Eur J Pediatr (2015) 174:1225–1235
DOI 10.1007/s00431-015-2523-7

ORIGINAL ARTICLE

Can the height-independent Pottel eGFR equation be used as a screening tool for chronic kidney disease in children?

Vandréa De Souza[1,2,3] · Hans Pottel[4] · Liesbeth Hoste[4] · Olga Dolomanova[1] · Regine Cartier[5] · Luciano Selistre[1,3,6] · Bruno Ranchin[7] · Aoumeur Hadj-Aïssa[1,8] · Sandrine Lemoine[1,8,9] · Pierre Cochat[7,8,10] · Laurence Dubourg[1,8,10]

Received: 30 October 2014 / Revised: 27 February 2015 / Accepted: 12 March 2015 / Published online: 7 April 2015

Abstract Determination of plasma creatinine (Pcr) should be associated to an estimation of glomerular filtration rate (eGFR). Pottel et al. established a height-independent equation, eGFR = 107.3/(Pcr/Q) where Q is the median of Pcr (Pottel–Belgium). The aims were to 1) determine a local height-independent equation (Pottel–Lyon), 2) evaluate the performance of these equations compared to the Schwartz 2009 and Schwartz–Lyon equations, and 3) evaluate the height-independent equations in laboratory routine. Therefore, 1) all first pediatric Pcr determination (December 2009–June 2011) were collected, and median of Pcr was determined for each 1-year age interval (Q-Lyon), 2) GFR was measured (mGFR) in 359 children (438 measures) and compared to eGFR, and 3) all first Pcr determination

Communicated by Jaan Toelen

Revisions received: 06 January 2015 / 27 February 2015

✉ Laurence Dubourg
laurence.dubourg@chu-lyon.fr

Vandréa De Souza
vandreasouza@gmail.com

Hans Pottel
Hans.Pottel@kuleuven-kulak.be

Liesbeth Hoste
Liesbeth.Hoste@kuleuven-kulak.be

Olga Dolomanova
dolomanova.olga@hotmail.fr

Regine Cartier
regine.cartier@chu-lyon.fr

Luciano Selistre
selistre71@gmail.com

Bruno Ranchin
bruno.ranchin@chu-lyon.fr

Aoumeur Hadj-Aïssa
aoumeur.hadj-aissa@chu-lyon.fr

Sandrine Lemoine
sandrine.lemoine01@chu-lyon.fr

Pierre Cochat
pierre.cochat@chu-lyon.fr

[1] Exploration Fonctionnelle Rénale, Groupement Hospitalier Edouard Herriot, Hospices Civils de Lyon, Lyon, France

[2] FAMED-Programa de Pós Graduação em Saúde da Criança e do Adolescente, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil

[3] CAPES Foundation, Ministry of Education of Brazil, Brasilia, DF, Brazil

[4] Interdisciplinary Research Facility Life Sciences, KU Leuven Kulak, Kortrijk, Belgium

[5] Groupement Hospitalier Est, Centre de Biologie et de Pathologie Est Biochimie et Biologie Moleculaire, Hospices Civils de Lyon, Lyon, France

[6] Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre, Brazil

[7] Centre de Référence des Maladies Rénales Rares, Service de Néphrologie et Rhumatologie Pédiatriques, Hospices Civils de Lyon, Lyon, France

[8] Université Claude-Bernard Lyon I, Lyon, France

[9] INSERM UMR 1060, Université Claude Bernard Lyon I, Lyon, France

[10] UMR 5305 CNRS/Université Claude-Bernard Lyon I, Biologie tissulaire et Ingénierie thérapeutique, Lyon, France

(January 2012–June 2013) were used to calculate eGFR with the Pottel–Lyon and the Pottel–Belgium equations. Pcr was determined by an IDMS-standardized enzymatic assay. In the population with a mGFR, the Pottel–Lyon and the Schwartz–Lyon showed the best performance (bias, P10 and P30). However, the performance in identifying patients with a mGFR<75 mL/min/1.73 m^2 was similar for all the studied equations.

Conclusion: The performance of the height-independent and dependent equations to identify mild renal dysfunction is similar. The height-independent Pottel equation could be proposed as an excellent screening tool for kidney disease when height information is not available.

"**What is Known:**"

- *Determination of plasma creatinine in children is rarely associated to an estimation of glomerular filtration rate due to the lack of height information.*
- *Pottel* et al. *developed a height-independent equation (eGFR= 107.3/(Pcr/Q) where Q is the median of Pcr for each age class.*

"**What is New:**"

- *The performance of the height-independent (Pottel) or height-dependent (Schwartz) equations is similar to identify renal dysfunction (GFR< 75 mL/min/1.73 m^2) in children.*
- *The height-independent Pottel equation could be an excellent screening tool for kidney disease in a general pediatric laboratory when height information is not available.*

Keywords Children · Adolescents · Estimated glomerular filtration rate · Height-independent GFR estimating equation · Schwartz equation · Chronic kidney disease

Abbreviations

AUC	Area under the curve
BMI	Body mass index
BSA	Body surface area
CCC	Concordance correlation coefficient
CKD	Chronic kidney disease
CKD-EPI	Chronic kidney disease epidemiology collaboration equation
eGFR	Estimation of glomerular filtration rate
GFR	Glomerular filtration rate
IDMS-traceable Pcr determination	Traceable to an isotope dilution mass spectrometry reference measurement procedure
KDIGO	Kidney disease improving global outcomes
LOA	Limit of agreement
MDRD	Modification of diet in renal disease equation
mGFR	Measured GFR
Pcr	Plasma creatinine
P10	10 % accuracy
P30	30 % accuracy
ROC	Receiver-operator characteristic
SDS	Standard deviation score
WHO	World Health Organization

