Risk and protective factors for severe COVID-19 infection in a cohort of patients with sickle cell disease

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ABSTRACT

Continued investigation of comorbid conditions that increase the mortality rate of COVID-19 is necessary to provide the best care for those affected. This continued push to find answers is even more important for populations with COVID-19 comorbidities that are historically under-researched. We performed a retrospective analysis of 30 patients with sickle cell disease (SCD) who tested positive for the COVID-19 virus. An analysis of each patient's history of SCD complications, hydroxyurea usage, comorbidities, and several other factors was performed to identify the trends that will allow the practitioners to better predict the outcomes of patients with SCD before and during hospitalization for COVID-19. Through these analyses, we found that patients receiving hydroxyurea before COVID-19 infection and patients with SCD-type HbSC had significantly milder COVID-19 disease courses than those not receiving hydroxyurea or with SCD-type HbSS. A history of acute chest syndrome (ACS), a complication seen in patients with SCD, appeared to be associated with a more severe COVID-19 disease course. By creating systems to better interpret what makes a patient with SCD at high risk for a poor prognosis, practitioners are better equipped to make data-supported recommendations for prevention, risk, and treatment. These recommendations should include beginning or maintaining hydroxyurea usage in all qualifying patients with SCD, advising patients with a history of ACS to take extra precautions to prevent initial COVID-19 infection, and initiating close monitoring in the hospital for patients with HbSS and a history of ACS.

Significance of this study

What is already known about this subject?

⇒ Sickle cell disease (SCD) has been identified as a comorbid condition that may increase severity of COVID-19 infection.
⇒ SCD is historically understudied.

What are the new findings?

⇒ Patients with SCD receiving hydroxyurea had milder COVID-19 infection.
⇒ Patients with a history of acute chest syndrome (ACS) had more severe COVID-19 infection.
⇒ Patients with SCD-type HbSC had milder COVID-19 disease courses than patients with SCD-type HbSS.

How might these results change the focus of research or clinical practice?

⇒ These findings suggest that beginning or maintaining hydroxyurea usage in all qualifying patients with SCD, advising patients with a history of ACS to take extra precautions to prevent initial COVID-19 infection, and initiating close monitoring in the hospital for patients with HbSS and a history of ACS may limit poor prognosis of patients with SCD and COVID-19.

INTRODUCTION

As the COVID-19 pandemic continues to infect millions of people, numerous investigations have been launched that aim to the key predictors of COVID-19 infection outcomes. Based on these investigations, several comorbid conditions have been identified, one of which is the category of blood disorders into which sickle cell anemia or sickle cell disease (SCD) falls.[1] Just over 1 year since the COVID-19 virus first presented in China, multiple studies have been conducted on the risks, disease processes, and treatments for patients with other COVID-19 comorbidities such as diabetes, cardiovascular disease, chronic obstructive pulmonary diseases, and asthma. However, the information available on the outcomes and options for patients with SCD infected with COVID-19 is limited to a handful of articles, many of which are case series consisting of 5 patients or fewer, which is in line with the historical trend of understudying SCD that only began to improve in 2015.[2–3] For this study, we gathered information on the history, disease progression, treatments, and outcomes of 30 patients with SCD infected with COVID-19 from February 2020 to February 2021 in the Greater Houston area. After carefully examining the presentation and hospital course of each patient, we identified which historical factors and long-term medications, such as a history of acute chest syndrome (ACS), history of vaso-occlusive crises (VOC) requiring hospitalization, and hydroxyurea use, that could be associated with the varied

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outcomes we saw in our patients. The goal of our study was to provide much-needed information about the interaction between COVID-19 infection and SCD, to decrease the mortality and morbidity of over 100,000 patients in the USA and millions of patients worldwide with SCD.[6]

MATERIALS AND METHODS

This was a retrospective case study of data from 30 patients with COVID-19 and SCD who were evaluated in the UTHealth System between February 2020 and February 2021. The diagnosis of COVID-19 was made based on positive SARS-CoV-2 reverse transcription PCR (RT-PCR) tests from nasopharyngeal swabs. None of the patients from the cohort were vaccinated against COVID-19. SCD and comorbidities were determined based on patient chart documentation at the time of admission or prior visits at the UT Physicians Comprehensive Sickle Cell Center. Data were reviewed by all authors.

