# Prevalence, Pattern and Risk Factors of Albuminuria among Adults Patients with Sickle Cell Anaemia in Maiduguri, Northeastern Nigeria.

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#### ABSTRACT -

Background: Sickle cell anaemia (SCA) is a common life-threatening haematological disorder that affects millions of people worldwide. Albuminuria has been identified as an early marker of sickle cell nephropathy. The study aimed to determine the prevalence, pattern and risk factors associated with proteinuria among patients with SCA in Maiduguri. Methods: This was a cross-sectional descriptive study that involved 240 patients with SCA attending the heamatology clinic, UMTH and 240 controls with Hb AA that fulfilled the inclusion criteria. The participants were screened for proteinuria (albuminuria or overt proteinuria) using spot urine to assess for albumin creatinine ratio (ACR). The glomerular filtration rate was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Albuminuria was defined as a UACR of 3.4 – 33.9 mg/mmol while overt proteinuria as a UACR of > 33.9mg/mmol. Results: The mean age of the SCA group was 23.95±5.93 years while that of the control group was 24.69±6.58 years (p =0.313). The prevalence of albuminuria and proteinuria were significantly higher among the SCA group compared with the control group, 23.3% vs 10.4% and 12.1% vs 4.2% respectively. (p-value < 0.001). Serum creatinine levels correlated positively with albuminuria (r = 0.178; p = 0.006), while PCV correlated negatively with albuminuria (r = -0.178; p=0.006). Albuminuria and high diastolic blood pressure were predictors of kidney disease (odds ratio 0.937, 95% CI 0.019 - 0.981, p = 0.002 and 0.971,95% CI 0.937 - 0.971, p = 0.001 respectively. Conclusion: Albuminuria is a marker of early-stage kidney disease in patients with SCA in Maiduguri. Albuminuria correlates with low PCV and elevated serum creatinine levels in SCA patients.

Keywords: Sickle cell anaemia, Albuminuria, kidney disease, northeastern Nigeria.

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#### Date Submitted 23th February 2024 Date Accepted 12th June 2024 Date Published online 30th June 2024

Access this article online				
QuickResponse Code				
	website:www.bornomedicaljournal.com			
	DOI: 10.31173/bomj.bomj_2424_21			

#### Introduction

Sickle cell Anaemia (SCA) is a genetic disorder characterized by the production of abnormal haemoglobin, predominantly affecting persons of African, Mediterranean, Indian, and Middle Eastern descent.<sup>1,2</sup>

Approximately 300,000 babies are born with SCA annually, and this figure is expected to rise to 400,000 by the year 2050.<sup>3,4</sup> The disorder is associated with many acute and chronic complications requiring immediate medical attention.5Acute complications of SCA include anaemic crisis, vaso-occlusive crisis (VOC) and acute chest syndrome, whereas chronic complications can manifest in virtually all systems of the body, including the brain, musculoskeletal system and the kidneys.5The two major risk factors for the progressive decline in kidney function are proteinuria involvement.6 and glomerular Proteinuria is an early manifestation of sickle cell nephropathy (SCN) and is a more sensitive marker

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in detecting glomerular injury and kidney dysfunction.7 It is also more sensitive in detecting glomerular injury than serum creatinine and has been reported to herald the manifestations of SCN.7,8The appearance of albumin in the urine [albumin to creatinine ratio (ACR)] >3.5mg/mmol can be detected in 20% of children with SCA, this prevalence increases to >60% in those 46 years or older. The prevalence of micro- or macroalbuminuria continues to increase with age and heralds the onset of established SCN.9 The prevalence of albuminuria is found to be 68% among adults with SCD.<sup>10</sup>In a study by Abdu et al.7 28% of adults with SCA had proteinuria, while Arogundade et al.11 reported a prevalence of 16.8%. A cross-sectional study in northwestern Nigeria showed that 30.89% of the children with SCA had proteinuria, of which 24.3% had microalbuminuria while the rest (6.59%) had overt proteinuria.12Sulaimanet al.13 in a crosssectional study of CKD among patients with SCA, observed that patients with proteinuria had significantly higher creatinine levels (332 mmol/L vs 255 mmol/L) and a higher proportion of them present with end-stage CKD. This study aimed to determine the prevalence, pattern and risk factors associated with proteinuria among patients with SCA and HbAA controls in Maiduguri.

