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ORIGINAL ARTICLE

Performance of creatinine and cystatin C-based equations to estimate glomerular filtration rate in African children with sickle cell anemia

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Abstract

Background Serum creatinine (SCr), the most used biomarker to evaluate glomerular filtration rate (GFR), might be inaccurate in children with sickle cell anemia (SCA). In this context, cystatin C (SCys) could be of interest. This study evaluated the performance of commonly used SCr- and SCys-based estimated GFR (eGFR) equations in African children with SCA.

Methods This cross-sectional study included 109 steady-state children with SCA aged 3–18 years, from the Democratic Republic of Congo. Measured GFR (mGFR) was obtained using iohexol plasma clearance. eGFR was calculated using commonly used SCr- and SCys-based equations in children. The performance of these equations was evaluated by calculating the bias, precision, and accuracy within 30% (P30) of mGFR.

Results The mean age of participants was 9.9 ± 4.2 years, and 48.6% were female. The median mGFR was 142 (IQR 119–169) mL/min/1.73 m^2. Of the equations studied, the FAS-Age SCr had the lowest bias (0.9 mL/min/1.73 m^2). However, the 95% limit of agreement was very wide (−80.3 to + 81.6). SCr failed to rise in an age-dependent manner, reflecting a progressive loss of muscle mass or increased tubular secretion. All SCys-based equations underestimated GFR and failed to detect hyperfiltration, but there was no age-related change in bias.

Conclusion These data show that all common eGFR equations using SCr or SCys poorly predict mGFR in African children with SCA. SCr-based equations potentially miss a decline in kidney function, which suggests that SCys could be the preferred marker in this population.

Keywords Creatinine · Cystatin C · Equations · Glomerular filtration rate · Sickle cell anemia

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Introduction

Sickle cell disease (SCD) is a group of inherited hemoglobin disorders with the highest prevalence observed in sub-Saharan Africa (SSA), where approximately 5.68 million people are affected [1, 2]. Individuals with SCD develop multiple alterations of kidney function, including hyperfiltration that begins in early childhood [3, 4]. Hyperfiltration can persist through adulthood and progress to albuminuria, chronic kidney disease (CKD), and ultimately kidney failure [5, 6]. In children with SCD, the prevalence of hyperfiltration varies between 16 and 98% [6]. It should be noted that there is no consensus for defining hyperfiltration in the SCD population since different thresholds and methods to determine glomerular filtration rate (GFR) have been used in this population [6].

Serum creatinine (SCr)-based estimated GFR (eGFR) equations are mostly used to determine GFR in patients with SCD [6]. However, this method has been shown to be less accurate in these patients [7]. These equations may overestimate GFR owing to increased tubular creatinine secretion and lower muscle mass seen in these patients [3, 7]. Moreover, the commonly used SCr measurement assay could affect the accuracy of these equations due to interference with some substances, especially bilirubin [7, 8]. Indeed, patients with SCD having a chronic hemolysis state tend to have elevated bilirubin concentrations, which could interfere with Jaffe SCr measurement, resulting in wrongly lower creatinine results. Therefore, the gold standard method to accurately determine GFR is the direct measurement of GFR using the clearance of an exogenous marker, such as inulin or iohexol [9, 10]. Iohexol is a non-ionic contrast agent that is not metabolized, reabsorbed, or secreted by the kidney, thus making it one of the reference markers for measuring GFR [9]. Although being the gold standard method, direct measurement of GFR is expensive, time-consuming, and challenging to perform, especially in the pediatric population [11, 12]. Notably, the usefulness of direct measurement of GFR in African children with SCD is understudied.

Furthermore, in the absence of the measured GFR (mGFR), serum cystatin C (SCys) has been reported as an alternative endogenous marker to SCr since it is independent of muscle mass, not secreted in the urine, and not affected by the presence of bilirubin [3]. In routine practice, GFR is estimated using various equations based on either SCr alone, SCys alone, or a combination of both in children with SCD. It is worth mentioning that none of these equations has been validated in these patients, especially those living in SSA. Ascertaining the most appropriate equation for estimating GFR in children with SCD is crucial for early detection and effective management of kidney disease [3]. Thus, the present study aimed to evaluate the performance of commonly used SCr- and SCys-based equations compared to the mGFR obtained with iohexol clearance in African children with sickle cell anemia (SCA), one of the most severe forms of SCD. In addition, this study aimed to determine the prevalence of hyperfiltration using mGFR compared to eGFR equations in this population.

Methods

Ethical considerations

The study protocol was approved by the Ethical Committee of the Public Health School of the University of Kinshasa (ESP/CE/131B/2021). Written informed consent was obtained from parents or legal guardians of children before enrollment.

