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Clinical Outcomes of COVID-19 in Sickle Cell Patients in the Hatay Province of Turkey

Türkiye'nin Hatay İlinde Orak Hücre Hastalarında COVID-19'un Klinik Sonuçları

ABSTRACT

Objective:

The COVID-19 caused by the severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) can be mortal particularly due to respiratory system involvement and coagulopathy. On the other hand, respiratory system involvement and coagulopathy are among the major causes of mortality in sickle cell patients as well. There are conflicting results in the literature on the mortality rates caused by COVID-19 in sickle cell patients. For this reason, we aimed to show the course of COVID-19 in sickle cell patients.

Material and Method:

Our study was created from the data of 21 sickle cell patients in the adult age group who were infected with SARS-COV-2. The laboratory and imaging results of these patients were reviewed.

Result:

The median age of the patients in the study was 34 years and 57% of the patients were male. 72% (n:15) of the patients needed to be admitted to the hospital and three of them died. The CRP level in individuals who died was found to be statistically significantly higher (HR, 1.02; 95% CI, 1.01-1.03; p=0.049).

Conclusion:

In this patient group, the requirement for hospitalization has increased significantly and mortality rates have increased in comparison to the general population. Patients with a high CRP value should be monitored closely since they can have a fatal outcome.

Key Words :

Sickle Cell Disease, COVID-19, Fatal Outcome

ÖZ

Amaç:

SARS-COV-2'nin sebep olduğu COVID-19 özellikle solunum sistemi tutulumu ve koagülopati nedeniyle mortal olarak seyredebilmektedir. Benzer şekilde orak hücre hastalarında da solunum sistemi ve koagülopati ilişkili ölüm mortalitenin önemli sebepleri arasında yer almaktadır. Yapılmış olan çalışmalarda COVID-19'un orak hücre hastalarındaki mortalite oranları ile ilgili çelişkili sonuçlar mevcuttur. Bu sebepten dolayı orak hücre hastalarında COVID-19'un seyrini göstermeyi hedefledik.

Gereç ve Yöntem:
Çalışmamız SARS-COV-2 ile enfekte olan erişkin yaş grubundaki 21 orak hücre hastasının verilerinden oluşturulmuştur. Bu hastaların laboratuvar ve görüntüleme sonuçları incelenmiştir.

Bulgular:
Çalışmaya alınan hastaların %57'si erkek cinsiyet olup medyan yaş 34 saptanmıştır. Hastaların %72'sinin (n:15) hastane yatış ihtiyacı gerekmiş olup 3 hasta hayatını kaybetmiştir. Hayatını kaybedenlerde CRP değeri istatistiksel olarak anlamlı bir şekilde yüksek saptanmıştır (HR, 1.02; %95 GA, 1.01-1.03; p=0.049).

Sonuç:
Normal popülasyona göre mortalite oranlarının arttığı bu hasta grubunda hastane yatış ihtiyacıda belirgin şekilde artmıştır. Özellikle CRP değeri yüksek seyreden hastaların mortal seyredebilmesi nedeniyle dikkatli olunmalıdır.

Anahtar Kelimeler:
Orak Hücre Hastalığı, COVID-19, Ölümcül Sonuç

INTRODUCTION

A new type of Coronavirus, which caused respiratory tract infection and is currently named as severe acute respiratory syndrome coronavirus 2 (SARS-COV-2), was detected in December 2019, in the Wuhan City of the People's Republic of China (1). According to the data of the World Health Organization, more than 127 million people have become infected with the coronavirus disease of 2019 (COVID-19) and more than 2.7 million of them have died, within the period between the onset of the outbreak till the day this article was written (2). Approximately 81% of patients infected with COVID-19 were shown to develop mild symptoms (either no pneumonia or mild pneumonia), 14% of them were shown to develop severe symptoms (shortness of breath, increased respiratory frequency 30/minute, O2 saturations less than 92%, and more than 50% lung involvement) and 5% of them were shown to develop critical symptoms (respiratory failure, septic shock and multi-organ failure) (3). Additionally, it has been shown in many studies that COVID-19 progresses more severe in individuals with pre-existing chronic conditions, such as heart disease, diabetes, chronic kidney disease and pulmonary disease and that presence of such pre-existing chronic conditions increases the rates of hospitalization and mortality if these patients become infected with COVID-19 (4,5).

