



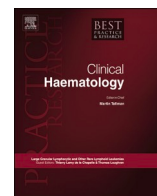
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COVID-19 outcomes in sickle cell disease and sickle cell trait

Jana Christian, Sophie Lanzkron, Rakhi P. Naik^{*}

Division of Hematology, Department of Medicine, Johns Hopkins School of Medicine, Baltimore, MD, USA

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ABSTRACT

Throughout the Coronavirus Disease 2019 (COVID-19) pandemic, understanding the effects of COVID-19 on persons with Sickle Cell Disease (SCD) and Sickle Cell Trait (SCT) has garnered interest. Patients with SCD diagnosed with COVID-19 utilize the emergency department and are hospitalized at significantly higher rates compared to the general population, with vaso-occlusive crisis and acute chest syndrome as the leading presentations. Whether SCD alone increases the likelihood of severe COVID-19 illness remains uncertain; however, potential risk factors for severe disease among patients with SCD include older age, frequent acute care visits for pain, haemoglobin SC disease, and pre-existing end-organ disease. SCT status may also influence COVID-19 outcomes, particularly among those with pre-existing co-morbidities. Corticosteroids in patients with SCD and COVID-19 should be used with extreme caution given strong associations between corticosteroid exposure and severe vaso-occlusive crisis, with prophylactic transfusion administered if corticosteroids are deemed necessary. Hydroxyurea may be protective in COVID-19.

1. Introduction

Sickle cell disease (SCD) encompasses a group of inherited haemoglobinopathies defined by a single nucleotide substitution in the β -globin allele leading to the formation of sickle haemoglobin (Hb S). Sickle cell disease is the most common monogenic disorder in the world, and in the United States, an estimated 100,000 persons have the disease [1]. Vaso-occlusive pain crises are considered the hallmark of SCD, and acute chest syndrome is the second most common cause of hospitalization and the leading cause of death in SCD. The pathophysiologic hallmark of SCD is Hb S polymerization during states of deoxygenation, which results in the sickling of red blood cells and subsequent vaso-occlusion, ischemic injury to tissues, and hemolysis. In addition, further mechanisms of disease in SCD include inflammation, augmented neutrophil adhesiveness, increased activation of platelets, hypercoagulability, functional nitric oxide deficiency, and vascular-endothelial dysfunction [1–3]. These mechanisms manifest in severe and progressive multiorgan disease for patients with SCD. Increased morbidity and mortality in SCD have been well documented, especially for patients who are homozygous for haemoglobin S [4–6].

Unlike SCD, sickle cell trait (SCT) is a carrier state characterized by the inheritance of a sickle cell gene from one parent and a normal gene from the other parent. Although the clinical significance of SCT remains under ongoing study, there have been associations found between SCT and clinically significant outcomes, such as the development of chronic kidney disease, exertional rhabdomyolysis, and venous thromboembolism [7,8].

Coronavirus Disease 2019 (COVID-19) is an illness caused by the severe acute respiratory coronavirus 2 (SARS-COV-2) that has rapidly become a global pandemic. Over the course of the COVID-19 pandemic, there have been over 590 million cases estimated

^{*} Corresponding author. 1830 E. Monument Street, Suite 7300, Baltimore, MD, 21230, USA.

E-mail address: rakhi@jhmi.edu (R.P. Naik).

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worldwide and over 6.4 million deaths, with over 1 million deaths in the United States alone, as of August 2022 [9].

At this time, the published data on COVID-19 outcomes among persons with SCD and SCT is limited, as the majority of investigations have been case series reports, retrospective study designs, and/or reliant on registry databases vulnerable to reporting biases. Nonetheless, these investigations have yielded meaningful observations regarding COVID-19 outcomes among patients with SCD and SCT.

1.1. Case presentation

Ms. H is a 57-year-old woman with sickle cell disease (Hb SS genotype) on hydroxyurea complicated by multiple prior hospitalizations for vaso-occlusive pain crises, stage 3 chronic kidney disease, and avascular necrosis of bilateral femoral heads who presents to the emergency department (ED) with fevers, rhinorrhea, non-productive cough, and pain in her lower back, bilateral hips, and bilateral thighs. Her symptoms first began with rhinorrhea and non-productive cough three days prior to presentation. However, for the last 12 h, Ms. H has had unrelenting pain not responsive to her home opioid regimen, which prompted her ED visit. Her pain is consistent with her prior vaso-occlusive pain crises. On exam, she is tired-appearing but in no acute distress. She has a normal oxygen saturation of 97% on room air. Her lungs are clear. Her labs reveal unchanged anemia and stable reduced estimated glomerular filtration rate. She tests positive for SARS-COV-2 infection. She is given intravenous hydromorphone, and is admitted to the hospital for further care.