Study design and participants

This cross-sectional study was conducted between March and December 2022, at the University Hospital of Kinshasa, the Democratic Republic of Congo (DRC). Participants included in the present study were recruited from our previous cohort of steady-state children with SCA aged 3 to 18 years [13]. This was a prospective observational study evaluating the progression and risk factors associated with kidney abnormalities in African children with SCA. Participants were enrolled in Kinshasa at SCD patient associations and SCD clinics recognized by the National SCD Control Program of the DRC. Participants were included in the study if they were in steady state (defined as the absence of acute SCA-related complications in the previous 4 weeks or more before the date of the visit) and after the confirmation of the SCA status by β-globin gene sequencing. Sociodemographic (age, gender), anthropometric (weight, height), clinical, and hematological parameters were collected from all participants, as previously described [13].

GFR measurement and estimation

GFR was measured using iohexol plasma clearance (Omnipaque®, 240 mg I/mL, GE Healthcare, Belgium), known as a reference method [9]. Details are described in the Supplementary Methods. The mGFR was calculated using the slope-intercept method and corrected using the Brochner-Mortensen equation [9]. All results of mGFR were indexed to body surface area (BSA) after the Brochner-Mortensen correction using the Gehan and George equation ($BSA = 0.0235 \times weight^{0.51456} \times height^{0.42246}$).

SCr was measured using a Jaffe method not IDMS-calibrated in Kinshasa, DRC, as previously described [14]. Serum samples were shipped to the Laboratory of Clinical Chemistry of the University Hospital of Liège (Belgium), where SCr was measured using an enzymatic method and SCys measured using a latex immunoturbidimetric method, both calibrated to the international standard reference material (Roche Diagnostics, Mannheim, Germany). GFR was estimated using different SCr- and SCys-based eGFR equations (Supplementary Table S1). Jaffe SCr was only used for the original Schwartz equation while all other SCr-based equations used IDMS-traceable enzymatic SCr. The latter was normalized (SCr/Q) using *Q* values designed for children of European descent, as previously described [14]. Indeed, due to the absence of specific *Q* values for African children, including those with SCA, we used *Q* values designed for European descent children. The latter has been shown to be effective in our previous cohort evaluating the applicability of different SCr-based eGFR equations in African children [14]. Since there is no consensus for defining hyperfiltration, we compared the proportion of patients with hyperfiltration using two different cutoffs with the first defined as a GFR > 135 mL/min/1.73 m^2, based on a literature review [15]. The second cutoff defined hyperfiltration as a GFR ≥ 180 mL/min/1.73 m^2 for children between 2 and 10 years of age and > 140 mL/min/1.73 m^2 for children more than 10 years of age as suggested by Lebensburger et al. for children with SCD [16].

Statistical analysis

Statistical analysis was performed using SAS 9.4 (SAS Institute, Inc., Cary, NC, USA) statistical package. Categorical variables were presented as counts and percentages, while continuous variables were presented as mean and standard deviation (SD) or median and interquartile range (IQR). The Student's *t*-test was used to compare the mean of two independent groups. The Mann–Whitney test was used to compare the median of two independent groups. Linear quantile regression analysis was used to investigate the age dependency of SCr/Q, eGFR equations, and mGFR. The correlation between eGFR and mGFR values was evaluated using Pearson's correlation coefficient. The performance of different equations was compared to mGFR using the following usual metrics: bias, precision, and P10/P30 accuracy. The median bias expressed the median difference between eGFR and mGFR (i.e., eGFR–mGFR) with a 95% confidence interval (CI). An absolute bias was considered small (< ± 5 mL/min/1.73 m^2), moderate (± 5–10 mL/min/1.73 m^2), or large (> ± 10 mL/min/1.73 m^2). The precision was evaluated by the interquartile range (IQR) of the bias, with higher IQR values reflecting greater imprecision [17]. P10 and P30 accuracy with a 95% CI described the percentage of eGFR values within ± 10% and ± 30% of mGFR [18, 19]. A P30 value of > 75% is considered "sufficient for good clinical decision-making" [19], although our goal was to achieve a P30 > 90%. To test whether an equation was different from another equation in the same population, we did not use statistical tests to avoid numerous *p*-value calculations, but the reader may consider an equation as different when the 95% CI between equations was not overlapping, which is a more conservative criterion.

Bland–Altman analysis was used to assess the agreement between the different eGFR equations compared with the mGFR. We presented the percentage agreement between the prevalence of hyperfiltration of mGFR and different eGFR equations using two definitions, with the first defined as a GFR > 135 mL/min/1.73 m^2, based on the literature review [15]. The second definition was a GFR ≥ 180 mL/min/1.73 m^2 for children between 2 and 10 years of age and > 140 mL/min/1.73 m^2 for children more than 10 years of age, suggested by Lebensburger et al. for children with SCD [16]. The threshold for statistical significance was 0.05.

