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REVIEW

Sickle cell disease and COVID-19: Susceptibility and severity

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Abstract

We surveyed published papers and an international sickle cell disease (SCD) registry to detect susceptibility and clinical course of coronavirus disease 2019 (COVID-19) in SCD patients. COVID-19 presentation was mild in children and moderate in many SCD adults. Regarding increased comorbidities with age, it seems severe COVID-19 to be more common in older SCD patients. Although the overall outcome of COVID-19 was favorable in SCD children, a high rate of pediatric intensive care unit admission should be considered in managing these patients. To explain COVID-19 outcome in SCD patients, the possible benefits of 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 the more severe form of disease, the effect of pre-existing comorbidities with multisystem organ damage, and the role of health socio-economic determinants.

KEYWORDS
COVID-19, HbF, hydroxyurea, hypercoagulation, sickle cell disease, splenectomy

1 | INTRODUCTION

Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for coronavirus disease 2019 (COVID-19), results in a 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 sixth position of the beta globin chain of hemoglobin. This alteration results in the polymerization of hemoglobin in low oxygen saturation, the deformity of red blood cells, and microvascular occlusion.[2] About 5% of the population in the world is the carrier of hemoglobinopathies, mainly sickle cell disease (SCD), with a carrier prevalence of 10–45% of sub-Saharan Africa population for sickle cell gene.[3]

COVID-19 pandemic emerged as a concern about greater susceptibility of SCD patients to COVID-19 and more severe form of disease. The Centers for Disease Control and Prevention have classified the SCD as one of the 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,[5] (2) are immunocompromised due to auto-infarction of their spleen or surgical splenectomy and especially prone to infectious diseases and acute chest syndrome (ACS),[6] and (3) have the comorbidities and secondary organ dysfunction,[7,8] there is concern about susceptibility and COVID-19 severity in these patients. The present review aimed to summarize and analyze the susceptibility of SCD patients to COVID-19 and its severity.

Abbreviations: ACS, acute chest syndrome; COVID-19, coronavirus disease 2019; HbS, hemoglobin S; HU, hydroxyurea; ICU, intensive care unit; LDH, lactate dehydrogenase; PICU, pediatric ICU; RT-PCR, real-time reverse transcription-polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SCD, sickle cell disease; WHO, World Health Organization.

2 | METHODS

In the present review, we surveyed the literature (PubMed, Web of Science, and Scopus) till January 21, 2021, and 27 published papers, including a paper from SECURE-SCD Registry of Medical College of Wisconsin, USA, along with international SCD registry, US registry, updated on April 2, 2021, related to SCD patients with confirmed COVID-19 were identified. In all studies, COVID-19 presence was confirmed using real-time reverse transcription-polymerase chain

reaction (RT-PCR). One study from Oman due to incomplete information and possible overlap with another study from this country reported in this review was omitted. Data presented in the text, the tables of scientific documents, and the website of international SCD registry,[9] and also US registry[10] were extracted and analyzed by researchers. To consider age effect on COVID-19 susceptibility and outcome, children and adults were separately discussed. The following important or available parameters including sample size, the mean age, the death rate due to COVID-19, intensive care unit (ICU) admission, hospitalization, SCD genotype, HbF level, hydroxyurea (HU) therapy, simple/exchange transfusion during hospitalization, and the history of comorbidities were extracted. In the final analysis of parameters, we separately discussed data from 27 published papers and international SCD registry to prevent possible duplication of data.

