International Journal of Contemporary Pediatrics
Minto'o S et al. Int J Contemp Pediatr. 2024 Jun;11(6):630-635
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20241285

Original Research Article

Evaluation of renal function of sickle cell children in Libreville by estimation of glomerular creatinine-cystatin C filtration rate: prevalence of acute kidney injury and associated factors

Steeve Minto'o[1]*, Fifi C. Loembe[1], Sylvie Mpira[1], Nathalie Nguemou[1], Joel Djoba Siawaya[2], Jean Koko[1], Simon J. Ategbo[1]

[1]Department of Paediatrics, Université des Sciences de la Santé, Libreville, Gabon
[2]National Public Health Laboratory, Libreville, Gabon

Received: 17 April 2024
Accepted: 02 May 2024

***Correspondence:**
Dr. Steeve Minto'o,
E-mail: Steeve.mintoo@yahoo.fr

ABSTRACT

Background: Sickle cell disease (SCD) is an important and growing global health problem. Kidney damage is one of the most common complications of SCD. We aimed to determine the prevalence of acute kidney injury (AKI) in children with SCD in our context.
Methods: Cross-sectional and analytical study from January 2022 to September 2022, including SCD children aged from 6 months to 17 years during their hospitalisation. We measured the estimated glomerular filtration (eGFR) rate using the combined creatinine and cystatin C formula for kids ($CKiD_{Scr\text{-}Cys\ C}$). 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, we included 82 boys (60%) and 55 girls (40%). The mean eGFR was 112±45.3 ml/min/1.73 m^2. A total of 36 subjects, or 26.3% (95% CI [18.9-33.6%)), had acute AKI. Comparison of characteristics by AKI status showed significant differences according the number of transfusions ($p<0.01$), and hemoglobin level ($p<0.027$), eGFR had a negative correlation with the number of transfusions r=-0.308 (-0.477; -0.117); $p<0.01$. Multivariate analysis showed that nutritional status was a protective factor of AKI ($p<0.01$), and the number of transfusions was a predictive factor of AKI in SCD in our context ($p<0.001$).
Conclusions: The results from our study are an urgent alarm to implement the existing management programs on SCD from screening to universal access of hydroxyurea in order to reduce complications and mortality related to this pathology.

Keywords: SCD, Children, CKD, Gabon

INTRODUCTION

Sickle cell disease (SCD) is a monogenic disease that affects millions of people worldwide. It is characterized by a mutation in the globin gene β, resulting in an abnormal version of adult haemoglobin. SCD is an important and growing global health problem, with nearly half a million children born in 2021 with the condition, and an increase in the overall number of sickle cell patients by approximately 44.4% between 2000 and 2021.[1] The pathophysiology of SCD is characterized by chronic haemolysis, vaso-occlusions, and organ dysfunction. Kidney damage is one of the most common complications of SCD, with approximately 30% of sickle cell patients developing chronic kidney disease (CKD) and 14-18% progressing to a terminal kidney.[2] SCD is a

particular challenge in the paediatric population, as it begins in early childhood with signs of structural changes detected as glomerular hyperfiltration leading to albuminuria, loss of renal function, and AKI.[2] However, these low-level changes can progress undetected to advanced CKD in late adolescence or early adulthood.[2,3]

Current improvements in the care of sickle cell patients allow for relatively longer survival, leading to an increased incidence of sickle cell nephropathy and AKI.[2] The monitoring of the renal function of the sickle cell sufferer thus becomes a key point in the overall management of the child with SCD. Tools for routine assessment of kidney function of SCD have been expanded over time and with a better understanding of certain biomarkers.[4] The most recent recommendations retain the evaluation of glomerular filtration rate of creatinine and cystatin C (eGFRcr-cys) as the reference method in chronic pathology situations such as de-nutrition, that is the case in SCD.[5]

Some studies in sub-Saharan Africa had already 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 CDK-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 the assessment of GFR in sub-Saharan Africa in sickle cell patients.

The aim of our study was therefore 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 secondary objective was to determine the epidemiological factors associated with renal impairment in sickle cell patients in Gabon. Our research hypothesis was that the majority of sickle cell children in Libreville were in acute kidney failure.

METHODS

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

These SCD patients were included during their hospitalization. Blood tests were performed within the regular tests.

The minimal size of the sample was calculated with Statcalc of Epi Info 7.2 software. We introduced as expected frequency of AKI 9,6% according to Ndour et al. We considered an acceptable margin error of 5%. The result was 136 patients.

