

**Original Article****Preliminary Data on COVID-19 in Patients with Hemoglobinopathies: A Multicentre ICET-A Study**

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Competing interests: The authors declare no conflict of Interest.

Abstract. Objectives: This study aims to investigate, retrospectively, the epidemiological and clinical characteristics, laboratory results, radiologic findings, and outcomes of COVID-19 in patients with transfusion-dependent β thalassemia major (TM), β -thalassemia intermedia (TI) and sickle cell disease (SCD).

Design: A total of 17 Centers, from 10 countries, following 9,499 patients with hemoglobinopathies, participated in the survey.

Main outcome data: Clinical, laboratory, and radiologic findings and outcomes of patients with COVID-19 were collected from medical records and summarized.

Results: A total of 13 patients, 7 with TM, 3 with TI, and 3 with SCD, with confirmed COVID-19, were identified in 6 Centers from different countries. The overall mean age of patients was 33.7 ± 12.3 years (range: 13-66); 9/13 (69.2%) patients were females. Six patients had pneumonia, and 4 needed oxygen therapy. Increased C-reactive protein (6/10), high serum lactate dehydrogenase (LDH; 6/10), and erythrocyte sedimentation rate (ESR; 6/10) were the most common laboratory findings. 6/10 patients had an exacerbation of anemia (2 with SCD). In the majority of patients, the course of COVID-19 was moderate (6/10) and severe in 3/10 patients. A 30-year-old female with TM, developed a critical SARS-CoV-2 infection, followed by death in an Intensive Care Unit. In one Center (Oman), the majority of suspected cases were observed in patients with SCD between the age of 21 and 40 years. A rapid clinical improvement of tachypnea/dyspnea and oxygen saturation was observed, after red blood cell exchange transfusion, in a young girl with SCD and worsening of anemia (Hb level from 9.2 g/dl to 6.1g/dl).

Conclusions: The data presented in this survey permit an early assessment of the clinical characteristics of COVID 19 in different countries. 70% of symptomatic patients with COVID-19 required hospitalization. The presence of associated co-morbidities can aggravate the severity of COVID-19, leading to a poorer prognosis irrespective of age.

Keywords: COVID-19; SARS-CoV-2; β -thalassemia; Sickle cell disease; Patients' characteristics; Clinical course; Risk factors.

Citation: de Sanctis V., Canatan D., Corrons J.L.V., Karimi M., Daar S., Kattamis C., Soliman A.T, Wali Y., Alkindi S., Huseynov V., Nasibova A., Tiryaki T. O., Evim M.S., Gunes A.M., Karakas Z., Christou S., Campisi S., Zarei T., Khater D., Oymak Y., Kaleva V., Stoyanova D., Banchev A., Galati M. C., Yassin M.A., Kakar S., Skafida M., Kilinc Y., Alyaarubi S., Verdiyevs N., Stoeva I., Raiola G., Mariannis D., Ruggiero L., Di Maio S. Preliminary data on COVID-19 in patients with hemoglobinopathies: a multicentre icet-a study. *Mediterr J Hematol Infect Dis* 2020, 12(1): e2020046, DOI: <http://dx.doi.org/10.4084/MJHID.2020.046>

Published: July 1, 2020

Received: May 30, 2020

Accepted: June 14, 2020

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Introduction. The recent COVID-19 outbreak has been deemed a global health emergency. From Dec 31, 2019, to May 20, 2020, 4,861,456 cases of COVID-19 (in accordance with the applied case definitions and testing strategies in the affected countries), and 322,483 deaths were reported (<https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases>).

The clinical presentation of COVID-19 disease is quite variable.^{1,2} A study from the Chinese Center for Disease Control and Prevention on 72,314 patients

with COVID-19 (44,672 laboratory-confirmed, 16,186 suspected, and 10,567 clinically diagnosed), reported that the clinical severity was mild in 81.4%, severe in 13.9%, and critical in 4.7%. Most patients were between 30 to 79 years of age (87%), 1% were less than 9 years, 1% between 10 and 19 years and 3% were 80 and above years.³

Subjects at higher risk for severe illness are: adults > 60 years, patients with chronic diseases [heart, lungs, and end-stage renal disease neuromuscular disorders, sickle cell disease (SCD), cirrhosis and diabetes],

immunocompromised patients, pregnant women or those immediately postpartum (<2 weeks), and patients who reside in nursing homes or long-term care facilities (<https://www.england.nhs.uk/coronavirus/wp-content/uploads/> sites; Updated:11 April 2020).