3 | RESULTS

3.1 | Children

There were four case series and case reports from United States of America. In a case series of seven SCD patients, six with HbSS and one with HbSC, four on HU therapy and one with splenectomy, COVID-19 outcome was favorable.[7] Moreover, in a case series that compared five American pediatric patients with HbSS developed ACS with three HbSS patients who did not have ACS, clinical presentation of COVID-19 was not severe. None of these patients required the ICU admission or significant respiratory support. All patients without ACS were on HU therapy compared to the lack of HU therapy in all SCD patients who developed ACS.[11] In two separate cases reports from American children, one with HbSC[12] and other with HbSS and without comorbidity,[13] COVID-19 presentation was mild with a good outcome during hospitalization. Considering SECURE-SCD Registry of Medical College of Wisconsin, USA, among 178 SCD patients, including 44 patients <19 years, mortality rate was 2.3% in children.[10]

In a multicenter study from France consisting of 12 inpatients, COVID-19 SCD with SS/Sβ^0-thalassemia genotypes,[14] no death was observed among hospitalized SCD patients. In two separate reports from France, including five SCD patients with COVID-19, no death was detected.[15,16] Three patients were on HU treatment,[15,16] one with splenectomy, and baseline HbF levels 8.3–16%[15]; all patients had favorable respiratory outcomes. There was one death based on a report from the national survey of United Kingdom consisting of 77 hospitalized SCD patients with RT-PCR-confirmed COVID-19, including 10 patients <20 years.[17] Furthermore, among three hospitalized SCD patients from Brazil, two SS on HU therapy and one SC, no ICU admission and death were reported. The mean level of HbF was 17% in two SS patients, and three patients required blood transfusion during hospital stay.[18] Finally, as per the international SCD registry, updated April 2, 2021, among 365 SCD patients <19 years with COVID-19, there was one death (0.3%)[9] (Table 1).

The death rate was 2.1% (two out of 94) among SCD cases based on published papers compared to 0.3% (one out of 365) according to the international SCD registry.[9] Due to available data related to simple/exchange transfusion during hospitalization and the presence of at least one comorbidity, 20 out of 39 (51.3%) and 25 out of 38 (65.8%) patients required the transfusion who had comorbidities, respectively. In international SCD registry,[9] 66 out of 365 (18.1%) needed transfusion. Although the presence of 327 comorbidities were reported in 365 patients in the registry,[9] it was not clear that each individual had one comorbidity or there might be more than one comorbidity in a patient. Pediatric ICU (PICU) admission was nine out of 40 (22.5%) in published papers, and in the report of international SCD registry[9] was 23 out of 365 (6.3%) (Table 1).

Regarding available data, 19 out of 38 pediatric patients were on HU therapy (50%), and in the international SCD registry report,[9] there were 203 out of 365 (55.6%) (Table 1). The mean HbF level was available in three studies[11,15,18] as 17.7%, 12.3%, and 11.3%, respectively.

3.2 | Adults

Considering SECURE-SCD Registry of the Medical College of Wisconsin, among 134 adult SCD patients, ICU admission rate was 11%, and mortality rate was 7%. Mortality rate was higher among milder SCD genotypes compared to severe genotypes. However, the presence of a bias toward a more severe form of disease in this registry and pre-existing comorbidities with multisystem organ damage in the exacerbation of COVID-19 and fatality rate in SCD patients should be considered.[10] Around 40% of deaths were among patients who had milder SCD genotypes (HbSC or HbSβ^+-thalassemia).[10] In one large study from five referral SCD centers in the United States, 66 SCD patients with COVID-19, including 57 adults, were detected from 3500 adult and pediatric patients with SCD. The median age was 34 years (the age range was 8 months to 69 years). The mortality rate was 10.6%, which was higher than the general population (3.3%).[19] HU was a protective factor, and all dead patients were not taking HU. The mortality rate was higher than the US-based registry (7%) and a European study, which seems to be due to this study's older age range. The study results showed older age with pre-existing chronic organ damage of kidneys, heart, lung, and brain were at high risk of morbidity regardless of hemoglobin genotype. SCD patients with pulmonary hypertension seem to be at the highest risk of mortality with COVID-19. Twelve out of 66 patients (18.2%) had a history of splenectomy. Moreover, patients with increased levels of lactate dehydrogenase (LDH) and D-dimer were at higher risk of death.[19]

