

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

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SUPPLEMENTAL MATERIALS

Supplemental methods

a) Exclusion criteria

To limit the probability of including sickle cell trait patients miscoded for SCD, patients with at least one of the following criteria were not included (n= 14,497):

- Patients with at least one in-hospital diagnosis of sickle cell trait (D57.3) and at least one hospitalisation with an in-hospital diagnosis of SCD and without any other SCD-related record or HU delivery or blood transfusions (n=1,022);
- Pregnant women with only one SCD hospitalisation and no other SCD-related record;
- Patients with no HU delivery and no blood transfusions, and less than 6 deliveries of folic acid, as well as with only one SCD hospitalisation and no other SCD-related record (n=10,435);
- Patients with LDD for SCD and no other SCD-related record, as well as with no delivery of HU and with less than 6 deliveries of folic acid and no osteonecrosis and no phlebectomy (n=3,684).

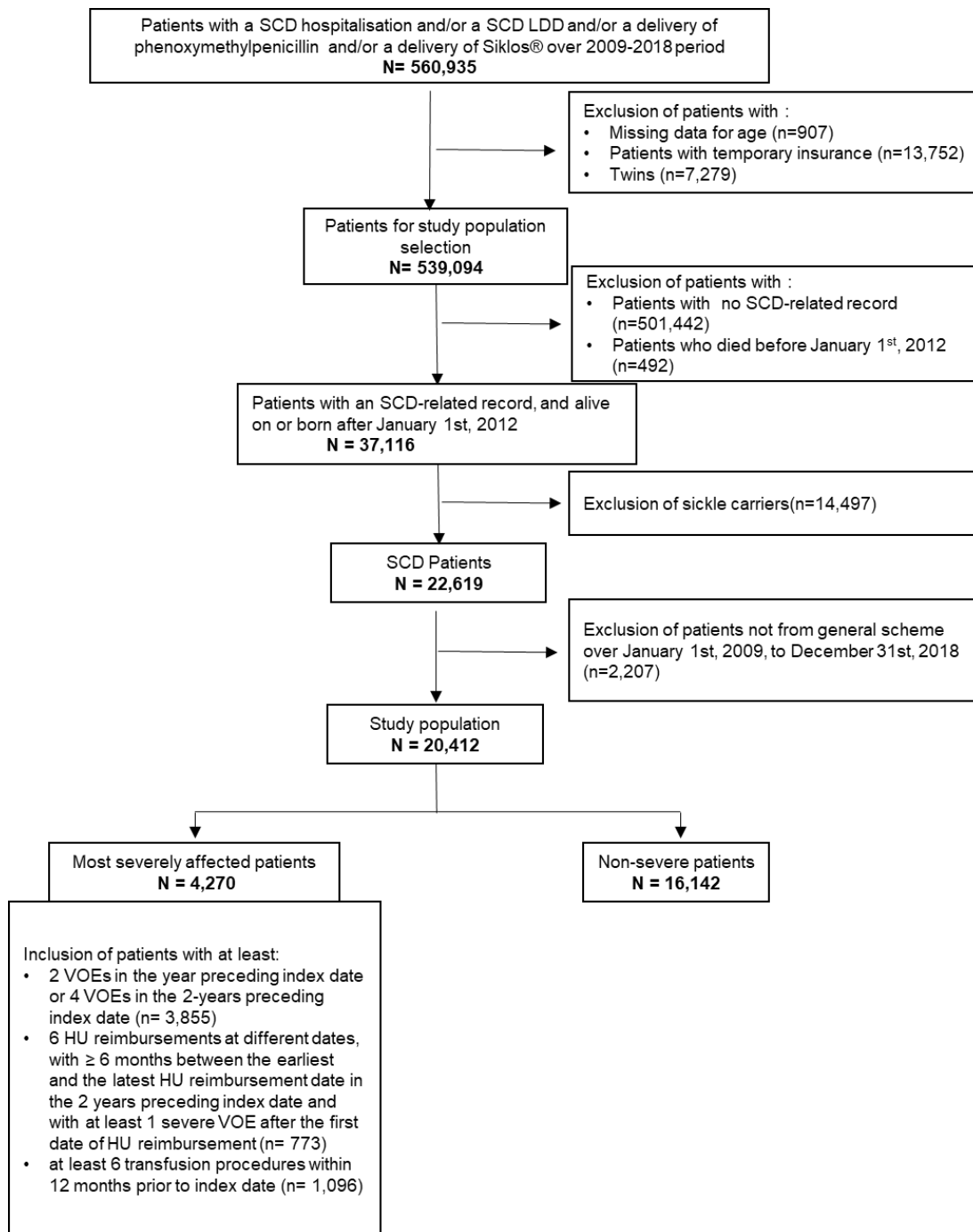
The French healthcare system includes several health insurance schemes providing universal coverage for its residents. The main schemes that provide health insurance are one specific to the agricultural sector and another more general scheme with the same coverage and benefit policies. For patients who cannot enrol in a classic health insurance scheme, a temporary health coverage exists. However, disparities exist between the different schemes concerning the information available in the SNDS. Vital status is not correctly entered for some insurance schemes other than the general scheme, and diagnoses of long-term and occupational diseases have been made available in the SNDS for schemes other than the general one only since 2014⁴². Consequently, patients not belonging to the general insurance scheme have been excluded. Furthermore, data from temporary health coverage cannot be linked to data from the classic health insurance schemes; consequently, patients under a temporary coverage have been excluded in order to avoid to double count them once they switch to a classic health insurance scheme. Finally, twins were excluded for identification difficulties within SNDS.

