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HAL Id: hal-04775160

https://hal.sorbonne-universite.fr/hal-04775160v1

Submitted on 10 Nov 2024

BJHaem
BRITISH JOURNAL OF HAEMATOLOGY

Shift in emergency department utilization by frequent attendees with sickle cell disease during the COVID-19 pandemic: A multicentre cohort study

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Summary

While the coronavirus disease-2019 (COVID-19) might have increased acute episodes in people living with sickle cell disease (SCD), it may also have changed their reliance on emergency department (ED) services. We assessed the impact of the COVID-19 pandemic and lockdowns on ED visits in adult SCD people followed in five French reference centres, with a special focus on 'high users' (≥10 visits in 2019). We analysed the rate of ED visits from 1 January 2015 to 31 December 2021, using a self-controlled case series. Among 1530 people (17 829 ED visits), we observed a significant reduction in ED visits during and after lockdowns, but the effect vanished over time. Compared to pre-pandemic, incidence rate ratios for ED visits were 0.59 [95% CI 0.52–0.67] for the first lockdown, 0.66 [95% CI 0.58–0.75] for the second and 0.85 [95% CI 0.73–0.99] for the third. High users (4% of people but 33.7% of visits) mainly drove the reductions after the first lockdown. COVID-19 lockdowns were associated with reduced ED visits. While most people returned to their baseline utilization by April 2021, high users had a lasting decrease in ED visits. Understanding the factors driving the drop in ED utilization among high users might inform clinical practice and health policy.

KEYWORDS
COVID-19, emergency medical services, public health, risk assessment, sickle cell anaemia

INTRODUCTION

The COVID-19 pandemic led to a massive number of hospital visits worldwide, often exceeding available resources.[1] Concomitantly, a reduction in hospital use for causes unrelated to COVID-19 has been reported in several countries.[2–4] This decrease in hospital use also affected emergency department (ED) visits for acute episodes of chronic diseases, such as chronic obstructive pulmonary disease,[5,6] asthma[3] and heart failure.[3,7]

People living with sickle cell disease (SCD) often resort to ED visits in case of acute painful episodes, acute chest syndrome or fever. These complications can be triggered by respiratory infections. People living with SCD may require subsequent hospitalization and, in some cases, intensive care unit (ICU) transfer.[8] The frequency of ED visits varies between people and in a given person over time.[9] While most people have less than three ED visits a year, some people, sometimes referred to as 'high users', have many more visits.[10] This small subgroup of people accounts for a large proportion of ED visits. Despite an apparent lack of severity, they are more at risk of death than other people living with SCD as reported in a recent national French study showing a higher mortality in people with a higher number of ED visits in the previous year.[11]

The impact of the pandemic and lockdowns on adult SCD people has not been described yet. On the one hand, it may have encouraged protective behaviours such as mask wearing, hand hygiene, better adherence to treatments and reduced exposure to cold weather, thus reducing the onset of SCD acute episodes.[12,13] On the other hand, COVID-19 and/or the limited and delayed access to care may have resulted in more adverse outcomes in SCD people.[14–16]

To analyse these effects, we evaluated the changes in ED utilization among SCD people in the Paris area before and during the different phases of the pandemic, considering the severity of episodes and comparing high users to other people.

METHODS

Study design

This is a multicentric cohort study using data routinely collected in the Clinical Data Warehouse of Greater Paris University Hospitals (GPUH). This report complies with the RECORD statement.[17]

Data sources, data access and cleaning methods

The Clinical Data Warehouse aggregates administrative, demographic, clinical and biological data from people treated in the GPUH.[18] It also integrates dates of deaths sourced from the French Epidemiology Centre on Medical Causes of Death, irrespective of the location of death.

Settings and participants

For the main analysis, the study period was from 1 January 2015 to 31 December 2021. We included people aged 18 or older as of 1 January 2015, with SCD based on ICD-10 (International Classification of Disease 10th edition) diagnostic codes D570-D572, receiving care at any of the five adult SCD centres within the GPUH (Avicenne, Kremlin-Bicêtre, Henri Mondor, Louis Mourier and Tenon Hospitals), and with at least one ED visit in the study period. Final data extraction was performed on 4 October 2022.

Variables

Exposures

We divided the study period into a pre-pandemic period (up to 16 February 2020) and a pandemic period (since 17 February 2020) (Figure 1). This latter period was further split into various stages according to lockdowns in France:

- pre-lockdown period from 17 February 2020 to 16 March 2020;
- first lockdown from 17 March 2020 to 10 May 2020;
- first post-lockdown period from 11 May 2020 to 29 October 2020;
- second lockdown from 30 October 2020 to 14 December 2020;
- second post-lockdown period from 15 December 2020 to 2 April 2021;
- third lockdown from 3 April 2021 to 2 May 2021;
- third post-lockdown period from 3 May 2021 to the end of the study (31 December 2021).

