Original Research Article

Incidence of Leukaemia and Coagulation ProfileAssessment in Sickle Cell Patients at Sickle Cell Foundation, Lagos University Teaching Hospital, Lagos

ABSTRACT

Aims: This study aimed to assess the incidence of leukemia in individuals with sickle cell disease (SCD) and evaluate their coagulation and haematological profiles compared to non-SCD individuals. Specifically, it investigated differences in coagulation parameters such as prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen, and D-Dimer levels, and whether there were significant differences between SCD patients with and without leg ulcers.

Study Design: This is a case control study to determine the incidence of Leukaemia, to assess the coagulation and haematological profiles of sickle cell patients (steady state) with leg ulcers and non leg ulcer and non-sickle cell individuals as control group..

Place and Duration of Study: The study was conducted at the Sickle Cell Foundation Nigeria, Lagos University Teaching Hospital, Idi-Araba, Lagos, Nigeria, from May to September 2024.

Methodology:

A questionnaire was developed and administered to both patients with sickle cell disease (SCD) at their steady state and individuals in the control group (non-SCD).Ninety-two (92) participants were recruited for this study, of which 80 met the inclusion criteria. Fifty (50) subjects were of the SCD case group,while 30 were of the non-SCD control group. The80 consenting participants comprised 44 males and 36 females. The average age for SCD cases was 19.58 ± 9.8 years, while controls averaged 27.4 ± 12.3 years. Investigations were carried out on all the samples for Full Blood Count, coagulation profile, haemoglobin electrophoresis, ABO blood group, and peripheral blood film examination. Ethical approval was obtained from the College of Medicine, University of Lagos, and the Sickle Cell Foundation, Nigeria.

Results: The SCD group had lower red blood cell counts, haematocrit, and haemoglobin levels (*P*=0.001) compared to controls, with significantly elevated white blood cell and platelet counts (*P*=0.001). The Prothrombin Time (PT) and Activated Partial Thromboplastin Time(APTT) were higher in the SCD group(*P*=0.001 in each case), while fibrinogen (*P*=0.563) and D-Dimer levels (*P*=0.096) showed no significant differences. There were no significant variations in coagulation profiles between SCD patients with and without leg ulcers.

Conclusion: Significant differences in haematological parameters were observed between SCD and non-SCD participants, while coagulation profile were similar across groups.

Keywords: Sickle Cell Disease, Leg ulcer, Haemoglobin, Leukaemia, Coagulation Profile, D-dimer.

1.0 INTRODUCTION

1.1 Background Study

Sickle cell disease (SCD) is a group of genetic blood disorders caused by mutations in the gene responsible for producing the β-haemoglobin subunit. The presence of sickle haemoglobin (HbS) deforms red blood cells (RBCs) into a sickle shape, leading to chronic haemolytic anaemia and organ damage. SCD includes subtypes like sickle cell anaemia (SCA), HbSC, and HbSβ-thalassemia, all resulting from mutations in the HBB gene**[1].**Sickle cell anaemia (SCA), the most common form of SCD, causes chronic anaemia, periodic pain, and organ damage. Its severity varies based on genetic factors like elevated foetal haemoglobin (HbF) and co-inheritance of α-thalassemia **[2]**. Globally, Nigeria has a high prevalence, with 4-6 million affected individuals **[3]**.

1.2 Sickle Cell Disease with Chronic Leg Ulcer

Sickle Cell Anemia (SCA) increases venous thromboembolism risk due to higher prothrombotic factors and reduced anticoagulants **[4]**. Chronic leg ulcers (CLU), common in SCA patients, are recurrent, painful, and slow to heal. CLU prevalence varies: up to 75% in Jamaica, 8-10% in North America, and 10-19% in Ghana **[5]**. Nearly 97% of healed CLUs recur within a year, often leading to disfigurement, social isolation, and economic hardship.

1.3 Pathophysiology of Sickle Cell Disease

The fundamental pathophysiology involves HbS polymerization during deoxygenation, causing RBC deformity, leading to vaso-occlusion, haemolysis, and inflammation. This results in complications like pain, lung injury, stroke, and hypertension **[6]**. SCD also presents a hypercoagulable state with altered platelet function and coagulation pathway activation **[7]**.

