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ORIGINAL ARTICLE

A Clinicohematological Study of Sickle Cell Disease Among Adult Patients in Makkah, Saudi Arabia

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Abstract

Background: **Sickle cell disease is an autosomal recessive disease characterized by an aberrant production of hemoglobin S (HbS). The disease's presentation and severity vary substantially between people from various socioeconomic backgrounds and geographical regions. The clinical picture includes hemolytic anemia, vascular occlusion events, acute and persistent pain, and varied organ damage.**

Objective: **To investigate the clinical and hematological characteristics of adult patients with sickle cell disease.**

Patients and methods: **The study was conducted using outpatient and inpatient data obtained retrospectively from a specialist hospital in Makkah City from January 2019 to December 2019. This study collected clinical and hematological data from all patients with sickle cell anemia (SCA) validated by high-performance liquid chromatography between the ages of 18 and 50 years. The data were gathered from the laboratory database and contained demographic and hematological findings of complete blood counts performed on a fully automated hematology analyzer, as well as high-performance liquid chromatography results for percentages of variant hemoglobins within the SCA group. This study included 130 participants with SCA. All of the aforementioned patients' clinical findings were documented from the hospital archives.**

Results: **The mean age for all of the patients was 30.5 ± 11.1 years. Pearson correlation for male patients showed significant positive correlations between HbS and leukocytes ($r = 0.503$, $P < 0.001$), platelets ($r = 0.164$, $P = 0.04$), MCH ($r = 0.304$, $P = 0.017$), and RDW_SD ($r = 0.34$, $P = 0.014$), whereas significant negative correlations between HbS and RBC ($r = -0.29$, $P = 0.023$), HBA2 ($r = -0.519$, $P \leq 0.001$), and HBA ($r = -0.84$, $P < 0.001$). Among females, the results displayed significant positive correlations between HbS and MCV ($r = 0.334$, $P = 0.005$) and MCH ($r = 0.438$, $P < 0.001$), whereas a significant negative correlation between HbS and RBC ($r = -0.472$, $P < 0.001$)). The associated clinical findings were pain crises in 40 (30.76%), gallstones in 38 (29.23%), infections in 26 (20%), and acute chest syndrome in 20 (18.46%).**

Conclusion: **There was a significant correlation between HbS and RBC count and MCH for both sexes, whereas a significant negative correlation between HbS and MCV was observed. Clinical findings were predominantly pain crises and acute chest syndrome.**

Keywords: Hemoglobin, Pain crises, Sickle cell disease

1. Introduction

Sickle cell disease (SCD) is a group of inherited disorders of the red blood cells that are characterized by defective hemoglobins.[1] SCD is an autosomal recessive disorder characterized by improper production of hemoglobin S (HbS). This form of hemoglobin is produced by swapping glutamic acid for valine in position six of the chain, resulting in deoxygenation-induced polymerization and the aberrant crescent shape of red blood cells.[2,3]

SCD can appear in a variety of haplotypes around the world, and even within a single haplotype, the clinical manifestations of SCD can vary significantly.[4] All age groups around the world are affected by sickle cell anemia (SCA).[5] The mechanisms driving the many phenotypes of SCA can be broken down into three main pathogenic processes:

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sickling of the erythrocytes, vaso-occlusion, and susceptibility to infections.[6] SCD is very common in the Arabian Peninsula.[7]

Overall, 2.7% of the population in Saudi Arabia has SCD, whereas another 2–27% has sickle cell traits.[8] The incidence of SCD is highest in the eastern part of Saudi Arabia, followed by the southern part of the country. Only 10.3% of the population in the north did not have SCD. There is a lack of definitive data on the prevalence of SCD in Saudi Arabia; however, analysis of data from the Saudi Premarital Screening Program database (which includes 488 315 individuals) showed that 4.2% of the screened population has the sickle cell trait, and 0.26% of these individuals have SCD.[9]