Introduction

There is a general consensus that screening for chronic kidney disease (CKD) in adults is of great importance, and according to the 2012 Clinical Practice Guidelines of the National Kidney Foundation (Kidney Disease Improving Global Outcomes; KDIGO) [17, 27], determination of plasma creatinine (Pcr) should be associated to an estimation of glomerular filtration rate (eGFR) with a GFR estimating equation based on characteristics of the patient, that is sex, age, ethnic origin. In the pediatric population, the last KDIGO recommends the use of the Schwartz 2009 formula to estimate GFR in children. However, this GFR predicting equation requires height information, which is normally not available in clinical laboratory databases. Therefore, Pcr determination is usually not associated to an eGFR which leads to miss many diagnosis of mild or moderate CKD. Pottel et al. [14, 20] developed a height-independent equation based on the determination of median Pcr for each age class. The concept of this formula can be applied in every laboratory with a large data base (i.e., large laboratory pediatric hospital) leading to an equation adapted to the laboratory and/or to the local population characteristics (independent of ethnicity). As the original equation was developed in a European population with an IDMS-traceable Pcr determination (traceable to an isotope dilution mass spectrometry reference measurement procedure), the published coefficients could, from a theoretical point of view, be used in every European laboratory if standardized Pcr method is used. Pottel et al. claimed that this equation can be used as a screening tool for a possible underlying kidney problem in a general population of children [20]. Therefore, the aims of this study were to estimate 1) the feasibility of determining a local height-independent equation based on results of the laboratory hospital; 2) the performance in estimating GFR and in identifying patients with a CKD (i.e., GFR <75 or <60 mL/min/1.73 m^2) of the locally adapted (Pottel–Lyon), the original height-independent equation (Pottel–Belgium), and the height-dependent (Pottel–L–Belgium) eGFR formulas compared to the internationally recommended Schwartz 2009 equation [24] and the locally adapted Schwartz–Lyon equation [9] (both height-dependent) in a population of children undergoing a reference GFR measurement in our department; 3) the practicability of using the height-independent GFR estimating equation in children either with the original (Pottel–Belgium) or the locally adapted (Pottel–Lyon) height-independent equation in laboratory routine.

Materials and methods

Clinical laboratory data set for determination of the adapted Pottel–Lyon equation

The databases were obtained from the laboratory of the pediatric hospital. All patient data were recorded in an anonymous manner such that subjects could not be identified directly or through identifiers linked to the subjects. The study was therefore exempted from institutional review board. All Pcr value determined in children aged between 1 and 18 years (either in outpatients or hospitalized ones) from December 2009 to June 2011 were collected. Only the first test result for each patient was used for further analysis. Also, data below the detection limit (12 μmol/L) and outliers (determined by Grubbs test for outliers) were not taken into account. This reduced the total amount of data from n=80,668 to n=12,219. The children were then further divided in subgroups according to sex and age (age in years is calculated as (day of test− day of birth)/365.25). Median Pcr values together with lower and upper limits may be calculated using nonparametric statistics (Pct 2.5 and Pct 97.5 are considered lower and upper limits). This allowed to determine the Q-Lyon value which is the median of healthy children at a specific age in our laboratory.

Population of patients with a measured GFR

To evaluate the performance of GFR estimating equations, we used a data set on 359 consecutive children (438 measurements) referred to our center between January 2010 and July 2013 to undergo a GFR measurement (inulin or iohexol clearance) as a routine procedure for renal evaluation because of suspected underlying kidney pathology. A written informed consent was obtained from all patients or their families prior to obtaining the measured GFR (mGFR). The consent form contained information referring to the procedure itself as well as the later use of the information in research. According to the French Law, concerning the use of a database without direct identification of patients, it was not necessary to obtain an ethical approval (law 2006–450, April 19th 2004; Commission nationale de l'informatique et des libertés-CNIL). All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Weight, height, as well as standard deviation of size for age (SDS) according to French pediatric growth charts [25], body mass index (BMI), and BMI Z-score were recorded. Weight categories were defined according to World Health Organization (WHO) cutoff points for BMI (BMI Z-score<−2: underweight patients, BMI Z-score between −2 and +2: normal weight, and BMI Z-score>+2: obese patients). Size categories were defined by a height<−2 SDS (undersized), between −2 and +2 SDS (normal size for age), and>+2SDS oversized for age. All patients had concomitant determinations of Pcr in our hospital laboratory allowing a GFR estimation using the five formulas (Table 1).

Testing data set for determination of eGFR with the Pottel equation in the general population

We determined eGFR with the height-independent GFR predicting equation either with the previously determined Q-Lyon value (Pottel–Lyon) or with the original Pottel formula (Pottel–Belgium). All the first determinations of Pcr performed in children in the laboratory of our hospital between January 2012 and June 2013 were included.

GFR measurement and laboratory methods

GFR determination was measured either by renal inulin or plasmatic iohexol clearance depending on the indication and clinical condition of the patients. Plasmatic iohexol clearance, which does not require urinary samples, was preferred in children younger than 6 years of age or patients with urological problems. By contrast, inulin clearance was chosen when a history of iodine allergy, extracellular overload, or severe level of CKD was present. However, as most studies indicate close agreement between GFR measured by inulin clearance and clearance of iohexol, measured as standard renal clearance or plasma disappearance [23], we consider the two methods as equivalent ones. A standard technique of renal clearance of inulin (polyfructosan, Inutest®, Fresenius Kabi, Graz, Austria) was used as previously described [9, 11]. The measurement of plasma and urine polyfructosan concentrations were performed using an enzymatic method which demonstrated very good specificity and reproducibility (within-run precision <1 % and between-run precision <3.5 %) [11]. Iohexol clearance was performed according to a standard technique of single-bolus injection method. Briefly, an IV injection of about 6 mL/1.73 m^2 (with a maximum dose of 6 mL) of iohexol (Omnipaque, 300 mg/mL) was administered, and blood samples were drawn from the contralateral arm after 120, 180, and 240 min. The GFR was calculated from the slope of plasma concentrations using a one-compartment model corrected using the Bröchner-Mortensen formula [3]. Plasma iohexol concentration was determined using HPLC according to the method published by Cavalier et al. [5] which showed high analytical performances. External quality control was provided by Equalis (Uppsala, Sweden) every 3 months. The results were expressed per 1.73 m^2 body surface area (Dubois formula: $BSA = height^{0.725} \times weight^{0.425} \times 0.007184$) [10].

