Adult sickle cell disease and SARS-CoV-2: an increasingly common comorbidity for a rare disease

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ABSTRACT

Sickle cell disease (SCD) is a collection of genetic lesions that manifest in the diminished effectiveness of hemoglobin. We collected and reviewed the recent and extant literature on SARS-CoV-2 (COVID-19) and SCD. We posit an answer to the question associated with any adaptive responses to COVID-19 in individuals with SCD. We collected papers from MEDLINE and all available published papers on COVID-19 and SCD. Unlike a formal meta-analysis, given the early phase of this review in the pandemic, we did not seek unpublished papers. We found an emerging literature where case studies dominated, and traditional large N epidemiological studies were absent. Patients with SCD share many comorbid illnesses with an increased risk of mortality associated with contracting COVID-19. There is sufficient empirical justification to accelerate research on the impact of a viral pathogen like COVID-19 on individuals with SCD.

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Introduction

SARS-CoV-2 infection, also known colloquially as COVID-19, is caused by the coronavirus.[1] COVID-19 can be characterized by acute respiratory distress syndrome (ARDS), multiple organ failure, severe cytokine release syndrome, altered olfaction and gustation, abdominal pain, and diarrhea to name a few.[2-4] The clinical spectrum of COVID-19 ranges from paucisymptomatic to cardiopulmonary failure and death. Since the beginning of the COVID-19 pandemic in and or around early 2020, many clinicians and researchers who worked with patients with sickle cell disease (SCD) wondered if the genetic lesion would promote an adaptive functional response to COVID-19, much like in the case of SCD and malaria. In contrast, many other clinicians and researchers suspected that individuals with SCD were at greater risk for developing severe infections and complications when contracting COVID-19. At the time, there was little data to answer such questions and guide clinical decision-making.

Today, almost three years into the pandemic, data has begun to emerge that demonstrates the impact of COVID-19 on patients with SCD. The current review paper evaluated all known published papers associated with COVID-19 and SCD to inform future clinical decision-making and better understand the interactive impact of both diseases.

Individuals with SCD are generally more susceptible to viral infections and are predisposed to contracting severe COVID-19.[5] The CDC classifies SCD as a condition that increases the risk of severe illness from COVID-19 infection.[6] Patients with SCD have underlying pathophysiology of i) chronic inflammation with increased risk of thrombosis; ii) are immunocompromised due to auto-infarction; iii) prone to infectious disease and acute chest syndrome (ACS) and have comorbidities and secondary organ dysfunction.[7-9] Nevertheless, it is unknown if COVID-19 can cause severe complica-

tions in individuals with SCD or if SCD-related complications are risk factors for severe COVID-19.

Transmission, structure, and pathophysiology of SARS-CoV-2

The World Health Organization declared the novel SARS-CoV-2 virus to be a national public health emergency by January 30th, 2020, with worldwide cases surpassing one million in early April 2020.[10] Though the initial case of SARS-CoV-2 is believed to be the result of zoonotic infection, human-to-human transmission via symptomatic or asymptomatic carriers is the primary route by which the virus is spread. Current understanding posits that viral transmission may be the result of either close contact with an infected person or through contact with a contaminated surface.

Close contact refers to the transference of respiratory droplets from an infected individual that has the potential to enter the mouth, nose, or eyes of a non-infected individual, typically from less than two meters.[1] It is also known that the SARS-CoV-2 virus can remain viable for a certain duration on various surfaces. Therefore, surfaces that have been contaminated with the respiratory droplets of an infected individual may also spread the virus if a non-infected person touches the surface, then touches their mouth, nose, or eyes.[1] Efforts to contain the transmission of the virus primarily involve proper hygiene practices (*e.g.*, hand washing, hand sanitizer, *etc.*), social distancing, mask usage, and quarantine for infected individuals.