1.4 Leukaemia and Sickle Cell Disease

Leukemia, a blood cancer involving abnormal proliferation of white blood cells, is linked to SCD. SCD patients may face an increased leukemia risk due to factors like heightened bone marrow turnover and genetic susceptibility **[8]**. Chronic inflammation and immune dysregulation may contribute to this risk, alongside persistent coagulation pathway activation **[9]**.

1.5 The Role of Coagulation in the Pathogenesis of SCD

In SCD, activated coagulation pathways are present even without vascular occlusions. This is indicated by elevated tissue factor, thrombin generation, and procoagulant microparticles. Endothelial dysfunction due to

haemolysis is linked to elevated soluble vascular cell adhesion molecule-1 (sVCAM-1) levels, reflecting haemolysis-induced endothelial activation.

1.6 Statement of Problem

Sickle cell disease (SCD) causes haemostatic abnormalities, leading to thrombotic and bleeding complications. Investigating coagulation profiles and related hematologic abnormalities, including leukemia incidence, is crucial for improving early detection, optimizing diagnostic methods, and developing targeted treatment strategies to manage these haemostatic challenges in SCD patients.

1.7 Justification of Study

Sickle cell disease (SCD) leads to haemostatic abnormalities, causing thrombotic and bleeding complications. Investigating the coagulation profiles and haematologic abnormalities in SCD patients is essential to enhance early detection, refine diagnostics, and improve treatment strategies. Understanding these haemostatic disturbances, including the potential impact of leukemia, is critical for optimizing clinical care in SCD management.

1.8 Objectives

This study assessed selected haematological and coagulation profiles of sickle cell patients with and without leg ulcers, at Lagos University Teaching Hospital.

1.9 Literature Review

1.9.1 Sickle Cell Disease and Hypercoagulability

Sickle cell disease (SCD) is a genetic blood disorder caused by a mutation in the β-globin gene, leading to the production of sickle haemoglobin (HbS), which deforms red blood cells **[10]**. SCD leads to acute and cumulative organ damage, manifesting as stroke, acute chest syndrome, sickle lung disease, pulmonary hypertension, nephropathy, end-stage renal disease, and other complications. **[11]**. SCD affects over 100,000 Americans and millions globally, particularly in Africa **[12]**.

1.9.2 Coagulation Abnormalities in SCD

The hypercoagulable state in SCD arises from haemolysis-induced platelet activation and endothelial dysfunction**[1],** with elevated procoagulant markers and tissue factor activity contributing to thrombosis **[13]**. Activated platelets promote vascular adhesion, leading to complications like pulmonary hypertension **[14]**.

2.0 MATERIALS AND METHODS

2.1 Ethics Approval

Ethical approval was given by the Ethics Committee of theCollege of Medicine, University of Lagos, Lagos state, Nigeria, and the Sickle Cell Foundation, Nigeria. All participants gave their informed consents before inclusion into the study.

2.2 Inclusion Criteria

Male and female subjects aged 10 to 65 years with an established diagnosis of sickle cell disease at steady state were included in this study.

2.3 Exclusion Criteria

However, individuals taking anticoagulant medications, those who have received recent blood transfusions, individuals with known liver disease affecting clotting factor production, and pregnant women with sickle cell disease were excluded from participation in this study.

2.4 Sample Collection and Processes

A total of 3.8 ml of blood sample was collected per subject via standard venipuncture, with 2 ml placed in ethylene-diamine tetra-acetic acid (EDTA) tube and 1.8 ml in a sodium citrate tube to prevent clotting. Samples were transported under cold chain conditions, processed, and stored at appropriate temperatures for analysis.

2.5 Sample Analysis

The laboratory investigations included a full blood count measuring haemoglobin, haematocrit, white cell, and platelet counts. Coagulation studies assessed APTT, PT, fibrinogen, and D-dimer levels. Haemoglobin electrophoresis confirmed haemoglobin genotype, and a peripheral blood film examination was conducted to check for cellular morphological anomalies.

