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Managing sickle cell patients with COVID-19 infection: the need to pool our collective experience

Coronavirus disease 19 (COVID-19) has posed unparalleled challenges for healthcare communities, the general population and, in particular, for patients suffering from various comorbidities. Patients with haematological disorders, both benign and malignant, need special attention during this crisis, to ensure uninterrupted delivery of optimal care.[1]

Sickle cell disease (SCD) is the most common inherited anaemia in the USA and the UK with an approximately 80 000–100 000 and 12 500–15 000 individuals living with the disease in the USA and UK respectively.[2,3] Patients with SCD are prone to an increased risk of infections that can trigger acute chest syndrome (ACS) and related pulmonary complications. Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), the agent responsible for the current COVID-19 pandemic, has been found to be a trigger for the development of ACS and veno-occlusive crisis (VOC) in patients with SCD.[4–8] We hereby discuss the recently reported literature on patients with SCD who developed COVID-19.

Our literature review showed 19 SCD patients with COVID-19 were reported from December 2019 till 17 May 2020,[2,5,6,9-11] (Table 1). The largest case series by McCloskey *et al*. included 10 patients, six with confirmed COVID-19 (laboratory-confirmed COVID-19, reverse transcription polymerase chain reaction (RT-PCR)-positive) and four with suspected COVID-19 (clinical COVID-19 based on laboratory/imaging findings).[7] Similarly, in Nur *et al*.'s two patient series, one patient with SCD required repeat RT-PCR swab testing to confirm COVID-19.[8] Patients received a varied combination of supportive care for SCD-VOC/ACS with hydration, analgesics, empirical broad-spectrum antibiotics, red blood cell exchange, and simple blood transfusions. With regard to COVID-19 pneumonia, most of the patients (15/19) required oxygen support ranging from low flow (2 l/min) to high flow, non-invasive and mechanical ventilation in critically ill patients. Only one patient from Hussain *et al*.'s series required mechanical ventilation. The patient improved and was discharged home after 13 days of hospital stay.[6] Tocilizumab (IL-6 inhibitor, an investigational drug for COVID-19) and hydroxychloroquine were used in two and three patients respectively.[4–6,12] A single dose of tocilizumab was used (8 mg/kg) in both the patients with a good response.[6,11]

Except for one death reported by McCloskey *et al*. (a 57-year-old person with a history of stroke, bedbound with a neurological compromise), the rest of the 18 patients had a complete recovery from COVID-19.[7] Barring one improved patient, reported by Nur *et al*., who was still hospitalized at the time of reporting of the case, the remaining 17 patients were successfully discharged home with a median hospital stay of 7·2 days.[8]

ACS is considered one of the leading causes of death in patients with SCD. Thromboembolism, pulmonary infection, rib infarction and fat embolism are common causes of ACS. Experience from the 2009 H1N1 influenza pandemic has shown the H1N1 influenza virus to be a trigger for ACS with a significant proportion of SCD patients requiring intensive care support.[9] In most of the COVID-19 patients, the disease presents in the milder form. Only in a small percentage of patients is COVID-19 pneumonia likely to cause hypoxia and ventilation-perfusion mismatch. SCD has a complex pathogenesis leading to vaso-occlusion and hypercoagulability, which can result in serious complications and multiple organ dysfunction (Fig 1). Based on this vicious cycle, it is likely that COVID-19 patients with SCD will have a poorer outcome than patients without COVID-19, but more evidence is required to confirm this.

From lessons learned from previous viral outbreaks and currently available literature on the COVID-19 pandemic, SARS-CoV-2 viral infection should be considered as one of the important triggering factors for sickle-cell crisis. Any patient with SCD presenting with ACS/VOC symptomatology should be evaluated for COVID-19 with a SARS-CoV-2 PCR testing.[8]

SCD is the most common genetic disease in the world, and we believe that SCD patients suffering from COVID-19 are underreported. Patients with SCD have various reasons (functional hyposplenism, vasculopathy and recurrent VOCs) for an impaired immune system, which puts them in the 'high-risk category' of acquiring SARS-CoV-2, like patients with other blood disorders.[13,14]

Table I. Description of the patients with sickle cell disease and COVID-19 (up to 17 May 2020).

