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Published online: 28 Jul 2020.

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ORIGINAL ARTICLE

Impact of COVID-19 Infection on 24 Patients with Sickle Cell Disease. One Center Urban Experience, Detroit, MI, USA

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ABSTRACT

The city of Detroit has a large population of individuals with sickle cell disease, and hospitals in Detroit have seen some of the highest numbers of cases of coronavirus disease-19 (COVID-19) in 2020. The purpose of this study was to examine the pathophysiological characteristics of COVID-19 in patients with sickle cell disease or trait to determine whether these patients have unique manifestations that might require special consideration. This retrospective analysis included 24 patients with confirmed COVID-19 and sickle cell disease or trait who were seen at the Henry Ford Hospital, Detroit, MI, USA, between March 1 and April 15 2020. Of the 24 patients, 18 (75.0%) had heterozygous sickle cell trait, one (4.0%) was a double heterozygote for Hb S (*HBB*: c.20A>T)/β^+-thalassemia (β^+-thal), four had sickle cell anemia (β^S/β^S) and one (4.0%) had Hb S/Hb C (*HBB*: c.19G>A) disease. A total of 13 (54.0%) patients required hospitalization. All four patients with sickle cell anemia, developed acute pain crisis. We observed one patient who developed acute pulmonary embolism and no patients developed other sickle cell associated complications. Additionally, three (13.0%) patients required packed red blood cell transfusion without the need of exchange transfusion, and one patient required admission to the intensive care unit (ICU), mechanical ventilation and subsequently died. Patients with sickle cell disease or trait and laboratory-confirmed COVID-19 had a generally mild, or unremarkable, course of disease, with lower chances of intubation, ICU admission and death, but with a slightly longer hospitalization.

Introduction

In December 2019, the first cases of respiratory disease attributable to a novel enveloped RNA β coronavirus, now known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), were identified in Wuhan, People's Republic of China [1]. The disease, referred to as COVID-19, has now spread to every continent, with the exception of Antarctica. According to the World Health Organization, at the time of writing this report, there were more than 5 million confirmed cases with over 350,000 deaths [2].

Patients infected with SARS-CoV-2 experience a broad spectrum of symptoms, with approximately 80.0% of infected patients being classified as mild, 15.0% of cases as severe (dyspnea, hypoxia, or >50.0% of lung involvement on imaging) and 5.0% percent of patients being classified as critical (respiratory failure requiring intubation or shock) [3]. Between 20.0 and 40.0% of patients with severe disease develop acute respiratory distress syndrome (ARDS) [4,5].

According to a recent retrospective analysis of 5700 patients hospitalized in New York City, the three most common comorbidities with COVID-19 were hypertension, obesity and diabetes. Those who required mechanical ventilation had the highest mortality rate [6]. Older age,

high sequential organ failure assessment (SOFA) score, and D-dimer greater than 1.0 μg/mL were associated with poor prognosis at an early stage in a retrospective multicenter cohort study from China [7].

Sickle cell disease is a general term that describes an inherited group of disorders characterized by the presence of abnormal hemoglobin (Hb), Hb S (*HBB*: c.20A>T), caused by a point mutation at codon 6 of the β-globin gene. Hb S becomes poorly soluble when deoxygenated [8], causing red blood cells (RBCs) to distort into a crescent or sickle cell shape. Inciting events such as infection may cause hypoxia, which may lead to a sickle cell crisis resulting in vascular occlusion and major organ complications. This predisposition to major organ complications and susceptibility to hypoxia in patients with sickle cell disease was cited as one of the most frequent comorbidities seen in hospitalized patients during the H1N1 pandemic [9]. Note that sickle cell disease encompasses multiple genotypes, including a specific genetic profile called sickle trait. Collectively, the term sickle cell disease or trait (sickle cell disease/sickle cell trait) encompasses all individuals with at least one copy of the sickle cell disease Hb S gene.

While the mechanisms leading to ARDS in COVID-19 need to be investigated, we wanted to study the effect of

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Table 1. Demographics and medical comorbidities of the studied patients.