Table 1 Overview of eGFR equations

Name	Full formula
Pottel–Lyon	eGFR=107.3/(Scr/Q) with Q=median of Pcr of healthy children at a specific age (Table 2)
Pottel–Belgium [14]	eGFR=107.3/(Scr/Q) with $Q=88.4\times(0.21+0.057\times Age-0.0075\times Age^2+0.00064\times Age^3-0.000016\times Age^4)$ for boys $Q=88.4\times(0.23+0.034\times Age-0.0018\times Age^2+0.00017\times Age^3-0.0000051\times Age^4)$ for girls
Pottel–L–Belgium [14]	eGFR=107.3/(Pcr/Q) with $Q=88.4\times(3.94-13.4\times L+17.6\times L^2-9.84\ L^3+2.04\times L^4)$ for boys and girls
Schwartz 2009 [24]	$eGFR=36.5\times L / PCr$
Schwartz–Lyon [9]	eGFR=k×L/PCr *k*=36.5 in males aged >13 years *k*=32.5 in others

L=Height, expressed in centimeter (cm) except for Pottel–L–Belgium where height is expressed in meter (m); PCr=Plasma creatinine, expressed in micromoles per liter (μmol/L) and age in years

All Pcr determinations were obtained with an enzymatic method (Multigent Creatinine Enzymatic kit purchased from Abbott Diagnostics) on the Architect cSystemS. The creatinine calibrators (ClinChem Cal) are traceable to the National Institute of Standards and Technology, Creatinine Standard Reference Materials 914 (verified with NIST SRM 967). Indicated quality control data showed intra- and interassay precision (CV) of 0.6 and 2.6 %, respectively at a creatinine concentration of 78 and 58 μmol/L, respectively.

Statistical analysis

The agreement between mGFR and eGFR values was evaluated by estimation of the mean bias (mean eGFR−mGFR), the agreement limits, and the 10 % (P10) and 30 % (P30) accuracies as recommended by Earley et al. [12] and according to the Clinical Practice Guidelines of the Kidney Disease Outcomes Quality Initiative (KDOQI) [18]. A random intercept model was used to estimate the mean bias and the standard deviation (SD) of the bias. This allowed for repeated measurements in the same patients and estimates of intra-patient and inter-patient variances. The concordance correlation coefficient (CCC) was used to test agreement [8, 15]. The ability of the formulas to predict a mGFR<60, <75 and <90 mL/min/1.73 m^2 was assessed using area under the ROC curves (AUC).

To compare the mean biases, the CCCs, the P10, and the P30, respectively, a paired *t* test, the bootstrap 95 % confidence intervals of the differences between CCCs, and a McNemar's test were used.

Based on the paper of Hoste et al. [14], a performance score for the eGFR formulas was calculated based on the following rules:

(i) absolute bias <5: score +5; between 5 and 10: score +3; between 10 and 15: score +1,

(ii) P30>80: score +5; between 70 and 80: score +3; between 60 and 70: score +1

(iii) P10>40: score +5; between 30 and 40: score +3; between 20 and 30: score +1.

All the analyses were performed using R for Windows, version 3.0.2. A value of $p<0.05$ was considered for statistical significance.

Results

Determination of median Pcr value in Lyon (Q-Lyon) according to age class and sex in the clinical laboratory data set population

Mean±SD, median, and percentile 2.5 and 97.5 % of Pcr were determined for each sex and for all 1 year interval age classes (Table 2). Comparison of the median values for each age and sex classes between the Belgian results of Pcr [21, 22] and those of our laboratory by a linear regression slope showed a slight but significantly higher median result of Pcr in the Belgian population (slope 1.06, $p<0.0001$). There is a 6 % systematic deviation between median Pcr values (Q values) between Lyon and Belgium with lower estimates for Lyon.

Performance of the GFR estimating equations in the population of children with a mGFR

The performance of the height-independent equations (Pottel–Lyon and Pottel–Belgium) and of the height-dependent equations (Schwartz 2009, Schwartz–Lyon, and Pottel–L–Belgium) and formulas has been evaluated in a population of 359 children (438 measurements) referred to our department for GFR determination. Characteristics of the children were

indicated in Table 3. Schwartz–Lyon and Pottel–Lyon showed the best performance in the whole population and in patients with a GFR <90 mL/min/1.73 m^2 giving significantly higher P30 and CCC and lower bias in comparison with other equations (Table 4). In patients with a GFR≥90 mL/min/1.73 m^2, the performance of the five predicting GFR equations is similar. To note, hyperfiltration (GFR ≥135 mL/min/1.73 m^2) [4] that was observed in 39 patients (42 measurements, mean GFR=153 mL/min/1.73 m^2) decreased performance (bias, P10 and P30) of all studied equations (data not shown). A performance score for the five different eGFR formulas in the whole population and in each subgroup (defined by a GFR<90 or ≥90 mL/min/1.73 m^2 was calculated (Table 4). In the overall cohort, as well in the two mGFR subgroups, the Schwartz–Lyon and the Pottel–Lyon get the highest score.

As shown by the areas under the ROC curves of GFR estimating equations (Table 5), all the studied equations have similar performance in identifying patients with renal dysfunction (mGFR<60 or <75 mL/min/1.73 m^2) in the present study. However, when mGFR<90 mL/min per 1.73 m^2, the AUC of Schwartz 2009 and Schwartz–Lyon formulas were significantly higher than those of the others formulas. Bland and Altman graphs show bias changes according to mGFR: the overestimation of mGFR increased when mGFR decreased with all equations (Fig. 1).

Finally, the performance of eGFR equations was evaluated according to weight and size subgroups (Table 6). All the equations have better performance in the normal group of weight or size. However, Pottel–Lyon and Schwartz–Lyon have a better score in all the subgroups, followed by the Pottel–L–Belgium equation. The performance of Schwartz 2009 and Pottel–Belgium are rather similar.

