

## Research Paper

# Evaluation of Renal Function of Sickle Cell Children in Libreville by Estimating Glomerular Creatinine-Cystatin C Filtration Rate



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## ABSTRACT

**Background and Aim:** Sickle cell disease (SCD) is a crucial and growing global health problem. Kidney damage is one of the most common complications of SCD. This study aimed to determine the prevalence of acute kidney injury (AKI) in children with SCD.

**Methods:** This cross-sectional and analytical study was conducted from January 2022 to September 2022. It included children with SCD aged 6 months to 17 years during their steady state. We measured the estimated glomerular filtration rate (eGFR) using the combined creatinine and cystatin C formula for kids (CKiD<sub>Scr-CysC</sub>). Univariate analyses were performed to measure the relationship between variables and AKI and eGFR, followed by a multivariate analysis using logistic regression.

**Results:** Of the 137 children, 82 (60%) were boys and 55 (40%) were girls. The mean eGFR was 112±45.3 mL/min/1.73 m<sup>2</sup>. A total of 36 subjects, or 26.3% (95% confidence level [CI], 18.9, 33.6%), had acute AKI. Comparison of characteristics by AKI status showed significant differences in the number of transfusions (P<0.01) and hemoglobin level (P<0.027). eGFR was negatively correlated with the number of transfusions (r=-0.308; 95% CI, -0.477%, -0.117%; P<0.01). Multivariate analysis showed that nutritional status was a protective factor for AKI (P<0.01), and the number of transfusions was a predictive factor of AKI in SCD (P<0.001).

**Conclusion:** The results of our study are an urgent call to implement existing management programs for SCD, from screening to universal access to hydroxyurea, to reduce complications and mortality related to this pathology.

**Keywords:** Sickle cell disease (SCD), Children, Acute kidney injury (AKI), Chronic kidney disease (CKD), Gabon



## Introduction

**S**ickle cell disease (SCD) is a monogenic disease that affects millions of people worldwide. It is characterized by a mutation in the  $\beta$ -globin gene, resulting in an abnormal form of adult hemoglobin. SCD is a crucial and growing global health problem, with nearly half a million children born in 2021, and an increase in the overall number of sickle cell patients by approximately 44.4% between 2000 and 2021 [1]. Chronic hemolysis, vaso-occlusions, and organ dysfunction characterize the pathophysiology of SCD. Kidney damage is one of the most common complications of SCD, with approximately 30% of patients with SCD developing chronic kidney disease (CKD) and 14%-18% progressing to a terminal kidney [2]. SCD is a particular challenge in the pediatric population because it begins in early childhood with signs of structural changes detected as glomerular hyperfiltration leading to albuminuria, loss of renal function, and acute kidney injury (AKI) [2]. However, these low-level changes can progress to advanced CKD in late adolescence or early adulthood [2, 3].

Current improvements in the care of patients with SCD have led to longer survival, increasing the incidence of sickle cell nephropathy and AKI [2]. Monitoring the renal function of the sickle cell sufferer thus becomes a key point in the overall management of children with SCD. Tools for routine assessment of kidney function in SCD have expanded over time, and with a better understanding of certain biomarkers [4]. The most recent recommendations retain the evaluation of glomerular filtration rate using creatinine and cystatin C (eGFR<sub>cr-cys</sub>) as the reference method in chronic disease setting, such as SCD [5].

Some studies in sub-Saharan Africa aimed to evaluate the glomerular filtration of sickle cell patients at the time of the democratization of online glomerular filtration rate (GFR) calculators, but they were limited to the Cockcroft and Gault formula, or that of the CKD-epidemiology (CKD-EPI) of 2009 which was based on the determination of creatinine, and are therefore obsolete [6]. We did not find any recent studies using the latest recommendations for GFR assessment in patients with SCD in sub-Saharan Africa.

Therefore, this study aimed to contribute to the improvement of care for children with SCD, and the main objective of our study was to determine the prevalence of AKI in children with SCD in our context. The sec-

ondary objective was to determine the epidemiological factors associated with renal impairment in patients with SCD in Gabon. Our research hypothesis was that the majority of sickle cell children in Libreville were in acute kidney failure.

## Materials and Methods

This cross-sectional, observational, and analytical study was conducted from January 2022 to September 2022. We selected SCD children aged 6 months to 17 years from the SCD follow-up registries of outpatients at 4 hospitals in Libreville (Gabon).