In a report of 24 SCD cases from United States, a mild clinical course of 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 patient with sickle cell trait who was on chronic immunosuppressive therapy and required ICU admission died. None of the SCD patients received HU therapy.[20] A mild clinical course of COVID-19 disease existed in an HbS/β^0-thalassemia patient on HU therapy[21] and four SCD cases from the United States.[22] In a multicenter study from France, consisting

TABLE 1 Characteristics of studies that reported children with SCD infected with SARS-CoV-2

Reference	Sample size	Mean age	COVID severity parameters			SCD-related parameters				
			Mortality *n*	ICU admission *n*	Hospitalization *N*	SCD genotype	HbF%	HU therapy *N*	Transfusion *N*	Comorbidity *N*
7	7	14	0	1	2 with and 2 without comorbidity	6 SS,1 SC	NA	4	4	5
12	1	0.5	0	1	1	SC	NA	NA	NA	NA
13	1	~3	0	0	1	SS	NA	1	1	0
11	8	16	0	0	5 with ACS	SS	17.7	3	1 with ACS	6
10	44	<19	1	19/178 Children and adults	122/178 Children and adults	SS/Sβ^0, SC/Sβ^+	NA	NA	84/178 Children and adults	[a]182 in all cases
15	4	14.5	0	4	4	SS	12.3	2	4	1
16	1	16	0	1	1	SS	NA	1	1	1
17	10	<20	1	NA	10	NA	NA	NA	NA	NA
9	365	<19	1	23	149	SS/Sβ^0, SC/Sβ^+-thalassemia/	NA	203	66	327
14	12	0–14	0	2	12	SS/Sβ^0, Sβ^+-thalassemia	NA	4	4	8
18	3	11	0	0	3	2 SS, 1 SC	11.3	2	3	3
30	2	13	0	0	1	SS	NA	1	1	1
31	2 Adults and one child	27.3	0	0	2	SS	NA	3	1	0
Total	459	<20	3	32	191	[b]25 SS/3 SC	13.8	221	86	352

Note: Comorbidity included ACS, anxiety, asthma/obstructive sleep apnea, atrial tachycardia, behavioral problems, bilateral ischemic retinopathy, chronic obstructive pulmonary disease, depression, hallucination, painful crisis, pulmonary hypertension, splenectomy, renal disease, stroke.

Abbreviations: ACS, acute chest syndrome; COVID-19, coronavirus disease 2019; HU, hydroxyurea; ICU, intensive care unit; NA, not available; SCD, sickle cell disease; SS, sickle cell homozygous.

[a]Some patients had more than one comorbidity.

[b]Except references 9, 10, 14, the percentage of SCD genotype was considered in all patients and presented in Table 2.

of 71 inpatient SCD with COVID-19 (15–74 years), mostly adults with SS/Sβ^0, SC, Sβ^+-thalassemia genotype[14] and a case with HbSS,[23] COVID-19 did not increase the risk of morbidity or mortality in these patients. Among patients, there were eight with SC genotype, five (63%) of them admitted to ICU, and two patients (25%) died with COVID-19 pneumopathy.[14] Comparing nine case series of COVID-19, including eight patients with HbSS and one patient with HbSC, from the United States, 67% with comorbidities, with 53 age-matched controls infected with SARS-CoV-2 indicated 35.9% of controls needed ICU admission, four individuals required intubation, and mortality rate was 5.6%. However, among SCD patients, 11.1% required ICU admission without need for intubation, and no death was observed.[24] In one case series of six SCD patients from the United Kingdom with COVID-19, none of the patients required admission to ICU, mechanical ventilation, or noninvasive ventilation. Only one patient with a previous stroke and multiple comorbidities died, and the overall outcome of COVID-19 infection was favorable in SCD patients.[25] Moreover, another UK study reported mild clinical symptoms of COVID-19 in 10 patients with HbSS and COVID-19 despite the presence of severe premorbid disease and previous ICU admission in 90% of them. Only one patient with multiple comorbidities died.[26] In a report from the national survey of the United Kingdom of 67 hospitalized SCD patients, mortality rate was lower than the general population of the United Kingdom (10.4% vs. 14.8%), the age-adjusted risk of death analysis indicated an increased risk of COVID-19-related deaths in SCD patients. In 75% of patients who died, there were comorbidities. Mortality was higher in mild genotypes of SCD (HbSC, HbSC, HbSβ^+-thalassemia, or HbSE) than severe genotypes (HbSS, HbSβ^0-thalassemia). In mild genotypes, higher proportion of patients required critical care, eight of 29 (27.6%), than severe genotypes, seven of 99 (7.1%).[17] Furthermore, two cases of HbSS with COVID-19 from the Netherlands were reported that recovered from the disease.[27] Among three patients with severe HbSS originating from Congo with COVID-19, the disease's clinical presentation was mild. All patients received HU therapy.[28] Moreover, in a Senegalese SCD woman positive for COVID-19, the disease's clinical course was mild.[29]