Ms. H is clinically stable with improving pain until day 4 of her hospitalization, when she begins to note worsening dyspnea and cough. She is started on nasal cannula at 2 L/min that is increased a few hours later to 6 L/min. By the evening, she has been transferred to the intensive care unit and is started on high-flow nasal cannula. A chest x-ray is obtained that shows new bilateral alveolar infiltrates. What are Ms. H's risk factors for severe COVID-19 illness and how should we best treat her?

2. Clinical presentations of COVID-19 in patients with sickle cell disease

2.1. Emergency department visits and hospitalizations

Across a number of studies in the United States and internationally, patients with SCD and SARS-COV-2 infection have been found to be significantly more likely to present to the emergency department [10,11] and to be hospitalized as a result of COVID-19 as compared to the general population [10,12,13]. A retrospective analysis across more than fifteen hospitals within a healthcare system in New York identified 12,659 patients with COVID-19 who presented to care between January 1, 2020 and January 21, 2021. Of these 12,659 patients, 53 patients had SCD. Patients with SCD were 3.5 times more likely to have visited the emergency department and approximately 7 times more likely to be hospitalized as compared to the general population of patients [10]. Similarly, a United Kingdom study found that patients with SCD were 4 times more likely to be hospitalized [13]. Furthermore, the hospitalization rate among patients with SCD and COVID-19 has been reported to range from 26% to as high as 85% [14,15]. In addition, the Medical College of Wisconsin established the SECURE-SCD registry to collect data on COVID-19 cases occurring globally in persons living with sickle cell disease, and of the 178 patients with SCD entered into this registry, 90% accessed COVID-19 related care in emergency departments [11].

2.2. Presentations and complications of hospitalized patients

Vaso-occlusive pain crisis, the hallmark presentation of SCD, has been shown to be the most common presentation among patients with SCD hospitalized with COVID-19 [10,12,16]. In a prospective, five academic center study in New York City, Boston, Chicago, and Detroit, pain was reported by 65% of patients with SCD during their hospitalization for COVID-19 [12]; and in the analysis of the SECURE-SCD registry, pain was reported 67.4% of adults with SCD and COVID-19 [16]. Notably, in the SECURE-SCD cohort, of patients with SCD who presented with pain during their COVID-19 illness, there was a subgroup of patients with SCD who had not experienced acute pain in the three years prior to their illness, suggesting that COVID-19 may induce pain even among those without significant prior history of acute pain [16]. Furthermore, adults with SCD and a history of pain had a 1.8-fold increased risk of COVID-19-related hospitalization as compared to those with SCD without a history of pain [16]. In addition, for some patients, pain was the only symptom experienced throughout their COVID-19 illness [16].

Acute chest syndrome is the second most common presentation and complication among patients with SCD hospitalized with COVID infection [10,12,17]. Minniti et al. revealed that 60% of patients with SCD and COVID-19 developed acute chest syndrome over the course of their hospitalizations [12]. Similarly, in the SECURE-SCD cohort, 28.5% of patients with SCD experienced acute chest syndrome as part of their COVID-19 illness [16]. In addition, Singh et al. demonstrated that patients with COVID-19 and SCD had a 2.5 times higher risk of developing of pneumonia compared to a matched cohort of Black patients with COVID-19 [17].

Additional documented presentations and complications of COVID-19 in hospitalized patients with SCD include bacterial superinfection, kidney failure, venous thromboembolism, heart failure, stroke, priapism, aplastic crisis, and splenic sequestration, but these outcomes were less frequently documented (<10% of patients) as compared to pain and acute chest syndrome [16]. Although SCD and COVID-19 are both known to be hypercoagulable states [18–22], rates of venous thromboembolism were not frequently reported in studies. One study conducted in France found a high rate of pulmonary emboli among their cohort of patients with haemoglobin SC (Hb SC) disease with 25% of patients with Hb SC disease and COVID-19 diagnosed with pulmonary emboli during their hospitalization compared to 5% in the remaining population of patients with SCD and COVID-19 [23]. Another study; however, when comparing patients with SCD hospitalized for COVID-19 (281 patients) with patients with SCD not hospitalized for COVID-19 (4873 patients)

found no significant difference in VTE rates within 6 months of the hospitalization, after adjusting for differences in baseline characteristics [24].

