

Accuracy of Different Equations in Estimating GFR in Pediatric Kidney Transplant Recipients

Vandréa de Souza,^{*,†‡§} Pierre Cochat,^{||¶**} Muriel Rabilloud,^{¶††††} Luciano Selistre,^{‡§†§§} Mario Wagner,^{§§§} Aoumeur Hadj-Aissa,^{‡¶} Olga Dolomanova,[‡] Bruno Ranchin,^{||} Jean Iwaz,^{¶††††} and Laurence Dubourg^{‡¶†††}

Abstract

Background and objective The knowledge of renal function is crucial for the management of pediatric kidney transplant recipients. In this population, the most commonly used plasma creatinine (PCr)-based or cystatin C (CystC)-based GFR-predicting formulas may underperform (*e.g.*, corticosteroids and trimethoprim may affect PCr concentration, whereas prednisone and calcineurin inhibitors may affect CystC concentration). This study evaluated the performance of six formulas in pediatric kidney transplant recipients.

Design, setting, participants, & measurements The study used PCr-based formulas (bedside Schwartz, Schwartz-Lyon), CystC-based formulas (Hoek, Filler), and combined PCr-CystC-based formulas (CKD in Children [CKiD] 2012 and Zappitelli). The performance of these formulas was compared using inulin clearance as reference and assessed according to CKD stages in a historical cohort that included 73 pediatric kidney transplant recipients (199 measurements). The ability of the formulas to identify GFRs <60, <75, and <90 ml/min per 1.73 m² was assessed.

Results At measured GFR (mGFR) ≥90 ml/min per 1.73 m² (nine patients; 23 measurements), the Zappitelli formula had the highest 30% accuracy (P30) (95% [95% confidence interval (95% CI), 87% to 100%]) and the bedside Schwartz had the highest 10% accuracy (P10) (56% [95% CI, 32% to 72%]). At mGFR ≥60 and <90 ml/min per 1.73 m² (22 patients; 91 measurements), all formulas had P30 values >80%. However, only the CKiD 2012 formula had a P10 value >50%. At mGFR <60 ml/min per 1.73 m² (42 patients; 85 measurements), the CKiD 2012 and Schwartz-Lyon formulas had the highest P10 (45% [95% CI, 34% to 55%] and 43% [95% CI, 33% to 54%]) and P30 (90% [95% CI, 84% to 97%] and 91% [95% CI, 86% to 98%]). All studied equations except Hoek and Filler had areas under the receiver-operating characteristic curves significantly >90% in discriminating patients with renal dysfunction at various CKD stages (GFR <60, <75, and <90 ml/min per 1.73 m²).

Conclusions In pediatric kidney transplant recipients, the CKiD 2012 formula had the best performance at mGFRs <90 ml/min per 1.73 m². CystC-based formulas were not superior to PCr-based formulas.

Clin J Am Soc Nephrol 10: 463–470, 2015. doi: 10.2215/CJN.06300614

Introduction

GFR is of major importance in the management of pediatric kidney transplant patients, but determining the GFR by the reference methods (*e.g.*, inulin, iothexol) is time-consuming and expensive, and entails some risks for the patients. Thus, measurement of endogenous blood markers to estimate GFR has become common. Currently, despite several limitations (1,2), plasma creatinine (PCr) is the marker most used for this purpose.

An important limitation with PCr is the variability of its levels between laboratories due to the variety of the assays used. The standardization of the PCr determination method (*i.e.*, isotope-dilution mass spectrometry [IDMS] standardization) is now part of the international recommendations and has overcome this limitation.

The influence of muscle mass on PCr remains the major restriction to the use of PCr in GFR evaluation in all patients. In kidney transplant patients, many

other factors may affect creatinine metabolism. For example, corticosteroids may alter the muscle mass-to-total body weight ratio (3), and the use of drugs, such as trimethoprim, may affect creatinine secretion in the proximal tubule (3,4).

Plasma cystatin C (CystC), an endogenous low-molecular-weight protein, overcomes PCr limitations (2,5–8). CystC meets only a few criteria of an ideal renal function marker because it is produced at a constant rate and is freely filtered in the glomerulus without tubular secretion; however, it is catabolized in the tubulus (9). The reports about the value of CystC as a GFR marker, particularly in pediatric kidney transplantation, have been contradictory because of the influence of prednisone and calcineurin inhibitors on CystC concentration (10,11). Therefore, CystC-based or combined PCr-CystC GFR-predicting equations have been established in various populations, especially in pediatric patients (12–15), but few equations have been specifically developed for transplant