There are five studies from Middle East, including a Saudi Arabian family with COVID-19, mother was sickle cell trait without significant symptoms of COVID-19, and two of her HbSS children, recovered from COVID-19 with good outcome.[30] In an international multicenter study, including 17 centers from 10 countries and a survey of 9499 patients with hemoglobinopathies, three out of 2000 SCD (0.15%), including one child and two adults with confirmed COVID-19, two out of three nonpneumonic COVID-19 were detected in Oman. However, in Oman general population, the rate of SARS-CoV-2 infection was 0.33%.[31] 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. Furthermore, the clinical course of disease in HbSS patients was not different as compared to normal population.[32] In an SCD patient from Egypt with a history of splenectomy and confirmed COVID-19, the clinical course of disease was moderate.[33] In a case with HbSS from Qatar on HU therapy and an HbF level of around 27%, the outcome of disease was favorable.[34] As per international SCD registry updated April 2, 2021, among 390 adult cases with SCD, the mortality rate was 4.6%. Most of the patients had various comorbidities. Mortality was higher in mild genotypes of SCD (HbSC/Sβ^+-thalassemia [2.8%]) than severe genotypes (HbSS/Sβ^0-thalassemia [2.1%])[9] (Table 2).

The death rate was 31 out of 409 (7.6%) in published papers compared to 18 out of 390 (4.6%) in international SCD registry.[9] Due to available data related to simple/exchange transfusion during hospitalization, 73 out of 200 patients (36.5%) required transfusion. There were 241 and 482 comorbidities among 201 SCD patients and 390 registered cases,[9] respectively, indicating the presence of more than one comorbidity in each patient. In international SCD registry,[9] there were 115 out of 390 (29.5%) who needed transfusion. ICU admission was 25 out of 208 (12%) among SCD patients reported in papers, and in the international SCD registry[9] was 33 out of 390 (8.5%) (Table 2).

HU therapy's available data indicated 79 out of 189 adult patients were on HU therapy (41.8%) (Table 2). In international SCD registry,[9] 193 out of 390 patients (49.5%) were on HU therapy. HbF level was available in three studies[24,26,34] as 1.5–30.4%, and the mean of 6.2% and 26.9%, respectively. One death occurred among 10 patients with a mean HbF level of 6.2%.[26]

3.3 | Symptoms

The most common symptoms in the symptomatic SCD children with COVID-19 were pain (120 out of 339, 35.4%) and pneumonia/ACS (52 out of 339, 15.3%). In adults, pain was detected in 249 out of 374 (66.6%), and pneumonia/ACS was prevalent in 108 out of 374 (28.9%).[9] In other studies, the most common symptoms among children were fever and ACS,[7] and in adults were cough, fever, myalgia, shortness of breath, chills,[20] fever, myalgia, back pain, and cough.[24]