2.3. ICU admissions, mechanical ventilation, and deaths

COVID-19 has been found to be a significant cause of death among patients with SCD. In 2020, of a total of 1023 SCD-related deaths that occurred in the United States, 86 (8.4%) had COVID-19 as the underlying or contributing cause of death [25]. However, whether patients with SCD are at *greater risk* for serious COVID-19 illness including ICU admission, mechanical ventilation, and death is uncertain. Early in the pandemic, there were a number of published case series of patients with SCD and COVID-19 that revealed that most adult patients with SCD had mild to moderate disease courses [26–29]. And one study concluded that although patients with SCD and COVID-19 visited the emergency department and were hospitalized more frequently than the general population, that SCD status did not carry an added risk of COVID-19 related severe illness or death compared to a population with similar demographics and comorbidities [10]. One research group hypothesized that because many patients with SCD and COVID-19 presented early in their disease course, especially those with pain requiring acute care visits, this allowed for earlier monitoring and care that prevented poor outcomes [29].

On the contrary, other studies found that SCD status was in fact associated with a higher risk of severe COVID-19 illness. In a cohort study utilizing a primary care database in England that included approximately 18% of the population, 5059 persons were found to have SCD and COVID-19. Researchers found that the adjusted hazard ratio for death for patients with SCD and COVID-19 was 2.6 times that of the general population [13]; however, this risk ratio was based on a small absolute number of deaths due to COVID-19 ($n = 10$ [0.2%]) [13]. The SECURE-SCD registry also found high rates of severe illness in their cohort of patients with SCD and COVID-19, with 20 patients (11%) admitted to the ICU and 13 patients (7%) who died [11]. Minitti et al. also noted that 7 patients (10.6%) with SCD and COVID-19 in their study population died, which was noted to be higher than the COVID-19 case fatality rate for the general population at that time of 3.3% [12]. However, matched controls were not utilized in Minitti et al. or the SECURE-SCD registry's analyses, so neither study directly compared ICU admissions or mortality rates to a population of patients without SCD.

Many studies have focused on identifying potential risk factors for severe disease among patients with SCD. Arlet et al. found that patients with SCD who were older than 40 years old had an 8.3-fold greater risk of intubation or death compared to patients with SCD between the ages of 20 and 40 [23]. Minitti et al. also found that older age contributed to increased risk of death in patients with SCD and COVID-19 [12]. After analyzing the 7 patients (10.6%) with sickle cell disease and COVID-19 who died, Minitti et al. found that older age and history of end organ damage such as pulmonary hypertension, congestive heart failure, chronic kidney disease, and stroke were more prevalent in those patients who died as compared to those who survived [12]. In the SECURE-SCD registry, patients who died from COVID-19 were found to have higher prevalence of pain episodes in the prior 3 years (85%), pulmonary hypertension (39%), stroke (31%), and decreased renal function (23%) [11]. Mucalo et al. found that frequent prior acute care visits for pain increased the risk for serious COVID-19 illness by 1.94 times in adults with SCD [16].

SCD genotype has also been examined as a risk factor for severe illness in patients with SCD and COVID-19. Notably, Panepinto et al. found that nearly 40% of the patients with SCD in their cohort who died had genotypes generally associated with milder disease