b) Methods

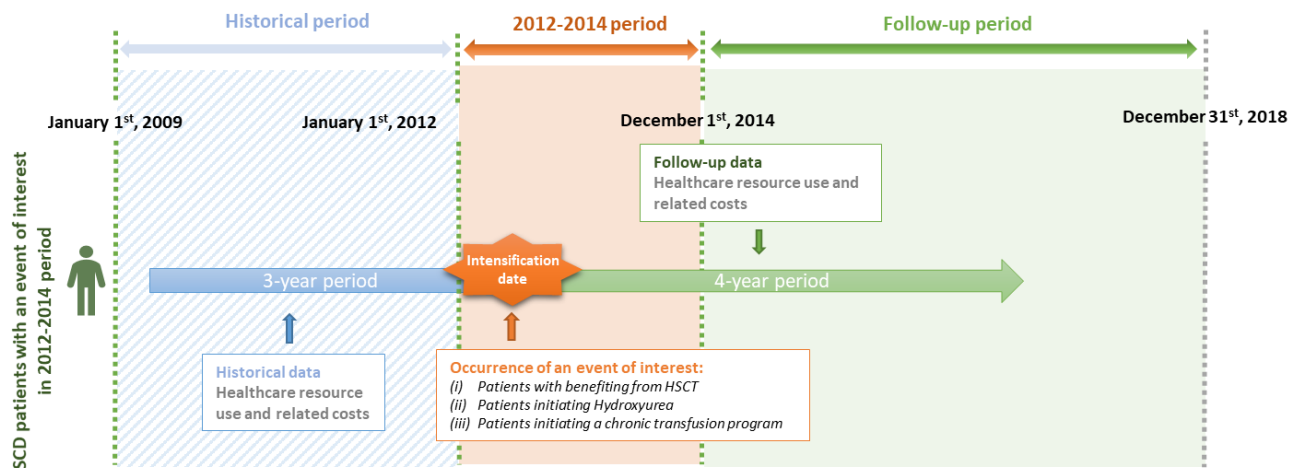
Baseline sociodemographic characteristics (age and gender) were described for patients from the study population and most severely affected patients. Rates of acute SCD-related hospitalisations for SCD, ACS, severe infections and cerebrovascular symptoms and 30-day readmission rates among patients with at least one related hospitalisation were calculated. The number of patients with chronic SCD-related events (cardiovascular disease, osteonecrosis, kidney disease, pulmonary thrombotic events, iron overload, and sequels of cerebrovascular events) was described. HCRU of interest included outpatient hospital visits (excluding same-day discharge and overnight hospitalisations), ambulatory medical visits including general practitioner visits, emergency room (ER) visits, hospitalisations in Medical, Surgical and Obstetrics Care units (Médecine, Chirurgie et Obstétrique, MCO), including same-day discharge hospitalisations, medication, sick leaves and medical transport.

