RESEARCH ARTICLE

Comparing different estimated glomerular filtration rate equations in assessing glomerular function in children based on creatinine and cystatin C

Seçil Conkar¹ | Sevgi Mir¹ | Fatma Nur Karaslan² | Gülden Hakverdi³

¹Faculty of Medicine, Department of Pediatric Nephrology, Ege University, Izmir, Turkey

²Faculty of Medicine, Fatma Nur Şirin Ege University, Izmir, Turkey

³Faculty of Medicine, Department of Biostatistics and Medical Informatics, Gülden Hakverdi Ege University, Izmir, Turkey

Correspondence

Seçil Conkar, Department of Pediatric Nephrology, Ege University School of Medicine, Izmir, Turkey.

Email: secilcankar@yahoo.com.tr

Background: Glomerular filtration rate (GFR) is the best marker used to assess renal function. Estimated GFR (eGFR) equations have been developed, and the ideal formula is still under discussion. We wanted to find the most practical and reliable GFR in eGFR formulas. We compared serum creatinine (Scr)- and cystatin C (cysC)-based eGFR formulas in the literature. We also aimed to determine the suitability and the reliability of cysC for practical use in determining GFR in children.

Methods: We have enrolled 238 children in the study. Measurement of 24-hour creatinine clearance was compared with eGFR equations which are based on Scr, cysC, and creatinine plus cysC.

Results: Of the patients (n = 238), 117 were males (49.2%), and 121 (50.8%) were females with a median age of 9.0 years. The areas under the ROC curves of Counahan-Barratt and Bedside Schwartz were equal and 0.89 (with a 95% CI 0.80-0.97). The areas under the ROC curves were not significantly different in all cystatin C-based eGFR equations. The highest AUC values for differentiating normal vs abnormal renal functions according to CrCl_{24} were for the CKiD-cysC and CKiD-Scr-cysC equations.

Conclusions: In our study, compared with creatinine-based ones, the cystatin C-based formulas did not show much superiority in predicting eGFR. Still, we think Bedside Schwartz is a good formula to provide ease of use because, in this equation, the constant k is same for all age groups. However, the most valuable equations in determining chronic kidney disease are the CKiD-cysC and CKiD-Scr-cysC equations.

KEYWORDS

children, cystatin C, estimating equations, glomerular filtration rate, serum creatinine

1 | INTRODUCTION

Glomerular filtration rate (GFR) is the best indicator of kidney function.¹ The change in glomerular filtration rate may be the only sign of kidney disease. Assessment of glomerular filtration rate allows medications to be administered at appropriate doses to prevent and identify early end-stage renal disease and initiate appropriate fluid therapy. The gold standard of GFR measurement

is inulin clearance. However, it is not suitable for routine use.² Therefore, estimated GFR (eGFR) calculated by various equations is used in many instances. Of these eGFR equations, the most commonly used ones are serum creatinine (Scr)-based eGFR equations. Furthermore, serum creatinine is affected by muscle mass, age, gender, race, and diet.³ Lately, cystatin C-based equations have been used. As cystatin C is not a simple-to-use biomarker of renal function, many different formulas have been published, potentially

confusing the general pediatricians. Thus, there is a search to find a formula to guess GFR value correctly using endogen indicators such as serum urea, creatinine, and cystatin C (CysC) in children.⁴

Our aim in this study was to assess correlations between eGFR equations based on Scr, CysC, CysC-Scr, and creatinine clearance. We ultimately wanted to determine the most reliable equation for children in measuring eGFR.

2 | METHODS

This study was conducted between September 2016 and March 2017 at Ege University Children Hospital. Two hundred and thirty-eight children were included in the study. Ethical approval was taken from the Ege University Medical Faculty Board of Ethics for Clinical Studies. Parents of all the participants gave verbal consent to join the study.

Inclusion criteria were children aged 2-18 years followed up at the nephrology outpatients, who came to their control visits with an appropriately collected 24-urine sample.

Children under 2 years of age; receiving glucocorticoids, cimetidine, or trimethoprim therapy within the previous 3 months;

diabetic patients with ketoacidosis, thyroid dysfunction (hypo- or hyperthyroidism), with known leukemia or other types of cancer, severe malnutrition; acute kidney injury; general oedema; severe heart failure receiving hemodialysis or peritoneal dialysis; absence of limbs; having high C-reactive protein levels; and non-cooperative patients (not complying with urine collection instructions) were excluded. To check for exclusion criteria, we measured from all patients fasting blood sugar, urinary ketone levels (only in diabetic patients), serum C-reactive protein, serum-free T4, and serum TSH levels.