Determination of eGFR in the testing data set of children

All the first Pcr measurements of 13,117 children (53.3 % of males) aged 8.7±5.2 years (1–18) were included. Mean Pcr was 55±28 μmol/L. Among them, 328 (2.5 %) and 949 (7.2 %) children have a Pcr value less the 2.5th and above the 97.5th percentile for age and sex, respectively. P97.5 corresponds to a mean eGFR of 76.4±3.4 mL/min/1.73 m^2 (70–83) with Pottel–Lyon and a Pcr/Q of 1.41±0.06 (1.3–1.5). Three thousand one hundred and four (23.7 %) and 908 (6.9 %) of children have a Pottel–Lyon estimated eGFR <90 and <75 mL/min/1.73 m^2, respectively.

Table 2 Mean, median, and lower and upper limit of Pcr in the training set population in Lyon (n=12,219) and median of Pcr in Belgium (Q-Belgium) for different age categories

	Girls				Boys			
	Lyon			Belgium	Lyon			Belgium
Age group (years)	Number	Mean Pcr±SD	Median Pcr=Q-Lyon [P2.5–P97.5]	Median Pcr Q-Belgium	Number	Mean Pcr±SD	Median Pcr=Q-Lyon [P2.5–P97.5]	Median Pcr Q-Belgium
1–2	682	22.9±4.5	22 [15–33]	24	765	23.1±4.9	23 [15–35]	24
2–3	504	24.9±5.1	25 [15–35]	27	547	25.3±5.3	25 [15–36]	27
3–4	332	27.6±5.4	27 [17–40]	29	439	27.7±5.2	28 [18–39]	29
4–5	356	29.7±5.7	30 [19–41]	32	389	30.8±5.9	30 [19–43]	32
5–6	299	31.9±5.8	31 [23–44]	34	382	32.7±6.3	32 [21–46]	34
6–7	249	34.2±6.6	34 [22–50]	37	334	34.1±6.9	34 [19–47]	37
7–8	300	36.9±6.6	36 [26–51]	39	323	38.2±6.7	38 [25–53]	39
8–9	307	38.9±6.8	39 [26–52]	40	327	40.4±7.4	40 [24–56]	40
9–10	272	40.9±7.5	40 [27–57]	43	310	41.8±6.9	42 [27–56]	43
10–11	291	41.8±7.9	41 [27–60]	46	353	44.7±7.3	44 [30–58]	46
11–12	276	43.7±6.6	43.5 [30–59]	47	355	46.5±7.2	46 [32–60]	47
12–13	261	46.6±7.6	46 [34–62]	50	375	47.5±8.4	48 [32–65]	50
13–14	307	48.5±9.5	48 [32–71]	54	334	52.8±9.6	52 [36–78]	54
14–15	332	53.0±8.8	52.5 [36–70]	55	369	57.0±11.2	57 [37–79]	60
15–16	399	55.1±9.2	55 [38–76]	59	382	63.9±12.4	64 [39–90]	69
16–17	302	56.5±9.2	56 [41–77]	62	236	68.6±11.8	69 [44–91]	72
17–18	292	57.1±10.1	57 [37–81]	62	238	72.2±11.9	72 [46–93]	75

Pcr is expressed in micromoles per liter (μmol/L)

P2.5 percentile 2.5, *P97.5* percentile 97.5

Table 3 Characteristics of the patients with GFR measurement

Characteristic of the patients	Database
n	359
Male (%)	58 %
Age (years)	9.5±3.3 (3–18)
Weight (kg)	30.5±13.2 (9–92)
Height (cm)	131.3±18.9 (77–182)
Height expressed in SDS	0.2±1.5(−6.5–4.2)
Growth retardation (<2SDS)	35 (8.0 %)
Growth advance (>2SDS)	26 (5.9 %)
BMI (kg/m^2)	17±3 (10–32)
BMI Z-score	0.07±1.4 (−4.9–5.2)
Underweight (BMI Z-score<−2)	25 (5.7 %)
Obese (BMI Z-score>2)	36 (8.2 %)
Method of GFR measurement (inuline/iohexol) (%)	43 %/57 %
Plasma creatinine (μmol/L)	55±28 (17–262)
mGFR (mL/min/1.73 m^2)	95±29 (18–204)
Indications of GFR measurement	
Congenital abnormality of the kidney and urinary tract	105 (29 %)
Glomerular nephropathy	40 (11 %)
Tubulo-interstial disease	19 (5 %)
Hereditary disease	22 (6 %)
Renal transplantation	44 (13 %)
Other transplantation	76 (21 %)
Other	53 (15 %)
CKD classification	
Stage I	204 (57 %)
Stage II	104 (29 %)
Stage III	44 (12 %)
Stage IV	7 (2 %)

Values are mean±standard deviation (range) or *n* (%) unless otherwise specified

Mean±SD eGFR estimated with Pottel–Lyon was significantly lower than those estimated with Pottel–Belgium (106.3 ±28.6 and 115.1±30.9 mL/min/1.73 m^2, respectively, $p<0.0001$). The difference between the two estimating formulae was −8.4±3.8 % and do not change with the Pcr/Q ratio. The use of Q-Belgium to estimate eGFR leads to a change of classification between decreased (eGFR<90) to normal eGFR (eGFR≥90) in 1315 children. However, mean Pottel–Lyon estimated eGFR of these 1315 patients was 86.3±2.7 mL/min/1.73 m^2 (78.6–89.9) that is close to the limit of 90.

Discussion

Pcr measurement is one of the most frequent biochemical parameters measured in patients even in children. However, eGFR is rarely determined by the laboratory due to the lack of height information, a necessary parameter in the Schwartz 2009 formula. To help clinicians, reference intervals of Pcr according to sex and age are provided such as those provided by Pottel et al. or Ceriotti et al. [6, 22]. However, identifying a mild or moderate CKD is challenging, and the use of a height-independent formula might be useful.

