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Assessment of D-dimer level among Yemeni Patients with Sickle Cell Anemia

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Abstract

Background: Sickle cell anemia (SCA) is a hereditary hemoglobin disorder characterized by chronic hemolysis, vaso-occlusive crises, and a hypercoagulable state. Elevated D-dimer levels have been associated with increased thrombotic risk in patients with SCA. However, limited data exists on D-dimer levels in Yemeni patients with SCA.

Objective: This study aimed to assess the plasma D-dimer levels in Yemeni patients with SCA and compare them with those of healthy controls.

Methods: A comparative cross-sectional study was conducted at the Yemen Society for Thalassemia and Genetic Blood Disorders in Sana'a, Yemen from August to December 2024. The study included 100 participants: 50 patients with SCA and 50 age- and sex-matched healthy controls. The plasma D-dimer levels were measured using an automated immunoturbidimetric assay. Hematological parameters were analyzed using an automated hematology analyzer. Statistical analysis was performed using SPSS version 26, and a p-value of <0.05 was considered significant.

Results: The mean D-dimer level in SCA patients was significantly higher (2.5±1.8 mg/L) compared to the control group (0.3±0.14 mg/L) ($p < 0.001$). Hemoglobin levels were significantly lower in the SCA group (9.5±1.5 g/dL) compared to controls (14.7±1.3 g/dL) ($p < 0.001$). SCA patients also exhibited significantly lower RBC counts (3.3±0.8)$10^{12}/L$ and higher platelet counts (368.3±133.8 ($10^{9}/L$) than controls (5.8±0.7) $10^{12}/L$ and (260.8±48.9)$\times 10^{9}/L$, respectively, ($p < 0.001$).

Conclusion: Yemeni patients with SCA exhibited significantly elevated D-dimer levels, suggesting increased coagulation activation and thrombotic risk. These findings highlight the need for further research on thromboprophylactic strategies in this population.

Article Info

Keywords:
Sickle cell anemia (SCA), chronic hemolysis, vaso-occlusive crises, D-dimer, thrombotic risk.

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1. INTRODUCTION

Sickle cell anemia (SCA) is a genetic disorder caused by a single nucleotide mutation in the gene coding for the β-globin chain of hemoglobin. This mutation substitutes negatively charged glutamate with a neutral, hydrophobic valine, which creates sticky areas on the surface of the protein [1]. The main aspect of sickle cell pathophysiology is the intracellular polymerization of deoxyhaemoglobin S. When hemoglobin (HbSS) is deoxygenated, it undergoes a structural change, exposing a hydrophobic valine at position β6 in contrast to the hydrophilic glutamate found in normal hemoglobin (HbAA). This shift results in decreased solubility and polymerization [2, 3]. Numerous factors, such as the inheritance of additional genetic factors, can exacerbate or lessen the severity of the disease's manifestations, resulting in a wide range of symptoms [4]. Sickle cell disease (SCD)