*Universidade Federal do Rio Grande do Sul, Programa de Pós-graduação em Saúde da Criança e do Adolescente, Porto Alegre, Brazil; †Universidade de Caxias do Sul, Centro de Ciências da Saúde, Caxias do Sul, Brazil; ‡Exploration Fonctionnelle Rénale et Métabolique, Groupement Hospitalier Edouard Herriot, Centre de Référence des Maladies Rénales Rares, Service de Néphrologie et Rhumatologie Pédiatriques, and ††Service de Biostatistique, Hospices Civils de Lyon, Lyon, France; ‡Fellow CAPES-Foundation, Ministry of Education of Brazil, Brasília/DF, Brazil; ¶Université Claude Bernard, Lyon 1, Lyon, France; **CNRS UMR 5305, Biologie tissulaire et Ingénierie thérapeutique, Lyon, France; ††CNRS UMR 5558, Laboratoire de Biométrie et Biologie Evolutive, Equipe Biostatistique-Santé, Villeurbanne, France; and ‡§Pontificia Universidade Católica do Rio Grande do Sul, Porto Alegre, Brazil

Correspondence:

Dr. Laurence Dubourg, Exploration Fonctionnelle Rénale et Métabolique - Pavillon P, Hôpital Edouard Herriot - 5 Place d'Arsonval - F-69437 Lyon Cedex 03-France. Email: laurence.dubourg@univ-lyon1.fr

patients. Only the Zappitelli formula has a correction factor for pediatric kidney transplant patients (15).

The recently published Kidney Disease Improving Global Outcomes (KDIGO) guidelines on kidney transplantation recommend estimating GFR in children and adolescent transplant recipients with PCr using the 2009 Schwartz formula, which has an adapted coefficient for determining IDMS-calibrated PCr (16). Because of the growth retardation in the studied population, this formula has a single coefficient for all age groups but was validated in children with and without CKD (17). In 2012, De Souza *et al.* described a locally adapted Schwartz formula (the Schwartz–Lyon formula, which has two coefficients for sex and age) and validated it in an external population (14). Finally, Schwartz *et al.* established a new combined PCr–CystC equation, the CKD in Children (CKiD) formula (16), which was updated in 2012 using immunonephelometric CystC determination (18).

The present study was conducted to assess the performance of the most commonly used PCr-based and CystC-based formulas in a cohort of pediatric kidney transplant recipients with a broad spectrum of GFRs. The predictive performance of these equations was compared with that of inulin clearance using the analytical method developed in the KDIGO guidelines. We also assessed the abilities of these GFR estimates to classify pediatric kidney transplant recipients into the different CKD stages according to the KDIGO recommendations.

Materials and Methods

Patients

Post-transplant eGFRs calculated with various formulas based on PCr and/or CystC were compared with GFRs measured by inulin clearance (mGFR) in a historical cohort of 73 pediatric kidney transplant recipients.

These children belonged to the French cohort used for establishing the Schwartz–Lyon formula (14). They had been referred to the Unit “Exploration Fonctionnelle Rénale et Métabolique” for measurement of inulin clearance at Hôpital Edouard Herriot (Lyon, France) between July 2003 and July 2010. The institutional review board of Hôpital Edouard Herriot approved this study (no. 11263), and the patients’ legal representatives provided appropriate informed consent.

In fact, inulin clearance was part of the post-transplantation routine follow-up and was performed at 1 year and 3 years, then every 5 years thereafter. In total, the patients underwent 199 inulin measurements (6 measurements in four patients, 5 in seven patients, 4 in nine patients, 3 in 15 patients, 2 in 21 patients, and 1 in 17 patients). All the patients were receiving a standard immunosuppressive regimen (corticosteroid doses <2.5 mg/m² per day). At the time of inulin clearance, none of them was receiving trimethoprim.

Measurement of PCr

PCr was obtained from a kinetic colorimetric compensated Jaffé technique (Roche Modular, Meylan, France). All PCr measurements were performed with the same method throughout the whole study period. The results were standardized by linear regression adjustment of the concentrations obtained by the compensated Jaffé assay and liquid chromatography–mass spectrometry.

The calibration equation was as follows:

$$\begin{aligned} \text{Standardized plasma creatinine} &= 0.9395x \\ &\times (\text{Jaffé compensated plasma creatinine in } \mu\text{mol/L}) \\ &+ 4.6964. \end{aligned}$$

The coefficient of correlation was $r=0.97$. These standardized creatinine values were used for the bedside Schwartz and the CKiD formulas.

Measurement of CystC

Before the advent of the European Reference Material by the International Federation of Clinical Chemistry and Laboratory Medicine (ERM-DA471/IFCC), CystC samples were assessed with the Siemens N–latex Cystatin C kit using the BN systems; however, the values obtained were recalculated according to the recommendations of the manufacturer. This required a correction factor of 1.11 to adjust the values to the new traceable International Reference Preparation-ERM-DA471/IFCC, as recommended by KDIGO (19).

