Impact of hospitalized vaso-occlusive crises in the previous calendar year on mortality and complications in adults with sickle cell disease: a French population-based study

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Summary

Background Historically, sickle cell disease (SCD) patients experiencing frequent hospitalized vaso-occlusive crises (HVOC) have been associated with increased mortality, yet recent data reflecting the widespread use of hydroxyurea and advancements in disease management remain limited. Our study aims to assess the association between HVOC and mortality or severe complications in patients with SCD in this new treatment landscape.

Methods This was a retrospective observational cohort study using the French national health data system. Between 01-01-2012 and 12-31-2018, all SCD patients ≥16 years old (ICD-10 codes D57.0–2) were included and followed until 12-31-2018. HVOC was defined as a hospitalization of ≥1 night with primary diagnosis of SCD with crisis, following an emergency room visit. The association between HVOC and severe complications was assessed with a Cox proportional hazards model.

Findings In total, 8018 patients (56.6% females; 4538/8018) were included. The 2018 SCD standardized one-year period prevalence was 17.9 cases/100,000 person-years [17.4; 18.3]. The mean rate was 0.84 (1.88) HVOC/person-year. In 2018, 70% (5323/7605), 22% (1671/7605), and 8% (611/7605) of patients experienced 0, 1–2, or 3+ HVOCs, respectively. The median survival time between HVOCs was 415 days [386; 439]. Overall, 312 patients died (3.9%) with a mean age of 49.8 (19.4). Compared to patients without HVOC, the hazard ratios of death in patients with 1–2 or 3+ HVOCs the year prior to death were 1.67 [1.21; 2.30] and 3.70 [2.30; 5.93], respectively. Incidence of acute chest syndrome, pulmonary embolism, osteonecrosis, and sepsis increased with the HVOCs category, but not stroke. In 2018, 29.5% (180/611) of patients with 3+ HVOCs did not take hydroxyurea.

Interpretation Patients must be closely monitored during their hospitalizations to intensify treatment and check treatment compliance. Innovative therapies are also required.

Funding The study was funded by Novartis.

Keywords: Sickle cell disease; Vaso-occlusive crisis; France; Mortality

Introduction

Sickle cell disease (SCD) is a lifelong, inherited condition with an incidence at birth of around 1 in 1300 in France.[1] France has the largest population of SCD patients in Europe.[2] In 2016, based on a sample of the French National Health Data System, the prevalence of SCD was estimated to be between 19,800 and 32,400 patients.[3] Another French study identified 22,619 SCD patients between 2012 and 2018.[4]

Patients with SCD experience a wide range of complications thought to be the consequences of the systemic impact of chronically inflamed vasculature,

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Translation: For the French translation of the abstract see Supplementary Materials section.

Research in context

Evidence before this study

Patients with sickle cell disease (SCD) suffer from vaso-occlusive crises (VOC) and early mortality. We searched *PubMed* for evidences of the association between VOC and death between January 2003 and December 2023 in English and French. The search was "(vaso-occlusive crisis OR vaso-occlusive event* OR vaso-occlusive episode* OR sickle cell pain crisis) AND (sickle cell disease OR drépanocytose OR anémie falciforme) AND mortality" and the filter "Humans" was added. Two hundred and sixty-six articles were retrieved. The association between VOC and mortality had been shown before in the US, prior the widespread use of hydroxyurea. Later, a long-term observational study on patients with SCD initially taking hydroxyurea for frequent VOCs as part of a clinical trial seemed to show a reduced mortality.

Added value of this study

The French national health insurance reimbursement system database used in this study is a large unbiased, well anonymised claims database that covers major part of the French population. This means that study data are robust and reflect population-wide practices. This study is, to our knowledge, the first national study based on real-world data to test and quantify the association between hospitalized VOC and death and severe SCD complications, in recent years, considering new SCD treatment landscape.

Implications of all the available evidence

Our findings support to intensify disease-modifying therapies in SCD adults' patients with recurrent annual HVOCs, during the hospital stay, to prevent sequelae and premature death. Our conclusions could serve as evidence to establish new patient management guidelines regarding the aggressive treatment of recurrent VOCs and ensure the patients comply with their treatments.

ongoing haemolysis, multicellular adhesion, and ischemic damage. These SCD-related complications are associated with poor health-related quality of life, reduced lifespan, and increased healthcare costs. One of the most impactful complications is the SCD pain crisis, also referred to as the vaso-occlusive crisis (VOC). An early study, before de hydroxyurea therapy, suggested a relationship between VOC occurrence and increased mortality.[5] Later, a long-term observational study on patients with SCD initially taking hydroxyurea for frequent VOCs as part of a clinical trial seemed to show a reduced mortality.[6] Since then, SCD management has improved and reviewing the strength of relationship between VOC and mortality is important.

