Original Article

# Comparison of CKD-EPI versus MDRD and Cockcroft-Gault Equations to Estimate Glomerular Filtration Rate among Stable Homozygous Sickle Cell Patients in Southwest Nigeria

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**Abstract**

**Background:** Homozygous sickle cell patients are prone to renal damage which can be on-going in and out of crises, therefore, there is a need to monitor renal status using glomerular filtration rate. Equations to estimate GFR are readily available. Cockcroft-Gault equation is widely used, while the MDRD formula is the currently accepted equation. The CKD-EPI equation is recently being recommended but has not been validated among HbSS patients. Therefore, we aim to compare estimated GFR using CKD-EPI versus MDRD and Cockcroft-Gault equations among HbSS patients. **Material and Methods:** This was a cross-sectional study of stable HbSS patients. Information on their age, sex, and weight was collected. Their venous blood samples were also obtained for plasma creatinine determination which was used to calculate estimated GFR using Cockcroft-Gault, MDRD and CKD-EPI equations. Student t-test, Pearson correlation, and Bland-Altman difference plots were performed. A p-value of $< 0.05$ was considered to be significant. **Results:** One hundred and twenty patients comprising 60 HbSS patients and 60 HbAA controls participated in the study. The HbSS patients had mean ± SD age of 26±6.7years, plasma creatinine 77 ± 17umol/L, eGFR: CG 93±31.6ml/min, MDRD 124 ± 34.8ml/min/1.73m$^2$, CKD-EPI 122 ± 25.1ml/min/1.73m$^2$ ($p<0.0001$). Hyperfiltration was observed in 20(33.3%) of the HbSS patients. CKD-EPI had stronger positive correlation with MDRD ($n = 60$, $r = 0.93$) and less bias (SD = 14.7) than with CG ($n = 60$, $r = 0.76$, SD = 20). **Conclusion:** CKD-EPI equation is best for individuals with GFR > 60ml/min/1.73m$^2$. This study has shown that it correlates well with the currently acceptable MDRD equation, therefore, can be used to monitor the renal status of stable HbSS patients. CG gives poor correlation and bias with CKD-EPI. Further validation studies on CKD-EPI equation are needed in different patient populations.

**Keywords:** *CKD-EPI, Cockcroft-Gault equation, Glomerular filtration rate, MDRD equation, sickle cell anaemia,*

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## Introduction

Sickle cell anaemia (SCA) is a disorder of the blood caused by an inherited abnormality of haemoglobin. It is classified as a sickle cell disorder that is associated with the inheritance of homozygous haemoglobin S gene (HbSS).[1] It has a prevalence of 20 per 1000 births in Nigeria, therefore 150,000 children are born with SCA annually.[2] Clinically, SCA exists in two states; steady state and crisis state, of which the steady state can be defined as periods of well-being during the management of HbSS patients.

Sickle cell anaemia is a multi-systemic disorder which may result in end-organ damage, including renal manifestations which range from various functional abnormalities to gross anatomic alterations of the kidneys.[3] The inner medulla's relatively hypoxic, hypertonic, and acidotic environment is known to be predisposed to sickling of red blood cells in these patients, which significantly decreases renal medullary blood flow through vaso-occlusion,[4] resulting in injuries to the

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vasa recta.[5] Patients may develop glomerulopathy with proteinuria which may progress to chronic renal failure in 20% of cases.[6] Similarly, a study involving 1056 SCA patients with a median age of 20 years showed that after 40 years of follow up, 12% developed renal failure at a median age of 37 years.[7]

The possibility of kidney damage in HbSS patients necessitates the monitoring of their renal status. Glomerular filtration rate (GFR) is accepted as the best measure of overall kidney function both in good health and disease because it is the sum of the filtration rates in each of the functioning nephrons.[8] Continuous infusion urinary clearance of exogenous inulin is widely regarded as the gold standard for measuring GFR, because it is physiologically inert, stable in plasma; freely filtered at the glomerulus, neither secreted, reabsorbed, synthesized nor metabolized by the kidney; thus the amount filtered at the glomerulus is equal to the amount excreted in urine.[9] But it is inconvenient, expensive and laborious.[10] Therefore, creatinine which is an endogenous product of muscle cells released into body fluids at a constant rate is preferred for measurement. The amount of plasma cleared of creatinine by the glomerular filtration mechanism of the kidneys per unit time measures creatinine clearance (CrCl) which is an effective tool to evaluate kidney function.[11] However, it overestimates GFR due to the renal tubular secretion of creatinine, and timed CrCl is limited by the inaccuracy of urine specimen collection especially in ambulatory patients; making it at best an approximation of renal status.