Measurement of GFR

The mGFR was obtained by the renal clearance of inulin method (polyfructosan, Inutest; Fresenius Kagi, Graz, Austria). A standard technique was used by a trained staff with a continuous infusion after a priming dose of polyfructosan (30 mg/kg). Water diuresis was induced by oral administration of 5 ml/kg water followed by 3 ml/kg every 30 minutes, combined with an intravenous infusion of 0.9% sodium chloride. This enabled the patients to spontaneously empty their bladder every 30 minutes. All patients needing intermittent urethral catheterization were excluded from this study. Three to four urine samples were collected, and a blood sample was drawn midway through each collection period. The clearance values, calculated by the standard UV/P formula (where U is the urinary concentration of the substance, V is the urine flow rate [urinary volume], and P is the average plasma concentration), were obtained from the mean values of the three to four clearance periods. Plasma and urine polyfructosan were measured using the same enzymatic method. The results were corrected to 1.73 m² body surface area according to the Dubois formula (20):

$$\text{Body surface area} = \text{height}^{0.725} \times \text{weight}^{0.425} \times 0.007184.$$

Estimation of GFR

The eGFR was obtained using six formulas: (1) two creatinine-based formulas (the bedside Schwartz [16] and Schwartz–Lyon [14] formulas); (2) two CysC-based formulas (the Hoek [13] and Filler [12] formulas); and (3) two combined formulas (the CKiD [18], which uses PCr, CystC, and urea, and the Zappitelli [15], which uses PCr and CystC). All the eGFRs were standardized for a body surface area of 1.73 m² and expressed in ml/min per 1.73 m². The equations used to determine eGFRs are shown in Table 1.

Statistical Analyses

The performances of the six formulas were compared regarding mGFR, first in the whole dataset and then in the following CKD subgroups: GFR >90 ml/min per 1.73 m², 60 ≤ GFR <90 ml/min per 1.73 m², and GFR <60 ml/min per 1.73 m².

Name (Reference)	Formula
PCr-based formulas	
Bedside Schwartz (16)	$K \times \text{height} / \text{PCr}$, with $K=0.413$
Schwartz–Lyon (14)	$K \times \text{height} / \text{PCr}$, with $K=0.413$ in boys >13 yr and $K=0.367$ in others
CystC-based formulas	
Hoek (13)	$-4.32 + (80.35 / \text{CystC})$
Filler (12)	$\text{Log}(\text{eGFR}) = 1.962 + [1.123 \times \text{log}(1 / \text{CystC})]$
Combined formulas	
CKiD 2012 (18)	$39.8 \times (\text{height} / \text{PCr})^{0.456} \times (1.8 / \text{CystC})^{0.418} \times (30 / \text{BUN})^{0.079} \times (1.076)^{\text{male}} \times (\text{height} / 1.4)^{0.179}$
Zappitelli (15)	$[43.82 \times e^{0.003 \times \text{height (cm)}}] / [\text{Cys}^{0.635}] \times [\text{PCr}^{0.547}]$ In kidney transplant recipients: $\times 1.165$ In patients with spina bifida: $1.57 \times \text{PCr}^{0.925}$

BUN is expressed in milligrams per deciliter. Height is expressed in centimeters in the bedside Schwartz, Schwartz-Lyon, and Zappitelli formulas, and in meters in the CKiD formula. Weight is expressed in kilograms, and age is expressed in years. PCr, plasma creatinine, expressed in milligrams per deciliter; CystC, cystatin C, expressed in milligrams per liter; CKiD, CKD in Children.

The agreement between mGFR and eGFR values (as obtained with the six formulas) was evaluated by the bias (mean of eGFR–mGFR differences), the agreement limits, and the 10% (P10) and 30% (P30) accuracies according to the clinical practice guidelines of the Kidney Disease Outcomes Quality Initiative (21). P10 and P30 are the proportions of the eGFR estimates that fall within the interval $\text{mGFR} \pm 10\%$ and the interval $\text{mGFR} \pm 30\%$, respectively. The concordance correlation coefficient (CCC) was also estimated to quantify the agreement. The CCC adjusts the Pearson correlation coefficient downward whenever there is a systematic bias between the methods being compared. It measures, at the same time, precision (the closeness to the best-fit line) and bias (how far the best-fit line deviates from the concordance line) (22).

The comparisons of the biases, the CCCs, the P10, and the P30 used, respectively, a paired *t* test, the bootstrap 95% confidence intervals (95% CIs) of the differences between CCCs, and a McNemar test.

A random intercept linear model without covariates was used to estimate the bias and the SD of the bias. This allowed taking into account the repeated measurements in the same patients and estimating inpatient and interpatient variances in order to estimate the variance of the bias (which is the sum of the two variances).

The ability of the formulas to predict a $\text{GFR} < 60$, < 75 , and < 90 ml/min per 1.73 m² was assessed using areas under the corresponding receiver-operating characteristic curves (AUCs). The percentages of patients well classified into the two classes of GFR, as determined by each of the three thresholds with each equation, were also calculated.

Bland and Altman graphs were built using the mGFR values on the x-axis because the mGFR (*i.e.*, clearance) is considered as the gold standard method for GFR measurement.

All the analyses were performed using R for Windows, version 2.15. A *P* value < 0.05 was considered to represent statistical significance.