Outcomes

The main outcome was the incidence of ED visits in one of the GPUH. Secondary outcomes were subtypes of ED visits: ED visits without further inpatient admission, ED visits with subsequent hospitalizations but without transfer to an ICU and ED visits with subsequent hospitalization including an ICU transfer. As the saturation of ICUs might have led to varying thresholds for ICU admission over time, we also analysed emergency hospitalizations with any criteria of severity: death, ICU transfer, red blood cell (RBC) transfusion or high flow oxygen/mechanical ventilation, including non-invasive ventilation. We also analysed visits that led to mechanical ventilation/high flow oxygen in the ICU or death to restrict the analysis to the most severe outcomes. Ventilatory supports were identified using their billing codes. RBC transfusions were identified using either an ICD-10 diagnostic code (Z5130 and Z5131) or a billing code for RBC transfusions.
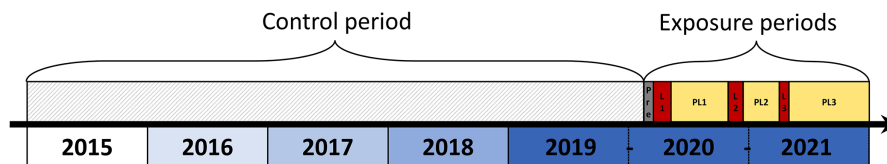
FIGURE 1 Diagram of the self-controlled case series model. Exposure periods: Pre, pre-lockdown period, 16 February 2020 to 16 March 2020; L1, first lockdown, 17 March 2020 to 10 May 2020; PL1, first post-lockdown period, 17 March 2020 to 29 October 2020, L2, second lockdown, 30 October 2020 to 14 December 2020; PL2, second post-lockdown period, 15 December 2020 to 2 April 2021; L3, third lockdown, 3 April 2021 to 2 May 2021; PL3, third post-lockdown period, 3 May 2021 to the end of the study (31 December 2021). Control period: 1 January 2015 to 15 February 2020. Adjustment variables: Calendar years (categorial, 5 levels shown on diagram, same level for years 2019, 2020 and 2021), months (categorial, 12 levels, not shown on diagram).

Descriptive data

People

The sex and age of people were obtained from the administrative data records. SCD beta-haemoglobin genotype was identified using free text analysis of medical records. Steady-state haemoglobin and lactate dehydrogenase (LDH) concentration were defined as the median of all available values obtained during outpatient follow-up visits up to 31 December 2019.

Stays

Hospitalizations with a COVID-19 infection were identified using the ICD-10 diagnostic codes U071.

Statistical analysis

All analyses were performed using R version 4.0.0.[19]

Self-controlled case series

We used the self-controlled case series method (SCCS package version 1.5[20]) to estimate the relative incidence of events during specific exposure periods.[21,22] More specifically, we compared each patient's ED visit frequency during the pandemic to their own baseline period before the pandemic. This approach is particularly effective as it inherently controls for individual factors that do not change over time, such as sex and genotype. We used multinomial conditional logistic regression to assess the relative incidence of ED visits during the various stages of the pandemic (pre-lockdown; lockdowns 1, 2, 3; and post-lockdown 1, 2, 3) compared to the pre-pandemic period. We further adjusted on the calendar month to account for seasonality, and on the calendar year to account for year-to-year change (Figure 1). To compute this year-to-year change in the frequency of ED visits, we pooled years 2019, 2020 and 2021 because 2020 included only two unexposed months (before the pandemic) and 2021 no unexposed period. Living people who did not attend one of the GPUH between 1 January 2022 and 4

October 2022 (last data extraction) were considered lost to follow up and censored at time of their last outpatient or in-patient visit in one of the GPUH. Likewise, people who died before the end of the study period (31 December 2021) were censored at the date of their death. We applied the same approach to analyse secondary outcomes.

Subgroup analyses

People with frequent ED visits, often referred as high users, might have a unique utilization trends. We defined here high users as people with 10 or more ED visits in a calendar year and compared them to other people. To assess if the effect observed was mainly driven by high users with the highest number of visits per year, we performed the analysis in the subgroup of high users with <15 visits per year in 2019 and in the subgroup of high users with ≥15 visits per year in 2019.

In France, care for rare diseases is organized such a way that people living with SCD are usually referred to the reference centre where they are followed up when they need urgent care. We also analysed data based on the follow-up centre, comparing the two largest centres separately and grouping the remaining centres, to assess any variations in ED usage across different hospital settings. For this analysis, people were allocated to the centre where they had the highest number of ED visits up to 31 December 2021.

Sensitivity analyses

We conducted sensitivity analyses to see how our results might change under different assumptions.

Outcome capture

In the main analysis, we censored people if they stopped attending the GPUH, assuming that their healthcare utilization behaviour did not differ from similar remaining people but took place elsewhere. However, people who stopped attending the GPUH during the study period may also simply have had no ED visits anywhere after they were censored. We therefore performed a first sensitivity analysis including all living people up to the end of the study period and considering that they had no ED visit if none was recorded.

