



Estimating glomerular filtration rate in children: evaluation of creatinine- and cystatin C-based equations

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Abstract

Background Glomerular filtration rate (GFR) estimated by creatinine- and/or cystatin C-based equations (eGFR) is widely used in daily practice. The purpose of our study was to compare new and old eGFR equations with measured GFR (mGFR) by iohexol clearance in a cohort of children with chronic kidney disease (CKD).

Methods We examined 96 children (median age 9.2 years (range 0.25–17.5)) with CKD stages 1–5. A 7-point iohexol clearance (GFR_{7p}) was defined as the reference method (median mGFR 66 mL/min/1.73 m², range 6–153). Ten different eGFR equations, with or without body height, were evaluated: Schwartz_{bedside}, Schwartz_{CKiD}, Schwartz_{cysC}, CAPA, LM_{REV}, (LM_{REV} + CAPA) / 2, FAS_{crea}, FAS_{cysC}, FAS_{combi}, FAS_{height}. The accuracy was evaluated with percentage within 10 and 30% of GFR_{7p} (P10 and P30).

Results In the group with mGFR below 60 mL/min/1.73 m², the Schwartz_{cysC} equation had the lowest median bias (interquartile range; IQR) 3.27 (4.80) mL/min/1.73 m² and the highest accuracy with P10 of 44% and P30 of 85%. In the group with mGFR above 60 mL/min/1.73 m², the Schwartz_{CKiD} presented with the lowest bias 3.41 (13.1) mL/min/1.73 m² and P10 of 62% and P30 of 98%. Overall, the Schwartz_{cysC} had the lowest bias – 1.49 (13.5) mL/min/1.73 m² and both Schwartz_{cysC} and Schwartz_{CKiD} showed P30 of 90%. P10 was 44 and 48%, respectively.

Conclusions The Schwartz_{cysC} and the combined Schwartz_{CKiD} present with lower bias and higher accuracy as compared to the other equations. The Schwartz_{cysC} equation is a good height-independent alternative to the Schwartz_{CKiD} equation in children and can be reported directly by the laboratory information system.

Clinical Trial Registration [ClinicalTrials.gov](https://clinicaltrials.gov), Identifier NCT01092260, <https://clinicaltrials.gov/ct2/show/NCT01092260?term=tondel&rank=2>

Keywords Glomerular filtration rate · Child · Chronic kidney disease · Renal function · Cystatin C

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Introduction

Glomerular filtration rate (GFR) is an important indicator of renal function in children and is widely used for classifying grade of kidney impairment [1, 2]. The gold standard for measurement of GFR (mGFR), renal inulin clearance, is often replaced by multipoint plasma clearance procedures with other markers than the hardly available inulin [3, 4]. Simplified mGFR methods using one or two blood samplings after marker injection have been shown to exhibit adequate performance for most clinical purposes [4–7]. To avoid time-consuming procedures in every day clinical practice, estimated GFR (eGFR) based on the natural biomarkers are widely used [1, 2].

Many different eGFR equations have been published, based on both plasma creatinine and cystatin C [8–12]. Schwartz et al. introduced two common ones; a combined equation with several parameters and the bedside equation based on only body height and serum creatinine [8, 9]. The plasma level of creatinine correlates with muscle mass [13, 14] and may be affected by the intake of protein [15], in addition to GFR. The biomarker cystatin C is less influenced by confounding factors and its plasma concentration remains relatively constant from approximately 1 year of age [16]. Cystatin C can thus be used as an alternative for estimating GFR in children and patients with abnormal muscle mass, or in other situations where renal tubular excretion of creatinine is modified (e.g., by the use of trimethoprim) [17, 18]. On the other hand, cystatin C may be influenced by factors such as corticosteroids and thyroid hormones [19–22]. The preferred choice is, according to guidelines, to use an eGFR value and not only to look at the absolute value of creatinine or cystatin C [23, 24]. This is easily done in adults because most parameters needed for GFR estimation are already present in the laboratory information systems. Several eGFR formulas for children are based on height, which is not readily available in the laboratory systems. During recent years, different height-independent eGFR equations have been published, e.g., FAS (full age spectrum) equations with or without cystatin C [10, 11].

The purpose of our study was to evaluate in total 10 formulae for eGFR: the four different FAS equations [10, 11, 25] (with or without cystatin C), the three commonly used Schwartz equations (with or without cystatin C) [8, 9], the CAPA (Caucasian, Asian, pediatric, and adult) equation based on cystatin C [12], the LM_{REV} equation (Lund-Malmø revised) [26], and the LM_{REV} -CAPA equation (mean of LM_{REV} and CAPA) in a cohort of children at different stages of chronic kidney disease (CKD) and with different kidney disorders.

Patients and methods

Patients

A total of 96 patients with CKD were recruited at Haukeland University Hospital and Oslo University Hospital (ClinicalTrials.gov Identifier NCT01092260). The children had a stable kidney function without edema and were distributed evenly over the different GFR stages: 28, 27, 23, and 18 patients in CKD stages 1, 2, 3, and 4–5, respectively. The patients included had various kidney disorders; congenital anomalies of kidney and urinary tract (CAKUT) ($n = 30$), hereditary kidney disorder ($n = 27$), acquired kidney disorder ($n = 12$), glomerulonephritis ($n = 9$), hydronephrosis/vesicoureteral reflux ($n = 9$), and CKD of unknown etiology/miscellaneous ($n = 9$). Median (range) demographic characteristics were age 9.2 years (3 months to 17.5 years), weight 28.3 kg (6.6–84.6), and height 134 cm (59–177). Median multipoint mGFR was 65.9 (range 6.3–153) mL/min/1.73 m². Forty-seven of the participants had proteinuria with urinary protein/creatinine ratio ≥ 30 mg/mmol, and seven of these had a ratio > 300 mg/mmol (Table 1). The study was approved by the Regional Ethics Committee of Western Norway and written informed consent was obtained in all cases before inclusion in the study. The procedures were in accordance with the Helsinki Declaration and Good Clinical Practice.