Sickle cell disease (SCD) is a hemoglobinopathy caused by a single amino acid change (β 6Glu → Val) in the 6th codon of beta-globin gene. This disease is the most common hemoglobinopathy affecting millions of people worldwide and has a particularly high prevalence in sub-Saharan Africa, the Middle East, India and in the Mediterranean basin, which also includes Turkey and mainly the Hatay Province in Turkey (6). Abnormal hemoglobin produced in people with SCD polymerizes in the erythrocyte at low oxygen levels, causing ischemia and reperfusion damage in the microvascular system, resulting in vaso-occlusive crises and also in multiple organ damage later on. Additionally, inflammation, hypercoagulopathy and vasculopathy develop in patients with SCD, and the increased susceptibility to recurrent infections, especially pneumonia (7). Therefore, individuals with SCD have high mortality and morbidity and their average life expectancy is 43-54 years (8,9).

The viral infections that develop in patients with SCD have been shown to trigger vaso-occlusive crises (VOC), especially Acute Chest Syndrome (ACS), which is a condition associated with high mortality rates (10,11). COVID-19 causes multiple organ failure by causing cytokine storm, progressive intravascular activation and disseminated intravascular coagulation (DIC), especially in critically ill patients (12). In this respect, COVID-19 bears an important risk for patients with SCD, as do the other viral infections. However, there are only a few studies available in the literature on the effects of COVID-19 on patients with SCD and thus only limited information. In view of the foregoing, it is aimed in this study to investigate the effects of COVID-19 on the prognosis of the SCD and on the mortality of sickle cell patients through scrutinizing the clinical and laboratory findings and the treatment needs of 21 adult sickle cell patients with COVID-19.

MATERIAL and METHODS

This study was carried out as a retrospective study using the data of 21 SCD patients, who were infected with SARS-COV-2 and applied to either Hatay Mustafa Kemal University Faculty of Medicine Hematology Clinic or Hatay Public Hospital, both of which are located in the Hatay Province of Turkey, between October 2020 and December 2020. This research complies with all the relevant national regulations, institutional policies and is in accordance with tenets of the Helsinki Declaration, and has been approved by the Hatay Mustafa Kemal University Ethics Committee (approval number:14/01/2021-01-22). All the participants' rights were protected and written informed consents were obtained before the procedures according to the Helsinki Declaration.

The COVID-19 diagnosis of these SCD patients were made based on the SARS-COV-2 positivity determined as a result of reverse transcription polymerase chain reaction (RT-PCR) test carried out using the nasopharyngeal swab sample. The SCD patients, who were suspected of having been infected with based on clilnical manifestation and imaging but tested negative for SARS-COV-2 based on the RT-PCR test , as well as the SCD carriers, were not included in the study. All of the 21 patients included in this study were in the adult age group. Hemoglobin electrophoresis and genotype records of 10 of these 21 patients could not be accessed, yet they were included in the study as their medical histories and clinical and laboratory findings clearly indicated SCD.

The complete blood counts and biochemical parameters of the patients (LDH (lactate dehydrogenase), CRP (C-Reactive Protein), Ferritin, and D-Dimer levels) as well as their imaging results were examined, and the clinical severity and

treatment needs of the patients were reviewed. Subsequently, these patients were categorized into four groups based on the severity of COVID-19, which are; asymptomatic cases, who were without clinical signs and symptoms; mild to moderate cases, who had symptoms of acute upper respiratory tract infection such as fever, fatigue, myalgia, cough, sore throat, runny nose and sneezing, or digestive symptoms such as nausea, vomiting, abdominal pain and diarrhea or non-hypoxic pneumonia; severe cases, who had symptoms such as dyspnoea and hypoxia (O2 saturations < 92%); and critical cases, who had symptoms such as acute respiratory distress syndrome, respiratory failure, encephalopathy, shock, coagulopathy and life-threatening multi-organ failure with lung, heart, kidney and/or brain involvement(s).

Accordingly, the main goal of this study has been set to evaluate the complaints of the adult SCD patients with COVID-19 at the time they were admitted to the hospital, as well as their laboratory and imaging findings, VOC and ACS histories, hydroxyurea usage rates, hospitalization rates, whether they required oxygen and transfusion and the extent of this requirements, if any, whether they required intensive care and mechanical ventilation and the extent of this requirements, if any, and their mortality rates. All cases that were determined to have met the inclusion criteria, were analyzed thereafter.

