RESEARCH ARTICLE

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Impact of COVID-19 on incidence, clinical presentation, and prognosis of acute chest syndrome in patients with sickle cell disease

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Abstract

Acute chest syndrome (ACS) is a frequent complication of sickle cell disease (SCD). Because coronavirus disease 2019 (COVID-19) increases mortality and morbidity in many diseases, we retrospectively analyzed the impact of SARS-CoV-2 infection on the incidence, the clinical presentation, and the prognosis of ACS in patients with SCD by comparing ACS episode before and during COVID-19 pandemic.

Ninety-nine episodes of ACS were registered over 24 months before pandemic versus 81 episodes over 24 months during the pandemic period. The number of ACS episodes varies among children regarding the two period of time: 26 episodes (26%) for the pre-pandemic period versus 11 episodes (13%) for the pandemic period ($p = 0.03$). Comparisons between adults and children showed a higher incidence of initial VOC (45% vs. 24%; $p = 0.04$) in adults, and a higher incidence of initial pneumonia (35% vs. 15%; $p = 0.01$) and documented infection (35% vs. 7%; $p < 0.001$) in children. One patient died during the pandemic period but without any relationship with ACS or COVID-19. During this pandemic period, 13 episodes of ACS (16%) were found related to coronavirus infection. These ACS episodes did not show any significant differences in terms of outcome when compared to the other ACS episodes observed during this period.

Overall, coronavirus infection did not demonstrate a negative impact on incidence, clinical presentation, and outcome of ACS in patients with SCD. Early management, chronic treatment with HU, and exchange transfusions could likely explain the low morbidity and mortality rates.

KEYWORDS

acute chest syndrome, COVID-19 infection, prognosis, severe acute respiratory syndrome-coronavirus 2, sickle cell disease, vaso-occlusive crisis

1 | INTRODUCTION

In contrast to low-income countries, the prognosis of sickle cell disease (SCD) has significantly improved over the last decades in developed countries because of newborn screening, prophylaxis with antibiotics, preventive therapy for strokes, conjugated vaccines, hydroxyurea, evidence-based supportive care, and allogenic hematopoietic stem cell transplantation [1]. However the disease still follows an unpredictable course. Acute chest syndrome (ACS) is one of the most frequent causes of hospitalization in SCD. ACS is associated with an increased risk of respiratory failure, and the potential for developing chronic lung disease, especially in children [2–5]. SCD patients may present with ACS or may develop ACS during the course of a vaso-occlusive crisis (VOC). This complication is associated with a higher risk of mortality and morbidity.

Several concerns were raised by the potential impact of the pandemic spread by the severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) in SCD patients [6–9]. Because patients with SCD can experience severe complications all of which being identified as risk factors for worse coronavirus disease 2019 (COVID-19) outcome, we retrospectively analyzed the impact of SARS-CoV-2 infection on the incidence, the clinical presentation, and the prognosis of ACS in patients with sickle cell disease seen at our Institution from March 2020 to February 2022.

2 | PATIENTS AND METHODS

2.1 | Patient population

This retrospective study involved SCD patients followed at the Constitutive Reference Center of Lyon University Hospital for major SCDs. All involved patients received an information notice regarding the study and gave a nonopposition approval to anonymous data collection and analyses. The study was approved by an institutional review board committee.

All episodes of ACS as defined below were recorded as they occurred. The ACS data analyzed were collected from March 2018 through February 2022. During this period, 127 patients (28 pediatric patients and 99 adult patients) were diagnosed with ACS. For the purpose of this study, the diagnosis of ACS was made each time a patient with SCD developed a new infiltrate on chest X-ray and/or on lung CT scan, combined with one or more of the following symptoms: fever (T ≥ 38.5°C), cough, sputum production, respiratory distress, chest pain, or hypoxia. Only hospitalized patients were included in the study.

ACS episodes were split into two equal period of time: the first one from March 2018 to February 2020 (before COVID-19 pandemic spread) and the second from March 2020 to February 2022 (during COVID-19 pandemic spread). March 2020 was chosen as cut-off as the date coronavirus infection was systematically performed by polymerase chain reaction (PCR) analysis. In this second period, ACS was considered related to coronavirus infection if PCR analysis was positive at most 14 days before the ACS episode.