Methods

Iohexol was administrated via an intravenous cannula as Omnipaque® 300 mg I/mL (647 mg iohexol/mL, GE Healthcare, Oslo, Norway) in doses according to the patient's weight; < 10 kg, 1 mL; 10–20 kg, 2 mL; 20–30 kg, 3 mL; 30–40 kg, 4 mL; ≥ 40 kg, 5 mL. Serum samples were collected from a vein of the contralateral arm of the iohexol injection at seven time points 10–300 min after injection for calculation of the seven-point reference mGFR (GFR_{7p}), using the method of Sapirstein [27]. GFR was normalized to body surface area calculated by the method of Haycock [28]. Details about the procedures and methods are described in earlier studies published on the same cohort [5, 7, 29]. Serum creatinine was measured by an enzymatic colorimetric method (reagents from Roche Diagnostics®), IDMS traceable. The coefficient of variation (CV) (i.e., total analytical imprecision) was $\leq 3.7\%$ and limit of detection was 5 μ mol/L. Serum cystatin C was measured by a turbidimetric immunoassay, traceable to the ERM-DA471/IFCC reference material (reagents from Gentian, Moss, Norway). The CV was $\leq 5.0\%$ and limit of detection was 0.03 mg/L. Serum urea was measured by a kinetic UV method. Urine protein and creatinine measurements were obtained in morning void urine. Urine protein was analyzed by an immunoturbidimetric method (CV $\leq 9\%$) and urine creatinine by an enzymatic colorimetric method

Table 1 Basic characteristics of the population

Variable	Value given as median (range) or number
Total number (<i>f/m</i>)	96 (41/55)
Age, years	9.2 (0.25–17.5)
< 2 years, <i>n</i>	9
2–12 years, <i>n</i>	68
13–18 years, <i>n</i>	19
Body weight, kg	28.3 (6.6–84.6)
Height, cm	134 (59–177)
S-creatinine, $\mu\text{mol/L}$	51 (14–465)
S-cystatin C, mg/L	1.11 (0.44–5.47)
S-urea, mmol/L	6.52 (2.4–27.7)
U-total protein/creatinine ratio, mg/mmol	29 (3–1084)
Proteinuria ≥ 30 mg/mmol, <i>n</i>	47
7-Point iohexol plasma clearance (mGFR), mL/min/1.73 m ²	65.9 (6.3–153)
mGFR < 60 mL/min/1.73 m ² , <i>n</i>	41
mGFR ≥ 60 mL/min/1.73 m ² , <i>n</i>	55

S serum, U urine, *f* female, *m* male, *mGFR* measured glomerular filtration rate

(CV $\leq 3.7\%$). All markers were analyzed on Modular P8000 (Roche Diagnostics®).

Formulae

Table 2 describes the 10 different eGFR equations evaluated in this study: Schwartz_{bedside} [8], Schwartz_{CKiD} [9], Schwartz_{cysC} [9], FAS_{crea} [11, 25], FAS_{cysC} [10], FAS_{combi} [10], FAS_{height} [25], CAPA [12], LM_{REV} [26], and the LM_{REV}-CAPA (mean of LM_{REV} and CAPA). The Schwartz_{bedside}, Schwartz_{CKiD}, and FAS_{height} equations require a height measurement, but the Schwartz_{cysC}, FAS_{crea}, FAS_{cysC}, FAS_{combi}, CAPA, LM_{REV}, and the LM_{REV}-CAPA equations are height-independent.

Statistics

The performance statistics are presented as bias, interquartile range (IQR), and accuracy. Bias was defined as the difference between the eGFR and mGFR, calculated as median absolute differences (mL/min/1.73 m²) in GFR. Precision was assessed as the IQR of the differences. Accuracy was defined by the percentage of eGFR results within 10 and 30% of the mGFR (mL/min/1.73 m²); P10 and P30. Confidence intervals were calculated by means of bootstraps methods with 1000 replicates. Bias, IQR, and accuracy were also evaluated in relation to two mGFR regions, below or above (including) 60 mL/min/1.73 m². A priori we defined bias ± 3 mL/min/1.73 m² as “clinically irrelevant.” Bland Altman plots, McNemars test

with Holm-Bonferroni method for multiple comparisons for accuracy, and *t* tests with Holm-Bonferroni method for multiple comparisons for bias were used for comparison of estimates between the equations [30]. Subgroup analyses with different age groups and proteinuria/non-proteinuria were also performed. We used R version 3.3.2 for all statistical analyses and making figures.