We included the subjects on a voluntary basis after their parents had signed the informed consent form, and kids also gave their approval. We included the subjects according the following criteria:

Inclusion criteria

Patients with SCD and formal Hb SS result and aged from 6 months to 17 years were included in the study.

Exclusion criteria

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 than Hb SS result; patients having encountered an acute situation in the past two months were excluded.

Data recorded were age, sex, history of transfusion, anthropometric data measured according to WHO standards, proteinuria and haematuria on urine strip tests; total blood count cell; urea; creatinine and cystatin C according to KDIGO standards.

We calculated the anthropometric z-scores with WHO Anthro© and WHO Anthro© Plus software that allowed us to obtain weight for age (WAZ), height for age (HAZ) and body mass index for age (BAZ).

The GFR was calculated with the formula:

$CKiD_{Scr\ +\ Cys\ C}$ (ml/min/1.73 m^2)=39.8×(height (m)/Scr (mg/dl)]$^{0.456}$ × (1.8/Cys C (mg/l)]$^{0.418}$ × 30/BUN (mg/dl)]$^{0.079}$ × [1.076]^{male} × [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^2, moderate if the GFR is between 30-60 mL/min/1.73 m^2.

We defined poly-transfusion as a number of transfusions greater than 2.

Data were collected on Epi Info 7.2. Descriptive analysis was conducted to determine the characteristics of the sample. Quantitative data were expressed as means and standard deviation, or as a median for the number of transfusions. We used the Welch test for the comparison of means, and the Wilcoxon Mann and Whitney test for the comparison of medians. Qualitative data were expressed as a given proportion with a 95% confidence interval calculated using the Miettinen method. The proportion of patients with renal impairment was compared using the two tails Chi-square test or a Fisher test when effective did not allow it. Quantitative variables were assessed by linear regression to assess their correlation with GFR with Pearson's test. We performed a multivariate linear regression analysis to determine the factors determining kidney failure in SCD. The significance threshold was a $p<0.05$ test.

The study protocol complied with the ethical guidelines of the declaration of Helsinki and was approved by the ministry of health of Gabon in absence of national ethic committee. An informed consent was obtained from adult parents or guardians prior to recruit the children by signing the informed consent form. Patients did not have to pay for GFR biomarkers.

RESULTS

We included 137 subjects, including 82 boys (60%) and 55 girls (40%), the mean age of the included children was 6.2±4.7 years. The minimum age was 6 months and the maximum age was 17 years.

The subjects' medical history reported that 123 subjects or 89.8% (95% CI [84.5%-94.9%]) had received a transfusion at least once in their lifetime. Median number of transfusions=3, minimum=0, maximum=8. Ninety-one subjects, or 66.4% (95% CI [58.5%-74.3%]) were poly transfused. A history of urinary tract infections was found in 6 subjects (4.4%), 3 (2.2%) subjects had a history of uretero-hydronephrosis, and 5 (3.7%) had high blood pressure.

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

Proteinuria was negative in 131 cases (95,6%), positive at one cross in 5 cases (3.6%), positive at two crosses in 1 case (0.8%). Haematuria was negative in 97.1% of cases (n=133), and positive for a cross in 2.9% (4 cases).

The mean haemoglobin level was 7.6±1.8 g/dl, the means of the biomarkers used to calculate the glomerular filtration rate are noted in Table 1.

Table 1: Haemoglobin 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

The mean GFR was 112±45.3 ml/min/1.73 m^2. A total of 36 subjects, or 26.3% (95% CI [18.9-33.6%]), had acute AKI, including 16% (n=22) with mild acute AKI, and 10.2% (n=14) with moderate acute failure.

Comparison of characteristics by AKI status showed significant differences by sex, number of transfusions, and haemoglobin 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% IC (1.05 [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% IC [1.3; 2,7]) p<0.001.

Table 2: Comparison of variables analysed by AKI status.

