Published in : Pediatric Nephrology (2024), vol. 39, pp. 3013–3022
DOI: 10.1007/s00467-024-06349-x
Status : Postprint (Author's version)

ESTIMATED GLOMERULAR FILTRATION RATE: APPLICABILITY OF CREATININE-BASED EQUATIONS IN AFRICAN CHILDREN

Agathe Bikupe Nkoy[1,2] , Therance Tobo Matoka[1], Justine Busanga Bukabau[3], Ernest Kiswaya Sumaili[3], Veerle Labarque[4,5], Lambertus P. van den Heuvel[2,6], Elena Levtchenko[2,7], Etienne Cavalier[8], Pierre Delanaye[10,9], Pépé Mfutu Ekulu[1], Hans Pottel[11]

[1]*Division of Nephrology, Department of Pediatrics, University Hospital of Kinshasa, University of Kinshasa, Kinshasa, Democratic Republic of Congo*
[2]*Laboratory of Pediatric Nephrology, Department of Development and Regeneration, KU Leuven, Leuven, Belgium*
[3]*Division of Nephrology, Department of Internal Medicine, University Hospital of Kinshasa, University of Kinshasa, Kinshasa, Democratic Republic of Congo*
[4]*Department of Pediatric Hematology, University Hospital Leuven, Leuven, Belgium*
[5]*Center for Molecular and Vascular Biology, Department of Cardiovascular Sciences, KU Leuven, Leuven, Belgium*
[6]*Department of Pediatric Nephrology, Radboud University Medical Centre, Nijmegen, Netherlands*
[7]*Department of Pediatric Nephrology, Amsterdam University Medical Centre, Amsterdam, The Netherlands*
[8]*Division of Clinical Chemistry, CHU Sart Tilman, University of Liège, Liège, Belgium*
[9]*Department of Nephrology, Dialysis, Hypertension and Transplantation, CHU Sart Tilman, University of Liège , Liège, Belgium*
[10]*Department of Nephrology-Dialysis-Apheresis, Hôpital Universitaire Carémeau, Nîmes, France*
[11]*Department of Public Health and Primary Care, KU Leuven Campus Kulak Kortrijk, Kortrijk, Belgium*

Abstract

Background The Schwartz equation is the most widely used serum creatinine (SCr)-based formula to estimate the glomerular filtration rate (GFR) in children of European descent, but whether this applies to African children is unclear.

Methods In a cross-sectional study, 513 apparently healthy African children aged 6 to 16 years were randomly recruited in school area of Kinshasa, the Democratic Republic of Congo (DRC). SCr was measured using calibrated enzymatic method. SCr was normalized using Q-values designed for European descent children, due to the absence of Q-values for African children. Commonly used eGFR equations were applied in this population.

Results Normalization of SCr using Q-values for European descent children was effective in this cohort. The majority of African children (93.4%) have normalized SCr (SCr/Q) values within the reference interval (0.67–1.33) of children of European descent. The bedside-Schwartz equation was associated with significant age and sex dependency. However, the FAS-Age formula showed no sex and age dependency. The new CKiDU25 equation did not show a significant sex dependency. The recently introduced EKFC and LMR18 equations also showed no age and sex dependency, although the distribution of eGFR-values was not symmetrical. On the other hand, the FAS-Height and the Schwartz-Lyon equations showed significant sex dependency but no age dependency.

Conclusions The reference interval for SCr designed for European descent children can be applied to African children. Of all the equations studied, FAS-Age performed best and is most suitable because no height measurements are required. Establishment of specific Q-values for the widespread Jaffe-measured creatinine in Africa can further broaden applicability.

Keywords

Serum creatinine ; Estimated glomerular filtration rate ; Enzymatic method ; African children

Introduction

Glomerular filtration rate (GFR) is a valuable tool and the best indicator for assessing kidney function [1]. Knowledge on GFR is critical for detecting and monitoring kidney disease and determining adequate medication doses [1, 2]. Early detection and prevention of kidney disease in children offer the best chance of preventing kidney failure, especially in those living in sub-Saharan Africa (SSA), where access to kidney replacement therapy is very limited [3, 4].

In clinical practice, GFR is estimated using equations based on the serum concentration of endogenous markers such as creatinine or cystatin C [1, 2]. Serum creatinine (SCr) is the most widely used endogenous marker to assess kidney function in children and adults [2]. Several methods have been developed to measure SCr, the most common and least expensive being the alkaline picrate Jaffe assay. However, this method is susceptible to interferences caused by non-creatinine chromogens. Enzymatic assays were developed to overcome these interferences and are less biased than Jaffe assays [2, 5].

Furthermore, to allow the estimation of GFR from these endogenous markers, a large number of different estimated GFR (eGFR) equations have been developed [2]. Creatinine-based eGFR equations are often used in children, with the Schwartz formula (original or updated version) being the most widely used SCr-based equation [3]. The original Schwartz formula, used for more than three decades, was developed using the Jaffe method for SCr measurement [6]. In 2009, Schwartz et al. developed an updated version of the Schwartz formula, the bedside-Schwartz equation, generated from SCr measured by the enzymatic method traceable to the gold standard isotope-dilution mass spectrometry (IDMS) [3, 7]. However, this equation was designed for children with chronic kidney disease (CKD) and growth retardation until the age of 16 years and does not perform well in healthy children, as acknowledged by the authors [1, 7].

Recent studies showed some unexpected observations when applying the bedside-Schwartz equation to children with normal and near-to-normal kidney function, especially an unexpected decline with age and an unexpected difference between boys and girls [8, 9]. Moreover, the bedside-Schwartz equation requires the height variable, which is mostly not available in clinical laboratory databases, preventing the automatic estimation and reporting of GFR by laboratories, as is the case in adults [10]. Using the bedside-Schwartz equation in children and Chronic Kidney Disease Epidemiology

Published in : Pediatric Nephrology (2024), vol. 39, pp. 3013–3022
DOI: 10.1007/s00467-024-06349-x
Status : Postprint (Author's version)

Collaboration (CKD-EPI) equation in adults also leads to implausible jumps in the estimation of eGFR at the transition between adolescence and adulthood [11]. Thus, a new equation for eGFR that guarantees continuity across all ages, called "the full age spectrum" (FAS) equation, was developed [10, 12, 13]. This FAS equation is based on the concept of normalized enzymatic SCr (SCr/Q), in which Q is the median SCr of the corresponding age-/sex-matched healthy population [10, 12, 13]. Although the FAS equation was developed to overcome the limitations of the bedside-Schwartz equation, it also overestimates the GFR when SCr values are low and in patients with CKD [14]. More recently, the European Kidney Function Consortium (EKFC) equation (the optimized FAS equation) was developed to address this issue. This new equation showed high accuracy and precision when compared to commonly used creatininebased equations [14].