People who had the opportunity to attend another ED department may have done so at different frequency depending on the study period, whether they were censored or not. We therefore performed a second sensitivity analysis excluding all people who had been transferred at least once in a GPUH from an outside hospital, as a proxy for occasionally attending ED outside the GPUH. During the pandemic, especially during first lockdown, hospital might have reorganized due to resource constraints. Thus, people might have been cared for in different units such as daycare hospital or might have been admitted directly in a ward rather than through the ED. To evaluate this possible compensatory shift in care during the pandemic, we assessed the effect of the different exposure periods on all inpatient visits, including ED visits as in the main analysis, plus direct hospitalizations (without ED visit) and daycare hospitalizations.

Death

Censoring to death could affect the findings because the death rate could be higher for those with more frequent ED visits. We therefore performed an analysis excluding people who died during follow-up.

Sickle cell disease identification

People living with a sickle cell trait are sometimes coded as having SCD. We performed a sensitivity analysis using only people with a haemoglobin genotype identified by free text analysis of medical records, in addition to an ICD-10 diagnostic code for SCD (D570–D572).

Regression to the mean effect

We selected high users as those with the highest number of visits in 2019, making it necessary to check that regression to the mean alone does not account for subsequent changes.[23,24] We therefore computed the expected reduction in number of visits due to regression to the mean for high users based on data from 2018 to 2019,[25] and compared it to the observed reduction in their number of visits between 2019 and 2020. Then, we also performed the analysis on persistently high users, defined as people that had ≥10 visits per year both in 2018 and 2019.

Ethics

The Greater Paris University Hospitals Clinical Data Warehouse Scientific and Ethics Committee (IRB00011591) granted access to the data for this study and no linkage was made with other databases.

RESULTS

Participants

There were 1575 adults with a diagnostic code for SCD at any time and followed up in one of the five SCD reference centres on 1 January 2015. Among them, 1530 had at least one ED visit during the study period and were included in the main analysis (Figure 2). Their characteristics are reported in Table 1.
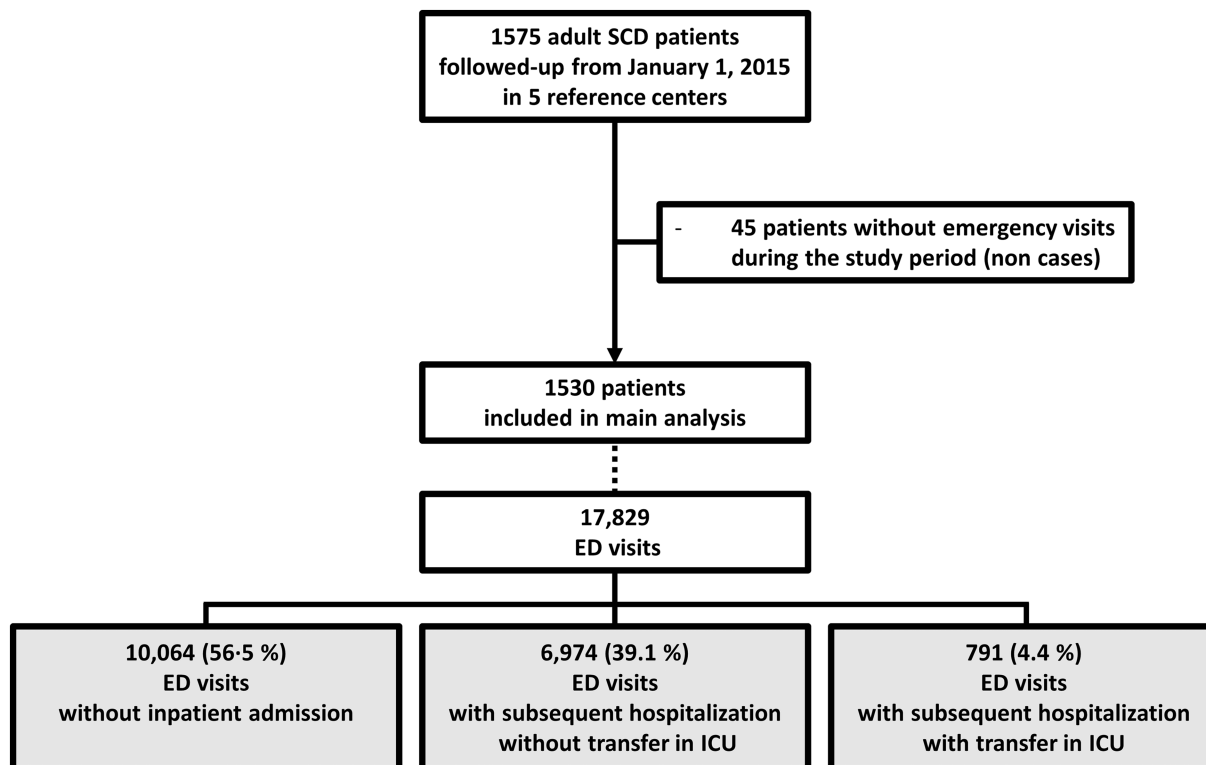

FIGURE 2 Flowchart of the study. ED, emergency department. ICU, intensive care unit. SCD, sickle cell disease.

TABLE 1 Characteristics of people before the COVID-19 pandemic.