Results

Patient characteristics are listed in Table 1. Median bias, IQR, and accuracy for the 10 tested equations are presented in Tables 3–4 and Figs. 1–2, both above and below mGFR 60 mL/min/1.73 m². In the group with mGFR below 60 mL/min/1.73 m², the Schwartz_{cysC} equation had the lowest bias (IQR) 3.27 (4.80) mL/min/1.73 m² and the highest accuracy with P10 of 44% and P30 of 85%. All other equations demonstrated P30 below 80% in this group. In the group with mGFR above 60 mL/min/1.73 m², the Schwartz_{CKiD} presented with the lowest bias (IQR) 3.41 (13.1), a P10 of 62% and P30 of 98%. In addition, the Schwartz_{cysC} showed a P30 of 93%. The FAS_{cysC}, FAS_{combi}, and LM_{REV} had P30 below 90% (82, 82, and 87%, respectively). Schwartz_{cysC} demonstrated a bias (IQR) of -7.46 (14.8) mL/min/1.73 m² (underestimation). The CAPA equation gave a bias of 7.45 (13.4) and 24.0 (33.4) mL/min/1.73 m² below and above 60 mL/min/1.73 m², respectively, and a P30 of 55% in the total group. For the whole group (*n* = 96), the Schwartz_{cysC} had the lowest bias (IQR) -1.49 (13.5) and both the Schwartz_{cysC} and the Schwartz_{CKiD} showed a P30 of 90%, whereas P10 was 44% and 48% respectively. All 10 equations overestimated eGFR as compared to mGFR, except the Schwartz_{cysC} equation which gave an underestimation in the GFR level above 60 mL/min/1.73 m² (Figs. 1–2). The Schwartz_{cysC} formula also performed relatively well in the subgroup with proteinuria (*n* = 47) with bias 1.98 (7.16), and a P10 of 45% and P30 of 87%. In the group without proteinuria, the Schwartz_{CKiD} formula had the lowest bias 3.84 (10.7) and a P10 of 55% and P30 of 98% (Fig. 3 and Online Resource 1). In the age group < 2 years, the Schwartz_{cysC} showed the best results with bias 3.27 (5.37), and a P30 of 89% (Fig. 4 and Online Resource 2). This formula also performed relatively well in the age group from 2 to 12 years with bias -1.46 (14.1) and P30 of 93%. The Schwartz_{CKiD} formula also demonstrated a relatively high accuracy with P30 of 91%. In the group with adolescents (age > 13 years), the LM_{REV} gave a very low bias -0.21 (11.3) mL/min/1.73 m² and a P30 of 89%, but also the Schwartz_{CKiD}, Schwartz_{cysC}, Schwartz_{bedside}, CAPA, LM_{REV}, and LM_{REV}-CAPA had a bias < 3 mL/min/1.73 m². The LM_{REV}-CAPA and Schwartz_{CKiD} had the highest accuracy in this group with P30 of 100 and 95%, respectively (Fig. 4 and Online Resource 2).

Table 2 Equations evaluated in this study

Equation	Formula (mL/min/1.73 m ²)	Assay	mGFR method used
Creatinine-based			
Schwartz _{bedside}	GFR = 41.3 × (L/crea)	Enzymatic	Iohexol plasma clearance
FAS _{crea}	GFR = 107.3/(crea/Qcrea) Qcrea: 0.21 + 0.057 × age − 0.0075 × Age ² + 0.00064 × age ³ − 0.000016 × age ⁴ for boys. 0.23 + 0.034 × age − 0.0018 × age ² + 0.00017 × age ³ − 0.0000051 × age ⁴ for girls	Enzymatic	Inulin urinary clearance
FAS _{height}	GFR = 107.3/(crea/Q) Q: 3.94 − 13.4 × L + 17.6 × L ² − 9.84 × L ³ + 2.04 × L ⁴ for boys and girls	Enzymatic	Inulin urinary clearance
LM _{REV}	GFR = exp[X − 0.0158 × age + 0.438 × ln(age)] with X = 2.50 + 0.0121 × (150 − crea), for females and crea < 150 μmol/L X = 2.50 − 0.926 × ln(crea/150), for females and crea ≥ 150 μmol/L X = 2.56 + 0.00968 × (180 − crea), for males and crea < 180 μmol/L X = 2.56 − 0.926 × ln(crea/180), for males and crea ≥ 180 μmol/L	Enzymatic	Iohexol plasma clearance
Cystatin C-based			
Schwartz _{cysC}	GFR = 70.69 × (cysC ^{−0.931})	PENIA	Iohexol plasma clearance
FAS _{cysC}	GFR = 107.3/(cysC/QcysC), with QcysC 0.82	Different PENIA/PETIA	Various
CAPA	GFR = 130 × (cysC ^{−1.069}) × (age ^{−0.117}) − 7	Different PENIA/PETIA	Iohexol plasma clearance, inulin plasma/urinary clearance
Combined creatinine and cystatin C			
Schwartz _{CKiD}	GFR = 39.8 × (L/crea) ^{0.456} × (1.8/cysC) ^{0.418} × (30/BUN) ^{0.079} × 1.076 ^{male} × (L/1.4) ^{0.179}	Enzymatic and PENIA	Iohexol plasma clearance
FAS _{combi} (< 40 years)	GFR = 107.3/(α × (crea/Qcrea) + (1 − α) × (cysC/QcysC)), with QcysC 0.82 and α set at 0.5. Qcrea: 0.21 + 0.057 × age − 0.0075 × Age ² + 0.00064 × age ³ − 0.000016 × age ⁴ for boys. 0.23 + 0.034 × age − 0.0018 × age ² + 0.00017 × age ³ − 0.0000051 × age ⁴ for girls	Enzymatic and different PENIA/PETIA	Various
LM _{REV} -CAPA	(LM _{REV} + CAPA)/2		

s-creatinine (crea) in mg/dL, if not specified otherwise. Conversion factor creatinine mg/dL to μmol/L: 88.4. s-blood urea nitrogen (BUN) in mg/dL. Conversion factor BUN mg/dL to mmol/L: 0.357. s-cystatin C (cysC) in mg/L. Height (L) in meter (m), weight in kg, and age in year. FAS full age spectrum, LM_{REV} Lund-Malmö revised, CAPA Caucasian, Asian, pediatric, and adult, PENIA particle enhanced nephelometric immune assay, PETIA particle enhanced turbidimetric immune assay, mGFR, measured glomerular filtration rate

