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The effect of COVID-19 on hematological disease diagnosis, management and outcomes

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The effect of COVID-19 on hematological disease diagnosis, management and outcomes

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Editorial: The effect of COVID-19 on hematological disease diagnosis, management and outcomes

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Editorial on the Research Topic
The effect of COVID-19 on hematological disease diagnosis, management and outcomes

Lee, Chieng, Lau et al. studied the effects of coronavirus disease-2019 (COVID-19) on the clinical presentation, radiological findings, and outcomes of the infection in patients with hemoglobinopathies. They found that the possibility of severe COVID-19 infection in patients with hemoglobinopathies was higher than in the general population, with a percentage of 35.8% with severe infection compared to (11.1–19.1%) in the general population. The mortality rate was also higher than in the general public, with 6.9% mortality in patients with hemoglobinopathies compared to (2.2–5%) in the population. They also reported that hemoglobinopathy patients had higher mortality rates than patients with comorbid conditions such as chronic kidney diseases, but lower mortality rates than patients with HIV and malignancies. However, it was found that other comorbid conditions such as respiratory and cardiovascular diseases within these patients significantly increased mortality. It has been previously shown in several studies that comorbidities like hypertension could lead to a more aggressive course of COVID-19 infection and possible ICU admission (1). In addition, healthcare disparity and socioeconomic status in patients may have also led to worsened outcomes. Nevertheless, the review showed that patients with hemoglobinopathies suffer the same common COVID-19 symptoms occurring in the population. In addition, patients with hemoglobinopathies suffered from increased rates of vaso-occlusive crises secondary to hypoxia. This review and its reported numbers, however, included studies published during the earlier phases of the COVID-19 pandemic that included small sample sizes. Long-term effects were also not recorded. Finally, the radiological findings were descriptive and did not include definitive diagnoses and causes of these findings, which could be a limitation to this study as some radiological features can be found in both COVID-19 and some hemoglobinopathies like sickle cell disease (SCD). The review provides valuable insights into the management of COVID-19 in patients with hemoglobinopathies and underscores the need for further research in this (Lee, Chieng, Lau et al.).

Similarly, Martin et al. reviewed the clinical outcomes of children and adolescents with SCD who were infected with COVID-19. The study was conducted in a metropolitan tertiary pediatric hospital. The study concluded that these patients had a higher risk of conducting severe disease and more complications when compared to the general pediatric population. Nearly half (47%) of the patients with SCD and COVID-19 required hospitalization, and 5% were admitted to the ICU. Two out of the three patients admitted to the ICU were not on hydroxyurea. Vaso-occlusive crises, fever, and acute chest syndrome were the most common symptoms in hospitalized patients. No mortality was reported in the study. Compared to adults, pediatric patients with SCD may have had lower mortality due to lower incidences of end-organ damage and most patients were on disease-modifying therapy. It was shown that hydroxyurea treatment had a protective effect. It was suggested that pediatric patients with SCD should perhaps be prioritized in taking the COVID-19 vaccine as it may contribute to reducing the rate of complications and hospitalizations that these groups of patients are more prone to experience. The limitation of this study is that it is a retrospective analysis from a single hospital with a small sample size, so further data may be necessary to confirm their findings (Martin et al.).

Both Lee, Chieng, Abdul Jalal et al. and Marhaeni et al. studied the association between COVID-19 infection and ferritin levels. Lee, Chieng, Abdul Jalal et al. conducted a meta-analysis to study the relationship between serum ferritin levels and COVID-19 outcomes in patients with SCD. They found that even though elevated serum ferritin levels were commonly observed in sickle cell disease patients with COVID-19, they could not be used as a reliable predictor of severe disease or poor outcomes. Nevertheless, they found that ferritin levels cannot be used reliably to predict severity, ICU admission, or mortality in SCD patients. The limitations of the review include having a small number of eligible studies and limiting the generalizability of data. The authors suggest the need for further analysis and studies with larger sample sizes and better designs to confirm their findings (Lee, Chieng, Abdul Jalal et al.). Marhaeni et al., on the other hand, studied the levels of ferritin in COVID-19 infections in transfusion-dependent thalassemia (TDT) patients. However, a limitation to any study involving this population is that high ferritin levels cannot be certainly considered a result of COVID-19 infection as TDT patients normally present with elevated ferritin levels. This study included fourteen pediatric patients. They found that ferritin levels increased significantly in the infection period and decreased during the recovery period compared to baseline ferritin levels. It showed that even though serum ferritin levels were markedly and significantly increased in TDT patients after getting a COVID-19 infection, this rise in ferritin did not reflect the severity of the disease or symptoms. This is further proof that ferritin levels may not be reliable to use as a prognostic value in patients with hemoglobinopathies (Marhaeni et al.).

Sekizawa et al. published a case report about an 80-year-old Japanese woman who experienced a malignant marginal zone B-cell lymphoma after receiving the BNT162b2 mRNA COVID-19 vaccine. The characteristics upon the initial visit, which was 1 day after vaccine administration, showed signs of vaccine-related cervical lymphadenopathy, increasing the suspicion of malignancy. The radiological findings showed that the mRNA COVID-19 vaccine-related lymphadenopathy can be indistinguishable from neoplastic lymphadenopathies except for the absence of irregular margins. The study suggests that even though lymphadenopathy was common after mRNA vaccine administration, patients with COVID-19 vaccine-related lymphadenopathy should be regularly followed up and get comprehensive care. They also suggest close observation of lymph node enlargement which might occur later (up to 4–6 weeks) after vaccination and to avoid overlooking slowly progressing lymphadenopathies. Further studies are also necessary to test the causal relationship between COVID-19 vaccination and lymphoma progression (Sekizawa et al.).

Another case report published by Gogia et al. describes a case of Rosai-Dorfman-Destombes disease (RDD) that occurred in a 55-year-old woman following COVID-19 infection. This describes a case in which COVID-19 may have caused a histiocytic disease which could be due to immune dysregulation. However, further research is needed to confirm this hypothesis. Interestingly, this case also had the mRNA vaccination months before being infected and contracting the histiocytic infection. The patient was treated with corticosteroids and showed significant improvement in his symptoms (Gogia et al.).

Abuawwad et al. reviewed the existing literature on the association between ABO blood groups, Rh-factor, and COVID-19. The review concluded that individuals with blood group O had a lower chance of being infected with COVID-19 in addition to less chance of worsening. Individuals with blood group A on the other hand were found to be more prone to complications and getting infected. This, however, was not consistent across all studies. Some of the studies also suggested that individuals with Rh-positive blood may be at higher risk for severe COVID-19 disease, although evidence is conflicting. The authors suggest that these associations may be related to the interaction between the virus and the ABO antigens on red blood cells, although the underlying mechanisms are not yet clear. The article also notes that while the association between ABO blood groups, Rh-factor, and COVID-19 is of scientific interest, it should not be used as a basis for discrimination or stigmatization of individuals based on their blood type or Rh-factor status (Abuawwad et al.).

Some studies also investigated the hematological manifestations of COVID-19. This could be an important aspect to understand disease processes in COVID-19 infections. Some studies have previously shown, for instance, a protective effect of eosinophilia in patients with COVID-19 (2). Elemam et al. studied the morphologic and quantitative abnormalities in the peripheral blood counts of patients with (COVID-19) infections in the United Arab Emirates (UAE). The most common feature they found was the presence of atypical lymphocytes. Other commonly seen features were monocytes with cytoplasmic vacuoles and neutrophilic changes. They did not find significant changes in platelet counts. RBC changes like anisocytosis and hyperchromicity were found in about 50% of patients. Morphological changes in RBCs were also seen in many samples. They also tested the significance of the association between these changes and disease severity. However, significant differences were only seen with thrombocytosis and microcytic RBCs being significantly more common in stable patients compared to critical patients. They

also showed that gender was associated with some specific abnormalities such as normochromic RBCs being associated with the male gender and a collateral decrease in hypochromic RBCs in males. The study had several limitations including the absence of any information regarding patient mortality as well as the absence of any healthy controls. Hence, further studies are needed to confirm these findings and to investigate the underlying mechanisms responsible for these hematological abnormalities in COVID-19 patients (Elemam et al.).

Aydemir and Ulusu performed a review of the available literature on the occurrence of thrombotic events after COVID-19 vaccination in patients with hematological disorders and hypercoagulable states. They found that these patients may be at increased risk of hypercoagulability after COVID-19 vaccination compared to the general healthy population. Thrombosis, portal vein thrombosis (PVT), immune thrombotic thrombocytopenia (ITT), deep vein thrombosis (DVT), vaccine-induced immune thrombocytopenia (VITT), and heparin-induced thrombocytopenia (HIT) are reported as vaccine-induced adverse effects in people with blood disorders. This led to the recommendation of administering anticoagulants following vaccination by the Expert Hematology Panel in March 2021. These findings were also supported by other studies that showed an increase in VTE prevalence in severe cases of COVID-19 infection (3). In conclusion, the study suggested closer monitoring during infection and after the administration of vaccines (Aydemir and Ulusu).

An article by Zomerdijk et al. investigates the factors associated with changes in healthy lifestyle behaviors among hematological cancer patients during the COVID-19 pandemic. The authors found that a considerable proportion of patients reported a decrease in physical activity and a decrease in the adoption of a healthy diet. The study highlights the importance of supporting healthy lifestyle behaviors among hematological cancer patients, particularly during the pandemic, to improve their overall health and wellbeing (Zomerdijk et al.).

An article by Böning et al. provides an update on the oxygen-carrying capacity and affinity in patients with COVID-19. The article discusses how COVID-19 affects the oxygen dissociation curve and can lead to hypoxemia, or low blood oxygen levels, which can contribute to respiratory failure and other complications. The authors also discuss potential treatment strategies to address hypoxemia in COVID-19 patients, including high-flow nasal cannula therapy and non-invasive positive pressure ventilation. They also note the importance of considering individual patient factors such as comorbidities and disease severity when choosing treatment strategies. A possible association was found between severity and the oxygen dissociation curve. To elaborate, they found that critical patients usually demonstrate a left shift of the curve which shows increased affinity. However, this feature was also associated with a good prognosis (Böning et al.).

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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SYSTEMATIC REVIEW
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COVID-19 and Hemoglobinopathies: A Systematic Review of Clinical Presentations, Investigations, and Outcomes

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This systematic review aimed to provide an overview of the clinical profile and outcome of COVID-19 infection in patients with hemoglobinopathy. The rate of COVID-19 mortality and its predictors were also identified. A systematic search was conducted in accordance with PRISMA guidelines in five electronic databases (PubMed, Scopus, Web of Science, Embase, WHO COVID-19 database) for articles published between 1st December 2019 to 31st October 2020. All articles with laboratory-confirmed COVID-19 cases with underlying hemoglobinopathy were included. Methodological quality was assessed using the Joanna Briggs Institute (JBI) critical appraisal checklists. Thirty-one articles with data on 246 patients with hemoglobinopathy were included in this review. In general, clinical manifestations of COVID-19 infection among patients with hemoglobinopathy were similar to the general population. Vaso-occlusive crisis occurred in 55.6% of sickle cell disease patients with COVID-19 infection. Mortality from COVID-19 infection among patients with hemoglobinopathy was 6.9%. After adjusting for age, gender, types of hemoglobinopathy and oxygen supplementation, respiratory (adj OR = 89.63, 95% CI 2.514–3195.537, $p = 0.014$) and cardiovascular (adj OR = 35.20, 95% CI 1.291–959.526, $p = 0.035$) comorbidities were significant predictors of mortality. Patients with hemoglobinopathy had a higher mortality rate from COVID-19 infection compared to the general population. Those with coexisting cardiovascular or respiratory comorbidities require closer monitoring during the course of illness. More data are needed to allow a better understanding on the clinical impact of COVID-19 infections among patients with hemoglobinopathy.

Clinical Trial Registration: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020218200.

Keywords: COVID-19, hemoglobinopathies, sickle cell disease, thalassemia, severe acute respiratory syndrome coronavirus 2, systematic review

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INTRODUCTION

The unprecedented coronavirus disease-2019 (COVID-19) pandemic has not abated since the first-ever reported case in Wuhan, China. The World Health Organization (WHO) declared the outbreak of Public Health Emergency of International Concern on 30th January 2020, and subsequent pandemic on 11th March 2020. According to WHO COVID Dashboard, as of 9th

August 2021, COVID-19 has impacted more than 200 million patients globally, with incidence and mortality rates of 2.58 and 2.12%, respectively. The emergence of new variants that are associated with higher severity and mortality has added more burden to the already exhausted health care system.

COVID-19 is known to spread through respiratory droplets, with recent evidence of airborne transmission. Published studies suggested 17.9–30.8% of infected patients may be asymptomatic (1, 2). Symptoms of COVID-19 infection vary from the common presentation of fever, cough, and shortness of breath, to the less common ones such as anosmia, ageusia, and diarrhea (3, 4). Several risk factors were identified to be associated with higher mortality including age more than 65 years old and the presence of chronic diseases such as diabetes mellitus and cardiovascular disease.

Haemoglobinopathy itself is a chronic disease. Patients with hemoglobinopathy are a specific population with special health needs. Cardiopulmonary comorbidities that arise as complications of the disease are one of the main causes of mortality and morbidity in this population (5). Concerns arise whether this group of patients is more susceptible to COVID-19 infection with a more severe course of illness given their immunocompromised state and its many comorbidities. Clinicians need to be aware of the potential differences in how COVID-19 infection manifests in patients with hemoglobinopathies, along with the possible risk factors associated with poorer outcomes. As most evidence is being published as case series or case reports, there is a need to synthesize these findings to guide clinicians in managing COVID-19 infection in patients with hemoglobinopathy.

Hence, this systematic review aims to provide an overview of the clinical profile, including the clinical presentations, laboratory, and radiological findings, as well as the outcome of COVID-19 infection among patients with hemoglobinopathy.

MATERIALS AND METHODS

Search Strategy and Selection Criteria

The study methods were in adherence to the guidelines established by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (Protocol number #CRD42020218200).

A systematic search was conducted in the following databases: PubMed, Scopus, Web of Science, Embase, and WHO COVID-19 database. The search terms included were "COVID-19" OR "severe acute respiratory syndrome coronavirus 2" OR "ncov" OR "2019-nCoV" OR "COVID-19" OR "SARS-CoV-2" AND "Hemoglobinopathies" OR "Thalassemia" OR "Anemia, Sickle Cell" OR Hemoglobin C Disease. The last search was performed on 30th October 2020.

Articles that were eligible for review included the following study designs: systematic review, cohort, case-control, cross-sectional, case report, and case series. Only articles published from 1st December 2019 to 31st October 2020, in English which reported laboratory-confirmed COVID-19 cases with underlying hemoglobinopathy were included in this review. In this review, hemoglobinopathies were defined as a heterogeneous group of inherited disorders characterized by structural alterations within the hemoglobin molecule, specifically sickle cell disease and thalassemia. This review included both the adult and pediatric populations. Articles that reported suspected COVID-19 cases without laboratory evidence, *in vitro* studies, animal experiments, or patients without hemoglobinopathy were excluded from this review. Papers that consisted of only an abstract were also excluded.

Outcomes of interest for this study were clinical presentation, laboratory, and radiological findings, and outcomes of COVID-19 infection among patients with hemoglobinopathies.

Data Collection and Risk of Bias Assessment

The studies extracted from the searches were identified by two independent reviewers. Citation records were managed with EndNote(R). Duplicate citations were deleted and the records were exported to an Excel sheet. Each citation was screened based on titles, abstracts, and keywords. Reasons for excluding citations were recorded. The full articles fulfilling the inclusion criteria were retrieved for review. A third investigator was consulted to resolve differences of opinion at any phase. Data retrieved from each article was cross-checked by at least two independent investigators.

The Excel data extraction form recorded the following information: author/s, study title, study design, country of study, year of publication, digital object identifier (DOI), sample size, comorbidities, clinical signs and symptoms, laboratory findings, imaging findings, outcomes.

The quality of studies included was appraised using the Joanna Briggs Institute (JBI) critical appraisal tools for the respective study designs (6). The studies were further classified into poor, moderate, or high quality based on selected criteria that would provide sufficient information for the purpose of this study (**Supplementary Material**). The risk of bias was assessed independently by two investigators and any discrepancies in opinions were resolved by a third investigator.

Operational Definitions

Symptoms were considered present if they occurred at any time from presentation to discharge. Duration of symptoms was presented in days.

All laboratory data results were categorized into high, normal, or low, according to the local laboratory reference values in the respective articles. This was done taking into consideration that different laboratories would have different reference ranges. For articles that reported mean values for multiple samples, the researcher attempted to email the original authors for their raw data for further analysis. In the event that raw data was not available, they were considered as missing data.

Radiological findings were categorized based on the descriptive changes reported by the authors: normal, ground glass opacity, consolidation, combined ground glass opacity/consolidation and others.

Clinical staging for COVID severity was based on the National Institute of Health guidelines category 1 for asymptomatic presentation, category 2 for mild illness (mild systemic and respiratory symptoms with no clinical evidence of lower

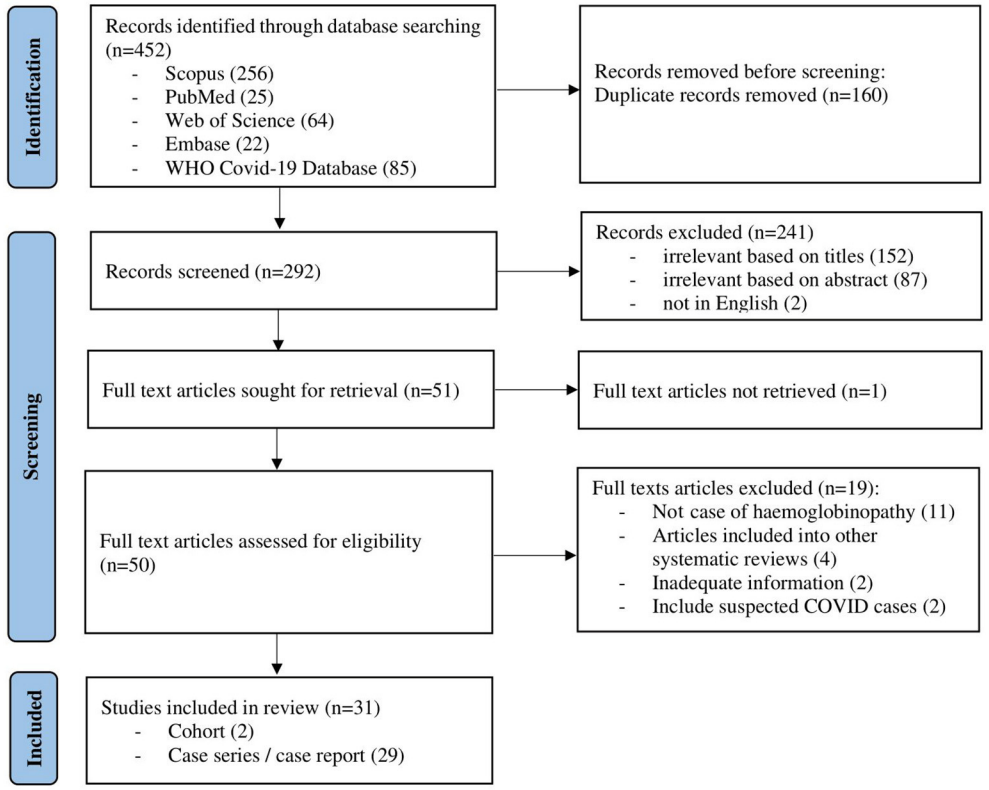

FIGURE 1 | Flow chart of study selection process (flow chart adapted from PRISMA).

respiratory involvement), category 3 for moderate illness (clinical signs and symptoms of lower respiratory involvement with oxygen saturation of or more than 95% on room air at sea level), category 4 for severe illness (lower respiratory involvement with oxygen saturation of <95% on room air at sea level) and category 5 for critical illness (presence of acute respiratory distress syndrome, septic shock or multiorgan involvement) (7).

Statistical Analysis

Descriptive statistics were reported using frequencies, percentages, and ranges. The proportion ratios and prevalence rates were also determined. Simple logistic regression was done to determine the crude odds ratio for various comorbidities and COVID-19 mortality. Comorbidities with p-value of <0.25 were included in the model for binary logistic regression. Binary logistic regression was conducted to determine the independent associations between selected predictors with COVID-19 mortality, with adjustment for age, gender, and need for oxygen supplementation. All statistical analyses were done using Statistical Package for the Social Sciences (SPSS) version 26. The α for statistical significance was set at 0.05.

RESULTS

The initial search of the electronic databases yielded 452 articles. Manual searching through the references of these articles yielded no additional eligible articles. After removing 160 duplicates, the titles and abstracts for 292 articles were screened. Following this, 50 full-text articles were retrieved with the full text of 1 article being unable to be retrieved. Finally, out of the 50 eligible full-text articles, 31 articles were included in this review (**Figure 1**). Of these, 2 were retrospective cohort studies, 13 were case series and 16 were case reports (**Table 1**). As the majority of the articles were case reports and case series, the level of evidence was low. The methodological quality for all of the studies is described in the supplementary data (**Supplementary Material**).

Overall, a total of 246 patients with hemoglobinopathies were reported to have COVID-19 infection. The patients' age ranged from 0.5 to 61 years old, with the majority (83.7%) being adults (age above 18 years old). Out of this, 140 (56.9%) had sickle cell anemia, 22 (8.9%) had sickle cell trait, 68 (27.6%) transfusion-dependent thalassemia and 16 (6.5%) non-transfusion-dependent thalassemia. Two-third (64.6%) of the patients had at least one underlying comorbidity and 22.4% had undergone splenectomy (**Table 2**). Among the sickle cell anemia patients, 42.6% had a history of vaso-occlusive crisis.

Table 3 summarized the reported clinical symptoms, laboratory markers, and radiological findings for COVID-19 infection in these patients. Twenty-nine (35.8%) patients had severe COVID-19 (Stage 4 or 5). The three most common presenting symptoms were fever (69.2%), vaso-occlusive crises (55.6%), and cough (54.2%). A small number of patients presented with mild non-respiratory symptoms such as gastrointestinal symptoms, conjunctivitis, and anorexia. Eight

TABLE 1 | Characteristics of studies included.

No	First Author	Study Type	Country	N	Age (Years)	Adult, *n*	Male, *n*	Types of Hemoglobinopathy		Mortality, *n*
								SCD, n	Thal, n	
1	Albagshi M (8)	Case Series	Saudi Arabia	2	37	2	1	2	0	0
2	Al-Hebshi A (9)	Case Series	Saudi Arabia	3	42.667	1	1	3	0	0
3	Allison D (10)	Case Report	United States	1	27	1	1	1	0	0
4	Appiah-Kubi A (11)	Case Series	United States	7	14.286	2	2	7	0	0
5	Arlet JB (12)	Case Series	France	83	Adult: 33.5 (median) Child: 12.0 (median)	66	38	83	0	2
6	Balanchivadze N (13)	Case Series	United States	24	52.9	24	6	24	0	1
7	Beerkens F (14)	Case Report	United States	1	21	1	1	1	0	0
8	Dagalakis U (15)	Case Report	United States	1	0.5	0	1	1	0	0
9	De Luna G (16)	Case Report	France	1	45	1	1	1	0	0
10	De Sanctis V (17)	Case Series	Multi-nation§	13	33.7	12	4	3	10	1
11	Ershler WB (18)	Case Report	United States	1	39	1	0	1	0	0
12	Fronza M (19)	Case Report	Italy	1	44	1	0	1	0	0
13	Heilbronner (20)	Case Series	France	4	14.55	0	1	4	0	0
14	Hussain FA (21)	Case Series	United States	4	33	4	2	4	0	0
15	Jacob S (22)	Case Study	United States	1	2.75	0	1	1	0	0
16	Justino (23)	Case Study	Brazil	1	35	1	0	1	0	0
17	Karimi M (24)	Cohort	Iran	15	36	15	7	0	15	4
18	Karimi M (25)	Cohort	Iran	43	35.3	42	22	0	43	8
19	Marhaeni W (26)	Case Report	Indonesia	1	17	0	0	0	1	0
20	Marziali M (27)	Case Report	Italy	1	46	1	1	0	1	0
21	Morrone KA (28)	Case Series	United States	8	16	2	4	8	0	0
22	Motta I (29)	Case Series	Italy	11	44.27	11	5	0	11	0
23	Nur E (30)	Case Series	Netherlands	2	22	2	1	2	0	0
24	Odievre MH (31)	Case Report	Netherlands	1	16	0	0	1	0	0
25	Okar L (32)	Case Report	Qatar	1	25	1	0	0	1	0
26	Pinto VM (33)	Case Report	Italy	1	57	1	1	0	1	0
27	Sasi S (34)	Case Report	Qatar	1	26	1	1	0	1*	0
28	Sheha D (35)	Case Report	Egypt	1	22	1	0	1	0	0
29	Stochino C (36)	Case Series	Italy	1	20	1	0	1	0	0
30	Subarna C (37)	Case Series	United Kingdom	10	38.25	10	3	10	0	1
31	Verdiyeva N (38)	Case Report	Russia	1	24	1	1	1	0	0

SCD, sickle cell disease; Thal, thalassemia; N, number.

§*Turkey, Italy, Cyprus, Iran, Oman, Azerbaijan.*

**Hemoglobin D disease.*

(6.7%) adult COVID-19 patients were detected through mass screening and were asymptomatic. Half (55.8%) of the patients had normal SpO_2 during admission. Complete blood counts and C-reactive protein (CRP) were the most commonly reported laboratory results (**Table 3**). Overall, 79.5% ($n = 105$) of patients were anemic at presentation and 50.7% ($n = 34$) had leukocytosis. Radiographic findings were only reported in a small number of patients ($n = 45$) with 64.1% and 76.4% having radiological features of COVID-19 in chest x-ray and computed tomography, respectively.

Twenty-eight articles reported treatment given to the patients ($n = 93$) (**Table 4**). Antibiotics (67.3%) and hydroxychloroquine (58.2%) were the more commonly administered drugs. The majority (82.4%) of patients required hospital admission with about 29.3% of them requiring supplemental oxygen (either non-invasive or invasive), and 31.9% required blood or exchange transfusion. There were 17 (6.9%) deaths reported; out of those, 13 (76.5%) were thalassemia patients while the remaining were patients with SCD.

Binary logistic regression analysis was done to determine the independent association between comorbidities and mortality, adjusting for age, gender, types of hemoglobinopathy, and oxygen supplementation. The model predicted between 8.0 and 36.5% variance in the outcome and was able to correctly predict 97.3% of mortality outcomes. The presence of respiratory and cardiovascular comorbidities was independently associated with mortality in patients with underlying hemoglobinopathies who were infected with COVID-19 (**Table 5**). Respiratory

TABLE 2 | Underlying comorbidities of the study population.

Underlying Medical Conditions	Thal, *n* (%) [*N* = 84]	SCD, *n* (%) [*N* = 162]
None	23 (27.4)	64 (39.5)
Hematology		
Vaso-occlusive crisis	N/A	69 (42.6)
Splenectomy	49 (58.3)	6 (3.7)
Cardiology		
Hypertension	2 (2.4)	12 (7.4)
Pulmonary hypertension	12 (14.3)	0 (0)
Heart Failure	8 (9.5)	0 (0)
Cardiomyopathy	5 (6.0)	1 (0.6)
Arrhythmia	1 (1.2)	1 (0.6)
Not specified	1 (1.2)	0 (0)
Respiratory		
Asthma	2 (2.4)	9 (5.6)
Pulmonary embolism	0 (0)	3 (1.9)
Obstructive sleep apnea	1 (1.2)	1 (0.6)
Chronic obstructive pulmonary disease	0 (0)	1 (0.6)
Sarcoidosis	1 (1.2)	0 (0)
Concurrent pulmonary tuberculosis	0 (0)	1 (0.6)
Not specified	1 (1.2)	0 (0)
Endocrinology		
Diabetes mellitus	19 (22.6)	10 (6.2)
Hypogonadism	20 (23.8)	0 (0)
Obesity	1 (1.2)	13 (8.0)
Hypothyroidism	9 (10.7)	0 (0)
Hypoparathyroidism	6 (7.1)	0 (0)
Growth failure	3 (3.6)	0 (0)
Orthopedics		
Osteoporosis	41 (48.8)	0 (0)
Avascular necrosis	0 (0)	2 (1.2)
Hepatobiliary		
Chronic liver disease	14 (16.7)	0 (0)
Hepatitis	10 (11.9)	0 (0)
Gallstone disease	1 (1.2)	0 (0)
Nephrology		
Chronic kidney disease / end stage renal failure	8 (9.5)	2 (1.2)
Vascular		
Venous thromboembolism	0 (0)	7 (4.3)
Recurrent leg ulcer	0 (0)	2 (1.2)
Neurology		
Stroke	0 (0)	6 (3.7)
Transient ischemic attack	0 (0)	1 (0.6)
Moya Moya syndrome	0 (0)	1 (0.6)
Oncology		
Non-Hodgkin lymphoma	1 (1.2)	0 (0)
Acute lymphoid leukemia	1 (1.2)	0 (0)
Not specified	0 (0)	5 (3.1)
Ophthalmology		
Retinopathy	0 (0)	2 (1.2)
Psychiatry		
Not specified	0 (0)	1 (0.6)

SCD, sickle cell disease; Thal, thalassemia; N, number; N/A, not applicable.

TABLE 3 | Summary of clinical presentations, laboratory investigations and radiological imaging of the study population.

Parameters	Thal, *n* (%)	SCD, *n* (%)
Clinical symptoms	***n* = 41**	***n* = 79**
Asymptomatic	1 (2.4)	7 (8.9)
Systemic symptoms		
Fever	31 (75.6)	52 (65.8)
Vaso-occlusive crisis	N/A	90 (55.6)
Fatigue	16 (39.0)	2 (2.5)
Anorexia	7 (17.1)	7 (8.9)
Respiratory		
Cough	30 (73.2)	35 (44.3)
Shortness of breath	13 (31.7)	23 (29.1)
Sore throat	10 (24.4)	2 (2.5)
Nasal symptoms (rhinorrhea, sneezing, sinusitis)	6 (14.6)	3 (3.8)
Gastrointestinal		
Nausea, vomiting, diarrhea	13 (31.7)	14 (17.7)
Musculoskeletal		
Myalgia	4 (9.8)	21 (26.6)
Neurological		
Headache	11 (26.8)	9 (11.4)
Anosmia	12 (29.3)	3 (3.8)
Ageusia	7 (17.1)	2 (2.5)
Ophthalmology		
Conjunctivitis	3 (7.3)	0 (0)
SpO_2	***n* = 41**	***n* = 79**
≥95%	15 (36.6)	52 (65.8)
<95%	26 (63.4)	27 (34.2)
Laboratory investigations*		
Hemoglobin	***n* = 68**	***n* = 64**
Normal	6 (8.8)	21 (32.8)
Low	62 (91.2)	43 (67.2)
White cell count	***n* = 42**	***n* = 25**
Normal	17 (40.5)	14 (56.0)
High	23 (54.8)	11 (44.0)
Low	2 (4.8)	0 (0)
Lymphocyte count	***n* = 14**	***n* = 30**
Normal	12 (85.7)	16 (53.3)
High	1 (7.1)	2 (6.7)
Low	1 (7.1)	12 (40.0)
Neutrophil count	***n* = 4**	***n* = 1**
Normal	2 (50.0)	0 (0)
High	1 (25.0)	1 (100.0)
Low	1 (25.0)	0 (0)
Platelet	***n* = 48**	***n* = 46**
Normal	27 (55.1)	31 (67.4)
High	21 (42.9)	8 (17.4)
Low	0 (0)	7 (15.2)
C-Reactive protein	***n* = 14**	***n* = 32**
Normal	8 (57.1)	8 (25.0)
High	6 (42.9)	24 (75.0)

(Continued)

TABLE 3 | Continued

Parameters	Thal, *n* (%)	SCD, *n* (%)
D-dimer	***n* = 4**	***n* = 17**
Normal	1 (25.0)	1 (5.9)
High	3 (75.0)	16 (94.1)
Lactate dehydrogenase	***n* = 11**	***n* = 10**
Normal	7 (63.6)	0 (0)
High	4 (36.4)	10 (100.0)
Erythrocyte sedimentation rate	***n* = 10**	***n* = 4**
Normal	7 (70.0)	0 (0)
High	3 (30.0)	4 (100.0)
Procalcitonin	***n* = 1**	***n* = 5**
Normal	1 (100.0)	1 (20.0)
High	0 (0)	4 (80.0)
Fibrinogen	***n* = 1**	***n* = 4**
High	1 (100.0)	4 (100.0)
Radiological findings		
Chest X-ray	***n* = 12**	***n* = 27**
Normal	4 (33.3)	10 (37.0)
Ground glass opacity	0 (0)	2 (7.4)
Consolidation	1 (8.3)	9 (33.3)
Combined ground glass opacity and consolidation	0 (0)	1 (3.8)
Others[§]	0 (0)	5 (18.5)
Not specified	7 (58.4)	0 (0)
Computed Tomography thorax	***n* = 8**	***n* = 9**
Normal	3 (37.5)	1 (11.1)
Ground glass opacity	1 (12.5)	0 (0)
Consolidation	0 (0)	2 (22.2)
Combined ground glass and consolidation	0 (0)	4 (44.5)
Others[†]	1 (12.5)	2 (22.2)
Not specified	3 (37.5)	0 (0)
COVID-19 staging[‡]	***n* = 26**	***n* = 55**
1	0 (0)	8 (14.5)
2	7 (26.9)	22 (40.0)
3	9 (34.6)	6 (10.9)
4	10 (38.5)	10 (18.2)
5	0 (0)	9 (16.4)

SCD, sickle cell disease; Thal, thalassemia; N, number; N/A, not applicable.
**Categorized into high, normal or low according to the articles' local laboratory reference values.*
[§]Described changes such as reticular opacity, atelectasis, perihilar streaking, interstitial or alveolar infiltration.
[†]Described changes such as interstitial or alveolar infiltration, halo sign.
[‡]Staging based on NIH guidelines (7).

comorbidities were associated with 89.63 times risk of death compared to those without respiratory comorbidities (adj OR = 89.63, 95% CI 2.514–3195.537, $p = 0.014$). Cardiovascular comorbidities were associated with 35.20 times risk of death compared to those without (adj OR = 35.20, 95% CI 1.291–959.526, $p = 0.035$).

TABLE 4 | Summary of treatments received and outcome of study population.

Parameters	Thal, *n* (%)	SCD, *n* (%)
Hospitalization	***n* = 26**	***n* = 162**
Yes	16 (61.5)	139 (85.8)
No	10 (38.5)	23 (14.2)
Treatments	***n* = 12**	***n* = 43**
Hydroxychloroquine	6 (50.0)	26 (60.5)
Antibiotics*	9 (75.5)	28 (65.1)
Anti-viral	5 (41.7)	0 (0)
Disease modifying agent		
Tocilizumab	1 (8.3)	4 (9.3)
Anakinra	1 (8.3)	3 (7.0)
Glucocorticoid	1 (8.3)	3 (7.0)
Oxygen support	***n* = 26**	***n* = 162**
No oxygen required	15 (57.7)	118 (72.8)
Non-invasive	11 (42.3)	33 (20.4)
Invasive	0 (0)	11 (6.8)
Transfusion	***n* = 26**	***n* = 162**
No transfusion required	21 (80.8)	107 (66.0)
Packed cell transfusion	5 (19.2)	45 (27.8)
Exchange transfusion	N/A	4 (2.5)
Packed cell and exchange transfusion	N/A	6 (3.7)
Treatment outcome	***n* = 84**	***n* = 162**
Recovered	71 (84.5)	158 (97.5)
Death	13 (15.5)	4 (2.5)

SCD, sickle cell disease; Thal, thalassemia; n, number; N/A, not applicable.
**Types of antibiotics used includes cephalosporin, macrolide, fluoroquinolone, beta-lactamase and tetracycline.*

DISCUSSIONS

Our review found that in terms of severity, more patients with hemoglobinopathy (35.8%) had severe COVID-19 infection compared to the general population (11.1–19.1%) (39, 40). This could explain the higher mortality due to COVID-19 in this review (6.9%) compared to the general population (2.2–5.0%) (3, 39, 40). The mortality of 6.9% in patients with hemoglobinopathy was higher than reported COVID-19 mortality in patients with chronic kidney disease (1.54%) (41). However, it was lower compared to other immunocompromised conditions such as HIV infection (12.65%) (42) and malignancy (25.6%) (43). Majority of the published cases in this review was from high-income countries (25 articles; 17 thalassemia and 159 SCD patients) with four (2.5%) deaths involving SCD patients reported. In contrast, most of the thalassemia cases reported were from the low-middle-income countries (5 articles; 63 thalassemia patients) of which, there were 13 (20.6%) deaths. As the type of hemoglobinopathy is not a significant predictor of mortality in our logistic regression, we postulate that the higher mortality rate among the thalassemia patients could be attributed to the low health care system capacity in the low-middle-income countries.

This review also found that the presence of respiratory and cardiovascular comorbidities were independent predictors of mortality in COVID-19 infection. COVID-19 infection can lead to multi-system inflammation, resulting in myocardial injuries such as myocarditis, arrhythmia, acute coronary syndrome, and

TABLE 5 | Predictors of COVID-19 mortality in patients with hemoglobinopathy.

Variables	Simple logistic regression			Binary logistic regression		
	Crude odds ratio	95% CI	*p*-value	Adjusted odds ratio	95% CI	*p*-value
Gender (female vs. male)	2.015	(0.741, 5.483)	0.170	1.225	(0.086, 17.391)	0.881
Age (pediatric vs. adult)	1.492	(0.328, 6.795)	0.605	0.171	(0.009, 3.179)	0.237
Types of hemoglobinopathy (Thal vs. SCD)	7.232	(2.278, 22.958)	0.001*	14.612	(0.425, 502.262)	0.137
Respiratory comorbidity (no vs. yes)	1.902	(0.398, 9.103)	0.421	89.625	(2.514, 3195.537)	0.014*
Cardiovascular comorbidity (no vs. yes)	4.081	(1.396, 11.930)	0.010*	35.199	(1.291, 959.526)	0.035*
Splenectomy (no vs. yes)	3.442	(1.260, 9.403)	0.016*	<0.001	–	0.998
Diabetes mellitus (no vs. yes)	2.511	(0.760, 8.296)	0.131	<0.001	–	0.998
Oxygen requirement (no vs. yes)	3.779	(0.614, 23.271)	0.152	8.912	(0.674, 117.824)	0.097

CI, confidence interval; Thal, thalassemia; SCD, sickle cell disease.

Simple logistic regression was performed for all comorbidities vs. mortality as an outcome. Comorbidities with p-value of <0.25 for simple logistic regression were included in the model for binary logistic regression.

**Indicate statistically significant $p < 0.05$.*

venous thromboembolism (44). COVID-19 related myocardial injury may further aggravate the burden of patients with underlying cardiovascular comorbidities, thereby putting them at higher risk of death (44). COVID-19 infection is primarily a viral respiratory illness. In chronic pulmonary disease, alteration of the pulmonary structures may result in a more severe COVID-19 infection. Up-regulation of ACE-2 expression in COPD, and delayed innate antiviral immune response in asthma (45) are mechanisms that possibly explain the higher risk of severe COVID-19 infection and mortality among those with respiratory comorbidities (40).

Several studies have found that SCD patients with heart and lung comorbidities were at higher risk of severe COVID-19 infections (46, 47). Similarly, the mortality rate among thalassemia patients with cardiovascular comorbidities was significantly higher when compared to its counterpart without underlying cardiovascular disease (48). Thalassemia patients are expected to be at higher risk of cardiovascular comorbidities compared to SCD patients. This is due to the higher risk of cardiomyopathy associated with iron overload compared to patients with sickle cell disease (49). Cardiomyopathy is also the leading cause of mortality and morbidity in thalassemia patients (50, 51). However, this excess risk of COVID-19 mortality due to the presence of cardiovascular comorbidity remained statistically significant despite statistically controlling for the type of hemoglobinopathy. Due to the relatively small number of samples, the precision of the adjusted OR was affected, resulting in an extremely wide confidence interval. As more evidence is being generated, a more precise estimate of the true adjusted odds ratio can be determined.

In this review, the clinical presentations of COVID-19 infection among patients with hemoglobinopathy were almost similar to the general population, with fever and cough being reported as the most common symptoms (52, 53). COVID-19 infection may also lead to hypoxia, triggering vaso-occlusive crisis, making this one of the common manifestations seen in patients with SCD. Anemia, leukocytosis, lymphopenia, thrombocytosis, and raised CRP were among the abnormal laboratory changes reported (54, 55). These are among the common non-specific findings in the presence of infections. The treatment and management of COVID-19 in these patients were similar to that of COVID-19 patients in the general population (56–58). Exchange transfusion was only required in a small number of patients with sickle cell disease who presented with vaso-occlusive crises and severe COVID-19 infections (n=10, 6.2%). Meanwhile, blood transfusion was generally required when patients with hemoglobinopathy had anemia during presentation (mean hemoglobin 8.2 ± 1.6 g/dL). As the data available was limited, we were unable to determine whether the requirement for transfusion was influenced by the severity of COVID-19 infection and oxygen requirement. None of the articles in this review reported on the impact of COVID-19 pandemic on blood transfusion services at their center, and whether this indirectly affect the management as well as the outcome of patients with hemoglobinopathy when they were admitted for COVID-19 infection. Two studies conducted in Eastern Mediterranean reported no interruption on blood transfusion services for patients with hemoglobinopathy despite the pandemic (59, 60). However, more data is needed especially from the low- and middle-income countries with regards to this matter.

This systematic review summarized the clinical manifestations, investigations, and outcomes of COVID-19 in the hemoglobinopathy population. One of the limitations

was that studies included in this review were published during the early phase of COVID-19 pandemic, thus most of them were case reports or case series with low levels of evidence. The small sample size also discouraged further analysis based on types of hemoglobinopathy. Furthermore, not all of the studies reported their laboratory and radiological findings, hence a meta-analysis was not feasible to conclusively determine the association between laboratory markers and disease outcomes. Another limitation in our review was that the radiological findings were categorized based on the descriptive changes reported by the authors. As both COVID-19 pneumonia and acute chest syndrome in SCD patients may have similar findings (consolidation, ground glass opacity, and atelectasis), we were unable to differentiate what causes these radiological changes. The outcome of the study population reported in this systematic review was limited to mortality rate as no follow-up data were available with regards to long term effects of COVID-19 infection to patients with hemoglobinopathy. Finally, the actual number of COVID-19 cases or deaths among patients with hemoglobinopathy may be underreported especially in developing or under-developed nations, given limitations of resources for testing. The development of an authoritative international registry to capture the data on COVID-19 infections among patients with hemoglobinopathy will allow a more accurate and impactful analysis.

