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Derivation of New Equations to Estimate Glomerular Filtration Rate in Pediatric Oncology Patients

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Abstract

Background and Objective—Monitoring renal function is critical in treating pediatric patients, especially when dosing nephrotoxic agents. We evaluated the validity of the bedside Schwartz and Brandt equations in pediatric oncology patients, and developed new equations for estimated glomerular filtration rate (GFR) in these patients.

Methods—A retrospective analysis was conducted on patients comparing the estimated GFR using the bedside Schwartz and Brandt equations to measured GFR (mGFR) from ^{99m}Technetium-DTPA (^{99m}Tc-DTPA) between January 2007 and August 2013. An improved equation to estimate GFR was developed, simplified, and externally validated in a cohort of patients studied from September 2013 to June 2015. Carboplatin doses calculated from ^{99m}Tc-DTPA were compared to doses calculated by GFR estimating equations.

Results—Overall, the bedside Schwartz and Brandt equations did not precisely or accurately predict mGFR in our pediatric oncology patient population. Using a subset of the data, we developed a 5-covariate equation, which included the covariates of height, serum creatinine, age,

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Compliance with Ethical Standards

Research Involving Human Participants

All procedures performed in studies involving human participants 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. For this type of study formal consent is not required.

Informed consent

For this type of study formal consent is not required because it was a retrospective study of patient electronic medical records.

Disclosure of potential conflicts of interest

The authors have nothing to declare.

BUN, and gender, and a simplified version (2-covariates), which only contained height and serum creatinine. These equations were used to estimate GFR in 2036 studies, resulting in precise and accurate predictors of the mGFR values. The equations were validated in an external cohort of 570 studies; both new equations were more accurate in calculating carboplatin doses than either the bedside Schwartz or Brandt equation.

Conclusions—Two new equations were developed to estimate GFR in pediatric oncology patients, both of which did a better job at estimating mGFR than published equations.

Keywords

renal; Schwartz; Brandt; carboplatin; technetium

Introduction

A readily available method to assess glomerular filtration rate (GFR) in pediatric patients is important for dosing renally excreted pharmaceuticals and monitoring drug therapy. In children with cancer, accurate GFR results are essential to adjust the dosage of renally cleared medications (e.g., carboplatin) and to monitor for acute or chronic renal insufficiency. While accurate measurements of GFR using radioisotope (e.g., technetium-99m-diethylenetriaminepentaacetic acid [^{99m}Tc -DTPA]) or inulin clearance studies are available, they are not feasible for all institutions and are limited by resources, time, and cost constraints. Equations used to estimate GFR are of great importance for daily use when it is impractical to perform more cumbersome procedures.

Prior to the creation of the Creatinine Standardization Program of the National Kidney Disease Education Program, estimation equations based on serum creatinine measurements have been shown to overestimate GFR as determined by isotope methods (iGFR) [1–3]. As a consequence, these first generation equations lost their utility and second generation equations were developed using serum creatinine measurements traceable to an isotope dilution mass spectrometry (IDMS) calibrated method [1]. One of the commonly used pediatric GFR equations was developed by Schwartz and colleagues from The Chronic Kidney Disease in Children study and is often referred to as the bedside Schwartz equation [4]. This equation was developed in children with chronic kidney disease, and although it has been shown to be useful in predicting renal function in a broader pediatric population including children with solid tumors [5], other studies suggest it may not be useful for populations other than those in which it was developed [6, 7].

An alternative second generation equation was developed in children with solid tumors by Brandt et al [8]. Subjects were studied prior to receiving chemotherapy ($n=111$), and GFR was measured using serum iothalamate clearance. The resulting equation had an $r^2 = 0.97$ for prediction of measured GFR (mGFR). A comparison of the original Schwartz equation in the same study group yielded an $r^2 = 0.24$. The study group later validated the Brandt equation in an additional cohort of 566 children (Adjusted $r^2 = 0.80$) [9]. While the Brandt equation had reasonable precision and accuracy characteristics when evaluated in all subjects, the authors did note the equation was less reliable for GFR values > 120 mL/min (regression $r^2=0.23$) compared with GFR < 120 mL/min (regression $r^2=0.76$). When

normalized to 1.73 m^2 , this GFR cutpoint (120 ml/min) is similar to that proposed by the National Kidney Foundation ($\sim 60 \text{ ml/min/1.73 m}^2$) and represents loss of half or more of the adult level of normal kidney function [10]. Investigators evaluating estimating equations compared with measured GFR often use this cutpoint as a method to determine performance characteristics.

Thus, the objectives of the present study were to determine the accuracy of the bedside Schwartz and Brandt equations to estimate the mGFR determined by $^{99\text{m}}\text{Tc}$ -DTPA clearance studies in our pediatric oncology population, and to develop a new GFR estimation equation, which would be externally validated in a separate pediatric oncology cohort. In addition, we sought to evaluate the clinical utility of calculating carboplatin doses based on the estimated GFR from all equations and compared it to the dose calculated from the mGFR.