Hemoglobin (Hb) genotype was determined in all patients at a central laboratory. Patients were diagnosed as having homozygous SCD (SS) if their Hb electrophoresis showed only Hbs S, A_2 and F, and if Hb A_2 was no greater than 3.5%. The diagnosis of sickle cell-β^0 thalassemia was made when Hb A_2 was greater than 3.5% and with a mean corpuscular volume (MCV) < 80 fL. The diagnosis of Hb SC disease was defined by the presence of an SC Hb electrophoretic pattern.

2.2 | Data collection methods

Data were retrospectively obtained directly from inpatient medical records and from the hospital-based computer system. Baseline characteristics including type of SCD, age, chronic medications, and prior history of ACS were collected for each patient. For each admission, the following were collected: period of ACS diagnosis, clinical features, documented infection, chest X-ray and/or CT scan findings, need of oxygen, opioid administration, nitrous oxide administration, admission in intensive care unit (ICU), breath support requirement, exchange transfusions, thromboembolic event, and duration of hospitalization. Pneumonia was defined by fever ≥ 38.5°C and an infiltrate on chest X-ray or CT scan. Furthermore, supplementary information regarding SARS-CoV-2 was systematically collected from March 2020: history of coronavirus disease, coronavirus vaccination, and the result of COVID-19 PCR test.

2.3 | Statistical analyses

The primary goal of the statistical analysis was the identification of variables with which ACS incidence varies. Descriptive statistics were used to characterize patients and their disease. Normal distribution and heteroskedasticity of continuous variables were assessed by Shapiro-Wilk and Levene's tests, respectively. Continuous variables were compared by ANOVA, Welch's ANOVA, or Kruskal-Wallis tests, according to data distribution. Differences among categorical variables were compared by the χ^2 test or Ficher's exact test accordingly. Odds ratios (OR) and 95% confidence intervals (CI) were calculated where appropriate. Multivariate analyses using logistic regression modeling was performed to assess the relationship between ICU admission and covariates postulated a priori to be important in the development of ACS. The same analyses were performed to assess the relationship between exchange transfusions as well as noninvasive respiratory support requirement and the same covariates. All analyses were two-sided, with a p value ≤ 0.05 considered statistically significant. Computations were performed using the online EasyMedStat 2022 statistical program.

3 | RESULTS

3.1 | Incidence of ACS

Among 665 SCD patients followed in our Constitutive Reference Center during the study period (March 2018 to February 2022), a total of 180 episodes of ACS occurred in 127 SCD patients: 37 episodes of ACS in 28 children (age ≤ 16 years) and 143 episodes of ACS in 99 adult (age > 16 years) patients. The mean number of episodes of ACS per patient was 1.4. One hundred and seven patients (84%) had SS genotype, 13 (10%) had SC genotype, and 7 (6%) had Sβ^{thal}. Fifty nine percent were treated by hydroxyurea (HU) and 6.2% have been previously treated according to a chronic exchange transfusion program. A prior history of ACS was present in 66.9% of cases.

3.2 | Initial characteristics of ACS episodes

One hundred and six hospitalizations (59%) were motivated by a direct ACS episode, while in 74 cases (41%) ACS was preceded by uncomplicated VOC. Nineteen percent of ACS episodes presented with a concomitant initial pneumonia. An infectious documentation was found in 15% of ACS episodes. Table 1 summarizes the initial characteristics of ACS episodes. Comparison of ACS episodes between children and adult patients showed a higher incidence of initial VOC (45% vs. 24%; $p = 0.04$) in adults, and a higher incidence of initial pneumonia (35% vs. 15%; $p = 0.01$), fever ≥ 38.5°C (41% vs. 11%; $p < 0.001$), and documented infection (35% vs. 7%; $p < 0.001$) in children (Table 2).

3.3 | Comparison of ACS episodes between pre-pandemic and pandemic periods

The incidence rate of ACS episodes in the SCD population followed in our center did not significantly vary between pre-pandemic (15%) and pandemic periods (12%). However the number of ACS episodes varies among children regarding the two period of time: 26 episodes (26%) for the prepandemic period versus 11 episodes (13%) for the pandemic period (OR = 2.27; 95% CI: 1.04–4.94; $p = 0.03$). Seventy-eight percent of patients presented with 2 or 3 affected lung lobes on X-ray and/or CT scan during the first period versus 57% during the second period ($p = 0.01$). There were no other significant differences among the two periods of time in terms of presenting clinical features and complications (Table 3). Thirty-eight percent of patients required exchange transfusions during the prepandemic period versus 42% during the pandemic period. One patient died during the pandemic period but without any relationship with ACS or COVID-19.

