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EVALUATION OF VONWILLIEBRAND FACTOR LEVELS IN SICKLE CELL DISEASE PATIENTS WITH LEG ULCERS IN SOUTH-SOUTH NIGERIA

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ABSTRACT

Background: Leg ulcers contribute to significant morbidity in patients with sickle cell disease (SCD). Nigeria has the highest burden of SCD with about one-third of the patients having leg ulcers. Although several factors contribute to the development of leg ulcer, the role of Von Willebrand factor (VWF) has not been adequately explored globally. **Aim:** This study aimed at determining the levels of VWF in SCD patients with leg ulcers in Benin City, Nigeria. **Methods:** This was a hospital based comparative study conducted at the University of Benin Teaching hospital (UBRH) between June 2023 and November 2023 among SCD patients and healthy controls. Eighty-eight subjects including 33 SCD patients with leg ulcer, 33 SCD patients without leg ulcers and 22 Haemoglobin (Hb) AA controls were recruited. Blood samples were analyzed for VWF, full blood count (FBC), Prothrombin time (PT) and Activated partial thromboplastin time (APTT). FBC parameters were estimated using an auto analyser (Sysmex Haematology Autoanalyser model KN21. Coagulation parameters (PT and APTT) were estimated manually and VWF concentration was estimated using the enzyme linked immunosorbent assay method (ELISA). Human von Willebrand Factor ELISA Kit (Cat: ELK5248) was used. Data were analyzed using the statistical package for social sciences (SPSS) version 23. **Results:** The mean age (SD) of SCD patients with leg ulcers, SCD controls and HbAA controls were 29±6.6yrs, 29.3±5.9yrs and 29.9±6.7yrs respectively. The differences in mean age across the study groups were not statistically significant (p=0.932). The peak age range of SCD patients with leg ulcer was 25-29 years. 14 (57.6%) individuals with SCD with leg ulcers were

females and 14 (42.4%) were males. There was no statistically significant difference in the sex distribution between the case group and controls (p=0.521). The median VWF levels was higher in SCLU and SCD control groups compared to age and sex matched HbAA controls (2.56ng/ml, 2.09ng/ml and 2.00ng/ml respectively). The differences in median were not statistically significant (p= 0.273). The study did not find any significant association between the levels of VWF and the severity of leg ulcer (p=00.321). **Conclusion:** There was no significant association between VWF levels and SCLU in our study population.

KEYWORDS: Vonwilliebrand factor, sickle cell disease, leg ulcer, Nigeria.

INTRODUCTION

Sickle cell disease (SCD) is a genetic disorder resulting from the inheritance of the sickle β-globin gene (HbS). It is a group of haemoglobin disorders resulting in the inheritance of the sickle β-globin gene either in the homozygous state or double heterozygous state. When inherited in the homozygous state, it is termed sickle cell anaemia (SCA). Other known SCD genotypes include haemoglobin SC disease, sickle cell beta plus (HbS/β^{+}) thalassaemia, and sickle cell beta zero (HbS/β^{0}) thalassemia, haemoglobin SD disease, haemoglobin SE, haemoglobin SO disease.

It is one of the most common genetic diseases worldwide and it has its highest prevalence in Sub-Saharan Africa which accounts for about 80% of cases.[1] A World Health Organization (WHO) report estimated that around 2% of newborns in Nigeria were affected by sickle cell anaemia (SCA); giving a total of 150,000 affected children born yearly in Nigeria.[2] Another study reports that SCD affects about 2 to 3% of the Nigeria population of more than 200 million.[3] Nwogoh et al. in Benin City, South-South Nigeria reported a prevalence of 2.39% for SCD and a carrier rate of about 23%.[4]