Patients and Methods

Study population and GFR determination

This retrospective chart review of patients undergoing a $^{99\text{m}}\text{Tc}$ -DTPA clearance study was conducted in two parts. First, estimated GFR (eGFR) values were calculated using the bedside Schwartz or Brandt equation and compared with mGFR values as determined by a $^{99\text{m}}\text{Tc}$ -DTPA. $^{99\text{m}}\text{Tc}$ -DTPA studies conducted from January 2007 to August 2013 that were part of a clinical trial or routine clinical care at St. Jude Children's Research Hospital were used for the analysis. Second, a new equation to estimate GFR using patient specific covariates was developed using a subset of $^{99\text{m}}\text{Tc}$ -DTPA studies from the initial population. All $^{99\text{m}}\text{Tc}$ -DTPA clearance studies conducted from September 2013 to June 2015 were used as an external validation cohort. This study and the waiver of informed consent were approved by the St. Jude Children's Research Hospital Institutional Review Board.

Patients were included in the study if they were <19 years of age with a successful $^{99\text{m}}\text{Tc}$ -DTPA study as defined below. The radioisotope method utilized to measure GFR involved a single injection of 2 mCi/m^2 of $^{99\text{m}}\text{Tc}$ -DTPA followed by three timed samples at 1, 2, and 4 hours post-injection [11]. Clearance of $^{99\text{m}}\text{Tc}$ -DTPA was determined by pharmacokinetic modeling using ADAPT II (University of Southern California, <https://bmsr.usc.edu/software/adapt/>). Patients were excluded if they had an unsuccessful $^{99\text{m}}\text{Tc}$ -DTPA clearance study, which was defined as a volume of distribution outside the range of $5\text{--}10 \text{ L/m}^2$, residuals exceeding 10% of the measured value, first blood sample drawn before hour 1, or results not consistent with clinical status of the patient as assessed by the clinical pharmacist. In addition, GFR measurements $< 10 \text{ mL/min/1.73m}^2$ or $> 200 \text{ mL/min/1.73m}^2$ were also excluded from the analysis because they were characterized as extreme values [12].

Estimation of GFR from bedside Schwartz and Brandt equations

Patient demographic and clinical covariates were extracted from the patient chart for each $^{99\text{m}}\text{Tc}$ -DTPA clearance study. Information included height, weight, age, gender, serum creatinine (SCr) concentration, and blood urea nitrogen (BUN) values. SCr was measured using an IDMS-traceable enzymatic method (CREP prior to September 2013 and CREP2 after September 2013, Cobas). These data were used to calculate an eGFR at the time of

each ^{99m}Tc -DTPA clearance study using both the bedside Schwartz [4] and Brandt [8] equations as follows:

$$\text{Bedside Schwartz (mL/min/1.73m}^2\text{)} = 0.413 * \frac{\text{height (cm)}}{\text{SCr}(\frac{\text{mg}}{\text{dL}})} \quad (1)$$

$$\text{Brandt (mL/min)} = k * \sqrt{\frac{(\text{age [months]} + 6) * \text{weight (kg)}}{\text{SCr}(\frac{\text{mg}}{\text{dL}})}} \quad (2)$$

where k is 0.95 for females and 1.05 for males. All estimated GFR calculations via the Brandt equation were normalized to a BSA of 1.73 m² to make them comparable to results of the ^{99m}Tc -DTPA clearance studies and the eGFR determined using the bedside Schwartz equation.

Development of a new equation and external validation

After comparing the bedside Schwartz and Brandt equation to the mGFR, we found it necessary to develop a new equation to estimate GFR in our patient population. A subset of the ^{99m}Tc -DTPA studies from January 2007 to August 2013 was used to develop two new equations (a more complex and a simplified version) by using univariate and multivariate linear regression. The overall performance of the equations and the performance in subgroups was evaluated for root mean square error (RMSE), predicted residual sum of squares (PRESS) statistics, number of parameters, and an adjusted r-squared. The equation was validated internally using the remainder of the studies from the January 2007 to August 2013 cohort, and also in an external cohort of patients studied from September 2013 to June 2015. The performance characteristics (bias and accuracy) of the new equation in the external validation cohort were compared with those observed in the development cohort.

Calculation of carboplatin dose

To evaluate the clinical utility of the new estimation equations compared with previously published equations, carboplatin dosages were calculated using a modified version of the Calvert equation as follows [13, 14]:

$$\text{Carboplatin dosage} \left(\frac{\text{mg}}{\text{m}^2} \right) = \text{AUC} * ([0.93 * \text{GFR}] + 15) \quad (3)$$

where AUC is the area under the concentration-time curve defined as 6 mg/mL*min and GFR units are mL/min/m². Measured GFR values from ^{99m}Tc -DTPA clearance studies from January 2007 to August 2013 served as the reference to calculate the “actual” carboplatin dosage. Carboplatin dosages using the estimated GFR following the bedside Schwartz, Brandt, and the newly developed equations were all compared to the “actual” carboplatin

dosage. Using the BSA for each patient, a carboplatin dose (mg) was also calculated for each individual.

