Original

Assessment of Haptoglobin, Creatinine and Novel Markers of AKI in Homozygous and Heterozygous Sickle Cell Disease Patients in Ekiti State.

[1]Kazeem Damilola Suleman, [1]Odeyinka Olufunsho Odewusi, [1]Adeola Olanrewaju Oluboyo, [1]Olajumoke Abosede Ekundayo, [1]Emmanuel Ewesim, [1]Jawadat Olalekan, [1]Gabriella Eyide, [1]Phillip-James Ifeanyichuckwu, [2]Ibrahim Folorunsho Abdulganeey

[1]*Department of Medical Laboratory Sciences, Afe Babalola University, Ado-Ekiti, Ekiti State.*
[2]*Medical Laboratory Department, Nigerian Navy College of Health Sciences, Offa, Kwara State.*
Corresponding author: Kazeem D. Suleman, Department of Medical Laboratory Sciences, Afe Babalola University, Ado-Ekiti, Ekiti State. kdsuleman@gmail.com: +2348056912317,

Article history: Received 30 June 2025, Reviewed 29 July 2025, Accepted for publication 10 March 2026

ABSTRACT

Background: Sickle cell disease (SCD) is characterised by the polymerisation of haemoglobin S (HbS) under low oxygen conditions, causing red blood cells to become rigid and sickle-shaped. The occurrence of renal complications following this abnormality has been a matter of concern. This study was conducted to assess serum haptoglobin, creatinine, markers of Acute Kidney Injury (AKI), and selected haematological parameters in subjects with sickle cell disease in Ekiti State.
Methods: A total of sixty-six (66) subjects, comprising thirty-seven (37) sickle cell disease patients and twenty-nine (29) controls, were recruited for this study. Their demographic data were collected, and 5 mL of venous blood was drawn for laboratory analysis. Human haptoglobin (HP), Kidney Injury Molecule-1 (KIM-1), Neutrophil Gelatinase-Associated Lipocalin (NGAL), and Interleukin-18 (IL-18) were measured using ELISA, while Creatinine (Cr) was analysed using Jaffe's alkaline picrate method. Full blood count was performed using a Mindray BC-5000 haematology analyser.
Results: The results from homozygous (HbSS) subjects, especially those in crisis, showed significantly ($p< 0.05$) worse anaemia, thrombocytosis, and higher AKI markers. The correlation analysis of this study revealed that total white blood cells correlated with creatinine, and HP correlated with NGAL among homozygous SCD subjects in crisis.
Conclusion: The findings indicate that inflammation and haematological abnormalities are hallmarks of SCD. There are notable renal and haematological changes in SCD, particularly in homozygous individuals during vaso-occlusive crisis. Therefore, KIM-1 and NGAL are more effective markers of kidney injury, as they can be elevated in both steady and crisis states, regardless of zygosity.

Keywords: sickle cell disease, acute kidney injury, KIM-1, NGAL, interleukin-18, haptoglobin, creatinine.

How to cite this article

Suleman KD, Odewusi OO, Oluboyo AO, Ekundayo OA, Ewesim E, Olalekan J, Eyide G, Ifeanyichukwu P, Abdulganeey IF. Assessment of Haptoglobin, Creatinine and Novel Markers of AKI in Homozygous and Heterozygous Sickle Cell Disease Patients in Ekiti State. The Nigerian Health Journal 2026; 26(1): 68 – 83.
https://doi.org/10.71637/tnhj.v26i1.1144

INTRODUCTION

Sickle cell disease is a genetic haemoglobin disorder present predominantly in Africans and Hispanics. The disease is defined by the inheritance of one mutated haemoglobin gene, HbS, alone or in combination with other sickle haemoglobin genes. The aetiology of sickle cell disease is due to a single-nucleotide mutation in the beta globin gene on the short arm of chromosome 11. It is the most prevalent inherited haematological disorder, affecting approximately 12,000 to 15,000 individuals and estimated to have 250,000 carriers of the sickle cell gene.[1] This inherited haematological disorder has a high prevalence in the Nigerian population [2]. The resultant haemoglobin S (HbS) tends to polymerise when oxygen tension is low, leading to rigidity of red blood cells and the adoption of a sickled morphology.[3] These deformed red cells trigger activation of other blood cells, for example, neutrophils, and also of the endothelial lining of blood vessels by similar mechanisms found in vasculopathies. Through this, the targeted tissues lose their blood perfusion, and the resulting ischemia leads to infarction of the tissues.[4] Clinical manifestations of sickle cell disease typically begin at the age of 5 to 6 months[3]. Sickle cell disease is a condition that may lead to death, and it has periodic pain crises and is highly associated with an increase in estimated glomerular filtration rate (eGFR) and CKD onset.[5]

Kidney presentations of SCD are typically less severe in compound heterozygous mutations like HbSC and HbSβ+-thalassemia. The illness is fairly mild or absent in individuals who have the sickle cell trait.[6] Whether sickle cell disease is associated with acute kidney injury (AKI) in sickle cell disease is a field not well studied.

Haptoglobin (HP) is a serum glycoprotein with significant functions in the prevention of blood toxicity and inflammation in SCD patients, in addition to playing a central role in the treatment of hemolysis secondary to SCD complications[7]. HP, being a natural scavenger, binds free haemoglobin (Hb) produced due to hemolytic processes, thereby preventing its deleterious effect on the vascular and renal system[8]. Experiments using the employment of haptoglobin in therapy have shown it to modulate nitric oxide signalling effectively, reduce oxidative stress, and enhance erectile function in mouse models of sickle cell disease (SCD), potentially excluding priapism[9]. Free heme, a byproduct of hemolysis, is an erythrocytic danger-associated molecular pattern (eDAMP) and exacerbates vaso-occlusive crises, acute lung injury, and other SCD-linked complications.[10] Current therapeutic strategies are largely aimed at raising levels of normal haemoglobin, stimulating fetal haemoglobin, and restoring nitric oxide signalling[11]. Current studies indicate that leveraging endogenous mechanisms of haemolysis product clearance, such as pathways for heme scavenging, may hold promise in the treatment of SCD.[11]

Creatinine is a nitrogenous non-protein metabolite resulting from the metabolism of creatine and creatine derivatives. Its production is in the liver, pancreas, and kidneys via transamination of amino acids arginine, glycine, and methionine.[12] Increased serum creatinine can occur through increased production of creatinine or impaired tubular secretion of creatinine.[13] The only major drawback of creatinine as a marker of glomerular and renal function is that serum creatinine level cannot accurately measure early glomerulopathy in sickle cell disease (SCD), owing to increased estimated glomerular filtration rate (eGFR), reduced muscle mass, and increased tubular secretion among SCD patients.[14] Although creatinine is traditionally used as a marker, it inherently possesses limitations in accurately measuring renal damage in SCD patients.[15] As new biomarkers like cystatin C, β2-microglobulin, NGAL, and KIM-1 have been found to be valuable for early detection of renal damage[16], they could potentially be employed to supplement monitoring with serum creatinine or enhance the diagnostic accuracy of AKI. The sources, physiological functions, kinetics, and sensitivity of these biomarkers after renal damage vary considerably.[17]

Neutrophil Gelatinase-Associated Lipocalin (NGAL) is a 25 kDa neutrophil gelatinase-associated glycoprotein. It is constitutively produced in tissues like the lungs, stomach, colon, and the proximal tubular epithelial lining. NGAL is induced early in injury as a response to nephrotoxicity or ischaemic kidney injury and also works as a prognostic marker for AKI.[18] The nephrotoxic or ischaemic kidney insults induce the up-regulation of NGAL transcription and protein expression, which can be measured by increased levels of urinary and plasma NGAL.[18] The predominant production sites of NGAL in the kidney are the Henle's loop thick ascending limb and the collecting duct intercalated cells.[19] The levels of NGAL can increase within three hours after injury, peak from six to twelve hours, and may last as long as five days, depending on the severity of injury.