Results

General characteristics of the study participants

A total of 115 children with SCA underwent iohexol measurements. Among them, 109 participants (56 boys and 53 girls) were included in the present study. The six remaining participants were excluded due to invalid results of mGFR. The general characteristics of the study participants are summarized in Table 1. The mean age was 9.9 ± 4.2 years. The median mGFR was 142 (IQR 119–169) mL/min/1.73 m^2. No difference was observed in the median mGFR, mean body mass index (BMI), and body surface area (BSA) between boys and girls ($p = 0.460$).

Serum creatinine and cystatin C values for age

While SCr values of young patients with SCA were between the reference band of healthy children, SCr failed to rise in older children, as shown in Fig. 1. This was also seen when SCr was normalized to mean SCr concentrations of healthy children (*Q* values calculated from the Hoste polynomials) [20] (Supplementary Fig. S1). There was no difference in the mean SCr/Q between boys (0.76) and girls (0.79) ($p = 0.452$), while both values were about 20–25% lower than the expected mean SCr/Q value of 1. Indeed, there was a clearly decreasing trend in SCr/Q with age after normalization of SCr.

Regarding SCys, there was no difference in mean values between boys (0.88 mg/L) and girls (0.89 mg/L) ($p = 0.890$).

Table 1 General characteristics of the study participants

Variables	Overall, $n=109$	Boys, $n=56$	Girls, $n=53$	p
Age (years)	9.9 (4.2)	10.0 (4.1)	9.7 (4.2)	0.884
Weight (kg), median (IQR)	24.0 (19.0–35.5)	25.5 (19.3–32.0)	23.0 (19.0–43.0)	0.707
Height (m)	1.32 (0.21)	1.30 (0.21)	1.33 (0.22)	0.451
BMI (kg/m^2)	15.4 (2.5)	15.4 (2.4)	15.5 (2.7)	0.862
BSA (m^2)	1.01 (0.27)	0.99 (0.24)	1.04 (0.30)	0.358
SBP (mmHg)	105.2 (11.8)	103.5 (12.2)	107.0 (11.3)	0.143
DBP (mmHg)	63.8 (9.7)	61.8 (10.1)	65.9 (8.8)	**0.031**
LDH (U/L), median (IQR)	680.3 (511.2–968.0)	704.3 (475.9–968.4)	671.3 (538.2–939.4)	0.912
Total bilirubin (mg/dL), median (IQR)	1.80 (1.40–3.10)	1.70 (1.40–3.30)	2.05 (1.48–2.83)	0.699
Indirect bilirubin (mg/dL), median (IQR)	1.30 (1.00–2.30)	1.30 (1.00–2.25)	1.40 (0.90–2.30)	0.963
SCr Jaffe (mg/dL)*	0.47 (0.21)	0.46 (0.18)	0.48 (0.23)	0.655
SCr Enz (mg/dL)	0.39 (0.09)	0.39 (0.09)	0.38 (0.10)	0.717
SCys (mg/L)	0.89 (0.19)	0.89 (0.18)	0.89 (0.20)	0.890
mGFR (mL/min/1.73 m^2), median (IQR)	142 (119−169)	141 (118–173)	143 (121–163)	0.939

Data are presented as mean (standard deviation) or unless otherwise noted. *BMI*, body mass index; *BSA*, body surface area; *DBP*, diastolic blood pressure; *IQR*, interquartile range; *SBP*, systolic blood pressure; *SCr Enz*, serum creatinine measured by the calibrated enzymatic method; *SCr Jaffe*, serum creatinine measured by the Jaffe method; *SCys*, serum cystatin C. *Data on SCr measured by the Jaffe method were available for 104 participants

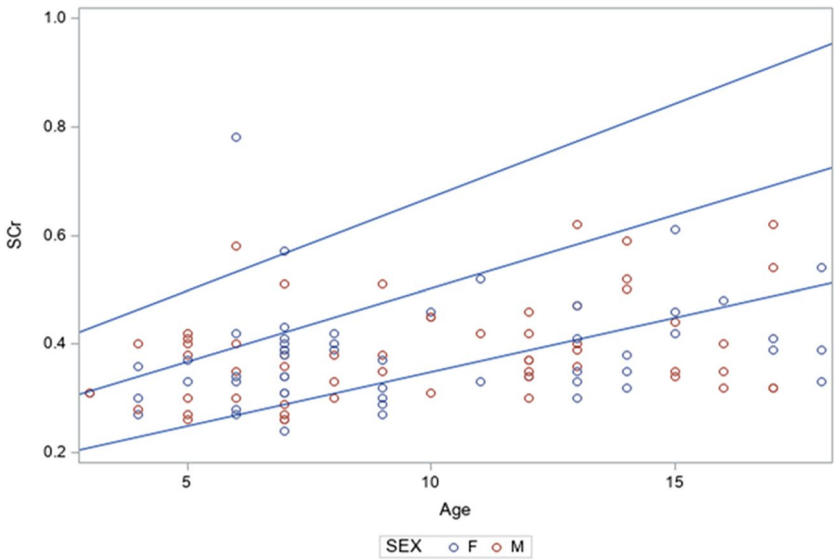

Fig. 1 Scatterplot of SCr (mg/dL) against age in children with SCA. The solid lines represent the median and reference interval for serum creatinine of healthy children. The linear lines for healthy children correspond to the linear equations: median SCr = 0.3679 + 0.027 × age, and lower and upper lines with SCr = 0.2499 + 0.0199 × age and SCr = 0.4987 + 0.0343 × age (as established by Pottel et al. (2008) Clinica Chimica Acta)