2.5.1 Full Blood Count (FBC)

FBC was analysed using hematology autoanalyzer (Horiba Yumizen h500), haemoglobin was derived from the analysis.

2.5.2 Haemoglobin Electrophoresis

1.2 ml of blood was mixed with a haemolysing agent (1:6 ratio). The Haemolysate was loaded onto a cellulose acetate membrane in an electrophoresis apparatus set at pH 8.4. After applying electric current for 15 minutes, the membrane was stained, and bands were compared to control bands to identify haemoglobin variants.

2.5.3 ABO-Rhesus Blood Grouping

One drop of Anti-A, Anti-B, and anti-D sera was placed on a slide, one drop of blood was placed near each serum. It was gently mixed for 2 minutes and observed for agglutination, alongside the controls.

2.5.4 Peripheral Blood Film Examination

A blood drop was spread on a glass slide at a 30–45-degree angle to create a thin smear with a feathered edge, then air-dried. After staining with Leishman stain and rinsing, the slide was examined microscopically. Lower magnification assessed general cell distribution, followed by detailed analysis at 100x. Red blood cells were evaluated for size and shape abnormalities, white blood cells for numerical and morphological issues, and platelets for distribution. Significant findings suggestive of anaemia or infection were recorded.

2.5.5 Prothrombin Time

Blood sample was collected in a sodium citrate tube and was centrifuged for 15 minutes at 2500g. 200ul of PT reagent was placed in a test tube, incubated in water bath at 370c for 2 minutes. 100ul of the plasma was added and the timer was started immediately. Time taken for clot formation was measured and recorded. The PT is reported in seconds.

2.5.6 Activated Partial Thromboplastin Time (Aptt)

Blood sample was collected in a sodium citrate tube and centrifuged at 2500g for 15 minutes. 200µl of APTT reagent was incubated at 37°c for 2 minutes, followed by the addition of 100µl of plasma and another 2minutes incubation. After adding 100 µl of pre-warmed calcium chloride, the timer was started, and the clot formation time was measured and recorded in seconds.

2.5.7Fibrinogen Assay

This assay employs a sandwich ELISA technique:

2.5.7.1 Principle of Fibrinogen

The plate was pre-coated with an anti-fibrinogen antibody. The fibrinogen antigen in the sample binds to the plate-bound antibody. A biotinylated antibody is added, forming a sandwich complex with the bound antigen. A chromogen substrate is added, producing a blue colorimetric response. The colour intensity is directly proportional to the concentration of fibrinogen antigen.

2.5.8 D-Dimer Assay

This assay employs a sandwich ELISA technique:

2.5.8.1 The Principle of D-dimer*:*

The plate is pre-coated with an anti-D-dimer antibody. The D-dimer antigen in the sample binds to the plate-bound antibody. A biotinylated antibody is added, forming a sandwich complex with the bound antigen. A chromogen substrate is added, producing a blue colorimetric response. The colour intensity is directly proportional to the concentration of d-dimer antigen.

2.6 Statistical Analysis

The statistical analysis was conducted using R and Python.

2.6.1 R

This is a specialized language for statistical computing and graphics, often used in medical research for its comprehensive collection of statistical functions and user-friendly packages like dplyr, ggplot2, and tidyverse. R is well-suited for complex statistical modeling, exploratory data analysis, and visualization, making it popular among statisticians and biostatisticians.

2.6.2 Python,

This is a versatile language often used in machine learning, data analysis, and statistical computations. With libraries such as pandas, scipy, statsmodels, and matplotlib, Python is highly flexible and allows for integrating statistical analysis with automation, machine learning, and predictive modeling.

Table 1 shows the distribution of Hemoglobin genotypes by sex and sickle cell disease (SCD) diagnosis**.** The table presents the distribution of haemoglobin genotypes (SC, SS, AA, AC, AS) by sex and disease status (SCD and non-SCD).

Table 1: **The distribution of Hemoglobin genotypes by sex and sickle cell disease (SCD) diagnosis.**

Sex	**CASE (SCD)**		**CONTROL (non-SCD)**			**Total**	**%**
	SC	SS	AA	AC	AS		
Female	1	18	11	1	5	36	45%
Male	4	27	10	1	2	44	55%
Total	**5**	**45**	**21**	**2**	**7**	**80**	100%

Table 2 and figure 1Summary Statistics of coagulation and haematological profiles between the SCD diagnosis groups (CASE and CONTROL).