According to international recommendations, Pcr measurement in children should be performed by an enzymatic method with calibration traceable to IDMS reference methodology [17] in order that results could be compared in all laboratories of most countries. Therefore, provided that the studied population is similar to the reference group, the use of GFR estimating equations with identical coefficients could be used with a relative confidence. In the present study, the predicting GFR equations (i.e., Schwartz 2009 and Pottel–Belgium or Pottel–L–Belgium) established in other countries (USA and Belgium, respectively) with comparable Pcr method of measurements and in comparable populations (Western countries children), give similar performance results. The good performance of Schwartz 2009, Pottel–Belgium, and Pottel–L–Belgium in our study is in accordance with previous reports [1, 11, 14, 24, 26].

Table 4 Statistical results for the prediction performance of eGFR equations and results of the performance scoring system (results between brackets) according to mGFR, subgroups

Group	Schwartz 2009	Schwartz–Lyon	Pottel–Lyon	Pottel–Belgium	Pottel–L–Belgium
All measurements (n=438/patients=359)—mGFR±SD=92.9±32.6					
Bias±SD	10.0±22.7 (3)	−0.5±21.6* (5)	0.3±21.4* (5)	8.2±23.3 (3)	4.4±21.9 (5)
30 % accuracy	81.0 (5)	87.6 * (5)	87.0 * (5)	79.6 (3)	85.2 (5)*
10 % accuracy	36.5 (3)	42.4 (5)	43.0 (5)	37.4 (3)	38.8 (3)
CCC	0.77 (0.73–0.80)	0.81 (0.77–0.84) *	0.80 (0.76–0.83) *	0.75 (0.71–0.79)	0.79 (0.76–0.82)*
Score[a]	11	15	15	9	13
According to mGFR					
Group 1 (GFR<90 mL/min/1.73 m^2) (n=206/patients=163)—mGFR±SD=65.3±17.1					
Bias±SD	12.4±18.7 (1)	5.0±16.8* (3)	7.4±16.8* (3)	14.0±18.7 (1)	9.1±17.3 (3)
30 % accuracy	74.8 (3)	85.4 * (5)	82.5* (5)	70.0 (3)	81.5 (5)
10 % accuracy	34.5 (3)	40.8 (5)	42.2 (5)	37.9 (3)	36.9 (3)
Score[a]	7	13	13	7	11
Group 2 (GFR≥90 mL/min/1.73 m^2) (n=232/patients=209)—mGFR±SD=117.4±21.3					
Bias±SD	8.1±25.7 (3)	−4.7±23.2 (5)	−5.1±23.1(3)	4.0±25.7 (5)	0.9±24.7 (5)
30 % accuracy	86.6 (5)	90.0 (5)	91.0 (5)	88.3 (5)	88.8 (5)
10 % accuracy	38.7 (3)	44.3 (5)	43.1 (5)	37.0 (3)	36.9 (3)
Score[a]	11	15	13	13	13

mGFR is expressed in mL/min/1.73 m^2

SD standard deviation, *CCC* concordance correlation coefficient

*p<0.05 between Schwartz–Lyon and other equations, favoring Schwartz–Lyon, but without difference with Pottel–Lyon

[a] Performance score for the eGFR formulas in the three subgroups according to Hoste et al.[14] and based on the following rules: (i) absolute bias <5: score +5; between 5 and 10: score +3; between 10 and 15: score +1, (ii) P30>80: score +5; between 70 and 80: score +3; between 60 and 70: score +1, and (iii) P10>40: score +5; between 30 and 40: score +3; between 20 and 30: score +1

However, a 6 % systematic deviation between median Pcr values (Q values) between Lyon and Belgium was observed with a mean difference between Q values for Lyon and Belgium of −2.7±1.5 μmol/L (−6 to 0), p<0.0001, leading to a small but significant difference in the mean eGFR estimation in the testing population with either the Pottel–Lyon or the Pottel–Belgium. Despite standardization of Pcr measurement method, this systematic deviation might be partly explained by the use of various manufacturer techniques of Pcr measurement (Roche enzymatic assay in Belgium, Abbott enzymatic assay in Lyon). In addition, differences (i.e., median size and height) between children from different European countries cannot be ruled out as suggested by Bonthuis et al. who reported a difference in mean height between Belgium and France [2]. These small but significant differences might explain the better performance of Pottel–Lyon which uses the locally adapted coefficient for our own children population. However, these differences are not significant on a clinical point of view. The same points (i.e., difference of Pcr measurement method and/or anthropometric differences between

Table 5 Performance of the formulas in identifying patients with mGFR <60, GFR <75, and <90 mL/min /1.73 m^2

	GFR <60 mL/min/1.73 m^2 n=69 (65)		GFR <75 mL/min/1.73 m^2 n=130 (98)		GFR <90 mL/min/1.73 m^2 n=206 (163)	
Formula	AUC (95 % CI)	Std. Error	AUC (95 % CI)	Std. Error	AUC (95 % CI)	Std. Error
Schwartz 2009	0.95 (0.92, 0.98)	0.02	0.94 (0.91, 0.96)	0.01	0.91 (0.88, 0.94) *	0.01
Schwartz–Lyon	0.95 (0.91, 0.98)	0.02	0.93 (0.90, 0.96)	0.01	0.91 (0.88, 0.93) *	0.01
Pottel–Lyon	0.94 (0.91, 0.97)	0.02	0.92 (0.89, 0.95)	0.01	0.88 (0.85, 0.91)	0.02
Pottel–Belgium	0.94 (0.90, 0.97)	0.02	0.91 (0.88, 0.94)	0.02	0.87 (0.84, 0.91)	0.02
Pottel–L–Belgium	0.95 (0.92, 0.98)	0.02	0.93 (0.90, 0.95)	0.01	0.89 (0.87, 0.93)	0.01

AUC area under ROC curves, *95 % CI* 95 % confidence interval

*p<0.05 between Schwartz 2009 and other formulas, favoring Schwartz 2009 (without difference for Schwartz–Lyon) n=Number of measurements (patients)

