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Review article

Hemoglobinopathy and pediatrics in the time of COVID-19

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ABSTRACT

Introduction: It is important to know if patients with hemoglobinopathy could be more susceptible to COVID-19.
Objective: Analyze SARS-CoV-2 infection in pediatric patients with hemoglobinopathy.
Methods: Using the online platforms LILACS, PUBMED and EMBASE, on 17- JUL-2020 a search was made for the terms COVID-19 and SARS-CoV-2 associated with "sickle cell", "thalassemia" and "hemoglobinopathy".
Results: There were 623 pediatric and adult patients with sickle cell disease (SCD) or beta thalassemia (BT) and COVID-19. Total mortality rate was 6.42%. No pediatric patient with BT has been described. So, our analysis focused on children and adolescents with SCD: there were 121 pediatric patients, one adolescent died, prophylactic anticoagulation was prescribed to six patients, 11.76% needed intensive care unit, blood transfusion was prescribed in 29.70%. Vaso-occlusive crisis (VOC) and acute chest syndrome (ACS) were the main clinical manifestations in SCD.
Discussion: Pediatric patients with SCD and COVID-19 have a low mortality rate when compared to adults, although is higher than the global pediatric population with COVID-19 (0–0.67%). The comorbidities associated with age and the long-term complications inherent to hemoglobinopathies may contribute to the increased mortality outside the pediatric age group. In SCD the clinical manifestations, both in children and adults, are VOC and ACS, and there was increase in blood requirement. Pediatric SCD patients with COVID-19 need more intensive care unit than the global pediatric population (3.30%).
Conclusion: Despite pediatric population with SCD needs more intensive care, the outcome after infection by COVID-19 is favorable.

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Introduction

In less than three months after the first case reported in China, the infection called coronavirus disease-2019 (COVID-19), caused by the new "Severe Acute Respiratory Syndrome Coronavirus 2" (SARS-CoV-2), was recognized by the World Health Organization (WHO) as a pandemic.[1] This is the worst pandemic in the last 100 years and is still uncontrolled.[2]

The epidemiology of the disease showed a higher lethality among elderly patients, mainly with chronic diseases such as diabetes mellitus, obesity, hypertension and cardiovascular disease.[3,4]

Thus, it is important to know if patients with hematological diseases that are predisposed to altered immune responses secondary to the disease itself or to the treatment could be more susceptible to this new pathology and present a higher risk of death.[5] This relationship proved to be true considering malignant hematological diseases.[6]

Considering the hematological diseases called benign, patients with sickle cell disease (SCD) have immunodeficiency[7] related to the disease itself, continuous use of medications or complications inherent to the disease.[8,9] Functional asplenia provides a greater risk of infections by encapsulated bacteria, however, there is no relation to the increase in infections caused by viruses.[8,10,11] Iron overload, both in beta thalassemia and in SCD, favors oxidative stress and in thalassemia can result in chronic organ damage, such as adrenal insufficiency, which could lead to immunodeficiency and increased risk of infections.[9]

Objective

As SARS-CoV-2 spread easily in the world, much remains unknown about this virus and the higher susceptibility to infection of the people with hemoglobinopathy. This review aims to analyze the behavior of SARS-CoV-2 infection in pediatric patients with hemoglobinopathy, based on data from scientific medical publications, comparing it with published data on adults with hemoglobinopathy.

Methods

Search

Using the online platforms LILACS, PUBMED and EMBASE as a database, a search was made on July 17, 2020 for the term "COVID-19", associated with "sickle cell", "thalassemia" and "hemoglobinopathy". To increase the number of publications found, the association of "SARS-CoV-2" with the same terms was also researched. The search returned 47 articles. Also included were an abstract presented at the European Hematology Association Congress 2020 (EHA25)[12] and data from the Surveillance Epidemiology of Coronavirus (COVID-19), under Research Exclusion - SECURE-SCD Registry (after being allowed by the investigator team),[13] bringing the total to 49 scientific documents.

Selection of scientific documents

The scientific documents were independently read by three researchers and then selected. Most of them were correspondences and letters to the editor. Of the 49 documents found, 26 were excluded because they did not present patient data and, therefore, 23 were selected.[12–34] Of these, three more articles were excluded, as one was a report on a patient with sickle cell anemia after hematopoietic stem cell transplantation[14] and two were published case reviews,[15,16] totalizing 20 eligible scientific documents. Finally, four were exclusively pediatric descriptions (between zero and < 19 years old),[17–20] five described both pediatric and adult data[12,13,21–23] and 11 exclusively reported on adults.[24–34] Fig. 1 shows the selection of scientific documents.

Results

Data on pediatric patients with hemoglobinopathy and COVID-19 are presented in Table 1, grouped pediatric and adult patients in Table 2 and adults in Table 3.

We excluded seven patients (one sickle cell trait and six rare inherited anemias) from this analysis. Hence, there are 623 pediatric and adult patients with hemoglobinopathy (SCD or beta thalassemia) and COVID-19 in the 20 selected documents. SCD was present in 553 patients (88.76%) and beta-thalassemia in 70 (11.24%). The total mortality rate in this review was 6.42% (40/623). The mortality rate in SCD ranged from 0% to 10% and in beta thalassemia between 0% and 26%, according to the evaluated report. A total of 12.82% (75/585) patients needed the intensive care unit during hospitalization and 47 advanced oxygen supply, being 30 by mechanical ventilation under orotracheal intubation (including two patients treated with extracorporeal membrane oxygenation), and 17 with non-invasive ventilation. Red blood cell transfusion (RBC) or exchange transfusion was performed in 35.57% (148/416) of the patients (Tables 1, 2 and 3).

