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COVID-19 infection among pediatric patients with hemoglobinopathies in Basrah, Iraq

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Abstract:

BACKGROUND: Patients with hemoglobinopathies are considered as immunocompromised; however, it is unclear if they are more susceptible to COVID-19 infection and experience a more severe illness course.

AIMS OF STUDY: The aims of this study were to evaluate the clinical presentation and severity of COVID-19 among pediatric patients with hemoglobinopathies, assess risk factors, and outcome among studied patients.

PATIENTS AND METHODS: An analytical, cross-sectional study has been carried out on children and adolescents with hemoglobinopathies, for the period from the first of May 2021 to September 2022. In addition to patient's data and thorough physical examination, patients were followed concerning the course, complications, and disease outcome. Investigations included complete blood count, inflammatory markers, liver, and renal function tests.

RESULTS: Out of 42 patients with hemoglobinopathies and COVID-19, the majority of patients 35 (83.3%) gave a history of COVID-19 exposure, with a median of 5 days for the presentation since exposure and 23 (54.8%) needed hospitalization. All studied patients had fever, followed by cough in 36 (85.7%) and shortness of breath (42.9%). No death was reported in studied patients. The lymphocyte count was significantly lower and C-reactive protein and D-dimer levels were significantly higher in sickle cell disease (SCD) patients with COVID-19 as compared to thalassemia patients, $P < 0.05$. Twenty-two patients (52.4%) had mild COVID-19 disease, 12 (28.6%) moderate, and 8 (19%) with severe disease. Regression analysis revealed that acute chest syndrome (ACS) as COVID-19 infection presentation, high white blood cells count, and elevated total serum bilirubin were significant variables associated with severe COVID-19 infection, $P < 0.05$.

CONCLUSION: The clinical course of hemoglobinopathy patients with COVID-19 infection is similar to that in the general population and no death was reported among studied patients. However, clinicians treating patients with SCD need to be aware of COVID-19 infection when diagnosing ACS.

Keywords:

Children, COVID-19, hemoglobinopathies, Iraq

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Introduction

Hemoglobinopathies, mainly sickle cell disease (SCD) and thalassemia, are a group of chronic genetic hemoglobin (Hb) disorders that are associated with pulmonary parenchymal damage and impaired vascular function. Cardiopulmonary comorbidities represent an important cause of mortality and morbidity in patients with hemoglobinopathies.[1]

Infections are a common and sometimes fatal consequence of hemoglobinopathies including thalassemia. The morbidity and mortality rates of diseases vary globally based on the epidemiology of each infection, the socioeconomic status of each country, and the preventive and therapeutic

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measures taken. Infection susceptibility in thalassemia and SCD can result from a wide range of immunological disorders: patients with SCD have immunodeficiency attributable to the disease itself, ongoing medication use, disease-specific consequences, and exposure to infectious pathogens.[2,3] Iron overload in both β-thalassemia and SCD also can cause chronic organ damage in thalassemia that may result in immunodeficiency and an increased risk of infections.[2]

A systematic review of hemoglobinopathy patients with COVID-19 infection has revealed that only 16.3% were within the pediatric age group. About 57% of these individuals had sickle cell anemia (SCA), 8.9% had sickle cell trait, 27.6% had transfusion-dependent thalassemia (TDT), and 6.5% had non-TDT (NTDT).[4]

Patients with SCD and TDT should be included in the "vulnerable" groups of every country's population. Patients with TDT can be divided into three risk groups concerning COVID-19 infection, while SCD are considered as the highest risk group,[5] while the disease is mild to moderate in most thalassemia cases.[6]

Patients with hemoglobinopathy exhibited nearly identical clinical manifestations of COVID-19 infection as the general population, with fever and cough being the most prevalent symptoms among patients with thalassemia and SCD.[4] There is increasing evidence that COVID-19 pneumonia can result in acute chest syndrome (ACS) in patients with SCD,[7] that increases the risk of disease severity and mortality.[8] The detection of SARS-CoV-2 RNA by the reverse transcription polymerase chain reaction (RT-PCR) of nasopharyngeal swab is still considered the reference standard for the diagnosis of acute COVID-19 infection in symptomatic and/asymptomatic children with COVID-19 exposure.[9]

Given the immunocompromised state and several comorbidities of patients with hemoglobinopathies, it is unclear if they are more susceptible to COVID-19 infection and experience a more severe illness course. Clinicians must be aware of the possibility of COVID-19 infection to manifest differently in these patients as well as the risk factors associated with worse outcomes.[4]

Therefore, this study aimed to evaluate the clinical presentation and severity of COVID-19 among pediatric patients with hemoglobinopathies, assess the risk factors, duration of hospitalization among studied patients, and explore the outcome of COVID-19 among hemoglobinopathy patients.