SCD is still one of Saudi Arabia's biggest problems that people do not talk about. It has one of the highest rates of incidence in the world.[10] The high rate of SCD in Saudi Arabia is likely caused by the country's high rate of first-degree consanguinity.[9,10]

The clinical picture includes symptoms such hemolytic anemia, vascular occlusion events, acute and persistent pain, and varying degrees of organ damage.[7] Owing to the obstruction of blood flow brought on by the abnormally shaped red cells, people with SCD experience hemolytic anemia for the rest of their lives and experience both acute and chronic tissue damage.[10,11] The disease's manifestation and severity varied considerably between socioeconomic groups and geographical regions.[7]

SCD can lead to a stroke, high blood pressure in the lungs, acute chest syndrome, organ damage, leg ulcers, gallstones, priapism, and problems during pregnancy.[9] Virulent bacterial infections and splenic sequestration crises are two life-threatening complications. Chronic hemolysis causes pigmented gallstones to form, and chronic organ damage can lead to cerebrovasculopathy, pulmonary and renal damage, leg ulcers, and avascular osteonecrosis.[7]

Patients with SCD have a lower quality of life than the general population and those with other chronic diseases. SCD pathophysiology causes lifelong problems for most patients.[9] Kingdom-wide haplotype, prevalence, and clinical manifestation vary. Thus, clinicians must understand the disease in their specialty to provide the best therapy and recommendations.[4]

High-performance liquid chromatography (HPLC) is the preferred approach for screening and confirming hemoglobinopathies such as SCA. It delivers sensitive, precise, and reproducible data that, when combined with a family history and well-defined hematological parameters, aid in the identification of various hemoglobinopathies. HPLC helps monitor and prevent hemoglobinopathies by determining their prevalence.[12]

We aimed to investigate the clinical and hematological characteristics of adult patients with SCA, as well as their prevalence in a tertiary care hospital in Makkah region of Saudi Arabia.

2. Patients and methods

This study was done using the outpatient and inpatient data collected retrospectively over a period of 1 year from January 2019 to December 2019 from a specialist hospital in Makkah City. Clinical and hematological data of all patients with SCA confirmed by HPLC in the age group of 18 and 50 years were included in this study. The data were collected from the laboratory database and includes demographic and hematological results of complete blood count performed on a fully automated hematology analyzer along with HPLC results for percentages of variant hemoglobins within the SCA group. The clinical findings of patients were recorded from the hospital archives of all the aforementioned patients. A total of 130 patients with SCA were included in this study. The institutional review board gave the ethical approval with IRB number 0449–131121 dated 12/12/2021.

Statistical analysis was done by SPSS, version 22 (Statistical Package Social Science; SPSS inc., Chicago, Illinois, USA). Continuous variables were presented in tables as mean ± SD, whereas noncontinuous variables were presented in tables as frequency and percent. The correlations between HbS and other variables were achieved by Pearson correlation test. Curve estimation for HbS and other significant hematological parameters was performed. A P value of less than 0.05 was considered statistically significant result.

3. Results

Table 1 shows the baseline characteristics of patients with SCA. The mean age for all the patients was 30.5 ± 11.1 years, and the mean ages for males and females were 28.3 ± 9.6 and 32.5 ± 12, respectively. The serum hemoglobin level for both sexes was lower than the normal range. Additionally, average serum levels for hematocrit, red blood cells (RBC), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC, and hemoglobin A (HBA) were lower than the normal values. On the contrary, the average serum levels for leukocytes, ferritin, hemoglobin (HBF), hemoglobin A2 (HBA2), red cell distribution width coefficient of variation (RDW_CV), and red cell distribution width standard deviation (RDW_SD) were higher than the normal values.

Table 1. Description of hematological parameters of 130 patients with sickle cell anemia.