It is worth mentioning that the reliability and validation of all these equations are understudied in African children. The present study aimed to evaluate the applicability of different creatinine-based eGFR equations and their agreement in this population.

Methods

ETHICAL CONSIDERATIONS

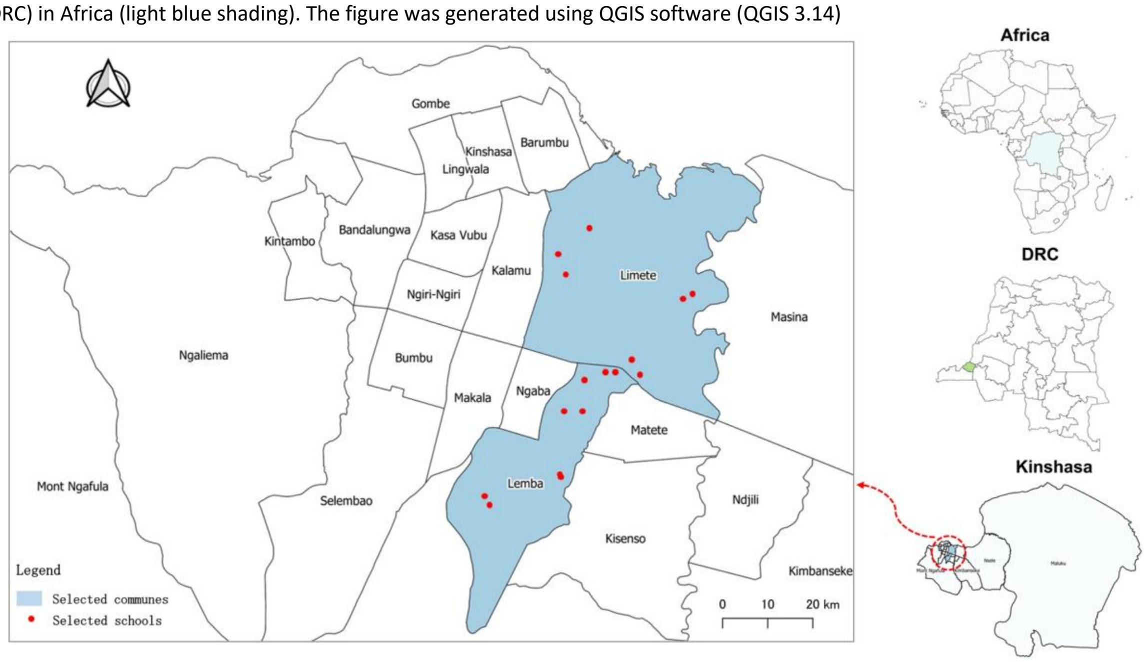
The study was approved by the Ethical Committee of the Public Health School of the University of Kinshasa (ESP/CE/256/2019) and was authorized by the relevant administrative and school authorities. Written informed consent was obtained from parents or legal guardians of children before the enrollment.

STUDY DESIGN AND PARTICIPANTS

This cross-sectional study was conducted in the framework of a school-based study evaluating the prevalence of CKD and its risk factors among healthy children living in Kinshasa, the capital of the Democratic Republic of Congo (DRC) (*unpublished data*). Between January and December 2019, healthy children aged 6–16 years were randomly recruited from 17 schools in Kinshasa (Fig. 1). Using a multistage sampling method [15], we randomly selected one district from the four main districts of Kinshasa. Next, within that district, two out of five communes were selected with a probability proportional to size (number of schools per commune). Then, 17 schools were randomly selected within the two communes. In each school, we randomly selected six grades using the complete list of pupils. Finally, at least five pupils in each grade were systematically selected. At enrollment, demographic (age, sex) and anthropometric data (weight, height) were obtained from all participants. A trained medical staff measured body weight and height using standard methods and calibrated devices. Body surface area (BSA) was calculated using the Du Bois formula [16].

Published in : Pediatric Nephrology (2024), vol. 39, pp. 3013–3022
DOI: 10.1007/s00467-024-06349-x
Status : Postprint (Author's version)

Fig. 1 Spatial distribution of selected schools. Selected schools are represented by red dots and selected communes are shaded in blue. Inset maps show location of Kinshasa in Democratic Republic of the Congo (green shading) and Democratic Republic of the Congo (DRC) in Africa (light blue shading). The figure was generated using QGIS software (QGIS 3.14)



LABORATORY MEASUREMENTS

Five milliliters of blood were collected from all participants. Blood samples were centrifuged and serum was stored at −20 °C. SCr was measured using a compensated Jaffe method (HumaLyser Primus 200, HUMAN Diagnostics Worldwide, Germany) at the Medical Biochemistry Laboratory of the Faculty of Pharmaceutical Sciences in Kinshasa (University of Kinshasa/DRC). In order to measure SCr by an IDMS traceable method, the same frozen samples were sent to the Laboratory of Clinical Chemistry of the University Hospital of Liège (Belgium), where SCr was measured using the Roche enzymatic method on a Cobas Integra 400 instrument (Roche Diagnostics, Mannheim, Germany). Due to samples lost during the shipment to Belgium, enzymatic SCr measurement (in mg/dL) was available for only 460 participants. For the remaining 53 children, since the Jaffe SCr results (mg/dL) were the only available, we used the regression equation derived on the 460 samples for which results for both methods were available to provide a recalibrated value in mg/dL ($SCr_{Enzymatic} = 0.7504 \times SCr_{Jaffe} - 0.11$). GFR was estimated using different creatinine-based eGFR equations, as displayed in Supplementary Table S1.