The aim of this study was to explore different factors that may predict the severity of COVID-19 outcomes in patients with SCD. To analyze these factors, we retrospectively separated our 30 patients with SCD into 2 populations: those with severe COVID-19 infections and those with mild/moderate COVID-19 infections. The severe infection group was defined in this report as symptoms warranting hospitalization, as determined by practitioners based on hypoxia, pain, or patient's overall presentation. The mild/moderate COVID-19 infection group consisted of those who were either asymptomatic or those who experienced symptoms that did not warrant hospitalization. We compared measures such as history of ACS, VOC, avascular necrosis, and SCD-related medications between these 2 groups.

Inclusion criteria included all patients with a previous diagnosis of SCD and a positive SARS-CoV-2 RT-PCR test.

RESULTS

Between February 2020 and February 2021, thirty patients with SCD and COVID-19 were evaluated at the UTHealth System. The median age of our study group was 31 years (range: 8–70 years); 15 (50%) were male and 15 (50%) were female. Among the 30 cases, 22 (73%) patients had SCD-type HbSS, 7 (23%) patients had HbSC, and 1 (3%) patient had HbSB0 (table 1).

The most common presenting symptom was cough (9 patients, 29%), followed by congestion (8 patients, 26%), shortness of breath (7 patients, 23%), fever (3 patients, 10%), and loss of taste or smell (3 patients, 10%). A total of 6 (19%) patients reported no symptoms at all (table 2). Comorbidities were present in 26 patients (87%), including pulmonary hypertension in 19 patients (61%), proteinuria in 6 patients (20%), and obesity (body mass index >30) in 3 patients (10%) (table 1).

Of this cohort, 20 patients (67%) had mild COVID-19 disease and did not require hospitalization. Only 3 patients (14%) with mild disease had a history of ACS, whereas of the 10 patients with severe disease, 5 (50%) had a history of ACS. History of VOC and avascular necrosis between the 2 groups was similar (table 1). The majority of patients in both mild and severe groups had at least 1 comorbidity

Table 1 Preinfection characteristics

	All patients			Mild group			Severe group		
Characteristic	n	Results	%	n	Results	%	n	Results	%
Demographic									
Age (y, median)	30	31		20	30.5		10	31	
Gender	30			20			10		
Male		15	50		9	45		6	60
Female		15	50		11	55		4	40
Sickle cell disease genotype	30			20			10		
HbSS		22	73		15	75		7	70
HbSC		7	23		4	20		3	30
HbS-beta zero thalassemia		1	3		1	5		0	0
Medical history									
Acute chest syndrome	30	8	27	20	3	15	10	5	50
Vaso-occlusive crisis	30	11	37	20	8	40	10	3	30
Avascular necrosis	30	9	30	20	6	30	10	3	30
Comorbidities									
Stroke	30	2	7	20	1	5	10	1	10
Pulmonary hypertension	30	19	63	20	13	65	10	6	60
Proteinuria	30	6	20	20	5	25	10	1	10
Pneumonia	30	7	23	20	5	25	10	2	20
CKD	30	1	3	20	1	5	10	0	0
BMI>30	30	3	10	20	3	15	10	0	0
Congestive heart failure	30	0	0	20	0	0	10	0	0
SCD medications									
Hydroxyurea	30	23	74	20	17	85	10	6	60
L-glutamine	30	1	3	20	0	0	10	1	10

BMI, body mass index; CKD, chronic kidney disease; SCD, sickle cell disease.