SARS and coronaviruses are not unique to the current pandemic; however, the structure and pathophysiology of the SARS-CoV-2 virus are novel and the subject of ongoing research. Structurally, SARS-CoV-2 is a single-stranded, positive ribonucleic acid (RNA) virus that features a nucleocapsid and an envelope with four distinct protein spikes.[1,11] The full length of the genome is approximately 30,000 nucleotides, or a diameter of 50-200 nm, with the ability to encode 27 different proteins.[1,11,12] The surface glycoprotein spike (S), matrix protein (M), small envelope protein (E), and nucleocapsid protein (N) comprise the structure of the SARS-CoV-2 viral envelope.[1,11]

The angiotensin-converting enzyme 2 (ACE2) receptor is most implicated in the cellular attachment and transmission of SARS-CoV-2.[1,11] Studies suggest that the S protein is responsible for attaching primarily to the ACE2 receptor of cells, thereby allowing the virus to bind to the host cell's membrane. More specifically, the S protein consists of an S1 receptor binding subunit and an S2 fusion subunit, split by the S cleavage site. The attachment and fusion processes are contingent upon the severance of the cleavage site. Furthermore, S proteins are activated by serine proteases, which are also implicated in the division of the cleavage site.[1]

SARS-CoV-2 RNA alters normal cellular functions, which forces the host cell to replicate the viral genome once fused. Other structural proteins play a role in the binding of the original RNA fragments, as well as the formation of the nucleocapsid and envelope.[1,11] The ACE2 receptors which facilitate these processes are found in most human tissues and organs. Of note, these receptors are found in venous and arterial endothelial cells, epithelial cells in the alveoli of the lungs, nasal epithelium, and in the smooth muscle cells of the brain, stomach, lungs, lymph nodes, and liver bile ducts, to name a few.[11] ACE2 receptors have been shown to have increased expression in individuals with hypertension and diabetes.[1]

COVID-19 and sickle cell disease

Several factors may contribute to an increased susceptibility to developing COVID-19. The elderly, those who are immunocompromised, and those who suffer underlying chronic medical conditions such as hypertension, diabetes, cardiovascular disease, and pulmonary dysfunctions have a greater propensity for contracting the virus.[13] With respect to the risk factors, many researchers have explored whether being diagnosed with SCD increases the likelihood of contracting COVID-19 and if it is associated with greater morbidity and mortality. Notable concerns include whether the respiratory involvement of COVID-19 would precipitate acute chest syndrome in SCD and which pathophysiological components of SCD may be exacerbated by SARS-CoV-2 infection.

Advanced age in patients with SCD is associated with a more severe clinical course and greater disease burden associated with COVID-19. In the asymptomatic population, older age is associated with an increase in medical comorbidities, whereas older age in the SCD population is associated with greater SCD-related disease morbidities. Aging in SCD has been shown to be related to an increased incidence of vaso-occlusive crises (VOCs), which cause chronic tissue and organ ischemia, reperfusion injury, endothelial activation, and inflammation.[14] In the setting of VOCs, immune cells respond to the site of tissue injury, promoting the extravasation of monocytes, subsequently releasing inflammatory cytokines such as interleukin-6, interleukin-1β, and tumor necrosis factor-α.[14-16]

Chronic proinflammatory states and the involvement of endothelial cells as a target of the SARS-CoV-2 virus to attach and replicate may put individuals with SCD at an increased risk for cytokine storm and thrombotic complications. Both events may be associated with increased morbidity and mortality if patients become infected with COVID-19.[13,14] Furthermore, individuals with SCD may have elevated rates of other comorbid medical conditions, including pulmonary hypertension and chronic lung disease, which may also place them in the high-risk category for COVID-19-related complications.[13] These complications may provoke VOCs, ACS, or organ failure in those with SCD.[13]

Symptoms associated with COVID-19 can include cough, fever, and shortness of breath. Once the infection progresses, individuals may develop multi-organ failure, pneumonia, and respiratory complications.[1] Of significant concern relating to SCD is the development of ACS, secondary to SARS-CoV-2 infection. ACS commonly presents with chest pain, fever, and pulmonary infiltrates and is associated with increased mortality in this population.[14] While contracting COVID-19 is not a significant predictor of the development of ACS; there is still a potential for chronic lung injury to trigger ACS in individuals with SCD.[13]

Diagnosis of SARS-CoV-2 and ICD-10 codes

The symptoms associated with SARS-CoV-2 infection are not unique to this virus and may be like that of other respiratory infections. Symptoms should not solely be used to make a diagnosis of COVID-19.[11] Nucleic acid testing is often the primary diagnostic tool used to make the most accurate diagnoses. By March 2020, scientists were able to identify the genome of SARS-CoV-2, which was foundational to the development of reverse transcription polymerase chain reaction (RT-PCR) testing.[11] Rapid testing techniques and computed tomography (CT) imaging may also be used for diagnosis.