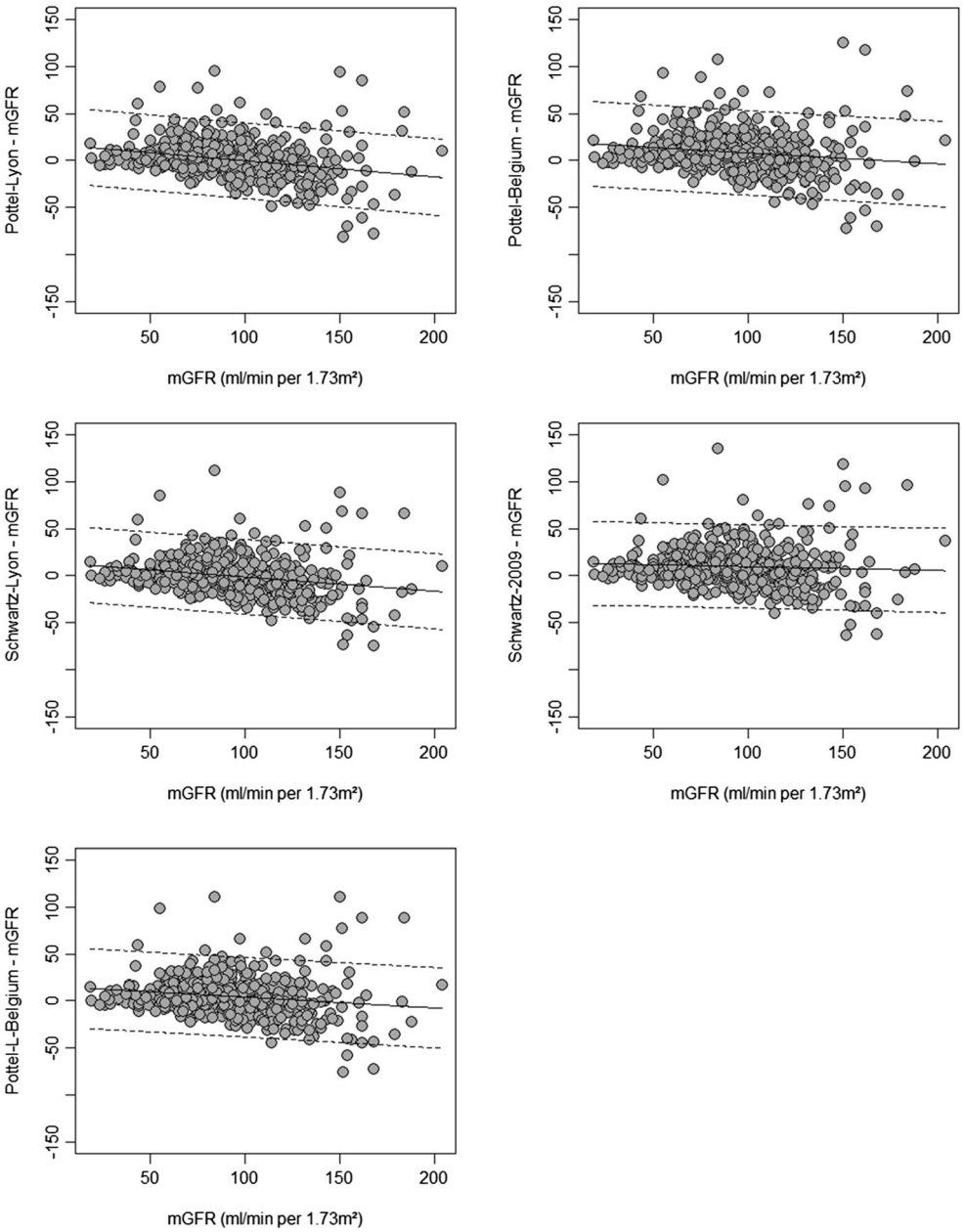

Fig. 1 Bland and Altman plots showing, for each formula, the estimated GFR minus the measured GFR bias in function of the measured GFR as gold standard in the whole population of children with a mGFR determination. The *solid line* represents the mean ratio. The *broken lines* represent the 95 % limits of agreement (i.e., ±1.96× the standard deviation)

children population) could explain the small but significant better performance of the locally adapted Schwartz–Lyon formula compared to Schwartz 2009. However, the performance of the adapted Pottel–Lyon and Schwartz–Lyon equations is similar.

The height-independent Pottel equation is built on the concept of a population-normalized Pcr and median Pcr (Q value) for age and sex can reliably be obtained from large hospital laboratory databases, as the majority of patients in these databases have normal kidney function [20]. In addition, with the systematic exclusion of patients with serial measurements and the use of specific statistical methods (a nonparametric method, the Bhattacharya procedure, and a nonlinear fit of the cumulative Gaussian distribution) which allowed to distinguish the normal from the abnormal data of Pcr, we can establish reliable and robust data of normal Pcr according to sex and age in a healthy population of children. However, in the testing data set as 7.2 % of children have a Pcr value above the 97.5 percentile for age and sex. This result could be explained by the fact that all first Pcr measurements of the pediatric hospital database were included, that is an increased proportion of children with an elevated Pcr compared to a normal healthy population.

In our population, 2155 (16.4 %) of children have a mild CKD according to the Pottel–Lyon equation (stage 2 of KDIGO classification) with a Pcr below the 97.5th percentile. In another way, 23.7 % of children of our testing set population have a Pottel–Lyon eGFR<90 mL/min/1.73 m^2 and

Table 6 Statistical results for the prediction performance of eGFR equations and results of the performance scoring system (results between brackets) according to weight and height subgroups