Statistical analysis

As the focus of the analysis was to assess the performance of the equations to estimate the GFR, all DTPA clearance studies were treated as independent observations. Linear regressions and Bland-Altman plots were applied to characterize the correlation between the ^{99m}Tc -DTPA mGFR and the eGFR for the bedside Schwartz, Brandt, and the newly developed equations. Overall and subgroup specific bias (defined as the difference between estimated and measured GFR values) and percent bias (defined as the bias relative to the measured GFR on a percentage scale) were calculated for the estimated GFR determined by the bedside Schwartz, Brandt, and the newly developed equations. Accuracy was assessed as the percent of the estimates within 30% of the measured GFR values (P_{30}), which takes into account higher errors at higher values and absolute values of the difference between measured and estimated GFR [15 individuals with CKD]. A receiver operator characteristic (ROC) curve analysis was performed to assess the performance of covariates in predicting dichotomized GFR (i.e., either $\leq$ or $> 60 \text{ mL/min/1.73m}^2$).

The actual and hypothetical carboplatin doses were compared by subtracting the dose determined from the ^{99m}Tc -DTPA clearance study from the dose determined from the equation estimated GFR, and the difference was expressed in terms of percentage error (%PE) and absolute percentage error (APE). The means of doses calculated using ^{99m}Tc -DTPA and eGFR equations were compared by paired-t tests, with effect sizes calculated as Cohen's d [16]. The %PEs between hypothetical and actual carboplatin doses are also shown as waterfall plots. The limits of underdosing (i.e., $< -10\%$ %PE) and overdosing ($> 25\%$ %PE) depicted in the waterfall plots were chosen based upon suggested clinical relevance in adult studies [17].

For all statistical analyses, a p-value less than 0.05 was considered statistically significant. Statistical analyses were performed and plots generated using SAS (SAS Institute, Cary, NC), Windows version 9.4.

Results

Estimation of GFR from bedside Schwartz and Brandt equations

From January 2007 to August 2013, 2036 ^{99m}Tc -DTPA clearance studies were performed in 1044 patients at St. Jude Children's Research Hospital. The demographics of these patients are described in Table 1. A total of 1044 patients were studied of which 397 (38%) patients had a diagnosis of leukemia/lymphoma or hematologic disorders, 421 (40%) patients had a diagnosis of solid tumors, 189 (18%) patients had tumors of the central nervous system, and 37 (4%) patients had a diagnosis of multiple primary diagnoses. As noted in Table 1, the median ^{99m}Tc -DTPA clearance for the study population was $114 \text{ mL/min/1.73 m}^2$ with extreme measurements excluded: one GFR measurement was $10 \text{ mL/min/1.73 m}^2$ ($2 \text{ mL/min/1.73 m}^2$) and 40 observations from 36 patients had GFR values greater than $200 \text{ mL/min/1.73 m}^2$ (~2% of the total number of observations).

The bedside Schwartz and Brandt equations were used to estimate GFR and compared to the mGFR from ^{99m}Tc -DTPA clearance studies. Comparisons of the eGFR by the bedside Schwartz or the Brandt equations with mGFR values are presented in Fig. 1a and 1b, respectively. The Bland-Altman analyses for the bedside Schwartz and the Brandt GFR equations compared with the mGFR are presented in Fig. 2a and 2b, respectively. As depicted in the Bland-Altman analysis, both equations had a positive bias, but the overall range of difference as presented by ± 2 standard deviations was less for the Brandt equation. The overall and group specific bias and accuracy results for both equations are summarized in Table 2 where the analysis is presented as the overall cohort (n=2036 observations), subdivided by age groups, gender, and GFR (i.e., $\leq$ or $> 60 \text{ mL/min/1.73m}^2$ (based on adult values for kidney dysfunction [10])). Although not listed in Table 2, we also analyzed the specific bias and accuracy results for both equations both primary diagnosis subdividing the population into the subgroups, hematological malignancies, brain tumors, and solid tumors. As noted in Online Resource Table 1, results of the study cohort were similar for all three types of malignancy. We also performed these analyses on index cases (distinct patients), and found similar results to the analyses with all patients (see Online Resource Table 2).