Parameters	Mean ± SD	Median (IQR)	Normal range
Age (all patients, $N = 130$)	30.5	29 (22–38)	
Age (males, $N = 61$)	28.3 ± 9.6	28 (21–36)	
Age (females, $N = 69$)	32.5 ± 12	32 (23–40)	
Hemoglobin (g/dl)			
Male	85 ± 24.1	85.7 (64.3–107.1)	Male: 130–170
Female	80.6 ± 25.4	80.9 (56.6–105.3)	Female: 120–150
Hematocrit (%)	3.5 ± 6.9	0.4 (0.3–3)	0.4–0.5
Leukocytes	11.3 ± 6.2	9.5 (7–14.5)	4–11
Platelets	348.9 ± 163.9	335 (237.8–473.3)	150–400
RBC count			
Male	4.2 ± 0.9	4.1 (2.7–5.5)	Male: 4.5–5
Female	4.1 ± 0.9	3.9 (2.8–5)	Female: 3.8–4.8
Ferritin (ng/dl)	1396.7 ± 29.58	531.9 (81–1495.4)	30–400
MCV	69.4 ± 6.7	69.1 (65–75.8)	83–101
MCH	22.8 ± 2.8	22.7 (21.3–25)	27–32
MCHC	293.7 ± 72.7	317 (396.4–332)	315–345
HBF	5.9 ± 6.4	4.1 (1.2–8.4)	0.0–1
HbS	54.4 ± 32.3	65.3 (29.4–83.2)	0.0–0.0
HBA2	7.5 ± 10.3	5.1 (4.1–6.1)	1.5–3.5
HBA	31.9 ± 32.8	15.4 (3.8–60.5)	95–98
RDW_CV	20.3 ± 3.9	19.9 (17.4–22.1)	11.6–14
RDW_SD	47 ± 8.6	46.2 (40.8–53.6)	39–46

HbS, hemoglobin S.

Table 2 demonstrates the Pearson correlations between HbS and other variables for both sexes. Male patients showed significant positive correlations between HbS and leukocytes ($r = 0.503$, $P < 0.001$), platelets ($r = 0.164$, $P = 0.04$), MCH ($r = 0.304$, $P = 0.017$), and RDW_SD ($r = 0.34$, $P = 0.014$), whereas significant negative correlations between HbS and RBC ($r = -0.29$, $P = 0.023$), HBA2 ($r = -0.519$, $P \leq 0.001$), and HBA ($r = -0.84$, $P < 0.001$). Regarding female patients, the results displayed significant positive correlations between HbS and MCV ($r = 0.334$, $P = 0.005$) and MCH ($r = 0.438$, $P < 0.001$), whereas a significant negative correlation between HbS and RBC ($r = -0.472$, $P < 0.001$).

Curve estimation for HbS and the most valuable parameters (RBC, MCV, and MCH) for males and females is presented in Figs. 1–6. The results showed significant correlations between HbS and RBC count and MCH for both sexes, whereas a significant negative correlation between HbS and MCV was observed.

The most common presenting clinical characteristic was painful episodes followed by gallstones. Infections and acute chest syndrome were also seen in a good number of patients. The least clinical presentation was priapism reported by only one patient (Table 3).

Table 2. Pearson correlations between hemoglobin S and other variables.

Parameters	Hemoglobin S r (P value)		
	All patients ($N = 130$)	Males ($N = 61$)	Females ($N = 69$)
Age	−0.169 (0.055)	0.021 (0.872)	−0.219 (0.07)
Hemoglobin (g/dl)	−0.073 (0.408)	−0.067 (0.61)	−0.125 (0.305)
Hematocrit (%)	−0.053 (0.548)	−0.062 (0.637)	−0.035 (0.775)
Leukocytes	0.296 (0.001)[a]	0.503 (<0.001)[a]	0.099 (0.42)
Platelets	0.248 (0.004)[a]	0.164 (0.04)[b]	0.211 (0.081)
RBC count	−0.36 (<0.001)[a]	−0.29 (0.023)[b]	−0.472 (<0.001)[a]
Ferritin	−0.022 (0.862)	−0.09 (0.649)	0.001 (0.995)
MCV	0.263 (0.003)[a]	0.219 (0.09)	0.334 (0.005)[a]
MCH	0.377 (<0.001)[a]	0.304 (0.017)[b]	0.438 (<0.001)[a]
MCHC	0.108 (0.221)	0.115 (0.376)	0.072 (0.557)
HBF	0.067 (0.45)	−0.164 (0.207)	0.222 (0.067)
HBA2	−0.334 (<0.001)[a]	−0.519 (<0.001)[a]	−0.216 (0.074)
HBA	−0.892 (<0.001)[a]	−0.84 (<0.001)[b]	−0.915 (<0.001)
RDW_CV	−0.008 (0.932)	0.023 (0.86)	−0.131 (0.284)
RDW_SD	0.251 (0.007)[a]	0.34 (0.014)[b]	0.173 (0.178)