The clinical manifestations of SCD are diverse and amongst them include leg ulcers which are relatively common and disabling. Chronic Leg ulcers are the commonest skin manifestation in SCD and they occur either spontaneously or as a result of local trauma. The healing rate of these ulcers is typically 3 to 16 times slower than for other forms of leg ulcers and they tend to reoccur.[5] The prevalence of leg ulceration varies with age and type of SCD. It rarely occurs before the age of 10 years and it is reported that between 8% and 10% of HbSS patients develop leg ulceration between the ages of 10 and 50 years.[6] It is most common in HbSS and less often seen in HbSC disease or HbS-β thalassemia. Its geographical

distribution is also variable, affecting 75% of HbSS patients in Jamaica but only 8–10% of North American patients.[7] Durosinmi et al reported a prevalence of 7.5% among 630 HbSS patients at Ibadan, Nigeria.[8]

Von Willebrand factor (VWF) is a large glycoprotein with multimers of about 2-50 dimeric subunits. It is synthesized by the endothelial cells and megakaryocytes. It is involved in the adhesion of sickled red blood cells to the endothelium by acting as an adhesive bridging molecule between red cell receptors and endothelial receptors.[9] Since endothelial dysfunction has been implicated in the pathophysiology of sickle cell leg ulcers (SCLU), VWF is a useful marker of endothelial dysfunction.[9] Several reports including those from Rees et al and Chen et al have demonstrated elevated levels of vWF in patients with SCD.[9-11] The plasma concentration of VWF is higher in patients with a genotype (HbSS or HbSβ°) compared to patients with a (HbSC or HbSβ+).[11]

The aetiology of leg ulcers in SCD is complex and multifactorial and not well understood, hence attempts at prevention have been disappointing. Management of sickle cell leg ulcers is often protracted, requiring a long stay in the hospital, thereby worsening both the economic and social well-being of affected persons. Thus, a clinical prediction based on biochemical markers seems a sensible approach to surveillance and prevention of complications of leg ulcers.

This study aims to evaluate the concentration of VWF as a marker of endothelial dysfunction in SCD patients with leg ulcers in Benin City, Nigeria with the hope of providing a baseline data for further research, including possible therapeutic interventions.

METHODOLOGY

Study Design

This study design was a comparative cross-sectional study.

Study Area

The study was conducted at the University of Benin Teaching Hospital (UBTH), Benin City, Nigeria. Participants were recruited from the Department of Haematology, Plastic and Burns Department both at UBTH and the Sickle cell centre Benin.

The University of Benin Teaching Hospital is a federal government owned hospital with over 800 bed spaces, located in Egor local government area, Benin City. The sickle cell centre is a

dedicated health facility with over 9 bed spaces established by the Edo State Government for the care of patients with SCD.

Study Duration

The study was terminated when the estimated sample size was realized. It was carried out within a period of 6 months (June 2023-November 2023).

Participants and Sampling Technique

Consecutive sampling technique was used for this study.The study participants were individuals with SCD aged 18 -45 years divided into two groups as follows

Group I: This consisted of SCD patients with leg ulcers aged between 18 and 45 years (both old and new). They were evaluated for VWF and haematological parameters like FBC and coagulation profile (Prothrombin time and Activated partial thromboplastin time).

Group II: This consisted of SCD patients in steady state without leg ulcers. They were matched for age and sex with those in group 1. They were also evaluated for VWF and similar haematological parameters as above.

Sample size estimation

Using the formula $n = \frac{z^2 pq}{d^2}$ to determine the mean sample size[12]

z = 1.96

p= 0.015

p=prevalence rate; (using a minimum prevalence of 1.5%)[13]

q =1-p =0.985

d= degree of error =0.05

n =minimum sample size = 23

M1inimum calculated sample size is 23; However 33 sickle cell patients with leg ulcer were recruited into the study.