Considering available pediatric data (Table 1), there are 121 patients, representing 19.42% of all patients. At the pediatric age, only one adolescent with SCD died (0.82% of the pediatric population). The main clinical manifestation at hospital admission or during hospitalization was the vaso-occlusive crisis (VOC), followed by the acute chest syndrome (ACS). A total of 41 pediatric patients had VOC, 27 ACS and two both VOC and ACS. Prophylactic anticoagulation was prescribed to six patients at two medical centers, with one report of pulmonary thromboembolism. There was a need in 14 of 119 patients for the pediatric intensive care unit (11.76%), with seven under advanced oxygen supply and two with mechanical ventilation by orotracheal intubation (1.68%). RBC or exchange transfusions were performed in 30 of 101 patients with accessible data (29.70%). An adolescent patient received tocilizumab and two patients Anakinra for cytokine storm syndrome, all with favorable outcomes. It is also worth mentioning that 47 (38.84%) of the pediatric patients were not hospitalized.

In Tables 2 and 3, the VOC was also the main clinical manifestation in SCD adult patients at hospital admission or during hospitalization, also followed by the ACS. There were no reg-

Table 1 – Summary data from pediatric patients with sickle cell disease and COVID-19 published in the literature.

Author/Country	Age (y) Gender	Hbpathy	Medical history	PCR-RT	Symptoms	Chest image	Anticoag	PICU	O_2	RBC	Management	Outcome
Heilbronner et al. Oualha et al. France	17/F	HbSS	None	+	ACS Fever	X-r: inferior lobe consolidation	Prophylactic	Yes	NIV	ET	Analgesics Antibiotics	Recovered
Heilbronner et al. Odièvre et al. Oualha et al. France	16/F	HbSS	HU	+	VOC ACS Fever	CT: Ground glass Consolidation Embolism	Therapeutic	Yes	NIV	RBC ET	Analgesics Antibiotics Tocilizumab	Recovered
Heilbronner et al. Oualha et al. France	11/M	HbSS	HU ET Splenectomy ACS	+	ACS Fever	X-r: inferior lobe consolidation	Prophylactic	Yes	NIV	RBC ET	Analgesics Antibiotics	Recovered
Heilbronner et al. Oualha et al. France	12/F	HbSS	None	+	ACS Fever	CT: Ground glass Consolidation	Prophylactic	Yes	NIV	RBC ET	Analgesics Antibiotics	Recovered
Appiah-Kubi et al. USA	15/M	HbSS	Splenectomy ET	+	Fever	NA	No	No	No	No	Antibiotics	Recovered (Not hospitalized)
Appiah-Kubi et al. USA	11/F	HbSS	HU	+	ACS Fever	NA	Prophylactic	No	NIV	RBC	Antibiotics HCQ Antivirals Anakinra *	Recovered
Appiah-Kubi et al. USA	2/M	HbSS	None	+	ACS Fever	NA	Prophylactic	Yes	NIV	RBC ET	Antibiotics Antivirals HCQ Antivirals Anakinra *	Recovered
Appiah-Kubi et al. USA	18/F	HbSC	Obesity	+	Fever	NA	No	No	No	No	Antibiotics	Recovered (Not hospitalized)
Appiah-Kubi et al. USA	14/F	HbSS	HU Atrial tachycar-dia	+	VOC Fever	NA	No	No	No	No	Analgesics Antibiotics	Recovered (Not hospitalized)
Al-Hebshi et al. Saudi Arabia	14/F	HbSS	HU	+	VOC	X-r: normal	No	No	No	No	Analgesics Antibiotics	Recovered
Al-Hebshi et al. Saudi Arabia	12/M	HbSS	HU Splenectomy	+	VOC / ACS Fever	X-r: Ground glass	No	NA	NIV	RBC	Analgesics Antibiotics Corticotherapy HCQ	Recovered
De Sanctis et al. Oman	13/F	HbSS	HU	+	Fever Worsening anemia	NA	NA	NA	NA	ET	NA	Recovered

– Table 1 (*Continued*)

Author/Country	Age (y) Gender	Hbpathy	Medical history	PCR-RT	Symptoms	Chest image	Anticoag	PICU	O_2	RBC	Management	Outcome
Pediatric data from group studies												
Data from April 16th 2020 Arlet et al. France	0–14 6M/6F	11 HbSS/Sβ0 1 Sβ+	4 HU	+	50% VOC 17% ACS	NA	NA	17%	No MV	33%	NA	All Recovered
Data from July 17th 2020 Panepinto et al. International Registry	<18	77 SCD	38 HU 4 Stroke 22 Asthma	NA	47% VOC 26% ACS	NA	NA	9%	2.6% MV	23%	NA	76 Recovered (44 not hospital-ized) 1 death (adolescent)
Data from May 6th 2020 Telfer et al. UK	≤18	20		NA	NA	NA	NA	None	No MV	NA	NA	All Recovered

ACS, acute chest syndrome; Anticoag, anticoagulation; CT, computerized tomography; ET, exsanguineo transfusion; F, female; Hbpathy, hemoglobinopathy; HbSβ^0, sickle cell disease Sβ^0; HbSβ$^+$, sickle cell disease Sβ$^+$; HbSC, sickle cell disease SC; HbSS, sickle cell anemia; HCQ, hydroxychloroquine; HU, hydroxiurea; M, male; MV, mechanical ventilation; NA: Not available; NIV, non invasive ventilation; O2, oxygen; PCR-RT, SARS-CoV2 reverse-transcriptase polymerase-chain-reaction; PICU, Pediatric Intensive Care Unit; RBC, red blood cell transfusion; VOC, vaso-oclusive crisis; X-r, X-ray; y, years; +, positive.

* for cytokine storm syndrome.

Table 2 – Summary data from pediatric and adult patients with hemoglobinopathy and COVID-19 described in group published in the literature.

