result in worsening of anemia. On the other hand, it led to both improvement of anemia as well as fairly rapid decrease in marrow fibrosis thereby demonstrating its potential effectiveness as a therapy for AIMF.

In summary, P-AIMF is a very rare disease which needs to be distinguished from the PMF. Although response rate to steroids is high, ruxolitinib should be considered in steroid refractory cases.

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CONFLICT OF INTEREST

H.A.: speakers bureau and advisory board for Incyte. G.M.: speakers' bureau for AbbVie and Novartis, advisory board with Janssen. V.P.: speakers Bureau for Jazz, Amgen, Novartis, AbbVie, advisory board for AbbVie and Jazz Pharmaceuticals. The rest of the authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the finding of this letter are available from the corresponding author upon reasonable request.

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SARS-CoV-2 infection in patients with β-thalassemia: Experience from Lebanon

To the Editor:

The outbreak of coronavirus disease 2019 (Covid-19) caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to a global health pandemic. Up until April 19, 2021 the World Health Organization reported around 141 057 106 cases and 3 015 043 deaths worldwide.[1]

The thalassemias constitute one of the most common monogenic diseases worldwide, characterized by inherited defects in the production of hemoglobin. Transfusion requirement is used to distinguish different phenotypes of thalassemia, with patients commonly classified as having transfusion-dependent thalassemia (TDT) or non-transfusion dependent thalassemia (NTDT). Patients with β-thalassemia suffer from different underlying comorbidities, stemming from ineffective erythropoiesis, chronic hemolytic anemia, and iron overload.[2] As a result, these patients can be considered among vulnerable patient-populations to the complications of the SARS-CoV-2 infection.[3]

Current data from the literature reporting outcomes of β-thalassemia patients with SARS-CoV-2 infection are limited.[4–7] Since disease severity of Covid-19 is associated with increased mortality and morbidity, identifying risk factors for adverse outcomes remains crucial for the timely management of patients. In this report, we investigate the severity of Covid-19 among β-thalassemia patients who are regularly followed up at the Chronic Care Center (CCC), a tertiary care thalassemia center in Lebanon.

Throughtout the Covid-19 pandemic which began in Lebanon in February, 2020 and up until April, 2021, 40 cases of β-thalassemia and Covid-19 were reported by CCC, and after patients informed the center of a confirmed diagnosis by real time-polymerase chain reaction (RT-PCR). Patients' clinical characteristics, Covid-19 signs and symptoms, treatment, disease course and outcomes were collected by analyzing patients' medical records and by directly calling the patients and checking on their well-being (Table S1). The mean age of patients was 30.7 years (range 9–61 years), including 21 (52.5%) males and 19 (47.5%) females. Twenty seven patients (67.5%) had TDT, and 13 patients (32.5%) had NTDT (Table 1). Covid-19 disease severity was classified according to the guidance issued by the National Health Commission of China.[8] Mild cases usually present with mild symptoms without radiographic features; while patients with a moderate disease present with fever, respiratory symptoms, and radiographic features. Patients with severe disease should meet one of three criteria: (a) dyspnea (≥30 breaths/min), (b) oxygen saturation ≤93% at rest, and (c) PaO_2/FiO_2 ≤300 mmHg. Critical patients show one of the following criteria: (a) respiratory failure, (b) septic shock, and (c) multiple organ failure and requring intensive care unit care. Based on this classification, disease severity in our sample was as follows: asymptomatic or mild ($n = 32$, 80%), moderate ($n = 4$, 10%), and severe or critical ($n = 4$, 10%).