STATISTICAL ANALYSIS

All statistical analyses were performed using SAS 9.4 (SAS Institute, Inc., Cary, North Carolina, USA) statistical package. Continuous variables are presented as mean ± standard deviation (SD) for normally distributed values or otherwise as median and interquartile range (IQR). Independent groups were compared using Student's t-test. Due to the absence of reference intervals (either for SCr or Q-values) available for African children, we used two different approaches to test whether the serum creatinine values of these African children can be considered normal for their age and sex. The first approach was by considering the reference intervals for SCr of European descent boys and girls [17], and the second approach was to normalize or rescale SCr by considering the so-called Q-values (median SCr-values) of

Published in : Pediatric Nephrology (2024), vol. 39, pp. 3013–3022
DOI: 10.1007/s00467-024-06349-x
Status : Postprint (Author's version)

healthy European descent boys and girls [12]. Minimum, maximum, and percentiles (P5, P25, P75, and P95) are presented for SCr/Q. Distributions of SCr/Q and eGFR predictions are presented as histograms. Linear quantile regression analysis was used to investigate the age dependency of SCr/Q and eGFR predictions. Linear correlation was used to compare the enzymatic versus the Jaffe-based creatinine. Bland-Altman analysis was used to assess the agreement between the different equations against the FAS-Age equation. A p-value less than 0.05 was considered statistically significant.

Results

GENERAL CHARACTERISTICS OF THE STUDY POPULATION

A total of 513 children (217 boys and 296 girls) were included in the present study. The general characteristics of the study population are summarized in Table 1. The mean age, weight, height, and BSA were significantly higher in girls than boys.

SERUM CREATININE VALUES FOR AGE

The majority (> 90%) of school children from Kinshasa have enzymatic SCr results within the reference ranges for SCr of children of European descent, as depicted in Fig. 2a. In addition, there was an increasing trend in SCr-values along with age, with some outliers in several age groups for both boys and girls.

Furthermore, SCr was normalized or rescaled to SCr/Q based on the Hoste formulas for the Q-value [12]. The histograms (Supplementary Fig. 1) peak at SCr/Q = 1, demonstrating that normalization or rescaling of SCr using the Hoste polynomials (designed for children of European descent) is effective. As shown in Fig. 2b, most children (481/515 = 93.4%) had rescaled SCr within the reference interval (0.67, 1.33) of children of European descent. A small number of 9 out of 515 (1.8%) had SCr/Q-values below the lower limit of 0.67. Twenty-five out of 515 (4.9%) had SCr/Q-values above the upper limit of 1.33.

In addition, there was no significant difference (p = 0.121) in the mean normalized SCr/Q between boys (1.04) and girls (0.99). Using the linear quantile regression (Supplementary Fig. 2), there was a slight age decline in median SCr/Q in boys (slope of − 0.0194 mg/dL per year, p = 0.006). After removing 3 outliers with SCr/Q > 2 in boys, the median regression line no longer shows an age dependency (slope of − 0.0153 mg/dL, p = 0.060). However, the median SCr/Q showed no age dependency in girls (slope of − 0.004 mg/dL per year, p = 0.323).

Published in : Pediatric Nephrology (2024), vol. 39, pp. 3013–3022
DOI: 10.1007/s00467-024-06349-x
Status : Postprint (Author's version)

Table 1 General characteristics of the study population

Variables	*n*	Overall	Boys	Girls	*p*
Age (years)	513	11.4 ± 2.9	10.9 ± 2.9	11.8 ± 3.0	< 0.001
Anthropometric data	513				
Weight (kg)		40.1 ± 15.8	36.2 ± 13.3	43.0 ± 16.8	< 0.001
Height (m)		1.44 ± 0.18	1.41 ± 0.18	1.46 ± 0.17	< 0.001
BMI (kg/m²)		18.5 ± 3.9	17.5 ± 2.9	19.2 ± 4.5	< 0.001
BSA (m²)		1.26 ± 0.31	1.19 ± 0.29	1.31 ± 0.31	< 0.001
Kidney function					
SCr Enz (mg/dL)	460*	0.56 ± 0.18	0.57 ± 0.23	0.55 ± 0.13	0.208

Data are presented as mean ± standard deviation

BMI body mass index, *BSA* body surface area, *SCr Enz* serum creatinine measured by the calibrated enzymatic method

* Blood samples for enzymatic creatinine measurement were not available for all participants due to samples lost during the shipment to Belgium; the characteristics of this subgroup are summarized in Supplementary Table S2

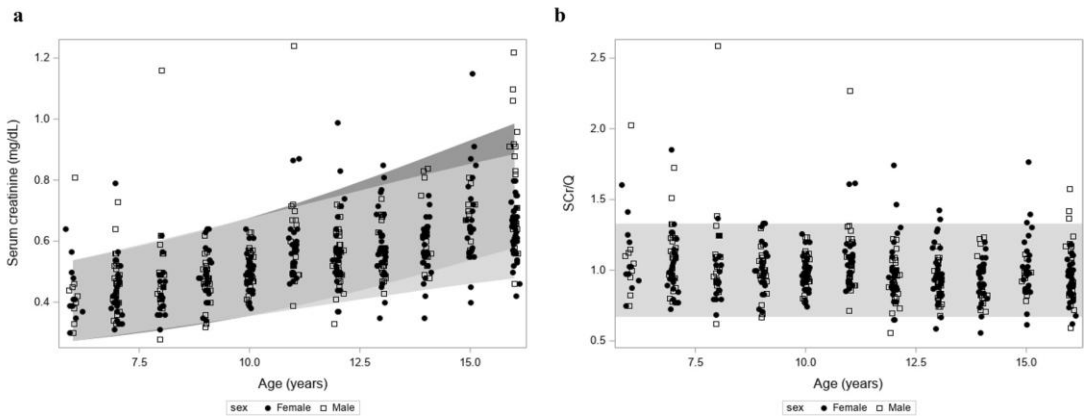


Fig. 2 **a** Serum creatinine (SCr, mg/dL) against age in African healthy children. Serum creatinine (SCr, mg/dL) against age in African healthy children. The confidence band (grey zone) represents the reference interval for serum creatinine of European descent children. b SCr/Q against age in African healthy children. Serum creatinine (SCr) was normalized or rescaled to SCr/Q, based on the Hoste formulas for the Q-values. The confidence band (grey zone) represents the reference interval for SCr/Q of European descent children

