Severity and burden of sickle cell disease in France: a nationwide real-world study

Valentine Brousse,[1*] Françoise Bernaudin,[2*] Asma Melaine,[3] Mélanie Goguillot,[3] Meghan Gallagher,[4] Stève Benard[3] and Anoosha Habibi[5]

[1]Centre de Référence MCGRE, Service d'Hématologie-Immunologie, AP-HP, Hôpital Robert Debré, Université Paris Cité and Université des Antilles, INSERM, BIGR, Paris, France; [2]French Referral Center for Sickle Cell Disease, SFGM-TC (Société Française de Greffe de Moelle et de Thérapie Cellulaire), DrepaGreffe Association, Nogent sur Marne, France; [3]Stève Consultants, Oullins, France; [4]bluebird bio, Inc., Somerville, MA, USA and [5]Sickle Cell Referral Center, Henri Mondor Hospital, AP-HP, UPEC, Laboratory of Excellence GR-Ex, INSERM Unit 955, Mondor Institute of Biomedical Research, Paris-Est Creteil University, Creteil, France

VB and FB contributed equally as first authors.

Correspondence: S. Benard
sbenard@steve-consultants.com

Received: September 30, 2022.
Accepted: March 6, 2023.
Early view: March 16, 2023.

https://doi.org/10.3324/haematol.2022.282098

Abstract

The burden of sickle cell disease (SCD) in France has been difficult to apprehend due to the paucity of reliable nationwide epidemiological data. We aimed to describe the epidemiology of SCD and evaluate its burden and costs. Patients with SCD and most severely affected patients were identified between 2012 and 2018 from the French National Health Data System database (SNDS, Système national des données de santé). Outcomes of interest included rates of acute and chronic complications, healthcare resource utilization and associated costs, and were compared in subpopulations of patients before and after hematopoietic stem cell transplantation, initiating hydroxyurea or a chronic transfusion program. Between 2012 and 2018, 22,619 patients with SCD were identified, among which 4,270 patients were defined as most severely affected. Rates of vaso-occlusion episodes and acute chest syndrome were 86.29 (95% confidence interval [CI]: 85.75-86.83] and 12.90 (95% CI: 12.69-13.11) per 100 person years in the study population and 166.9 (95% CI: 165.4-168.4) and 22.71 (95% CI: 22.16-23.27) per 100 person years in most severely affected patients. Median (Q1-Q3) annualized total costs were €5,073.63 (range, €1,633.74-14,000.94) and €13,295.67 (range, €5,754.67-26,385.23) in the study population and most severely affected patients. Median annualized costs were ten times lower after treatment intensification for hematopoietic stem cell transplantation (€29,011.75 *vs*. €2,465.98; *P*<0.001), they slightly decreased after hydroxyurea initiation (€13,057.79 *vs*. €12,752.44; *P*=0.003) and were five times higher after chronic transfusion program initiation (€4,643.11 *vs*. €22,715.85; *P*<0.001). SCD still places a significant demand on health resources, even after therapeutic intensification.

Introduction

Sickle cell disease (SCD) is the most frequent genetic disease in the world[1] and is considered a major public health topic. It is caused by a single mutation in the β-*globin* gene, resulting in an abnormal hemoglobin S (HbS).[2] The most common and impactful form of SCD is the homozygous (SS) HbSS genotype. Other forms of SCD include the association of hemoglobin S (HbS) and other genetic *β-globin* variants, including hemoglobin C (HbSC) or β-thalassemia (S/β0-thalassemia and S/β$^+$-thalassemia). The expression of the SCD phenotype varies greatly and can range from moderate to severe across genotypes, but also within the same genotype. Sickle carriers (HbAS), also known as patients with sickle cell trait, do not have pathological manifestations. In contrast, patients with SCD experience a myriad of acute and chronic events ranging from painful vaso-occlusive crises (VOC) and acute chest syndrome (ACS) to chronic complications, including organ failure, life-threatening infections and stroke.

The management of SCD relies on the prevention and treatment of SCD complications and is mainly supportive. Disease-modifying therapies for patients with SCD include chronic transfusion programs (CTP), hydroxyurea (HU), and more recently, L-glutamin, crizanlizumab in 2021, and voxelotor in 2022. Potentially curative therapy includes hematopoietic stem cell transplantation (HSCT) and gene therapies.[3] SCD has a significant negative impact on the quality of life of patients and requires high levels of healthcare resource utilization, resulting in a significant economic burden.[4,5]

As there is limited data on the epidemiology and the burden of SCD in France, the purpose of this study was to collect up-to-date epidemiological data on SCD on a nationwide basis, to evaluate the clinical burden as well as the annual healthcare resource use and costs in patients with SCD, with a specific focus on most severely affected patients and a comparison before and after disease-modifying treatment initiation.

Methods

The French healthcare system offers universal coverage for nearly 99% of French residents in mainland France and overseas territories.[6] Reimbursed medical services are captured in an exhaustive pseudonymized patient-level collection of claims data: the French National Health Data System database (SNDS, Système national des données de santé). SNDS is a suitable tool for epidemiological and population-based medical resource utilization research.[6,7] The study population consisted of patients identified in SNIIRAM (Système national d'information inter-régimes de l'Assurance maladie) from the French general healthcare insurance system, alive on or born after January 1st, 2012, with at least one SCD-related record between 2009 and 2018 (Figure 1):

-hospitalization for SCD (ICD-10 code D57 excluding D57.3-sickle-cell trait);

-long duration diseases (LDD) for SCD (ICD-10 code D57);

-dispensation of phenoxymethylpenicillin for at least 6 months, initiated before 1 year of age.

CIM-10 coding theoretically allows to differentiate SCD phenotypes, but the absence of clinical data and imprecise coding led us to include all patients with SCD with no ge-