In addition, no age dependency was observed ($p=0.545$) (Supplementary Fig. S2).

GFR values in the study population

Table 2 shows the results of GFR values obtained from the mGFR and different equations. When regressing mGFR against age (Fig. 2), the slope was −1.02 ($p=0.306$), not significantly different from zero. However, the distribution of mGFR was shifted to higher values, from 107 (i.e., the mean mGFR of healthy children) to a median of 142 mL/min/1.73 m^2.

Overall, the highest eGFR was observed with original Schwartz and the lowest eGFR with LMR18 (Table 2). The effect of age dependency on the bias of SCr- and SCys-based eGFR is visualized in Fig. 3A and B, demonstrating a linear rise in bias for FAS-Age (slope = 6.49, $p<0.0001$), which was observed in all SCr-based and SCr-containing eGFRs (Supplementary Table S2). By contrast, pure SCys-based eGFR was independent of age. For instance, as shown in Fig. 3A, children with SCA aged < 5 years had relatively normal SCr and eGFR. However, beyond that age, SCr does not increase to the same extent as in healthy children, resulting in overestimations of predicted eGFR.

Table 2 Distribution of GFR values from mGFR and different equations

Equations	Mean (SD)	Median (LQ–UQ)	Min–max
Measured GFR	149 (43)	142 (119–169)	73–358
Creatinine-based equations			
FAS-Age [20]	149 (41)	144 (120–175)	55–275
FAS-Height [20]	140 (33)	137 (115–159)	88–246
EKFC [21]	117 (15)	118 (111–126)	49–144
EKFC-Height [21]			
Bedside Schwartz [22]	146 (29)	145 (124–167)	88–213
Original Schwartz* [23, 24]	181 (66)	173 (144–218)	52–369
CKiDU25 [25]	135 (33)	133 (109–152)	74–238
Schwartz-Lyon [26]	133 (28)	134 (110–149)	79–212
LMR18 [27]	115 (18)	117 (104–129)	47–149
MSMS eGFR [7]	124 (25)	123 (105–141)	75–181
Cystatin C-based equations			
FAS_SCys [28]	102 (23)	100 (87–113)	58–174
EKFC_SCys [29]	98 (16)	102 (87–110)	55–126
Combined equations			
FAS_Mean [28]	126 (28)	122 (104–143)	57–214
EKFC_Mean [29]	107 (13)	110 (99–116)	52–132

GFR is expressed in mL/min/1.73 m^2. SD, standard deviation; *LQ* lower quartile (25th percentile); UQ, upper quartile (75th percentile). *Data on SCr measured by the Jaffe method were available for 104 participants

Performance of different eGFR equations based on creatinine, cystatin C or both

The bias, precision, correlation coefficient, and accuracy of different eGFR equations compared to mGFR are summarized in Table 3. The Bland–Altman plots of mGFR vs. different eGFR equations are depicted in Supplementary Fig. S3. Overall, all eGFR equations were weakly correlated to the mGFR, with the original Schwartz equation showing the lowest correlation coefficient ($r = -0.177$, 95% CI [−0.357; 0.016]), while the EKFC combining SCr and SCys had the highest correlation coefficient ($r = 0.457$ [0.294; 0.594]). When comparing the bias from different equations, the FAS-Age (0.9 mL/min/1.73 m^2) and the bedside Schwartz (−2.7 mL/min/1.73 m^2) had the smallest bias. The original Schwartz equation clearly overestimated the mGFR. In contrast, all other equations (based on enzymatic SCr, SCys, or both) clearly underestimated the mGFR. The original Schwartz equation had the lowest accuracy, while the enzymatic SCr-based equations had comparable P30-performance, which was below the threshold of 75% in all but two (bedside Schwartz and Schwartz-Lyon). The bias and accuracy of the SCys-based equations were even worse than those of the SCr-based equations, and equations combining both biomarkers had no added value.