Table 2 Presenting symptoms at time of COVID-19 testing

	All patients			Mild group			Severe group		
Presenting symptoms	n	Results	%	n	Results	%	n	Results	%
Fever (>38°C)	30	3	10	20	1	5	10	2	20
Cough	30	9	29	20	8	40	10	1	10
Congestion	30	8	26	20	8	40	10	0	0
Shortness of breath	30	7	23	20	2	10	10	5	50
Loss of taste	30	3	10	20	3	15	10	0	0
Loss of smell	30	3	10	20	3	15	10	0	0
No symptoms	30	6	19	20	5	25	10	1	10

(85% and 90%, respectively) prior to presentation with COVID-19.

When comparing patients with mild disease versus patients with severe disease, more patients in the mild group (17 of 20, 85%) were taking hydroxyurea for SCD management. Of the 10 patients with severe disease, only 6 (60%) were taking hydroxyurea, and 1 (10%) was taking L-glutamine. The patients on hydroxyurea in the mild group had higher baseline hemoglobin and hemoglobin F prior to COVID-19 infection than patients on hydroxyurea in the severe group (9.3% and 13.9% vs 8.6% and 10.9%) (table 3).

Among the 10 patients with severe disease, 1 required admission into the intensive care unit (ICU). Nine patients tested positive for COVID-19 at time of hospital admission, and 1 patient tested positive 11 days prior to admission. None of the patients required intubation. None of the hospitalized patients experienced a red cell aplastic crisis. Of the 10 patients who required hospitalization, the mean reticulocyte count percentage was 7.7% (range 3.9%–16.8%). There were no patient deaths related to the diagnosis of COVID-19. Patients spent an average of 6 days in the hospital. Patients with HbSS had a longer average hospital stay than those with HbSC (9.14 days vs 2.67 days). Of the 10 patients with severe disease, 5 (50%) received packed red blood cell (RBC) transfusions, and 2 (20%) received dexamethasone. Only 1 patient, the one that required ICU admission, received remdesivir. None of the hospitalized patients received monoclonal antibodies, as this product was not approved by the Food and Drug Administration or readily available at time of data collection. None of the hospitalized patients received red cell exchange therapy. The mainstay of treatment for hospitalized patients was intravenous fluids, pain control, and packed RBC transfusion.

DISCUSSION

The COVID-19 pandemic has greatly affected the global population, and understanding the role that the COVID-19 virus plays in patients with pre-existing conditions is imperative. In this retrospective case study of 30 patients, we describe the clinical factors affecting the course and outcomes of patients with SCD infected with COVID-19. In this cohort, 20 (67%) patients did not require hospitalization and had mild disease, and 10 (32%) patients required hospitalization, categorized as severe disease. Only 1 patient required ICU admission, no patients required intubation, and no patients died.

A recent cohort study of 178 patients with SCD with COVID-19 reported that 69% of patients required hospitalization, 11% required ICU admission, and 7% died.[7] Despite similarities in mean patient age (<40 years), our cohort showed a lower rate of hospitalization, ICU admission, and mortality.[7] We believe that many different factors, such as treatment with long-term SCD-specific therapy, history of ACS, and SCD genotype, may be associated with the varied outcomes seen in our cohort. We believe that our results may also be affected by the fact that our patient population receives specialized care at a comprehensive sickle cell center.

Compared with the severe group (those requiring hospitalization), more patients in the mild symptom group (those not requiring hospitalization) were receiving disease-modifying therapy with hydroxyurea (60% vs 85%, respectively). Hydroxyurea has been shown in numerous clinical trials to decrease the mortality and morbidity of patients with SCD.[8]

Hydroxyurea's primary mechanism of action is the reversible inhibition of ribonucleotide reductase, an enzyme necessary for the synthesis and repair of DNA.[9] The cytotoxic effects of hydroxyurea reduce hemolysis, platelets, leucocytes, and mediators of inflammation.[9] Hydroxyurea decreases the rate of painful episodes, ACS episodes, and blood transfusions by 50% in adults with SCD.[9] The protective effects of hydroxyurea may contribute to milder COVID-19 outcomes and should be considered in future studies.