In subjects with SCD, this is probably due to impaired immunity resulting from impaired function of the spleen, systemic vasculopathy that predisposes to end-organ dysfunction, and an increased risk of thrombosis. Patients with thalassemias could have multiple organ impairment due to iron overload and chronic anemia (chronic hypoxemia) of the heart, lungs (pulmonary artery hypertension), liver and endocrine glands. Both groups of patients have been considered vulnerable to COVID-19 and at potentially higher risk for severe complications compared to the general young population (especially in the older age group).⁴ Moreover, coexistent immune system impairment in patients with thalassemia also predisposes to more severe COVID-19 disease.⁴ However, there is limited information available on COVID-19 infection in patients with hemoglobinopathies.⁴⁻⁹

We report the preliminary results of an International Multicentre Study (IMS), promoted by the International Network of Clinicians for Endocrinopathies in Thalassemia and Adolescence Medicine (ICET-A). The survey aimed to investigate the COVID-19 retrospectively in patients with hemoglobinopathies, namely β -thalassemias (TM and TI) and SCD, followed in 17 Centers from 10 countries.

Survey Design and Participants

Questionnaire development. A. First step

In April 2020, the Coordinator of the ICET-A (VDS) with DC and JLVC designed and promoted a survey questionnaire to collect, as a primary aim, data on confirmed COVID-19 in patients with hemoglobinopathies and as a secondary aim, the numbers of suspected or probable COVID-19 cases,¹⁰ without performing the test, registered from Jan 1, 2020, to 7th June 2020.

For a uniform collection of data, the diagnosis of β -thalassemias was based on the definitions proposed by Kattamis et al.¹¹ in TM patients, Karimi et al.¹² in TI cases, and by Quinn¹³ for the diagnosis of SCD.

Before the distribution to the ICET-A members, the questionnaire was revised and discussed with the ICET-A Board (SD, CK, and MK).

A. Second step. The final questionnaire was sent by mail to 12 Thalassemia Centers of the ICET-A Network.

Each ICET-A member was free to distribute the questionnaire to other Thalassemia Centers within their own country. The deadline for returning the requested data was fixed to 7th June 2020.

Definitions of confirmed COVID-19 and close contact. A patient was classified as confirmed COVID-19 in the presence of laboratory confirmation of COVID-19 infection, documented by at least one nasal/pharyngeal swab specimen positive for SARS-CoV-2 nucleic acid testing (NAT) using reverse-transcriptase polymerase-chain-reaction (RT-PCR) technology,¹⁴ irrespective of clinical signs and symptoms, according to the European Centre for Disease Prevention and Control as of Mar 2, 2020. Close contact definition was based on the current WHO available information.¹⁰

Data collection. The collected data included: demographic data, medical history, exposure history, underlying comorbidities, symptoms, signs, laboratory findings, chest X-ray and/or computed tomography (CT) scans, treatment schedules, and outcomes. The disease onset was defined as the day when the first symptoms appeared before the first medical contact/examination. Time (in days) from the onset of disease to hospital discharge was also recorded. Laboratory data included: complete blood cell count (CBC), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), liver enzymes and serum creatinine, D-dimer, levels of procalcitonin, serum lactate dehydrogenase (LDH), and serum ferritin levels.