Author/Country	Age (y) Gender	Hbphaty	Medical history	PCR-RT	Symptoms	Chest image	Anticoag	ICU	O_2	RBC	Management	Outcome
Appiah-Kubi et al. USA	Total 7 Age: 2–20 Adults = 2 Pediatric = 5 2M/5F	6 HbSS 1 HbSC	1 splenectomy 1 obesity 1 Atrial tachycardia 1 Hallucinations 1 Asthma 57% HU	+	28.6% VOC 28.6% ACS	NA	4	1	2 NIV	4	7 Antibiotics 3 Anakinra 4 HCQ 3 Remdesivir	85.7% hospitalized No death
De Sanctis et al. Turkey, Italy, Bulgaria, Azerbaijan, Cyprus, Greece, India, Iran, Oman, Qatar	Total 13 Mean age: 33.7 ± 12.3 (13–66) Adults = 12 Pediatric = 1 4M/9F	9 TDT 1 NTDT 3 HbSS	Thal –4 splenectomized –3 diabetes mellitus –1 hypogonadism, renal disease and hypertension SCD –1 asthma –1 renal disease	+	80% fever 70% cough 60% headache 60% fatigue 50% diarrhea, vomiting, abdominal pain 40% tachypnea/dyspnea 40% anosmia/hyposmia 10% myalgia 1 VOC 3 no symptoms	NA	2	NA	4	1 ET (HbSS 13y)	Thal: Antibiotics (3) Antiviral (1) HCQ (2)	7 hospitalized 1 death (7.69%; TDT)
Data from April 16th 2020 Arlet et al. France	Total 83 Median age: 30 (0.3–68) ≥ 15 y = 71 ≤ 14 y = 12 38 M/45F	71 HbSS/Sβ0 8 HbSC 4 HbSβ+	38 HU	+	54% VOC 28% ACS	NA	NA	20% (≤14y = 2.4%)	11% MV 2.4% ECMO Obs: none ≤14y	7% RBC 11% ET Obs: 4.5% ≤14y	NA	2.4% deaths (2 HbSC adults)
Data fromJuly 17th 2020 Panepinto et al. International Registry	Total 260 Mean age: 26,83 ± 15,12 ≥ 18 y = 183 <18 y = 77 116 M/140F	181 HbSS 54 HbSC 12 HbSβ0 13 HbSβ+	135 HU 28 Stroke 56 Asthma 19 Cardiovascular disease 13 diabetes	NA	59% VOC 30% Pneumonia	NA	30.6%	10.4%	4.6% MV	36.1%	31.2% Azitromicin 14% HCQ 3.5% Remdesivir 3.5% corticosteroid 1.7% plasma 1.16% tocilizumab	66% hospitalized 6.15% deaths (15 adults, 1 adolescent)

– Table 2 (*Continued*)

Author/Country	Age (y) Gender	Hbphaty	Medical history	PCR-RT	Symptoms	Chest image	Anticoag	ICU	O_2	RBC	Management	Outcome
Data from May 6th 2020 Telfer et al. UK	Total 195 Median age: 33 (6w-92y) Adults = 175 ≤ 18y = 20 86 M/109F	164 SCD - 124 HbSS - 30 HbSC - 10 other 25 Thal −20 TDT −5 NTDT 6 RIA	Comorbidity: 7/13 deaths −5 SCD −1 TDT −1 NTDT	98/154 tested +	NA	NA	NA	10.5% (all adults)	4.9% NIV 2.8% MV 2.8% both	NA	NA	74% hospitalized 7.7% deaths (all adults) −11 SCD −1 NTDT −1 TDT

ACS, acute chest syndrome; Anticoag, anticoagulation; ECMO, Extracorporeal Membrane Oxygenation; ET, exsanguineo transfusion; F, female; Hbpathy, hemoglobinopathy; HbSβ^0, sickle cell disease Sβ^0; HbSβ^+, sickle cell disease Sβ^+; HbSC, sickle cell disease SC; HbSS, sickle cell anemia; HCQ, hydroxychloroquine; HU, hydroxiurea; ICU, Intensive Care Unit; M, male; MV, mechanical ventilation; NA: Not available; NIV, non invasive ventilation; NTDT, non transfusion dependente talassemia; O_2, oxygen; PCR-RT, SARS-CoV2 reverse-transcriptase polymerase-chain-reaction; RBC, red blood cell transfusion; RIA, rare inherited anemias; TDT, transfusion dependente talassemia; Thal, thalassemia; VOC, vaso-oclusive crisis; y, years; +, positive.

Table 3 – Summary data from adult patients with hemoglobinopathy and COVID-19 published in the literature.

Study/Country	Age/Gender	Hbpathy	Medical history	PCR-RT	Symptoms	Chest image	Anticoag	ICU	O2	RBC	Management	Outcome
Beta Thalassemia												
Pinto et al. Italy	57/M	TDT	Splenectomy Severe pulmonary arterial hypertension Chronic heart failure	+	Dessaturation	CT: bilateral ground glass	Yes	Yes	Yes	RBC	Antibiotics Antivirals HCQ	Recovered
Motta et al. Italy	49/F	NTDT	Obesity Hyperparathyroidism	+	Fever, cough, anosmia, ageusia pain, fatigue, diarrhea, headache	X-r: thickening	No	low-intensity	No	NA	HCQ	Recovered
Motta et al. Italy	48/F	TDT	Splenectomy	+	Fever, cough, anosmia, ageusia pain, fatigue	X-r: thickening	No	low-intensity	No	No	No drugs	Recovered
Motta et al. Italy	31/M	TDT	Cardiomyopathy, chronic hepatopathy, diabetes, Hypothyroidism, Osteoporosis, Hypogonadism	+	Fever, cough, anosmia, ageusia, pain, fatigue, headache, neutropenia	CT: thickening	No	No	Yes	RBC	No drugs	Recovered
Motta et al. Italy	42/M	TDT	Splenectomy, asthma, hypogonadism	+	Fever, cough, pain, diarrhea	X-r: thickening	No	No	No	No	No drugs	Recovered
Motta et al. Italy	33/F	TDT	Splenectomy Hypothyroidism	+	Cough, pain, diarrhea	Not done	No	No	No	No	No drugs	Recovered
Motta et al. Italy	59/F	TDT	Splenectomy, cardiomyopathy, renal impairment, chronic hepatopathy, diabetes, hypothyroidism, osteoporosis, hypogonadism, previous NHL	+	Fever, cough, difficulty breathing	X-r: thickening	No	High-intensity	Yes	No	Canaquinumab HCQ	Hospitalized