Prevalence of hyperfiltration depending on the method and the definition used

Table 4 shows the performance of different eGFR equations in detecting hyperfiltration. Overall, the proportion of hyperfiltration was highly dependent on the method (mGFR vs. eGFR) and the cutoff used. Using mGFR, glomerular hyperfiltration was found in 65 (59.6%) and 34 (31.2%) participants with the cutoff of Lebensburger and the fixed cutoff of 135, respectively. Regarding eGFR equations, the prevalence of hyperfiltration was also variable depending on the equation used. Using both cutoffs, the lowest prevalence

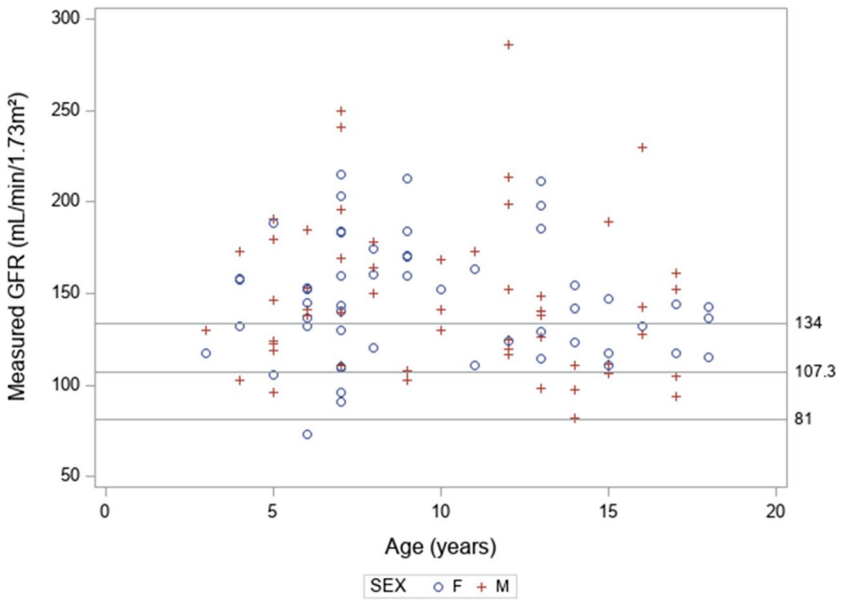

Fig. 2 Reference lines for mGFR against age. The middle line in the figure corresponds to 107.3 mL/min/1.73 m^2, and the lower and upper horizontal lines correspond with 81 and 135 mL/min/1.73 m^2

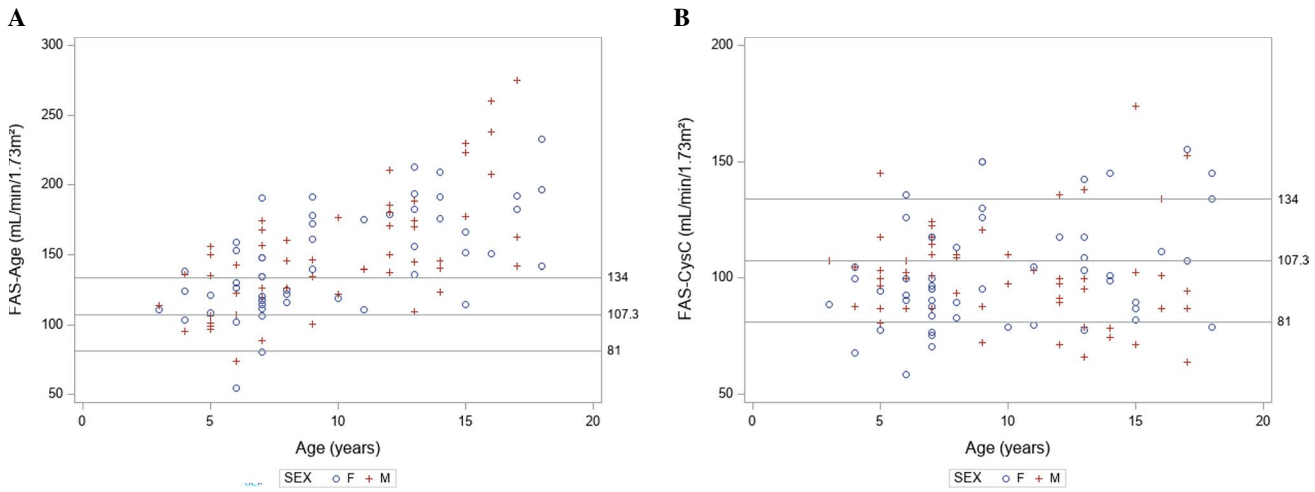

Fig. 3 Reference lines for FAS-Age SCr and FAS-Age SCys against age. The middle line corresponds to eGFR = 107.3 mL/min/1.73 m^2 (corresponding to SCr/Q = 1); the lower limit corresponds to eGFR = 81 (corresponding to SCr/Q = 1.33), and the upper limit corresponds to the value symmetrical with 81 (vs. 107.3) and corresponding to the hyperfiltration limit of 135 mL/min/1.73 m^2