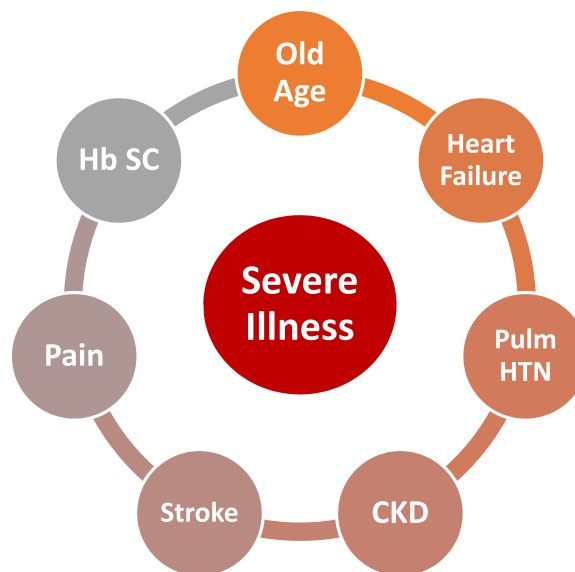


Fig. 1. Risk Factors for Severe Illness in SCD and COVID-19: Severe illness in patients with SCD and COVID-19 has been found to be associated with older age (age >40 years old), presence of pre-existing end-organ disease (including heart failure, pulmonary hypertension, chronic kidney disease, and stroke), history of prior acute care visits for pain, and Hb SC disease.

Treatments	Considerations
Vaccination	<ul style="list-style-type: none"> Vaccines against COVID-19 are safe and effective, and patients with SCD should be encouraged to seek vaccination. COVID-19 vaccines are not associated with increased rates of vaso-occlusive pain crisis.
Corticosteroids	<ul style="list-style-type: none"> Corticosteroids in patients with SCD and COVID-19 should be used with extreme caution given strong associations between corticosteroid exposure and severe vaso-occlusive crisis. If corticosteroid use is deemed necessary, then prophylactic transfusion therapy should be employed to decrease Hb S and mitigate negative effects of corticosteroid use.
Remdesivir	<ul style="list-style-type: none"> Remdesivir is suggested for patients with mild, moderate, and severe disease due to COVID-19 and should be given to patients with SCD who meet criteria for its use.
IL-6 Inhibitors	<ul style="list-style-type: none"> IL-6 inhibitors are suggested for severe and critical disease due to COVID-19 and should be given to patients with SCD who meet criteria for its use. Case studies suggest use of IL-6 inhibitors for patients with SCD and severe acute chest syndrome may result in favorable outcomes.
Disease Modifying Therapy	<ul style="list-style-type: none"> Hydroxyurea may be protective against ICU admission and death. Hydroxyurea may lower the risk of presenting with pain during COVID-19 illness. Crizanlizumab has been shown to remarkably decrease P-selectin levels in patients with COVID-19 without SCD, which may lead to decreased microvascular complications. Unless contraindications emerge, patients with SCD and COVID-19 should be continued on their disease-modifying therapy.
Transfusions	<ul style="list-style-type: none"> Transfusions are the mainstay of treatment for acute chest syndrome. Patients with COVID-19 and moderate to severe acute chest syndrome should be cared for in hospital settings that are able to provide exchange transfusions for optimal outcomes.
Antibiotics	<ul style="list-style-type: none"> Patients with SCD are considered at increased risk for certain bacterial infections due to functional hypo-splenism due to splenic auto-infarction. In conjunction with exchange transfusion therapy and other measures, patients who develop worsening hypoxemia with moderate to severe acute chest syndrome may warrant antibiotics.
Anticoagulation	<ul style="list-style-type: none"> All hospitalized patients with SCD and COVID-19 should receive prophylactic anticoagulation given increased risk of thrombosis associated with both conditions. Whether certain patients with SCD and COVID-19 may benefit from therapeutic dosing of anticoagulation is uncertain and requires further investigation.

Fig. 2. Treatment considerations for hospitalized patients with sickle cell disease.

such as Hb SC or Hb S β^+ thalassemia [11]. Minniti et al. also replicated that serious illness secondary to COVID occurred irrespective of haemoglobin genotype [12]. Arlet et al. found that after employing multivariate analysis adjusting for a number of variables including age, sex, weight, hydroxyurea use, and transfusion prior to hospitalization that Hb SC genotype was associated with a 6.99-fold increased risk for mechanical ventilation and death as compared to SS or S β^0 genotypes [23]. When hypothesizing what contributed to this almost 7-fold increase in intubation and death, researchers attributed a portion of the excess risk to an increased rate of venous thromboembolism and pulmonary embolism in patients with Hb SC genotype. Nine of 32 patients (28.1%) with Hb SC disease were diagnosed with an episode of thrombosis compared to 15 of 237 patients (6.3%) with SS or S β^0 genotypes. Furthermore, pulmonary embolism was found in 25% of patients with Hb SC disease as compared to 5% of patients with SS or S β^0 disease [23].