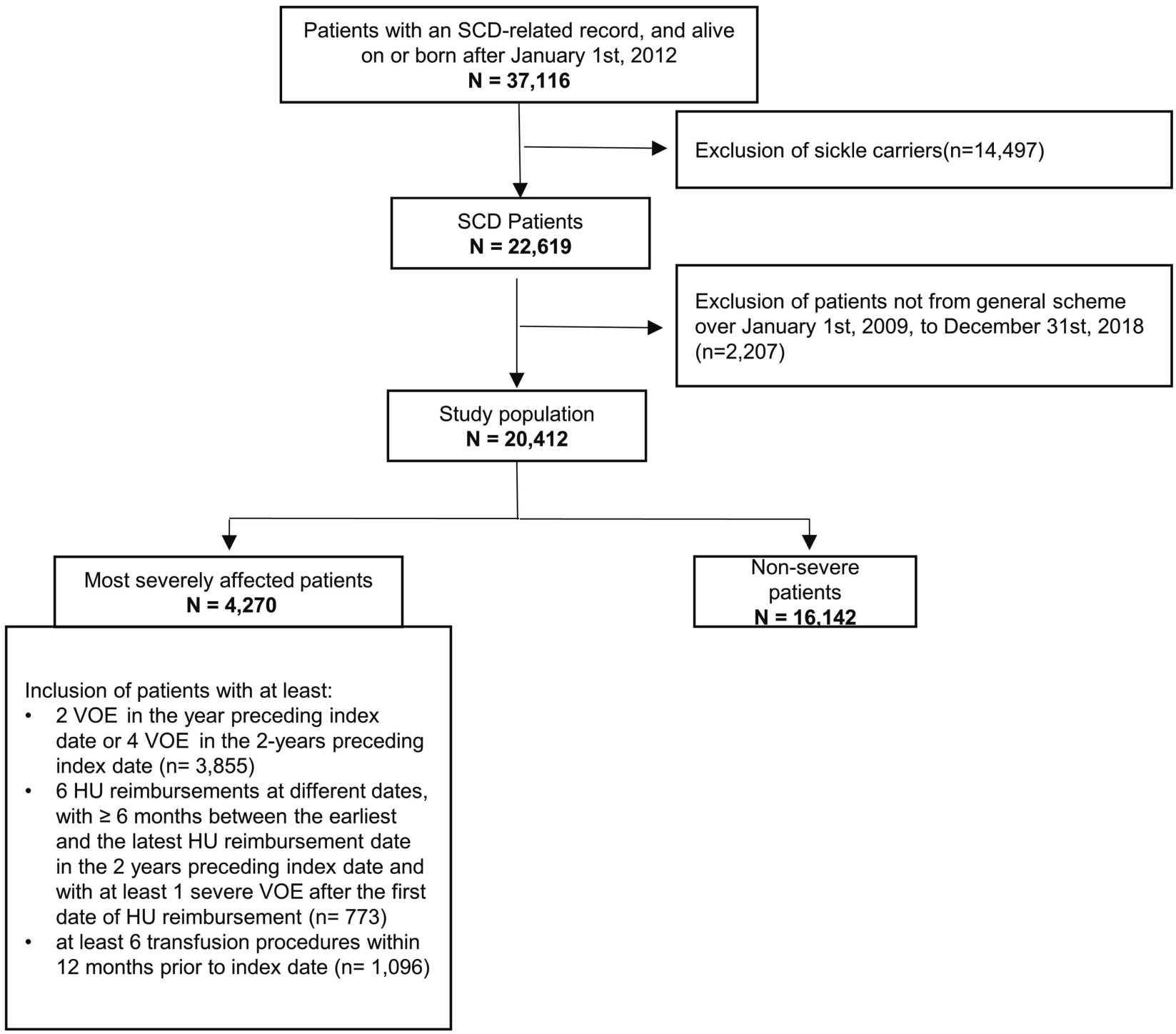


Figure 1. Flow chart of study population selection. SCD: sickle cell disease; VOE: vaso-occlusive event; HU: hydroxyurea.

notype/phenotype distinction. In order to limit the inclusion of patients miscoded for SCD, patients susceptible to being sickle carriers were excluded (*Online Supplementary Figure S2*). Patients with temporary health insurance coverage, missing data for age, and twins were excluded.

Index date was the date of the first SCD-related record during the study period, or January 1st, 2012, for patients with SCD-related records prior to 2012. Patients were followed from the index date till death or December 31st, 2018.

A subgroup of most severely affected patients was defined at index date as patients meeting at least one of the following criteria:

- two VOE in the year preceding the index date or four VOE in the 2 years preceding the index date. VOE corresponded to inpatient hospitalizations (excluding day-care hospitalizations) for VOC, hepatic sequestration, splenic sequestration, severe priapism or ACS;
- six HU reimbursements with ≥6 months between the earliest and the latest HU reimbursement in the 2 years preceding the index date and with at least one VOE after the first HU reimbursement;
- six transfusion procedures within 12 months prior to the index date.

Subpopulations of patients with therapeutic intensification (defined as disease-modifying therapy treatment initiation [CPT or HU] or curative treatment [HSCT]) were defined (Figure 2). In order to ensure ensure 4 years of follow-up after the treatment intensification date (date of the first record of therapeutic intensification), patients with at least 6 months of medical history were selected between 2012 and 2014 and followed-up for 4 years or until death (*Online Supplementary Figure S1*). Outcomes were compared considering a 3-year period before and 4 years after the intensification date. In order to exclude HSCT procedure costs for HSCT patients, outcomes were compared on a period of 3 years before HSCT *versus* a period of 1 and 4 years after HSCT.

Quantitative values will notably de described as median, first (Q1) and third (Q3). Quartiles correspond to value superior to that of 25% (Q1) or 75% (Q3) of the population.

Rates per person years were calculated by dividing the number of events by the sum of person years. Quantitative variables were compared using paired Student's t-test or Wilcoxon signed-rank test, depending on data distribution. Analyses were performed using SAS® 9.4 (SAS Institute Inc. Cary, NC, USA).

Results

The prevalence of SCD was 15,203 patients in 2012 and slightly increased over the years to 21,668 patients alive in 2018 (*Online Supplementary Figure S2*). Overall, between 2012 and 2018, a total of 22,619 patients with SCD were identified in the national database. Among these, 2,207 patients were not covered by the general health insurance system and were excluded, resulting in a study population of 20,412 patients with SCD. A subpopulation of 4,270 most severely affected patients was identified at the index date.

Male/female sex ratio was 0.74, with 8,702 (42.6%) male and 11,710 (57.4%) female patients. Mean (standard deviation [SD]) age at the index date was 24.0 (21.0) years, and 45% of patients were younger than 18 years old. Most severely affected patients tended to be younger, with a mean age at the index date of 21.8 years (15.7) and had a men/women sex ratio of 0.89 (Table 1). Median (Q1–Q3) follow-up duration was 7.0 (4.2-7.0) years. During follow-up, 5.2% (n=1,062) of patients with SCD died, among whom 23.4% (n=248) were most severely affected. The median (Q1–Q3) age at death of patients with SCD was 58 (range, 39-73) years old, contrasting sharply with the age at death of 44 (range, 28-57) years in most severely affected patients.

VOC and ACS were the most frequent causes of hospitalization (Table 2), with a rate of 86.29 (95% CI: 85.75-86.83)

