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Original Research

Factors Associated with Microalbuminuria among Children with Sickle Cell Disease in a Tertiary Centre in South-South Nigeria

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Abstract

Background: Microalbuminuria, an early indicator of kidney damage in Sickle Cell Disease (SCD) patients, is linked to a heightened risk of chronic kidney disease (CKD) in adulthood. This study investigates the determinants of microalbuminuria in paediatric SCD patients in South-South Nigeria.

Methodology: This cross-sectional study was conducted over six months at the Rivers State University Teaching Hospital, Nigeria, involving 60 children with [HbSS genotype, SCD] in a steady state. Data collection included demographics, past medical history, clinical measurements, and laboratory assessments of urine and blood samples. 'Steady state' was defined as SCD with a known 'steady state' haemoglobin level and stable clinical state for ≥ 3 months. Microalbuminuria was defined spot urine albumin-creatinine ratio of 30mg/g to <300 mg/g.

Results: Of the 60 children recruited, 31 children (51.7%) were males. The mean age was 9.6 ± 4.3 years. The prevalence of microalbuminuria was 16.7% (CI: 8.29 – 28.5%) and associated risk factors were hypertension (p = 0.017), use of Hydroxyurea (p = 0.008), and Ciklavit (p = 0.025), but not NSAIDs (p = 0.046). There was a significant negative correlation (r = -0.28; p = 0.032) between haemoglobin level and microalbuminuria.

Conclusion: This study provides insights into the factors associated with microalbuminuria in children with SCD in our setting and highlights the need for early screening for markers of CKD among children with SCD. Further research is needed to ascertain the potential benefits of addressing anaemia and reducing haemolysis in mitigating the occurrence of microalbuminuria among children with SCD.

Keywords: Children; Microalbuminuria; Risk Factors; Sickle Cell Disease; Sickle Cell Nephropathy.

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Introduction:

Sickle cell disease (SCD) is a genetic disorder characterized by abnormal haemoglobin production, leading to the formation of sickle-shaped red blood cells. It affects millions globally, particularly those of African descent, impacting multiple bodily systems, including the kidney and urinary system.[1,2]SCD-related kidney changes, termed sickle cell nephropathy, manifest as microalbuminuria, an early sign of kidney damage linked to a heightened risk of chronic kidney disease later in life. [1,3]

The kidney involvement in SCD stems from haemoglobin S polymerization-induced sickling and subsequent vaso-occlusion.[4] This process triggers chronic inflammation, oxidative stress, and endothelial dysfunction, culminating in glomerular hypertension and damage to the glomerular filtration barrier, resulting in microalbuminuria. [5,6] This subtle yet chronic urinary abnormality can progress to chronic kidney disease. [7]

Various predisposing factors contribute to microalbuminuria in children with sickle cell anaemia. These include a mix of non-modifiable factors like genetics[2,6], age[8-13], sex[2,11], and intrinsic levels of Hemoglobin F [14,15], as well as modifiable factors such as hyperfiltration [2,8], haemoglobin levels[8,9,11,12], frequency of crises[16], blood transfusions[2], and blood pressure[11,13]. Some studies suggest that hydroxyurea usage may modify glomerular leakage of microalbuminuria.[15,17] While predictors for chronic kidney disease in adults include lower haemoglobin levels, increased age, and albuminuria,[18] such associations in paediatric cohorts are still inconclusive due to disparities among studies.

This study, therefore, set out to determine the risk factors of microalbuminuria among children with sickle cell disease in steady state seen at the Rivers State University Teaching Hospital, Nigeria.

Subjects and Methods

This was a cross-sectional study carried out at the Departments of Paediatrics, Haemato-oncology and general outpatient clinic of the Rivers State University Teaching Hospital. The study was conducted over 6 months from 1st April 2022 to 30th September 2022. The study population: Consisted of children with sickle cell disease (SCD) in steady-state, aged 3 to less than 18 years being followed up at the haemato-oncology clinic. All cases previously had a genotype determined and were already enrolled in the sickle cell disease registry. Steady state was defined as SCD with a known 'steady state' haemoglobin level and stable clinical state in the absence of infection, pain, acute clinical symptoms or crisis for ≥ 3 months.