RT-PCR testing requires the reverse transcription of the viral RNA into complementary deoxyribonucleic acid (cDNA) strands.[11] Certain sections of the strands are then magnified to determine the presence of specific gene sequences that are consistently observed in patients diagnosed with SARS-CoV-2 infection. Most implicated are the RNA-dependent RNA polymerase (RdRP) gene, the E gene, and the N gene. Of interest, the former two genes are known to have increased sensitivity, allowing for greater detection when compared to the N gene.[11]

Within the United States, the CDC utilizes a one-step, real-time RT-PCR assay. A sample of the viral RNA is placed into a mixture of nuclease-free water, forward and reverse primers, and a probe containing fluorescent dye.[11] The mixture contains an additional reaction mix consisting of nucleotides, polymerase, magnesium, and reverse transcriptase.[11] The extracted sample, including potential viral RNA, is then placed in a temperature-controlled PCR thermocycler for incubation. Standards for temperature and cycle duration have been outlined by the CDC.[11] During the assay, the severance of the fluorophore-quencher probe then allows for the illumination of fluorescent light to be recognized by the thermocycler. The illumination of fluorescent light in the mixture indicates the presence of viral RNA, thus conferring a positive test result.

Other diagnostic tools can be utilized to detect SARS-CoV-2 and diagnose COVID-19. Of note, rapid testing procedures and CT imaging tend to be common second-line testing options. Rapid testing allows for a faster turnaround time to provide results, which is beneficial for time-sensitive testing. However, due to the low accuracy associated with them, rapid tests that yield positive results typically require additional RT-PCR testing to confirm the diagnosis. CT imaging may be beneficial in detecting lung involvement which is typically most significant around 10 days following symptom onset.[11] Bilateral or peripheral lung opacities and consolidations are most indicative of SARS-CoV-2 infection.[11]

The International Statistical Classification of Diseases and Related Problems, 10th revision (ICD-10) provides independent coding for SCDs and COVID-19. Coding should include the specific genotype of SCD, modified by "with other specified complication", in addition to the code for COVID-19 (Table 1).

Impact of COVID-19 on black communities

SCD and sickle cell trait (SCT) are the most inherited hematologic diseases, primarily affecting black Americans or individuals with ancestors from sub-Saharan Africa, Spanish-speaking countries in the Western Hemisphere, and Mediterranean countries.[17-18] In the United States, black Americans are affected by COVID-19 at disproportionate rates. At the peak of the pandemic, there were initially higher mortality rates among black Americans due to COVID-19. Due to the pathophysiology mentioned above, concerns as a result of COVID-19, such as ACS caused by pneumonia or SCD-related concerns as a result of COVID-19, like higher risk of venous thromboembolism, black Americans and African descendants with SCD are an at-risk population.[19-22]

Historically, this population has an increased risk of hypertension, heart disease, and obesity when compared to other racial groups, which also places them at greater risk for severe COVID-19 complications or death.[23-25] Previous research suggests that this trend is consistent within other racial populations; however, black Americans are more likely to experience three or more of these comorbidities, placing them in a higher risk category.[26-29]

Psychosocial factors and vaccination hesitancy

The COVID-19 pandemic has caused irreparable damage to black Americans due to health factors and social and economic factors. Initially, when COVID-19 emerged, it was not acknowledged as an international issue, with the solution being to close the borders and authorize travel restrictions. In January 2020, the first US case was reported; by March, the US had succumbed to the virus and became the pandemic's epicenter. The virus spread to cities such as Detroit, New Orleans, Philadelphia, Chicago, and Boston, where a larger part of the population consisted of black Americans.[30] Due to the proximity of housing within black communities, the population is at an increased risk of COVID-19's infectious nature. This population also accounts for a disproportionate amount of poverty, mass incarceration, and limited health care access

Table 1. ICD-10 codes for sickle cell disease and COVID-19.

ICD-10 code	Disorder
D57.09	Hb-SS disease with other specified complication
D57.218	Sickle-cell/Hb-C disease with other specified complication
D57.418	Sickle-cell thalassemia, unspecified, with other specified complication
D57.438	Sickle-cell thalassemia beta zero with other specified complication
D57.458	Sickle-cell thalassemia beta plus with other specified complication
D57.818	Other sickle-cell disorders with other specified complication
U07.1	COVID-19

Hb-SS, hemoglobin SS.

while also being more likely to work service jobs, therefore becoming more susceptible to exposure.[31,32]

