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Review Article

Poor Prognostic Factors in Sickle Cell Disease Patients Infected with Covid-19 – Review of Literatures

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Abstract: Sickle cell disease (SCD) is the co-inheritance of HbS with other abnormal haemoglobin. COVID-19 is a severe acute respiratory distress syndrome caused by coronavirus 2 infections. The immunosuppression and chronic inflammatory states in patients with SCD predispose them to severe form of COVID-19. The few case studies on sickle cell disease patients infected with COVID-19 mostly discuss the pattern of clinical presentations and laboratory changes in patients with SCD infected with COVID-19. This review of literature assesses the prognostic indicators in sickle cell disease patients infected with COVID 19 in three major case series. Some presenting symptoms and signs, presence of comorbidities and certain laboratory parameters were compared with poor outcome of patients. Poor clinical outcomes of patients in this review included: 1. Duration of admission of ≥10 days, 2. A week or more of intensive care unit admission, 3. Death of patient despite intervention while on admission, and 4. Deterioration in the presenting comorbid clinical condition. The presenting symptoms and signs, presence of comorbidities and certain laboratory parameters associated with these poor clinical outcomes were considered as poor prognostic factors. The presence of comorbidities, markedly elevated pro-inflammatory markers such as leukocytosis, IL-6, C-reactive proteins, marked elevated D-Dimer and high serum creatinine are poor prognostic factors in sickle cell disease patients with COVID-19 infection.

Keywords: Sickle Cell Disease, COVID-19, Poor prognostic Factors, Comorbidities

1. Background

Sickle cell disease (SCD) is a spectrum of disorder characterized by co-inheritance of HbS with other abnormal haemoglobins such as haemoglobin C, S, E, D and beta thalassemia. The most common of this disorder in the sub-Saharan region especially Nigeria is sickle cell anaemia (SCA) [1]. The prevalence rate of SCA among Yoruba people in Nigeria is about 2-3% and with about one in four Lagos Yoruba's having sickle cell trait [2]. Sickle cell disease is not only associatedwith high morbidity and mortality, It is also associated with high physical and financial burden on the patients and their relatives [3].

The symptoms and signs of sickle cell anaemia are due to polymerization of deoxygenated HbS within the red blood cells [4]. The polymerized deoxygenated haemoglobin S subsequently damages the red cell membrane and makes it to become sickled. The sickled red cell can occlude microvasculature to cause vaso-occlusive crisis or be destroyed in the intravascular and extravascular compartment to cause hyperhaemolytic crisis [4].

Sickle cell disease is a chronic inflammatory state and also a disorder of impaired immune system [5, 6]. The chronic inflammatory state in sickle cell disease is induced by

increased oxidative stress caused by: 1. Increase xanthine oxidase generated during ischaemic reperfusion injury and increased auto-oxidation of HbS more than normal HbA. 2. Reduction in nitric oxide which prevents expression of adhesion molecules on the endothelial cells responsible for inflammation [7]. Sickle cell disease and other conditions associated with chronic inflammatory states such as hypertension, diabetis mellitus, obesity and coronary artery disease can predispose patients infected with COVID-19 to a syndrome call Cytokine storm which is characterized by worsening fever, cough, worsening breathlessness and shock, hypoxia that might necessitates intensive care unit admission and ventilation [8, 9]. Cytokine storm is characterized by excessive and abnormal release of cytokines, it is associated with high morbidity and mortality in patients with sickle cell disease [10].

Paradoxically, sickle cell anaemia is associated with some degree of immunosuppression affecting the innate and adaptive immunity [11]. The immunosuppression in patients with sickle cell disease is due to autosplenectomy, defective alternate complement pathways and reversal of CD4/CD8 count [12]. This immunosuppression can predispose sickle cell anaemic patient to different types of encapsulated bacterial infections such as streptococcus pneumonia, Neisseria meningitides, Haemophillus influenza infection and viral infections [12].

COVID-19 is also known as SARS – COV2 infection, it is a severe acute respiratory distress syndrome caused by coronavirus 2[11]. The outbreak of this infection was first discovered in the city of Wuhan china in December 2019. It was included as a disease of public Health emergency on January 30, 2020 and a pandemic disease on March 11, 2020 by World Health Organisation (WHO) [13, 14]. As at 28th June, 2020 it has affected 213 countries with over 10 mllion people infected, about 50% of these people have been discharged with about 5% mortality rate globally. In Nigeria, Over 24 thousand people were infected, more than 9 thousand people recovered and 566 people dead [15].