ASSESSMENT OF DIFFERENT EGFR FORMULAS FOR CHILDREN

The results of the eGFR calculated with different equations are shown in Table 2. In addition, Fig. 3 shows histograms and linear quantile regression lines for the different creatinine-based eGFR equations. As mentioned above, there was no difference between males and females for SCr/Q_Age. It follows logically that there are no differences between males and females for the age-based eGFR-equations FAS-Age, EKFC, and LMR18 (Table 3). Moreover, as there was a significant difference between males and females for SCr/Q_Ht (p = 0.010), it follows that the height-based equations

Published in : Pediatric Nephrology (2024), vol. 39, pp. 3013–3022
DOI: 10.1007/s00467-024-06349-x
Status : Postprint (Author's version)

(FASHeight, bedside-Schwartz, CKiDU25) also show a difference (or borderline no difference for CKiDU25) between males and females (Table 3)

Table 2 Comparison of the eGFR calculated with different equations

Formula	Mean (SD)	Median (LQ-UQ)
FAS-Age [12]	111 (21)	110 (98–123)
FAS-Height [12]	109 (21)	108 (96–121)
EKFC [14]	103 (14)	108 (97–112)
Bedside-Schwartz [7]	111 (21)	110 (99–122)
CKiDU25 [18]	102 (19)	101 (90–112)
Schwartz-Lyon [19]	101 (19)	99 (90–110)
LMR18 [20]	98 (14)	99 (91–107)

eGFR is expressed in mL/min/1.73 m²

SD standard deviation, *LQ* lower quartile (25th percentile), *UQ* upper quartile (75th percentile)

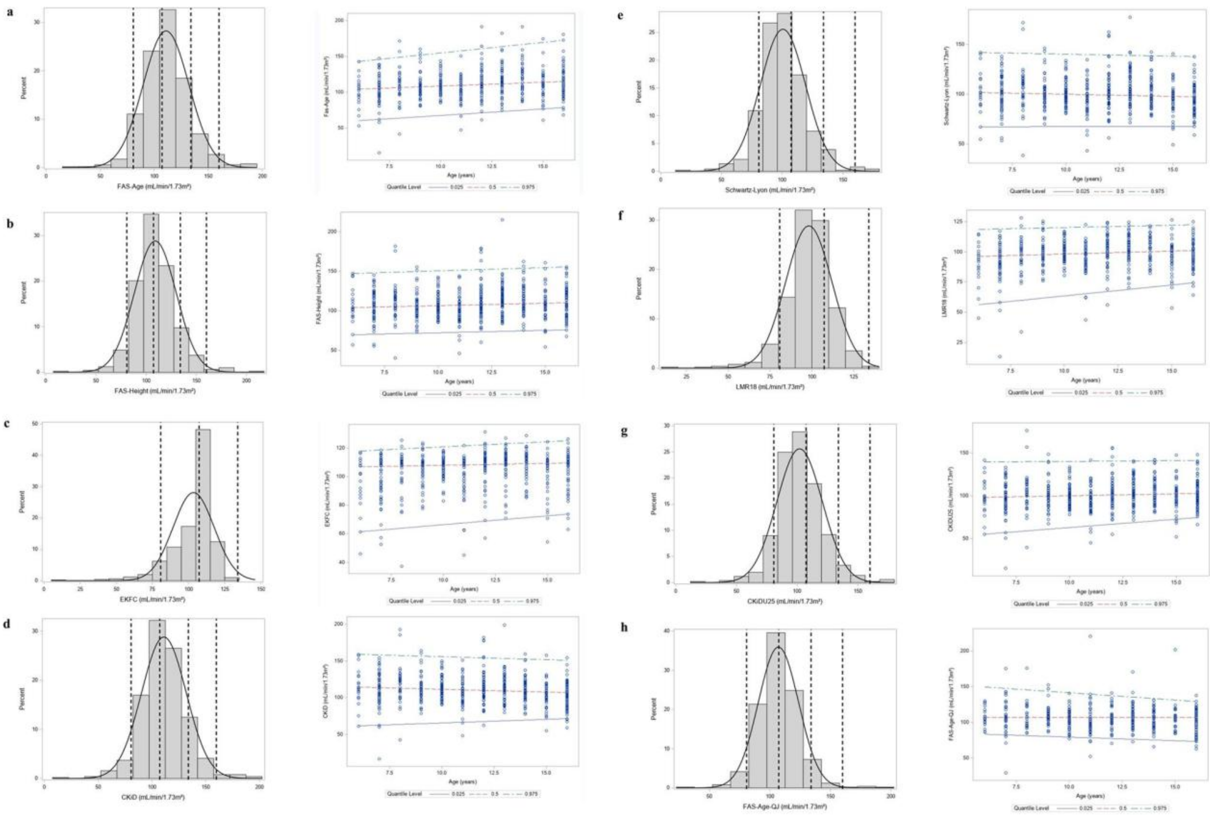


Fig. 3 Histograms and linear quantile regression lines for the different creatinine-based eGFR formulas. a FAS-Age, b FAS-Height, c EKFC, d Bedside-Schwartz, e Schwartz-Lyon, f LMR18, g CKiDU25, h FAS-Age-Jaffe (QJ): FAS-Age was applied to the 513 African children using specific Q-values derived from the Jaffe creatinine. Vertical dashed lines in the histograms are drawn at FAS = 107.3/1.33 = 80.7, at 107.3, at 134 (corresponding to the symmetrical limit with 80.7 with 107.3 as the center value), and 160 (= 107.3/0.67)

.

