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RESEARCH ARTICLE

IMPACT OF COVID-19 ON SICKLE CELL DISEASE PATIENTS; A NARRATIVE REVIEW

Dr. Hussien Abdullmohsen Alnasser[1] and Dr. Essa Mohammed Alsaleh[2]

1. Senior Preventive Medicine Resident, Joint Program of Preventive Medicine, Al-Ahsa, Community Medicine Department, Al-Ahsa Health Cluster, Saudi Arabia.
2. Consultant Physician of Epidemiology and Public Health, Infection Control Administration at AlAhsa Health Directorat,Saudi Arabia.

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Abstract

Objective: The review aimed to examine the evidence for the impact of COVID-19 on Sickle Cell Disease (SCD) patients.

Background: Corona virus disease (COVID-19) continues to ravage various parts of the world, with increasing cases of morbidity and mortality. The coronavirus primarily targets therespiratory system, although it affects other organs. Evidence shows that patients with pre-existing conditions, such as SCD, are a to higher risk of developing severe COVID-19 illness and death.

Methods: A narrative review was conducted through a computerized search on the PubMed database. Ten articles met the inclusion criteria and were included in the synthesis.

Discussion: The findings of the review show that SCD patients are at increased risk of severe illness and death when infected with COVID-19 due to their immunocompromised state.

Although there is heterogenicity in results, most studies concur that SCD complications such asVaso-occlusive crisis (VOC), Acute Chest Syndrome (ACS), stroke, and acute anemia pose the greatest risk of morbidity and mortality. However, most patients show favorable outcomes when provided with proper intervention.

Conclusion: Based on the findings of this review, patients with SCD have significantly adverse COVID-19 outcomes.

Introduction:-

A recently discovered coronavirus (SARA-CoV-2) caused coronavirus disease 2019(COVID-19). It affected millions of individuals around the world and caused challenges to healthcare frameworks(18).

The novel coronavirus disease (COVID-19) infected more than 177 million people and caused the deaths of 3.83 million up to the date. The disease that is caused by the SARS-CoV-2 virus primarily targets the respiratory system, resulting in distress syndrome that leads to mortality and morbidity (1). The clinical manifestation of severe COVID-19 include acute respiratory distress syndrome (ARDS),sepsis, multi-organ failure, systemic inflammation and death(19).. Moreover, coronavirus disease (COVID-19) has been shown to affect the gastrointestinal tract that may lead to diarrhea, abdominal pain, and altered taste (1). Besides, different other organs can be affected due to the presentation of severe cytokine release syndrome.

Corresponding Author:- Dr. Hussien Abdullmohsen Alnasser

Sickle cell disease (SCD) which caused by genetic mutation in a single amino acid in the beta-chain of the human hemoglobin protein is an inherited red blood cell disorder. Sickle cell disease is a result of the homozygous inheritance of a mutated gene (β-globin). Heterozygous inheritance of the mutated gene leads to a condition known as sickle cell trait, which is more common (2). Polymerization of hemoglobin in low oxygen saturation will result from this alteration that lead to deformity of blood cells and vascular occlusion. Worldwide 5% affected by hemoglobinopathies (mainly SCD). SCD affects around one in every 400 African-Americans in the USA (5). 10 – 45% of sub-Saharan Africa population are carrier of sickle cell gene)(20). Growing evidence shows that people who have pre-existing conditions, such as cancer, obesity, acute organ dysfunction, diabetes, cardiovascular disease, and hypertension, are at a higher risk of death and severe illness when infected by COVID-19 (6). However, limited research evidence exists concerning the risk of COVID-19 for people with SCD and sickle cell trait.

Some researches explore that patients who suffer from sickle cell disease (SCD) prone to high risk of developing severe complications when expose to the new disease of COVID-19 (2).

Therefore, the purpose of the present review is to examine the impact of COVID-19 on SCD patients and assess whether SCD is a risk factor for severe cases of coronavirus.

The narrative review is important because the COVID-19 pandemic presents serious challenges for individuals with chronic conditions, including those suffering from SCD due to disease-related comorbidities, the complexity of the condition, and the need for regular medical intervention (3). To the review date, only a few studies have explored the impact of COVID-19 on SCD patients (4). Moreover, there is a paucity of narrative reviews on the subject, which necessitates the need for the present review.