Clinical and diagnostic classification. Patients with a nasal/pharyngeal swab specimen positive for SARS-CoV-2, fever, respiratory symptoms, and radiologic changes consistent with diffuse pneumonitis were defined as having **pneumonic COVID-19**. Positive patients, with fever and respiratory symptoms without radiologic changes, were defined as having **non-pneumonic COVID-19**. Positive patients, without fever and respiratory symptoms, were defined as **asymptomatic**. Furthermore, according to the latest recommendations of the National Health Commission of the People's Republic of China¹⁴ and WHO,¹⁰ COVID-19 disease was classified into four types: **mild**, **moderate**, **severe** and **critical**. **Type 1 mild:** mild clinical symptoms without pneumonia at chest computed tomography; **Type 2 moderate:** fever and other respiratory symptoms with pneumonia seen at imaging; **Type 3 severe:** respiratory distress (≥ 30 breaths per min), hypoxia (oxygen saturation: $\leq 93\%$), or abnormal results of blood gas analysis; and **type 4 critical:** respiratory failure requiring mechanical ventilation, shock, or other organ(s) failure requiring intensive care unit monitoring and treatment.

Study approval. Ethical approval and informed patient or guardian consent were obtained in accordance with local institutional requirements and with Good Clinical Practice and the Declaration of Helsinki principles for ethical research, and its later amendments.

Data presentation. Descriptive statistics of the participants' baseline characteristics are provided as mean and standard deviation (SD) for continuous variables and frequency and percentages for categorical variables. A detailed description of confirmed COVID-19 patients is also provided.

Results. A total of 17 Centers, 5 from Turkey, 3 from Italy, 2 from Bulgaria, and 1 each from Azerbaijan, Cyprus, Greece, India, Iran, Oman, and Qatar, following 9,499 patients with hemoglobinopathies (β -thalassemias and SCD), participated in the survey. The distribution by age groups, sex, and type of hemoglobinopathy are listed in **table 1**. The largest group of patients with TM and TI was reported in Azerbaijan (TM:1,304; TI:605) and for SCD in Oman (SCD: 2,000).

A total of 13 patients with confirmed COVID-19 by RT-PCR, 7 with TM, 3 with TI, and 3 with SCD, were retrospectively identified from 6 Centers (Azerbaijan, Cyprus, Iran, Italy, Turkey, and Oman) (**Table 2**). The overall mean age of patients was 33.7 ± 12.3 years (range:13-66); 9 (69.2%) were females.

The general characteristics of patients with thalassemias, SCD, and confirmed COVID-19 are reported in **table 3**. None of them were overweight.

The mean serum ferritin level in 12/13 patients was $1,428 \pm 1,538$ ng/ml. Four patients with thalassemia had been splenectomised; 4 had endocrine complications: 3 had insulin-dependent diabetes mellitus (2 with TM and in 1 with TI), and one hypogonadal female patient had a history of renal disease with hypertension. One patient had arrhythmia (**Table 2**).

Three asymptomatic patients had laboratory-confirmed positive results for SARS-CoV-2 (based on nucleic acid testing of pharyngeal swab samples). All had had close contact with an infected family member or community exposure. These patients remained asymptomatic throughout quarantine and clinical monitoring.

In symptomatic patients, the mean interval between symptoms onset and first medical evaluation was 5.0 ± 3.4 days (range: 3–14).

Fever was present in 8 out of 10 (80%) symptomatic patients (peak 38.1°C - 39.5°C). Other common signs and symptoms were: cough (70%), headache (60%), fatigue (60%), gastrointestinal symptoms (diarrhea /vomiting/abdominal pain; 50%), tachypnea/dyspnea (40%), sore throat (40%), anosmia/hyposmia (40%), conjunctivitis (30%), rhinorrhea (20%) and myalgia (10%). Back and chest pain were reported in a patient with SCD. Six patients had pneumonia (unilateral in 3,

Table 1. Total number of patients with hemoglobinopathies enrolled in the ICET-A survey.

Hemoglobinopathy	Age group 1 < 21 yrs	Age group 2 21-40 yrs	Age group 3 > 40 yrs
1. Thalassemia major (TM)	2,659	1,598	705
No. males / . females; total	1,007/937; 1,944 (*)	680/801;1,481 (*)	302/342;644 (*)
Age range	=	=	41-69
2. Thalassemia intermedia (TI)	530	577	182
No. males / . females; total	295/231;526 (*)	258/273;531 (*)	87/94;181 (*)
Age range	=	=	41-87
3. Sickle cell disease (SCD)	1,309	1,677	262
No. males/ females; total	587/480;1,067 (*)	624/598;1,222 (*)	97/145;242 (*)
Age range	=	=	40-70

(*) Data not fully available.