4 | DISCUSSION

SCD patients are immunocompromised with multiple comorbidities and a hypercoagulable state. SCD patients with COVID-19 show a wide range of severity, which might be associated to a higher risk of morbidity and mortality. It seems severe COVID-19 to be common in older SCD patients, because the comorbidities are increased once SCD patients become older.[19] However, as per most reports, COVID-19 had a 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. A survey of literature indicated a death rate of 2.1% in SCD children with COVID-19; however, the mortality rate of pediatric patients with COVID-19 as per the international SCD registry[9] was 0.3%. The difference among overall mortality rates in published papers and US registry might be due to introducing severe SCD cases in the published papers, while in international SCD registry, 40.8% of patients[9] were hospitalized (Table 1). Although mortality rate of SCD children with COVID-19 was higher than that in pediatric patients infected with SARS-CoV-2 in general population (0.09%),[35] the

TABLE 2 Characteristics of studies that reported adults with SCD infected with SARS-CoV-2

Reference	Sample size	Mean age	COVID severity parameters			SCD-related parameters				
			Mortality *N*	ICU Admission *n*	Hospitalization *N*	SCD genotype	HbF%	HU therapy *N*	Transfusion *N*	Comorbidity *N*
10	134	19	12	19/178 children and adults	122/178 children and adults	135 SS/Sβ^0, 42 SC/Sβ^+ in all cases	NA	NA	84/178 Children and adults	[a] 182 in all cases
17	67	20–59	7	NA	67	NA	NA	NA	NA	NA
9	390	19 to ≥65	18	33	227	524 SS/Sβ^0, 212 SC/Sβ^+-thalassemia in all cases	NA	193	115	[a] 482
19[b]	66, 57 Adults	34	7	5	50	47 SS/Sβ^0, 19 SC/Sβ^+	NA	28	25	[b] #137
20	24	52.9	1	1	13	4 SS, 1 SC, 1 S/β^+-thalassemia, 18 AS	NA	0	3	15
21	1	21	0	0	1	HbS/β^0-thalassemia	NA	1	1	1
22	4	33	0	1	4	2 SS, 1 Sβ^0-thalassemia and 1 SC	NA	NA	1	4
14	71	15–74	2	15	71	71 SS/Sβ^0, 8 SC,4 Sβ^+-thalassemia	NA	34	27	59
23	1	45	0	0	1	SS	NA	1	1	1
24	9	27.9	0	1	9	8 SS, 1 SC	1.5–30.4	6	6	6
25	6	36	1	0	6	SS, Sβ^0-thalassemia, SC	NA	NA	NA	2

(Continues)

TABLE 2 (Continued)

Reference	Sample size	Mean age	COVID severity parameters			SCD-related parameters				
			Mortality *N*	ICU Admission *n*	Hospitalization *N*	SCD genotype	HbF%	HU therapy *N*	Transfusion *N*	Comorbidity *N*
26	10	40	1	1	5	SS	6.2	2	2	10
27	2	22	0	0	2	SS	NA	NA	0	1
28	3	30	0	0	3	SS	NA	3	3	1
29	1	44	0	0	1	SS	NA	1	1	NA
31	2 Adults and 1 child	27.3	0	0	2	SS	NA	3	1	2 Overall
32	6	30.8	0	0	6	SS	NA	NA	1	NA
33	1	22	0	0	0	SCD	NA	NA	1	1
34	1	22	0	1	1	SS	26.9	1	1	1
Total	790	Adults	49	58	469	[c]819 SS/Sβ^0 (72.7%), 289 SC/S/β^+-thalassemia (25.7%), 18 AS (1.6%)	1.5–30.4	273	189	723

Note: Comorbidity included ACS, asthma, avascular necrosis, cardiovascular disease, chronic obstructive pulmonary disease, diabetes, obesity, hypertension, painful crisis, pulmonary embolism, pulmonary hypertension, splenectomy, chronic kidney disease, malignancy, seizure, sickle cell nephropathy, stroke, venous thromboembolism.

