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Evaluation du taux de filtration glomérulaire chez l'enfant: étude clinique et perspectives

THESE

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par

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Evaluation du taux de filtration glomérulaire chez l'enfant: étude clinique et perspectives

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Résumé de thèse

L'enjeu et le contexte de la recherche :
Déterminer le taux ou le débit de filtration glomérulaire (en anglais « GFR » ou «glomerular filtration rate») est crucial en pédiatrie afin de pouvoir adapter les posologies des médicaments prescrits et suivre l'évolution de la fonction rénale chez les patients souffrant d'une maladie rénale ou présentant le risque de développer une insuffisance rénale. La manière la plus précise pour déterminer le GFR est de le mesurer. Cependant les méthodes utilisées pour mesurer le GFR sont coûteuses, contraignantes et elles ne sont pas disponibles dans tous les hôpitaux, d'où l'importance de développer une formule fiable permettant d'estimer le GFR.

L'article:
Plusieurs formules pour estimer le GFR (eGFR) à partir de marqueurs endogènes comme la créatinine plasmatique et/ou plus récemment la cystatine C sanguine ont été développées chez l'enfant. La formule la plus couramment utilisée en pédiatrie est la formule de Schwartz qui a été révisée en 2009 en se référant à une cohorte d'enfants avec un GFR mesuré par des clearances à l'iohexol entre 15 et 75 ml/min x 1,73 m². Dans cet article, nous avons étudié la validité de la nouvelle formule de Schwartz dans une population d'enfants présentant un plus large spectre de degré d'insuffisance rénale en y incluant des enfants avec un GFR normal ou une hyperfiltration glomérulaire. Nous avons comparé 551 clairances à l'inuline (le « gold standard » pour mesurer le GFR) de 392 enfants âgés de 3 à 18 ans avec leurs eGFRs selon Schwartz dans une étude rétrospective et prospective. La créatinine sérique est mesurée en utilisant la méthode de Jaffe compensée. Selon nos résultats, la formule de Schwartz est applicable jusqu'à une valeur de taille/créatinine sérique de 251 qui correspond à un iGFR de 103ml/min x 1,73m². Cependant, cette formule manque de précision chez les enfants présentant un iGFR au-delà de cette valeur, ce qui correspond soit à une insuffisance rénale légère, soit à un GFR normal ou encore à une hyperfiltration glomérulaire. En effet, la corrélation entre les iGFRs et la variable de la formule de Schwartz (taille/créatinine sérique) n'est pas linéaire comme décrite par Schwartz mais plutôt quadratique, raison pour laquelle nous avons développé la formule suivante à l'aide d'un modèle de régression quadratique :
0.68 x (taille(cm)/ créatinine sérique (mg/dl)) - 0.0008 x (taille (cm)/ créatinine sérique (mg/dl))² + 0.48 x âge (années) - (25,68 pour les filles ou 21,53 pour les garçons).
Nous avons validé cette nouvelle formule quadratique par la méthode de validation interne croisée et par une nouvelle étude prospective incluant 127 iGFRs de 127 enfants (validation externe). En conclusion, la nouvelle formule quadratique est applicable à toutes les classes du GFR chez l'enfant et pourrait remplacer la formule de Schwartz.

Les conclusions et les perspectives :
Cette étude contribue à affiner le champ d'application de la formule révisée de Schwartz et propose une nouvelle formule certes plus complexe, mais facilement utilisable de nos jours grâce aux nouvelles technologies informatiques. Néanmoins, d'autres études sont nécessaires, par exemple afin d'évaluer la possibilité d'appliquer cette formule quadratique chez les enfants de moins de trois ans. En attendant, la formule quadratique, en tenant compte du contexte clinique, peut aider le pédiatre à prendre des décisions thérapeutiques et à suivre les enfants.