Results

The cohort of pediatric kidney transplant recipients included 73 patients (55% of whom were male) whose median

Table 2. Baseline characteristics of the pediatric kidney transplant recipients

Characteristics	Values
Total patients (<i>n</i>)	73
Male patients, <i>n</i> (%)	40 (55)
Median age (yr)	11.5 (7.7–15.1)
Boys > 13 yr (<i>n</i>)	26
Median weight (kg)	35.6 (22.0–48.0)
Median height (cm)	140.0 (119.5–154.0)
Median BSA (m ²)	1.2 (0.9–1.4)
Median creatinine (mg/dl)	0.87 (0.67–1.20)
Patients (measurements)	
per mGFR subgroup, <i>n</i> (<i>n</i>)	
mGFR ≥ 90 ml/min per 1.73 m ²	9 (23)
60 ≥ mGFR 90 ml/min per 1.73 m ²	22 (91)
mGFR < 60 ml/min per 1.73 m ²	42 (85)
Median transplantation –mGFR delay (yr)	4.0 (2.2–6.0)

Median values are expressed with interquartile range. BSA, body surface area; mGFR, measured GFR.

age was 11.5 years. These patients contributed 199 measurements (one to six measurements per patient). In this cohort, 57% (*n*=42) of the patients had an mGFR < 60 ml/min per 1.73 m² (Table 2).

Formula Performance in Whole Kidney Transplant Population

The CKiD 2012 and Schwartz–Lyon formulas were the most accurate in estimating GFR in the pediatric kidney transplant cohort. They showed the highest P30 values: 98% (95% CI, 96% to 99%) and 97% (95% CI, 94% to 98%), respectively. However, the CKiD 2012 formula had the lowest variability in eGFR–mGFR difference, as shown by the narrowest 95% limits of agreement (Figure 1). In

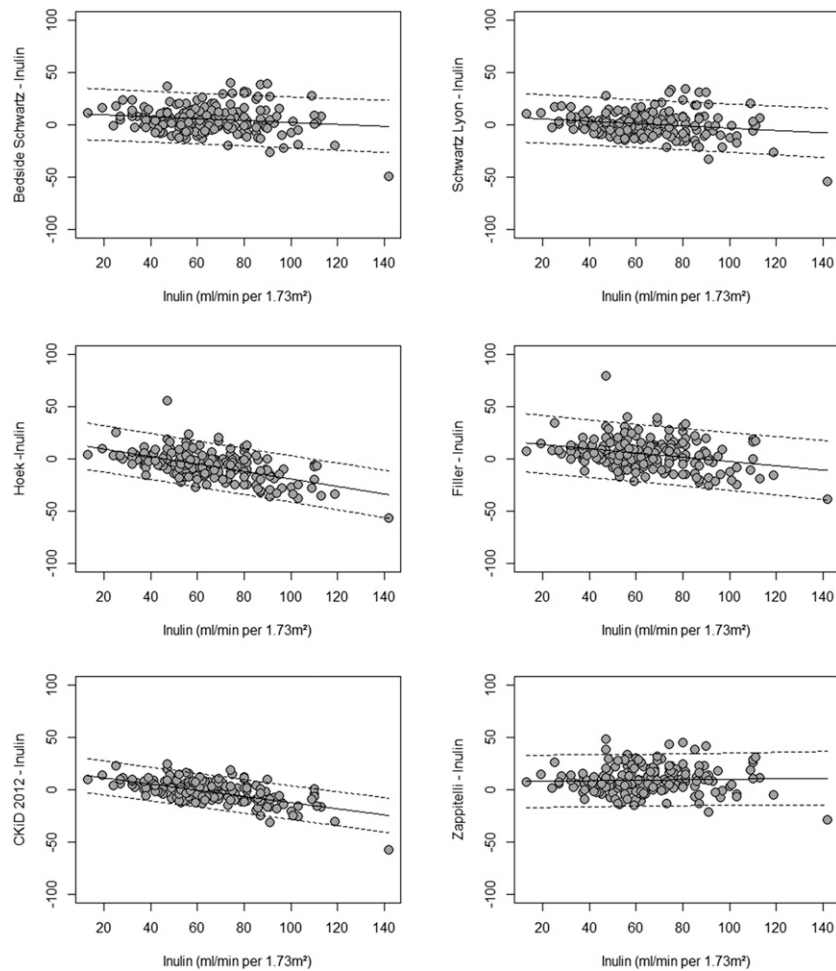


Figure 1. | Bland and Altman plots showing the bias. eGFR—measured GFR (on the y-axis) versus measured GFR as gold standard (on the x-axis). The solid lines represent the bias eGFR—measured GFR; the dotted lines represent the 95% limits of agreement. CKiD, CKD in Children.

addition, the CCCs for the CKiD 2012 and Schwartz–Lyon formulas were significantly higher than those for the other formulas. In Figure 1, Bland and Altman plots with inulin clearance on the x-axis allowed us to see the trend of the bias of each formula according to the mGFR. Bias changed according to inulin clearance: The overestimation of mGFR increased with the decrease of GFR with all tested equations except the Zappitelli formula.