Kidney Injury Molecule-1 (KIM-1) is a transmembrane type 1 protein with mucin and immunoglobulin-like extracellular domains. Under constitutive expression in normal kidney, it is low but is up-regulated in the

Print ISSN: 0189-9287 Online ISSN: 2992-345X

proximal tubule after post-ischemic injury. KIM-1 is increased in expression following ischemic damage to the proximal tubular cells, and its extracellular domain is secreted to urine.[20]

Interleukin 18 (IL-18), a cytokine of 22 kDa molecular weight with pro-inflammatory activity. It is detectable in distal collecting tubule cells following ischemic events. IL-18 has been recognised as an early and sensitive AKI biomarker, with its levels increasing dramatically before any increase in creatinine.[21]

New markers like kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL) have been evaluated as potential markers to evaluate kidney function in SCD.[22,23] Increased levels of cystatin C and KIM-1 have been documented in patients with SCD compared to controls and are potential markers for the detection of kidney injury.[16] However, results for NGAL and KIM-1 have been inconsistent across studies.[23] Further research is needed to establish the most effective biomarkers for the early detection of kidney complications in SCD patients.

This study assessed serum haptoglobin, creatinine, markers of AKI (NGAL, KIM-1 & Interleukin-18) and haematological parameters in homozygous and heterozygous sickle cell disease subjects in Ekiti State, Nigeria.

METHODOLOGY

***Study Design*:** This was a comparative cross-sectional and case-control study among heterozygous and homozygous sickle cell disease subjects in Ekiti State. It was carried out in the departments of Haematology and Chemical Pathology of the Federal Teaching Hospital, Ido-Ekiti (FETHI), over a period of four months. FETHI is a tertiary hospital situated within the jurisdiction of Ido-Osi Local Government Area in Ekiti State, Nigeria. It is a tertiary healthcare facility established to provide sophisticated medical services, function as a referral institution, and facilitate clinical research and medical education. The diagnostic laboratories within the hospital are equipped with state-of-the-art facilities for comprehensive haematological and biochemical evaluations and biomarker assessments. Given its capacity and access to a substantial cohort of patients suffering from sickle cell disease (SCD), FETHI represents an exemplary environment for conducting research aimed at evaluating haptoglobin levels, creatinine, and novel markers of acute kidney injury (AKI) in individuals diagnosed with sickle cell disease.

Sample Size: The sample size was calculated using Fisher's formula for a cross-sectional study.

$$N = \frac{Z^2P(1-P)}{d^2},$$

where N = Minimum sample size,

Z = Normal standard deviation at 95% confidence interval = 1.96,

d = degree of precision = 5%, and

P = proportion of the SCD patient, which was 3.0% from a previous study[24].

This formula gave a minimum sample size of 50 after including a 10% attrition rate.

Study Participants: A total of sixty-six (66) subjects, comprising thirty-seven (37) sickle cell disease and twenty-nine (29) control subjects, made up of a mix of other genotypes, were recruited for this study. However, the test group comprised twenty-eight (28) homozygous SCD subjects and nine (9) heterozygous SCD subjects. The homozygous SCD subjects comprised two groups of twelve (12) subjects who were in vaso-occlusive crisis and sixteen (16) who were at steady state. The heterozygous SCD subjects comprised two groups of five (5) subjects who were in crisis and four (4) who were at steady state.

Data Collection: A self-administered questionnaire was used to obtain information on demography and medical history. Five (5) mL of venous blood was collected from the antecubital fossa of each subject, and 2.5 mL of blood was dispensed into serum separator bottles. The samples were allowed to clot, and then spun at 5,000 rpm for 5 minutes. The serum was separated and then kept frozen at -20°C until analysis. 2.5 millilitres of blood were dispensed into EDTA anticoagulant bottles. It was mixed gently by inversion and then immediately taken to the laboratory for a full blood count. Human haptoglobin (HP), Kidney Injury Molecule -1 (KIM-1), Neutrophil Gelatinase-Associated Lipocalin (NGAL) and Interleukin-18 (IL-18) were assayed using the ELISA technique (ElabScience kit), and creatinine (Cr) was assayed using Jaffe's alkaline picrate method (Agappe kit). Haematological parameters were determined through a full blood count on a Mindray BC-5000 haematology analyser.

Statistical Analysis: The Statistical Package for Social Sciences (SPSS version 25.0 software by SPSS Inc., Chicago, Illinois, USA) was used to analyse the data generated from this study. All data were expressed as mean ± SD. Student's t-test was used to compare biomarker levels. One-way analysis of Variance

The Nigerian Health Journal, Volume 26, Issue 1
Published by The Nigerian Medical Association, Rivers State Branch.

Print ISSN: 0189-9287 Online ISSN: 2992-345X

(ANOVA) and post-hoc Tukey's test were used to assess group differences, and Pearson's correlation test was used to test the association between continuous variables. The threshold for acceptable significance was set at $p < 0.05$. All results were presented in tables and charts.

Ethical Approval: Ethical approval was obtained from the Ethics and Research Committee, College of Medicine and Health Sciences, Afe Babalola University, Ado-Ekiti, Ekiti State (ABUADHREC/27/03/2025/626) and the Human Research and Ethics Committee, Federal Teaching Hospital, Ido Ekiti (ERC/2025/03/24/1227B). Informed consent was obtained from all participants, and the confidentiality of the provided information was ensured throughout the study.

RESULTS

Demographic characteristics of the SCD subjects: Table 1 outlines the demographic characteristics of the study participants. Findings reveal that within the age classifications, 18 participants (48.65%) are in the 5 – 10 years category, 14 (37.84%) are in the 11 – 20 years category, 4 (10.81%) fall within the 21 – 30 years category, and 1 (2.70%) belongs to the 31 – 40 years category. In terms of gender classification, 18 participants (48.65%) were identified as male, whereas 19 (51.35%) were classified as female. Regarding genotype classification, 28 participants (75.68%) were identified as homozygous SCD, while 9 participants (24.32%) were categorised as heterozygous SCD. At the time of the study, 17 participants (45.95%) were suffering from a vaso-occlusive crisis, while 20 participants (51.3%) were in a stable condition.