Comparison of the glomerular filtration rate in children by the new revised Schwartz formula and a new generalized formula

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The most widely used formula for estimating glomerular filtration rate (eGFR) in children is the Schwartz formula. It was revised in 2009 using iohexol clearances with measured GFR (mGFR) ranging between 15 and 75 ml/min×1.73 m^2. Here we assessed the accuracy of the Schwartz formula using the inulin clearance (iGFR) method to evaluate its accuracy for children with less renal impairment comparing 551 iGFRs of 392 children with their Schwartz eGFRs. Serum creatinine was measured using the compensated Jaffe method. In order to find the best relationship between iGFR and eGFR, a linear quadratic regression model was fitted and a more accurate formula was derived. This quadratic formula was: 0.68× (Height (cm)/serum creatinine (mg/dl)) − 0.0008×(height (cm)/serum creatinine (mg/dl))^2 + 0.48×age (years) − (21.53 in males or 25.68 in females). This formula was validated using a split-half cross-validation technique and also externally validated with a new cohort of 127 children. Results show that the Schwartz formula is accurate until a height (Ht)/serum creatinine value of 251, corresponding to an iGFR of 103 ml/min×1.73 m^2, but significantly unreliable for higher values. For an accuracy of 20 percent, the quadratic formula was significantly better than the Schwartz formula for all patients and for patients with a Ht/serum creatinine of 251 or greater. Thus, the new quadratic formula could replace the revised Schwartz formula, which is accurate for children with moderate renal failure but not for those with less renal impairment or hyperfiltration.

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KEYWORDS: children; chronic renal failure; glomerular filtration rate; quadratic formula

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The exact determination of the glomerular filtration rate (GFR) is often critical to patients in clinical practice, for instance in the intensive care unit, after organ transplantation, or for drug dosage adjustment. Several methods for assessing true GFR exist and require the administration of exogenous markers such as inulin, iohexol, ^{51}Cr-EDTA, or ^{99m}Tc-diethylenetriaminepentaacetic acid. All these markers are freely filtered by the glomerulus and are neither reabsorbed nor secreted by tubules. Measuring GFR with the above-mentioned techniques can be difficult to perform, invasive, time-consuming, and costly, and they are not available in all health-care facilities. To avoid these drawbacks, various bedside formulas to estimate GFR were developed using serum creatinine (SCreat) as a marker of the renal function.

In adults, the commonly used formulas are the well-known Cockcroft Gault formula,[1] the Modification of Diet in Renal Disease formula,[2] and the more recently developed Chronic Kidney Disease Epidemiology Collaboration formula.[3] It is recognized that these formulas are not applicable to the pediatric population. Several formulas were therefore developed for this population group.[4-6] The most widely used formula is the Schwartz formula,[7] developed in the 1970s and recently revised to take into account the new methods of SCreat measurements.[8] Since its publication, several studies have assessed the external validity of the revised Schwartz formula. Staples *et al.*[9] found a good agreement when applying this formula to children with no renal insufficiency. Similarly, Bacchetta *et al.*[10] concluded from their data set of children with moderate renal failure and normal GFR that the Schwartz bedside formula is accurate. However, Pottel *et al.*[11] suggested adding an age-dependent modification to the constant k for healthy children.

The revised Schwartz formula[8] was derived from data obtained in children with measured GFR (mGFR) between 15 and 75 ml/min×1.73 m^2 (using iohexol clearance), and thus its applicability to children with less renal insufficiency or

to children with normal renal function remains questionable at best.

Because of these limitations to the widespread application of the Schwartz formula, the aim of the study was to provide additional data to assess the accuracy of the revised Schwartz formula by using another gold-standard method of mGFR determination, i.e., inulin clearance (iGFR), in a cohort of children with renal failure, but also in children with normal renal function or even supra-normal GFR, i.e., hyperfiltration.