Demographics	Patients ($n = 24$)	%
Ethnicity:		
African American	22	92.0
not African American	2	8.0
Age (years):		
>60	9	38.0
<60	15	63.0
Gender:		
Men	6	25.0
Women	18	75.0
Sickle cell disease types:		
Hb S (HBB: c.20A>T)	4	17.0
Hb S/Hb C (HBB: c.19G>A)	1	4.0
sickle cell trait	18	75.0
Hb S/β-thal trait	1	4.0
Comorbidities:		
COPD	1	4.0
Asthma	3	13.0
HIV positive	0	0.0
Hypertension	12	50.0
Diabetes	9	38.0
BMI >30	12	50.0
End-stage renal disease	3	13.0
History of malignancies	5	21.0
History of VTE	6	25.0

COPD: chronic obstructive pulmonary disease; HIV: human immunodeficiency virus; BMI: body mass index; VTE: venous thromboembolism.

SARS-CoV-2 on patients who have sickle cell disease/sickle cell trait due to these patients' unique Hb phenotype and the prevalence of hypoxia as a hallmark of COVID-19. Importantly, individuals with sickle cell disease/sickle cell trait may or may not be manifesting anemia- or sickle cell-related symptoms, and our study sought to investigate the sickle cell disease/sickle cell trait process within the context of COVID-19. Many case series of COVID-19 infected hospitalized patients have been published so far, but studies of patients with sickle cell disease/sickle cell trait are sparse.

Here we present a retrospective analysis of all patients with sickle cell disease/sickle cell trait who presented at the Henry Ford Health System, Detroit, MI, USA, from 1 March to 15 April 2020. We examined these patients' hospital course, laboratory findings, need for hospitalization, intensive care unit (ICU) admission, packed RBC (PRBC) transfusion, and mortality.

Methods

This was a retrospective case study of data from adult patients with laboratory-confirmed COVID-19 and sickle cell disease/sickle cell trait who were evaluated at the Henry Ford Health System between March 1 and April 15 2020. The diagnosis of COVID-19 was made based on typical clinical and radiographic findings and a positive SARS-CoV-2 reverse-transcription polymerase chain reaction (RT-PCR) test from nasopharyngeal swab specimens performed at the Henry Ford Hospital. Sickle cell disease/sickle cell trait and comorbidities were determined based on patients' report and chart documentation on admission. Not all patients had Hb electrophoresis available for confirmation. All cases that met our inclusion criteria were analyzed. Data were reviewed by all authors.

Table 2. Presenting symptoms and triage vital signs.

Triage Vital Signs	n (%)	Total Tested (n)
Temperature >38.0 °C	10 (40.0)	24
Temperature (median °C)	37.0 (36.4-39.9)	24
Oxygen saturation:		
<90.0% on room air	3 (12.0)	24
median saturation on room air	94.0	24
Received supplemental oxygen	7 (28.0)	24
Respiratory rate >24/min.	2 (8.0)	24
Heart rate:		
>100 beats/min.	9 (36.0)	24
Median	94 beats/min.	24
Presenting symptoms:		
Fever	19 (79.0)	
Chills	14 (58.0)	
Headache	7 (29.0)	
Myalgia	16 (67.0)	
Change in taste	3 (13.0)	
Change in smell	2 (8.0)	
Shortness of breath	15 (63.0)	
Cough	20 (83.0)	
Nausea	5 (21.0)	
Vomiting	4 (17.0)	
Anorexia	7 (29.0)	

Sickle cell trait is the term used to refer to sickle cell disease patients who are heterozygous for Hb S, while patients who are homozygous are referred to as having sickle cell anemia (β^S/β^S). Additionally, patients with one copy of the Hb S gene and one copy of the Hb C (HBB: c.19G>A) gene are referred to as having Hb S/Hb C, and patients who are heterozygous for two blood disorders have Hb S/β^+-thalassemia (Hb S/β^+-thal). All four genotypes were represented in our study group and are collectively referred to as sickle cell disease/sickle cell trait patients.