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

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

Variables	Correlation coefficient (95% CI)	P value	Test
Age (in years)	-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
Haemoglobin level (g/dl)	0.172 (-0.0271; 0.358)	0.09	Pearson
WAZ	0.0853 (-0.138; 0.301)	0.45	Pearson

DISCUSSION

Renal function of subjects included in our study was impaired in 26.3% of cases had GFR below established norms. Epidemiological context of Gabon alone justifies constant research and care improvement efforts in the management of sickle cell patients. Gabon has a prevalence of nearly 1.5% of sickle cell patients and 25% of carriers of the trait. Gabon is located in the heart of the geographical area where both the haplotype of sickle cell anemia associated with more clinical severity (Bantu or CAR) are found, as well as *P. falciparum,* which is fatal or severe, including kidney damage.[7-9]

Some series report that 12% of children with SCD with renal kidney disease will progress to end-stage renal disease.[10] This treatment makes the conventional management of the steady state more cumbersome.[11] This prevalence is quite high compared to that of Ndour et al who found 9.68% AKI but using the eGFRcr. 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 difference between our series and that of Ndour et al can result in the diagnostic tool chosen (eDFGcr vs eDFG cr-cys), but also in the haplotype of our region (Bantu-CAR). Estimation of renal function using the simultaneous assessment of GFR of cystatin C and creatinine is more suitable for chronic situations mainly with malnutrition, which is the case for SCD, 99.9% of sickle cell patients in Gabon are Bantu-CAR haplotype, presenting with more severe clinical forms, while the Senegal haplotype is the one with the least clinical severity.[1,5,7,8]

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 the causes in our settings can be grouped into two categories: the lack of national recommendations and the severe clinical expression of our haplotype. There are no national recommendations for the management of SCD in Gabon. There is no transfusion exchange program, no government-recommended administration of hydroxyurea, nor is there access to other molecules recommended elsewhere.[1,12,13] In our African context, 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 countries, 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 resolutions recently taken on birth screening, but also on early access to different therapies.[13,17] Transfusion exchange programs could be revived due to new data on efficacy, low cost-to-carbon footprint ratio, and whole blood utilization.[15,18,19]

Denutrition were 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 denutrition 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 between the proportion of malnourished sickle cell children in these two countries may be based on GDP per capita.[21] The 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 take into account the nutrition of the sickle cell patient, but also the 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 abnormality processes that include recurrent hypoxia-reperfusion lesions induced by vaso-occlusive crises, which could also lead to a reduction in the ability to absorb nutrients.[24]

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

CONCLUSION

The kidney function of the subjects included in our study was in about 3 out of 10 subjects had GFR below established norms. This is a high proportion. Given their