These SCD patients underwent systematic consultation during their steady-state period, away from any acute episode for at least 2 months. Blood tests were performed during regular control tests. The minimum sample size was calculated using StatCalc in Epi Info 7.2. As expected, we observed an AKI frequency of 9.6% according to Djite et al. [6]. An acceptable margin of error of 5% was considered. The result was 136 patients. We included the subjects voluntarily after their parents had signed the informed consent form, and the kids also gave their approval. We included the subjects according to the following criteria:

1) Inclusion criteria included SCD with a formal hemoglobin (Hb) SS result, aged 6 months to 17 years. 2) exclusion criteria included children whose parents refused their inclusion, patients aged more than 17 years and less than 6 months at inclusion, patients with no formal Hb SS or with another result other than Hb SS, and patients who had encountered an acute situation in the past two months.

The data recorded included age, sex, history of transfusion, anthropometric data measured according to [World Health Organization \(WHO\)](#) standards, proteinuria and hematuria on urine strip tests, total blood cell count, urea, creatinine, and cystatin C according to KDIGO standards. We calculated anthropometric z-scores using the [WHO Anthro<sup>®</sup>](#) and [WHO Anthro<sup>®</sup> Plus](#) software, which allowed us to obtain weight-for-age Z score (WAZ), height-for-age Z score (HAZ) and body mass index-for-age Z score (BAZ).

The GFR was calculated with [Equation 1](#):

$$1. \text{CKiD}_{\text{Scr+Cys C}} (\text{ml/min}/1.73 \text{ m}^2) = 39.8 \times [\text{height (m)}/\text{Scr (mg/dl)}]^{0.456} \times [1.8/\text{Cys C (mg/l)}]^{0.418} \times [30/\text{BUN (mg/dl)}]^{0.079} \times (1.076)^{\text{male}} \times [\text{height (m)}/1.4]^{0.179}$$

According to the KDIGO classification, AKI is mild if the GFR is between 60-100 mL/min/1.73 m<sup>2</sup>, moderate if the GFR is between 30-60 mL/min/1.73 m<sup>2</sup>.

We defined polytransfusion as receiving more than 2 transfusions.

Data were collected using Epi Info 7.2. A descriptive analysis was conducted to characterize the sample. Quantitative data were expressed as Mean±SD or as median for the number of transfusions. We used the Welch test for the comparison of means, and the Wilcoxon Mann-Whitney test for the comparison of medians. Qualitative data were expressed as proportions with 95% confidence intervals (CIs) calculated using the Miettinen method. The proportion of patients with renal impairment was compared using the two-tailed chi-square test or a Fisher test when effects did not allow it. Quantitative variables were assessed for correlation with GFR using Pearson's test. We performed a multivariate linear regression analysis to identify factors associated with kidney failure in SCD. The significance level was set at P<0.05.

The study protocol complied with the ethical guidelines of the Declaration of Helsinki and was approved by the Ministry of Health of Gabon in the absence of a National Ethics Committee. Informed consent was obtained from adult parents or guardians prior to recruiting the children by having them sign the informed consent form. The patients did not have to pay for GFR biomarkers.

## Results

This study included 137 participants, comprising 82 boys (60%) and 55 girls (40%). The mean age of the children was 6.2±4.7 years, ranging from 6 months to 17 years.

The subjects' medical history showed that 123 subjects or 89.8% (95% CI, 84.5%, 94.9%) had received at least one transfusion in their lifetime. The median number of transfusions was 3, with a minimum of 0, a maximum of 8. Ninety-one subjects (66.4%, 95% CI, 58.5%, 74.3%)

were polytransfused. A history of urinary tract infections was reported in 6 subjects (4.4%), ureterohydronephrosis in 3 subjects (2.2%), and high blood pressure in 5 subjects (3.7%).

The means of the anthropometric indices were -0.02±1.51 for WAZ, 0.03±2.28 for HAZ, and -0.70±1.64 for BAZ. According to the HAZ index, 119(86.8%) were in the median, 13 (9.5%) were stunted, and 5(3.7%) were taller than average. According to the BAZ index, 98 patients (71.5%) had good nutritional status, 2(1.5%) were overweight, 16(11.7%) were moderately undernourished, and 21(15.3%) were severely acutely undernourished.

Proteinuria was negative in 131 cases (95.6%), positive at one cross in 5 cases (3.6%), and positive in two crosses in 1 case (0.8%). Hematuria was negative in 133 cases (97.1%) and positive in 4 cases (2.9%).