Thus, among patients with SCD, existing evidence suggests risk factors for severe COVID-19 disease include older age (>40 years), pre-existing end-organ damage, history of frequent acute care visits for pain, and Hb SC disease, and these factors should be considered when assessing a patient's risk for development of severe disease [Fig. 1]. It is also important to note that these cohort studies occurred across various time points during the COVID-19 pandemic with varying SARS-COV-2 strains and largely unreported vaccination statuses of the patients, and these two factors may also contribute to some of the observed differences in outcomes among cohorts.

3. Treatment of COVID-19 in hospitalized patients with sickle cell disease

Since the COVID-19 pandemic began, significant knowledge has been established regarding effective treatment against COVID-19. However, specific treatment considerations for patients with SCD are largely uncertain. We will discuss some important considerations that are also represented in Fig. 2.

3.1. Vaccination

Prior to discussions on treatment, the importance of prevention with vaccination must be emphasized. On December 11, 2020, the Food and Drug Administration issued an emergency use authorization for the first COVID-19 vaccination from Pfizer-BioNTech for individuals 16 years of age and older. Since then, as of August 2022, over 12 billion COVID-19 vaccination doses have been administered worldwide [9]. Vaccination against COVID-19 is safe and effective in protecting against severe COVID-19 illness including hospitalization, mechanical ventilation, and death [30] and patients with SCD should be encouraged to receive COVID-19 vaccinations. Additionally, COVID-19 vaccination is not associated with increased rates of vaso-occlusive pain crises [31].

3.2. Corticosteroids

Among patients with COVID-19 and moderate to severe acute respiratory distress syndrome, the use of dexamethasone, in addition to standard care, has demonstrated superiority to standard care in ventilator free days [32] and in decreased 28-day mortality among hospitalized patients [33]. As such, the Infectious Diseases Society of America (IDSA) provides a strong recommendation to administer dexamethasone to hospitalized patients with COVID-19 and severe illness, defined as oxygen saturation less than or equal to 94% on room air, including patients on supplemental oxygen [34]. However, in patients with SCD and COVID-19, exposure to corticosteroids may lead to significant adverse effects. Systemic corticosteroid use in patients with SCD has been associated with increased length of hospital stay and increased likelihood of re-admission due to the occurrence of severe vaso-occlusive crises in patients exposed to corticosteroid therapy [35,36]. As such, many experts advise extreme caution in the use of corticosteroids in patients with SCD diagnosed with COVID-19. In patients with SCD and COVID-19, we recommend that systemic corticosteroid use be avoided if possible. If necessary to administer corticosteroids given lack of acceptable alternatives, then systemic corticosteroids should be given in conjunction with transfusion therapy in order to lower the percentage of Hb S and mitigate the negative effects and likelihood of severe pain [37,38].

3.3. Remdesivir

Remdesivir is suggested for treatment of mild, moderate, and severe disease in ambulatory and hospitalized patients with COVID-19 [34]. Unlike the concerns associated with corticosteroids, there are no particular considerations when utilizing Remdesivir in patients with SCD, and Remdesivir should be provided for patients who meet criteria for its use.

3.4. IL-6 inhibitors

IL-6 inhibitors (e.g. Tocilizumab) are suggested for use in hospitalized patients with COVID-19, elevated markers of systemic inflammation, and severe or critical disease, with critical disease defined as end-organ dysfunction, use of mechanical ventilation, or use of extracorporeal membrane oxygenation [34]. Notably, there have been case reports in which patients with SCD and COVID-19 have experienced significant improvement in clinical outcomes and respiratory status after tocilizumab administration [12,39].