young age, these patients will therefore require monitoring and perhaps management of this anomaly to prevent progression to chronicity and a terminal phase. Management programs exist and need to be implemented in order to reduce complications and mortality related to this pathology.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2021 Sickle Cell Disease Collaborators. Global, regional, and national prevalence and mortality burden of sickle cell disease, 2000-2021: a systematic analysis from the Global Burden of Disease Study 2021. Lancet Haematol. 2023;10(8):E585-99.
2. Adebayo OC, Van den Heuvel LP, Olowu W, Levtechenko EN, Labarque V. Sickle cell nephropathy: insights into the pediatric population. Pediatr Nephrol. 2022;37(6):1231-43.
3. Afangbedji N, Jerebtsova M. Glomerular filtration rate abnormalities in sickle cell disease. Front Med. 2022;9:1029224.
4. Belisário AR, Dda Silva AA, Silva CV, De Souza LM, Wakabayashi EA, et al. Sickle cell disease nephropathy: an update on risk factors and potential biomarkers in pediatric patients. Biomark Med. 2019;13(11):967-87.
5. Kidney Disease Improving Global Outcomes (KDIGO). KDIGO 2023 clinical practice guideline for the evaluation and management of chronic kidney disease. Available at: KDIGO-2023-CKD-Guideline-Public-Review-Draft5-July-2023.pdf. Accessed on 28 January, 2024.
6. Ndour EHM, Dione R, Gueye Tall F, Mazandu GK, Mnika K, et al. Determination of glomerular filtration rate during sickle cell disease in Senegal: Schwartz, Cockcroft and Gault, MDRD, CKD-EPI or JSCCS? Int J Biol Chem Sci. 2021;15(6):2283-96.
7. Delicate-Loembet LM, Elguero E, Arnathau C, Durand P, Ollomo B, Ossari S, et al. Prevalence of the sickle cell trait in Gabon: a nationwide study. Infect Genet Evol. 2014;25:52-6.
8. Piel FB, Steinberg MH, Rees DC. Sickle Cell Disease. N Engl J Med. 2017;377(3):305.
9. Zoleko Manego R, Koehne E, Kreidenweiss A, Nzigou Mombo B, Adegbite BR, Dimessa Mbadinga LB, et al. Description of Plasmodium falciparum infections in central Gabon demonstrating high parasite densities among symptomatic adolescents and adults. Malar J. 2019;18(1):371.
10. Roy NB, Carpenter A, Dale-Harris I, Dorée C, Estcourt LJ. Interventions for chronic kidney disease in people with sickle cell disease. Cochrane Database Syst Rev. 2023;8(8):CD012380.
11. Amarapurkar P, Roberts L, Navarrete J, El Rassi F. Sickle Cell Disease and Kidney. Adv Chronic Kidney Dis 2022;29(2):141-8.
12. Directorate-General for Statistics (DGS). Third Demographic and Health Survey (2019-2021) 2023 (French). Gabon-Third Demographic and Health Survey 2019-2021. Available at: https://dhsprogram.com/publications/publication-FR371-DHS-Final-Reports.cfm. Accessed on 28 January, 2024.
13. World Health Organization, African Region. African health ministers launch drive to curb sickle cell disease toll 2022. Available at: https://www.afro.who.int/news/african-health-ministers-launch-drive-curb-sickle-cell-disease-toll. Accessed on 28 January, 2024.
14. WHO. Blood safety and availability. 2020. Available at: https://www.who.int/news-room/fact-sheets/detail/blood-safety-and-availability. Accessed on 28 January, 2024.
15. Maitland K, Kiguli S, Olupot-Olupot P, Opoka RO, Chimalizeni Y, Alaroker F, et al. Transfusion management of severe anaemia in African children: a consensus algorithm. Br J Haematol. 2021;193(6):1247-59.
16. Payán-Pernía S, Ruiz Llobet A, Remacha Sevilla ÁF, Egido J, Ballarín Castán JA, Moreno JA. Sickle cell nephropathy. Clinical manifestations and new mechanisms involved in kidney injury. Nefrologia (Engl Ed). 2021;41(4):373-82.
17. Piel FB, Rees DC, DeBaun MR, Nnodu O, Ranque B, Thompson AA, et al. Defining global strategies to improve outcomes in sickle cell disease: a Lancet Haematology Commission. Lancet Haematol. 2023;10(8):E633-86.
18. Doughty HA, Hervig TA. Whole blood for transfusion in sub-Saharan Africa. Lancet Glob Health. 2022;10(3):E303-4.
19. George EC, Uyoga S, M'baya B, Kyeyune Byabazair D, Kiguli S, Olupot-Olupot P, et al. TRACT trial study group. Whole blood versus red cell concentrates for children with severe anaemia: a secondary analysis of the Transfusion and Treatment of African Children (TRACT) trial. Lancet Glob Health. 2022;10(3):E360-8.
20. Islam MR, Moinuddin MD, Ahmed A, Rahman SM. Association of sickle cell disease with anthropometric indices 1 among under-five children: evidence from 2018 Nigeria Demographic and Health Survey. BMC Med. 2021;19(1):5.
21. The World Bank. GDP per capita. 2022. Available at: https://data.worldbank.org/indicator/NY.GDP.PCAP.CD. Accessed on 28 January, 2024.
22. Alexandre-Heymann L, Dubert M, Diallo DA, Diop S, Tolo A, Belinga S, et al. Prevalence and correlates of growth failure in young African patients with sickle cell disease. Br J Haematol. 2019;184(2):253-62.

23. Williams TN. Undernutrition: a major but potentially preventable cause of poor outcomes in children living with sickle cell disease in Africa. BMC Med. 2021;19(1):17.
24. Dutta D, Methe B, Amar S, Morris A, Lim SH. Intestinal injury and gut permeability in sickle cell disease. J Transl Med. 2019;17(1):183.
25. Olaniran KO, Eneanya ND, Allegretti AS, Zhao SH, Achebe MM, Thadhani RI. Cardiovascular Outcomes in African Americans with Sickle Cell Trait and Chronic Kidney Disease. Am J Nephrol. 2019;49(2):93-102.
26. Neugarten J, Golestaneh L. Sex Differences in Acute Kidney Injury. Semin Nephrol. 2022;42(2):208-18.

Cite this article as: Minto'o S, Loembe FC, Mpira S, Nguemou N, Siawaya JD, Koko J, et al. Evaluation of renal function of sickle cell children in Libreville by estimation of glomerular creatinine-cystatin C filtration rate: prevalence of acute kidney injury and associated factors. Int J Contemp Pediatr 2024;11:630-5.