Weight and height were measured from all participants. The body mass index (BMI) was calculated, and participants with a BMI of above 95 percentile were excluded as well. Seventy applicants met some exclusion criteria (Figure 1).

Serum urea, creatinine, and cystatin C were measured in all children. The blood urea nitrogen (BUN) was also calculated using urea values ($BUN = \text{urea} \times 0.467$). Simultaneously, the 24-hour urine volume was measured, followed by a calculation of the 24-hour urinary creatinine clearance as creatinine excretion per kilogram of body weight (total urinary creatinine/patient's weight). If the 24-hour urinary creatinine was at least 20 mg/kg/24 hours, the amount of urine

FIGURE 1 Patient flow diagram

collected was regarded as adequate.⁵ The 24-hour urinary creatinine clearance (CrCl₂₄) was calculated by the following formula:

$$\text{CrCl}_{24} \left(\frac{\text{mL}}{\text{min}} / 1.73 \text{ m}^2 \right) = \frac{\text{Ucr (mg/dL)} \times \text{Urine volume (mL)} \times 1.73}{\text{Scr (mg/dL)} \times 1440 \times \text{Patient body surface (m}^2\text{)}}$$

Ucr = Urinary creatinine, Scr = Serum creatinine

Urine creatinine, serum creatinine, and serum urea measurement were performed by Synchron (Beckman Coulter) brand urea and creatinine kits, which were photometrically measured on a DxC800 model, Beckman Coulter brand autoanalyzer using the Jaffé method. CysC was measured by the "Particle Enhanced Nephelometric Immunoassay" (PENIA) method.

2.1 | Estimation of GFR equations

In this study, we calculated eGFR by the following serum creatinine-based equations: Original Schwartz,⁶ Bedside Schwartz (eGFR),⁷ Counahan-Barratt,⁸ British Columbia Children's Hospital (BCCH 1 and 2),⁹ Gao,¹⁰ and the Lund-Malmö.¹¹

We also calculated eGFR using the following cystatin C-based equations: Hoek,¹² Bricon et al,¹³ Larsson et al,¹⁴ Rule et al,¹⁵ Filler and Lepage,¹⁶ Zappitelli et al,¹⁷ and the CKiD-eGFR-cysC.¹⁸ CKiD-eGFR-Scr-cysC was calculated using the CKiD study formula utilizing cystatin C and serum creatinine.¹⁸ For the CKiD-eGFR-Scr-cysC equation, the enzymatic serum creatinine measurements were converted into isotope dilution mass spectroscopy (IDMS) standard values.⁷ The formulas for the different equations are given in Table 1.

We accepted CrCl₂₄ as a gold-standard test. CysC-based eGFR Equations and Scr-based eGFR equations were evaluated for their own correlation. GFR <90 mL/min/1.73 m² was regarded as abnormal kidney function. We identified the specificity and sensitivity of each equation in differentiating abnormal kidney functions.

2.2 | Statistical analysis

As the distribution of all variables was skewed, results were presented as mean ± standard deviation (SD) and as median and min-max. IBM SPSS Statistics 22 Program was used for statistical analysis. *P* values less than .05 were accepted significant. The Shapiro Wilk test was used to evaluate normality. Spearman correlation analysis was performed to check correlations between variables.

The overall classification performance of a test was assessed via the ROC curve where an area under the ROC curve of 1.0 shows perfect discrimination, while an area of 0.5 shows that the test is not good to distinguish. The sensitivity and specificity of each formula were calculated by determining CrCl₂₄ cutoff level 90 mL/min/1.73 m².

3 | RESULTS

The clinical characteristics of the participants (*n* = 238) are shown in Table 2. One hundred and seventeen participants were males (49.2%), 121 (50.8%) were females, and the median age was 9.0 years (min. 3, max. 18).