– Table 3 (*Continued*)

Study/Country	Age/Gender	Hbpathy	Medical history	PCR-RT	Symptoms	Chest image	Anticoag	ICU	O2	RBC	Management	Outcome
Motta et al. Italy	32/M	TDT	Splenectomy, osteoporosis, previous ALL	+	Fever, cough, anosmia, ageusia, fatigue, headache	X-r: normal	No	No	No	No	No drugs	Recovered
Motta et al. Italy	61/F	TDT	Splenectomy, respiratory disease, cardiomyopathy, renal impairment, chronic hepatopathy, diabetes, osteoporosis, hypogonadism, sarcoidosis	+	Pain, fatigue difficult breathing	X-r and CT: thickening	No	low-intensity	No	No	No drugs	Recovered
Motta et al. Italy	56/M	TDT	Splenectomy, cardiomyopathy, chronic hepatopathy, osteoporosis, hypogonadism, pulmonary arterial hypertension	+	Fever, cough, pain, difficult breathing	X-r and CT: thickening	No	low-intensity	Yes	No	Antivirals HCQ	Recovered
Motta et al. Italy	40/F	TDT	Splenectomy, cardiomyopathy, chronic hepatopathy, hypothyroidism, hypoparathyroidism, hypogonadism	+	Fever, cough, anosmia, ageusia, pain, fatigue	Not done	No	No	No	No	No drugs	Recovered
Motta et al. Italy	36/M	TDT	Hypothyroidism	+	Fever, cough, anosmia, ageusia, pain, fatigue	X-r: thickening	No	low-intensity	No	No	No drugs	Recovered
Data from April 29th 2020 Karimi et al. Iran	Mean age: 36 (22–66) 39 (30–54): suspected COVID-19 14 M/9F	18 TDT 5 NTDT	16 Splenectomy 17 comorbidities	15 +	Fever, shortness of breath, fatigue, dry cough	CT: SARS-CoV-2 pneumonia	NA	NA	NA	NA	Antivirals HCQ	17 recovered 6 deaths - 26% (2 TDT; 4 NTDT)

– Table 3 (*Continued*)

Study/Country	Age/Gender	Hbpathy	Medical history	PCR-RT	Symptoms	Chest image	Anticoag	ICU	O2	RBC	Management	Outcome
Sickle cell disease												
Alisson et al. USA	27/M	HbSC	–	+	VOC ACS	X-r: bilateral SARS-CoV-2 pneumonia	Yes	Yes	Yes	ET	Analgesics Antibiotics Corticosteroids HCQ Tocilizumab	Recovered
Nur et al. NL	24/M	HbSS	Minor pain episodes	+	VOC ACS	CT: double-sided infiltrates in the lower lobes	No	No	Yes	No	Analgesics Antibiotics	Recovered
Nur et al. NL	20/F	HbSS	VOC	+	VOC	CT: normal	No	No	No	No	Analgesics	Recovered
Beerkens et al. USA	21/M	$HbS\beta^0$	Hydroxyurea Avascular necrosis	+	Severe anemia (Hb 2 g/dL)	X-r: ground glass	No	No	Yes	RBC ET	Analgesics Antibiotics HCQ	Recovered
Hussain et al. USA	32/M	HbSS	VOC ACS Extremity ulcers	+	VOC	X-r: pneumonia	No	Yes	MV	RBC ET	Analgesics Antibiotics HCQ	Recovered
Hussain et al. USA	37/F	$HbS\beta^+$	VOC Venous thromboembolism	+	VOC	X-r: normal	No	No	No	No	Analgesics	Recovered
Hussain et al. USA	22/F	HbSS	ACS, VOC Asthma	+	VOC	Not done	No	No	No	No	Analgesics Antibiotics	Recovered
Hussain et al. USA	41/M	HbSC	Avascular Necrosis Pulmonary embolism	+	VOC	Not done	No	No	No	No	Analgesics	Recovered
McCloskey et al. UK	Mean age: 36 (23–57) 8M/2F	9 HbSS or HbSβ0 1 HbSC	1 stroke 1 nephropathy 6 VOC	6 +	80% VOC	5 X-r and/or CT: infiltrates	Yes (all)	No	10	3 RBC	Antibiotics	9 recovered 1 death (10%)
De Luna et al. France	45/M	HbSS	Nephropathy Retinopathy Priapism Cardiac remodeling	+	VOC	CT: Ground glass	No	No	Yes	RBC	Antibiotics HCQ Tocilizumab	Recovered
Chakravorty et al. UK	36/M	HbSS	ACS Chronic pain	+	VOC	NA	Yes	No	No	No	Antibiotics	Recovered
Chakravorty et al. UK	38/F	HbSS	Recurrent leg ulcers	+	VOC	NA	Yes	No	Yes	RBC	Antibiotics	Recovered
Chakravorty et al. UK	34/F	HbSS	Stroke	+	VOC	NA	Yes	No	No	No	Antibiotics	Recovered

– Table 3 (*Continued*)