Patients and Methods

Patients

An analytical, cross-sectional study has been carried out on children and adolescents with hemoglobinopathies, who have consulted the emergency department at Basrah Maternity and Children Hospital and the Center of Hereditary Blood Diseases over 16 months during the period from the first of May 2021 to the end of September 2022.

The total number of patients with hemoglobinopathies and COVID-19 infection confirmed by either polymerase chain reaction (PCR) or computed tomography (CT) scan or both was 42, their age ranged from 2 to 18 years, 32 patients had SCD, while 10 patients had thalassemia.

Data included selected patient's demographic data, type of hemoglobinopathy, age of diagnosis, previous disease-related complications, comorbidities, for patients with SCD these included past medical and surgical history, SCD-related complications including ACS, vasoocclusive crises (VOC), acute splenic sequestration, and stroke, and drug history. While for patients with thalassemia, data included a history of respiratory problems such as asthma, diabetes mellitus, detailed blood transfusion history, history of splenectomy, and iron chelation therapy. Data were also obtained concerning the features and the clinical course of COVID-19 and history of COVID-19 vaccination. All patients were examined thoroughly, including growth measures and systemic examination.

Patients were followed concerning the course, complications (e.g., development of pneumonia, hospitalization, and/or the need for intubation), management, and disease outcome.

Patients with hemoglobinopathies who are >18 years old and those with symptoms suggestive of COVID-19 infection, but with negative PCR and/chest CT were excluded from the study.

An informed consent was obtained from patients and or one of their parents for participation in the study. The study has been approved by the Scientific and Ethical Committee of Basrah Medical College (Ref. number 03041172-2021, S/272 on June 29, 2021), and Basrah Health Directorate.

Definitions of variables

Transfusion-dependent thalassemia

This term is used to describe thalassemic patients who require lifelong regular blood transfusions for survival starting before the age of 2 years.[10]

Nontransfusion dependent thalassemia

This term is used to label thalassemic patients who may require blood transfusion occasionally or for limited periods of time, such as during periods of growth and development, surgery, pregnancy, or to prevent or manage disease-related complications.[10]

Type of sickle cell disease

- The diagnosis of Hb SS is established when 80–96% of total Hb is Hb S, Hb F 2–20%, normal Hb A2, and no Hb A
- The diagnosis of Hb S/ß° thalassemia is established if 50–85% of the total Hb is Hb S, 2–30% is Hb F, the amount of Hb A_2 is elevated (> 3.5%), and no Hb A
- S/β^+ Thalassemia is diagnosed if 50–80 of the total Hb is Hb S, 0–20% is Hb F, amount of Hb A_2 is < 3.5 %, and 10–30% of Hb is Hb A.[11]

COVID-19 disease severity

The COVID-19 severity was estimated depending on the clinical manifestation during infection:

- Asymptomatic: No sign or symptoms, only the PCR is positive
- Mild: Symptoms of upper respiratory tract infection in which the patient complained of fever, myalgia, sore throat, and sometimes gastrointestinal symptoms such as nausea, vomiting, and abdominal pain
- Moderate: Pneumonia, but no hypoxia
- Severe: Dyspnea and hypoxia (O_2 saturation <92%) with respiratory or gastrointestinal symptoms
- Critical: Acute respiratory distress syndrome, respiratory failure, encephalopathy, shock, and multiorgan failure.[12]

Methods

A portion of each blood sample was added to EDTA tubes and sent for complete blood count analysis by a hematology analyzer (Mindray BC-5300, Shenzhen, China). The remainder was transferred to plain tubes for the rest of the biochemical analyses. After sera separation, specimens were either immediately analyzed or stored in freezing conditions until analysis within 2 days. Inflammatory markers include serum ferritin, lactate dehydrogenase (LDH), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and D-dimer. LDH enzyme and serum electrolytes (serum potassium and sodium), total serum bilirubin (TSB), alanine aminotransferase, aspartate aminotransferase (AST), and alkaline phosphatase were assessed by Roche Cobas C111 Biochemistry analyzer, Germany. The blood urea was measured by RANDOX United Kingdom, kit ref. UR2316, while serum creatinine was estimated spectrophotometrically using an alkaline picrate assay kit from Spectrum, Egypt.