Discussion

Among the 10 eGFR equations evaluated in this study, the Schwartz_{cysC} and Schwartz_{CKiD} equations were superior to the other eight eGFR equations and performed equally well with P30 of 90% for the total group ($n = 96$) (Figs. 1–2 and Table 3–4). Based on P30 and P10, the Schwartz_{cysC} equation seemed to give a higher accuracy in the group with mGFR below 60 mL/min/1.73 m² (P10 44% and P30 85%) and the Schwartz_{CKiD} in the group with mGFR above 60 mL/min/1.73 m² (P10 62% and

P30 98%) (Table 4). The commonly used Schwartz_{bedside} equation based solely on creatinine as endogenous metabolite showed low accuracy with P30 of 53% and a median bias of 15.5 mL/min/1.73 m² for the total group of patients. The creatinine-based equation with the best accuracy was the LM_{REV} equation with a P30 of 72% (Fig. 1 and Table 4). The new height-independent FAS equations showed lower accuracy and higher bias than the Schwartz_{cysC} and the Schwartz_{CKiD} equations, and the Schwartz_{cysC} equation had the lowest bias of −1.49 mL/min/1.73 m² (Figs. 1–2 and Tables 3–4).

Table 3 Comparison of the equations: bias and IQR

	mGFR (7-point iohexol plasma clearance)		
	mGFR < 60 mL/min/1.73 m ² (n = 41)	mGFR ≥ 60 mL/min/1.73 m ² (n = 55)	mGFR total group (n = 96)
Median bias (2.5–97.5 CI)			
<i>FAS_{crea}</i>	10.6 (− 4.81–35)**	15.3 (− 14.3–50.6)**	13.3 (− 13.2–46.6)**
<i>FAS_{cysC}</i>	9.64 (− 0.78–27.3)**	14.1 (− 23.1–48.6)**	10.4 (− 16.8–48.3)**
<i>FAS_{combi}</i>	10.4 (0.10–27.4)**	12.9 (− 15.0–42.3)**	11.9 (− 6.0–40.0)**
<i>FAS_{height}</i>	9.67 (− 5.17–34.8)**	13.8 (− 15.8–50.4)**	10.8 (− 11.6–45.8)**
<i>CAPA</i>	7.45 (− 7.60–43.3)**	24.0 (− 14.3–86.7)**	14.2 (− 8.79–78.6)**
<i>LM_{REV}</i>	10.1 (− 8.75–31.9)**	8.02 (− 34.0–27.6)*	8.99 (− 23.4–30.3)**
<i>LM_{REV}-CAPA</i>	8.71 (− 4.35–31.6)**	16.7 (− 17.9–44.7)**	14.7 (− 9.54–44.6)**
<i>Schwartz_{bedside}</i>	9.57 (− 4.78–37.6)**	19.4 (− 21.3–62.5)**	15.5 (− 17.1–57.9)**
<i>Schwartz_{cysC}</i>	3.27 (− 5.31–10.4)*	− 7.46 (− 45.4–17.9)*	− 1.49 (− 37.6–17.5)*
<i>Schwartz_{CKiD}</i>	6.54 (− 4.08–14.1)**	3.41 (− 26.8–23.6)	5.14 (− 9.94–23.6)*
IQR (2.5–97.5 CI)			
<i>FAS_{crea}</i>	14.2 (8.86–20.2)	23.8 (14.9–31.3)	18.2 (12.6–26.5)
<i>FAS_{cysC}</i>	6.42 (4.12–9.46)	20.3 (14.2–26.6)	12.3 (9.01–17.9)
<i>FAS_{combi}</i>	9.65 (5.11–13.1)	17.0 (9.80–22.0)	12.7 (9.0–17.4)
<i>FAS_{height}</i>	12.0 (7.58–20.5)	17.5 (12.2–27.7)	15.9 (10.5–20.7)
<i>CAPA</i>	13.4 (7.85–19.9)	33.4 (22.5–43.1)	28.9 (22.2–40.0)
<i>LM_{REV}</i>	18.1 (11.9–26.7)	20.8 (13.9–26.0)	19.1 (14.8–23.5)
<i>LM_{REV}-CAPA</i>	14.3 (8.66–19.9)	15.9 (10.9–21.8)	15.0 (12.2–18.8)
<i>Schwartz_{bedside}</i>	16.4 (9.58–24.5)	19.3 (12.4–30.0)	19.3 (14.8–25.8)
<i>Schwartz_{cysC}</i>	4.80 (2.78–8.08)	14.8 (11.5–19.0)	13.5 (8.90–17.9)
<i>Schwartz_{CKiD}</i>	6.43 (3.51–9.45)	13.1 (8.70–17.9)	9.13 (6.68–12.4)

Bold; lowest bias and interquartile range (IQR)

FAS full age spectrum, *LM_{REV}* Lund-Malmö revised, *CAPA* Caucasian, Asian, pediatric, and adul, *mGFR* measured glomerular filtration rate

*Statistically significant difference between eGFR and mGFR, *p* < 0.05

**Statistically significant difference between eGFR and mGFR, *p* < 0.001

Most eGFR-studies state error as a percentage, that includes the majority of estimations, and a commonly used criterion is error within ± 30% compared with the gold standard, which allows for a quite wide limit. Ideally, the majority of the estimations (90%) should be included in a 10% difference limit of a gold standard method as recommended recently by Lima et al. [31]. A new review from Levey and Inker recommends, on the other hand, P30 of > 90% as an adequate standard [32]. In our study, the *Schwartz_{cysC}* and the *Schwartz_{CKiD}* equations were the only formulae with P30 > 90% in the complete cohort, but in the group with mGFR < 60 mL/min/1.73 m² none of the formulas fulfilled these requirements (Table 4). In the adolescent group, however, the *Schwartz_{cysC}* equation demonstrated a P30 of just 79% (Online Resource 2).