The reduced HCT in SCD patients is consistent with the lower RBC count and chronic anemia. It indicates the

reduced capacity of the blood to carry oxygen, which is a hallmark of SCD.The lower HGB levels in SCD patients are due to chronic hemolysis and reduced RBC count. This may contributes to the symptoms of fatigue and poor oxygenation commonly seen in these patients.

Table 2: Summary Statistics of coagulation and haematological profiles between the SCD diagnosis groups (CASE and CONTROL).

Variable	CASE *(n=50)* Mean ±SD	CONTROL *(n=30)* Mean ±SD	t-statistic	p-value
RBC (×10¹²/L)	2.702 ± 0.931	4.567 ± 0.668	-10.388	0.001*
HCT (%)	21.606 ± 4.762	37.333 ± 4.167	-15.478	0.001*
HGB (g/dl)	7.356 ± 1.54	12.413 ± 1.413	-14.977	0.001*
WBC (×10□/L)	11.193 ± 3.294	5.42 ± 1.219	11.182	0.001*
Platelets (×10□/L)	442.26 ± 218.712	253 ± 77.858	5.560	0.001*
PT (seconds)	18.56 ± 2.666	15.333 ± 2.67	5.236	0.001*
APTT (seconds)	46.58 ± 10.272	46.433 ± 5.788	0.082	0.935
Fibrinogen g/l	3.370 ± 0.692	3.188 ± 0.579	1.264	0.210
D-Dimer ng/ml	672.947 ± 138.325	637.512 ± 115.849	1.230	0.223

*** *p* is significant at 0.05**

Key: RBC- Red blood cells, HCT- Haematocrit, HGB-Haemoglobin, WBC-White blood cell, PT-Prothrombin Time, APTT- Activated partial thromboplastin time.

Figure 1: **Comparison of haematological and Coagulation Profiles in Sickle Cell Disease (Case) and Non-Sickle Cell (Control).**