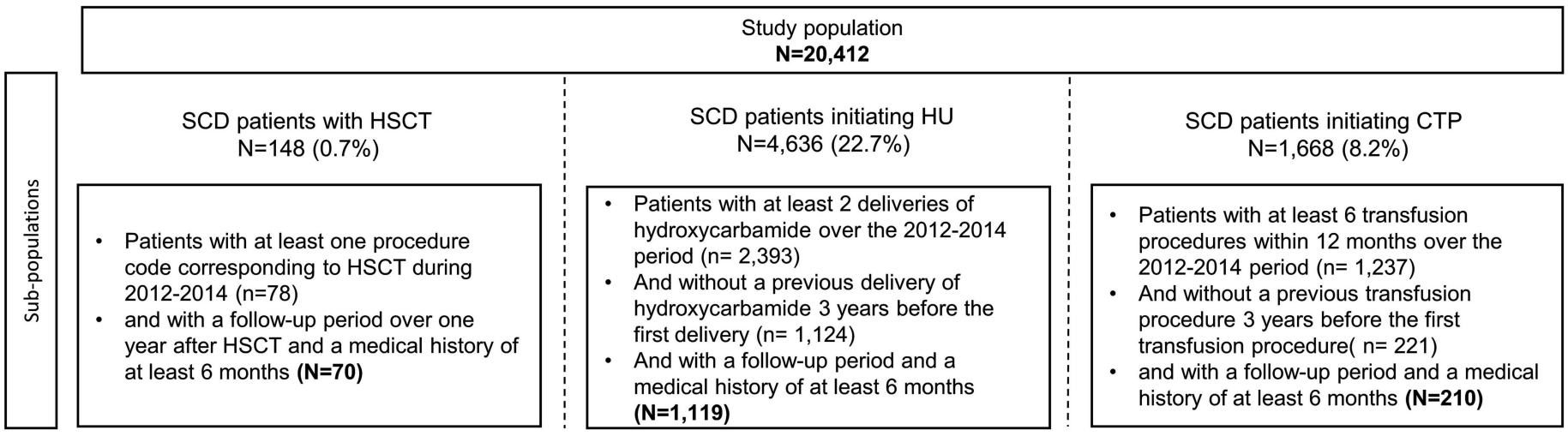


Figure 2. Patients initiating disease-modifying therapy over the period 2012-2014. Modifying therapy: hematopoïetic stem cell transplantation (HSCT), hydroxyurea (HU), chronic transfusion program (CTP). SCD: sickle cell disease.

and 12.90 (95% CI: 12.69-13.11) per 100 person years, respectively, and a 30-day readmission rate of 19.9% and 8.7%, respectively. These events were more frequent in most severely affected patients, with 166.9 (95% CI: 165.4-168.4) per 100 person years for hospitalizations for VOC and 22.71 (95% CI: 22.16-23.27) per 100 person years for ACS, and a 30-day readmission rate of 28.9% and 9.9%, respectively.

Chronic SCD-related events prevalence increased with age (Table 3) and were more important in most severely affected patients than in the whole SCD population, with respectively 15.4% (n=656) *versus* 8.1% (n=1,651) for car-

Table 1. Patient demographics and characteristics.

Characteristics	Study population (N=20,412)	Most severely affected patients (N=4,270)
Age in years at index date Mean (SD) Median (Q1-Q3)	 24.0 (21.0) 20.0 (5.0-37.0)	 21.8 (15.7) 19.0 (9.0-31.0)
Age in years at index date, N (%) ≤5 6-11 12-17 18-24 25-39 40-59 ≥60	 5,229 (25.6) 2,150 (10.5) 1,862 (9.1) 2,237 (11.0) 4,388 (21.5) 3,079 (15.1) 1,467 (7.2)	 564 (13.2) 759 (17.8) 652 (15.3) 677 (15.9) 1,056 (24.7) 459 (10.7) 103 (2.4)
Sex, N (%) Male Sex ratio, M/F	 8,702 (42.6) 0.74	 2,008 (47.0) 0.89
Geographical area of residence at index date, N (%) Mainland Overseas regions	 15,891 (83.8) 3,063 (16.2)	 3,438 (83.6) 676 (16.4)
Death, N (%)	1,062 (5.2)	248 (5.8)
Death, age in years Mean (SD) 95% CI Median (Q1-Q3)	 55.0 (23.9) (53.5-56.4)] 58.0 (39.0-73.0)	 43.5 (21.0) (40.9-46.1) 44.0 (28.0-57.0)

SD: standard deviation; Q: quartile; M: male; F: female; CI: confidence interval.

Table 2. Acute events during follow-up.

Events	Study population (N=20,412)	Most severely affected patients (N=4,270)
Acute chest syndrome N (%) Rate per 100 person years (95% CI)	 6,787 (33.3) 7.62 (7.44-7.80)	 2,331 (54.6) (12.16-13.19)
Vaso-occlusive crisis N (%) Rate per 100 person years (95% CI)	 15,346 (75.2) 33.55 (33.03-34.09)	 3,804 (89.1) 57.09 (55.29-58.93)
Septicemia, sepsis or meningitis N (%) Rate per 100 person years (95% CI)	 1,315 (6.4) 1.19 (1.13-1.26)	 481 (11.3) 1.78 (1.62-1.95)
Cerebrovascular symptoms N (%) Rate per 100 person years (95% CI)	 589 (2.9) 0.53 (0.49-0.57)	 190 (4.4) 0.68 (0.59-0.79)
Gallstones and cholecystitis N (%) Rate per 100 person years (95% CI)	 2,014 (9.9) 1.89 (1.81-1.98)	 770 (18.0) 3.04 (2.83-3.26)

Cerebrovascular symptoms include transient cerebral ischemic attacks along with intracerebral and intracranial hemorrhage. CI: confidence interval.

diovascular disease, 15.5% (n=662) *versus* 6.6% (n=1,351) for osteonecrosis, 13.9% (n=593) *versus* 4.0% (n=819) for iron overload, 7.9% (n=338) *versus* 6.6% (n=1,350) for kidney disease and 9.3% (n=399) *versus* 4.7% (n=961) for pulmonary thrombotic events.

Patients with SCD had a median of 2.0 (range, 0.3-4.4) ambulatory medical visits per year and 1.3 general practitioner visits (range, 0.0-3.3), but 21.3% and 27.9% of the total population as well as the most severely affected patients had no visits, respectively (Table 4). However, there was a median of 0.4 (range, 0.0-1.3) outpatient hospital visits per year, with 36.9% of patients not having any outpatient visits. These numbers were similar in most severely affected patients. Regarding emergency room (ER) visits, 71.4% of patients had at least one ER visit followed by a hospitalization (n=14,571) and 87.4% for most severely affected patients (n=3,733), with a median of 0.9 (range, 0.3-1.9) ER visit per year that were almost all followed by hospitalization.

Overall, 93% of patients (n=18,988) and 97.9% of most severely affected patients (n=4,179) had at least one hospitalization during follow-up, including day-care unit hospitalizations, with a median of 1.3 (range, 0.6-2.9) hospitalization per year for a cumulative duration of 3.3 (range, 2.0-5.0) days per year. This number doubled in the most severely affected patients, with 2.9 (range, 1.4-6.4) hospitalizations per year with a similar cumulative duration.

The dispensation of pain medication concerned 63.6% (n=12,992) and 81.3% of the most severely affected patients (n=3,470). HU dispensation (Siklos® and/or Hydrea®) concerned 24.8% (n=5,061) of patients and more than half of the most severely affected patients (56,0%, n=2,390).

Regarding sick leaves in patients aged between 15-64 years (n=2,528), 37.9% (n=4,189) of patients had at least one sick leave during follow-up, with a median duration of 9.1 (range, 2.8-27.4) days per year. Results were similar for most severely affected patients. The use of reimbursed medical transport concerned 39.7% (n=8,110) of patients with a median of 0.6 (range, 0.2-2.0) per year annually. Results were similar for most severely affected patients.

In the study population, the median annualized total health care costs per patient were €5,073.63 (range, €1,633.74-14,000.94) and were driven at 90% by hospitalization costs with €4,140.66 (range, €1,145.06-12,114.41) (Table 5; Figure 3). Medication costs accounted for €115.19 (range, €23.30-419.36), and medical consultation costs accounted for €81.94 (range, €23.83-162.85). Total health care costs tended to be twice higher in most severely affected patients with a median of €13,295.67 (range, €5,754.67-26,385.23), similarly driven by hospitalization costs €10,983.70 (range, €4,414.01-22,403.95).