TABLE 1 Characteristics of ACS episodes.

ACS characteristics	Results (180 ACS episodes)
Presentation at admission	
Direct ACS	106/180 (59%)[a]
Uncomplicated VOC	74/180 (41%)
Pneumoniae	35/180 (19%)
Initial laboratory values	
Hemoglobin (g/L)	87.6 (85.4–89.8)[b]
WBC (x10^9/L)	15.2 (14.2–16.3)
PMN (x10^9/L)	12.2 (7.6–16.9)
Platelets (x10^9/L)	371 (346–395)
C-reactive protein (mg/L)	73.3 (61.1–85.6)
LDH (U/L)	588 (538–638)
Affected lung lobes on chest X-ray or CT scan	
1	58/180 (33%)
2	101/180 (57%)
3	17/180 (10%)
NA	4/180
Infectious documentation[c]	27/180 (15%)
Streptococcus pneumonia	2
Legionella sp.	1
Influenza A or B	4
Mycoplasma pneumonia	3
SARS-CoV-2	13
Other viruses	4
Pain management during hospitalization	
Nitrous oxide	79/180 (44%)
Opioids	138/180 (77%)
Benzodiazepines	5/180 (3%)

Abbreviations: ACS, acute chest syndrome; LDH, lactodehydrogenase; PMN, polymorphonuclear cells; VOC, vaso-occlusive crisis; WBC, white blood cells.

[a]Number of episodes (%);.
[b]Mean [95% confidence interval];.
[c]No patients had more than one infectious agent identified.

3.4 | ACS episodes concomitant with coronavirus infection

Thirteen episodes of ACS between March 2020 and February 2022 were found related to coronavirus infection. They represented 16%

TABLE 2 Comparison of ACS episodes between children and adult patients.

ACS characteristics	Adults (>16 years old) 143 ACS episodes	Children (≤16 years old) 37 ACS episodes	p-Value
Direct ACS at admission	79 (55%)	27 (73%)	NS
Uncomplicated VOC	65 (45%)	9 (24%)	0.04
Pneumoniae at admission	22 (15%)	13 (35%)	0.01
Fever ≥ 38.5°C	16 (11%)	15 (41%)	<0.001
Documented infection (excluding coronavirus)	10 (7%)	13 (35%)	<0.001

Abbreviations: ACS, acute chest syndrome; NS, not significant; VOC, vaso-occlusive crisis.

of ACS episodes registered during this pandemic period and involved six males and seven females. Mean age was 30 years. Two patients were ≤16 years old and 11 were >16 years old. Two ACS episodes concerned children and 11 concerned adults. Two patients (15%) had complete COVID vaccination. Seven adults (54%) developed pulmonary infection. Seven patients (54%) were admitted in intensive care unit. Comparison of ACS episodes related to coronavirus infection with the other ACS episodes observed during this period did not show any significant differences in terms of symptoms at admission and complications (Table 4).

3.5 | Multivariate analyses

Potential predictors were examined in multivariable models. SS genotype (OR = 2.55; 95% CI: 1.05 – 6.21; p = 0.03), and documented infection (other than coronavirus infection) (OR = 3.69; 95% CI: 1.18–11.52; p = 0.02) were associated with a higher rate of admission in intensive care unit (ICU). Infection (other than coronavirus infection) was also associated with a higher rate of noninvasive pulmonary support requirement (OR = 3.94; 95% CI: 1.29–11.99; p = 0.01), while use of opioids was associated with a lower rate of noninvasive breast support requirement (OR = 0.17; 95% CI: 0.07–0.39; p < 0.001). The prescription of exchange transfusions was associated with the presence of more than one lung lobe affected on X-ray (OR = 3.97; 95% CI: 1.84–8.59; p < 0.001), a documented infection (other than coronavirus infection) (OR = 5.3; 95% CI: 1.47–19.11; p = 0.01), the use of opioids (OR = 7.31; 95% CI: 2.29–23.33; p < 0.001), and transcutaneous oxygen saturation < 94% (OR = 4.73; 95% CI: 1.09–20.52; p = 0.03).