TABLE 1 Demographic data and clinical characteristics of our cohort of β-thalassemias patients infected with SARS-CoV-2

Demographic data and clinical parameters	Thalassemia patients infected with SARS-CoV-2 ($N = 40$)
Disease type (TDT/NTDT)	27/13
Age (year)[a]	30.7 ± 10.7
Gender (M/F)	21/19
BMI (kg/m^2)[a]	22.7 ± 2.9
Splenectomy, *N* (%)	26 (65.0)
Presence of ≥1 comorbidity, *N* (%)	37 (92.5)
Hemoglobin (g/dl)[a]	8.6 ± 1.2
Serum Ferritin (μg/l)[b]	1041 (359–6000)
LIC ≥3 (mg/g d.w), N (%)	26 (65%)
Covid-19 disease severity, *N* (%)	Asymptomatic or mild: 32 (80) Moderate: 4 (10) Severe or critical: 4 (10)
Hospital admission required, *N* (%)	4 (10)
Covid-19 clinical course (days)[a]	14.5 ± 3.8
O2/CPAP required, *N* (%)	4 (10)
Patients enrolled in clinical trial, *N* (%)	7 (17.5)
Dead, *N* (%)	0 (0)

Abbreviations: BMI, Body mass index; Covid-19, Coronavirus disease 2019; F, Female; LIC, Liver iron concentration; M, Male; NTDT, Non-transfusion dependent thalassemia; O2/CPAP, Oxygen/Continuous positive airway pressure; TDT, Transfusion dependent thalassemia.
[a]Values represented as mean ± SD.
[b]Values are presented as median and range.

The comorbidities present among our β-thalassemia patients are reported in the Table S1. Overall, 37 (92.5%) patients had at least one comorbidity. Most of our patients suffered from iron overload. Liver iron concentration (LIC) (mg/g) was classified as: mild (LIC 3–7 mg/g), moderate (LIC >7–14 mg/g), and severe overload (LIC >15 mg/g). In our patient cohort 13 (32.5%) patients had mild iron overload, seven (20.6%) patients had moderate iron overload, and six (17.6%) patients had severe iron overload. Eight patients never had their LIC determined. Twenty six patients (65%) were splenectomized. Of the 26 splenectomized patients, 19/26 (73.1%) were on aspirin, 1/26 (3.8%) was on warfarin for his co-existing atrial fibrillation, and 3/26 (11.5%) were switched to low molecular weight heparin (enoxaparin) in the hospital setting. Among our cohort of 40 patients, 35 (87.5%) were on iron chelation therapy. According to a set of recommendations by the American Society of Hematology, if a thalassemia patient is exposed to SARS-CoV-2 but is asymptomatic there is no reason to interrupt iron chelation. If a patient becomes symptomatic, especially in the case of moderate and severe disease, then interruption of iron chelation is advisable.[9] In our group of patients, mild to moderate disease was treated similar to asymptomatic, thus patients continued iron chelation therapy. However, iron chelation therapy was interrupted in all patients with severe disease and who were admitted to the hospital until resolution of symptoms or until a confirmatory negative PCR.

In terms of signs and symptoms, four patients (10%) were asymptomatic. The remaining 36 (90.0%) patients had signs and symptoms, most notably in the form of fatigue, fever, ageusia, and anosmia (Table S1). Four (10%) patients were hospitalized, but none required intubation or mechanical ventilation. Among the four hospitalized patients, only one splenectomized TDT patient received antiviral treatment with remdesivir and favipiravir without hydroxychloroquine in addition to azithromycin and levofloxacin for concurrent pneumonia and enoxaparin after a drop in her oxygen saturation. The other three hospitalized patients received symptomatic treatment and specific therapy for their coexisting comorbidities. None of the hospitalized patients required invasive respiratory support. The disease clinical course across all 40 patients ranged from 10 to 28 days. All 40 (100%) patients have clinically recovered, and no deaths were reported.

Of the 40 infected patients, seven (17.5%) were part of ongoing clinical trials. Of these seven patients, three (42.8%) (two TDT and one NTDT) were on luspatercept therapy at a dose of 1.25 mg/kg. Luspatercept treatment was halted for these patients until resolution of their symptoms and until a documented negative PCR test. Luspatercept dose interruption ranged from 16 to 20 days in the two TDT patients and was 30 days in the NTDT patient. A drop of 1.9 g/dl in Hb level was evident in the NTDT patient, and the patient eventually required blood transfusion. Two (28.6%) TDT patients were receiving IMR-687, a phosphodiesterase 9 inhibitor that increases intracellular cyclic guanosine monophosphate levels and stimulates the production of HbF. Treatment with IMR-687 was stopped until a confirmatory negative PCR test was obtained. The remaining two (28.6%) patients were on the improved deferasirox formulation (granules) which was also withheld during their Covid-19 disease course.