Published in : Pediatric Nephrology (2024), vol. 39, pp. 3013–3022
DOI: 10.1007/s00467-024-06349-x
Status : Postprint (Author's version)

Table 3 Comparison of SCr/Q and the eGFR mean values between boys and girls

Formula	Mean boys	Mean girls	p-value
SCr/Q_Age	1.04	0.99	0.121
SCr/Q_Ht	1.08	0.99	0.010
FAS-Age [12]	109.8	111.9	0.287
FAS-Height [12]	105.4	111.7	0.001
Bedside-Schwartz [7]	108.2	113.4	0.005
CKiDU25 [20]	103.8	100.6	0.063
EKFC [14]	103.4	103.5	0.983
LMR18 [20]	99.1	97.4	0.184
Schwartz-Lyon [19]	99.9	101.0	0.512

SCr is expressed in mg/dL; eGFR is expressed in mL/min/1.73 m ^{2}

FAS-AGE

FAS is designed so that the expected eGFR-value for the average healthy child (the child with SCr/Q = 1) equals 107.3 mL/min/1.73 m ^{2} [21]. Vertical dashed lines are drawn at FAS = 107.3/1.33 = 80.7, at 107.3, at 134 (corresponding to the symmetrical limit with 107.3 as the center value), and 160 (= 107.3/0.67) mL/min/1.73 m^2 (Fig. 3a). Children with SCr/Q below the lower limit (of 0.67) have FAS-eGFR > 160 mL/min/1.73 m ^{2} and children with SCr/Q above the upper limit (of 1.33) have FASeGFR < 80.7 mL/min/1.73 m^2. The interval (80.7–134) may be considered the eGFR-reference interval for children. In addition, there was a slight increase with age for FAS-Age (slope of 0.98, p = 0.014).

FAS-HEIGHT

The distribution of eGFR values appears symmetrical (Fig. 3b) and there was no age dependency for median FAS-height (slope is 0.62, p = 0.082).

EKFC

The distribution of eGFR-values appears to be skewed to the left (Fig. 3c). However, no age dependency was observed for the median EKFC (slope = 0.27, p = 0.095).

BEDSIDE-SCHWARTZ

The distribution of eGFR-values is slightly skewed to the right, although relatively symmetrical (Fig. 3d). A slight age dependency of median eGFR-value (slope = − 0.75, p = 0.016) was observed. However, we noted a fast decrease in median eGFR for boys above 14 years old (data not shown).

SCHWARTZ-LYON EQUATION

This formula did not show an age dependency (slope = − 0.43, p = 0.122), but the histogram is relatively shifted to the left (Fig. 3e).

LUND-MALMÖ REVISED (LMR18)

Published in : Pediatric Nephrology (2024), vol. 39, pp. 3013–3022
DOI: 10.1007/s00467-024-06349-x
Status : Postprint (Author's version)

The histogram is relatively symmetrical, although shifted to the left (Fig. 3f). This formula demonstrated no age dependency of median eGFR (slope = 0.49, p = 0.051).

CKIDU25

The histogram appears to be skewed to the left (Fig. 3g) and there was no significant difference between males and females (p = 0.063).

AGREEMENT BETWEEN DIFFERENT EGFR FORMULAS

Results from the Bland-Altman analysis are summarized in Supplementary Table S3. Plots for the agreement between different equations against the FAS-Age equation are depicted in Fig. 4. The findings show that the bedsideSchwartz (− 0.14 ml/min/1.73 m^2) and the FAS-Height (2.0 ml/min/1.73 m^2) formulas had the lowest average difference from FAS-Age, compared to the other equations.

It is worth mentioning that in many African countries, SCr is commonly measured using the uncalibrated Jaffe method and the Schwartz formula is the most used SCrbased formula in children. Thus, we tested whether the bedside-Schwartz could be applied to both Jaffe-based creatinine and enzymatic-based creatinine in this context. The results showed a moderate linear correlation (r = 0.759) between both creatinine measurements, but the agreement was poor. Moreover, the correlation between the bedsideSchwartz equation calculated as 0.413 × Height / SCr, once for enzymatic based-creatinine and once for Jaffe-based creatinine, was poor (r = 0.286), as shown in Supplementary Fig. 3. In addition, the FAS-Age formula had the highest bias when applied to uncalibrated Jaffe-based creatinine with Q-values of European descent children (Supplementary Table S3).

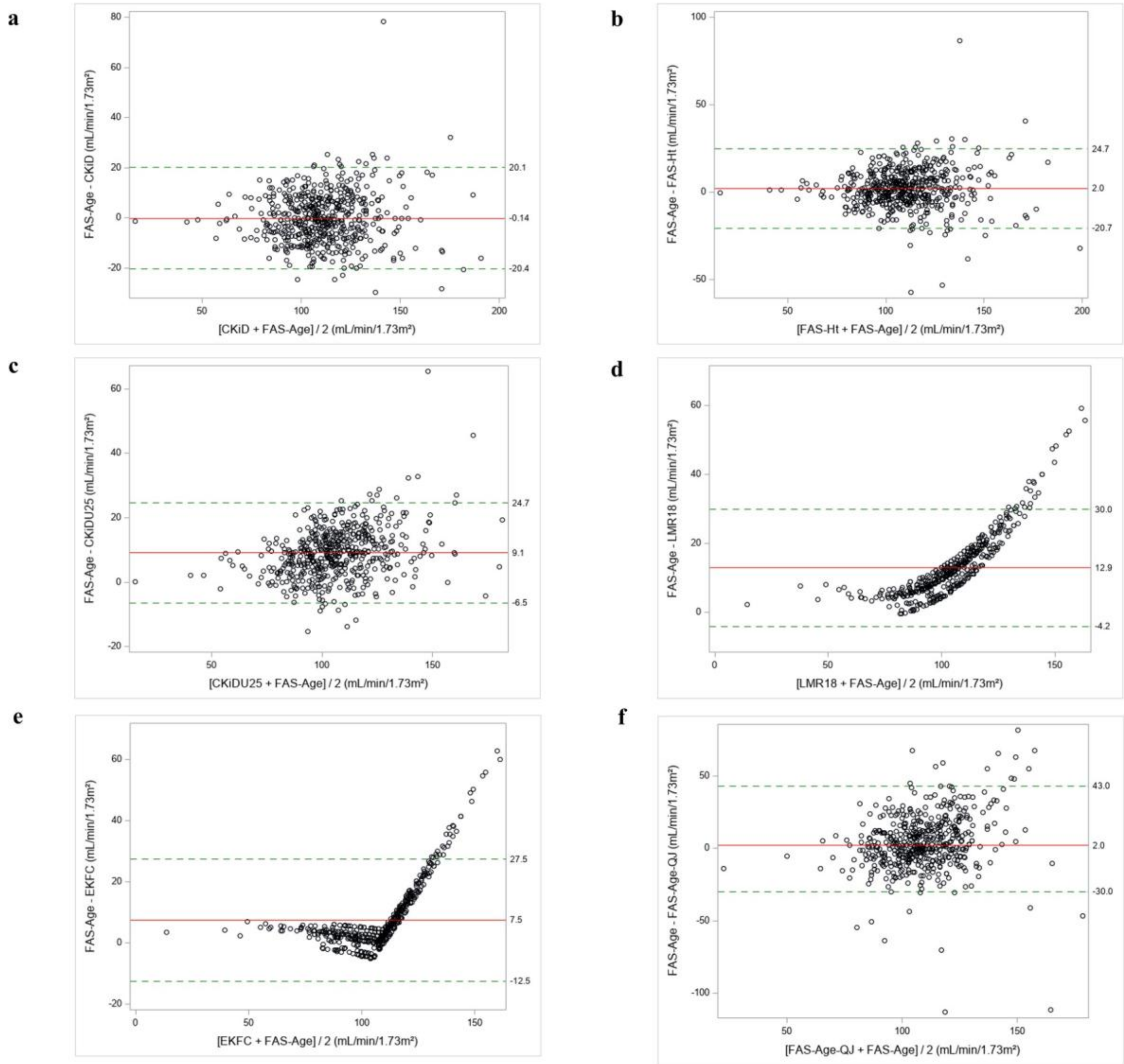
Given the fact that Jaffe creatinine is very different from enzymatic creatinine (as demonstrated above), we proposed to use the FAS equation with appropriate Q-values from Jaffe creatinine of African children (Q_J). We performed median quantile regression for Jaffe creatinine against age on the dataset (Supplementary Fig. 4.) and obtained the following expression for the median Q-values:

$$Q_J = 1.4963 - 0.22753 \times \text{Age} + 0.02297 \times \text{Age}^2 - 0.000668 \times \text{Age}^3$$

Then, we applied the FAS-Age to the 513 African children using these specific Q-values. The results showed a minor difference in SCr/Q_J between boys and girls (p = 0.037) but not in FAS-Age with Q_J (p = 0.470). In addition, the distribution of eGFR values was symmetrical (Fig. 3h) and there was no age dependency, although a very minor sex dependency was noted (data not shown). The Bland-Altman analysis showed that rescaling with Jaffe specific Q-values (Q_J) reduced the bias from FASAge. However, the 95% limits of agreement are still much wider compared to the other equations (Supplementary Table S3 and Fig. 4f).

Published in : Pediatric Nephrology (2024), vol. 39, pp. 3013–3022
DOI: 10.1007/s00467-024-06349-x
Status : Postprint (Author's version)

Fig. 4 Bland-Altman plots for the agreement between different formulas against the FAS-Age. **a** Bedside-Schwartz, **b** FAS-Height, **c** CKiDU25, **d** LMR-18, **e** EKFC, **f** FAS-Age (Jaffe), **g** FAS-Age (Q_J): FAS-Age was applied to the 513 African children using specific Q-values derived from the Jaffe creatinine. In each plot, the central red line represents the mean difference between different eGFR formula and the FAS-Age, while the upper and lower green dotted lines represent the 95% limits of agreement



Discussion

Population-based studies investigating kidney function in the general pediatric population are limited, especially in SSA, and most data come from hospital-based studies [22]. The present study described the evaluation of kidney function in a large cohort of Central African healthy children. The main message from this study is that the reference intervals for enzymatic SCr, as defined for children of European descent, seem to be applicable to African healthy children. Also, the Q-values defined for European children can be applied to rescale enzymatic SCr for African healthy children, suggesting that the reference interval for SCr/Q of (0.67–1.33) is applicable for African children and can be used to evaluate the normality of rescaled SCr in these children.

Published in : Pediatric Nephrology (2024), vol. 39, pp. 3013–3022
DOI: 10.1007/s00467-024-06349-x
Status : Postprint (Author's version)

In addition, the results of eGFR calculated using different formulas showed that the commonly used equation to estimate GFR in children (the bedside-Schwartz equation) was associated with a significant age and sex dependency in healthy African children. However, the recently introduced CKiDU25 equation did not show a significant sex dependency in these children. Currently, the Kidney Disease: Improving Global Outcomes (KGIDO) guidelines recommend using the bedside-Schwartz equation to estimate GFR in children and adolescents until 18 years [23]. It should be noted that this formula was derived from US children with established kidney disease and notable growth retardation [1]. Thus, many authors have questioned the applicability of this equation in children without kidney disease and from other ethnic origins since differences exist in kidney function and body composition between ethnic groups, especially during adolescence [1, 24, 25].

In this cohort, the FAS-Age equation showed age (although a very slight increase with age was noted in boys) and sex independency, suggesting that this equation could be applied to the entire age spectrum in African children. Indeed, normalization of enzymatic SCr using the Hoste polynomials (designed for European descent children) was effective in our population, as demonstrated above. The newly introduced EKFC and the LMR18 equations also showed age and sex independency, although the distribution of eGFR was not symmetrical. On the other hand, the FAS-Height and the Schwartz-Lyon formulas showed significant sex dependency but no age dependency. As mentioned above, there was a significant difference between boys and girls for SCr/Q_Ht, resulting in sex differences in the height-based eGFR equations (FAS-Height, bedside-Schwartz, CKiDU25). This finding seems to show that the relationship between height as a surrogate of muscle mass and sex could be different in African compared to European and US children and may point to possible racial differences in the creatinine growth curves.

Furthermore, Bland-Altman analysis was performed to evaluate the relative bias of these different eGFR equations against the FAS-Age formula. The bedside-Schwartz and FAS-Height equations had the lowest average difference from FAS-Age, compared to the EKFC, CKiDU25, and LMR18. This discrepancy could be explained by the fact that these latter formulas contain power coefficients depending on SCr growth curves to avoid overestimating the eGFR for low SCr values [26]. Notably, the FAS-Age equation showed a significant bias when applied to SCr measured by the Jaffe method.