The *Schwartz_{cysC}* formula performed best when mGFR was < 60 mL/min/1.73 m² and the *Schwartz_{CKiD}* when mGFR was > 60 mL/min/1.73 m². All the *FAS* equations were inferior to these equations (Figs. 1–2 and Tables 3–4) with

P30 between 56 and 66%, and bias between 10.4 and 13.3 mL/min/1.73 m². Pottel et al. recently published a study on new equations; *FAS_{cysC}* and *FAS_{combi}*, where they in contrast to us found better performance in children and adolescents with *FAS_{cysC}* than with *CAPA* or *Schwartz_{cysC}* (P30 86.1, 76.6, and 68.8%, respectively) [10]. When mGFR was below 60 mL/min/1.73 m², however, their results were in accordance with our study where the *Schwartz_{cysC}* equation gave the lowest bias and highest accuracy; bias of − 2.4 mL/min/1.73 m² and P30 of 86% in their study and 3.27 mL/min/1.73 m² and 85% in our study (Tables 3–4). The *FAS_{combi}* outperformed all equations included in the Pottel study, with a P30 of 92.1%; however, the *Schwartz_{CKiD}* equation was not included in their evaluation [10].

In our study, the *Schwartz_{CKiD}* performed relatively well with P30 of 90%, but the other combined equations, *LM_{REV}-CAPA* and *FAS_{combi}*, did not have acceptable accuracy (P30 of 65 and 66%, respectively) (Table 4). A recent study from the Schwartz-group compared *Schwartz_{bedside}* and

Table 4 Comparison of the equations: accuracy

	mGFR (7-point iohexol plasma clearance)			<i>p</i> value total group (Mc Nemars test)
	mGFR < 60 mL/min/1.73 m ² (<i>n</i> = 41)	mGFR ≥ 60 mL/min/1.73 m ² (<i>n</i> = 55)	mGFR total group (<i>n</i> = 96)	
Accuracy P10 (2.5–97.5 CI), %				
<i>FAS_{crea}</i>	17 (7–29)	33 (22–45)	26 (18–35)	0.286
<i>FAS_{cysC}</i>	12 (4–22)	33 (20–45)	24 (16–32)	0.284
<i>FAS_{combi}</i>	22 (10–34)	27 (16–40)	25 (17–34)	0.286
<i>FAS_{height}</i>	10 (2–20)	31 (18–44)	22 (14–30)	0.223
<i>CAPA</i>	20 (7–32)	22 (11–33)	21 (14–28)	0.207
<i>LM_{REV}</i>	12 (2–22)	38 (25–51)	27 (19–36)	0.286
<i>LM_{REV}-CAPA</i>	12 (2–22)	25 (15–36)	20 (13–27)	0.189
<i>Schwartz_{bedside}</i>	17 (7–29)	9 (2–17)	13 (6–20)	0.044*
<i>Schwartz_{cysC}</i>	44 (29–59)	42 (29–58)	44 (34–53)	1.00
<i>Schwartz_{CKiD}</i>	29 (17–44)	62 (49–75)	48 (36–58)	1.00 (reference)
Accuracy P30 (2.5–97.5 CI), %				
<i>FAS_{crea}</i>	32 (20–44)	75 (62–85)	56 (47–67)	< 0.001*
<i>FAS_{cysC}</i>	46 (32–61)	82 (71–91)	67 (59–76)	0.005*
<i>FAS_{combi}</i>	44 (29–59)	82 (71–91)	66 (55–75)	0.005*
<i>FAS_{height}</i>	49 (34–63)	78 (65–87)	66 (56–74)	0.005*
<i>CAPA</i>	59 (44–72)	53 (40–65)	55 (46–66)	< 0.001*
<i>LM_{REV}</i>	51 (37–66)	87 (78–95)	72 (63–81)	0.026*
<i>LM_{REV}-CAPA</i>	51 (34–66)	75 (64–86)	65 (55–75)	0.004*
<i>Schwartz_{bedside}</i>	39 (24–54)	64 (53–76)	53 (44–64)	< 0.001*
<i>Schwartz_{cysC}</i>	85 (76–95)	93 (85–98)	90 (83–96)	1.00 (reference)
<i>Schwartz_{CKiD}</i>	78 (65–90)	98 (95–100)	90 (83–96)	1.00 (reference)

Bold; highest P10 and P30 (percentage of eGFR results within 10 and 30% of mGFR, respectively)

FAS full age spectrum, *LM_{REV}* Lund-Malmö revised, *CAPA* Caucasian, Asian, pediatric, and adult, *mGFR*, measured glomerular filtration rate

*Statistically significant difference

Schwartz_{CKiD} with mGFR by iohexol plasma clearance in 730 children and adolescents, and reported that Schwartz_{CKiD} closely approximated mGFR to describe relationships with CKD severity indicators and progression, and concluded that this formula should be the preferred eGFR method for research studies of pediatric CKD [33]. Deng et al. published a study evaluating 14 published eGFR equations with iohexol-GFR. They found that the combined formulas with creatinine and cystatin C, including the Schwartz_{CKiD}, outperformed equations that used serum creatinine or cystatin C alone. The Schwartz_{cysC} equation also performed relatively well in their study with median bias 1.9 mL/min/1.73 m² and P30 of 79% [34]. From others, it has previously been demonstrated that combination of creatinine and cystatin C for GFR estimation increases the performance [35, 36].

Overall, the height-independent Schwartz_{cysC} equation showed better performance than the other height-independent formulas in our study (*FAS_{crea}*, *FAS_{combi}*, *FAS_{cysC}*, *LM_{REV}*, *CAPA*, *LM_{REV}-CAPA*) (Figs. 1–2 and Table 3–4). Another recent study found that by combining

the height-independent *FAS_{crea}* and Schwartz_{cysC} equations, the accuracy improved and that these two equations performed comparably to height-dependent equations [37]. A study from 2018 recommends reporting eGFR by calculating the geometric mean between the height-independent *FAS_{crea}* and *FAS_{cysC}* equations when Δ eGFR is smaller than 40%. If there was a large disagreement between the two, weighted means based on diagnosis improved accuracy [38]. This facilitates direct eGFR reporting by the laboratory information system.