Haptoglobin, creatinine, AKI markers and haematological parameters of SCD subjects and controls: Table 2 shows the haptoglobin, creatinine, haematological parameters and AKI markers of SCD subjects and the controls. The results obtained showed that the creatinine concentration for SCD subjects and controls was 194.3 ± 180.0 and 73.5 ± 33.1, KIM-1 was 5.4 ± 4.9 and 0.7 ± 0.4, NGAL was 73.4 ± 20.2 and 48.7 ± 4.8, IL-18 was 165.7 ± 92.7 and 58.4 ± 18.0, HP was 80.7 ± 47.1 and 140.6 ± 32.4, PCV was 30.2 ± 8.7 and 37.8 ± 2.9, Hb was 10.5 ± 3.7 and 13.7 ± 1.9, WBC was 12.8 ± 8.6 and 7.5 ± 2.3, while PLT was 435.9 ± 8.6 and 279.2 ± 83.3 respectively. Creatinine, KIM-1, NGAL, IL-18, WBC, and PLT levels were significantly ($p<0.05$) high in the SCD subjects compared to the controls, while PCV, Hb, and HP levels were notably reduced in the SCD participants in contrast to the controls.

Table 1: Demographic characteristics of the SCD subjects

Variables	Number Observed	Frequency (%)
Age (years)		
5 – 10	18	48.65
11 – 20	14	37.84
21 – 30	4	10.81
31 – 40	1	2.70
Gender		
Male	18	48.65
Female	19	51.35
Status		
Homozygous	28	75.68
Heterozygous	9	24.32
Health Condition		
Crisis	17	45.95
Steady	20	24.32

The Nigerian Health Journal, Volume 26, Issue 1
Published by The Nigerian Medical Association, Rivers State Branch.

Print ISSN: 0189-9287 Online ISSN: 2992-345X

Table 2: Haptoglobin, creatinine, AKI markers and haematological parameters of SCD subjects and controls.

Variables	SCD Subjects Mean ± SD N = 37	Controls Mean ± SD N = 30	t-value	p-value
Creatinine (µmol/L)	194.3 ± 180.0	73.5 ± 33.1	2.096	0.042*
KIM-1 (pg/mL)	5.4 ± 4.9	0.7 ± 0.4	4.027	0.000*
NGAL (pg/mL)	73.4 ± 20.2	48.7 ± 4.8	6.068	0.000*
IL-18 (pg/mL)	165.7 ± 92.7	58.4 ± 18.0	5.455	0.000*
HP (ng/mL)	80.7 ± 47.1	140.6 ± 32.4	6.770	0.000*
PCV (%)	30.2 ± 8.7	37.8 ± 2.9	8.908	0.000*
Hb (g/dL)	10.5 ± 3.7	13.7 ± 1.9	9.272	0.000*
WBC (x10⁹ cells/L)	12.8 ± 8.6	7.5 ± 2.3	5.541	0.000*
PLTs (x10⁹ cells/L)	435.9 ± 225.7	279.2 ± 83.3	5.192	0.000*

*Values are significantly different at $p<0.05$

Keys: KIM-1: Kidney Injury Molecule-1, **NGAL**: Neutrophil Gelatinase-associated Lipocalin, **HP**: Haptoglobin, **PCV**: Packed Cells Volume, **Hb**: Haemoglobin concentration, **WBC**: White Blood Cells Count, **PLTs**: Platelets count.

Haptoglobin, creatinine, AKI markers and haematological parameters of homozygous SCD subjects and controls.

Table 3 shows the haptoglobin, creatinine, novel AKI markers and haematological parameters of homozygous SCD (HbSS) subjects and controls. The results obtained showed that the creatinine concentration for homozygous SCD subjects and controls was 200.1 ± 197.7 and 73.5 ± 33.1, KIM-1 was 7.9 ± 5.1 and 0.7 ± 0.4, NGAL was 84.5 ±14.7 and 48.7 ± 4.8, IL-18 was 209.2 ± 70.4 and 58.4 ± 18.0, HP was 55.6 ± 25.0 and 140.6 ± 32.4, PCV was 22.0 ± 3.8 and 37.8 ± 2.9, Hb was 7.1 ± 1.0 and 13.7 ± 1.9, WBC was 18.5 ± 9.2 and 7.5 ± 2.3, while PLT was 603.7 ± 208.8 and 279.2 ± 83.3 respectively. KIM-1, NGAL, IL-18, WBC, and PLT levels were notably elevated in subjects with SCD compared to the control group, whereas PCV, Hb, and HP values were significantly reduced in homozygous SCD subjects relative to the controls. Nonetheless, there was no statistically significant difference observed in the creatinine levels between homozygous individuals and the controls.

Haptoglobin, creatinine, novel AKI markers and haematological parameters of heterozygous SCD subjects and controls.

Table 3 showed that the creatinine concentration for heterozygous SCD subjects and controls was 182.01 ± 65.13 and 73.5 ± 33.1, KIM-1 was 3.48 ± 0.92 and 0.7 ± 0.4, NGAL was 65.20 ± 6.28 and 48.7 ± 4.8, IL-18 was 140.00 ± 58.40 and 58.4 ± 18.0, HP was 90.78 ± 29.00 and 140.6 ± 32.4, PCV was 35.22 ± 6.38 and 37.8 ± 2.9, Hb was 12.47 ± 1.90 and 13.7 ± 1.9, WBC was 11.47 ± 5.95 and 7.5 ± 2.3, while PLT was 248.44 ± 55.51 and 279.2 ± 83.3 respectively. The levels of creatinine, KIM-1, NGAL, IL-18, and WBC were notably elevated in the heterozygous SCD participants compared to the control group, while HP was significantly lower in the heterozygous SCD participants in relation to the controls. However, there were no statistically significant differences observed between the WBC, Hb, and PCV values of the heterozygous SCD participants and those in the control group.

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Table 3: Haptoglobin, creatinine, AKI markers and haematological parameters of homozygous SCD (HbSS) subjects, Heterozygous SCD (HbSC) and controls.