Several formulae have been composed to estimate GFR by correcting for confounding variables that make the relationship between serum creatinine and GFR non-linear. Use of these equations has been shown to give more valid estimate of GFR than serum creatinine alone.[12] Of these, the National Kidney Foundation in USA had recommended Cockcroft-Gault (CG) and Modification of Diet in Renal Disease (MDRD) study equations in adults.[12] But recently, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation has been developed in order to create a formula more precise than the MDRD formula, especially when GFR is >60 mL/min per 1.73 m2,[13] as seen in healthy individuals.[14] This recent equation has been applied in several populations such as: obese individuals,[15] patients with scleroderma,[16] stroke,[17] and renal transplanted patients.[18]

Therefore, we aim to compare estimated GFR (eGFR) by CKD-EPI equation to that by MDRD and CG equations among steady-state HbSS patients.

## Materials and Methods

### Study design

The study was a cross-sectional study of eGFR of HbSS patients in steady state attending the Haematology clinic of the Obafemi Awolowo University Teaching Hospital Complex (OAUTHC) Ile-Ife, located in Osun state, Southwest Nigeria. The study was reviewed and approved by the Health Ethics Research Committee of the institution.

### Study population

Patients aged 18-54 years with confirmed HbSS haemoglobinopathy, who had not experienced any episode of crisis (painful/vasocclusive, sequestration, hyperhaemolytic and aplastic) in the last three months were included in the study. Those who had received blood transfusion in the previous three months; or had concomitant medical illnesses such as. hypertension, diabetes mellitus; or smoked cigarettes, were excluded. Age and sex- matched HbAA healthy individuals were recruited as controls. Informed consent was obtained from all the participants.

### Sample size determination

Using the formula $n = (z^2pq)/d^2$, where n = sample size, z= critical value at 95% confidence level, usually set at 1.96, p= Prevalence, q = 1-p, d = precision of 5% (0.05)[19] Prevalence of 3% was used as SCA affects 2-3% of Nigerians.[2] Inputting variables in formula, $n = (1.96^2 \times 0.03 \times 0.97/0.0025 = 45$. Extra 30% respondents were included to compensate for attrition,[19] leading to a calculated total sample size of 59. We aimed to exceed this sample size. Equal number of controls was included to ensure case: control ratio of 1:1.

### Data collection

The age and sex of participants were noted, and then their weights were measured using a calibrated weighing scale to the nearest 0.1 kg. Thereafter, 5mls of venous blood was collected via venipuncture into lithium heparin specimen tube, which was centrifuged at 4000xg for 10 minutes to obtain plasma for creatinine analysis. Plasma creatinine was analyzed by Jaffe-kinetic method using Randox kit (USA) calibrated with an isotope dilution mass spectrometry-traceable calibrator and reported in umol/L.

### Calculations

Estimated GFR (eGFR) was calculated using these formulae:

**Cockcroft-Gault**[20]:[(140-age) x weight in kg x 0.85 if female]/ (0.814 x plasma Cr in umol/L)

**MDRD equation**[21]: 186 x (plasma Cr in umol/L x 0.011312)-1.154 x age-0.203 x 1.210 if black x 0.742 if female

**CKD-EPI equation**[13]: 141 x min(Cr/k, 1)α x max(Cr/k, 1) -1.209 x 0.993age x 1.018 if female x 1.159 if black; where k= 0.7 for females, 0.9 for males; α= -0.329 for females, -0.411 for males.