Inclusion Criteria

- Sickle cell disease patients with leg ulcers, either bilaterally or unilateral with no history of trauma prior to onset. Ages between 18 – 45 years.
- Sickle cell disease patients in steady state, matched for sex and age
- Healthy individuals who have genotype AA matched for age and sex

Exclusion Criteria

- Participants on hydroxyurea due to its anti-inflammatory effect
- Participants on antiplatelet and anticoagulants
- Participants with co-existing illnesses that could contribute to inflammation. These include chronic hepatitis, lupus, arthritis, inflammatory bowel disease, chronic osteomyelitis, and other similar conditions
- Participants who have had an exchange transfusion either manual or automated in the last 3 months
- Ulcers secondary pentazocine abuse

Study Instrument

After obtaining consent, a study proforma was used to collect demography of study participants, medical history, drug history and history of complications. Thereafter, blood samples were collected for blood count, clotting profile and assessment of VWF.

Sample collection and analysis

Eight millilitres (mls) of venous blood was drawn aseptically from the antecubital vein of each subject with minimal stasis.

Four and a half (4.5mls) of whole blood for VWF and coagulation test (Prothrombin time and activated partial thromboplastin time) was dispensed into a sample bottle containing 0.5mls of 0.109M sodium citrate (3.2%). This was to obtain a blood: citrate ratio of 9:1. The sample was mixed by gentle inversion at least six times to ensure adequate mixing of the anticoagulant with the blood. The sample was transported in an ice pack to maintain viability from point of collection to the laboratory within two hours. The sample was centrifuged at room temperature at a speed of 2000 gravities (g) for 10mins to obtain platelet poor plasma. The plasma was carefully removed to prevent cell lysis with a plastic pipette into a plane bottle. The specimen was divided into three aliquots; one aliquot was used for Prothrombin and activated thromboplastin time assays, the other aliquot was used for VWF assay. The PT and APTT assays were analyzed immediately while that for VWF was immediately frozen at -80^0C till the study was completed.

The remaining volume of whole blood was dispensed into commercially prepared ethylene di-amine tetra-acetic acid (EDTA) bottle for full blood count. The sample was mixed gently

but thoroughly to prevent cell lysis and ensure anticoagulation. The EDTA sample was analysed immediately.

All specimens were labelled with personally generated identification numbers and recorded in the datasheet.

Test Procedures

Basic Haematological Parameters: Full blood count includes haematocrit, haemoglobin concentration, total white cell count and platelet counts was obtained from the EDTA sample, using automated blood cell counter (Sysmex Haematology Autoanalyser model KN21). The basic principles underlying this techniques are electronic impedance and light scatter. This was done in the main haematology laboratory, UBTH. Blood sample is aspirated and proportioned, then diluted to a pre-set ratio and labelled with a proprietary fluorescence marker that binds specifically to nucleic acids. Next the sample is transported into the flow cell. The sample is illuminated by a semiconductor laser beam, which can separate the cells using different signals.

The intensity of the forward scatter indicates the cell volume. The side scatter provides information about the internal cell structure and its content, such as nucleus and granules. The side fluorescence indicates the amount of nucleic acids present in the cell.

Haemoglobin Electrophoresis: The haemoglobin phenotypes of both subjects and healthy participants was confirmed using haemoglobin electrophoresis.

Determination of coagulation tests: Prothrombin time and activated partial thromboplastin time test was carried out for study group. This was done in the haematology Laboratory in UBTH Benin. See appendix II for materials and methodology.

Determination of VWF: The plasma level of VWF was evaluated using ELISA quantitation assay.

Data Analysis

Data obtained was analysed using Statistical Package for the social sciences (SPSS) version 23. Continuous variables (age, PT, APTT, VWF) were tested for normality. Normally distributed variables (age, WBC count and differentials, platelet count, HCT, PT, APTT) were summarized as mean, standard deviation and ranges while skewed variables (VWF

levels) were summarized as median and interquartile ranges. Comparison of mean between the groups for normally distributed continuous variables was done with the student t-test while Mann Whitney U test was used to compare differences in Median.