[a] Highly significant at P value less than 0.01.
[b] Significant at P value less than 0.05.

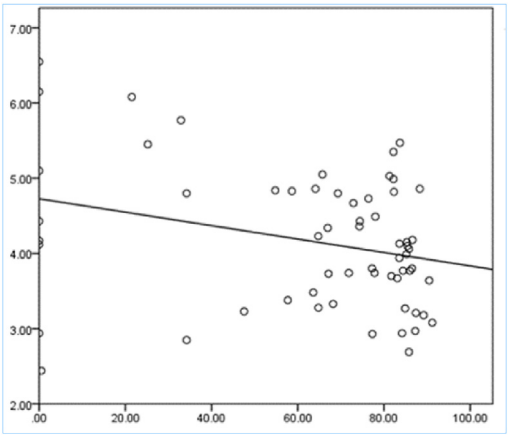

Fig. 1. Curve estimation for hemoglobin-S (Y axis) and RBC (X axis) for males ($R^2 = 0.084$, $P = 0.023$).

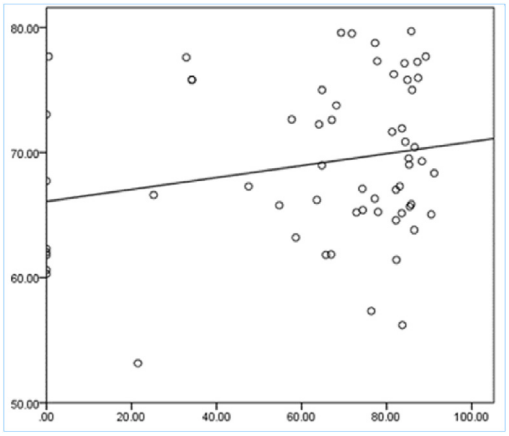

Fig. 3. Curve estimation for hemoglobin-S (Y axis) and MCV (X axis) for males ($R^2 = 0.048$, $P = 0.09$, not significant).

4. Discussion

SCD is a category of inherited red blood cell abnormalities defined by abnormal hemoglobin levels. The prevalence of SCD varies greatly across Saudi Arabia, with the Eastern province having the highest prevalence, followed by the southern provinces.[1,13–15] There are significant regional disparities in hemoglobinopathies among adult Saudis.[16] In Saudi Arabia, there are two distinct SCD patterns: one in the country's southwest, which resembles the African form, and the other in the Eastern Province, which follows a more milder course.[17,18] In Saudi Arabia, the first case of SCD was found in the early 1960s in the Eastern Province.[19]

Patients in this study had a mean age of 30.5 ± 11.1 years, with men having a mean age of 28.3 ± 9.6 years and women averaging 32.5 ± 12 years. Another study has indicated a lower mean age of 18.81 ± 11.05 years owing to the inclusion of all age groups in their research.[3] Pain crisis due to vaso-occlusive phenomenon was the most common presenting symptom, followed by gallstones, infections, and acute chest syndrome. These findings are consistent with those of another study conducted in the Jazan Region, which identified vaso-occlusive crisis and acute chest syndrome as the most common presenting symptoms of SCA in adult patients.[3]