Formula Performance according to CKD Subgroups

The results revealed an underestimation of mGFR at $\text{GFRs} \geq 90$ ml/min per 1.73 m^2 , except with the Zappitelli formula (-0.5 ± 17.2 , -5.4 ± 16.5 , -22.9 ± 13.4 , -6.3 ± 17.3 , -5.9 ± 12.1 , and 7.6 ± 17.8 , respectively) (Table 3). At this level of mGFR, the Zappitelli formula had the highest P30 (95%) and the bedside Schwartz formula had the highest P10 (56%).

At mGFR values ranging between 60 and 90 ml/min per 1.73 m^2 , the bias of the CKiD formula was statistically lower than those of all other formulas except the Schwartz–Lyon formula. However, the CKiD formula showed the lowest bias variability (*i.e.*, the narrowest interval between the 95% limits of agreement). In this range of mGFR, all formulas

had P30 values $>80\%$. Meanwhile, the CKiD 2012 formula was the only one with a P10 value $>50\%$ (Table 3).

The mGFR value was overestimated at $\text{mGFRs} < 60$ ml/min per 1.73 m^2 , except with the Hoek formula (Table 3). For the bedside Schwartz, Schwartz–Lyon, Hoek, Filler, CKiD 2012, and Zappitelli formulas, the mean \pm SD biases were 5.7 ± 9.4 , 1.3 ± 8.2 , -0.2 ± 11.7 , 8.2 ± 14.5 , 2.7 ± 7.6 , and 8.0 ± 11.8 , respectively. The CKiD 2012 and Schwartz–Lyon formulas had the highest P10 (45% and 43%, respectively) and P30 (90% and 91%, respectively).

Table 4 shows that all the studied equations, except the Hoek and Filler equations, had AUCs significantly $>90\%$ in discriminating patients with renal dysfunction at various CKD stages ($\text{GFR} < 60$, < 75 , and < 90 ml/min per 1.73 m^2). The CKiD 2012 and Schwartz–Lyon equations had the greatest AUCs whatever the CKD stage. Table 4 also shows the percentages of correct classifications of each formula versus inulin at various mGFR thresholds (90, 75, or 60 ml/min per 1.73 m^2).

Discussion

In comparing the performance of eGFR formulas in pediatric kidney transplant recipients, the present study

Table 3. Concordance correlation coefficient, 10% accuracy, and 30% accuracy of the six eGFR formulas (compared with mGFR) in the whole cohort and bias in the three CKD subgroups.

Variable	PCr-Based Equations		CystC-Based Equations		Combined PCr-CystC to Based Equations	
	Bedside Schwartz	Schwartz-Lyon	Hoek	Filler	CKiD 2012	Zappitelli
All measurements (n=199)						
mGFR=64.3±20.8 ml/min per 1.73 m ²						
eGFR (ml/min per 1.73 m ²)	69.8±22.5 ^a	65.0±21.8	57.8±17.4 ^a	69.0±21.6 ^a	62.5±16.8	73.4±24.7 ^a
CCC	0.81 (0.68 to 0.89)	0.85 (0.80 to 0.88) ^b	0.72 (0.65 to 0.77)	0.75 (0.68 to 0.80)	0.85 (0.81 to 0.88) ^b	0.79 (0.74 to 0.83)
10% accuracy	38 (31 to 46)	44 (36 to 53)	34 (28 to 41)	32 (26 to 39)	47 (40 to 58)	35 (28 to 43)
30% accuracy	92 (85 to 95)	97 (94 to 98)	85 (78 to 89)	82 (75 to 87)	98 (96 to 99)	85 (77 to 90)
GFR ≥ 90 ml/min/1.73 m² (n=23)						
mGFR=102.2±12.4 ml/min per 1.73 m ²						
eGFR (ml/min per 1.73 m ²)	101.7±19.9	96.7±19.1	79.2±13.7 ^a	95.9±14.5	86.8±14.4 ^a	109.8±17.4
Bias±SD	-0.5±17.2	-5.4±16.5	-22.9±13.4	-6.3±17.3	-5.9±12.1	7.6±17.8
10% accuracy	56 (32 to 72)	52 (19 to 84)	17 (2 to 33)	34 (15 to 54)	35 (15 to 54)	48 (27 to 68)
30% accuracy	91 (80 to 99)	86 (73 to 100)	69 (50 to 88)	50 (29 to 70)	91 (79 to 98)	96 (87 to 100)
60≥GFR<90 ml/min per 1.73 m² (n=91) mGFR=71.8±8.7 mL/min/1.73 m²						
eGFR (ml/min per 1.73 m ²)	78.6±15.7 ^a	73.5±15.5	63.6±12.6 ^a	76.1±15.8 ^a	69.1±10.6	82.3±16.3 ^a
Bias±SD	6.7±12.8	1.7±12.8 ^b	-8.2±10.7	4.3±14.5	-2.7±8.1 ^b	10.5±14.3
10% accuracy	42 (31 to 51)	46 (36 to 56)	38 (28 to 48)	37 (27 to 47)	51 (41 to 62)	39 (29 to 50)
30% accuracy	87 (79 to 93)	93 (88 to 98)	88 (81 to 95)	90 (84 to 96)	100 (100 to 100)	83 (76 to 91)
GFR< 60 ml/min per 1.73 m² (n=85) mGFR=46.0±8.7 ml/min per 1.73 m²						
eGFR (ml/min per 1.73 m ²)	51.7±12.7 ^a	47.3±11.0	45.8±13.7	54.2±16.7 ^a	48.7±10.1	54.0±15.5 ^a
Bias±SD	5.7±9.4	1.3±8.2 ^c	-0.2±11.7 ^c	8.2±14.5	2.7±7.6 ^c	8.0±11.8
10% accuracy	29 (19 to 39)	43 (33 to 54)	35 (25 to 45)	26 (16 to 35)	45 (34 to 55)	29 (20 to 39)
30% accuracy	81 (73 to 89)	91 (86 to 98)	82 (74 to 90)	66 (56 to 76)	90 (84 to 97)	76 (67 to 85)