Table 3 Performance of different eGFR equations

Equations	R (95% CI)	Bias, mL/min/1.73 m^2 (95% CI)*	IQR, mL/min/1.73 m^2 (P25–P75)**	P10***, % (95% CI)	P30***, % (95% CI)
Creatinine-based equations					
FAS-Age [20]	0.291 (0.109; 0.455)	0.9 (−10.0; 8.2)	−27.2; 31.8	27.5 (19.0; 36.0)	71.6 (63.0; 80.2)
FAS-Height [20]	0.266 (0.082; 0.432)	−8.7 (−14.7; 3.7)	−29.9; 16.5	24.8 (16.5; 33.0)	71.6 (63.0; 80.2)
EKFC [21]	0.344 (0.167; 0.500)	−24.9 (−33.3; −17.0)	−54.8; −7.2	22.0 (14.1; 29.9)	71.6 (63.0; 80.2)
EKFC_Height [21]	0.323 (0.144; 0.482)	−24.5 (−35.7; −20.5)	−57.6; −8.9	21.1 (13.3; 28.9)	70.6 (62.0; 79.3)
Original Schwartz**** [23, 24]	−0.177 (−0.357; 0.016)	29.2 (9.9; 51.4)	−20.9; 75.7	22.0 (14.1; 29.9)	45.0 (35.5; 54.4)
Bedside Schwartz [22]	0.360 (0.184; 0.513)	−2.7 (−7.5; 10.1)	−21.8; 21.2	37.6 (28.4; 46.9)	78.9 (71.1; 86.7)
CKiDU25 [25]	0.265 (0.081; 0.431)	−12.2 (−19.2; −0.2)	−38.2; 9.8	29.4 (20.7; 38.0)	70.6 (62.0; 79.3)
Schwartz-Lyon [26]	0.307 (0.127; 0.468)	−13.9 (−19.2; −5.2)	−38.3; 8.3	33.9 (24.9; 43.0)	76.2 (68.0; 84.3)
LMR18 [27]	0.341 (0.163; 0.497)	−26.0 (−36.1; −17.6)	−54.4; −9.9	19.3 (11.7; 26.8)	67.0 (58.0; 75.9)
MSMS eGFR [7]	0.360 (0.184; 0.513)	−21.2 (−25.1; −11.9)	−44.0; 1.4	27.5 (19.0; 36.0)	73.4 (65.0; 81.8)
Cystatin C-based equations					
FAS_SCys [28]	0.392 (0.221; 0.540)	−38.4 (−53.3; −31.0)	−68.0; −21.0	12.8 (6.5; 19.2)	47.7 (38.2; 57.2)
EKFC_SCys [29]	0.417 (0.248; 0.561)	−39.3 (−52.8; −33.4)	−66.8; −24.2	6.4 (1.8; 11.1)	45.9 (36.4; 55.4)
Combined equations					
FAS_Mean [28]	0.380 (0.207; 0.531)	−17.8 (−24.5; −10.2)	−46.2; 0.8	26.6 (18.2; 35.0)	74.3 (66.0; 82.7)
EKFC_Mean [29]	0.457 (0.293; 0.594)	−29.5 (−45.3; −23.6)	−57.4; −17.1	12.8 (6.5; 19.2)	62.4 (53.2; 71.6)

R is Pearson's correlation coefficient. *Bias expresses the mean difference between eGFR minus mGFR with a positive bias indicating overestimation of the mGFR and a negative bias indicating underestimation of the mGFR. **IQR (interquartile range) expresses the precision of the bias. ***P10 and P30 define the percentage of eGFR values within ± 10% and ± 30% of mGFR. FAS_Mean and EKFC_Mean combined SCr and SCys. ****Data on SCr measured by the Jaffe method were available for 104 participants

was observed with the EKFC equations, while the highest prevalence was observed with the original Schwartz equation (Table 4).

Discussion

The present study compared different SCr- and SCys-based eGFR equations to mGFR obtained with plasma iohexol

Table 4 Prevalence of hyperfiltration (count (%)) based on mGFR and eGFR from different equations