The primary endpoint of our study was a composite measure that consisted of the admission to the hospital, admission to intensive care unit (ICU), duration of hospitalization, requirement of supplemental oxygen (by any means) or invasive ventilation, requirement of blood transfusion (simple or exchange), and death. The secondary endpoint was the mortality rate.

Inclusion criteria included all adult patients with a previous diagnosis of sickle cell disease/sickle cell trait with confirmed SARS-CoV-2 RNA RT-PCR testing. We excluded patients with suspected but not confirmed COVID-19 or hospitalization at an outside hospital for their initial diagnosis. The study protocol was approved by the Henry Ford Institutional Review Board.

Results

Between March 1 and April 15 2020, 40 patients sickle cell disease/sickle cell trait suspected to have COVID-19, were evaluated at Henry Ford Health System. A total of 24 patients with laboratory-confirmed COVID-19 who met our criteria were included (Table 1) in this study. The mean age of our study group was 52.9 years (range: 24–87 years). Of our patients, 18 (75.0%) were women, six (25.0%) were men, 22 (92.0%) were African American, and 13 (54.0%) required hospital admission.

The most common presenting symptom was a cough (20 patients, 83.0%), followed by fever (19 patients, 79.0%).

Shortness of breath and myalgia were reported in 15 (63.0%) and 16 (57.0%) patients, respectively. Loss of taste or smell and gastrointestinal and neurologic complaints were less common (Table 2). Duration of symptoms varied with a mean of 7 days (range 1–28 days). All hospitalized patients were treated with hydroxychloroquine and/or systemic steroids in addition to supportive measures. A total of seven patients (29%) required supplemental oxygen administration, and only one patient (4.0%) required intubation and ICU admission (Table 3).

Of the 24 cases, 18 (75.0%) patients had heterozygous sickle cell trait, four (17.0%) patients had sickle cell anemia (β^S/β^S), one (4.0%) patient was a double heterozygote for Hb S/β-thal, and one (4.0%) had Hb S/Hb C disease (Table 1). Only two (8.0%) patients were taking folic acid supplementation as outpatients, while no patients reported taking hydroxyurea (HU).

Of the 24 patients, 15 (63.0%) reported having at least one comorbidity, while 12 patients (50.0%) reported hypertension, 12 (50.0%) had a body mass index (BMI) of >30. Only one patient was receiving immunosuppressive medications due to renal transplant. No patients had a reported history of chronic respiratory failure requiring oxygen supplementation at home, and six patients (25.0%) had a history of venous thromboembolism (VTE). All tested patients were negative for human immunodeficiency syndrome and were negative for influenza H1N1. There were two patients (8.0%), who had reported non metastatic solid malignancies, but were not receiving active chemotherapy (Table 1).

Notable laboratory findings included absolute lymphocyte count (ALC) $<1.0 \times 10^9$/mL in 40.0% of cases. The mean presenting ferritin level was found to be 820.14 ng/dL, with >1000.0 ng/dL found in 40.0% of patients tested during hospitalization. Average presenting D-dimer was reported as 3.59 μg/mL with >10 μg/mL in 23.1% patients tested during hospitalization. Serum troponin was elevated in 26.7% of patients at initial triage. Only one patient had a Hb level of <7.0 g/dL, and 20.0% of patients tested had Hb levels of <10.0 g/dL during their hospital stay (Tables 4 and 5).

All sickle cell anemia patients required hospitalization and developed acute sickle cell pain crisis. Of the 18 patients with sickle cell trait, 11 (61%) were hospitalized. Only one of the 18 patients with sickle cell trait (5.5%) required ICU admission, intubation and mechanical ventilation, and subsequently died. This patient had been on chronic immunosuppressive therapy due to history of a failed renal transplant, had extensive cardiac disease, and was requiring intermittent renal replacement therapy. Average length of stay of hospitalization for patients with sickle cell trait was 7.6 days (range 2–21 days), while the average length of stay of patients with sickle cell anemia was 4.75 days (range 2–8 days). Of the three patients that required PRBC transfusions, only one hospitalized patient had sickle cell trait and required >5 units PRBC transfusions (Table 3). None of the patients developed acute chest syndrome (ACS) or needed exchange transfusions. A single patient that was a double heterozygote for Hb S/β-thal trait developed pulmonary embolism but did not require invasive ventilation or ICU admission and was discharged home without supplemental oxygen.