Statistical analysis

Statistical analysis was performed using the SPSS software version 17 (SPSS Inc., Chicago, IL, USA). Data are presented as the mean ± standard deviation or number and percentage (*n* and %) as appropriate. The comparisons of the proportions were performed with crosstabs using the Chi-square test and Fisher's exact test. The statistical comparison between means was measured by paired *t*-tests and one-way analysis of variance. For all tests, a $P < 0.05$ was considered statistically significant.[13] Binary logistic regression analysis was done to look for the potential risk factors associated with severe COVID-19 infection. For statistical purposes, the severity of COVID-19 was classified as not severe and severe. Not severe includes mild and moderate cases.

Results

A total of 42 children and adolescents with various hemoglobinopathies and COVID-19 were included in this study. The mean age of patients was 10.48 ± 4.05 years with 33 (78.6%) of patients were at school age, and a male-to-female ratio of 1.6:1. SCD was the most common hemoglobinopathy 32 (76.2%), with SCA 22 (52.4%) being the most common type of SCD, followed by S/β° thalassemia in 7 (16.7%) and hemoglobin S/D in 3 (7.1%). All patients with TDT have β-thalassemia major 8 (10%), while concerning NTDT patients; one have β-thalassemia intermedia (β-TI), and the other with α-thalassemia.

All studied patients had fever during their infection course. Cough was the second most common symptom in 36 (85.7%), followed by shortness of breath in 18 (42.9%). Loss of taste and smell were present in 14 (33.3%) of patients. Gastrointestinal symptoms were significantly more common in SCD patients compared to those with thalassemia, $P < 0.05$. Regarding SCD patients, 14 (43.8%) had VOC and 7 (21.9%) presented with ACS in addition to COVID-19-related symptoms [Table 1].

The majority of patients 35 (83.3%) gave a history of COVID-19 exposure, ranging from 1 to 10 days with a median of 5 days for the presentation since exposure. A total of 33 (78.6) patients were diagnosed by PCR and 23 (54.8%) needed hospitalization. Only two patients have received COVID-19 vaccine; one of them is a 15-year-old boy with SCA and the other was a 16-year-old boy with β-thalassemia major. All patients recovered and discharged well. No death was reported in studied patients [Table 2].

Table 3 reveals that the lymphocyte count was significantly lower in SCD patients with COVID-19 in comparison with thalassemia patients, $P < 0.05$. Other hematological indices were not significantly different in both types of hemoglobinopathies.

Table 1: Clinical features of patients with COVID-19 in relation to the type of hemoglobinopathy

Variables	SCD (*n*=32), *n* (%)	Thalassemia (*n*=10), *n* (%)	Total (*n*=42), *n* (%)	*P*
Fever	32 (100.0)	10 (100.0)	42 (100)	0.922*
Cough	28 (87.5)	8 (80.0)	36 (85.7)	0.616*
Shortness of breath	16 (50.0)	2 (20.0)	18 (42.9)	0.084**
Nausea and vomiting	15 (46.9)	1 (10.0)	16 (38.1)	0.024**
Diarrhea	11 (34.4)	0	11 (26.2)	0.008**
Loss of taste and smell	11 (43.4)	3 (30.0)	14 (33.3)	0.798**
Skin rash	3 (9.4)	0	3 (7.1)	0.991**
Other disease-related presentation				
VOC	14 (43.8)	0	14 (33.3)	0.017**
ACS	7 (21.9)	0	7 (16.7)	0.04**

*Chi-squared test was used, **Fisher's exact test was used. ACS=Acute chest syndrome, VOC=Vaso-occlusive crises, SCD=Sickle cell disease

Table 2: Selected COVID-19 infection-related variables in relation to the type of hemoglobinopathy

