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Impact of COVID-19 on vasoocclusive crisis in patients with sickle cell anaemia

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Abstract

Objectives: The study aimed to assess COVID-19 impact on the morbidity and mortality of vasoocclusive crisis (VOC) in sickle cell anaemia (SCA) patients.

Methods: A prospective cohort study of 100 SCA patients; 50 with COVID-19 (COVID group) and 50 without (non-COVID group). All patients signed written informed consent.

Results: The COVID group had a significantly higher VOC episode median per year; 3 (IQR,1-6) vs 2 (IQR,2-12) (P < 0.05). The need for hospitalisation was similar in both groups. The non-COVID group had more history of culture-proven infection (P < 0.05). The COVID-group had more osteonecrosis (P < 0.05), splenic sequestration, splenomegaly and hepatic crisis (P < 0.05, 0.006, 0.02, respectively) and significantly higher (P < 0.05) symptoms of fever, cough, fatigue, abdominal pain and anemia. Mean haemoglobin, lymphocyte subset, platelets, and reticulocytes were reduced in both groups, while lactate dehydrogenase and ferritin levels were significantly elevated. In the COVID group, the rise in white blood cell count, reticulocyte percentage, platelets and ferritin was subdued (P < 0.05). Two patients in the COVID group and 3 in the non-COVID group died; there was no statistically significant difference in mortality.

Conclusions: Although COVID-19 may have triggered the onset of VOC, it did not significantly influence VOC-related morbidity or mortality in this SCA cohort.

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Introduction

COVID-19, caused by SARS-CoV-2 (Gorbalevna et al., 2020), has spread to 191 countries and all continents (https://coronavirus.jhu.edu/map.html), and the pandemic shows no signs of coming under control, despite global efforts. The pandemic has resulted in an unprecedented number of deaths globally, with widespread lockdowns and disruption to world economies and businesses (Fauci et al., 2020). The clinical features of SARS-CoV-2 vary from mild in approximately 80% of cases, severe in 15% and critical in 5%. More severe illness is predominantly seen in adults with advanced age and those with underlying comorbidities, although it has been reported in all ages (Wu and McGoogan, 2020). Sickle cell anaemia (SCA) patients are prone to pulmonary complications such as acute chest syndrome (ACS) and thromboembolic complications (Steinberg, 1999). Due to their underlying immunocompromised state, SCA patients are also at a higher risk of overwhelming inflammation and cytokine-associated lung injury (Hussain et al., 2020). COVID-19 has been reported in persons with SCA, with a variable
impact on morbidity and mortality (Beerkens et al., 2020; Chakravorty et al., 2020; De Sanctis et al., 2020; Nur et al., 2020; Odière et al., 2020). Vasooclusive crisis (VOC) is among the most common SCA manifestations that bring patients to medical facilities. The impact of COVID-19 on morbidity and mortality associated with SCA VOC is not clear. We prospectively enrolled SCA patients who presented to the emergency department with VOC and signs and symptoms suggestive of COVID-19. All of the patients were tested for COVID-19 by reverse transcriptase-polymerase chain reaction (RT-PCR) during their emergency department visits for VOC over the 6-month study period.

Material and methods

Design and setting

In this prospective cohort study, we enrolled consecutive SCA patients presenting with VOC to the emergency department. The study was approved by the local medical research and ethics committees, and patients gave written informed consent.

Population

SCA patients presenting with VOC and signs and symptoms suggestive of COVID-19 with a confirmed positive RT-PCR were the cases (COVID group), and those testing negative for COVID-19 were the control group (non-COVID group). Some of the non-COVID group presented with a sickle crisis on multiple occasions during the study period.

Outcomes

Our data collection included demographics, previous SCA-related complications, other comorbidities, presenting signs and symptoms, baseline laboratory findings including haematological tests (white blood cell (WBC) count, platelet count, haemoglobin (Hb) F, S and A2 levels), and biochemical tests including renal and hepatic function and serum ferritin (S. ferritin) and lactate dehydrogenase (LDH) levels. We also collected each patient’s laboratory data at VOC episode presentation and captured the medical therapy received and the outcome. Complete blood counts were obtained using Sysmex XN9100 automated blood cell counter (SYSMEX, Europe GmbH, Hamburg Germany) within 4-12 hours of collection, and high-performance liquid chromatography (HPLC) was carried out with the Bio-Rad VARIANT II™ instrument (Bio-Rad Laboratories, Hercules, CA, USA) applying the “j-thalassemia short program”. RT-PCR for COVID-19 testing was performed according to the manufacturer’s instructions and following the national case definition and clinical guidelines in the Sultanate of Oman using either the QuantStudio 5 Real-Time PCR System (Applied Biosystems, Life Technologies, and Foster City, CA, USA) or, for emergency cases, the GeneXpert machine (Cepheid, Sunnyvale, CA USA).