RESULTS

Demographics

Original data set. Five hundred and fifty-one iGFRs performed between 2005 and 2010 in 392 children were evaluated. Demographic characteristics of the population are summarized in Table 1a. Mean values ± s.d. for age, body weight (BW), and Ht were 11.44 ± 3.93 years (range 2.9–17.98), 40.62 ± 17.85 kg (range 13–113.2), and 144.8 ± 21.43 cm (range 94.5–188.5), respectively. Twenty-three children presented with growth retardation for BW (5.8% of all patients), 14 presented with growth retardation for Ht (3.5% of all patients), and 34 presented with combined growth retardation for both BW and Ht (8.6% of all patients). Renal disorders are summarized in Table 2.

Complementary data set. In a prospective manner, an external validation data set was conducted. One hundred and twenty-seven iGFRs were analyzed between 2010 and 2012 in 127 children. Children included in the original cohort were excluded from this complementary cohort. Demographic characteristics of this complementary data set are as follows: Mean values ± s.d. for age, BW, and Ht were 12.42 ± 4.1 years (range 3–18.0), 39.5 ± 16 kg (range 15–95), and 149.6 ± 21.88 cm (range 93.8–194.5), respectively. For the whole cohort, mean values ± s.d. for iGFRs and eGFRs using the new quadratic formula and the revised Schwartz formula were 85.66 ± 21.67, 89.44 ± 20.88, and 90 ± 24.78, respectively (Table 1b).

Correlation between iGFRs and the revised Schwartz formula

The revised Schwartz formula depends on the ratio of the two following variables: the Ht and SCreat. The distribution of iGFRs corresponding to this variable ratio (Ht/SCreat) is presented in Figure 1a and b. When applying the revised Schwartz formula to our original data set, we observed a linear correlation between eGFRs and iGFRs and a symmetric distribution of iGFRs along this line until a point from which eGFR systematically overestimates true iGFR (Figure 1a). To better define the points of change where the revised Schwartz formula overestimates iGFR, we applied the circular binary segmentation method for all the bias values of the revised Schwartz formula. This method demonstrates the presence of a one point of change equals to 251 of the variable ratio of Ht/SCreat corresponding to an iGFR of 103 ml/min × 1.73 m^2 (Figure 2a).

In fact, the best relation between the iGFR and the variable ratio of Ht/SCreat is quadratic (Figure 1b). For these reasons, we derived a new quadratic equation by fitting a robust linear quadratic model, applicable to all GFR values and taking into account the age and the sex of the patient. Of note, and contrary to the revised Schwartz formula, when applying the circular binary segmentation method to all bias values of our new quadratic formula, no change points were detected

Table 1b | Mean ± s.d. for iGFRs and eGFRs using the new quadratic and the revised Schwartz formulas in the validation data set

Ht/SCreat	Mean of iGFR	s.d. of iGFR	Mean of eGFR using quadratic formula	s.d. of eGFR using quadratic formula	Mean of eGFR using Schwartz formula	s.d. of eGFR using Schwartz formula
<251	81	22	83.26	20.24	80.72	19.51
⩾251	100.10	11.88	108.57	5.92	118.74	15.91
Total	85.66	21.67	89.44	20.88	90	24.78

Abbreviations: eGFR, estimated glomerular filtration rate; iGFR, inulin clearance; Ht/SCreat, height/serum creatinine.
iGFRs and eGFRs are expressed in ml/min × 1.73 m^2.

Table 2 | Characteristics and classification of patients' renal disorders

Etiologies	CKD stage 1	CKD stage 2	CKD stage 3	CKD stages 4 and 5
Obstructive or reflux uropathy	150	86	11	2
Congenital and acquired single kidney	57	38	4	0
Polycystic kidney disease	9	6	4	0
Glomerulopathies	19	8	4	2
Hemolytic and uremic syndrome	1	8	1	4
Metabolic disease	2	4	6	2
Post-chemotherapy	6	6	11	0
Post-pyelonephritis	12	6	0	0
Other	39	24	15	4
Total: 551	295	186	56	14

Abbreviation: CKD, chronic kidney disease.
CKD stages 1, 2, 3, 4, and 5 denote glomerular filtration rate (GFR) ⩾90, 60–89, 30–59, 15–29, and <15 ml/min × 1.73 m^2, respectively.