We had a particular interest in how well the equations performed in patients less than 24 months as well as patients with a GFR $\leq 60 \text{ mL/min/1.73m}^2$. As shown in Table 2, both the bedside Schwartz and Brandt equations performed poorly when estimating GFR in patients with reduced renal function defined as a GFR $\leq 60 \text{ mL/min/1.73m}^2$. The mean ($\pm$ SD) percent bias for the bedside Schwartz equation was 71% (90%), and only 30% of calculated values were within 30% of the measured GFR values (P_{30}). Similarly, the Brandt equation had a mean ($\pm$ SD) percent bias of 144% (93%), and the P_{30} was only 4%. Conversely, the bias and accuracy for both equations was much better for the subgroup of studies with GFR $> 60 \text{ mL/min/1.73m}^2$. For the younger populations, the Brandt equation performed much better than the bedside Schwartz equation with lower percent bias and greater P_{30} values in all ages ≤ 24 months (Table 2).

Development of a new equation and external validation

The first step to develop our new equation was to randomly divide the GFR values into an equation development group (two-thirds) and equation validation group (one-third). The covariates in this equation were age, gender, height/serum creatinine, blood urea nitrogen and weight. Although it performed well in the development and validation groups, it had similar bias and P_{30} characteristics to the bedside Schwartz and the Brandt equations (data not shown). Thus, as our next step we decided to use the subgroup of patients with reduced renal function (GFR $\leq 60 \text{ mL/min/1.73m}^2$; n=105 studies) to develop a new equation. Although this new equation performed well in that subgroup, it performed poorly in all other subgroups (data not shown). In this same analysis, we analyzed patient specific characteristics that differed by GFR groups (i.e., GFR ≤ 60 and $> 60 \text{ mL/min/1.73m}^2$) and found that not surprisingly serum creatinine and the ratio of height to serum creatinine were statistically different between the two subgroups ($p<0.001$). The receiver operating characteristics curve (ROC) analysis of the ratio of height/serum creatinine showed excellent accuracy with an area under the curve (AUC) of 0.90 predicting GFR $> 60 \text{ mL/min/1.73m}^2$.

The accuracy was slightly improved when the combination of age, height, serum creatinine, male gender, BUN, and height/serum creatinine was used (AUC 0.92).

Thus, in our next attempt to develop a new equation including the 5 covariates found to improve the accuracy of the estimated GFR, we used all our studies with GFR values ≤ 60 mL/min/1.73m² (n=105) and only one-tenth of the GFR studies > 60 mL/min/1.73m² (randomly selected; n=194). The new equation was as follows:

$$GFR \text{ (mL/min/1.73m}^2\text{)} = 0.748 * \left(\frac{HT}{SCr} \right)^{0.870} * Age^{0.063} * \frac{1}{BUN}^{0.104} * 1.092^{Male} \quad (4)$$

where *HT* is height in cm, *SCr* is serum creatinine in mg/dL, *Age* is in years, *BUN* is blood urea nitrogen in mg/dL, and *Male* is a categorical covariate with yes = 1 and no = 0. The 5-covariate equation was then used to estimate the measured GFR in all of the 2036 ^{99m}Tc-DTPA studies from January 2007 to August 2013. This equation did very well at estimating GFR in patients with a measured GFR ≤ 60 mL/min/1.73m² and > 60 mL/min/1.73m², with a mean ($\pm$ SD) percent bias 37% (68%) and -5% (25%), respectively (Table 3). Accuracy was better using this equation as well, with a P₃₀ for measured GFR ≤ 60 mL/min/1.73m² and > 60 mL/min/1.73m² of 61% and 81%, respectively. Furthermore, this 5-covariate equation was much better than the bedside Schwartz at predicting GFR in patients < 24 months, but performed equally as well as the Brandt equation (Table 2 compared to Table 3). Overall, the 5-covariate equation was much more accurate in all the subgroups evaluated than the bedside Schwartz or Brandt.

While the initial equation performed well in this patient cohort, it did require five patient covariates to estimate GFR. Though this would not be a problem for an electronic medical record where the equation could be programmed into a dashboard setting, it could be challenging for a bedside application. Therefore, we sought to determine which of these covariates could be eliminated and still provide an equation that would be accurate at estimating GFR in pediatric oncology patients. Online Resource 1 shows a linear relationship between the ratio of height to serum creatinine and measured GFR. Therefore, a univariate analysis was performed using a simple linear regression model without an intercept with the resulting equation:

$$GFR \text{ (mL/min/1.73m}^2\text{)} = 0.33 \left(\frac{HT}{SCr} \right) \quad (5)$$

where *HT* is height in cm and *SCr* is serum creatinine in mg/dL. This simplified equation was evaluated with all 2036 ^{99m}Tc-DTPA clearance studies and the bias, percent bias, and percent accuracy values are presented in Table 3. While this equation has fewer covariates than the original equation, it performed similarly, making it a more practical equation to use at the bedside.

We compared the performance of the two new equations by completing an external validation in 570 ^{99m}Tc-DTPA clearance studies completed from September 2013 to June

2015. The characteristics of these patients are presented in Table 1. The Bland-Altman plot for the simplified equation is shown in Online Resource 2. As depicted in Table 4, the 5-covariate and simplified equations had similar percent bias and P_{30} in the overall population and in the reduced renal function group (e.g., $GFR < 60 \text{ mL/min/1.73m}^2$), but both equations had greater bias and poorer accuracy (i.e., P_{30}) in the < 12 month old subgroup than in the equation development population (Table 3).