Equations	With cutoff defined by Lebensburger [16]	With cutoff of 135 mL/min/1.73 m^2	% agreement with mGFR**
Measured GFR	34 (31.2)	65 (59.6%)	-
Creatinine-based equations			
FAS-Age [20]	41 (37.6%)	66 (60.5%)	69.7/64.2
FAS-Height [20]	32 (29.4%)	57 (52.3%)	76.1/63.3
EKFC [21]	3 (2.8%)	8 (7.3%)	69.7/42.2
EKFC_Height [21]	1 (0.9%)	4 (3.7%)	69.7/38.5
Bedside Schwartz [22]	35 (32.1%)	69 (63.3%)	75.2/65.1
Original Schwartz* [23, 24]	56 (53.9%)	81 (77.9%)	56.0/54.1
CKiDU25 [25]	33 (30.3%)	51 (46.8%)	75.2/63.3
Schwartz-Lyon [26]	29 (26.6%)	54 (49.5%)	75.2/62.4
LMR18 [27]	8 (7.3%)	11 (10.1%)	70.6/45.0
MSMS eGFR [7]	19 (17.4%)	40 (36.7%)	73.4/60.6
Cystatin C-based equations			
FAS_SCys [28]	6 (5.5%)	12 (11.0%)	74.3/49.5
EKFC_SCys [29]	0 (0%)	0 (0%)	68.8/40.4
Combined equations			
FAS_Mean [28]	22 (20.2%)	36 (33.0%)	78.0/58.7
EKFC_Mean [29]	0 (0%)	0 (0%)	68.8/40.4

*Data on SCr measured by the Jaffe method were available for 104 participants. **Percent of agreement with mGFR using two cutoffs, the first number with the cutoff of Lebensburger and the second with the cutoff of 135. For instance, regarding the FAS-Age, the agreement with mGFR was 69.7% with Lebensburger and 64.2% with the 135 as cutoff

clearance in a cohort of African children with SCA. To the best of our knowledge, our study is the first to evaluate the GFR using a gold standard method in children with SCA living in SSA. As expected, a high proportion of participants had hyperfiltration, as demonstrated by mGFR.

The main finding from this study is that all eGFR equations (both based on SCr and SCys) poorly predict mGFR in children with SCA and fail to detect hyperfiltration. Furthermore, SCr-based equations progressively overestimate eGFR in older children, which potentially hampers detection of any loss of kidney function. This is not the case for SCys-based equations.

It should be emphasized that the presence of hyperfiltration can affect the accuracy of commonly used eGFR equations since these equations were not developed for patients with increased GFR but rather with mild to moderate kidney failure [30, 31]. For instance, in a cohort of hyperfiltrating adult patients with type 2 diabetes, Gaspari et al. found that all SCr-based equations tested poorly in predicting the mGFR (assessed using iohexol clearance), questioning the utility of any eGFR equation to assess and monitor kidney function in hyperfiltrating patients [32]. Therefore, it has been suggested that correct GFR values can only be determined by directly measuring the GFR, which is in line with our findings [10, 33]. However, routine access to direct GFR measurement will be challenging in patients with SCA, especially those living in resource-limited settings.

We found a large proportion of participants having hyperfiltration using the gold standard measurement of GFR regardless of the cutoff used. More so, we observed a substantial difference in the categorization of hyperfiltration based on eGFR equations that was dependent on the equation and the cutoff used. The presence of hyperfiltration in this population reflects the natural evolution of GFR in patients with SCD, characterized by an initial phase of increased GFR during early childhood, which peaks during adolescence and finally declines during adulthood [6]. Therefore, annual monitoring of GFR in those children presenting with hyperfiltration is crucial. The age spectrum of our study participants was largely limited to the hyperfiltrating stage.

Indeed, we observed a clearly decreasing trend in SCr with age, resulting in the overestimation of GFR with SCr-based equations, especially in older children. This observation could reflect the reduced muscle mass (likely reflecting undernutrition) observed in patients with SCD [34], or an increase in tubular secretion of creatinine [3]. It is not due to hyperfiltration, in which case the difference between mGFR and FAS-Age should remain zero across the entire age spectrum. We found no age dependency with SCys-based equations, probably because SCys is not dependent on muscle mass and does not undergo tubular secretion. In a prospective study assessing the nutritional status of children with SCA, Zemel et al. reported a decline in height and weight

over time [34]. These findings are consistent with several other studies showing that undernutrition is common among children with SCA and worsens with increasing age [35, 36]. Taken together, these data suggest that SCr is not a good marker for kidney function in this population and potentially misses the decline of GFR when patients get older. In this respect, SCys might be a more sensitive, albeit a much more expensive, alternative.

Studies evaluating the performance of common eGFR equations are very limited in patients with SCD. In the pediatric SCD population, a few studies compared eGFR equations with mGFR using the 99-technetium diethylenetriaminepentaacetate (^{99m}Tc-DTPA) plasma clearance [37–40] or plasma iohexol clearance [7]. Most of these studies found poor to moderate correlation between common SCr-based eGFR equations and mGFR in children with SCD [37–40]. Similarly, in the present study, all eGFR equations based on SCr alone were weakly correlated with mGFR. The same trend was observed with SCys or combined equations. The poor correlation commonly observed between usual eGFR equations and mGFR might probably be due to the fact that all these equations were designed and validated in non-SCD patients with normal or decreased kidney function [39].