The primary objective of this study was to assess the association between hospitalised VOCs (HVOCs) and mortality, in SCD patients aged after 16, using the French National Health Data System (Système National des Données de Santé, SNDS).[7] The secondary objectives were to investigate the association between some SCD complications and HVOC, to assess the prevalence of HVOC and to report hydroxyurea dispensings according to HVOC frequency.

Methods

Study design and data sources

This was a retrospective national observational cohort study using claims data from the SNDS. This database provides information on healthcare expenses including outpatient and in-patient care and drug dispensing in all French pharmacies. The data were extracted for individuals covered by the General Scheme (salaried employees of the private sector and their dependants) and local mutualist sections in France. In all, the study covered 87% of the French population. In addition, the SNDS provides the diagnoses (International Classification of Disease 10th revision codes [ICD-10]) of patients with severe and costly long-term diseases (LTD) (Affection de Longue Durée, ALD). SCD falls under LTDs.

Study population and study period

Individuals aged 16 years and above, with either an LTD status or a hospital record with diagnostic ICD-10 codes D57.0–2 as a principal diagnosis (PD), a valid social security number, and ≥1 healthcare expense reimbursement during the year prior to inclusion were included in the study. To limit the probability of including patients with sickle cell trait miscoded as SCD, patients with LTD for SCD but no other SCD-related claim, as well as no dispensing of hydroxyurea and/or folic acid and/or phlebotomy were excluded.[4]

The inclusion period started on 01 January 2012 and ended on 31 December 2018. In addition, healthcare data were collected starting on 01 January 2011 to allow for the detection of HVOCs and comorbidities. As SCD is a genetic disease, the index date was defined as 01 January of the year following the first interaction with the French healthcare system (any reimbursement or hospitalization, whether related to SCD, HVOC, or not) within the inclusion period. Individuals were followed until the end of the study, loss to follow-up (2 years without healthcare expense reimbursement), or death, whichever occurred first. All individuals were followed for at least 1 year.

The SNDS covers a major part of French population and the study included all individuals meeting the

selection criteria. No sample size calculation was performed.

Assessments

Sociodemographic data (age at index date, sex, region of residence, affiliation to the free complementary healthcare) and LTD benefit were collected to describe patients.

HVOC were defined as a visit to the emergency room (ER) followed by a hospital stay of ≥1 night with a PD of D57.0 (SCD with crisis). The number of HVOCs was grouped into three categories (0, 1–2 per year, 3+ per year), based on a previous study which observed different survival trajectories for individuals who experienced an average of 0, 1–2 and 3+ HVOCs per year.[5] Every year, individuals were allocated to the category corresponding to the number of HVOCs they had experienced the previous calendar year.

The following severe SCD-related complications were examined during the follow-up period: acute chest syndrome (ACS), sepsis, stroke, osteonecrosis, and pulmonary embolism (ICD-10 codes in Supplement Table S1). A complication was considered as present in the year of interest if there was ≥1 day of hospitalization with the complication as a PD, related diagnosis, or significant associated diagnosis.

The date of death (month and year, in hospital and out of hospital) was extracted for all deceased study patients.

Finally, hydroxyurea dispensings were collected (two drugs used in France: Siklos® or Hydrea®) during the follow-up.

Statistical methods

Continuous data were summarized by their mean, standard deviation (SD), median, and first (Q1) and third (Q3) quartiles. Categorical data were summarized by percentage.

The one-year period prevalence rate was defined as the number of SCD patients identified each year divided by the number of people ≥16 years old residing in France the corresponding year, multiplied by 1 year. The one-year period prevalence rate was standardized by sex and by 5-year age category using the population residing in France (https://www.insee.fr) as the standard population.

The duration between HVOC was calculated using a Kaplan Meier model.

The time-varying effect of HVOC on subsequent HVOCs, other complications, and death hinders the use of classical models to examine a possible causal relationship between HVOC and death. Following Hernán et al., the presence of complications were considered as time-varying confounders and models were adjusted for measured confounders (i.e., sex and age).[8] A three-levelled categorical exposure variable was used (0, 1–2, and 3+ HVOCs) based on the number of HVOCs during the calendar year preceding the event of interest [death or a complication]) (Supplement Figure S1) and a marginal structural Cox proportional hazards model (MSM) was performed. Each patient was allocated a time-specific weight. The weight is the inverse of the probability of the patient's history of number of HVOCs each year, hence the weights are known as inverse probability weights.[9] Weights were truncated at the 99th percentile. The association between the category of HVOC counts the calendar year before and death or a complication was reported as hazard ratio (HR).

Given that all healthcare consumptions are reported in the database, no replacement of missing values was performed.

Statistical analyses were performed using SAS version 9.4.