### Data analysis

Data was entered into a Microsoft Excel spread sheet and analyzed with SPSS statistical package (version 20). Continuous variables were presented as means and standard deviation (SD). Student t-test was used to compare mean values of HbSS cases with HbAA controls. Pearson correlation was used to determine relationship between CG and MDRD with the new CKD-EPI; and Bland-Altman difference plots were drawn to display bias between them. The mean values of the three eGFR were compared using ANOVA. A p-value < 0.05 was considered to be statistically significant.

## Results

A total of one hundred and twenty(120) subjects participated in this study. Sixty(60) were HbSS comprising of 33 females and 27 age-matched males (p = 0.57) [Table 1]. Plasma creatinine concentration of 73 ± 15umol/L among the females was significantly lower than that of the males 82 ± 19.2umol/L (p < 0.04), as well as the MDRD and CKD-EPI eGFR (p < 0.02 respectively) [Table 1].

Despite the fact that the HbSS patients were age-matched to the HbAA controls(p = 0.07), their mean ± SD plasma creatinine concentration of 77 ± 17umol/L and 103 ± 24umol/L respectively differed significantly (p < 0.0001). Similarly, the HbSS patients' mean ± SD weight of 53 ± 9.6kg was significantly lower than that of the HbAA controls 65 ± 13kg (p < 0.0001) [Table 2].

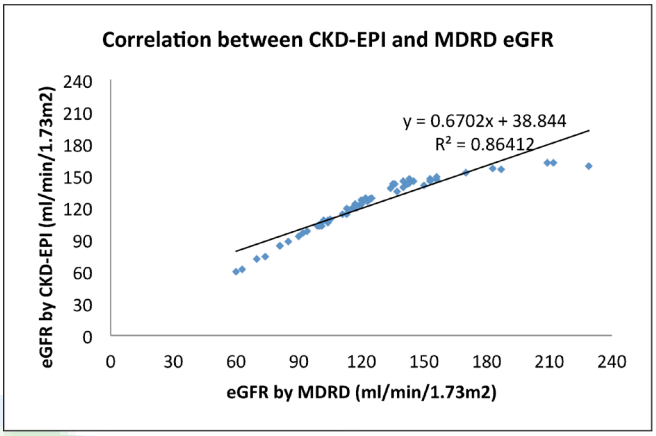


**Figure 1:** Correlation between CKD-EPI and MDRD eGFR

**Table 1: Demographics of HbSS patients (n=60)**

| | Females (n=33) | | Males (n=27) | | |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | p-value |
| Age (years) | 26 | 7.9 | 25 | 4.7 | 0.57 |
| Weight (kg) | 52 | 9.3 | 54 | 10 | 0.43 |
| Plasma Creatinine (umol/L) | 73 | 15.0 | 82 | 19.2 | 0.04* |
| Cockcroft-Gault eGFR (ml/min) | 91 | 33.3 | 97 | 29.3 | 0.47 |
| MDRD eGFR (ml/min/1.73m$^2$) | 116 | 33.2 | 137 | 34.5 | 0.02* |
| CKD-EPI eGFR (ml/min/1.73m$^2$) | 116 | 25.5 | 131 | 22.6 | 0.02* |

**Table 2: Comparison of variables between HbSS patients and HbAA controls**

| | HbSS patients (n=60) | | HbAA controls (n=60) | | |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | p-value |
| Age (years) | 26 | 6.7 | 29 | 8.7 | 0.07 |
| Weight (kg) | 53 | 9.6 | 65 | 13 | <0.0001* |
| Plasma Creatinine (umol/L) | 77 | 17 | 103 | 24 | <0.0001* |
| Cockcroft-Gault eGFR (ml/min) | 93 | 31.6 | 87 | 20 | 0.31 |
| MDRD eGFR (ml/min/1.73m$^2$) | 124 | 34.8 | 89 | 34 | <0.0001* |
| CKD-EPI eGFR (ml/min/1.73m$^2$) | 122 | 25.1 | 88 | 26 | <0.0001* |