Table 1a | Populations' demographic characteristics for the original data set

Ht/SCreat	*n*	Number of female	Percentage of female	Mean of age (years)	s.d. of age	Minimum of age (years)	Maximum of age (years)	Mean of height (cm)	s.d. of height	Mean of weight	s.d. of weight	Mean of creatinine (mg/dl)	s.d. of creatinine
<251	414	185	44.69	12.17	3.77	2.9	17.98	148.1	20.7	43.3	18	0.85	0.42
⩾251	137	59	43.07	9.24	3.59	3.34	17.26	134.9	20.6	32.6	14.9	0.48	0.09
Total	551	244	44.28	11.44	3.93	2.9	17.98	144.8	21.43	40.62	17.85	0.76	0.40

Abbreviation: Ht/SCreat, height/serum creatinine.

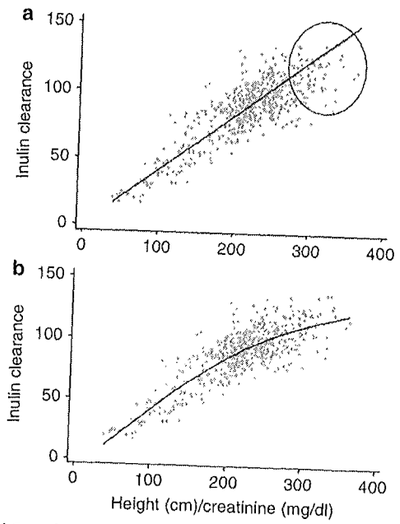

Figure 1 | Correlation between the variable ratios of height/serum creatinine (Ht/SCreat) and inulin clearances (iGFRs). (**a**) The solid line represents the best fit by applying the linear regression model of the revised Schwartz formula. The circle depicts estimated glomerular filtration rate (eGFR) values systematically overestimating true inulin clearance (iGFR). (**b**) The solid line represents the best fit using the quadratic regression model.

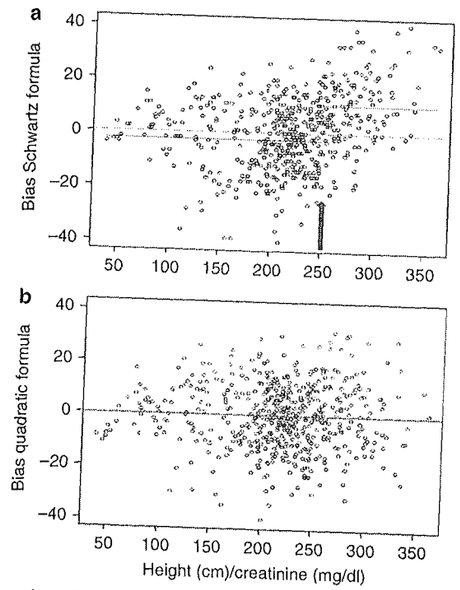

Figure 2 | Application of the circular binary segmentation (CBS) method to bias values of the Schwartz and the quadratic formulas. (**a**) Arrow shows the point of change at height/serum creatinine of 251, corresponding to an iGFR of 103 ml/min × 1.73 m^2, when using the Schwartz formula. (**b**) No point of change was detected when using the quadratic fomula.

(Figure 2b), which means that the new quadratic formula is applicable to all GFR values.

The new quadratic formulas for female and male individuals are as follows:

Females:

$$0.68 \times (\text{Height/serum creatinine}) - 0.0008 \times (\text{height/serum creatinine})^2 + 0.48 \times \text{age} - 21.53$$

Males:

$$0.68 \times (\text{Height/serum creatinine}) - 0.0008 \times (\text{height/serum creatinine})^2 + 0.48 \times \text{age} - 25.68$$

(Ht in cm, SCreat in mg/dl, age in years).