As may be expected, eGFR formulas are shown to work better in the same kind of cohort from which they were developed [39]. Differences among equations using the same filtration markers reflect differences in the variables in the equations and their coefficients. For equations using different filtration markers, differences in the validation will on the other hand also reflect differences regarding biological variations, error in assay measurements, or the influence of non-GFR determinants [32]. The Schwartz_{bedside} equation is similar to the two former equations, generated from the CKiD study.

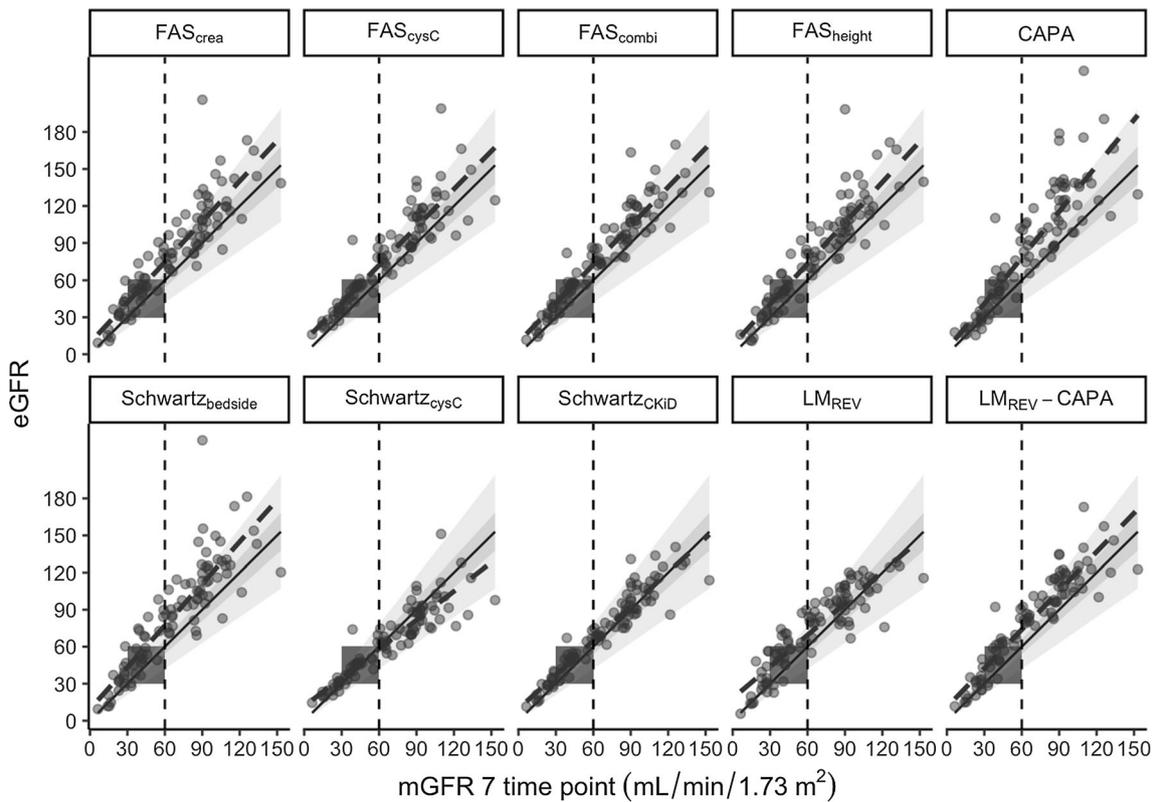


Fig. 1 Scatter plots of estimated glomerular filtration rate (eGFR) and measured GFR (mGFR) in children. Correlation between the 10 different eGFR equations and mGFR in children with chronic kidney disease (CKD) ($n = 96$). The dark gray area represents P10 (the percentage of eGFR results within 10% of the mGFR ($\text{mL}/\text{min}/1.73 \text{ m}^2$)) and the light

gray area P30 (the percentage of eGFR results within 30% of the mGFR ($\text{mL}/\text{min}/1.73 \text{ m}^2$)). The black line represents the multipoint mGFR and the dashed line the regression line. The gray box represents the CKD stage 3 ($30\text{--}60 \text{ mL}/\text{min}/1.73 \text{ m}^2$)