Study/Country	Age/Gender	Hbpathy	Medical history	PCR-RT	Symptoms	Chest image	Anticoag	ICU	O2	RBC	Management	Outcome
Chakravorty et al. UK	46/F	HbSS	Renal disease Hemodialysis Chronic pain Asthma	+	VOC	NA	No	No	No	No	Antibiotics	Recovered (Not admitted)
Chakravorty et al. UK	37/M	HbSS	Stroke	+	VOC	NA	No	No	No	No	Antibiotics	Recovered (Not admitted)
Chakravorty et al. UK	52/F	HbSS	Hydroxyurea Chronic shoulder pain	+	VOC	NA	No	No	No	No	Antibiotics	Recovered (Not admitted)
Chakravorty et al. UK	25/M	HbSS	Recurrent TIA	+	VOC	NA	No	No	No	No	Antibiotics	Recovered (Not admitted)
Chakravorty et al. UK	35/F	HbSS	Hydroxyurea Chronic hip pain	+	VOC	NA	No	No	No	No	Antibiotics	Recovered (Not admitted)
Chakravorty et al. UK	54/F	HbSS	Hyperhaemolysis, asthma, Avascular necrosis	+	VOC	NA	Yes	Yes	Yes	No	Antibiotics	Died (10%)
Chakravorty et al. UK	44/F	HbSS	ACS Stroke	+	VOC	NA	Yes	No	No	RBC	Antibiotics	Recovered
Justino et al. Brazil	35/F	HbSS	28 weeks pregnant.	+	Myalgia Fever Cough Dyspnea Hypoxia	CT: Ground glass	No	Yes	Yes	RBC	Antibiotics	Recovered
Sickle cell disease (already described in Table 2)												
Appiah-Kubi et al. USA	20/F	HbSS	Hallucinations Hydroxyurea	+	Hypoxia, Psychosis	NA	Yes	No	No	No	Anakinra Antibiotics HCQ	Recovered
Appiah-Kubi et al. USA	20/F	HbSS	Asthma Hydroxyurea	+	VOC	NA	Yes	No	No	RBC	Analgesics Antibiotics HCQ	Recovered

ACS, acute chest syndrome; ALL, acute lymphocytic leucemia; Anticoag, anticoagulation; ET, exsanguineo transfusion; F, female; Hbpathy, hemoglobinopathy; HbSβ^0, sickle cell disease Sβ^0; HbSβ$^+$, sickle cell disease Sβ$^+$; HbSC, sickle cell disease SC; HbSS, sickle cell anemia; HCQ, hydroxychloroquine; ICU, Intensive Care Unit; M, male; MV, mechanical ventilation; NA: Not available; NHL, non-Hodgkin lymphoma; NTDT, non transfusion dependente talassemia; O2, oxygen; PCR-RT, SARS-CoV2 reverse-transcriptase polymerase-chain-reaction; RBC, red blood cell transfusion; TDT, transfusion dependente talassemia; Thal, thalassemia; TIA, transient ischemic attack; VOC, vaso-oclusive crisis; X-r, X-ray; y, years; +, positive.

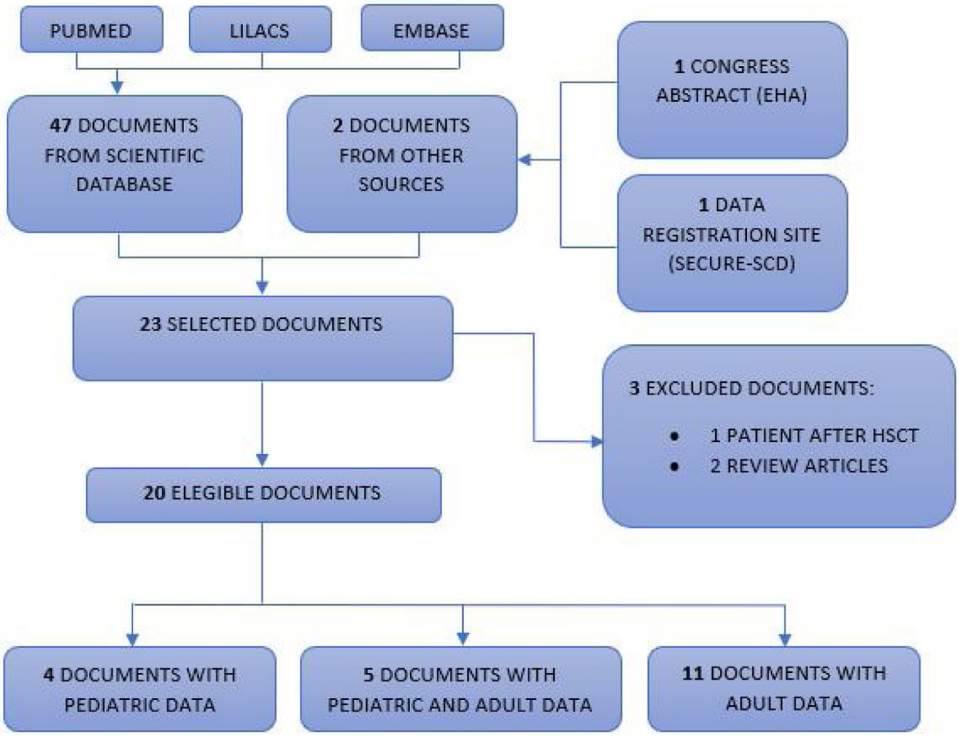

Fig. 1 – PRISMA flow diagram.
Flowchart of publications included in this review. Our database searches identified a total of 47 unique records for the initial screening of abstracts and two documents from another source (congress summary and SECURE-SCD website), of which 20 were selected for full-text screening. Subsequently, three studies were excluded. Four pediatric articles and five articles with data on the pediatric population were included, totalizing 121 pediatric patients with hemoglobinopathies and COVID-19.

istries of children and adolescents with beta thalassemia and COVID-19 in this review.