TABLE 1 Estimation of GFR equations

Equation name	Formula
Original Schwartz	$k^* \times \text{Ht}/\text{Scr}$
Counahan-Barratt	$0.43 \times \text{Ht}/\text{Scr}$
Bedside Schwartz	$0.413 \times (\text{Ht}/\text{Scr})$
BCCH 1	$1.18 + 0.0016 \times \text{Wt} + 0.01 \times \text{Ht} + 149.5/(\text{Scr} \times 88.4) - 21.41/(\text{Scr} \times 88.4)^2$
BCCH 2	$-61.56 + 58.86/(\text{Scr} \times 88.4) + 4.83 \times \text{Age} + (10.02 \text{ if male})$
Gao et al	$0.68 \times \text{Ht}/\text{Scr} - 0.0008 \times (\text{Ht}/\text{Scr})^2 + 0.48 \times \text{Age} - (21.53/25.68 \text{ M/F})$
Lund-Malmö et al	$\text{Exp} (4.62 - 0.0112 \times \text{Scr} \times 88.4 - 0.0124 \times \text{Age} + 0.339 \times (\ln \text{Age}))$
Hoek et al	$-4.32 + 80.35 \times \text{CysC}^{-1}$
Bricon et al	$78 \times \text{CysC}^{-1} + 4$
Larsson et al	$77.24 \times \text{CysC}^{-1.2623}$
Rule et al	$76.6 \times \text{CysC}^{-1.16}$
Filler and Lepage	$91.62 \times \text{CysC}^{-1.123}$
Zappitelli et al	$75.94 \times \text{CysC}^{-1.17}$
CKiD-eGFR-cysC	$75.94 \times \text{CysC}^{-1.17}$
CKiD-eGFR-Scr-cysC	$39.8 \times (\text{Ht}/\text{Scr})^{-0.456} (1.8 \times \text{CysC})^{-0.418} (30/\text{BUN})^{-0.079} 1.076^{\text{male}}$ $(\text{Ht}/1.4)^{0.179}$

eGFR, estimated glomerular filtration rate; *k**, 0.33 in preterm infants, 0.45 in full-term infants, 0.55 in children and adolescent girls, and 0.70 in adolescent boys; Ht (cm), length; Scr (mg/mL), creatinine serum concentration; BCCH, British Columbia Children's Hospital; CKiD, chronic Kidney Disease in Children; CysC, cystatin C; Wt, Weight; M, Male; F, Female.

TABLE 2 Clinical features of participants

	Mean $\pm$ SD	Median (Min-Max)
Age (y)	9.91 $\pm$ 5.7	9 (0.5-18)
Weight (kg)	40.99 $\pm$ 48.13	31.75 (4.35-148)
Height (cm)	131.46 $\pm$ 29.1	134 (53-185)
Body mass index (kg/m ²)	19.55 $\pm$ 10.75	17.58 (10.77-21.61)
Cystatin C (mg/L)	0.97 $\pm$ 0.86	0.76 (0.35-1.23)
Creatinine (mg/dL)	0.53 $\pm$ 0.56	0.5 (0.10-1.38)
Urea (mg/dL)	31.6 $\pm$ 22.8	26 (6-197)
CrCl ₂₄	132.7 $\pm$ 67.7	137 (45-166)
Original Schwartz	179.1 $\pm$ 79.5	163.75 (64-206)
Bedside Schwartz	132.1 $\pm$ 60.4	116 (48-208)
CKiD-eGFR-cysC	99.6 $\pm$ 27.4	99 (36-188)
CKiD-eGFR-Scr-cysC	110.7 $\pm$ 67.7	108.5 (40-180)
Counahan-Barratt	123 $\pm$ 63.13	120.9 (50-200)

SD, standard deviation; CrCl₂₄, 24 hour urinary Cr clearance; eGFR, estimated glomerular filtration rate; CKiD, Chronic Kidney Disease in Children study

3.1 | Performance of the Creatinine-based eGFR Equations

Creatinine-based estimations of eGFR were presented as median (min-max). The patient counts and percentages were displayed according to GFR at a cutoff level of 90 mL/min/1.73 m². Sensitivity and specificity were evaluated by each equation (Table 3).

The areas under the ROC curves of the Counahan-Barratt and Bedside Schwartz equations were equal and 0.89 (with a 95% CI for the area between 0.80 and 0.97). Sensitivity and specificity of the equations were 97% vs 90% and 97% vs 90%, respectively. The areas under the ROC curves for BCCH 1, BCCH 2, Gao, Lund-Malmö were 0.79 (95% CI 0.68-0.91), 0.86 (95% CI 0.77-0.95), 0.83 (95% CI 0.72-0.94), and 0.87 (95% CI 0.78-0.97), respectively (Figure 2).