Acute chest syndrome which is an acute pulmonary complications of sickle cell anaemia shares clinical similarity of cough, breathlessness and hypoxia with severe COVID -19 infection [16]. Also one of the major infectious precipitating factors to acute chest syndrome is viral respiratory infections [17]. The management of acute chest syndrome in sickle cell anaemia is similar in that they both require oxygen therapy, antibiotic and exchange blood transfusion [16]. Despite the highly contagious nature of this COVID-19 and the immunosuppression in sickle cell disease, there were few studies done on COVID-19 in patients with sickle cell disease [18, 19, 20, 21]. Most of these studies were case reports and case series that discussed the pattern of presentations and treatment modalities of COVID-19 in patients with sickle cell disease. None of them extensively discussed the prognostic factors of COVID-19 in patients with sickle cell disease, [19, 20, 21]. The knowledge of prognostic factors in patients with sickle cell disease with COVID-19 can help to predict the clinical outcome such as possibility of prolonged hospital admission, need for intensive care, worsening of comorbid clinical condition and mortality in this group of patient. Hence, this review will discuss the prognostic factors of COVID-19 in patients with sickle cell disease.

2. Method

The clinical presentations, comorbidities, laboratory parameters, interventions, duration of admission and outcome of sickle cell disease patients with COVID-19 infection were reviewed in three different case series presentations by McCloskey *et al*, 2020, Hussain *et al*, 2020 and Heilbronner et al, 2020 [18, 19, 20]. The clinical presentations, comorbidities and laboratory parameters were compared with outcome of patients. Poor clinical outcomes of patients in this study include: 1. Duration of admission of ≥10 days, 2. A week or more of intensive care unit admission, 3. Death of patient despite intervention while on admission, and 4. Deterioration in the presenting comorbid clinical condition. The clinical presentations, comorbidities and laboratory parameters associated with these poor clinical outcomes were considered as poor prognostic factors.

3. Result

A total of 18 patients were reviewed, 4 were teenagers between the ages of 12 to 18 years (Table 1). All the teenagers had dysphnoea and hypoxia that necessitated oxygen therapy and intensive care unit admission, they also had exchange blood transfusion and the duration of their stay on admission was 6 to 11 days before they were all discharged. However, patient 2 and 4 were discharged on day 11 and 10 respectively and 7 days of intensive care unit admission. Only patient 4 had tocilizumab therapy (Tables 1 and 2).

Fourteen patients were adult to middle age with age range of 23-57 years. Majority of the adult patients presented with fever, patient 6 and 7 presented had multiple morbidities and chronic kidney disease respectively. Only patient 15 of the adult patients had intensive care unit admission, exchange blood transfusion and discharged after 13 days. Patient 6 died, patient 7 had deterioration in renal function that necessitated peritoneal dialysis (Tables 1 and 2).

3.1. Comparison of Clinical Parameters with Poor Clinical Outcome of Patients

The presence of multiple comorbidities in patient 6 was associated with mortality in the patient. Also the presence of co-existing chronic kidney disease in patient 7 was associated with mortality (Tables 1 and 2).

Table 1. *Clinical Parameters of Patients with Sickle Cell Disease with COVID -19.*

	AGE (years)	Hb Phenotype	Fever	Cough	Dysphnoea	Hypoxia	Comobidities/PMH	References
1	17.5	HbS	NP	NP	+	+	NP	[20]
2	11.6	HbS	NP	NP	+	+	NP	[20]
3	12.5	HbS	NP	NP	+	+	NP	[20]
4	16.6	HbS	NP	NP	+	+	NP	[20]
5	AD	NP	+	+	+	+	NP	[18]
6	AD	NP	+	-	+	+	STROKE*, MULTIPLE COMOBIDITIES	[18]
7	AD	NP	+	+	-	+	CKD	[18]
8	AD	NP	+	-	-	+	NP	[18]
9	AD	NP	+	-	-	-	NP	[18]
10	AD	NP	+	+	-	-	NP	[18]
11*	AD	NP	+	-	+	+	NP	[18]
12*	AD	NP	+	-	-	-	NP	[18]
13*	AD	NP	-	+	-	-	NP	[18]
14*	AD	NP	+	-	-	-	NP	[18]
15	32	HbS	+	NP	NP	-	ACS*, CHRONIC LOWER LIMB ULCER, RECURRENT VOC	[19]
16	37	HbSβ+	+	NP	NP	-	ACS*, VTE*, RECURRENT VOC*	[19]
17	22	HbS	+	NP	NP	-	ACS*, RECURRENT VOC*, ASTHMA*	[19]
18	41	HbSC	+	NP	NP	-	BILATERAL AVN, PE*	[19]