Among HSCT patients (n=70), healthcare resource utilization (HCRU) was significantly lower between 1 and 4 years after HSCT compared to 3 years before HSCT. The median number and duration of hospitalizations significantly decreased from 9.0 (range, 5.7-13.0) to 1.0 (range, 0.3-3.0) hospitalizations per year (*P<0.001*) and from 2.3 (range, 1.5-4.8) to 1.2 (range, 1.0-2.7) days per hospitalization (*P<0.001*) (Table 6). The number of ER visits followed by hospitalization decreased from 0.7 (range, 0.0-1.4) to 0.0 (range, 0.0-0.3) (*P<0.001*) and concerned fewer patients (73.3%, n=55 *vs.* 37.3%, n=28; *P<0.001*). Patients with pain medication dispensation decreased from 44.0% (n=33) to 24.0% (n=18) (*P*=0.002). The median annualized costs were ten times lower after HSCT (€29,011.75 *vs.* €2,465.98; *P<0.001*; Figure 3), mostly represented by a decrease in hospitalization costs that accounted for 96% of total costs (€26,576.97 *vs.* €1,915.70; *P<0.001*). Medication costs also decreased significantly (€216.62 *vs.* €132.66; *P*=0.035).

Table 3. Chronic complications during follow-up.

	Cardiovascular diseases N (%)	Pulmonary thrombotic events N (%)	Sequels of cerebrovascular events N (%)	Chronic kidney disease N (%)	Iron overload N (%)	Osteonecrosis N (%)	Pulmonary hypertension N (%)
Study population (N=20,412)	1,651 (8.1)	961 (4.7)	748 (3.7)	1,350 (6.6)	819 (4.0)	1,351 (6.6)	507 (2.5)
Age in years							
≤5 (N=5,229)	122 (2.3)	105 (2.0)	15 (0.3)	28 (0.5)	86 (1.6)	51 (1.0)	33 (0.6)
6-11 (N=2,150)	89 (4.1)	71 (3.3)	19 (0.9)	25 (1.2)	88 (4.1)	108 (5.0)	13 (0.6)
12-17 (N=1,862)	133 (7.1)	80 (4.3)	56 (3.0)	32 (1.7)	77 (4.1)	150 (8.1)	24 (1.3)
18-24 (N=2,237)	240 (10.7)	114 (5.1)	134 (6.0)	65 (2.9)	103 (4.6)	205 (9.2)	37 (1.7)
25-39 (N=4,388)	449 (10.2)	203 (4.6)	271 (6.2)	222 (5.1)	259 (5.9)	466 (10.6)	129 (2.9)
40-59 (N=3,079)	372 (12.1)	210 (6.8)	178 (5.8%)	445 (14.5)	173 (5.6)	305 (9.9)	185 (6.0)
Most severely affected patients (N=4,270)	656 (15.4)	399 (9.3)	289 (6.8)	338 (7.9)	338 (7.9)	662 (15.5)	218 (5.1)

Among patients initiating HU (n=1,124), there were fewer ambulatory medical visits per year in the 3 years before HU initiation compared to 4 years after, with a median of 2.3 *versus* 3.0 (*P=0.003*), including general practitioner visits (1.7 *vs*. 2.2; *P=0.004*), while the number of outpatient hospital visits did not differ. Patients with a dispensation of pain medication increased from 76.2% (n=856) to 91.6% (n=1,030) (*P<0.001*). The proportion of patients using medical transport significantly increased after HU initiation from 40.0% (n=450) to 52.9% (n=595) (*P<0.001*), but the median annual number of medical transport and duration of sick leaves did not differ. Median annualized costs slightly decreased after HU initiation (€13,057.79 *vs*. €12,752.44; *P=0.003*), while median medication costs significantly increased after HU initiation (€156.68 *vs*. €2,180.05; *P<0.001*).

Among patients initiating a CTP (n=210), the median number of hospitalizations per year, including day care unit hospitalizations, significantly increased from 1.3 (range, 0.7-2.7) in the 3 years before CTP initiation to 9.0 (range, 5.7-12.7) in the 4 years following CTP initiation (*P<0.001*), but the hospitalizations were twice as short with a reduction from 4.0 (range, 2.5-5.5) to 2.1 (range, 1.3-3.5) days (*P<0.001*). Other HCRU significantly increased were hospitalizations after an ER visit (63.3%, n=140 *vs*. 82.4%, n=182; *P<0.001*), the number of patients using pain medication (45.7%, n=101 *vs*. 64.3%, n=142; *P<0.001*) and the number of patients using medical transport that doubled (21.7%, n=48 *vs* 49.8%, n=110; *P<0.001*). The median annualized costs for patients initiating CTP were more than five times higher after CTP initiation (€4,643.11 *vs*. €22,715.85; *P<0.001*), with a significant increase in hospitalization costs (€3,054.45 *vs*. €19,934.54; *P<0.001*) and medication costs (€113.43 *vs*. €798.28; *P<0.001*).

Table 4. Healthcare resource utilization during follow-up in patients with sickle cell disease and most severely affected patients.

Events	Study population (N=20,412)	Most severely affected patients (N=4,270)
Medical consultations		
Outpatient hospital consultations		
N (%)	12,873 (63.1)	2,757 (64.6)
Median annualized number (Q1-Q3)	0.4 (0.0-1.3)	0.3 (0.0-1.0)
Ambulatory medical consultations		
N (%)	16,064 (78.7)	3,525 (82.6)
Median annualized number (Q1-Q3)	3.1 (0.9-6.0)	1.9 (0.4-4.3)
General practitioner consultations		
N (%)	14,708 (72.1)	3,345 (78.3)
Median annualized number (Q1-Q3)	1.3 (0.0-3.3)	1.3 (0.1-3.4)
Hospitalizations in MCO		
N (%)	18,988 (93.0)	4,179 (97.9)
Median annualized number (Q1-Q3)	1.3 (0.6-2.9)	2.9 (1.4-6.4)
Median duration in months (Q1-Q3)	3.3 (2.0-5.0)	3.3 (2.0-4.9)
Opioid medication*		
N (%)	12,992 (63.6)	3,470 (81.3)
Emergency room visits		
N (%)	14,753 (72.3)	3,733 (87.4)
Median annualized number (Q1-Q3)	0.4 (0.0-1.0)	0.9 (0.3-1.9)
Emergency room visits followed by a hospitalization		
N (%)	14,571 (71.4)	3,712 (86.9)
Median annualized number (Q1-Q3)	0.3 (0.0-1.0)	0.7 (0.3-1.9)
Medical transports		
N (%)	8,110 (39.7)	2,378 (55.7)
Median annualized number (Q1-Q3)	0.6 (0.2-2.0)	0.6 (0.3-1.9)
	Study population aged between 15 and 64 years (N=11,053)	**Most severely affected patients aged between 15 and 64 years (N=2,505)**
Sick leaves		
N (%)	4,189 (37.9)	1,010 (40.0)
Median annualized number (Q1-Q3)	9.1 (2.8-27.4)	9.1 (3.0-25.6)

Q: quartile; MCO: médecine, chirurgie, obstetrique; SCD: sickle cell disease. *Opioid medication excluding morphine.