The mean hemoglobin level was 7.6±1.8 g/dL. [Table 1](#) presents the means of the biomarkers used to calculate the glomerular filtration rate.

The mean GFR was 112±45.3 mL/min/1.73 m<sup>2</sup>. A total of 36 subjects, or 26.3% (95% CI, 18.9%, 33.6%), had acute AKI, including 22 (16%) with mild acute AKI, and 14(10.2%) with moderate acute failure.

Comparison of characteristics by AKI status showed significant differences by sex, number of transfusions, and hemoglobin level ([Table 2](#)).

Univariate analysis of quantitative data of sample characteristics showed a negative correlation between the number of transfusions and GFR ([Table 3](#)).

Multivariate analysis showed that when the BAZ increased by 0.1 units, the score of AKI=No was multiplied by an average of 1.05, (95% CI, 1.01%, 1.09%) (P<0.01). When the number of transfusions increases by 1 unit, the score of AKI=Yes is multiplied by an average of 1.7 (95% CI, 1.3%, 2.7%), (P<0.001).

**Table 1.** Hemoglobin and biomarker parameters of renal function of study subjects

Markers	Mean±SD	Min	Max
Hemoglobin (g/dL)	7.6±1.8	2.6	9.6
BUN (mg/dL)	13.4±7.6	4.7	50.4
Creatinine (mg/dl)	0.7±0.5	0.06	3
Cystatin C (mg/L)	0.53±0.3	0.1	1.4

**Table 2.** Comparison of variables analyzed by AKI status

Variables	Mean±SD/ Median/ No. (%)		P	Test	
	AKI				
	No (n=101)	Yes (n=36)			
Age (y)	5.53±3.91	7.41±5.74	0.086	Welch	
HAZ	0.388±2.92	0.174±2.68	0.71	Welch	
WAZ	-0.110	-0.560	0.1	Welch	
BAZ	-0.531±1.60	-0.992±1.69	0.19	Welch	
Number of transfusions	2.35	4	<0.01	Wilcoxon	
Hemoglobin level (g/dL)	7.84±1.92	7.05±1.49	0.027	Welch	
Sex	Male	55(64)	17(47)	0.45	Chi <sup>2</sup>
	Female	46(36)	19(53)	-	-
Proteinuria (strips)	No	97(96)	34(94.4)	0.7	Fisher
	+	4(4)	1(2.8)		
	++	0	1(2.8)		
Hematuria (strips)	No	99(98)	34(94.4)	0.3	Fisher
	+	2(2)	2(5.6)		

Abbreviations: AKI: Acute kidney injury; HAZ: Height-for-age Z score; WAZ: Weight-for-age Z score; BAZ: Body mass index-for-age Z score.

## Discussion

The renal function of subjects included in our study was impaired in 26.3% of cases, with GFR below established norms. The epidemiological context in Gabon alone justifies ongoing research and improvement efforts in the management of patients with SCD. Gabon has a prevalence of nearly 1.5% for SCD and 25% for carriers of the trait. Gabon is located in the heart of the geographic

area where both the haplotype of sickle cell anemia associated with more clinical severity (Bantu or CAR) are found, and *Plasmodium falciparum*, which is fatal or severe, including kidney damage [7-9], are found.

Some series report that 12% of children with SCD with renal disease will progress to end-stage renal disease [10]. This treatment makes the conventional management of the steady state more cumbersome [11]. This

**Table 3.** Correlation between quantitative characteristics of the sample and GFR

Variables	Correlation Coefficient (95% CI)	P	Test
Age (y)	-0.0877 (-0.281, 0.113)	0.39	Pearson
BAZ	0.0843 (-0.116, 0.278)	0.41	Pearson
HAZ	-0.000391 (-0.199, 0.198)	1	Pearson
Number of transfusions	-0.308 (-0.477, -0.117)	<0.01	Pearson
Hemoglobin level (g/dL)	0.172 (-0.0271, 0.358)	0.09	Pearson
WAZ	0.0853 (-0.138, 0.301)	0.45	Pearson

Abbreviations: GFR: Glomerular filtration rate; HAZ: Height-for-age Z score; WAZ: Weight-for-age Z score; BAZ: Body mass index-for-age Z score; CI: Confidence interval.