Variables	HbSS Subjects Mean ± SD N = 28	Controls Mean ± SD N = 30	t-value	p-value	HbSC Subjects Mean ± SD N = 9	Controls Mean ± SD N = 30	t-value	p-value
Creatinine (µmol/L)	200.1 ± 197.7	73.5 ± 33.1	1.883	0.068	182.01 ± 65.13	73.5 ± 33.1	4.655	0.000*
KIM-1 (pg/mL)	7.9 ± 5.1	0.7 ± 0.4	4.419	0.000*	3.48 ± 0.92	0.7 ± 0.4	8.713	0.000*
NGAL (pg/mL)	84.5 ±14.7	48.7 ± 4.8	7.259	0.000*	65.20 ± 6.28	48.7 ± 4.8	6.457	0.000*
IL-18 (pg/mL)	209.2 ± 70.4	58.4 ± 18.0	6.354	0.000*	140.00 ± 58.40	58.4 ± 18.0	4.212	0.001*
HP (ng/mL)	55.6 ± 25.0	140.6 ± 32.4	8.096	0.000*	90.78 ± 29.00	140.6 ± 32.4	3.517	0.003*
PCV (%)	22.0 ±3.8	37.8 ± 2.9	17.766	0.000*	35.22 ± 6.38	37.8 ± 2.9	1.727	0.093
Hb (g/dL)	7.1 ± 1.0	13.7 ± 1.9	16.504	0.000*	12.47 ± 1.90	13.7 ± 1.9	1.764	0.086
WBC (x10^9 cells/L)	18.5 ± 9.2	7.5 ± 2.3	6.374	0.000*	11.47 ± 5.95	7.5 ± 2.3	3.092	0.004*
PLTs (x10^9 cells/L)	603.7 ± 208.8	279.2 ± 83.3	7.873	0.000*	248.44 ± 55.51	279.2 ± 83.3	1.036	0.307

*Values are significantly different at $p<0.05$
Keys: KIM-1: Kidney Injury Molecule-1, **NGAL**: Neutrophil Gelatinase-associated Lipocalin, **HP**: Haptoglobin, **PCV**: Packed Cells Volume, **Hb**: Haemoglobin concentration, **WBC**: White Blood Cells Count, **PLTs**: Platelets count.

Haptoglobin, creatinine, novel AKI markers and haematological parameters of steady homozygous SCD and homozygous SCD subjects in crisis.

Table 4 presents the concentrations of serum haptoglobin, creatinine, novel acute kidney injury (AKI) biomarkers, and haematological parameters among stable homozygous sickle cell disease (SCD) subjects and those experiencing a crisis. The findings indicated that the creatinine levels for stable homozygous SCD and SCD subjects in crisis were recorded at 132.3 ± 54.6 and 206.9 ± 173.0, respectively; KIM-1 values were 5.8 ± 3.8 and 9.5 ± 5.0; NGAL measured 75.1 ± 9.5 and 98.1 ± 9.1; IL-18 concentrations were 168.7 ± 39.9 and 268.1 ± 63.8; haptoglobin (HP) levels were 68.3 ± 22.9 and 37.3 ± 14.7; packed cell volume (PCV) was consistent at 22.0 ± 3.9 and 22.0 ± 3.6; hemoglobin (Hb) was recorded at 7.6 ± 1.1 and 6.4 ± 0.3; white blood cell (WBC) counts were 20.3 ± 11.1 and 16.0 ± 5.2; and platelet (PLT) counts were 615.0 ± 214.9 and 588.8 ± 208.6, respectively. The levels of creatinine, KIM-1, NGAL, and IL-18 were found to be markedly higher in the homozygous SCD subjects experiencing a crisis compared to those in a steady state, while HP and Hb levels were notably lower in the crisis-affected homozygous SCD subjects in comparison to their steady counterparts. However, there were no statistically significant differences observed in the PCV, WBC, and PLT measurements between the two groups.

Haptoglobin, creatinine, AKI markers and haematological parameters of steady heterozygous SCD and heterozygous SCD in crisis.

Table 4 shows the levels of serum haptoglobin, creatinine, novel AKI markers and haematological parameters of steady heterozygous SCD and heterozygous SCD subjects in crisis. The results obtained showed that the creatinine concentration for steady heterozygous and heterozygous SCD subjects in crisis was 129.0 ± 20.0 and 224.4 ± 55.9, KIM-1 was 3.1 ± 0.5 and 3.8 ± 1.1, NGAL was 61.2 ± 6.7 and 68.4 ± 4.0, IL-18 was 83.5 ± 17.3 and 185.2 ± 29.2, HP was 109.8 ± 28.4 and 75.6 ± 20.7, PCV was 41.0 ± 2.9 and 30.6 ± 3.8, Hb was 14.0 ± 0.8 and 11.2 ± 1.6, WBC was 5.6 ± 0.6 and 16.2 ± 2.8, while PLT was 287.8 ± 46.1 and 217.0 ± 42.3 respectively. The values of creatinine, IL-18 and WBC were significantly higher in the heterozygous SCD subjects in crisis relative to the steady heterozygous SCD subjects, while PCV, Hb and PLT were significantly lower in the heterozygous SCD subjects in crisis relative to the steady homozygous SCD subjects. However, there was no statistically significant difference between the KIM-1, NGAL, and HP values of the two groups.

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Table 4: Haptoglobin, creatinine, novel AKI markers and haematological parameters of homozygous SCD (HbSS) and heterozygous SCD (HbSC) in steady and crisis.

	HbSS Subjects				HbSC Subjects			
Variables	**Steady Mean ± SD N = 16**	**Crisis Mean ± SD N = 12**	**t-value**	**p-value**	**Steady Mean ± SD N = 4**	**Crisis Mean ± SD N = 5**	**t-value**	**p-value**
Creatinine (µmol/L)	132.3 ± 54.6	206.9 ± 173.0	2.075	0.049*	129.0 ± 20.0	224.4 ± 55.9	3.212	0.015*
KIM-1 (pg/mL)	5.8 ± 3.8	9.5 ± 5.0	2.081	0.049*	3.1 ± 0.5	3.8 ± 1.1	1.312	0.321
NGAL (pg/mL)	75.1 ± 9.5	98.1 ± 9.1	6.524	0.000*	61.2 ± 6.7	68.4 ± 4.0	2.005	0.085
IL-18 (pg/mL)	168.7 ± 39.9	268.1 ± 63.8	7.200	0.000*	83.5 ± 17.3	185.2 ± 29.2	6.114	0.000*
HP (ng/mL)	68.3 ± 22.9	37.3 ± 14.7	4.891	0.000*	109.8 ± 28.4	75.6 ± 20.7	2.094	0.074
PCV (%)	22.0 ± 3.9	22.0 ± 3.6	0.000	1.000	41.0 ± 2.9	30.6 ± 3.8	4.444	0.003*
Hb (g/dL)	7.6 ± 1.1	6.4 ± 0.3	3.675	0.001*	14.0 ± 0.8	11.2 ± 1.6	3.167	0.016*
WBC (x10⁹ cells/L)	20.3 ± 11.1	16.0 ± 5.2	1.226	0.231	5.6 ± 0.6	16.2 ± 2.8	7.497	0.000*
PLTs (x10⁹ cells/L)	615.0 ± 214.9	588.8 ± 208.6	7.873	0.000*	287.8 ± 46.1	217.0 ± 42.3	2.399	0.048*

*Values are significantly different at $p<0.05$

Keys: KIM-1: Kidney Injury Molecule-1, **NGAL**: Neutrophil Gelatinase-associated Lipocalin, **HP**: Haptoglobin, **PCV**: Packed Cells Volume, **Hb**: Haemoglobin concentration, **WBC**: White Blood Cells Count, **PLTs**: Platelets count.