3.5. Sickle cell disease modifying therapy

Initial research suggests SCD modifying therapy may improve COVID-19 outcomes for patients with SCD. For example, Minniti et al. found in their cohort of patients with SCD and COVID-19 that treatment with hydroxyurea was more common in non-hospitalized

patients than hospitalized patients. Furthermore, they found that among the 10 patients with SCD chronically prescribed hydroxyurea who continued hydroxyurea during their hospitalization, there were no deaths, ICU admissions, or need for invasive ventilation [12]. In addition, all patients with SCD who died in the cohort were not on disease-modifying therapy prior to hospitalization [12]. In a study in the Northwell healthcare system, of 27 patients with SCD and COVID-19, 85% (23 persons) were hospitalized and 17% (4 persons) required ICU admission [15]. After multivariate analysis on the outcome of ICU admission, hydroxyurea use was found to be protective against ICU admission [15]. In contrast, Mucalo et al. found in their cohort of patients with SCD and COVID-19 that use of hydroxyurea only lowered the risk of presenting with pain during COVID-19 illness but did not have an effect on COVID-19 disease severity [16]. Nonetheless, all authors encouraged continuation of hydroxyurea in patients with SCD unless a contraindication emerged given possible beneficial effect of therapy.

In addition, Crizanlizumab, a selective P-selectin inhibitor utilized to decrease the occurrences of vaso-occlusive crises in patients with SCD, was studied in a population of patients without SCD who had mild to moderate COVID-19 illness. In this placebo-controlled, randomized trial of patients without SCD and with COVID-19, investigators found that a single infusion of crizanlizumab resulted in an 89% reduction in P-selectin, a significant reduction in levels [40]. This reduction in P-selectin levels could correlate clinically to less endothelial activation, decreased systemic microvascular inflammation, and reduced microthrombi formation which may improve clinical outcomes in COVID-19 [40]. Given these promising findings of Crizanlizumab in patients with COVID-19, patients with SCD prescribed Crizanlizumab should continue on this disease-modifying therapy.

3.6. Transfusions

In SCD, transfusions are an important aspect of therapy for a number of acute and chronic conditions including symptomatic anemia, splenic sequestration, and stroke [41]; and despite a lack of randomized controlled trials supporting their use [42], transfusions are the mainstay of treatment for acute chest syndrome. Among one cohort of patients with SCD and COVID-19, 60% of patients received blood transfusion therapy over the course of their hospitalization; making transfusion therapy the third most common treatment after antibiotics (71%) and prophylactic or therapeutic anticoagulation (64%) among the cohort [12]. A case report early in the pandemic, published in June 2020, details the case of a 27-year-old man with SCD and genotype SC who was transferred to the authors' institution on hospital day 11 given severe acute chest syndrome due to COVID-19. He received an emergency exchange transfusion on arrival to their hospital, and within 2 h of completing his procedure, he was able to be weaned from 6 to 10 L/min to 2 L/min via nasal cannula, and ultimately successfully discharged from the hospital without requiring mechanical ventilation [43]. We; therefore, recommend that patients who develop moderate to severe acute chest syndrome from COVID-19 be cared for in hospital settings able to coordinate exchange transfusions for optimal outcomes.

3.7. Antibiotics

Minniti et al. found antibiotic therapy to be the most common therapy provided to patients with SCD and COVID-19 with 71% of patients in their analysis receiving antibiotic therapy during their hospital stay [12]. Patients with SCD are thought to be at increased risk for certain bacterial infections given functional hyposplenism and auto-infarction of the spleen, and as such, close monitoring for bacterial superinfection is crucial to the care of patients with SCD and COVID-19 [44]. Although bacterial superinfection tends to be a later and less frequent complication of COVID-19 in the general population, patients with SCD who develop acute chest syndrome may warrant empiric antibiotics regardless of time course, especially in persons with moderate to severe respiratory illness.

3.8. Anticoagulation

Both COVID-19 and SCD have been associated with hypercoagulability and increased risk of venous thromboembolism [18–22]. Despite this, there is no clear guidance on the use of prophylactic versus therapeutic anticoagulation in patients with COVID-19 and SCD. Given the increased risk of venous thromboembolism among patients with SCD, prophylactic anticoagulation has been strongly recommended for all patients hospitalized with SCD and COVID-19 [12]. However, whether a certain subset of patients with SCD without evidence of venous thromboembolism may benefit from therapeutic anticoagulation is unclear.