Furthermore, a history of ACS was more common in patients with severe disease. Although previous studies have demonstrated that ACS on presentation with COVID-19 was significantly more common in hospitalized patients,[6] our findings suggest that a history of ACS may be a factor contributing to COVID-19 disease severity as well. Repeated events of ACS may be linked to the development of chronic lung disease, and adults with higher ACS rates

Table 3 Baseline hemoglobin and hemoglobin F prior to COVID-19 infection

	All patients			Mild group			Severe group		
	n	Hemoglobin	Hemoglobin F (%)	n	Hemoglobin	Hemoglobin F (%)	n	Hemoglobin	Hemoglobin F (%)
Hydroxyurea use									
Yes	23	9.1	13.1	17	9.3	13.9	6	8.6	10.9
No	7	10.4	2.2	3	10.8	2.7	4	10.1	2.4

have a higher rate of mortality than those with low ACS rates.[10] This suggests that patients with a history of ACS may be more likely to experience severe disease due to COVID-19 infection and should be evaluated accordingly.

Among patients with severe disease, the average length of hospital stay was 7.2 days, which is similar to the existing literature on SCD cohorts.[6 11] Patients with SCD-type HbSS had a longer average length of hospital stay than patients with type HbSC (9.14 days vs 2.67 days). Furthermore, the one patient in our study who required ICU admission had the HbSS genotype. Although the molecular basis of HbSC is similar to that of HbSS, HbSC is generally thought to be a milder disease than HbSS.[11] The clinical manifestations of SCD, such ACS, pain crises, and VOC, are typically more common in patients with HbSS than in patients with HbSC.[12] The increased length of hospital stay in patients with HbSS that we observed may also be related to the increased hemolysis and inflammatory parameters that are typically associated with HbSS disease.[12]

Finally, we recognize the potential impact of social determinants of health and healthcare disparities on our observed outcomes. SCD predominantly affects individuals of African descent, and there is evidence that African American individuals in the USA are contracting SARS-CoV-2 at higher rates and that they have higher mortality rates.[13] Patients with SCD may experience socioeconomic and healthcare access barriers that further complicate infection and outcomes with COVID-19.[14]

CONCLUSION

In conclusion, there are several factors historical and current that appear to impact the COVID-19 disease progression of a patient with SCD. We found that patients with SCD with a history of ACS appeared to be at an increased risk of severe COVID-19 infection. This association between ACS, a complication of SCD caused by sickled RBCs blocking the blood vessels in the lungs, leading to decreased oxygenation, is in line with the results from other studies of SCD and COVID-19.[6] HbSC and hydroxyurea have been associated with a lower incidence of VOC, ACS, and several other SCD complications, and it also appeared to decrease the severity of COVID-19 infection in the patients we studied.[9 12] Patient hydroxyurea usage before COVID-19 infection, as well as SCD with HbSC genotype rather than HbSS, was associated with a milder/moderate COVID-19 disease course.

From these findings, we recommend that patients with SCD should begin or maintain hydroxyurea usage if there are no contraindications to its usage. We also recommend advising patients with a history of ACS to take extra precautions to prevent initial COVID-19 infection, since they are at a higher risk for severe disease. Finally, we suggest close monitoring for hospitalized patients with SCD, particularly those with type HbSS and a history of ACS, since they are more likely to have severe disease. By implementing these recommendations and continuing the research on the factors that impact the mortality and morbidity of patients with SCD with COVID-19, such as socioeconomic factors,[13 14] new disease-modifying medications, and the impact of inpatient treatments during hospitalizations, we can better protect and treat our patients with SCD.

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