Table 2. Number of confirmed COVID-19 in patients with hemoglobinopathies reported from 6 countries in comparison to the number of patients in the general population, updated to 8 th June 2020 (<https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases>).

Countries and number of participating Centers	Number of patients with hemoglobinopathies: TM - TI and SCD	Number (%) of confirmed Covid-19 positive cases in patients with hemoglobinopathies	Number of Covid-19 positive cases in general population
Italy (3 Centers)	306 - 79 - 37	1 TM (F - 34 yrs) (0.3 %)	234,998
Turkey (5 Centers)	658 -164 -335	1 TM (M - 22 yrs); 1 TM asymptomatic (F - 30 yrs) (0.3 %)	170,132
Azerbaijan (1 Center)	1,304 - 605 -124	2 TM asymptomatic (1 F - 29 yrs and 1M - 31 yrs) (0.15 %)	7,553
Iran (1 Center)	720 - 311 - 0	3 TM (F - 30, 31 and 38 yrs) (0.41 %) 1 TI (F- 66 yrs) (0.32 %)	171,789
Cyprus (1 Center)	247- 44 - 28	1 TM (M - 46 yrs) (0.4%)	964
Oman (1 Center)	300 - 44 - 2,000	3 SCD (2 F -13 and 43 yrs, and 1 M -26 yrs) (0.15%)	16,882

Legend. TM:Thalassemia major; TI: Thalassemia intermedia; SCD: Sickle cell disease; M: males; F: females.

Table 3. General characteristics in thalassemic and SCD patients with confirmed COVID-19..

Clinical and laboratory variables	Thalassemias (10)	Sickle cell anemia (3)
Total number		
Clinical phenotype: TM and/ TI	8 /2	3 severe
Gender male (M) / female (F)	3 /7	1/2
Age in yrs mean SD (range)	35.7±11.7 (22-66)	27.3 ±12.2 (13-43)
Blood group	5: A+; 4: B+; 1: AB+	2: 0 +; 1: NR
Household or community exposure	4/10	1/10
Hospitalization in symptomatic patients	5/7	2/3
Isolation and follow-up at home	4/10	1/3
Splenectomy	4/10	1/3 Functional hyposplenism
Last serum ferritin level mean±SD (ng/ml, range)	1,653 ± 1,592 (Range: 225-5,960)	2/3: 289 and 316 1/3:NA
Body mass index (Kg/m ²)	19.39 ± 3.5	1/3 (17.8)
LIC: MRI T2* (mg Fe/g d.w.)	Mild: 3/10; Moderate 2/10; Severe 3/10	NA
HCV Ab + HCV-RNA +	3/10 =	= 1/3 (treated)
Cardiac complications	1/10 (Arrythmia)	2/3: NR
Myocardial T2* (ms)	6/10 >20 ms; 1/10: 16 ms	3/3: NA
Chronic kidney disease before Covid-19	1/10 (Nephropathy and hypertension)	1/3
Respiratory disease before Covid-19	0/10	1/3 (Asthma)
Pulmonary hypertension	0/10	0/3
Endocrine complications	3/10: IDDM; 1/10 HH; 1/10 HT	0/3
Iron chelation therapy and other treatments	DFO: 3/10; DFP: 1/10; DFX: 6/10; DFO-DFX: 1/10; HU: 4/10	HU:3/3

Legend = TM: β-thalassemia major; **TI:** β-thalassemia intermedia; **NA:** Not available; **LIC:** liver iron concentration, was classified as mild (LIC > 3 and < 7), moderate (LIC > 7 and < 14) and severe (LIC > 14 mg/g.d.w.); **HCV Ab:** hepatitis C antibodies; **Myocardial T2* value:** normal >20 ms, mild to moderate iron overload:10 -20 ms and severe : <10 ms; **DFO:** desferrioxamine; **DFP:** deferiprone; **DFX:** deferasirox; **HU:** hydroxyurea; **IDDM:** Insulin Dependent Diabetes mellitus; **HH:** Hypogonadotropic Hypogonadism; **HT:** primary hypothyroidism.

bilateral in 2, and multiple opacities in 1 patient), and four needed oxygen therapy, and four patients (2 with SCD) had non-pneumonic COVID-19.