Analysis of variance and post-hoc test for effects of SCD in crisis on haptoglobin, creatinine, markers of AKI and haematological parameters.

Table 5 shows the analysis of variance (ANOVA) between HbSS subjects in crisis, HbSC subjects in crisis, and the control for the mean ± SD values of their haptoglobin, creatinine, KIM-1, NGAL, IL-18 and haematological parameters. The mean ± SD values of PCV, Hb, WBC, and HP of the HbSS subjects undergoing crisis are significantly lower (p values < 0.05) than those of HbSC subjects undergoing similar crises and those of controls.

Similarly, the mean ± SD of PLTs, NGAL, KIM-1 and IL-18 for HbSS subjects undergoing crisis were significantly higher (p-value < 0.05) than those of the HbSC subjects undergoing crisis and those of the control. However, the mean ± SD of creatinine in the HbSS subjects undergoing crisis had no significant difference from the HbSC subjects undergoing a similar crisis.

The post-hoc analysis showed that the statistically significant differences in the means of HbSS subjects undergoing crisis and HbSC subjects undergoing crisis for WBC (x 10^6 cells/L) were not truly significant (p-value > 0.05). Also, the mean difference observed between HbSC subjects undergoing crisis and controls for platelet counts (x 10^9 cells/L) was not significant (p-value > 0.05). As for the mean creatinine concentration (µmol/L), the mean difference observed was only significant (p-value < 0.05) for HbSS subjects undergoing crisis and control, while KIM-1 mean differences were also not statistically significant for HbSC subjects undergoing crisis and control.

Analysis of variance and post-hoc test for effects of steady SCD on haptoglobin, creatinine, markers of AKI and haematological parameters.

Table 5 showed the analysis of variance (ANOVA) for steady HbSS and HbSC SCD subjects and controls for their mean ± SD values of haptoglobin, creatinine, KIM-1, NGAL, IL-18 and haematological parameters. The findings of the study showed that the mean ± SD values of creatinine, KIM-1, NGAL, IL-18, and WBC for HbSS subjects in steady state were significantly higher (p-values < 0.05) than their HbSC counterparts and the control. However, the mean ± SD values of haptoglobin, PCV and Hb for HbSS subjects in steady state were significantly lower (p-value < 0.05) than those of HbSC subjects in steady state and the control.

The post-hoc analysis showed that the statistically significant differences observed for the effects of SCD on PCV (%), Hb (g/dL), PLTs (x 10^9 cells/L), and WBC (x 10^6 cells/L) do not apply to heterozygous subjects and controls, as the mean differences between them are not statistically significant (p value > 0.05). Similarly, the observed statistical difference in the mean creatinine concentration (µmol/L) and KIM-1(ng/mL) is not applicable between homozygous subjects and

Print ISSN: 0189-9287 Online ISSN: 2992-345X

heterozygous subjects in steady states. In addition, the mean differences between heterozygous subjects in steady state and control were not significant for IL-18 (ng/mL) and Haptoglobin (ng/dL) since their p-values were greater than 0.05.

Table 5: Analysis of variance for effects of SCD in crisis and steady state on haptoglobin, creatinine, markers of AKI and haematological parameters**.**

	Crisis state					**Steady state**				
Variables	**HbSS Mean ± SD SCD (N = 28)**	**HbSC Mean ± SD SCD (N = 9)**	**Controls Mean ± SD SCD (N = 30)**	**F-value**	**p-value**	**HbSS Mean ± SD SCD (N = 28)**	**HbSC Mean ± SD SCD (N = 9)**	**Controls Mean ± SD SCD (N = 30)**	**F-value**	**p-value**
Creatinine (µmol/L)	206.9 ± 173.0	224.4 ± 55.9	73.5 ± 33.1	3.337	0.054	132.8 ± 56.5	129.0 ± 20.0	73.5 ± 33.1	5.250	0.012*
KIM-1 (pg/mL)	9.5 ± 5.0	3.48 ± 0.92	0.7 ± 0.4	18.546	<0.001*	5.8 ± 3.9	3.1 ± 0.5	0.7 ± 0.4	9.587	0.001*
NGAL (pg/mL)	97.4 ± 9.7	68.4 ± 4.0	48.7 ± 4.8	117.769	<0.001*	73.8 ± 8.2	61.2 ± 6.7	48.7 ± 4.8	37.961	<0.001*
IL-18 (pg/mL)	281.7 ± 62.1	185.2 ± 29.2	58.4 ± 18.0	67.140	<0.001*	159.8 ± 18.7	83.5 ± 17.3	58.4 ± 18.0	98.563	<0.001*
HP (ng/mL)	34.8 ± 16.2	75.6 ± 20.7	140.6 ± 32.4	46.077	<0.001*	71.5 ± 19.6	109.8 ± 28.4	140.6 ± 32.4	21.896	<0.001*
PCV (%)	22.0 ± 3.6	30.6 ± 3.8	37.8 ± 2.9	103.135	<0.001*	22.0 ± 3.9	41.0 ± 2.9	37.8 ± 2.9	129.694	<0.001*
Hb (g/dL)	6.4 ± 0.3	11.2 ± 1.6	13.7 ± 1.9	87.354	<0.001*	7.6 ± 1.1	14.0 ± 0.8	13.7 ± 1.9	79.359	<0.001*
WBC ($x10^9$ cells/L)	16.0 ± 5.2	16.2 ± 2.8	7.5 ± 2.3	37.119	<0.001*	20.3 ± 11.1	5.6 ± 0.5	7.5 ± 2.3	22.008	<0.001*
PLTs ($x10^9$ cells/L)	588.8 ± 208.6	217.0 ± 42.3	279.2 ± 83.3	29.541	<0.001*	615.0 ± 214.9	287.8 ± 46.1	279.2 ± 83.3	31.807	<0.001*

*Values are significantly different at p<0.05

Keys: KIM-1: Kidney Injury Molecule-1, **NGAL**: Neutrophil Gelatinase-associated Lipocalin, **HP**: Haptoglobin, **PCV**: Packed Cells Volume, **Hb**: Haemoglobin concentration, **WBC**: White Blood Cells Count, **PLTs**: Platelets count.

Correlation of all parameters of SCD subjects in crisis.

Figures 1 and 2 display the scatterplot showing correlations among variables in homozygous sickle cell subjects in crisis. There was a statistically significant positive Pearson's correlation between haptoglobin (HP) and NGAL (r = 0.648, p = 0.043) in homozygous SCD subjects. Similarly, there was a statistically significant positive Pearson's correlation between total WBC and creatinine levels in homozygous sickle cell subjects (r = 0.649, p = 0.042), all at a 95% confidence level. This suggests that an increase or decrease in total WBC in homozygous sickle cell subjects could indicate a corresponding change in creatinine levels, and the same applies to the relationship between NGAL and HP among HbSS subjects in crisis. However, no statistically significant correlation was observed among the parameters of heterozygous subjects in crisis at a 95% confidence level. This indicates that all haematological parameters and markers of acute AKI in heterozygous SCD patients in crisis could not be used to predict the outcome of one another in this study.