NP, data not available; +, present; -, Absent; Hb, Haemoglobin; ACS, Acute chest syndrome; VOC, vaso-occlusive crisis; AVN, Avascular necrosis of the head of femur; PE, Pulmonary embolism, AD; Adult with age range 23-57; CKD, chronic kidney disease; 1-10 and 15-18 confirmed COVID-19 cases; 11*-14*, suspected COVID-19 cases

Table 2. *Treatments And Outcome of Sickle Cell Disease Patients with COVID -19.*

Patients Number	Oxygen Therapy	Duration of icu Admission (days)	Exchange Blood Transfusion	Tocilizumab (8 mg/kg/dose)	Duration of Days on Admission	Outcome	References
1	+	4	+	-	6	DICHARCHED	[20]
2	+	7	+	-	11	DICHARCHED	[20]
3	+	5	+	-	8	DICHARCHED	[20]
4	+	7	+	+	10	DICHARCHED	[20]
5	+	-	-	-	NS	DICHARCHED	[18]
6	+	-	-	-	NS	DIED	[18]
7	+	-	-	-	NS	DISCHARCHED*	[18]
8	+	-	-	-	NS	DICHARCHED	[18]
9	+	-	-	-	NS	DICHARCHED	[18]
10	+	-	-	-	NS	DICHARCHED	[18]
11*	+	-	-	-	NS	DICHARCHED	[18]
12*	+	-	-	-	NS	DICHARCHED	[18]
13*	+	-	-	-	NS	DICHARCHED	[18]
14*	+	-	-	-	NS	DICHARCHED	[18]
15	+	NS	+	-	13	DICHARCHED	[19]
16	-	-	-	-	8	DICHARCHED	[19]
17	-	-	-	-	2	DICHARCHED	[19]
18	-	-	-	-	4	DICHARCHED	[19]

NS- Not Specified but between 3- 17 days with mean duration of days of 7.2 days; +, present; -, Absent DISCHARCHED*-Discharged but transient deteriotation in renal function that necessitated peritoneal dialysis; ICU; Intensive care unit; 1-10 and 15-18 confirmed COVID-19 cases; 11*-14*, suspected COVID-19 cases

3.2. Comparison of Biochemical and Some Haematological Parameters with Poor Clinical Outcome of Patients

Patient 4 has the high concentration of C-reactive protein, IL-6 and D-dimer at 355mg/L, 724pg/ml and 23600ng/ml respectively. This was also associated with admission for 10days despite administration of tocilizumab. Patient 6 had the most markedly elevated elevated serum creatinine of 1941 µmol/l before the demise. Patient 2 had marked elevated C-reactive protein and IL-6 of 246mg/L and 215pg/ml respectively. This was also associated with a week of intensive care unit admission and total inpatient care length of 11 days despite exchange blood transfusion (Tables 2 and 3).

Patient 15 had white cell count of 22.7 X 10^3/ul and had longest duration of admission of 13 days despite the exchange blood transfusion done on this patient (Tables 2 and 3).

Table 3. *Immunological/Biochemical and Some Haematological Parameters of Sickle Cell Disease Patient with COVID-19.*

Patients Number	CRP (mg/l)	IL-6 (pg/ml)	D-Dimer (ng/ml)	Maximum WBC (10^3/ul)	Lymphocytes (10^9/l) Nadir	Creatinine (µmol/l)	References
1	100	NP	2007	NP	NP	NP	[20]
2	246	215	7115	NP	NP	NP	[20]
3	145	37.5	7564	NP	NP	NP	[20]
4	355	724	23600	NP	NP	NP	[20]
5	221	NP	NP	NP	1.61	81	[18]
6	320	NP	871	NP	2.08	1941	[18]
7	46	NP	NP	NP	2.84	513	[18]
8	205	NP	9253	NP	0.54	34	[18]
9	63	NP	NP	NP	1.11	76	[18]
10	<5	NP	1246	NP	0.45	70	[18]
11*	64	NP	157	NP	0.81	52	[18]
12*	9	NP	NP	NP	3.71	54	[18]
13*	10	NP	NP	NP	4.31	49	[18]
14*	319	NP	NP	NP	0.84	44	[18]
15	NP	NP	NP	22.7	NP	NP	[19]
16	NP	NP	NP	5.3	NP	NP	[19]
17	NP	NP	NP	16	NP	NP	[19]
18	NP	NP	NP	8.1	NP	NP	[19]