Group	Schwartz 2009	Schwartz–Lyon	Pottel–Lyon	Pottel–Belgium	Pottel–L–Belgium
According to weight					
Obesity (n=36/patients=32)—mGFR±SD=92.2±28.4					
Bias±SD	14.2±27.5 (1)	3.0±24.5 (5)	2.6±24.8 (5)	11.5±25.8 (1)	9.6±26.0 (3)
30 % accuracy	69.4 (1)	83.3 (5)	83.3 (5)	63.9 (1)	77.8 (3)
10 % accuracy	27.8 (1)	38.9 (3)	33.3 (3)	22.2 (1)	30.6 (3)
Score[a]	3	13	13	3	9
Normal weight (n=377/patients=311)—mGFR±SD=95.3±32.9					
Bias±SD	8.9±22.3 (3)	−1.4±20.7 (5)	−0.8±20.5 (5)	6.9±22.3 (3)	3.2±21.5 (5)
30 % accuracy	83.6 (5)	88.6 (5)	88.1 (5)	82.2 (5)	86.7 (5)
10 % accuracy	38.5 (3)	42.2 (5)	44.6 (5)	40.6 (5)	40.3 (5)
Score[a]	11	15	15	13	15
Underweight (n=25/patients=22)—mGFR±SD=90.4±30.0					
Bias±SD	17.6±23.1 (0)	7.0±20.2 (3)	13.4±25.6 (1)	23.3±29.4 (0)	13.9±22.4 (1)
30 % accuracy	60.0 (0)	80.0 (3)	72.0 (3)	64.0 (1)	72.0 (3)
10 % accuracy	24.0 (1)	44.0 (5)	28.0 (1)	12.0 (0)	28.0 (1)
Score[a]	1	11	5	1	5
According to size					
Oversized for age (n=26/patients=24)—mGFR±SD=107.3±33.2					
Bias±SD	25.9±29.5(0)	11.8±24.8 (1)	1.5±22.4 (5)	10.4±24.3 (1)	18.4±27.8 (0)
30 % accuracy	53.8 (0)	80.8 (5)	92.3 (5)	76.9 (3)	61.5 (1)
10 % accuracy	30.8 (3)	30.8 (3)	38.5 (3)	34.6 (3)	23.1 (1)
Score[a]	3	9	13	7	2
Normal size for age (n=377/patients=311)—mGFR±SD=95.0±31.9					
Bias±SD	9.2±22.3 (3)	−1.1±20.8* (5)	−0.6±21.4* (5)	7.2±23.2 (3)	3.6±21.6 (5)
30 % accuracy	83.0 (5)	88.3 (5)	87.0 (5)	80.9 (5)	86.7 (5)
10 % accuracy	36.9 (3)	44.3 (5)	43.0 (5)	37.7 (3)	40.8 (5)
Score[a]	11	15	15	11	15
Short size for age (n=35/patients=31)—mGFR±SD=81.7±31.8					
Bias±SD	4.0±16.6 (5)	−3.9±16.8 (5)	9.1±19.4 (3)	17.6±21.7 (0)	0.7±16.8 (5)
30 % accuracy	80.0 (3)	85.7 (5)	80.0 (3)	68.6 (1)	85.7 (5)
10 % accuracy	40.0 (3)	25.7 (1)	42.9 (5)	37.1(3)	28.6 (1)
Score[a]	11	11	11	4	11

mGFR is expressed in mL/min/1.73 m^2

SD standard deviation, *CCC* concordance correlation coefficient

*p<0.05 between Schwartz–Lyon and other equations, favoring Schwartz–Lyon, but without difference with Pottel–Lyon

[a] Performance score for the eGFR formulas in the three subgroups according to Hoste et al. [14] and based on the following rules: (i) absolute bias <5: score +5; between 5 and 10: score +3; between 10 and 15: score +1, (ii) P30>80: score +5; between 70 and 80: score +3; between 60 and 70: score +1, and (iii) P10>40: score +5; between 30 and 40: score +3; between 20 and 30: score +1

6.9 % an eGFR<75 mL/min/1.73 m^2. These results are in accordance with those of Fadrowski et al. [13] who found that 8.9 % of adolescents from the National Health and Nutrition Examination Survey (NHANES), in the USA, had an eGFR< 75 mL/min/1.73 m^2 (the reporting cutoff used by pediatric eGFR calculators on the National Kidney Disease Education Program (NKDEP) web site) when the bedside Schwartz 2009 formulae is used. Chavers et al. found comparable results with the Chronic Kidney Disease in Children formula, which includes Pcr, cystatin C, and blood urea nitrogen concentration [7].

Finally, we can demonstrate that all the studied equations have a better performance in children with a normal weight and/or size for age and that the performance of most of the equations decreases in children with extreme size and/or BMI.

Therefore, the height-independent equation, with or without an adaptation to the local laboratory, could be used as screening tool in a general population and as a warning sign

for a possible underlying kidney problem. Pediatric considerations of KDIGO guidelines [19] recommend to report an individual child's eGFR value of less than 60 mL/min/1.73 m^2 as "decreased." However, according to KDIGO [16], pediatric practice would suggest a higher level of kidney function for referral than that for adults, although there is no specific value in children. As suggested in a recent paper [19], abnormal GFR in children and adolescents starts below 75 mL/min/1.73 m^2; we can suggest that all children with an eGFR<75 mL/min per 1.73 m^2 could be indicated to the practitioner as potentially decreased GFR. This may trigger the attention of the general practitioner and may be the reason for sending this particular child to the pediatric nephrologist as for adult patients with the MDRD or CKD-EPI.

Several strengths of the present study can be pointed out: 1) the use of a reference standard method for GFR measurement (i.e., inulin or iohexol clearance) to evaluate performance of the various GFR estimating equations; 2) the use of an IDMS-standardized Pcr to validate the Pottel–Belgium, the Pottel–L–Belgium, and Schwartz 2009 equations; and 3) the demonstration of the practicability of determining an adapted height-independent equation to the local method of determination of Pcr and to the anthropometric characteristics of the French children population and its performance. However, the study presents also some limitations: 1) the lower age limit of 2.7 years of the children with a measured GFR limiting the validity of our results for children aged between 1 and 3 years; 2) the effect of ethnicity could not be tested because this information was not regularly available for all patients.

Conclusion

The performance of the height-independent equation is similar to those of the Schwartz 2009 or Pottel–L–Belgium equation in a Western country population of children when IDMS-standardized Pcr determination is used. Therefore, this equation could be easily used by every laboratory to give an eGFR in children and provide a screening tool to detect CKD in a general population of children.