RESULTS

The median age of the patient group included in this study was determined as 34 years. 57.1% (n:12) of the patients were male. 9 of the patients were determined to have Hgb SS, 2 of them were determined to have Hgb S-Beta genotype, whereas the genotype of the remaining 10 patients was unknown. 14.3% (n:3) of the patients died. It was determined that these 3 patients died within the first 2 days (range: 1-2 days) from their admission to the hospital. On the other hand, it was determined that the surviving patients stayed in hospital for a mean duration of 2 days (range:1-15 days). Patients age, gender and genotype information were not found to have been associated with their survival (Table I).

Table I : Age, gender and genotype information of the patients.

	Entire population N= 21	Survival		Univariable Cox Regression		
		Alive N= 18	Exitus N= 3	HR	%95CI	P
Age (years)	34(23-50)	33.5(23-50)	42(28-44)	1.04	0.91-1.19	0.592
Gender, n (%)						
Female	9(42.9)	9(50.0)	-	Ref		
Male	12(57.1)	9(50.0)	3(100.0)	39.58	0.10-1075.8	0.48
Genotype, n (%)						
Hb SS	9(42.9)	8(44.4)	1(33.3)	Ref		
Hb S Beta	2(9.5)	2(11.1)	-	0.43	0.01-18.38	0.992
Unknown	10(47.6)	8(44.4)	2(66.7)	0.75	0.06-9.46	0.826

Abbreviations: HbSS: Homozygous sickle cell disease, that is generally associated with a severe clinical picture, HbSB-thalassemia: compound heterozygous sickle cell thalassemia, that is generally associated with a mild clinical picture and is clinically indistinguishable from sickle cell disease, HR: Hazard Ratio, CI: Confidence Interval, ref: Reference

Of the 21 patients included in the study group, 15 (72%) patients required hospitalization after having become infected with SARS-COV-2. In terms of severity of the COVID-19, 1 patient was assessed as an asymptomatic case, 12 patients were assessed as mild to moderate cases, 4 patients were assessed as severe cases, and the remaining 4 patients were assessed as critical cases. Of the 15 patients, who required hospitalization due to COVID-19, 8 patients required oxygen support. Additionally, 4 of these 8 patients required mechanical ventilation support and were transferred to intensive care unit (ICU). No correlation was found between patients' disease severity, the need for O2 support, ICU admission and mortality rates (Table II).

Table II: Disease severity, follow-up and treatment results of the patients.

	Entire population n =21	Survival		Univariable Cox Regression		
		Alive n =18	Exitus n = 3	HR	%95 CI	P
COVID-19 severity n(%)						
Asymptomatic	1(4.8)	1(5.6)	-	Ref	-	-
Mild to Moderate	12(57.1)	12(66.7)	-	0.95	0.01-2864.5	0.999
Severe	4(19.0)	4(22.2)	-	0.92	0.01-3135.6	0.999
Critical	4(19.0)	1(5.6)	3(100.0)	62.5	0.01-3582.5	0.898
Hospitalization, n (%)	15(71.4)	12(66.7)	3(100.0)	34.2	0.01-3117.2	0.706
Need for O_2 support	8(38.1)	5(27.8)	3(100.0)	63.01	0.01-8651.9	0.394
Need for ICU, n (%)	4(19.0)	1(5.6)	3(100.0)	48.5	0.01-606.4	0.388
A history of hydroxyurea use, n (%)	16(76.2)	14(77.8)	2(66.7)	0.95	0.08-10.67	0.966
VOC (more than 3 times in the last 3 years), n (%)	7(33.3)	7(38.9)	-	0.03	0.01-47.8	0.462
ACS (in the last 3 years), n (%)	7(33.3)	7(38.9)	-	0.03	0.01-1038.6	0.507
Presence of painful VOC at the time of admission, n (%)	7(33.3)	5(27.8)	2(66.7)	2.87	0.25-32.18	0.392
Presence of ACS at the time of admission, n (%)	5(23.8)	2(11.1)	3(100.0)	371.4	0.01-1694.6	0.373
Erythrocyte transfusion, n (%)	8(38.1)	7(38.9)	1(33.3)	0.66	0.06-7.33	0.736
Erythrocyte exchange, n (%)	3(14.3)	2(11.1)	1(33.3)	2.47	0.22-27.350	0.461