Age/Gender	SCD genotype	Chief complaints	COVID RT-PCR Test	Radiology imaging (Chest X ray/CT chest)	Laboratory data	Maximum oxygen requirement	Management	Outcome
32/M[6]	HbSS	Typical VOC symptoms	+ve	Plate-like atelectasis above the left lower lobe	WBC-22·7 10^3/µl Hb-7·3 g/l	Mechanical ventilation	Analgesics, antibiotics, HCQ, RBCX	Improved, discharged after 13 days
37/F[6]	HbSBeta	Typical VOC symptoms	+ve	Normal	WBC 5·3 10^3/µl Hb-10·1 g/l	No O_2 support required	Analgesics	Improved, discharged after 8 days
22/F[6]	HbSS	Severe pain, nausea, vomiting, diarrhea	+ve	Normal	WBC-16·0 10^3/µl Hb-7·3 g/l	No O_2 support required	Analgesics, antibiotics	Improved, discharged after 2 days
41/M[6]	HbSC	Cough, dyspnoea	+ve	Normal	WBC-8·1 10^3/µl Hb-11·4 g/l	No O_2 support required	Analgesics	Improved, discharged after 4 days
21/M[4]	HbS/β0-thalassemia	Worsening left hip pain X 4 months New onset fever, cough and hypoxia during hospital stay	+ve	Multifocal ill-defined opacities in the left mid-lung, retro-cardiac portion of the left lower lobe and right lung base	WBC-6·0 10^3/µl ALC-1·4 $\times 10^9$/l Hb-8·6 g/l LDH-664 IU/l	O_2 support (4 l/min)	RBCT RBCX HCQ	Improved, discharged after 11 days
45/M[5]	HbSS	VOC related symptoms at admission followed by fever and hypoxia	+ve	Consolidation, crazy-paving pattern with GGOs and interlobar septal thickening	CRP-189 mg/l Hb-7·0 g/l WBC-20 10^3/µl	Venturi mask (15 l/min and a 100% FiO_2)	Antibiotics HCQ Tocilizumab dose 8 mg/kg) RBCT	Improved, discharged after 15 days
16/F[11]	HbSS	Fever, acute chest pain	+ve	B/l consolidation with halo sign on right side B/l PE	CRP-355 mg/l LDH-446 IU/l; Hb-6·4 g/l D-Dimer-23·611 ng/ml IL6-629 pg/ml (normal <8·5)	NIV	Intensive care support RBCT, RBCX Therapeutic anticoagulation Tocilizumab (1 dose 8 mg/kg)	Improved, discharged after 11 days
24/M[8]	SCD	Severe right thoracic pain, dyspnoea, Fever	1st test −ve 2nd test +ve	Bilateral infiltrates without GGOs or crazy paving	NA	0_2 support up to 5 l/min	Antibiotics, analgesics	Improved, discharged after 4 days
20/F[8]	SCD	Severe back pain and extremity pain	+ve	Normal	NA	No O_2 support required	Analgesics	Improved, not discharged at time of reporting
10 cases (9) [Mean age 36 years, range 23–57)][7]	9 with HbSS or HbSBeta 1 with HbSC	Chest pain, fever, dry cough	+ve in 6 patients −ve in 4 patients	Typical findings in 5 and normal in 5 patients	Mean values (10 patients) Nadir ALC-1·36 $\times 10^9$/l Max CRP −63·5 mg/l Max LDH-802·5 IU/l Max Ferritin-2485 µg/l	All patients required O_2 support	All patients received analgesics antibiotics. 3 patients required RBCT	1 death, remaining 9 recovered and discharged after mean hospital stay of 7·2 days

