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*Original Article*

# Association between renal function parameters, clinical severity score and mortality risk among adult Sudanese sickle anemia patients

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**Abstract:** Background: Sickle Cell Anemia (SCA) is an autosomal recessive haemoglobinopathy with high morbidity and mortality. Global survival of sickle patients is increased due to advances in management; and subsequently, prevalence of chronic complications including renal manifestations also increased. Therefore, early detection and management of these complications is mandatory. This study aimed to investigate the estimated Glomerular Filtration Rate (eGFR), proteinuria and serum uric acid as markers of renal involvement in Sudanese sickle adults and association between these parameters and clinical severity score of sickle cell disease. Methods: Cross-sectional hospital-based study included thirty-two adult Sudanese patients diagnosed with SCA and twenty-three as controls. Written informed consent was obtained from each participant. Blood and urine samples were collected. Severity score was calculated using Bios online calculator and eGFR was calculated using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula without adjustment for ethnicity. Associations between the severity score and renal parameters were tested using unpaired T test and Mann Whitney test for normally and non-normally distributed data and correlations between variables were tested using SPSS version 23. Results: Protein/Creatinine Ratio (PCR) was significantly higher ($p$-value < 0.001) in sickle cell anaemia group compared to controls. Hyper-filtration and Hyperuricemia were manifested in 75% and 6.3% of SCA group respectively. There was no association between the severity score and renal manifestations in the SCA group. Conclusions: Hyper-filtration and proteinuria were the most prevalent renal manifestations in SCA group. Further studies are recommended to determine the predictors of renal complications and ensure early management of such complications.

**Keywords:** Sickle cell anemia, glomerular hyper-filtration, proteinuria, hyper-uricemia

## Introduction

Sickle cell anemia (SCA) is an autosomal recessive disease resulting from substitution of amino acid glutamate by valine in position 6 of beta-globin chain [1]. Sickle Cell Disease is the most inherited blood disorder worldwide [2]. In USA approximately one in every thirteen African American have sickle cell trait and in some African regions the prevalence of SCA may reach up to 30% [3].

Sickling of the RBCs, hemolysis, increase viscosity, vaso-occlusion, hypoxia, and ischemia-reperfusion injury are the hallmarks of the SCD [4]. Survival age increases in patients with SCA due to advances in management leading to widespread tissue necrosis and end organ damage [5]. Renal impairment predominates organs failure among adult SCA patients [6]. Sickle cell disease should be considered as syndrome affecting all body organs rather than just hematological disease [7].

This study aimed to measure proteinuria, uric acid level, and estimated GFR as markers of renal function in steady state SCA adult patients, and to identify the associations between these parameters and the clinical severity score of SCA. Studying renal parameters in SCA enables early detection and management of renal complications to decrease morbidity, mortality and improve quality of life (QOL). Best to our knowledge this is the first study that investigated renal parameters and their association with the severity score among sickle cell anemia patients.

## Methods

*Study area and population*

This study is a cross sectional hospital-based study. A total sample of 32 SCA adult patients (13 males, 19 females) in a steady state, who attended the hematology referred clinic in the hospital during the study period from October to December 2017. Control group (11 males, 12 females) were healthy students recruited from Faculty of Medicine, Al Neelain University.

*Inclusion and exclusion criteria*

Adult (≥ 18 years) SCA Hb SS as evidenced by electrophoresis. Patients in steady state who attended the clinic and accepted to participate in the study were included in the study. Healthy control was Hb AA. Diabetic patients, Chronic Kidney Disease (CKD) patients, patients with acute illness or need hospital admission and pregnant women were excluded.

*Characteristics of the study population*

Participants were classified according to the last American Heart Association classification of hypertension into: normal BP, elevated BP, stage 1 and stage 2 hypertension; if their BP < 120/80, 120-129/80, 130-140/80-90 and > 140/90 respectively [8].

Patients were classified according to the WHO classification of BMI available at (http://apps.who.int/bmi/index).

Venous blood sample (5 ml) was obtained from each participant and sent to the laboratory for CBC, RFT, UA, bilirubin and reticulocyte count using Automated Hematology Analyzer (BC-2800 Mindary, Nanshan, China). Random spot urine collected and analyzed for PCR using colorimetric method. Study population classified according to their PCR using NICE Guidelines to a group with significant proteinuria if PCR ≥ 50 mg/mmol and another with non-significant proteinuria when PCR < 50 mg/mmol [9].