Variables	SCD (*n*=32), *n* (%)	Thalassemia (*n*=10), *n* (%)	Total (*n*=42), *n* (%)	*P*
COVID-19 exposure	26 (81.3)	9 (90.0)	35 (83.3)	0.993*
Duration since exposure (days)				
Mean±SD	4.51±2.54	4.67±1.22	4.12±2.56	0.867***
Median	5	4	5	
Range	0–10	3–7	0–10	
Method of diagnosis				
PCR	24 (75.0)	9 (90.0)	33 (78.6)	0.516**
CT	5 (15.6)	1 (10.0)	6 (14.3)	
Both	3 (9.4)	0	3 (7.1)	
Hospitalization	18 (56.3)	5 (50.0)	23 (54.8)	0.923*
Length of stay at hospital (*n*=23)				
Range	2–7	1–7	1–7	0.372***
Mean±SD (days)	3.7±1.32	3.0±2.35	3.57±2.3	
COVID-19 vaccination	1 (3.12)	1 (10)	2 (4.76)	0.410

*Chi-squared test was used, **Fisher's exact test was used, ***Independent sample *t*-test. SCD=Sickle cell disease, PCR=Polymerase chain reaction, CT=Computed tomography, SD=Standard deviation

Although acute phase reactants are elevated among both groups, patients with SCD and COVID-19 have significant higher CRP and D-dimer levels, $P < 0.05$ [Table 4]. All studied biochemical parameters related to renal and liver function tests were not significantly different between SCD and thalassemia patients with COVID-19 infection, except for the TSB which was significantly higher among thalassemia patients, $P < 0.05$ [Table 3].

Concerning COVID-19 disease severity, 22 (52.4%) had mild disease, 12 (28.6%) moderate, and 8 (19%) with severe disease. Analysis of hematological data has revealed that the lymphocyte count was lower significantly while the total WBC and neutrophils count were significantly higher in severe COVID-19 infection, $P < 0.05$ [Table 4]. The levels of CRP, LDH, and D-dimer have increased significantly with increasing severity of COVID-19 infection, with those with severe disease having the highest levels, followed by moderate and then mild disease, $P < 0.05$. Furthermore, TSB, AST, and alkaline phosphatase were significantly higher in patients with severe COVID-19 disease, followed by those with moderate disease and then mild disease, $P < 0.01$ [Table 4].

Binary logistic regression analysis was done to look for the potential risk factors associated with severe COVID-19 infection and it revealed that ACS as COVID-19 infection presentation, high WBC count, and elevated TSB are significant variables associated with severe COVID-19 infection were, $P < 0.05$ [Table 5].

Discussion

Basrah has a high prevalence of hemoglobinopathies, SCD being the most common form. Other hemoglobinopathies, such as thalassemia is prevalent in this region. The prevalence of SCD in Basrah is estimated to be around 6.48%, making it one of the highest in Iraq, while the prevalence for β-thalassemia carrier rates was 4.6%.[14]

The emergence of COVID-19 has influenced the management and treatment of hemoglobinopathies by disrupting health-care services and changing blood donation patterns. Furthermore, individuals with hemoglobinopathies may be more susceptible to COVID-19 due to their underlying condition and may be at higher risk of severe illness and mortality.[15]

Table 3: Hematological, inflammatory, and biochemical indices of patients with COVID-19 in relation to type of hemoglobinopathy