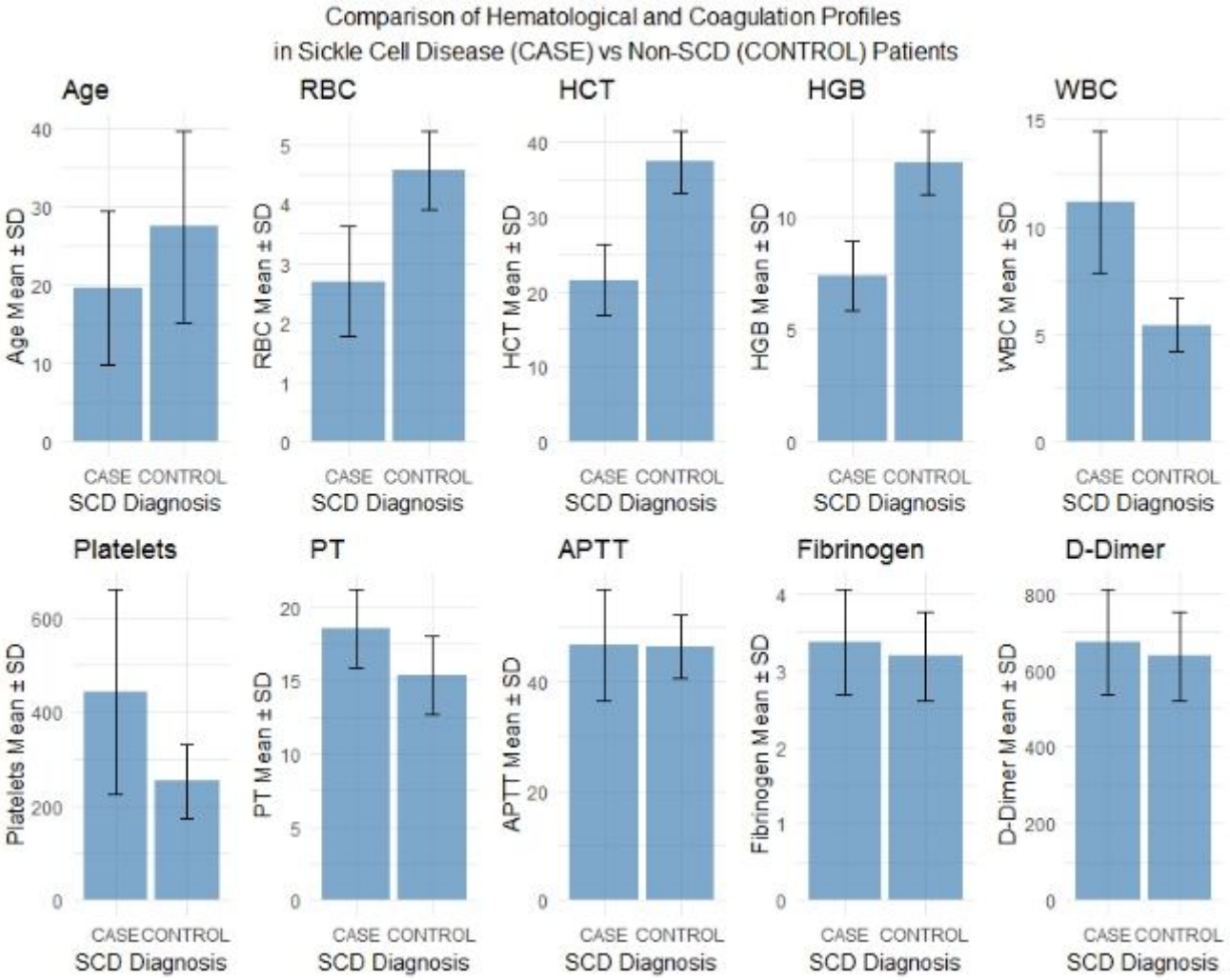

Table 3: T-test results comparing haematological profiles between sickle cell patients with and without leg ulcers

Statistical analysis of variables were compared in SCD with leg ulcer and non-leg ulcer with the corresponding *P* value.

Table 3: T-test results for comparing haematological profiles between sickle cell patients with and without leg ulcers.

Variables	t-statistics	*P*-value
RBC	-2.065	0.045*
HCT	-1.129	0.265
HGB	-0.676	0.503
WBC	2.330	0.024*
Platelets	3.303	0.002*
PT	1.281	0.206
APTT	-0.533	0.596
Fibrinogen	0.788	0.435
D-Dimer	0.842	0.406

***p* is significant at 0.05**

Figure 2 Coagulation profile in SCD Patients with and without Leg Ulcers

Figure 2. presents a boxplot to compare Prothrombin Time, APTT, Fibrinogen, and D-Dimer levels between SCD patients with and without leg ulcers.