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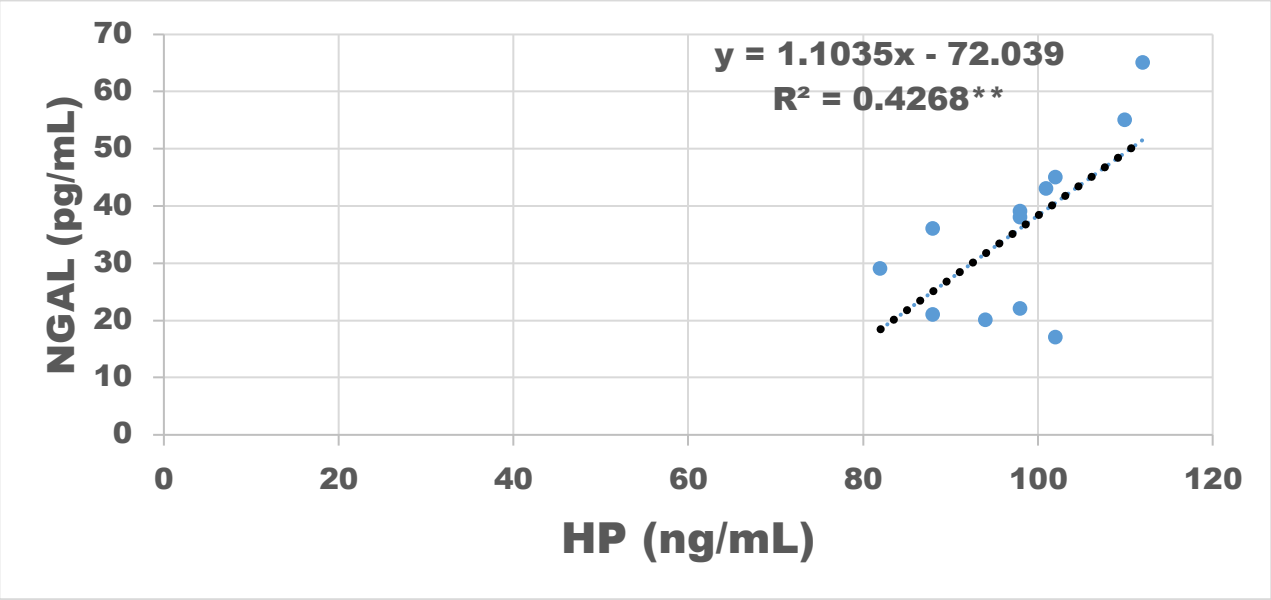
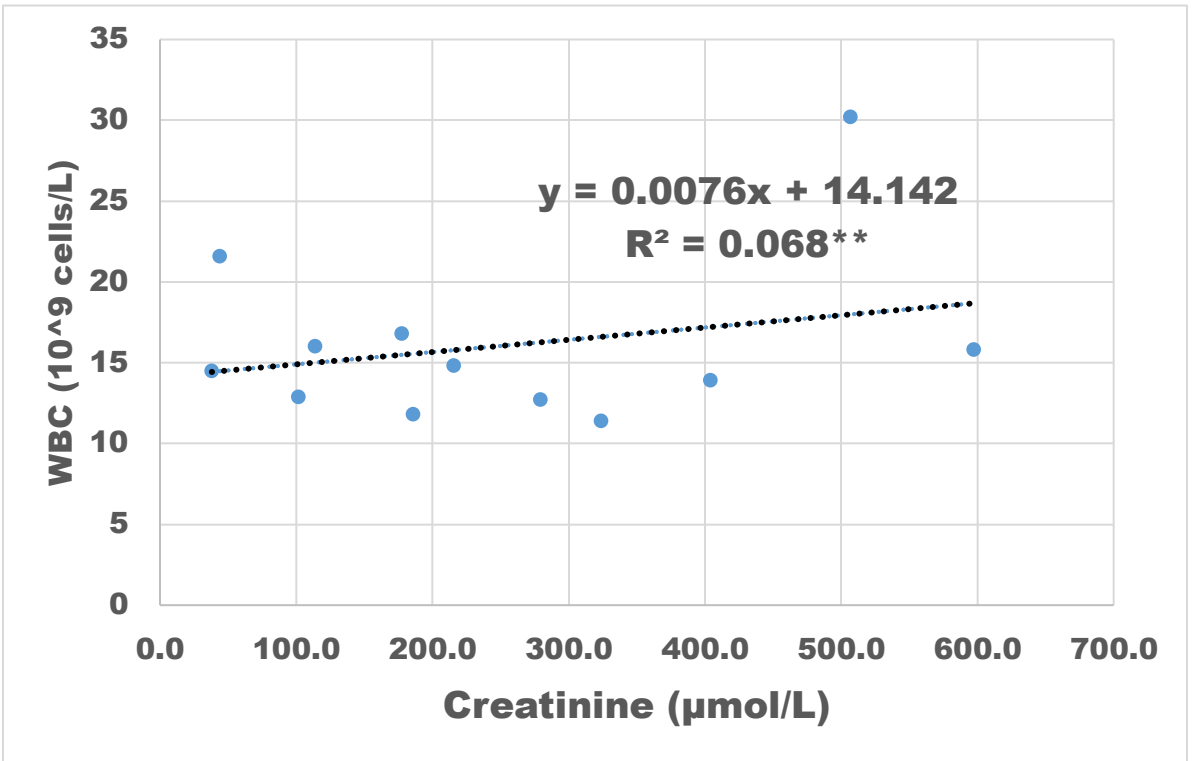


Keys: **Correlation is significant at the 0.01 level (2-tailed), *Correlation is significant at the 0.05 level (2-tailed), **NGAL**: Neutrophil Gelatinase-associated Lipocalin, **HP**: Haptoglobin

Figure 1: Scattered plot showing Pearson's correlation between NGAL and haptoglobin of HbSS subjects in crisis.



Published by The Nigerian Medical Association, Rivers State Branch.

Print ISSN: 0189-9287 Online ISSN: 2992-345X

Keys: **. Correlation is significant at the 0.01 level (2-tailed).
*. Correlation is significant at the 0.05 level (2-tailed).
WBC: White Blood Cells

Figure 2: Scattered plot showing Pearson's correlation between WBC and creatinine of HbSS subjects in crisis.