Variables	Mean±SD			*P*
	SCD (*n*=32)	Thalassemia (*n*=10)	Total (*n*=42)	
HB (g/dL)	8.59±1.66	8.74±1.56	8.63±1.61	0.807
MCV (fL)	80.56±9.3	75.14±8.80	79.27±9.38	0.112
MCH (pg/cell)	27.39±3.62	25.63±4.92	26.97±3.98	0.226
WBC (×10^3/μL)				
Total	14.04±10.3	7.67±5.79	12.52±9.38	0.124
Neutrophils	6.39±5.53	7.43±3.98	6.64±4.50	0.740
Lymphocytes	2.86±1.72	8.85±3.04	4.28±2.18	0.001
Reticulocyte count (%)	3.36±2.11	2.60±1.22	3.18±1.95	0.296
Platelet (×10^3/μL)	245.21±162.56	263.0±168.12	249.45±162.0	0.766
Serum ferritin (ng/mL)*	2057.28±370.9	2853.0±917.1	2246.74±355.02	0.346
ESR (mm/h)*	23.72±5.47	26.2±8.44	24.31±4.58	0.821
CRP (mg/dL)*	25.88±11.69	7.91±4.44	21.60±9.01	0.001
LDH (μ/L)*	582.53±71.7	382.5±85.3	534.90±384.31	0.050
D-dimer (mg/dL)*	1248.23±446.2	423.7±185.5	1051.92±550	0.030
Blood urea (mmol/L)	6.70±3.64	5.65±0.73	6.46±3.21	0.371
Serum creatinine (mmol/L)	70.64±22.31	74.5±16.79	71.56±21.00	0.618
Serum potassium (mmol/L)	4.32±0.53	4.38±0.59	4.34±0.54	0.765
Serum sodium (mmol/L)	137.16±22.85	141.1±3.07	138.1±19.99	0.593
TSB (mmol/L)	20.20±2.47	36.55±5.78	32.66±5.53	0.013
ALT (μ/L)	55.31±36.83	54.19±35.06	55.05±27.28	0.969
AST (μ/L)	57.19±40.6	47.43±23.23	54.86±38.86	0.495
ALP (μ/L)	201.96±115.1	219.7±113.7	206.19±113.64	0.627

Values were assessed as mean±SE. Independent sample *t*-test. Hb=Hemoglobin, MVC=Mean corpuscular volume, MCH=Mean corpuscular hemoglobin, WBC=White blood cells count, ESR=Erythrocyte sedimentation rate, CRP=C-reactive protein, LDH=Lactate dehydrogenase, TSB=Total serum bilirubin, ALT=Alanine transaminase, AST=Alanine aspartate transaminase, ALP=Alkaline phosphatase, SD=Standard deviation, SCD=Sickle cell disease, SE=Standard error

Table 4: Hematological, inflammatory, and biochemical indices of hemoglobinopathies patients with in relation to COVID-19 severity

Variables	Mean±SD				*P**
	Mild (*n*=22)	Moderate (*n*=12)	Severe (*n*=8)	Total (*n*=42)	
Hb (g/dL)	9.12±1.31	8.33±1.94	7.73±1.53	8.63±1.61	0.046
MCV (fL)	77.92±8.12	82.59±9.17	77.96±12.6	79.27±9.38	0.357
MCH (pg/cell)	26.39±4.12	27.83±3.39	27.29±4.62	26.97±3.98	0.599
WBC (×10^3/μL)					
Total	7.78±3.36	14.49±9.35	22.63±18.12	12.52±9.38	0.003
Neutrophils	6.27±0.86	4.05±0.79	11.53±6.36	6.64±4.50	0.004
Lymphocytes	5.55±1.44	3.09±0.64	2.58±0.33	4.28±0.80	0.035
Reticulocyte count (%)	2.89±1.63	3.82±2.69	3.01±1.40	3.18±1.95	0.414
Platelet (×10^3/μL)	264.18±170.55	211.33±138.32	266.13±172.64	249.45±162.0	0.639
Serum ferritin (ng/mL)	1794.36±477.7	2835.00±708.3	2608.38±798.1	2246.74±355.1	0.912
ESR (mm/h)	17.14±3.93	28.91±9.76	37.12±16.7	24.31±20.72	0.008
CRP (mg/dL)	5.51±2.1	26.08±12.9	59.13±9.12	21.60±9.0	0.07
LDH (μ/L)	335.09±38.9	751.33±139.2	759.75±130.4	534.90±59.31	0.001
D-dimer (mg/dL)	304.85±47.9	573.06±134.4	3824.62±1498.9	1051.92±345.7	0.001
Blood urea (mmol/L)	6.81±3.41	5.26±1.00	7.26±4.53	6.46±3.21	0.305
Serum creatinine (mmol/L)	67.86±4.02	73.55±6.44	78.75±8.83	71.56±3.24	0.432
Serum potassium (mmol/L)	4.28±0.53	4.44±0.51	4.34±0.63	4.34±0.54	0.711
Serum sodium (mmol/L)	141.55±3.83	130.93±36.87	139.38±5.88	138.1±19.99	0.337
TSB (mmol/L)	20.09±1.47	33.30±6.11	66.25±17.57	32.66±4.56	0.001
ALT (μ/L)	39.4±6.10	72.42±4.3	71.98±6.03	55.05±11.9	0.398
AST (μ/L)	41.5±5.7	55.25±12.1	91.04±15.3	54.86±5.99	0.006
ALP (μ/L)	167.32±18.2	208.75±27.9	309.25±53.2	206.19±17.5	0.007