The sample size was estimated to be forty-five children using the sample size calculator: ClinCal, with statistical parameters from a previous study[8], using an anticipated incidence in cases: 26% and using alpha at 0.05%, power 80% and attrition rate of 10%. However, sixty children were recruited into the study.

A systematic random sampling technique was employed to recruit the children with confirmed HBSS presenting to the Haemato-oncology clinic [on Wednesdays]. The sampling frame was obtained from the haematology register of 208 SCD children who are on regular follow-up visits. Hence the sampling interval was [208/60] = 3.4. The starting child was randomly selected and the interval - every 3rd SCD child who presented for follow-up was assessed for eligibility and subsequently recruited.

Children with a confirmed genotype HBSS who were in a ‘steady state,’ had documented blood haematocrit values, and were in an otherwise stable clinical state for at least three months preceding the study were included. However, **c**hildren with SCD who had experienced an episode of painful vaso-occlusive crises as evidenced by bone pains, jaundice, the passage of bloody urine, and stroke, who received a blood transfusion in the last 3 months were excluded. Also, SCD children with co-existing comorbid disease like cardiac disease, primary renal disease, obesity, severe malaria, Hepatitis B or C and Clinical AIDS or Human Immunodeficiency Virus infections were excluded.

A semi-structured questionnaire was used to collect the information on demographics and clinical measurements after duly explaining the aim and relevance of the study and obtaining written consent from parents/caregivers and assent for children above 7 years of age. All information obtained was handled with the utmost confidentiality. Participants were informed of their choice to withdraw at any time during the study. Clinical measurements obtained included three measurements of blood pressure (5 minutes apart) using a standard mercury sphygmomanometer with an appropriate paediatric cuff using the patient's right arm while sitting in a relaxed position and arms at the level of the heart. The average of the last two of three consecutive readings, taken 5 minutes apart, was taken as the blood pressure. The weight was measured using an electronic scale with readings allowed to the nearest 0.1kg, height (in meters) was measured with the participant standing erect without shoes using a stadiometer and the headpiece, oxygen saturation using a paediatric pulse oximeter finger probe, axillary temperature using a mercury thermometer was read off to the nearest 0.1^{o}C after 120 seconds and pulse rate obtained by palpation of the radial artery and reported after 60 seconds respectively.

Sample Collection and Assay Methods:

Spot urine specimens and venous blood samples were collected from study participants. The urine was used for urinalysis, urine albumin, urine creatinine, and spot urine albumin-creatinine ratio estimation. The blood samples were used for plasma urea and creatinine estimation. Specimens were stored at –20°C until analysis, which was conducted within 48 hours of collection. Serum creatinine was measured using a semi-automated chemistry analyzer, and urine albumin was assayed using Fluoro-immunoassay methods.

Statistical Analysis:

The data collected was checked for completeness and entered to IBM's SPSS for analysis. Categorical and continuous variables were summarized. Microalbuminuria prevalence among HBSS children was calculated and defined as spot urine albumin creatinine ratio > 30 - <300mg/g. The modified Schwartz formula was used to determine the estimated glomerular filtration rate (eGFR). Factors associated with microalbuminuria were investigated using statistical tests with a significance level of $p < 0.05$.

Ethical Consideration: Ethical approval was obtained from the Rivers State University Teaching Hospital Research Ethics Committee (RSUTH/REC/2022158) and consent was obtained from parents and accent obtained from children over 7 years.

Results:

Prevalence of Microalbuminuria among children with HBSS in RSUTH, Port Harcourt.

Of the 60 HBSS children who participated in the study, 10 children were observed to have microalbuminuria giving a prevalence rate of 16.7% (CI: 8.29 – 28.5%) among HBSS children in this locality.

Association between Microalbuminuria and Sociodemographic characteristics, nutritional and hypertensive status among children with HBSS in RSUTH, Port Harcourt.

Table 1 shows that 31 children (51.7%) were boys while 29 (48.3%) were girls. The mean age of children in the study was 9.6 ± 4.3 years while 32 children (53.3%) were less than 10 years. The mean weight and height were 30.7 ± 14.0kg and 1.33 ± 0.23m respectively. Three children (5.0%) were classified as having hypertension. Concerning nutritional status, 8 children (13.3%) were underweight, 3 (5.0%) were overweight and 2 (3.4%) were obese. The other children had healthy weight for age and sex (78.3%).