Black Americans are likely accustomed to a marginalized status because of the disparities in the healthcare system throughout American history. The Food and Drug Administration issued an emergency use authorization in 2020 for COVID-19 vaccines; this provided a path to lessen the strain on the black population. However, according to the CDC, as of July 2022, 55.9% of black non-Hispanic people did not receive a booster dose once eligible.[33] Although black Americans are affected by the virus at alarming rates, there were a plethora of ethical concerns and questions that caused hesitancy towards the vaccines. There is an overarching lack of trust in black Americans' perception of the healthcare system.[34] This mistreatment of the black population throughout the history of medicinal practice has and continues to cause health disparities.[35]

Medical misconceptions about black patients are a form of mistreatment that continues to hurt the health of black Americans. A previous study found that 50% of active medical students believed at least one false biological difference between black and white patients.[36] Often, black patients are under-treated for pain at systematic rates due to an assumption that black people perceive pain differently at a biological level compared to white counterparts due to a difference in skin thickness or the sensitivity of nerve endings.[37-39] The examples of mistreatment shown in the lack of care given to black men in the Tuskegee syphilis study and the forced sterilization of black women are often used to describe why black people are so distrustful of physicians and the entire healthcare system.[40,41] Past experiences have created a cultural distrust in medical research and trials within black communities. Due to historical negligence or lack thereof medical care that black people in the US have received, there is suspicion about information concerning the COVID-19 virus and vaccine, which puts an already marginalized community at much higher risk.[42,43]

There were also issues with healthcare availability. In many cases, protective measures were put in place in order to decrease unnecessary exposures for both providers and patients.[44,45] Further, there were problems due to healthcare avoidance and delaying of care among patients due to multiple factors such as fear of the virus, disruption of employment, and financial barriers.[44] These factors also had an impact on patients avoiding and delaying care for acute crises that would have usually prompted immediate care. Avoidance and delay were associated with fewer receiving hospitalizations, but those who were eventually admitted experienced longer stays.[45]

Complications, treatment, and mortality

Complications

It is known that SCD symptoms could complicate the COVID-19 disease course. It has been theorized that adults with a history of chronic pain are at higher risk of worse disease severity.[46] Another major concern unique to patients with SCD is pulmonary thrombosis, which is prevalent in both SCD and COVID-19. A severe disease course is typically characterized by patients needing escalated care and prolonged hospitalization due to severe COVID-19 symptoms (*e.g.*, hypoxia, pneumonia, prolonged fever, multisystem inflammation), or severe SCD-related complications (*e.g.*, ACS, severe pain crisis), or both.

One study observed increased hospitalization, mild to moderate pneumonia, and intubation among SCD patients. Another study identified older patients, pre-existing conditions, and end-organ damage as high-risk factors for severe COVID-19 disease course and poor outcomes. Observational cohort studies and case reports suggest that advanced age, pre-existing conditions, and male sex are risk factors for unfavorable COVID-19 outcomes in patients with SCD, like the reported risk factors in the general population.[47-50]

Marked differences in disease severity between different sickle genotypes may result in different COVID-19 outcomes. Various studies observed that genotypes associated with milder SCD [*i.e.*, hemoglobin C disease (HbSC), HbSE, HbSβ+] had no different or worse outcomes than genotypes associated with more severe SCD [*i.e.*, hemoglobin SS (HbSS), HbSβ0]. Having both conditions could conceivably result in an even higher risk of severe disease. Persons with SCD would benefit from individual risk assessment for poor COVID-19 outcomes, although a history of SCD complications does not necessarily lead to unfavorable outcomes. Studies have suggested that prior sickle cell complications such as avascular necrosis of the joints, hypersplenism requiring splenectomy, and cerebrovascular accident were not associated with the outcome of patients with COVID-19.[51]

Treatment

Previous observational cohort studies reported that a simple or exchange blood transfusion was the primary therapy. Regularly scheduled chronic transfusion prior to COVID-19 diagnosis and/or received transfusion during the COVID-19 disease course was reported in 47% of SCD patients (60 out 129 individuals).[47,52-55] Early red blood cell exchange has reportedly been successful in the treatment of severe COVID-19 pneumonia, severe hemolysis, and VOC and might prevent patients with SCD from further clinical deterioration and intubation experiences. Another common therapy for SCD was Hydroxyurea. This treatment was received by 32% of SCD patients (41 out of 129 individuals) in case studies.[56,57] Beneficial effects of hydroxyurea were noted to include lower morbidity and mortality rates compared to SCD patients that were not on hydroxyurea or other SCD-modifying therapies. Patients on hydroxyurea also did not develop ACS.[50]