is the most common monogenic disorder in the world is sickle cell disease [5]. There are notable regional variations in the prevalence of SCD worldwide. The estimated prevalence in the United States is 329 cases per million people. The prevalence in the United Kingdom is 217 cases per million people [5]. According to Bin Zuair et al. [6], the prevalence is significantly higher in other regions, with over 20,000 cases per 1,000,000 people in Nigeria, over 45,100 cases per 1,000,000 adults in Saudi Arabia, and 2,400 cases per 1,000,000 Saudi children and adolescents. It was estimated that 2.2% of Yemenis had sickle cell disease, with the frequency of the gene surpassing 4.0% in people from the governorates of Taiz and Hajjah [7]. The causes of coagulation activation in sickle cell disease (SCD) appear to be complex and involve several factors, including ischemia-reperfusion injury, inflammation, hemolysis, nitric oxide deficiency, and increased expression of phosphatidylserine in sickle red blood cells. Individuals with SCD show enhanced platelet activation, higher plasma levels of thrombin generation markers, decreased natural anticoagulant proteins, dysregulated activation of the fibrinolytic system, and elevated tissue factor expression, even during periods of "steady state" when they are not experiencing a crisis [8]. SCA is associated with hypercoagulability, which can result in certain health issues such as vaso-occlusion and cerebrovascular system incidents. It has been shown that people with SCA have lower levels of natural anticoagulant proteins, specifically during episodes of vaso-occlusive crisis. These Proteins C and S, two plasma proteins that are dependent on vitamin K and work together as a natural anticoagulant mechanism [9]. Compared to healthy people with normal hemoglobin levels, patients with SCD in a stable state show persistent coagulation system activation [10]. Prothrombin fragment 1.2, fibrinopeptide A, thrombin-antithrombin complexes (TAT), D-dimers, and plasmin-antiplasmin complexes (PAP) are markers that frequently show increased production and elevated plasma levels in these patients, indicating ongoing thrombin and fibrin generation[11]. Previous studies have indicated that patients with sickle cell anemia (SCA) exhibit abnormal D-dimer levels compared to individuals without the condition. However, there is a lack of data on D-dimer status in SCA patients in Yemen. Therefore, this study aimed to fill this critical knowledge gap and improve clinical care by determining D-dimer levels in patients with SCA.

2. METHODS

2.1. Study Design

This research employed a comparative cross-sectional study design.

2.2. Study Population

The study population consisted of patients with sickle cell anemia (HbSS) and healthy individuals with Hemoglobin A (HbAA). The healthy controls were matched for age and sex.

2.3. Study Setting

The study was conducted at the Yemen Society for Thalassemia and Genetic Blood Disorders in Sana'a City, Yemen, from August to December 2024.

2.4. Sample Size

The sample size for this study included 100 participants (both males and females). The calculation was performed using the OpenEpi program (Version 2.3.1) with a 95% confidence level, 80% power of the study, and an expected mean ± standard deviation of D-dimer of 0.56±0.33 for the patient group and 0.33±0.14 for the control group, as reported by Elnaim et al. [2]. The final sample size was rounded to 100 to improve accuracy.

2.5. Data Collection

Sociodemographic information, including age, sex, and occupation, along with medical data such as blood transfusion history and number of crises in the previous year were gathered from each participant using a standardized questionnaire.

2.6. Sample Collection

Five milliliters of venous blood were collected from each subject. This was distributed as follows: 1.8 milliliters into a trisodium citrate tube and 3 milliliters into an Ethylene Diamine Tetraacetic Acid (EDTA) tube. The blood collected in the trisodium citrate tube was analyzed for D-dimer levels, while EDTA blood was used for complete blood count (CBC) and hemoglobin phenotype determination via Hb electrophoresis using the cellulose acetate technique in an alkaline medium.

2.7. Statistical Analysis

The collected data were analyzed using the Statistical Package for Social Sciences (SPSS) version 26 (LEAD Technologies, Inc., USA). Quantitative data were expressed as mean values ± standard deviation (SD) when the data were normally distributed. Qualitative data were expressed as percentages. The independent samples t-test was used to compare the means between the two groups, and a p-value of less than 0.05 was considered statistically significant.

2.8. Ethics Statement

All the participants provided written informed consent. The study objectives and procedures were explained to each participant. Approval for this study was obtained from the Faculty of Medicine and Health Sciences Committee on Postgraduate Studies and Scientific Research.