A few studies attempted to identify the most suitable equation (with the least bias and highest precision compared to mGFR) to estimate GFR in children with SCD. The results of the bias, precision, and accuracy of eGFR equations in these studies are variable. For instance, a recent study from Inusa et al. evaluated the reliability of different eGFR equations compared to mGFR obtained with iohexol plasma clearance in children with SCA living in the UK. The authors found that the FAS SCr-based equations had good accuracy and precision profiles [7]. In addition, they developed a revised constant for the bedside Schwartz equation from SCr measured using tandem mass spectrometry (MSMS), by lowering the *k*-value from 36.5 to 31 to compensate for the lower SCr values in patients with SCD. While the new equation "called MSMS eGFR" had good accuracy and precision in their hands, this new equation showed poor correlation with mGFR and underestimated mGFR in our cohort. In contrast, another study found that the CKiD Schwartz equation (combining SCr and SCys) had better precision and accuracy than the other equations tested in children with SCA [37].

Remarkably, the original Schwartz equation significantly overestimated GFR and showed the lowest accuracy profile compared to the equations using enzymatic SCr. This is unfortunate as the Jaffe assay is the most widely used SCr measurement method in resource-limited settings [8]. This equation was developed based on the Jaffe method, resulting in higher *k*-values than those used in later equations developed for enzymatic SCr assays. It is well known that the Jaffe method is hampered by interference with non-creatinine chromogens, particularly bilirubin, which results in higher SCr readings [41]. However, the present study found no correlation between Jaffe SCr and bilirubin (total, direct, or indirect bilirubin) concentration (data not shown). In addition, no correlation was found between mGFR, SCys on one hand and total bilirubin, direct, or indirect bilirubin on the other. It is worth mentioning that the results of eGFR based on Jaffe SCr should be interpreted with caution since this assay is not IDMS-calibrated, as previously reported [14]. Nevertheless, in the absence of mGFR, some efforts could be made to make IDMS-calibrated enzymatic SCr measurement more accessible in resource-limited settings.

Despite being the first study to evaluate the GFR using a gold standard method in African children with SCA, this study has some limitations that should be pointed out. First, the relatively small sample size with participants recruited in the city of Kinshasa does not allow us to generalize our findings to the entire pediatric SCA population living in DRC or SSA. Second, SCr was normalized using *Q* values designed for healthy children of European descent. Although these *Q* values have been shown to be valid in our previous cohort of healthy African children [14], more extensive studies measuring the GFR and endogenous markers (SCr and SCys) in a larger number of healthy African children and those with SCA are still needed. Such studies could allow the establishment of normal reference intervals for GFR, derive specific *Q* values, and generate eGFR equations that will be validated in these populations.

Third, the mGFR was obtained on a single occasion. Recently, in a cohort of 198 children with SCA who had repeated assessments of mGFR and eGFR, Lebensburger et al. observed high intra-patient variability in bias on repeated testing [37], underlining the importance of repeated evaluations of GFR in patients with SCD. However, it should be kept in mind that also the "golden standard" methods have significant variability and represent only an approximation of the "true GFR" [42]. This might account for some of the intra-patient variability observed by Lebensburger et al. Given the limited accessibility to mGFR in routine practice, especially in SSA, repeated measurements of SCys in children with SCA could be considered to detect changes in kidney function, which are potentially missed due to the age-dependent bias of SCr-based equations. Still, this potential benefit of SCys cannot be proven based on our data, as all patients were still in the hyperfiltration stage of sickle cell nephropathy. This calls for extension of our study to older individuals with SCA.

Conclusion

Accurate assessment of GFR remains challenging in children with SCA. Data from this study showed that SCr- or SCys-based equations should be used with caution in African

children with SCA. While direct GFR measurement is the only reliable method to assess kidney function in this hyperfiltrating population, monitoring SCys might be an alternative to detect a decline in kidney function.

Added value

The present study is the first to evaluate the GFR using a gold standard method in children with SCA living in a low-resource setting of SSA and to do an extensive head-to-head comparison between the endogenous GFR markers SCr and SCys in this population.

Clinical relevance of the study

This study demonstrates the shortcomings of SCr as a marker of GFR in patients with SCA because of age-dependent changes in non-glomerular factors affecting SCr concentrations, such as tubular secretion and a decrease in muscle mass. Although SCys does not measure hyperfiltration, it might be a safer alternative to detect a loss of kidney function in SCA. However, financial constraints will be a challenge for using mGFR or SCys in a low-resource setting. Therefore, awareness of the shortcomings of SCr-based equations is very important.

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Data availability The datasets generated and analyzed during the current study can be made available by the corresponding author upon reasonable request and approval by the Kinshasa School of Public Health Ethics Committee.

Declarations

Conflict of interest Pierre Delanaye and Etienne Cavalier are consultants for Nephrolyx. Hans Pottel is a consultant for Bayer. These funders were not involved in the design, analysis, presentation, or interpretation of the study results. None of the other authors have a relevant conflict of interest.

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