Methods:-

A computerized literature search was conducted in June 2021 surveyed the PubMed database for English language-based publications between January 2020 and May 2021. PubMed, Cochrane Library, National Library of Medicine, and Embase databases were selected because of their specificity, reputation, comprehensiveness, and their recognition as a credible repository of quality, peer-reviewed research articles. The literature search was informed by a framework that identified concepts pertinent to the study objective. The question included terms that described COVID-19 and its impact on patients with SCD. The search was divided into two theme, as shown in table 1. For identification of COVID-19, a Boolean search was conducted using the term “OR” to explore and map headings as shown under S1 in the table. For identification of Sickle Cell Disease, a Boolean search was done using the term “OR” as indicated in the table (S2). The two themes were combined by using the Boolean operator “AND” as indicated in S3. The following inclusion criteria were used for the search: studies discussing the co-occurrence of COVID-19 and SCD, full-text articles, primary studies, and published in the English language. Studies that did not meet the inclusion criteria were excluded, such as those published before January 2020 and studies without English-language abstracts.

Table 1:- Key terms used in the search.

Type of Search	Key word Syntax
S1	“Coronavirus” OR “COVID-19”OR“SARS-CoV-2”
S2	“Sickle Cell Disease” OR “Sickle Cell Trait” OR "Sickle Cell Anemia” OR “SCD” or “SCT”
S3“combined”	S1 AND S2

The retrieved articles were screened for abstracts and titles, which were followed by full-text analysis. All studies that met the inclusion criteria and had full text available were downloaded and collected into one Mendeley library for deletion of duplicates. Data extraction was done using a specified form, which captured information that included authors, year of publication, setting, design, sample size, measurement of outcomes, and results. The extracted data was used for the preparation of the evidence synthesis table and subjected to the Matic analysis.

Results:-

The database search yielded 25 potential articles based on the search terms used. All articles were obtained from PubMed as the search in the other databases such as Cochrane Library, Medline national library of medicine, and EMBASE did not produce significant results. We excluded some publications because they did not meet the inclusion criteria. After the removal of studies with irrelevant topics ,those not authored in English and those whose full texts were not available, ten (10) articles remained and were included in the synthesis and the Matic analysis.

The summary of the characteristics of included studies is presented in Table2.
The main Outcome Recorded on the Articles

Infection with COVID-19 for patients with SCD leads to various complications, hospitalization, and, in some cases, mortality. The findings of this review show that COVID-19 triggers the development of Acute Chest Syndrome (ACS)and Veno-Occlusive Crisis (VOC) in patients suffering from Sickle Cell Disease (7,8,9). The largest case series that of McCloskey et al. had 10 patients with COVID-19 who were given supportive case for SCD-ACS/VOC (9). In the majority of the cases reviewed, ACS was the leading complication in SCD patients suffering from COVID-19 infection (8, 10). In the series presented by Hussein et al., the patients' requiredmechanical ventilation due to ACS (8). Other complications caused by COVID-19 includepriapism, splenic sequestration, stroke, hepatobiliary, acute respiratory distress syndrome(ARDS), and acute anemia (11, 12). In the case series by McCloskey et al., one patient who hada history of stroke died (9). In Minniti et al., seven of the patients in the prospective cohort study died, all of them presenting with ACS and VOC (13).

Table2:- Characteristicsof includedstudies.

Author (Year)	Design/ Setting	Objective	Sample size/ Demographics	Intervention/ Outcome Measures	Results
Hussain et al. (2020)	Case series The Universityof Illinois at Chicago	To describe cases of SCD patients infected with COVID-19 and the approaches used for treatment.	4 SCD patients, 2 Male and 2female Mean age: 33	Different case managementand treatment for each patient. Outcome: Recovery and discharging from hospital.	The patients were discharged from the hospital after 13, 8, 2,and 4 days respectively.
McCloskey et al. (2020)	Case Series Homerton University Hospital, UK	To report pathological features, treatment, and outcomes of patients with SCD and COVID-19.	10 SCD and COVID-19 patients Mean age: 36years	Case Management andtreatment. Measurement of clinical, laboratory, and radiological features.	The outcome was favorable, nine patients recovered, one died. The mean length of hospital staywas 7.2 days.
Appiah-Kubi et al. (2020)	Case series Cohen Children's Medical Center, USA	To compare the outcomes of the case series of COVID-19 infections in SCD patients to previously reported cases.	7 children andyoung adults	Different treatment interventions based on symptom presentation. Data collected from routineclinical practice.	Most of the reported cases had afavorable outcome.