*Renal parameters among participants*

GFR was calculated using CKD-EPI formula without adjustment for ethnicity which is the best GFR formula for SCD [10]. GFR < 60 ml/min/1.73 $m^2$ regarded as CKD. Despite there is no consensus about the cut-off point of hyper-filtration; more than 130 ml/min/1.73 $m^2$ in females and > 140 in males is regarded as glomerular hyper-filtration based on previous reported literature [11].

*CKD-EPI without adjustment of ethnicity formula*

GFR (ml/min/1.73 $m^2$) = 141 min (S.Cr/k, 1)$^{\alpha}$ × max (S.Cr/k, 1)$^{-1.209}$ × 0.993$^{age}$ × 1.018 (if female), whereas S.Cr is Serum Creatinine, k is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min: indicates the minimum of S.Cr/k or 1, and max indicates the maximum of S.Cr/k or 1.

*Severity score of SCA patients*

Severity score is an estimation of 5-year risk of death among SCD was calculated using a validated online clinical severity score calculator based on study made by Sebastian et al. [12, 13], available freely online at *http:/bios.ugr.es/dss-calculator*. Fifteen out of sixteen clinical and laboratory characteristics were entered to the online calculator. Severity Score Variables include: Stroke, blood transfusion times, pain, priapism, acute coronary syndrome, avascular necrosis, systolic blood pressure, Hemoglobin, Hb genotype, MCV, TWBCs, Reticulocyte count, and Serum bilirubin beside age and gender. Patients were classified in to high, moderate and low risk of death if they score > 0.72, (0.55-0.72) and < 0.55 respectively according to Sebastiani et al. study [13].

*Data analysis and ethical considerations*

Data were summarized and analysed using SPSS version 23. One-sample Kolmogorov-Smirnov Test was used to test the distributions of variables. Unpaired T. Test was used to study association for normally distributed variables and Mann Whitney U test for non-normally distributed ones. A correlation analysis was applied in SPSS to investigate the relation between study variables. *P*-value < 0.05 was considered as statistically significant cut off point.

Study was ethically approved from Institutional Review Board (IRB) of Al Neelain University. Informed written consents were obtained from participants after explaining the purpose, pro-

**Table 1.** Basic characteristics of study population

| Variable | SCA group | Control | *P*. Value |
|---|---|---|---|
| Gender | | | |
| Male | 13 (40.6%) | 11 (47.8%) | |
| Female | 19 (59.4%) | 12 (52.2%) | |
| Age (years) | 23.9±6.1 | 22.1±4.1 | 0.34 |
| BMI (Kg/m$^2$) | 17.6±2.6 | 23±4.8 | < 0.001* |

**p*-value is significant; BMI: Body mass index.

**Table 2.** Severity score laboratory characteristics of SCA group

| Variables | Mean ± SD |
|---|---|
| Hb (mg/dl) | 7.6±1.6 |
| MCV (fl) | 88.9±11.6 |
| Retics (%) | 2.5±0.6 |
| TWBC (× 10$^9$/l) | 13.2±3.4 |
| D. bilirubin (mg/dl) | 0.7±0.8 |
| I. bilirubin (mg/dl) | 1.3±1.6 |

cedures and measurement needed for the study.

## Results

*Characteristics of study population*

Most of our participants were < 25 years. According to WHO classification 71.9% of SCA group were underweight and only 3.1% were overweight. In control group 21.7% were underweight and 56.6% had normal BMI (**Table 1**). **Table 2** represented laboratory characteristic of SCA patients.

*Renal parameters among SCA patients*

Hyper-filtration was observed in 75% and significant proteinuria was reported in 12.5% while hyperuricemia reported in 6.3% of SCA patients. **Table 3** illustrates renal parameters among SCA patients and the control group. According to the guidelines, 84.4% of SCD group have normal BP, 12.5% have elevated BP and 3.1% have stage II systolic HTN, while 87% of the control have normal systolic BP, 13% have an elevated BP. 6.3% of SCD group have stage I diastolic HTN and none of the control group have diastolic HTN.