RESULTS

Demographics of the study population

A total of eighty-eight individuals participated in this study, comprising 33 SCD patients with sickle cell leg ulcers, 33 SCD controls (without leg ulcers) and 22 HbAA controls.

The age range of the SCD individuals with sickle cell leg ulcers (SCLU) was 20 – 45 years with a mean (SD) of 29.7±6.6yrs. The SCD controls had a mean(SD)age of 29.3±5.9yrs and HbAA controls 29.9 ± 6.7yrs. The differences in mean age across the study groups were not statistically significant (p=0.932). The peak age range of SCD SCLU was 25 – 29yrs. Nineteen (57.6%) individuals with SCD SCLU were females and 14 (42.4%) were males. The differences in the sex distribution between the study population was not statistically significant (p = 0.521) (Table 1).

The median age (IQR) at diagnosis of the disease was 4.0 (2.0-6.5)years. Majority (18, 54.5%) of the SCD SCLU population had secondary level education and 12 (36.4%) had tertiary level education.

Table 1: Sociodemographic characteristics of the study population.

	SCD SCLU n = 33	**SCD Control n = 33**	**HbAA Control n = 22**	χ^2	**P-value**
Age group (in years)					
20 – 24	6 (18.2)	6 (18.2)	4 (18.2)		
25 – 29	15 (45.5)	15 (45.5)	8 (36.4)		
30 – 34	5 (15.2)	6 (18.2)	5 (22.7)	0.731	0.999
35 – 39	4 (12.1)	3 (9.1)	3 (13.6)		
≥40	3 (9.1)	3 (9.1)	2 (9.1)		
Mean ± SD Range	29.7±6.6 20 – 45	29.3±5.9 21 – 45	29.9 ± 6.7 20 – 44	0.071	0.932
Age at SCD diagnosis(in years) Median IQR	4.0 2.0 – 6.5	4.0 2.0-6.0			0.553
Sex					
Male	14 (42.4)	13 (39.4)	12 (54.5)	1.305	0.521
Female	19 (57.6)	20 (60.6)	10 (45.5)		
Education					
Primary	3 (9.1)	3(9.1)		0.167	0.920

Secondary	18 (54.5)	19(57.6)			
Tertiary	12 (36.4)	11(33.3)			

Laboratory Parameters

Blood counts

The mean (SD) white blood cell count in the SCD SCLU group was higher than that of the SCD controls (12.9±7.3 x 10^9/L versus 9.7±3.6 x 10^9/L, p = 0.027). Similarly, the mean absolute neutrophils count (7.1±5.2 x 10^9/L vs. 5.2±2.2 x 10^9/L, p = 0.058) and mean absolute lymphocyte counts (4.8±2.2 x 109/L vs. 3.6±1.3 x 109/L, p = 0.009) were higher in the SCD SCLU group (Table 2). The mean monocyte count was however lower in the study group than in the SCD control group (0.7±0.4 x10^9 /L vs 0.8±1.1 x 10^9 /L) but the difference in mean was not statistically significant (p=0.573).

The mean haematocrit in the study group was 24.8±4.5% and that of the SCD control was 26.5±4.8 % and the mean difference was not statistically significant (P=0.148). The mean platelet count was higher in the SCD SCLU group (296.8±138.7x10^9 /L vs 272.5±82.7x10^9/L, p=0.391). (Table 2).

The mean prothrombin time in the SCD SCLU group was 16.6 ±1.2secs and in the SCD control 16.5±1.7 secs. The mean difference was not statistically significant (p= 0.869). The mean Activated prothrombin time was higher in SCD SCLU compared to SCD controls (45 ± 3.4secs versus 40.9± 4.4secs) and the mean difference was statistically significant, p= 0.001. (Table 2).

Table 2: Comparison of Haematological parameters between SCLU patients and SCA controls.