Quantitative variables were described in terms of mean, standard deviation, and extreme values, and qualitative variables in terms of absolute frequency and percentage by category. Annualised numbers and costs of healthcare resource use were calculated by dividing the number of healthcare resources of interest during the follow-up period (or the sum of costs of interest) by the number of person-years

during the follow-up period. 30-day readmission rates were calculated by dividing the number of patients presenting with at least one 30-day readmission event by the total number of patients presenting at least one acute SCD-related event of interest.

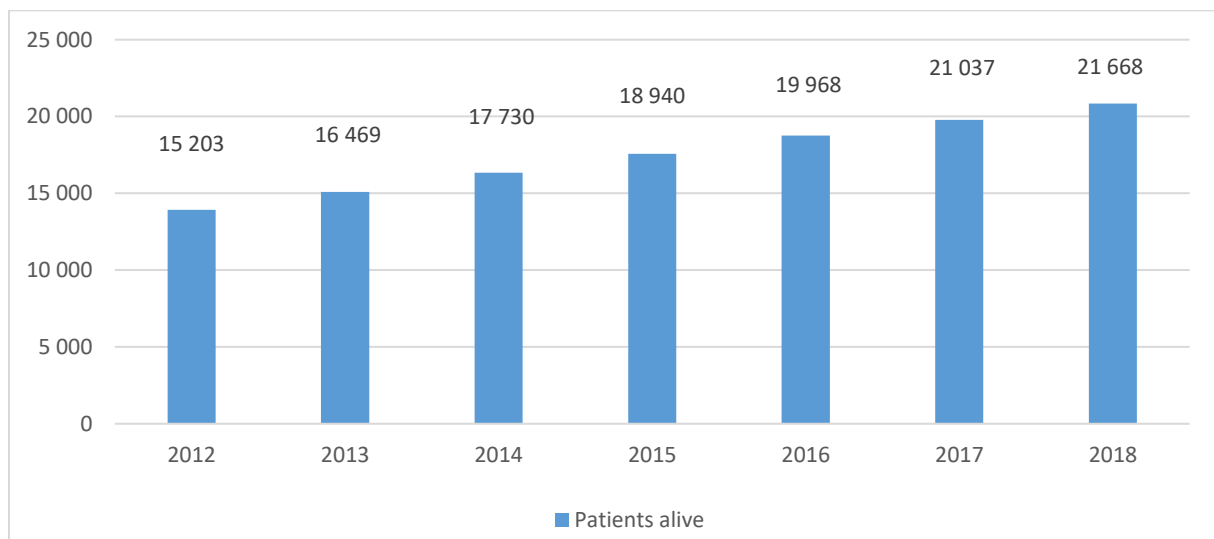


Supplemental figure 1. Detailed flow chart of study population selection



Supplemental figure 2. Comparison design

SCD: sickle cell disease, HSCT: Hematopoietic stem cell transplantation.



Supplemental figure 3. Yearly evolution of the number of alive patients between 2012 and 2018

Patients alive each year are represented in the figure above.