In the majority of patients (6), the course of COVID-19 was defined as moderate, and severe in 3. Oxygen saturation of ≤ 93% was documented in 3 patients. One of them, a 30-year-old female with TM developed critical type 4 COVID-19, according to the National Health Commission of the People's Republic of China¹⁴ and WHO,¹⁰ characterized by progressive respiratory and renal insufficiency, followed by death in an Intensive Care Unit.

Increased C-reactive protein (6/10), high LDH (6/10), high ESR (6/10), and high D-dimers, in 4 out of 5 tested patients, were the most common laboratory findings. Six patients with confirmed COVID-19 (1 with SCD) had a reduction of hemoglobin levels, three patients had lymphopenia (low absolute number of lymphocytes), and 1 SCD patient had thrombocytopenia.

Experimental treatments for SARS-CoV-2 infection, including hydroxychloroquine (2.5 mg/kg twice daily; 2 patients), azithromycin (10 mg/kg once daily)/clarithromycin (7.5 mg/kg twice daily) or

moxifloxacin (3 patients), were given to 5 of 6 patients with TM. Low molecular weight heparin and antiviral drugs (2 and 1 out of 10 patients, respectively) were less commonly used. A rapid clinical improvement of tachypnea/dyspnea and oxygen saturation was observed, after red blood cell exchange transfusion, in a 13-year-old girl with SCD and COVID-19. At hospital admission, she presented with high fever, cough, worsening of anemia (decreased Hb level from 9.2 g/dl to 6.1g/dl) and elevated D-Dimers).

None of the SCD patients received hydroxychloroquine or convalescence plasma transfusion.

The average time from the onset of disease to hospital discharge was 12.8 ±5.4 days.

Seven Centers did not report cases of suspected or probable COVID-19, and 5 Centers did not respond with the requested information. One Center reported detailed information (data are presented in **Table 4**). The majority of cases were observed in patients with SCD, between 21- 40 years (5.5%).

Discussion. People of all ages are susceptible to SARS- CoV-19 infection. Clinical manifestations of

Table 4. Number of suspected or probable COVID-19 in patients with hemoglobinopathies in Oman.

Group of patients and demographic data	Age group < 20 yrs (Total no.)	Age group 21-40 yrs (Total no.)	Age group > 40 yrs (Total no.)	Total and %
1. Thalassemia major (TM) - No.	120	170	10	300
No. of males and No. females	50/70	60/110	5/5	=
Age range	=	=	41-47	=
WHO - Suspected Covid 19 -M/F	3/2	1/0	0/0	6 (2.0%)
WHO - Probable Covid 19 - M/F	1/0	0/0	0/0	1 (0.3%)
2. Thalassemia intermedia (TI) - No.	28	10	6	44
No. of males and No. females	14/14	4/6	5/1	=
Age range	5-20	21-28	41-43	=
WHO - Suspected Covid 19 - M/F	0	0	0	0
WHO - Probable Covid 19 - M/F	0	0	0	0
3. Sickle cell disease (SCD) - No.	800	1,000	200	2,000
No. of males and No. females	430/370	510/490	80/120	=
Age range	=	=	40-61	=
WHO - Suspected Covid 19 - M/F	10/21	20/30	2/3	86 (4.3%)
WHO - Probable Covid 19- M/F	2/0	3/2	0/1	8 (0.4%)

SARS-CoV-19 infection range from asymptomatic to severe pneumonia and respiratory failure. Severe disease can lead to death. Hospitalization rates are higher for people of advanced age (> 60 years). Although age and comorbidities have been described as the main determinants of disease progression towards severe respiratory distress, the high diversity in clinical severity among patients could suggest a possible role of the host genetic background contributing to the observed inter-individual clinical variability associated with COVID-19 in black and ethnic minority people.