Mortality

The reported COVID-19-related mortality rates for persons with SCT vary significantly between studies, from 2.2% to 28.6%.[47,58,59] In one of the most extensive studies, including patients with both SCD and SCT, individuals with SCD were found to be almost four times as likely to succumb to COVID-19-related complications, whereas those with SCT may be nearly three times as likely to die from similar complications. Contrarily, vast cohort studies have shown no difference in mortality rates between individuals with or without SCT and COVID-19.[47,59,60] A single study analyzed mortality risk factors and found preexisting diabetes to increase the risk of death in SCT patients.[58]

Summary of case reports

We identified and reviewed five published case reports of COVID-19 in patients with SCDs at the time of our paper construction (last week of December 2022). There does not seem to be a gender bias in cases. Three of five cases reported a medical history of recurring VOC episodes (*Supplementary Table 1*). One patient who experienced 3-4 VOC episodes per year also required hospitalization. Patients presented a range of symptoms, including right lower extremity pain, cough, fever, chronic lower back pain, icteric sclera, nasal congestion, loss of taste, intermittent frontal headache, intermittent musculoskeletal pain, febrile dyspnea, acute respiratory distress, pain in arms and chest walls (*Supplementary Table 1*). At the time of admission, four of the five patients were noted to have HbSS, while one was identified as sickle cell HbSC.

Presenting symptoms at the emergency room (ER) often included fever, shortness of breath, cough, headaches, and pain in both arms and chest walls. After the initial ER or telemedicine visit, three out of five patients were hospitalized for the duration of their sickness. During the time of hospitalization, laboratory tests were performed on patients with SCD (*Supplementary Tables 2-4*). Treatment options were mentioned in each case but varied from patient to patient.

In these cases, patient one was started on prophylactic enoxaparin to prevent deep vein thrombosis, followed by a simple transfusion of 1 unit of packed RBCs for the treatment of hypoxia and pain, and advised to self-quarantine following a positive COVID-19 test. In the second case, treatment was albuterol MDI, Dextromethorphan 20 mg every 4 hours as needed for cough, and Lidocaine patch as needed for pain. The third case was a more severe treatment; the patient was administered 4 L O2 via nasal cannula, azithromycin, ceftriaxone, I.V. morphine, dexamethasone, and enoxaparin 80 mg for 12 hours for thrombosis prophylaxis because of high D-dimer levels. Patient three was hospitalized for four days and had an elaborate treatment plan (*Supplementary Table 5*). Patent four had a mild case, being the only patient out of five not hospitalized and had pain management treated via OTC analgesics. In the case of patient five, there was a severe case with an intricate treatment course over the 34 days of hospitalization, including blood exchange transfusion, among many other treatments (*Supplementary Table 5*).

Conclusions

To better understand the interactive effect of COVID-19 in patients with SCD, we collected, reviewed and summarized all available published data to aggregate the status of the literature in this area into one paper. As the JN.1 and other variants of COVID-19 emerge and rates of infection again increase, understanding how this virus interacts with rare diseases like SCD is increasingly important. Understanding which profiles of genetics and behavioral patterns of healthcare utilization and comorbid disease are associated with the greatest risk of severe morbidity and mortality is critical to understand.

For example, if adult patients with β-thalassemia, a history of complicated depression with anxiety, and a pattern of high emergency room utilization seem to be at greater risk for hospitalization and mortality from COVID-19, proactively developing public health inoculation strategies for that group would seem warranted and a good investment. Almost four years into the pandemic/post-pandemic era, our review suggests that we are in our infancy in terms of knowledge of the interactive effects of COVID-19 and SCD across the lifespan of patients who are potentially affected. More research is needed to better understand a comorbidity that is likely to be around for many years to come. The sooner we understand the many common and rare comorbidities that impact SCD,[63-67] the more effective our public health and individual evaluation and intervention efforts become. Towards the reduction of health disparities researchers and clinicians should see the advancement of knowledge in this area as an eminent priority.

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Online supplementary material:

Table S1. Medical history, current medications, presenting symptoms, and hemoglobin values.

Table S2. Vital signs.

Table S3. Relevant hematologic values, D-dimer levels, and total bilirubin.

Table S4. Imaging and testing results and SARS-CoV-2 reverse transcription polymerase chain reaction testing results.

Table S5. Complications during hospitalization and treatment.