Unless otherwise noted results are expressed as mean±SD. Values expressed in parentheses are 95% confidence intervals. CCC, concordance correlation coefficient.

^ap<0.05 between mGFR and eGFR.

^bp<0.05 for the difference between CKiD formula and other equations (without difference with Schwartz-Lyon formula).

^cp<0.05 for the difference between CKiD formula and other equations (without difference with Schwartz-Lyon and Hoek formulas).

Table 4. Area under the receiver-operating curves and percentages of well classified patients versus inulin at different mGFR thresholds (<90, <75, and <60 ml/min per 1.73 m²)

mGFR Threshold	AUC (95% CI)	Well Classified Patients (%)
mGFR < 90 ml/min per 1.73 m² (n=64)		
Bedside Schwartz	0.94 (0.92 to 0.96)	90
Schwartz–Lyon	0.95 (0.93 to 0.96)	93
Hoek	0.91 (0.88 to 0.94)	89
Filler	0.91 (0.88 to 0.93)	89
CKiD 2012	0.96 (0.94 to 0.97)	98
Zappitelli	0.93 (0.91 to 0.95)	83
mGFR < 75 ml/min per 1.73 m² (n=59)		
Bedside Schwartz	0.94 (0.92 to 0.96)	82
Schwartz–Lyon	0.95 (0.93 to 0.97)	89
Hoek	0.92 (0.89 to 0.95)	96
Filler	0.92 (0.89 to 0.95)	79
CKiD 2012	0.96 (0.94 to 0.98)	94
Zappitelli	0.93 (0.91 to 0.95)	73
mGFR < 60 ml/min per 1.73 m² (n=42)		
Bedside Schwartz	0.96 (0.94 to 0.98)	75
Schwartz–Lyon	0.97 (0.95 to 0.98)	96
Hoek	0.92 (0.89 to 0.95)	88
Filler	0.92 (0.89 to 0.95)	70
CKiD 2012	0.96 (0.95 to 0.98)	96
Zappitelli	0.94 (0.92 to 0.96)	70

AUC, area under the receiver-operating characteristic curve; 95% CI, 95% confidence interval.

found (1) a better performance of the CKiD 2012 and Schwartz–Lyon formulas versus the other formulas when mGFR was <90 ml/min per 1.73 m² and (2) nonsuperiority of CystC-based formulas over creatinine-based formulas whatever the mGFR (or CKD) subgroup.

As previously shown (23,24), the bedside Schwartz formula overestimated the GFR by 10% on average. This is in agreement with a report by Tsampalieros *et al.* (23), who found that in kidney transplant recipients the bedside Schwartz formula overestimated the mGFR by 9%. This finding also agrees with a recent study by Kivelä *et al.* (24), who found that in pediatric liver transplant patients the bedside Schwartz formula overestimated the mGFR by 11%. In addition, in the present cohort, the bedside Schwartz formula showed a significantly lower performance than the CKiD 2012 formula.

Conversely, the present study demonstrated that the Schwartz–Lyon formula (a PCr-based formula) and the CKiD 2012 formula (a combined PCr-CystC prediction equation) have similar biases and P30s; the latter values were, respectively, lower and higher than those of other formulas (*i.e.*, performance in estimating GFR in pediatric kidney transplant recipients was higher than that of the other formulas). The use of specific coefficients with the Schwartz–Lyon formula ($k=32.5$ in children age <13 years and girls age ≥ 13 years because of a lower muscle mass in female than in male adolescents) might improve the performance of the Schwartz–Lyon formula up to the level of the CKiD 2012 formula. Furthermore, the population of the present study contributed 20% of the cohort used to establish the Schwartz–Lyon formula.

Up to now, few studies have compared PCr- and CystC-based equations in pediatric kidney transplant recipients.