Up to 7th June 2020, the impact of COVID-19 in thalassaemic or SCD patients had only been preliminarily evaluated in different countries.^{3-9,15}

A study of a small cohort of patients with thalassemia from Northern Italy, which was the epicenter for coronavirus COVID-19 in Europe, showed relatively mild to moderate COVID-19 disease in 11 patients (10 with TM and 1 with TI) compared to the general population with all infected thalassemia patients recovered.⁹ The mean age of this cohort of the thalassaemic patients was 44 ± 11 years (range 31-61 years), and 55% (6/11) were females. One patient, with severe symptoms, required ventilation with continuous positive airway pressure (CPAP). All patients had associated comorbidities, and 70% were splenectomised. The likely source of infection was found in 64% of cases, while the clinical course ranged from 10 to 29 days.⁹

A multicenter, retrospective, cross-sectional study was obtained across all comprehensive thalassemia centers in Iran, from January to Apr 29, 2020. All suspected and confirmed COVID-19 cases from a total of 15,950 TM and 2,400 TI patients were evaluated. Fifteen confirmed cases (12 TM and 3 TI; mean age 36.1 ± 12.1; range 22-66 years). Moreover, eight asymptomatic suspected β-thalassemia patients (6 TM

and 2 TI) of COVID-19 were detected. Seventeen patients (73.9%) had mild to moderate symptoms and recovered, while six patients died (26.1%, 2 TM, and 4 TI). More than 60% of all patients had at least one comorbidity, and 80% were splenectomised. The prevalence of COVID-19 in thalassemia patients was less than the general population, but the mortality rate was significantly higher, also taking into consideration the lower age.¹⁵ Therefore, these findings provide further objective evidence to take into account the comprehensive risk assessment and prognosis among thalassaemic patients with COVID-19.

The clinicopathological features, management, and outcomes of 10 SCD patients (8 male and 2 female), with COVID-19 infection (6 with confirmed COVID-19 and 4 with suggestive clinical, laboratory and radiological features, but a negative swab) with a mean age of 36 years, were reported by McCloskey et al.⁵ A 57-year-old patient with several pre-existing comorbidities including severe neurological impairment as a result of a previous stroke, died. Another patient with chronic kidney disease (CKD) stage III developed significant deterioration of renal function and required temporary peritoneal dialysis, but otherwise had a full recovery, as did the remaining patients.⁵

To our knowledge, this is the first preliminary multicenter study evaluating the COVID-19 in patients with hemoglobinopathies, namely β-thalassemsias and SCD. Approximately 90% of COVID-19 cases are associated with household or community exposure, and 10% are associated with travel.^{1,2} In the present survey the likely source of infection was detected in only 5/13 (38.4%) of patients.

A recent review of data from 59,254 patients from 11 countries has shown a positive association between male sex and a higher mortality rate.¹⁶ Although adult

men are more susceptible to COVID-19 infection and adult females produce more robust inflammatory responses as compared to men,¹⁷ 10 out of 13 of patients (76.9%) in our survey were females. Therefore, further studies are needed to elucidate this particular gender aspect of COVID-19 in hemoglobinopathies.

Asymptomatic infection at the time of laboratory confirmation has been reported in many settings.^{18,19} Some of these cases developed symptoms at a later stage of infection; the proportion of these cases has not yet thoroughly evaluated.²⁰ There are also reports of patients remaining asymptomatic throughout quarantine, as observed in our patients.

Four of our patients (2 with SCD) had non-pneumonic COVID-19, 6 had pneumonic COVID-19, and five patients, in addition to fever and cough, had gastrointestinal symptoms, such as diarrhea, vomiting and/or abdominal pain.

In the majority of patients (90%) worldwide, the outcome of COVID-19 infection has been defined as a mild or moderate disease, but severe, and especially critical cases are accompanied by a high mortality rate. Current knowledge has shown that the mortality rate is high in people with chronic underlying diseases.^{21,22}

Blood groups were known in 12 of our 13 confirmed COVID-19 patients: 5 were blood group A (41.6%), 33.3% blood group B, 16.6% blood group O, and 8.3% blood group AB. Therefore, it is plausible that different blood groups might vary in their susceptibility to COVID-19, as reported by Zhao et al.²³ However, more evidence is needed to confirm this observation, taking into consideration the specific distribution of blood groups among populations.

