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ORIGINAL ARTICLE

Cardiac and other systemic complications in sickle cell anemia patients with COVID 19 infection

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) has been a major source of health-related morbidity and mortality worldwide. Several recent reports emerged from evaluating large cohorts of patients infected with SARS-CoV-2 have shown that a small number of COVID-19 positive patients had a severe disease course. Reports have indicated that COVID-19 positive patients with cardiovascular disease are at a higher risk of developing severe phenotypes following hospitalization. Sickle cell disease (SCD) is very common in the Eastern Province of Saudi Arabia, and cardiovascular complications and acute chest syndrome are commonly associated with SCD. The main objective of the present study was to evaluate the severity of COVID-19 infection in sickle cell anemia patients compared to a non-SCD COVID-19 cohort.

Methods: Demographic, clinical, biochemical, and follow-up data were collected for 20 sickle cell anemia patients infected with COVID-19 and 50 normal COVID-19 patients at King Fahd Hospital of the University, Al Khobar.

Results: Analysis of the data showed that acute cardiovascular symptoms, acute respiratory distress syndrome, acute kidney syndrome, and shock were absent in the SCD patients compared to the normal COVID-19 cohort. The average temperature was lower, while the platelet count was higher in the SCD cohort than in non-SCD patients.

Conclusion: SCD patients infected with the COVID-19 virus showed a less severe course of COVID-19 than non-SCD patients with COVID-19.

Keywords: COVID-19, sickle cell disease, cardiovascular, severity.

Introduction

Coronavirus disease 2019 (COVID-19) has spread worldwide, with an estimated 225 million infected cases and over 4.7 million deaths as of September 2021 [1]. The World Health Organization announced that COVID-19 has emerged as a global pandemic and the severity and the outcome of COVID-19 have a very complex relationship with the heart, lung, liver, brain, and kidney [2]. Since the beginning of 2020, several reports have shown that a large number of patients who develop the severe phenotype of the disease had other comorbidities, including cardiovascular disease (CVD) and lung and kidney diseases [3,4]. Moreover, studies have reported that patients with pre-existing CVDs were at a higher risk of a severe course of the disease when compared to patients without CVDs [5,6]. A study on a large cohort of patients hospitalized with COVID-19 infection reported that CVD was found to be significantly associated with severe morbidity and mortality [4,5].

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Sickle cell disease (SCD) is a common monogenic disease highly prevalent in the Eastern Province of Saudi Arabia [7,8]. Sickle cell anemia patients in the Eastern Province exhibit a mild course of the disease compared to their counterparts in Africa, which was characterized as benign [9]. This is attributed to the high level of fetal hemoglobin maintained by these patients even at old age [9,10]. However, it was indicated that most of these patients were children and that this phenotype is not extended to adulthood. Furthermore, several studies have indicated that the level of fetal hemoglobin decreases with an increase in age of these patients, leading to a more severe form of the disease [11-13]. Cardiovascular complications and acute chest syndrome (ACS) are commonly associated with SCD [7]. The main objective of the present study was to evaluate the severity of COVID-19 in sickle cell anemia patients compared to a normal COVID-19 infected cohort.

Subjects and Methods

This retrospective observational study was conducted among 26 SCD patients with COVID-19, and 50 non-SCD patients with COVID-19 admitted to King Fahd Hospital of the University, Al Khobar, Saudi Arabia. Data were collected between October 2020 and November 2021, with a 1-month follow-up period for each patient. Patients aged >18 years, with a confirmed diagnosis of SARS-CoV-2 and a clinical diagnosis of SCD, were included in the study. The demographical, clinical, and laboratory data of the selected patients were collected from the patient case report forms and hospital data management systems on a pre-designed datasheet after Institutional Review Board approval. The follow-up data were also entered onto the same datasheet.

The acquired data were coded to protect the identity of each patient and stored in a protected Microsoft excel document. The relationship between the categorical variables and the cohorts was tested using the chi-square test/Fisher's exact test. The independent *T*-test tested differences between the continuous variables with the disease cohorts. The statistical analysis was performed using IBM Statistical Package for the Social Sciences statistics software (version 20), and the statistical significance is considered if the *p*-value is <0.05.