The present study showed that PCr-based equations or combined PCr-CystC-based equations were more in agreement with mGFR than CystC-based ones. Similar results were obtained by the pilot study conducted by Krieser *et al.* (11) in 19 pediatric kidney transplant recipients (median age, 13.5 years), which did not support the use of serum CystC measurements for monitoring renal function in pediatric kidney transplant recipients (11). Recently, Papez *et al.* (25) demonstrated an acceptable performance of the bedside Schwartz, CKiD 2009, and Zappitelli equations in a Hispanic-dominant pediatric renal transplant population ($n=47$) with a mean GFR (iothalamate) of 90 ml/min per 1.73 m². In a systematic review evaluating 14 different CystC-based equations in adult kidney transplant recipients, Harman *et al.* (26) found considerable heterogeneity in the performance of CystC-based equations. In addition, by analyzing data on 240 children, Sharma *et al.* (27) found that the diagnostic accuracy of various CystC-based equations varied with mGFR. Some equations performed better at low mGFR levels and others at high mGFR levels. Franco *et al.* (28) reported superiority of the CystC-based Zappitelli equation over a PCr-based equation in 50 pediatric kidney transplant recipients, but these authors used the previous Schwartz equation established in 1976 (15,29).

In the present study, conducted with both an IDMS-standardized PCr measurement and a standardized method for CystC determination, the performance of the CKiD 2012 formula (a combined PCr-CystC equation) was similar to that of the Schwartz–Lyon formula. In fact, Schwartz *et al.* have used an immunonephelometric method of CystC measurement but could not use the standardized CystC calibrators; this might have decreased the performance of

their formula in the present cohort. Moreover, despite the use of a specific correction factor for pediatric kidney transplant recipients, the Zappitelli formula showed better performance than other equations, but only at mGFR \geq 90 ml/min per 1.73 m². However, this group had a very small number of patients (23 measurements in nine patients), which was also reflected by the large confidence intervals for P30 and P10.

One strength of the present study is the use of the reference standard for GFR measurement (*i.e.*, inulin clearance) and the standardization of PCr and CystC measurements according to the international recommendations. However, the study had a few limitations: (1) Very few patients ($n=7$) had CKD stage IV or V; (2) the performance of eGFR equations in patients with mGFR $<$ 30 ml/min per 1.73 m² could not be examined because of the small number of patients; (3) the influence of the immunosuppressive regimen could not be tested because this information was not regularly available for all patients (14); and (4) the study population included French patients and thus the results cannot be readily extrapolated to non-European pediatric populations.

In conclusion, the present evaluation of eGFR formulas suggests that the CKiD 2012 formula has the best performance in pediatric kidney transplant recipients at mGFR $<$ 90 ml/min per 1.73 m². In addition, the use of both PCr and CystC is obviously more expensive than PCr alone in routine clinical evaluation. PCr-based equations remain reliable for the assessment of renal function when an IDMS-standardized measurement of PCr is used. The cost/performance ratio must be evaluated in specific clinical conditions, such as transplantation.

Finally, despite continuous refinements of the GFR-predicting equations, these equations remain insufficiently reliable in pediatric kidney transplant recipients at high mGFR levels. The ability to accurately estimate post-transplant GFR—when it is expected to be at its highest levels—is important to monitor the progression of CKD, especially at its early stages. The reference methods of GFR determination (inulin or other method) should then be performed whenever a reliable measurement is needed.

Acknowledgments

The fellowship period during which the study was supported by a grant from the Brazilian government (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior [CAPES] Process 11083-13-1 and 3677-14-1).

Disclosures

None.