Furthermore, in patients with hemoglobinopathies, several factors may be associated directly or indirectly with the triggering of a severe outcome of the COVID-19.³⁻⁶ Both intravascular and extravascular hemolysis can occur in thalassemia patients. Clinicians should, therefore, closely monitor blood counts of thalassemia patients with COVID-19, and caution should be maintained towards the possibility of exacerbated hemolytic anemia in the setting of acute viral infection.

Moreover, there is a significant concern that the overlap of lung disease from COVID-19 with acute chest syndrome (ACS) may result in increased complications among individuals with SCD.²⁴

Splenectomy is a common therapeutic intervention in β -thalassemias, while many SCD patients have a hypo-functional spleen. Splenectomy was reported in 6/13 of our patients with thalassemias.

Based on the knowledge of the immunological functions of the spleen, there is no evidence that asplenic/hyposplenic patients are at higher risk of having severe COVID-19 infection.

Nevertheless, since fever could indicate bacterial as well as viral infection, all patients should be instructed to seek medical advice by contacting their clinical team

if they develop fever. Medical consideration should be given to the presence of superimposed infection, particularly with encapsulated pathogens.^{25,26}

In patients with SCD, hypoxia, dehydration, or acidosis due to respiratory infection may trigger a vaso-occlusive and hemolytic crisis and acute chest syndrome (ACS), with a high risk of thrombosis in pulmonary arteries.²⁷ Thus, measures to prevent and treat ACS early in the event of viral infection, require particular alertness by physicians treating infected patients.²⁸

Another relevant aspect for COVID-19 infection in hemoglobinopathies, mainly SCD and TI, relates to current therapy with hydroxycarbamide (hydroxyurea), a cytotoxic agent, with possible immune-compromising effects contributing to an adverse outcome of these patients.²⁸ Risk stratification recommendations for children and adults hospitalized with COVID are available from the American Society of Hematology (<https://hematology.org/covid-19/covid-19-and-vte-anticoagulation>).

The current study has some limitations. First, only 13 patients with confirmed COVID-19 infection were identified. However, the data presented in this study permit an early assessment of the clinical characteristics of COVID-19 in different countries. Second, though the sample of patients with COVID-19 was small, we observed a prevalence of females versus males. These data contrast with the reduced susceptibility of females, probably linked to the X chromosome and sex hormones, which play an important role in innate and adaptive immunity.²⁹ Nevertheless, this is a preliminary report of a rapidly evolving condition, as the parameters discussed here are changing quickly with time. Third, our survey included mainly young adult patients with an age range between 20 and 40 years. Lastly, the number of reported COVID-19 cases has certainly underestimated the real burden of disease, given the widespread unavailability and accuracy of tests, and also the significant proportion of infected persons, who develop asymptomatic or mild unidentified forms of the disease, remain undiagnosed. The high number of suspected or probable COVID-19 in patients with SCD sustain this hypothesis. Therefore, we should be careful when measuring the prevalence of confirmed COVID-19, acknowledging that the rate will be likely higher once the denominator is adjusted to the correct number of individuals who acquired the infection.

Conclusions. It is reasonable to say that few cases of COVID-19 have so far been reported in thalassemias and SCD patients in the literature. Is this due to a lack of testing or a real lack of infection/susceptibility? In our survey, a total of only 13 patients with confirmed COVID-19 were identified in 17 Centers, from 10 countries, following 9,499 patients with

hemoglobinopathies. However, our provisional data should be interpreted cautiously because only 20% of patients with thalassemias and 8.7% of SCD patients were in the higher age group (> 40 years) for SARS-CoV-2 infection. Despite their age, 70% of symptomatic COVID-19 patients required hospitalization, and the clinical outcome in one patient confirmed that associated comorbidities could

aggravate the severity of infection, leading to death. Automated exchange transfusion improved the outcome of COVID-19 respiratory failure in a young girl with SCD. In the forthcoming weeks, we will continue to monitor the epidemiology of the COVID-19 outbreak collecting data from the participating Centers. Any further international participation is welcomed.

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