Tezol and Unal (2020)	Cross-sectional study Mersin, Turkey	To examine COVID-19 and SCD-related experiences and the anxiety levels of patients.	47 patients, 70.2 % male Mean age:18.2	A survey was done usingthe State-Trait Anxiety Inventory forms.	66% of patients had negative COVID-19 experiences of anxiety symptoms.
(Sahu et al., 2020)	Literature Review	To report the impact of COVID-19 on SCD patients as reported in recent literature.	NA	NA	The review of the literature showed that SCD patients are ata higher risk of COVID-19 complications.
Okar et al. (2021)	Case Report	To present a case report of an SCD patient who tested positive for COVID- 19.	1 patient Male 48 years	Favipiravir + Amoxicillin/ Clavulanic acid for COVID-19 treatment.	A favorable outcome for the patient. Patient was discharged after 22 days.
Minniti et al. (2021)	Cross-sectional study 4 Covid-19 centers in the USA	To identify predictors of survival and outcomes of patients with SCD and COVID-19.	66 SCD patients with COVID-19	Pre-Post test A standardized form was used to collect data from the patients at baseline and during clinical cause.	75% of SCD patients infected with COVID-19 required hospitalization. Mortality rate was 10.6%. Patients with preexisting renal conditions were more vulnerable. ACS occurred in 60% of hospitalized patients
Alkindi et al. (2021)	Prospective Cohort Study	To assess the impact of COVID-19 on mortality and morbidity of VOC in SCD patients.	100 SCD patients (50 with Covid-19 and 50 without)	Data collected included demographics, comorbidities, SCD complications, baseline. laboratory assessments.	The Covid group had significantly more episodes of VOC, Osteonecrosis, hepatic crisis, splenomegaly, and splenic sequestration.
Teulier et al. (2021)	Case Report	To report the case of a patient with SCD and COVID-19.	1 patient Male 33 years	Laboratory assessments Treatment was done through intubation, curarization, and transfusion. exchange.	The patient was discharged from the hospital after one month.

(Arlet et al., 2020)	Prospective Cohort Study 24 centers in France	To examine outcomes of patients with SCD and COVID-19.	83 patients Mean age: 33.5	A standardized form was used to collect data on outcomes.	In 54% of the participants, VOC was associated with COVID-19. 20% of the patients were admitted to ICU. 53% of patients in ICU needed ventilation. Two patients died of pneumopathy.

Discussion:-

Vulnerability of SCD Patients for Increased COVID-19Morbidity and Mortality

Data obtained from the reviewed studies show that individuals are at risk of developing severe complications if they are of advanced age or have medical comorbidities, which include SCD. Patients who are critically ill from COVID-19 often develop a cytokine storm, which increases the risk of macro-and microthrombi, as well as disseminated intravascular coagulation, which eventually leads to multiple organ failure (10).In particular ,patients with SCD ,especially those with advanced age, have multiple comorbidities, including chronic lung disease, hypertension, and progressive renal insufficiency. As such, viral infection triggers acute chest syndrome (ACS), which causes multi-organ failure. According to Okar et al., ACS is similar toCOVID-19 pneumonia as they both share features such as chest pain, shortness of breath, cough, and fever (12). Also, due to underlying dysfunction of the endothelium, the patients are also at increased risk of thrombotic events and thrombus inflammation when they get infected with COVID-19. According to Appiah-Kubi et al., the most common presenting symptoms are VOC, ACS, and fever(10).