Compliance with ethical standards

In accordance with the regulations in force, patient consent was not necessary because this study uses secondary data, there was a public interest in assessing, for the first time to our knowledge, the impact of HVOC on SCD patient death in France, and the protection of patients' rights and freedom were guaranteed. The study protocol obtained approval from the committee for research, studies, and evaluations in the field of health (Comité d'expertise pour les recherches, les études et les évaluations dans le domaine de la santé, CEREES) (File TPS 506323 bis) and the authorization to use the data was granted by the French data protection authority (Commission Nationale de l'Informatique et des Libertés, CNIL) (Decision DR-2019-207, and authorization No. 919281).

The STROBE cohort reporting guidelines were used.[10]

Role of the funding source

Novartis founded the study but was not involved in the work on the article, which is the sole responsibility of the authors.

Results

Study population

A total of 28,834 individuals with a hospitalization with a PD of D57.0–2 or LTD status for SCD between 01 January 2012 and 31 December 2018 were identified in the database. Of these, 8018 met all selection criteria (Supplement Figure S2).

Patients were followed for 5.8 years, on average, (median 7.0 years) and for a cumulative time of 46,825 patient-years. In all, 7552 patients (94.2%) were followed until the end of the study, 312 (3.8%) died, and 154 (2.0%) were lost to follow-up (Supplement Table S2).

Patient characteristics

The age of all patients at inclusion was on average 30.1 ± 13.4 years (median 28 years; Q1–Q3 18; 38)

(Supplement Table S3). More women (56.6%) were included (Supplement Figure S3). More than half (4068 patients, 51.6%) of patients lived in Ile-de-France (Paris area). Overseas territories had large numbers of patients (1514 patients, 18.9%) relative to their small population sizes (3.2% of the French population). Overall, 22.0% (1680) of patients were affiliated to the free complementary healthcare and 61.7% (4946) of patients had an LTD status for SCD. Despite their young age, 13.1% (1049) and 4.8% (385) of patients had a Charlson index score of 1–2 and 3–15, respectively. A history of cardiac or renal disease was present in 9.3% (742) of patients.

Sickle cell disease prevalence in France

The standardized one-year period prevalence of adult SCD increased over time from 14.6 cases/100,000 person-years [95% CI 14.2; 15.0] in 2012 to 17.9 cases/100 000 person-years [17.4; 18.3] in 2018 (Fig. 1).

Hospitalized vaso-occlusive crises

Between 2012 and 2018, 5341 patients (66.6%) experienced ≥1 HVOC (2885 patients (36.0%) at least 3+ HVOCs) and the mean number of HVOC was 0.8/person-year (±1.88) (median 0.3, Q1–Q3 0.0–1.0) (Supplement Table S4). The annual proportion of patients experiencing no HVOC declined from 73.0% to 70.0%. Consequently, the proportion of patients experiencing 1–2 or 3+ HVOCs increased over time from 21.2% to 22.0%, and from 6.6% to 8.0%, respectively.

The Sankey graph reports the transition between the HVOC categories each year over time (Fig. 2). We found that patients with 3+ HVOCs remained more frequently in this category (between 48% and 53% irrespective of years) compared to 1–2 HVOCs category (between 34% and 37%). In addition, 468 patients (5.8% of the patients) remained in the 3+ HVOC category during at least 3 successive years.

The annual number of hospital admissions and ER visits by HVOC category is shown in Fig. 3. The mean survival duration between the first HVOC (occurring during the study period) and the second HVOC was 690 days (9.5) and the median duration (95% CI) was 415 days (386; 439) (Fig. 4).

Deaths and hospitalized vaso-occlusive crises

Over the study period, 312 patients died (237 in-hospital [76.0%] and 75 out-of-hospital deaths [24.0%]) (all causes). The mean age at death was 49.8 years (19.4) and the median 49 (34.–63). The annual mortality of this adult cohort increased from 0.4% to 0.7% in 2018 (Table 1).

Association between death and hospitalized vaso-occlusive crises the calendar year prior to death

The HR of death increased with the HVOC category the calendar year prior to death (Fig. 5). Compared to patients without any HVOC the year prior to death, the HRs of death in patients who had experienced 1–2 or 3+ HVOCs were 1.67 [1.21; 2.30] and 3.70 [2.30; 5.93], respectively. The HR of patients with 3+ HVOC vs the patients with 1–2 HVOCs was 2.21 [1.34; 3.65]. Compared to the patients aged 16–29, the HR of death consistently increased with age class, from 1.66 [1.11; 2.47] for patients aged 30–39 to 22.27 [15.22; 32.56] for patients aged 60 and above (Supplement Table S5). Women had a lower HR of death (0.74 [0.58; 0.94]) compared to men.