Abbreviations: ACS, acute chest syndrome; COVID-19, coronavirus disease 2019; HU, hydroxyurea; ICU, intensive care unit; NA, not available; SCD, sickle cell disease; SS, sickle cell homozygous

[a]Some patients had more than one comorbidity.

[b]Study included 57 adults and nine children, and except for mortality other parameters were not separately described in patients, and the numbers were based on all 66 patients.

[c]In references 9, 10, 14, and 19, the percentage of SCD genotype was considered in all patients.

presence of comorbidities in 65.8% of pediatric SCD patients should be considered for a higher mortality rate. The death rate increased in the presence of comorbidities as a death rate of 4% was reported in children infected with SARS-CoV-2; 83% of them had pre-existing comorbidity.[36] Furthermore, in a report of 46 children and adolescents positive for COVID-19, 28.3% were admitted to PICU and the death rate was 2.2%, and the most prevalent comorbidities were obesity and asthma.[37] The overall outcome of COVID-19 was favorable in SCD children; the high rate of PICU admission (22.5%) and need for PICU support should be considered in managing these patients. ICU admission was 12%, and the death rate was 7.6% in SCD adults infected with SARS-CoV-2. As per the World Health Organization (WHO) report updated on April 5, 2021, the overall death rate from COVID-19 in adults and children was 2.17%.[38] Although the mortality rate due to COVID-19 in the general population was lower than that in adult SCD patients with COVID-19, we should consider the presence of a high rate of comorbidities in SCD patients as most of the adults with SCD and COVID-19 had comorbidity, some patients had multiple comorbidities, and a premorbid condition existed in these patients. ICU admission rate was 23.6%, and the death rate was 21.1% among 1000 hospitalized confirmed COVID-19 patients from New York City, with a high rate of baseline comorbidities and a mean age of 63 years.[39] Moreover, in another report from adults >18 years and mean age of 58 years, most of them had at least one comorbidity, mortality rate of ICU-admitted patients was 53.3%.[40] Comparing three cohorts of adult SCD patients with COVID-19 from the United Kingdom, France (all patients were hospitalized),[14,17] and the United States (69% of patients were hospitalized)[10] indicated higher mortality rates in US (9%) and UK cohorts (10.4%) than France cohort (2.8%). Moreover, the interaction between genetic and environmental factors determines the overall clinical outcomes of human diseases, and health socio-economic determinants have a crucial role in health inequities and disease outcomes. In the United States, it seems among African Americans, there were higher mortality rates due to COVID-19, and SCD mostly affects Black/African Americans in the United States.[41] In recent American Society of Hematology abstract, comparing COVID-19 outcomes between sickle cell trait/SCD and Blacks without sickle cell complication indicated that SCD could be an additional risk for severe COVID-19. However, mortality rate among SCD patients (8%) was not significantly different compared to Blacks without SCD (3%).[42] Based on the reports on SCD patients with COVID-19, there were limited data from Africa. SCD has a high prevalence among African descent people, Indian subcontinent, some parts of Middle East, and Mediterranean region. Sub-Saharan Africa accounts for approximately 79% of around 300,000 infants born annually with SCD in the world. Despite the high prevalence of SCD in sub-Saharan Africa, the data related to SCD and COVID-19 are limited.[43] As per WHO report, globally Africa has the least affected individuals with 1.5% of world's reported COVID-19 cases and 0.1% of the world's death. However, WHO estimated up to 15% of mortality in Africa due to SCD.[44]

Our survey of published papers shows 51.3% of SCD children and 36.5% of SCD adults with COVID-19 required simple/exchange transfusion during hospitalization. Benefit of early simple/exchange transfusion in the patients with ACS was indicated with rapid clinical improvement of tachypnea/dyspnea and oxygen saturation,[31] and it affected the clinical course of disease in patients who required respiratory support in the ICU.[7]