Laboratory Parameters	SCA SCLU n = 33 Mean ± SD	SCA Control n = 33 Mean ± SD	T test	P-value
WBC (x10^9/l)	12.9±7.3	9.7±3.6		0.027
ANC (x10^9/l)	7.1±5.2	5.2±2.2		0.058
ALC (x10^9/l)	4.8±2.2	3.6±1.3		0.009
Monocytes (x10^9/l)	0.7±0.4	0.8±1.1		0.573
Haematocrit (%)	24.8±4.5	26.5±4.8		0.148
Platelet count(x 10^9/l)	296.8±138.7	272.5±82.7		0.391
Stable HCT (%)	24.0±4.0	24.4±2.7		0.648
Prothrombin time(s)	16.6±1.2	16.5±1.7		0.869
APTT(s)	45.0±3.4	40.9±4.4		0.001

Compared to age- and sex-matched HbAA controls, SCD patients with leg ulcers, the median VWF level was also higher in the sickle cell disease population than HbAA controls (Table 3).

Table 3: Comparison of VWF levels between SCA SCLU, SCA controls and HBAA controls.

	SCD SCLU n = 33	SCD Control n = 33	HbAA Control n = 22	Statistics	P-value
VWF(ng/ml)	2.56 1.78 – 4.85	2.09 1.17 – 3.36	2.00 1.12 – 4.42	Kruskal Wallis	0.273

VWF Concentration and Severity of Leg ulcers

The differences in the median VWF levels between different stages of SCLU were not statistically significant (p value: 0.321 and 0.442 respectively).

Table 4: VWF and severity of leg ulcer.

	SCLU			
	Stage II	Stage III	Statistics	P –value
VWF (ng/ml)	3.10 1.11 – 5.79	2.46 1.90 – 3.35	Mann Whitney U	0.321

Correlations between VWF with haematological parameters, PT and APTT in SCD SCLU

There was no significant correlation between VWF in the SCD population with leg ulcers (r = -0.346, p = 0.146). However, there was a negative correlation between VWF and prothrombin time (r = -0.344, p = 0.050) and this was statistically insignificant. There were no statistically significant correlations between vWF and full blood count parameters.(Table 5)

Table 5: Correlations between VWF with Full blood count parameters, prothrombin time and activated partial thromboplastin time in SCD with SCLU.

	Vwf	
	R	p-value
WBC	-0.016	0.928
HCT	-0.100	0.581
ANC	-0.062	0.731
ALC	.115	0.522
Monocyte	-0.116	0.519
Platelet	-0.129	0.474
PT	-0.344	0.050*
APTT	-0.086	0.641

Correlations between VWF with FBC parameters, PT and APTT in SCD Controls

There were no statistically significant correlations between VWF, PT, APTT and haematologic parameters in the SCD controls. (Table 6).

Table 6: Correlations between VWF with FBC parameters, PT and APTT in SCA Controls.

	VWF	
	R	**p-value**
WBC	0.229	0.207
HCT	0.052	0.777
ANC	0.221	0.225
ALC	0.200	0.272
Monocyte	-0.132	0.471
Platelet	-0.084	0.649
PT	-0.045	0.808
APTT	0.004	0.981

DISCUSSION

Sickle cell leg ulcer contributes to significant morbidity in patients with SCD. Although there are various studies to understand the factors which contribute to the development of leg ulcers, the role of VWF has not been adequately explored globally (with Nigeria inclusive). This study was to determine the levels of VWF in SCD patients with leg ulcer and to determine the association of the concentrations of these markers with the severity of leg ulcer.