Calculation of carboplatin dose

To further assess the clinical utility of our new equations, we calculated carboplatin dosages according to Equation 3 using measured GFR from ^{99m}Tc -DTPA clearance studies compared to the carboplatin dose determined from the GFR estimating equations. The mean (SD) carboplatin dose using measured GFR from ^{99m}Tc -DTPA ($n=2036$) and AUC of $6 \text{ mg/mL} \cdot \text{min}$ was 447 mg (250 mg). Mean (SD) carboplatin doses calculated using eGFR equations for the bedside Schwartz, Brandt, 5-covariate, and simplified equations were 500 mg (250 mg), 528 mg (296 mg), 418 mg (224 mg), and 417 mg (208 mg), respectively.

Due to a large sample size ($n=2036$), a statistically significant difference between the mean ^{99m}Tc -DTPA calculated dose and the mean dose obtained using eGFR was found for all four equations ($p<0.05$ each). However, the difference was small when the 5-covariate (Cohen's $d=0.29$) or the simplified (Cohen's $d=0.26$) equation was used. In contrast, a medium to large difference was observed for the bedside Schwartz (Cohen's $d=0.43$) or Brandt (Cohen's $d=0.68$) equations.

Doses calculated using estimating formulas were compared to those obtained with the ^{99m}Tc -DTPA approach using both percentage error (%PE) and absolute percentage error (APE). The 5-covariate and simplified equations tended to slightly underdose patients (mean %PE -3.4% and -0.9% , respectively; Fig. 3), whereas the bedside Schwartz and Brandt equations tended to overdose patients (mean %PE 18.7% and 19.2% , respectively; Fig. 3). The 5-covariate equation had the lowest APE (15.7%), followed by the simplified equation (mean APE 17.6%), and Brandt and bedside Schwartz equations had the highest mean APE (24.1% and 24.8% , respectively). Patients with an APE $<10\%$ were considered to have received an equivalent dose of carboplatin, and 40.8% and 38.1% of patients would have received equivalent dose of carboplatin using the 5-covariate and the simplified equations, respectively, compared with 29.8% of patients using bedside Schwartz equation and 31.5% of patients using Brandt equation (Fig. 3). We performed a similar analysis using just our external validation data set ($n=570$ observations), and the results were similar to those obtained with the development group (see Online Resource Table 3).

Discussion

This study sought to first, determine how well the bedside Schwartz and Brandt equations estimated measured GFR by ^{99m}Tc -DTPA clearance studies in children with cancer, and second, to develop a new equation to accurately estimate GFR in pediatric patients with a particular interest in children less than 24 months and patients with a measured $GFR < 60 \text{ mL/min/1.73m}^2$. Furthermore, the optimal equation would also accurately estimate GFR in patients with normal renal function. The results from this analysis showed that eGFR using

the bedside Schwartz and the Brandt equations in pediatric oncology patients were biased and poorly accurate (Table 2), confirming results from similar studies [18, 19]. Therefore, a new equation was developed using available patient covariates (Equation 4), and further simplified (Equation 5) to estimate GFR in our patient cohort. Both of these equations were more accurate at estimating GFR than the bedside Schwartz and Brandt equations (Table 3), and were successfully externally validated in a separate pediatric oncology cohort (Table 4). Furthermore, evaluating these equations in a clinical setting demonstrated the 5-covariate and simplified equations were better at matching the carboplatin dose using measured GFR from ^{99m}Tc -DTPA clearance studies than the bedside Schwartz and Brandt equations (Fig. 3).

Andersen and colleagues compared the ability of GFR models to discriminate normal and reduced renal function in 119 children with nephro-urological disorders [20]. The authors used ^{51}Cr -EDTA as the index measure of GFR, and variations on eight published GFR models. Different from our study, the authors only used the GFR models to categorize renal function into normal, reduced, or needing a more precise test to be determined (or so called gray zone). They found that the GFR models were in general adequate to screen for normal or reduced renal function, but only 9 patients had $\text{GFR} < 60 \text{ mL/min/1.73 m}^2$ limiting their ability to identify patients with severely impaired renal dysfunction.

Bernhardt and colleagues performed a retrospective evaluation of the performance of three equations (i.e., original Schwartz, bedside Schwartz, and Counahan-Barratt) to estimate GFR in 174 children with leukemia, lymphoma, or histiocytosis [18]. Similar to our study, they used ^{99m}Tc -DTPA as the index measure of GFR and found that none of the three equations reliably estimated GFR. Using logistic regression analysis, they identified age and prior reception of chemotherapy to predictors of the observed estimation bias in the GFR equations. However, the authors did not develop a new equation using this information.