Print ISSN: 0189-9287 Online ISSN: 2992-345X

DISCUSSION

The onset of complications, inability, disability, and the gradual deterioration of essential organs in sickle cell disease (SCD) have consistently raised concerns. SCD is widely prevalent in sub-Saharan Africa, India and the Middle East, with about 300,000 infants born with the disease worldwide annually[25]. Recurrent vaso-occlusive pain crises, characterised by sickled erythrocytes obstructing capillaries and causing sudden severe pain and tissue ischemia, are the hallmark of SCD. Over time, ongoing haemolysis and ischaemia increase the risk of stroke, pulmonary hypertension, renal failure, retinopathy, avascular necrosis, and organ damage[26]. Individuals with SCD frequently have kidney injury, resulting in complications, with approximately 18% advancing to end-stage renal failure[27]. Given the necessity for enhanced clinical results and tailored care for SCD patients, this research was intended to assess the levels of creatinine, KIM-1, NGAL, and IL-18 in both homozygous and heterozygous SCD patients. Additionally, the research aimed to assess and compare the haptoglobin levels between these two patient groups. This study comprised 37 sickle cell disease (SCD) subjects, predominantly children and adolescents (86.5% aged ≤20 years), with a near-equal gender distribution. Most were homozygous (75.68%), and 45.95% were in vaso-occlusive crisis during the study. This finding aligns with Kato *et al.'s* (2018)[28] study on SCD epidemiology, where pediatric populations bear the highest disease burden, and homozygous (HbSS) genotypes experience more severe complications.

Anaemia markers (Hb and PCV) were significantly lower in SCD ($p < 0.001$), while WBC and platelet count were significantly elevated ($p < 0.001$). This finding was consistent with SCD-related inflammation and compensatory erythropoiesis reported by Achebe *et al.* (2022), who noted that leukocytosis in SCD reflects a chronic inflammatory state[29]. A positive correlation between WBC and creatinine levels in homozygous crisis subjects indicates that inflammation may worsen renal dysfunction. PCV and Hb were significantly lower in HbSS patients relative to the controls. This reflects the chronic anaemia observed in SCD due to increased haemolysis, bone marrow suppression, and nutrient deficiencies. An increased TWBC was observed, most notably in HbSS patients. An increased white blood cell count is recognised as being linked to systemic inflammation and serves as a sign of stroke risk and early mortality in SCD.[30,31] Additionally, platelet counts were markedly higher in homozygous patients, particularly during crises. This thrombocytosis may be reactive due to splenic dysfunction or inflammation. High PLT counts can contribute to vaso-occlusion crises (VOC) and are linked to an increased thrombotic risk in SCD. This supports Conran and Belcher (2020), who described thrombocytosis as part of the pro-thrombotic state in SCD[4]. Similarly, in HbSC patients, vaso-occlusive events resulted in elevated levels of creatinine and IL-18, but these increases were not as pronounced as those observed in HbSS. Supporting this observation, Conran and Belcher (2013) proposed that significantly elevated platelet counts during crises in HbSS may worsen VOC by enhancing clot formation and endothelial adhesion[32]. The correlation analysis in this study revealed that TWBC correlated with creatinine ($r = 0.649$; $p = 0.042$) among HbSS subjects in crisis, suggesting a leukocyte-driven renal injury during crises.[33] Likewise, haptoglobin correlated with NGAL ($r = 0.648$; $p = 0.043$), implying that haemolysis intensifies tubular damage.[34] Significant correlations observed in homozygous patients during crises, particularly between WBC and creatinine ($r = 0.649$, $p < 0.05$), and between HP and NGAL ($r = 0.648$, $p < 0.05$), justify the interplay between inflammation, haemolysis, and renal injury in severe SCD phenotypes.[35] However, no significant correlations were observed between the newer AKI markers and haematological parameters in heterozygous SCD patients, indicating less predictable biomarker interactions in this group, potentially due to milder pathophysiology.

Haptoglobin (HP) is a liver-derived acute-phase plasma glycoprotein whose major role is to bind free haemoglobin (Hb) released during erythrocyte breakdown.[36,37] By sequestering Hb, HP reduces the formation of free heme and iron-driven reactive oxygen species (ROS); this antioxidant function helps protect blood vessels and organs from oxidative stress.[36] Haptoglobin (HP) was significantly reduced in SCD (80.7 ± 47.1 vs. 140.6 ± 32.4 ng/mL; $p< 0.001$), indicating chronic haemolysis and haemoglobin scavenging.[8] The levels remained consistently lower in SCD subjects, especially HbSS individuals, due to their consumption during intravascular haemolysis, a hallmark of SCD. According to Nnodu *et al.* (2021), lower levels of haptoglobin indicate a greater severity of haemolysis[38], which supports the conclusions of the present study. Additionally, the observed negative correlation between NGAL and haptoglobin in HbSS individuals experiencing a crisis implies a connection between haemolytic processes and indicators of renal

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stress. A decrease in haptoglobin is widely recognised as a signal of haemolysis among those with sickle cell disease.[35]

Creatinine is a non-protein nitrogenous waste product of the metabolism of creatine and its derivatives. The synthesis of creatinine occurs in the liver, pancreas, and kidneys, which involves the transamination of amino acids.[12] One limitation of using creatinine to evaluate glomerular and kidney function is that serum creatinine levels do not serve as reliable markers for early-stage glomerulopathy in individuals with SCD due to increased estimated glomerular filtration rate (eGFR), reduced muscle mass, and increased tubular secretion of creatinine in these patients.[14] In this study, creatinine levels were notably higher in both homozygous and heterozygous SCD patients relative to the control group, indicating impaired renal function. Although creatinine is a traditional marker for kidney function, this result contradicts the findings of Gausch *et al.* (2006), who indicated that using creatinine levels to assess kidney injury may underestimate early renal damage in SCD because of hyperfiltration and variations in muscle mass[39]. On the other hand, the findings in this study agree with Alkhunaizi *et al.* (2021), who concluded that increased creatinine levels are a prevalent sign of renal dysfunction in patients with SCD.[40] Nevertheless, various studies have indicated more severe renal impairment in homozygous individuals due to the compounded impact of frequent sickling events.[41]

Neutrophil gelatinase-associated lipocalin, also referred to as lipocalin-2, is a newly discovered adipokine which is an integral member of the lipocalin superfamily. The recognition of NGAL as a critical biomarker for renal pathology has been progressively acknowledged within the scientific community. Specifically, NGAL has been delineated as a pertinent biomarker for acute kidney injury, even among individuals with pre-existing chronic kidney disease. Notably, its concentrations rise within hours post-injury, preceding any alterations in serum creatinine levels.[42] Empirical investigations have demonstrated that NGAL levels are significantly increased in patients with SCD when compared to healthy control subjects ($p<0.05$); particularly, elevated levels were observed in both HbSS and HbSC phenotypes relative to controls, indicating the potential presence of subclinical renal impairment. Findings articulated by Ware *et al.* (2023) corroborate that NGAL concentrations were also markedly increased in HbSS and HbSC patients when juxtaposed with controls, with the most pronounced levels identified in homozygous patients undergoing a crisis.[43] This observation is consistent with the assertions made by Batte *et al.* (2022), who indicated that NGAL possesses significant applicability in crises for SCD patients.[44] Consequently, NGAL is recognised for its rapid elevation after tubular injury and has been substantiated as a valuable biomarker for the detection of AKI in SCD. These results imply that renal stress is amplified during vaso-occlusive crises, with NGAL acting as a sensitive biomarker for acute sickle cell nephropathy.[45]