Nevertheless, due to its high cost, the enzymatic creatinine measurement is not routinely available in SSA. Thus, the Jaffe method for SCr measurement remains the only option [5, 27]. In addition, the Schwartz formula is mainly applied to estimate GFR in children living in this setting. In the DRC, as in many African countries, due to a lack of appropriate information and the simplicity of the bedsideSchwartz equation (with a unique coefficient in comparison with the original Schwartz equation), most clinicians often use this latter formula in children, regardless of the creatinine assay method (*unpublished data*). This raises the question of the reliability of the eGFR values in this context.

Therefore, we evaluated whether the bedside-Schwartz equation could be applied to Jaffe-based and enzymaticbased creatinine. The correlation between the bedside-Schwartz equation calculated once for enzymatic-based creatinine and once for Jaffe-based creatinine was poor. This finding demonstrated that the bedside-Schwartz equation is not appropriate when SCr is measured using the Jaffe method, as previously reported [3, 7]. Likewise, the FAS-Age formula applied to uncalibrated Jaffe-based creatinine with Q-values of European descent children is not appropriate, as demonstrated

Published in : Pediatric Nephrology (2024), vol. 39, pp. 3013–3022
DOI: 10.1007/s00467-024-06349-x
Status : Postprint (Author's version)

above. It is worth mentioning that all other eGFR equations were only evaluated with enzymatic creatinine measurement, and the use of Jaffe creatinine with other equations also led to faulty results, even with the original Schwartz equation. Indeed, after applying the original Schwartz to Jaffe-based creatinine, the results were clearly underestimating GFR and there was an age dependency in boys (due to the switch at age 13 from k = 0.55 to 0.70) but not in girls (*data not presented*).

On the other hand, since the Jaffe assays are mainly used in SSA and knowing that the FAS equation has been developed for enzymatic creatinine, as with the bedside-Schwartz equation, we proposed to normalize the Jaffe creatinine with the specific Q-value derived above (Q_J), before applying the FAS-Age equation. This normalization allowed estimation of eGFR from the FAS-Age, with results showing no age dependency and a minor sex dependency, although the limits of agreement between FAS-Age with FAS-Age-Q_J were so much wider than those of the other pediatric equations. The reason for this is that all equations, except FAS-Age-Q_J, were calculated from the enzymatic SCr, while FAS-AgeQ_J was calculated from the Jaffe SCr. Indeed, in the first situation, we compare eGFR-equations calculated from the same SCr-measurements, while in the latter case, we compare eGFR-equations calculated from different SCr measurements. Nevertheless, this result suggests that this specific Q-value derived from African children (Q_J) could also be applied to EKFC since this equation is based on the same concept of Q-value as the FAS-Age.

It is worth mentioning that these Q-values may not be generalized to all Jaffe assays in Africa, given the heterogenicity observed in SCr measurement across laboratories in African countries (differences in manufacturers, reagents, calibrators). Thus, locally derived Q-values can be obtained from hospital databases with data restricted to children with normal kidney function after appropriate selection procedures. Future studies with a large and representative number of African children are needed to validate this observation. In addition, such studies would allow evaluation of the distribution of the Jaffe creatinine values in healthy African children.

STRENGTH AND LIMITATIONS

To the best of our knowledge, this is the first population-based study evaluating and comparing several equations used to estimate GFR in a large cohort of African healthy children, using creatinine measured by an enzymatic method, traceable to the international standard reference material. However, this study had some limitations that should be pointed out. The GFR was estimated by using formulas rather than a direct measurement. This could underestimate or overestimate the actual value of GFR since all these formulas were not validated in healthy African pediatric populations. Therefore, future studies measuring the GFR are needed in order to evaluate the relevance of these different eGFR formulas in these children. More so, such studies could help to establish normal reference GFR values for African children and generate eGFR formulas that will be validated in this specific population. Furthermore, the number of subjects between 14 and 16 years was limited in the present cohort, and thus we could not propose a sex-specific Q-value derived from Jaffe creatinine (Q_J) for this age range where SCr begins to be different between males and females. Future studies including more adolescent subjects would probably allow calculation of sex-specific (Q_J) from this population. Lastly, since the study was conducted in the city of Kinshasa, the results might not be generalizable to the entire pediatric population from the DRC or from SSA. Nevertheless, this study provides first data that will be useful for future studies evaluating kidney function in African children.

Conclusion

This study shows that enzymatic SCr values of African children fall mostly within the reference interval of children of European descent. In addition, the normalization of enzymatic SCr using Q-values defined for children of European descent works very well in this cohort. After evaluating different formulas, the FAS-Age equation is of interest in this population. However, EKFC and LMR18 showed some concerns about the skewness of the distribution, that is not the case for FAS-Age. In contrast, the commonly used bedside-Schwartz equation was associated with a significant age and sex dependency. Furthermore, equations using the concept of Q-value could potentially be used with such Q-values developed locally in Africa, even with uncalibrated creatinine results.

Acknowledgements The authors would like to thank all study participants and are grateful to the team of medical doctors, students, laboratory technicians, and nurses for their assistance in data acquisition. The authors also thank the team of Clinical Chemistry of CHU Sart Tilman in Liège. The authors are grateful to Caroline Nkoy-Ihomi for her valuable contribution to field logistics and to Yannick Munyeku-Bazitama for his assistance in field logistics and the elaboration of Figure 1.

Author contribution A.B.N., P.M.E., and E.K.S. conceived and designed the study. A.B.N. and T.T.M. recruited participants and collected data and samples. P.M.E., E.K.S., J.B.B., and E.L. provided field supervision. H.P. performed statistical analysis. H.P., A.B.N., P.D., and E.C. interpreted the results. A.B.N. wrote the first version of the manuscript. All authors revised the manuscript and approved the final version.

Funding This project was funded by the Flemish Inter-University Council (VLIR) of KU Leuven (Leuven, Belgium). A.B.N. is supported by the Global Minds Scholarship of VLIR-UOS and DGD (Belgium partner in development).