4 | DISCUSSION

ACS remains a frequent complication of SCD, especially in patients hospitalized with VOC. Approximately 20% of SCD patients followed in our reference center between March 2020 and February 2022 developed at least one episode of ACS. Most of them were adults with SS genotype and more than half of them were treated with HU or received prophylactic exchange transfusions. Infection is a major cause for ACS. Twenty percent of our patient had pneumonia and one patient in six demonstrated a documented infection. This is less than what was reported in previous cohorts [2, 10], but this could be explained by the absence of systematic bronchoalveolar lavage in our series. We, however, confirmed a higher infection rate in children [11], especially of viral origin.

Chronic organopathies of SCD have been identified as potential risk factors for worse COVID-19 outcomes [12-14]. The hypercoagulable state sickling pathophysiology in hypoxic environments could be at higher risk for severe COVID-19 outcomes. Although not statistically significant, we found more ACS episodes during the prepandemic period than during the pandemic period. The lower incidence of ACS during the pandemic period mainly concerned children, and was likely related to a lower virus transmission in this patient population due to the closure of schools during this period and the national lockdown. Furthermore the availability of Pfizer vaccine by the end of 2020 may have provided some protection and possibly accounted for a lower incidence of transmission. A large Italian study showed recently a significant reduction in emergency room access and hospitalizations for severe SCD complications, such as ACS, compared to the previous year, especially in regions that were the most impacted by the pandemic [15]. In the general population, children are less likely to experience severe COVID-19 outcomes as compared to adults, but few large studies have examined children with SCD [9, 16]. It seems that most children with SCD-related comorbidities and coronavirus infection are more likely to be hospitalized and require escalated care than children without SCD, but they were less likely to experience COVID-19-related severe illness and death than adults with SCD [9].

In our study, COVID-19 infection did not impact on the incidence of ACS and confirmed the absence of negative impact on the morbidity and mortality of this SCD complication. Indeed, prior SCD cohort studies with matched controls for pre-existing conditions or comparing SCD patients with or without COVID-19 did not report any significant differences in terms of mortality rates [17–19]. The overall mortality of SCD patients hospitalized with coronavirus infection was even lower than that in the general population [20]. In a recent large series, SCD patients with confirmed SARS-CoV-2 infection were at higher risk of severe disease than the general population. A prior history of recent ACS was associated with a higher risk of severe disease. However it was reported favorable outcomes as no deaths occurred [21]. In our series, only one death was registered in SCD patients hospitalized for ACS during the pandemic period, and was not due to COVID-19. While viral infections can trigger SCD symptoms, favorable COVID-19 outcomes could be explained by a timely intervention by anemia-specific therapies via a high hospitalization rate, but also protective effects due to certain pathophysiological characteristics of SCD, such as an unexpected activation of the interferon-α signaling pathway [22, 23]. However, a longer duration of hospitalization has been reported in SCD

TABLE 3 Comparison of ACS episodes between the pre-pandemic (March 2018–February 2020) and the pandemic (March 2020–February 2022) periods.

ACS characteristics	Prepandemic period 99 episodes	Pandemic period 81 episodes	p-Value
Age (years)	22.5 ± 11.3[a]	25.3 ± 11.6	NS
ACS in patients ≤ 16 years	26 (26%)[b]	11 (13%)	0.03
Presentation at admission			NS
Direct ACS	57 (58%)	49 (60%)	
Uncomplicated VOC	41 (41%)	32 (40%)	
Duration of hospitalization (days)	9.7 ± 6.3	10.3 ± 7.2	NS
Number of affected lung lobes			0.01
1	40 (41%)	18 (23%)	
2	46 (47%)	55 (69%)	
3	10 (10%)	7 (9%)	
NA	3	1	
Admission in ICU	61 (62%)	43 (53%)	NS
Infection (other than coronavirus infection)	16 (16%)	7 (9%)	NS
Pulmonary management			NS
Invasive pulmonary support	4 (4%)	1	
NI pulmonary support	35 (35%)	19 (23%)	
Oxygen saturation < 94%	7 (7%)	6 (8%)	
Exchange transfusions	38 (38%)	34 (42%)	NS
Thromboembolic events	5 (5%)	7 (9%)	NS

Abbreviations: ACS, acute chest syndrome; ICU, intensive care unit; neg, negative; NA, not available; NI, noninvasive; NS, not significant; pos, positive; VOC, vaso-occlusive crisis.