CONCLUSION

This review has shown that there is no difference in terms of clinical manifestations, laboratory and imaging findings for COVID-19 infections among patients with hemoglobinopathy compared to the general population. There is higher COVID-19 mortality among patients with hemoglobinopathy compared to the general population. Clinicians who manage COVID-19 infections in patients with underlying hemoglobinopathy should therefore exercise greater caution, especially in the presence of coexisting cardiovascular or respiratory comorbidities. Further large-scale, longitudinal studies are needed to evaluate the impact and long-term morbidity of COVID-19 infection on patients with hemoglobinopathy.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

JL, WC, CT, and SL contributed to the conception and design of the study. JL and WC conducted the systematic search of the study. JL, WC, and CT contributed to the data analysis. All authors contributed to the drafting and revising the article and gave final approval of the version for publication.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.757510/full#supplementary-material

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SYSTEMATIC REVIEW
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Role of Serum Ferritin in Predicting Outcomes of COVID-19 Infection Among Sickle Cell Disease Patients: A Systematic Review and Meta-Analysis

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Patients with sickle cell disease (SCD) are at higher risk of getting severe COVID-19 infection. This systematic review and meta-analysis aimed to determine the role of serum ferritin in predicting ICU admission and mortality among patients with SCD following COVID-19 infection. A systematic search was conducted in PubMed, Scopus, Web of Science, Embase, WHO COVID-19 database, ProQuest, and Cochrane Library for articles published between 1st December 2019 to 31st November 2021. Methodological quality was assessed using the Joanna Briggs Institute (JBI) critical appraisal checklists. Eleven articles (7 cohorts and 4 case series) were included in this review. Pooled mean serum ferritin level on admission was 1581.62 ng/mL while pooled proportion of ICU admission and mortality were 0.10 (95% CI 0.06; 0.16, prediction interval 0.04; 0.23, $p = 0.29$, $I^2 = 17\%$) and 0.07 (95% CI 0.05; 0.11, prediction interval 0.04; 0.12, $p = 0.68$, $I^2 = 0\%$) respectively. Meta-regression showed that serum ferritin did not predict for both ICU admission (regression coefficient = 0.0001, $p = 0.3523$) and mortality (regression coefficient = 0.0001, $p = 0.4029$). Our analyses showed that serum ferritin may not be a useful marker to predict the outcomes of COVID-19 infection among patients with SCD. More data are required to identify a reliable tool to identify patients with SCD who are at risk of getting severe COVID-19 infection.

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Keywords: sickle cell disease, COVID-19, ferritin, ICU, mortality

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INTRODUCTION

By the end of year 2021, global reported deaths from COVID-19 pandemic have reached a devastating number of 5.9 million (1). Patients with chronic illness such as chronic kidney disease, chronic respiratory or cardiovascular disease, diabetes mellitus, and hypertension were identified as high-risk groups with 2–8 fold increased risk of mortality compared to general population (2). Published data have identified several clinical and laboratory parameters which were useful to predict the outcomes of COVID-19 infection (3). High serum ferritin has been associated with

immune dysregulation and cytokine storm in severe COVID-19 infection, and thus has been reported to be a useful tool to predict the disease severity in the general population (4–6).

Sickle cell disease (SCD) is an inherited blood disorder characterized by chronic anemia, acute painful crisis and organ infarction (7). International data revealed 20–25 million individuals worldwide have homozygous SCD, majority of which resides in sub-Saharan Africa and India (8). High risk patients with SCD require chronic exchange or blood transfusion as part of their treatment protocol, leading to iron overload and its multiple complications (9). Several studies reported an increased risk of severe COVID-19 infection and mortality among patients with SCD (10–13). However, with the existing chronic iron overload in this cohort of patients, we hypothesized that in patients with SCD, serum ferritin may not be a useful outcome predictor for COVID-19 infection.

This systematic review aimed to determine the role of serum ferritin in predicting outcomes of COVID-19 infection among patients with SCD. The outcomes of interest are intensive care unit (ICU) admission and mortality.

MATERIALS AND METHODS

Study Protocol and Guideline

This systematic review and meta-analyses were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (14). For data that could not be meta-analyzed, the findings from narrative synthesis were reported using the Synthesis without meta-analysis (SWiM) guideline (15). The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (Protocol number #CRD42021287792).

Search Strategy and Selection Criteria

Systematic searches were performed in the following databases: PubMed, Scopus, Web of Science, Embase, WHO COVID-19 database, ProQuest Dissertations, and Theses Global and Cochrane Library. The combinations of search terms were #1: "COVID-19" [MeSH] AND "Anemia, Sickle Cell [MeSH]; #2: "Covid-19 [MeSH]" AND "Anemia, Sickle Cell [MeSH] AND "Ferritins [MeSH]; #3: "Covid-19 [MeSH]" AND "Anemia, Sickle Cell [MeSH] AND "Ferritins [MeSH] OR "Predictor" OR "Prognostic factor"; #4: "Covid-19 [MeSH]" AND "Anemia, Sickle Cell [MeSH] AND "Ferritins [MeSH] OR "Survival." Manual searching was also conducted to identify potential articles from the reference list of included articles. The last search was conducted on the 30th November 2021.

Studies extracted from the searches were identified by two independent reviewers. All citation records were managed with EndNote(R) version 20 (The EndNote Team, Philadelphia, USA) and duplications were removed. The authors independently screened for relevant articles by analyzing the research title, abstract and index terms of the manuscripts. Studies that reported sufficient estimates of clinical parameters of interest and COVID-19 outcomes among SCD patients with the following study designs were included: systematic reviews, cohort studies, case control studies including nested case control studies, analytical cross-sectional studies, and case series. Case reports, editorials, opinion pieces, articles that reported suspected COVID-19 cases without laboratory evidence, *in vitro* studies and patients without SCD were excluded from this review. For published articles that reported data obtained from overlapping populations, only the most recent publication was selected.

Data Collection and Methodological Quality Assessment

Full-text articles fulfilling inclusion criteria were retrieved to assess their eligibility. For studies that reported laboratory parameters without serum ferritin, the authors attempted to contact the corresponding authors to obtain the raw data, failing which these studies were excluded. The included citations were exported to an Excel spreadsheet and coded as following: author/s, study title, study design, country of study, year of publication, sample size, age, gender, comorbidities, current treatment with hydroxyurea, serum ferritin, ICU admission and mortality. Serum ferritin was presented as means and standard deviations, using reported values or estimated using standard formulas for studies that reported median and interquartile range (16). The data extracted from each article was cross-checked by at least two independent investigators. An independent third reviewer evaluated the data and provided the final decision in the event of any dispute.

The methodological quality of studies included was assessed using the Joanna Briggs Institute (JBI) critical appraisal tools for the respective study designs (17). The studies were further classified into poor (0–49%), moderate (50–69%), or high (70% and above) quality (18, 19). The risk of bias was assessed independently by two investigators and any discrepancies in opinions were resolved by a third investigator.

Operational Definitions

In this review, serum ferritin referred to the ferritin level during admission for COVID-19 infection. Comorbidities were categorized based on respective systems namely cardiovascular, respiratory, endocrine, renal, oncology, musculoskeletal, and others. History of acute chest syndrome (ACS), vaso occlusive crisis, splenectomy, and transfusion frequency were also recorded. Outcomes of COVID-19 infection were determined by ICU admission and mortality rate. ICU admission signified severe (at least Category 4) COVID-19 infection.

Statistical Analysis

R packages, metafor version 3.0, meta, and dmetar were used for meta-analysis and meta-regression (20, 21). Both packages were implemented in R version 4.1.1 (R Core Team, Vienna, Austria) using RStudio version 1.4.1106 (RStudio Team, Boston, USA).

Using random effects models, pooled means, and standard deviations for serum ferritin and pooled proportions with logit transformation (22) for severity and mortality rate of COVID-19 infection in patients with SCD were computed. Restricted Maximum Likelihood (REML) and the Hartung-Knapp adjustments were used to estimate the variances, $\tau 2$ for both effect measures and to calculate the confidence intervals of

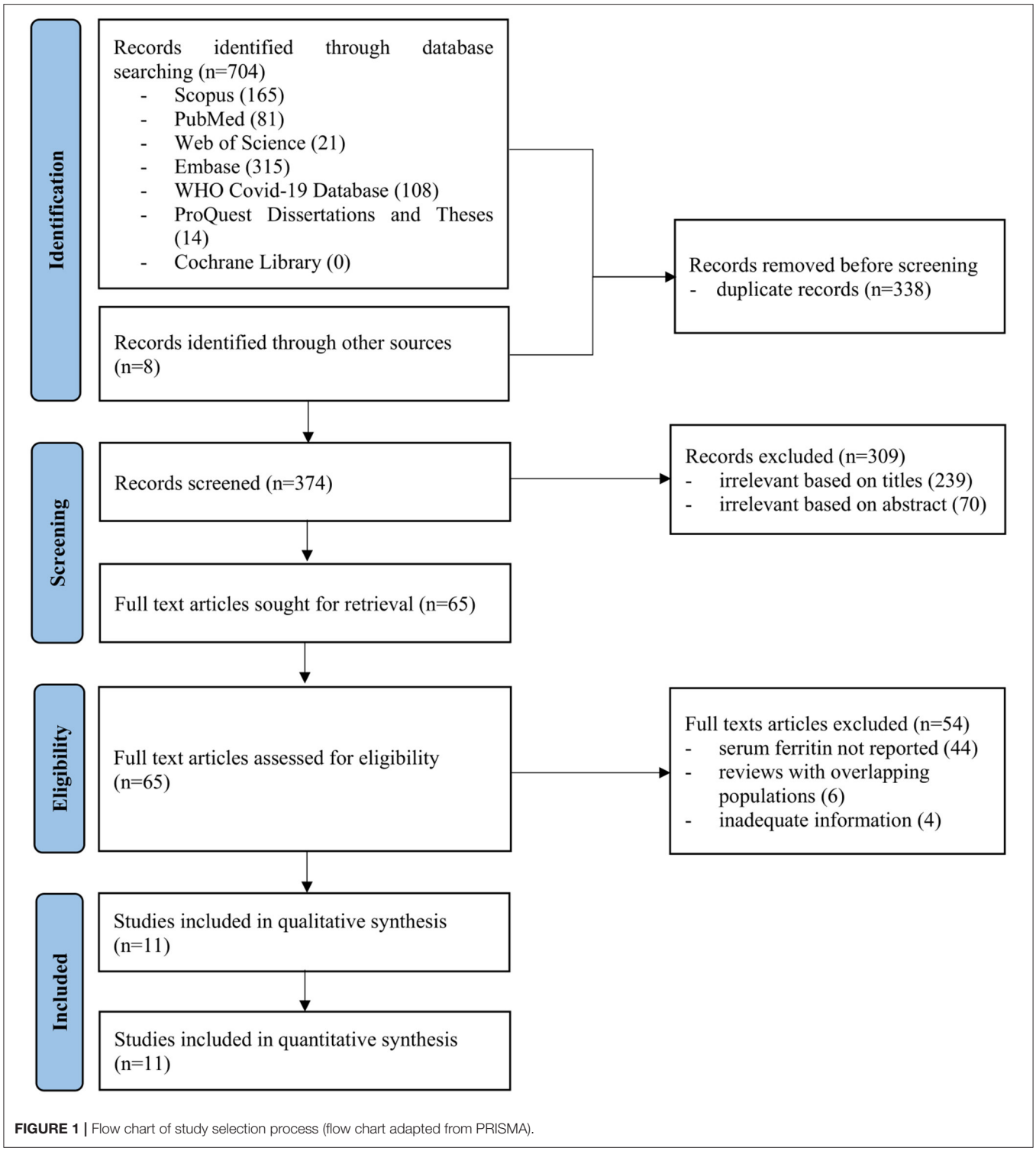

FIGURE 1 | Flow chart of study selection process (flow chart adapted from PRISMA).

summary effects, respectively. The 95% confidence interval for $\tau 2$ was obtained using the Q-profile method.

Heterogeneity was assessed using the Cochran χ^2-test ($p < 0.1$ indicates significant heterogeneity), and the I^2 statistic which was classified as following: (i) 0–40%: possibly unimportant; (ii) 30–60%: moderate heterogeneity; (iii) 50–90%: substantial heterogeneity, and (iv) 75–100%: considerable heterogeneity (23). Subgroup and sensitivity analyses were performed in the presence of substantial heterogeneity (Cochran χ^2 $p < 0.1$ or $I^2 > 50\%$).

Publication bias was evaluated by subjective visual inspection of the funnel plots for the lack of small-size studies with small

TABLE 1 | Characteristics of studies included.

No.	Reference	Study type	Country	N	Age in years, mean (range)	Male, *n*	Ferritin (ng/mL) on admission, mean (SD)	ICU admission, *n*	Mortality, *n*
1.	Alhumaid et al. (25)	Cohort	Saudi Arabia	31	NR	NR	965 (617)	14	NR
2.	Alkindi et al. (26)	Cohort	Saudi Arabia	50	31*	27	1,829 (78)	2	2
3.	Anusim et al. (27)	Case series	United States	11	44 (22-60)	4	5,571 (4,110)	2	2
4.	Balanchivadze et al. (28)	Case series	United States	24	53 (24-87)	6	820 (494)	1	1
5.	Boga et al. (29)	Cohort	Turkey	39	35 (18–64)	17	847 (908)	4	2
6.	Devarashetty et al. (30)	Cohort	United States	51	30*	20	787 (544)	2	2
7.	McCloskey et al. (31)	Case series	United Kingdom	10	36 (23–57)	8	4,669 (6,123)	0	1
8.	Minniti et al. (13)	Cohort	United States	66	33 (24-40)	30	1,035 (615)	6	7
9.	Ramachandran et al. (32)	Case series	United States	9	28 (19-40)	5	2,026 (1,550)	1	0
10.	Sewaralthahab et al. (33)	Cohort	United States	21	42*	5	1,141 (857)	5	2
11.	Yurtsever et al. (34)	Cohort	United States	40	30 (2–66)	17	4,166 (7,730)	6	1

*N, number; SD, standard deviation; ICU, intensive care unit. *Studies reporting age in median.*

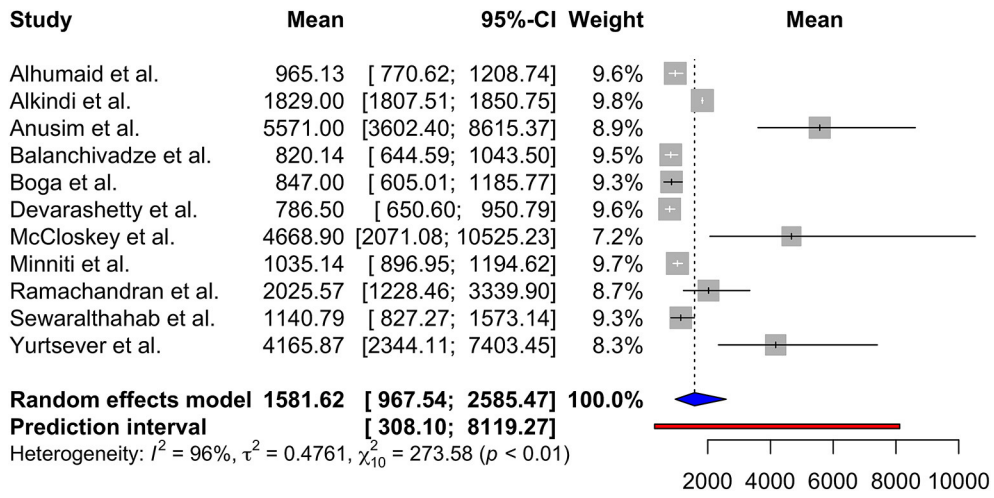

FIGURE 2 | Forest plot showing mean serum ferritin (ng/mL) on admission.

effect size and objectively by Egger's test. The Galbraith plot was used to detect the presence of outlier studies (24).

Serum ferritin was evaluated as a predictor for COVID-19 outcomes among patients with SCD using meta-regression. All tests were two-tailed, and *p*-values of 0.05 or lower were considered to be statistically significant.

RESULTS

Systematic Search Results

The searches of electronic databases yielded 704 articles while manual search through the references of these articles contributed additional 8 articles (**Figure 1**). Overall, 374 titles and abstracts were screened after removing 338 duplicates. Following this, 65 full-text articles were retrieved and reviewed. Eleven studies which consisted of 7 cohorts and 4 case series were finally included in this review (**Table 1**). The methodological quality for all the studies were summarized in the **Supplementary Table 1**.

Overall, a total of 352 patients with SCD contracted COVID-19 infection. The patients' mean age was 34.5 years (range from 2 to 87 years old) with male patients making up 43.3% (n = 139) of the cohort. Only one paper published data on 13 pediatric patients. The most common genotype reported was HbSS genotype (n = 159, 45.2%) followed by HbS/thalassemia (n = 65, 18.5%). Approximately half of the patients (n = 187, 58.3%) did not have any comorbidities (**Supplementary Table 2**). One-third (n = 122; 38.0%) of the patients were on hydroxyurea therapy while 45 patients (14.0%) were on regular blood transfusion. None of the studies reported on the patients' COVID-19 vaccination status.

Serum Ferritin on Admission for COVID-19 Infection

Using random effects model, the pooled mean serum ferritin was 1581.62 ng/mL (95% CI 967.54; 2585.47, prediction interval

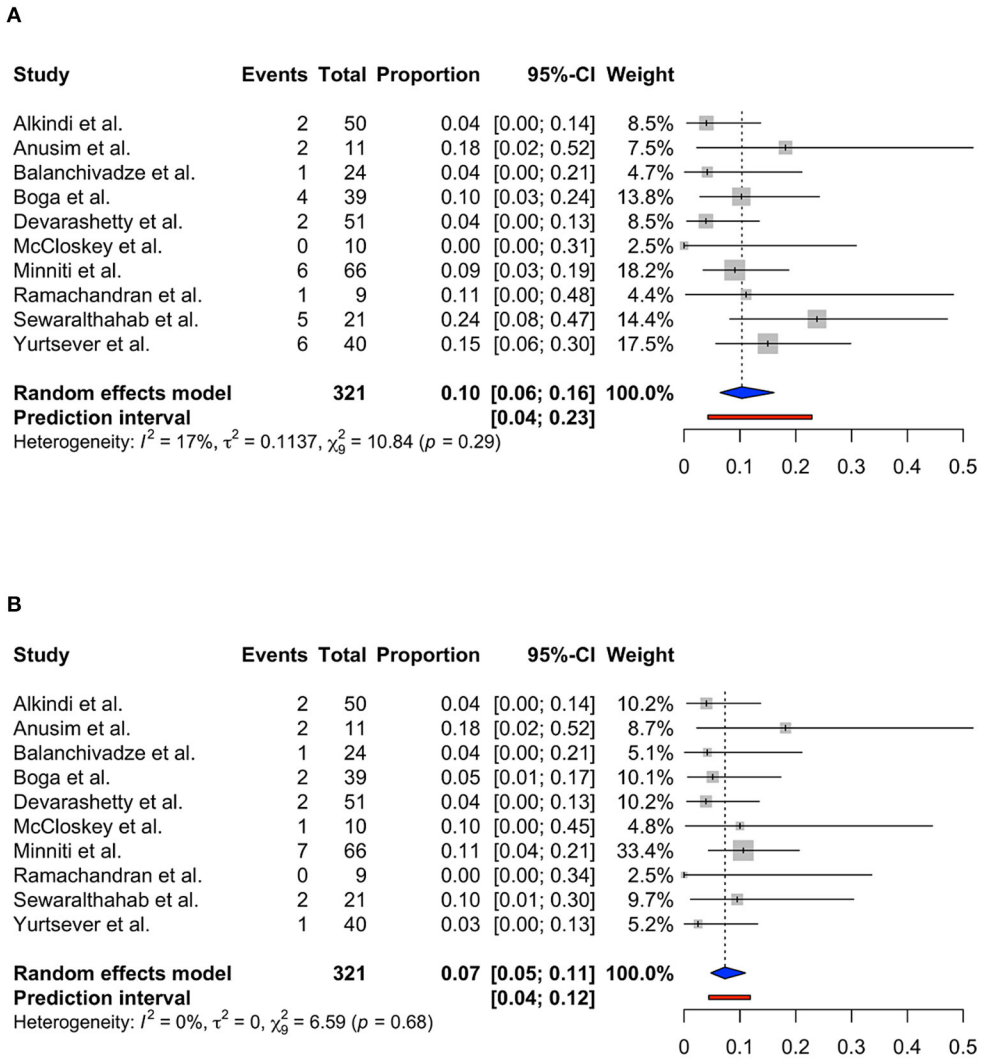

FIGURE 3 | Forest plot showing **(A)** ICU admission and **(B)** mortality due to COVID-19 infection.

308.10; 8119.27, $p < 0.01$). There was substantial between-study heterogeneity ($I^2 = 96\%$) (**Figure 2**).

COVID-19 Outcomes in Patients With SCD

Only 10 studies were included into the meta-analysis to determine the role of serum ferritin as a predictor for ICU admission and mortality among patients with SCD. Study by Alhumaid et al. was not included as the data required for meta-analysis was insufficient (25). Using the random effects model, the pooled proportion of ICU admission was 0.10 (95% CI 0.06; 0.16, prediction interval 0.04; 0.23, $p = 0.29$) with low heterogeneity ($I^2 = 17\%$) (**Figure 3A**). The pooled proportion of COVID-19 mortality in patients with SCD was 0.07 (95% CI 0.05; 0.11, prediction interval 0.04; 0.12, $p = 0.68$) with no heterogeneity ($I^2 = 0\%$) (**Figure 3B**).

Our meta-regression showed that serum ferritin on admission for COVID-19 did not predict for ICU admissions (regression coefficient = 0.0001, OR = 1, 95% CI 1.00; 1.00, $p = 0.3523$) and mortality (regression coefficient = 0.0001, OR = 1, 95% CI 1.00; 1.00, $p = 0.4029$) (**Figure 4**). Further subgroup analysis and meta-regression revealed no significant associations between serum ferritin and study characteristics, sociodemographic factors or underlying comorbidities.

Publication Bias

The funnel plots and Egger's test showed no publication bias for serum ferritin ($p = 0.1532$), ICU admission ($p = 0.2099$) and mortality ($p = 0.1925$) (**Supplementary Figure 1**). Galbraith plots showed no outlier studies were detected in the meta-analysis (**Supplementary Figure 2**).

DISCUSSION

Our study showed that serum ferritin levels on admission for COVID-19 infection did not predict ICU admission and mortality among patients with SCD. The role of serum ferritin

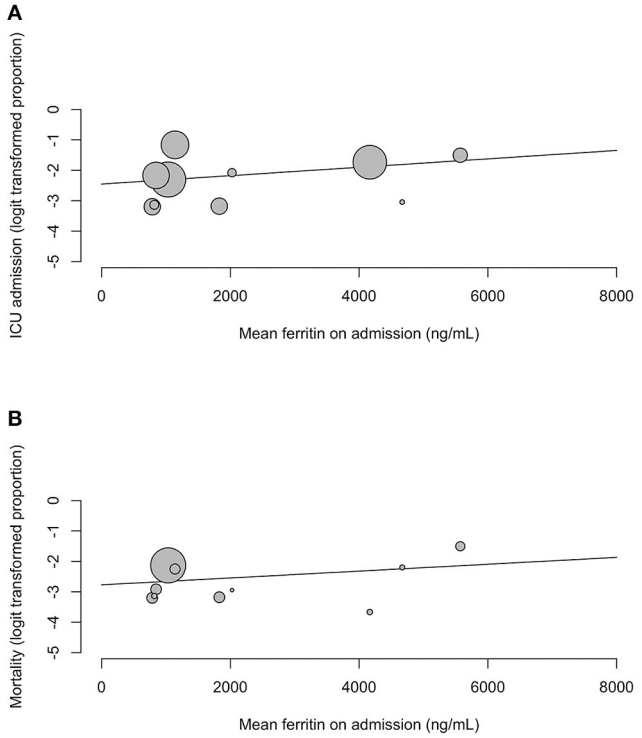

FIGURE 4 | Meta-regression bubble plots for **(A)** ICU admission and **(B)** mortality against mean serum ferritin on admission.

in predicting severity and mortality of COVID-19 infection has been inconsistent in other studies. Two previous meta-analyses done on general population reported significantly higher levels of serum ferritin among patients with severe COVID-19 and among those who succumbed (4, 35). The heterogeneity among these studies and publication bias were, however, significant and no risk ratio was reported to suggest the directionality of ferritin in predicting severity and mortality of COVID-19 infection. Conversely, other studies demonstrated that although elevation of serum ferritin to over 25th percentile had significantly higher odds of more severe lung involvement (36), serum ferritin was neither associated with COVID-19 severity (36–38) nor mortality (36, 37). Our findings concurred that serum ferritin did not predict COVID-19 severity or mortality among patients with SCD.

Ferritin is an acute phase reactant, as well as a mediator of immune dysregulation during cytokine storms in severe COVID-19 infection (39). Inflammatory cytokines such as interleukins, tumor necrosis factors, and interferons are rapidly secreted during cytokine storms, which in turn upregulate the production of ferritin by hepatocytes, Kupffer cells, and macrophages (40). Concurrently, ferritin also induces the release of pro-inflammatory and anti-inflammatory cytokines (36). The role of ferritin in the cytokine storm explained its role as a predictor for poor outcomes in various conditions (41–44). However, our review found that it did not predict for ICU admission or mortality among patients with SCD who were infected with COVID-19. One possible explanation for this could be the central role of chronic inflammation in the pathophysiology of SCD (45, 46). This ongoing inflammatory process leds to a higher baseline serum ferritin among patients with SCD compared to the general population, and further elevation happens during acute painful crises (47–49). Frequent blood transfusions, shorter duration of red cells survival and chronic intravascular hemolysis further contribute to a significantly higher levels of ferritin in these patients (50, 51). Therefore, it is possible that the higher baseline serum ferritin level in patients with SCD may have diminished its ability to predict the outcome of COVID-19 infection.

This meta-analysis provided evidence that serum ferritin may not be a useful marker to predict the outcomes for COVID-19 infection among patients with SCD with regards to ICU admission and mortality. However, our review is limited by the small number of eligible studies for meta-analysis, and insufficient reported details such as stratification of serum ferritin levels by disease severity and clinical outcomes. High between-study effect heterogeneity for the serum ferritin results was also observed, although our sensitivity analysis revealed no "outlying" studies which may have led to this (**Supplementary Figure 3**). Therefore, we postulate that this high heterogeneity could be contributed by other factors such as time-point of ferritin measurement after admission, varying laboratory analyzers to determine serum ferritin level, and the differences in the study population's disease control. Hence, our findings need to be interpreted with caution.

CONCLUSION

Our study showed that serum ferritin level on admission for COVID-19 infection did not predict the risk for ICU admission and mortality among patients with SCD. More data are required to identify other reliable clinical and laboratory markers as COVID-19 outcome predictors in this group of patients.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

JL, WC, MA, CT, and SL contributed to the conception and design of the study. JL and WC conducted the systematic search of the study. JL, WC, and MA contributed to the data analysis. All authors contributed to the drafting and revising the article and gave final approval of the version for publication.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.919159/full#supplementary-material

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Rapid progression of marginal zone B-cell lymphoma after COVID-19 vaccination (BNT162b2): A case report

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B-cell lymphomas are neoplastic diseases occasionally associated with chronic inflammation. mRNA vaccines for coronavirus disease 2019 (COVID-19) induce inflammatory responses, which often lead to fever and lymphadenopathies indistinguishable from lymphomas. Although both lymphadenopathies and lymphomas can be influential, the correlation between them is unclear. Herein, we present the first case of marginal zone B-cell lymphoma following mRNA COVID-19 vaccination. An 80-year-old Japanese woman presented with a right temporal mass that appeared the morning after she was administered her first mRNA COVID-19 vaccination (BNT162b2). The mass gradually decreased in size but persisted over 6 weeks after her first vaccination (3 weeks after her second vaccination). At her first visit to our hospital, ultrasound revealed the size of the mass to be 28.5 × 5.7 mm, and computed tomography revealed multiple lymphadenopathies in the right parotid, submandibular, jugular, and supraclavicular regions. Initially, we suspected head-and-neck benign lymphadenopathy as a side effect of vaccination. Nine weeks later, the number of swollen submandibular and parotid glands increased, and the lymph nodes further enlarged. Finally, the right temporal mass was diagnosed as marginal zone B-cell lymphoma based on immunohistochemical and flow cytometry findings of biopsy specimens. Our findings suggest that although 4–6 weeks of observation for lymph node inflammation after the second vaccination is recommended, malignancy should also be considered in the differential diagnosis of lymphadenopathy following vaccination.

KEYWORDS

mRNA vaccine, B cell, lymphoma, COVID-19, lymphadenopathy, BNT162b2, marginal zone B-cell lymphoma

Introduction

During the coronavirus disease 2019 (COVID-19) pandemic, the mRNA COVID-19 vaccines, BNT162b2 and mRNA-1273, were administered worldwide. The clinical trials of the mRNA COVID-19 vaccines reported them as safe for administration, and their relationship with malignant diseases was rare (1, 2). Although a few cases of recurrence, progression, or regression of T-cell lymphoma after mRNA COVID-19 vaccinations were reported (3–5), an influence of these vaccines on B-cell lymphomas has not been reported to date.

In the abovementioned clinical trials, the incidence of lymphadenopathy after the administration of the BNT162b2 vaccine was 0.3% (1), while the incidence of lymphadenopathy after the administration of the mRNA-1273 vaccine was 6.1–11.6% (2). To avoid unnecessary invasive tests, such as biopsy of enlarged or hypermetabolic benign lymph nodes detected on ultrasound (US), computed tomography (CT), or ^{18}F-fluorodeoxyglucose positron emission tomography-CT, close observation of vaccinated patients for inflammation of lymph nodes 4–6 weeks after the second dose (6) or at least 6 weeks after the booster dose (7–9) of COVID-19 vaccines is recommended. However, information about neoplastic lymphadenopathy derived from lymphoid hyperplasia following vaccinations remains unclear. Moreover, lengthy observations of clinical symptoms could lead to delayed diagnoses of malignant diseases, including fatal conditions.

Herein, we present a case of marginal zone B-cell lymphoma (MZL) in a patient after the administration of the BNT162b2 mRNA COVID-19 vaccine, which progressed during the 15-week follow-up from the first vaccination.

Case description

An 80-year-old Japanese woman with a medical history of hypertension, angina pectoris, mitral valve regurgitation, and ovarian tumor resection was referred for further examination of a right temporal mass (Figure 1) that suddenly appeared the morning after she received her first COVID-19 vaccine (BNT162b2) in her left deltoid muscle. She had no fever, night sweats, weight loss, sticky sensation in her mouth, burning sensation in her eyes, or joint pain. Her elder sister had systemic lupus erythematosus, and her daughter had Sjögren's syndrome. She presented to her family doctor on the day that the mass first appeared and was prescribed acetaminophen and fexofenadine for this presumed side effect of the vaccination. The mass gradually decreased in size, but it did not disappear completely. She was asymptomatic except for a sore arm. Thereafter, she was administered the second vaccine. She was referred to our hospital 6 weeks after her first vaccination (3 weeks after her second vaccination) because the right temporal mass had not disappeared.

A physical examination identified a hard, immovable right temporal mass (∼30.0 × 30.0 mm) and three palpable cervical lymph nodes. There was no tenderness or redness of the skin. US revealed the size of the mass to be 28.5 × 5.7 mm (Figures 2A,B), and the palpable lymph nodes were ≤10.2 mm in diameter. Laboratory test results of her blood and urine were unremarkable, including normal values of erythrocyte sedimentation rate and C-reactive protein, lactate dehydrogenase, and soluble interleukin-2 receptor levels. She tested negative for rheumatoid factor, SS-A and SS-B antibodies, and her antinuclear antibody titer was 1:40 (speckled pattern). CT of the neck, thorax, abdomen, and pelvis revealed 14 lymphadenopathies in the right parotid, submandibular, jugular, and supraclavicular regions, all of which were ≤7.5 mm (Figures 3A–C). At this time, the right temporal mass was suspected to be an asymptomatic benign lymphadenopathy after the administration of COVID-19 vaccination (BNT162b2). We decided on close monitoring without any treatment. We recommended that the patient return to our hospital if the mass increased in size or if she developed any other symptoms.

Although the size of the mass did not change for 9 weeks after the first visit to our hospital (from weeks 6 to 15 after the first vaccination), she subsequently presented with a sudden enlargement of the mass over the course of a few days. Contrast-enhanced CT was performed again 15 weeks after the first vaccination. The size of the right temporal mass had increased from 28.5 × 5.7 mm to 68.3 × 17.1 mm in 10 weeks (from weeks 6 week 16 after the first vaccination) (Figure 3D). The number of swollen submandibular and parotid glands had also increased from 14 glands at the last visit to >22 glands, and the maximum size of the pre-existing lymphadenopathies had enlarged from 7.5 to 13.3 mm (Figures 3E–G). ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography-CT demonstrated abnormal FDG uptake in the mass, right parotid glands, and lymphadenopathies (maximum standardized uptake value, 6.92) (Supplementary Figure 1). A biopsy of the temporal mass was performed. Pathological examination showed diffuse proliferation of small- to medium-sized lymphoid cells with slightly enlarged round nuclei (Figure 4A). There were no indications of a lymphoepithelial lesion. In the immunohistochemical analysis, the lymphoid cells were positive for CD20 (Figure 4B), CD79a, and bcl-2 (Figure 4C) and negative for CD3, CD5 (Figure 4D), CD10 (Figure 4E), bcl-6, MUM1, cyclin D (Figure 4F), IgA, IgG, and IgM. In flow cytometry, the tumor cells were positive for CD19, CD20, CD22, and cyCD79a and negative for CD5, CD10, CD11c, CD23, CD25, and CD103. Immunoglobulin kappa light-chain restriction was detected (kappa: lambda ratio, 24:1). Therefore, the right temporal mass was diagnosed as a subtype of MZL (extranodal marginal zone lymphoma of the mucosa-associated lymphoid tissue or nodal marginal zone lymphoma) stage IIE,

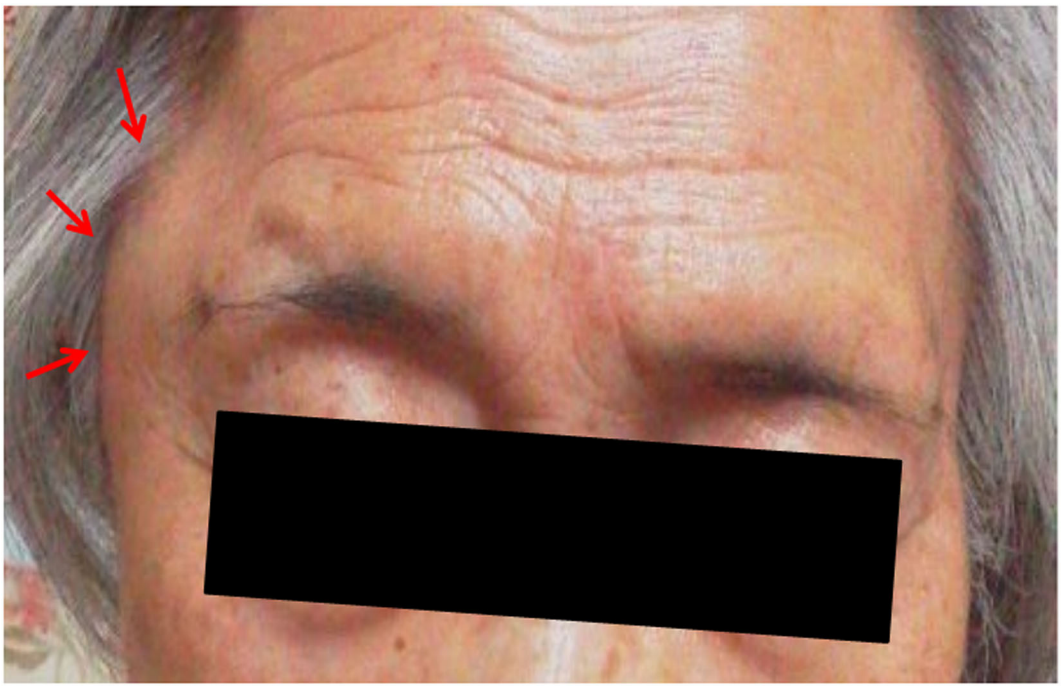

FIGURE 1
Photograph of the right temporal mass (red arrows) seen the morning after the patient's first coronavirus disease 2019 vaccination (BNT162b1) (photograph taken by the patient's family member).

according to the Lugano classification (10). Careful observation or chemotherapy was suggested to the patient. The patient preferred careful monitoring over treatment for lymphoma and is now being followed up monthly as an outpatient. Because she had no symptoms, except difficulty in wearing glasses, and no functional abnormality in the liver, kidneys, or bone marrow, she was recommended watchful waiting for her lymphoma to avoid the risk of adverse effects of therapy. No significant changes in the size of the right temporal mass, which was 70.0 × 20.0 mm at the last follow-up, have been detected in the 10 months following the first vaccination.

Discussion

To the best of our knowledge, this is the first report of B-cell lymphoma after mRNA COVID-19 vaccination, while three cases of T-cell lymphomas after mRNA COVID-19 vaccinations have been reported (3–5). Two of these three cases were of recurrence or progression of a CD30-positive T-cell lymphoma induced by mRNA COVID-19 vaccinations (3, 4), and one was of the spontaneous regression of a CD30-positive T-cell lymphoma (5). Although the precise mechanisms for T-cell lymphomas induced by the mRNA COVID-19 vaccines are still unknown, mRNA COVID-19 vaccines may have the capability to overstimulate the immune system as well as trigger autoimmune responses.

In our case, the same mechanism by which T-cell lymphomas are induced by the COVID-19 vaccine could be considered for the pathogenesis of MZL. mRNA COVID-19 vaccines are reported to induce T follicular helper cells with a Th1 functional profile, which is associated with selective generation of neutralizing antibodies, and stimulate germinal center B-cells, long-lived plasma cells, and memory B-cells. Therefore, these vaccines induce a stronger germinal center reaction than recombinant protein vaccines (11). However, the continuous stimulation of T- and B-cells by mRNA COVID-19 vaccines can trigger aberrant inflammatory responses, leading to lymphoma or accelerating its progression. MZLs are indolent lymphomas; their progression usually occurs over many years, and they are associated with chronic inflammation, including infections and several autoimmune diseases (12). A meta-analysis of five cohort studies reported that the standardized incidence rate of non-Hodgkin's lymphoma in patients with Sjögren's syndrome ranged from 8.7 to 44.4% (13). However, our patient showed no evidence of associated autoimmune diseases, including Sjögren's syndrome. A rare case has been reported in which the skin was induced by the antigenic stimulus of influenza vaccine components, causing MZL (14). A case of evolution of a cutaneous lymphoid hyperplasia, possibly due to a chronic inflammatory response to the antigenic stimulus of

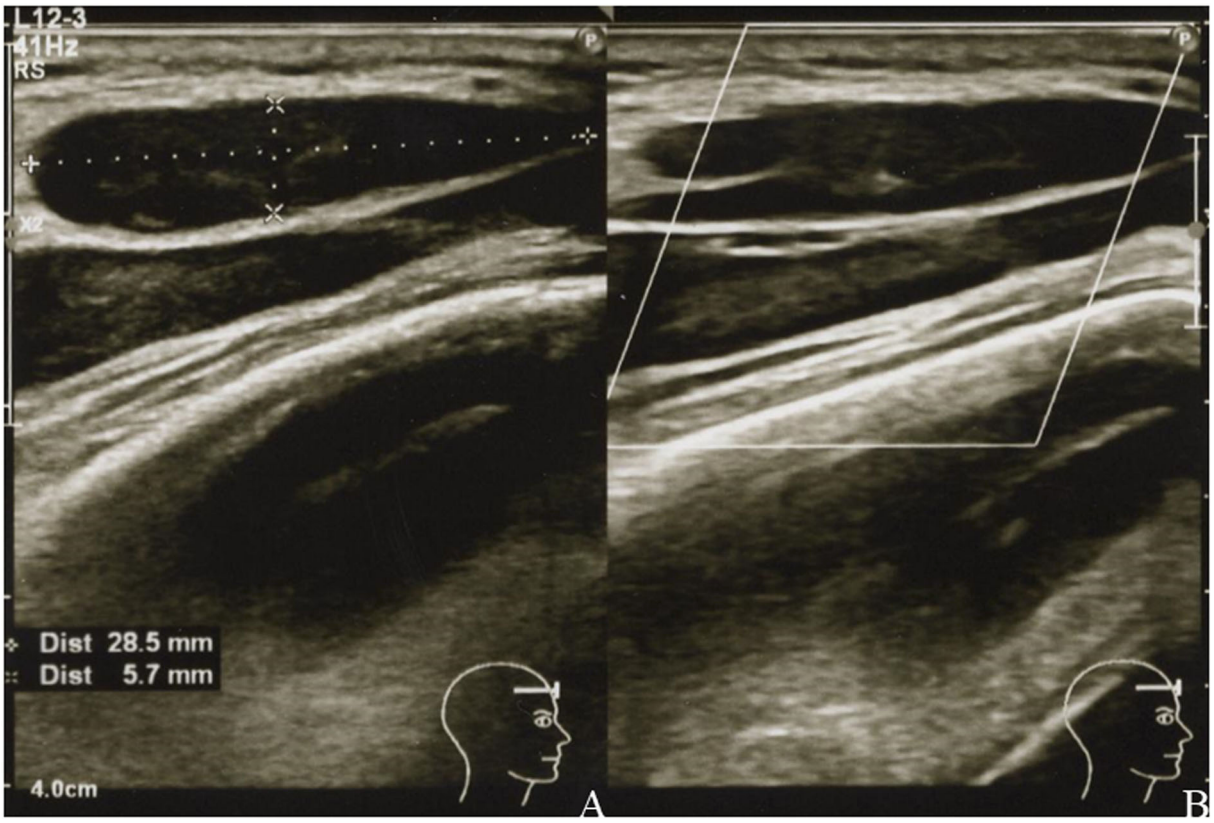

FIGURE 2
Grayscale **(A)** and color Doppler **(B)** images of the right temporal mass showing a uniformly hypoechoic teardrop-shaped mass with well-defined margins **(A)** and decreased vascularity **(B)**.

tattoo dye to a B-cell lymphoma, has also been reported (15). The pathogenesis of MZL in the present case could be similar to that in the abovementioned cases.