The potential role of blood type in predicting risk and complications of Covid-19 infection has emerged as an important scientific question.[10] According to a recent retrospective study, blood type O may offer some protection against Covid-19 infection. The study suggested that people with blood types A, B, or AB may be more likely to be infected with Covid-19 than people with type O.[11] Another retrospective study showed that people with blood groups A or AB appear to exhibit greater Covid-19 disease severity than people with blood groups O or B.[12] In our cohort of thalassemia patients, blood groups were as follows: 19 (47.5%) patients were O^+, 10 (25.0%) patients were A^+, six (15.0%) patients were B^+, three (7.5%) patients were A^-, and two (5.0%) patients were O^-. A chi-square test showed no statistical significance when comparing blood group to the clinical course of the disease (p value = 0.631). Obesity (BMI >30 kg/m^2) has also been shown to significantly increase the chances of severe outcomes for patients with Covid-19. The latest scientific evidence shows that Covid-19 patients with obesity, especially those hospitalized experienced substantially higher rates of severe outcomes, such as requiring intensive care treatment, mechanical ventilation, and death.[13] Among our 40 confirmed Covid-19 thalassemia cases, only nine were overweight (25.0 ≤ BMI ≤ 29.9 kg/m^2) and none were obese (BMI ≥30) (Table S1).

Low levels of immune-related micronutrients have been identified in β-thalassemia patients, reducing the body's ability to eliminate SARS-CoV-2 and leading to further pathology of Covid-19.[14] One systematic review found six observational and five interventional studies supporting the importance of supplementing vitamins and minerals among β-thalassemia patients.[14] It was shown that vitamin C, vitamin E, vitamin D, zinc and selenium supplementations might bring advantages for immunity in β-thalassemia by reducing reactive oxygen species and improving proliferation, differentiation, maturation, and gene expression of innate and adaptive immune cells.[14] In our cohort of SARS-CoV-2 infected patients, 39 (97.5%) patients, 39 (97.5%) patients and 30 (75%) patients were on vitamin C, vitamin D and zinc, respectively (Table S1). Because no established guidelines are available regarding the susceptibility or the immunity of patients with β-thalassemia to SARS-CoV-2 infection, prevention is crucial. Vitamin and mineral supplementation could thus provide benefits for patients with β-thalassemia patients infected with SARS-CoV-2.

Our findings were overall similar to the preliminary data reported from the Italian experience.[5] Unlike our study, data from the Iranian group confirmed that the coexistence of underlying disorders, including obesity and cardiovascular disease (heart failure and pulmonary artery hypertension), are associated with the disease severity of thalassemic patients affected by Covid-19.[4] While no deaths were reported among our patient cohort, and the cohort of the Italian group, eight thalassemic patients with severe or critical Covid-19 died from the Iranian cohort.

Based on the current limited evidence and the lack of national registries, no definite conclusions can be made regarding the prevalence of SARS-CoV-2 infection in β-thalassemia patients compared to the general population.[15] Moreover, the clinical impact of Covid-19 in β-thalassemia patients is not yet well defined and thus all infected cases should be under careful observation with a detailed reporting of their clinical outcomes. International efforts must also be made to better understand the effects of SARS-CoV-2 infection in β-thalassemia patients and accordingly develop a set of recommendations for better monitoring and optimization treatment of future infected patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Rayan Bou-Fakhredin and Ali T. Taher designed the study; Rayan Bou-Fakhredin, Hisham Daadaa, Suzanne Koussa, Therese Abou Nasr and Peter Noun performed research; Rayan Bou-Fakhredin and Hisham Daadaa collected the data, performed the statistical analysis, analyzed and interpreted the data and wrote the manuscript. Suzanne Koussa, Therese Abou Nasr and Peter Noun analyzed and interpreted the data and edited the manuscript; Ali T. Taher critically reviewed and edited the manuscript and supervised the whole work; all authors approved the final manuscript.