Data availability The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors declare no competing interests.

References

1. Pottel H (2017) Measuring and estimating glomerular filtration rate in children. Pediatr Nephrol 32:249–263. https://doi.org/10.1007/s00467-016-3373-x
2. den Bakker E, Gemke RJBJ, Bökenkamp A (2018) Endogenous markers for kidney function in children: a review. Crit Rev Clin Lab Sci 55:163–183. https://doi.org/10.1080/10408363.2018.1427041
3. Schwartz GJ, Work DF (2009) Measurement and estimation of GFR in children and adolescents. Clin J Am Soc Nephrol 4:1832–1843. https://doi.org/10.2215/CJN.01640309
4. Harambat J, Ekulu PM (2016) Inequalities in access to pediatric ESRD care: a global health challenge. Pediatr Nephrol 31:353–

358. https://doi.org/10.1007/s00467-015-3263-7

5. Ezegbogu M, Abdulsalam K (2018) Creatinine assay methods in resource-limited settings: a review. BJMLS 3:37–47
6. Schwartz J, Haycock GB, Edelmann CM Jr, Spitzer A (1976) A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. Pediatrics 58:259–263
7. Schwartz GJ, Munoz A, Schneider MF et al (2009) New equations to estimate GFR in children with CKD. J Am Soc Nephrol 20:629–637. https://doi.org/10.1681/ASN.2008030287
8. Pottel H, Björk J, Delanaye P, Nyman U (2022) Evaluation of the creatinine-based chronic kidney disease in children (under 25 years) equation in healthy children and adolescents. Pediatr Nephrol 37:2213–2216. https://doi.org/10.1007/s00467-022-05429-0
9. van Dam MJCM, Pottel H, Vreugdenhil ACE (2022) Creatininebased GFR-estimating equations in children with overweight and obesity. Pediatr Nephrol 37:2393–2403. https://doi.org/10.1007/s00467-021-05396-y
10. Pottel H, Dubourg L, Goffin K, Delanaye P (2018) Alternatives for the bedside Schwartz equation to estimate glomerular filtration rate in children. Adv Chronic Kidney Dis 25:57–66. https://doi.org/10.1053/j.ackd.2017.10.002
11. Pottel H, Björk J, Bökenkamp A et al (2019) Estimating glomerular filtration rate at the transition from pediatric to adult care. Kidney Int 95:1234–1243. https://doi.org/10.1016/j.kint.2018.12.020
12. HosteL, Dubourg L, Selistre L et al (2014) A new equation to estimate the glomerular filtration rate in children, adolescents and young adults. Nephrol Dial Transplant 29:1082–1091. https://d oi. org/ 10. 1093/ ndt/ gft277
13. Pottel H, Delanaye P, Schaeffner E et al (2017) Estimating glomerular filtration rate for the full age spectrum from serum creatinine and cystatin C. Nephrol Dial Transplant 32:497–507. https://doi.org/10.1093/ndt/gfw425
14. Pottel H, Björk J, Courbebaisse M et al (2021) Development and validation of a modified full age spectrum creatinine-based equation to estimate glomerular filtration rate. Ann Intern Med 174:183–191. https://doi.org/10.7326/M20-4366
15. World Health Organization (2005) WHO STEPS surveillance manual: the WHO STEPwise approach to chronic disease risk factor surveillance. Geneva, World Health Organization
16. Du Bois D, Du Bois EF (1916) Clinical calorimetry: tenth paper a formula to estimate the approximate surface area if height and weight be known. Arch Intern Med 17:863–871. https://doi.org/10.1001/archinte.1916.00080130010002
17. Pottel H, Vrydags N, Mahieu B et al (2008) Establishing age/sex related serum creatinine reference intervals from hospital laboratory data based on different statistical methods. Clin Chim Acta 396:49–55. https://doi.org/10.1016/j.cca.2008.06.017
18. Pierce CB, Muñoz A, Ng DK et al (2021) Age- and sex-dependent clinical equations to estimate glomerular filtration rates in children and young adults with chronic kidney disease. Kidney Int 99:948–956. https://doi.org/10.1016/j.kint.2020.10.047
19. Selistre L, De Souza V, Cochat P et al (2012) GFR estimation in adolescents and young adults. J Am Soc Nephrol 23:989–996. https://doi.org/10.1681/ASN.2011070705
20. Björk J, Nyman U, Delanaye P et al (2020) A novel method for creatinine adjustment makes the revised Lund-Malmö GFR estimating equation applicable in children. Scand J Clin Lab Invest 80:456–463. https://doi.org/10.1080/00365513.2020.1774641
21. Pottel H, Hoste L, Martens F (2012) A simple height-independent equation for estimating glomerular filtration rate in children. Pediatr Nephrol 27:973–979. https://doi.org/10.1007/s00467-011-2081-9
22. Harambat J, Madden I (2022) What is the true burden of chronic kidney disease in children worldwide? Pediatr Nephrol 38:1389–1393. https://doi.org/10.1007/s00467-022-05816-7
23. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO (2012) (2013) Clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl 3:19–62. https://doi.org/10.1038/kisup.2012.71A
24. Uemura O, Honda M, Matsuyama T et al (2012) Is the new Schwartz equation derived from serum creatinine and body length suitable for evaluation of renal function in Japanese children? Eur J Pediatr 171:1401–1404. https://doi.org/10.1007/s00431-012-1772-y
25. Uemura O, Nagai T, Ishikura K et al (2015) Reference glomerular filtration rate levels in Japanese children: using the creatinine and cystatin C based estimated glomerular filtration rate. Clin Exp Nephrol 19:683–687. https://doi.org/10.1007/s10157-014-1042-6
26. Schellekens P, Verjans M, Janssens P et al (2023) Low agreement between various eGFR formulae in pediatric and young adult ADPKD patients. Pediatr Nephrol 38:3043–3305. https://doi.org/10.1007/s00467-023-05926-w
27. George C, Mogueo A, Okpechi I et al (2017) Chronic kidney disease in low-income to middle-income countries: the case for increased screening. BMJ Glob Health 2:e000256. https://doi.org/10.1136/bmjgh-2016-000256