A strength of our new equations, which were derived in a population of pediatric oncology patients, is that we have a large enough population of patients to have a diversity of ages, diagnoses, and renal function. In both our model derivation and external validation data set, we have patients that range in age from 1 month to 19 years. In addition, our patient population includes patients with leukemia/lymphoma, other hematologic disorders, solid malignancies, and brain tumors. Approximately 5% (105 ^{99m}Tc -DTPA studies) of the model derivation population had a $\text{GFR} < 60 \text{ mL/min/1.73 m}^2$, which enhanced the likelihood the new equations would accurately estimate GFR for patients with renal dysfunction. In fact, our results clearly show that for the group of $\text{GFR} < 60 \text{ mL/min/1.73 m}^2$ both our new equations (either the 5-covariate or the simplified 2-covariate) have less bias and better accuracy than either the bedside Schwartz or the Brandt equation. Specifically the accuracy as measured by the P30% for the 5-covariate and simplified equations is 60.95 compared with 29 for the Bedside Schwartz and only 3 for the Brandt. Thus, this represents at worst a 2-fold increase in accuracy and at best a 30-fold increase. Furthermore, this equation was developed using SCr measurements from an IDMS traceable method, improving its clinical utility.

The 5-covariate equation accurately estimated GFR compared to the measured GFR by ^{99m}Tc -DTPA clearance studies and may be the equation of choice by a clinician practicing in an environment with access to an electronic medical record (EMR). It could easily be coded to pull each patient characteristic within the EMR to estimate the GFR. However, a caveat is that the patient covariates have to be available within a reasonable time frame of each other to estimate GFR. The simplified equation with only two patient covariates (height and serum creatinine) had slightly lower accuracy, but performed similarly, improving its clinical utility.

Although the methods to measure serum creatinine were similar between the bedside Schwartz and our new equations, it is well known that such methodological aspects may alter the coefficient of serum-based equations to estimate GFR. In a mini-review by Schwartz and Work [21], they summarized several published GFR equations and demonstrated how the covariates in each equation are similar (e.g., serum creatinine, height), but that over time and presumably with changes in the methods of measuring serum creatinine the coefficient has changed. In our study, we noted that our equation differed from that of the bedside Schwartz by only the coefficient. However, this change in the coefficient significantly increases the accuracy of the estimated GFR in pediatric oncology patients (Tables 2 and 3).

As with all retrospective studies, ours has limitations that must be considered when interpreting the results. The patients studied to develop our equations all had various malignancies, so it is unknown whether these equations would perform well in other pediatric settings. Therefore, further validation in other pediatric cohorts is warranted. In addition, the generally lower serum creatinine concentration in children makes the influence of a measurement error proportionally larger than the same magnitude error in an adult sample. However, this limitation applies to any equation to estimate GFR that includes serum creatinine.

In conclusion, this study developed a 5-covariate equation and further simplified this equation to one with 2-covariates to estimate GFR in pediatric oncology patients with better accuracy than the bedside Schwartz and Brandt equations. We recommend using the simplified new equation on a daily basis for estimating GFR in pediatric oncology patients due to its accuracy and ease of use.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1. Correlation plots comparing glomerular filtration rate (GFR) estimated by the bedside Schwartz (a) or Brandt (b) equation to measured GFR. The dotted line is the line of identity and the solid line is the best fit linear correlation.

Fig. 2. Bland-Altman plots for the bedside Schwartz (a) and Brandt (b) equations. The solid line represents the mean of the difference and the dashed lines represent ± 2 standard deviations.

Fig. 3. Waterfall plots of percentage error (PE) of glomerular filtration rate (GFR) estimation by different formulas (a. bedside Schwartz, b. Brandt, c. 5-Covariate, and d. Simplified) versus the individual observations (n = 2036). The dashed lines represent the limits of underdosing [$<90\%$ of actual target dose (ATD) and overdosing ($>125\%$ ATD)].

Table 1

Characteristics of the patients from the technetium studies included in the equation building dataset and external validation data set.

Characteristic	All Studies (n=2036)			External Validation Data Set (n=570)		
	Median	IQR	Range	Median	IQR	Range
Age (years)	6.1	2.3 to 12.4	0.1 to 18.9	5.8	2.4 to 11.8	0.1 to 18.9
Height (cm)	114	86.2 to 150.9	49.3 to 198.9	111.7	88.4 to 148	53.7 to 196.7
Weight (kg)	21	12.3 to 44.4	3.5 to 131.7	19.5	12.4 to 41.1	3.8 to 119.7
Serum creatinine (mg/dL)	0.3	0.2 to 0.5	0.1 to 2.2	0.3	0.2 to 0.5	0.1 to 1.9
Blood urea nitrogen (mg/dL)	10	7 to 13	2 to 155	11	8 to 14	2 to 74
Body surface area (m ²)	0.8	0.6 to 1.4	0.2 to 2.7	0.8	0.6 to 1.3	0.3 to 2.5
99mTc-DTPA GFR (ml/min/1.73 m ²)	114	92 to 136	11 to 200	108.5	88 to 133	11 to 200

IQR – interquartile range, GFR glomerular filtration rate, 99mTc-DTPA - technetium-99m- diethylenetriaminepentaacetic acid

Table 2
Bias and accuracy of estimated glomerular filtration rate (eGFR) from the bedside Schwartz and Brandt equations.