Results

The study cohort included 76 patients with a confirmed diagnosis of COVID-19 infection (50% male, 50% female). The patients were classified into two groups, one group comprising patients with SCD (n = 26) and another one comprising non-SCD patients (n = 50). In the SCD group, 69% were homozygous (HbSS), and the remainder were heterozygous (HbSA). In the SCD and non-SCD groups, male participants represented 46.1% and 51%, respectively. The mean age of the SCD group was 30.69 and 34.57 years in the non-SCD group. Patients in the SCD group were Saudi nationals. In contrast, in the non-SCD group, 77.5% were Saudi nationals, and the remainder were from Asian countries, including India, Palestine, Jordan, Sudan, Ethiopia, and Bangladesh. G6PD deficiency (p = <0.001) and β-thalassemia (p = 0.006) were noted in 30.1% of the patients from SCD group. However, in the non-SCD group, none had G6PD deficiency, and only 2% were β-thalassemia carriers. Pulmonary embolism was observed in the non-SCD group only (2%) (Tables 1 and 2).

Major admission complaints in the SCD group included fever, cough, body pains, sore throat, and vaso-occlusive crisis (VOC). One SCD patient visited the hospital with labor pains and was subsequently found to be positive with COVID-19 infection. Among the non-SCD group, complaints included fever, cough, dyspnea, sore throat, and gastrointestinal symptoms. Prior to admission, 12.2% of cases in the non-SCD group were on non-steroidal anti-inflammatory drugs (NSAID) therapy followed by lipid-lowering agents (8.2%), beta-blockers (8.2%), antiplatelet agents (6.1%), and Angiotensin-converting enzyme (ACE) inhibitors (4.1%). Upon physical examination during admission, cardiology consultation was requested for 16.3% of the patients from the non-SCD group based on abnormal findings and results of electrocardiograph, echocardiogram, and laboratory tests [Troponin and creatine kinase myocardial band (CKMB)]. None of the patients in the SCD group required a cardiology consultation (Table 1).

Comorbidities observed in the SCD group included diabetes, hypothyroidism, hypertension, dyslipidemia, mixed connective tissue disease, chronic kidney disease, and bronchial asthma. Similarly, major comorbidities observed in the non-SCD group included diabetes, hypertension, and CVD. Vital signs and blood biochemical parameters revealed significant differences between the two groups, namely temperature (p = 0.004), hemoglobin (p < 0.005), and platelet count (p = 0.002). Low temperature, low hemoglobin, and high platelet count were observed in the SCD group compared to the non-SCD group.

After the diagnosis of COVID-19 infection, one patient had cardiomyopathy, and one had heart failure; both of these patients were from the non-SCD group. Bacterial infection was seen in 15.4% and 12.2% of the SCD and non-SCD groups. Furthermore, clinical pneumonia was seen among 36.7% and 23% of patients in the non-SCD and SCD groups, respectively. Other infections, acute respiratory distress syndrome, acute kidney injury, and shock were not seen in the SCD group. ICU admissions were 8.2% in the non-SCD group; however, no patients in the SCD group were admitted to the ICU. Of the patients admitted to the ICU, 75% were discharged within 1-4 days. The total duration of hospital admission, including in the general ward and ICU, was 1-42 days (average: 5.38 days) in the non-SCD group and 1-19 days (average: 6.39 days) in the SCD group (Table 2).

During the hospital stay, none of the patients from the SCD group were given oxygen therapy, invasive ventilation, prone positioning, tracheostomy, extracorporeal membrane oxygenation, and dialysis. In contrast, in the

non-SCD group, 20% of patients were given oxygen therapy for an average of 5.6 days with a dose up to a maximum of <10 l/minute. Hydroxychloroquine was administered among 30.8% and 32.6% of patients in the SCD and non-SCD groups, respectively. The ability of patient self-care was monitored post-discharge, and it was found that there was no difference in the abilities of the patients regarding self-care (Table 1).