Discussion

To the best of our knowledge, this is the first real-world study in France describing and comparing nationwide epidemiology, HCRU, overall costs, before and after disease-modifying therapy and HSCT initiation. Our study highlights the progressive increase of SCD prevalence over the years, from 15,203 patients in 2012 to 21,668 in 2018, with figures in line with recent literature data reporting a prevalence between 19,800 and 32,400 patients in 2016.[5] The increasing number of patients can be explained by the implementation of newborn screening for SCD, which has allowed the identification of 9,260 children with SCD since 1989,[8] by the inclusion of new adults due to emigration and overall better survival of patients. Early diagnosis, followed by prophylactic measures, has allowed for better prevention of disease complications and improved quality of care, delaying the median age of death from 35.1 years for the 1995-2010 period[9,10] to 58.0 years for the 2012-2018 period. These results are in line with the global trends of improved survival in SCD,[11,12] although mortality estimates for the most severely affected patients remain dramatically unimproved at 43.5 years.

Results from our study stratified by age and sex are consistent with the literature.[13] The most severely affected patients were younger and had a more pronounced clinical burden, reflected by high frequencies of acute complications, including hospitalizations for VOE, ACS, and ER visits, followed by hospitalizations and pain symptoms that were captured through pain medication dispensation that concerned two-thirds of the study population and almost all of the most severely affected patients. Of note, pain medication dispensation did not include morphine treatment as the latter is not prescribed outside hospital

Table 5. Annualized cost (€) in the study population and of most severely affected patients.

	Study population	Most severely affected patients
Overall costs Median (Q1-Q3) Mean (SD)	5,073.63 (1,633.74-14,000.94) 16,025.18 (129,468.19)	13,295.67 (5,754.67-26,385.23) 23,163.76 (36,410.53)
Medical consultations Median (Q1-Q3) Mean (SD)	81.94 (23.83-162.85) 120.96 (179.57)	69.47 (20.30 - 142.23) 106.98 (174.88)
Hospitalizations Median (Q1-Q3) Mean (SD.)	4,140.66 (1,145.06-12,114.41) 14,441.84 (128,741.03)	10,983.70 (4,414.01-22,403.95) 20,332.07 (34,500.10)
Medication Median (Q1-Q3) Mean (SD)	115.19 (23.30-419.36) 772.68 (2,282.00)	436.53 (75.03-2,313.75) 1,999.72 (3,995.10)
Emergency room visits not followed by hospitalization Median (Q1-Q3) Mean (SD)	0.00 (0.00-0.00) 0.72 (6.13)	0.00 (0.00-0.00) 1.34 (11.55)
Medical transports Median (Q1-Q3) Mean (SD)	0.00 (0.00-27.64) 256.16 (2,176.37)	13.82 (0.00-85.00) 287.07 (2,106.35)
Clinical imaging Median (Q1-Q3) Mean (SD)	33.56 (0.00-104.23) 77.79 (222.48)	60.81 (11.47-143.29) 112.91 (426.23)
Paramedical care Median (Q1-Q3) Mean (SD)	5.22 (0.00-60.67) 293.62 (1,559.84)	5.81 (0.00-75.12) 308.14 (1,951.64)
Laboratory tests Median (Q1-Q3) Mean (SD)	25.77 (0.00-93.45) 86.94 (227.30)	21.41 (0.92-76.44) 80.81 (246.41)
Medical devices Median (Q1-Q3) Mean (SD)	0.00 (0.00-0.00) 6.79 (156.67)	0.00 (0.00-0.00) 6.50 (59.89)

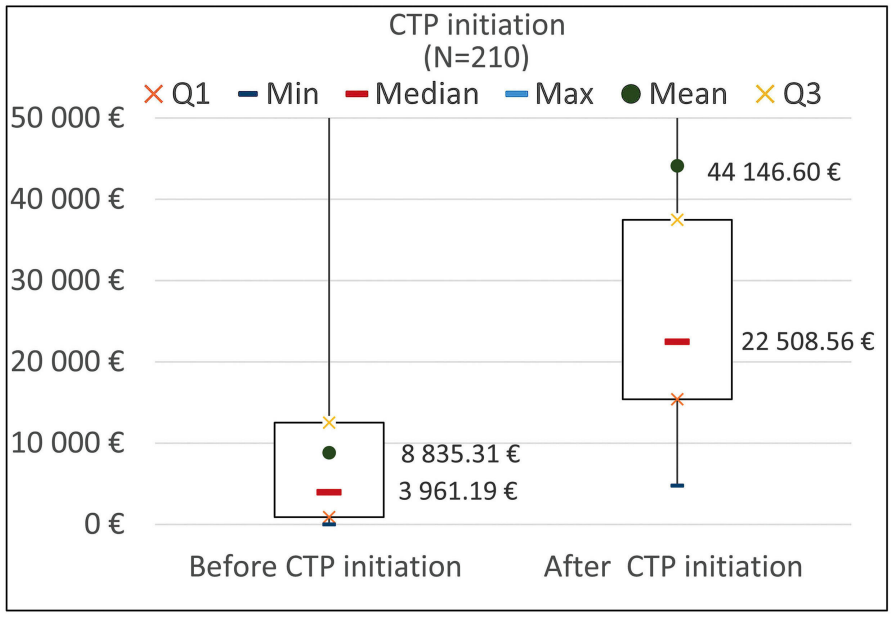
Q: quartile; SD: standard deviation.

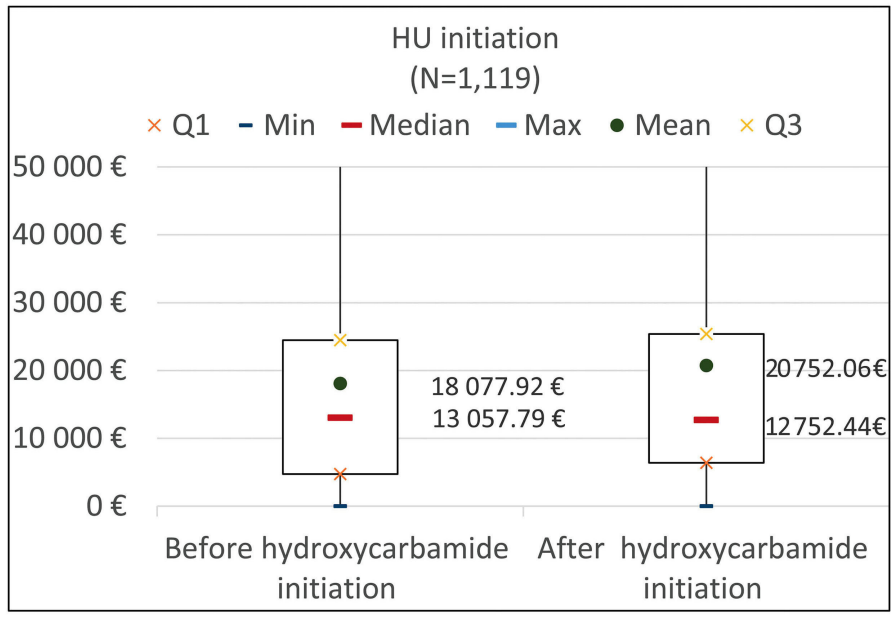
settings in France, in line with national guidelines that do not recommend ambulatory prescription of morphine. We confirm in this study that severe outcomes are more frequent in younger patients,[5,13] with rates of complications consistent with previously reported data on VOC rates ranging between 53.91 and 142.20 VOC events per 100 person years and ACS rates between 8.8 events and 25.3 events per 100 patient years.[14,15] More than half of the most severely affected required disease-modifying treatment by HU, in line with the substantial disease severity in this subgroup.

