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COVID-19 infection and beta thalassemia; a single center experience in Iran

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Abstract

Introduction: COVID-19 infection is a contagious acute respiratory syndrome, leading to a high mortality rate; it is also a systemic disease, and all people are at risk of being infected, including hemoglobinopathies patients. Thalassemia is one of the most prevalent hemoglobinopathies while Beta-thalassemia patients, are at risk for the deadly effects of the coronavirus.
Objectives: This study examines the prevalence, severity, and mortality rate of COVID-19 infection in thalassemia patients of the southwest of Iran.
Patients and Methods: In this descriptive cross-sectional study, from March 2019 to September 2020, 1000 beta-thalassemia patients, referred to Shahid Baqaei 2 hospital, Ahvaz, Iran, were screened for COVID-19.
Results: Findings showwd 80% of thalassemia patients were women. Fever, body aches, weakness, and dizziness were the main symptoms of patients.
Conclusion: This result suggests that hemoglobinopathies may affect infections and mortality from COVID-19 infection. However, our findings do not support a direct association between hemoglobin disease and COVID-19, and further research is needed to confirm this, but this might state the hemoglobin's role in the pathophysiology of COVID-19 infection.

Introduction

Around a month after the first diagnosis of severe acute respiratory syndrome-related coronavirus (SARS-CoV-2), on January 31, 2020, the World Health Organization (WHO) announced that SARS-CoV-2 is becoming a severe health threat to humans. Unfortunately, in a short time, it was turned into a deadly pandemic disease (1). The SARS-CoV-2 (COVID-19) has the positive-strand RNA, which encoded structural and non-structural proteins (ORF8, ORF7a, ORF6, ORF3a, ORF10, and orf1ab). The primary structural proteins include the envelope protein (E), spike surface glycoprotein (S), nucleocapsid phosphoprotein, and matrix protein (M) (2). The angiotensin-converting enzyme 2 (ACE2) protein is the central COVID-19 receptor in the host, binds to the spike protein (3), and identified in various human organs, including the respiratory system, thymus, bone marrow, gastrointestinal tract, liver, spleen, kidney, lymph nodes and brain (4). Therefore, it can cause infections in various systems of the human body

Key point

The result of our study showed that hemoglobinopathies might affect COVID-19 mortality.

(5). The main presentation of infection includes fatigue, dry cough, dizziness, fever above 37.3°C, sore throat, headache, myalgia, difficulty breathing or shortness of breath, hemoptysis, and gastrointestinal symptoms (6,7). Examination of biochemical parameters performed on some patients with novel coronavirus-induced pneumonia revealed an abnormal phenomenon associated with hemoglobin biochemical indexes (8). These studies have shown that COVID-19 patients' hemoglobin is declined (5, 9). As the COVID-19 virus needs many porphyrins, it is thought that some specific COVID-19 proteins (ORF8, ORF10, and ORF3a) could coordinately attack red blood cells (RBCs) and lead to its hemolysis. The heme molecule is a vital component of RBC hemoglobin, composed of porphyrin and iron. COVID-19 proteins could capture heme and dissociate the porphyrin and

release the iron ions (10). On one hand, a decrease in hemoglobin concentration in COVID-19 patients leads to decreased oxygen delivery to the tissues involved in the infection. It can lead to septic shock or multiple organ dysfunction syndromes, and on the other hand, the body has faced over-accumulating harmful iron ions that cause inflammation. Thereby, the cells producing large amounts of ferritin to bind to free iron ions and reduce damage (11, 12). People with diabetes have extreme inflammation due to excess iron, carbon dioxide, and oxygen. Patients with respiratory distress will worsen, and organs and tissues of the whole body encounter varying degrees of damage (10).

β-thalassemia is the most common monogenic recessive disease worldwide caused by decreased or complete absent synthesis of β-globin chains (responsible for hemoglobin production in the RBC) (13). Besides, the immune system of thalassemia patients is altered. It is associated with the decreased neutrophil count, changes in the number and function of natural killer cells, macrophage dysfunction and phagocytosis, and the production of interferon-gamma (IFN-γ) which can lead to hypersensitivity to infectious agents (14, 15). Followed by, some other comorbidities may make them vulnerable to the virus, including liver disease, diabetes, and severe iron overload (16). Thus, thalassemia patients are expected to be more exposed to severe symptoms of the COVID-19 (19,21). Iran is on the thalassemia world belt map with around two million β-thalassemia carriers and 25000 β thalassemia major patients. Khuzestan province is located in southwest Iran, and the frequency of β-thalassemia is too high due to the existence of different ethnicities (Arab, Bakhtiari, Qashqai, Persian, and Lor) and consanguineous marriages (17).

Objectives
This study investigates the prevalence, severity, and mortality rate of COVID-19 in thalassemia patients referred to Baqaei 2 hospital in Iran's southwest.

Patients and Methods
Study design
Baqaei 2 hospital is a referral center for patients with hemoglobin disorders in Khuzestan province. The beta-thalassemia patients referred to this center were screened for COVID-19 from March 2019 to September 2020. To this end, some leading indicators were evaluated, such as their lung CT scan, CBC, C-reactive protein (CRP); lactate dehydrogenase (LDH); creatine phosphokinase (CPK). tests, and blood oxygen levels.