As presented in Table 1, age and sex were not significantly associated with the occurrence of MA in these children. However, of the 3 HBSS children with elevated blood pressure, 2 children (66.7%) had MA, reflecting a significant association (Fisher's exact = 5.68; 0.017) between hypertension and MA in the study.

Table 1: Demographic characteristics and occurrence of microalbuminuria in HBSS children

Characteristics	Total	Microalbuminuria		Fisher's exact test
	N = 60 (%)	Present	Absent	(p-value)
		N = 10 (%)	N = 50 (%)	
Gender				
Male	31 (51.7)	4 (12.9)	27 (87.1)	0.65 (0.419)
Female	29 (48.3)	6 (20.7)	23 (79.3)	
Age				
≤ 10 years	32 (53.3)	5 (15.6)	27 (84.4)	0.05 (0.817)
> 10 years	28 (46.7)	5 (17.9)	23 (82.1)	
Age in years – Median (Range)	8.9 (3.0 – 16.0)	8.5 (3.0 – 16.0)	10.0 (3.0 – 16.0)	221.5[a] (0.571)
Social class				
Upper class	5 (8.3)	1 (20.0)	4 (80.0)	0.58 (0.750)
Middle class	37 (61.7)	7 (18.9)	30 (81.1)	
Lower class	18 (30.0)	2 (11.1)	16 (88.9)	
Blood pressure status				
Normotensive	57 (95.0)	8 (14.0)	49 (86.0)	5.68 (0.017*)
Hypertensive	3 (5.0)	2 (66.7)	1 (33.3)	
Weight in Kg – mean ± SD	30.7 ± 14.0	30.7 ± 14.2	30.8 ± 14.0	0.02[a] (0.984)
Height in m – mean ± SD	1.33 ± 0.23	1.34 ± 0.22	1.35 ± 0.25	0.12[a] (0.907)
Nutritional Status				
Underweight	8 (13.3)	1 (12.5)	7 (87.5)	1.89 (0.285)
Healthy weight	47 (78.3)	7 (14.9)	40 (85.1)	

Overweight	3 (5.0)	1 (33.3)	2 (66.7)	
Obese	2 (3.4)	1 (50.0)	1 (50.0)	

Note: [a]Mann-Whitney U-test

Association between microalbuminuria and routine medication useamong children with HBSS in RSUTH, Port Harcourt.

Table 2 reveals that the most common routine drugs among children in the study were folic acid (98.3%), Astymin (95.0%) and Paludrine (91.7%). Other drugs used include NSAIDs (75.0%), hydroxyurea (38.3%) herbal medication (5.0%) and Ciklavit (3.3%).

In Table 2, the use of hydroxyurea (Fisher's exact = 6.92; p – 0.008), and Ciklavit (Fisher's exact = 4.53; p – 0.025) in HBSS children were significantly associated with the occurrence of MA. The two children using Ciklavit had MA. A significantly higher proportion of HBSS children using hydroxyurea (26.1% Vs. 10.8%) than those not using hydroxyurea were found to have MA (Table 2). The children who used NSAIDs also had significantly (χ^2 = 4.08; 0.046) lower prevalence of MA than those not using NSAIDs (11.1% Vs 33.3%).

Table 2: Relationship between routine medication use and microalbuminuria among HBSS children

Characteristics	**Total**	**Microalbuminuria**		**Fisher's exact test (p-value)**
		Present	**Absent**	
	N = 60 (%)	**N = 10 (%)**	**N = 50 (%)**	
Hydroxyurea				
Yes	23 (38.3)	8 (26.1)	15 (73.9)	6.82 (0.008*)
No	37 (61.7)	2 (10.8)	35 (89.2)	
Folic Acid				
Yes	59 (98.3)	9 (15.3)	50 (84.7)	1.83 (0.167)
No	1 (1.67)	1 (100.0)	0 (0.0)	
Astymin				
Yes	57 (95.0)	9 (15.8)	48 (84.2)	0.63 (0.427)
No	3 (5.0)	1 (33.3)	2 (66.7)	
Paludrine				
Yes	55 (91.7)	9 (16.4)	46 (83.6)	0.17 (0.676)
No	5 (8.3)	1 (20.0)	4 (80.0)	
Ciklavit				
Yes	2 (3.3)	2 (100.0)	0 (0.0)	4.53