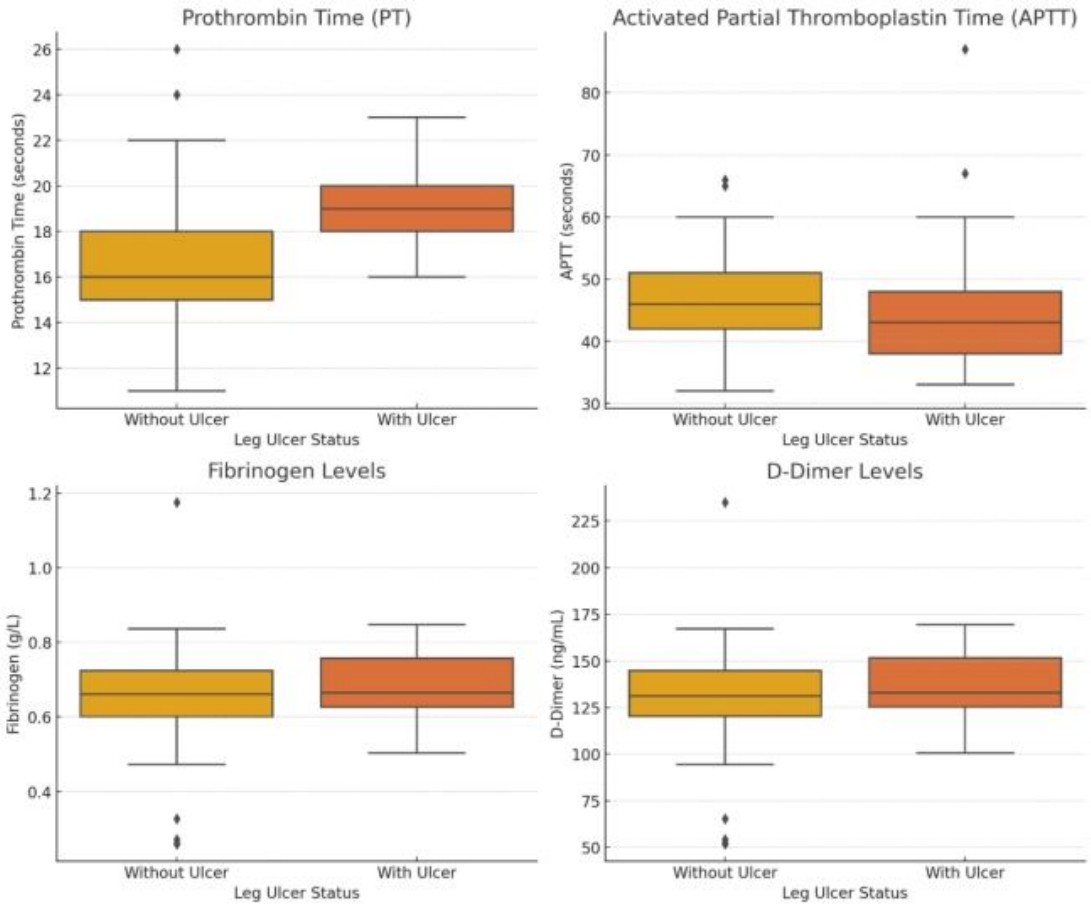

Figure 2Coagulation profile in SCD Patients with and without Leg Ulcers

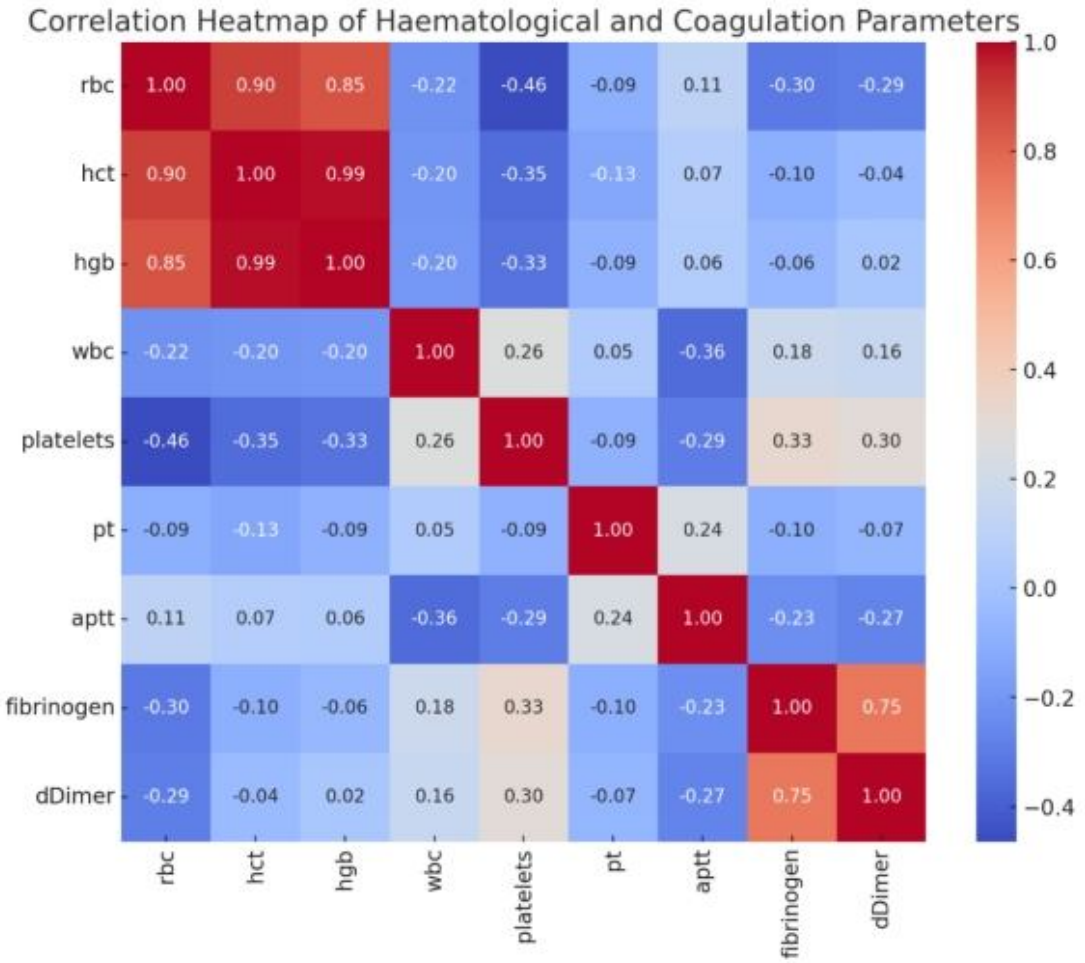

Figure 3 shows the correlation heatmap of all the variables. Indicating the correlation among them.

3.0 RESULTS AND DISCUSSION

3.1 The distribution of Hemoglobin genotypes by sex and sickle cell disease (SCD) diagnosis (Table 1).

The predominance of HbSS in the SCD group aligns with known epidemiology, as HbSS is the most common variant associated with sickle cell anaemia. HbSC, a milder variant, still leads to complications such as haemolysis and pain crises. The control group's high frequency of HbAA reflects the general population. Our study corroborates **[1]**, reporting Sickle cell anaemia as the most common form of SCD. The higher prevalence in males (62%) compared to females (38%) is clinically significant, with studies indicating increased incidence of complications like priapism **[15]**.

3.2 (Table 2 and Figure 1) Summary Statistics of coagulation and haematological profiles between the SCD diagnosis groups (CASE and CONTROL)

The summary statistics **(Table 2)** of haematological and coagulation profiles in Sickle Cell Disease (SCD) and controls show significantly lower mean RBC (*P*=.001), HCT (*P*=.001), and haemoglobin (*P*=0.001) in SCD individuals. Sickle cells are fragile, with a lifespan of 10–20 days, leading to chronic haemolysis. This aligns with **[16]**, who found lower Hb levels in HbSS compared to HbSC and HbAA participants.