According to another study, acute chest syndrome and sepsis were the two main causes of death among Saudi patients.[20] There are numerous known etiologies linked to the onset of acute chest syndrome, such as infection, pulmonary or lipid embolism, or opiate overdose. Most of the time, the cause cannot be ascribed to a single agent, and if it can, the only reliable way to determine it is by autopsy. The typical occurrence of an acute pain event coming before the onset of acute chest syndrome is one possible commonality. Even though there is

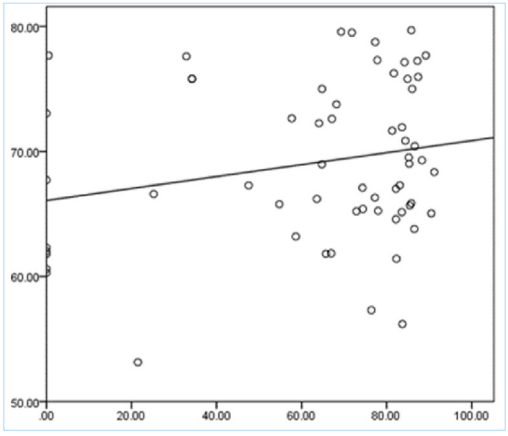

Fig. 2. Curve estimation for hemoglobin-S (Y axis) and RBC (X axis) for females ($R^2 = 0.223$, $P < 0.001$).

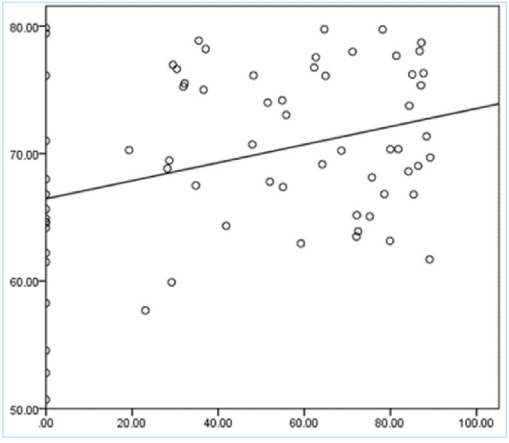

Fig. 4. Curve estimation for hemoglobin-S (Y axis) and MCV (X axis) for females ($R^2 = 0.112$, $P = 0.005$).

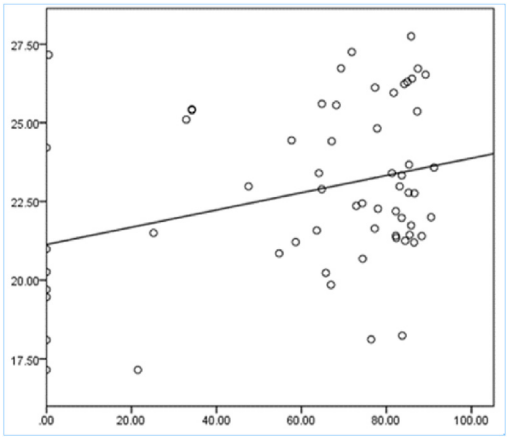

Fig. 5. Curve estimation for hemoglobin-S (Y axis) and MCH (X axis) for males ($R^2 = 0.092$, $P = 0.017$).

obviously still plenty to learn, acute pain occurrences are one of the more well-known symptoms of SCD. In most instances, inflammatory markers and signs of endothelial dysfunction rise. Both platelet activation and inflammation-related indicators produced from platelets are increased during painful events.[21]

According to a study, a significant sequestration of platelets in the pulmonary vasculature may be a contributing factor in the development of acute chest syndrome.[21] Now that it has been discovered that SCD vaso-occlusion is a complex, multifactorial process characterized by recurrent vaso-occlusion, ischemia-reperfusion injury, and oxidative stress with subsequent vascular endothelial cell activation, chronic inflammation in patients with SCD is induced, and this chronic inflammation is sustained by elevated levels of circulating inflammatory cytokines.[22] According to a different study, having a history of asthma and having a high steady state