In non-SCD patient populations, there has been mixed data on whether therapeutic anticoagulation is beneficial in hospitalized, non-critically ill patients with COVID-19. One study showed increased probability of survival until hospital discharge and a reduced need for organ support among those with therapeutic anticoagulation as compared to usual care thromboprophylaxis [45]; however, other trials have found no difference in outcomes between those on therapeutic dose anticoagulation and those on prophylactic dose anticoagulation [46]. Among patients who are critically ill or outpatients with COVID-19, therapeutic anticoagulation has not been shown to improve outcomes, and in critically ill patients, therapeutic anticoagulation may be associated with an increased risk of major bleeding as compared to usual thromboprophylaxis [47,48]. Based on this evidence, the International Society for Thrombosis and Haemostasis made recommendations to consider the use of therapeutic heparin in hospitalized, non-critically ill patients with low risk of bleeding and risk factors for thromboembolism or organ failure, including elevated D-dimer or increasing oxygen requirements [49].

4. Treatment of COVID-19 in ambulatory patients with sickle cell disease

As SCD is regarded as a medical condition with a potential increased risk for severe COVID-19 disease, ambulatory patients with

mild to moderate COVID-19 symptoms and SCD qualify for COVID-19 directed therapies. Options for treatment of ambulatory patients include nirmatrelvir/ritonavir, three-day treatment with remdesivir, molnupiravir, and SARS-COV-2 neutralizing monoclonal antibodies (bebtelovimab). Decision-making on choice of agent depends on patient driven factors such as drug interactions, preference, and renal function and systems-driven ones such as product availabilities [34].

5. COVID-19 and patients with sickle cell trait

As SCT is significantly more common than SCD, the effect of SCT on SARS-COV-2 infection outcomes has also been the topic of scientific exploration, with conflicting results. A multicenter, retrospective analysis performed by Harvard Medical School researchers endeavored to understand how the COVID-19 outcomes of patients who identified as Black or African American differed based on SCT status. One hundred sixty-six Black patients were identified, and 20 patients were found to have SCT. Among patients without SCT, 13% (19/146) died in the hospital compared with 15% (3/20) of patients with SCT, which was a non-significant difference between those with SCT and those without SCT [50]. Another study from the Medical College of Wisconsin identified 312 patients with COVID-19 and SCD, 449 patients with COVID-19 and SCT, and 45,517 Black patients with COVID-19 and without SCD or SCT. After 1:1 propensity score matching based on age, sex, and other preexisting comorbidities, SCT did not lead to significantly different COVID-19 outcomes [17].

However, a few studies do suggest an increased risk of morbidity in individuals with SCT with COVID-19 infection. One observational study performed in Detroit, Michigan, followed 24 patients with SCD and SCT with COVID-19, and of the 24 patients, only 1 patient died, who notably had SCT. This patient had been on chronic immunosuppression given history of a failed renal transplant, had extensive cardiac disease, and was on renal replacement therapy [51]. In addition, a large database study with 25,682 SCT carriers showed a 1.38-fold increased risk of COVID-related hospitalization and 1.51-fold increased risk of COVID-related death among patients with SCT as compared to the general population [13]. Similarly, a large analysis using the Million Veteran Program (MVP) cohort with 2729 individuals with SCT demonstrated a 1.77-fold increased risk of COVID-related mortality in SCT [52]. Furthermore, this increased risk of mortality appeared to be related, in part, to an increased risk of development of acute renal failure among SCT carriers. Similar to prior studies, this analysis also found that individuals with SCT had an increased prevalence of pre-existing chronic kidney disease and history of pulmonary embolism prior to their COVID-19 infection [52].

Thus, our existing knowledge suggests that SCT may influence COVID-19 outcomes for people with SCT, especially among those with pre-existing co-morbidities such as chronic kidney disease or those who develop acute renal failure over the course of their COVID-19 illness. Although most individuals with SCT are unaware of their status, SCT testing in patients with COVID-19 is not yet warranted as testing will likely not change management.

6. Case conclusion

Ms. H presented with acute pain, the most common presentation at hospital admission for patients with COVID-19 and SCD. She has risk factors for severe COVID-19 illness given her chronic kidney disease, prior acute care visits for pain, and older age. She also has protective factors including hydroxyurea use and perhaps her Hb SS genotype. She unfortunately develops acute hypoxemic respiratory failure with impending need for invasive ventilation. Ms. H would benefit from both COVID-19 directed therapies, such as Remdesivir and IL-6 inhibitors, and SCD directed therapies, including continuation of her hydroxyurea therapy and coordination of exchange transfusion given severe acute chest syndrome. She should also be started on empiric antibiotics given new alveolar opacities and possibility of bacterial superinfection. Corticosteroids, given her presentation with vaso-occlusive crisis, should be avoided if possible. With these treatments, Ms. H is weaned off oxygen over the subsequent days and discharged home. On her follow-up appointment one week after discharge, her pain remains well-controlled and all COVID-19 related symptoms have abated.