EVENTS	HSCT (N=70)		HU INITIATION (N=1,124)		CTP INITIATION (N=221)				
	Before HSCT	1 year after HSCT	P-value	Before HU initiation	After HU initiation	P-value	Before CTP initiation	After CTP initiation	P-VALUE
n(%)	18 (24.0%)	36 (48.0%)	p=0.004	79 (35.7%)	115 (52.0%)	P<0.001	150 (67.9%)	180 (81.4%)	P<0.001
median annualised number (O1 - O3)	0.0 (0.0 - 0.3)	0.0 (0.0 - 1.0)	p=0.122	0.0 (0.0 - 0.7)	0.2 (0.0 - 1.2)	p<0.001	0.0 (0.0 - 0.7)	0.2 (0.0 - 1.1)	P=0.106
n(%)	54 (72.0%)	61 (81.3%)	p=0.108	150 (67.9%)	218 (31.0%)	p<0.001	150 (67.9%)	29 (81.9%)	P=0.251
median annualised number (O1 - O3)	3.0 (0.0 - 7.0)	3.0 (0.3 - 5.0)	p=0.713	2.3 (0.0 - 6.0)	0.0 (0.0 - 6.7)	p=0.003	2.3 (0.0 - 6.0)	0.0 (0.0 - 4.0)	P=0.009
n(%)	51 (68.0%)	56 (74.7%)	p=0.251	140 (63.3%)	110 (49.8%)	p<0.001	140 (63.3%)	110 (49.8%)	P<0.001
median annualised number (O1 - O3)	2.0 (0.0 - 5.3)	2.2 (0.0 - 4.0)	p=0.691	1.3 (0.0 - 4.7)	0.2 (0.0 - 0.7)	p=0.004	1.3 (0.0 - 4.7)	0.2 (0.0 - 1.2)	P=0.106
n(%)	74 (98.7%)	66 (88.0%)	p=0.005	194 (87.8%)	180 (81.4%)	p=0.011	194 (87.8%)	180 (81.4%)	P<0.001
median annualised number (O1 - O3)	9.0 (5.5 - 12.7)	1.0 (0.3 - 3.0)	p<0.001	1.3 (0.7 - 2.7)	2.5 (0.5 - 5.0)	p<0.001	1.3 (0.7 - 2.7)	2.5 (0.5 - 5.0)	P=0.993
Median duration (O1 - O3)	2.3 (1.5 - 4.8)	1.2 (1.0 - 2.7)	p<0.001	4.0 (2.5 - 5.5)	1.015 (90.3%)	p<0.001	4.0 (2.5 - 5.5)	173 (78.3%)	P<0.001
n(%)	33 (44.0%)	18 (24.0%)	p=0.002	101 (45.7%)	2.2 (0.7 - 4.7)	p<0.001	101 (45.7%)	2.0 (0.2 - 4.2)	P=0.845
n(%)	55 (73.3%)	28 (37.3%)	p<0.001	141 (63.8%)	1.084 (96.4%)	p=0.052	141 (63.8%)	221 (100.0%)	NA
median annualised number (O1 - O3)	0.7 (0.0 - 1.7)	0.0 (0.0 - 0.3)	p<0.001	0.3 (0.0 - 1.3)	2.5 (1.2 - 5.0)	p=0.002	0.3 (0.0 - 1.3)	9.0 (5.7 - 12.7)	P<0.001
n(%)	54 (72.0%)	24 (32.0%)	p<0.001	140 (63.3%)	3.3 (2.0 - 4.9)	p=0.098	140 (63.3%)	2.1 (1.3 - 3.5)	P<0.001
median annualised number (O1 - O3)	0.7 (0.0 - 1.4)	0.0 (0.0 - 0.3)	p<0.001	0.3 (0.0 - 1.3)	1.030 (91.6%)	p=0.003	0.3 (0.0 - 1.3)	9.0 (5.7 - 12.7)	P<0.001
n(%)	1 (6.3%)	4 (25.0%)	p=0.083	24 (26.4%)	183 (82.8%)	p<0.001	24 (26.4%)	142 (64.3%)	P<0.001
median annualised number (O1 - O3)	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.7)	p=0.125	0.0 (0.0 - 0.3)	0.7 (0.2 - 2.0)	p=0.004	0.0 (0.0 - 0.3)	0.7 (0.2 - 1.7)	P=0.041
Emergency room visits/n(%)	23 (30.7%)	17 (22.7%)	p=0.180	48 (21.7%)	902 (80.2%)	p=0.001	48 (21.7%)	182 (82.4%)	P<0.001
median annualised number (O1 - O3)	0.0 (0.0 - 0.7)	0.0 (0.0 - 0.0)	p=0.970	0.7 (0.2 - 2.0)	0.7 (0.2 - 2.0)	p<0.001	0.0 (0.0 - 0.0)	0.7 (0.2 - 1.5)	P=0.017
Sick leaves	218 (31.0%)	269 (38.2%)		269 (38.2%)			269 (38.2%)		
Medical transports	0.0 (0.0 - 2.7)	0.0 (0.0 - 6.7)		0.0 (0.0 - 6.7)			0.0 (0.0 - 6.7)		
	450 (40.0%)	595 (52.9%)		595 (52.9%)			110 (49.8%)		
	0.0 (0.0 - 0.7)	0.2 (0.0 - 0.7)		0.2 (0.0 - 0.7)			0.2 (0.0 - 1.2)		