Imaging and clinical features characteristic of malignancy that are useful in differential diagnosis include >11 enlarged lymph nodes, lymph nodes with short-axis diameters >15 mm, lymphadenopathy on the contralateral side of the vaccination site, and/or lymphadenopathy in a region other than the axial and supraclavicular regions. Cervical lymphadenopathy after administration of mRNA COVID-19 vaccines is not rare, with a reported prevalence of 9% on CT (16) and 5 and 14.8% on US (17, 18). The number of cervical lymphadenopathies ranged from 1 to 10 on CT (16) and 1–5 on US (19). The median short-axis diameter of the largest node in the cervical lymphadenopathy was 7 mm (range, 5–14 mm) on CT (16) and 5.2 mm (range, 3.4–8.2 mm) on US (18). mRNA COVID-19 vaccine-related lymphadenopathy was mostly identified on the injected side (1, 2) and in the axial and/or supraclavicular regions (20, 21). Cocco et al. also reported that lymph node swelling after COVID-19 vaccination most commonly appeared in the axillary and/or supraclavicular regions; however, 5/64 (7.8%) patients in their study had swollen lymph nodes in an atypical location [6/170 (3.5%) lymph nodes] (22). In our case, most of the lymph nodes [13/14 (93%) at the first visit; 20/22 (91%) at the second visit] were in atypical locations, such as in the parotid, submandibular, and jugular regions. Therefore, cervical lymphadenopathy with >11 enlarged lymph nodes, lymph nodes with short-axis diameters >15 mm, and/or lymph nodes on the contralateral side of the injection site or in a region other than the axial and/or supraclavicular regions is considered atypical, and these clinical findings could be suggestive of a malignancy.

In our case, the patient's CT at the first visit showed 14 lymphadenopathies in the right parotid, submandibular, jugular, and supraclavicular regions on the contralateral side of the COVID-19 vaccination site. The mass was 28.5 × 5.7 mm in size, and the diameter of the largest lymph node was 7.5 mm on CT and 10.2 mm on US. Therefore, the number and location of the lymphadenopathies and the size of the mass were atypical for a vaccine-related cervical lymphadenopathy, which contributed to suspicion of malignant disease and further examinations.

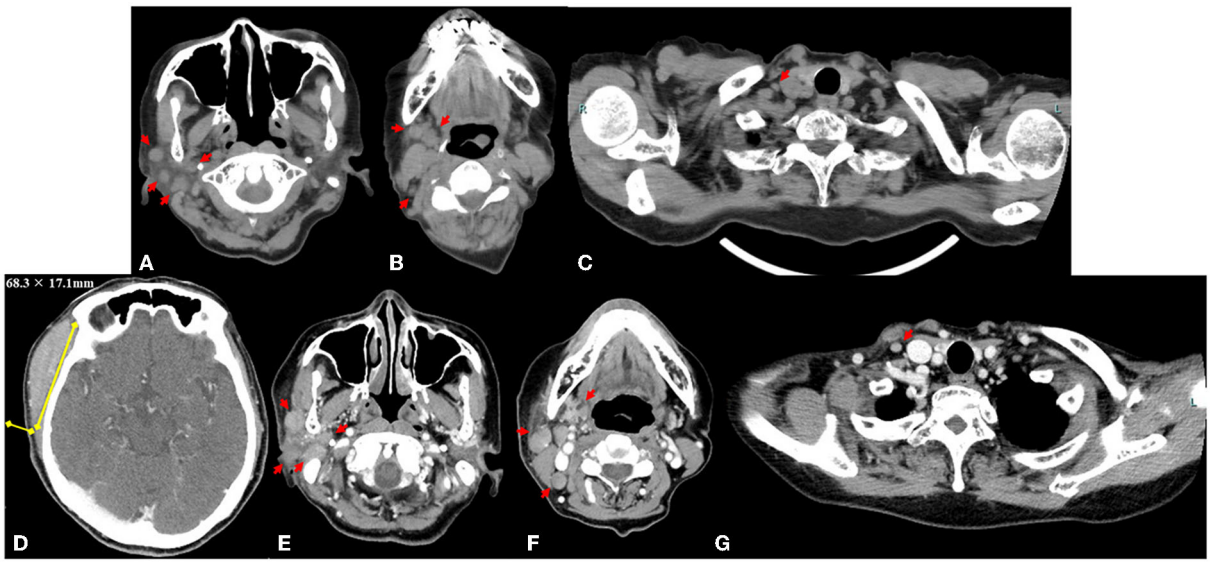

FIGURE 3
Axial computed tomography image obtained at the first visit shows 14 lymphadenopathies, with a maximum diameter ≤7.5 mm (red arrows) in the right parotid region **(A)**, submandibular and jugular regions **(B)**, and supraclavicular region **(C)**. Measurement of the right temporal mass (68.3 × 17.1 mm) on an axial contrast-enhanced computed tomography image 9 weeks after the first visit to our institution **(D)**. The lymphadenopathies (maximum size ≤ 13.3 mm, yellow arrows) in the right parotid region **(E)**, submandibular and jugular region **(F)**, and supraclavicular region **(G)**.

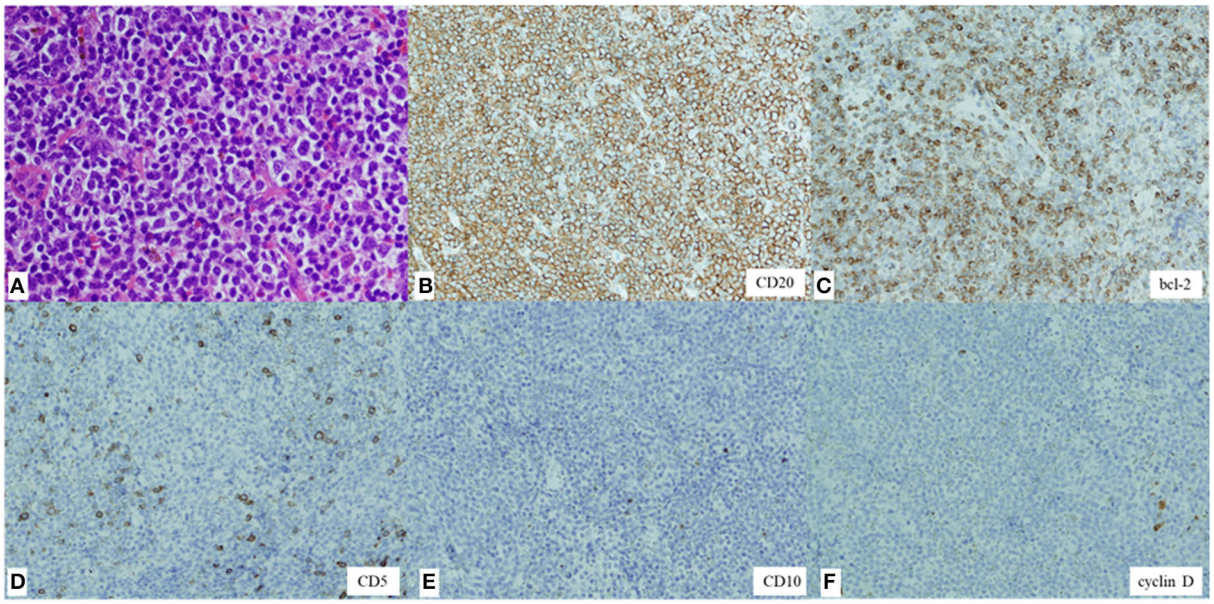

FIGURE 4
Hematoxylin and eosin staining of the biopsy specimen showing diffuse proliferation of small- to medium-sized lymphoid cells with slightly enlarged round nuclei (magnification, ×200) **(A)**. Immunohistochemical staining showing lymphoid cells positive for CD20 (×100) **(B)** and bcl-2 (×100) **(C)** and negative for CD5 (×100) **(D)**, CD10 (×100) **(E)**, and cyclin D (×100) **(F)**.

The shape of the lymphadenopathy on US, findings of eccentric cortical thickness, irregular margins, loss of an echogenic hilum, and increasing peripheral vascularity on a color Doppler scan are generally suggestive of malignancy (23, 24). Of these findings, the mass in our case showed eccentric cortical thickness. However, many mRNA COVID-19 vaccine-related lymphadenopathies show asymmetric eccentric cortical thickening, loss of an echogenic hilum, and increased vascularity on US (18, 19). Therefore, other than the irregular margin, mRNA COVID-19 vaccine-related lymphadenopathies can be indistinguishable from neoplastic lymphadenopathies.

In a previous study, no significant differences in US findings were detected among patients with COVID-19 vaccine-related lymphadenopathies who received the Pfizer/BioNTech BNT162b2 mRNA, AstraZeneca ChAdOx1, and Moderna mRNA-1273 vaccines (25). In contrast, the US features of lymph nodes post-vaccination, such as round morphology, absence of hilum, and hard pattern, have been found to mimic those of pathological lymph nodes (25). However, in the patients in that study, features of COVID-19 vaccine-related lymphadenopathy were found to be superimposed on those of malignant pathologies, representing a potential pitfall for patients belonging to high-risk categories. Therefore, patients with COVID-19 vaccine-related lymphadenopathy should receive comprehensive care and follow-up.

Recommendations by the Canadian Society of Breast Imaging, Society of Breast Imaging, and European Society of Breast Imaging for the treatment of lymphadenopathy after the administration of mRNA COVID-19 vaccines advise waiting and monitoring for over 4–6 weeks (6, 8, 9). However, opinions differ on whether a long-term observation is acceptable for distinguishing benign from neoplastic lymphadenopathy because lymph node swelling after the administration of mRNA COVID-19 vaccines has been reported to persist for over 4 weeks in 50% (18) and 20% (26) of patients on US. In particular, lymphadenopathy in an atypical region (such as the upper cervical region), involvement of multiple lymph nodes, and extraordinary enlargement of lymph nodes may need to be observed for a shorter duration of ∼4 weeks before treatment, as recommended by the three societies (6, 8, 9). On the contrary, lymphomas that are relatively benign and have a long progression (as seen in this case) pose a risk of misdiagnosis or a missed diagnosis if the lymphoma develops after vaccination. Therefore, we recommend careful observation of post-COVID-19 vaccination lymph node enlargements, even if they occur 4–6 weeks after the second vaccination.

In conclusion, we reported a case of MZL following mRNA COVID-19 vaccination. This is the first report of a malignant lymphoma of B-cell lineage that developed after COVID-19 vaccination. Lymphadenopathy induced by mRNA COVID-19 vaccination is not rare; therefore, clinicians should be aware of the atypical features of lymphadenopathy to prevent delayed diagnosis during monitoring of the signs and symptoms listed above. We suggest that malignant lymphoma may be differentiated from benign lymphadenopathy if there are >11 enlarged lymph nodes, lymph nodes with short-axis diameters >15 mm, and lymphadenopathy contralateral to the vaccination site and/or in a region other than the axial and supraclavicular regions. Attention should be paid to the development of lymphoma within 4–6 weeks after COVID-19 vaccination. Moreover, care should be taken to avoid overlooking relatively benign, slowly progressing lymphomas, such as MZLs, after 4–6 weeks of follow-up.

Patient perspective

This patient wanted to notify the possibility of neoplastic lymphadenopathy mimicking lymphadenopathy following the mRNA COVID-19 vaccinations as a caution. Moreover, she wanted to utilize our therapeutic experience for other patients with COVID-19 vaccine-related lymphadenopathies to prevent negligence or delayed diagnoses.

Data availability statement

The data that support the findings of this article/Supplementary material are available from the corresponding author upon reasonable request.

Ethics statement

This study was reviewed and approved by the Ethics Committee at National Defense Medical College in Japan. The patient provided written informed consent to participate in this study. Written informed consent was obtained from the patient for the publication of any potentially identifiable images or data included in this article.

Author contributions

AS and KH wrote the first draft of the manuscript and sections of the revised manuscript. SKob was consulted for the diagnosis and hematological problems. KH contributed to funding acquisition. AS, SKob, KH, SKoz, TK, YK, MK, NF, YOn, YOb, and YT were responsible for the clinical care of the patient and supervised the writing of the manuscript. All authors contributed to manuscript revision and read and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.963393/full#supplementary-material

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Peripheral blood cell anomalies in COVID-19 patients in the United Arab Emirates: A single-centered study

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Introduction: In this study, we aimed at exploring the morphologic and quantitative abnormalities in the peripheral blood counts of coronavirus disease 2019 (COVID-19) patients.

Methods: A cohort of 131 COVID-19 patients was recruited at University Hospital Sharjah (UHS), UAE. Their peripheral blood smears were examined for morphological evaluation. Also, their clinical laboratory investigations and radiological findings were retrieved from the medical records. Our cohort consisted of 63 males and 68 females with an age of 63.6 ± 18.6 years.

Results: The presence of atypical lymphocytes was observed in around 80% of the recruited COVID-19 patients. Further, monocytes with toxic cytoplasmic vacuoles were identified in 55% of the cases. Neutrophil-associated changes, including pseudo-Pelger-Huët, bands, and long nuclear endoplasm, were reported in around 25–35% of the patients. RBCs associated changes such as microcytic and hypochromic RBCs, as well as targetoid, dacrocytes, ovalocytes, echinocytes/burr cells, and schistocytes, were described. According to disease severity, RBCs chromicity was found to be significantly different between stable and critical patients. COVID-19 patients with CO-RADS 5 showed a similar change in RBCs as well as a decrease in the neutrophils with hypogranular cytoplasm.

Conclusion: Peripheral blood smear assessment in COVID-19 patients could provide information about the disease state and pulmonary involvement.

KEYWORDS

CO-RADS, COVID-19, lymphocytes, neutrophils, peripheral smears, UAE

Introduction

Coronavirus disease 2019 (COVID-19) remains a global pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which affects multiple organs (1). In the United Arab Emirates (UAE), the first case of COVID-19 was identified on 29 January 2020 (2). The most common symptoms in COVID-19 patients include fever, fatigue, cough, and dyspnea (3). However, some cases could be asymptomatic carriers while others fall into mild, moderate, and severe categories. In critical COVID-19 patients, fatal acute respiratory distress syndrome (ARDS) occurs, leading to intensive care unit (ICU) admission (4, 5).

It was found that COVID-19 pathogenesis was associated with an activation of the immune system and subsequent immune dysregulation (6). A major clinical feature of COVID-19 was neutrophilia with concomitant lymphopenia, that were linked to the severity of the disease (7). Despite the known quantitative abnormalities in the peripheral blood, little is known about the morphologic changes in circulating blood cells in COVID-19 (8). Such changes could aid in the diagnosis of COVID-19 and management decisions in COVID-19 patients. The reported abnormalities in peripheral blood smears include a range of atypical lymphocytes, acquired Pelger-Huët anomaly, and fetus-shaped neutrophils (9). Furthermore, abnormal platelets and red blood cells (RBCs) morphology were also reported in peripheral blood of COVID-19 infected patients, thus inducing coagulopathies and malfunction of oxygen carrying capacity (10). In this study, we aim to explore the morphologic and quantitative abnormalities in the peripheral blood counts of COVID-19 patients recruited to a single center in the UAE.

Subjects and methods

This is a retrospective study conducted on 131 COVID-19 patients that were recruited at University Hospital Sharjah (UHS), UAE. Our cohort was composed of 63 males and 68 females, aged 63.6 ± 18.6 years (mean ± SD). The cases were diagnosed based on a positive nasopharyngeal swab result using reverse transcriptase-polymerase chain reaction (RT-PCR). Out of 270 patients that were admitted from July 2020 to July 2021, 131 COVID-19 patients were selected as they were not previously vaccinated for SARS-CoV-2. The study was approved by the Ethics and Research Committee of UHS (UHS-HERC-035-03052020).

Peripheral blood samples were collected from COVID-19 patients in EDTA sterile vacutainers, after which peripheral blood smears were prepared, and laboratory investigations were performed. These tests included complete and differential blood such as platelets, white blood cells (WBCs), neutrophils, lymphocytes, monocytes count, oxygen saturation and hemoglobin that were done using Sysmex XN 20 Hematology Analyzer (Sysmex, Germany). Also, prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (aPTT), and D-dimer were measured using STA Compact Max 3 (Stago, France). Moreover, lactate dehydrogenase (LDH) and C-reactive protein (CRP) were measured using Atellica® CH 930 Analyzer (Siemens Healthineers, Germany), while procalcitonin and ferritin were measured Atellica® IM 1300 Analyzer (Siemens Healthineers,

TABLE 1 Clinical and demographic of 131 coronavirus disease 2019 (COVID-19) patients recruited in this study.

Total COVID-19 cases	***n* = 131**	
Gender	63 males and 68 females	
Age (years) (Mean ± SD)	63.6 ± 18.6	
	Normal range	**Mean ± SD**
Oxygen saturation	≥95	91.9 ± 5.3
Hemoglobin (g/L)	13.0–17.5	11.9 ± 2.2
Platelet count ($\times 10^9$/L)	125–350	262.2 ± 172.1
White blood cell count ($\times 10^9$/L)	3.5–9.5	9 ± 17.6
Neutrophil count ($\times 10^9$/L)	1.8–6.3	7.9 ± 17.6
Lymphocyte count ($\times 10^9$/L)	1.1–3.2	1.3 ± 1.3
Monocyte count ($\times 10^9$/L)	0.1–0.6	0.6 ± 0.7
Lactate dehydrogenase (U/L)	135–225	302.6 ± 192.4
Prothrombin time (seconds)	11.5–14.5	14.8 ± 2.2
International normalized ratio – INR	0.8–1.2	1.1 ± 0.3
Activated partial thromboplastin time (seconds)	29–42	38.4 ± 7
D-dimer (μg/mL)	<0.5	2.5 ± 5.5
Procalcitonin (ng/mL)	0.02–0.05	4.9 ± 42.7
C-reactive protein (CRP) (mg/L)	<1	83.2 ± 73.4
Ferritin (μg/L)	30–400	462.5 ± 511.1

TABLE 2 COVID-19 Reporting and Data System (CO-RADS) interpretation with level of suspicion for pulmonary involvement of COVID-19 infection and its corresponding CT findings.

CO-RADS	**Level of suspicion for pulmonary involvement of COVID-19 infection**	**CT findings**
1	Highly unlikely	Normal or non-infectious abnormalities
2	Unlikely	Abnormalities consistent with infections other than COVID-19
3	Equivocal	Unclear whether COVID-19 is present
4	Probable	Abnormalities suspicious of COVID-19
5	Highly likely	Typical COVID-19
6	PCR proven	–

Germany). All these tests are summarized in Table 1. Blood films were prepared and stained using the Leishman stain standard protocol. The smears were examined under the light microscope (Olympus BX43, Japan) by a hematopathologist for morphological evaluation, and images were captured using the digital camera (Olympus SC50, Japan). The evaluation was done blindly in terms of laboratory investigations.

Radiological evaluation was done using chest X-ray and high-resolution computed tomography (CT) scans, followed by an assessment using the COVID-19 Reporting and Data System (CO-RADS) as a standardized assessment of pulmonary involvement of COVID-19 (11). The CO-RADS classification is described in Table 2.

Values represent mean ± SD for the continuous variables, or percentage relative to the total number of patients in each group for the categorical variables. Statistical analysis was performed using GraphPad Prism 6 software (GraphPad Software, San Diego, CA, USA). Chi-square test was used for the comparison between the categorical variables. P-value < 0.05 was considered statistically significant.

Results

Our cohort was composed of 131 patients that were proven to be COVID-19 positive by RT-PCR of the nasopharyngeal

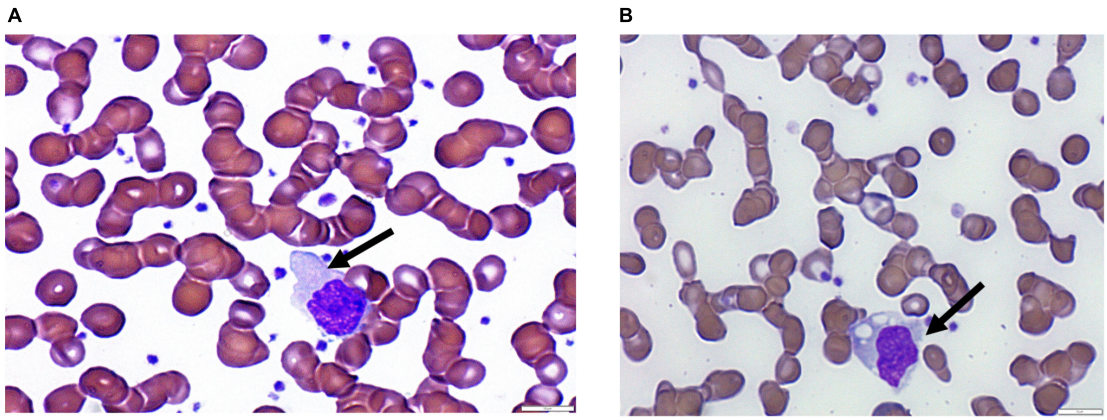

FIGURE 1
Images showing peripheral changes in lymphocytes and monocytes. **(A)** Atypical lymphocytes and **(B)** monocytes with vacuolated cytoplasm.

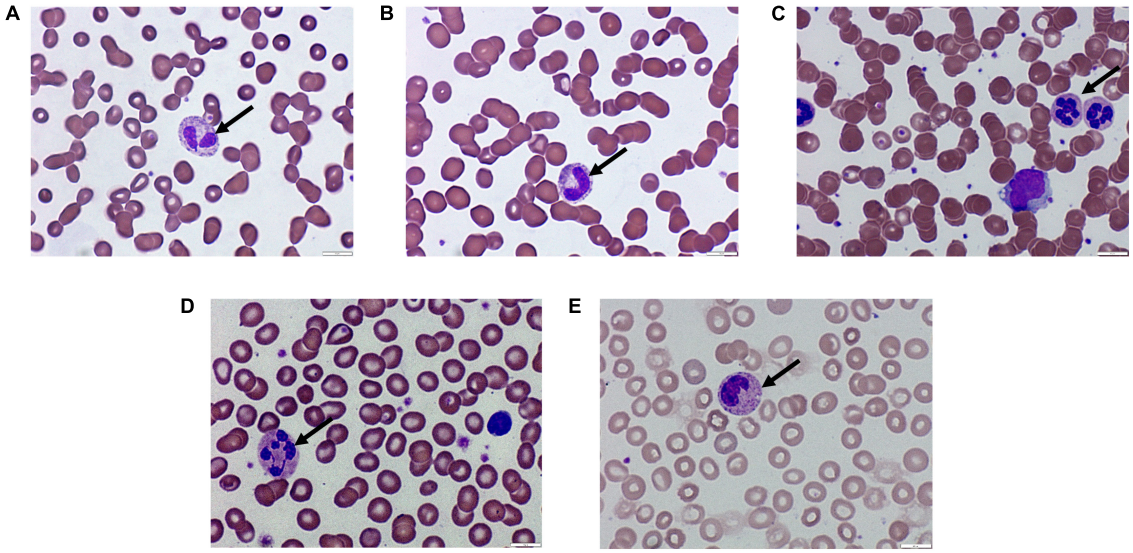

FIGURE 2
Images showing peripheral changes in neutrophils. **(A)** Pseudo-Pelger-Huët, **(B)** bands, **(C)** hypersegmented, **(D)** long nuclear cytoplasm, and **(E)** fetus-shaped nuclei in neutrophils.

swabs. Their quantitative hematologic abnormalities were documented along with the microscopic examination of the peripheral smears to include various anomalies such as changes in WBCs, RBCs, and platelets.

The most common reported morphologic finding was the presence of atypical lymphocytes in around 80% of the COVID-19 patients (Figure 1A). This was followed by the presence of monocytes with toxic cytoplasmic vacuoles in 55% of the cases. As shown in Figure 1B, activated monocytes were observed showing prominent cytoplasmic vacuolization and few granules. Also, the nuclei were large, having fine chromatin with nuclear blebbing.

Neutrophil-associated changes, including pseudo-Pelger-Huët (Figure 2A), bands (Figure 2B), hypersegmented (Figure 2C), and long nuclear endoplasm (Figure 2D), were observed in some of the recruited COVID-19 patients. Such neutrophilic-associated changes were reported in around 25–35% of the patients, as shown in Table 3. Also, C-shaped, fetus-like nuclei were noted with aberrant nuclear projections (Figure 2E).

Regarding platelet counts, the mean number was within the normal range in COVID-19 patients, which aligns with the coagulation parameters (PT, INR, and aPTT) that were almost in their normal ranges. Around half of the COVID-19 patients presented with normocytic RBCs along with anisocytosis and hyperchromicity (Table 4). Other common RBCs associated changes included erythrocytopenia and microcytic RBCs as well as targetoid, dacrocytes, ovalocytes, echinocytes/burr cells, and schistocytes (Figures 3A–E).

The COVID-19 patients were classified into different groups according to their CO-RADS score. Almost 77% of the patients fell into the CO-RADS 5 category (Figure 4), indicating pulmonary involvement and a high probability of COVID-19 infection before confirmatory tests by qRT-PCR (Table 5).

In order to search for a relation between morphological changes in peripheral blood cells and disease severity, COVID-19 patients were classified into stable (patients not requiring ICU admission, $n = 48$) and critical (ICU admitted patients, $n = 83$) groups. No statistical significance was found between the two groups except for RBCs changes and platelets' thrombocytosis (Table 6). There was a significant increase in the percentage of patients showing normocytic ($p = 0.0301$), normochromic ($p = 0.0246$), with a significant decrease in the patients' microcytic ($p = 0.0109$), and hypochromic RBCs ($p = 0.0158$)

TABLE 3 Changes in the white blood cells (WBCs) count and morphological anomalies including lymphocytes, monocytes, and neutrophils.

	Frequency (*n*)	Percent (%)
WBC changes		
Leucocytosis	4	3.1
Leukopenia	4	3.1
Lymphocyte changes		
Lymphocytosis	2	1.5
Lymphopenia	26	19.8
Atypical lymphocytes	105	80.2
Granular lymphocyte cytoplasm	5	3.8
Basophilic cytoplasm lymphocytes	6	4.6
Plasmacytoid lymphocytes	0	0.0
Monocyte changes		
Monocytosis	4	3.1
Monocytes with vacuoles	72	55.0
Neutrophils changes		
Neutrophilia	19	14.5
Neutropenia	2	1.5
Pseudo-Pelger-Huët	33	25.2
Bands	34	26.0
Long nuclear endoplasm	33	25.2
Fetus-shaped nucleus	30	22.9
Macrogranular neutrophil cytoplasm	12	9.2
Karyorrehxis neutrophils	3	2.3
Drumstick nucleus	2	1.5
Hypogranular neutrophil cytoplasm	48	36.6

TABLE 4 Changes in the platelets and red blood cells (RBCs) count and their associated morphological anomalies.

	Frequency (*n*)	Percent (%)
Platelets changes		
Platelets thrombocytosis	17	13
Platelets thrombocytopenia	15	11.5
RBCs changes		
Normocytic RBCs	66	50.4
Anisocytosis	65	49.6
Hypochromic RBCs	55	42
Targetoid	47	35.9
Normochromic RBCs	44	33.6
Dacrocytes	42	32.1
Erthrocytopenia	35	26.7
Ovalocytes	35	26.7
Microcytic RBCs	34	26
Echinocytes/Burr cells	34	26
Schistocytes	33	25.2
Bite cells	28	21.4
Stomatocytes	24	18.3
Acanthocytes/Spur	24	18.3
Rouleaux RBCs	23	17.6
Mushroom RBCs	21	16
Polycythemia	10	7.6
Polychromasia	5	3.8
Normoblasts	4	3.1
Macrocytic RBCs	2	1.5

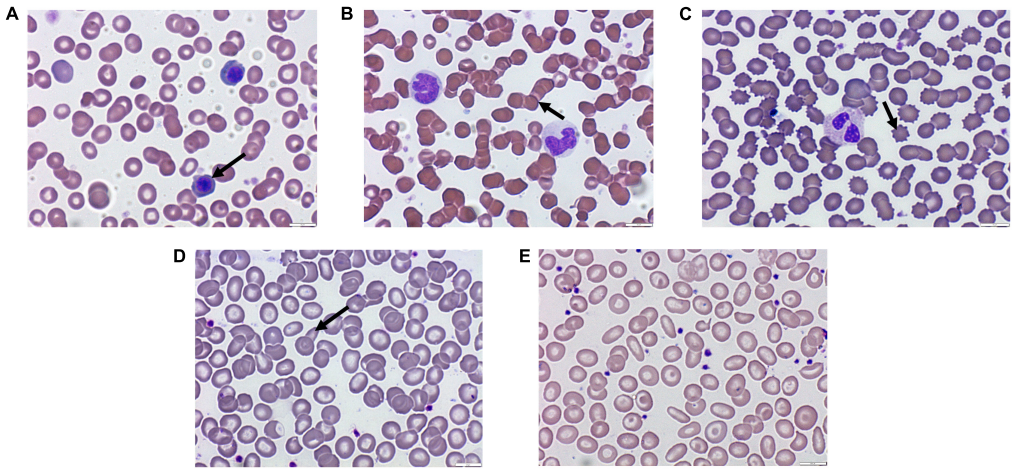

FIGURE 3
Images showing peripheral changes in red blood cells (RBCs). **(A)** Normoblasts, **(B)** rouleaux, **(C)** acanthocytes, **(D)** mushroom-like, and **(E)** anisopoikilocytosis, ovalocytes, schistocytes, and targetoid cells.

in critical ICU-admitted patients. Furthermore, stable COVID-19 patients showed higher levels of platelets' thrombocytosis compared to critical COVID-19 patients ($p = 0.0209$).

Another possible classification was to divide COVID-19 patients into those belonging to CO-RADS 5 group ($n = 99$) versus others ($n = 30$). There was an observed significant decrease in the neutrophils showing hypogranular cytoplasm in CO-RADS 5 group ($p = 0.049$). Also, there was a significant increase in the percentage of patients showing normocytic ($p = 0.0431$) and normochromic ($p = 0.0135$) RBCs in the CO-RADS 5 group. Further, there was a significant decrease in the percentage of patients showing ovalocytes in the CO-RADS 5 group ($p = 0.0194$, **Table 7**).

Since gender plays a critical role in the COVID-19 pathogenesis (11, 12), it was interesting to explore if there is any difference in the peripheral blood anomalies between males ($n = 63$) and females ($n = 68$). There was a statistical significance in the chromicity of RBCs, where males showed a higher significant percentage of normochromic ($p = 0.0093$), with a concomitant decrease in the percentage of hypochromic RBCs ($p = 0.0054$, **Table 8**).

Discussion

This study highlights the quantitative and morphological changes in the peripheral blood cells of COVID-19 patients. To our knowledge, this is the first study to report these changes in the UAE, which has taken extraordinary precautionary measures to restrict the spread of COVID-19 and guarantee the safety of citizens. Furthermore, this study explored if there is an association between disease severity and peripheral blood anomalies.

The most common morphological anomalies in our cohort were atypical lymphocytes, large monocytes with vacuoles, and hypogranular neutrophil cytoplasm of the peripheral blood smears. Despite the small number of reports on the peripheral morphological anomalies associated with COVID-19 infection, our findings go in line with a study by Zhang et al. where large monocytes with vacuoles were observed in peripheral smears of COVID-19 patients (13). In addition, our observed morphological anomalies were consistent with the findings by Zini et al. that reported various peripheral morphological blood changes, specifically in the neutrophils (14). Further, the presence of atypical lymphocytes was highly found to be similar to the previous reports (15–17). In addition, granulocytes and particularly neutrophils showed a pseudo-Pelger-Huët anomaly affecting 25% of the recruited COVID-19 patients, both stable and critical cases, unlike the observed findings by Ahnach et al. (18). Similarly, another type of neutrophil-associated anomaly was the presence of hypogranular cytoplasm in more than 30% of the patients (18).

Despite the advances in COVID-19 research, little information about the morphological changes in peripheral blood smears of infected individuals and their association with patients' clinical outcomes is still unknown. Thus, we were interested in correlating the difference in these peripheral anomalies in ICU-admitted and stable COVID-19 patients. An increase in the percentage of patients showing neutrophilia, neutrophils with pseudo-Pelger-Huët, bands, long nuclear endoplasm, and fetus shaped nucleus, as well as large vacuolated monocytes, was recognized in the critical/ICU admitted group; however, such changes did not reach statistical significance. An increase in the percentage of aforementioned anomalies was also observed in COVID-19 patients with a CO-RADS score 5 compared to others. On the other hand, upon the

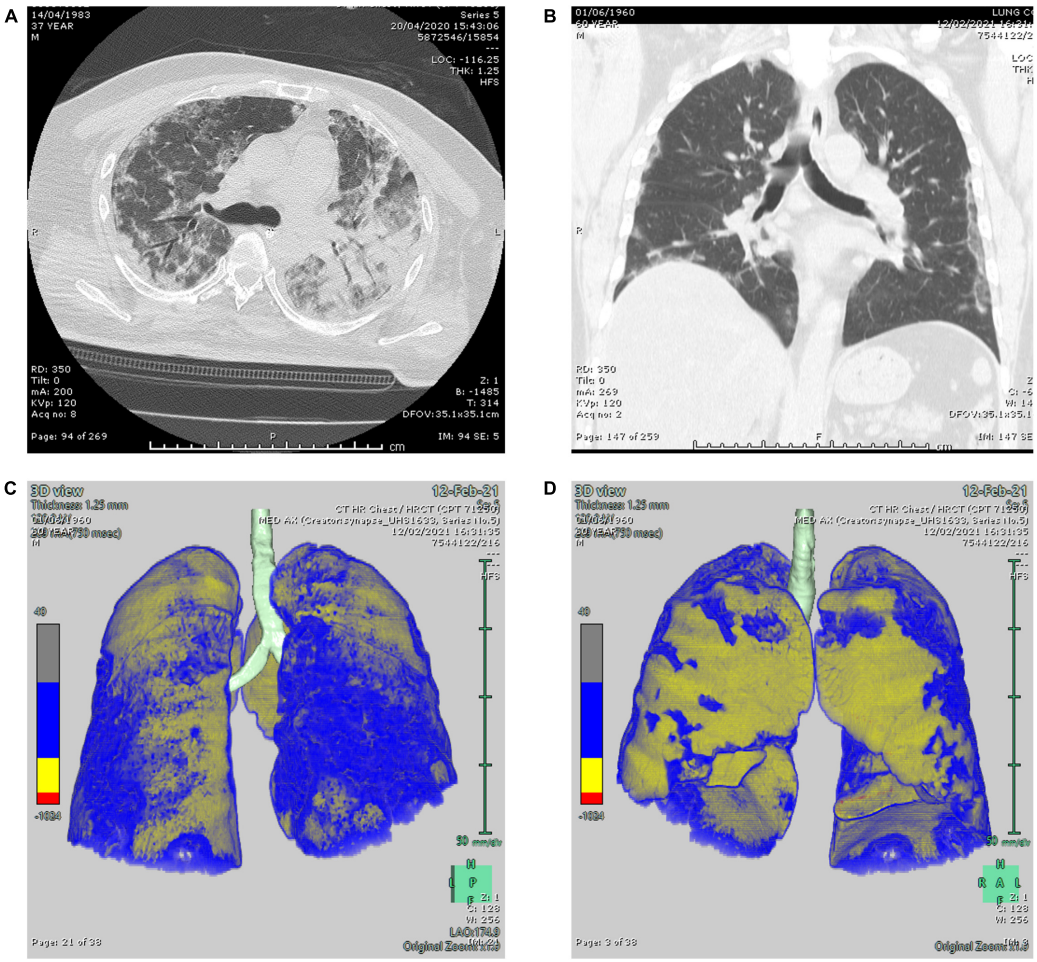

FIGURE 4
Two representative computed tomography (CT) lung window images. **(A)** Axial and **(B)** coronal lung window CT images showing bilateral scattered ground-glass attenuation opacities with an area of pneumonic consolidation at the left lower lobe (CO-RADS 5). **(C,D)** 3D reconstructed images of the lungs showing bilateral subpleural ground-glass attenuation opacities (CO-RADS 5) with 27.6% parenchymal high attenuation areas in both lungs (calculation performed on Fujifilm Synapse 4D PACS dedicated application).

classification of COVID-19 patients according to the severity of the disease or CO-RADS, there was a decrease in the number of patients showing hypogranular neutrophilic cytoplasm, which could be a sign of pulmonary deterioration. On the contrary, a study by Gabr et al. reported that the abundance of peripheral morphological abnormalities was significantly associated with unfavorable clinical outcomes in COVID-19 patients (17).

A plethora of abnormalities associated with RBCs was previously described in COVID-19 patients (19, 20). Morphological changes in COVID-19 patients were detected, along with a comparison between stable and critical cases. There was a significant decrease in the percentage of COVID-19 patients in the critical group with microcytic and hypochromic RBCs, along with a significant increase in the percentage of patients with normocytic and normochromic RBCs. A similar pattern was observed in the classification of COVID-19 according to CO-RADS. Additionally, there was a concomitant decrease in hemoglobin concentration in stable COVID-19 patients (11.4 ± 2.3) compared to critical (12.2 ± 2.0) cases. Hence, this could be attributed to other factors such as ferritin

TABLE 5 Radiological assessment of COVID-19 patients using the CO-RADS.

	Frequency (*n*)	Percent (%)
CO-RADS 1	17	13.2
CO-RADS 2	6	4.7
CO-RADS 3	4	3.1
CO-RADS 4	3	2.3
CO-RADS 5	99	76.7
Presence of acute respiratory distress syndrome	18	13.8

TABLE 6 Count and morphological changes in WBCs, platelets, and RBCs between stable and critical COVID-19 patient groups.

	Stable (n = 48)		Critical (n = 83)		
	Frequency	Percentage	Frequency	Percentage	P-value
WBC changes					
Leucocytosis	2	4.2	2	2.4	0.2867
Leukopenia	2	4.2	2	2.4	0.2867
Neutrophils changes					
Neutrophilia	5	10.4	14	16.9	0.1562
Neutropenia	1	2.1	1	1.2	0.3464
Pseudo-Pelger-Huët	11	22.9	22	26.5	0.3242
Bands	11	22.9	23	27.7	0.2732
Long nuclear endoplasm	10	20.8	23	27.7	0.1911
Fetus shaped nucleus	9	18.8	21	25.3	0.195
Macroganular neutrophil cytoplasm	5	10.4	7	8.4	0.3523
Karyorrehxis neutrophils	0	0.0	3	3.6	0.0913
Drumstick nucleus	1	2.1	1	1.2	0.3464
Hypoganular neutrophil cytoplasm	19	39.6	29	34.9	0.2975
Lymphocyte changes					
Lymphocytosis	1	2.1	1	1.2	0.3464
Lymphopenia	10	20.8	16	19.3	0.4148
Atypical lymphocytes	39	81.3	66	79.5	0.4054
Granular lymphocyte cytoplasm	3	6.3	2	2.4	0.1345
Basophilic cytoplasm lymphocytes	2	4.2	4	4.8	0.4317
Plasmacytoid lymphocytes	0	0.0	0	0.0	–
Monocyte changes					
Monocytosis	2	4.2	2	2.4	0.2867
Monocytes with vacuoles	24	50.0	48	57.8	0.1927
Platelets changes					
Platelets thrombocytosis	10	20.8	7	8.4	0.0209*
Platelets thrombocytopenia	5	10.4	10	12.0	0.3888
RBCs changes					
Normocytic RBCs	19	39.6	47	56.6	0.0301*
Normochromic RBCs	11	22.9	33	39.8	0.0246*
Erthrocytopenia	13	27.1	22	26.5	0.4713
Polycythemia	5	10.4	5	6.0	0.1808
Normoblasts	1	2.1	3	3.6	0.3118
Polychromasia	1	2.1	4	4.8	0.2155
Microcytic RBCs	18	37.5	16	19.3	0.0109*
Macrocytic RBCs	1	2.1	1	1.2	0.3464
Hypochromic RBCs	26	54.2	29	34.9	0.0158*
Rouleaux RBCs	9	18.8	14	16.9	0.3925
Anisocytosis	20	41.7	45	54.2	0.0831
Targetoid	18	37.5	29	34.9	0.3842
Stomatocytes	12	25.0	12	14.5	0.0664
Mushroom RBCs	9	18.8	12	14.5	0.2594
Acanthocytes/Spur	7	14.6	17	20.5	0.2002
Ovalocytes	14	29.2	21	25.3	0.315
Dacryocytes	18	37.5	24	28.9	0.1552
Schistocytes	14	29.2	19	22.9	0.2127
Echinocytes/Burr cells	9	18.8	25	30.1	0.0763
Bite cells	12	25.0	16	19.3	0.2207

*$p < 0.05$, significant results.

TABLE 7 Count and morphological changes in WBCs, platelets, and RBCs between COVID-19 patients with CO-RADS 5 and other CO-RADS.

	CO-RADS 5 (n = 99)		Other CO-RADS (n = 30)		
	Frequency	Percentage	Frequency	Percentage	P-value
WBC changes					
Leucocytosis	3	3.0	1	3.3	0.4666
Leukopenia	2	2.0	2	6.7	0.0992
Neutrophils changes					
Neutrophilia	16	16.2	3	10.0	0.2021
Neutropenia	1	1.0	1	3.3	0.1834
Pseudo-Pelger-Huët	27	27.3	6	20.0	0.2119
Bands	27	27.3	6	20.0	0.2119
Long nuclear endoplasm	26	26.3	7	23.3	0.3737
Fetus shaped nucleus	24	24.2	6	20.0	0.315
Macroganular neutrophil cytoplasm	8	8.1	4	13.3	0.1928
Karyorrehxis neutrophils	3	3.0	0	0.0	0.1673
Drumstick nucleus	1	1.0	1	3.3	0.1834
Hypogranular neutrophil cytoplasm	33	33.3	15	50.0	0.049*
Lymphocyte changes					
Lymphocytosis	2	2.0	0	0.0	0.2163
Lymphopenia	17	17.2	9	30.0	0.0625
Atypical lymphocytes	78	78.8	25	83.3	0.2933
Granular lymphocyte cytoplasm	3	3.0	2	6.7	0.183
Basophilic cytoplasm lymphocytes	4	4.0	1	3.3	0.4302
Plasmacytoid lymphocytes	0	0.0	0	0.0	–
Monocyte changes					
Monocytosis	2	2.0	2	6.7	0.0992
Monocytes with vacuoles	56	56.6	15	50.0	0.2633
Platelets changes					
Platelets' thrombocytosis	11	11.1	5	16.7	0.2093
Platelets' thrombocytopenia	11	11.1	4	13.3	0.3697
RBCs changes					
Normocytic RBCs	54	54.5	11	36.7	0.0431*
Normochromic RBCs	38	38.4	5	16.7	0.0135*
Erthrocytopenia	24	24.2	10	33.3	0.161
Polycythemia	7	7.1	3	10.0	0.2996
Normoblasts	3	3.0	1	3.3	0.4666
Polychromasia	3	3.0	2	6.7	0.183
Microcytic RBCs	23	23.2	10	33.3	0.1333
Macrocytic RBCs	2	2.0	0	0.0	0.2163
Hypochromic RBCs	38	38.4	16	53.3	0.073
Rouleaux RBCs	16	16.2	7	23.3	0.1843
Anisocytosis	49	49.5	15	50.0	0.4807
Targetoid	35	35.4	11	36.7	0.4477
Stomatocytes	17	17.2	6	20.0	0.3615
Mushroom RBCs	14	14.1	7	23.3	0.1161
Acanthocytes/Spur	16	16.2	8	26.7	0.0976
Ovalocytes	21	21.2	12	40.0	0.0194*
Dacryocytes	28	28.3	13	43.3	0.0605
Schistocytes	24	24.2	9	30.0	0.2633
Echinocytes/Burr cells	27	27.3	7	23.3	0.3339
Bite cells	21	21.2	7	23.3	0.4025

*$p < 0.05$, significant results.