Or

Females:

$$60 \times (\text{Height/serum creatinine}) - 6.25 \times (\text{height/serum creatinine})^2 + 0.48 \times \text{age} - 21.53$$

Males:

$$60 \times (\text{Height/serum creatinine}) - 6.25 \times (\text{height/serum creatinine})^2 + 0.48 \times \text{age} - 25.68$$

(Ht in cm; SCreat in μmol/l; age in years).

New quadratic formula: checking for overfitting

To check for overfitting, first we calculated a shrinkage coefficient 'γ', which measures the flattening of the plot of predicted (eGFR) versus observed (iGFR) values away from 45°.[12,13] We obtained a γ value of 0.0055281 (<1%); this indicates that <1% of the model fit is noise. In addition, we performed an internal and an external validation of this new formula.

Model validations

Internal model validation (original data set). A split-half cross-validation technique was performed to assess our model fit/accuracy.[14] We divided our data set into two halves: the training set, on which the model was fitted, and the testing set, on which the model was evaluated. The estimated coefficients on the training set are then used to predict outcome scores of the training set, as well as of the testing set. The residual squared errors (RSEs) were then calculated for the training set and for the testing set using the new quadratic formula and the revised Schwartz formula. This allows the comparison of the RSE between the training set and the testing set for the new quadratic formula and also for the comparison of RSE between the new quadratic and the revised Schwartz formulas on the same data set (testing set). In addition, the correlation coefficient between predicted and observed values was calculated for the new quadratic and for the revised Schwartz formulas on the same testing set.

The split-half cross-validation was done with 500 bootstrap replications, and the results are summarized in Table 3. The calculated mean error (mean RSE) of the quadratic formula on the testing set is slightly larger than the mean RSE calculated on the training set (mean difference = 156–149.7 = +6.3). However, for the revised Schwartz formula, the mean RSE is very large (mean difference = 197.5–149.7 = +47.8). The mean correlation coefficient between the predicted and the observed values on the testing set is 0.85 and 0.82 for the quadratic formula and the revised Schwartz formula, respectively.

When the new quadratic formula and the revised Schwartz formulas were applied to the whole population, we found a mean RSE of 151.5 and 196.4, with a mean correlation coefficient of 0.86 and 0.83, respectively.

External model validation (complementary data set). The estimated coefficients for the new quadratic formula from the original cohort were used to predict scores on the complementary cohort. The RSE of the new quadratic formula on the complementary cohort is 157.2 (compared with 156 in the original cohort), and the correlation between the predicted and observed values is 0.84. These results show an excellent performance of the new quadratic formula. In addition, the RSE of the revised Schwartz formula on this complementary data set is 267.17, which confirms the low performance of this formula for eGFR. A scattered plot depicting the relationships between iGFRs and eGFRs using the new quadratic formula (Figure 3a) and the revised Schwartz formula (Figure 3b) shows an overall better performance of the quadratic formula, whereas the Schwartz formula overestimates GFR, and this again at high iGFR values.

Comparison of the revised Schwartz formula and the quadratic formula

Table 4 summarizes the results and shows the different performances of the revised Schwartz formula and the new quadratic formula. Considering all patients, there is no significant difference between the two formulas ($P = 0.9$) for an accuracy within 10%. However, when considering an accuracy within 20%, the new quadratic formula shows significantly better results ($P = 0.04$) than the revised Schwartz formula. The higher precision and accuracy of the new quadratic formula was especially more appropriate for patients with Ht/SCreat over 251, corresponding to a mGFR $\geqslant$ 103 ml/min×1.73 m^2 (P-values of 0.02 and 0.001 for an accuracy of 10% and 20%, respectively).