*Severity score*

The mean severity score of SCA group was 0.69. SCA patients were stratified according to their severity score in to: Mild, moderate and severe according to Sebastiani et al. [13]. (**Table 4**) shows severity score grading of SCA group.

There is no correlation observed between the severity score and renal parameters in this study, but there is positive correlation between: PCR and systolic BP (*P* value = 0.01) and age with systolic and diastolic BP (*P* value = 0.001 and 0.03 respectively). (**Table 5**) shows the correlation between renal parameters, age, BP and severity score.

## Discussion

This study proposed to investigate renal characteristics (proteinuria, eGFR and uric acid level) among sickle cell anemia patients and their association with severity score of SCA. Hyper-filtration and glomerular hypertrophy dominate early onset renal involvement in Sickle Cell Anemia; as the disease progress with time, eGFR decreases due to increased fibrosis and glomerulosclerosis [14]. Low eGFR was not reported in this study among SCA patients unlike other studies [14-16]; this may be due to the low BMI and younger age of the patients. In contrast, all control groups had normal eGFR (**Table 3**).

Significant proteinuria was detected in 12.5% of SCA patients while none of the control group had significant proteinuria; this might have resulted from tubular damage, increase glomerular permeability related to repeated vaso-occlusive crisis and poor management of SCA [4]. A retrospective study conducted in inpatients adult Sudanese with SCD, reported proteinuria in 81.8% of patients [17]; this may indicate a higher level of proteinuria in SCA patients during crisis. Proteinuria is a prevalent complication of SCD, it was detected in variable proportions in many previous studies for example: Jamaican's (65.3%) [15], North American's (42.8% [16] and 65.6% [14]) and Nigerian's (51%) [18], this variation may result from specific nucleotide polymorphism [19]. Further studies are necessary in this area to identify if there are specific genetic polymorphisms in Sudanese SCA patients related to proteinuria. In this study, proteinuria grade was determined through a spot urine PCR as an acceptable alternative for ACR [20].

**Table 3.** Renal parameters comparison among SCA and control groups

| Variable | SCD | Control | *P*-value |
|---|---|---|---|
| | Mean ± SD | Mean ± SD | |
| Urea (mg/dl) | 21.6±8.4 | 33.8±5.9 | < 0.001* |
| Creatinine (mg/dl) | 0.65±0.18 | 0.7±0.03 | 0.386 |
| eGFR (ml/min) | 149.7±29.6 | 127.5±5.1 | < 0.001* |
| PCR (mg/mmol) | 30.9±25.2 | 17.3±3.4 | < 0.001* |
| UA (mg/dl) | 5.3±3.3 | 4.1±1 | 0.086 |
| Systolic BP (mmHg) | 112±14 | 114±10 | 0.45 |
| Diastolic BP (mmHg) | 67±11 | 72±6 | 0.02* |
| MAP | 82.2±10.2 | 86.7±6.5 | 0.06 |

*: Statistically significant; GFR: glomerular filtration rate; PCR: protein creatinine ratio; UA: uric acid; MAP: mean arterial pressure.

**Table 4.** Severity score grading of SCA group

| MORTALITY | N | % |
|---|---|---|
| HIGH (> 0.72) | 17 | 53.1 |
| MODERATE (0.55-0.72) | 11 | 34.4 |
| LOW (< 0.55) | 4 | 12.5 |

N: number of SCA patients; %: percentage among SCA group.

More than 50% of SCA patients in this study scored a high risk of death (severity score > 0.72) (**Table 4**). Using the same calculator, a previous investigation conducted in referral center of hemoglobinopathies in London found that only 12% of SCA had severe risk of death [21]. This high severity score among Sudanese study population requires early preventive measures to decrease morbidity and mortality among adults Sudanese SCA patients.

Significant reduction in diastolic Blood Pressure (BP) was noted (*p* value 0.02) in SCA group compared to the control group. Other studies also showed similar observations [14, 22, 23]. This may be due to loss of sodium and water related to medullary tonicity defects [24]. In addition to, high levels prostaglandin, decrease vascular reactivity and systemic vaso-dilatation response to micro-vascular dysfunction [4] or might be due to chronic activation of Nitric Oxide system (NO) [12, 22].