No	58 (96.7)	8 (13.8)	50 (86.2)	(0.025*)
Herbal Medication				
Yes	3 (5.0)	1 (33.3)	2 (66.7)	0.63 (0.427)
No	57 (95.0)	9 (15.7)	48 (84.3)	
NSAIDS				
Yes	45 (75.0)	5 (11.1)	40 (88.9)	4.08
No	15 (25.0)	5 (33.3)	10 (66.7)	(0.046*)

Note: NSAIDs mean non-steroidal anti-inflammatory drugs e.g. Ibuprofen and Diclofenac; *Statistically significant.

Association between Microalbuminuria and Blood and urine parameters

As presented in Table 3, mean spot urine albumin, mean spot urine creatinine and mean UACR were 45.1 ± 36.8 mg/L, 4.3 ± 2.5 mmol/L and 14.1 ± 16.8mg/g respectively, as seen in Table 4. The spot urine albumin (98.7 ± 41.1 mg/L Vs 34.4 ± 24.8 mg/L) and UACR (47.2 ± 18.4 mg/g Vs 7.5 ± 3.3 mg/g) were significantly higher (p – 0.001) among children with MA than those without MA. However, the reverse was the case for Spot urine creatinine (2.2 ± 0.9mmol/l Vs 4.8 ± 2.5mmol/l).

The mean serum creatinine, mean haematocrit and mean total white cell count were 44.3 ± 12.3 µmol/L, 27.0 ± 3.5%, and 12.9 ± 4.6 x 10^9/L respectively. Furthermore, Table 3 revealed that haematocrit level was significantly lower (t-test – 2.37; p – 0.021) in children with MA than those without MA (24.7% ± 2.9% Vs 27.5 % ± 3.4%).

Table 3: Blood and Urine indicators among HBSS children with and without microalbuminuria

Characteristics		**Microalbuminuria**		**Student's**
	Total, n = 60	**Present, n = 10**	**Absent, n = 50**	**t-test**
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	**(p-Value)**
Urine parameter				
Specific gravity	1.01 ± 0.01	1.02 ± 0.01	1.01 ± 0.01	1.73 (0.088)
Urine pH	6.1 ± 0.5	6.2 ± 0.2	6.1 ± 0.4	0.67 (0.508)
Spot Urine Creatinine (mmol/L)	4.3 ± 2.5	2.2 ± 0.9	4.8 ± 2.5	3.21 (0.002*)
Spot Urine Albumin (mg/L)	45.11 ± 36.8	98.7 ± 41.1	34.4 ± 24.8	6.64 (0.001*)
Urine Albumin Creatinine ratio (mg/g)	14.1 ± 16.8	47.2 ± 18.4	7.5 ± 3.3	14.62 (0.001*)
eGFR	115.7 ± 27.9	108.5 ± 22.7	117.2 ± 28.8	0.89 (0.374)

Blood parameter				
Plasma Creatinine (mmol/L)	44.3 ± 12.3	47.6 ± 16.1	43.6 ± 11.5	0.92 (0.360)
Haematocrit (%)	27.0 ± 3.5	24.7 ± 2.9	27.5 ± 3.4	2.37 (0.021*)
Total WBC Count (10^9/L)	12.9 ± 5.7	12.4 ± 4.6	13.0 ± 5.9	0.33 (0.745)
Neutrophils (%)	45.8 ± 7.5	45.8 ± 4.7	45.8 ± 7.9	0.01 (0.994)
Lymphocytes (%)	45.9 ± 8.3	46.9 ± 5.8	45.7 ± 8.8	0.41 (0.685)
Platelets (10^9/L)	454.6 ± 221.7	493.4 ± 404.4	446.9 ± 169.7	0.60 (0.549)

*Statistically significant

Table 4 shows that spot urine albumin correlated strongly and positively with UACR (ɼ = 0.73; p – 0.001) while spot urine creatinine had a moderate negative correlation with UACR (ɼ = -0.39; p – 0.002). Haematocrit level had a weak negative correlation with UACR (ɼ = -0.28; p – 0.032).