We also divided our original data set into three groups for bias analysis: group 1, iGFR $\leqslant$ 75 ml/min×1.73 m^2 ($n = 116$); group 2, iGFR between 75 and 103 ml/min×1.73 m^2 ($n = 298$); and group 3, iGFR $\geqslant$ 103 ml/min×1.73 m^2 ($n = 137$). With the revised Schwartz formula, there is a significant difference in bias between groups 1 and 3 ($P < 0.00$) (mean values ± s.d. of bias for groups 1 and 3 are −2.38 ± 12.96 and 10.72 ± 13.81, respectively). There is also a significant difference in bias between the groups 2 and 3 ($P < 0.00$) (mean values ± s.d. of bias for groups 2 and 3 are −2.6 ± 12.25 and 10.72 ± 13.81, respectively), but there is no significant difference between groups 1 and 2 ($P = 0.5$) (mean values ± s.d. of bias for groups 1 and 2 are −2.38 ± 12.96 and −2.6 ± 12.25, respectively). With the new quadratic formula, there is no significant difference in bias between all groups (mean values ± s.d. of bias for groups 1, 2, and 3 are 0.44 ± 11.97, −1.13 ± 11.95, and 1.82 ± 13.23, respectively).

Furthermore, in contrast to the new quadratic formula, the revised Schwartz formula was not adjusted for age and sex. Figure 4a and b compare these formulas at two extreme ages (4 and 17 years), and demonstrate the effect of age and sex on the eGFR. They also show the range of reliability using the Schwartz formula in these two extreme ages.

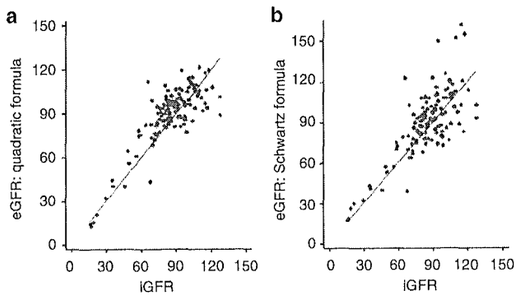

Figure 3 | Relationships between inulin clearances (iGFRs) and estimated glomerular filtration rates (eGFRs) in the complementary data set. Using (**a**) the new quadratic formula and (**b**) the revised Schwartz formula.

Table 3 | RSEs in the training set and testing set, correlation coefficient between iGFRs and eGFRs using the new quadratic and the revised Schwartz formulas

	Training set RSE	RSE; correlation coefficient using the quadratic formula on the testing set	RSE; correlation coefficient using the revised Schwartz formula on the testing set
Minimum	123.9	129.1; 0.796	161.5; 0.766
1st quartile	143.9	150.3; 0.843	188.8; 0.814
Median	149.4	155.9; 0.853	197.6; 0.825
Mean	149.7	156.0; 0.851	197.5; 0.824
3rd quartile	155.5	162.1; 0.861	205.5; 0.837
Maximum	175.2	189.2; 0.884	236.7; 0.872

Abbreviation: RSE, residual squared error.

Table 4 | Performances of the revised Schwartz formula and the new quadratic formula

	n	Accuracy within 10% of iGFR	Accuracy within 20% of iGFR
All patients			
Schwartz formula	551	47%;	79%;
Quadratic formula	551	50%;	83%;
P-value		0.9	0.04
Patients with height/creatinine <251			
Schwartz formula	414	46%;	80%;
Quadratic formula	414	47%;	81%;
P-value		0.4	0.2
Patients with height/creatinine ⩾251			
Schwartz formula	137	48%;	75%;
Quadratic formula	137	60%;	89%;
P-value		0.02	0.001

Height in cm; iGFR; inulin clearance; *n*, patient number; serum creatinine in mg/dl. Significance was defined as $P < 0.05$.