Discussion

A large proportion of patients who developed severe COVID-19 and required hospitalization had an underlying CVD or other comorbidities [5]. This study aimed to describe and compare the disease course and outcomes in hospitalized COVID-19 patients with and without pre-existing SCD.

Prior studies based on multiple case reports have suggested that SARS-CoV-2 does not have a greater risk in developing ACS compared to other viral infections in SCD. Another study claimed that sickled RBCs might prevent severe clinical presentation as most cases had presented with mild-unprogressive symptoms [13,14]. Moreover, no significant correlation between SARS-CoV-2 infection and venous thromboembolic incidence in sickle cell anemia was concluded in the literature [14,15]. Our study showed that out of the thirteen SCD patients, no deep vein thrombosis/

Table 1. *Clinical and therapeutic characteristics of the patient cohorts.*

Variables	SCD patients, *n* (%)	Non-SCD patients, *n* (%)	*p*-value
Before admission, disease			
G6PD deficiency	8 (30.7%)	0 (0%)	<0.001
Beta thalassemia carrier	8 (30.7%)	1 (2%)	0.001
Healthcare worker	2 (7.7%)	3 (6%)	1
Pulmonary embolism	0 (0%)	1 (2%)	1
Before admission, therapy			
NSAID	2 (7.7%)	6 (12%)	0.155
Beta blockers	0 (0%)	4 (8%)	0.292
ACE inhibitors	0 (0%)	2 (4%)	0.544
Antiplatelet agent	0 (0%)	3 (6%)	0.547
Lipid lowering agents	2 (7.7%)	4 (8%)	1
During admission			
Cardiology consultation	0 (0%)	8 (16%)	0.045
Bleeding	2 (7.7%)	1 (2%)	0.268
Bacterial infection	4 (15.4%)	6 (12.2%)	0.864
Other infection	0 (0%)	2 (4%)	0.252
Clinical pneumonia	6 (23%)	18 (36%)	0.305
Acute respiratory distress syndrome	0 (0%)	2 (4%)	0.544
Acute kidney injury	0 (0%)	3 (6%)	0.547
Shock	0 (0%)	1 (2%)	1
Admission to ICU	0 (0%)	4 (8%)	0.292
During admission, tests performed			
Troponin	2 (7.7%)	8 (16%)	0.479
CKMB	0 (0%)	3 (6%)	0.547
During admission therapy			
Oxygen therapy	0 (0%)	10 (20%)	0.013
Invasive ventilation	0 (0%)	2 (4%)	0.544
Prone positioning	0 (0%)	5 (10%)	0.159
Tracheostomy	0 (0%)	1 (2%)	1
Extracorporeal membrane oxygenation	0 (0%)	1 (2%)	1
Dialysis	0 (0%)	2 (4%)	0.544
Hydroxychloroquine	8 (30.7%)	16 (32%)	1
Post diagnosis			
Cardiomyopathy	0 (0%)	1 (2%)	1
Heart failure	0 (0%)	1 (2%)	1
Post-discharge Ability of self-care			
Same as before	12 (46.1%)	32 (64%)	**0.032**
Better	8 (30.7%)	16 (32%)	
Worst	6 (23%)	2 (4%)	
Other treatment	14 (53.8%)	26 (52%)	1

Statistically significant values were given in bold (*p*-value below 0.05).

Table 2. *Laboratory parameters comparison within the two groups at the time of admission.*

Variables	Patient group	Mean	Std. deviation	*p*-value
Age (years)	SCD	30.69	11.18	0.069
	Non-SCD	34.52	6.88	
Duration of stay in hospital (days)	SCD	5.38	6.12	0.618
	Non-SCD	6.28	7.96	
Temperature (°C)	SCD	36.73	0.35	**<0.005**
	Non-SCD	37.44	0.82	
Heart rate (bpm)	SCD	90.92	14.96	0.097
	Non-SCD	98.32	19.68	
Systolic blood pressure (mmHg)	SCD	126.38	11.62	0.470
	Non-SCD	129.56	20.62	
Diastolic blood pressure (mmHg)	SCD	77.69	11.30	0.557
	Non-SCD	79.82	16.45	
Respiratory rate (breaths per minute)	SCD	20.38	0.85	0.088
	Non-SCD	22.66	6.66	
Oxygen saturation (%)	SCD	97.85	1.69	0.466
	Non-SCD	97.24	4.02	
C-reactive protein (mg/l)	SCD	4.42	3.75	0.854
	Non-SCD	4.02	7.04	
Hemoglobin (g/dl)	SCD	9.13	1.93	**<0.005**
	Non-SCD	12.48	2.64	
Platelet at admission ($\times 10^3$/ µl)	SCD	355.46	116.85	**<0.005**
	Non-SCD	248.91	92.02	