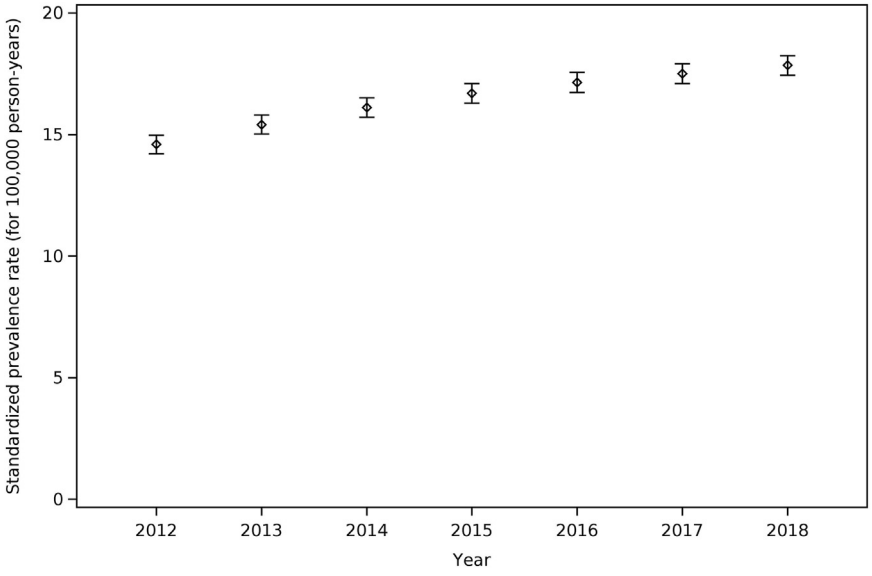

Fig. 1: French standardized one-year period prevalence sickle-cell disease rate in patients aged 16 and above.

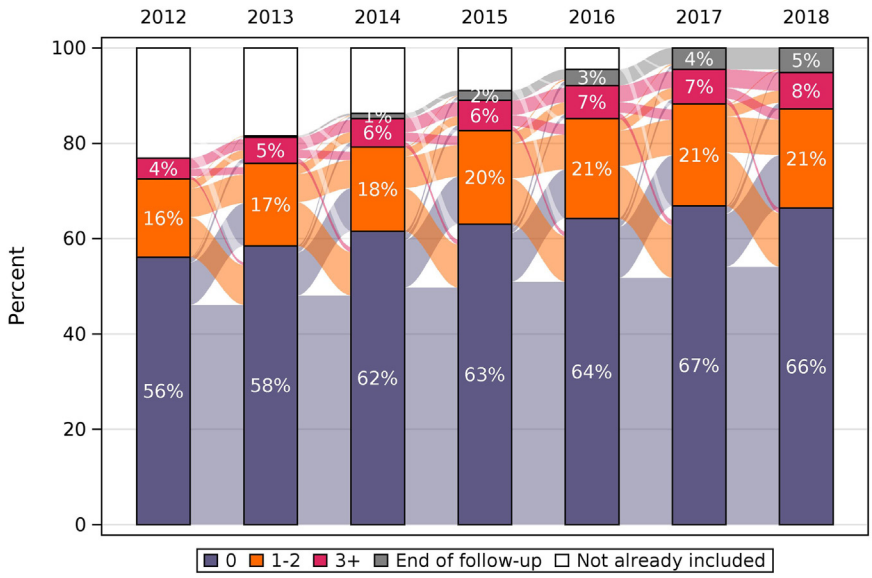

Fig. 2: Hospitalized vaso-occlusive crisis (HVOC) evolution across years.

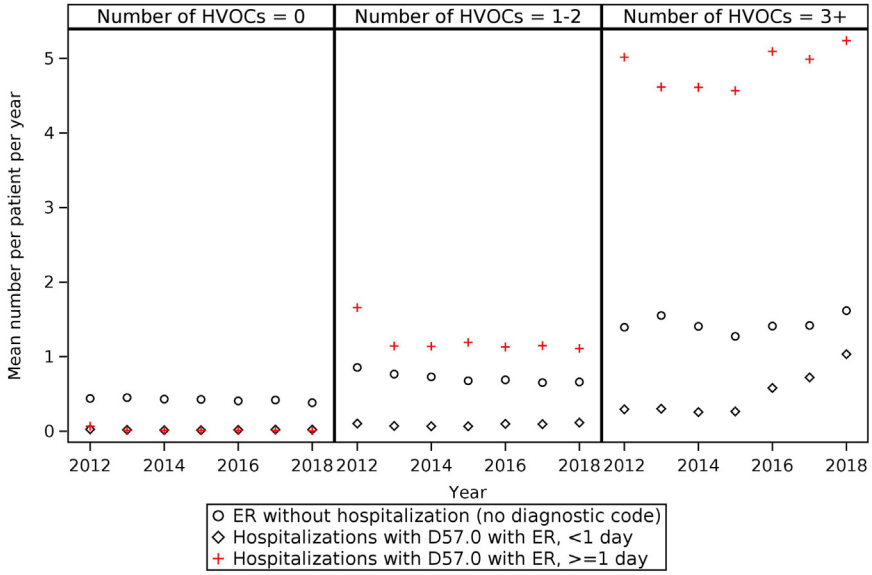

Fig. 3: Hospitalizations and emergency room visits per patient, per category of hospitalized vaso-occlusive crisis, per calendar year. HVOC, hospitalized vaso-occlusive crisis; ER, emergency room visit.