DATA AVAILABILITY STATEMENT

The dataset used and analyzed during the current study are available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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Hemolytic crisis due to Covid-19 vaccination in a woman with cold agglutinin disease

To the Editor:

A 57-year-old Caucasian female was diagnosed of primary cold agglutinin disease (CAD) in 2016. At that time, she presented with weakness, fatigue, jaundice and distal acrocyanosis when exposed to cold temperatures. Laboratory findings showed a regenerative anemia (hemoglobin of 9.0 g/dl, reticulocyte count of 175 000/μl), red blood cell agglutination on peripheral blood smear, undetectable haptoglobin and elevated bilirubin and lactate dehydrogenase (1.73 mg/dl and 427 U/L respectively). The direct antiglobulin test (DAT) was strongly positive for complement protein C3D and negative for IgG. A cold agglutinin with anti-I specificity was identified, with a titer of 128 and a high thermal amplitude. There was evidence of a serum monoclonal protein IgM lambda (352 mg/dl), a clonal lymphocyte population (0.4% of total leukocytes) and low titer antinuclear antibodies (1:80) at diagnosis. A recent history of infection was excluded. A complete body computed tomography scan ruled out an underlying malignancy.

Her symptoms improved with a short course of corticosteroids and she did not require any other pharmacological therapy or blood transfusion. For the past 5 years, she has presented compensated hemolysis with intermittent mild anemia that occasionally required 5–10 mg of prednisone to control flare-ups. Haptoglobin levels consistently remained undetectable. Although corticosteroid therapy is not an adequate long-term treatment for CAD, rituximab plus/minus bendamustine was not required due to the good response to low dose short-course intermittent prednisone.

During this last pandemic year, she received follow-up every 3 months, and her blood work showed very mild compensated hemolysis, with a hemoglobin greater than 11 g/dl. She did not refer fever or SARS-CoV-2-like symptoms at any time.

As she worked in a nursing home, in January, 2021 she was scheduled to receive a mRNA Covid-19 vaccination. Two days after the inoculation of the first dose, she began with chills, weakness, shortness of breath upon exertion, lumbar pain, jaundice and mild hemoglobinuria. Physical examination showed paleness and mucous jaundice. Laboratory findings revealed a hemoglobin of 8.6 g/dl, increased reticulocyte count, bilirubin (2.9 mg/dl), LDH (462 U/L), and spherocytes on the peripheral blood smear. Inflammation parameters such as ferritin or D-dimer were elevated at 426 and 726 ng/ml respectively. Serologic testing for known viruses and bacteria were negative. Autoimmunity screen was only positive for antinuclear antibodies, as previously detected. Real time PCR detection for SARS-CoV2 was also negative. The patient was treated with prednisone 20 mg daily with improvement of the hemolytic parameters and hemoglobin level to baseline values. Seven days before the second dose of the vaccine, prednisone was reduced to 10 mg daily to avoid dampening of the immune response. Two days after the second inoculation, again, she presented the same signs, symptoms and laboratory findings observed after the first dose, which were consistent with an exacerbation of autoimmune hemolytic anemia (Figure 1).

Five days after receiving the second dose, a serological study was performed, demonstrating the production of >40 000 AU/ml of SARS-CoV-2 IgG by the chemiluminescence immunoassay (CLIA). Prednisone was then increased to 20 mg per day with a subsequent improvement of all clinical and laboratory parameters, which allowed gradual tapering of steroids until discontinuation.

The cryoagglutinin titer increased after the first dose of the vaccine from 256 (4°C), to 512 with a wide range thermal amplitude. The DAT remained positive for CD3. Flow cytometric detection of