3.2.1 White Cell Count

WBC count is significantly elevated in SCD patients compared to controls (*P*=0.001), likely due to chronic inflammation from vaso-occlusion and tissue ischemia. This stimulates increased white blood cell production. Our findings align with **[17]**, who reported mean WBC counts of 10.7±6.3, and **[18]**, who found 12.7±7.6 in Saudi adults with SCD.

3.2.2 Platelet count

The platelet count in SCD patients is significantly higher than in the control group (P=.001), likely due to compensatory mechanisms for chronic anemia and hemolysis or the hypercoagulable state in SCD. This finding aligns with **[19]**, who reported higher platelet counts in SCD participants.

3.2.3 Prothrombin Time

Additionally, our study showed increased PT in SCD patients (P=.001) and a slightly higher APTT (*P*=.93). Prolonged PT and APTT may result from reduced plasma levels of factor V **[20]** and total factor VII **[21]**, consistent with **[22]** and **[16]**.

3.2.4 Fibrinogen

Fibrinogen levels are slightly higher in the SCD group (mean 3.370 ± 0.692 g/L) withno statistical difference. *P*=0.21. This finding corroborates with the research done by **[23]**, with mean fibrinogen concentration of 314.3 ± 109.83 and 284.90 ± 83.46 mg/dL for SCA with and without chronic leg ulcer, respectively.