Association between hospitalized vaso-occlusive crises and complications

Over the study follow-up (2012–2018), the following complications were recorded as PD, related diagnosis, or significant associated diagnosis (ICD-10 codes) during ≥1 hospitalization: ACS in 2371 patients (29.6%), sepsis in 1782 patients (22.2%), acute kidney injury episode in 1163 patients (14.5%), osteonecrosis in 902 patients (11.3%), pulmonary embolism in 529 patients (6.6%), stroke in 371 patients (4.6%), and ≥1 dialysis session in 213 (2.7%) patients. In detail for patients with strokes: 193 patients (2.4%) had an ischemic stroke, 13 patients (0.2%) had an hemorrhagic stroke, 178 patients (2.2%) had a stroke sequelae, and 173 patients (2.2%) had an unknown/unspecified stroke.

The strength of the association between the HVOC category the calendar year prior and other complications varied by complication (Fig. 6). The HR of the following complications for patients in the category 3+ HVOCs vs patients in the category 0 HVOC were: 4.38 [3.95; 4.87]

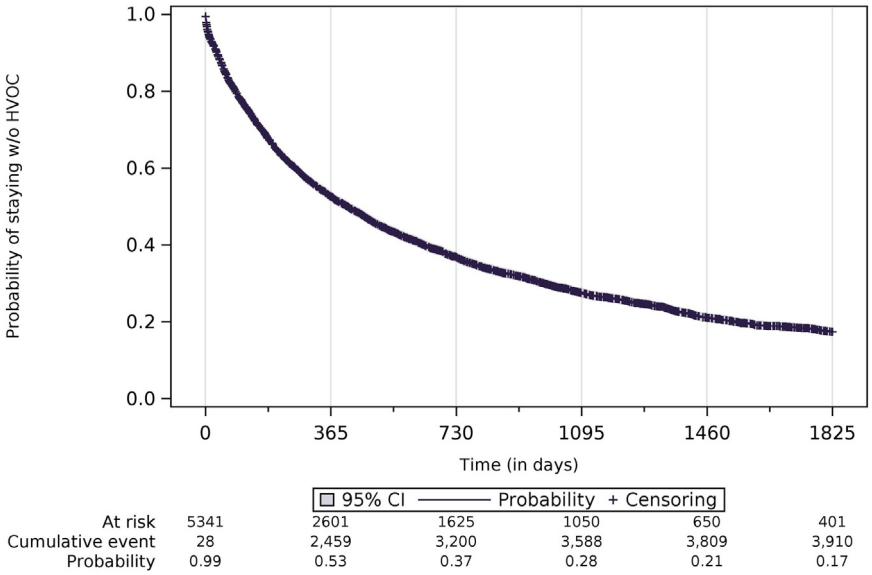

Fig. 4: Kaplan Meier curve of the probability of patients with one hospitalized vaso-occlusive crisis (HVOC) during the study period of staying without a second HVOC.

for ACS, 4.70 [4.13; 5.34] for sepsis, 4.43 [3.62; 5.41] for osteonecrosis, 3.40 [3.20; 3.61] for ≥1 dialysis session, 3.06 [2.49; 3.76] for acute kidney injury episode, 3.07 [2.32; 4.07] for pulmonary embolism. There was no association between the category 3+ HVOCs and stroke (1.04 [0.67; 1.62]).

Hydroxyurea (HU) treatment and hospitalized vaso-occlusive crises

HU dispensing by pharmacies regularly increased during the study period in the entire cohort (Supplement Figure S4). The proportion of treated patients with 3+ HVOCs during the previous calendar year increased by 11% each year (from 55.4% in 2012 to 69.8% in 2018) ($p < 0.0001$).

Discussion

In this nationwide study on a large adult SCD population, we demonstrated that the probability of dying increased with the number of HVOCs the previous calendar year of the death. Several hospitalized complications were also associated with HVOC except for stroke. The strength of the association was highest for ACS, sepsis, acute kidney injury, and osteonecrosis.