7. Summary

Despite high utilization of emergency department care and hospitalizations, many patients with SCD and COVID-19 experience only mild to moderate illness, with vaso-occlusive pain crisis as the most common presentation and complication. Risk factors for severe COVID-19 disease among patients with SCD include older age, prior acute care visits for pain, and pre-existing end-organ disease, including heart failure, chronic kidney disease, pulmonary hypertension, and stroke. Although haemoglobin SC disease is considered a milder form of SCD, emerging literature suggests that haemoglobin SC disease may be associated with worse outcomes in COVID-19, potentially due to increased rates of venous thromboembolism. SCT has also been shown to affect COVID-19 outcomes, especially among those with pre-existing co-morbidities such as chronic kidney disease.

Although we have gained significant knowledge about COVID-19 outcomes in patients with SCD and SCT, many clinical questions still necessitate further investigation. Given that the majority of current studies are small and single center without matched controls, future studies of COVID-19 in patients with SCD/SCT should focus on expanding patient sample sizes and including appropriately matched controls. Treatment considerations in COVID-19 and SCD also require ongoing study. Given known associations between systemic corticosteroid use and severe vaso-occlusive crisis, we caution against the use of corticosteroids unless there are no other alternatives for the treatment of severe COVID-19. However, use of prophylactic transfusion therapy to mitigate the negative effects of corticosteroid use when deemed necessary should be further explored. Further study should also be devoted to understanding the potential effect of hydroxyurea and crizanlizumab to protect against severe COVID-19 illness in SCD.

8. Practice points

- Vaso-occlusive crisis is the most common presentation and complication of COVID-19 in patients with SCD. Consider COVID-19 testing in patients with SCD who present with acute pain, especially if their clinical picture is otherwise suspicious for COVID-19 (fevers, rhinorrhea, cough, etc.).
- Patients with SCD who are older (approximately age >40 years old), have multiple prior acute care visits for pain, and have pre-existing end-organ disease are at the highest risk for progression to severe COVID-19 disease and should be monitored closely.
- Haemoglobin SC disease may be associated with increased risk of severe COVID-19 illness, potentially due to increased rate of thrombosis and pulmonary emboli.
- SCT status may influence COVID-19 outcomes, especially in those with pre-existing co-morbidities such as chronic kidney disease; however, patients with SCT can be triaged and managed similarly to general population, as SCT status may not influence treatment decisions.
- Corticosteroids, although routinely recommended for patients with COVID-19 and severe disease, should be used with extreme caution in patients with SCD given strong associations between corticosteroid exposure and severe vaso-occlusive crisis. If corticosteroids are deemed necessary, prophylactic transfusion should be strongly considered.
- Continue patients with SCD on disease modifying therapy unless contraindications emerge, as there may be a protective effect of hydroxyurea and crizanlizumab against severe disease in COVID-19.

9. Research agenda

- As the majority of current studies in patients with SCD/SCT and COVID-19 are small and single site, investigators should attempt to study large, multicenter cohorts of patients with SCD/SCT and COVID-19.
- Future studies on SCD/SCT and COVID-19 should prioritize including matched controls to better compare the COVID-19 outcomes of patients with SCD/SCT to that of the general population.
- Further guidance regarding the treatment of COVID-19 in patients with SCD/SCT is crucial, especially the use of corticosteroids in patients with SCD given associations with vaso-occlusive pain crisis and requires ongoing study.
- Possible protective effects of hydroxyurea and crizanlizumab in patients with SCD and COVID-19 should be further evaluated to guide the use of disease modifying therapy.

Declaration of competing interest

S Lanzkron reports consultancy at Bluebird bio, Novo Nordisc, Pfizer, Novartis, GMI; research funding from Imara, Novartis, GBT, Takeda, CSL-Behring, HRSA, PCORI; and stocks with Pfizer and Teva. J Christian and R Naik have no relevant conflicts of interest to disclose.

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