References

- Delanghe JR: How to estimate GFR in children. *Nephrol Dial Transplant* 24: 714–716, 2009
- Filler G, Sharma AP: How to monitor renal function in pediatric solid organ transplant recipients. *Pediatr Transplant* 12: 393–401, 2008
- White CA, Knoll GA, Poggio ED: Measuring vs estimating glomerular filtration rate in kidney transplantation. *Transplant Rev (Orlando)* 24: 18–27, 2010
- Berglund F, Killander J, Pompeius R: Effect of trimethoprim-sulfamethoxazole on the renal excretion of creatinine in man. *J Urol* 114: 802–808, 1975
- Pöge U, Gerhardt T, Stoffel-Wagner B, Palmedo H, Klehr HU, Sauerbruch T, Woitas RP: Cystatin C-based calculation of glomerular filtration rate in kidney transplant recipients. *Kidney Int* 70: 204–210, 2006
- Yang Q, Li R, Zhong Z, Mao H, Fan J, Lin J, Yang X, Wang X, Li Z, Yu X: Is cystatin C a better marker than creatinine for evaluating residual renal function in patients on continuous ambulatory peritoneal dialysis? *Nephrol Dial Transplant* 26: 3358–3365, 2011
- Xu H, Lu Y, Teng D, Wang J, Wang L, Li Y: Assessment of glomerular filtration rate in renal transplant patients using serum cystatin C. *Transplant Proc* 38: 2006–2008, 2006
- Maillard N, Mariat C, Bonneau C, Mehdi M, Thibaudin L, Laporte S, Alamartine E, Chamson A, Berthouix F: Cystatin C-based equations in renal transplantation: Moving toward a better glomerular filtration rate prediction? *Transplantation* 85: 1855–1858, 2008
- Filler G, Bökenkamp A, Hofmann W, Le Bricon T, Martínez-Brú C, Grubb A: Cystatin C as a marker of GFR—history, indications, and future research. *Clin Biochem* 38: 1–8, 2005
- Bökenkamp A, Domanetzi M, Zinck R, Schumann G, Byrd D, Brodehl J: Cystatin C serum concentrations underestimate glomerular filtration rate in renal transplant recipients. *Clin Chem* 45: 1866–1868, 1999
- Krieser D, Rosenberg AR, Kainer G, Naidoo D: The relationship between serum creatinine, serum cystatin C and glomerular filtration rate in pediatric renal transplant recipients: A pilot study. *Pediatr Transplant* 6: 392–395, 2002
- Filler G, Lepage N: Should the Schwartz formula for estimation of GFR be replaced by cystatin C formula? *Pediatr Nephrol* 18: 981–985, 2003
- Hoek FJ, Kemperman FA, Krediet RT: A comparison between cystatin C, plasma creatinine and the Cockcroft and Gault formula for the estimation of glomerular filtration rate. *Nephrol Dial Transplant* 18: 2024–2031, 2003
- De Souza VC, Rabilloud M, Cochat P, Selistre L, Hadj-Aissa A, Kassai B, Ranchin B, Berg U, Herthelius M, Dubourg L: Schwartz formula: Is one k-coefficient adequate for all children? *PLoS ONE* 7: e53439, 2012
- Zappitelli M, Parvex P, Joseph L, Paradis G, Grey V, Lau S, Bell L: Derivation and validation of cystatin C-based prediction equations for GFR in children. *Am J Kidney Dis* 48: 221–230, 2006
- Schwartz GJ, Muñoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, Furth SL: New equations to estimate GFR in children with CKD. *J Am Soc Nephrol* 20: 629–637, 2009
- Staples A, LeBlond R, Watkins S, Wong C, Brandt J: Validation of the revised Schwartz estimating equation in a predominantly non-CKD population. *Pediatr Nephrol* 25: 2321–2326, 2010
- Schwartz GJ, Schneider MF, Maier PS, Moxey-Mims M, Dharnidharka VR, Warady BA, Furth SL, Muñoz A: Improved equations estimating GFR in children with chronic kidney disease using an immunonephelometric determination of cystatin C. *Kidney Int* 82: 445–453, 2012
- Chapter 1: Definition and classification of CKD. *Kidney Int Suppl*, 3: 19–62, 2013
- Du Bois D, Du Bois EF: A formula to estimate the approximate surface area if height and weight be known. 1916. *Nutrition* 5: 303–313, 1989
- National Kidney Foundation: K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. *Am J Kidney Dis* 39[Suppl 1]: S1–S266, 2002
- Lin LI: A concordance correlation coefficient to evaluate reproducibility. *Biometrics* 45: 255–268, 1989
- Tsampalieros A, Lepage N, Feber J: Intraindividual variability of the modified Schwartz and novel CKiD GFR equations in pediatric renal transplant patients. *Pediatr Transplant* 15: 760–765, 2011
- Kivelä JM, Räisänen-Sokolowski A, Pakarinen MP, Mäkisalo H, Jalanko H, Holmberg C, Lauronen J: Long-term renal function in children after liver transplantation. *Transplantation* 91: 115–120, 2011
- Papez KE, Barletta GM, Hsieh S, Joseph M, Morgenstern BZ: Iothalamate versus estimated GFR in a Hispanic-dominant pediatric renal transplant population. *Pediatr Nephrol* 28: 2369–2376, 2013
- Harman G, Akbari A, Hiremath S, White CA, Ramsay T, Kokolo MB, Craig J, Knoll GA: Accuracy of cystatin C-based estimates

- of glomerular filtration rate in kidney transplant recipients: A systematic review. *Nephrol Dial Transplant* 28: 741–757, 2013
27. Sharma AP, Yasin A, Garg AX, Filler G: Diagnostic accuracy of cystatin C-based eGFR equations at different GFR levels in children. *Clin J Am Soc Nephrol* 6: 1599–1608, 2011
28. Franco MC, Nagasako SS, Machado PG, Nogueira PC, Pestana JO, Sesso R: Cystatin C and renal function in pediatric kidney transplant recipients. *Braz J Med Biol Res* 42: 1225–1229, 2009
29. Brochard K, Boyer O, Blanchard A, Loirat C, Niaudet P, Macher MA, Deschenes G, Bensman A, Decramer S, Cochat P, Morin D, Broux F, Caillez M, Guyot C, Novo R, Jeunemaître X, Vargas-Poussou R: Phenotype-genotype correlation in antenatal and neonatal variants of Bartter syndrome. *Nephrol Dial Transplant* 24: 1455–1464, 2009

Received: June 24, 2014 **Accepted:** December 8, 2014

Published online ahead of print. Publication date available at www.cjasn.org.