Discussion

The emergence of a rapidly spreading viral disease around the world, as in 2009 with the H1N1 Influenza virus, is of great concern among patients with chronic pathologies. During the H1N1 outbreak, 50% of the SCD pediatric cases with H1N1 went to the hospital and 25% developed ACS.[28,35] Therefore, a new virus with a high risk for respiratory complications in adult and elderly patients and which, unlike H1N1, does not have a developed available vaccine, has a catastrophic potential, especially in the poorest regions of the planet.[36]

As there were no reports of pediatric patients with thalassemia, our analysis focused on children and adolescents with SCD. When assessing mortality in pediatric and adult patients with hemoglobinopathy, a higher percentage was found when compared to the general population (estimated at 4.30% on July 17th 2020 according to WHO)..[37] Fortunately, in pediatric patients there has been a low mortality rate, with one case of an adolescent observed in this review. The presence of comorbidities associated with age,[3,4,38] as well as the known long-term complications inherent to hemoglobinopathies, may contribute to the increased mortality out of the pediatric age group bracket.[39,40] The clinical course of COVID-19 in pediatric patients has been favorable, but data on children and adolescents with chronic diseases are still scarce.[41]

In children and adolescents with SCD and COVID-19, the presence of VOC and ACS were common at hospital admission or during hospitalization. It is known that these acute events are preceded in most cases by infection.[42] The ACS is epidemiologically a complication of the VOC,[43] having a complex pathophysiology and resulting in an acute lung injury indistinguishable from a multilobed pneumonia.[44] The radiological evaluation by computed tomography shows consolidation in most cases, but the presence of the ground glass image, as well as commonly present in patients with COVID-19,[45] appears in practically a quarter of the patients with ACS.[46] In the absence of a positive real-time polymerase chain reaction (RT-PCR) test for SARS-CoV-2, the same appearance of the radiological image can make the diagnosis difficult.[47] In contrast, in patients with SCD and confirmed SARS-CoV2 infection, the diagnosis of ACS may be underestimated.

Another important pathophysiological mechanism in the ACS is the presence of fat embolism and/or bone marrow embolism in the circulation.[44] For this reason, some medical centers include prophylactic anticoagulation in ACS as an institutional protocol. This is the reality of one of the pediatric centers described in this review, where four patients received Low Molecular Weight Heparin (LMWH).[17] In this report, one adolescent receiving prophylactic anticoagulation changed to a therapeutic dose after the chest computed tomography

showed a pulmonary embolism. The other two patients on anticoagulation, from the six described in Table 1, received prophylactic doses, following thromboprophylaxis guidelines for COVID-19.[20] In COVID-19, the presence of microvascular thrombosis, mainly pulmonary, was also observed, although its mechanism has not yet been clarified.[48] This evidence resulted in the recommendation for anticoagulation for adult patients with COVID-19.[49] However, there is no such evidence in pediatrics and furthermore, there is controversy regarding the need for anticoagulation, even if prophylactic, for all patients.[50]

Patients with hemoglobinopathy usually need transfusion therapy when hospitalized. Among patients with SCD, hemolysis intensifies in the presence of infectious processes[51] and for patients with ACS, there is a suggestion to maintain hemoglobin levels stable at 9–11 g/dL or hemoglobin S levels below 30%.[52,53] In this review, all seven SCD pediatric patients described individually in Table 1 who presented with ACS required RBC transfusion and/or exchange transfusion, with a good outcome after the procedure. Therefore, blood transfusion seems to rapidly improve oxygen saturation[20,23] and it is possible that early and aggressive transfusion for ACS may be beneficial to COVID-19 patients.[21]

The clinical course of COVID-19 in pediatric patients with SCD requires some attention regarding the need for an intensive care unit, which seems to make no difference, when compared to adults with hemoglobinopathy. However, compared to global pediatric data, in which the average intensive care unit need is 3.30%,[54] SCD pediatric patients seem to have a greater requirement for intensive care support. This is in line with the data that 83% of patients admitted to a pediatric intensive care unit have chronic diseases.[55] In this review, advanced oxygen supply in pediatrics was relatively lower, when compared to adults, mainly in mechanical ventilation, corroborating the pediatric best outcome. Finally, mortality rate in pediatrics varied between 0−0.67%[56] and in this review, for SCD pediatric patients, it was 0.82%, suggesting the need of further studies and case reports on pediatric patients with hemoglobinopathy for better understanding. Although we did not perform the statistical analysis to determine whether this difference in the severity of the disease is statistically significant, our hypothesis is that the underlying disease may be responsible for the need for more intensive care during hospitalization for any infection in patients with SCD. Thus, the greater need for the ICU can be explained by clinical manifestations, such as ACS, or by the comorbidities that the disease can cause.

The identification of possible duplicate data in a few case reports and reviews was considered a limitation of this review, making it difficult to accurately number the patients. All the data found were described in the Tables. Thus, we suggest to future authors that they specify in their articles whether the patient reported was part of a larger registry, such as the UK Haemoglobinopathy Coordinating Centres[12] and the SECURE-SCD.[57]

In conclusion, the pediatric population with SCD needs more intensive care during hospitalization, but with a favorable outcome after infection by COVID-19. National and international registries of pediatric patients with hemoglobinopathy should be prioritized to obtain robust data on this population.

Conflicts of interest

The authors declare no conflicts of interest.