This study demonstrates that the Q coefficient can be locally determined by large laboratories leading to a better performance of the locally adapted Pottel equation. A locally adapted equation might be very useful when enzymatic Pcr determination is not possible and/or in other population preventing the inappropriate use of formula established in Western countries patients.

Conflict of interest The authors declare that they have no conflict of interest.

Authors Contribution All authors have contributed in various degrees to the collection of data, to the research design, to the analysis performance and to the manuscript writing: V. De Souza and L. Dubourg designed the study, collected the data, performed the analysis and wrote the manuscript; H. Pottel and L. Hoste developed the methodology and wrote the manuscript; O. Dolomanova, R. Cartier, L. Selistre, B. Ranchin, A. Hadj-Aïssa, S. Lemoine and P. Cochat designed the study, collected the data and discussed the manuscript.

References

1. Blufpand HN, Westland R, van Wijk JA, Roelandse-Koop EA, Kaspers GJ, Bokenkamp A (2013) Height-independent estimation of glomerular filtration rate in children: an alternative to the Schwartz equation. J Pediatr 163:1722–1727
2. Bonthuis M, van Stralen KJ, Verrina E, Edefonti A, Molchanova EA, Hokken-Koelega AC, Schaefer F, Jager KJ (2012) Use of national and international growth charts for studying height in European children: development of up-to-date European height-for-age charts. PLoS One 7:e42506
3. Brochner-Mortensen J (1972) A simple method for the determination of glomerular filtration rate. Scand J Clin Lab Invest 30:271–274
4. Cachat F, Combescure C, Cauderay M, Girardin E, Chehade H (2015) A systematic review of glomerular hyperfiltration assessment and definition in the medical literature. Clin J Am Soc Nephrol 10:382–389
5. Cavalier E, Rozet E, Dubois N, Charlier C, Hubert P, Chapelle JP, Krzesinski JM, Delanaye P (2008) Performance of iohexol determination in serum and urine by HPLC: validation, risk and uncertainty assessment. Clin Chim Acta Int J Clin Chem 396:80–85
6. Ceriotti F, Boyd JC, Klein G, Henny J, Queralto J, Kairisto V, Panteghini M, Intervals ICoR, Decision L (2008) Reference intervals for serum creatinine concentrations: assessment of available data for global application. Clin Chem 54:559–566
7. Chavers BM, Rheault MN, Foley RN (2011) Kidney function reference values in US adolescents: national health and nutrition examination survey 1999–2008. Clin J Am Soc Nephrol 6:1956–1962
8. Crawford SB, Kosinski AS, Lin HM, Williamson JM, Barnhart HX (2007) Computer programs for the concordance correlation coefficient. Comput Methods Prog Biomed 88:62–74
9. De Souza VC, Rabilloud M, Cochat P, Selistre L, Hadj-Aissa A, Kassai B, Ranchin B, Berg U, Herthelius M, Dubourg L (2012) Schwartz formula: is one k-coefficient adequate for all children? PLoS One 7:e53439
10. Dubois D, Dubois EF (1916) A formula to estimate the approximate surface area if height and weight be known. Arch Intern Med 17:863–871
11. Dubourg L, Hadj-Aissa A, Ferrier B (2010) Adaptation of an enzymatic polyfructosan assay to clinical practice. Anal Biochem 405:266–268
12. Earley A, Miskulin D, Lamb EJ, Levey AS, Uhlig K (2012) Estimating equations for glomerular filtration rate in the era of creatinine standardization: a systematic review. Ann Intern Med 156:785–795
13. Fadrowski JJ, Neu AM, Schwartz GJ, Furth SL (2011) Pediatric GFR estimating equations applied to adolescents in the general population. Clin J Am Soc Nephrol 6:1427–1435
14. Hoste L, Dubourg L, Selistre L, De Souza VC, Ranchin B, Hadj-Aissa A, Cochat P, Martens F, Pottel H (2014) A new equation to estimate the glomerular filtration rate in children, adolescents and young adults. Nephrol Dial Transplant Off Publ Eur Dial Transplant Assoc Eur Renal Assoc 29:1082–1091
15. King TS, Chinchilli VM, Carrasco JL (2007) A repeated measures concordance correlation coefficient. Stat Med 26:3095–3113

16. Members-KB (2013) Chapter 5: referral to specialists and models of care. Kidney Int Suppl 3:112–119
17. Members KB (2013) KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl 3:19–62
18. National Kidney F (2002) K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 39:S1–S266
19. Pottel H, Hoste L, Delanaye P (2014) Abnormal glomerular filtration rate in children, adolescents and young adults starts below 75 mL/min/1.73 m. Pediatr Nephrol 30:821–828
20. Pottel H, Hoste L, Martens F (2012) A simple height-independent equation for estimating glomerular filtration rate in children. Pediatr Nephrol 27:973–979
21. Pottel H, Mottaghy FM, Zaman Z, Martens F (2010) On the relationship between glomerular filtration rate and serum creatinine in children. Pediatr Nephrol 25:927–934
22. Pottel H, Vrydags N, Mahieu B, Vandewynckele E, Croes K, Martens F (2008) Establishing age/sex related serum creatinine reference intervals from hospital laboratory data based on different statistical methods. Clin Chim Acta Int J Clin Chem 396:49–55
23. Schwartz GJ, Furth SL (2007) Glomerular filtration rate measurement and estimation in chronic kidney disease. Pediatr Nephrol 22: 1839–1848
24. Schwartz GJ, Munoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, Furth SL (2009) New equations to estimate GFR in children with CKD. J Am Soc Nephrol 20:629–637
25. Sempé M, Pédron G, Roy-Pernot M-P (1979) Auxologie: méthode et séquences. Théraplix, Paris
26. Staples A, LeBlond R, Watkins S, Wong C, Brandt J (2010) Validation of the revised Schwartz estimating equation in a predominantly non-CKD population. Pediatr Nephrol 25:2321–2326
27. Stevens PE, Levin A, Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group M (2013) Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. Ann Intern Med 158:825–830