	N	Median [IQR] or No. (%)
Age (years)[a]	1530	31 [25–39]
Sex (F)	1530	893 (58.4%)
Genotype	1530	
SS/Sβ0		1152 (75.3%)
SC/Sβ+		286 (18.7%)
Unknown		92 (6.0%)
Haemoglobin (g/dL)[b]	1326	8.8 [8.0–9.9]
LDH (iu/L)[b]	1497	413 [315–546]

Abbreviations: IQR, interquartile range; LDH, lactate dehydrogenase.

[a]Age on 1 January 2015.

[b]Biological variable at steady state was defined as the median of all available outpatient measurements up to 31 December 2019 for each individual; people with missing data: 204 (13.3%) for haemoglobin, 33 (2.2%) for LDH, none for age and sex.

Sixty-seven people (4.4%) died during the study period, after a median follow-up of 4.8 [2.2–5.7] years (Tables S1–S3 for details). Three hundred and eighty-six other people (25.2%) were censored after a median follow-up of 5.9 [4.5–6.7] years because they had no documented inpatient or outpatient hospital visit after the study period.

Outcome data

People had a median of 1 [0–2] ED visits per year, totalling 17 829 ED visits over 7 years. This included 10 064 (56.5%) ED visits only, 6974 (39.1%) ED visits followed by a hospitalization without transfer to the ICU and 791 (4.4%) ED visit followed by a hospitalization with transfer to the ICU. RBC transfusion was required in 709 visits (4.0% of all visits), including 275 (39%) in the ICU. Mechanical ventilation or high-flow oxygen was required in 327 visits (1.8% of all visits), mainly non-invasive mechanical ventilation or high-flow oxygen (91%), including 223 (68%) in the ICU. In 2020 and 2021, a diagnosis (primary or associated) of COVID-19 was present in 10.4% of hospitalizations without transfer to the ICU and 21.8% of hospitalization with transfer to the ICU.

Main analysis

All ED visits

There was a reduction in ED visits during all lockdown periods (Figures 3 and 4) relative to the pre-pandemic period. The reduction waned with time, with an incidence rate ratio (IRR), compared to the pre-pandemic period, of 0.59 [95% CI 0.52–0.67] for the first lockdown, 0.66 [95% CI 0.58–0.75] for the second lockdown and 0.85 [95% CI 0.73–0.99] for the third lockdown. The null hypothesis that all lockdowns had a similar effect was rejected based on a likelihood ratio test ($p < 0.001$). The reduction persisted during the post-lockdown periods, with IRR 0.78 [95% CI 0.73–0.84] for the first post-lockdown, 0.68 [95% CI 0.63–0.75] for the second post-lockdown and 0.79 [95% CI 0.75–0.85] for the third post-lockdown.

Subtypes of hospital visits

The change over time was similar for the three subtypes of hospital visits (Figures S1 and S2). Results were similar when hospitalizations that needed a transfer to the ICU were complemented with hospitalizations requiring a transfusion or high flow oxygen/mechanical ventilation and hospitalization that ended with death (Figure S2).

Calendar years

The incidence of ED visits per patient increased with time, the IRR was 1.48 [1.40–1.56] for 2019–2021 compared to the reference year 2015 (Figure 4). The median age of people with active follow-up increased as expected due to the ageing of the initial population (Table S1).

High users versus other people

The percentage of people with ≥10 visits per year increased from 1.83% in 2015 to 4.42% in 2019, as did their median number of visits per year: 14 [12–26] in 2015 versus 18 [13–29] in 2019 (Table S2). The number of people with ≥10 visits per year decreased in 2020 and 2021. The 61 people with ≥10 visits in 2019 (4.1% of all people), referred as high users, had 6032 ED visits, 33.8% of all ED visits over the whole study period: 4245 out of 13 307 (31.9%) ED visits up to the 31 December 2019, and 1754 out of 4522 (38.8%) ED visits after 31 December 2019.

When these 61 high users were removed from the analyses, the yearly number of visits became stable from 2015 to 2019 (Figure 5). The reduction in the number of visits during the pandemic period remained, but was smaller and waned more rapidly over time. These constatations were similar across centres (Figure S3). On the opposite, the analysis limited to the 61 high users showed an increasing incidence of ED visits before the pandemics but a sharp decrease in the incidence of ED visits during all pandemic periods.

The increasing incidence of ED visits over time before the pandemic was present in all centres. However, the associations of the different pandemic periods with the incidence of ED visits differed across centres (Figure S3).