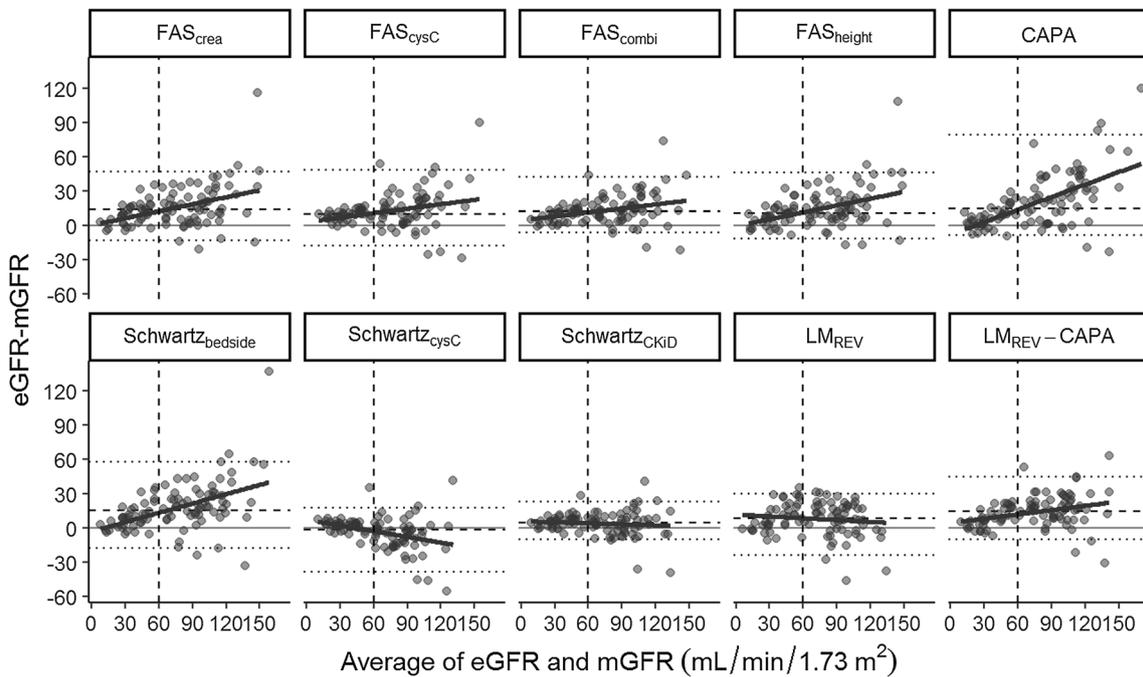


Fig. 2 Bland Altman plots with absolute bias between estimated glomerular filtration rate (eGFR) and measured GFR (mGFR) for the different equations in children ($n = 96$) with chronic kidney disease

(CKD). The solid line represents the regression line. The dashed line represents the median bias and the dotted line the 2.5–97.5% confidence interval for all points

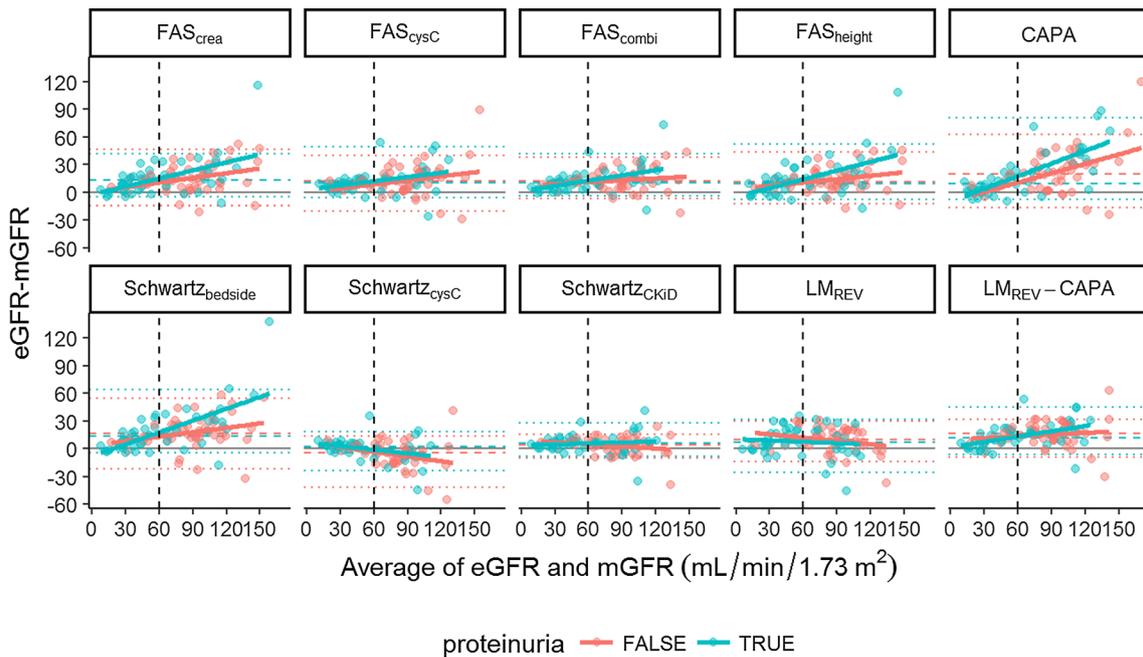


Fig. 3 Bland Altman plots with absolute bias between estimated glomerular filtration rate (eGFR) and measured GFR (mGFR) for the different equations in children ($n = 96$) with chronic kidney disease (CKD). The blue lines represent the group with proteinuria ≥ 30 mg/

mmol ($n = 47$) and the red lines the group with non-proteinuria ($n = 49$). The solid lines represent the regression line, the dashed lines the median bias, and the dotted lines the 2.5–97.5% confidence interval for all points

This study included patients from 1 to 16 years of age with eGFR in the range of 30–90 mL/min/1.73 m² [8, 9]. The CAPA equation was developed from a cohort of children with median age (2.5th, 97.5th percentile) 12 (2.0, 17.5) years and

median mGFR 103 mL/min/1.73 m², with 88% of the mGFR > 60 mL/min/1.73 m² [12]. The CAPA equation did not perform well in our study, neither below nor above mGFR 60 mL/min/1.73 m², with a P30 of only 55% (Figs. 1–2,