Our findings are also consistent with existing data on chronic SCD-related complications that report a prevalence of around 6% of pulmonary hypertension in adult patients, between 8% and 22% for osteonecrosis and 12% for end-stage chronic kidney disease.[16,17] Expectedly, organ damage increased across age groups, notably for chronic kidney disease, pulmonary hypertension, cardiac complications, sequels of cerebrovascular events, and osteonecrosis. With 99% of children who now reach adulthood[8] and around half of the patients in the study population aged under 18 years, an increasing proportion of children treated for SCD are expected to transition from pediatric to adult care, with, expectedly, an increasing burden related to chronic organ complications such as kidney or heart failure.

In addition to the important morbidity highlighted through acute and chronic complications, healthcare resource utilization was high and increased in most severely affected patients, with a median of 2.9 hospital stays per patient per year and 3.3 days per stay, corresponding to an average of 9.5 total days per year, including same-day discharge hospitalizations. These results are inferior to those from previous studies of SCD-related healthcare utilization, reporting a mean of 2.83 hospitalizations and 14.69 total days during a 12-month follow-up period,[4,18] a discrepancy possibly attributable to the differing inclusion/exclusion criteria, which favored in our study specificity over sensitivity. This study also offers a perspective on the importance of ambulatory settings in the clinical follow-up of patients with 0.4 outpatient hospital visits per year and 2.0 ambulatory medical visits per year, among which 1.3 general practitioner visits, meeting the French recommendations of quarterly follow-up for optimal patient treatment pathways.[19,20]

The median annualized costs estimated for SCD was €5,073.63 and was coherent with reported costs in previous retrospective studies.[5] Mean costs were estimated





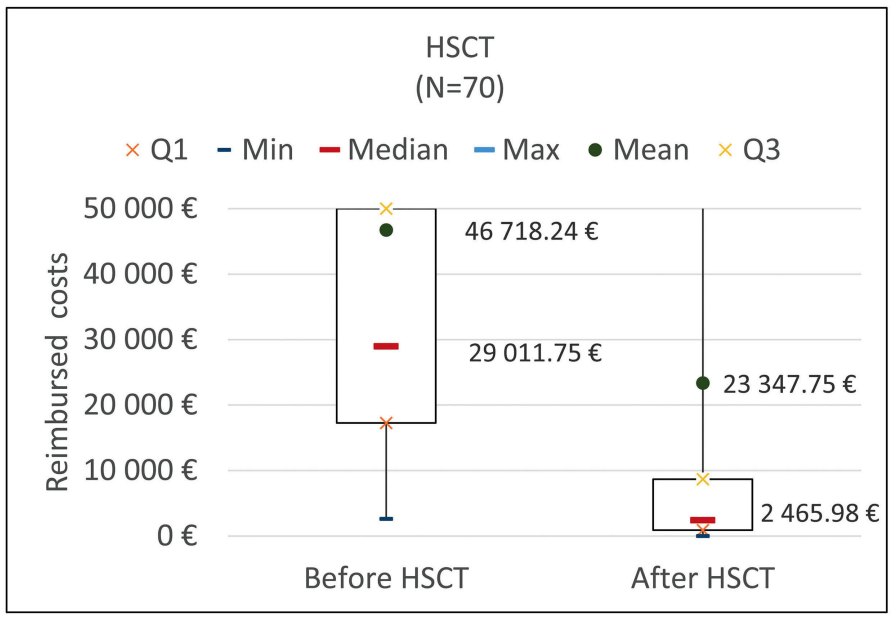


Figure 3. Annualized overall cost comparison after treatment intensification. Comparison 3 years before hematopoïetic stem cell transplantation (HSCT) to cost between 1 year and 4 years after HSCT (P<0.001), 3 years before *vs.* 4 years after hydroxyurea (HU) initiation (P=0.003) and chronic transfusion program (CTP) initiation (P<0.001).

to be €16,025.18, highlighting a wide variability of HCRU among patients with SCD, with a small fraction of patients driving a significant increase in HCRU and costs as previously observed in pediatric patients,[21] notably for most severely affected patients with a median annualized total cost of €12,562.34, mainly driven by hospitalization costs. On a national scale and considering the prevalence of SCD in France, this cost per patient remains higher than cystic fibrosis, another rare genetic disease with a prevalence of 7,000 patients in France,[22] which is associated with an average annual cost of €29,746,[23] highlighting the significant economic burden of SCD in France. It should be noted that SNDS allows for the exact cost of medications calculation so that the figures include real-life costs, allowing to take into consideration both Siklos® and Hydrea® for the study of HU and treatment costs overall.

Regarding non-transplant intensive therapeutic strategies, CTP is mainly indicated in patients with neurological complications and severely symptomatic patients despite HU, as well as acute splenic sequestration prevention in children.[24,25] HU prescription practices have been described in the European, multi-centered non-interventional ESCORT-HU cohort, conducted over a 10-year period, including 1,906 participants, among which 74% were prescribed HU for VOC or ACS while 26% were treated for other non-VOC complications, including severe chronic anemia and conditional transcranial Doppler velocities.[26]

While the decrease in hospitalization duration after CTP initiation suggests a benefit in preventing SCD-related complications, total costs were, however, multiplied by five highlighting the burden of CTP on the healthcare system and on patients who require regular hospital attendance for same-day discharge care. Similarly, our study underlined a minor impact of HU in decreasing costs and did not capture the positive disease-modifying effects of HU therapy in reducing the overall HCRU.[27–29] In line with results from real-world studies, a high economic burden was still associated with patients treated by HU.[4] This burden could be partly explained by low treatment adherence since important rates of treatment discontinuation have been reported in previous studies ranging from 58.9% to 87.8%.[4,30] Another explanation could pertain to the increasing severity of the disease with time, requiring more follow-up and more hospitalizations and limiting the effect of non-curative treatments, as highlighted by the ESCORT-HU cohort where initial HU dose was progressively increased in 44% of patients during follow-up because of recurrent VOC events.[26] Altogether, these findings corroborate the persisting economic burden on the healthcare system following non-transplant intensive therapy initiation, with remaining acute and chronic disease-related complications and potential adverse effects such as iron overload, allo-immunization, and delayed hemolytic transfusion reactions.[25]

Post-HSCT median costs were ten times lower starting from the 2nd year post-HSCT (€2,465.98); however, HSCT is only available for a small subgroup of patients. Important improvements have been obtained over time with HSCT from a matched-sibling donor (MSD), reaching 98% of disease-free survival in SCD patients younger than 30 years following myeloablative conditioning regimen[31] and have expanded the indications to less severe patients. Non-myeloablative conditioning regimens have allowed for an increased frequency of adult transplants, even in the presence of organ dysfunction, offering 87% chances of cure with no graft-*versus*-host disease (GvHD) risk.[32,33] However, such transplants are still limited by the lack of matched sibling donors. Recently, haplo-identical HSCT using post-transplant cyclophosphamide has allowed to strongly increase the pool of donors.[34–36] Recent results with gene therapy are also promising, giving access to a potentially curative treatment to patients with no available donor and without the risk of GvHD.