Statistics

We used descriptive statistics and univariate comparisons with the t2 test to determine differences between SCA patients with and without COVID-19. Paired and unpaired Students t tests were used to compare continuous variables. The primary outcome was to measure the impact of COVID-19 on VOC in SCA with a P-value of <0.05 considered statistically significant.

Results

Table 1A shows the demographic data, medical history, clinical presentation, treatment and outcome in this study cohort. Fifty patients had COVID-19 RT-PCR positive tests (n = 50 episodes) (COVID group), and 50 had COVID-19 RT-PCR negative tests (non-COVID group), some of the non-COVID group presented with a sickle crisis on multiple occasions during the study period (n = 67 episodes).

The severity of SCA was classified, based on the number of VOC episodes, as mild (0-3 episodes per year), moderate (>3-6) and severe (>6). The COVID group had a significantly higher median of VOC episodes per year, i.e. 3 (IQR, 1-6) vs 2 (IQR, 2-12) (P < 0.05; Mann–Whitney test). There was no significant difference in age or gender between the 2 groups. The median length of hospital stay was relatively longer in the non-COVID group, while the percentage of hospital admissions was similar in both groups. Patients with Sickle β+ were more likely to be infected with COVID-19 than HbSS patients (P < 0.009, Chi-square test). The non-COVID group had more history of culture-proven infection (P = 0.05, Chi-square test), including bacterial and viral infections (P = 0.04 for both). The COVID group were more likely to have more osteonecrosis of joints (P < 0.05, Chi-square test), splenic sequestration, splenomegaly and hepatic crisis (P = 0.05, 0.006, 0.02, respectively, Chi-Square test). The number of intermittent simple blood transfusions was relatively higher in the COVID group; however, 6% of the non-COVID group were on regular blood transfusions.

The presenting symptoms of fever, cough, fatigue, abdominal pain and anosmia were significantly higher (P < 0.5, Chi-Square test) in the COVID group. The COVID group had milder disease severity with less frequent pain. Although hospital admission rates were similar for both groups, intensive care unit (ICU) admission and ventilator support were relatively higher in the non-COVID group.

In both groups, there was a fall in the mean haemoglobin, lymphocyte subset, and platelets, while the mean serum LDH (S. LDH) and S. ferritin were significantly elevated (P < 0.5, paired students’ t test) (Table 1B). The mean WBC count and reticulocyte percentage rose significantly in the non-COVID group during the VOC episode leading to their emergency department visit, but this was not seen in the COVID group. The other significant differences during the presenting VOC episode were a lower mean total for WBC count, lymphocytes, reticulocyte percentage, platelet count and S. ferritin in the COVID group (Table 1C). C-reactive protein, fibrinogen and D dimers were elevated in both groups. There was 1 confirmed pulmonary embolism in the COVID group and 2 thrombosis episodes in the non-COVID group, but this was not statistically significant.

Therapeutic interventions between the 2 groups were significantly different only in the use of azithromycin and convalescent plasma. Two patients died in the COVID group and 3 in the non-COVID group; this difference in mortality was not statistically significant (Table 1D).

Discussion

Due to the immune-compromised status and the known chest complications of SCA, it was feared that SCA patients would be adversely affected by COVID-19. To our knowledge, this is the first study to evaluate the impact of COVID-19 on the morbidity and mortality of SCA patients presenting with VOC, where 2 groups of SCA patients are compared within the same study cohort.

The 2 groups were comparable in age, gender and the need for hospital admission; however, the COVID group had more severe SCA, determined by a significantly higher VOC frequency. Conversely, the non-COVID group had significantly more history of culture-proven infections, including bacterial and viral, potentially explaining their longer hospital stay duration.
The Sickle^p^ genotype was more prevalent in the COVID group, with significantly higher HbA2-. The reason for this is unclear, and it would require a larger study sample to infer the relevance of this observation. There was a higher prevalence of osteonecrosis, splenic and hepatic complications in the COVID group. The significance of these findings is not clear, but it may relate to the higher prevalence of Sickle^p^ genotype in the COVID group, analogous to Adesina et al.'s (2017) report of a higher incidence of osteonecrosis in SCA patients who co-inherited α-thalassemia with SCA. Splenomegaly is generally not seen in adult SCA patients, as

**Table 1A**

Demographics, medical history, clinical presentations, treatment and outcome.