DISCUSSION

SCreat is, and remains, the most commonly used endogenous marker of renal function. It is easily measured and therefore available in most laboratories worldwide. To evaluate GFR, several formulas were developed, extrapolating from the SCreat values. The most commonly used formula in children is the Schwartz formula, revised in 2009.[8] There are several limitations to the widespread use of the revised Schwartz formula, mainly its precision and accuracy in children with a GFR above 75 or below 15 ml/min×1.73 m^2. Furthermore, the revised formula is not adjusted for age or sex, in contrast to the previous Schwartz formula. Our data set provides a further validation of the revised Schwartz formula, as we found a good agreement for children with a GFR between 15 and 103 ml/min×1.73 m^2, confirming what other studies have also found. However, we observed that the revised Schwartz formula performs poorly at Ht/SCreat values exceeding 251, corresponding to higher GFR levels. Above that value, the Schwartz formula significantly overestimates mGFRs. Our results are in line with previously published reports. Bacchetta *et al.*[10] and Pottel *et al.*[11] already showed that for a GFR above 90 ml/min×1.73 m^2 the new Schwartz formula loses its accuracy. Staples *et al.*[9] and Berg *et al.*[15] both observed an underestimation in GFR above 90 and 60 ml/min×1.73 m^2, respectively, but authors questioned whether their findings were related to the small number of patients studied. In addition, we found a significant effect of age and sex on the prediction of GFR. Therefore, and in contrast to the revised Schwartz formula, the new quadratic formula has been adjusted for age and sex.

Our study is the first one to describe a precise cutoff for the validity of the revised Schwartz formula, and allows deriving a new generalized formula, applicable to all GFR values.

The new quadratic formula, validated against iGFRs in two independent cohorts, assessed GFR equally well or more precisely than the revised Schwartz formula across a wide variety of clinical conditions. It is the first one to take into account children with normal or supra-normal GFR. The bias and accuracy improvements for higher estimated GFRs in which Ht/SCreat are above 251, corresponding to iGFRs above 103 ml/min×1.73 m^2, have important implications for public health and clinical practice. This is particularly important in conditions such as diabetes mellitus, where hyperfiltration has an important role in the progressive deterioration of the renal function and puts the children at risk for secondary glomerulosclerosis if left untreated.

Although more complex than the revised Schwartz formula, the new quadratic formula can readily be implemented into daily clinical work, at the bedside, with the use of personal computers. We have developed a JavaScript application that can be downloaded from our website using the following link: http://www.chuv.ch/quadraticformula. We also developed a calculator for applying this formula, which can also be found on this website.

All creatinine-based formulas for calculating eGFR depend strongly on the accuracy of SCreat measurement. The most important problem is that the methods used to assay creatinine in the blood differ widely in their susceptibility to nonspecific chromogens, which causes the creatinine value to be overestimated. The National Kidney Disease Education Program in the United States has attempted to solve this problem by trying to get all laboratories to calibrate their measurements of creatinine against a 'gold standard', which is isotope dilution mass spectrometry. In our study, all plasma creatinine assays were performed in one laboratory with one method (compensated Jaffe technique, which is standardized against the isotope dilution mass spectrometry method). However, we cannot rule out that some of the differences in performance between the new quadratic formula and the revised Schwartz formula could be secondary to the different creatinine measurement methods used (the compensated Jaffe method vs. the enzymatic method).