Positive correlation was observed in the current study between SBP and PCR among SCA patients (*P* value = 0.013) (**Table 3**). This correlation was documented among hypertensive patients in a previous study which also stated that both proteinuria and hypertension can increase cardiovascular and renal risks independently [25]. There was also positive correlation between SBP and age which can be explained by aging process and chronic depletion of nitric oxide due to its consumption in SCA patients [26].

Uric acid was used as a marker of renal function [27]. In SCA high uric acid level may result from increased haemolysis and rapid turnover of the RBCs and decreased uric acid clearance by the kidneys [28]. No significant difference regarding UA between sickle and control group (**Table 3**), this finding is similar to former study among Sudanese population [23]. In this study hyperuricemia is reported only in 6.3% of SCA group; this likely due to the compensation of the high GFR i.e. high UA clearance among those young group; as age increases, GFR decreases and they may develop higher rates of hyperuricemia [29]. Hyperfiltration, proteinuria, high UA levels and lower BP were also reported in similar study conducted in Congo SCD pediatrics populations [30]; which indicated the early onset of renal pathophysiological processes in SCD patients.

This report demonstrated that patients with SCA in spite having normal urea, creatinine, UA levels and lower diastolic BP in compere to control group, but they suffered from hyper-filtration and proteinuria. Eventually they may end up with CKD, hypertension and hyperuricemia. Therefore, physician of SCA patients should consider those early signs of SCN and manage them appropriately to prevent further complications. In spite of lack of association of severity score with each individual renal parameter but we observed that both impaired renal parameters and severity score were high among our SCA group; so, modified severity score may be implemented and validated to address these renal manifestations among sickle cell anemia patients as potential risk factors.

In conclusion, Proteinuria and hyper-filtration were the most prevalent renal manifestation in SCA patients. SCA patient had higher UA level and lower BP compared to control group. There was lack of association between the clinical severity score and renal manifestations of SCA.

**Table 5.** Correlation of Renal Parameters, BP, Age and severity score among SCA

| | | AGE | SBP | DBP | Uric acid | eGFR | PCR | S.SCORE |
|---|---|---|---|---|---|---|---|---|
| AGE | R | 1 | .573* | .378* | 0.324 | -0.315 | 0.273 | 0.239 |
| | *P*-value | | 0.001 | 0.033 | 0.071 | 0.079 | 0.13 | 0.187 |
| SBP | R | .573 | 1 | 0.347 | 0.147 | -0.155 | .436* | 0.316 |
| | *P*-value | 0.001 | | 0.052 | 0.421 | 0.396 | 0.013 | 0.078 |
| DBP | R | .378* | 0.347 | 1 | -0.026 | 0.029 | -0.092 | -0.036 |
| | *P*-value | 0.033 | 0.052 | | 0.886 | 0.876 | 0.615 | 0.846 |
| Uric acid | R | 0.324 | 0.147 | -0.026 | 1 | -0.303 | -0.031 | 0.153 |
| | *P*-value | 0.071 | 0.421 | 0.886 | | 0.092 | 0.865 | 0.403 |
| eGFR | R | -0.315 | -0.155 | 0.029 | -0.303 | 1 | -0.055 | -0.123 |
| | *P*-value | 0.079 | 0.396 | 0.876 | 0.092 | | 0.766 | 0.501 |
| PCR | R | 0.273 | .436* | -0.092 | -0.031 | -0.055 | 1 | 0.142 |
| | *P*-value | 0.13 | 0.013 | 0.615 | 0.865 | 0.766 | | 0.437 |
| S.SCORE | R | 0.239 | 0.316 | -0.036 | 0.153 | -0.123 | 0.142 | 1 |
| | *P*-value | 0.187 | 0.078 | 0.846 | 0.403 | 0.501 | 0.437 | |

*Correlation is significant at the 0.05 level (2 tailed).

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## Disclosure of conflict of interest

None.

## Abbreviations

BP, Blood Pressure; CKD, Chronic kidney Disease; eGFR, Estimated Glomerular Filtration Rate; GFR, Glomerular Filtration Rate; PCR, Protein to Creatinine Ratio; SCA, Sickle Cell Anemia; UA, Uric Acid; SCD, Sickle Cell Disease; SCN, Sickle Cell Nephropathy; WBC, White Blood Count.

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