The observed increase in SCD one-year period prevalence over time may be due to the method to identify patients. Patients were captured as they were admitted to the hospital or obtained LTD status (an administrative procedure to acknowledge the special healthcare needs of patients with chronic diseases). Indeed, the number of inclusions is higher during the first study years and reaches a plateau after 4 years. It may be also explained by the steady increase of SCD births, evidenced in the same period by the French systematic neonatal screening, and by the immigration of adults with SCD from African countries to France.[11]

The association between HVOC and mortality had been shown before in the US, prior the widespread use of hydroxyurea,[5] and more recently among Medicaid beneficiaries (eligible low-income adults, children, pregnant women, elderly adults and people with disabilities).[12,13] In the latter population (mean age of 16 years), the HR for 2–4 HVOC vs <2 HVOC the preceding year and death was 1.26 [1.14–1.40]. We observed that the proportion of patients treated with HU increased over time in France, irrespective of the number of HVOCs the previous calendar year. Our findings imply that, despite the availability of hydroxyurea (free for all patients with sickle cell anemia in France), SCD patients still suffer from HVOCs and that their accumulation is associated with higher mortality. Moreover, the annual proportion of patients with 3+ HVOCs slightly increased during the period of our study. This paradox of a greater severity in adult patients in recent years, even as patients have benefited from therapeutic advances, is probably a survival bias. This had already been highlighted in an American study which showed that the death rate among children with SCD has declined over time in the US (1979–2005), while it has increased among adults. It showed the effect of interventions targeting children with SCD to increase their life expectancy, but leading to more severe patients in adulthood.[14] Interestingly, we observed that compared to older adults, young patients in the pediatric–adult transition period (16–24 years) experienced more

	2012	2013	2014	2015	2016	2017	2018	2012–2018 7 years
No. of patients	5782	6139	6459	6751	7028	7297	7605	8018[a]
All deaths	21 (0.36%)	33 (0.54%)	38 (0.59%)	64 (0.95%)	50 (0.71%)	53 (0.73%)	53 (0.70%)	312 (3.89%)
In-hospital deaths	16 (0.28%)	27 (0.44%)	28 (0.43%)	45 (0.67%)	46 (0.65%)	40 (0.55%)	35 (0.46%)	237 (2.96%)
Out-hospital deaths	5 (0.09%)	6 (0.10%)	10 (0.15%)	19 (0.28%)	4 (0.06%)	13 (0.18%)	18 (0.24%)	75 (0.94%)
Age at death								
Mean (SD)	50.9 (21.4)	51.6 (19.2)	44.9 (17.2)	47.3 (17.4)	50.9 (18.0)	47.6 (21.7)	55.8 (20.3)	49.8 (19.4)
Median (Q1; Q3)	36 (34; 48)	54.5 (47; 66)	45 (31; 52)	50 (33; 56)	36 (21.5; 50.5)	39 (26; 61)	48.5 (34; 63)	46 (33; 58)

[a]8018 patients correspond to 7605 patients still followed in 2018 and 154 patients lost to follow-up before 2018 and 259 patients dead before 2018.

Table 1: **Patient deaths over time (all causes).**

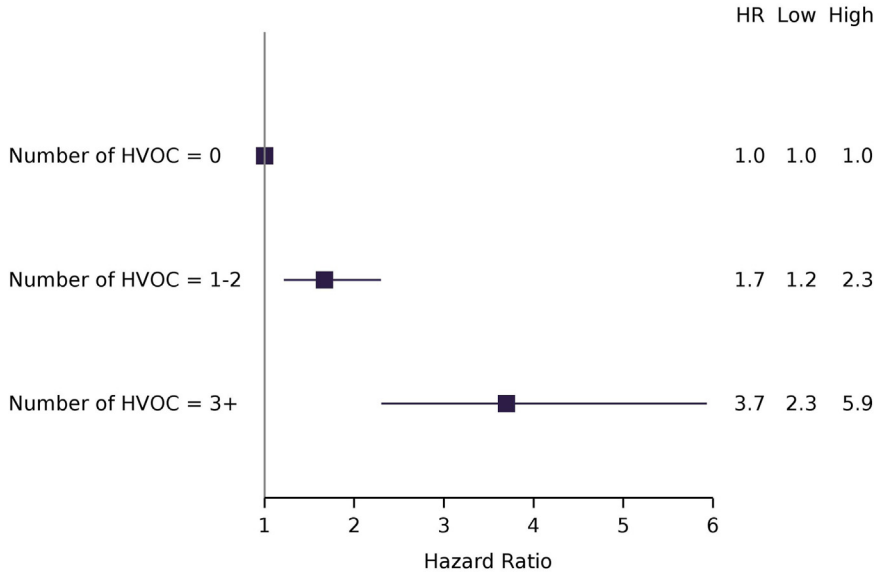

Fig. 5: Hazard ratio of the risk of death and the HVOC category the calendar year before death. HVOC, hospitalized vaso-occlusive crisis (visit to the ER followed by a hospital stay of ≥1 night with a primary diagnosis of D57.0).