*ANOVA test was used. Hb=Hemoglobin, MVC=Mean corpuscular volume, MCH=Mean corpuscular hemoglobin, WBC=White blood cells count, ESR=Erythrocyte sedimentation rate, CRP=C-reactive protein, LDH=Lactate dehydrogenase, TSB=Total serum bilirubin, ALT=Alanine transaminase, AST=Alanine aspartate transaminase, ALP=Alkaline phosphatase, SD=Standard deviation

Table 5: Predictors of severe COVID-19 disease

Variables	*B* coefficient	OR	95% CI		*P*
			Lower limit	Upper limit	
ACS	4.049	57.33	4.162	80.82	0.002
WBC	1.08	3.083	1.031	7.124	0.05
TSB	1.58	4.007	1.236	5.302	0.04

CI=Confidence interval, ACS=Acute chest syndrome, WBC=White blood cells count, TSB=Total serum bilirubin, OR=Odds ratio

The current study involved 42 hemoglobinopathy patients infected with COVID-19. Fever and cough were the most common symptoms of COVID-19 disease in patients with hemoglobinopathies, which is comparable to the general population.[16] In patients with SCD, VOC was one of the most common features which could be triggered by COVID-19-induced hypoxia.[17]

In almost half of patients with SCD, symptoms such as vomiting and diarrhea were observed, which is significantly more common than in patients with thalassemia. These gastrointestinal symptoms are also prevalent in the general population. Pan *et al*., in China, have reported that almost half of the participants experienced symptoms related to the digestive system.[18]

The current study revealed that about half of patients, regardless of the type of hemoglobinopathy, were admitted to the hospital and required admission to the intensive or respiratory care units. This finding is consistent with a study conducted by Mucalo *et al*., which also reported a comparable hospitalization rates among patients with SCD and COVID-19 infection.[19] Martin *et al*. in the USA reported a hospitalization rate of 47% with no mortality was observed among studied patients and they attributed the absence of mortality to the lower end-organ damage probably due to the use of disease-modifying agents.[20]

RT-PCR testing is the preferred diagnostic method for COVID-19 infection in both the general population and the current study sample. This is likely due to its higher sensitivity and specificity in detecting COVID-19 infections, which are estimated to be around 70% and 95%, respectively. In addition, RT-PCR is a noninvasive method that spares patients from the potentially harmful effects of radiation, making it a safer and more accessible diagnostic tool.[21,22]

Lee *et al*. have reported that 40% of patients with SCD had a low lymphocyte count, while only 7% of thalassemia patients had the same condition,[4] which is in agreement with the results of this study where a significantly lower lymphocyte count was found in individuals with SCD compared to those with thalassemia. The lower lymphocyte count associated with higher D-dimer and LDH may indicate bone marrow suppression driven by the inflammatory process that is seen during in COVID-19 cases and also in SCD during VOC episodes.[23] Lee *et al*. also noted a higher frequency of raised CRP and D-dimer levels in SCD patients compared to those with thalassemia.[4] In the present study, a significant increase in CRP and D-dimer levels was found among individuals with SCD. Both COVID-19 and SCD are thrombogenic conditions and can lead to multi-systemic inflammation. Thus, the elevation of these parameters is higher when the two diseases exist.[4,24]

Thalassemia patients may experience both intravascular and extravascular hemolysis. As a result, health-care providers should carefully monitor the blood counts of thalassemia patients with COVID-19 and be alert to the potential for worsened hemolytic anemia in the context of an acute viral infection.[25]

Another finding of the current study is the significantly higher TSB levels reported among patients with thalassemia compared to SCD patients reflecting more liver involvement. However, studies specifically comparing the effects of COVID-19 on bilirubin levels in thalassemic patients versus SCD patients are currently limited.

As patients with hemoglobinopathies suffer many comorbidities, there is a concern that these patients may be more vulnerable to COVID-19 infection and experience a more severe course of illness. It is important for clinicians to be aware about the presentation of COVID-19 in these patients and the potential risk factors that may contribute to adverse outcomes.