#### Methods

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This was a cross-sectional study conducted at GOPD and haematology clinic(s) of the University of Maiduguri Teaching Hospital from January 2022 to June 2022. Two hundred and forty consenting adults with SCA who were in a steady clinical state and an equal number of age- and sex-matched control groups with Hb AA were recruited. Excluded from the study were those with hepatitis B surface antigen (HBsAg) positivity, antibody to hepatitis C virus (anti-HCV), human immunodeficiency virus (HIV), diabetes mellitus (DM) hypertension, or on haemodialysis. Their Maintenance sociodemographic data, Hemoglobin genotype, frequency and types of crises per year, number of units of blood transfused, and symptoms of kidney disease including haematuria, frothiness of urine, nocturia and recurrent body swelling were obtained and recorded in a well-structured questionnaire. Blood pressure was measured in both arms, in supine and standing positions, using an Accoson mercury-in-glass sphygmomanometer (England)

with an appropriate cuff size. Blood samples were also obtained and analyzed for serum electrolytes, creatinine, urea and packed cell volume. Patients were taught how to collect fresh early morning urine samples in a sterile universal bottle. Urinalysis was carried out using a urinary dipstick, Combi-Uriscreen® 10SL (Germany) to assess for protein, leucocytes and nitrite. Female subjects were instructed to void fresh urine at times outside of their menstrual periods. In subjects with leucocyturia or positive dipstick nitrite test, the presence of proteinuria was confirmed after treatment with antibiotics.

The urinary albumin: creatinine ratio was determined using Clinitek® 50 (Bayer diagnostics) specifically for urine samples that were dipstick negative for proteinuria. The urine Albumin Creatinine ratio (ACR) of each sample was calculated in milligrams per mmol (mg/mmol). Albuminuria was defined as an ACR of 3.4 – 33.9 mg/mmol. Overt proteinuria was defined as an ACR of > 33.9 mg/mmol.

#### **Data Processing and Analysis**

Data entry and analysis were done using the IBM-SPSS (International Business Machines-Statistical Package for the Social Sciences) Statistics for Windows, Version 21.0. Continuous variables were expressed as mean  $\pm$  SD, median (range), and categorical variables were expressed as percentages. The relationship between continuous variables was determined using the Student's t-test and Chi-square test for discrete variables. Multiple regression analysis was used to assess the weight of different variables. Results were presented as tables and graphs where appropriate. P-values of <0.05 was considered statistically significant at a 95% confidence interval.

#### **Ethical Consideration**

Ethical approval for the study was sought and obtained from the UMTH Health Research Ethics Committee with approval reference UMTH/REC/24/672. Informed written consent was obtained from each study participant.

#### Results

Out of a total of 480 study participants recruited in the study; 240 were patients with Hb SS recruited from GOPD and haematology clinic (SCA Group) and 240 were patients with Hb AA (Control Group) recruited from GOPD.

#### Socio-demographic Characteristics of Study Participants

The age of the study population ranged between 18 and 50 years with a mean age of  $23.95\pm5.93$  years for the SCA group and  $24.69\pm6.58$  years for the controls (p-value = 0.313). The age group 21-30 years constituted the highest proportion of subjects 118 (49.2%). There were 131 (54.6%) males in the SCA

group while 136 (56.7%) were males in the control group (p-value = 0.170).

The majority of the subjects were students in both the cases and control accounting for 180 (75%) and 106 (44.6%) of the study subjects. Table 1 shows the distribution of socio-demographic characteristics between cases and controls.