Statistically significant values were given in bold (*p*-value below 0.05).

pulmonary embolism was encountered during admission. The present study results are aligned with previous studies. Comparison between SCD and non-SCD patients with reference to the viral clearance found no significant difference between the two cohorts. Regarding VOC, it has been shown that there is no significant correlation in those patients with COVID-19 [6]. In our study, no SCD patient had VOC during their hospital stay. These results support the theory that COVID-19 infection in SCD patients may not trigger VOC.

According to the Saudi Ministry of Health guidelines, ICU admission for COVID-19 patients was indicated in certain situations, such as the need for invasive mechanical ventilation, requiring more than 2 hours of non-invasive ventilation or high flow nasal cannula, development of acute respiratory distress syndrome, hemodynamic instability, the need for vasopressor support, metabolic complication (e.g., acidosis) or signs of organ failure [16]. ICU admission rate among non-SCD patients was 8.2% (n = 4) compared to 0% (n = 0) in SCD patients. In the non-SCD patient cohort, 8% (n = 4) were admitted to the ICU due to the need for invasive mechanical ventilation or the development of acute respiratory distress syndrome. A study by Shekerdemian et al. [18] reported that ICU admissions were 4% (n = 2) among patients with ages ranging from 4.2 to 16.6 years. In the present study, the age of the SCD patients ranged between 15 and 54 years [17]. The higher age range may be a factor that resulted in the SCD patients avoiding admission to the ICU.

In our study, out of the four patients who were admitted to the ICU, only one patient had diabetes mellitus as comorbidity, while the remaining patients did not present with any comorbidity. The patients with COVID-19 and pre-existing comorbidity, namely, pulmonary hypertension, chronic kidney disease, and congestive heart failure, irrespective of hemoglobin genotype, should be hospitalized and managed accordingly [18].

We found that generalized body pain was the most common complaint in SCD patients (30.1%), followed by cough (23%). In the SCD group, no patients presented with temperature >38°C. However, in the non-SCD group, 24.4% presented with a temperature >38°C. A study by Kashari et al. [14] indicated that VOC, fever, and ACS are the most common reasons for admission to hospital in SCD patients with COVID-19. Our results show that none of the COVID-19 SCD patients were admitted due to VOC and ACS.

Lower hemoglobin levels were observed in SCD patients compared to non-SCD patients ($p < 0.005$) since the low hemoglobin phenomenon is commonly seen in SCD. Platelet counts were higher in SCD patients compared

to non-SCD patients (p = 0.002). This may be due to the activation of platelets and neutrophils by the pro-inflammatory process [20].

Conclusion

Severe complications were not seen among SCD patients with COVID-19 infection. None of the SCD patients required supportive therapy post admission or required admittance to the ICU. Symptoms of ACS and SARS-CoV-2 infection might overlap and must be carefully diagnosed and closely followed. COVID-19 infection in SCD patients may not induce the increased risk of COVID-19 complications and may have a better prognosis.

List of Abbreviations

ACE	Angiotensin-converting enzyme
CKMB	Creatine kinase myocardial band
CVD	Cardiovascular disease
NSAID	Non-steroidal anti-inflammatory drugs
VOC	Vaso-occlusive crisis

Conflict of interest

The authors declare that there is no conflict of interest.

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None.

Consent to participate

Informed consent was obtained from all the participants.

Ethical approval

Institutional review board approval was obtained from Imam Abdul Rahman bin Faisal University (IRB-UGS-2021-01-001), dated 10/1/2021.

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