3. RESULTS

Fifty individuals with sickle cell anemia (HbSS) comprising 33 males and 17 females, with a mean age of 19.1 ± 9.7 years, were included in the study. The control group consisted of 50 individuals with normal hemoglobin genotype (HbAA), including 31 males and 19 females, with a mean age of 21.4 ± 9.4 years (P = 0.23). The mean body mass index (BMI) was significantly lower in the HbSS group (17.7 ± 3.3 kg/m^2) compared to the HbAA group (21.4 ± 5.2 kg/m^2; P < 0.001). The mean frequency of pain crises among HbSS individuals was 4.6 ± 2.1 episodes per year, and the mean number of blood transfusions was 1.4 ± 1.1 per year. Regarding employment status, a significantly higher proportion of individuals with HbAA were employed (42%) than those with HbSS (8%; P = 0.001). Gender distribution and unemployment status did not differ significantly between the groups (Table 1). The mean D-dimer levels were significantly higher

Table 1. Demographic and clinical characteristics of sickle cell anemia patients and controls

Parameter	HbSS n(%)	HbAA n(%)	p-value
Mean age (years)	19.1 ± 9.7	21.4 ± 9.4	0.23
BMI (kg/m^2)	17.7 ± 3.3	21.4 ± 5.2	<0.001
Pain crisis/year	4.6 ± 2.1	-	-
Blood transfusion/year	1.4 ± 1.1	-	-
Gender			0.67
Male	33 (66%)	31 (62%)	
Female	17 (34%)	19 (38%)	
Occupation			<0.001
Employed	4 (8%)	21 (42%)	
Unemployed	46 (92%)	29 (58%)	

BMI, body mass index

in the sickle cell anemia (SCA) group (2.5±1.8 mg/L) compared to the control group (0.3±0.14 mg/L), with a p-value of 0.000. Similarly, hemoglobin (HGB) levels were significantly lower in the SCA group (9.5±1.5 g/dL) compared to the control group (14.7±1.3 g/dL, p < 0.001). Red blood cell (RBC) counts were also significantly lower in the SCA group (3.3±0.8)$10^{12}/L$ compared to the control group (5.8±0.7)$10^{12}/L$, p < 0.001). In contrast, white blood cell (WBC) counts were significantly higher in the SCA group (9.9±5.8 $)10^9/L$ than in the control group (4.9±1.8 $)10^9/L$, p < 0.001). Platelet counts were elevated in the SCA group (368.3±133.8 $)10^9/L$ compared to the control group (260.8±48.9 $)10^9/L$, and this difference was statistically significant (p < 0.001) (Table 2).

Table 2. D-dimer and hematological parameters in sickle cell anemia and controls

Parameters	SCA	Control	p-value
D-dimer	2.5 ± 1.8	0.3 ± 0.14	<0.000
Hemoglobin g/dl	9.5 ± 1.5	14.7 ± 1.3	<0.001
Red blood cell count $(10^{12}/L)$	3.3 ± 0.8	5.8 ± 0.7	<0.001
White blood cell count $(10^9/L)$	9.9 ± 5.8	4.9 ± 1.8	<0.001
Platelet count $(10^{12}/L)$	368.3 ± 133.8	260.8 ± 48.9	<0.001

4. DISCUSSION

This study investigated plasma D-dimer levels in patients with SCA. Plasma D-dimer levels were assessed in patients with SCA and controls. In this study, patients with sickle cell anemia (SCA) exhibited significantly higher D-dimer levels than those in the control group. Similar results were reported by Kusfa et al. [12], Fakunle et al. [13], Hagger et al. [14], and Francis RB [15], all of which indicated elevated D-dimer levels in SCA patients relative to controls. The pronounced increase in D-dimer levels may be attributed to multiple thrombus formation sites of varying severity in individuals with SCA (Ataga, K. I., & Orringer) [16]. Additionally, some patients might have experienced crises during the study period, which could explain their elevated D-dimer levels. Conversely, a study by Akinola et al. found that SCA patients in a steady state exhibited biochemical and rheological changes indicative of minor microvascular stasis episodes, which were not severe enough to trigger overt vaso-occlusive crises [17]. This study assessed plasma D-dimer levels and hematological parameters in patients with sickle cell anemia (SCA) compared to healthy controls. The findings revealed that plasma D-dimer levels were significantly elevated in patients with SCA, indicating an ongoing hypercoagulable state. This result aligns with previous studies by Kusfa et al. [12], Fakunle et al. [13], Hagger et al. [14], and Francis RB [15], all of which reported heightened D-dimer levels in individuals with SCA. The elevated levels may be attributed to multiple sites of thrombus formation and the pro-inflammatory and pro-thrombotic environments associated with SCA [16]. Additionally, the presence of patients experiencing crises during the study may have contributed to elevated D-dimer levels. In contrast, Akinola et al. [17] observed that even in the steady state, patients with SCA exhibit microvascular stasis, which may not manifest as overt vaso-occlusive crises, yet could still influence hemostatic markers such as D-dimer. Interestingly, Ekwere et al. [18] found no significant difference in D-dimer levels between patients with SCA and controls, possibly due to their rela-

