**Abstract**

Sickle cell disease (SCD) patients are immunocompromised with multiple comorbidities and a hypercoagulation state. On the other hand COVID-19 is associated with cytokine storm and hypercoagulability. To find the susceptibility and the clinical course of COVID-19 in SCD patients we surveyed related published papers from USA, Europe, Middle East, few African patients and international SCD registry. The COVID-19 presentation was mild in children and moderate in many SCD adults. To explain these findings, possible benefits of high HbF level, and hydroxyurea therapy could be considered. The obtained results should be interpreted considering low cases from sub-Saharan people, younger age of SCD patients compared to general population, a bias toward registry of more severe form of the disease, the influence of preexisting comorbidities with multisystem organ damage in exacerbation of the COVID-19 and the fatality rate in SCD patients and the role of health socio-economic determinants.

**Key words**: Sickle cell disease, COVID-19, hypercoagulation, HbF, splenectomy, hydroxyurea

## Introduction

Infection with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) that is responsible for coronavirus disease 2019 (COVID-19) results in cytokine storm with damage to organs, mainly lungs in severely affected patients (1).

Hemoglobin S (HbS), an abnormal structural hemoglobin variant, results from valine substitution for glutamic acid at the 6$^{th}$ position of the beta globin-chain of hemoglobin. This alteration results in polymerization of the hemoglobin in low oxygen saturation, deformity of the red blood cells and microvascular occlusion (2). Around 5% of the world's populations are carriers of hemoglobinopathies, mainly sickle cell disease (SCD) with a carrier prevalence of 10–45% of the sub-Saharan Africa population for the sickle cell gene (3).

The pandemic of COVID-19 emerged concern about greater susceptibility of SCD patients to COVID-19 and more severe form of the disease. Centers for Disease Control and Prevention have classified SCD as one of conditions to be considered at increased risk of severe illness from COVID-19 infection (4). Since SCD patients 1) have underlying pathophysiology of chronic inflammation with increased risk of thrombosis, 2) are immunocompromised due to autoinfarction of their spleen or surgical splenectomy and especially prone to infectious diseases and acute chest syndrome (ACS), and 3) have comorbidities and secondary organ dysfunction (5) there is concern about susceptibility and the severity of COVID-19 in these patients. The aims of present review were to summarize and analyses the susceptibility of SCD patients to COVID-19 and its severity.

## Methods

In the present review we surveyed the literature (PubMed, Web of Science, and Scopus) till November 19, 2020 and 24 published papers along with the international SCD registry related to SCD and COVID-19 were identified. To consider the influence of age on COVID-19 susceptibility and outcome, children (<19 years) and adults (≥19 years) were separately discussed. The following information, if was available, including sample size, the mean age, Hb F level and the history of splenectomy, the genotype of SCD, hydroxyurea (HU) therapy and the clinical course of COVID-19 were extracted and summarized in Tables 1 and 2.

## Results

### Children

There were five case report and case series from United States of America (USA) including a case series of 6 patients with HbSS and one with HbSC, 4 on HU therapy and one with splenectomy that had favorable outcome of COVID-19 (5). Also, there were 2 American children, one with Hb SS (7) and other with HbSC (5), positive for COVID-19 that had mild disease presentation and good outcome during hospitalization. Also, comparing 5 American pediatric patients with HbSS developed ACS with 3 HbSS patients that did not have ACS, indicated the clinical presentation of COVID-19 was not severe and none of these patients required intensive care unit (ICU) management or significant respiratory support. Patients without ACS all were on HU therapy compared to the absence of HU therapy in all SCD patients developed ACS (8). Based on the SECURE-SCD Registry of the Medical College of Wisconsin among 178 SCD patients including 44 patients <19 years, the mortality rate was 2.3% in children (9). In three separated reports from France including 9 SCD patients with COVID-19 no death was detected (10-12). Three patients were on HU treatment (11,12), one with splenectomy, and

the baseline HbF levels were 8.3-16% (11), all patients had favorable respiratory outcome. In a report from national survey of United Kingdom (UK) consisted of 77 hospitalized SCD patients with COVID-19 including 10 patients < 20 years, there was one death (13). Finally, according to international SCD registry updated November 6, 2020 among 186 SCD patients <19 years with COVID-19 there was one death (0.5%) (14) (Table 1).