3.2 | Performance of the CysC-based eGFR equations

Analysis of ROC curves was performed to confirm the prediction capability of the cysC-based eGFR equations. The areas under the

TABLE 3 GFR calculated from serum creatinine-based equations

	Median (Min-Max)	Mean $\pm$ SD	<90 mL/min/1.73 m ² n (%)	Sens. (%)	Spec. (%)
Original Schwartz	163.75 (64-206)	179.12 $\pm$ 79.52	35 (6.8%)	85	100
Bedside Schwartz	116.22 (48-208)	132.11 $\pm$ 60.41	58 (24.4%)	97	90
Counahan-Barratt	120.91 (50-200)	123.21 $\pm$ 63.13	53 (22.3%)	97	90
BCCH 1	119.52 (36-234)	108.12 $\pm$ 53.12	87 (36.6%)	97	74
BCCH 2	137.42 (26-223)	160.12 $\pm$ 98.73	36 (15.1%)	82	96
Gao	107.13 (75-127)	96.12 $\pm$ 34.21	62 (26.1%)	100	90
Lund-Malmö	114.82 (60-163)	104.91 $\pm$ 32.21	51 (21.4%)	88	90

FIGURE 2 ROC curves of serum creatinine-based eGFR equations

ROC curves were 0.89 (95% CI 0.83-0.96) and equal for all cysC-based eGFR equations (Figure 3).

Sensitivity vs specificity of the Larrson, Hoek, Bricon, Rule, Zappitelli, CKiD-cysC, and Filler were calculated as 71% vs 83%, 75% vs 83%, 71% vs 83%, 71% vs 83%, 75% vs 83%, 88% vs 77%, and 58% vs 93%, respectively.

3.3 | Performance of all eGFR equations

Correlation analysis demonstrated that eGFR obtained by all equations had a significant correlation with CrCL₂₄ ($P < .001$). The correlation coefficients (r) between CrCL₂₄ and Original Schwartz, Bedside Schwartz, Counahan-Barratt, CKiD-cysC, and CKiD-Scr-cysC were 0.704, 0.713, 0.711, 0.620, and 0.914, respectively. CKiD-cysC had the highest AUC value. Areas under the ROC curves and sensitivity/specificities are given in Table 4.

Correlation analysis also demonstrated that eGFR obtained by all equations had significant correlations with the Original Schwartz estimation ($P < .001$). Correlations of the Original Schwartz formula with Bedside Schwartz, Counahan-Barratt, CKiD-cysC, CKiD-Scr-cysC, and CrCL₂₄ had r values of .955, .955, .741, .914, and .704, respectively ($P < .001$ for all pairwise correlations).

FIGURE 3 ROC curves of CysC-based eGFR equations

Correlation coefficients (r) between Bedside Schwartz and Original Schwartz, CKiD-cys, CKiD-creat-cys, CrCL_{24} , and Counahan-Barratt were 0.95, 0.74, 0.91, 0.71, and 1.0, respectively ($P < .001$ for all pairwise correlations). Bedside Schwartz was most compatible with the Original Schwartz and Counahan-Barratt formulas.

The area under the ROC curves for Original Schwartz, Bedside Schwartz, Counahan-Barratt, CKiD-cys, and CKiD-Scr-cysC formulas were 0.868, 0.887, 0.885, 0.891, and 0.889, respectively. Highest AUC values for differentiating normal vs abnormal renal functions according to CrCL_{24} were for the CKiD-cysC and CKiD-Scr-cysC equations (Figure 4).

4 | DISCUSSION

New eGFR equations have been improved for better GFR guess and practical usage. The accuracy of these equations is essential. In clinical practice, eGFR calculated by these equations is used to regulate the dosage of nephrotoxic drugs and to determine chronic renal disease. The eGFR value is associated with the performance of the eGFR equation.¹⁹ The most common Scr-based eGFR equations used in practice depend on anthropometric measurements. Of these, the Schwartz equation is usually used to assess eGFR

FIGURE 4 Roc curve analysis for all eGFR equations

value. It is believed that Scr-based eGFR will not be reliable, and its usage in children with conditions which affect muscle mass (such as malnutrition, obesity, anorexia, cachexia, and loss of extremities) is not suitable.²⁰ Because of this, eGFR equations which use cystatin C (cysC) have been developed.²¹ Compared with Scr-based eGFR, cysC-based eGFR equations have been found to be more reliable in several adult clinical studies.²² A study conducted among children has demonstrated that prediction equations based on CysC levels are likely to provide more accurate estimates of GFR than Scr-based equations.¹⁷ Another study carried out in renal transplant patients has revealed a better performance of cystatin C-based formula compared with the traditional creatinine-based equations in predicting GFR among patients with kidney transplantation.²³ However, as the cost of cysC measurement is approximately eight times more than serum creatinine, it is not recommended for clinical practice.²⁴

In this study, we determined the value of cysC-based eGFR equations in children. All of the cysC-based eGFR equations were correlated with each other; neither one was superior. However, the CKiD-cysC and CKiD-Scr-cysC equations were more valuable concerning the areas under the ROC as well as sensitivity and specificity values.