Bedside Schwartz	N	Bias				Bias (%)				P30%
		Mean	SD	Median	IQR	Mean	SD	Median	IQR	
Overall	2036	23.00	39.94	19.20	42.88	25.02	42.64	18.23	41.92	60.76
Age: 6 months	85	43.01	37.17	40.87	26.33	55.06	46.69	46.27	35.65	27.06
Age: 7–12 months	164	42.87	42.17	39.58	31.64	45.47	46.20	38.14	36.47	39.02
Age: 13–24 months	213	34.34	47.48	30.86	51.20	33.54	42.37	27.50	50.82	52.11
Age: 2–12 years	1031	23.75	38.43	18.79	40.79	23.69	38.19	17.14	37.31	64.11
Age: Females > 12 years	242	17.25	27.90	15.01	34.02	22.25	35.50	15.94	37.31	67.77
Age: Males > 12 years	301	0.57	34.95	0.89	39.95	6.13	48.68	0.77	37.94	71.10
GFR: 60 mL/min/1.73m ²	105	30.03	35.78	19.04	24.14	71.06	89.98	43.02	55.95	29.52
GFR: > 60 mL/min/1.73m ²	1931	22.62	40.12	19.29	44.35	22.52	36.87	16.78	41.02	62.45
Brandt										
Overall	2036	20.86	30.47	21.27	39.60	27.13	45.14	18.77	40.42	63.26
Age: 6 months	85	6.07	18.15	7.66	19.57	13.88	31.28	8.58	29.07	76.47
Age: 7–12 months	164	1.61	21.80	0.62	24.06	5.68	27.34	0.69	25.50	85.98
Age: 13–24 months	213	−1.43	31.87	−1.69	38.49	6.74	37.79	−1.67	30.94	77.00
Age: 2–12 years	1031	22.27	28.32	23.74	36.44	26.26	39.08	19.85	36.37	64.50
Age: Females > 12 years	242	38.23	25.64	38.36	32.34	49.10	48.63	38.65	44.77	40.50
Age: Males > 12 years	301	32.49	30.74	32.15	36.98	42.32	61.39	28.85	41.26	51.50
GFR: 60 mL/min/1.73m ²	105	57.61	26.27	54.86	28.10	143.76	92.78	124.68	81.82	3.81
GFR: > 60 mL/min/1.73m ²	1931	18.86	29.40	19.30	38.38	20.79	30.07	16.84	37.33	66.49

IQR – interquartile range, GFR glomerular filtration rate, SD – standard deviation

Table 3
Bias and accuracy of estimated glomerular filtration rate (eGFR) from the 5-covariate and simplified equations.

5-Covariate	N	Bias				Bias (%)				P30%
		Mean	SD	Median	IQR	Mean	SD	Median	IQR	
Overall	2036	-7.95	29.35	-7.50	33.14	-3.27	30.00	-6.86	28.42	79.86
Age: 6 months	85	4.02	24.05	3.79	18.84	7.30	29.45	4.62	26.39	84.71
Age: 7-12 months	164	0.76	28.14	-1.87	26.98	3.34	30.39	-2.13	25.61	81.71
Age: 13-24 months	213	-12.02	35.30	-14.69	38.39	-6.14	28.24	-11.78	32.61	72.77
Age: 2-12 years	1031	-8.69	28.65	-8.83	33.43	-4.53	26.36	-7.83	27.31	81.96
Age: Females > 12 years	242	-6.07	24.42	-5.71	28.62	-0.95	27.32	-5.51	26.70	82.23
Age: Males > 12 years	301	-12.17	30.92	-10.78	35.12	-5.38	41.68	-9.72	31.53	73.42
GFR: 60 mL/min/1.73m ²	105	14.74	24.72	7.67	17.93	36.89	68.48	20.38	45.07	60.95
GFR: > 60 mL/min/1.73m ²	1931	-9.19	29.08	-9.16	33.12	-5.45	24.58	-7.98	27.68	80.89
Simplified										
Overall	2036	-4.47	33.96	-5.58	37.09	-0.11	34.07	-5.53	33.50	76.33
Age: 6 months	85	17.73	29.97	14.65	22.81	23.90	37.30	16.88	28.49	72.94
Age: 7-12 months	164	13.80	34.25	11.61	27.01	16.24	36.92	10.38	29.14	79.88
Age: 13-24 months	213	3.17	40.26	1.02	46.48	6.70	33.86	1.87	40.60	76.06
Age: 2-12 years	1031	-4.90	32.47	-7.06	35.14	-1.16	30.52	-6.40	29.81	79.53
Age: Females > 12 years	242	-7.23	25.34	-6.51	29.87	-2.32	28.37	-7.36	29.81	81.40
Age: Males > 12 years	301	-22.40	31.02	-22.04	37.87	-15.20	38.90	-19.48	30.31	60.47
GFR: 60 mL/min/1.73m ²	105	14.95	28.53	5.85	19.89	36.68	71.90	14.28	44.71	60.95
GFR: > 60 mL/min/1.73m ²	1931	-5.53	33.92	-6.97	38.13	-2.11	29.46	-6.69	32.78	77.16