KIM-1 is a type 1 transmembrane glycoprotein characterised by the presence of immunoglobulin-like and mucin domains. Typically, the expression of this protein within the renal system is minimal; however, it exhibits a significant elevation in instances of ischemic or toxic renal injury.[20] In this study, the levels of KIM-1 were markedly higher in subjects diagnosed with SCD relative to the control ($p < 0.05$), thereby suggesting the existence of subclinical renal impairment. This biomarker was particularly elevated in homozygous patients and during episodes of vaso-occlusive crises. These observations align with findings from other correlational studies, such as Ataga *et al.* (2020), which demonstrated the predictive validity of KIM-1 and NGAL as early indicators of acute kidney injury (AKI) in patients with SCD, particularly during periods characterised by ischemia or inflammation.[46] The results of this study underscore that KIM-1 serves as a sensitive and specific biomarker for proximal tubular damage and was significantly heightened in individuals afflicted with SCD, particularly among homozygous patients and during vaso-occlusive crises. This is consistent with investigations that have established KIM-1 as an outstanding biomarker for the early identification of tubular injury in chronic hemoglobinopathy conditions.[47]

IL-18 is a pro-inflammatory cytokine that is generated by damaged tubular cells and macrophages, with levels increasing in acute kidney injury before the rise in serum creatinine.[42] However, no published African studies have directly assessed IL-18 for AKI in SCD patients (pediatric or adult). Thus, its role remains theoretical. It is often measured alongside NGAL/KIM-1 in AKI research, but currently, IL-18 is not established for SCD-AKI detection. IL-18 was notably elevated in homozygous and heterozygous patients, particularly during crisis, consistent with Akinkunmi *et al.* (2023).[48] Its elevation indicates an underlying chronic inflammatory environment and renal ischaemia characteristic of SCD.[49]

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Strengths and Weaknesses of the Study

The study area is a research-oriented hospital that supports clinical research and medical education through rigorous ethical review by an independent ethics board and meticulous patient documentation. The hospital's patient demography spans Ekiti State and neighbouring areas, which ensures a comprehensive and varied clinical population.

The research was affected by the prevalence of sickle cell disease and the literacy levels of potential subjects, which contributed to the difficulty of recruiting participants for the study.

Implications of the Findings of the Study

Effective management of sickle cell disease requires thorough assessment of AKI markers such as KIM-1, NGAL, and IL-18. Sickle cell disease (SCD) frequently culminates in nephropathy and acute kidney injury (AKI). However, AKI is often insufficiently recognized during episodes of vaso-occlusive crises due to the inadequacy of the traditionally employed marker, creatinine, which serves as a late indicator in SCD given the phenomena of hyperfiltration and tubular secretion, thus underscoring the necessity for innovative biomarkers. KIM-1 and NGAL demonstrate a correlation with renal impairment in SCD, as they facilitate the detection of early tubulointerstitial injury prior to a significant elevation in creatinine levels. These biomarkers exhibit sensitivity to tubular damage and hold considerable potential as early indicators of nephropathy in SCD, although they require validation in extensive, prospective cohorts of SCD patients. IL-18 has been documented to increase during vaso-occlusive episodes in SCD and is associated with hemolysis and inflammatory responses, indicating that it may also be elevated during renal crises. The standard management protocol for SCD predominantly centers on monitoring albuminuria and creatinine levels. There exists a pressing necessity to integrate novel biomarkers into standard clinical practice.

The understanding of the newer AKI markers and a complete blood count in sickle cell disease is needed for the development of more efficient therapeutic drugs for addressing kidney injury in sickle cell disease. It is noteworthy that the incorporation of these biomarkers alongside standard complete blood count findings has the potential to augment risk stratification, as studies have established a correlation between diminished hemoglobin levels and elevated hemolysis markers with sickle cell disease nephropathy. Consequently, a biomarker–CBC profile could effectively identify SCD patients who are at the highest risk for renal complications, thereby facilitating timely intervention. Nonetheless, significant deficiencies remain in the literature, as the majority of available data are either cross-sectional in nature or derived from small sample sizes.

A genotypic-specific management strategy is required for the treatment of sickle cell disease. Sickle cell disease genotypes exhibit notable variations in their pathophysiological mechanisms and clinical trajectories, thereby rendering a universal treatment strategy inadequate. Erythrocytes bearing the HbSC genotype are predisposed to dehydration, resulting in the formation of target cells, which consequently increases blood viscosity significantly. Clinically, individuals with the HbSC genotype experience less severe anaemia and a reduced incidence of acute crises or cerebrovascular accidents compared to those with the HbSS genotype. However, they demonstrate markedly elevated rates of certain complications. Summarily, the genotype-specific pathophysiology exerts a profound influence on the risk of complications and the response to treatment, thereby underscoring the necessity for individualized management approaches.

Additional research into the link between haptoglobin and NGAL is essential to improve their application as predictive indicators for evaluating oxidative stress in the kidneys and protein damage in red blood cells among sickle cell disease patients in crisis.

CONCLUSION

This study concluded that zygosity could affect the severity of SCD. There are significantly higher markers of AKI in SCD subjects compared to the controls. It was also found that homozygous SCD shows considerable renal and haematological dysfunction, which worsens during crises, while heterozygous SCD exhibits intermediate severity, with notable increases in inflammation and newer renal markers during crises. Post-hoc tests confirmed significant differences between homozygous and heterozygous groups in PCV, Hb, PLTs, and AKI markers ($p < 0.05$), although creatinine levels did not differ by genotype during crises ($p = 0.777$). Steady-state homozygous individuals still showed elevated AKI markers and cytopenia compared to controls ($p < 0.001$), whereas heterozygous steady-state values often overlapped with controls, indicating milder baseline pathology. It was also found that KIM-1 and NGAL are better markers of kidney injury, as they can

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be elevated in both steady and crisis states, regardless of zygosity.

Ethical Approval: Ethical approval for this study was obtained from the Ethics and Research Committee, College of Medicine and Health Sciences, Afe Babalola University, Ado-Ekiti, Ekiti State (ABUADHREC/27/03/2025/626) and Human Research and Ethics Committee, Federal Teaching Hospital, Ido Ekiti (ERC/2025/03/24/1227B).

Informed Consent: Written informed consent was obtained for anonymised patient information to be published in this article.

Conflict of Interest: The authors whose names are listed above certify that they have no affiliations with or involvement in any organisation or entity with any financial or non-financial interest in the subject matter or materials discussed in this manuscript.

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Print ISSN: 0189-9287 Online ISSN: 2992-345X