[a]Mean ± standard deviation.
[b]Number of episodes (percentage).

patients with coronavirus infection [24], and the long-term effects of SARS-CoV-2 among patients with SCD remain unknown. The beneficial effects of HU treatment on SCD-related morbidity and mortality are well known, and it was found that all deaths occurred in patients not on HU or other SCD-modifying therapies [8] and that HU has no effect on hospitalization or COVID-19 disease severity [9]. The use of exchange transfusions could have participated to the favorable patient outcome with advantages of this procedure compared to simple transfusions, such as a large volume transfused on a short time, a reduction of inflammatory mediators, and the nonexpansion of blood volume [25]. Although less frequent than in previous publications that question whether a transfusion is needed in all cases of ACS [26, 27], exchange transfusions were required in 38% and 42% for prepandemic and pandemic periods, respectively. This could indicate that improved outcome of ACS was not simply due to more transfusions, but possibly to an early and coordinated intervention and careful attention to all aspects of care. We can, however, not exclude potential erroneous ACS diagnosis, which is a pitfall of all retrospective analysis.

Because of the overall favorable outcome of ACS in our series, we attempted to identify risk factors for severity. Documented infection (excluding coronavirus) was associated with a higher risk for ICU admission, exchange transfusions, and noninvasive breath support requirement. Patients with an SS genotype were also at higher risk of ICU admission. This was opposed to a prior study that demonstrated a higher mortality in patients displaying a SC genotype [20]. Receiving opioids appeared associated with exchange transfusion requirement, which could be explained by a following hypoventilation that can worsen ACS [28].

Overall, coronavirus infection did not demonstrate a negative impact on ACS in patients with SCD. Although our study has several limitations related to the small number of ACS episodes and to its retrospective nature, incidence, clinical presentation, and outcome did not vary significantly compared to the pre-pandemic period. However, the long-term effects of SARS-CoV-2 infection are unknown and may affect SCD patients differently as compared to the general population. Long-term follow-up studies with longitudinal assessment of post-COVID-19 symptoms are therefore warranted. Early management with hospitalization in ICU and SCD-directed therapies, such as HU and exchange transfusions, appear to be associated with favorable outcomes and could likely explain the low morbidity and mortality rate in our series. Furthermore, comparing our study population to the US sickle cell patients, there are fewer diabetes and low obesity frequency, explaining a lower rate of death than that described in the US national registry of SCD [17, 18].

TABLE 4 Comparison of ACS episodes with positive or negative testing for Coronavirus.

ACS characteristics	PCR COVID-neg 67 episodes	PCR COVID-pos 13 episodes	*p*-Value
Age (years)	24.4 ± 10.9[a]	30.3 ± 14.7	NS
Presentation at admission			NS
Direct ACS	38 (57%)[b]	10 (77%)	
Uncomplicated VOC	29 (43%)	3 (23%)	
Duration of hospitalization (days)	10.5 ± 7.7	10 ± 4.8	NS
Number of affected lung lobes			NS
1	13 (20%)	5 (38%)	
2	47 (71%)	7 (54%)	
3	6 (9%)	1 (8%)	
NA	1	0	
Admission in ICU	36 (54%)	7 (54%)	NS
Pulmonary management			NS
Invasive pulmonary support	1	0	
NI pulmonary support	16 (24%)	3 (23%)	
Oxygen saturation < 94%	5 (8%)	1 (8%)	
Exchange transfusions	29 (43%)	5 (38%)	NS
Thromboembolic events	4 (6%)	3 (23%)	NS

Abbreviations: ACS, acute chest syndrome; ICU, intensive care unit; neg, negative; NA, not available; NI, noninvasive; NS, not significant; pos, positive; VOC, vaso-occlusive crisis.

[a]Mean ± standard deviation;.

[b]Number of episodes (percentage).

AUTHOR CONTRIBUTIONS

GD treated patients, performed statistical analyses, interpreted the data, and drafted the manuscript. EV, MM, and SP treated patients. GC treated patients, interpreted the data, and wrote the manuscript; and AH designed the study, treated patients, and reviewed the manuscript. All authors gave final approval of the version to be submitted.

CONFLICT OF INTEREST STATEMENT

The authors do not have any competing financial interest in relation with the work described.

FUNDING INFORMATION

The authors received no specific funding for this work.

ETHICS STATEMENT

The study was conducted in accordance with the declaration of Helsinki. All patients received an information notice regarding the study and gave a nonopposition approval to anonymous data collection and analyses.

CLINICAL TRIAL REGISTRATION

The study was approved by an institutional review board committee (Hospices Civils de Lyon, Edouard-Herriot Hospital, Lyon, France).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available upon request from the corresponding author.

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