Table 4 further shows that a unit change in spot urine albumin brings about a 53.3% change in the level of UACR. Meanwhile, a unit increase in spot urine creatinine leads to a 15.2% drop in the level of UACR.

Table 4: Relationship between Urine Albumin Creatinine ratio (microalbuminuria) and other blood and urine indicators of renal function of HBSS children

Characteristics	**Correlation co-efficient - ɼ**	**$ɼ^2$**	**p-Value**
Urine parameter			
Specific gravity	-0.11	0.012	0.396
Urine pH	0.13	0.017	0.319
Spot Urine Creatinine (mmol/L)	-0.39	0.152	0.002*
Spot Urine Albumin (mg/L)	0.73	0.533	0.001*
eGFR	-0.16	0.026	0.222
Blood parameter			
Plasma Creatinine (mmol/L)	0.04	0.002	0.745
Haematocrit (%)	-0.28	0.078	0.032*
Total WBC Count (10^9/L)	-0.14	0.020	0.281
Neutrophils (%)	-0.05	0.003	0.715
Lymphocytes (%)	0.10	0.010	0.427

Platelets (10^9/L)	-0.06	0.004	0.655

*Statistically significant

Association between Microalbuminuria and hyperfiltration, SCD severity among children with HBSS in RSUTH, Port Harcourt.

The majority of children with HBSS genotype in the study had no hospital admission (56.7%), no episode of blood transfusion (53.3%), and no bone pain crisis (43.3%) in the last year preceding the study. Forty-three (71.7%) were regular with their follow-up appointments and a quarter (25.0%) were found with glomerular hyperfiltration (As seen in Table 5).

Furthermore, Table 5 shows that hyperfiltration (χ^2 =1.44; p – 0.426), number of pain crises (χ^2 =1.44; p – 0.426), number of hospital admissions (χ^2 =1.44; p – 0.426), number of blood transfusions (χ^2 =1.44; p – 0.426), and regularity of follow-up (χ^2 =1.44; p – 0.426), were not significantly related to the occurrence of microalbuminuria among HBSS children in stable state in this locality.

Table *5*: Relationship between hyperfiltration, severity factors of HBSS and microalbuminuria among HBSS children

Characteristics		**Microalbuminuria**		**Fisher's exact test**
	Total	**Present**	**Absent**	**(P-value)**
	N = 60 (%)	**N = 10 (%)**	**N = 50 (%)**	
Regular follow-up appointments				
Yes	43 (71.7)	7 (16.3)	36 (83.7)	0.02 (0.898)
No	17 (28.3)	3 (17.6)	14 (82.4)	
Number of pain crises in the last one year				
1 pain crisis	11 (18.3)	2 (18.2)	9 (81.8)	2.04 (0.723)
2 pain crises	10 (16.7)	2 (20.0)	8 (80.0)	
3 pain crises	7 (11.7)	2 (28.6)	5 (71.4)	
> 3 pain crises	6 (10.0)	0 (0.0)	6 (100.0)	
No pain crisis	26 (43.3)	4 (15.4)	22 (84.6)	
Number of Hospital admissions in the last one year				
No hospital admission	34 (56.7)	7 (20.6)	27 (79.4)	1.87 (0.760)
1 hospital admission	17 (28.3)	2 (11.8)	15 (88.2)	
2 hospital admission	4 (6.7)	0 (0.0)	4 (100.0)	
3 hospital admission	1 (1.7)	0 (0.0)	1 (100.0)	
> 3 hospital admission	4 (6.7)	1 (25.0)	3 (75.0)	