TABLE 8 Count and morphological changes in WBCs, platelets, and RBCs between male and female COVID-19 patients.

	Male (n = 63)		Female (n = 68)		
	Frequency	Percentage	Frequency	Percentage	P-value
WBC changes					
Leucocytosis	1	1.6	3	4.4	0.2032
Leukopenia	2	3.2	2	2.9	0.3906
Neutrophils changes					
Neutrophilia	13	20.6	6	8.8	0.074
Neutropenia	0	0.0	2	2.9	0.1249
Pseudo-Pelger-Huët	15	23.8	18	26.5	0.4562
Bands	17	27.0	17	25.0	0.3125
Long nuclear endoplasm	17	27.0	16	23.5	0.2271
Fetus shaped nucleus	13	20.6	17	25.0	0.4025
Macroganular neutrophil cytoplasm	6	9.5	6	8.8	0.438
Karyorrehxis neutrophils	1	1.6	2	2.9	0.1903
Drumstick nucleus	0	0.0	2	2.9	0.1249
Hypoganular neutrophil cytoplasm	23	36.5	25	36.8	0.3703
Lymphocyte changes					
Lymphocytosis	0	0.0	2	2.9	0.1249
Lymphopenia	16	25.4	10	14.7	0.2869
Atypical lymphocytes	52	82.5	53	77.9	0.4305
Granular lymphocyte cytoplasm	2	3.2	3	4.4	0.2195
Basophilic cytoplasm lymphocytes	3	4.8	3	4.4	0.4405
Plasmacytoid lymphocytes	0	0.0	0	0.0	–
Monocyte changes					
Monocytosis	1	1.6	3	4.4	0.2032
Monocytes with vacuoles	38	60.3	34	50.0	0.1391
Platelets changes					
Platelets' thrombocytosis	7	11.1	10	14.7	0.0794
Platelets' thrombocytopenia	9	14.3	6	8.8	0.2715
RBCs changes					
Normocytic RBCs	33	52.4	33	48.5	0.0903
Normochromic RBCs	28	44.4	16	23.5	0.0093*
Erthrocytopenia	15	23.8	20	29.4	0.347
Polycythemia	6	9.5	4	5.9	0.438
Normoblasts	1	1.6	3	4.4	0.4228
Polychromasia	4	6.3	1	1.5	0.1415
Microcytic RBCs	16	25.4	18	26.5	0.0853
Macrocytic RBCs	2	3.2	0	0.0	0.3627
Hypochromic RBCs	19	30.2	36	52.9	0.0054*
Rouleaux RBCs	13	20.6	10	14.7	0.4025
Anisocytosis	27	42.9	38	55.9	0.45
Targetoid	20	31.7	27	39.7	0.2634
Stomatocytes	9	14.3	15	22.1	0.0767
Mushroom RBCs	11	17.5	10	14.7	0.4305
Acanthocytes/Spur	16	25.4	8	11.8	0.0819
Ovalocytes	21	33.3	14	20.6	0.3199
Dacryocytes	22	34.9	20	29.4	0.3896
Schistocytes	18	28.6	15	22.1	0.4727
Echinocytes/Burr cells	18	28.6	16	23.5	0.1161
Bite cells	13	20.6	15	22.1	0.2927

*$p < 0.05$, significant results.

concentration or other underlying chronic diseases in such patients. Further, such findings suggest that anemia could be linked to inflammation, a known manifestation of COVID-19 infection. This was further confirmed with a higher percentage of female COVID-19 patients presenting hypochromic RBCs, which supports previous findings by Bergamaschi et al. (21).

Conclusion

To our knowledge, this is the first study in the UAE describing the morphological changes in the peripheral blood smears of COVID-19 patients and their association with disease severity. Peripheral blood smear assessment at the time of diagnosis in COVID-19 patients could provide information about the disease state and pulmonary involvement. One of the limitations of this study is the lack of information about the recruited patients' mortality and the lack of peripheral smears of healthy controls for comparative investigation. Also, another limitation of this study is the lack of functional analysis of the aforementioned peripheral blood cells (including oxygen-carrying capacity of RBCs, ROS generation by leukocytes and immunoglobulin production by lymphocytes, phagocytosis capacity of macrophages/monocytes and leukocytes), that should be explored in future studies to further understand their role in the fight against SARS-CoV-2. Additionally, future studies could explore the association between antibody titers against SARS-CoV-2 proteins and hematological abnormalities that will aid in understanding the effect of infection and vaccinations on various blood cells.

Data availability statement

The original contributions presented in this study are included in this article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics and Research Committee of University Hospital Sharjah in June 2020 (UHS-HERC-035-03052020). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

NE and IT designed the study, analyzed, interpreted the results, and wrote the original draft. FB interpreted the slides of the peripheral blood smears. RG assessed the radiological imaging of the patients. DZ, AAl, NA, AH, FA, AE, AAh, and SA recruited and collected the data of the patients. RB designed the study. FB, RG, and RB reviewed the manuscript. All authors read and approved the final manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Case report: A rare case of Rosai–Dorfman–Destombes disease after the COVID-19 infection

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Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is known to cause immune dysregulation and, therefore, has varied and often rare presentations. Rosai–Dorfman–Destombes disease (RDD) is an unusual non-Langerhans cell (non-LC) histiocytosis presenting with massive lymphadenopathy and various systemic symptoms. A 55-year-old Asian-American woman with no significant medical history or recent use of new drugs initially presented with cervical lymphadenopathy and urticarial rash 1 week after receiving the COVID-19 messenger RNA (mRNA) vaccine (Moderna, mRNA-1273) against SARS-CoV-2. The biopsy of the skin rash was consistent with a drug reaction. Approximately 2 months later, she developed mild flu-like symptoms and was diagnosed with a COVID-19 infection. Her symptoms were mild and self-resolving. Approximately 3 months later, she developed a generalized patchy erythematous rash on the face and the body that gradually worsened; diffuse lymphadenopathy involving the bilateral cervical, axillary, and inguinal areas; and constitutional symptoms. Laboratory results were consistent with lymphopenia, anemia, and an elevated sedimentation rate. Supraclavicular lymph node biopsy showed Rosai–Dorfman disease with a marked polyclonal plasmacytosis. She was started on a tapering dose of corticosteroids and showed clinical improvements over the next few weeks. Herein, we present a rare case of a histiocytic disorder that developed after contracting the SARS-COV2 infection in the event of receiving a recent mRNA COVID vaccination.

KEYWORDS

COVID-19, COVID-19 vaccination, Rosai–Dorfman disease, sinus histiocytosis with massive lymphadenopathy, Moderna vaccine

Introduction

Rosai–Dorfman–Destombes disease (RDD) is a rare systemic macrophage-related disorder characterized by sinus histiocytosis and massive lymphadenopathy (1). The etiology of RDD is not fully understood and varies across the spectrum of phenotypes (2).

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a virus that has caused an outbreak of the illness Coronavirus disease 2019 (COVID-19), which has been declared a public health emergency by the World Health Organization (WHO), an agency of the United Nations responsible for international public health (3). In individuals infected with COVID-19, there is a dysregulation of the adaptive immune response that leads to a cytokine storm and widespread multi-organ involvement (4). A recent case report described a sinus histiocytosis with massive lymphadenopathy (Rosai–Dorfman disease) that developed after contracting a COVID-19 infection (5).

Messenger RNA (mRNA) vaccines against SARS-CoV-2 have been widely used, and several case reports of patients with vaccination-induced lymphadenitis have been published. In a retrospective study, unilateral lymphadenopathy was identified at the vaccination site in about 44% of patients after they received the COVID-19 vaccination with the aid of imaging studies, and persistent lymphadenopathy was observed at 43 weeks after vaccination (6). We identified a case report of the development of cutaneous RDD after 10 days of receiving Pfizer vaccination against COVID-19 (7). A few cases of histiocytic necrotizing lymphadenitis after vaccination against COVID-19 have been reported in the literature (8). Another case of Langerhans cell (LC) hyperplasia associated with the COVID-19 mRNA vaccine has also been reported (9). Here, we present a rare, biopsy-confirmed case of RDD after receiving the COVID-19 mRNA vaccine and then contracting a COVID-19 infection.

Case report

Our patient is a 55-year-old woman of Chinese descent with no known medical history who initially presented to the office with chief complaints of painless swelling in the left side of the neck and a generalized rash persisting for the past 1 month. She is a lifetime non-smoker, has never abused alcohol, and has never used illicit drugs. No recent prescription or over-the-counter (OTC) drug or herbal supplement was used. Her only distant medical history was infectious mononucleosis at 24 years of age. She has a history of allergic reactions to cefaclor and reported developing an itchy rash. The patient reported to be healthy until she received her COVID-19 vaccine booster shot with Moderna's mRNA vaccination (mRNA-1273) against SARS-CoV-2 on the left arm. Prior vaccination history was uneventful. Approximately 4 days after the vaccination, she developed left arm pain and swelling at the site of injection. Approximately 1 week later, she developed swelling on the left side of the neck, and 2 weeks later, she developed a diffuse urticarial rash. She underwent a skin biopsy of a rash about a month later since presentation in the left mid-back that showed a perivascular cell infiltrate with eosinophils consistent with a drug reaction. Blood work performed on the same date showed a white blood cell (WBC) count of 2.5×10^9/L, a hemoglobin level of 10.9 g/L, and a platelet count of 296,000/mm^3. Absolute lymphocyte count (ALC) was 1.79×10^9/L, absolute neutrophil count (ANC) was 0.54×10^9/L, MCV was 71 femtoliter, red blood cell (RBC) count was 5.04×10^9/L, and red cell distribution width (RDW) was 15.8%. Her comprehensive metabolic panel was within normal limits. Approximately 15 days later, after the biopsy, she developed a fever and mild cough and was tested positive for SARS-COV-19; however, her symptoms resolved completely within a few days. Repeat blood work done a month later since contracting COVID-19 was also consistent with bi-cytopenia with a hemoglobin level of 9.6 g/L and a WBC count of 1.8×10^9/L with ANC of 1.16 and ALC of 0.40×10^9/L. Liver transaminases were mildly elevated to alanine transaminase/aspartate transaminase (ALT/AST) of 49/59 units/L. Iron studies were within normal limits. Approximately 3 months later, after her COVID-19 infection, she presented again with a painless rash on her face, mainly in the nose and around the mouth and the chin, extending to the upper chest area. She reported worsening of her cervical lymphadenopathy and progressively worsening of lymphadenopathy in the neck, the axilla, and the groin and also developed a rash that progressed to involve the extremities and the back. She also described constitutional symptoms including fatigue and a weight loss of 4 kg over the last 3 months. She declined experiencing fever, chills, or significant night sweats. On physical examination, vitals were within normal limits except for tachycardia of 102 beats/min. Head and neck examination showed a patchy erythematous plaque-like rash on the face and around the nose, the perioral area, and the chin, extending to involve the upper chest and the arms. A patchy erythematous plaque-like rash was also observed in the back and the upper extremities, as shown in Figure 1. Lymph node examination showed diffuse adenopathy of the bilateral cervical area (levels I to V) more in the left than the right with a maximum size of 2×2 cm, palpable lymph nodes in bilateral axillae with a maximum size of 3×2 cm more in the left than in the right, and lymph nodes palpable in the bilateral inguinal area. Lymph nodes were soft in consistency and mildly tender. The rest of the examination was within normal limits. Further tests were performed, which showed a WBC count of 2.3×10^9/L (ANC of 1.66×10^9/L, ALC of 0.340×10^9/L, absolute monocyte count of 0.22×10^9/L, and absolute eosinophil count of 0.7×10^9/L), a hemoglobin level of 9 (MCV 75 femtoliter), and an erythrocyte sedimentation rate (ESR) of 46 mm. The chest x-ray was within normal limits. Cytomegalovirus (CMV) IgM and IgG antibodies were positive, Epstein–Barr virus (EBV) IgM antibody was negative, IgG was positive, the hepatitis panel (both B and C) was negative except Hep A IgG, which was positive, and rapid plasma reagin (RPR) was negative. Complement C3 was decreased to 49, and complement C4 was also decreased to 4 mg/dl, and total complement CH50 was <10 units/ml. ANA was positive, ANA titer was 1 to 320, and

an ANA pattern of homogeneous and double-stranded DNA antibodies was negative. QuantiFERON TB was indeterminate. Histoplasma antibodies were negative, and toxoplasmosis IgG antibodies were negative. A computed tomography (CT) scan of the neck 1 month later showed extensive bilateral levels of 1–4 lymphadenopathy, the largest of which was the left base of neck level IV, which was approximately 3 × 2.7 × 2.0 cm. A CT scan of the chest with contrast showed bilateral axillary lymphadenopathy. The largest one on the right axilla was 2.6 ×1.2 cm. The largest one on the left axilla was 2.7 ×1.3 cm. There is no mediastinal or hilar lymphadenopathy. There is no pulmonary nodule or mass. She subsequently underwent a left supraclavicular lymph node biopsy. A supraclavicular lymph node biopsy showed atypical interfollicular B-cell proliferation associated with Rosai–Dorfman disease and a marked polyclonal plasmacytosis, as shown in Figure 2. Flow cytometry showed polyclonal B-cells, and T cells demonstrated no pan-T-cell antigen loss. Polymerase chain reaction (PCR) performed for Ig and T-cell receptor (TCR) gamma gene rearrangement showed a clonal rearrangement for Ig and a polyclonal pattern for TCR gamma.

Treatment was initiated with methylprednisolone at a dose of 24 mg a day, which was slowly tapered down over 3 weeks to 8 mg daily. The patient showed clinical improvements, her skin rash improved, and her lymphadenopathy clinically improved by 80%. She also reported improvements in fatigue and exercise tolerance and then continued on a slow taper of steroids over the next 3 weeks. After 2 months of taking steroids, the patient reported a complete resolution of her symptoms.

Discussion

Rosai–Dorfman–Destombes disease is a rare histiocytic disorder named after Juan Rosai and Ronald Dorfman who analyzed 34 cases under the name sinus histiocytosis with massive lymphadenopathy in 1969 but was first described in 1965 by the French pathologist Pierre Paul Louis Lucien Destombes (2). It is a non-Langerhans cell histiocytosis (LCH) characterized by the accumulation of activated histiocytes within the affected tissues and is associated with a wide clinical spectrum of presentation. It can occur as an isolated disorder or in association with autoimmune, hereditary, and malignant diseases (2). Most patients present with bilateral, massive, and painless cervical lymphadenopathy with or without systemic symptoms. Other lymph nodes that can be involved are mediastinal, axillary, inguinal, and rarely retroperitoneal lymph nodes (10). In our case report, the patient had bilateral cervical, axillary, and inguinal lymphadenopathy associated with fatigue and weight loss. The skin may be involved in 10% of cases, and lesions can be variable but are usually described as painless, non-pruritic nodules, plaques, or erythematous papules that have a coloration varying from yellow to red to brown (11). Our patient had a patchy erythematous rash on the face, around the nose, and on the periorbital area. Other sites of involvement are extranodal, including the central nervous system, the head and the neck, the ophthalmic, intrathoracic, retroperitoneal, genitourinary, gastrointestinal sites, and the bone. Hematological studies may reveal an elevated ESR, normochromic normocytic anemia, leukocytosis (typically neutrophilia), thrombocytopenia, and eosinophilia, although bone marrow infiltration is rare (2). In the abovementioned case report, the patient had microcytic anemia and leucopenia, which are not seen in classically described RDD. The lab results, however, were consistent with an elevated ESR. Her laboratory findings could be explained by the recent COVID-19 infection (12).

The immunophenotype of RDD histiocytes is characterized by cytoplasmic and nuclear S100, fascin, and CD68 positivity. In contrast to LCH, the cells are CD1a-and CD207 negative (13). In the present case report, the patient's cervical node biopsy histopathology was consistent with polytypic plasmacytosis, which is usually observed with RDD. The histopathology was also consistent with the areas of fibrosis rich in S100-positive cells that show evidence of emperipolesis consistent with RDD. IgG4 diseases are often difficult to distinguish from RDD, especially when the hallmark features such as emperipolesis may not be seen in RDD and when obliterative phlebitis and storiform fibrosis might not be abundant in IgG4 diseases. However, in this case, the pathological features of the specimen were diagnostic, and IgG4-positive cells, although increased, are insufficient, neither in their absolute number nor as a percentage, for a diagnosis of IgG4 diseases. In addition, there is also an increase in IgM-positive cells that are more suggestive of hypergammaglobulinemia (14).

Treatment differs depending on the involvement of nodal areas and symptoms. The disease can be self-limiting but can take many months to years for spontaneous resolution, as reported in 20–50% of patients with nodal/cutaneous disease (15). The response to corticosteroids varies, although they have helped in reducing nodal size and symptoms. Other therapies in patients refractory to steroids include immunosuppressants like sirolimus, chemotherapy with cladribine, methotrexate, vinca alkaloids, immunomodulatory agents like thalidomide, lenalidomide, rituximab, and imatinib, and enrollment in clinical trials (2). Immunomodulatory agents have been explored in the treatment of cutaneous RDD. In a recent case report, a patient who developed cutaneous RDD after receiving an mRNA vaccine was successfully treated for 6 months with thalidomide (7). The National Comprehensive Cancer Network (NCCN) guidelines recommend thalidomide as an option for cutaneous RDD (16). According to a few case reports, lenalidomide has a similar response rate and is more tolerable than thalidomide (17, 18). The optimal duration of steroids or other systemic therapies

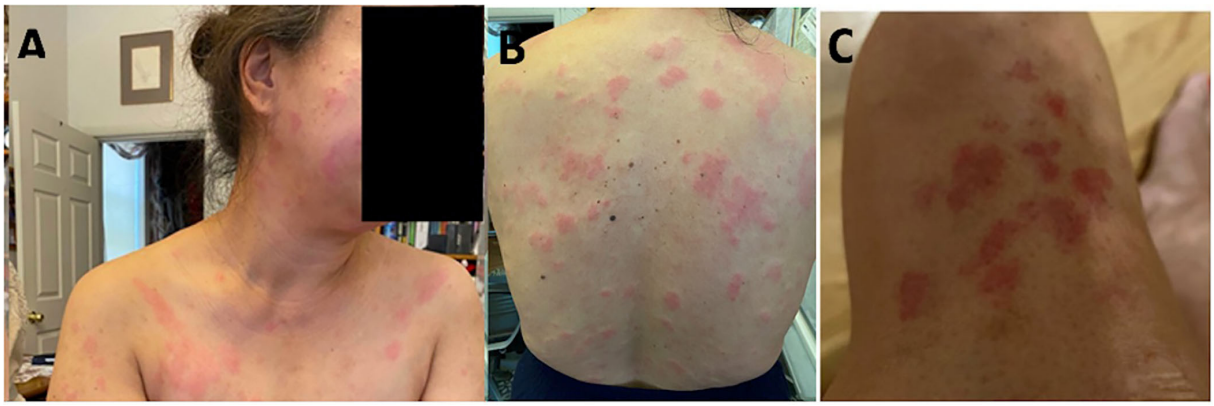

FIGURE 1
Illustration of a patchy erythematous plaque-like rash on the face **(A)** and an erythematous plaque-like rash on the body **(B,C)**.

is not determined, although some clinicians recommend 6–12 months of systemic therapy followed by observation as a reasonable approach (2).

Targeted therapies have also been studied. An activating BRAF V600E mutation is seen in 38–64% of LCH and Erdheim–Chester disease (ECD) cases and more frequently in mixed LCH/ECD (16). In RDD, however, no single dominant mutation has been found, though Kirsten rat sarcoma virus (KRAS) and MAP2K1 mutations have been described in 33% of cases of Rosai–Dorfman disease (3, 19). A published case report of a patient with RDD and a *KRAS* mutation responded well to targeted therapy with cobimetinib (20). A phase II trial evaluating the MEK inhibitor cobimetinib, which included 18 adult patients diagnosed with a histiocytic neoplasm (only two with RDD), demonstrated an overall response rate of 89% with a complete response in 72% of patients. After a follow-up of 11.9 months, the median progression-free survival was not reached. The most common adverse events were a decrease in ejection fraction (27.8%), rash (11.1%), and diarrhea (11.1%) (21). Our patient, as mentioned, had an excellent response to corticosteroids within 3 weeks of treatment initiation.

The Coronavirus disease 2019 infection is a world pandemic, and the spectrum of disease manifestations ranges from asymptomatic disease with mild respiratory tract illness to severe pneumonia, acute respiratory distress syndrome (ARDS), multi-organ failure, and death (22). Various rare manifestations and associations of the disease have been reported in various case reports. So far, only one published case report has depicted an association between RDD and COVID-19. The mechanism of action was hypothesized to be an altered immune response and a cytokine storm caused by interferon dysregulation (5). Another case report describing an LCH presenting as a post-COVID-19 multisystem inflammatory syndrome was published (23). Histiocytic disorders, in particular hemophagocytic lymphohistiocytosis have been postulated as an etiology for triggering cytokine storm in patients with severe COVID-19 and both these diseases demonstrate clinical similarities (24, 25).

Various studies on lymph node autopsy reports have shown the histopathological appearance of decreased total lymphocytes with the absence of germinal centers (26), increased reactive plasmablasts in the interfollicular zone, histiocytic hyperplasia with hemophagocytosis (26, 27), and, in rare cases, necrotizing granulomas (28). Cutaneous manifestations have been described in up to 20% of patients with COVID-19, including erythematous rash, widespread urticaria, varicella-like rash, and purpura (29). Histopathologic examinations of skin biopsies revealed a superficial and deep perivascular infiltrate of lymphocytes or neutrophils, with some eosinophils or plasma cells (29). Endothelial cell injury and thrombotic vasculopathy with fibrinoid or inflammatory thrombi are the most frequent dermal vascular lesions (30).

Widespread vaccination against SARS-CoV-2 has been considered the most promising approach to curbing the pandemic. mRNA vaccines have been widely used and show a high degree of immunogenicity, a high safety profile, and high efficacy in inducing immune responses against SARS-CoV-2 (3). Multiple case reports of patients with vaccination-induced lymphadenitis after COVID-19 vaccination have been published, as described in a systematic review (31). Though most of the studies have shown ipsilateral axillary lymphadenopathy as the site of injection, a few case reports have been published to suggest cervical lymphadenopathy after vaccination (32, 33). Reports of lymphadenopathy are more common in those receiving the Moderna vaccine compared to the placebo and typically occur 2–4 days after vaccination (34).

Histopathologically, in these lymph nodes, there will be an expansion of the paracortex with abundant T cells, B cells,

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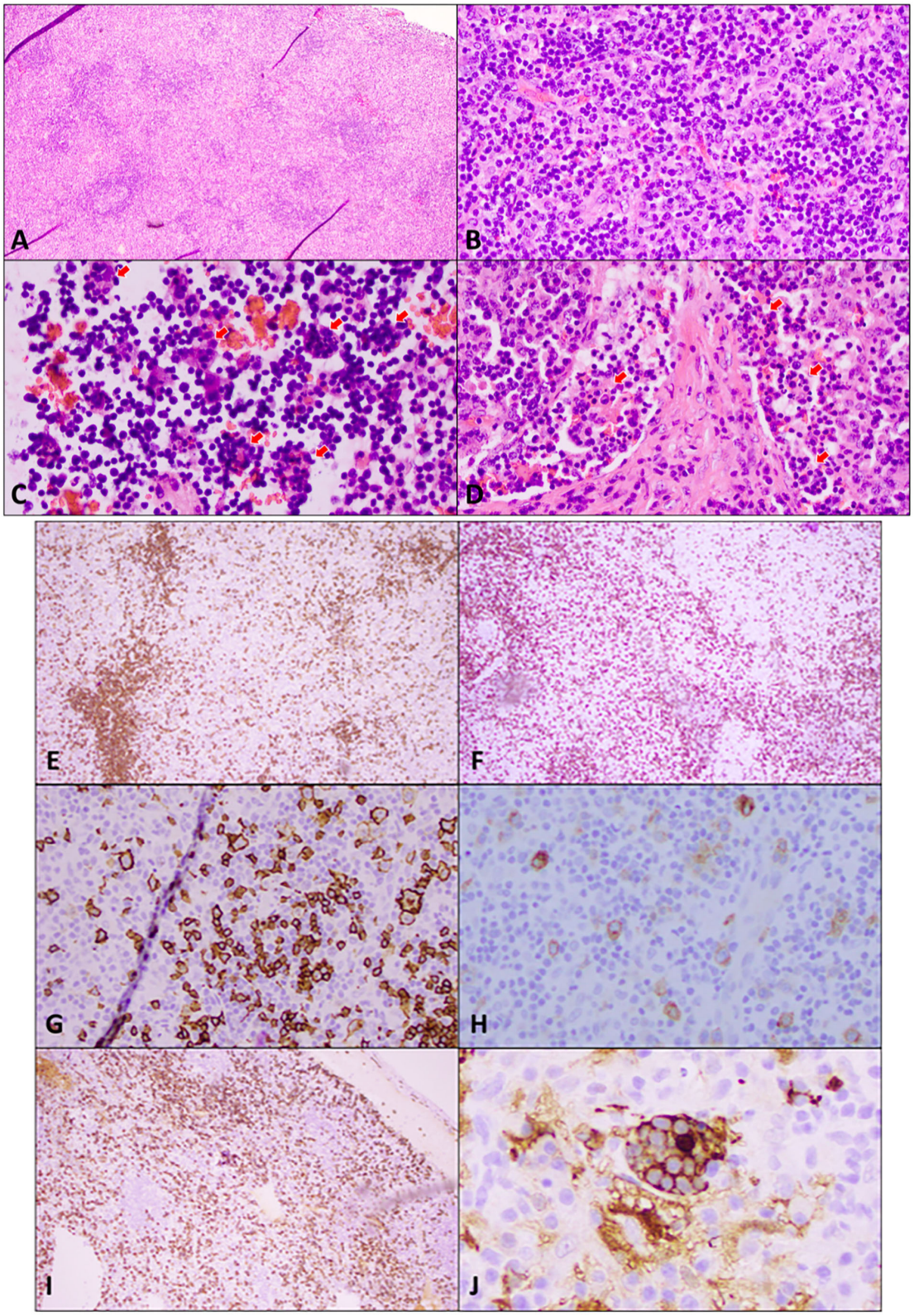

FIGURE 2
Excisional biopsy of an enlarged supraclavicular lymph node. **(A)** Hematoxylin and eosin (H&E) staining at low power (4×) shows widely spaced reactive follicles with a prominent paracortex expansion. **(B)** H&E medium power (20×) view demonstrates a mixed small and large atypical lymphocytic infiltrate in the paracortex against the background of abundant plasma cells, immunoblasts, and histiocytes. **(C)** H&E high power

(Continued)

FIGURE 2 (Continued)
(40×) view of cells in sinuses shows numerous histocytes with vacuolated nuclei and abundant cytoplasm engulfing lymphocytes and other cells in a process termed emperipolesis (red arrows). **(D)** H&E high power (40×) view of the stain demonstrates emperipolesis (red arrows) in sinuses with adjacent areas of fibrosis. Immunohistochemical studies: **(E)** A low power (10×) view of CD20 immunostaining shows disrupted reactive follicles and scattered large atypical B-lymphocytes. **(F)** A lower power (10×) view of CD3 immunostaining highlights the admixed paracortical T-cells. **(G)** A medium power (20×) view of the CD20 immunostaining is positive in atypical lymphocytes. PAX 5 also stains the large atypical cells (not shown). **(H)** CD30 immunostaining (20× power) highlights the large atypical lymphocytes in interfollicular areas, which were negative for CD15 (not shown). This makes Hodgkin's lymphoma unlikely. **(I)** CD138 immunostaining (10×) demonstrates the presence of abundant plasma cells, which are also positive for CD79a, MUM1 with polyclonal kappa, or lambda by *in situ* hybridization (not shown). Plasma cells are often associated with Rosai–Dorfman disease. **(J)** Areas of emperipolesis are better demonstrated with S100 stain (high power, 60×), which highlights histiocytes with an abundant cytoplasm that have engulfed lymphocytes and other cells (emperipolesis). Engulfed cells do not stain but are outlined by S100 staining when engulfed.

immunoblasts, and plasma cells with increased vascularity, which are similar to those seen with acute viral infections or angioimmunoblastic T-cell lymphoma (35). The detection of clonal B-cell IgH gene rearrangements in the abovementioned patient's lymph node may be related to the patient's exposure to viruses or COVID-19 vaccination.

Enlarged lymph nodes after the COVID-19 vaccine may be mistaken for malignancy, necessitating unnecessary biopsies. However, in patients with associated systemic symptoms, skin manifestations, and progressive diffuse lymphadenopathy, it is imperative to perform a biopsy for a definitive diagnosis and further management. Also, variable cutaneous reactions, including a delayed urticarial rash after receiving mRNA vaccines against COVID-19, have been reported, and most of them are mainly self-limited (36).

In our case report, the patient initially developed cervical lymphadenopathy and urticarial rash 1 week after receiving the mRNA COVID-19 vaccination. A few months after contracting mild respiratory symptoms from COVID-19, the patient developed progressive bilateral cervical, axillary, and inguinal lymphadenopathy associated with fatigue, weight loss, and an erythematous rash on the face, the extremities, and the back.

Conclusion

In conclusion, the pathophysiology of COVID-19 disease and its association with rare histiocytic disease is incompletely understood but can be hypothesized as immune dysregulation associated with the infection. Recently, a few case reports are evolving suggesting associations between contracting SARS-CoV-2 virus and development of histiocytic disorders with varied presentations. Herein, as described we present a rare case of histiocytic disorder Rosai-Dorfman-Destombes disease manifesting months after receiving mRNA vaccine and further after contracting COVID-19 infection.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

PG and YH: concept and design. PG, FT, and YH: data acquisition. PG, JC-G, NC, and YH: drafted the article. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Effects of ABO blood groups and RH-factor on COVID-19 transmission, course and outcome: A review

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ABO and Rh blood grouping systems are two of the non-modifiable risk factors that play an important role in the susceptibility, severity and outcomes of COVID-19 infection. This review explores these associations all over the world, in an attempt to conclude a clear idea for future reference in clinical practice. In the present review, a link has been drawn between blood groups and COVID-19 transmission, course and prognosis, as literature suggests that blood group O plays a protective role against the infection, while blood group A exhibits a higher risk of exacerbation. In contrast with Rh negative individuals, Rh positive individuals are prone to more severe infection and complications, despite the fact that the underlying mechanisms of this association remain understudied. Nevertheless, the connection remains subject to controversy; since some studies report doubts about it. Thus, this association requires further investigation.

KEYWORDS

ABO blood groups, COVID-19, hematology, RH factor, SARS-CoV-2

1. Introduction

Coronavirus disease 2019 (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in late December 2019, causing a global pandemic as declared by World Health Organization in March 2020 (1). Since then, evidence from medical research is growing regarding the risk factors that may increase the susceptibility, morbidity and mortality of the infection which could help decrease the burden of this crisis on medical services and guide public health recommendations and interventions.

One of these risk factors is the ABO blood group system, which is considered an inheritable and a non-modifiable risk factor. The ABO system is one of the most important systems among 33 other blood group systems listed by the international

society of blood transfusion, dividing blood into four groups: A, B, AB, and O (2). Blood groups are determined by carbohydrates present on the surface of red blood cells (RBCs), giving them the ability to act as receptors for different microorganisms and toxins (3). The first suggestion of a link between ABO blood group and clinical COVID-19 manifestations was reported by Zhao et al. (4). From then on, many studies tackled this association (5). Moreover, the Rhesus (RH) factor which is another RBC surface protein is suspected to have a role in the COVID-19 infection (6). As a consequence, to the aforementioned data, several hypotheses have been suggested in a trial to explain the underlying mechanisms behind this association.

This work aims at reviewing available research that investigated the correlation between ABO blood groups and RH factor with transmission, course, and outcome of COVID-19 infection. A brief worldwide overview of studies handling this topic was introduced, and the mechanisms by which this effect is exerted are described.

2. Method

In this research, we collected the most relevant papers to our chosen title and keywords. Search was conducted through major platforms like "Scopus", "Google Scholar", "Cochrane library", and "PubMed" using the following keywords: "ABO blood group", "blood groups", "COVID-19", and "SARS-CoV-2" and combinations between them. The search was conducted between 13 and 25th of August, 2022.

Our eligibility criteria are (A) Studies that investigated the relationship between COVID-19 and ABO blood groups, (B) Studies that investigated the relationship between COVID-19 and RH factors. (C) Studies published in international peer-reviewed journals and (D) English language-only. We excluded animal studies, studies writer in languages other than English, and commentary articles. Later and more robust articles were prioritized. For the section on worldwide sample, the largest and most major studies from each country were elected.

3. Association between blood groups and COVID-19 transmission

The relationship between ABO blood groups and SARS-CoV-2 infection susceptibility was reported at the beginning of the pandemic in China (4). It is reported that blood group A may be associated with an increased risk of infection and blood group O may play a protective role against SARS-CoV-2 transmission (4). Therefore, many studies have been conducted to investigate the relationship between ABO groups and COVID-19. A systematic review conducted by Bing-Bing Wu and his team concluded the same results; individuals with blood group A are more likely to get infected in comparison with non-A blood groups, while on the other hand, blood group O individuals are less liable to get COVID-19 (7). Several global studies support this relationship and report similar results regarding blood group A and blood group O and their impact on COVID-19 infection (4, 8, 9). In retrospect, looking back on the previous SARS-CoV-1, an association between ABO blood groups and the susceptibility to SARS-CoV-1 was also detected, as blood group O played a protective role against transmission similar to SARS-CoV-2, but the data for the effects of blood group A was insufficient as far as our search goes (10).

The ability of anti-A antibodies to inhibit the adhesion between SARS-CoV-2 virus with angiotensin converting enzyme 2 (ACE2)-expressing cells was one of the main hypotheses that explain this relationship (Figure 1) (11). This also sheds light on the idea that the antibody itself, not the blood group, determines the relationship. For example, both B and O blood groups have anti-A antibodies, and according to Christiane Gerard who conducted a study on the antibody itself; it was found that subjects with anti-A in serum (i.e., B and O blood groups) are significantly less reported as the COVID-19 patients than those who do not have the anti-A antibody. However, in the same study, when comparing the anti-A antibody in O and B blood groups, a significant difference was found in the anti-transmission effect where blood group O plays more protective role than blood group B, which suggests other contributing factors that relate to the increased presence of Immunoglobulin G (IgG), anti-A, and anti-B in group O plasma (Figure 1) (12). In addition, the lifestyle and the local climate besides blood type distribution may also affect the infectivity onset and initial growth rate of the virus (13).

A meta-analysis studied 10 articles and found that the susceptibility to infection by COVID-19 increases in blood group A compared to non-A types, and that this result still applies in different racial groups (5). Many other studies found the same results, but these papers reported relatively contradicting minor results regarding blood groups B and AB where they showed various effects on COVID-19 ranging from low to high risk (4, 14–16).

4. Effects of ABO blood groups on the course, clinical presentation, and prognosis of COVID-19

Evidence from research reported that patients with blood group A are at a higher risk of developing severe COVID-19 infection compared to the other blood groups, while patients with blood group O are at a lower risk of developing severe infection compared to the other blood groups. According to a study conducted by Heit et al., blood group O individuals have lower plasma levels of procoagulant factor VIII and Von Willebrand factor compared to other blood

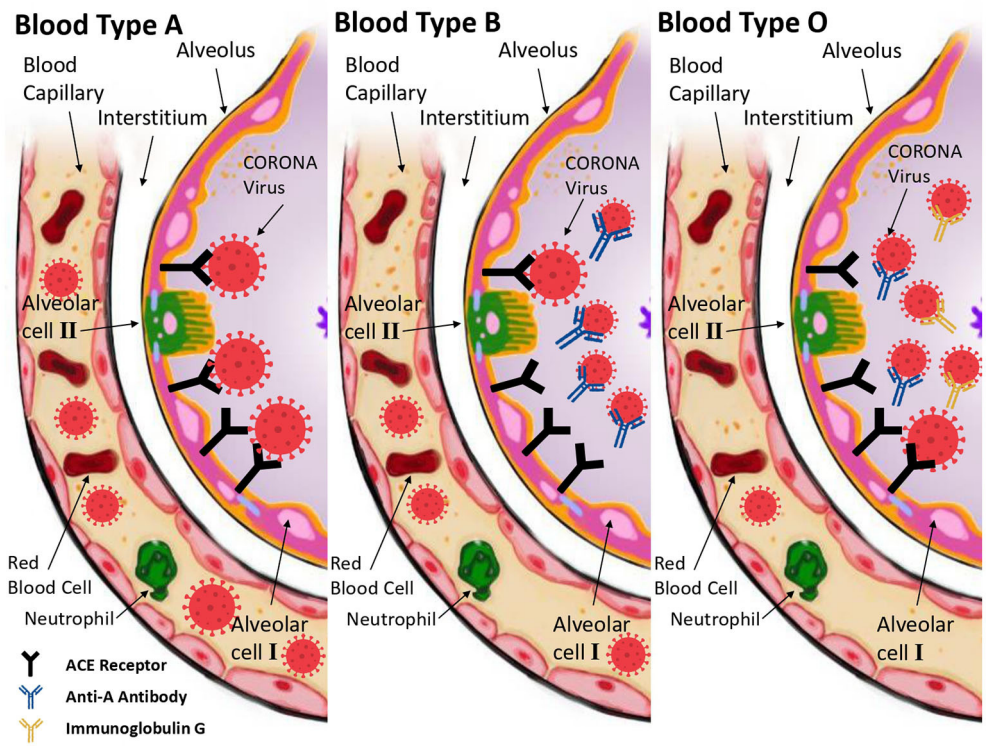

FIGURE 1
The molecular mechanism that explains how and why the ABO blood group affects a human's vulnerability to COVID-19 disease. The A blood group's lack of antibodies makes it easier for SARS-CoV-2 to enter the host cell and cause the subsequent viral infection **(Left side)**. Anti-A antibodies prevent the S protein of the virus from interacting with ACE-Receptors on the cell surface in blood group B cells **(Middle)**. Finally, blood group O provides further protection against COVID-19 infection due to the presence of anti-A antibodies and IgG antibodies **(Right side)**.

groups (17), rendering them less likely to develop venous thromboembolism. This is an important fact to consider when thinking about COVID-19 infection related coagulopathy and pulmonary thromboembolism, which are important issues in the context of COVID-19 infection and must be handled carefully (18). Li et al. reported in his study that individuals with blood group O are less likely to develop COVID-19 pneumonia and pulmonary microthrombi (19). On the contrary, patients with blood group A who have hypertension or other cardiovascular diseases are more likely to develop a severe form of SARS-CoV-2 infection and should receive ultra-care (20, 21).

In a study conducted in three hospitals in Wuhan, China in the period between February 1 and March 25, 2020 on patients who were diagnosed with COVID-19, resulting either in their death, or discharge from the hospital demonstrated that blood group A was associated with a higher risk of hospitalization following SARS-CoV-2 infection, while blood group O corresponded to lower risk of hospitalization (19). Another study conducted by Zhao et al. in Wuhan also found that blood group A had a higher rate of death in contrast to blood group O which was associated with a lower death rate (4).

Nevertheless, a systematic review described a significant association between COVID-19 and ABO groups, as more than a half (62.5%) of them found a better prognosis for blood group O, and almost a half (54.17%) found a worse prognosis for blood group A, yet only 33.33% reported both results together. There has also been a contradiction in the results of the other blood groups (B and AB) (22).

Overall, the respective blood group of patients are suspected to have an effect on the course of COVID-19 infection, either by prolonging/reducing their hospital stay or by imposing a more/less severe manifestations. Moreover, the outcome of the infection is also influenced by the blood type, as better prognosis was linked to blood group O, while worse outcome was associated with A blood group.

5. Main underlying mechanisms of association

Since the pandemic, a lot of studies have shed light on the molecular mechanisms explaining SARS-CoV-2 interaction with host cells. Viral particle entry is mediated through binding of the virus's Spike (S) protein, which is a glycoprotein emerging

from the viral envelope, to the ACE2-receptors that are present on several human cells (23). Several hypotheses were suggested to explain the mechanism behind the association of ABO blood groups and SARS-CoV-2 infection. A study conducted by Cooling, proved that blood group antigens, which are determined by oligosaccharides, act as receptors for several microorganisms including coronaviruses. The study showed that blood group A cells contain an additional sugar, N-acetyl galactosamine, which is not present on blood group O cells (3). Hence, Zaidi et al. suggested that this could explain the increased cell pathogen exposure in individuals with blood group A (24).

It is reported that anti-A antibodies that are present in individuals with blood groups O and B, block the interaction between the Spike protein and ACE2 receptors, thus inhibiting the virus entry and attachment, which leads to an attenuated infectivity of the virus. Therefore, blood group O and B individuals exhibit partial or complete protection against the virus, whereas blood group A individuals have a higher risk of infection since they lack anti-A antibodies (5). Another note is that anti-A antibodies in blood group B present Immunoglobulin M (IgM) while the antibodies from group O present Immunoglobulin G (IgG), giving more protection in blood group O (12). Moreover, it was reported that non-O blood groups, specifically group A, have increased levels of angiotensin-converting enzyme (ACE), which plays a role in promotion of the inflammatory response, meaning that O blood groups have lower ACE levels and a higher protection against the virus (20).