**Table 3: Distribution of HbSS patients according to Chronic Kidney Disease staging[13]**

| CKD staging | GFR (ml/min/1.73m$^2$) | CG | MDRD | CKD-EPI |
|---|---|---|---|---|
| | | n (%) | n (%) | n (%) |
| Stage 1 | ≥90 | 32 (53.3) | 53 (88.3) | 53 (88.3) |
| Stage 2 | 60 – 89 | 20 (33.3) | 7 (11.7) | 7 (11.7) |
| Stage 3 | 30 – 59 | 8 (13.4) | 0 | 0 |

No HbSS patients were classified in Stages 4 (GFR 15 – 29ml/min/1.73m$^2$) and 5 (GFR <15ml/min/1.73m$^2$)

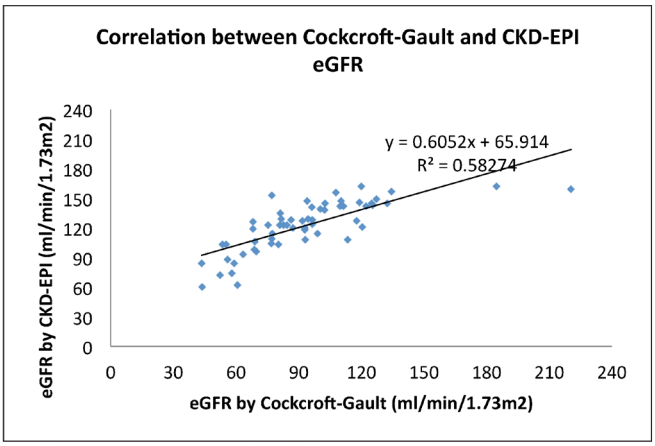


**Figure 2:** Correlation between Cockcroft-Gault and CKD-EPI eGFR

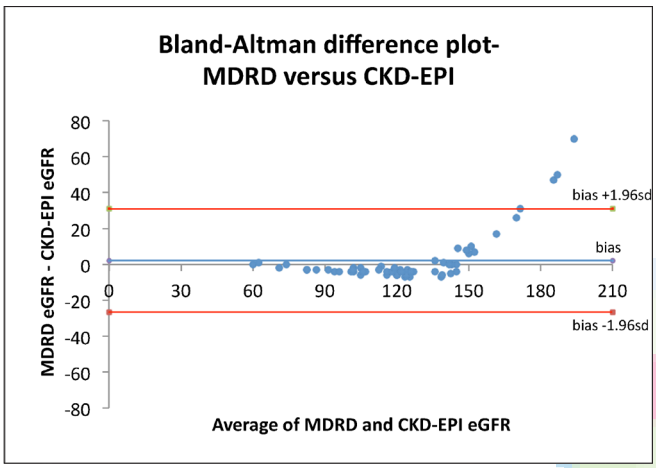


**Figure 3:** Bland-Altman difference plot: MDRD versus CKD-EPI eGFR

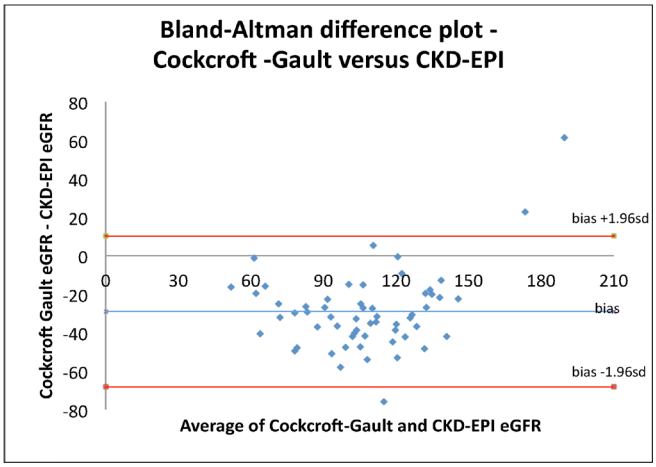


**Figure 4:** Bland-Altman difference plot: Cockcroft-Gault versus CKD-EPI eGFR

Inputting the plasma creatinine concentrations in the various equations resulted in mean ± SD eGFR of CG: 93 ± 31.6ml/min; MDRD: 124 ± 34.8ml/min/1.73m$^2$; CKD-EPI: 122 ± 25.1ml/min/1.73m$^2$ among the HbSS patients ($p < 0.0001$).