We are aware of a few limitations in our study. Although some authors prefer cystatin C–based formulas or combined cystatin C and creatinine formulas[16] and challenge the use of creatinine formula, these formulas have not proven to be superior to creatinine-based formulas.[17] We could not compare formulas using cystatin C, as cystatin C was not measured. Furthermore, our new formula does not overcome limitations of SCreat in some patients, which depend on muscle mass levels. It is important to note that we did not have muscle mass evaluations in our population, but no infant was diagnosed with myopathy. Moreover, we did not

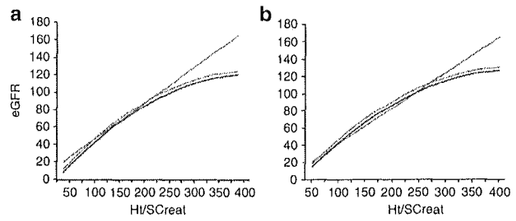

Figure 4 | Relationships between estimated glomerular filtration rates (eGFRs) and the variable ratios of height over serum creatinine (Ht/SCreat) using the revised Schwartz formula (green line) and the new quadratic formula (blue curve for boys and pink curve for girls). (**a**) Children aged 4 years. (**b**) Children aged 17 years. eGFR is expressed in ml/min×1.73 m^2, height (Ht) in cm, SCreat in mg/dl.

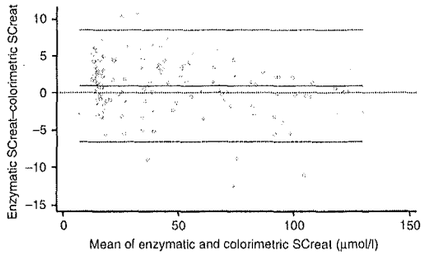

Figure 5 | Bland–Altman agreement between enzymatic and colorimetric serum creatinine (SCreat) measurements. SCreat is expressed in μmol/l.

include children below the age of 2 years in our study; therefore, we cannot make any conclusions for that age category. Several studies suggest that GFR estimation in infants is different from that of older children.[18,19] In the same vein, the influence of Tanner stages was not assessed, as Tanner stages were not recorded. Further studies will be needed to determine whether pubertal status impacts further on the new quadratic formula. Finally, 159 children were studied twice; however, this group was included several years apart, with a minimum time frame of 2 years between the two exams. Given the major demographic differences between the two exams (age, Ht, and renal disease progressions), this should not weaken the conclusions of our study.

In conclusion, using the data of more than 500 clearances with values ranging between 17 and 150 ml/min×1.73 m^2, in children with various renal diseases, we have been able to generate a more precise and generalizable quadratic formula, applicable to all GFR values and also to children with failure to thrive. Although less exact than iGFR, this new quadratic formula is a good alternative for GFR estimation in children.

MATERIALS AND METHODS

Population

Demographic characteristics and patients' renal disorders are presented in Tables 1 and 2.

Details of methods and population section are available on line in a supplementary file at www.nature.com/ki

Analytical analysis

SCreat was measured using the kinetic colorimetric compensated Jaffe method, which is closely aligned with the enzymatic assay (Figure 5) and standardized against the reference isotope dilution mass spectrometry method. iGFR was measured using the anthrone test. eGFR was calculated according to the revised Schwartz formula as follows: eGFR (ml/min×1.73 m^2) = 0.413×Ht (cm)/SCreat (mg/dl).

Statistical analysis

To overcome the problem of overestimation of eGFR calculated by the Schwartz formula, a robust linear quadratic regression model was fitted and a more accurate quadratic formula was derived. The cutoff at which the eGFR using the revised Schwartz formula tends to overestimate iGFR was determined using the circular binary segmentation method.[20] To quantify the quadratic model overfitting, we calculated the shrinkage coefficient γ.[12,13] An internal validation method using the split-half cross-validation technique was performed with 500 bootstrap replications to assess the fit and/or predictive accuracy of the new elaborated formula and to evaluate the Schwartz formula. Our sample was randomly split into two independent groups: the training set, on which our model was fitted, and the testing set, on which our model and the Schwartz formulas were evaluated. An external validation of the quadratic formula with a complementary data set was also conducted. The RSE and the correlation coefficient for the quadratic and the Schwartz formulas were calculated in the internal and the external validation data set. The quadratic formula was also compared with the Schwartz formula in terms of bias, precision, and accuracy. Statistical significance was defined as $P<0.05$.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/ki

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