Regarding the severity of the infection in different ABO phenotypes; blood group A and AB patients were found to have elevated levels of D-dimer, this might be of significance in the development of severe respiratory manifestations in the SARS-CoV-2 infection (25). Furthermore, blood groups O and B have reduced levels of factor VIII and von Willebrand factor. Reduced levels of these factors provide protective mechanisms against complications from SARS-CoV-2 such as pulmonary vasculopathies, therefore blood group A individuals are more susceptible to a more severe infection by SARS-CoV-2 (26). This mechanism requires further work to be better understood.

Another important aspect of association between specific ABO types and increased COVID-19 severity is the genomic aspect of each group. A few genome-wide association studies (GWAS) on the association between ABO groups and COVID-19 severity were performed. Upon studying the ABO group locus, it was found that blood group A has a higher risk of developing respiratory failure, while blood group O has a protective role (27). Similar findings were observed regarding the allelic variants of the ABO phenotype (28). A trans-ethnic GWAS of COVID-19 severity found that the allele TC is a risk allele for COVID-19, and that its carriers belong to blood groups other that O (29). On the other hand, homozygote T/T carriers who belong to blood group O are relatively protected against the severe infection.

6. The role of Rhesus (RH) factor

Regarding the RH factor, Rh-negative (Rh-) individuals had a lower risk of initial infection in comparison to Rh-positive (Rh+) individuals (9). This is also found in a study that reported Rh+ individuals were more likely to test positive for SARS-CoV-2 (30). Furthermore, a study on 825 hospitalized COVID-19 patients showed that 95% of patients were Rh+ (31).

RH factor also plays a role in the severity of the COVID-19 infection. Ray et al. reported that Rh– blood group is associated with lower risk of developing severe COVID-19 infection, suggesting that Rh– blood group may have a protective effect against severe SARS-CoV-2 illness (18). Similar results were reported in a study conducted by Zietz et al., where it concluded that COVID-19 patients with negative RH were less likely to develop infection, intubation, and death (9).

7. A worldwide comparison between different studies regarding its final results and findings

Table 1 illustrates studies from different countries around the world distributed among 6 regions according to the world health organization (WHO) classification of the world (32). These studies investigated the relationship between COVID-19 and ABO blood groups among their respective populations. A map illustrating the final conclusion of each paper and its corresponding country is provided in Figure 2.

According to our sample, all studies around the world supported the protective role of blood group O, except for one study from Turkey that reported opposite findings, but the authors explained that by the fact that this group of people were not subject to curfews and traveled outside their country (41). The results of the Turkish study, however, are questionable, since a major study from Canada, analyzing the data of 225,556 patients support the protective role of O blood group (18).

On the other hand, regarding A blood group, studies vary in their conclusions. Most studies support the relationship with blood group A and the increased susceptibility and severity of the COVID-19 diseases. In this context, we highlight the Turkish, as it analyzes the data of 39,850 patients and concludes that intensive care unit (ICU) admission was higher for COVID-19 patients with A blood type (40). However, a study from Nigeria reported blood groups AB and B to be more susceptible to COVID-19 rather than A (33). In addition, a study from Spain reported the role of blood group B in increasing the risk of post-COVID complications (42).

TABLE 1 A summary of population-based studies sampled from each region in the world.

Country (32)	Sample Size (Positive COVID test)	COVID-19 cases per blood group	Main conclusion
African Region (AFR)			
Nigeria (33)	297	A: 58 (19.1%) B: 77 (25.3%) AB: 17 (5.6%) O: 145 (47.7)	Blood groups AB and B were more susceptible to the disease. Blood group O has a protective role (Statistically insignificant finding)
Region of the Americas (AMR)			
United States of America (34)	4968	A: 1,473 (29.6%) B: 846 (17.0%) AB: 204 (4.1%) O: 2,445 (49.2%).	Patients vary in admission rates based on ABO groups but not in discharge. Blood type A was associated with the increased cause-specific hazard of all-cause in-hospital mortality com-pared to type O.
Canada (18)	225,556	A: 81,797 (36.3%) B: 33,536 (14.9%) AB: 10,221 (4.5%) O: 100,002 (44.3%)	O-negative blood group is associated with lower risk of both COVID-19 infection and complication. A person with O- blood group may remain asymptomatic.
Columbia (26)	95 (ICU due to COVID-19)	A: 35 (37%) B: 16 (17%) AB: 3 (3%) O: 41 (43%)	Critically ill COVID-19 patients with blood group A or AB are prone with an increased risk for requiring mechanical ventilation, CRRT, and prolonged ICU length of stay compared with patients with blood groups O or B.
Brazil (35)	31	A: 15 (48.4%) B: 4 (12.9%) AB: 1 (3.2%) O: 11 (35.5%)	Authors detected an association of being blood type A with recurrence of COVID-19.
South-East Asian Region (SEAR)			
India (36, 37)	2,586	A: 774 (29.93%) B: 1,081 (41.80%) AB: 183 (7.08%) O: 548 (21.19 %)	Blood group A and Rh+ are more susceptible to infection while blood group O and B have a lower risk of infection.
	509	A: 112 (22%) B: 158 (31%) AB: 183 (36%) O: 56 (11%)	Neutralizing antibodies significantly more in AB and least in O. Blood group AB are at higher risk of infection. Blood group O have lowest risk of infection.
Bangladesh (38)	771	A: 288 (37.35%) B: 134 (17.38%) AB: 204 (26.46%) O: 145 (18.81%)	Blood group A had the greatest need for supplemental oxygen and mechanical ventilation. Blood group A is associated with higher severity, complications and death from COVID-19 while blood group O had the least risk of complications.
European Region (EUR)			
United Kingdom (39)	968	N/A	Blood group A are more liable to get COVID-19 infection than blood group O. The role of ACEI in increasing the risk of COVID-19.
Turkey (40)	39,850	A: 15,663 (39.3%) B: 5,865 (14.7%) AB: 4,359 (10.9%) O: 13,963 (35.1%)	Increased intensive care unit (ICU) admission in blood group A.
Turkey (41)	220	A: 100 (45.45%) B:32 (14.55%) AB: 12 (5.45%) O: 76 (34.55%)	Blood group O and young age are more susceptible to COVID-19 infection. Authors suspect that this age group was not subject to curfews and traveling outside their country.
Spain (42)	483	A: 220 (45.5%) B: 44 (9.1%) AB: 19 (3.9%) O: 200 (41.4%)	Blood group O has a protective role. The B-group patients are more liable to post-COVID complications.
Austria (43)	336	A: 151 (44.9%) B: 54 (16.1%) AB: 31 (9.2%) O: 100 (29.8%)	Blood group O has a protective role, while blood type AB is associated with a higher risk of COVID-19. An association between Lewis-antigen and COVID-19.

(Continued)

TABLE 1 (Continued)

Country (32)	Sample Size (Positive COVID test)	COVID-19 cases per blood group	Main conclusion
Eastern Mediterranean Region (EMR)			
Saudi Arabia (44)	404	A: 103 (25.5%) B: 41 (10.1%) AB: 8 (2%) O: 252 (62.4%)	Blood group O is protective against infection and has a lower risk of positive COVID-19.
Saudi Arabia (45)	373	A: 102 (27.35%) B: 88 (23.59%) AB: 20 (5.36%) O: 163 (43.70%)	
United Arab Emirates (UAE) (46)	303	A: 84 (27.7%) B: 76 (25.1%) AB: 21 (6.9%) O: 122 (40.3%)	Among COVID-19 patients with blood group B, the age-related risk for pneumonia and mortality was lower than that of patients with blood group O. Authors found a significant increase in creatinine among patients with blood group AB compared to other blood groups.
Iraq (14)	1,014	A: 360 (35.5%) B: 221 (21.8%) AB: 109 (10.7%) O: 324 (32%)	Blood group A carries have an increased risk of COVID-19 infection.
Egypt (47)	547	A: 153 (28%) B: 139 (25.4%) AB: 28 (5.1%) O: 227 (41.5%)	Blood group A is susceptible to more severe forms of pneumonia. Blood group O is considered protective.
Lebanon (16)	146	A: 59 (40.4%) B: 25 (17.1%) AB: 10 (6.9%) O: 52 (35.6%)	Higher infection rates in blood group A and lower in blood group O (statistically insignificant).
Sudan (48)	557	A: 180 (32.3%) B: 102 (18.3) AB: 34 (6.1%) O: 241 (43.3%)	A blood group is more vulnerable to contracting the disease, whereas blood group O are the least exposed to the severe symptoms. RH+ has a negative impact on blood group A, but positive impact on blood group O.
Western Pacific Region (WPR)			
China (49)	105	A: 45 (42.8%) B: 28 (26.7%) AB: 9 (8.57%) O: 23 (21.9%)	Higher susceptibility for infection in blood group A. No significant associations for other blood groups.
Japan (50)	461	A: 199 (43.2%) B: 101 (21.9%) AB: 47 (10.2%) O: 114 (24.7%)	Blood groups A, B and AB have significantly higher risks of acquiring COVID-19 infection. Blood group O is less likely to get infected by COVID-19.
Total		280,580	A: 101,971 (36.3%) B: 42,668 (15.2%) AB: 15,723 (5.6%) O: 119,250 (42.5%)

8. Discussion

Since the beginning of the COVID-19 pandemic, the associated risk factors that affect the transmission, course, outcome, and late complications were of interest for medical research. Both modifiable and nonmodifiable factors were extensively investigated. In this review, we try to summarize the role of one of the nonmodifiable factors. ABO blood group types have been established to have a role in many diseases, and their role in COVID-19 transmission, course, and outcome has been investigated in several previous primary and secondary research articles. In addition, we took a worldwide sample from different countries around the world according to WHO region classification, choosing the largest sample in each country of each region.

The overall outcome of this review can be summed up to the following: O blood group individuals have additional protective features against acquiring COVID-19, and against its worsening, contrary to individuals with blood group A, who are more prone to the virus's infectivity and exacerbation. Results get more confusing regarding patients with blood groups B and AB, because their associations with the incidence, course and

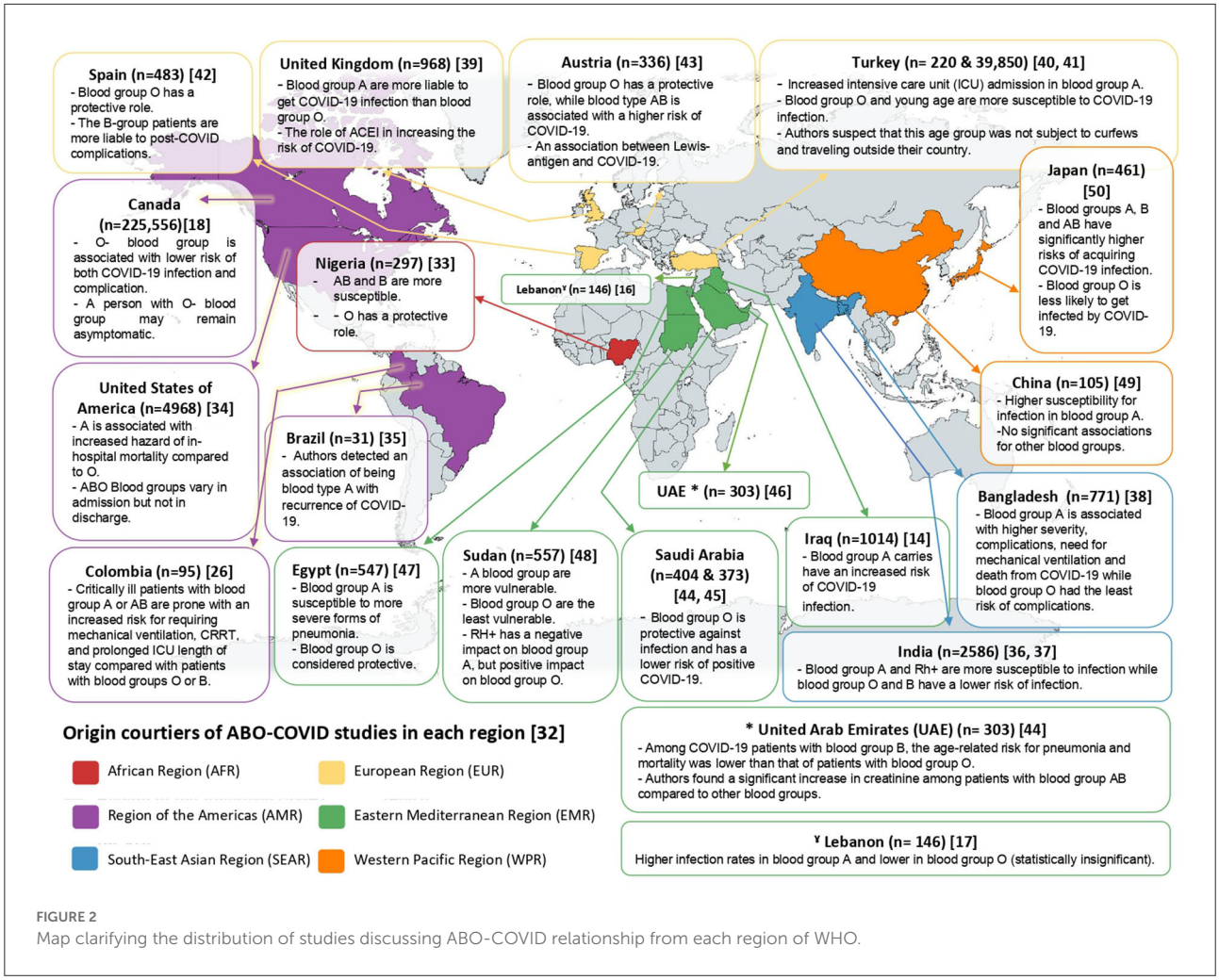

FIGURE 2
Map clarifying the distribution of studies discussing ABO-COVID relationship from each region of WHO.

outcome of COVID-19 are still not fully understood. Despite these findings, it is important to read these results keeping in mind the percentage of each blood group in population. A blood group has a higher frequency compared to B and AB groups, meaning that more COVID-19 cases are expected to have A blood group. The frequency of each blood group varies according to population, but A and O blood groups are generally of higher frequency, in contrast with B and AB groups, which are less prevalent (51).

Many hypotheses were proposed in literature in order to explain these results. People with blood group O were less likely to get infected with the virus, mainly due to the presence of anti-A antibodies in their serum, which block the interaction of the virus's S protein with the ACE2-receptor, thus preventing cellular entry of the virus (11). This explanation was reported in many studies, but it could not explain why blood group B does not play the same protective role as blood group O, despite the presence of anti-A antibodies in blood group B serum as well. This suggests that other factors like increased presence of IgG, anti-A and anti-B antibodies in group O plasma are involved (12). The contradiction regrading B and AB groups could be referred to the rarity of both group among population (51), therefore; a very large sample is needed to achieve a relatively robust analysis.

The RH factor, in addition to the ABO blood group, had a significant impact on COVID-19 transmission and outcome. The role of Rh+ in transmission requires further explanation and research, as systematic reviews and numerous studies have reported that Rh+ individuals are far more common than Rh− individuals (52), implying that the normal population was originally composed primarily of Rh+ individuals, making those people more vulnerable to infection. This also could be combined with the fact that there is no clear explanation why Rh− people are less likely to get infected as far as our research goes. Similar to ABO groups, the percentage of Rh+ individuals in population is significantly higher than Rh− type (51). This difference in frequency need should not be forgotten when interpreting the results of the present review.

Other studies also reported the other associated factors that may have an important role besides the blood groups. A

meta-analysis conducted by Nanyang Liu found that the overall results of COVID-19 infection with blood group B in Caucasians were shown to have limited alteration (5) while in contrast Jori E. May et al. conducted a study on 165 most of them were African American and Cacusian and she found that there was no association between ABO type and admission to an intensive care unit, diagnosis of thrombosis during hospitalization, or death (53). Moreover, ABO blood groups are affected by gender too, as Muñiz-Diaz reported that the male gender is associated with worse prognosis, especially when associated with other comorbidities (21). Khalil et al. reported that male gender is not considered as a significant risk factor for developing a severe form of the disease, but had a higher incidence of infection (16). In contrast, Fan et al. reported that the association between blood group A and increased susceptibility to COVID-19 infection reaches statistical significance only in females (49).

9. Conclusion

We conclude that there is a strong association between ABO blood groups and COVID-19 transmission, course and outcome. Blood group O plays a protective role while blood group A is associated with an increased risk of COVID-19 infection and worse prognosis in comparison to other blood groups. To add, there are many other associated factors that may play a significant role alongside ABO blood groups, such as the RH factor. However, the role of the RH factor needs further research and investigation as its role is not yet fully understood, hence, it is highly recommended that the formerly mentioned association be considered in medical care units, and that cases are dealt with accordingly. Moreover, case-control studies targeting this issue are needed, and the lack of such studies is a limitation for understanding and addressing this topic. We suggest the following manner of benefiting from the ABO grouping when dealing with COVID-19 patients: people with blood group A should receive higher consideration if confirmed as COVID-19 positive patients, whereas those with blood group O should not hesitate to follow the protective measures against the infection, all whilst maintaining control over the cases. Individuals are also recommended to adopt a healthy lifestyle with a good nutritious diet in order to benefit maximally from the protective antibodies against the virus.

Author contributions

MA and MT: figures design. MA, MT, WA, SS, IA, AN, and YA-B: literature search and manuscript preparation. All authors have read and agreed to the published version of the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Comparing serum ferritin levels during COVID-19 infection and recovery period in pediatric patients with transfusion-dependent thalassemia, a single-center study

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Background: Ferritin has been recognized as a predictor of severity among Coronavirus-19 disease (COVID-19) patients. Studies have shown higher levels of ferritin in patients with COVID-19 than in healthy children. Patients with transfusion-dependent thalassemia (TDT) basically have high ferritin level due to iron overload. It is uncertain whether serum ferritin level in these patients is associated with COVID-19 infection.

Objective: To evaluate ferritin levels in TDT with COVID-19 before, during, and after the course of infection.

Methods: This retrospective study enrolled all TDT children with COVID-19 infection that were hospitalized in Ulin General Hospital Banjarmasin during the COVID-19 pandemic (March 2020 to June 2022). Data were collected from medical records.

Results: There were 14 patients included in this study, 5 patients had mild symptoms and 9 patients were asymptomatic. The mean of hemoglobin level upon admission was 8.1 ± 3 g/dL and serum ferritin level were 5148.5 ± 2651.8 ng/mL. The average serum ferritin level during COVID-19 infection was 2373.2 ng/mL higher than before infection and then decreased by 952.4 ng/mL after infection. We found no association of increasing serum ferritin with patients' symptoms (p = 0.27). The severity of anemia also was not correlated with the presentation of COVID-19 infection (p = 0.902).

Conclusion: Serum ferritin levels in TDT children may not reflect disease severity or predict poor outcomes during COVID-19 infection. However, the presence of other co-morbid conditions/confounders warrants cautious interpretation.

KEYWORDS

transfusion-dependent thalassemia, thalassemia, pediatric, hyperferritinemia, ferritin, COVID-19

1. Introduction

Coronavirus disease 2019 (COVID-19) pandemic has been going on since December 2019 and affected many people from neonates to elders (1, 2). Clinical symptoms of COVID-19 vary from asymptomatic infection to severe form of the acute respiratory syndrome, even death (3). Although SARS-CoV-2 infection in children was less severe as compared to adults, children with comorbid disease may develop severe disease (4, 5). Hematological disease has been known as one of the risk factors related to the severity of COVID-19 (5, 6).

β-thalassemia is one of the most common hematological diseases in the world, with approximately 1.5% of the global population carrying the β-thalassemia trait (7, 8). β-thalassemia is divided into two groups: transfusion-dependent β-thalassemia (TDT) and non-transfusion-dependent β-thalassemia (NTDT) (6, 9). TDT children might be at risk for severe disease of COVID-19 because of several complications like iron overload, ineffective erythropoiesis, hypercoagulability, splenectomy, and multiple organ damage due to excess iron (6, 10). These complications may increase the susceptibility to infection in TDT children (11). Ferritin is a marker for iron storage status in humans. High serum ferritin levels indicate increased or normal iron storage (12). Ferritin also known as an acute phase reactant, is elevated in acute and chronic inflammation and/or infection (12, 13). In cases of COVID-19, ferritin has been correlated with disease severity that may serve as a biomarker (14, 15). Measurement of serum ferritin is used to diagnose iron overload in β-thalassemia children (16). Thus, ferritin levels in these children are already elevated due to iron overload (9).

No study compares serum ferritin levels during COVID-19 infection and recovery period in pediatric patients with TDT. In this study, we aim to compare and analyze serum ferritin levels in children with TDT and COVID-19. Clinical severity and hemoglobin levels were also described.

2. Materials and methods

2.1. Methods and study criteria

A single-center retrospective study was conducted in Ulin General Hospital, Banjarmasin. We included all TDT children aged 0–18 years that were diagnosed with confirmed COVID-19 at Ulin General Hospital Banjarmasin between June 2020 and June 2022. Data were collected from the isolation registry book and patients' medical records. Incomplete medical record data were excluded from the study.

2.2. Operational definitions

TDT is defined as the need for repeated blood transfusion regularly with the assumption of 2–4 units of packed red cells monthly (17). Diagnosis COVID-19 was confirmed by SARS-CoV-2 polymerase chain reaction (PCR) test results. Clinical symptoms were considered present if developed at the beginning of hospitalization to discharge. Laboratory data collected are the laboratory results before, during, and after COVID-19. The results of laboratory data before and after COVID-19 were collected from previous and afterward hospitalization, which was 1–two 2 months before and after COVID-19 infection.

2.3. Outcome

The outcome of this study was serum ferritin levels before, during, and after COVID-19 infection among children with TDT. Presentation of clinical symptoms, hemoglobin levels, and association of serum ferritin levels in TDT children with COVID-19 were also of interest.

2.4. Statistical analysis

Baseline characteristics were reported using frequencies, percentages, mean and ranges. Independent *t*-test was used to determine the association between numeric variables. All statistical analyses were done using Statistical Package for the Social Sciences (SPSS) version 23. Results were considered statistically significant if $\alpha < 0.05$. Informed consent was obtained from all parents of the study participants. This study was approved by the Ethics Committee of Ulin General Hospital (register number 198/X-RegRiset/RSUDU/22).

3. Results

A total of 15 children with TDT were reported to have COVID-19 infection from 205 thalassemia children registered in Ulin General Hospital. Generally, there were 65 patients diagnosed with confirmed COVID-19 infection and hospitalized at Ulin General Hospital from June 2020 to June 2022. One child was excluded because of incomplete laboratory data. The characteristics of these patients was described in **Table 1**.

The youngest TDT child with COVID-19 infection was 1-year old and the oldest was 18 years old. No patient had severe signs and symptoms of COVID-19 infection in this study. Five patients (35.7%) were symptomatic. Fever presented in 4 patients (80%) and other symptoms were cough (40%), anosmia (20%), ageusia (20%), and myalgia (20%).

The range of hematological parameters from 14 patients upon admission were hemoglobin 2.6 to 13.2 g/dl, white blood cell (WBC) 2400 to 18700/μL, platelet 73 to 441 × 10^3/μL, and lymphocyte count 1210 to 3430/μL, respectively. Serum ferritin levels were 980.51 to 8974.82 ng/mL. The average serum ferritin level changes in TDT children during COVID-19 infection was 2373.2 ng/mL higher than before infection and after COVID-19 infection was 952.4 ng/mL lower than during infection. Six patients had pneumonia from radiological findings, two (33.3%) of which were asymptomatic and none needed oxygen supplementation.

The comparison of serum ferritin level changes before and during COVID-19 infection vs. during and after COVID-19 infection were statistically significant ($p = 0.003$; mean differences 3371.84 ng/mL; 95% CI 1421.26 to 5322.43). Although there were increasing serum ferritin levels in TDT children during COVID-19 infection, these changes were not associated with the patient's symptoms ($p = 0.27$), and no severe disease was presented. The severity of anemia also was not correlated

TABLE 1 Baseline characteristic.

Characteristic	Total
Gender (n, %)	
Male	11 (78.6)
Female	3 (21.4)
Age (years) (mean, SD)	11 ± 5
Symptoms (n, %)	
Symptomatic	5 (35.7)
Asymptomatic	9 (64.3)
Iron chelating agent (n, %)	
Deferiprone (DFP)	8 (57.1)
Deferasirox (DFX)	6 (42.9)
Hemoglobin (g/dL) (mean, SD)	
Pre-COVID-19	9 ± 2.1
During COVID-19	8.1 ± 3
Post-COVID-19	8.4 ± 1.9
White blood cell (/uL) (mean, SD)	
Pre-COVID-19	7735.7 ± 2389.9
During COVID-19	6928.6 ± 3813.2
Post-COVID-19	8293 ± 3243.3
Platelet (10^3/uL) (mean, SD)	
Pre-COVID-19	256.3 ± 143.3
During COVID-19	281.3 ± 123.1
Post-COVID-19	267.6 ± 151.2
Ferritin (ng/mL) (mean, SD)	
Pre-COVID-19	3934.5 ± 1804
During COVID-19	5148.5 ± 2651.8
Post-COVID-19	4264 ± 2516.1
Ferritin changes (ng/mL) (mean, SD)	
Pre- vs. during COVID-19	2373.2 ± 1320.9
During vs. post-COVID-19	952.4 ± 2978.1
Radiologic findings (n, %)	
Pneumonia	6 (42.9)
Normal	8 (64.3)
Outcome (n, %)	
Self-isolation	11 (78.6)
Recovered	3 (21.4)

with the presentation of COVID-19 infection (p = 0.902). Data were presented in Table 2. We also found that the serum ferritin elevation was not associated with pneumonia (p = 0.554).

4. Discussion

Serum ferritin levels in transfusion-dependent β-thalassemia patients were higher compared to healthy people as a result of regular transfusions (9, 18, 19). The higher level of ferritin was directly associated with iron accumulation in tissue which commonly involves the heart, liver, lungs, and endocrine glands (12, 18, 20). During iron overload, transferrin saturation percentage that leaves non-transferrin-bound iron as free iron. This free iron enters some cells and pooled within the cells. Intracellular iron is stored either in ferritin or in hemosiderin (12, 13). Ferritin plays a major role in iron homeostasis, which acts as the main iron storage mechanism and releases iron when the level decreased (12). Therefore, ferritin is used to identify iron overload in β-thalassemia patients and the need for iron chelation agent therapy initiation. Iron chelation agent was indicated if serum ferritin levels exceed 1000 ng/mL in TDT children (17, 21). The raise of serum ferritin above 1000 ng/mL is considered hyperferritinemia (21, 22).

Ferritin also represents an acute-phase protein that is elevated in the course of inflammation, both infectious and non-infectious (14, 21). In inflammatory conditions, serum ferritin may be within normal or increased even though the actual iron stores are absent. Increased ferritin levels are associated as a biomarker of cell damage, oxidative stress, the presence of disease processes, and the severity of chronic disease processes (23). Hyperferritinemia in inflammatory and infective disorders is believed to be cytokine-mediated that implicate interleukin (IL) 1β, IL-6, IL-18, interferon (IFN)-γ, tumor necrosis factor-α (TNF-α) and macrophage-colony stimulating factor (22). These pro-inflammatory cytokines induced the liver to produce several proteins including C-reactive protein (CRP) and ferritin. Ferritin sources during inflammation include macrophage secretion and damaged cells. Also, ferritin may have an active pathogenic role by stimulating pro-inflammatory pathways (24). It means that there might be a feedback mechanism between cytokines and ferritin (25).

While serum ferritin in normal children represents a biomarker of cell damage, TDT children already present with high serum ferritin levels. A high level of ferritin serum was identified in those patients with COVID-19 with severe disease and poor outcomes (23, 24). In this study, an increase in serum ferritin in TDT children was observed. However, this noticeable increase before and during COVID-19 infection, although was statistically significant, was not correlated either with disease severity or poor outcome, statistically. A nationwide study in Iranian adults showed no difference of serum ferritin level between the death group and the recovery group of thalassemia patients with confirmed COVID-19 (20).

SARS-CoV-2 virus primarily affects the respiratory system with wide range of symptoms, from asymptomatic or mild nasopharyngeal symptoms to severe pneumonia. Hemoglobin disorders, particularly thalassemia, are not directly related with respiratory conditions. However, thalassemia patients are divided into three risk groups of developing severe SARS-CoV-2 infection. Highest risk group included thalassemia patients with 2 or more of the following criteria: age more than 50 years, suboptimal transfusion pre-transfusion

TABLE 2 Laboratory changes in thalassemia children with confirmed COVID-19.

Laboratory variables	Symptomatic (n = 5)	Asymptomatic (n = 9)	P-value	95% CI
Hemoglobin (g/dl)	8.22 ± 1.48	8.04 ± 3.68	0.902	−2.88 to 3.23
Ferritin (mg/dl)	6235.1 ± 3075	4544.8 ± 2356.2	0.27	−1491.14 to 4871.65

Hb < 7.0 g/dL (currently and in the last 2–3 years), serum ferritin >4000 ng/mL (currently and in the last 2–3 years), one or more comorbidity such as diabetes, cardiac, endocrine, respiratory or hepatic disease, splenectomy with at least one comorbidity (26). Several studies showed that the susceptibility to severe disease and mortality were more profound in non-TDT patients (7, 8, 20). Thus, patients with TDT were associated with less severe disease and improved outcomes (27). These patients regularly received blood transfusions which could decrease the occurrence of anemia-related complications and compensation for bone marrow expansion. Iron chelation therapy also reduces iron overload related to multiple transfusions (27). Severe diseases of COVID-19 in TDT patients are shown to be due to the coexistence of organ damage associated with iron overload including cardiomyopathy and heart failure (5, 28).

Several possible explanations were suggested for the less severe disease and susceptibility to COVID-19 in thalassemia patients. During SAR-CoV-2 infection, the beta chain of Hb was attacked, resulting separation of iron from the porphyrin ring, and impairing the oxygen transfer process. It could be that the viral protein competes with iron to bind to this porphyrin ring, interfering the normal heme anabolic pathway (27, 29). A study had suggested that some proteins of this coronavirus attacked the heme on the beta chain of hemoglobin, both oxygenated and deoxygenated hemoglobin. The higher the hemoglobin content, the higher risk of disease. However, in case of abnormal hemoglobin (abnormal structure of Hb), it is not clear whether the viral proteins could attack this heme and then bind with this porphyrin to form a complex (29). Further research is needed to verified this theory. A national survey in French reported 16 cases of β-thalassemia patients that included 4 pediatric patients. All of pediatric patients were having few signs and symptoms during the disease course. Furthermore, the severity of COVID-19 in β-thalassemia patients, young and middle-aged patients, remained mild to moderate (30). A meta-analysis determined that the incidence rate of TDT patients with COVID-19 infection, in general, was 1.28/100,000 people per day. This number was surprisingly lower than the incidence rate in the general population which was 2.89/100,000 people per day (6).

Other hematological and biochemical parameters were also associated with poor outcomes in COVID-19 patients. A meta-analysis showed that lymphopenia (lymphocyte count < 1500/μL; OR 3.33; 95% CI: 2.51–4.41), thrombocytopenia (platelet level < 150 × 10^3/μL; OR 2.36; 95% CI: 1.64–3.40), elevated AST (>40 IU/L; (OR 2.36; 95% CI: 1.64–3.40) and elevated AST (>40 IU/L; OR 1.71; 95% CI: 1.32–2.20), elevated creatinine (>1.18–1.5 mg/dL; OR 2.84; 95% CI: 1.8–4.46) were associated with poorer outcome (31). In this study, we have three patients with thrombocytopenia, two patients with lymphopenia, five patients with elevated AST and ALT, and one patient with elevated creatinine. However, none was presented either with severe disease nor poor outcome. Previous study reported that significant mortality rate was observed when the platelet count dropped below 100 × 10^3/μL. Mortality rates were 61.2% with platelet counts 50–100 × 10^3/μL and 92.1% with platelet counts < 50 × 10^3/μL (32). Another study about lymphopenia and COVID-19 severity was observed below 800–1100/μL (33). As for the unavailable results of AST, ALT and creatinine in this study, were not provided because of the incomplete data.

This study has several limitations such as the small number of participants because the incidence rate of COVID-19 infection in β-thalassemia was shown to be lower than in the general population. As for disease severity, children were generally present with mild disease and many of thalassemia patients didn't visit the hematology-oncology clinic in our center during COVID-19 pandemic. This mild presentation also happens in TDT children, as seen in our study. Therefore, we couldn't observe how far the "hyperferritinemia" state occurs in TDT children with severe disease.

5. Conclusion

Hyperferritinemia is usually observed in TDT children due to iron overload. Our data suggest that ferritin in TDT children may not reflect disease severity or predict poor outcomes during COVID-19 infection. However, the presence of other co-morbid conditions/confounders warrants cautious interpretation. Further studies with more participants are required to determine if there's any role of ferritin for the assessment of disease severity and outcome.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethical Committee of Ulin General Hospital. Written informed consent for participation was not provided by the participants or their legal guardians/next of kin because: Data were collected from the isolation registry book and patients' medical records. Written informed consent was not obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

Author contributions

WM: principal investigator, supervision, data curation, and writing – review and editing. FF: investigation, data curation, writing draft, software, and formal analysis. AS: investigation, data curation, writing draft, and formal analysis. EH: investigation, methodology, formal analysis, and data curation. PA: investigation and data curation. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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People having hematological disorders and hypercoagulability state need extra precautions because of the increased risk of thrombosis after COVID-19 vaccination

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Introduction

Millions of people have been infected and died because of the COVID-19 pandemic since December 2019, which is not the first pandemic the world has faced (1). Older people and individuals with comorbidities such as cancer, diabetes mellitus, cardiovascular diseases, hematological disorders, immune disease, enzyme deficiencies, and chronic respiratory diseases are reported to be more vulnerable to COVID-19, making them major risk groups (2–5). According to the literature, people with hematological disorders and hypercoagulability states are more vulnerable to COVID-19 infection because of the increased risk of adverse health effects and mortality. However, the impact of the COVID-19 vaccination has not been widely investigated in patients having hematological disorders such as glucose 6-phosphate dehydrogenase (G6PD) deficiency, thalassemia, sickle cell disease (SCD), pyruvate kinase enzyme deficiency (PKD), thrombophilia, hypereosinophilic syndromes, Glanzmann syndrome, sticky platelet syndrome, immune thrombocytopenia, and antithrombin deficiency (6, 7).

COVID-19 infection and COVID-19 vaccines can trigger endothelial damage, inflammation, platelet activation, cytokine storm, oxidative stress, and altered coagulation, contributing to thrombosis in patients (8). Platelets play a major role in thrombosis and inflammatory and immune processes; thus, they have a frontline effect on COVID-19 pathogenesis. Platelet hyperactivity, platelet aggregation, increased platelet–platelet interaction, increased gene expression, adhesion, and spreading in the platelets have been reported in patients infected with COVID-19. On the other hand, platelet hyperactivation has been found in both severe and non-severe forms of COVID-19 disease (9–11). Endothelial injury, coagulation, and thrombosis are directly associated with the disease severity and increased mortality risk in patients infected with COVID-19 and people with hypercoagulability (12, 13). Despite COVID-19 vaccines, people are still infected and die since the virus mutates and spreads quickly. Although vaccination reduces the mortality rate, the severity of the disease, and hospitalization, several studies reported that some COVID-19 vaccines might cause adverse health effects in people having hematological disorders or hypercoagulability state because of increased risk of thrombosis and hemolysis (14).

Therefore, extra caution and supportive care can be crucial for those patients after COVID-19 vaccination (12–15). The severity of COVID-19 infection and possible post-vaccination complications can be monitored *via* coagulation and thrombosis-inducing factors (15) such as increased levels of factor VIII, fibrinogen, plasmin activator inhibitor-1 (PAI-1), Willebrand factor (VWF), tissue factor expression, thrombin generation, and platelet activation and

decreased concentrations of antithrombin, protein C, and thrombomodulin (16). In this context, we discussed the possible impact of the COVID-19 vaccination on people with hematological and hypercoagulability disorders correlated with the increased risk of thrombosis.

COVID-19 vaccine-induced thrombotic events

People are vaccinated against COVID-19 infection *via* several types of vaccines, including inactivated, viral vector, and mRNA; however, there is an increasing concern about COVID-19 vaccines about their safety. Thrombosis, platelet aggregation, platelet activity, embolism, and thrombocytopenia have been investigated in healthy individuals vaccinated with adenoviral or mRNA vaccines. Several studies have reported that no vaccine-induced side effects such as persistent platelet aggregation, activation, or plasma thrombin generation have been observed in healthy individuals after COVID-19 vaccination in the long or short term (17–19). On the contrary, viral vector and mRNA COVID-19 vaccines might cause mild-to-severe adverse health effects in people with blood disorders, according to the literature. Thrombosis, portal vein thrombosis (PVT), immune thrombotic thrombocytopenia (ITT), deep vein thrombosis (DVT), vaccine-induced immune thrombocytopenia (VITT), and heparin-induced thrombocytopenia (HIT) are reported as vaccine-induced adverse effects in people with blood disorders; thus, anticoagulation treatment following vaccination (non-heparin anticoagulant and intravenous immunoglobulin) has been recommended by the Expert Hematology Panel in March 2021 and the National Institute for Health Care Excellence (Figure 1) (20). NETosis is reported as the major contributor to VITT and HIT in patients with COVID-19, and NETs formed by neutrophils are involved in the innate immunological response as a first-line defense against pathogens. Increased levels of NETs' formation result in the overactivated immune cells and platelets associated with increased coagulation and endothelial damage, according to the literature (Figure 1) (21). Further studies should be conducted to reveal the mechanisms behind COVID-19 vaccine-induced thrombosis in patients having hematological disorders to prevent vaccine-related complications.

The impact of COVID-19 vaccines on people with hematological and hypercoagulability state disorders

People with hematological or hypercoagulability disorders such as G6PD deficiency, thalassemia, SCD, pyruvate dehydrogenase deficiency, thrombophilia, and sticky platelet syndrome have a higher risk of developing thrombosis, anemia, hemolysis, and embolism than healthy individuals. G6PD enzyme is the rate-limiting enzyme in the pentose phosphate pathway responsible for producing NADPH involved in maintaining the redox balance in the cell (22–25). Therefore, G6PD enzyme deficiency causes enhanced oxidative stress directly associated with hemoglobin denaturation and intravascular hemolysis (23, 25–27). According to the literature, people with G6PD deficiency can develop life-threatening hemolytic anemia and thrombosis after COVID-19 vaccination or during COVID-19 infection (2–4, 28). On the contrary, PKD is the second most common enzyme deficiency associated with hemolytic anemia, following G6PD deficiency. Since PKD shows clinical heterogeneity due to the type of the mutation, either autosomal recessive or dominant, the disease can be asymptomatic, and hemolysis occurs under stress conditions. Hemolysis, thrombosis, and decreased glycolysis have been found in people with PKD; however, no publication correlates PKD with COVID-19 infection or vaccination. Further studies should be conducted to evaluate the impact of the COVID-19 disease and vaccines on those patients (29, 30).

Thalassemia and SCD are the most common hemoglobin disorders or hemoglobinopathies, and people with hemoglobinopathies require lifelong follow-up and therapy (31). Thrombosis, hypercoagulability state, hemolysis, anemia, and embolism are clinical symptoms of hemoglobinopathies that increase those patients' mortality risk (32). Thalassemia is characterized by the defects of one or more hemoglobin chains and phenotypes of the disease ranging from severe anemia to asymptomatic individuals classified as thalassemia major, intermedia, and minor (33, 34). SCD is another type of hemoglobinopathy characterized by chronic anemia, hemolysis, and vasculopathy (35). Since people with thalassemia or SCD are more vulnerable to COVID-19 infection, they have a higher risk of hospitalization, mortality, and complications (36). Although vaccination enables immunity in both thalassemia and patients with SCD, some people with thalassemia showed vaccine-related adverse effects, including decreased hemoglobin levels and hemolysis (37). Those patients should be followed up closely following the vaccination because of vaso-occlusive crisis (VOC) along with increased levels of white blood cells (WBC) and liver enzyme; in contrast, a significant decrease in hemoglobin and platelet levels has been observed after COVID-19 vaccination (38).

Thrombophilia is characterized by abnormal blood coagulation in almost 50% of people with past thrombotic events. It can be congenital or acquired with clinical symptoms including deep vein thrombosis (DVT) and pulmonary embolism (PE). Protein S deficiency, protein C deficiency, antithrombin deficiency, antiphospholipid syndrome, factor V Leiden (FVL), and hereditary thrombophilia are the types of thrombophilia. Patients with thrombophilia have an increased tendency to clot, venous thrombosis, and thromboembolism because of the hypercoagulability observed in some patients with COVID-19 (39, 40). Antiphospholipid syndrome, also known as Hughes syndrome, is characterized by arterial, venous, or small vessel thrombosis associated with an increased risk of mortality in the patients. It has been reported that antiphospholipid antibodies are found in healthy individuals at approximately 1–5%, which is associated with antiphospholipid syndrome. On the contrary, these antibodies are also determined in patients infected with COVID-19; also Seeley et al. (41) reported that a woman with antiphospholipid syndrome has catastrophic episodes following COVID-19 vaccination (41).