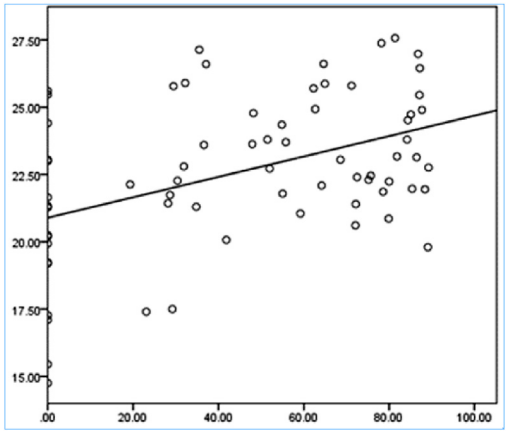

Fig. 6. Curve estimation for hemoglobin-S (Y axis) and MCH (X axis) for females ($R^2 = 0.192$, $P < 0.001$).

white blood cell count were linked to an increased chance of developing acute chest syndrome.[23]

The most frequent presenting symptoms, according to Alsultan *et al.*[23] were gallstones in 34% of patients and vaso-occlusive crises in 98% of patients. However, in their study from Yemen, Al-Ghazaly et al.[24] found that pain was present in 73.4% of patients, followed by jaundice and infection as the most common presenting symptoms. Anemia crisis and acute chest syndrome were observed in 15.8 and 10.7% of cases, respectively, in another study conducted in Yemen, where 35.95% of the patients had pain7.

Thus, other studies have documented a similar pattern of presentation in patients with SCA, with pain/vaso-occlusive crises being the most prevalent. The most prevalent finding in a study conducted in Nigeria was hepatomegaly (64%), followed by frequent bouts of vaso-occlusive crises (30%) and dactylitis in infants (26%). Another study conducted on female patients in Maharashtra, India, identified recurrent infections (37.5%), followed by joint pain (28.9%) as the most prevalent symptom.[25] A large proportion of patients (20%) had recurrent infection, according to our findings. Loss of splenic function is associated with reduced splenic immunoglobulin production, which increases the risk of infection.[13] The bone pain crisis is a frequent consequence of SCD that typically affects the long bones, including the femur and humerus, vertebrae, pelvis, ribs, and sternum.[26] Recent research suggests that sickled erythrocytes promote the production of adhesion molecules by the vascular endothelium, which in turn encourages intravascular cellular adhesions, stasis, and a prolonged blood flow transit time.[27]

The culmination of these processes is the occlusion of microcirculation, which causes tissue infarctions and manifests clinically as the painful vaso-occlusive crises, which typically manifest in the bones. Vascular occlusion in SCD has far-reaching consequences, not just for the bones. Multiple organs may be damaged as a result of this, including the central nervous system, the lungs, the penis, and

Table 3. The presenting clinical characteristics of all patients with sickle cell anemia.

Clinical characteristics	*n* (%)
Pain crisis	40 (30.76)
Acute chest syndrome	24 (18.46)
Osteonecrosis	16 (12.30)
Gall stones	38 (29.23)
Deep vein thrombosis	3 (2.3)
Infections	26 (20)
Splenomegaly	10 (7.6)
Priapism	1 (0.76)

the kidneys. Chronic hemolytic anemia, jaundice, and the development of bilirubin gallstones are all possible outcomes of sickling, which also substantially reduces the red cell life span.[28] The current study found that gallstones were the second most common problem among patients with SCD, affecting 38 (29.3%).

Only one participant in our study reported experiencing priapism. In the past, several alterations in hematological parameters had been described as major risk factors for the emergence of priapism in patients with SCD. Low hemoglobin F (HbF) levels and high platelet counts were found to be substantially related to priapism in Jamaican patients with SCA.[29] One American study found no statistically significant changes between hematological parameters of patients with SCD with and without priapism.[28]

Priapism is an underreported complication, despite the fact that it may exacerbate the condition.[30] Similar to our findings, another study from Bisha, Saudi Arabia, revealed a low frequency of leg ulcers and priapism.[31]

