clinical Complications by Number of VOCs

Acute Complication	VOCs PPPY			
	<2 VOCs (n = 1,638)		⩾2 VOCs (n = 2,964)	
	Mean Rate PPPY (SD)	Proportion, n (%)[a]	Mean Rate PPPY (SD)	Proportion, n (%)[a]
VOCs	1.19 (0.48)	1,638 (100)	5.27 (3.71)	2,964 (100)
Infections[b]	0.12 (0.29)	483 (29.5)	0.30 (0.67)	1,448 (48.9)
Multiorgan failure[c]	0.11 (0.30)	433 (26.4)	0.32 (0.79)	1,325 (44.7)
Gallstones	0.05 (0.17)	225 (13.7)	0.09 (0.27)	548 (18.5)
Acute renal failure	0.01 (0.05)	30 (1.8)	0.04 (0.22)	182 (6.1)
Strokes	0.02 (0.27)	31 (1.9)	0.05 (0.50)	153 (5.2)
Leg ulcers	0.01 (0.15)	25 (1.5)	0.08 (0.71)	131 (4.4)

PPPY, per patient per year; SD, standard deviation; VOC, vaso-occlusive crisis.
[a]Proportion of patients with any incidence of an acute complication that occurred during the variable follow-up period; [b]Inclusive of bacteremia, osteomyelitis, septicemia, and viral infections; [c]Inclusive of cardiac, hepatic, kidney, ovarian, cerebrovascular, polyglandular, and respiratory failures.

Table 7. Subgroup Analyses: Acute Clinical Complications by Age

Acute Complication[a]	Age Group					
	0–11 Years (n = 1,561)		12–35 Years (n = 2,464)		⩾36 Years (n = 577)	
	Mean Rate PPPY (SD)	Proportion, n (%)[b]	Mean Rate PPPY (SD)	Proportion, n (%)[b]	Mean Rate PPPY (SD)	Proportion, n (%)[b]
VOCs	3.26 (2.77)	1,561 (100)	4.25 (3.96)	2,464 (100)	3.52 (3.53)	577 (100)
Infections[c]	0.23 (0.38)	697 (44.7)	0.22 (0.53)	1,027 (41.7)	0.31 (1.01)	207 (35.9)
Multiorgan failure[d]	0.16 (0.29)	525 (33.6)	0.24 (0.60)	988 (40.1)	0.52 (1.29)	245 (42.5)
Gallstones	0.10 (0.25)	339 (21.7)	0.07 (0.24)	365 (14.8)	0.05 (0.21)	69 (12.0)
Acute renal failure	0.00 (0.03)	13 (0.8)	0.02 (0.17)	103 (4.2)	0.11 (0.34)	96 (16.6)
Strokes	0.04 (0.54)	37 (2.4)	0.04 (0.37)	109 (4.4)	0.05 (0.32)	38 (6.6)
Leg ulcers	0.00 (0.03)	-	0.05 (0.61)	81 (3.29)	0.22 (1.00)	73 (12.7)

PPPY, per patient per year; SD, standard deviation; VOC, vaso-occlusive crisis.
[a]Values with patient numbers <10 were masked (i.e., "-") to protect patient confidentiality; [b]Proportion of patients with any incidence of an acute complication that occurred during the variable follow-up period; [c]Inclusive of bacteremia, osteomyelitis, septicemia, and viral infections; [d]Inclusive of heart, hepatic, kidney, ovarian, polyglandular, and respiratory failures.

LIMITATIONS

- As with any claims database analysis, this study utilized ICD-10 codes to identify patients with SCD with recurrent VOCs and was thus subject to misclassification bias due to inaccurate coding; however, the effect of this bias was limited given the significant requirements for inclusion (e.g., 2 VOCs in 2 consecutive years)
  - The number of patients with SCD could have been overestimated due to patients with a sickle cell trait being coded as having SCD
- Patients with SCD who have recently emigrated to France might be overrepresented in the 1% of the French population not recorded in the SNDS
- Given the minimum 12-month post-index period for patients with SCD, individuals who died during this period were excluded, which may have led to an underestimation of mortality

CONCLUSIONS

- Despite available care, patients with SCD with recurrent VOCs in France experience numerous disease-related clinical complications and increased mortality, underscoring the need for innovative therapies in this space
- Increased rates of VOCs and older age were associated with higher mortality and number of clinical complications

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AUTHOR DISCLOSURES

JB, CU, NL and LD are employees of Vertex Pharmaceuticals Incorporated and may hold stock or stock options in the company. LB is a former employee of Vertex Pharmaceuticals and may hold stock or stock options in the company. GP, NQ and HJ are employees of Certara France and may hold stock or stock options in the company. FG is an employee of the Sickle Cell Referral Center, Henri Mondor Hospital Paris, France. Approval for use of SNDS data was granted by all relevant authorities and governing bodies. Analyses for this study were performed through remote access on the Caisse Nationale de L'assurance Maladie (CNAM) portal to comply with national security guidance (Le Référentiel de Sécurité). The final protocol was reviewed and approved by a scientific committee and the National Informatics and Liberty Commission (CNIL, decision DR-2022-065, March 2, 2022). All patient data were pseudonymized, which according to applicable legal requirements renders the data exempt from privacy laws; therefore, obtaining informed consent from patients was not required. The interpretation and conclusions contained in this study are those of the authors alone.

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