Factor V Leiden is the most common hereditary thrombophilia characterized by a decreased anticoagulant response, increased risk of deep venous thrombosis, and pulmonary embolism (42). People with FVL are more vulnerable to COVID-19 infection since the increased risk of pulmonary embolism and thrombosis; moreover, deep vein thrombosis has been reported after COVID-19 vaccination

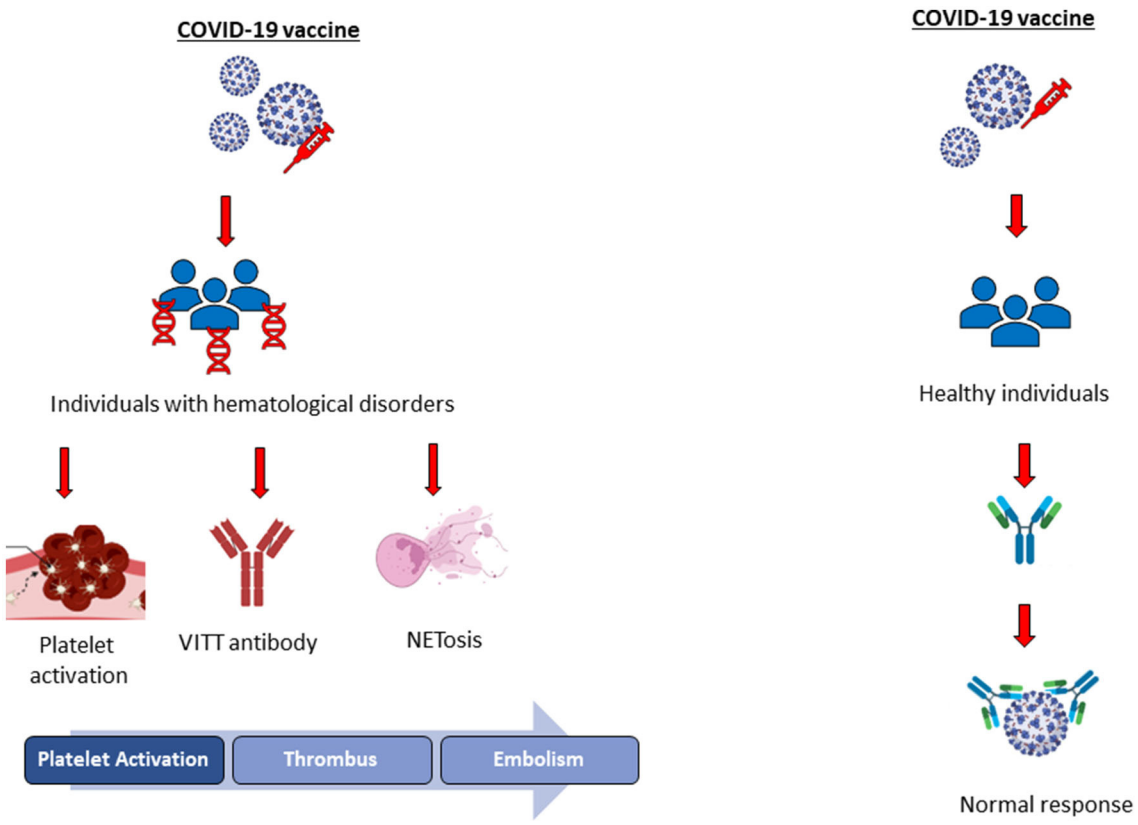

FIGURE 1
Illustration of COVID-19 vaccine-induced adverse health effects in healthy individuals and people with hematological disorders.

in a patient with FVL (43). Protein C deficiency is a rare hereditary or acquired life-threatening risk factor that can cause various health problems, such as thrombophilia to venous thromboembolism; it can also be asymptomatic (44). However, there is no publication about protein C deficiency and COVID-19 infection and/or the COVID-19 vaccine in the literature. Protein S deficiency is one of the hypercoagulability syndromes, and the synthesis of this plasma protein depends on vitamin K. Protein S has a central role in protein coagulation, and deficiency of protein S causes thrombotic complications in COVID-19-infected individuals (45, 46). On the contrary, cerebral venous sinus thrombosis has been reported in a patient with protein S deficiency following COVID-19 vaccination; thus, people with thrombophilia should be followed closely after vaccination or during COVID-19 (47).

Immune thrombocytopenia (ITP) is a rare autoimmune disorder with an incidence rate between 1.6 and 3.9 per 100 000 and is commonly found in women. In this disorder, the immune system destroys platelets; therefore, blood cannot clot accurately, leading to the increased risk of venous and arterial thromboembolism. People with ITP are reported to be more vulnerable to COVID-19 vaccination (48–50). Thrombocytopenia and purpuric lesions were observed after several mRNA COVID-19 vaccines, and adverse health effects were reported in patients with ITP (51, 52). Moreover, hyperviscosity syndrome (HVS) is a rare syndrome characterized by high immunoglobins and proteins, which cause an increase in blood thickness. Plasma hyperviscosity has been found in both COVID-19 infection and after vaccination, correlated with disease severity; therefore, people with HVS syndrome can be more vulnerable to COVID-19 infection and vaccination (53, 54).

Sticky platelet syndrome is an autosomal dominant disease characterized by platelet aggregation leading to the increased risk of thrombosis and embolism. According to the literature, people with this syndrome have a higher risk of developing thrombosis during COVID-19 infection (55, 56). Glanzmann thrombasthenia (GT) is a rare autoimmune disorder that can be inherited in an autosomal recessive manner or acquired. Platelet aggregation and decreased coagulation lead to bleeding in patients because of the defects in integrin αIIbβ3. Since thrombosis and embolism are observed in people with GT, they can have severe illness and increased mortality risk during COVID-19 infection, according to the literature (56). However, no detailed study or information about the impact of the COVID-19 infection or vaccination on those patients should be further investigated.

Conclusion

People are still infected and die because of the COVID-19 virus despite vaccination since the virus mutates and spreads very quickly. Therefore, as major risk groups, older people and individuals with comorbidities should be followed up carefully. People with hematological disorders and hypercoagulability are more vulnerable to COVID-19 infection and vaccination because of the increased

risk of thrombosis according to the literature. This is a knife-edge situation because viral vector and mRNA COVID-19 vaccines might cause mild-to-severe adverse health effects but also provide immunity in patients. Therefore, people with hematological disorders are required close follow-up during COVID-19 infection and after COVID-19 vaccines.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Clinical outcomes of children and adolescents with sickle cell disease and COVID-19 infection: A year in review at a metropolitan tertiary pediatric hospital

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Background: COVID-19 was declared a global pandemic in March 2020. Early reports were primarily in adults, and sickle cell disease (SCD) was classified as a risk factor for severe COVID-19 disease. However, there are a limited number of primarily multi-center studies reporting on the clinical course of pediatric patients with SCD and COVID-19.

Methods: We conducted an observational study of all patients with SCD diagnosed with COVID-19 at our institution between March 31, 2020, and February 12, 2021. Demographic and clinical characteristics of this group were collected by retrospective chart review.

Results: A total of 55 patients were studied, including 38 children and 17 adolescents. Demographics, acute COVID-19 clinical presentation, respiratory support, laboratory findings, healthcare utilization, and SCD modifying therapies were comparable between the children and adolescents. Seventy-three percent (N = 40) of all patients required emergency department care or hospitalization. While 47% (N = 26) were hospitalized, only 5% (N = 3) of all patients required intensive care unit admission. Patients frequently had concurrent vaso-occlusive pain crisis (VOC) (N = 17, 43%) and acute chest syndrome (ACS) (N = 14, 35%). Those with ACS or an oxygen requirement had significantly higher white blood cell count, lower nadir hemoglobin, and higher D-dimers, supporting a pro-inflammatory and coagulopathic picture. Non-hospitalized patients were more likely to be on hydroxyurea than hospitalized patients (79 vs. 50%, p = 0.023).

Conclusion: Children and adolescent patients with SCD and acute COVID-19 often present with ACS and VOC pain requiring hospital-level care. Hydroxyurea treatment appears to be protective. We observed no mortality despite variable morbidity.

KEYWORDS

sickle cell disease (SCD), COVID-19, SARS-CoV-2, pediatrics—children, morbidity, mortality

Introduction

COVID-19 (SARS-CoV-2) was declared a global pandemic by the World Health Organization in January 2019 leading to over 500 million confirmed cases and greater than >6 million deaths worldwide (1). During the earlier phases of the pandemic, higher morbidity and mortality were concentrated within the elderly and patients with underlying chronic conditions, including diabetes, obesity, and sickle cell disease (SCD) (2). In children, the majority presented either asymptomatic or with mild symptoms (3). A study of 277,285 school-aged children with laboratory-confirmed COVID-19 in the United States (U.S.) from March 2020-September 2020 reported only 1.2% were hospitalized and 40% were asymptomatic (3). However, children with an underlying medical condition accounted for 16% of hospitalizations, 27% of Intensive Care Unit (ICU) admissions, and 28% of the mortality (3). A multi-center study stratifying 2,293 hospitalized SARS-CoV-2 positive children by specific underlying conditions revealed those with chronic lung disease and neurologic disorders were associated with highest risk for severe COVID-19 infection (4). Children's National Hospital (CNH) also confirmed this association reporting higher hospitalization rates within their cohort of 177 SARS-CoV-2 positive children and adolescents with an underlying medical condition (5).

Sickle cell disease has been identified as a risk factor for severe COVID-19 disease. The effects of COVID-19 on the clinical course of SCD are emerging most notably through case reports, multi-center and single-center experiences, and through the international SECURE Sickle Cell COVID-19 registry (6–8). A published report of the 750 SCD COVID-19 cases from the SECURE registry revealed that SARS-CoV-2 severely affects SCD with an increase in morbidity and a higher case fatality rate than the general population (7). Sixty-nine percent of adults and 40% of children were hospitalized, in addition to 5.8 and 8.8% admitted to the intensive care unit, respectively (7). With a reported mortality rate of 2.5% from the SECURE registry, COVID-19 SCD patients suffered higher hospitalizations and case-fatality rates than those of similar ages within the US population (7). To comprehensively evaluate the impact of COVID-19 on pediatric patients, we conducted this study describing our one-year experience caring for a large number of patients with SCD and COVID-19 early in the COVID-19 pandemic.

Methods

This was a single-center, observational, prospective cohort study describing the clinical course of COVID-19 in pediatric (age <18 years) and adolescents (age 18–21 years) SCD patients. CNH is a free-standing 323-bed quaternary academic medical center that serves over 223,000 unique patients primarily from Maryland (59%) and Washington DC (23%), including over 1,500 pediatric and adolescent patients with sickle cell disease through outreach with local hospitals and clinics. We started our CNH Sickle Cell Disease COVID-19 Registry in March 2020 to collect real-time clinical information in SCD patients aged 0–21 years old (y/o) presenting with polymerase chain reaction (PCR) confirmed SARS-CoV-2 infection either in their community or at our hospital and associated clinics. As adapted by the Sickle Cell SECURE registry, we classified patients by level of severity (five levels) during their COVID-19 clinical course (6).

The study was approved by the CNH Institutional Review Board. We collected demographics, clinical characteristics, presenting symptoms, management, treatment, and clinical outcomes prospectively in patients with SCD and COVID-19 infection admitted between March 2020 and February 2021. In April 2020, we implemented standardized COVID-19 management and treatment guidelines for patients with SCD treated at our institution. As the pandemic progressed and updated treatment guidelines were published there was an evolution of our outpatient and inpatient guidelines for screening of SCD patients for COVID-19, laboratory, and clinical guidelines for suspected versus confirmed COVID-19, and eligibility criteria for monoclonal antibody therapy, antiviral treatment, and prophylactic anticoagulation (9–11). Inpatient prophylactic anticoagulation was initiated at the time of positive SARS-CoV-2 PCR and continued throughout hospitalization until 30 days post discharge with a telehealth visit with a hematology provider at 2 weeks.

Statistical analysis

Analysis was performed using descriptive statistics with categorical variables presented as proportions and continuous variables presented with their median and interquartile ranges. Differences were tested using the Chi-Square test or Fisher's Exact test for categorical variables and the Wilcoxon Rank Sum Test for continuous variables. All tests were two-sided and the values of $p < 0.05$ were considered statistically significant. The statistical analysis was done using SAS V9.4 (Cary, NC, USA).

Results

Demographics and clinical characteristics

Fifty-five patients with SCD had PCR-confirmed SARS-CoV-2 during the study time period, representing ~3.7% of our patient population, of which 69% were children (N = 38, <18 years) versus 31% were adolescents (N = 17, 18–21 years) (**Table 1**). The mean age was 11.6 years for the study population with mean ages of 8.3 and 19.2 years in children and adolescents, respectively. Gender was evenly matched with 51% females and 49% males. Hemoglobin SS (Hgb SS) was the most common genotype with 74% of the cases (79% of pediatrics, 65% of adolescents) followed by Hemoglobin SC (Hgb SC) (15%) and Sickle -Beta Zero Thalassemia (Hgb Sβ0 Thal) SCD (11%). Hydroxyurea (HU) was the most common disease-modifying therapy in 66% of children and 65% of adolescents; 7% were on chronic blood transfusions, 5% on crizanlizumab, and 4% on voxelotor (**Table 1**). All patients receiving crizanlizumab or voxelotor were also on HU.

Abbreviations: ACS, acute chest syndrome; CBC, complete blood count; CNH, Children's National Hospital; ED, emergency department; Hgb, hemoglobin; HU, hydroxyurea; 02 Sat, oxygen saturation; PCR, polymerase chain reaction; RBC, red blood cell; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; S β0 Thal, sickle beta zero thalassemia; SCD, sickle cell disease; VOC, vaso-occlusive crisis; WBC, white blood cell; y/o; years old; U.S., United States.

TABLE 1 Demographics and baseline characteristics.

	All patients *N* = 55	Children <18 y/o (*N* = 38, 69%)	Adolescents ≥18 y/o (*N* = 17, 31%)
Age mean (SD)	11.6 (6.7)	8.3 (5.2)	19.2 (1.2)
Age, median (IQR)	13.0 (5.0–18.0)	7.0 (4.0–14.0)	19 (18.0–20.0)
Gender *N* (%)			
Female	28 (51)	21 (55)	7 (41)
Male	27 (49)	17 (45)	10 (59)
Genotype (*N* = 55) *N* (%)*			
Hgb SS	41 (74)	30 (79)	11 (65)
Hgb SC	8 (15)	4 (11)	4 (24)
Hgb Sβ0 Thal	6 (11)	4 (11)	2 (12)
Disease modifying therapies *N* (%)			
Chronic blood transfusion	4 (7)	4 (11)	0 (0)
Hydroxyurea	36 (65)	25 (66)	11 (65)
Crizanlizumab	3 (5)	0 (0)	3 (18)
Voxelotor	2 (4)	1 (3)	1 (6)

*Numbers may not add up to 100% due to rounding.
Hgb, hemoglobin; Sβ0 Thal, sickle beta zero thalassemia; ED, emergency department; Hosp, hospitalization; ICU, intensive care unit.

Health care utilization

Twenty-seven percent (*N* = 15) of SCD patients with positive SARS-CoV-2 PCRs remained at home and were tested in an outpatient or community setting for mild symptoms or asymptomatic screening (Figure 1). The remaining 73% (*N* = 40) received emergency department (ED) care or were hospitalized (Figure 1). Twenty-six percent (*N* = 14) were discharged from the ED, of which the majority were children (*N* = 10). Approximately half (47%, *N* = 26) of the SCD patients with COVID-19 were hospitalized (45% of children, 53% of adolescents). Only 3 patients (5% of all patients) required Intensive Care Unit (ICU) level care for management of multi-lobar ACS and hypoxia requiring BiPAP (Supplementary Tables 3, 5). The median length of hospitalization was 5 days (4 days for children, 6 days for adolescents) (Table 2).

COVID-19 exposures and clinical presentation

Figure 2A shows the monthly patterns of COVID-19 cases in our SCD patients from March 2020 through February 2021. There were 3 peaks of COVID-19 cases represented in spring 2020 (*N* = 11 April-May 2020), summer 2020 (*N* = 6 July-August 2020), and winter 2020–21 (*N* = 21 December 2020-January 2021). Classification of symptoms at presentation (Figure 2B) and type of exposure (Figure 2C) were based on classifications from the SECURE registry. Fever (45%) was the most common presenting symptom in our SCD patients with COVID-19. Cough (22%), rhinorrhea (18%), abdominal pain (16%), chest pain (16%), sore throat (9%), and myalgias (11%) were among the other symptoms (Figure 2B). Only 7% percent reported a loss of taste or smell. Conversely, 24% of patients were asymptomatic at time of positive SARS-CoV-2 PCR. Among the 40 patients with SCD and COVID-19 who were hospitalized or had ED visits, 60% (*N* = 24) presented with fever, 43% (*N* = 17) with vaso-occlusive pain crisis (VOC), 35% (*N* = 14) with acute chest syndrome (ACS), 3% (*N* = 1) with splenic sequestration and 3% (*N* = 1) with venous thromboembolism (Table 2).

Exposure to COVID-19 was primarily community-acquired (56%, *N* = 31), followed by close contact of laboratory-confirmed COVID-19 (37%, *N* = 20), and close contact of a probable case of COVID-19 in 7% (Figure 1C). Sixty-nine percent (*N* = 38) of patients reported reasons for COVID-19 testing were predominately for symptoms, 24% (*N* = 13) were tested for exposure, and 7% (*N* = 4)

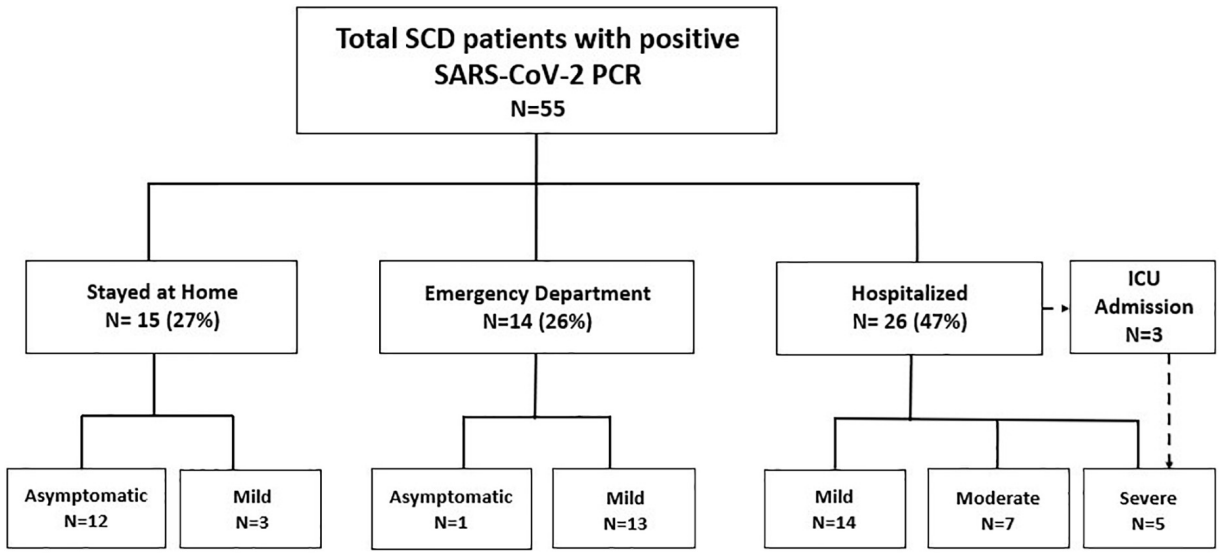

FIGURE 1
Healthcare utilization.

TABLE 2 Clinical presentation and characteristics of hospitalized and ED patients.

N (%)	All patients *N* = 40	Children, <18 y/o (*N* = 27)	Adolescents ≥18 y/o (*N* = 13)
Fever ≥38°C during hospitalization or ED visit	24 (60)	19 (70)	5 (38)
Oxygen saturation <95%	15 (38)	6 (22)	9 (69)
Sickle cell disease presentation			
Vaso-occlusive crisis (Pain)	17 (43)	11 (41)	6 (46)
Acute chest syndrome	14 (35)	7 (26)	7 (54)
Splenic sequestration	1 (3)	1 (4)	0 (0)
Venous thromboembolism	1 (3)	0 (0)	1 (8)
Length of stay** (day) median (IQR)	5 (3–6)	4 (2–5)	6 (4–6)

**Only hospitalized patients (*N* = 26) included.
ED, emergency department.

on pre-anesthesia assessment for procedures or diagnostic studies (Figure 2D).

Clinical severity and laboratory presentation

Twenty-four percent were asymptomatic (severity), while 54% experienced mild severity, primarily with an upper respiratory infection or gastrointestinal symptoms during their COVID-19 infection (Table 3). Moderate severity defined by pneumonia without hypoxia was exhibited in 13%, and severe presentation [dyspnea and hypoxia, oxygen saturation (02 sat) <92%] occurred in 9% of COVID-19 SCD patients (Table 3). A complete blood cell count (CBC) in 43 patients revealed a median white blood cell (WBC) count 10.4 × 10^3/μL (7.6–14.9 IQR), hemoglobin (hgb) 8.4 g/dL (7.3–10.2 IQR), and platelet count 277 × 10^3/μL (190–380 IQR) (Supplementary Table 1). Elevated median d-dimers of 1.7 μg/mL (0.5–4.7 IQR) and CRP of 2.0 mg/dL (0.4–6.2 IQR) were found within a subset of SCD patients with COVID-19 (Supplementary Table 1).

COVID-19 and sickle cell supportive treatment

Fifty-one percent of SCD patients received antibiotics, including ceftriaxone (51%) and azithromycin (25%) [Data not shown]. Only 6 SCD patients were treated with Remdesivir and 1 with convalescent plasma as early in the pandemic inpatient use was restricted to those with an oxygen requirement and higher clinical severity. Consequently, all patients that received these therapies carried a diagnosis of ACS. Blood transfusions were given to 29% (*N* = 16), which represented 61.5% of admitted patients. One patient received both simple and exchange transfusions. Twenty-six percent (*N* = 17) of hospitalized patients with SCD and COVID-19 received anticoagulant thromboprophylaxis with either enoxaparin or rivaroxaban according to the CNH COVID-19 anticoagulation treatment protocol. Inhaled or nebulized albuterol and budesonide were given to 37 and 22% of COVID-19 SCD patients, respectively. No patients received oral steroids.

Acute chest syndrome (ACS) vs. no acute chest syndrome

Thirty-five percent of SCD patients with COVID-19 were diagnosed with ACS and 92% of those had multi-lobar infiltrates on CXR. Lower 02 Sat <95% (86% vs. 8% $p < 0.001$), higher WBC count (14.1 vs. 8.7 × 10^3/μL, $p = 0.033$), lower hgb nadir (6.8 and 9.6 g/dL, $p = 0.064$), and elevated D-dimers (3.6 vs. 0.48 μg/mL, $p = < 0.001$) were significantly associated with ACS patients (Supplementary Table 2). One patient required an automated exchange blood transfusion.

Oxygen requirement vs. no oxygen requirement

All SCD patients with COVID-19 requiring supplemental oxygen received a blood transfusion compared to only 38% of those who were not on supplemental oxygen ($p < 0.001$) (Supplementary Table 3). Additionally, 90% of patients with oxygen requirement showed pneumonia on CXR (all with multi-lobar infiltrates) vs. only 14% who were not on oxygen (Supplementary Table 4). One patient exhibited bilateral pleural effusions but without pulmonary infiltrates. Higher WBC count (8.8 vs. 14 × 10^3/μ, $p = 0.002$), lower hgb (9.0 vs. 7.1 g/dL, $p = 0.002$), higher D-Dimer (0.8 vs. 4.1 μg/mL, $p = 0.002$), higher fibrinogen (270 vs. 601 mg/dL, $p = 0.013$), higher prothrombin time (14.5 vs. 16 s, $p = 0.006$) were all associated with supplemental oxygen requirement (Supplementary Table 4).

Potential risk/protective factors for severe COVID-19

Hospitalized vs. non-hospitalized patients

Hemoglobin SS and Hgb SC showed similar proportion of patients hospitalized vs. non-hospitalized with COVID-19 (Table 4). Fever (69% vs. 24%, $p = 0.001$), VOC pain crisis (50% vs. 24%, $p = 0.047$), and ACS (54% vs. 0%, $p < 0.001$) were more common in hospitalized SCD patients (Table 4). Hematologic studies including CBC, coagulation labs, inflammatory markers were not significantly different between hospitalized and non-hospitalized patients (Supplementary Table 1).

Children vs. adolescent patients

The demographics and clinical presentation between our SCD children and adolescent patients with COVID-19 were similar overall. Symptoms of COVID-19, SCD genotype, HU use, voxelotor use, sickle cell symptoms, hospitalization rate, length of stay, respiratory support, oxygen requirement, blood transfusions, ACS episodes, CBC, inflammatory markers were not significantly different in children vs. adolescents in our cohort. However, adolescents were more likely to be on crizanlizumab treatment (0% vs. 18%, $p = 0.026$)

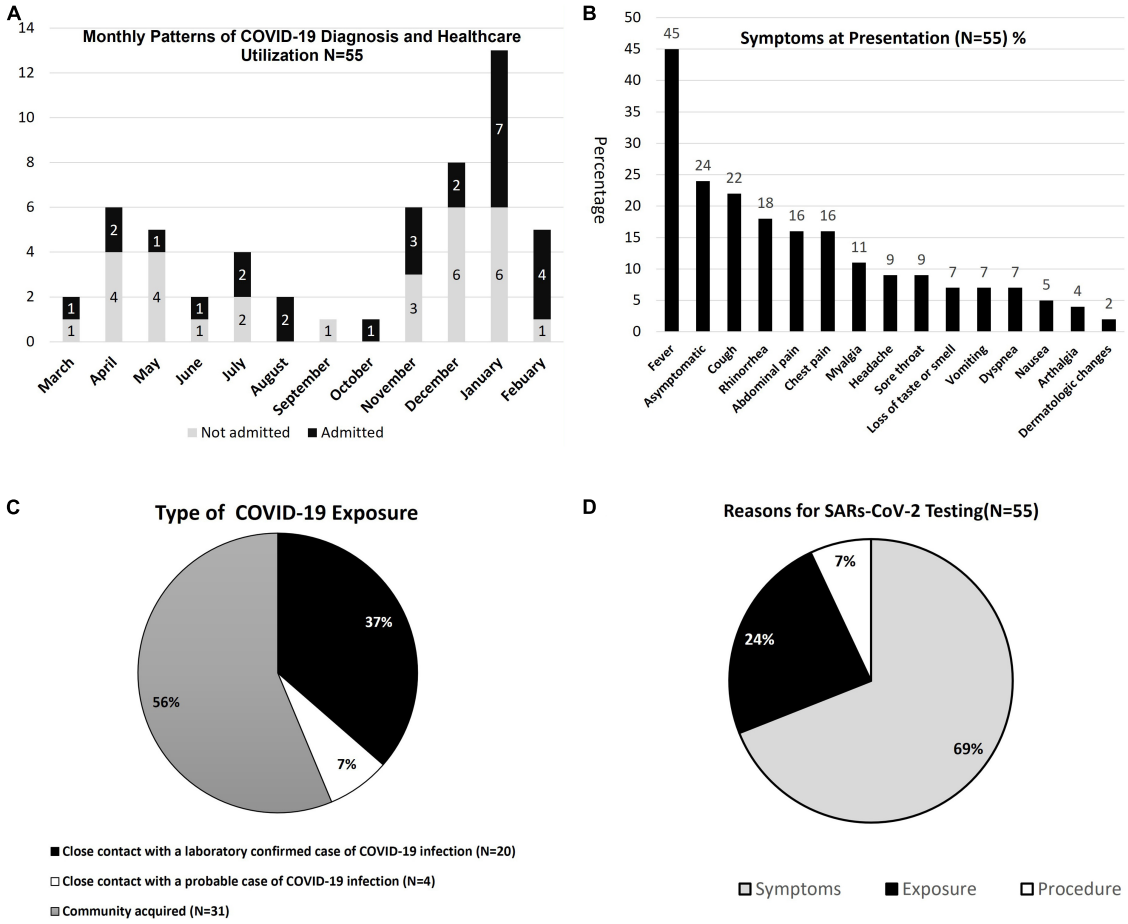

FIGURE 2
(A–D) COVID-19 admission patterns, symptoms, exposures, and testing.

and have an elevated D-Dimer (1.0 vs. 4.0 μg/mL, $p = 0.012$) on laboratory studies (Supplementary Table 5).

Hydroxyurea

Thirty-six patients (65%) were on HU. The median age on HU was 14 y/o versus 9.5 y/o not on HU ($p = 0.166$). Seventy-six percent ($n = 31$) of patients with HbSS and 33% ($n = 2$) of HbSB0 patients were on HU while the remaining HU patients were Hgb SC (38%, $n = 3$) ($p = 0.017$). No significant differences in length of stay, the prevalence of ACS, respiratory support, oxygen requirement, blood transfusions, CBC, coagulation labs, and inflammatory markers were found between those on HU at baseline, compared to those not on HU. However, patients taking HU were less likely to be hospitalized than those not taking HU (79%% vs. 50%, $p = 0.023$) (Table 4). Furthermore, 2 of the 3 patients requiring ICU level care were not on HU.

Discussion

Our study is one of a few pediatric comprehensive reports on the 1-year experience of patients with SCD and COVID-19 during the pandemic. We report that SCD remains a significant risk factor for morbidity in patients with COVID-19 disease. Specifically, the majority of pediatric and adolescent patients with SCD and COVID-19 sought medical care and nearly half required hospitalization. Patients not on HU were more likely to be hospitalized. While VOC, fever, and ACS were the most common presenting symptoms in those evaluated in the hospital setting, overall COVID-19 clinical severity was mild in most patients. COVID-19 infection rates in our SCD cohort mirrored the incidence of reported COVID-19 infection in our region (5). Comparatively, clinical severity reported from the SECURE registry showed that 18% of SCD patients with COVID-19 were asymptomatic, 56% had mild disease severity, 13% had moderate disease severity, 11% had severe disease severity, and 2% had critical disease severity (7). VOC was the most common SCD-specific presenting symptom and mechanical ventilation was required in 2.4% of their cohort.

One of the largest (non-SECURE registry) case series of COVID-19 SCD cases to date was the French experience which reported 83 hospitalized SCD patients infected by SARS-CoV-2 (12). They included 24 different centers with patients ranging from 3 months to 74 y/o (12). Fifty-four percent of patients presented with VOC and 28% with ACS. Among the 20% ($N = 17$) who were admitted to the ICU, 53% ($N = 9$) required Mechanical Ventilation, and 12% ($N = 2$) required extracorporeal membrane oxygenation (12). Previously non-SECURE registry published reports on COVID-19 SCD patients have primarily been adults, and reports in pediatrics

have been lacking in larger numbers (13, 14). A study from the US Peds COVID-19 registry, evaluated 27 pediatric patients with SCD and demonstrated increased morbidity and hospitalization rates although no patients required ICU level care (15). Minniti et al. published the largest US study (4 metropolitan areas) to date reporting on cases but included only 9 pediatric patients confirming a higher mortality rate in adults and those with pre-existing end-organ damage (13).

TABLE 3 Severity of sickle cell disease during+COVID-19 period*.

Level of severity	Definition	N	%
Asymptomatic	No clinical signs or symptoms during the positive COVID-19 period	13	24%
Mild	Symptoms of acute upper respiratory tract infection, including fever, fatigue, myalgia, cough, sore throat, runny nose, and sneezing or gastrointestinal symptoms or digestive symptoms such as nausea, vomiting, abdominal pain and diarrhea	30	54%
Moderate	Pneumonia, with or without clinical symptoms, no hypoxia	7	13%
Severe	Early respiratory symptoms or gastrointestinal symptoms followed by dyspnea and hypoxia (oxygen saturation less than 92%)	5	9%
Critical	Acute respiratory distress syndrome, respiratory failure, encephalopathy, shock, coagulopathy, multiorgan impairment (lung, heart, kidney, brain) that may be life threatening	0	0%

*Adapted from the SECURE registry (7).

TABLE 4 Sickle cell disease (SCD) COVID-19 patients non-hospitalized vs. hospitalized.

	Non-hospitalized (*N* = 29)	Hospitalized (*N* = 26)	**P*-value
Age median (IQR)	11 (6–18)	14 (5–18)	0.473
Sex (N,%)			
Male	13 (45%)	14 (54%)	0.504
Female	16 (55%)	12 (46%)	
Sickle cell genotype *N* (%)			
Hgb SS	22 (76%)	19 (73%)	0.553
Hgb SC	5 (17%)	3 (12%)	
Hgb Sβ0 Thal	2 (7%)	4 (15%)	
Hydroxyurea use	23 (79%)	13 (50%)	0.023
Oxygen saturation *N* (%) <95%	2 (10%) *N* = 20	13 (62%) *N* = 21	<0.001
Symptoms *N* (%)			
Fever	7 (24%)	18 (69%)	<0.001
Sickle cell disease presentation *N* (%)			
Vaso-occlusive crisis (any)	7 (24%)	13 (50%)	0.047
Acute chest syndrome	0 (0%)	14 (54%)	<0.001

**P*-value: Non-hospitalization vs. hospitalization. Hgb, hemoglobin; Sβ0 Thal, sickle beta zero thalassemia.

As compared to the general US population, our rate of hospitalization (47%) and need for Intensive Care-ICU (5%) is much higher than that reported (2.5% admission, 0.8% ICU) for children and adolescents (ages 0–24 years) (16) but in line with what has previously been reported for pediatric patients with SCD in a report of pediatric hematology/oncology patients in Texas (17) (47% hospitalization, 7% ICU) as well as for 0–18 years old in the SECURE registry (40.1% hospitalization, 5.8% ICU) (7). We had no mortality or need for mechanical ventilation or extracorporeal membrane oxygenation therapies despite sickle cell patients being relatively immunosuppressed. Our absence of mortality is also consistent with an investigation using the TriNetX database which demonstrated that even though patients with SCD have significantly higher rates of hospitalization, ACS, and VOC due to COVID-19, they do not have increased rates of mortality when a 1:1 propensity score matched comparison to the non-SCD Black population with COVID-19 was performed (18).

Of patients evaluated in a hospital setting (ED or inpatient), VOC (50%), and fever (45%) were the most common symptoms seen, and these same symptoms along with ACS were statistically more likely to lead to hospitalization. Patients with ACS and/or an oxygen requirement had significantly higher WBC count, lower nadir hemoglobin, and higher D-dimers. The D-dimer finding, though hard to interpret given its fluctuation with sickling of red blood cells (RBCs), is interesting as it has been shown to be an independent risk factor for death in both sickle cell and non-sickle cell patients with COVID (6, 13, 19). Also notable is that thromboembolism occurred in only a single adolescent patient (2%), despite there being an association between thromboembolism and both SCD (20) and COVID-19 (21). Some of this can possibly be explained by an early recognition of the risk of clotting, and proactive adherence to prophylactic anticoagulation at our institution without major or clinically relevant non-major bleeding. Hydroxyurea was the most common disease-modifying therapy which has been shown to decrease ACS and need for RBC transfusion in pediatric patients with SCD (22, 23). Two-thirds of our cohort was on HU and were less likely to be hospitalized than patients not receiving it confirming the protective effect of HU. This HU usage level was higher than both the SECURE registry (56% for children 0–18 y/o) (7) and the French experience (46% of total, 33% in children 0–14 y/o) (12). The beneficial effect of HU in our study contrasts with the SECURE registry study, where HU showed no effect on hospitalization and COVID-19 severity. However, both single-center (17) and multi-center publications (12, 13) demonstrated that the use of HU was associated with decreased hospitalization rates (17), need for ICU admission (12) or death (13).

Our cohort spans 12 months (March 2020–February 2021), during which time the medications used to treat COVID-19-related respiratory complications evolved significantly. From an early embrace and subsequent rejection of hydroxychloroquine to the recognition that the oral steroids (usually contraindicated in patients with SCD) are beneficial in respiratory failure patients (24) to the FDA approval and increased usage of the antiviral remdesivir (25). ACS was our most common admission diagnosis,

present in almost two-thirds of those admitted and treated per our institution's expert opinion established ACS pathway that included therapies such as antibiotics, inhaled corticosteroids in conjunction with bronchodilators, and supplemental oxygen when indicated. Intravenous or oral corticosteroid use was considered a mainstay of inpatient COVID-19 therapy but was limited in SCD patients given the known association with rebound VOC (26–28). Despite a low rate of dexamethasone usage, inhaled corticosteroids, which we commonly use as part of an established ACS pathway, were used, and may have contributed to low ICU utilization, given their demonstrated association with good outcomes if initiated early in COVID-19 infection (29).

Over 200 million in the United States have been fully vaccinated against COVID-19, with children 5–11 years old recently being approved through Emergency Use Authorization as of October 2021 (30). Given the morbidity observed within our SCD cohort of children and adolescents, COVID-19 vaccination within this age group may prove beneficial in reducing unwanted SCD complications and hospitalizations. Additional end-organ damage resulting from an acute COVID-19 infection in SCD within the 1st two decades of life is unknown but may contribute to future SCD morbidity in an infection that has already exhibited subacute and chronic complications in the form of Long COVID-19 syndrome (31).

At the beginning of the pandemic, there was a poor understanding of the impact of COVID-19 in pediatric patients with SCD. Management guidelines stemmed from early reports conducted primarily in adult patients and evolved with an improved understanding of the disease pathology. Our study was a non-comparative observational study; thus, it was difficult to make comparisons due to confounding by indication. Additionally, our registry captures only those patients that either presented to CNH for care during their COVID-19 infection or provided documentation to their provider if tested out in the community. Patients received standardized therapies based on the severity of their COVID-19 disease, much of which was supportive and not disease-directed. Routine laboratory evaluation encompassing inflammatory and coagulation markers was not universally obtained early in the pandemic. We also have limited information on how the use of blood transfusions and supplemental oxygen compares to other respiratory viral infections and global viral pandemics. While our study cohort included asymptomatic patients with SCD who were tested for various reasons and found to have COVID-19, it is likely there were more patients with SCD at our institution who had COVID-19 and were asymptomatic or had only minimal symptoms. Our study thus likely over-estimates the morbidity associated with COVID-19. Further investigation into the clinical presentation and outcomes with the emergence of variants is needed and may inform long-term sequelae of COVID-19 infection.

Conclusion

Our study describes one of the largest, SCD single-center experiences of pediatric SCD patients during the COVID-19 pandemic. It will add to a growing body of literature on pediatric SCD and COVID-19 cases describing the impact of specific SCD and COVID-19 related therapies on clinical outcomes. We report similar morbidity patterns (ACS, Pain/VOC) between SCD pediatric and adolescent patients with COVID-19. While morbidity was variable in our cohort, we saw no mortality within our pediatric and adolescent SCD patients with COVID-19 infection similar to observations made by the Quebec registry which spanned 2 years (32). In comparison to previously published adult reports, the absence of mortality may be attributable to lower end-organ damage in our adolescent cohort or the fact that approximately two-thirds of patients were on some form of disease-modifying therapy. Additionally, we saw a wide array of adjunctive therapies (i.e., remdesivir, anticoagulant thromboprophylaxis) added to routine SCD management. Future studies will compare the impact of best practices throughout consecutive years of the pandemic as well as investigate the emergence of long-COVID in patients with SCD.

Data availability statement

The datasets presented in this article are not readily available because restrictions are provided by our CNH hospital IRB of record. Requests to access the datasets should be directed to AC, acampbell@childrensnational.org.

Ethics statement

The studies involving human participants were reviewed and approved by Children's National Hospital Institutional Review Board. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

OM, DD, StM, MS, and AC wrote and critically edited the manuscript, designed the study, performed the research, and analyzed the data. RN, AL, BS-B, BM, JB, JW, and SuM critically edited the manuscript and analyzed the data. JB provided statistical analysis. All authors contributed to the article and approved the submitted version.

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Conflict of interest

AC: consultancy and research: Global Blood Therapeutics, Novartis Pharmaceuticals, Forma Pharmaceuticals, and Agios Pharmaceuticals. DD: consultancy: Novartis, Global Blood

Therapeutics and Hilton Publishing Inc.; research: Novartis. BS-B: consultancy: Novartis and Chiesi.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2023.987194/full#supplementary-material

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The oxygen dissociation curve of blood in COVID-19–An update

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An impressive effect of the infection with SARS-Co-19 is the impairment of oxygen uptake due to lung injury. The reduced oxygen diffusion may potentially be counteracted by an increase in oxygen affinity of hemoglobin. However, hypoxia and anemia associated with COVID-19 usually decrease oxygen affinity due to a rise in [2,3-bisphosphoglycerate]. As such, COVID-19 related changes in the oxygen dissociation curve may be critical for oxygen uptake and supply, but are hard to predict. A Pubmed search lists 14 publications on oxygen affinity in COVID-19. While some investigations show no changes, three large studies found an increased affinity that was related to a good prognosis. Exact causes remain unknown. The cause of the associated anemia in COVID-19 is under discussion. Erythrocytes with structural alterations of membrane and cytoskeleton have been observed, and virus binding to Band 3 and also to ACE2 receptors in erythroblasts has been proposed. COVID-19 presentation is moderate in many subjects suffering from sickle cell disease. A possible explanation is that COVID-19 counteracts the unfavorable large right shift of the oxygen dissociation curve in these patients. Under discussion for therapy are mainly affinity-increasing drugs.

KEYWORDS

hemoglobin oxygen affinity, sickle cells, anemia, erythroblasts, *in vivo* oxygen dissociation curve

1. Introduction

Infection with SARS-CoV-19 causes multiple organ failure. An especially impressive effect is the impairment of oxygen uptake. The underlying general pathophysiology of COVID-19 has been previously reviewed by various authors, e.g. (1, 2). The impairment of oxygen uptake specifically relates to (a) impaired oxygen diffusion due to edema formation in the injured lung, (b) V/Q mismatch due to microvascular thrombosis, loss of hypoxic pulmonary vasoconstriction, or bronchopulmonary anastomoses, and (c) impaired oxygen transport in blood due to anemia resulting from cell damage or reduced cell production. In addition, ECMO treatment may cause hemolysis and a rise in COHb concentration. Further, changes in oxygen affinity of hemoglobin occur [reviewed by 3] which may affect oxygen uptake and delivery: In the lung an increase in affinity may facilitate O_2 uptake while oxygen delivery to consuming cells is enhanced by decreasing affinity.

Pubmed searches for COVID-19 AND hemoglobin (1,090 articles), COVID-19 AND erythrocytes (559 articles) or COVID-19 AND erythrocyte function (310 articles) yield a

large body of publications. Most decisive for red cell function is, however, hemoglobin oxygen affinity. Yet, only 14 publications address COVID-19 AND hemoglobin oxygen affinity, which is still 2 times more than in the first quarter of 2021, when we wrote our first review (3). Only 8 of these publications, however, contain actual measurements, the remaining are reviews, comments or letters to the editor. Some aspects in the more recent articles are new and help to refine our understanding of oxygen uptake, transport and delivery in COVID-19. In particular, the presence of the ACE2 receptor in part of the erythroblasts which allows binding of SARS-CoV-2 may be relevant (4). Similarly, binding of SARS-CoV-2 to Band 3 has been suggested by *in silico* data. Before discussing the most recent findings on the oxygen dissociation curve, a description of the physiological basis and a summary of the previous review are useful.

2. Determinants of hemoglobin oxygen affinity

Oxygen affinity is an intrinsic property of hemoglobin in red blood cells that can be modified by a variety of factors [reviewed e.g., by 5]. For determination of oxygen affinity the oxygen dissociation curve (ODC) has to be measured. Characteristic properties of the ODC are the half saturation pressure P_{50} and the slope n (see below) in the logarithmic Hill plot. A low P_{50} is favorable for oxygen binding to Hb in the lung capillaries, while a high P_{50} is favorable for oxygen delivery to the consuming cells. *In vivo* variations in pH (higher in the lungs than the consuming tissues), PCO_2 (lower in the lungs) and temperature (lower in the lungs than in tissues with high energy turnover) as well as additional, partly unknown factors may cause such variations in affinity. The resulting *in vivo* ODC is therefore steeper than the standardized *in vitro* curve (see below).