Table	1: Socio-	demographic	Characteristics	of Study Parti	icipants	
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Characteristics	n=240(%)   n=240(%)   n=240(%)		X <sup>2</sup>	p-value	
MeanAge(Mean±S.D)	23.93±5.93 years	24.69±6.58 years		0.313	
Age group					
< 00					
\$ 20	91 (37.9)	80 (33.3)	3.559	0.313	
21-30	118 (49.2)	119 (49.6)			
31-40	27 (11.3)	31 (12.1)			
> 40	4 (1.7)	10 (4.2)			
Sex					
Male	121 (50.4)	136 (56.7)	1.884	0.170	
Female	119 (49.6)	104 (43.3)			
Occupation					
Student	180 (75.0)	176 (73.3)	2.686	0.443	
Civil Servant	19 (7.9)	24 (10.0)			
Housewife	14 (5.8)	8 (3.3)			
Others	27 (11.3)	32 (13.3)			
Ethnic group					
Kanuri	119 (49.6)	126 (52.5)	1.292	0.936	
Hausa	31 (12.9)	27 (11.3)			
Shuwa	24 (10.0)	21 (8.8)			
Babur/Bura	23 (9.6)	19 (7.9)			
Fulani	11 (4.6)	11 (4.6)			
Others	32 (13.3)	36 (15.0)			
Religion		/			
lslam Christianity	224 (93.3)	203 (84.6)	1.033	0.314	
Citionality	10 (0.7)	57 (15.4)			
Level of Educational					
Informal Primary Sal1	22 (9.2)	15 (6.3)	3.556	0.314	
Secondary School	0 (1.3) 114 (47 5)	0 (2.1) 93 (38 7)			
Tertiary	101 (42.0)	127 (52.9)			
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#### Distribution of Albuminuria Among SCA Group

The prevalence of albuminuria and proteinuria were 23.3% (56) and 12.1% (29) respectively in the SCA group. However, there was no significant difference in the prevalence among males and females. (p- value 0.797). (Table 2)

#### Table 2: Pattern of albuminuria among SCA group

Gender	Normoalbuminuria	Albuminuria	Proteinuria	X <sup>2</sup>	p value
	n (%)	n (%)	n (%)		
Male	80 (51.6)	28 (50)	13 (44.8)	0.455	0.797
Female	75 (48.4)	28 (50)	16 (55.2)		
Total	155 (100)	56 (100)	29 (100)		

## Comparison of Markers of Kidney Damage between Cases and Controls

There was significant difference in the prevalence of albuminuria among SCA and control groups (p = < 0.001), with the prevalence of normoalbuminuria, albuminuria and overt proteinuria of 64.6%, 23.3% and 12.1% in SCA group and 85.4%, 10.4% and 4.2% in the controls, respectively.

The prevalence of hyperfiltration (GFR >120mil/min), normal GFR (90-120ml/min) and reduced GFR (<60ml/min) were 17.5% vs 1.7%, 21.3% vs 68.8% and 38.3% vs 12.1% in the SCA and control groups respectively. There was a significant difference in the prevalence of GFR subgroups among the study participants. P = < 0.001 (Table 3)

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Table 3. Pattern	of kidney	Damage/function	among study	narticinante
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Kidney Damage/function	SCA Group	Control Group	X2	p value
	n (%)	n (%)		
By Albuminuria			28.065	< 0.001
Normoalbuminuria	155 (64.6)	205 (85.4)		
Albuminuria	56 (23.3)	25 (10.4)		
Proteinuria	29 (12.1)	10 (4.2)		
By GFR			126.987	< 0.001
Hyperfiltration (>120ml/min)	42 (17.5)	4 (1.7)		
Normal (90-120ml/min)	51 (21.3)	165 (68.8)		
Reduced GFR (<60ml/min)	92 (38.3)	29 (12.1)		

GFR (Glomerular filtration Rate), Normoalbuminuria: ACR < 3.4mg/mmol, Albuminuria: ACR 3.4 – 33.9 mg/mmol,

Overt Proteinuria: ACR > 33.9 mg/mmol, \*(Significant p value)