Abbreviations: VOC: vaso-occlusive crisis, ACS: acute chest syndrome, HR: Hazard Ratio, CI: Confidence Interval, ref: Reference

It was found that 76.2% (n:16) of the patients regularly used hydroxyurea. It was also found that 33.3% (n:7) of the patients suffered painful VOC more than three times per year in the last 3 years, which required their hospitalization, and that 33.3% (n: 7) had a history of ACS in the last 3 years. Additionally, it was determined that painful VOC was detected in 33.3% (n:7) of the patients at the time of their admission to the hospital, whereas ACS was detected in 23.8% (n:5) of the patients. Furthermore, it was determined that erythrocyte transfusion was performed in 38.1% (n:8) of the patients and that erythrocyte exchange was performed in 14.3% (n:3) of the patients (Table II).

In terms of their laboratory findings it was found that the increase in CRP levels was associated with mortality (HR, 1.02; 95% CI, 1.01-1.03; p=0.049) whereas no correlation was found between other laboratory findings and mortality. Analysis of the imaging findings of the patients indicated lung infiltration findings in the chest X-Rays of 4 patients and in computed tomography images of 12 patients (Table III).

Table III : Laboratory findings and imaging results of the patients.

	Reference Range	Entire population n=21	Survival		Univariable Cox Regression		
			Alive n=18	Exitus n=3	HR	%95 GA	p
Imaging Results							
X-ray	-	4(19.0)	2(11.1)	2(66.7)	6.28	0.56-70.17	0.136
CT	-	12(57.1)	9(50.0)	3(100.0)	39.58	0.01-1075.8	0.480
Laboratory Findings							
WBC, 109/ L	3.8-10.6	13(3.7-71.2)	13.8(3.7-71.2)	13(8.5-38)	0.99	0.98-1.01	0.805
Lymphs, 109/L	1.00-4.80	2.2(0.2-42)	2.2(0.2-42)	4.0(8.9-9.9)	1.02	0.97-1.10	0.757
Hemoglobin, g/L	12.00–15.00	7.9(4.7-11)	8.1(4.7-11)	7.7(4.8-10.4)	1.02	0.58-1.76	0.970
CRP, mg/dL	<5	22(4.6-323)	13.6(4.6-209)	190(157-323)	1.02	1.01-1.03	0.049*
LDH, IU/L	<250	565(225-2042)	505.5(225-2042)	957(771-1128)	1.01	0.99-1.03	0.387
D-dimer, mg/mL	<500	2150(270-20000)	1885(270-9940)	>20000	1.00	0.99-1.01	0.420
Ferritin, ng/dL	24-336	1285(287-10700)	1208.5(287-10700)	4664.5(4485-4844)	1.00	0.98-1.03	0.381

Abbreviations: Hgb: hemoglobin, WBC: white blood cell count, Lymphs: Lymphocyte, LDH: lactate dehydrogenase, CRP: C-reactive protein, CT: computed tomography, HR: Hazard Ratio, CI: Confidence Interval, ref: Reference

DISCUSSION

A review of the literature revealed that there are only few studies available on sickle cell patients with COVID-19 and that most of these studies were based on case series (13-16). It was determined that patients of all ages were included in two of the three studies conducted in large patient groups and that sickle cell carriers were included in the third study. There are significant differences between the mortality rates reported in these studies (17-19). Hence in this study, it was decided to create a homogenous group of adult patients to determine the mortality rates in this group and to share the experience with regards to SCD patients with COVID-19.