ACS, acute chest syndrome; AVN, avascular necrosis; CKD, chronic kidney disease; CRP, C reactive protein; F, female; GGOs, ground glass opacities; FiO_2, Fraction of inspired oxygen; Hb, haemoglobin; HCQ, hydroxychloroquine; HDU, hydroxyurea; LDH, lactate dehydrogenase; M, male; NIV, Non-invasive ventilation; PE, pulmonary embolism; RBCX, red blood cell, exchange transfusion; RBCT, red blood cell simple transfusions; SCD, sickle cell disease; VOC, veno-occlusive crisis; VTE, venous thromboembolism.

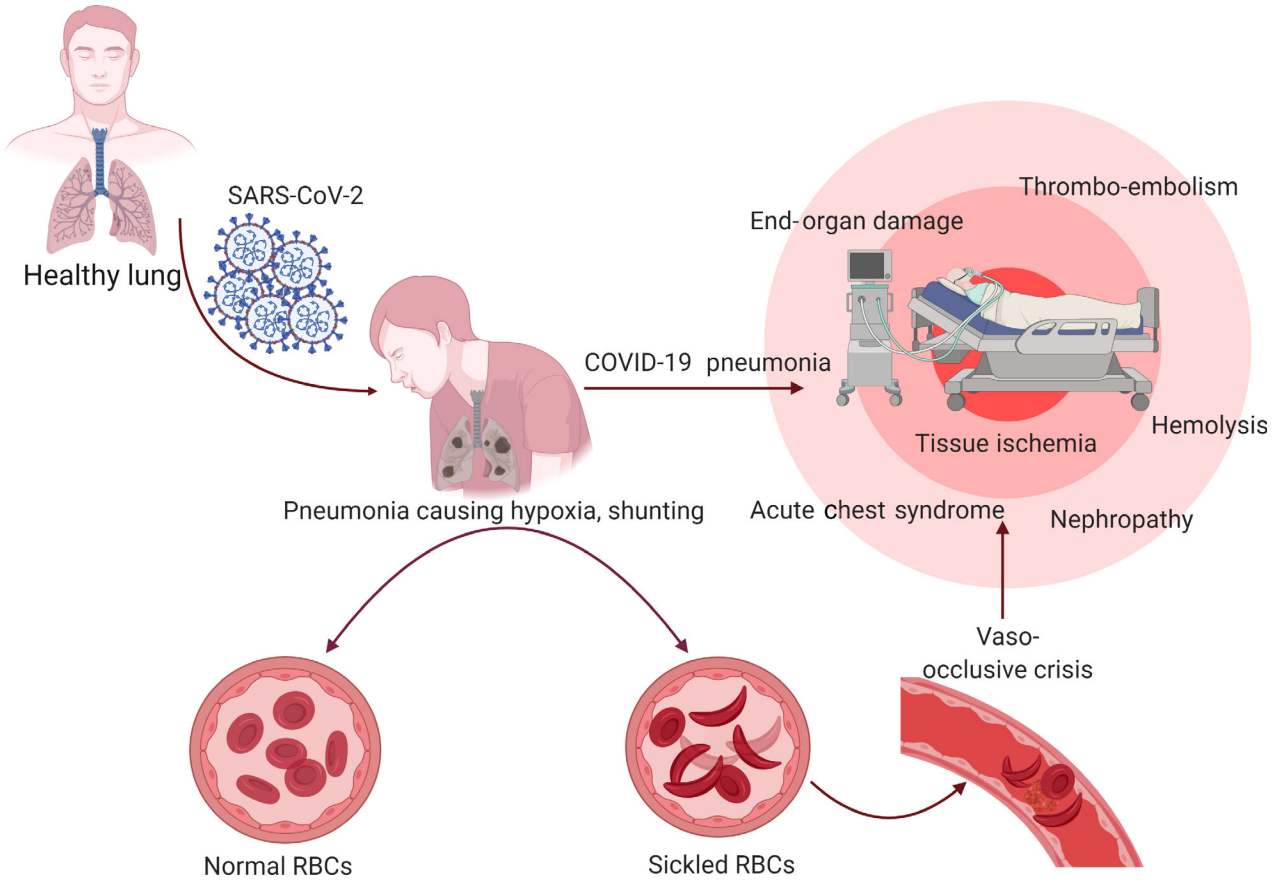

Fig 1. Pathogenesis of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection in a patient with sickle cell disease (created with biorender.com).