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Association Between Febrile Illness, Blood
Transfusion and VOC and Albuminuria
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Table 4. Showed the relationship between the prevalence of transfusion, frequency of febrile illness and VOC and degree of albuminuria among patients with SCA. There was no significant difference in the

prevalence of blood transfusion between the different groups, with multiple transfusions occurring in 74.8% of those with normoalbuminuria, 85.7% of those with albuminuria and 89.7% of those with Overt proteinuria, (p= 0.076)

level of albuminuria					
	Normoalbuminuria(%)	Albuminuria(%)	Proteinuria (%)	p value	
	n = 155	n = 56	n = 29		
Transfusion	116 (74.8)	48(85.7)	26(89.7)	0.076	
Febrile illness	150 (96.8)	53(94.5)	29(100)	0.424	
VOC frequency					
0-2/year	100 (64.5)	42 (75.0)	17(58.6)	0.137	
3-5/year	31 (20.0)	7 (12.5)	10(34.5)		
≥6/year	24 (15.5)	7 (12.5)	2(6.9)		

Table 4: Prevalence of transfusion, febrile illness and frequency of VOC according to

VOC (Vaso-occlusive crisis)

**Biochemical Parameters in Patients with Sickle Cell** Anaemia

There was a significant positive correlation between albuminuria and serum creatinine

(p= <0.006, r= 0.178). Albuminuria correlated negatively

Correlation Between Albuminuria and Clinical and with PCV (p= <0.001, r = -0.251) and GFR (p= <0.001, r = -0.251). There was no correlation between albuminuria and BMI (p= 0.503, r = -0.043), systolic blood pressure (p=0.003, r = -0.207) and diastolic blood pressure (p = 0.956, r = 0.003). (Table 5)

> Table 5: Correlation between albuminuria and clinical and biochemical characteristics in patients with SCA.

Parameter	R	p value
Age (years)	0.085	0.188
Body mass index (kg/m²)	- 0.085	0.187
Systolic blood pressure (mmHg)	-0.043	0.503
Diastolic blood pressure (mmHg)	0.003	0.956
Packed cell volume (%)	-0.251	<0.001*
Serum creatinine (mg/dl)	0.178	0006*
Estimated GFR (mls/min/1.73m <sup>2</sup> )	-0.251	<0.001*

\*(Significant p value of< 0.05)

#### Logistic Regression to Determine Predictors of predicting kidney disease with odd ratios (confidence Kidney Disease among SCA Group

Using logistic regression analysis, the diastolic blood pressure (BP) and Albuminuria were significant in

interval) of 0.937 (0.019 - 0.981) and 0.971 (0.937 - 0.971) respectively (Table 6).

#### Table 6: logistic regression for predictors of kidney disease

Factors	OR	95% Confidence interval		P value
		Lower limit Upper limit		
Age	0.985	0.948	1.023	0.425
Sex	0.908	0.568	1.448	0.683
BMI	0.967	0.984	1.157	0.119
Systolic BP	1.002	0.997	1.048	0.081
Diastolic BP	0.937	0.019	0.981	0.002*
Albuminuria	0.971	0.937	0971	< 0.001*

BMI (Body Mass Index), BP (Blood pressure), OR = Odd ratio. Significance at p < 0.

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#### Discussion

prevalence, pattern and risk The factors of albuminuria were studied among the study participants using UACR. Albuminuria was more prevalent in SCA patients than controls. Proteinuria is an early manifestation of sickle cell-related kidney disease. 14,15,16 The prevalence of albuminuria in patients with SCA in this study is 23.3%. This is comparable to 17.4% and 26% reported in the Ivory Coast and Jamaica respectively.<sup>17.18</sup> This is, however, lower than the prevalence of 44.4% and 40% reported in South Western Nigeria and Brazil.7,18 The prevalence of proteinuria in the index study was 12.1%, similar to 16.8% reported by Arogundade et al.7 in a retrospective study in Ile-Ife, but lower than reports from other studies. 12,19,20 A much higher prevalence of 41% was, however, reported in adults with SCD in Saudi Arabia.<sup>21</sup>The varied prevalence reports across different locations could be explained by the differences in patients' characteristics and SCD behavior in different parts of the world. This is evidenced by the observation that variable associations have been found in patients with similar origins studied at different centres.<sup>18</sup> This may also be related to the differences in the haplotypes of the patients in these differing populations. Disease severity may vary among different haplotypes and this is thought to be due to additional genetic modifiers and environmental factors that influence the expression of the disease phenotype.22,23 The Senegalese haplotype which is associated with a higher haemoglobin F (HbF) concentration has a better prognosis than others. The Benin haplotypes were detected in 92.3% of a sample population in Nigeria, associated with an intermediate clinical course.23