Comparison of these values with the HbAA eGFR showed statistically significant differences in eGFR by MDRD and CKD-EPI ($p < 0.0001$) but not CG ($p = 0.31$) [Table 2].

Majority of the HbSS eGFR were in CKD stage 1 where GFR is ≥ 90ml/min/1.73m2 [Table 3]. The three eGFR equations classified HbSS patients into stages 1 and 2; but only CG classified up to stage 3 CKD. No HbSS patients was classified in Stages 4 (GFR 15-29ml/min/1.73m$^2$) and 5 (GFR < 15ml/min/1.73m$^2$) [Table 3].

Using the CKD-EPI equation, 20 (33.3%) HbSS patients comprising 9 females and 11 males showed hyperfiltration, defined by GFR > 130ml/min/1.73m$^2$ in females and >140ml/min/1.73m$^2$ in males.[22] The maximum eGFR values observed were 159ml/min/1.73m$^2$ and 162ml/min/1.73m$^2$ among the females and males, respectively.

We observed a strong positive correlation of HbSS CKD-EPI versus MDRD n = 60, r = 0.93 [Figure 1] which was statistically significant $p < 0.001$. A weaker correlation was observed with CG: r = 0.76 [Figure 2].

Bland-Altman difference plot showed less bias between CKD-EPI and MDRD [Figure 3] than with CG [Figure 4] especially between GFR 60-150ml/min/1.73m$^2$.

## Discussion

The equations for estimating GFR include plasma creatinine concentration which is endogenously produced from the skeletal muscle. For this reason, females who have less muscle mass than males would have lower plasma creatinine concentrations and consequently lower eGFR which our study demonstrates. This is corroborated by Madu et al. who observed lower eGFR in females than males.[23]

We also observed lower plasma creatinine levels in HbSS patients 77 ± 17umol/L than the HbAA controls 103 ± 24umol/L ($p < 0.0001$) despite ensuring that our patients were age-matched to our controls ($p = 0.07$). This may be due to the asthenic build of sicklers, who typically have long bones and less muscle bulk as a compensatory mechanism to increase bone marrow for more erythropoiesis.

Classification of HbSS patients according to CKD staging showed majority of them were in stage 1 where GFR is ≥ 90ml/min/1.73m$^2$. This may be because our HbSS patients were in steady-state and therefore, their kidneys were not decompensated. Also, these patients were relatively young with a mean age of 26years. Older age has been identified as a socio-demographic factor

for susceptibility to and initiation of CKD resulting in lower GFR.[12]

Using the same cut-off values[22] we observed glomerular hyperfiltration in 33.3% of our HbSS patients, which was more than the 30.5% described by Marouf et al.,[22] but less than the 51% described by Haymann et al.,[24] although they both used the MDRD equation to generate their eGFR, while we used CKD-EPI. The hyperfiltration may be due to chronic haemolysis resulting in glomerular vasculopathy.[24] Also, in a study on adult SCA patients, hyperfiltration status was significantly associated with young age (median of 24.1years for men and 26.3years for women)(OR:0.79, 95% CI:0.71 to 0.89, p=0.0001),[24] which is similar to our patient's mean age of 26years.