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REFERENCES

1. World Health Organization [updated 2020 Mar 12; cited 2020 Jul 17] Available at: https://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19/news/news/2020/3/who-announces-covid-19-outbreak-a-pandemic, 2020.
2. Gates B. Responding to Covid-19 - A once-in-a-century pandemic? N Engl J Med. 2020;382(18):1677–9.
3. Liu H, Chen S, Liu M, Nie H, Lu H. Comorbid chronic diseases are strongly correlated with disease severity among COVID-19 patients: a systematic review and meta-analysis. Aging Dis. 2020;11(3):668–78.
4. Simonnet A, Chetboun M, Poissy J, Raverdy V, Noulette J, Duhamel A, et al. High prevalence of obesity in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation. Obesity (Silver Spring). 2020;28(7):1195–9.
5. Malard F, Genthon A, Brissot E, van de Wyngaert Z, Marjanovic Z, Ikhlef S, et al. COVID-19 outcomes in patients with hematologic disease. Bone Marrow Transplant. 2020:1–5.
6. Weinkove R, McQuilten ZK, Adler J, Agar MR, Blyth E, Cheng AC, et al. Managing haematology and oncology patients during the COVID -19 pandemic: interim consensus guidance. Med J Aust. 2020;212(10):481–9.
7. Loggetto SR, Pellegrini-Braga JA, Costa-Carvalho BT, Solé D. Immunological disorders in sickle cell disease. Rev. Bras. Alerg. Imunolpatol. 1999;22(3):77–82.
8. Vives Corrons JL, De Sanctis V. Rare anaemias, sickle-cell disease and COVID-19. Acta Biomed. 2020;91(2):216–7.
9. Karimi M, De Sanctis V. Implications of SARSr-CoV 2 infection in thalassemias: Do patients fall into the ḧigh clinical riskc̈ategory? Acta Biomed. 2020;91(2):50–6.
10. Gavillet M, Rufer N, Grandoni F, Carr Klappert J, Zermatten MG, Cairoli A, et al. L'hématologie au temps du COVID-19 [Hematology in the time of COVID-19]. Rev Med Suisse. 2020;16(691-692):823–6.
11. Roy NBA, Telfer P, Eleftheriou P, de la Fuente J, Drasar E, Shah F, et al. Protecting vulnerable patients with inherited anaemias from unnecessary death during the COVID-19 pandemic. Br J Haematol. 2020;189(4):635–9.
12. Telfer P, De La Fuente J, Sohal M, Brown R, Eleftheriou P, Roy N, et al. Real-time national survey of COVID-19 in hemoglobinopathy and rare Inherited anemia patients. EHA Library. Telfer P. 06/14/20; 303394; LB2606. Oral presentation at the 25th European Hematology Association Annual Congress; 2020. Jun 11-21; Virtual Edition.
13. Panepinto J, Brandow A, Singh A, Mucalo L [updated 2020 Jul 17; cited 2020 Jul 17]. Available from: https://covidsicklecell.org/updates-data/, 2020.

14. André N, Rouger-Gaudichon J, Brethon B, Phulpin A, Thébault É, Pertuisel S, et al. COVID-19 in pediatric oncology from French pediatric oncology and hematology centers: High risk of severe forms? Pediatr Blood Cancer. 2020;67(7):e28392.
15. Sahu KK, Siddiqui AD, Cerny J. Managing sickle cell patients with COVID-19 infection: the need to pool our collective experience. Br J Haematol. 2020;190(2):e86–9.
16. Kehinde TA, Osundiji MA. Sickle cell trait and the potential risk of severe coronavirus disease 2019—A mini-review. Eur J Haematol. 2020;105:519–23.
17. Heilbronner C, Berteloot L, Tremolieres P, Dupic L, de Saint Blanquat L, Lesage F, et al. Patients with sickle cell disease and suspected COVID-19 in a paediatric intensive care unit. Br J Haematol. 2020;190(1):e21–4.
18. Odièvre M-H, de Marcellus C, Ducou Le Pointe H, Allali S, Romain A-S, Youn J, et al. Dramatic improvement after tocilizumab of severe COVID-19 in a child with sickle cell disease and acute chest syndrome. Am J Hematol. 2020;95(8):E192–4.
19. Oualha M, Bendavid M, Berteloot L, Corsia A, Lesage F, Vedrenne M, et al. Severe and fatal forms of COVID-19 in children. Arch Pediatr. 2020;27(5):235–8.
20. Al-Hebshi A, Zolaly M, Alshengeti A, Al Qurainees G, Yamani S, Hamdan N, et al. A Saudi family with sickle cell disease presented with acute crises and COVID-19 infection. Pediatr Blood Cancer. 2020;67(9):e28547.
21. Appiah-Kubi A, Acharya S, Fein Levy C, Vlachos A, Ostovar G, Murphy K, et al. Varying Presentations and Favourable Outcomes of COVID-19 Infection in Children and Young Adults with Sickle Cell Disease: An Additional Case Series with Comparisons to Published Cases. Br J Haematol. 2020;190:e221–4.
22. Arlet J-B, de Luna G, Khimoud D, Odièvre M-H, de Montalembert M, Joseph L, et al. Prognosis of patients with sickle cell disease and COVID-19: a French experience. Lancet Haematol. 2020;7(9):e632–4.
23. de Sanctis V, Canatan D, Corrons JLV, Karimi M, Daar S, Kattamis C, et al. Preliminary data on COVID-19 in patients with hemoglobinopathies: a multicentre ICET-a study. Mediterr J Hematol Infect Dis. 2020;12(1), e2020046.
24. McCloskey KA, Meenan J, Hall R, Tsitsikas DA. COVID-19 infection and sickle cell disease: a UK centre experience. Br J Haematol. 2020;190(2):e57–8.
25. Chakravorty S, Padmore-Payne G, Ike F, Tshibangu V, Graham C, Rees D, et al. COVID-19 in patients with sickle cell disease - a case series from a UK Tertiary Hospital. Haematologica. 2020;105(11):254250.
26. De Luna G, Habibi A, Deux J-F, Colard M, Pham Hung d'Alexandry d'Orengiani A-L, Schlemmer F, et al. Rapid and severe Covid-19 pneumonia with severe acute chest syndrome in a sickle cell patient successfully treated with tocilizumab. Am J Hematol. 2020;95(7):876–8.
27. Nur E, Gaartman AE, van Tuijn CFJ, Tang MW, Biemond BJ. Vaso-occlusive crisis and acute chest syndrome in sickle cell disease due to 2019 novel coronavirus disease (COVID-19). Am J Hematol. 2020;95(6):725–6.
28. Beerkens F, John M, Puliafito B, Corbett V, Edwards C, Tremblay D. COVID-19 pneumonia as a cause of acute chest syndrome in an adult sickle cell patient. A Am J Hematol. 2020;95(7):E154–6.
29. Hussain FA, Njoku FU, Saraf SL, Molokie RE, Gordeuk VR, Han J. COVID-19 infection in patients with sickle cell disease. Br J Haematol. 2020;189(5):851–2.
30. Pinto Vm, Derchi Ge, Bacigalupo L, Pontali E, Forni Gl. COVID-19 in a patient with β-thalassemia major and severe pulmonary arterial hypertension. Hemoglobin. 2020;44(3):218–20.
31. Motta I, Migone De Amicis M, Pinto VM, Balocco M, Longo F, Bonetti F, et al. SARS-CoV-2 infection in beta thalassemia: Preliminary data from the Italian experience. Am J Hematol. 2020;95(8):E198–9.
32. Karimi M, Haghpanah S, Azarkeivan A, Zahedi Z, Zarei T, Akhavan Tavakoli M, et al. Prevalence and mortality in β-thalassaemias due to outbreak of novel coronavirus disease (COVID-19): the nationwide Iranian experience. Br J Haematol. 2020;190(3):e137–40.
33. Allison D, Campbell-Lee S, Crane J, Vidanovic V, Webb S, Fraidenburg D, et al. Red blood cell exchange to avoid intubating a COVID-19 positive patient with sickle cell disease? J Clin Apher. 2020;35:378–81.
34. Justino CC, Campanharo FF, Augusto MN, de Morais SC, Figueiredo MS. COVID-19 as a trigger of acute chest syndrome in a pregnant woman with sickle cell anemia. Hematol Transfus Cell Ther. 2020;42(3):212–4.
35. Inusa B, Zuckerman M, Gadong N, Afif M, Arnott S, Heath P, et al. Pandemic influenza A (H1N1) virus infections in children with sickle cell disease. Blood. 2010;115(11):2329–30.
36. Dexter D, Simons D, Kiyaga C, Kapata N, Ntoumi F, Kock R, et al. Mitigating the effect of the COVID-19 pandemic on sickle cell disease services in African countries. Lancet Haematol. 2020;7(6):e430–2.
37. World Health Organization. Coronavirus disease 2019 (COVID19) – situation report 179; 2020 [updated 2020 Jul 17; cited 2020 Jul 17] Available at: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200717-covid-19-sitrep-179.pdf?sfvrsn=2f1599fa_2.
38. Rezende LFM, Thome B, Schveitzer MC, de Souza-Júnior PRB, Szwarcwald CL. Adults at high-risk of severe coronavirus disease-2019 (Covid-19) in Brazil. Rev Saude Publica. 2020;54:50.
39. Farmakis D, Giakoumis A, Cannon L, Angastiniotis M, Eleftheriou A. COVID-19 and thalassaemia: a position statement of the Thalassaemia International Federation. Eur J Haematol. 2020;105:378–86.
40. Chowdhury SF, Anwar S. Management of hemoglobin disorders during the COVID-19 pandemic. Front Med (Lausanne). 2020;7:306.
41. Safadi MA. The intriguing features of COVID-19 in children and its impact on the pandemic. J Pediatr (Rio J). 2020;96(3):265–8.
42. Ahmed SG. The role of infection in the pathogenesis of vaso-occlusive crisis in patients with sickle cell disease. Mediterr J Hematol Infect Dis. 2011;3(1):e2011028.
43. Vichinsky EP, Neumayr LD, Earles AN, Williams R, Lennette ET, Dean D, et al. Causes and outcomes of the acute chest syndrome in sickle cell disease. National Acute Chest Syndrome Study Group. N Engl J Med. 2000;342(25):1855–65.
44. Sundd P, Gladwin MT, Novelli EM. Pathophysiology of sickle cell disease. Annu Rev Pathol. 2019;14:263–92.
45. Kong W, Agarwal PP. Chest imaging appearance of COVID-19 infection. Radiol Cardiothorac Imaging. 2020;2(1):e200028.
46. Mekontso Dessap A, Deux J-F, Habibi A, Abidi N, Godeau B, Adnot S, et al. Lung imaging during acute chest syndrome in sickle cell disease: computed tomography patterns and diagnostic accuracy of bedside chest radiograph. Thorax. 2014;69(2):144–51.
47. Parekh M, Donuru A, Balasubramanya R, Kapur S. Review of the chest CT differential diagnosis of ground-glass opacities in the COVID era. Radiology. 2020:202504.
48. Bray MA, Sartain SE, Gollamudi J, Rumbaut RE. Microvascular thrombosis: experimental and clinical implications. Transl Res. 2020;225:105–30.