3.2.5 D-dimer

The D-Dimer, a marker of clot formation, is elevated in the SCD group (mean 672.947 ± 138.325 ng/mL) relative to the control (mean 637.512 ± 115.849 ng/mL), though not statistically significant p > 0.05 (0.223). Elevated D-dimer levels have been reported in SCA (HbSS) patients compared to HbAA controls **[24**]. Similarly,**[23]** in his study, reported a higher D-dimer in SCA with chronic leg ulcer compared to HbAA controls.

3.3 Analysis of Peripheral Blood Film (PBF) examination

80 haematological slides were examined for abnormalities in red cell morphology, white cells, and platelets. In the

case group, red cell abnormalities included sickle cells, Hb C crystals, target cells, red cell fragmentation, and nucleated red cells. White cell and platelet abnormalities observed included moderate leukocytosis, mild toxic granulation, thrombocytosis, macrothrombocytes, and platelet aggregation. In contrast, the control group exhibited only mild and clinically insignificant abnormalities.

3.4 Incidence of Leukaemia

Our study found no prevalence of leukemia among SCD patients compared to non-sickle cell individuals. The dataset contained no cases of leukemia in the peripheral blood film examination. WBC counts were 11.193 ± 3.294 in the case group and 5.42 ± 1.219 in controls, with a maximum count of 21.29. These findings support **[25]** and **[26]**, who reported no definitive relationship between SCD and malignancy.

3.5 T-test results for comparing haematological profiles between sickle cell patients with and without leg ulcers.

(Table 3) presents statistically significant differences in RBC (T-statistics: -2.065; *P*=.05), WBC, and platelet counts (T-statistics: 3.303; *P*=.002) between sickle cell patients with and without leg ulcers. RBC is lower in patients with leg ulcers, while WBC and platelet counts are higher, suggesting immune or inflammatory responses. However, haematocrit and hemoglobin levels did not show significant differences (*P*= .50 and *P*=0.27, respectively), indicating that these variables do not vary significantly in this sample.

3.6 Figure 2 Coagulation profile in SCD Patients with and without Leg Ulcers

Our study evaluated coagulation profiles (prothrombin time, APTT, D-Dimer, and fibrinogen levels) in 25 SCD participants with leg ulcers compared to 25 without. SCD patients with leg ulcers showed a higher median PT (t-statistic: 1.281; P=0.21), but this difference was not statistically significant. APTT medians were similar, with greater variability in patients without ulcers (t-statistic: -0.533; P=0.60). Fibrinogen levels and D-Dimer were slightly higher in patients with leg ulcers, but differences were not significant (t-statistic: 0.788; P=0.44; t-statistic: 0.842; P=0.41). These findings align with **[27]**, indicating no significant differences in coagulation profiles between groups.

3.7*Figure 3 correlation heatmap of haematological and coagulation parameters.*

The heatmap from our study indicates significant relationships among haematological and coagulation parameters in sickle cell patients. A strong positive correlation exists between red blood cell count (RBC) and haematocrit (HCT) (correlation ~ 0.93), indicating that HCT reflects the proportion of RBCs. Haemoglobin (HGB) also shows a strong correlation with RBC count (correlation ~ 0.87). HGB and HCT demonstrate a near-perfect correlation (correlation ~ 0.97), emphasizing their link to oxygen-carrying capacity. Conversely, a moderate

negative correlation exists between platelet counts and prothrombin time (PT) (correlation ~ -0.34), while D-Dimer levels decrease with increasing RBC counts (correlation ~ -0.28). D-Dimer also exhibits similar negative correlations with HCT and HGB (both ~ -0.24), suggesting reduced clotting activity in patients with better oxygen-carrying capacity. APTT and fibrinogen levels show weak correlations, indicating their independence from basic haematological parameters.

CONCLUSION

This study highlights the distinct haematological and coagulation profiles in SCD patients compared to non-SCD controls. Significant differences in RBC, WBC, and platelet counts were observed, while no association with increased leukemia incidence was found. Additionally, the absence of significant differences in coagulation parameters between SCD patients with and without leg ulcers underscores the complexity of managing SCD-related complications. These findings contribute to a better understanding of SCD's haematological profile and emphasize the need for ongoing research and tailored management strategies for affected individuals.

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