Currently, many unanswered questions remain and need attention. For example, do compound heterozygous patients (e.g. sickle cell-beta thalassemia) have a higher risk of acquiring SARS-CoV-2 and how does their clinical course of COVID-19 compare with homozygous sickle cell disease patients? We also need to understand more about the role of hydroxyurea. Does it increase the risk of SARS-CoV-2 infection owing to the myelosuppressive property? And what is its specific impact on red cell–endothelial cell interaction in COVID-19? What is the impact of iron overload on COIVD-19? Given the complex logistics of red cell exchange in COVID-19-positive individuals, and the fall in Hb that accompanies severe illness such as COVID-19 infection, would it be advantageous to treat SCD patients with preventative simple transfusions instead of red blood cell exchange? Unfortunately, answers to these questions are not possible until all the data on SCD patients with COVID-19is pooled and we capture their disease course and outcome. Experts from the Medical College of Wisconsin have created a voluntary reporting system (https://covidsicklecell.org/) to study the impact of COVID-19 on the wellness of patients with SCD.[2] Such collaborative efforts should not only involve haematologists but also primary care providers, family physicians and emergency physicians. The increased awareness about how to approach a sickle-cell crisis is of extreme importance, especially amongst the physicians in the emergency departments who might overlook the sickle-cell crisis and treat the patients for COVID-19 only, thereby missing the inciting factor.[10,15,16]

To date, there are no specific clinical trials on patients with SCD and COVID-19. We aim to draw the attention of research bodies and scholars to the need to develop a well-structured global portal for data gathering and sharing to aid in providing optimal care to patients with SCD during the COVID-19 pandemic.

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Keywords: viruses, sickle cell anaemia, anaemia, pandemic, coronavirus

First published online 11 June 2020
doi: 10.1111/bjh.16880

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Clinical significance of blue-green neutrophil and monocyte cytoplasmic inclusions in SARS-CoV-2 positive critically ill patients

Identification of blue-green cytoplasmic inclusions in neutrophils and/or monocytes on peripheral blood smears is a rare, and likely underreported, finding described in few case reports and small case series studies in critically ill patients with acute liver dysfunction and lactic acidosis.[1–11] As these inclusions are thought to herald poor prognosis and death shortly after identification, they have been referred to as 'green crystals of death' or 'critical green inclusions'.

The coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to hundreds of thousands of deaths worldwide as of May 2020. Though many patients have mild symptoms, a subset develop severe pneumonia, acute respiratory distress syndrome (ARDS), multiorgan failure, and death. Over one-third of patients with COVID-19 have elevated serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST), however, it is unclear whether liver dysfunction is directly caused by viral infection, sequelae of sepsis, or a complication of other comorbidities.[12,13]

To better understand and manage COVID-19, it is imperative that biological indicators associated with adverse outcomes be identified. One such indicator that has been described in approximately 80% of critically ill patients with COVID-19 is lymphocytopenia.[14] As a result, emerging COVID-19-related studies emphasize lymphocyte counts, but do not readily provide information on blood smears. One group described COVID-19-related leukocyte morphologic changes that could provide further insights into the inflammatory process associated with the disease; however it remains unknown whether there are distinct morphologic changes that can aid in identifying patients at risk of poor outcomes.[15] Given the liver dysfunction and leukocyte morphologic changes associated with SARS-CoV-2 infection, blue-green inclusions may be underreported in this population and may correlate with short-term mortality.