It should be noted that for all of the above-mentioned treatments, cost comparison was restricted to a few years after treatment intensification and does not reflect the lifetime cost of patients undergoing HSCT or initiating HU and CTP. Cost distribution was skewed, with a small number of patients with very high costs, driving mean costs to €23,347.75 after HSCT, €45,075.85 after CTP initiation and €20,752.06 after HU initiation. Even though the median gives a better indication of cost distribution among patients, this difference between the two measures highlights a high variability in HCRU within these subpopulations, notably among HSCT patients. Mean costs might be considered a better measure of the economic burden since the costs of these outliers are also presented for reimbursement

The use of the SNDS database allowed to include a majority of patients with SCD in France and enabled adequate power for analysis of this population, but our study has some limitations inherent to secondary database analysis. Because of the absence of genotype data, a conservative selection algorithm was used to minimize the risk of including sickle carriers miscoded for SCD, resulting in a possible underestimation of the prevalence of SCD in France. Although the general scheme of health insurance covers more than 80% of the French population,[37] the overall prevalence of the disease might be underestimated regarding patients covered by other health insurance schemes. Furthermore, patients with SCD under temporary health insurance coverage (i.e., for patients who recently emigrated) were not included because of identification difficulties. The non-inclusion of this population in the study might further underestimate the population size and overall HCRU and costs. The most frequent and severe SCD genotype (SS/Sβ0-thalassemia) accounts for approximately 70% of patients in France,[38] while the most se-

verely affected patients in our study accounted for only 21% of the study population. This difference results from the lack of clinical and biological data in SNDS that allows to precisely estimate disease severity in clinical practice. Consequently, the definition of most severely affected patients relied on acute events and treatment utilization in a real-life setting rather than chronic comorbidities. Altogether, this resulted in a possible inclusion of non-severe patients in the most severely affected patients subgroup. The availability of both genotype data and biological variables would have allowed a more precise identification of severity profiles and assessment of the burden related to severe SCD and provided additional insights into the therapeutic management of the disease and overall burden reported in this study. Our results nevertheless confirm the severity subgroup definition and are coherent with existing literature that highlights that the most severely affected patients share characteristics that are associated with more acute and chronic pain, more hospital re-admissions and an accumulation of organ damage.[39,40] Because this study is descriptive, the relationship between the severity and outcomes is yet to be demonstrated. Results for the age at death are challenged by the study design that does not allow the longitudinal follow-up of patients, causing a possible overestimation of life expectancy. Furthermore, severity status was defined on index date only, resulting in a potential underestimation of the number of most severely affected patients by not including patients whose severity status appeared during follow-up. Finally, French medical-administrative databases do not allow to control the data validity and quality. Some studies have reported some unreliability in the ICD-10 diagnoses coded in the PMSI database.[6,41] There is a risk of information bias related to coding errors in hospitalization diagnosis; however, considering the important number of patients included, this bias is expected to have a limited impact.

Despite the limitations and biases identified, this study gives a reliable overview of the current prevalence and the continuous life-long management of patients with SCD in France. The mainstay of SCD treatment remains blood transfusion or HU therapy, but SCD still places a significant demand on health resources, even more importantly in the most severely affected patients and over time. Treatment advances that address underlying disease pathogenesis and can halt acute and chronic disease manifestation are needed to improve the lives of those affected and to alleviate the associated healthcare system burden.

Disclosures

FB is a consultant of bluebirdbio, Pfizer and Vertex; is part of the advisory board of GBT; has received honorary from AddMedica, Anoosha Habibi; has received ASH congress funding from Addmedica; is a consultant and trainer of their team of Novartis; is a consultant of GBT and has received congress funding from GTB, was a consultant of bluebirdbio up to 2000. VB was an advisory committee member up to 2018 of Addmedica, is a consultant for Beam Therapeutics; is an advisory committee member of Forma therapeutics and GBT; was a consultant of bluebirdbio up to 2020. SB is the executive director of Steve consultants and does contract work with bluebirdbio. MG is employed by Steve consultants and does contract work with bluebirdbi. AM is employed by Steve consultants and does contract work with bluebirdbio. MG is employed by bluebirdbio.

Contributions

VB and FB equally contributed to the manuscript development. VB, FB and AH drafted the manuscript. MG performed statistical analysis. All authors developed the concept and design of the research and supervised the study. All authors acquired, analyzed and interpreted data. All authors participated in the interpretation of the data, provided critical feedback and final approval for submission, and took responsibility for the accuracy, completeness, and protocol adherence of data and analyses.

Data-sharing statement

All original data are included in the manuscript.

References

1. Mattioni S, Stojanovic KS, Girot R, Lionnet F. La drépanocytose en France. Rev Francoph Lab. 2016;2016(481):61-66.
2. Sundd P, Gladwin MT, Novelli EM. Pathophysiology of sickle cell disease. Annu Rev Pathol. 2019;14:263-292.
3. Carden MA, Little J. Emerging disease-modifying therapies for sickle cell disease. Haematologica. 2019;104(9):1710-1719.
4. Shah N, Bhor M, Xie L, et al. Treatment patterns and economic burden of sickle-cell disease patients prescribed hydroxyurea: a retrospective claims-based study. Health Qual Life Outcomes. 2019;17(1):155.
5. Leleu H, Arlet JB, Habibi A, et al. Epidemiology and disease burden of sickle cell disease in France: A descriptive study based on a French nationwide claim database. PLoS One. 2021;16(7):e0253986.
6. Bezin J, Duong M, Lassalle R, et al. The national healthcare system claims databases in France, SNIIRAM and EGB: powerful tools for pharmacoepidemiology. Pharmacoepidemiol Drug Saf 2017;26(8):954-962.
7. Tuppin P, Rudant J, Constantinou P, et al. Value of a national administrative database to guide public decisions: From the système national d'information interrégimes de l'Assurance Maladie (SNIIRAM) to the système national des données de santé (SNDS) in France. Rev Epidemiol Sante Publique. 2017;65(Suppl 4):S149-S167.
8. Brousse V, Allaf B, Benkerrou M. Dépistage néonatal de la drépanocytose en France. médecine/sciences.