**Adults**

Based on the SECURE-SCD Registry of the Medical College of Wisconsin among 134 adult SCD patients, the rate of ICU admission was 11% and the mortality rate was 7%. However, the rate of mortality was higher among milder SCD genotypes compared to severe genotypes. However, the presence of a bias toward more severe form of the disease in this registry and the preexisting comorbidities with multisystem organ damage in exacerbation of the COVID-19 and fatality rate in SCD patients should be considered (9). In a report of 24 SCD from USA a mild clinical course of the COVID-19, low rate of intubation, ICU admission and death, was observed. Ninety-two percent of patients were African-American and 63% had at least one comorbidity. Only one sickle cell trait that had been on chronic immunosuppressive therapy and required ICU admission died. None of SCD patients received HU therapy (15). Mild clinical course of the COVID-19 disease existed in a HbS/$\beta^0$-thalassemia on HU therapy (16), and 4 SCD cases from USA (17). In a multicenter study from France consisted of 83 inpatients SCD with COVID-19, mostly adults with SS/S$\beta^0$-thalassemia genotype (18), and a case with HbSS (19) COVID-19 did not increase the risk of morbidity or mortality in these patients. Two patients who died with COVID-19 pneumopathy had the milder HbSC genotype (18). Comparing 9 case series of COVID-19 including 8 patients with HbSS and one patient with HbSC from the USA, that

67% of them had comorbidities, with 53 age-matched controls infected with SARS-CoV-2 indicated 35.9% of controls needed ICU admission, 4 individuals required intubation and the mortality rate was 5.6%. However, among SCD patients 11.1% required ICU admission without need for intubation and no death was observed (20). In one case series of 10 SCD patients from UK with COVID-19, none of patients required admission to ICU, mechanical ventilation or non-invasive ventilation. Only one patient with previous stroke and multiple co-morbidities died. The overall outcome of COVID-19 infection was favorable in SCD patients (21). Also, another UK study reported mild clinical symptoms of COVID-19 in 10 patients with HbSS and COVID-19 in spite of presence severe pre-morbid disease and previous ICU admission in 90% of them. Only one patient with multiple co-morbidities died (22). In a report from national survey of UK consisted of 67 hospitalized SCD patients, the mortality rate was lower than general population of the UK (10.4 vs. 14.8%) but the age adjusted risk of death analysis indicated an increased risk of COVID-19 related death in SCD patients. In 75% of patients who died there were comorbidities. The mortality was higher in mild genotypes of SCD (HbSC, HbSC, HbS$\beta^+$-thalassemia or HbSE) than severe genotype (HbSS, HbS$\beta^0$-thalassemia) (13). Also, two cases of HbSS with COVID-19 from the Netherlands recovered from the disease (23). Among three patients with severe HbSS originating from Congo with confirmed COVID-19 the clinical presentation of the disease was mild. All patients received HU therapy (24). Further, in a Senegalese SCD woman positive for COVID-19 the clinical course of the disease was mild (25).

There are 4 studies from Middle East including a Saudi-Arabian family with COVID-19, mother was sickle cell trait without significant symptoms of the COVID-19 and two her HbSS children, recovered from COVID-19 with good outcome (26). In an international multicenter study including 17 centers from 10 countries and a survey of 9,499 patients with hemoglobinopathies

using a questionnaire, 3 out of 2000 SCD (0.15%) including one child an 2 adults with confirmed COVID-19, two out of 3 were non-pneumonic COVID-19, were detected in Oman. However, in the Oman general population the rate of SARS-CoV-2 infection was 0.33% (27). In a report from Bahrain, 38,092 people including 387 SCD patients were tested for COVID-19. The infection rate of normal population was 1.83% compared to 1.6% in SCD patients. Also, the clinical course of the disease in HbSS patients was not different compared to normal population (28). In a SCD patient from Egypt with a history of splenectomy and confirmed COVID-19 the clinical course of the disease was moderate (29). According to international SCD registry updated November 6, 2020 among 252 adult cases with SCD the mortality rate was 6.3% and around 43% expired patients were on HU therapy. Most of patients had various comorbidities (**14**) (Table 2).

**Discussion**

SCD patients are immunocompromised with multiple comorbidities and a hypercoagulable state. However, according to most reports, COVID-19 had mild clinical course in SCD children and many reports, but not all, suggested a mild to moderate clinical presentation of COVID-19 in SCD adults. These findings could be interpreted considering the following matters:

1) The SCD has high prevalence among African descent people, Indian subcontinent, some parts of the Middle East and in the Mediterranean region. Sub-Saharan Africa accounts for approximately 79% of around 300,000 infants born annually with SCD worldwide. In spite of high prevalence of SCD in sub-Saharan Africa data related to SCD and COVID-19 are limited (30). Also, according to the WHO report, globally Africa has the least affected individuals with

1.5% of the world's reported COVID-19 cases, and 0.1% of the world's death. However, WHO estimated up to 15% of mortality in Africa is due to SCD (31).