The study by Hussain et al. reported that after testing 14 SCD patients, four of them were positive for COVID-19 (8). The four patients had different SCD genotypes, but they all had a history of ACS, VOC, and other respiratory complications, which have been shown to be risk factors for severe COVID-19 illness. Besides, all the patients in the study first reported to the Emergency Department for VOC and associated pain, but the clinical course of their COVID-19 infection was mild, except for the first case. The findings of the study corroborate the results of Appiah-Kubi et al., who noted that patients with SCD are at a greater risk of serious illness from COVID-19 because of chronic inflammation, which enhances the risk of thrombosis (10).

Moreover, Alkindi et al. Also reported that thromboembolic disease is strongly associated with COVID-19 and SCD, with cases of coagulopathy and pulmonary embolism reported in the former (7).

Similarly, McCloskey et al. reported on the management and outcome of patients with SCD and COVID-19 infection treated in their institution (9). Out of the ten patients included in the study, nine had Hb SS, and one had Hb SC disease. Besides, one patient had severe comorbidities that included a previous stroke and severe neurological impairment. Another patient had severe nephropathy and staged III chronic renal disease. For the rest of the patients, there was no end-organ damage, although six had VOC and five were on regular transfusion.

Moreover, the patients had varying degrees of pain and other features such as hypoxemia, dry cough, and fever.

The cross-sectional survey by Tezol and Unal sought to examine COVID-19 and SCD-related experiences and the anxiety levels of patients (14). The study was based on the understanding that SCD patients are aware of their vulnerability to severe COVID-19 illness, and as such, they are susceptible to anxiety. From the sample of 47 young adults and adolescents, the survey that used the State-Trait anxiety Inventory instrument revealed that a majority of the participants (66%) exhibited negative COVID-19 anxiety symptoms. Due to the pandemic, some SCD patients have encountered disruptions and difficulties accessing their routine medical services, a situation that has exacerbated anxiety rates.

In a related cross-sectional study, Minniti et al. explored outcomes and survival of SCD patients with COVID-19 (13). The researchers collected data at baseline, during treatment, and after three months of follow-up. They noted that 75% of the patient's needed hospitalization, out of which 10% died. The study noted that the probability of death was higher in people patients with chronic kidney disease, and the main symptom was Vaso-occlusive pain. ACS was reported in 60% of the hospitalized patients, including all those who died. Moreover, risk factors for death

included older age and histories of stroke, chronic kidney disease, congestive heart failure, and pulmonary hypertension. Nonetheless, the study did not find a significant correlation between SCD and overall higher mortality rates.

To investigate outcomes for SCD patients infected with COVID-19, Arlet et al. invited physicians involved in treating patients with SCD to report those with COVID-19 (15). The study prospectively collected data on SCD patients 'outcomes and compared the prevalence with other COVID-19 inpatients. The study noted that out of the 83 enrolled patients, 48 had ACS, which required hydroxyurea treatment at admission. In 54% of the patients, there was an association of VOC with COVID-19. Moreover, 20% of the patients were admitted to the Intensive Care Unit (ICU), out of whom 53% needed mechanical ventilation, and two died.

However, Arlet et al. asserted that although COVID-19 is potentially severe, it does not increase the risk of mortality and morbidity for patients with SCD (15). In contrast, the case report by Teulier et al. assessed the impact of COVID-19 and Acute Respiratory Distress Syndrome (ARDS) on SCD patients (11). The patient in the case was an adult male with homozygous sickle cell anemia. After presenting in the emergency department (ED), his respiratory symptoms worsened, which necessitated a transfer to the ICU after suffering from severe ARDS.

In a study that sought to examine the impact of COVID-19 on morbidity and mortality of VOC in SCD patients, Alkindi et al. (2021) conducted a prospective cohort study of SCD patients (n=100), 50 with COVID-19 and 50 without. The results showed that patients withCOVID-19 had significantly higher episodes of VOC annually. However ,mortality rates were not significantly different ,which corroborates Arlet et al.'s findings that COVID does not significantly increase the risk of morbidity and mortality with SCD (15).