Various factors are important for oxygen affinity. There are intraerythrocytic (e.g., cell age) and extraerythrocytic (e. g. plasma concentrations of influencing substances) effects. An overview is presented in Table 1.

TABLE 1 Internal (erythrocytes) and external (plasma and interstitial fluid) regulators of Hb-O_2 affinity.

Parameter	Change of P_{50}	Known change during COVID-19
Internal		
Type of Hb	∧ or ∨	No change
2,3-BPG	∧	Slight increase?
ATP	∧	∧?
GSH	∨	No change
Production of acids (e.g., lactic acid)	∧	Possibly increased
Cellular concentration of non-diffusing substances (Donnan equilibrium)	∧	?
Non-diffusing anions (Donnan equilibrium)	∨	Depending on plasmaprotein concentration
Cell age	∨	?
External		
Temperature	∧	∧
Osmolality	?	?
pH	∨	Variable
PCO_2,	∧	Variable, initially low
HCO_3^-	∨	Variable
Other diffusible anions (mainly Cl^-. La^-)	∧	Variable
Non-diffusing anions (Donnan equilibrium)	∨	Depending on plasmaprotein concentration

Data from sources evaluated in Böning et al. (3) and Mairbäurl and Weber (5).

2.1. Intraerythrocytic effects

Besides the type of Hb (HbA in most subjects), the following substances produced in the red cells are especially relevant: While 2,3- bisphosphoglycerate (2,3-BPG) and adenosin triphosphate (ATP) increase P_{50}, glutathione (GSH) reduces it moderately. A new analysis of the GSH effect was published recently (6). Additionally all not freely diffusing anions (especially Hb^- because of its high concentration) influence the Donnan equilibrium and increase the intraerythrocytic $[H^+]$.

2.2. Extraerythrocytic effects

In addition to intraerythrocytic factors, properties of blood plasma are also influential. In contrast to *in vitro* investigations exchange with the interstitial space is relevant *in vivo* especially in the oxygen consuming tissues. In COVID-19 the small extracellular space in the lungs may be increased by the accumulation of interstitial or even alveolar edema fluid. The concentrations of CO_2, Cl^-, lactic and other fixed acids as well as water (osmolality) in the erythrocyte equilibrate with the surrounding fluid; but because of the Donnan effect especially of Hb the concentrations of freely exchangeable anions are lowered compared to the plasma. All acids and bases influence the pH, but those entering the red cell (e.g., CO_2, Cl^-, lactic acid) can additionally bind to Hb at its end-terminal nitrogen. Lactic acid is produced not only in the muscles, but also within the red cells and interchanges slowly after binding to the monocarboxylate-transporter 1 (7–9). A relevant influence of nitric oxide on hemoglobin oxygen affinity on the other hand is disputed because of its very low concentration compared to Hb (5).

3. Methods for the determining O_2 affinity

The classical method for the determination of O_2 affinity is measurement of oxygen saturation (SO_2) or content *in vitro* after equilibration of blood with varying PO_2 at standard conditions (pH 7.4, PCO_2 40 mmHg, temperature 37°). While PCO_2 and temperature can be set by the investigator, pH varies slightly because of the Haldane effect and has to be corrected for (see below). These *in vitro* conditions resemble the situation in the

healthy lungs with a very small extracellular volume. The influence of temperature and acids can be studied by equilibration at different conditions (PCO_2, temperature) or after addition of acids or bases (e.g., HCl, lactic acid). A drawback is the required volume of blood; approximately a minimum of 5 ml is necessary for one curve with five points when using sphere tonometers. We have previously reduced this to 2–3 ml for 10 points by adding oxygen to desaturated blood in a syringe (10). A frequently used apparatus is the Hemox-Analyzer (11–13) where only 50 µl of blood are added to 50 ml buffer solution (100 mmol/l sodium chloride, 5 mmol/l potassium chloride, 30 mmol/l imidazole buffer, 5 mmol/l sodium phosphate, 5 mmol/l glucose) and equilibrated with oxygen or nitrogen. Advantages are the ability to investigate minimal red cell volumes as well as isolated erythrocytes, and possible manipulation of experimental conditions. The lack of CO_2 in this assay has rightfully been criticized by Harutyunyan et al. (14). In addition, the buffer lacks Ca^{++}, bicarbonate, proteins, and lipids. Further, substances in the plasma which interchange with red cells or influence the membrane potential (e.g., bicarbonate and lactate) are largely diluted resulting in their efflux from the erythrocytes into the buffer solution. As such, characteristic *in vivo* effects of these compounds may completely disappear *in vitro*. Some of the drawbacks can be abolished by using a plasma-like solution and adding CO_2 to the equilibration gas, as previously described by e.g., (15). A new apparatus where only some microliters of undiluted native blood are necessary might be useful in the future (16).

Because of lacking laboratory facilities, small available blood volumes or risk of infection, most investigators of COVID-19 have calculated P_{50} values from single blood samples after routine blood gas analysis. The following equations published by Severinghaus (17) are most often applied for correction to standard conditions (pH 7.4, base excess 0 mequ/l, 37°C):

Correction for Bohr shift by CO_2 and fixed acid (e.g., lactic acid):

$$\Delta \log PO_2 = -0.48\Delta pH + 0.0013\Delta \text{base excess} \quad (1)$$

Correction for temperature shift:

$$\Delta \log PO_2 = 0.024\Delta T \quad (2)$$

Presentation in the Hill diagram (18):

$$\log SO_2/(100 - SO_2) = n^*\log PO_2 + K \quad (3)$$

The slope n is rather constant over a large range of SO_2 [e.g., (19)] allowing to calculate a standard P_{50} from one pair of PO_2 and SO_2 measurements. However, n may be influenced by additional factors such as physical training (20) or illness, e.g., peripheral artery disease (21) or cystic fibrosis (19).

Yet, various modulating factors were initially not known and are therefore not considered in these equations, especially the effect of organic phosphates like 2,3-BPG (22, 23) and the modulation of the Bohr effect as a function of oxygen saturation at values below 20 as well as above 90% SO_2 (24, 25). To avoid influences of the latter, Severinghaus (17) suggested to use only samples between 20 and 80% SO_2 for the P_{50} calculation. As long as the deviations from the standard conditions are small, these effects are of no major relevance. A more important problem is, however, whether these factors are equally large *in vivo*. Specifically, we have observed considerably *in vivo* deviations of P_{50} as well as of the Bohr coefficients in various studies [discussed e.g., in (19, 26)], which may be attributable to the constant exchange of substances between blood, interstitial fluids, and even parenchymal cells.

4. Summary of our first review

In our initial review on the topic (3), four papers containing measurements of oxygen affinity were considered (27–30). The techniques used in these for the determination of O_2 affinity were either the Hemox-Analyzer or calculation from single arterial or venous blood samples applying Severinghaus' equations to obtain the standard half saturation pressure P_{50}.

In these reports, no right shift of the ODC was detected as would normally be expected in patients with hypoxia due to a counterregulatory increase in [2,3-BPG] (5). The largest investigation (30) even showed a left shift calculated from thousands of venous or arterial blood samples (23.4 mmHg compared to the accepted value of 26.7 mmHg in healthy subjects). This was astonishing since the patients additionally suffered from marked anemia. Anemia might cause an increase in P_{50} to more than 30 mmHg resulting from high 2,3-BPG concentrations (15); additionally Hill's n tended to higher values at SO_2 above 50% in this investigation. At that time, we speculated that a high concentration of methemoglobin (MetHb) as observed in some investigations [summarized by Scholkmann et al. (31)] might have reversed the anemia effect in COVID-19 patients and caused a left shift of the ODC. Additionally we suggested that various commonly observed, yet not very well-understood *in vivo* effects might have caused a further left shift in Vogel's (30) investigation.

In this context, the following methodological problems have to be considered: P_{50} in COVID-19 patients was compared to values obtained in patients with other (non-COVID) diseases, while a comparison with healthy subjects would have been preferable. Measurement of complete ODCs at different physiological conditions (pH, PCO_2, temperature) with established methods especially including determination of 2,3-BPG had not been performed. The latter has been measured only in one study on erythrocytic metabolism in moderate COVID-19, but only arbitrary units were presented hinting to slightly elevated concentrations (32). Reasons for the surprising paucity of data on [2,3-BPG] in COVID-19 might be that the appropriate commercial test kits are no longer available and that the physiological laboratories specialized in [2,3-BPG] measurements are not prepared for work with infectious samples.

5. New publications on hemoglobin oxygen affinity in COVID-19

Pubmed and Google Scholar were searched up to December, 2022 for "COVID-19 AND oxygen dissociation curve" as well as "COVID-19 AND hemoglobin oxygen affinity." An overview is presented in **Table 2**.

Early after the publication of our review Vogel et al. (33) communicated that they had meanwhile measured methemoglobin levels and detected no increase in the majority of cases. Specifically,

TABLE 2 Oxygen affinity in COVID-19 patients.

Authors	COVID-19 group	Comparison group	P_{50} (mmHg) COVID-19	P_{50} (mmHg) comparison	Signif. *p*	[Hb] (g/dl)	Method	Annotations
De Martino et al. (27)	12m, 9f	10m, 11f ARDS	Data lacking	26.7	ns	~13	G	v. No clear deviation from theoretical standard ODCs, but tendency for a right shift
Daniel et al. (28)	7m, 7f	5m, 6f no diagnosis	29.0 ± 2.3	28.5 + 1.8	ns	9.3 ± 2.3 14.3 ± 1.1	H	Anemia in COVID-19 patients
Renoux et al. (29)	7	7 healthy 7 sepsis	29.7 [27.2; 31.0]	26.7 [26.3; 29.3]; 27.6 [27.0; 30.6]	ns	11.6 [9.0; 14.4] 10.7 [9.8; 12.4]	H	v. SO_2 of all and Hb of healthy subjects not communicated
Vogel et al. (30)	43m and f	828 critically ill	23.4 ± 3.1	24.6 ± 5.4	< 0.001	8.1 ± 1.2 9.4 ± 2.0	C	a and v. Comparison to standard P_{50} 26.7 $p < 0.0001$
Gille et al. (38)	70m, 30f	69m, 31f histor. control	26 [25.2–26.8]	25.9 [24.0–27.3]	ns	14 [12.6; 15.2] 13.2 [11.4; 14.7]		a. Diagnosis in historical control not communicated!
Pascual-Guàrdia et al. (42)	79m, 60f	73, historical control or negative PCR	not calculated	not calculated		13.3 ± 1.8 11.8 ± 2.4	C	a. P_{50} not calculated, but many PO_2 values differ > 2 SD from mean. Sex of comparison patients not communicated.
Pascual-Guàrdia et al. (42)	110m, 105f	379, historical control or negative PCR	not calculated	not calculated			C	v. P_{50} not calculated, but many PO_2 values differ more than 2 SD from mean. Sex of comparison patients not communicated.
Laredo et al. (45)	89m, 35f	104m, 37f	27.4 ± 0.3	27.5 ± 0.2	< 0.05	11.1 [9.6; 13.2] 10.8 [9.4; 12.7]	C	Probably a and v. Lower Bohr coefficient in COVID-19.
Ceruti et al. (50)	25 survivors	7 deceased	23.0 ± 1.6	32.2 ± 7.9	< 0.01	11.5 ± 2.0	C	a. Comparison deceased vs. survivors
Hlutkina et al. (51)	15	15 healthy	31.8 [29.5; 34.3]	27.9 [27.5; 28.9]	< 0.05	12.1 [9.2; 13.0] 14.1 [11.7; 14.4]	C	v. SO_2 not communicated
Valle et al. (56)	517	314	26.3 ± 1.2 vitro 25.7 ± 1.4 vivo	26.8 ± 2.9 vitro 27.1 ± 2.8 vivo	0.001 0.001	13.0 ± 1.8 13.0 ± 2.3	C	a. Higher survival in patients with initial P_{50} < 27 mmHg
Bergamaschi et al. (57)	289m *In vivo*	289m *In vitro*	25.4 [24.5–6.4] *in vivo*	27.2 [26.3–28.2] *in vitro*	0.01	12.9 [11.7–141]	C	Mild form of illness, age 75 (63–82) years

Explanations: m, male; f, female; ARDS, viral pneumonia-induced acute respiratory distress syndrome; ns, not significant. P_{50} calculated for standard conditions. vitro, *in vitro*; vivo, *in vivo*. Methods: H, Hemoxanalyzer; C, calculation from arterial or venous measurements by applying Hill or Severinghaus equations; D, calculation from arterial or venous measurements by applying Dash equations; G, graphical representation in the SO_2-PO_2 diagram. Annotations: a, arterial; v, venous.

MetHb exceeded 3% in only 30 of 3,518 samples. This finding was also supported by Gille et al. (34) in a comment (see below). In other studies, however, elevated MetHb levels might play a relevant role: Alamdari et al. (35) reported an average of 16.4 ± 9.1 SD% in 21 severely ill patients treated in the intensive care unit. Caution is warranted as some MetHb formation may also occur during the time between blood sampling and measurement. In our own investigations (30) measurements were performed immediately after blood sampling. Alamdari et al. (35), however, state that their samples were transported on ice to the laboratory. But formation of MetHb is an autoxidative process without molecule collisions which cannot be prevented by cooling. As such, MetHb may cause a left shift of the ODC in patients with COVID-19, especially when treated with drugs favoring MetHb formation such as chloroquine and hydrochloroquine. These substances were not applied in the patients studied by Vogel et al. (30).

Hence, the cause for the low P_{50} in Vogel's paper remains unknown and the measurement of 2,3-BPG becomes ever more important. Unfortunately, we had to recognize that previously utilized commercial test kits are no longer produced (36), which

is likely the reason why none of the above mentioned papers on oxygen affinity in COVID-19 with the notable exception of the report by Thomas et al. (32) measured [2,3-BPG], and even the Thomas paper determined only relative concentrations (Personal communication A. D'Alessandro). As such, it remains unclear whether the detected left shift in Vogel′s study occurred because of a lack of the (physiologically expected) increase in 2,3-BPG or whether it was caused by unknown factors despite elevated [2,3-BPG]. Various substances (e.g., ATP, Cl^-, lactate, glutathione) may have influenced oxygen affinity in this investigation (36). The concentration of NO in blood is low but its binding mechanism to Hb is similar to MetHb formation at high oxygen saturation; as such NO may possibly influence the position of the ODC during the lung passage (37); this effect, however, disappears at low oxygen saturation in the tissue capillaries.

While our first review was in press, Gille et al. (38) published a similar study as Vogel et al., but did not detect a change in the ODC in their COVID-19 patients compared to a non-uniform group of patients with infection, airway disease, interstitial lung disease, or heart failure. MetHb was also not increased, similar to Vogel's investigation. Subsequently the authors also wrote a letter to the editor with respect to our review (34). A careful analysis of both papers yields the following conclusions (39):

(1) Gille et al. evaluated data from 100 patients with COVID-19 and compared them to 100 patients with acute respiratory failure (infection, airway disease, interstitial lung disease, or heart failure) who had been assessed prior to the emergence of the COVID-19 pandemic. They did not detect differences in the P_{50} [median 26 (25.2–26.8) versus 25.9 (24–27.3) mmHg]. The number of measurements was, however, much smaller than in Vogel's study (19.463 from 43 COVID-19 patients and 828 critically ill patients with acute respiratory failure), and the average Hb concentration was markedly higher (median 14.0 g/l versus mean value 8.1 g/dl).

As PO_2 scatters markedly at saturations higher than 97%, Gille et al. excluded these values. According to various investigations, [e.g., (24, 25)] also the Bohr effect is markedly reduced above 90% SO2. Therefore, this exclusion is reasonable.

Vogel et al. (30) did not exclude data, instead, they evaluated all measurements between 20 and 100% SO_2. Mean values of approximately 94% SO_2 were similar for COVID-19 patients and the control group. The Bohr effect correction was negligible (pH 7.382 ± 0.077 SD). Outliers were present in both groups, therefore the detected P_{50} difference can be assumed to be real. One may conclude that the different results in the studies by Vogel et al. and Gille et al. do not seem to be caused by different methods, but to depend on other causes such as different severity of the illness; this notion is supported by the fact that all patients in Vogel's study received ventilator support, and that [Hb] was much lower than in Gille's study.

In Figure 2 Gille et al. present the time course of the standard P_{50} over 18 days in COVID-19 patients and non-COVID patients. They do not find a significant difference, albeit a tendency for lower mean values in the COVID-19 patients relative to the control group is visible (e.g., a 2 mmHg difference on days 8–10). Possibly the number of measurements (maximally 15 on each day) was too low or the variability of diseases in the non-COVID patients (infections, airway disease, interstitial lung disease, heart failure, surgical interventions) too high. In any case lack of significance does not proof the absence of an effect.

Surprisingly Gille et al. added COHb to O_2Hb for the calculation of SO_2. This is not correct in our eyes, but used in some apparatus (40). Accordingly, the calculated P_{50} is lowered, but [CO-Hb] is rather small in this investigation and therefore the effect presumably negligible.

Additionally, 55 subjects with high CO-Hb and 30 subjects with sickle cell disease (see below) were studied. As expected, the ODC was left shifted in the CO-Hb group.

(2) Similar to the previous report by Vogel et al., the findings of Gille et al. exclude MetHb as main factor for a left shift of the *in vivo* ODC in COVID-19. As mentioned above, a possible influence of variable NO-binding to Hb might yield an alternative explanation for the reported left shift (36). On the other hand, erythroblasts express ACE2 on the plasma membrane and are therefore potentially vulnerable to SARS-CoV-2 infection in cases of viremia (41); this, again, might influence oxygen affinity.

Pascual-Guàrdia et al. (42) published a rather large investigation (approximately 1,100 arterial or venous samples) in COVID-19 patients who in most cases were not critically ill (no mechanical ventilation, mean Hb concentrations of 13.3 ± 1.8 SD g/dl) and compared them to an even larger group of patients with pulmonary dysfunction caused by other illnesses. The authors did not observe a significant change in oxygen affinity, but scattering was very large. In 35 venous samples the difference between measured and calculated SO_2 (by use of three published standard curves) was larger than two standard deviations (approx. ± 6%).

In a letter to the editor we (43) therefore suggested that changes in Hb-concentration or other indicators of severe illness (e. g. mechanical ventilation) might have influenced P_{50} in these patients. Possibly the effects of critical illness with profound anemia were similar to those reported by Vogel et al. (30), and might thus have caused the large scatter in the study by Pascual-Guàrdia et al.

Subsequently Pascual-Guàrdia et al. (44) presented data for severely ill patients only. In this group, again, no significant change in P_{50} was detectable, but the scattering remained improbably large. Therefore, the data of Pascual-Guàrdia neither supports nor contradicts those measured by Vogel et al. (30).

Laredo et al. (45) published a letter to the editor reporting a large investigation comparing patients treated in the intensive care unit (5,291 measurements in COVID-19 patients in 2020 versus 3,449 measurements in Non-COVID patients in 2018–2019); more than 60% were mechanically ventilated. The reference group suffered from bacterial pneumonia (n = 80, 56%), influenza (n = 32%), and non-infectious injuries; this selection is similar to that by Gille et al. (38). Average arterial SO_2 was high in both groups [95.7 (93.9–96.8)% in COVID-19 patients vs. 95.1 (91.7–96.3)% in Non-COVID patients with slightly higher values in COVID-19 patients (p = 0.03), the corresponding PO_2 amounted to 107 mmHg (91–128) and 95 mmHg (77–115), respectively (p = 0.002)]. Yet, at least 100 SO_2 values were lower than 70%. The medians of PCO_2 [43 mmHg (38–48) vs. 42 mmHg (37–49), (p = 0.87)] and pH [7.41 (7.38–7.45) vs. 7.40 (7.34–7.44), (p = 0.04)] were in the normal range, but individual values scattered considerably.

The authors applied a relatively complicated equation for P_{50} calculation: the constants for correction to standard conditions (P_{CO2} = 38 mmHg, pH = 7.4) were obtained from each patient′s data, for comparison the median was used. Hb concentration amounted to 11.1 [9.6–13.2] and 10.8 [9.4–12.7] g/dl, respectively, corresponding to moderate anemia.

In COVID-patients, the calculated standard curves were only slightly yet significantly left-shifted by 0.1 mmHg as compared to the reference group (27.5 ± 0.2 SD mmHg). This shift is physiologically negligible. Interestingly, however, the calculated Bohr coefficient for CO_2 was slightly reduced in COVID-19 patients, which reduces the *in vivo* P_{50} further.

The main problem with P_{50} calculation in this investigation is that many PO_2 were very high (up to > 300 mmHg in Figure 1 of Laredo's article). The large scattering as well as the disappearance of the Bohr effect reduce the probability of a correct P_{50}-calculation from these values. Laredo er al. did not exclude values above 95% like some other authors. But when considering all single standardized values (SO_2 versus PO_2) presented in Figure 1 of Laredo's article, it is visible that below 95% saturation the majority of points in the COVID-patients are left-shifted compared to the Non-COVID group.

To summarize: This investigation shows only a minor effect of COVID-19 on the ODC, but experimental limitations may have obscured a potentially larger effect. Specifically, a potential left shift at high oxygen saturation and a corresponding right shift at low saturation levels may have cancelled each other out and resulted in a seemingly unchanged mean value.

An article possibly clarifying the discrepancies in preceding publications might be "Temporal Changes in the Oxyhemoglobin Dissociation Curve of Critically Ill COVID-19 Patients" by Ceruti et al. (46). Arterial blood gases were repeatedly assessed in the intensive care unit (3,514 analyses in 32 patients) and the standard P_{50} values of the first 3 days were compared to those measured over the last 3 days. Most patients showed a left shift similar to the study by Vogel et al. (30). A difference between early P_{50} and late P_{50} was detected (20.63 ± 2.1 vs. 18.68 ± 3.3 mmHg, $p = 0.03$ for all patients); however, when values of deceased patients (the number is not communicated) were analyzed, an increase in median P_{50} was observed compared to data in survivors (24.1 vs. 18.45 mmHg, $p = 0.01$).

This decrease of arterial P_{50} in the majority of patients which supports oxygenation in the lungs might be an important advantage for survivors and explain the differing results in former studies. Unfortunately, however, these P_{50} values are improbably low which we have criticized in a letter to the editor (47). Ceruti et al. (46) used equations published by Dash et al. (48) which are rather complicated compared to those of Severinghaus. As they presented no comparing measurements in healthy subjects, a check for a possible calculating error was impossible. Yet, we had never seen such low values in human blood of adults with normal HbA. According to Duhm (49) the standard P_{50} for human red cells completely depleted of 2,3-BPG decreases to only 16 mmHg.

We have therefore recalculated the results using the Hill equation (equ. 3) after correction to standard conditions and assuming $n = 2.7$ (47). When applying this procedure to Ceruti's data for all patients in their Table 1 (probably means of initial values), we obtained an average P_{50} of 26.9 + 1.9 SD mmHg, which is almost equal to Severinghaus' standard value of 26.7 mmHg. Similarly, the individual values for each patient in their Table 2 were much higher after recalculation (22.9–32.3 mmHg) than those given in Ceruti's paper. Only 7 single values were lower than 25 mmHg. We evaluated also the data for the 25 and the 75% percentile of SO_2 in Ceruti's Table S1. The P_{50} calculated from these values are lower (23.0 and 22.5 mmHg) but still higher than the means in Ceruti's paper (initially 20.6, at the end 18.7 mmHg). Exclusion of samples with SO_2 higher than 95% to avoid the large scattering of PO_2 did not change the mean standard P_{50}.

As such, it became obvious that the P_{50} values calculated by Ceruti et al. cannot be correct. Yet, the observed temporal decrease in survivors is likely real as a systematic error should similarly affect all calculated values during the stay on the intensive care unit. Unfortunately, a control group of patients with other illnesses as in the paper by Vogel et al. (30) was not included in this study.

In their answer to our letter, Ceruti et al. (50) conceded that the originally reported low P_{50} values resulted from a calculation error and announced a revised paper. They communicated that at the end of the stay surviving patients presented a P_{50} of 23.0 + 1.6 compared to 32.2 + 7.9 mmHg in deceased patients. A possible cause might be that anemia was less severe in the recovered patients and therefore [2,3-BPG] concentration lower.

One recently published paper by Hlutkina et al. (51) shows an increase in the standard P_{50} in 15 patients at admission to the hospital compared to 15 healthy subjects (median 31.8 versus 27.9 mmHg) calculated from venous measurements with rather low saturations (median 60%). The authors suggest an effect of increased NO concentrations, which had been previously reported by Mortaz et al. (52).

Since right shifts of the ODC in venous blood have been observed during exercise, e.g., (20, 53, 54) as well as in disease (21, 55), this is not entirely surprising. Such a right shift facilitates oxygen delivery to consuming tissues, yet it simultaneously impacts oxygen uptake in the lungs. Notably, in the investigation by Vogel et al. (30) the reported left shift is only visible in samples with saturations above 50%. Yet, when we recalculated P_{50}-values from the medians in the article of Hlutkina and Zinchuk applying Severinghaus' equations for correction to standard values and Hill's equation for calculation of P_{50}, we obtained for both groups 30.1 mmHg. We contacted the authors who assured us that their measurements and calculations were correct. A possible explanation for this discrepancy might be that the medians for PO_2, SO_2 and pH were measured in different blood samples, a problem which does not exist for mean values. Yet, as a consequence the results of this article have to be taken with a huge grain of salt. In Vogel′s et al. article (30) the left shift is not very pronounced when calculated from means, but clearly visible in the apparently not normal distribution of the single values.

The last paper that came to our knowledge was written by Valle et al. (56). They evaluated arterial blood gas measurements below 92% SO_2 for P_{50} calculation at entry to the hospital before treatment in 552 COVID-19 patients (75 were accepted into the intensive care unit) and 314 non-COVID respiratory patients applying the equations also used by Vogel et al. (30). Mean standard P_{50} was slightly lower in COVID-19 patients (26.3 ± 1.2 versus 26.8 ± 2.9 mmHg, $p < 0.001$). This difference was more pronounced for *in vivo* conditions, i.e., blood pH, temperature, PCO_2, and carboxyhemoglobin levels of the patient (25.7 ± 1.4 versus 27.1 ± 2.8 mmHg, $p < 0.001$). In spite of this still small general effect arterial oxygen content was markedly higher in COVID-patients compared to the Non-COVID group with *in vivo* P_{50} below 27 mmHg [17.2 (15.7–18.7) vs. 15.2 (13.0–16.6) mL/dL ($P < 0.001$)]. Interestingly, however, [Hb] was negatively correlated

with both *in vitro* and *in vivo* P_{50} showing that the known right-shift effect of anemia was preserved. The prevalence of hypoxemia (73.3 vs. 57.3%, $p < 0.001$), hypocapnia (59.4 vs. 35.7%, $p < 0.001$), combined hypoxemia and hypocapnia (59.4 vs. 27.8%, $p < 0.001$) and alkalosis (53.4 vs. 30.9%) was greater in COVID-19 patients than in the reference group.

Surprisingly, both P_{50s} and P_{50i} increased significantly over 18 days in the hospital in a subgroup of 33 subjects with regular measurements every 3 days from 25.8 to 27.5 mmHg. The percentage of patients with $P_{50i} < 27$ mmHg decreased from 78.8% at baseline to a minimum of 21.2% 6 days later and still amounted to only 45.5% after 18 days. In 6 patients P_{50} rose by more than 4 mmHg. An important result is that mortality was significantly lower (12.9 versus 23.7%, $p = 0.014$) in patients with low (< 27 mmHg) as compared to those with high P_{50i} (> 27 mmHg) at entrance to the hospital.

It seems astonishing that these relatively small changes may have affected survival, yet it should be considered that in the lungs at approximately 90% saturation the PO_2 differences are increased (see Table 3). It is also possible that the changes are larger during movements or vary during the day. Since anemia was positively correlated with P_{50}, this seems to be an additional factor for bad outcome.

Interestingly mortality correlates with body temperature during the stay in the hospital (57). One causal factor might be the decreasing oxygen affinity hindering O_2 uptake in the lungs when the temperature rises. The authors suggest cooling (e. g. of the inspired gas) as a possible therapeutic means.

Very recently Bergamaschi et al. (58) published a letter to the editor about measurements in 289 COVID-19 patients. They observed no change of *in vitro* standard P_{50}, but low *in vivo* P_{50}. This effect was more marked in surviving than in deceased patients [25.2 (24.4–26.3) versus 25.8 (24.7–26.9) mmHg; $p < 0.012$].

5.1. Comparison of methods

So far, the results from the various studies on hemoglobin oxygen affinity in COVID-19 are rather heterogeneous. A probable cause is that according to Ceruti et al. (46) changes partly depend on the severity or prognosis of the illness. In line with this notion, in the study by Pascual-Guardia et al. (44) the P_{50}-outliers mainly belonged to the critically ill group. Further likely causes for these variations may comprise: mixtures of venous and arterial samples, inequality of comparison groups, time delay until measurement, treatment of samples (on ice?), treatment of patients, or acidotic pH in arterial blood due to hypercapnia in severe cases.

Existing studies so far comprise 3 types of analyses: measurement of complete ODCs, calculation of P_{50} from single values determined in arterial blood, calculation of P_{50} from single values determined in venous blood. An overview is presented in Table 2.

TABLE 3 PO_2 to obtain 90% oxygen saturation in dependence on P_{50} (all values in mmHg).

P_{50}	PO_2 for 90% SO_2	Difference against P_{50} = 27 mmHg
24	54.2	−6.8
25	56.4	−4.5
26	58.7	−2.3
27	60.9	0.0
28	63.2	2.3
29	65.4	4.5
30	67.7	6.8
31	69.9	9.0
32	72.2	11.3

5.2. Complete ODCs

We detected only 2 publications which measured complete ODCs, both using the Hemox Analyzer. In the study by Daniel et al. (28) P_{50} was rather high (29,0 ± 2.3 mmHg) in 14 COVID-19 patients, but not significantly different from a reference group of 11 patients with unknown diagnosis (28.5 ± 1.8 mmHg). As mentioned above, in this assay all potential *in vivo* effects from soluble factors outside the red blood cells are extremely diluted (1:1000) in the buffer solution. However, [2,3-BPG] in the red cells should remain rather stable during the short-lasting experiments. At first glance one may hypothesize that its concentration should be increased due to anemia (Hb 9.4 g/l). The number of COVID-19 patients is rather small (14) and the reference group consists of severely ill patients, too, yet without anemia (14.3 ± 1.1 g/dl). Renoux (29) measured similar P_{50} values in seven COVID-19 patients, but the values of their reference group consisting of healthy subjects did again not differ. Additional problems might be that variations of buffer composition (and thus different pH) and type of anticoagulant (e. g. acid citrate dextrose) can influence the P_{50} values (59). The standard deviation of the method is ± 1.1 mmHg with the original buffer according to Mawjood (60). General problems for all measurements are storage duration (when did the blood arrive in the laboratory?) and conditions (e.g., storage temperature).

5.3. P_{50} calculation from single arterial samples

Three large studies using P_{50} calculation from arterial samples show a left shift of the ODC (30, 33, 46, 56). In two the outcome is positively correlated to a low half saturation pressure (46, 56), in one P_{50} was higher in anemic subjects with a bad prognosis (56). Patients in whom oxygen affinity-and thus, oxygen loading in the lungs - increased over the hospital stay had a higher probability of survival (56). In the patients reported by Ceruti et al. (50) the P_{50} difference between surviving and deceased patients is dramatic: P_{50} of 23.0 + 1.6 compared to 32.2 + 7.9 mmHg in the corrected version of their paper!

5.4. P_{50} calculation from single venous samples

Hlutkina and Zinchuk (51) calculated an increased P_{50} in COVID-19 patients from venous blood samples [SO_2 59.9 (44.7;

72.8)]. Other authors like Vogel et al. measured also venous saturations but did not present them separately. On their figures, however, a rightward deviation at low SO_2 from the standard curve is visible. Similarly in the article by DeMartino and colleagues (27) a tendency for a right shift in both patients and control subjects can be seen.

5.5. Confounding factors

Further complicating the interpretation of the published results is the fact that the investigated patients are often old and suffering from various additional health problems. On the other hand, the comparison with critically ill subjects with various non-COVID-19 diagnosis may be misleading, if their illnesses also affect hemoglobin oxygen affinity. In various articles the diagnoses and comorbidities of the reference groups are variable or not clearly defined. In chronic obstructive pulmonary disease P_{50} is often markedly decreased (61) due to a systemic inflammatory response.

The changes of the mostly calculated *in vitro* P_{50} for standard conditions are partly rather small and therefore not always statistically provable; *in vivo* the left shift is probably more relevant and, importantly, seems to increase survival rate, as indicated e.g., in 56. When hyperventilation diminishes arterial PCO_2 leading to a lower *in vivo* P_{50} as is often the case during the initial phase of the illness, this may have a transitory positive result.

Especially problematic is the impaired oxygen uptake in the injured lungs, i.e., in a situation where oxygen saturation is physiologically high. Here, a change of only 1 mmHg in P_{50} reduces or increases the P_{O2} necessary to obtain 90% saturation by 2.3 mmHg (**Table 3**), for 80% saturation the corresponding value is 1.7 mmHg. The same calculation for 95% increases this effect to 3 mmHg. When considering the results of Ceruti et al. (P_{50} of 23.0 ± 1.6 compared to 32.2 ± 7.9 mmHg in surviving vs. deceased patients), the corresponding P_{90} varies by 20 mmHg, a physiologically important effect in injured lungs (50).

5.6. Causes for the left shift

Causes for the reported left shift might be reduction of 2,3-BPG and/or concentration changes of other ODC-modulating molecules in the erythrocyte (e.g., ATP, glutathione, chloride, CO_2). Changes in red cell age because of hemolysis or altered erythropoiesis may also be important: The half saturation pressure of old erythrocytes is reduced due to lower [2,3-BPG] (62). Another factor might be that effective hyperventilation with reduction of alveolar PCO_2 and an increase in red cell pH as commonly seen in anemia is not possible in many COVID-19 patients. This failure of an adaptive ventilatory response might reduce 2,3-BPG synthesis and thus, promote a left shift in spite of anemia. In any case, even a "normal" standard P_{50} in anemic patients is in fact already a reduced one. Damages of the red cell membrane, as described e.g., in Thomas et al. (32), might change substance concentrations in the erythrocyte or allow exit of Hb molecules which influences affinity (e.g., plasma pH is about 0.2 units higher than cell pH). If erythropoiesis is suppressed because of cell damages already in the bone marrow (see Chapter 6), the proportion of old erythrocytes with low [2,3-BPG] rises resulting in lowered P_{50}. Finally MetHb as cause for P_{50} changes probably plays no important role. In 4 of the articles described in this chapter (38, 46, 56, 58) mean values did not exceed 1%.

An interesting aspect is that measurements in venous blood show no significant effect on P_{50} (27, 29) or even a rise in P_{50} (29, 51). This finding is reminiscent of the results of Vogel et al. (30), where the P_{50} values calculated for low SO_2 tended to lie to the right of the standard curve. Similarly, measurements in venous blood during physical exercise often show a deviation to the right [e.g., (21, 63, 64)]. The causes for this right-shift are not fully explained. A possible cause are shifts of anions (Cl^- or HCO_3^-), which enter red cells in the peripheral tissues and exit them again in the lungs. The decrease in Cl^- might be further enhanced in COVID-19 due to an increase in the pulmonary distribution space resulting from interstitial or alveolar edema fluid.

Astonishingly no author has considered a possibly varied Donnan effect caused by changes in the intraerythrocytic Hb concentration. A reduction of $[Hb]_{ery}$ increases pH_{ery} resulting in lowered P_{50} when applying pH_{plasma} for the calculation. But this effect is probably negligible. In the studies with P_{50} determinations only 3 (29, 30, 46) communicate Hct values necessary for the calculation. The resulting $[Hb_{ery}]$ is only slightly decreased (mean values 29.7–32.9 g/l compared the normal value of 33 g/l).

5.7. Conclusion from chapter 5

According to 4 studies in more than 600 patients COVID-19 has a remarkable effect on the ODC, causing in arterial blood a left, and in venous blood a right shift. This notion is based on measurements in several thousand blood samples. Lacking effects in other (mostly smaller) studies might result from a variety of confounding influences, e.g., comorbidities. Since extended laboratory measurements (complete ODCs and 2,3-BPG determinations) or comparative measurements between laboratories have been rarely performed, exact causes remain unknown.

6. Effects of COVID-19 on erythropoiesis and oxygen supply

SARS-CoV-2 infectivity has been demonstrated in erythroid progenitor cells (41). This invasion of erythroid precursors and progenitors by SARS-CoV-2 is a cardinal feature of COVID-19 disease which may in part explain the evolving hypoxia (65). The infection of erythroid progenitor cells can lead to hematopoietic stress which may result in RBC morphological abnormalities, inability to respond to environmental cues, and premature egress from the bone marrow. These findings provide a mechanistic concept for the association of COVID-19 disease with RBC abnormalities. For example, dysregulated iron homeostasis has been reported and unusual RBC morphological abnormalities have been observed in COVID-19 patients. The recognition of RBC precursors as a direct target of SARS-CoV-2 has led to the hypothesis that SARS-CoV-2 induced dysregulation of

hemoglobin- and iron-metabolism may contribute to severe systemic courses of COVID-19 (66). The premature egress from the bone marrow may in part reflect a physiological response to hypoxia. Indeed, COVID-19 patients appear to have elevated RBC distribution width (RDW) and altered erythrocyte shape (67). Moreover a differential impact of SARS-CoV-2 variants on erythropoiesis in COVID-19 patients with a more prominent impact of the original Wuhan variant compared with the Delta and Omicron variants has been proposed (68). Altered RBC morphology and composition due to impaired erythropoiesis could be one reason for the modulation of RBC function including oxygen binding in COVID-19. Additional mechanisms by which SARS-CoV-2 infection may affect mature RBCs are presently under discussion and may potentially explain functional alterations including changes in the ODC.

7. Possible pathomechanisms underlying functional and structural damage of red blood cells

The viral infection with SARS-CoV-2 causes significant damage to RBCs that are altered in number, size, rigidity, morphology, hemoglobin content, and distribution width. These changes are associated with functional alterations of RBCs such as changes in RBC metabolism, hemolysis, oxidative stress, NO-metabolism, and oxygen dissociation (3, 69). Damages of RBC membranes and cytoskeleton could be involved in several of the functional and structural RBC abnormalities induced by SARS-CoV-2 infection (69). One cause for the morphological alteration of RBCs could be related to the SARS-CoV-2 virus binding to membrane cluster of differentiation 147 (CD147) receptors and Band3 protein, the most abundant transmembrane protein in the RBCs, on the RBC membrane (70, 71). It should be pointed out that experimental proof for the predicted interaction between red blood cells and SARS-CoV-2 based on *in silico* modeling is lacking so far. However, should SARS-CoV-2 indeed bind directly to red blood cells, devastating consequences in terms of hemolytic activity and RBC properties may be expected.

These proposed mechanisms reduce the functional capacity of erythrocytes for oxygen transport and result in the development of tissue hypoxia (70). Oxygen delivery to tissues can also be decreased by hyperviscosity due to impaired RBC deformability and increased oxidative stress in RBCs (67, 72). The mechanisms leading to increased oxidative stress and impaired deformability of RBCs are not fully resolved up to now. Thomas et al. (32) describe several possible mechanisms which could lead to functional and structural alterations of RBCs. The authors propose that increases in glycolytic metabolites in COVID-19 RBCs are consistent with a theoretically improved capacity of hemoglobin to off-load oxygen as a function of allosteric modulation by high-energy phosphate compounds, possibly as an adaptive response to counteract COVID-19-induced hypoxia. The N-terminus of AE1/Band 3 stabilizes deoxyhemoglobin and fine-tunes oxygen off-loading. RBCs from COVID-19 patients may be incapable of responding to environmental variations in hemoglobin oxygen saturation when traveling from the lungs to peripheral capillaries and, as such, may have a compromised capacity to transport and deliver oxygen. Moreover a damage of the N-terminus of AE1 may compromise the RBC's capacity to inhibit glycolysis and activate the pentose phosphate pathway in response to oxidative stress, making the RBCs from COVID-19 patients more susceptible to increased oxidative stress. ROS can then react with membrane lipids and proteins, causing lipid peroxidation and modifying membrane proteins, resulting in phosphatidylserine exposure on the RBC surface. This membrane rearrangement is expected to generate an imbalance in cation homeostasis and a concomitant decrease in deformability and–together with oxidative damage of the endothelium–provides a mechanistic explanation for the high incidence of thromboembolic complications and coagulopathies in COVID-19 patients (69). Furthermore, RBCs of COVID-19 patients contain increased levels of glycolytic intermediates, accompanied by oxidation and fragmentation of ankyrin, β-spectrin, and the N-terminal cytosolic domain of Band 3 (AE1). Significant alterations in RBC glycolysis in COVID-19 (67) must also be considered in relation to the ODC shift discussed above. Significantly altered RBC metabolism of lipids, in particular short- and medium-chain saturated fatty acids, acyl-carnitines, and sphingolipids, has been observed (73). A further indicator for RBC membrane alterations are changes in the polyunsaturated fatty acid composition of the RBC membrane which correlate with inflammatory marker expression in COVID-19 patients (74). Further, RBCs of COVID-19 patients reveal increased levels of intraerythrocytic NO and reduced amounts of NO in the serum. This finding could be related to the development of silent hypoxia in some cases of severe disease, as the high levels of intraerythrocytic NO may counteract the release of oxygen at the tissue level and provide an explanation for the reported left shift of the ODC. Damage to AE1 and alterations of the erythrocyte membrane and cytoskeleton by SARS-CoV-2 infection are irreversible. As RBCs circulate for up to 120 days without *de novo* protein synthesis capacity, these effects may not only explain alterations of gas exchange and oxygen affinity properties in COVID-19 patients, but also some of the long-lasting sequelae of COVID-19 (32). It can further be assumed that damage of the erythrocyte membrane reduces the life time of red blood cells, and the resulting anemia will aggravate tissue hypoxia in COVID-19 patients.

8. COVID-19 and sickle cell anemia

COVID-19 is surprisingly important in patients suffering from Sickle Cell disease (SCD). SCD results from the exchange of one amino acid (valin for glutamic acid) in one or two β-chains of Hb (75). This exchange causes aggregation of Hb molecules impairing oxygen binding and reducing the deformability of the erythrocytes, the latter resulting in microvascular occlusion and hemolysis, e.g., after sequestration in the spleen. End-organ ischemia or even infarction, anemia, and sterile inflammation are subsequent complications. Yet, *Plasmodium falciparum*–the mosquito-borne parasite invading erythrocytes and causing malaria–has minimized ability to complete its reproductive cycle and cause severe disease in heterozygote carriers of the sickle cell trait. This evolutionary benefit has led to the wide distribution of SCD in equatorial

Africa and regions with populations originating from slave trade (76).