Discussion

In this retrospective case analysis, we describe the impact of COVID-19 on patients with sickle cell disease/sickle cell trait, who had presented to our institution. Overall, we found that the effect of COVID-19 on this patient population was mild, such that we did not observe any unusually severe outcomes compared to a general course of the infection. Surprisingly, despite a large population of patients with sickle cell disease/sickle cell trait in Detroit, the proportion of patients with sickle cell disease/sickle cell trait and laboratory confirmed COVID-19 infection that presented to the emergency department to seek care during our study period was, in our view, quite small. A total of 4688 patients with a diagnosis of COVID-19 were seen at the Henry Ford Health System from March 1 and April 15 2020, and patients with sickle cell disease/sickle cell trait represented only 0.5% of the total patient population. Considering that hypoxia is a troubling complication of COVID-19, we note that one sickle cell disease/sickle cell trait patient required ICU admission, mechanical ventilation, and subsequently died of multi organ failure. This patient also had multiple comorbidities, including chronic immuno-suppressed state due to prior renal transplant, worsening chronic renal disease requiring intermittent hemodialysis, and a history of cardiac disease. None of the patients developed ACS or any other complications to warrant exchange transfusions.

A recent large case series of all sequentially hospitalized patients with confirmed COVID-19 demonstrated that 14.2% required ICU care, 12.2% received invasive mechanical ventilation, and 21.0% died, and overall length of stay was 4.1 days [6]. Our findings within a specific sickle cell disease/sickle cell trait population showed a lower percentage of patients requiring ICU admission, fewer mechanical ventilations and a lower rate of mortality. The hospital length of stay was longer in our cohort, which can be explained in part by the presence of one critically ill patient who had a 21-day hospitalization.

We think the low number and unremarkable course of the COVID-19 infection on our patient population could be explained by several interventions. First, the overall number of COVID-19 affected patients with sickle cell disease/sickle cell trait could be lower due to social distancing that was put in effect early in the pandemic in the State of Michigan. Second, at the Henry Ford Hospital, we have a specialized Sickle Cell Disease Clinic with well-established guidance for our patients, including prompt outpatient management of painful crises, infusion room-based intravenous hydration, pain control, and outpatient management of mild viral illnesses. It is possible that some of the patients had been using outpatient resources rather than presenting to the hospital for evaluation and therefore did not get tested for COVID-19 due to presentation of acute painful crisis, which could mimic COVID-19 presentation. In a similar fashion, we do not know how many patients that presented to our

Table 3. Clinical measures and outcomes for the studied patients.

Outcome Measures ($n = 24$)	n (%) with Outcome	Total Patients
Hospitalizations	13 (54.0)	24
Sickle cell trait hospitalizations	11 (61.0)	18
Hb S, Hb S/Hb C, Hb S/β-thal hospitalizations	4 (100.0)	4
ICU admissions	1 (4.0%)	24
ICU admissions (het. sickle cell trait)	1 (5.5%)	18
Oxygen supplementation	5 (21.0)	24
Intubation/mechanical ventilation (het. sickle cell trait)	1 (5.5)	18
Sickle cell acute pain crisis	4 (17.0)	24
Sickle cell acute pain crisis (het. sickle cell trait)	0 (0.0)	18
PRBC transfusions	3 (13.0)	24
PRBC transfusions (het. sickle cell trait)	1 (5.5)	18
30-day readmission[a]	2 (15.4)	13
Death	1 (4.0)	24
Death (het. sickle cell trait)	1 (5.5)	18

ICU: intensive care unit; het.: heterozygous; PRBC: packed red blood cell transfusions.
[a]Readmission rates were calculated for patients who were initially admitted.