| Parameter                              | COVID (N = 50) | Non-COVID (N = 67) | P-value |
|----------------------------------------|----------------|--------------------|---------|
| Median age, yr (IQR)                   | 31             | 31                 | 0.85**  |
| Gender                                 | M:F=27:23      | M:F=29:21          |         |
| Genotype                               | SS, n (%)      | 10(20)             | 28(56)  | 0.07*  |
|                                        | SJ^p^, n (%)   | 16(32)             | 0.01*   |
| Treated at                             | Home, n (%)    | 16(32)             | 20(59.8)| 0.85*  |
|                                        | Admitted, n (%)| 34(68)             | 47(70.2)| 0.99*  |
| Length of stay                         | Median, days (IQR) | 5(3.5-7.5)          | 8(5-12) | 0.18** |
| Comorbidities                          | Previous infections, n (%) | 23(46)          | 56(86.3)| 0.05*  |
|                                        | Bacterial, n (%)| 18(36)             | 47(70.1)| 0.04*  |
|                                        | Viral, n (%)   | 13(26)             | 37(55.2)| 0.04*  |
|                                        | Fungal, n (%)  | 9(18)              | 17(25.4)| 0.44*  |
|                                        | Median VOC/year| 3 (3)              | 2       | 0.02** |
|                                        | IQR           | 1-6                | 2-12    |         |
|                                        | H/o Acute chest syndrome, n (%) | 37(74)         | 39(58.2)| 0.41*  |
|                                        | Splenectomy, n (%) | 21(42)             | 28(41.8)| 0.99*  |
|                                        | Cholecyctectomy, n (%) | 16(32)           | 15(22.4)| 0.37*  |
|                                        | Joint Necrosis, n (%) | 17(34)             | 9(13.4) | 0.03*  |
|                                        | Sequestration, n (%) | 2(4)               | 0(0)    | 0.05*  |
|                                        | Splenomegaly, n (%) | 12(24)              | 3(4.5)  | 0.006* |
|                                        | Hepatomegaly/Crisis, n (%) | 8(16)            | 2(2.9)  | 0.02*  |
|                                        | Transfusions-Intermediate, n (%) | 43(86)         | 35(52.2)| 0.08*  |
|                                        | Transfusions-Regular, n (%) | 0(0)             | 4.5(9)  | 0.03*  |
| Presenting features                    | Pain, n (%)    | 32(64)             | 55(84)  | 0.02*  |
|                                        | Fever, n (%)   | 40(80)             | 26(38.8)| 0.02*  |
|                                        | Cough n (%)    | 23(46)             | 13(19.4)| 0.02*  |
|                                        | Reduced saturation, n (%) | 8(16)            | 15(22.4)| 0.47*  |
|                                        | Fatigue, n (%) | 14(28)             | 3(4.5)  | 0.002* |
|                                        | Tachypnea, n (%)| 7(14)              | 13(19.4)| 0.31*  |
|                                        | Pharyngitis, n (%)| 10(20)          | 6(8.9)  | 0.13*  |
|                                        | Headache, n (%)| 9(18)              | 4.5(9)  | 0.07*  |
|                                        | Abdominal pain, n (%) | 6(12)             | 0(0)    | 0.001* |
|                                        | Anosmia, n (%)  | 6(12)              | 0(0)    | 0.001* |
| Clinical course                        | Mild, n (%)    | 24(48)             | 12(17.9)| 0.01*  |
|                                        | Moderate, n (%)| 18(36)             | 20(29.8)| 0.61*  |
|                                        | Severe, n (%)  | 1(2)               | 5(7.4)  | 0.20*  |
| Treatment                              | Transfusions - Simple n (%) | 20(40)           | 22(16.8)| 0.28*  |
|                                        | - Red blood cell exchange | 6(12)         | 9(13.4) | 0.84*  |
|                                        | Medication - HCQ therapy, n (%) | 6(12)           | 4.5(9)  | 0.29*  |
|                                        | - Azithromycin, n (%) | 24(48)             | 10(23.8)| 0.05*  |
|                                        | - Dexamethasone, n(%) | 1(2)               | 0(0)    | 0.16*  |
|                                        | - Antiviral therapy, n (%) | 7(14)            | 8(11.9) | 0.77*  |
|                                        | - Convalescent Plasma, n (%) | 2(4)              | 0(0)    | 0.05*  |
|                                        | - Antibiotics, n (%) | 34(68)             | 30(44.7)| 0.18*  |
| Outcome                                | ICU admission, n (%) | 2(4)              | 4.5(9)  | 0.64*  |
|                                        | Ventilated, n (%) | 1(2)               | 4.5(9)  | 0.31*  |
|                                        | Acute chest syndrome, n (%) | 20(40)          | 20(29.8)| 0.42*  |
|                                        | Mortality, n (%) | 2(4)               | 3(6)    | 0.98*  |

Key: IQR – Interquartile range, * Chi Square test (COVID group vs non-COVID group); HCQ – Hydroxychloroquine; LMWH – low molecular weight heparin.