In a study involving 4226 patients with COVID-19 among normal population both hospitalizations and the need for intensive care unit were observed to be at a low level in the adult age group and the respective mortality rate was found to be below 1% (20). There are reports in which it is stated that use of hydroxyurea due to beta chain-related diseases, such as SCD and beta thalassemia may be protective against COVID-19. Nevertheless the results of this study did not support the said hypothesis, since the rates of hospitalization, need for intensive care unit and mortality were found to be as high as 71.5%, 19% and 14% respectively, in the patient group, who were determined to have been using hydroxyurea, which made up 76% of all the patients included in this study. Analysis of the study findings indicated that most of the patients (57%) were male and interestingly that all 3 patients who died were also male and that 2 of these 3 patients have been receiving hydroxyurea treatment regularly. The SCD genotype of 2 of these 3 patients was unknown. Analysis of these 3 patients in terms of the severity of COVID-19 revealed that they were all assessed as critical cases having required intensive care units and mechanical ventilation. Additionally, it was determined that all of these 3 patients, who lost their lives, had ACS, and that 2 of them also had painful VOC in addition to ACS. Furthermore, it was determined that erythrocyte exchange was performed in 1 of these patients, that erythrocyte transfusion was performed in another 1 patient, whereas that none of the transfusion treatments could be administrated to the 3rd patient as he died very quickly within hours (Table I-II).

SCD, which is a chronic inflammatory disease, can cause acute and chronic complications and damages to all organ systems. Particularly the damages it inflicts upon the respiratory system are very effective on mortality (21). In our investigation, it was also observed that, despite the presence of painful VOC in the foreground, mortality was related to ACS and CRP was found to be significantly higher in patients who died (HR, 1.02; 95% CI, 1.01-1.03; p=0.049). Ferritin, D-dimer and LDH levels were found to be quite high in patients with mortality, albeit not statistically significantly due to the small number of the patients included in the study, which was also emerged as the main limitation of this study. Our experience with patients who had a fatal course has shown that, if imaging and clinical progression are considered, switching to transfusion treatments before the need for an intensive care unit and mechanical ventilation can save lives in patients with laboratory findings (elevated CRP, Ferritin, D-dimer and LDH). Erythrocyte exchange would also be beneficial in these patients, nevertheless simple transfusions may also be administered instead if it is concluded that erythrocyte exchange would be a loss of time. Additionally, it has been reported that use of tocilizumab yielded positive results in this patient group (22,23).

It is well understood that SCD, which has a variable disease course, does not progress in all patients in the same way. While some patients suffer severe frequent episodes, others have only a minor illness. One of the scenarios in the study that drew our attention was that no mortality was observed in the patient groups with a history of VOC (7 patients were found to have a history of VOC) or with a history of ACS (7 patients were found to have a history of ACS). Because of this reason that SCD patients without a history of VOC and ACS has a much higher risk of mortality, if VOC, and particularly ACS, is caused by COVID-19. To date, although we don't know why COVID-19 is more deadly in persons with a milder history of sickle cell illness, we believe that due to the high mortality rate in patients with this background, greater attention should be paid.

Coagulopathy is one of the major causes of mortality in individuals with SCD who are infected with COVID-19. Effective anticoagulation is required in these patients unless there is any contraindicated situation due to the coagulopathy caused by both SCD and COVID-19. Of the 21 patients included in this study, the 3 patients that died were found to have D-dimer levels above 20.000 mg/mL despite having received full-dose anticoagulant therapy in the form of low-molecular-weight heparin. The reason for the said high D-dimer levels in this patient group may be attributed to coagulopathy caused by complex multifactorial causes that stemmed from COVID-19, SCD and ACS (24-27).

CONCLUSION

In conclusion, despite the small number of patients in our study, we found that in sickle cell patients with COVID-19, the requirement for hospitalization increased proportionally. We found that mortality increased significantly in individuals with a high CRP value. We found that LDH, Ferritin, and D-dimer values were high in patients who had a fatal course, despite the fact that we couldn't show this statistically. Finally, we believe that the history of SCD disease influences mortality.

Ethics Committee Approval:
This research complies with all the relevant national regulations, institutional policies and is in accordance with the tenets of the Helsinki Declaration, and has been approved by the Hatay Mustafa Kemal University Ethics Committee (approval number:14/01/2021-01-22).

Informed Consent:
All the participants' rights were protected and written informed consents were obtained before the procedures according to the Helsinki Declaration

Author Contributions:
Concept – M.K., G.İ.; Design – M.K., G.İ., G.O.; Supervision – G.İ.; Resources – M.K., G.O.; Materials - M.K., G.O.; Data Collection and/or Processing – M.K., G.O.; Analysis and/ or Interpretation – M.K., G.İ., G.O.,; Literature Search – M.K.; Writing Manuscript - M.K.; Critical Review – M.K., G.İ., G.O.

Conflict of Interest:
The authors have no conflict of interest to declare.

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