49. Atallah B, Mallah SI, AlMahmeed W. Anticoagulation in COVID-19. Eur Heart J Cardiovasc Pharmacother. 2020;6(4):260–1.
50. Loi M, Branchford B, Kim J, Self C, Nuss R. COVID-19 anticoagulation recommendations in children. Pediatr Blood Cancer. 2020:e28485.
51. Booth C, Inusa B, Obaro SK. Infection in sickle cell disease: a review. Int J Infect Dis. 2010;14(1):e2–12.
52. Miller ST. How I treat acute chest syndrome in children with sickle cell disease. Blood. 2011;117(20): 5297–305.
53. Jain S, Bakshi N, Krishnamurti L. Acute chest syndrome in children with sickle cell disease. Pediatr Allergy Immunol Pulmonol. 2017;30(4):191–201.
54. Hoang A, Chorath K, Moreira A, Evans M, Burmeister-Morton F, Burmeister F, et al. COVID-19 in 7780 pediatric patients: a systematic review. EClinicalMedicine. 2020;24:100433.
55. Shekerdemian LS, Mahmood NR, Wolfe KK, Riggs BJ, Ross CE, McKiernan CA, et al. Characteristics and outcomes of children with coronavirus disease 2019 (COVID-19) infection admitted to US and Canadian pediatric intensive care units. JAMA Pediatr. 2020;174(9):868–73.
56. Hon KLE, Leung KKY. Pediatric COVID-19: what disease is this? World J Pediatr. 2020;16(4):323–5.
57. Panepinto JA, Brandow A, Mucalo L, Yusuf F, Singh A, Taylor B, et al. Coronavirus disease among persons with sickle cell disease, United States, March 20–May 21, 2020. Emerg Infect Dis. 2020;26(10):2473–6.