High users with <15 ED visits per year in 2019 (24 people, 1318 ED visits), and those with ≥15 visits per year in 2019 (37 people, 4681 ED visits) had a similar association between the different pandemic periods and the incidence of ED visits (Figure S4).
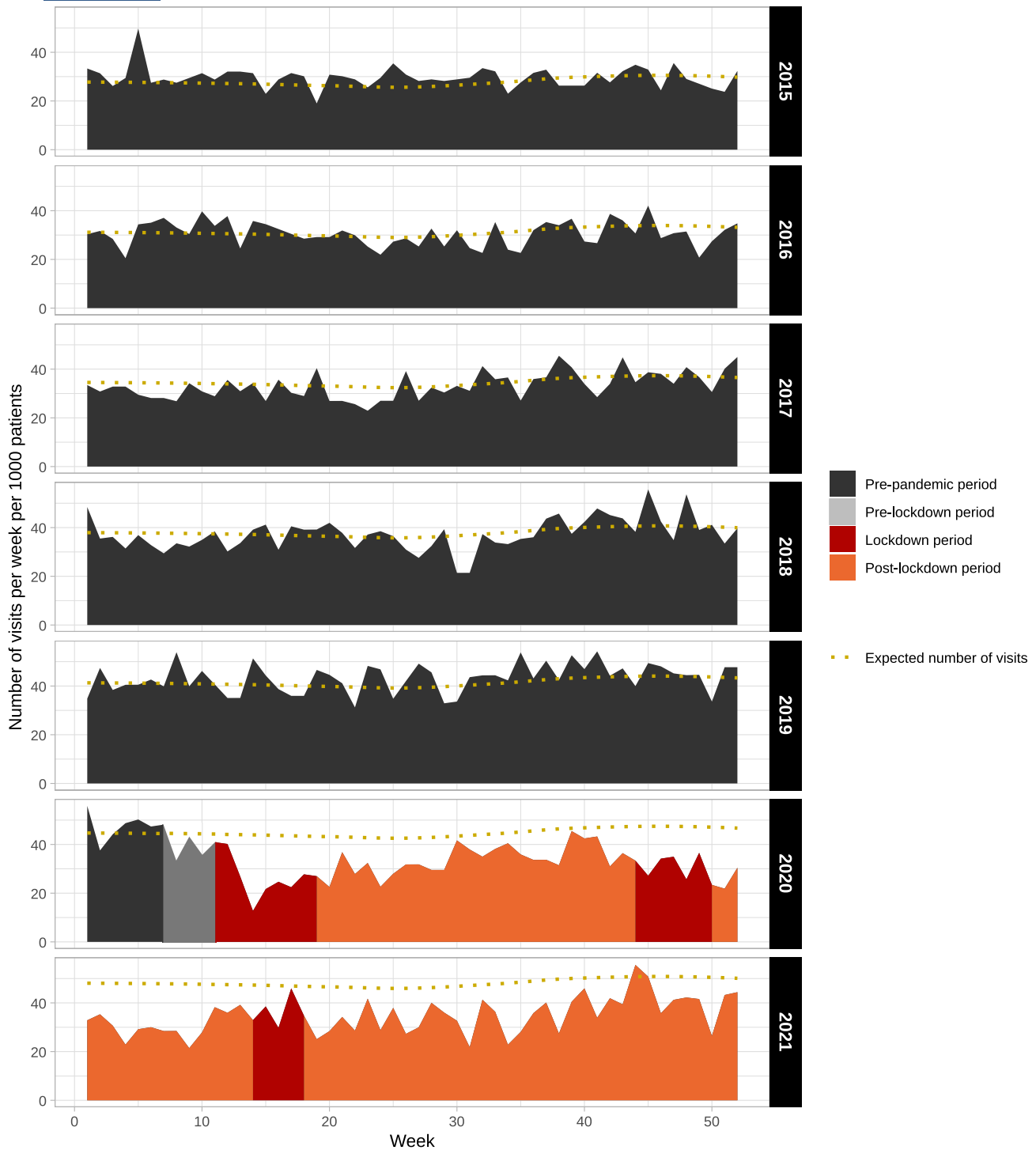
FIGURE 3 Number of emergency department visits per week from 1 January 2015 to 31 December 2021. Grey areas represent period outside lockdowns, red areas represent the three lockdowns and the orange dotted line represents the expected number of emergency visits per week using a linear model with calendar years (numeric, linear effect) and calendar weeks (numeric, natural spline) as covariates, derived on years 2015–2019.

Sensitivity analyses

Considering all inpatient visits (17 829 ED visits, 2863 direct hospitalizations and 9424 daycare hospitalization) rather than ED visits only, did not change the direction of the association but the reduction was smaller (Figure S5).

The percentage of transfers from hospitals outside GPUH did not increase during the pandemic period (Table S1). Sensitivity analysis considering that living people with incomplete follow-up (386 people) had no ED visits after their date of last news and sensitivity analyses excluding people with a history of transfer (158 people