The median levels of VWF were higher in the SCD population compared to controls, however, the difference in the median across the study groups did not reach statistical significance This is consistent with findings in other studies that reported an increase in VWF in both steady state and in acute crises.[14-16] Nwagha et al. and Omer et al. reported a significantly higher level of VWF in the plasma of SCD than in controls.[17,18] The higher levels of VWF in SCD patients can be attributed to the fact that VWF is an acute phase protein and its level in the plasma can be elevated in several clinical situations especially those affecting the blood vessels. VWF is released in plasma due to the inflammatory process induced by the adhesion of sickled red blood cells to the endothelium leading to the narrowing of the vessel lumen and creating a high sheer effect. Adhesion of platelets to the adherent sickled cells and their activation will release more VWF.[18] The adhesion of sickle erythrocytes to VWF immobilized with endothelial cells increases haemolysis by reducing the transit time of sickled erythrocytes sufficiently to induce hemoglobin deoxygenation and

polymerization. Patients with high haemolytic rates are at risk of developing a syndrome characterized by pulmonary hypertension, priapism and leg ulcers.

This study did not find any correlation between the mean serum concentrations of VWF with the severity of leg ulcers. There was no other study to compare this finding in our study, hence there is need for further studies to demonstrate this relationship.

The mean WBC and its differentials were significantly higher in respondents with chronic leg ulcers than those with stable disease. This is similar to the studies by Nolan et al., Hassan et al. and Babalola et al. who reported the same trend in the United States of America (USA), Zaria and Ibadan respectively.[13,17,18] The difference in the level of WBC between the two groups could reflect an increased haemopoiesis associated with haemolysis and/or due to microbial colonization or infection of ulcers.[17]

The mean haematocrit (HCT) of leg ulcer patients in this study was lower than those of the control (SCA) group, however this was not statistically significant. This was consistent with similar studies by Babalola et al., Hassan et al. and Bazuaye et al.[13,19,20] As reported in these studies, the index study also noted a lower stable HCT level of the sickle cell leg ulcer population in comparison to the stable SCD group.[13,18,20] Chronic haemolysis is one of the major causes of reduced steady state haemoglobin in non-leg ulcer controls. Studies have shown that sickle cell anaemia patients with a low steady-state HCT are at increased risk of developing chronic leg ulcers and the HCT is a marker of the severity of haemolysis.[17]

The sickle cell leg ulcer group had higher number of platelets than the control group. This finding was similar to studies by Babalola et al. and Hassan et al in their different researches.[13,19] Hypercoagulability contributed by elevated platelet count may have a possible role in the causation of leg ulcer formation as it contributes to skin ischemia, resulting in friability and ulceration.[21] Sickle cell ulcers are characterized partly by an increase in clotting ability as a result of increased platelets, hypercoagulability and a measured increase in clotting factors at the wound itself.[21] Babalola et al. in their study noted that platelet was positively correlated with wound size.[13] Some authors, including Wirth et al. assert that an efficient decrease in the concentration of platelets may be therapeutic in the management of ulcers.[22,23]

Limitation of the study

Limited financial resources hindered recruitment of participants into the HbAA control group.

CONCLUSION

The following conclusions can be drawn from this study

1. VWF levels are higher in SCD patients with leg ulcer compared to those without leg ulcer but it is not statistically significant.
2. There was no statistically significant association between VWF levels and the severity of leg ulcers.

Recommendation

1. Routine evaluation of VWF levels in SCD patients with leg ulcers may not be justified.
2. A large sample size study probably a multicenter study is recommended to validate the findings of this study.

Conflict of interest

There was no conflict of interest between the authours.

REFERENCES

1. Vos T, Allen C, Arora M, Barber R. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *The Lancet*, 2016; 388(10053): 1545-1602.
2. World Health Assembly, 59. (2006). Sickle-cell anaemia: report by the Secretariat. World Health Organization. Available from https://iris.who.int/handle/10665/20890
3. Adewoyin AS. Management of sickle cell disease: a review for physician education in Nigeria (sub-Saharan Africa). Anemia, 2015; 2015(1): 791498.
4. Nwogoh B, Adewoyin AS, Iheanacho OE, and Bazuaye GN. Prevalence of haemoglobin variants in Benin City, Nigeria. Annals of Biomed. Sci., 2012; 11(2): 60–64.
5. Oluwatosin OM. Management of chronic leg ulcers in Nigeria; An update. J. Surg. Sci., 2007; 1: 6-13.
6. Durosinmi MA, Gevao SM, Esan GI. Chronic leg ulcers in sickle cell disease: experience in Ibadan, Nigeria. Afr., J. Med. Sci., 1991; 20(1): 11-14.