tively small sample size, approximately half of that in our study. In contrast, Nsiri et al. [19] and Philips et al.[20] reported reduced fibrinolytic activity in patients with steady-state SCA, suggesting that the coagulation-fibrinolysis balance in SCA may vary depending on the disease phase and individual variability. Some studies have suggested no impairment in fibrinolytic function during the steady state [21]. It is important to note that elevated D-dimer levels do not exclusively indicate thrombosis; they can also result from infections, inflammation, or recent surgery. However, normal D-dimer levels are useful for excluding thrombosis, with a negative predictive value of approximately 90% [12]. In this study, hemoglobin (Hb) concentrations were significantly lower in SCA patients, consistent with the findings of Kusfa et al.[12], Ladu et al. [22], Omoti [23], and Chikhlikar et al. [24] These reductions are typically attributed to chronic hemolysis and splenic sequestration. Red blood cells (RBCs) in SCA patients showed a similar reduction, corroborating the results of Ugwu et al. [25] and Okocha et al.[26]. These hematological changes reflect the underlying pathophysiology of SCA, which is marked by ongoing hemolysis and ineffective erythropoiesis. The total white blood cell (WBC) count was significantly elevated in SCA patients compared to controls, in agreement with the observations of Kusfa et al. [12], Ladu et al. [22], Ahmed [27], and Okpala [28] Leukocytosis, even in the absence of infection, may result from chronic inflammatory stimuli that induce cytokine production and bone marrow stimulation [17] However, Elgari et al. [29], in a pediatric-focused study, found no significant difference in leukocyte counts, suggesting that age and maternal health factors could influence hematologic profiles in patients with SCA. Additionally, platelet count was significantly higher in patients with SCA. This aligns with the reports by Kusfa et al. [12], Aliyu et al. [30], Liesner et al. [31], Walters et al. [32], Hagger et al. [14], and Platt et al.[33] Increased platelet counts may be linked to functional asplenia and elevated thrombopoietin levels, which are common in chronic hemolytic conditions. Moreover, this finding supports prior suggestions for increased cellular activation and pro-thrombotic tendencies in patients with SCA [34]. This study is limited by the inability to assess additional coagulation parameters, such as fibrinogen, Protein S, and other specific clotting factors, which could have provided a more comprehensive view of the coagulation profile in patients with sickle cell anemia. Moreover, we did not evaluate other fibrin degradation products (FDPs) and C-reactive protein (CRP), both of which could help identify markers of intravascular clotting activation and ongoing clot lysis.

5. CONCLUSION

This study demonstrates that Yemeni patients with sickle cell anemia have significantly elevated D-dimer levels compared to healthy controls, indicating increased coagulation activation and heightened thrombotic risk. Additionally, the observed hematological abnormalities, including lower hemoglobin and RBC counts along with elevated platelet counts, further support the hypercoagulable state in SCA. These findings emphasize the need for increased awareness and further research on thromboprophylactic strategies to mitigate potential thrombotic complications in this population. Future studies should explore the clinical implications of elevated D-dimer levels and assess the effectiveness of anticoagulation therapy in reducing thrombotic events in Yemeni patients with SCA.

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