frequently 3+ HVOC (44.3%, 1478/3339) during the follow up compared to 27.5% (1286/4679) for older adults (>24 years) (Supplement Table S3). Furthermore, at the end of the study, in 2018, still 29.5% of adult patients with 3+ HVOCs did not take hydroxyurea, although this treatment has clearly demonstrated its great efficacy in decreasing VOC and ACS. Of note, our study is original in that it presented HU treatment dispensed by pharmacies and not just prescribed by the clinician. Firstly, these facts highlight the need to pay close attention during the hospital stay (and, of course, at every consultation) to the patient' therapeutic compliance and the prescription of HU. Secondly, clinician should not hesitate to increase the dose of HU (data not collected here) up to the maximum tolerated dose (neutrophils target around 2000/mm^3) in those patients with high risk of mortality. Nevertheless, evidence regarding the "maximum tolerated dose" regimen in adults is poor and depends on the patient's renal function,[15] but well demonstrated in children.[16,17] If this strategy fails, exchange transfusion programs or bone marrow transplantation may be proposed. However, the cost, access, and side effects of these treatments make it impossible to treat all patients properly. This leaves room for other therapeutic innovations.

It should be noted that, in this study, we also chose a very strict definition of severe crisis, considering only hospitalizations (without taking into account simple ER visits and VOC managed at home with opioids). It could explain the high proportion of patients with no HVOC. However, we still identified ER visits for these patients, which demonstrates the quality of the population selection. In a systematic review, the VOC frequency varied widely depending on the study population, study design, and the definition of VOCs.[18] Due to the strict definition of HVOC adopted for the study, comparisons with other studies are limited.

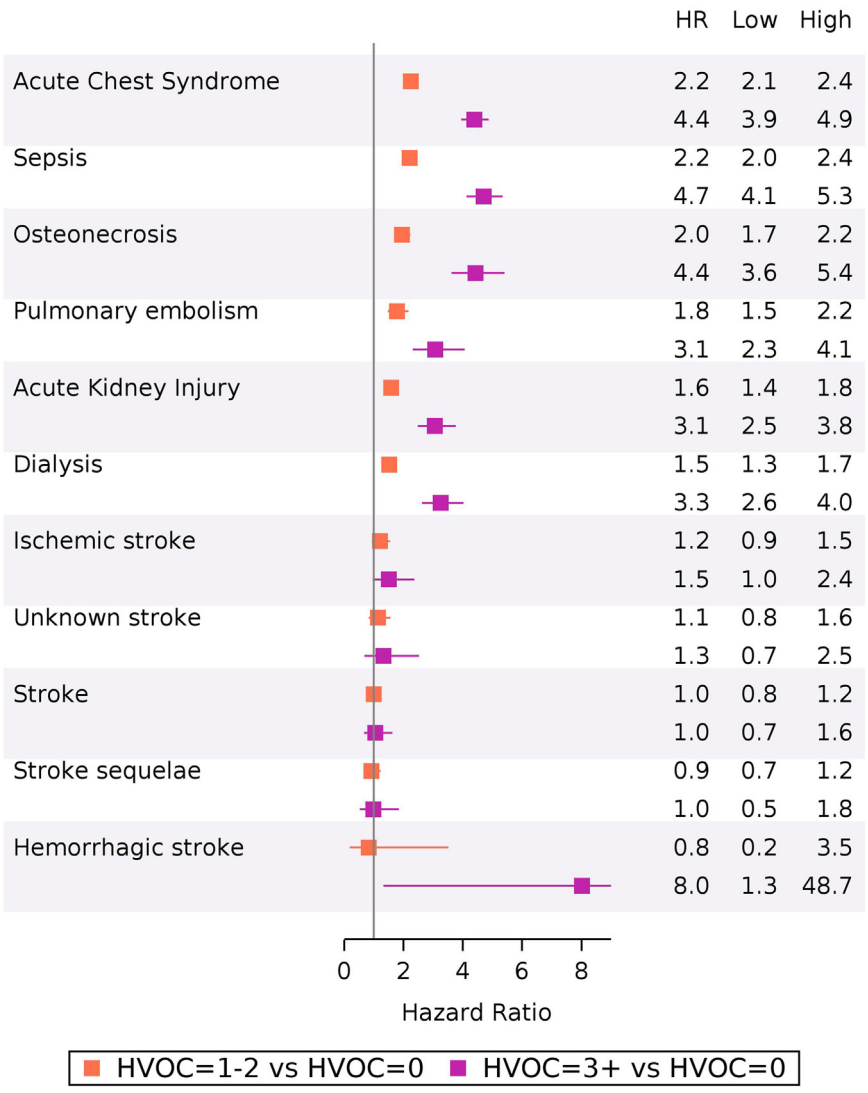

Fig. 6: Hazard ratio of the risk of sickle-cell disease severe complications and the HVOC category the calendar year before. HVOC, hospitalized vaso-occlusive crisis (visit to the ER followed by a hospital stay of ≥1 night with a primary diagnosis of D57.0).