Table 4. Presentation of laboratory results of patients diagnosed with COVID-19 ($n = 24$).

Parameters	Assay Mean (range) or % Patients (n)	Patients Tested (n)	Reference Ranges
Admission Laboratory Values			
WBC (10^9/L)	9.03 (2.50–27.8)	20	3.80.10.6
ALC (10^9/L)	1.45 (0.10–6.32)	20	1.10–4.00
ALC <1.0, % (n)	40.0 (4)	20	
Plateles (10^9/L)	248.25 (39.00–450.00)	20	150.00–450.00
Platelets <150.00, % (n)	15.00 (3)	20	
AST (IU/L)	65.33 (14.00–276.00)	15	<35.00
ALT (IU/L)	37.40 (12.00–101.00)	15	<52.00
CPK (IU/L), total	218.50 (22.00–1048.00)	14	<250.00
CPK (IU/L), total, (maximum)[a]	272.71 (22.00–1048.00)	14	<250.00
Ferritin (ng/dL)	820.14 (63.00–2038.00)	15	24.00–336.00
Ferritin (ng/dL) (maximum)	1312.32 (88.00–5218.00)	15	24.00–336.00
Ferritin <1000.00 ng/dL, % (n)	40.0 (6)	15	
CRP (mg/dL)	7.40 (0.40–19.70)	14	<0.50
CRP (mg/dL) (maximum)	10.40 (0.50–43.00)	15	<0.50
LDH (IU/L) total	381.73 (173.00–742.00)	15	<250.00
LDH (IU/L) total, (maximum)	499.27 (243.00–1022.00)	15	<250.00
LDH <250.00 IU/L, % (n)	26.7 (4)	15	
LDH >250.00 IU/L, % (n)	93.3 (14)	15	
Procalcitonin (ng/mL)	1.66 (0.10–15.28)	12	<0.25
D-dimer (μg/mL)	3.59 (0.29 to >20.00)	13	<0.80
D-dimer (μg/mL) (maximum)	5.52 (0.88 to >20.00)	13	<0.80
D-dimer >1.00 μg/mL, % (n)	69.2 (9)	13	
D-dimer >5.00 μg/mL, % (n)	23.1 (3)	13	
D-dimer >10.00 μg/mL, % (n)	23.1 (3)	13	
Troponin above test-specific upper limit of normal[b]	26.7 (4)	15	
Venous lactate (nmol/L)	1.76 (0.80–3.10)	10	<2.10
Hemolysate Markers			
Hb (g/dL)	11.68 (6.40–15.10)	20	12.00–15.00
Hb <10.00 g/dL, % (n)	20.0 (4)	20	
Haptoglobin (mg/dL)	213.15 (<30.00–475.20)	4	30.00–200.00
Haptoglobin <30.00 mg/dL, % (n)	25.0 (1)	4	
Haptoglobin >30.00 mg/dL, % (n)	75.0 (3)	4	
Total bilirubin (mg/dL)	2.61 (0.40–9.10)	15	<1.2
LDH (IU/L) total	381.73 (173.00–742.00)	15	<250.00

WBC: white blood cell count; ALC: absolute lymphocyte count; AST: aspartate aminotransferase; ALT: alanine aminotransferase; CPK: creatine phosphokinase; CRP: c-reactive protein; LDH: lactate dehydrogenase; Hb: hemoglobin.
[a]Maximum indicates the highest laboratory values obtained during the patient's hospitalization for that respective laboratory test.
[b]For simplicity, we present the number and percentage of troponin test results that were above the upper limit of normal for any of the different troponin tests currently in use, including troponin I, troponin T, and high-sensitivity troponin.

hospital with acute pain crises did not get tested for COVID-19. Additionally, those patients who were admitted to the hospital were treated early and aggressively, as our hospital had the unfortunate advantage of being one of the national 'hot-spots' for COVID-19. This resulted in rapid, effective training of staff and implementation of structured protocols for care of patients with COVID-19.