NP- Data not available; CRP, C-reactive protein; WBC, white blood cells; CRP, C-reactive proteins; IL-6, Interleukin 6; 1-10 and 15-18 confirmed COVID-19 cases; 11*-14*, suspected COVID-19 cases
C-reactive protein (CRP), normal range 0–10; D-Dimers, normal range 0–200; lymphocytes, normal range 0–4; creatinine, normal range 45–90/variable

4. Discussion

This study shows that SCD patients with COVID-19 that had multiple comorbidities (such as hypertension, diabetis and stroke) and chronic renal failure are likely to have poor clinical outcome. The finding in this study was identical to that conducted by Yeruva *et al*, 2016, which demonstrated that chronic kidney disease in patients with sickle cell disease was associated with increase length of inpatient admission and increase mortality compared with sickle cell disease patients without renal failure [22]. Also, the finding in this study was synonymous to some other studies by Panepinto and Amr in 2009 and 2011 respectively, which observed that comorbidities in patients with sickle cell disease confer poor outcome in them [23, 24]. Furthermore, the observation in this study was in support of the studies by Guan *et al* in 2020 which showed that presence of comorbidities such as hypertension, obesity, chronic lung disease, diabetes, and cardiovascular disease adversely affect and directly correlates with poor clinical outcome of patients with COVID-19 [25, 26]. Similarly, this study was also analogous to other studies by Oyelade *et al* and Uribarri *et al* in 2020 which show that renal failure in patients with COVID-19 is associated with increase in severity and in-patient mortality [27, 28].

The observation of markedly elevated pro-inflamatory markers (C-reactive proteins and IL-6) in patient with sickle cell disease and COVID-19 that was associated with prolonged inpatient and intensive care unit hospitalization in this study was in agreement with discovery by Conran *et al,* 2018 and Taylor *et al*, 1995 who noticed elevated interleukin 6 in patient with sickle cell disease and elevated IL-6 and C-reactive proteins in patients with sickle cell disease with vaso-occlusive crisis [6, 29]. Also the observation of markedly elevated C-reactive proteins and IL-6 in was identical to the finding by Mehta et al. who noticed SARS-COV 2 induces upregulation of pro-inflammatory cytokines such as (IL-1, IL-6 and TNF-α) [30], this finding was also comparable with the study by Zhang *et al* in 2020 that demonstrated increase in total number of mortality in patients with condition associated with exaggerated release of cytokine known as cytokine release syndrome [10]. This was also in agreement with the study by Kewan *et al* in 2020 that has shown the efficacy of Tocilizimab (an anti-human IL-6 receptor monoclonal antibody), which inhibits signal transduction through the IL-6 receptor by binding to sIL-6 receptor and mIL-6 receptor [31].

Markedly elevated D-dimer in sickle cell disease patient with COVID-19 was associated with prolonged hospital admission of 10 days despite the use of Tocilizumab was comparable with the study by Litao in 2020 who demonstrated that elevated D-Dimer is associated with severe COVID-19 [32]. No study that compared the clinical outcome of sickle cell disease with D-Dimer was found. However, there were studies by Zhang *et al* in 2020 and Hagger in 1995 that demonstrated elevated D-dimer in patients with sickle cell disease compared to HbA, the elevation is even more marked when they have vaso-occlusive crisis [33, 34].

The findings of leukocytosis associated with prolonged hospital admission in sickle cell patient with COVID-19 infection in this study was consistent with the observation of significant correlation between leukocytosis and the severity of COVID 19 infection in a study by Gleng *et al* in 2020 [31]. It can also be explained by the study of Suwa *et al* that demonstated that IL-6 induces both neutrophil demargination in the blood vessel and reduction in neutrophil transit time to

exit the bone marrow [35].

5. Conclusion

Presence of comorbidities, elevated pro-inflammatory markers, elevated D-Dimer levels and a very high serum creatinine are poor prognostic indices in sickle cell disease patients with COVID-19 infection.

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Nil

Conflicts of Interest

All the authors do not have any possible conflicts of interest

Limitations of the Study

This reviewed was done on retrospective studies carried out on few case series.

Not all the data were provided for all the patients reviewed

The phenotypic variation in the participants with sickle cell anaemia as a result of genetic modifiers mainly from the haplotypes and co-inheritance with thalassaemias was not investigated.

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