Supplemental table 1. HCRU comparison after treatment intensification

HSCT: Hematopoietic stem cell transplantation, HU: hydroxyurea, CTP: chronic transfusion program ER : emergency room, , MCO: médecine, chirurgie, obstetrique; *Opioid medication excluding morphin

LIST OF CODES

Event	Type of code	Code
HSCT	CCAM procedure code	FELF009 "Intravenous injection of a cellular therapy product for allograft transplantation"
Transfusions	ICD-10 codes	Z51.3 Blood transfusion (without reported diagnosis)
	CCAM procedure code	<ul style="list-style-type: none"> • FELF011 <i>Transfusion of concentrated red blood cells with a volume less than half a blood mass</i> • FELF006 <i>Transfusion of non-erythrocytic labile blood product</i> • FELF003 <i>Simultaneous intravenous administration of two of the following blood products: fresh frozen plasma, platelets, antihemophilic factor, fibrinogen, antithrombin III for the supply of coagulopathy, per 24 hours</i> • FELF004 <i>Transfusion of red blood cell concentrate with a volume greater than half a blood mass in adults or 40 milliliters per kilogram [ml/kg] in newborns in less than 24 hours</i> • FELF008 <i>Transfusion of red blood cell concentrate, at home</i> • FEJF006 <i>Therapeutic bloodletting with transfusion of red blood cell concentrate</i> • FEJF005 <i>Therapeutic erythrapheresis session with infusion [intentional normovolemic hemodilution]</i> • FEJF003 <i>Therapeutic erythropheresis session with transfusion of red blood cells [erythrocyte exchange]</i> • FELF012 <i>Exchange transfusion for purification or substitution</i> • FELF005 <i>Exchange transfusion for purification or substitution, for a newborn</i>
acute chest syndrome	ICD-10 codes	<ul style="list-style-type: none"> • J96.0 Acute respiratory failure • J80 Adult respiratory distress syndrome • I26 Pulmonary embolism • J09 Influenza due to identified zoonotic or pandemic influenza virus • J10 Influenza due to identified seasonal influenza virus • J11 Influenza, virus not identified • J12 Viral pneumonia, not elsewhere classified • J13 Pneumonia due to Streptococcus pneumoniae • J14 Pneumonia due to Haemophilus influenzae • J15 Bacterial pneumonia, not elsewhere classified • J16 Pneumonia due to other infectious organisms, not elsewhere classified • J17 Pneumonia in diseases classified elsewhere • J18 Pneumonia, organism unspecified
Cerebrovascular symptoms	ICD-10 codes	<ul style="list-style-type: none"> • G45 Transient cerebral ischaemic attacks and related syndromes • G45.0 Vertebro-basilar artery syndrome • G45.1 Carotid artery syndrome (hemispheric) • G45.2 Multiple and bilateral precerebral artery syndromes • G45.3 Amaurosis fugax • G45.4 Transient global amnesia • G45.8 Other transient cerebral ischaemic attacks and related syndromes • G45.9 Transient cerebral ischaemic attack, unspecified • I60 Subarachnoid haemorrhage