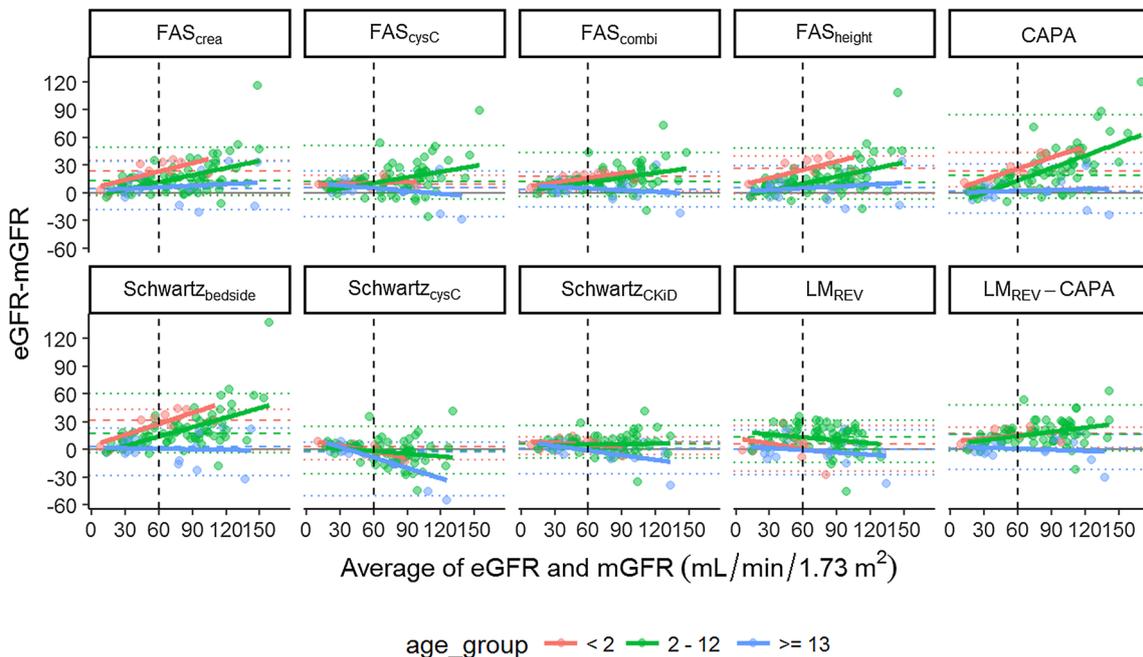


Fig. 4 Bland Altman plots with absolute bias between estimated glomerular filtration rate (eGFR) and measured GFR (mGFR) for the different equations in children ($n = 96$) with chronic kidney disease (CKD). The red lines, green lines, and blue lines represent the age group

< 2 years ($n = 9$), 2–12 years ($n = 68$), and ≥ 13 years of age ($n = 19$), respectively. The solid lines represent the regression line, the dashed lines the median bias, and the dotted lines the 2.5–97.5% confidence interval for all points

Tables 3–4). The FAS_{crea} and FAS_{height} were evaluated for subjects aged between 2 and 25 years [25, 40], and in our study, we included nine patients < 2 years. The $Schwartz_{cysC}$ equation was the only equation with P30 around 90% in patients below 2 years of age (Fig. 4 and Online Resource 2). The study of FAS_{cysC} and FAS_{combi} equations included children between 1 and 18 years with mean (\pm SD) mGFR 89.2 (30.4) [10], but these equations showed low P30 in patients < 13 years of age in our study (Fig. 4 and Online Resource 2). LM_{REV} formula was however developed in a cohort ($n = 850$) of Swedish adults (> 18 years), and in the present study, this formula performed best in the group of adolescents with P30 of 89% (Fig. 4 and Online Resource 2).

In our study, the highest P10 was 62% with the $Schwartz_{CKiD}$ formula in the group with mGFR > 60 mL/min/1.73 m² (Table 4). eGFR equations are hampered by low accuracy compared to mGFR, and the preferred method should be to measure GFR, if possible. We have previously published studies on simplified mGFR methods with validation of multiple formulas, single-point and two-point sampling times as well as capillary blood spot method [5, 7, 41], and we found that the highest P10 for children with CKD stage 1–5 was 95.8%, using the formula of Jødal and Brøchner-Mortensen from 2009 with blood sampling 2 and 5 h after marker injection [5, 42]. Single-point sampling at 3 h using the Fleming formula [43] showed a P10 of 92.3% in children with GFR \geq 30 mL/min/1.73 m². For children with GFR < 30 mL/min/1.73 m², two blood samples were needed to achieve sufficiently high accuracy [5, 7]. The use of simplified mGFR methods is of great clinical importance especially in patient groups where exact level and change in GFR are important to monitor and where muscle mass might change significantly due to disease, e.g., children with cancer. Oncology remains one important area where mGFR is still the gold standard instead of eGFR [18]. For clinical studies in children, simplified mGFR methods can also be an essential supplement to eGFR.

A limitation of our study is the relatively low number of patients, but on the other hand, there are few other studies with multipoint reference mGFR from children with CKD. One patient was younger than 1 year, but nine patients were < 2 years. Another limitation is that the last plasma sampling of mGFR at 5 h may be too early in patients with severely reduced kidney function. However, our study has a high number of blood samples at different time points obtained during daytime at the outpatient clinic, and multipoint iohexol clearance has proven to be close to the gold standard inulin clearance [1]. The creatinine and cystatin C were calibrated against a standardized reference method. However, important differences still remain despite the fact that only since 2010, a certified reference material ERM-DA471/IFCC has been available for cystatin C [44].

In conclusion, we recommend the $Schwartz_{cysC}$ and the $Schwartz_{CKiD}$ as preferred eGFR equations when mGFR is not performed in children with CKD. In addition, the height-independent $Schwartz_{cysC}$ equation can be implemented to be reported directly by most laboratory information systems. The commonly used creatinine-based equations, like $Schwartz_{bedside}$ equation, showed relatively low accuracy.

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Compliance with ethical standards

Financial disclosure The authors have no financial relationships relevant to this article to disclose.

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

Ethical approval The study was approved by the Regional Ethics Committee of Western Norway and an informed consent form was obtained by all patients and/or their designees. The study was performed in accordance with the Declaration of Helsinki.

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