The strong association between HVOC incidence and osteonecrosis is also interesting, as very little data are available on osteonecrosis. Both HVOC and osteonecrosis are associated with bone vasculopathy in SCD (acute and chronic, respectively). Hyperviscosity and inflammation are probably both involved in their pathophysiology. With our data, we could not determine the origin of pulmonary embolism. However, it has been recently shown in France that ACS was associated with pulmonary thrombosis in 3%–17% of cases.[19] Other causes of thrombosis in SCD are mainly represented by venous catheters due to poor venous access,[20] often during a hospitalisation for VOC. The lack of association between HVOC and stroke is probably due to the chronic blood exchange transfusions in patients with cerebral vasculopathy and possibly a different pathophysiology.

The main strength of the study is to be able to study almost the entire French population using two comprehensive databases providing prospectively and independently collected complementary data. Furthermore, the dataset is quasi exhaustive, and the data are routinely collected for reimbursement purposes and not specifically for this study. ICD-10 coding does not allow for a clear differentiation between SCD genotypes (SS, SC, S-beta-thalassemia), so we include all patients with SCD regardless of the genotype distinction. To limit the inclusion of patients miscoded for SCD, patients susceptible to being sickle carriers were excluded based on a algorithm adapted from a recent French study.[4] This

approach might inadvertently exclude SCD patients without specific treatments (like folic acid, hydroxyurea, or phlebotomy) and without HVOC or ER visits over 7 years. These could be the less severe genotypes (SC or S-beta + thalassemia) with well-controlled conditions without any treatment. Although difficult to estimate, we have considered the number of these patients likely minimal. However, we thought that the risk of including misclassified sickle cell traits as SCD in LTD coverage was greater than the risk of omitting some atypical, asymptomatic SCD patients not receiving disease-modifying therapies. Finally, a validation study reported that VOC were correctly coded as principal diagnosis on the hospital discharge form 98.6% of the time,[21] showing the reliability of the hospital database of the SNDS. Unlike previous studies, a stricter definition of HVOC was chosen because it was hypothesized that an ER visit not followed by a night at the hospital denoted a less severe VOC (ER is easy to access in France and anxious patients may go for mild causes). Conversely, direct hospitalizations of VOC (without ER visit) were excluded because it is not common practice in France. This precaution further guaranteed the exclusion of hospitalizations for planned surgery, pregnancy monitoring or delivery, or exams, sometime miscoded as D57.0 (SCD with crisis) as primary diagnosis.

This study also has limitations that must be considered when interpreting the results. As genotypes/phenotypes are likely to have an impact on the number of HVOCs a patient experiences, reliable information would have been valuable to inform on the genotypes/subtypes at the highest risk of HVOCs-associated death. As the analysis could only identify patients who were hospitalized for VOC, patients that were treated in the emergency room (e.g., with intravenous morphine) were not included. This likely lead to the underestimation of VOCs requiring hospital treatment (10–15%). However, it is unlikely that this underestimation would alter the magnitude or direction of the exposure–outcome relationship. Patients who recently migrated to France have a temporary social security number and were excluded from the analysis. Some immigrants are from African descent and a higher chance of suffering from SCD than the general French population. Consequently, the SCD one-year period prevalence is slightly underestimated.

The analyses were performed using cause-specific Cox models. It would have been also interesting to use also Fine&Gray models for complications, in order to consider the competing risk of death. As the number of deaths is low and the confounding factors are similar for death and complications, the difference between two methods are expected to be minimal in this study.

Conclusion

This nationwide study, based on the largest European population of patients with SCD, showed a clear association between HVOC and death and several SCD complications. Despite improved management of patients with SCD and of HVOCs, patients still experience an increased hazard of death with a higher number of HVOCs. The hazard of severe complications also raises as the number of HVOCs increases, particularly ACS, sepsis, osteonecrosis, acute kidney injury episode, and pulmonary embolism. Better management of HVOCs is needed not only to improve the patients' quality of life, but also to prevent premature mortality, and debilitating complications. In particular, patients need to be closely monitored during their hospitalizations to intensify treatment and check treatment compliance. Innovative treatments are also needed.

Contributors

JBA, FR, and PB contributed to the study conception and design. Data management and analyses were performed by EH. EH had full access and verified the data. JBA, FR, and PB commented on all versions of the manuscript. All authors read and approved the final manuscript and agreed with submission of the manuscript.

Data sharing statement

The data supporting the study findings are part of the National health data system (SNDS, Système national des Données de Santé) and are available from the HDH (Health Data Hub https://www.health-data-hub.fr/). Restrictions apply to the availability of these data containing potentially identifying and sensitive patient information. Special permission to access these data for this study was granted by the committee for research, studies, and evaluations in the field of health (Comité d'expertise pour les recherches, les études et les évaluations dans le domaine de la santé, CEREES) and the French data protection authority (Comité National de l'Informatique et des Libertés, CNIL).

Declaration of interests

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanepe.2024.100901.

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