The Cockcroft-Gault equation (CG) is one of the earliest GFR equations in use[20] and it has been the most widely used because it is easy to compute and produces a more accurate and precise estimate of GFR than measured CrCl, [25] although it is not normalized to body surface area. In this study, mean CG eGFR in the HbSS patients (93ml/min) was much less than that obtained with MDRD (124ml/min/1.73m$^2$) and CKD-EPI (122ml/min/1.73m$^2$) equations using the same serum creatinine concentration (n = 60, p < 0.0001). This was probably due to their low mean body weight which is a component of the CG equation, as this difference was not seen across the three eGFR from the HbAA controls (n = 60, p = 0.92)

In our study, using CG equation 8 (13.4%) of our HbSS patients were classified into Stage 3 CKD with GFR 30-59ml/min/1.73m2, which was not seen with the other formulas. This is similar to studies which showed classification of their HbSS patients up to CKD Stage 3 and 4, even when MDRD did not.[23,26]

After correlating eGFR from the 3 equations, our study showed a positive correlation between CG and CKD-EPI (r = 0.76), but a stronger correlation between MDRD and CKD-EPI (r = 0.93), especially when GFR is between 60-150ml/min/1.73m2. The Bland-Altman difference plots showed greater bias and more variation between CKD-EPI and CG than with MDRD. Asnani *et al*. compared the three formulas to 99mTc-DTPA-measured GFR and showed that they all differed from the target values with an overestimation of eGFR with increasing variability at higher GFR values, but CKD-EPI was the closest in its estimates over a wide range of GFR.[27] They explained that the differences in eGFR were due to differences in handling glomerular filtration by the sickled kidney.[27]

The MDRD study equation was developed as a better estimate of GFR than CG, and it had been validated extensively in Caucasian and African American populations between the ages of 18 and 70 with impaired kidney function (GFR < 60mL/min/1.73 m$^2$) and showed good performance in patients with all common causes of kidney disease.[28] Also, in a study of pooled clinical populations, MDRD and CKD-EPI were equally accurate in the subgroup with eGFR < 60ml/min/1.73m$^2$; but CKD-EPI was substantially more accurate in a subgroup with eGFR > 60ml/min/1.73m$^2$.[13] The results were consistent across studies and subgroups defined by age, sex, race, diabetes, transplant status and body mass index.[13] Therefore, CKD-EPI is a more appropriate equation to use for healthy or stable individuals where GFR is > 60ml/min/1.73m$^2$.

The major advantage of the MDRD study equation is its use in laboratories without IDMS-traceable calibration for creatinine measurement. But this is becoming obsolete due to standardization and improved laboratory quality practices. CKD-EPI is applied when serum creatinine concentration has been obtained from IDMS-traceable calibration.[13]

This study was limited in patients with eGFR < 60 mL/min/1.73m$^2$. It would have been interesting to see the correlation of the various eGFR at lower values of GFR. This was due to the stable status of the patients whose GFR tends to be > 60mL/min/1.73m$^2$. Also, we did not compare our calculated eGFR to a measured urine clearance method. Other studies have used radiologic (125I-iothalmate, 51Cr-EDTA, 99mTc-DTPA)[5,13,24] or non-radiologic materials (creatinine)[25] as their gold-standard. The former provide excellent measures of GFR but are not readily available, while the latter is subject to variations due to posture, diet, circadian rhythm,[29-31] as well as inaccurate urine collection. Furthermore, Aparicio *et al.* observed creatinine clearance underestimates GFR proportionally in SCA patients when compared to urinary clearance of 51Cr-EDTA, probably because renal tubular handling of creatinine is altered in SCA.[32]

Since measured GFR is not consistently superior to either creatinine-based or cystatin C-based equations in estimating GFR and explaining comorbidities related to renal disease,[33] and the CG and MDRD are the current eGFR methods in use by most clinicians, we compared the new CKD-EPI equation to them.

Equations are unsuitable for estimating GFR in patients with acute renal disorders because serum creatinine concentrations are changing rapidly, but they can be used for steady-state HbSS patients and health controls. CKD-EPI and MDRD equations can be used to estimate GFR more effectively than Cockcroft-Gault equation. CKD-EPI is the best choice for stable patients with GFR > 60 mL/min/1.73 m$^2$.

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IDO conceived the study; CLU obtained the data; IDO and CLU analyzed the data and drafted the article; IDO critically revised it for intellectual content. Both authors approved the final version to be published. Ethnical approval was obtained from the Health Research and Ethics committee of Obafemi Awolowo University Teaching Hospital Complex, Ife- Ife.

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## Conflicts of interest

There are no conflicts of interest

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