		<ul style="list-style-type: none"> • I61 Intracerebral haemorrhage • I62 Other nontraumatic intracranial haemorrhage • I63 Cerebral infarction • I64 Stroke, not specified as haemorrhage or infarction • I65 Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction • I66 Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction • R56 Convulsions, not elsewhere classified • F44.5 Dissociative convulsions
Vaso-occlusive crisis	ICD-10 codes	<ul style="list-style-type: none"> • D57.1 Sickle-cell anaemia without crisis • D57.0 Sickle-cell anaemia with crisis • D57.2 Double heterozygous sickling disorders (Hb-SC, Hb-SD, Hb-SE, sickle-cell thalassemia), • D57.8 Other sickle-cell disorders;
septicemia, sepsis or meningitis	ICD-10 codes	<ul style="list-style-type: none"> • A40 Streptococcal sepsis • A41 Other sepsis • A41.0 Sepsis due to Staphylococcus aureus • A41.1 Sepsis due to other specified staphylococcus • A41.2 Sepsis due to unspecified staphylococcus • A41.3 Sepsis due to Haemophilus influenzae • A41.4 Sepsis due to anaerobes • A41.5 Sepsis due to other Gram-negative organisms • A41.8 Other specified sepsis • A41.9 Sepsis, unspecified • B37.7 Candidal sepsis • G00 Bacterial meningitis, not elsewhere classified • G01 Meningitis in bacterial diseases classified elsewhere • G02 Meningitis in other infectious and parasitic diseases classified elsewhere • G03 Meningitis due to other and unspecified causes
Gallstone and cholecystitis	ICD-10 codes	<ul style="list-style-type: none"> • K80.0 Calculus of the gallbladder with acute cholecystitis • K80.1 Calculus of gallbladder with other cholecystitis • K80.2 Calculus of gallbladder without cholecystitis • K80.3 Calculus of bile duct with cholangitis • K80.4 Calculus of bile duct with cholecystitis • K80.5 Calculus of bile duct without cholangitis or cholecystitis • K80.8 Other cholelithiasis • K81.0 Acute cholecystitis • K81.8 Other cholecystitis
Iron overload	ICD-10 codes	<ul style="list-style-type: none"> • E83.1 Haemochromatosis
Osteonecrosis	ICD-10 codes	<ul style="list-style-type: none"> • M90.4 Osteonecrosis due to haemoglobinopathy (D50-D64+) • M90.5 Osteonecrosis in other diseases classified elsewhere • M87 Osteonecrosis
Pulmonary hypertension	ICD-10 codes	<ul style="list-style-type: none"> • I27.0 Primary pulmonary hypertension • I27.2 Other secondary pulmonary hypertension
Chronic kidney disease	variables from the CNAM medical cartography	<ul style="list-style-type: none"> • sup_RIRCT_cat including codes for chronic renal dialysis and renal transplantations
Cardiovascular diseases		
Sequels of cerebrovascular events	variables from the CNAM medical cartography	<ul style="list-style-type: none"> • top_CvAVC_seq
	ICD-10 codes	<ul style="list-style-type: none"> • G08 <i>Intracranial and intraspinal phlebitis and thrombophlebitis</i>

Cardiac thrombotic events	ICD-10 codes	<ul style="list-style-type: none">• I24.0 <i>Coronary thrombosis not resulting in myocardial infarction</i>• I51.3 <i>Intracardiac thrombosis, not elsewhere classified</i>
Pulmonary thrombotic events	ICD-10 codes	<ul style="list-style-type: none">• I26 <i>Pulmonary embolism</i>