**Table 1B**

Laboratory features – baseline and at presentation to the emergency department

| Parameters at baseline | COVID group (N = 50 episodes) (50 patients) | Non-COVID group (N = 67 episodes) (50 patients) |
|------------------------|---------------------------------------------|-----------------------------------------------|
|                        | Basal                                       | AE visit                                      | **P value**                                  | Basal                                       | AE visit                                      | **P value**                                  |
| Hemoglobin, g/dL, Mean ± SD | 9.2 ± 1.05                                  | 7.4 ± 1.8                                    | P<0.001**                                   | 9.8 ± 1.2                                  | 7.9 ± 1.5                                    | <0.001**                                    |
| White Blood Cells, X10^9/L, Mean ± SD | 9.8 ± 3.8                                   | 9.8 ± 1.4                                    | P=0.67**                                    | 11.3 ± 2.3                                 | 12.8 ± 1.6                                    | 0.01**                                      |
| Lymphocytes, X10^9/L, Mean ± SD | 3.1 ± 1.4                                   | 2.4 ± 1.2                                    | P<0.03**                                    | 3.6 ± 1.7                                  | 3.1 ± 1.9                                    | 0.05**                                      |
| Platelets, X10^9/L, Mean ± SD | 350 ± 34                                    | 212 ± 23                                     | P<0.001**                                   | 333 ± 89                                   | 278 ± 56                                     | 0.009**                                     |
| Reticulocytes, %, Mean ± SD | 7.5 ± 1.2                                   | 5.0 ± 1.3                                    | P=0.004**                                   | 6.3 ± 1.3                                  | 8.76 ± 1.2                                   | 0.006**                                     |
| Lactate Dehydrogenase, u/l, Mean ± SD | 420 ± 32                                    | 1030 ± 42                                    | P=0.01**                                    | 415 ± 57                                   | 1009 ± 332                                   | 0.01**                                      |
| Ferritin, ng/mL, Mean ± SD | 797 ± 189                                   | 1829 ± 78                                    | P=0.003**                                   | 2659 ± 215                                 | 1619 ± 157                                   | 0.15**                                      |

Key: #Unpaired Students ‘t’ test (COVID group vs non-COVID group); $paired Students ‘t’ test (in COVID group and non-COVID group).
the spleen is progressively lost in patients due to periodic splenic infarction with splenic atrophy. However, spleens can persist in SCA patients to adult life where the thalassaemia gene is carried in association with the sickle gene mutation, and the COVID group had a high prevalence of both the alpha and beta thalassemia genes (Alkindi et al., 2010).

Fever, cough, fatigue, abdominal pain and anemia were the lead presenting symptoms in the COVID group (P < 0.5, Chi-Square test), similar to the general population and as reported among sickle cell disease cohorts (Al Wahabi et al., 2020; Balanchivadze et al., 2020; Khamis et al., 2020). In their report from the same population, Khamis et al. (2020) reported that 95.9% of cases were mild, 3.6% moderate and 0.5% severe, with a case fatality rate of 0.5% in the non-SCA population. In the present study, pain was less frequent in the COVID group, while abdominal pain and anemia, defining symptoms of COVID-19 in the general population (Aziz et al., 2020), were only reported in this group. In their meta-analysis, Aziz et al. (2020) showed that anemia is a highly prevalent symptom with an odds ratio of 14.7 in COVID-19 patients.

Comparing the baseline vs laboratory parameters at the time of admission, a fall in the mean haemoglobin, lymphocyte subset, and platelets, and elevation in the mean S. LDH and S. ferritin were seen in both groups (P < 0.5, paired students’ t test) (Table 1B). These parameters indicate bone marrow suppression driven by the inflammatory process which is classically seen during SCA VOC episodes and in COVID-19 cases (Balanchivadze et al., 2020). The mean WBC count and reticulocytes rose significantly in the non-COVID patients during their VOC episodes, but this was subdued in the COVID patients. Other significant differences were the lower mean total WBC count, reticulocyte percentage, platelet count and S. ferritin in the COVID group compared to the non-COVID group (Table 1C). This significant observation could help us to better understand COVID-19 infection, but it requires a detailed analysis of the underlying cytokine interplay to explain the observed differences and should be evaluated with a larger study sample. It is known that numerical and morphological changes within WBC are associated with COVID-19 infection severity (Pozdnyakova et al., 2021).
Approximately one-third of patients in both groups were managed at home after their emergency department visit. Hospital admission rates were similar in both groups, with 2% of the COVID-19 patients classified as severe, of whom 2 (4%) required ICU admission and 1 (2%) required ventilator support. These outcomes contrast with a US study where 69% of COVID-19 patients with SCA were hospitalised, 11% admitted to the ICU, and 7% died (Panepinto et al., 2020).