Sickle cell disease (SCD) patients typically present a large right shift of the ODC, which impedes oxygen loading in the lungs. This property of HbS is further amplified by a high 2,3-BPG concentration (76, 77). Standard P_{50} of up to 42 mmHg have been observed [reviewed e.g., by Milner et al. 1974 (78)], of which 4 mmHg may be caused by 2,3-BPG according to Henry et al. (75). Interestingly, high affinity hemoglobins (HbF and thalassemia Hb) are occasionally also present in the blood of SCD patients and may reduce symptoms (76).

In their recent study on oxygen affinity in COVID-19, Gille et al. (38) also assessed the ODC in 30 subjects with SCD. As expected, the ODC was right-shifted but the extent of this shift was rather low [30 (26.9–31.9) mmHg]. Hydroxycarbamide reduced the right shift [28.2 (27–31.2) mmHg, $p = 0.014$], while blood transfusion had no significant effect. Unfortunately, no information about the state of the transfused blood (2,3-BPG content normal or reduced due to potential loss during conservation) or the time of measurement after transfusion–which may both influence [2,3-BPG]–are provided.

Various authors [e. g. Parsons et al. (79)] consider SCD a complication of COVID-19 based on the common finding of microthrombosis with occlusion of individual capillaries in critically ill patients (vaso-occlusive crisis). Yet, if COVID-19 decreases P_{50} in arterial blood as often observed (see Chapters 4 and 5), this effect should reverse the characteristic right shift of the ODC in SCD. Indeed COVID-19 presentation is mild in children and moderate in many adults suffering from SCD [reviewed by 80]. Measurements of oxygen affinity in these patients are necessary to test this hypothesis.

9. Drugs modulating oxygen affinity in COVID-19

9.1. Potential therapeutic agents to modify Hb-O_2-affinity

When exploring potential agents or methods to modify Hb-O_2-affinity in a therapeutic way, three questions emerge: Firstly, in which patients could it be desirable to modify Hb-O_2-affinity? Secondly, what should be the targeted P_{50}? Thirdly, by which means is it possible to achieve this target without detrimental side effects?

9.2. In which patients could it be desirable to modify O_2-Hb affinity?

To a certain degree impairment of pulmonary oxygen uptake can be compensated by increased work of breathing and in a clinical setting by delivery of oxygen. However, in some patients these compensatory mechanisms reach their limit. Either because work of breathing becomes harmful (81), or because enriching the alveolar oxygen concentration becomes insufficient to outweigh the degree of lung pathology. In these circumstances sedoanalgesia and mechanical ventilation are indicated to reduce the work of breathing (thereby also reducing oxygen consumption) and to deliver oxygen with positive pressure and lung protective ventilation (81, 82). Once this becomes insufficient, too, and other strategies [e.g., proning (83), pulmonary vasodilators] prove insufficient, extracorporeal membrane-oxygenation (ECMO) can be initiated to remove deoxygenated blood from the venous system, enrich it with oxygen outside the human body, and return it to the patient's circulation (84). However, this is not without risks and its availability is limited especially in a pandemic setting. Hence, it is a subgroup of critically ill patients with severe respiratory failure in whom modification of Hb-O_2-affinity may be worth exploring.

9.3. What should be the targeted P_{50}?

Which Hb-O_2-affinity is optimal for tissue oxygen delivery under various environmental and pathophysiological conditions has been debated for decades (85). In patients with normal oxygen content but impaired cardiac output, decreasing Hb-O_2-affinity may appear desirable to improve oxygen delivery in peripheral tissue, e.g., during cardiac surgery performed in a state of deep hypothermia (86–88). However, in a hypoxic environment or when pulmonary oxygen uptake is the limiting factor in the oxygen cascade, increasing Hb-O_2-affinity may be considered the desired target (85).

In his study on physiology at extreme altitudes on Mount Everest carried out in 1981, John B. West described the progressive left shift of the ODC at increasing altitude reaching an *in vivo* P_{50} of 20 mmHg in an individual climber (89). Dominelli et al. studied humans with high affinity hemoglobin and compensatory polycythemia and were able to show that a left shifted ODC mitigated the decline in exercise performance in acute hypoxia through a higher arterial oxygen content (90). The authors concluded that increased Hb-O_2-affinity is a superior strategy for preserving exercise tolerance in acute hypoxia. Similar conclusions had already been drawn in the 1970s by Eaton et al. (91) as well as Hebbel et al. (92), and more recently by Yalcin et al. (93). According to mathematical modeling, an increase in Hb-O_2-affinity resulting from a P_{50} change of -3 mmHg only slightly increases SO_2 (by 1%) in arterial blood in normoxia (PaO_2 90 mmHg), while in hypoxia (PaO_2 45 mmHg), the increased Hb–O_2 affinity increases arterial SO_2 by 4–5% (5) (see also **Table 3**: PO_2 required to obtain 90% saturation as a function of P_{50}). A review on the influence of high Hb-O_2-affinity on humans in hypoxia was recently published by Webb et al. (94). In COVID-19 patients, Valle et al. showed an association of an increased Hb-O_2-affinity with a lower mortality rate (56). To define a therapeutic target, more research is needed with regards to balancing the benefits of more rapid pulmonary oxygen uptake (and increased arterial oxygenation) with the associated reduced rate of peripheral oxygen unloading. In this context, it will also be important to consider that the *in vivo* P_{50} alterations in the lungs will be dissimilar to the changes in peripheral tissue due to differing acid-base and temperature conditions (54). As such, in hypoxic respiratory failure an increased Hb-O_2-affinity appears beneficial. However, the optimum degree of the desired ODC left-shift still needs to be identified.

9.4. By which means is it possible to achieve this target without detrimental side effects?

9.4.1. "Old" blood transfusions

Storage of red blood cells for transfusion increases Hb-O_2 affinity with time due to 2,3-BPG depletion (95, 96). Three large randomized controlled trials (RCTs) compared transfusion of fresh versus stored red blood cells in critically ill adults: the ABL (97), INFORM (98), and TRANSFUSE (99) trial with the latter recruiting almost 5,000 patients. None of these showed a difference in outcomes between the groups and in a meta-analysis no effect on mortality was found (100). However, the TRANSFUSE trial showed a lower mortality for older transfusions in a pre-specified subgroup with more severely ill patients. In ARDS patients, an observational study found no association between transfusion of older units and survival. Nevertheless, transfusion of "old" red cell units was associated with a lower chance for successful weaning from renal replacement therapy (101). Free hemoglobin acts as a potent vasoconstrictor, even at low concentrations (102). Indeed, transfusion of "old" red cell units was associated with increased plasma hemoglobin levels and increased pulmonary artery pressure (103). Furthermore, only a fraction of transfused red cells remains in the circulation for more than 24 h (104) and this proportion is lower following transfusion of "older" blood (105). In addition, storage of red cells alters their rheological properties unfavorably (106) and may disrupt physiologic vasodilatory responses (107). Thus, while it is possible to increase Hb-O_2 affinity with the transfusion of 2,3-BPG depleted blood, multiple confounding properties and side effects of transfusions exist.

9.4.2. 5-Hydroxymethylfurfural (5-HMF)

5-Hydroxymethylfurfural (5-HMF) is an aromatic aldehyde formed during non-enzymatic browning and caramelization of carbohydrate-containing foods after thermal treatment (the so called "Maillard" reaction) (108). Yalcin et al. showed that 5-HMF increases Hb-O_2 affinity (93). Woyke et al. demonstrated this dose dependent effect *in vitro* in whole blood and discussed its potential use in COVID-19 patients (109, 110). Mahon et al. demonstrated that 5-HMF increased the Hb-O_2 affinity in a swine model of hypoxia, resulting even in beneficial effects on pulmonary artery pressure and a trend toward improved mortality (111). Similar results were obtained by Lucas et al. (108) in a hamster model. In combination with α-ketoglutaric acid, 5-HMF has been shown to increase maximal aerobic capacity during the peri-operative period in lung surgery (112), and resulted in a predictable left-shift in healthy volunteers (109). Hence, while further research is still needed, 5-HMF (with or without α-ketoglutaric acid) is available and may represent a potential agent of choice to increase Hb-O_2 affinity in patients with severe respiratory failure.

9.4.3. Voxelotor (GBT440)

Voxelotor (previously known as GBT440), a specific agent for use in patients with sickle cell disease, has been approved by the US Food and Drug Administration (FDA) in 2019. Data from animal models had shown that GBT440 binds specifically to Hb, increases the Hb-O_2 affinity, prevents sickling and prolongs red blood cell half-life (113). Voxelotor causes a dose dependent left shift in Hb-O_2-affinity. Howard et al. (114) and the multicenter, randomized controlled HOPE trial (115) showed a disease-modifying potential. However, the lack of reduction of clinically important pain episodes has been criticized (77). Voxelotor has also been tested in healthy volunteers exercising under hypoxic conditions and showed the expected increase in oxygen content (116), however, it has not been trialed in respiratory failure or ARDS models.

9.4.4. GBT1118

GBT1118, a voxelotor analogue, is a small molecule that reversibly binds to the NH_2-terminal chain of Hb and increases Hb-O_2-affinity. In a mouse model of ARDS, Putz et al. (117) showed that a single dose of GBT1118 improved oxygen saturation, severity of illness, and survival. the effect was associated with reduced hypoxia in the kidney and liver, but was independent of airspace inflammation and alveolar-capillary barrier permeability (117). Similar findings were reported by Dufu et al. (118). Thus, GBT1118 represents a promising agent to induce a left shifted ODC in respiratory failure once further research is available.

9.4.5. Nebulized epoprostenol

Woyke et al. exposed venous blood samples from healthy volunteers to the pulmonary vasodilators epoprostenol and iloprost (119). With epoprostenol, they detected an increased Hb-O_2 affinity in all subgroups under laboratory conditions, however, further research is required to validate this effect *in vivo*.

9.4.6. Volatile anesthetic agents

According to Ronzani et al. (120), the volatile anesthetic agents isoflurane, desflurane and sevoflurane affect the ODC in a concentration dependent manner. While low to medium concentrations of isoflurane or desflurane were associated with a right shift, high concentrations of desflurane and sevoflurane increased Hb-O_2 affinity. Sevoflurane might be of particular interest as it has been studied in ARDS patients where it not only improved oxygenation but also decreased levels of markers of epithelial injury and inflammation (121).

9.5. Conclusion concerning the treatment of COVID-19

While it is possible to increase Hb-O_2 affinity with the transfusion of 2,3-BPG depleted blood, multiple confounding properties and side effects of transfusions exist. Meanwhile, several agents that specifically increase Hb-O_2 affinity are available. The voxelotor analogue GBT1118 has shown reliable effects on the ODC, even with promising outcomes in murine respiratory failure models. Further research is still required; yet, 5-HMF (with or without α-ketoglutaric acid) is available and may represent a potential agent of choice to increase the Hb-O_2 affinity in patients with severe respiratory failure. Finally, nebulized epoprostenol and sevoflurane (inhaled at high doses)–two agents which are already used in ARDS patients–increase Hb-O_2 affinity under laboratory conditions, and studying whether these can be exploited in a therapeutic way may be of particular interest in the near future.

9.6. Treatment of COVID-19 in sickle cell disease

According to Safo and Kato (122) the main therapeutic strategy for sickle cell anemia should aim to stabilize the R-state of hemoglobin, which has higher oxygen affinity and would be expected to have slower kinetics of polymerization. 5-HMF forms a high-affinity Schiff-base adduct with HbS and inhibits red cell sickling by allosterically shifting oxygen equilibrium curves toward the left (123). Therefore, similar drugs as in the treatment of COVID-19 have been suggested, for instance 5-HMF and Voxeletor (124).

Another possible strategy seems to be the reduction of iron supply, because this element is important for replication of the virus (66). Interestingly the severety of COVID-19 in SCD children with sickle cell disease is low (80). In this paper the authors state that "COVID-19 presentation was mild in children and moderate in many SCD adults."

The postulated therapeutic strategy by Safo and Kato (122) has stimulated the laboratory investigation of aromatic aldehydes, aspirin derivatives, thiols and isothiocyanates that can stabilize the R-state of hemoglobin *in vitro*. One representative aromatic aldehyde agent, 5-hydoxymethyl-2-furfural (5-HMF, also known as Aes-103) increases oxygen affinity of sickle hemoglobin and reduces hypoxia-induced sickling *in vitro* and protects sickle cell mice from effects of hypoxia. 5-HMF has completed pre-clinical testing and has entered clinical trials. The development of Hb allosteric modifiers as direct anti-sickling agents is an attractive investigational goal for the treatment of SCD.

10. General conclusion

SARS-CoV-19 damages red cells as early as during their production in the medulla ossea. Studies on the effects of COVID-19 on hemoglobin oxygen affinity have been performed in some hundred patients with contrasting results, probably due to varying methods and non-uniform groups of COVID-19 patients as well as comparison subjects. Most investigators have calculated half saturation pressures from single blood samples, only few have analyzed complete dissociation curves but with rather artificial methods. In the majority of severely ill patients a left shift of the curve was found, especially in those with a good prognosis. This change favors oxygen loading into the blood in the lungs. The cause for the changes is unknown because an analysis of red cell constituents was rarely performed.

In SCD the negative effects of COVID-19 seem to be mitigated, possibly because the effects of a SARS-CoV-2 infection counteract the unfavorable large right shift of the ODC by the hereditary illness. In the long term, further investigations will prove increasingly difficult, as most controls will no longer be real non-infected controls once a majority of the population has been infected by SARS-CoV-2 over the past years (125). Also, comparison with other illnesses may be misleading, if those also affect hemoglobin oxygen affinity.

Author contributions

DB, DV, and WB wrote sections of the manuscript. WK contributed to each section. All authors contributed to conception and design of the study, manuscript revision, read, and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Factors associated with changes in healthy lifestyle behaviors among hematological cancer patients during the COVID-19 pandemic

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Background: There is a paucity of research examining the effects of the COVID-19 pandemic on the healthy lifestyle behaviors of hematological cancer patients. We examined changes in healthy lifestyle behaviors since the pandemic and identified factors associated with these changes among members of this high-risk population.

Methods: Hematological cancer patients (n=394) completed a self-report online survey from July to August 2020. The survey assessed pandemic-related changes in exercise, alcohol consumption, and consumption of fruit, vegetables, and wholegrains. Information relating to several demographic, clinical, and psychological factors was also collected. Factors associated with changes in healthy lifestyle behaviors were analyzed using logistic regression.

Results: Just 14% of patients surveyed reported exercising more during the pandemic (39% exercised less). Only a quarter (24%) improved their diet, while nearly half (45%) reported eating less fruit, vegetables, and wholegrains. Just over a quarter (28%) consumed less alcohol (17% consumed more alcohol). Fear of contracting COVID-19 and psychological distress were significantly associated with reduced exercise. Younger age was significantly associated with both increased alcohol consumption and increased exercise. Being a woman was significantly associated with unfavorable changes in diet and being married was significantly associated with decreased alcohol consumption.

Conclusion: A substantial proportion of hematological cancer patients reported unfavorable changes in healthy lifestyle behaviors during the pandemic. Results highlight the importance of supporting healthy lifestyle practices among this particularly vulnerable group to ensure health is optimized while undergoing treatment and when in remission, particularly during crisis times like the COVID-19 pandemic.

KEYWORDS

hematology patients, cancer, diet, exercise, alcohol, COVID-19 pandemic

Introduction

The COVID-19 pandemic has created challenges that have profoundly impacted society. In countries with widespread community transmission of COVID-19, strict public health responses such as school closures, stay-at-home orders, border restrictions, and mandated self-isolation were enforced (Moss et al., 2020; Parliament of Victoria, 2022). Although the aim of these measures was to protect the population and the health system that serves them, they have disrupted all segments of the population. There is increasing recognition of the negative psychosocial consequences of these measures, including increased loneliness, reduced social support, depression, anxiety, and financial concerns (Ongaro et al., 2021). Certain subgroups of the population have been impacted more than others.

There is now considerable evidence demonstrating that hematological cancer patients are at particular risk of contracting COVID-19 and mortality from COVID-19 (Lee et al., 2020). A meta-analysis of data from 3,377 adult patients with both hematological cancer and COVID-19 reported a mortality risk of 34% (Vijenthira et al., 2020), which is significantly higher than the mortality rate reported in patients with solid tumors (22%; Zhang et al., 2021) and the average population aged 75 years (5%; Levin et al., 2020). Studies conducted during the early stages of the pandemic have shown that fears of contracting COVID-19 have contributed to heightened levels of psychological distress in hematological cancer patients (Zomerdijk et al., 2021a,b; Gates, 2022). There is also evidence that COVID-19 vaccines may yield less protection for people living with hematological cancers when compared to the general population (Lee et al., 2022; Re et al., 2022). With the progressive relaxation of public health measures, hematological cancer patients remain vulnerable to infection, highlighting the importance of ongoing COVID-19 protective behavioral measures, such as mask wearing, physical distancing, and working from home.

There is some evidence to suggest that COVID-19 related impacts have contributed to changes in healthy lifestyle behaviors, including physical activity, healthy diet, and alcohol consumption. For the general public, restrictions such as stay-at-home orders and the closure of sport facilities and public parks have contributed to a decline in exercise and fostered sedentary behavior (Wilke et al., 2021). A recent US study reported that one-third of cancer patients reduced their physical activity during the pandemic, with stressors such as disruptions to daily life being a key contributor to the decline among those surveyed (Himbert et al., 2022). Another survey study found that 17% of cancer survivors reported consuming more alcohol during the pandemic, which was associated with higher levels of anxiety and depression (Beebe-Dimmer et al., 2022).

These preliminary findings are concerning given the well documented body of evidence demonstrating the beneficial effects of healthy lifestyle behaviors on outcomes in cancer patients (Newton et al., 2020). For example, there is compelling evidence from over 30 randomized controlled trials that participating in regular exercise has benefits for preventing and managing the physical and psychosocial effects associated with cancer and its treatment (Buffart et al., 2017). These effects have also been identified in hematological cancers, with significant improvements found in treatment-related toxicities, physical functioning, and quality of life (Knips et al., 2019; Sitlinger et al., 2020). For patients undergoing planned stem cell transplantation, exercise has been shown to be beneficial for maintaining physical fitness, which is a requirement for transplant eligibility (Morishita et al., 2019). After transplantation, loss of muscle strength is highly prevalent and may cause disabilities (Morishita et al., 2013). Additionally, in the pre-and post-transplant phase, patients are hospitalized in a single-bed isolation room for several weeks, thereby aggravating the already low strength capacity induced by transplant treatment and contributing to increased fatigue (Kovalszki et al., 2008). Maintaining exercise before and after treatment is therefore key to preserving functioning in hematological cancer patients. As such, the consequences of reduced engagement in healthy lifestyle behaviors during the COVID-19 pandemic may be far reaching. However, results to date apply primarily to patients with solid tumors.

Despite their vulnerability and marked differences to patients living with solid cancers, those with hematological cancers have been largely overlooked, leaving some to call them the "Prisoners of the Pandemic" (International COVID-19 Blood Cancer Coalition, 2022). The concern for their physical and mental health was highlighted in the recent patient impact statement from the International COVID-19 Blood Cancer Coalition (2022), which calls for greater research attention to the specific impact of the pandemic on hematological cancer patients. To inform the improvement of support for those living with hematological cancers, the present study aimed to evaluate changes in healthy lifestyle behaviors among hematological cancer patients during the pandemic and the factors associated with these changes.

Materials and methods

Participants and recruitment

The present study formed part of a broader research program that aimed to investigate the experiences of hematological cancer patients during the COVID-19 pandemic. Participants were eligible for inclusion if they were aged ≥ 18 years, currently have, or previously have had, a confirmed diagnosis of hematological cancer, and had sufficient English language skills to participate without an interpreter. Participants who resided outside of Australia were excluded.

Participants were recruited between July and August 2020 through a study advertisement distributed *via* email and/or social media platforms by a national blood cancer community group (Leukaemia Foundation), a professional member working group (Victorian COVID-19 Cancer Network), and a clinical trial group (Australasian Leukaemia & Lymphoma Group). The advertisement included a link to an online information sheet, consent form, and survey. The University of Melbourne Human Research Ethics Committee approved the study protocol (Ref: 2057125.1).

Measures

After providing informed consent, participants completed an online cross-sectional survey that included the items outlined below.

Socio-demographic characteristics

The assessed socio-demographic variables were age, gender, postcode, marital status, and education level. Residential postcode

was used to classify respondents' location (Major cities/Inner regional/Outer regional/Remote/Very remote) as per the Australian Bureau of Statistics Australian Statistical Geography Standard (Australian Bureau of Statistics, 2016). For analysis purposes, location (major cities vs. regional), marital status (single vs. married/defacto), and education (tertiary vs. non-tertiary) variables were dichotomized.

Fear of contracting COVID-19

A single item – 'How concerned are you about being infected with COVID-19 yourself?' – was created by the research team to investigate respondents' concern about their perceived risk of contracting COVID-19. Responses were made on a 5-point scale that ranged from 1 (not at all concerned) to 5 (very concerned).

Psychological distress

Psychological distress was assessed using the Kessler 10-item assessment (K10; Kessler et al., 2003). Respondents indicated the extent to which they experienced various emotional states since the beginning of the pandemic using a 5-point Likert scale that ranged from 1 (none of the time) to 5 (all the time). Cronbach's alpha in this sample was 0.92 (95% CI = 0.90–0.93), indicating excellent internal consistency. Scores were divided into three categories representing mild (range 20–24), moderate (range 25–29), and severe psychological distress (range 30–50; Kessler et al., 2003).

Exercise

Respondents completed the Godin Leisure-time Exercise Questionnaire (GODIN; Godin and Shephard, 1985) and were asked to estimate the frequency with which they engaged in mild (e.g., bowling, golf, easy walking), moderate (e.g., fast walking, easy swimming), and strenuous physical activity (e.g., running, vigorous swimming) over a typical 7-day period before and during the COVID-19 pandemic. Higher scores indicate higher overall activity levels.

Diet

Questions relating to diet, adapted from the National Health Survey (Australian Bureau of Statistics, 2018), asked respondents to report on the average number of servings of fruit, vegetables, and wholegrains consumed per day before and during the COVID-19 pandemic. A composite diet score for each respondent was calculated as the total servings of fruit, vegetables, and wholegrains consumed per day. For example, a respondent who reported consuming 2 servings of fruit, 5 of vegetables, and 3 of wholegrains would receive a composite diet score of 10.

Alcohol

Respondents were presented with the Australian Guidelines' standard drink definitions (National Health and Medical Research Council, 2020) and were asked (i) how often they consumed an alcoholic drink of any kind before and during the COVID-19 pandemic and (ii) how many standard drinks (defined as 10 g of alcohol as per Australian guidelines) they usually consumed on a day that they had an alcoholic drink. Total standard drinks consumed per week was calculated for each respondent using the quantity–frequency method.

Statistical analysis

Survey data were collected in Qualtrics and de-identified prior to being exported to R version 4.2.0 for analysis (R Core Team, 2022). One respondent did not meet age eligibility and was removed from the data set, leaving only eligible participants for the data analyses. Descriptive statistics (e.g., proportions, frequencies, means, standard deviations) were calculated for all variables of interest. Differences between pre-COVID-19 and during-COVID-19 scores were calculated for each health behavior variable (exercise, diet, alcohol consumption). Binary variables were then created to: (1) identify those who increased their engagement with each health behavior (i.e., those that had a positive difference score) versus no change or a decrease (i.e., those that had a negative or zero value for their difference score), and (2) identify those who decreased their engagement in a health behavior (i.e., those that had a negative difference score) versus no change or increase (i.e., a difference score of zero or a positive score). This resulted in a total of six dichotomized outcome variables. Predictor variables were factors potentially associated with each dichotomized health behavior variable (age, gender, location, marital status, education, fear of contracting COVID-19, psychological distress). A total of six multivariate logistic regression analyses were conducted (i.e., one for each binary outcome variable). Parameter estimates of log odds and p-values were examined, and a significance level of $p < 0.05$ was used to determine significance.

Results

Sample characteristics

A total of 394 respondents (210 men, 184 women) aged 20–84 years ($M = 60.4$, SD = 12.8) completed the survey. Respondents were included in logistic regression analyses only if they had completed all questions related to the lifestyle behavior being examined. Consequently, 308 participants were included in the exercise analysis, 330 in the diet analysis, and 232 in the alcohol consumption analysis. Chi-squared tests (for categorical variables) and t-tests (for continuous variables) were used to identify any demographic differences between respondents included in analyses and those with missing data. Respondents with missing exercise data were older and less likely to be tertiary educated than those included in analyses. Respondents with missing alcohol consumption data were more likely to be female than those included in analyses. No other significant demographic differences were found. Participant characteristics are summarized in Table 1.

Descriptive results

Most participants reported exercising less during the pandemic (39%), while 14% reported exercising more. Nearly half (45%) reported eating less fruit, vegetables, and wholegrains, while 24% improved their diet. Most participants (55%) did not change their consumption of alcohol, while 17% consumed more alcohol and 28% consumed less.

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TABLE 1 Demographic and medical characteristics of respondents by changes in healthy lifestyle behaviors (n= 394).

	Exercise			Diet			Alcohol consumption		
	Increase	No change	Decrease	Increase	No change	Decrease	Increase	No change	Decrease
n	42	145	121	78	105	147	40	128	64
Age, *M* (*SD*)	56.5 (15.4)	62.8 (10.4)	57.1 (13.2)	61.8 (12.9)	59.9 (11.7)	59.8 (13.0)	54.5 (13.6)	62.7 (11.6)	59.7 (12.0)
Gender									
Men, *n* (%)	20 (48)	66 (46)	66 (55)	46 (59)	63 (60)	69 (47)	24 (60)	72 (56)	56 (88)
Women, *n* (%)	22 (52)	79 (54)	55 (45)	32 (41)	42 (40)	78 (53)	16 (40)	56 (44)	23 (36)
Postcode									
Regional, *n* (%)	16 (38)	87 (60)	54 (45)	34 (44)	53 (50)	81 (55)	18 (45)	66 (52)	33 (52)
Metro, *n* (%)	26 (62)	56 (39)	66 (55)	44 (56)	53 (50)	63 (43)	21 (53)	60 (47)	31 (48)
Marital status									
Married, *n* (%)	26 (62)	113 (78)	86 (71)	52 (67)	74 (70)	111 (76)	28 (70)	90 (70)	55 (86)
Not married, *n* (%)	16 (38)	32 (22)	35 (29)	26 (33)	31 (30)	36 (24)	12 (30)	38 (30)	9 (14)
Education									
Tertiary, *n* (%)	21 (78)	71 (49)	71 (59)	41 (53)	52 (50)	79 (54)	21 (53)	63 (49)	41 (64)
Non-tertiary, *n* (%)	6 (14)	72 (50)	49 (41)	36 (46)	52 (50)	66 (45)	18 (45)	64 (50)	23 (36)
Primary diagnosis									
Leukaemia, *n* (%)	16 (38)	35 (24)	33 (27)	16 (21)	31 (30)	43 (29)	17 (43)	29 (23)	13 (20)
Lymphoma, *n* (%)	17 (40)	47 (32)	47 (39)	29 (37)	38 (36)	49 (33)	13 (33)	46 (36)	29 (45)
Myeloma, *n* (%)	5 (12)	33 (23)	18 (15)	14 (18)	16 (15)	32 (22)	6 (15)	28 (22)	7 (11)
Other hematological cancers[a], *n* (%)	4 (10)	30 (21)	23 (19)	19 (24)	20 (19)	23 (16)	4 (10)	25 (20)	15 (23)
Treatments									
Stem cell transplant, *n* (%)	15 (36)	71 (49)	44 (36)	32 (41)	44 (42)	63 (43)	11 (28)	55 (43)	29 (45)
Chemotherapy, *n* (%)	38 (90)	110 (76)	99 (82)	62 (79)	89 (85)	117 (80)	31 (78)	103 (80)	54 (84)
Radiation therapy, *n* (%)	11 (26)	31 (21)	24 (20)	21 (27)	17 (16)	27 (18)	8 (20)	24 (19)	15 (23)
Other treatments[b], *n* (%)	25 (60)	86 (59)	66 (55)	51 (65)	55 (52)	78 (53)	23 (58)	67 (52)	28 (44)
Treatment Status									
Not yet started, *n* (%)	2 (5)	11 (8)	6 (5)	7 (9)	1 (1)	11 (7)	4 (10)	11 (9)	2 (3)
Currently undergoing, *n* (%)	0 (0)	19 (13)	19 (16)	15 (19)	8 (8)	15 (10)	0 (0)	9 (7)	16 (25)
Completed and in remission, *n* (%)	22 (52)	51 (35)	40 (33)	27 (35)	46 (44)	50 (34)	17 (43)	50 (39)	18 (28)
Ongoing management, *n* (%)	13 (31)	44 (30)	38 (31)	17 (22)	35 (33)	51 (35)	17 (43)	36 (28)	22 (34)
Other, *n* (%)	5 (12)	20 (14)	18 (15)	12 (15)	15 (14)	20 (14)	2 (5)	22 (17)	6 (9)
Psychological distress, *M* (*SD*)	18.2 (6.4)	17.8 (6.1)	21.2 (7.1)	19.1 (7.2)	19.6 (7.8)	19.2 (6.2)	18.8 (5.8)	18.6 (6.7)	19.9 (7.2)
Fear of contracting COVID-19, *M* (*SD*)	3.1 (1.1)	2.8 (1.1)	3.5 (1.2)	3.1 (1.2)	3.2 (1.2)	3.1 (1.2)	3.1 (1.2)	3.1 (1.2)	3.3 (1.2)

[a]Other hematological cancers include myelodysplastic syndrome, myeloproliferative neoplasms, amayloidosis.
[b]Other treatments include targeted therapy, immunotherapy, surgery.

Factors associated with lifestyle behavior changes

Table 2 presents the results from the logistic regression analyses assessing relationships between predictor variables and lifestyle behavior changes during the COVID-19 pandemic. Six significant relationships were observed. Specifically, (i) higher levels of fear of contracting COVID-19 and psychological distress were significantly associated with reduced exercise, (ii) being a woman was significantly associated with reduced consumption of fruit, vegetables, and whole grains, (iii) younger age was significantly associated with increased alcohol consumption and increased exercise, and (iv) being married was significantly associated with reduced alcohol consumption during the pandemic.

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TABLE 2 Parameter estimates of log odds, measures of deviation, and *p*-values for logistic regression analyses.

Predictor Variables	Unfavorable lifestyle behavior changes								
	Exercise decrease[a]			Diet decrease[a]			Alcohol increase[a]		
	β [95% CI]	SE	*p*	*β* [95% CI]	SE	*p*	*β* [95% CI]	SE	*p*
Categorical variables									
Gender (male = 0; female = 1)	−0.08 [−0.58, 0.42]	0.26	0.77	0.54 [0.08, 0.99]	0.23	0.02	−0.12 [−0.90, 0.62]	0.39	0.75
Location (metro = 0; regional = 1)	−0.29 [−0.80, 0.21]	0.26	0.26	0.33 [−0.14, 0.80]	0.24	0.17	−0.18 [−0.97, 0.59]	0.40	0.64
Marital status (partnered = 0; single = 1)	0.11 [−0.47, 0.67]	0.29	0.71	−0.26 [−0.78, 0.25]	0.26	0.32	0.41 [−0.44, 1.21]	0.42	0.32
Education (non-tertiary = 0; tertiary = 1)	0.28 [−0.22, 0.80]	0.26	0.27	0.15 [−0.31, 0.62]	0.24	0.52	−0.10 [−0.86, 0.66]	0.39	0.79
Continuous variables									
Age	−0.01 [−0.03, 0.01]	0.01	0.52	−0.01 [−0.03, 0.01]	0.01	0.51	−0.05 [−0.08, −0.02]	0.02	<0.01
Psychological distress	0.05 [0.01, 0.09]	0.02	0.01	0.00 [−0.04, 0.03]	0.02	0.88	−0.03 [−0.10, 0.03]	0.03	0.33
Fear of contracting COVID-19	0.36 [0.13, 0.58]	0.11	<0.01	−0.06 [−0.26, 0.14]	0.10	0.57	−0.17 [−0.52, 0.17]	0.18	0.32
	Favorable lifestyle behavior changes								
Predictor variables	**Exercise increase [b]**			**Diet increase[b]**			**Alcohol decrease[b]**		
	β [95% CI]	**SE**	***p***	**β [95% CI]**	**SE**	***p***	**β [95% CI]**	**SE**	***p***
Categorical variables									
Gender (male = 0; female = 1)	0.26 [−0.43, 0.95]	0.35	0.46	−0.29 [−0.83, 0.24]	0.27	0.29	−0.37 [−1.02, 0.27]	0.33	0.26
Location (metro = 0; regional = 1)	−0.64 [−1.37, 0.07]	0.36	0.08	−0.33 [−0.88, 0.22]	0.28	0.24	0.16 [−0.47, 0.79]	0.32	0.62
Marital status (partnered = 0; single = 1)	0.53 [−0.21, 1.24]	0.37	0.15	0.28 [−0.31, 0.85]	0.30	0.34	−0.98 [−1.85, −0.2]	0.42	0.02
Education (non-tertiary = 0; tertiary = 1)	−0.28 [−0.98, 0.42]	0.36	0.43	−0.01 [−0.55, 0.53]	0.28	0.96	0.52 [−0.10, 1.16]	0.32	0.10
Continuous variables									
Age	−0.03 [−0.06, 0.00]	0.01	0.03	0.01 [−0.01, 0.04]	0.01	0.24	0.00 [−0.03, 0.03]	0.01	0.94
Psychological distress	−0.06 [−0.13, 0.00]	0.03	0.05	0.00 [−0.05, 0.04]	0.02	0.84	0.03 [−0.02, 0.07]	0.02	0.28
Fear of contracting COVID-19	−0.04 [−0.36, 0.28]	0.16	0.81	0.01 [−0.23, 0.24]	0.12	0.96	0.18 [−0.09, 0.46]	0.14	0.20

β, parameter estimate of log odds; CI, Confidence interval [lower, upper]; SE, Standard error; $p < 0.05$ considered significant. Each column represents a single logistic regression analysis conducted with a binary outcome variable, defined in the column header.[a]Compared to exercise no change/increase, diet no change/increase, alcohol no change/decrease.
[b]Compared to exercise no change/decrease, diet no change/decrease, alcohol no change/increase.

Discussion

This study sought to examine changes in healthy lifestyle behaviors among hematological cancer patients during the COVID-19 pandemic and identify factors associated with these changes. In this cross-sectional survey study, we found that a substantial proportion of the study population reported unfavorable changes in lifestyle behaviors. Specifically, more than one-third reported a decrease in the amount of exercise in which they engage and nearly half reported consuming a less healthy diet. By contrast,

only a small proportion increased their exercise and consumed a healthier diet. The present study also demonstrated that a small but notable proportion of respondents reported increased alcohol use during the pandemic.

The observed reductions in healthy lifestyle behaviors are concerning as engagement in such behaviors has been shown to positively affect physical and psychosocial functioning in hematological cancer patients (Knips et al., 2019; Sitlinger et al., 2020). Furthermore, recent evidence has shown that exercise can influence survival rate in patients undergoing allogeneic stem cell transplantation (Morishita et al., 2019). As such, the reduced engagement in healthy lifestyle behaviors during the COVID-19 pandemic observed in this study may be far reaching. Our results emphasize the importance of encouraging patients to maintain healthy lifestyle practices to ensure health is optimized while they are undergoing treatment and when in remission, particularly during crisis times like the COVID-19 pandemic. The benefits of engaging in physical activity in people with cancer should be properly outlined and existing evidence-based programs for maintaining a healthy lifestyle should be promoted by healthcare providers in all settings, including primary healthcare (Buffart et al., 2017; Knips et al., 2019; Sitlinger et al., 2020).

Our results revealed that psychosocial challenges associated with the pandemic emerged as barriers to exercise participation. In particular, patients who reported higher levels of psychological distress and fears of contracting COVID-19 significantly reduced their exercise during the pandemic. Hematological cancer patients, due to their risk of developing severe illness if contracted with COVID-19, are considered a serious risk group for COVID-19 (Vijenthira et al., 2020; International COVID-19 Blood Cancer Coalition, 2022). In addition, evidence shows COVID-19 vaccination may give less effective protection for people with hematological cancer (Lee et al., 2022; Re et al., 2022). Emerging studies reported behavior changes among this population such as increased isolation to cope with fears of contracting COVID-19 (Zomerdijk et al., 2021a,b). It is possible that hematological cancer patients may have reduced their exercise due to concerns about contracting the virus in public spaces. Additionally, government-imposed public health measures included the closure of public parks and fitness facilities, which may have limited opportunities for exercise and fostered sedentary behavior.

To reduce fears of acquiring COVID-19, clinicians should adapt exercise programs for hematological cancer patients to ensure these are conducted in a safe environment (Newton et al., 2020). This is especially important in fitness facilities given coronavirus appears to exhibit strong stability on surfaces such as stainless steel that are often found in these settings (Aboubakr et al., 2021). Public awareness of the ongoing vulnerability of hematological cancer patients along with continued protective measures such as masking in exercise settings should also be encouraged, especially as public rules are being relaxed (International COVID-19 Blood Cancer Coalition, 2022). These measures could provide some reassurance for hematological cancer patients and help them to resume a normal exercise regime.

Our findings support existing evidence demonstrating significant inverse associations between physical activity levels and psychological distress (Stubbs et al., 2017; Wilke et al., 2021; Himbert et al., 2022) and suggest hematological cancer patients experiencing psychological distress are less inclined to engage in physical activity. In these patients, symptoms of psychological distress, such as lack of energy and motivation may lead to increased avoidance of physical activity (Stults-Kolehmainen and Sinha, 2014; Stubbs et al., 2017; Durosini et al., 2021). It has been reported that COVID-19 related challenges, such as concerns about treatment delays, feelings of isolation, and increased financial hardship have contributed to heightened distress in cancer patients (Zomerdijk et al., 2021a; Beebe-Dimmer et al., 2022; Gates, 2022). A recent study reported that cancer patients who felt lonely and had fewer social interactions during the pandemic were less likely to engage in exercise (Himbert et al., 2022). Taken together, these findings highlight the need to be vigilant in screening for and managing distress during crisis times like the COVID-19 pandemic, which continues to present challenges for hematological cancer patients. Clinicians can help by promoting community services that address the unique psychosocial challenges and needs within this population (Leukaemia Foundation, 2022). Additionally, group-based exercise programs can serve as a meaningful avenue for patients to develop important social relationships that can improve their psychological wellbeing as much as the physical intervention activities itself (Newton et al., 2020; Durosini et al., 2021). Remote, group-based exercise interventions can be considered for patients who remain isolated due to the risks posed by COVID-19.

Younger age emerged as a significant contributor to increased exercise among those surveyed in the present study. This finding aligns with previous studies conducted with cancer patients both pre-and during-the pandemic (Himbert et al., 2022). Younger patients advised to work or study from home may have spent less time commuting and seized the opportunity to exercise more. They may have also spent more time online and found more appropriate health related information during the pandemic than older patients. This is consistent with research reporting higher levels of digital skills and digital health literacy among younger people compared to older people (Berens et al., 2016; Thomas et al., 2018).

However, in our study, younger age was also associated with increased alcohol consumption. Indeed, while restrictions may have served as a renewed source of motivation for exercise, confinement to the home, employment changes, and lack of social connections may have also triggered increased alcohol use among young people. This is consistent with the data reported by Australia's Foundation for Alcohol Research and Education, showing alcohol purchases during the early stages of the pandemic increased by 20%, with 33% of Australians aged under 50 years drinking more to cope with distress (Foundation for Alcohol Research and Education, 2020). Taken together, the increased exercise observed among younger patients in our study is encouraging, but the increased alcohol use is concerning. Given the established benefits of preventative health measures such as limiting alcohol consumption, additional strategies are needed to enhance awareness of the increased risk of cancer resulting from alcohol consumption (World Health Organization, 2010). These may include clinician delivered education about treatment complications associated with alcohol use (LoConte et al., 2018) and public health strategies, including educational programs highlighting the link between alcohol and cancer for young people and incorporating this messaging in school-based alcohol education programs (Bates et al., 2018).

Limitations

There are several limitations in our study. First, the findings should be interpreted with caution due to the retrospective and self-reported nature of the data collected. Responses are subject to recall bias and causative links cannot be assumed. Longitudinal studies are needed to observe the impact of the COVID-19 pandemic on the lifestyle changes of hematological cancer patients over time. Second, our findings only illustrate the lifestyle behaviors of hematology patients within Australia during the early stages of the pandemic. The behaviors of patients in other countries are likely to differ, owing to varying degrees of COVID-19 restrictions in place at the time. Third, a number of other factors may have influenced the observed reductions in healthy lifestyle behaviors among this patient cohort. Many hematological cancer patients experience a decline in nutritional status and weight due to the side effects associated with aggressive treatments such as stem cell transplantation which can lead to reduced exercise vitality (Morishita et al., 2019).

Additionally, both patients and survivors of all hematological cancer types were included in this sample. Future studies should conduct stratified analyses by hematological cancer subtypes and treatment status. Finally, this study did not explicitly ask patients about perceived challenges in maintaining healthy lifestyle behaviors during the COVID-19 pandemic and this should be a direction of future research to inform prevention efforts. Investigating in more detail the influence of psychological factors including fears of contracting COVID-19 on physical activity would be beneficial. Future studies should expand on our results and continue to monitor health behaviors to investigate if unfavorable changes persist.

Conclusion

The COVID-19 pandemic has had far-reaching effects on the general well-being of hematological cancer patients. Although maintaining healthy lifestyle behaviors is important for preventing and managing the physical and psychosocial effects associated with hematological cancer and its treatment, our results indicate that a significant proportion of hematological cancer patients experienced unfavorable changes in healthy lifestyle behaviors during the early stages of the pandemic. This was more common among patients who reported experiencing fear of contracting COVID-19 and increased psychological distress and patients who were younger. Supporting healthy lifestyle practices is important to ensure health is optimized while undergoing treatment and when in remission, particularly during crisis times like the COVID-19 pandemic which continues to present challenges for this group.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by The University of Melbourne Human Research Ethics Committee (Ref: 2057125.1). The patients/participants provided their written informed consent to participate in this study.

Author contributions

NZ, MJ, BC, JT, CS, AS, and KH contributed to the study conception and design. Material preparation, data collection, and analysis were performed by NZ, MJ, and BC. The first draft of the manuscript was written by NZ. All authors contributed to the manuscript revision, read, and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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