Hemoglobin, hematocrit, and red blood cell count were all below the normal range in this study's participants (Table 1). Significant correlations were found between the increase in HbS levels and decrease in HBA and the decrease in RBC count and MCH (Fig. 1). Possible contributors to the low hemoglobin and hematocrit levels were chronic hemolysis, decreased RBC survival, and a diminished erythropoietin response associated with SCD. Reduced RBC counts were found, which is consistent with the majority of studies and may be explained by the patients' persistent chronic hemolytic anemia.[32–34] In contrast to a study conducted in Ghana that found a greater level of MCV, MCH, and MCHC among patients with HbS steady state compared with controls, MCV, MCH, and MCHC were considerably lower among all patients in the current study.[33] The HbS molecule polymerization in SCD is critically dependent on the mean corpuscular hemoglobin concentration, and its minor drop may have significant physiologic effects.[35]

Serum ferritin levels in our study were quite high in both sexes, with a mean of 1396.7 ± 29.58, indicating iron excess. As iron overload problems are a major cause of death in these patients, significant efforts are required to improve this area of their care. In their study,[35] Alsuliman and colleagues observed a lower mean blood ferritin content of 587 ± 547 (18.49–2660 ng/dl). However, a different study revealed mean ferritin levels of 2075 ng/ml, which are similar to those in the current study.[36] An excess of iron is hazardous to numerous tissues, especially the heart and endocrine system.

Several studies have demonstrated that iron depletion or less iron in the body is beneficial by reducing painful crises and hemolysis. These investigations suggested that this effect's mechanism is likely complex.[35]

The white blood cell count was above the normal range in both male and female patients (11.3 ± 6.2) (Table 1). Even in steady state, SCD is characterized by a mild leukocytosis, which is believed to be caused by a transfer of leukocytes from a marginal pool to a pool of circulating granulocytes.[28] However, other investigations have shown a median white blood cell (lymphocyte, monocyte, and granulocyte) count in patients with SCD that is twice as high as in matched controls[32] or a considerable leukocytosis in the absence of infection.[33,37]

Rise in the count was highly correlated with the HbS level for all patients combined and for male patients (Table 2). Thrombocytosis is frequent in SCD and is caused by the disease's background hemolytic anemia and autosplenectomy.[28] However, the platelet counts in this study were within normal limits although on the high end (348.9 ± 163.9) (Table 1). HbF levels were substantially higher in both sexes (5.9 ± 6.4) (Table 1). HbF lowers the severity of SCD, however the specific mechanism is unknown. HbS gelation duration is enhanced in the presence of HbF. The increased synthesis of HbF postnatally and its continuation are genetically controlled and also depend on the patient's age, which decreases dramatically with age.[38]

Other results indicate that fetal hemoglobin (HbF) influences the phenotype of SCA by preventing the polymerization of deoxy sickle hemoglobin (HbS).[39] Targeting BCL11A has been recommended as a treatment for the majority of illness problems if overall HbF levels of 30% can be obtained.[39]

Consanguinity is strongly linked to the high prevalence and mortality of SCD among Saudis. One of the several countries that took proactive measures to combat SCG and other hemoglobin disorders was Saudi Arabia. The prevalence of SCD and other prevalent hemoglobinopathies in Saudi Arabia was found to be reduced by a premarital screening program initiated by the government in 2003.[40]

5. Conclusions

In Saudi Arabia, SCD is one of the most common autosomal recessively inherited blood disorders.

SCD consequences and severity vary depending on genotype and environmental variables. Our study is limited in that we did not assess the genotype of SCD and we only included patients aged 18–50 years. In this study, at least, we can say for sure that hereditary hemoglobin disorders are very common in Saudi Arabia, which is what the health authorities should focus on. Some success was gained through the premarital program and screening for SCD and thalassemia, but much more work is needed to accomplish a satisfying goal.

Author contributions

The following are the author contributions: conceptualization, methodology, software, validation, formal analysis, investigation, resources, data curation, writing—original draft preparation, writing – review and editing, visualization, supervision, and project administration have been performed by A.F.A.

Conflict of interest

There are no conflicts of interest.

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