Number of blood transfusions in the last one year				
1 transfusion episode	13 (21.7)	0 (0.0)	13 (100.0)	5.51 (0.110)
2 – 3 transfusion episodes	10 (16.7)	2 (20.0)	8 (80.0)	
4 – 5 transfusion episodes	3 (5.0)	0 (0.0)	3 (100.0)	
> 5 transfusion episodes	2 (3.3)	1 (50.0)	1 (50.0)	
No episode	32 (53.3)	7 (21.9)	25 (78.1)	
Hyperfiltration				
Present	15 (25.0)	1 (6.7)	14 (93.3)	1.44 (0.426)
Absent	45 (75.0)	9 (20.0)	36 (80.0)	

Discussion

This study looked to uncover the factors associated with microalbuminuria (MA) among children with SCD in a tertiary hospital in Southern Nigeria. This study reveals that MA occurred as frequently as one in six children with sickle cell disease in a steady state, with occurrence linked to low levels of haematocrit, use of hydroxyurea, and hypertension. MA was noted to develop early in childhood buttressing the need for clinicians managing children with sickle cell disease to actively screen for MA in this chronic kidney disease-prone population.

In this study, the overall prevalence of microalbuminuria in children with the HBSS genotype was 16.7% and was comparable to estimates from other studies; 15.5% in the USA[21], 16% in Ivory Coast[22], 18.5% in Nigeria[6], and 19.2% in India.[25] However, our estimate was much higher than the 9.6% found among SCD children in Saudi Arabia.[19] Also, we report a prevalence that is lower than the 20.3% to 26% found in other Nigerian studies[7,8,26,27], 23% to 39.1% in other African studies [22,28,29] and 26.5% in the USA.[30] The variations could be due to differences in the age of children studied, the category of children (steady state Vs general cohort), the albumin quantification assay method employed and other co-existing genetic and environmental factors.

This study found that a relationship exists between MA and the haematocrit of children with SCD. The haematocrit levels correlated negatively with the occurrence of microalbuminuria. Similarly, other studies[7–9,20–22] have shown such negative associations between the severity of anaemia and MA. Chronic haemolysis has been suggested as being central to the pathophysiology of MA in children with SCD as evidenced by low haemoglobin concentrations/haematocrit levels and high levels of the markers of haemolysis including bilirubin, and lactate dehydrogenase.[9,23] Although, in some cross-sectional studies, authors observed a trend towards haemoglobin/Haematocrit levels of < 8g/dl[8] after data were subcategorized, the exact haematocrit level above which MA may be averted remains to be established. Nevertheless, variations in the individual underlying drivers of the haematocrit level such as the presence of foetal haemoglobin, severity of ongoing haemolysis, endothelial dysfunction, response to erythropoietin, genetic variations in spectra of SCD and environmental factors, will likely affect the desirable threshold. Therefore, interventions to improve anaemia which reduces the frequency of ongoing haemolysis may be integral to reducing the incidence of MA and sickle cell-related kidney disease.

Consistent with observations from other studies conducted in Nigeria[8,24,25], this study also found that MA was seen among children as young as 3 years (which was the lower limit for this study). In other African

series, SCD children with MA were as young as 2 to 4 years old[10,26]Therefore, it is plausible that microalbuminuria starts soon after infancy and gets worse as children get older. This was also suggested by the findings of an increasing occurrence of MA with age in our study, though not statistically significant. The increase in the prevalence of MA in the second decade of life over the first decade observed in this study is worthy of note. The lack of statistical significance could be because this cohort had fewer complications of severe SCD. Nonetheless, the increasing prevalence with age is in tandem with reports in other studies within and outside Nigeria.[8,10,27,28] Although some studies reported much higher estimates of MA[8,12,29] within the first decade than what we found, the findings give credence to the fact that structural glomerular changes[23] such as mesangial expansion, glomerular basement membrane thickening, podocyte effacement of the foot processes, glomerular size increase and even hyperfiltration occur at a much earlier age in children with HBSS. This implies that screening for MA in these cohorts of children should be prioritized being a marker of renal disease even before serum creatinine derangements are observed. This is especially prudent in the light of the often inescapable, yet early unrestricted overexposure to NSAIDs and other herbal-based unorthodox medications in our setting, during treatment for recurring ischaemic/ bone pain crises.[30,31]

In this study, the occurrence of microalbuminuria tended to be higher in girls than in boys – albeit, non-significant. This is consistent with observations in previous studies.[10,21,25,32,33] Interestingly, there was also no statistically significant relationship between microalbuminuria and sex in these reports. The exact explanation for this is unknown. However, in studies where healthy females have been suggested to be more likely to develop microalbuminuria, the females were observed to have precocious puberty when compared to the males. Authors suggested that a causal role in the occurrence of microalbuminuria could be puberty due to increased expression of IGF-1.[34] However, among children with HBSS, researchers have suggested increased confounders like leucocyturia, haematuria and urinary tract infection as plausible reasons for an increased occurrence in females.