7. Minniti CP, Eckman J, Sebastiani P. Leg ulcers in sickle cell disease. AJH, 2010; 85(10): 831-833.
8. Konotey-Ahulu FID. Torrential epistaxis with symmetrical Facial-skin ulceration in Sickle-cell Anaemia. *BMJ*., 1965; 2(5466): 859-860.
9. Sins JWR, Schimmel M, Luken D. Dynamics of von Willebrand factor reactivity in sickle cell disease during vaso-occlusive crisis and steady state. J. Thromb Haemost, 2017; 15(7): 1392–1402.
10. Rees DC, Williams TN, Gladwin MT. Sickle cell disease. *The Lancet*, 2010*;* 376 (9757): 2018–2031.
11. Oladele SO, Olatunya OS, Ogundare EO, Fadare JO, Oluwayemi IO, Adeyefa EJ. The financial burden of sickle cell disease on households in Ekiti, Southwest Nigeria. Cli., Outcomes Res., 2015; 545-553.
12. Habibi A, Maryse E, Emmanuelle B, Maria D, Pagona F, Ersi V. Leg ulcers in sickle cell disease patients undergoing hydroxyurea therapy:insights from two large cohort studies. Blood, 2023; 142(1): 2500.
13. Babalola OA. Haematological indices of sickle cell patients with chronic leg ulcers on compression therapy. Afr J Lab., Med., 2020; 9(1): 1037.
14. Schnogj JJBJ, Kremer Hovinga JA, Krieg S, Akin S. ADAMTS13 activity in sickle cell disease. AJH, 2006; 81(7): 492–498.
15. Van der Land V, Peters M, Biemond BJ. Markers of endothelial dysfunction differ between subphenotypes in children with sickle cell disease. Thromb. Res., 2013; 132(6): 712–717.
16. Chen J, Hobbs WE, Le J, Lenting PJ. The rate of hemolysis in sickle cell disease correlates with the quantity of active von Willebrand factor in the plasma. Blood, 2011; 117(13): 3680–3683.
17. Nwagha TU, Nweke M, Ezigbo ED. Contributions of von Willebrand factor to clinical severity of sickle cell disease: a systematic review and metanalysis. Hematology, 2022; 27(1): 860-866.
18. Omer NE, Satti MH, Mohammed AO. Plasma level of von Willebrand factor: An indicator of severity in sickle cell disease. Sudan J. med. sci., 2009; 4(2).
19. Hassan A, Gayus DL, Abdulrasheed I, Umar MA, Ismail DL, Babadoko AA. Chronic leg ulcers in sickle cell disease patients in Zaria, Nigeria. Arch. Int. Surg., 2014; 4(3): 141–145.

20. Bazuaye GN, Nwannadi AI, Olayemi EE. Leg Ulcers in Adult sickle cell disease patients in Benin City, Nigeria. GJMS, 2010; 8(2): 190–194.
21. Cumming V, King L, Fraser R, Serjeant G, Reid M. Venous incompetence, poverty and lactate dehydrogenase in Jamaica are important predictors of leg ulceration in sickle cell anaemia. Br J Haematol, 2008; 142(1): 119–125.
22. Madu AJ, Ubesie A, Madu KA, Okwor B, Anigbo C. Evaluation of clinical and laboratory correlates of sickle leg ulcers. WRR., 2013; 21(6): 808-812.
23. Dirisu IM, Awodu OA, Nwogoh B. Evaluation of Endothelin-1 as a marker of endothelial activation in patients with sickle cell anaemia in a tertiary hospital in South-South Nigeria. African Journal of Tropical Medicine and Biomedical Research, 2023; 6(2): 20-34.