In a study by Bacchetta et al, cysC-based eGFR equations were not shown to be superior to Scr-based eGFR equations in

TABLE 4 Performance of eGFR Equations

	GFR <90 mL/ min/1.73 m ² (n)	GFR >90 mL/ min/1.73 m ² (n)	Area under the curve	Sens. (%)	Spec. (%)
CrCL_{24}	77	161			
Original Schwartz	35	203	0.868	54	97
Bedside Schwartz	58	180	0.887	75	87
Counahan-Barratt	53	185	0.885	67	89
CKiD-cysC	103	135	0.891	88	77
CKiD-Scr-cysC	72	166	0.889	75	85

determining eGFR.⁴ In another study, they found that the CKiD-cysC and CKiD-Scr-cysC equations were better than the Scr-based eGFR equation.²⁵ In our research, cysC-based eGFR equations had no major superiority in evaluating eGFR compared to the Scr-based formulas. From the Scr-based GFR formulas, the Bedside Schwartz and Counahan-Barratt were identified as closest to the Original Schwartz formula. eGFR values calculated with these three formulas were similar to each other.

In this study, we found high sensitivity, specificity, and ROC values in all cysC-based equations. Zweig et al have shown that for GFR values between 60 and 90 mL/min/1.73 m², all cystatin C equations had excellent ROC AUC values ranging from 0.98 to 0.99, while for GFR values between 135 and 150 mL/min/1.73 m² they had less performance, with AUC values ranging from 0.80 to 0.89.²⁶

Sharma et al have evaluated the sensitivity and specificity of the eGFR equations measured by technetium-99 m–diethylene-triamine penta-acetic acid (99mTc DTPA). For GFR values of <60 and <90 mL/min/1.73 m², the CKiD, Zappitelli-CysEq, and Zappitelli-cysC equations had 90% sensitivity for categorizing the GFR.²⁷

In our study, the CKiD-cysC equation had a sensitivity of 88% and a specificity of 77% in estimating GFR <90 mL/dk/1.73 m². Similarly, Yang et al from China have demonstrated that the CKD-EPlscr-cys equation had sensitivity and specificity values of 79.8% and 93% to diagnose CKD.²⁸ In practice, it is often important to distinguish between children having normal (GFR ≥ 90 mL/min/1.73 m²) and abnormal GFR (GFR <90 mL/min/1.73 m²). Scr-based formulas are suitable for use in patients with normal renal function. The CKiD-cysC equation had higher sensitivity compared with the CKiD-Scr-cysC, Bedside Schwartz, and Counahan-Barratt equations in determining abnormal eGFR. In cases such as abnormal renal function recognition, CysC-based eGFR formulas can replace the Scr-based eGFR formulas. In particular, the CKiD-Scr-cysC equation, in which Scr and cystatin C are combined and the CKiD-cysC equation has high accuracy rates.

5 | CONCLUSIONS

The “Chronic Kidney Disease in Children” (CKiD) Scr-cysC and Scr-cysC formula were identified as the most valuable ones. However, in our study, Scr-based formulas were not much superior to the cysC-based formulas in predicting eGFR in children. It has been found that the use of Scr-based eGFR formulas in estimating GFR in children is more reliable. We think Bedside Schwartz is a good formula to provide ease of use in the daily practice, as the constant *k* in the formula is the same for all age groups. The use of eGFR formulas in identifying chronic kidney disease has been shown to be more reliable for the formulas using cysC and Scr in combination. We think that the CKiD-cysC and the CKiD-Scr-cysC equations are more effective eGFR equations in the early recognition of chronic kidney disease. Future research will probably be concerned with the identification of new formulas, novel exogenous

agents, and new endogenous markers that are used to determine GFR in children.

The most important limitation of this study is having used the GFR as gold standard. We also could categorize GFR values as above 90, 60–90, and <60 mL/min/1.73 m², which could provide extra valuable information concerning sensitivity and specificity thresholds. The heterogeneity of the study population with variability in the age, height, and weight, as well as the relatively low sample size, can be listed as additional limitations.

ORCID

Seçil Conkar <http://orcid.org/0000-0001-9189-0480>

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