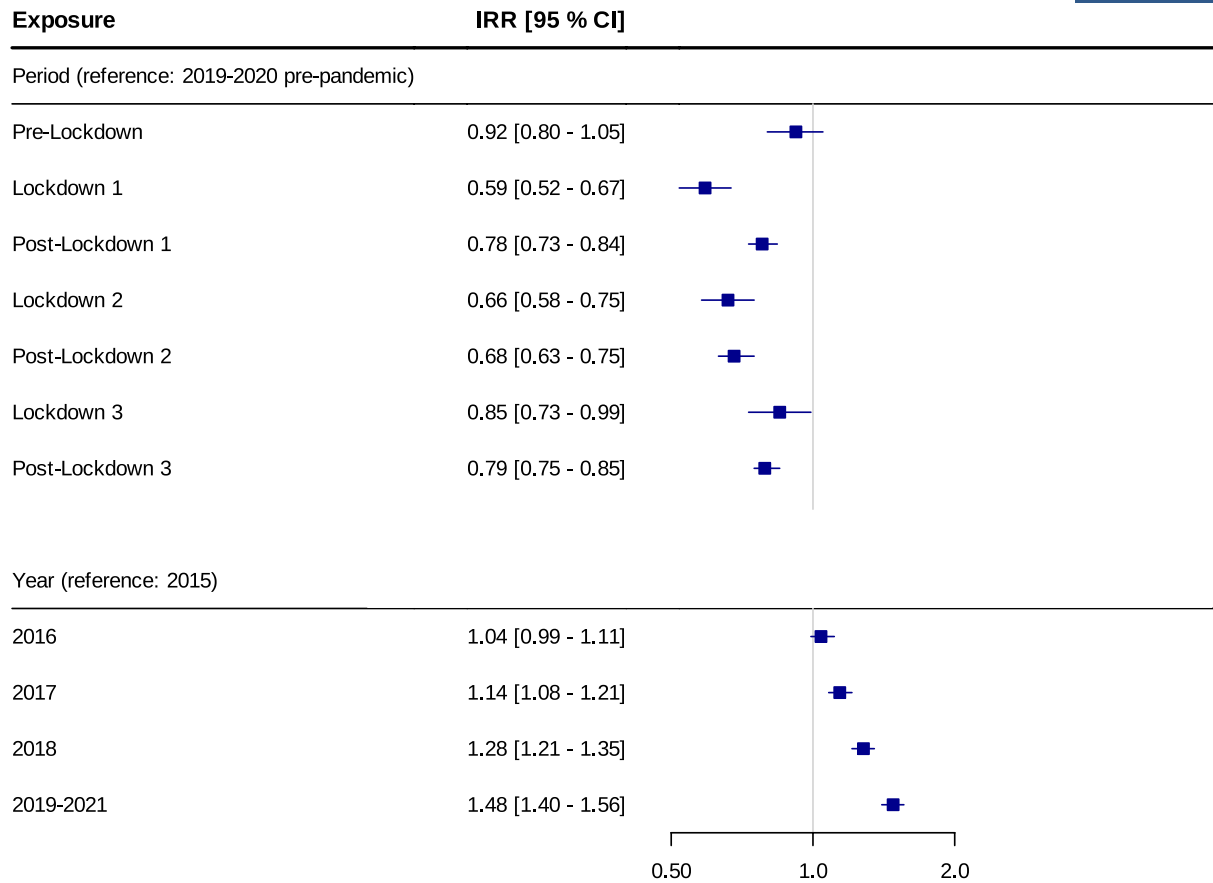| Exposure	IRR [95 % CI]	
Period (reference: 2019-2020 pre-pandemic)		
Pre-Lockdown	0.92 [0.80 - 1.05]	
Lockdown 1	0.59 [0.52 - 0.67]	
Post-Lockdown 1	0.78 [0.73 - 0.84]	
Lockdown 2	0.66 [0.58 - 0.75]	
Post-Lockdown 2	0.68 [0.63 - 0.75]	
Lockdown 3	0.85 [0.73 - 0.99]	
Post-Lockdown 3	0.79 [0.75 - 0.85]	
Year (reference: 2015)		
2016	1.04 [0.99 - 1.11]	
2017	1.14 [1.08 - 1.21]	
2018	1.28 [1.21 - 1.35]	
2019-2021	1.48 [1.40 - 1.56]	

FIGURE 4 Incidence rate ratio (IRR) of emergency department visits according to each risk period and calendar year in the whole population. Self-controlled case series design with conditional logistic regression (stratified on patient) and adjusted on calendar year and calendar month. CI, confidence interval.

(A)

Exposure	IRR [95 % CI]	
Period (reference: 2019-2020 pre-pandemic)		
Pre-Lockdown	1.01 [0.83 - 1.23]	
Lockdown 1	0.64 [0.53 - 0.78]	
Post-Lockdown 1	0.65 [0.58 - 0.72]	
Lockdown 2	0.50 [0.41 - 0.62]	
Post-Lockdown 2	0.56 [0.48 - 0.65]	
Lockdown 3	0.74 [0.57 - 0.96]	
Post-Lockdown 3	0.50 [0.45 - 0.55]	
Year (reference: 2015)		
2016	1.16 [1.03 - 1.31]	
2017	1.45 [1.29 - 1.63]	
2018	2.20 [1.97 - 2.45]	
2019-2021	3.17 [2.87 - 3.52]	

(B)

Exposure	IRR [95 % CI]	
Period (reference: 2019-2020 pre-pandemic)		
Pre-Lockdown	0.85 [0.70 - 1.03]	
Lockdown 1	0.56 [0.47 - 0.67]	
Post-Lockdown 1	0.89 [0.81 - 0.97]	
Lockdown 2	0.79 [0.67 - 0.93]	
Post-Lockdown 2	0.79 [0.71 - 0.89]	
Lockdown 3	0.97 [0.80 - 1.17]	
Post-Lockdown 3	1.07 [0.99 - 1.15]	
Year (reference: 2015)		
2016	1.01 [0.95 - 1.08]	
2017	1.06 [0.99 - 1.13]	
2018	1.03 [0.96 - 1.10]	
2019-2021	1.00 [0.94 - 1.07]	