Statistical analysis
Data were analyzed using SPSS software version 22. Mann-Whitney U, chi-square and Pearson's correlation tests were applied. Data were expressed as mean ± standard deviation. $P < 0.05$ was considered statistically significant.

Results
Out of 1000 β-thalassemia patients referred to Baqaei 2 hospital, 10 patients were positive for COVID-19. Eighty percent of thalassemia patients infected were women, and their age range was from 10 to 49 years. Fever, body aches, weakness, and dizziness were the main symptoms of patients, and in terms of laboratory indexes, increased WBC count and ESR and decreased platelets were observed in most patients. Fortunately, no mortality was observed among them (Table 1).

Discussion
In a similar study, Karimi et al have evaluated the COVID-19 severity among 48 β-thalassemia patients and observed that 73.9% had mild to moderate symptoms and recovered; however 26.1% of their patients died. More than 60.0% of patients had at least one comorbidity in this study. Diabetes, hypertension, pulmonary artery hypertension, and heart disease in dead patients were significantly higher. According to their reports, the prevalence of COVID-19 in thalassemia patients is 8.17 per 10 000 versus 11.01 per 10 000 in the general population (18). Some studies have focused on the hemoglobin targeting by SARS-CoV-2 and its mechanism of action. They have shown that it may attack hemoglobin, target the heme, and acquire porphyrins so it is believed that β-thalassemia might protect patients against COVID-19 (10, 19). Liu et al found that the orf1ab, ORF3a, and ORF10 viral proteins have participated in attacks to heme. Through analysis, they found that in oxidized hemoglobin, the orf1ab (His300) first attacked the alpha chain, and then the ORF3a (Gln303) and ORF10 successively attacked the beta chain, and at last IIe304 connects to the iron heme. This state leads to a decrease in hemoglobin levels and, consequently, a decrease in oxygen supply. For de-oxyhemoglobin, the possible mechanism is that orf1ab first attacks the 1-beta chain, and then ORF3a and ORF10 directly docked to the heme of the beta chain and dissociated it, therefore increasingly decreased hemoglobin that can carry carbon dioxide and blood sugar. These results show that the higher hemoglobin content could be associated with a higher risk of disease (20). In this regard, Lansiaux et al, suggested that the heterozygous ß-thalassemia patients may develop immunity to SARS-CoV-2 viral infection (using multiple linear regression analysis) (21). Another study was conducted in 17 centers in 10 countries, and the results confirmed our data (22). In this study, 9499 patients with hemoglobinopathies (β-thalassemia and sickle cell disease) were enrolled and identified only 13 patients with COVID-19 with clinical manifestations ranging from asymptomatic to severe pneumonia and respiratory failure (22). However, there is no strong clinical evidence and validated studies to support that hemoglobinopathies patients are less at risk for the relatively severe form of COVID-19, and achieving this result requires further research in this area. Therefore,

Table 1. Information of thalassemia patients with COVID-19

No.	Gender	Age	Type of disease	Sign	Lab. Index
1	F	34	Thalassemia intermediate	Weakness and lethargy	ESR↑, PLT.N, Increased blood bilirubin↑
2	F	28	Thalassemia intermediate	Cough, epigastric pain	ESR↑, PLT↑, lymph↑
3	M	10	Thalassemia major	Fever, body pains, weakness and lethargy, cough, fatigue	ESR↑, Hypoglycemia↓, PLT.N
4	M	20	Thalassemia major	Fever, abdominal pain, diarrheal,	PLT↓
5	F	28	Thalassemia major	Body pain, high fever	PLT.N, Blood in the urine lymph↓, ESR↑, FBS↑
6	F	27	Thalassemia major	Weakness and lethargy	WBC↑
7	F	39	Thalassemia major	Fever, cough	WBC↑
8	F	29	Thalassemia major	Headache, body pains, nausea, vomiting	Increase CRP, PLt.WBC↑
9	F	8	Thalassemia major	Fever, headache, unconsciousness	PLT↓, ESR↑
10	F	49	Thalassemia major	Fever, chills	PLT.↑, WBC↑

thalassemia patients should be taken care of with extra caution.

Conclusion

According to the results of several studies, it can be concluded that hemoglobinopathies may affect COVID-19 mortality. Of course, various studies have displayed inconsistent results, which indicates the need for further investigations in this regard. Although our finding does not prove the direct association between hemoglobin structure and COVID-19 mortality definitively, we suggest evaluation of hemoglobin's role in the pathophysiology of COVID-19.

Authors' contribution

AA, RSK and BKD were the principal investigators of the study. AK and MAN were included in preparing the concept and design. AA and RSK revised the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The Ethics Committee of Ahvaz Jundishapur University of Medical Sciences approved this study. The institutional ethical committee at Ahvaz Jundishapur University of Medical Sciences approved all study protocols (IR.AJUMS.REC.1399.723). Accordingly, written informed consent was taken from all participants before any intervention. This study was extracted from M.D., thesis of (Grant # Th-9913 (at this university. Moreover, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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