ACS, one of the severe complications of SCD, was an independent predictor of severe COVID-19 infection in this study. The association between ACS and severe COVID-19 infection was also reported in other studies. Cai *et al*. suggested that patients with SCD who had a prior ACS were more likely to experience severe COVID-19 infection.[26] While Elia *et al*. in Brazil[27] found that SCD pediatric patients with COVID-19 may be at a higher risk of experiencing painful VOC and ACS with a worse course. The symptoms of COVID-19, such as fever, desaturation, and dyspnea can be similar to those of ACS, this overlap in symptoms could affect medical decisions. In addition, since the presentation of COVID-19 pneumonia and ACS in SCD patients may have similar radiological features such as consolidation, ground-glass opacity, and atelectasis, it can be challenging to differentiate between the two conditions.[4]

Nearly one-fifth of hospitalized patients experienced severe disease. This rate was slightly lower than that reported by Preston *et al*. in the USA, where about one-third of admitted patients had severe disease, most of whom had an underlying medical condition.[28] On

the other hand, a study by Woodruff *et al*. concluded that some blood disorders, including SCD, were not associated with an increased risk of severe COVID-19.[29]

The present study found that patients with severe COVID-19 infection had a significantly lower Hb level. This observation is consistent with the findings of a study by Cai *et al*., among SCD patients.[26]

Previous studies found that in the general population COVID-19 patients with severe symptoms generally have lower lymphocyte counts and higher leukocyte counts; in addition, lymphopenia has been identified as a prognostic indicator in COVID-19 patients. Moreover, the WBC count at admission has been found to be significantly correlated with mortality in patients with COVID-19.[30-32] In the current study, similar associations were seen in relation to COVID-19 severity among hemoglobinopathies patients.

No association was found between serum ferritin level and COVID-19 severity. According to a systematic review conducted by Lee *et al*., the serum ferritin level at admission for COVID-19 infection did not serve as a predictor for ICU admission or mortality – as an indirect measure of the severity – in patients with SCD.[33]

Other acute-phase reactants, including ESR, CRP, LDH, and D-dimer, were significantly higher in more severe disease. Ji *et al*., in their meta-analysis found that, in the general population, elevated levels of inflammatory markers, including WBC, CRP, LDH, and ESR, have been linked to the severity of COVID-19.[34] He *et al*. have reported that D-dimer is a predictive factor for COVID-19 in the general population, with a higher likelihood of elevated D-dimer levels in severely and critically ill patients compared to milder cases.[35] Moreover, higher levels of LDH and D-dimer were found in patients who died pediatric and adult patients with SCD.[36]

Furthermore, Karimi *et al*. in Iran observed that the frequency of elevated CRP levels was higher in the severe/critical and moderate COVID-19 thalassemia patients with compared to the asymptomatic or mild groups.[37]

Hepatic involvement in COVID-19 may correlate with overall disease severity, especially among those with preexisting liver disease, which can be partially explained by the fact that ACE2, which is present in liver cells, makes them susceptible to COVID-19 infection, potentially explaining the hepatocellular damage observed in COVID-19 patients.[38]

Regression analysis demonstrated that TSB serves as a predictor of severe COVID-19 infection among hemoglobinopathies patients. A pooled analysis by Paliogiannis and Zinellu has demonstrated that patients with severe COVID-19 in the general population exhibit a significant rise in their total bilirubin levels.[39] While, Cosgun, reported that TSB levels may be an independent predictor of worse outcomes in patients with COVID-19 and could serve as an early marker for myocarditis.[40] Other possible risk factors such as age, gender, clinical, and laboratory variables were not found to be associated with COVID-19 severity.

This study has many limitations including the relatively small number of patients especially thalassemia patients and also the number of patients with severe COVID-19 disease.

Conclusion

From this study, it can be concluded that the clinical course is of hemoglobinopathy patients with COVID-19 infection is similar to that in the general population of the same age groups and no death was reported among studied patients. Therefore, it is recommended that clinicians treating patients with SCD need to be aware of COVID-19 infection when diagnosing ACS in such patients. Furthermore, studies including larger number of thalassemia patients and detailed treatment practice used for hemoglobinopathy patients are needed.

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Conflicts of interest

There are no conflicts of interest.

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