FIGURE 5 Incidence rate ratio (IRR) of emergency visits according to each risk period and calendar year in high users (A) and other people (B) groups. Self-controlled case series design with conditional logistic regression (stratified on patient) and adjusted on calendar year and calendar month. CI, confidence interval.
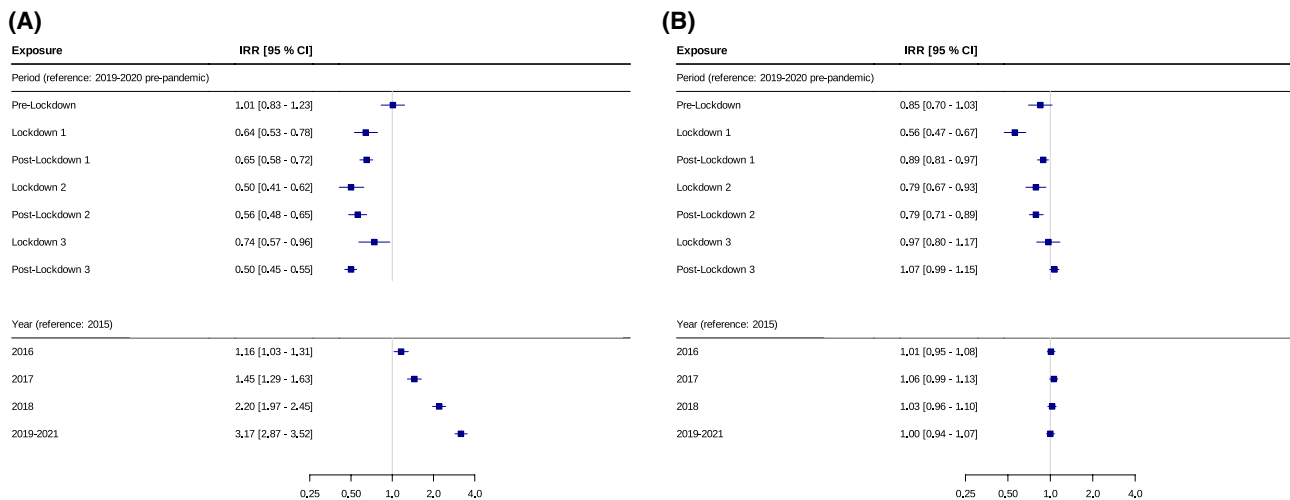
when only transfers before 2020 were considered, 179 people when transfers during the whole study period were considered), those who died during follow-up (67 people) or those without established genotype (92 people), led to similar results (Figure S6). The regression to the mean effect, computed based on data from 2018 to 2019, was estimated at 0.71 visits per year between year 2019 and year 2020 in the high-user group while the observed annual number of visits actually decreased by 5.5 [0–12] visits per year per patient in the high-user group between 2019 and

2020. Considering only persistent high users, that is, people with ≥10 visits per year both in 2018 and in 2019, lead to similar results as in main analysis (Figure S7).

DISCUSSION

Key results

Lockdown and post-lockdown periods were associated with a decrease in the incidence of ED visits and subsequent hospitalizations in adult people with SCD. The decrease waned progressively with time and the successive lockdowns. This reduction was observed across ED visits regardless of the outcome (discharge, hospitalization, ICU transfer). It was primarily driven by a small subgroup of people with a previously high ED utilization, in whom ED visits dramatically and persistently decreased after the onset of the pandemic.

Limitations

Various factors may contribute to the frequency and severity of ED visits in SCD people.[12,13] They include factors that can be assumed to be stable over the study period, such as sex, genotype, socio-economic level or distance from the reference centre, as well as factors that can vary during the study period, such as treatment and treatment adherence, and psychosocial factors.[8,12,13] By design, the self-controlled case series analysis controls for individual characteristics that are stable over time whether they are measured or not[21,22] and it can also adjust for recorded time-dependent factors. However, changes in time-dependent factors that were not recorded in our study, such as treatment adherence, may have influenced the frequency and severity of ED visits.[26]

The reduction in the frequency of visits during the first lockdown was not explained by a compensatory increase in daycare hospitalization or direct hospitalization, but it could be explained by people seeking care in neighbouring hospitals not in the GPUH network. Indeed, these hypothetical ED visits outside the GPUH are not recorded in the GPUH Clinical Data Warehouse. However, people followed in a reference centre are typically referred there, and no change in referral policy occurred during the pandemic. Moreover, transfers from other hospitals to the GPUH, involving 179 (11.6%) people, did not increase during the pandemic period, and removing people with a history of transfer did not change our conclusions. Finally, change in referral practice was not expected outside the first lockdown period, since the health system was not overwhelmed anymore.