Other factors linked to the occurrence of MA among the HBSS children in this study were the use of Ciklavit© and hydroxyurea. Ciklavit©, a phytomedicine is yet to demonstrate clinical efficacy among HBSS children.[35] This study revealed that all children on the phytomedicine had MA, suggesting it likely has no renoprotective role. Also, although previous studies[36] have suggested a beneficial role of hydroxyurea in limiting the frequency of vaso-occlusive crises via increases in the levels of haemoglobin F and reduction in the polymerization of haemoglobin S, which in turn minimizes the occurrence of MA[37,38]; this was not observed in this study. A plausible explanation could be that the hydroxyurea use was mainly for those with very severe diseases and those who could afford the medication, as consistent use remained a challenge considering the high cost of the medication in this environment. This is supported by a recent study[39] that assessed hydroxyurea use among SCD children in this facility, which reported that hydroxyurea use was predominantly among children from the upper socioeconomic class and those with complications. Comparably, a study by Aygun and colleagues[40] did not find any change in MA among children in their study even after hydroxyurea use for three years. Yet, studies among adults with SCD report improved MA levels within 3 – 6 months.[36,37] However, the benefit of hydroxyurea is suggested to be more noticeable after consistent use, but the exact duration remains to be determined in children with SCD.[36,41,42]

In this study, we also found a non-significant association between the presence of MA and GFR among the children irrespective of age. This suggests the possibility of glomerular changes leading to MA occurring with or without detectable hyperfiltration among these groups of the population, emphasizing again, the role of screening for early detection of renal compromise among HBSS children. Our findings are similar to reports from other studies which also found no significant association between MA and hyperfiltration among HBSS children.[10,32,43] Our study, albeit, compared unfavourably to other studies

that found that GFR was higher among children with MA.[8] The authors attributed their findings to the possibility of the existence of early-onset glomerular hypertrophy.

Unexpectedly, we found that children with a history of NSAID use also had a significantly lower prevalence of MA compared to those not using NSAIDs. This may be explained by the fact that overall, the study participants had less severe disease with a less frequent need for sustained analgesic use, it may also be that the right recommended doses of NSAIDs for acute pain episodes were used in our series. However, our study may have been underpowered. A study among children with HBSS in Uganda documented NSAID use was associated with the occurrence of MA[43] and others have shown an association with renal, gastrointestinal and cardiovascular adverse effects among people with SCD and should be used cautiously in them.[44] This is because NSAIDs substantially decrease the glomerular filtration rate and renal blood flow.[45] In addition, in this study, although a trend was observed towards a higher prevalence of MA among children who had more than 5 sessions of blood transfusions, between 1 - 3 episodes of bone pain crises in the previous year and more than three hospital admissions – none of these were statistically significantly related with MA.

This study also revealed that elevated blood pressures were significantly higher among the HBSS children with microalbuminuria compared to those without microalbuminuria. This was consistent with the reports by Aloni and colleagues in Kinshasa, DRC[10] but differed from earlier studies by Abhulimen-Iyoha and colleagues in Nigeria.[25] Masked hypertension has been documented among children with HBSS and linked to vascular disease which increases the risk for sickle cell nephropathy. [46,47]

The limitations of this study include its single-centred cross-sectional design which impacts the ability to infer causality. One other limitation is that biological measurements were performed once during the study. Despite the limitations, it is a pioneering study emerging from this setting that examined MA among this cohort of children. It adds to the body of evidence which can be used to advocate for instituting strategic preventative measures like ensuring early screening for sickle cell nephropathy and associated risk factors among children with SCD in Rivers State and Nigeria.

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