Lastly, we wonder if chronic sickle cell disease therapy might have a protective effects on the sickle cell disease/ sickle cell trait patient population. In our cohort, we did not have any patients with sickle cell disease taking HU. It is possible that those patients who have sickle cell anemia and are compliant with HU did not develop symptomatic disease needing emergency room evaluation and admission.

Most of our patients had sickle cell trait, which could have been a contributing factor to the relatively mild course of disease we observed. A potential mechanism explaining this phenomenon may be hinted at in a previous study [10],

Table 5. Presentation of laboratory results for sickle cell trait patients with COVID-19 ($n = 18$).

Parameters	Assay Mean (range) or % Patients (n)	Patients Tested (n)	Reference Ranges
Hb (g/dL)	12.8 (7.4–15.9)	15	12.0–15.0
Hb <10.0 g/dL, % (n)	13.33 (2)	15	
Hb <7.0 g/dL, % (n)	0.0 (0.0)	15	
Haptoglobin (mg/dL)	288.4 (93.7–475.2)	4	30.0–200.0
Haptoglobin <30.0 mg/dL, % (n)	0.0	4	
Haptoglobin >30.0 mg/dL, % (n)	100.0	4	
Total bilirubin (mg/dL)	0.6 (0.4–9.1)	11	<1.2
LDH (IU/L)	320.0 (173.0–646.0)	9	<250.0
LDH (IU/L) (maximum)	434.0 (275–1022)	11	
LDH <250.0 IU/L (at admission), % (n)	33.0 (3)	9	
LDH <250.0 IU/L, % (n)	91.0 (10)	11	
Reticulocytes (K/μL)	170.0 (135.7–288.8)	3	20.7–83.2

Hb: hemoglobin; LDH: lactate dehydrogenase.

which suggested that viral proteins ORF1ab, ORF10 and ORF3a might cause the porphyrin-associated iron molecule in heme, on the β1 chain of Hb, to dissociate. This would affect the amount of oxygen that Hb could carry while in the bloodstream. However, as sickle cell patients have a mutation in the β chain of Hb, we wonder if this mutation could potentially prevent the SARS-CoV-2 viral proteins from binding, thus preventing the dissociation of iron. The biochemical dynamics of the SARS-CoV-2 interaction with sickle cell disease/sickle cell trait isoforms of heme would be an extremely interesting avenue of research.

Another interesting observation was that only one sickle cell disease patient in our study was diagnosed with VTE. Multiple reports have shown that COVID-19 infection is associated with high risk of VTE. Lodigiani et al. [11] found that 21.0% of 388 consecutive COVID-19 patients (27.6% ICU, 6.6% general ward) treated at a large hospital in Italy developed thromboembolic complications. Sickle cell disease itself is a well-described hypercoagulable state. A cross-sectional analysis of 404 sickle cell disease patients at Johns Hopkins University, Baltimore, MD, USA, showed that one quarter of the patients had a history of VTE, and that sickle cell variant genotypes conferred a higher risk of non catheter related VTE relative to patients with sickle cell disease, which the authors attributed to increased whole blood viscosity [12]. We hypothesized that the low number of VTE in our cohort was possibly due to under-testing for VTE and also possibly due to the overall number of patients with non severe, non critical COVID-19 disease who did not require ICU care.

Currently there are no published guidelines for patients with sickle cell disease/sickle cell trait in regard to the COVID-19 pandemic, although the American Society of Hematology provides guidance for frequently encountered questions by health care providers [13]. Continued patient social distancing measures, vigilance in recognizing COVID-19 symptoms by providers, and preemptive management with hydration/pain control will likely help mitigate the effect of COVID-19 on our sickle cell patient population. Limitations of our study were its retrospective nature, overall low number of the patients, and the self-report of comorbidities on admission.

Conclusions

In this report, patients with sickle cell disease/sickle cell trait and laboratory-confirmed COVID-19 had a generally mild, or unremarkable, course of disease, with lower chances of intubation, ICU admission and death, but with longer hospital stay. Further large-scale studies are needed to establish the impact of COVID-19 on sickle cell disease/sickle cell trait patients and the underlying mechanisms of disease in this unique population.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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