As the GPUH Data Warehouse only record visits in the GPUH, people having all their visits in hospitals out of the GPUH are not included in the study. Yet, in France, sickle cell disease, considered as a rare disease, is essentially cared in reference centres, which are all members of the GPUH for the Ile de France Region. Unlike the main outcome, some of the secondary outcomes, like mechanical ventilation or red blood cell transfusion, are exposed to miscoding. Yet, misclassification of these outcomes is expected to be rare due to financial incentives depending on the appropriate coding of this event. Polymerase chain reaction assay results were not available to assess COVID-19 positivity, but ICD-10 code U071 showed a sensitivity as high as 94.19% [95% CI 93.49%–94.82%] and a positive predictive value of 92.9% (92.4%–93.4%) to identify inpatients stays with a COVID-19 positive test.[27]

Interpretation

Many ED visits due to COVID-19 could have been expected in SCD people, considered a high-risk population.[28,29] However, the majority of ED visits by SCD people in 2020 and 2021 were not due to COVID-19, as evidenced by <5% of hospitalizations with symptomatic COVID-19 in our study, and their decrease followed the global pattern of ED visits unrelated to COVID-19 reported in the French population.[4]

The reduction in ED visits was large in all SCD people during the first lockdown. A similar reduction in ED visits has been reported by previous studies in SCD children.[30–32] Several factors may have contributed to these findings. A first hypothesis is that lockdowns and other preventive measures reduced exposure to other pathogens, such as influenza and streptococcus pneumoniae[30,33,34] which are known risk factors for SCD acute complications.[13,30,35,36] A second possibility is that staying at home reduced weather and physical activity-related triggers of acute painful episodes.[26,37–39] Home-bound and sedentary behaviours may have persisted, to a lesser extent, after lockdowns.[40,41] Third, the fear of complications may have boosted adherence to SCD treatment and preventive measures, as reported in other diseases.[42] Fourth, people may have avoided the ED for milder acute painful episodes due to fear of catching COVID-19 there.[26] However, severe acute episodes (resulting in hospitalization, ICU transfer or transfusion) should not have decreased as much in this case.

High users had a larger reduction in ED visits than other SCD people, which pertained during all pandemic periods. A sharp decrease in the number of high-ED users during the pandemic has been previously reported among young adults with chronic illness.[43] Social and psychological risk factors of ED visits are frequent in high users.[12,44] They also receive high doses of short-acting strong opioids almost every time they visit the ED. Some of their acute painful episodes may therefore be linked to central nervous system pain sensitization, rather than SCD-related vaso-occlusion.[45–47] The effect of the pandemic and related lockdowns on the incidence of ED visits for SCD acute painful episodes could differ according to their main mechanism of pain.

Generalizability and perspective

This study focuses on French adult SCD people. Further quantitative and qualitative studies in different settings are needed to confirm and clarify how lockdowns and their possible consequences on behaviour reduced the number of ED visits across settings. If the main impact on high-users is confirmed, this would suggest that they can change their healthcare-seeking behaviour under specific conditions. Interventions, such as cognitive-behavioural therapy or patient education programmes, could reshape how these people perceive and use the ED as well or even better than the pandemic did, and may be used broadly in clinical practice and promoted by heath policy.

AUTHOR CONTRIBUTIONS

JSR had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All the authors participated in the design of the study, edited and reviewed the manuscript. JSR, PB, AS, CCA, LA, SLJ, JBA and OS participated in the provision of people data. JSR and AC performed data extraction and statistical analysis. JSR, PYB and OS interpreted the data and wrote the original draft. PYB and OS supervised the study. All the authors had full access to all the data in the study and accept responsibility for the decision to submit for publication.

CONFLICT OF INTEREST STATEMENT

PB reports being a member of steering committee for NOVARTIS, ROCHE, ADDMEDICA and PFIZER; receiving research support from ADDMEDICA, foundation Fabre, NOVARTIS, Bluebird and EMMAUS; receiving personal fees from and serving as a consultant for ADDMEDICA, NOVARTIS, ROCHE, GBT, Bluebird, EMMAUS, HEMANEXT and AGIOS; and lecture fees for NOVARTIS, ADDMEDICA and JAZZPHARMA all outside the submitted work. The other authors report no biomedical financial interests or potential conflicts of interest.

DATA AVAILABILITY STATEMENT

Raw data cannot be transmitted to persons outside the staff of the Greater Paris University Hospitals (GPUH) without specific authorization from the GPUH Clinical Data Warehouse Scientific and Ethics Committee. Contact the corresponding author (jsrech@hopital-saint-joseph.fr) for request.

ETHICS STATEMENT

The Greater Paris University Hospitals Clinical Data Warehouse Scientific and Ethics Committee (IRB00011591) granted access to the data for this study and no linkage was made with other databases.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Rech JS, Cohen A, Bartolucci P, Santin A, Chantalat Auger C, Affo L, et al. Shift in emergency department utilization by frequent attendees with sickle cell disease during the COVID-19 pandemic: A multicentre cohort study. Br J Haematol. 2024;205(2):463–472. https://doi.org/10.1111/bjh.19556