Available data from published papers indicated 50% of children and 41.8% of adults with SCD and COVID-19 were on HU therapy. HU as an FDA-approved pharmacologic treatment for SCD (HbSS, and HbS/β^0-thalassemia) is safe and cost-effective, which reduces the frequency and intensity of painful events in these patients. This drug decreases the rate of ACS events, transfusion requirements, and hospitalization. HU mildly increases HbF and metabolizes to nitric oxide increasing vasodilation and enhancing blood flow.[45] HU therapy improves hemolysis markers, increases the HbF level, decreases HbS level, and also reduces the monocyte counts. Furthermore, HU decreases the frequency and activation of classical inflammatory monocytes responsible for multiple proinflammatory cytokine production, which has overall anti-inflammatory function[46] and reduces plasma D-dimer level in SCD patients.[47] Since cytokine storm and increased monocytes and macrophages are implicated in COVID-19 lung injury, HU therapy could have an advantage in lowering absolute monocyte counts, decreasing inflammatory cytokines, and reduction of endothelial adhesive markers.[11] Moreover, HU decreases 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.[48] Furthermore, HbSS patients treated with HU compared to untreated patients had reduced coagulation activation and fibrinolysis.[49] Finally, the antiviral effect of HU with chloroquine or its analog hydroxychloroquine was indicated.[49] However, more reports are required to establish the benefit of HU therapy on COVID-19 severity in SCD patients.

Other hypotheses related to mild to moderate presentation of COVID-19 in SCD patients are as follows. (1) Decreased circulating CD4+ and CD8+ T lymphocytes in SCD patients, which 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 result in the milder course of disease.[29] However, the levels of circulating CD4+ and CD8+ T lymphocytes and their alterations should be detected in SCD patients with COVID-19 to confirm the above hypothesis. (2) Benefit of splenectomy in animal models, with decreased proinflammatory/anti-inflammatory ratio through a decrease in spleen-originated inflammatory cells.[51] Since only four SCD patients with splenectomy and good outcomes were reported,[7,11,15,30] the possible benefit of splenectomy against the produced cytokine storm in COVID-19 patients needs to be elucidated. (3) Although none of the reports discussed the ferritin levels and iron chelation therapy in SCD patients with COVID-19, high ferritin levels represent a negative prognostic factor in patients with COVID-19 and iron chelation with deferiprone or deferoxamine, which was proposed for COVID-19 therapy, reduced viral replication and related proinflammatory pathways.[52] Hence, iron chelation in SCD patients who need transfusion might also be beneficial against COVID-19, and it should be further confirmed.

5 | CONCLUSION

SCD patients are immunocompromised with multiple comorbidities and a hypercoagulation state. Older patients with pre-existing multiple organ damage are at higher risk of morbidity and mortality from COVID-19, and hemoglobin genotype, or gender seems to be not associated to COVID-19 disease severity. On the other hand, COVID-19 is associated with cytokine storm and hypercoagulability. As per the literature and comparing overall outcome of SCD patients positive for COVID-19 to the outcome of hospitalized and PICU-admitted non-SCD children with COVID-19, COVID-19 presentation was mild in children. Although the overall outcome of COVID-19 was favorable in SCD children, the high rate of PICU admission should be considered in managing these patients. COVID-19 outcome was variable from mild to severe in adults with SCD, and chronic disease-modifying therapy including HU can protect them from death. The possible benefits of HU include a high level of HbF, reduced hemolysis, platelet, leukocyte, and inflammatory parameters such as interleukin 6. On the other hand, the higher case fatality rate of SCD with COVID-19 than the general population shown in US studies underline older age above 50, multiple end-organ diseases, higher levels of D-dimer, creatinine, LDH, and not taking HU as risk factors should be considered. However, obtained results should be interpreted considering low cases from sub-Saharan people, younger age of SCD patients compared to the general population, a bias toward report and registry of the more severe form of disease, the effect of pre-existing comorbidities with multisystem organ damage in the exacerbation of COVID-19, fatality rate in SCD patients, and the role of health socio-economic determinants.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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