2) Although, interaction between genetic and environmental factors determine the overall clinical outcomes of the human diseases but health socio-economic determinants have crucial role in health inequities and disease outcome. In the US it seems among African American there are higher mortality rates due to COVID-19, and SCD mostly affects Black/African Americans in the US (32).

3) In addition to the association of Arab-Indian and Senegal haplotypes linked to the $\beta^S$ gene with high HbF levels and milder disease, some SS patients with other haplotypes also had a very high HbF level (**33**). Unique structural properties of the HbF tetramer make HbF-containing red blood cells as inadequate hosts for Plasmodium falciparum (34). So, it might high level of Hb F in SCD patients had an advantage against viral infection including infection with SARS-COV-2. In few studies the high levels of HbF in SCD patients with COVID-19 has been reported. The role of HbF in susceptibility and the severity of COVID-19 in these patients needs to be confirmed with more reports. Also, a possible potential role for beta chain mutation in prevention of binding the SARS-CoV-2 viral proteins to the hemoglobin and inhibition of iron dissociation from heme has been suggested (**15).**

4) Hydroxyurea as the only FDA-approved pharmacologic treatment for SCD (HbSS, and HbS/ $\beta^0$-thalassemia) is safe and cost effective and reduces the frequency and the intensity of painful events in these patients. This drug decreases the rate of ACS events, transfusion requirements, and hospitalization. HU mildly increased HbF and metabolized to nitric oxide which could increase vasodilation and enhance blood flow (35). HU therapy improved hemolysis markers,

increased the HbF level and decreased HbS level and also reduced the monocyte counts. Also, HU decreased the frequency and activation of the classical inflammatory monocytes responsible for multiple pro-inflammatory cytokine production and had overall anti-inflammatory function (36) and reduced the plasma D-dimer level in SCD patients (37). Since, cytokine storm and increased monocytes and macrophages are implicated in COVID-19 lung injury the HU therapy could have an advantage in lowering absolute monocyte counts, decrease inflammatory cytokines, and reduction of endothelial adhesive markers (8). Further, HU decreased the levels of factors II, V, VII, VIII, X, and XI with a significant rate of decrease in FVIII and protein C by 54.8 and 12.5%, respectively (38). Furthermore, HbSS patients treated with HU compared to untreated patients had reduced coagulation activation and fibrinolysis (**39)**. Finally, antiviral effect of HU with chloroquine or its analog hydroxychloroquine has been indicated (**40).** Some studies reported the history of HU therapy in SCD patients with COVID-19 and its benefit (5,7,8,11,12,16,19,20,24,26).

5) In patients with SCD circulating CD4+ and CD8+T-lymphocytes are decreased that results in reduced humoral immune response or a cell-mediated immune response by CD4+T-lymphocytes with reduced cytokines storm after SARS-CoV-2 infection that might results in milder course of the disease (25).

6) Patients with SCD considered as high risk individuals for respiratory infections including SARS-CoV-2 infection and subsequent pulmonary complication of ACS because of impaired immunity due to functional hyposplenism, systemic vasculopathy predisposing to end organ dysfunction and a high risk of thrombosis (17,21). However, in animal models, splenectomy decreased the proinflammatory/anti-inflammatory ratio through a decrease in spleen-originated

inflammatory cells (41). Since, only 4 SCD patients with splenectomy and good outcome have been reported (5,8,11,26) the possible benefit of splenectomy against produced cytokine storm in COVID-19 patients needs to be elucidated.

7) Although, none of reports discussed about the ferritin levels and the iron chelation therapy in SCD patients with COVID-19 but high ferritin levels represents a negative prognostic factor in patients with COVID-19 and iron chelation with deferiprone or deferoxamine that has been proposed for COVID-19 therapy reduced viral replication and related pro-inflammatory pathways (42). So, iron chelation in those SCD patients who needs transfusion might also be benefit against COVID-19 that should be confirmed.

**Conclusion**

SCD patients are immunocompromised with multiple comorbidities and a hypercoagulation state. On the other hand COVID-19 is associated with cytokine storm and hypercoagulability. According to the literature, the COVID-19 presentation was mild in children and was moderate in many adults with SCD. To explain these findings we discussed possible benefits of high level of HbF, and HU therapy that needs to be confirmed in future researches. Also, the obtained results should be interpreted considering low cases from sub-Saharan people, younger age of SCD patients compared to general population, a bias toward registry of more severe form of disease, the influence of preexisting comorbidities with multisystem organ damage in exacerbation of the COVID-19 and fatality rate in SCD patients and the role of health socio-economic determinants.

**Conflict of interest**: None

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