ACS is a lead cause of death in SCA, and COVID-pneumonia is a complication for 15–20% of COVID-19 patients (Gladwin and Vichinsky, 2008; Jain et al., 2017; Zhou et al., 2020). The aetiology of ACS is variable and includes infections and thrombosis, the 2 prominent elements of COVID-19 disease. COVID-19 symptoms such as fever, desaturation and dyspnoea are often similar to ACS symptoms and may affect clinical decisions. ACS incidence in this study cohort was similar in both groups (28% [COVID] vs 30.8% [non-COVID]) and consistent with other respiratory viral infections (Allkindi et al., 2020). Red blood cell transfusions or exchange were not significantly different with use in 40.2% and 52% of the non-COVID and COVID group, respectively. Red blood cell transfusions are the mainstay of therapy for patients with SCA but pose significant clinical challenges, including alloimmunisation, which can lead to life-threatening acute and delayed transfusion reactions (Nzuzanbaksh, 2016; Zimmerman and Hudson, 2016). Shortage of blood supply during the pandemic, is another challenge for SCA patients, and the judicious use of red blood cell exchange may help ameliorate COVID-19-related pulmonary complications in SCA patients with pulmonary infiltrates (Okar et al., 2020).

Several studies have reported pulmonary embolism and coagulopathy in patients with COVID-19 (Balanchivadze et al., 2020; Edler et al., 2020; Lodigiani et al., 2020). SCA and COVID-19 are strongly associated with thromboembolic disease. Both studies groups had raised C-reactive protein and fibrinogen; however, only 1 patient in the COVID group had a pulmonary embolism, treated with anticoagulation per the standard protocol (Balanchivadze et al., 2020; Okar et al., 2020). Two patients in the non-COVID group had thrombosis, 1 with a pulmonary embolism and 1 with cerebral sinus thrombosis. Low molecular weight heparin was given to 42% of the COVID group and 31.3% of the non-COVID group. The difference in thromboembolic disease between the 2 groups was not statistically significant; these findings are similar to those reported in a Detroit (USA) study (Balanchivadze et al., 2020).

There were 2 deaths in the COVID group (4%). A 19-year-old presented with a headache, had a cerebral haemorrhage and died in the operating room 12 hours after hospital admission. The other patient died with COVID-related pneumonia, renal failure and occipital infarction. Both patients had a history of asthma, ACS (2 factors also seen in COVID-19 in the general population) and splenectomy (Al Wahabi et al., 2020). The COVID group mortality rate is consistent with a French study where COVID-19 mortality among SCA patients was not severe (Arlet et al., 2020); this is thought to be partly due to SCA patients being young and self-isolated, and may also be a protective effect against COVID-19 driven by cytokine profile (Arlet et al., 2020). In Oman in 2nd January 2021, there were 1499 COVID-19 related deaths out of 128 867 PCR-confirmed COVID-19 cases, indicating a 1.16% mortality rate (https://coronavirus.jhu.edu/map.html). The non-COVID group deaths (n = 3) indicate an exaggerated inflammatory response with ensuing multiorgan failure, consistent with SCA VOC pathophysiology.

In conclusion, although the mortality in this study is higher than the COVID-19 mortality rate in the general population, COVID-19 did not significantly impact the morbidity or mortality of SCA patients with VOC. SCA patients with COVID-19 did not have a higher risk for a severe disease course or a higher case-fatality rate, consistent with reports elsewhere in the literature (Arlet et al., 2020).

Conflict of interests

The authors report no conflicts of interest relating to the contents of this article. The authors alone are responsible for the content and writing of this article and received no financial support.

Author contributions

All authors have made substantial contributions and have seen and approved the final version of the manuscript. SAK, RAE, AAM, MAM, SYA, GAK, BAR, SAR, JAY, YAW, SAS and MAR, were fully involved in the study’s conception and design, recruitment and care of patients, acquisition of data, or analysis and interpretation of data. SAK and AVP were instrumental in drafting the article and critical appraisal before submission.

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