prevalence is quite high compared to that reported by Djite et al. [6], who found 9.68% AKI using the estimated glomerular filtration rate of creatinine (eGFR<sub>cr</sub>). Nevertheless, the prevalence of acute AKI in our sample is supported by the KDIGO estimate of approximately 27% of sickle cell patients with CKD [5]. The differences between our series and that of Djite et al. [6] can result in the diagnostic tool chosen (eDFG<sub>cr</sub> vs. eDFG<sub>cr-cys</sub>) and in the haplotype of our region (Bantu-CAR). Estimation of renal function using simultaneous assessment of GFR with cystatin C and creatinine is more suitable for chronic conditions, particularly in the presence of malnutrition, such as SCD [5]. A total of 99.9% of sickle cell patients in Gabon carry the Bantu-CAR haplotype, presenting with more severe clinical forms, while the Senegal haplotype is the least severe [1, 7, 8].

Renal impairment was significantly related to the number of transfusions in our setting. This was true in both qualitative univariate analysis and multivariate linear regression. The glomerular filtration rate decreased as the number of transfusions increased, and the risk of kidney failure nearly doubled after each transfusion episode. We also hypothesize that the causes in our settings can be grouped into two categories: The lack of national recommendations and the severe clinical expression of our haplotype. National recommendations for the management of SCD are not established in Gabon. The country lacks a transfusion exchange program, does not recommend the administration of hydroxyurea, and other molecules recommended in other settings are also unavailable [1, 12, 13]. In Africa, transfusion is an emergency therapeutic alternative. It is administered in cases of severe, life-threatening anemia [14, 15]. Apart from seizures, young people with SCD are under permanent renal stress due to both anemia and hemolysis, which is toxic to podocytes [16]. Both of these factors are more severe in carriers of the Bantu-CAR haplotype [1]. In our country, transfusion in sickle cell patients is consequently a sign of extreme severity, and therefore, of uncontrolled sickle cell anemia [1, 17]. Hence, it is time for decision-makers to implement the resolutions recently adopted on birth screening and on early access to different therapies [13, 17]. Transfusion exchange programs could be revived due to new data on efficacy, a low cost-to-carbon footprint ratio, and whole-blood utilization [15, 18, 19].

Denutrition was correlated with kidney failure and decreased GFR. Nearly 25% of the children included in our study are suffering from denutrition, a proportion higher than that of all children of the same age in Gabon, which was 4% in the same period [12]. The proportion of malnutrition in our sample is nevertheless lower than that

of Islam et al. in the last demographic survey in Nigeria, with 55.4% of sickle cell children under 5 years of age malnourished [20]. The difference in the proportion of malnourished sickle cell children between these two countries may be explained by gross domestic product per capita [21]. Undernutrition of sickle cell patients has been the subject of several studies and recommendations for decades. The observation of this nutritional status is a sign of a specific failure to address the nutrition of the sickle cell patient, but also an expression of the clinical severity of the pathology [22, 23]. Indeed, as with all organ systems, the gut can be damaged in children with SCD by vascular abnormalities, including recurrent hypoxia-reperfusion lesions induced by vaso-occlusive crises, which could also lead to a reduction in the ability to absorb nutrients [24].

Gender has not been identified as a factor associated with the occurrence of acute AKI in sickle cell patients in our context. Rather, recent data from the literature show that the male sex is implicated in sickle cell patients [25]. Neugarten and Golestaneh argued that, contrary to the consensus view, male sex is more associated with kidney failure regardless of the associated or underlying pathology [26].

## Conclusion

About three out of ten subjects in our study had a GFR below the established norms, indicating reduced kidney function. This is a high proportion. Given their young age, these patients will therefore require monitoring and management of this anomaly to prevent progression to chronicity and a terminal phase. Management programs should be implemented to reduce complications and mortality related to this pathology.

## Ethical Considerations

### Compliance with ethical guidelines

Ethical approval was obtained from the [Ministry of Health](#), Libreville, Gabon.

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### Authors' contributions

Study design and writing the original draft: Steeve Minto'o, Fifi Claire Loembe and Sylvie Mpira; Inves-

tigation: Nathalie Nguemou; Recruiting patients: Fifi Claire Loembe and Sylvie Mpira; Data collection: Joel Djoba Siawaya; Review and editing: Jean Koko and Simon Ategbu; Project administration: Jean Koko and Simon Ategbu.

### Conflict of interest

The authors declared no conflict of interest.

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