The difference in prevalence of albuminuria between each gender was not statistically significant in this study. This finding is similar to the report by Eke et al,<sup>24</sup> but different from reports of previous studies that found а significantly higher prevalence of females. 25,26 Confounders albuminuria in of proteinuria such as haematuria and urinary tract infections which are known to be commoner in females were part of the exclusion criteria in this study. This may explain the absence of significant gender differences in the prevalence of albuminuria. Kidney involvement tends to occur more in subjects who have frequent vaso-occlusive crises.27 This is often compounded by the fact that patients with SCA

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commonly use NSAIDs intermittently to relieve of the painful crises which can cause a significant reduction in kidney blood flow and glomerular filtration rate; and thus, affect kidney function. There was a positive association between transfusion and severity of albuminuria in this study. The need for recurrent transfusion in SCA may indirectly reflect the severity of the disease. This cross-sectional study, however, did not observe an association of frequent vasoocclusive crisis and febrile illness with the progression of kidney dysfunction in contrast with previous reports.<sup>6,28,29</sup> It is possible that a large proportion of these patients were diagnosed early and may have received care that reduced their risk of developing these complications.

This study found a positive correlation between albuminuria and serum creatinine on one hand and a negative correlation between albuminuria and GFR on the other. Thus, worsening albuminuria in this study was a pointer to worsening renal function and hence increasing albuminuria in SCA patients can predict progressive renal damage. This finding has been supported by previous studies.<sup>15,16</sup>

There was no correlation between albuminuria and elevated BP in this study. This finding is in contrast to reports by Thompson,<sup>16</sup> and Guash *et al*,<sup>30</sup> who found a positive correlation between albuminuria and BP. Similarly, a previous study reported a positive correlation between albuminuria and systolic BP.<sup>31</sup>Although there is an association between albuminuria and high BP in many kidney diseases, patients with SCA with kidney disease may exhibit a different pattern. The mechanism of kidney damage in SCA is multifactorial, therefore, the relationship between albuminuria and BP might not follow the typical patterns seen in other kidney diseases.

This study identified some predictors of kidney dysfunction among patients with SCA. An increase in Urinary albumin excretion and high diastolic BP were shown to be associated with the risk of developing kidney disease among patients with SCA.<sup>12</sup> In contrast to other studies, this study neither showed age as a predictor nor was associated with the development of kidney disease, this may not be unrelated to the study population as this study focused only on adults while previous studies included children and adults.

#### Conclusion

Albuminuria is a marker of early kidney disease in patients with SCA in Maiduguri, correlated with low

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### PCV and elevated serum creatinine levels. Further studies are recommended to evaluate its long-term impact on kidney survival. Regular screening and treatment with established agents can help reduce albuminuria and ESRD progression.

#### **Conflict of Interest**

The authors declare no conflict of interest

#### Recommendations

- 1. The results indicate a high prevalence of albuminuria and proteinuria amongst the sickle cell population, indicating an additional impact of HbSS on the prevalence of kidney disease. Albuminuria should be included as part of routine investigations in patients with SCA and should be regularly assessed to detect early kidney dysfunction.
- 2. Screening for albuminuria and instituting measures to prevent severe anaemia in addition to the use of established therapeutic agents such as ACEI, ARB and hydroxyurea early in SCA patients will help to reduce albuminuria and subsequent progression to ESRD.

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**Cite this Article as**: Lawan M, Loskurima U, Ndahi AA, Habib AG, Ladu AI, Shettima J, Amali AO, Chiroma I, Dungus MM, EmeanwuCH, Tijjani ZM, Ummate I. Prevalence, Pattern and Risk Factors of Albuminuria among Adults Patients with Sickle Cell Anaemia in Maiduguri, Northeastern Nigeria. **Bo Med J** 2024; 21 (1):94-101 **Source of Support**: Nil, **Conflict of Interest**: None declared

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