2021;37(5):482-490.
9. Gomes E, Castetbon K, Goulet V. Mortalité liée à la drépanocytose en France: Âge de décès et causes associées (1979-2010). Bull Épidémiologique Hebd. 2015;2015(8):142-150.
10. Lanzkron S, Carroll CP, Haywood C. Mortality rates and age at death from sickle cell disease: U.S., 1979–2005. Public Health Rep. 2013;128(2):110-116.
11. Quinn CT, Rogers ZR, McCavit TL, Buchanan GR. Improved survival of children and adolescents with sickle cell disease. Blood. 2010;115(17):3447-3452.
12. Platt OS, Brambilla DJ, Rosse WF, et al. Mortality in sickle cell disease. Life expectancy and risk factors for early death. N Engl J Med. 1994;330(23):1639-1644.
13. Masson E. Sévérité des patients drépanocytaires à travers la prise en charge hospitalière en France: résultats rapportés du Programme de médicalisation des systèmes d'information (PMSI). EM-Consulte. https://www.em-consulte.com/article/1292574/severite-des-patients-drepanocytaires-a-travers-la. Accessed December 8, 2021.
14. Sysol JR, Machado R. Sickle cell disease and acute chest syndrome: epidemiology, diagnosis, management, outcomes. In: Lee JS, Donahoe MP, editors. Hematologic abnormalities and acute lung syndromes. Cham: Springer International Publishing. p67-87.
15. Shah N, Bhor M, Xie L, et al. Evaluation of vaso-occlusive crises in United States sickle cell disease patients: a retrospective claims-based study. J Health Econ Outcomes Res. 2019;6(3):106-117.
16. Powars DR, Chan LS, Hiti A, Ramicone E, Johnson C. Outcome of sickle cell anemia: a 4-decade observational study of 1056 Patients. Medicine (Baltimore). 2005;84(6):363-376.
17. Akgül F, Yalçin F, Seyfeli E, et al. Pulmonary hypertension in sickle-cell disease: comorbidities and echocardiographic findings. Acta Haematol. 2007;118(1):53-60.
18. Kauf TL, Coates TD, Huazhi L, Mody-Patel N, Hartzema AG. The cost of health care for children and adults with sickle cell disease. Am J Hematol. 2009;84(6):323-327.
19. Haute Autorité de Santé. 2006 - Prise en charge de la drépanocytose chez l'enfant .pdf. https://www.has-sante.fr/jcms/c_272479/fr/prise-en-charge-de-la-drepanocytose-chez-l-enfant-et-l-adolescent. Accessed January 12, 2022.
20. Haute Autorité de Santé. ald_10_guide_drepano_adulte_web.pdf. https://www.has-sante.fr/upload/docs/application/pdf/2010-04/ald_10_guide_drepano_adulte_web.pdf. Accessed January 25, 2022.
21. Thielen FW, Houwing ME, Cnossen MH, et al. Cost of health care for paediatric patients with sickle cell disease: an analysis of resource use and costs in a European country. Pediatr Blood Cancer. 2020;67(9):e28588.
22. Burgel P-R. Epidemiological trends of cystic fibrosis in France: 10-year perspective. Arch Pediatr Organe Off Soc Francaise Pediatr. 2016;23(Suppl 12):12S4-12S8.
23. Chevreul K, Berg Brigham K, Michel M, Rault G. Costs and health-related quality of life of patients with cystic fibrosis and their carers in France. J Cyst Fibros. 2015;14(3):384-391.
24. Howard J. Sickle cell disease: when and how to transfuse. Hematol Am Soc Hematol Educ Program. 2016;2016(1):625-631.
25. Chou ST. Transfusion therapy for sickle cell disease: a balancing act. Hematol Am Soc Hematol Educ Program. 2013;2013:439-446.
26. de Montalembert M, Voskaridou E, Oevermann L, et al. Real-Life experience with hydroxyurea in patients with sickle cell disease: results from the prospective ESCORT-HU cohort study. Am J Hematol. 2021;96(10):1223-1231.
27. Charache S, Terrin ML, Moore RD, et al. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. Investigators of the multicenter study of hydroxyurea in sickle cell anemia. N Engl J Med. 1995;332(20):1317-1322.
28. Rodgers GP, Dover GJ, Noguchi CT, Schechter AN, Nienhuis AW. Hematologic responses of patients with sickle cell disease to treatment with hydroxyurea. N Engl J Med. 1990;322(15):1037–1045.
29. Yawn BP, John-Sowah J. Management of sickle cell disease: recommendations from the 2014 expert panel report. Am Fam Physician. 2015;92(12):1069-1076.
30. Candrilli SD, O'Brien SH, Ware RE, Nahata MC, Seiber EE, Balkrishnan R. Hydroxyurea adherence and associated outcomes among Medicaid enrollees with sickle cell disease. Am J Hematol. 2011;86(3):273-277.
31. Bernaudin F, Dalle J-H, Bories D, et al. Long-term event-free survival, chimerism and fertility outcomes in 234 patients with sickle-cell anemia younger than 30 years after myeloablative conditioning and matched-sibling transplantation in France. Haematologica. 2020;105(1):91-101.
32. Hsieh MM, Kang EM, Fitzhugh CD, et al. Allogeneic hematopoietic stem-cell transplantation for sickle cell disease. N Engl J Med. 2009;361(24):2309-2317.
33. Hsieh MM, Fitzhugh CD, Weitzel RP, et al. Nonmyeloablative HLA-matched sibling allogeneic hematopoietic stem cell transplantation for severe sickle cell phenotype. JAMA. 2014;312(1):48-56.
34. de la Fuente J, Dhedin N, Koyama T, et al. Haploidentical bone marrow transplantation with post-transplantation cyclophosphamide plus thiotepa improves donor engraftment in patients with sickle cell anemia: results of an international learning collaborative. Biol Blood Marrow Transplant. 2019;25(6):1197-1209.
35. Bolaños-Meade J, Fuchs EJ, Luznik L, et al. HLA-haploidentical bone marrow transplantation with posttransplant cyclophosphamide expands the donor pool for patients with sickle cell disease. Blood. 2012;120(22):4285-4291.
36. Bolaños-Meade J, Cooke KR, Gamper CJ, et al. Effect of increased dose of total body irradiation on graft failure associated with HLA-haploidentical transplantation in patients with severe haemoglobinopathies: a prospective clinical trial. Lancet Haematol. 2019;6(4):e183-e193.
37. Direction de la Sécurité Sociale. Les chiffres clés de la Sécurité sociale 2019.pdf. https://www.securite-sociale.fr/files/live/sites/SSFR/files/medias/DSS/2019/CHIFFRES%20CLES%202019.pdf. Accessed December 08, 2021.
38. Brousse V, Arnaud C, Lesprit E, et al. Evaluation of outcomes and quality of care in children with sickle cell disease diagnosed by newborn screening: a real-world nation-wide study in France. J Clin Med. 2019;8(10):1594.
39. Ballas SK, Lusardi M. Hospital readmission for adult acute sickle cell painful episodes: frequency, etiology, and prognostic significance. Am J Hematol. 2005;79(1):17-25.
40. Ballas SK, Lieff S, Benjamin LJ, et al. Definitions of the phenotypic manifestations of sickle cell disease. Am J Hematol. 2010;85(1):6-13.
41. Misset B, Nakache D, Vesin A, et al. Reliability of diagnostic coding in intensive care patients. Crit Care. 2008;12(4):R95.