Taken together, these studies suggest serious implications of COVID-19 in SCD. Most studies have confirmed that SCD causes a decline in pulmonary functions, which is caused by a repeated chest infection that changes the lung parenchyma's geometry and collagen fibers' physical properties (16). Besides, patients with SCD are vulnerable to infection due to their immunocompromised state caused by the loss of both cell-mediated and humoral immunity (17). Consequently, COVID-19 exacerbates pulmonary symptoms in patients with SCD by enhancing complications such as the ACT, VOC, and acute respiratory distress syndrome (ARDS) (8).

Generally, older patients and those with chronic comorbidities like cardiovascular diseases ,lung diseases ,diabetes, and hypertension are at increased risk of complications. Management of SCD patients infected with COVID-19.

The case reports by Hussain et al. provide insights on the management of SCD patients who get infected with COVID-19 (8). The study noted that SCD is an immunocompromised condition, which means that patients are at increased risk of serious respiratory infections and complications. In the first case, the patient (male, 32) had a history of ACS, ulcers, and Vaso-occlusive crises (VOC). Upon admission, he was given morphine (IV) and fluids. After that, he was treated with ceftriaxone, hydroxychloroquine, and azithromycin for seven days(8).The three other cases were treated with morphine and fluids and improved after a short hospital stay. Insights from this study show that COVID-19 severe pulmonary symptoms fit in the definition of ACS for SCD patients, which calls for urgent blood transfusion.

In the study by McCloskey et al., all the patients were given oxygen therapy, broad-spectrum antibiotics ,and thromboprophylaxis (enoxaparin) due to evidence of increased risk of thrombosis in COVID-19 cases (9). Blood transfusion was done for three patients whose hemoglobin had dropped from baseline. Unfortunately, one patient died due to a history of stroke and multiple comorbidities ,but the rest of the patients attained full recovery after a mean hospital stay of seven days. The study shows that SCD patients who get infected with COVID-19 can recover, except if they have significant pre-existing co-morbidities. Similarly, Appiah-Kubiet al. noted that successful treatment could be achieved for children and young adults with COVID-19 and SCD comorbidity ,especially through transfusion and antiviral therapy(10).

Arletet al.also reported that SCD/COVID-19 patients often require mechanical ventilation ,automated exchange, and treatment with hydroxyurea(15).

In the case report by Okar et al., the patient was treated with Favipiravir and Cluvalanic acid for the infection, and enoxaparin was given because he was presented with deep vein thrombosis (DVT) (11). After four days, he was transferred to the ICU due to intolerable back pain, and Cluvulanic acid was substituted with Tazobactam /Piperacillin.

After that, an exchange transfusion was done, and dexamethasone was given, with the patient improving after two days.

In sum, it is important for all SCD patients to be informed about the signs, symptoms, and mode of transmission of COVID-19. They ought to be aware of the increased risk of getting infected since they are immunocompromised, and they should adhere to isolation policies ,social distancing, hand washing, and face mask use. Besides, it is critical that they keep adequate medication for SCD, including antipyretic and analgesic drugs, L-glutamine, hydroxyurea ,Crizalizumab , and Voxelotor, to avoid unnecessary hospital visits where they can be exposed(17). Once infected with COVID-19, SCD patients should receive special attention because studies have shown that their respiratory status can worsen to include ARDS, which requires intubation ,venovenous ECMO ,and curarization (11).In some cases of ACS ,patients require oxygen supplementation and mechanical ventilation.

Conclusion:-

The narrative review has contributed to the understanding of the clinical features that contribute to a higher risk of mortality and morbidity for SCD patients infected with COVID-19. It has been noted that older patients, especially those with pre-existing chronic conditions of the lungs, heart, brain, and kidney, are at the highest risk of hospitalization. SCD-related pulmonary hypertension is the highest risk for COVID-19 deaths. Evidence from reviewed studies shows that ACS is the most significant cause of morbidity and mortality in patients. Patients in studies that informed this review received a varied combination of supportive care, including analgesics, hydration, exchange, broad-spectrum antibiotics, blood transfusions, intubation, and ventilation. Although most studies report favorable outcomes for patients infected with COVID-19, some SCD individuals are at risk of deterioration and death due to an immunocompromised state.

There is a need for future research to explore many unanswered questions to increase awareness and understanding of outcomes for SCD patients infected with COVID-19. Presently, no clinical trial has been carried out specifically with COVID-19 and SCD patients.

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