IQR – interquartile range, GFR glomerular filtration rate, SD – standard deviation

Table 4

Bias and accuracy of estimated GFR for the external validation cohort.

Bedside Schwartz	N	Bias				Bias (%)				P30%
		Mean	SD	Median	IQR	Mean	SD	Median	IQR	
Overall	570	28.92	40.69	26.22	42.36	31.69	45.44	24.15	44.84	54.56
Age: 6 months	17	67.62	79.48	44.03	34.54	87.34	94.70	77.67	53.97	17.65
Age: 7–12 months	36	59.88	31.48	55.76	38.35	67.06	43.21	59.13	52.71	13.89
Age: 13–24 months	67	44.44	28.22	46.42	36.03	40.46	28.67	42.41	31.26	37.31
Age: 2–12 years	312	31.16	38.66	27.18	37.14	33.28	42.01	25.30	39.83	54.81
Age: Females > 12 years	58	14.46	29.25	11.35	36.94	17.02	29.50	12.71	36.63	70.69
Age: Males > 12 years	80	−4.44	27.92	−9.14	31.65	1.08	39.28	−6.99	30.48	82.50
GFR: 60 mL/min/1.73m ²	37	34.96	28.79	29.03	29.67	77.29	65.61	59.01	52.24	18.92
GFR: > 60 mL/min/1.73m ²	533	28.50	41.38	25.08	44.52	28.53	41.98	22.49	41.75	57.04
Brandt										
Overall	570	26.15	29.48	25.04	35.92	34.42	53.45	23.31	38.87	60.18
Age: 6 months	17	11.98	20.33	18.72	19.54	20.92	24.98	25.40	40.18	64.71
Age: 7–12 months	36	12.63	19.35	13.26	23.78	17.56	26.62	14.08	25.95	80.56
Age: 13–24 months	67	5.33	21.53	6.48	31.61	8.70	24.59	4.82	30.46	86.57
Age: 2–12 years	312	29.77	30.82	28.63	34.07	39.89	61.79	25.59	41.88	55.45
Age: Females > 12 years	58	35.82	26.00	37.77	33.90	42.96	38.99	32.74	43.24	43.10
Age: Males > 12 years	80	31.57	27.39	28.61	31.98	38.89	50.83	24.36	37.31	58.75
GFR: 60 mL/min/1.73m ²	37	64.36	25.40	63.33	22.40	157.08	117.48	129.49	60.79	0.00
GFR: > 60 mL/min/1.73m ²	533	23.50	27.87	22.85	33.66	25.90	31.67	22.06	34.68	64.35
5-Covariate*										
Overall	568	−3.67	28.47	−3.41	32.22	0.89	30.34	−3.51	29.46	81.75
Age: 6 months	17	20.68	50.49	10.26	14.93	28.16	58.40	16.76	19.13	76.47
Age: 7–12 months	36	13.94	23.51	10.38	31.67	18.44	29.82	11.41	36.30	66.67
Age: 13–24 months	67	−4.36	22.17	0.17	30.61	−1.59	20.79	0.20	25.72	92.54
Age: 2–12 years	311	−2.61	28.40	−3.04	30.82	1.85	29.66	−3.23	28.26	81.73

Bedside Schwartz	N	Bias				Bias (%)				P30%
		Mean	SD	Median	IQR	Mean	SD	Median	IQR	
Age: Females > 12 years	58	-8.80	23.94	-7.62	27.26	-4.91	22.24	-5.97	27.02	84.48
Age: Males > 12 years	79	-16.78	24.73	-19.94	34.52	-10.42	30.02	-16.55	25.22	78.75
GFR: 60 mL/min/1.73m ²	37	17.54	19.31	12.33	12.87	40.62	47.14	26.24	25.94	56.76
GFR: > 60 mL/min/1.73m ²	531	-5.15	28.43	-5.12	31.67	-1.88	26.76	-4.83	28.29	83.49
Simplified										
Overall	570	1.06	34.27	-1.06	37.53	5.23	36.31	-0.80	35.83	73.86
Age: 6 months	17	37.16	64.13	22.22	34.41	49.69	75.67	41.97	43.13	41.18
Age: 7-12 months	36	28.19	26.58	26.56	34.88	33.49	34.52	27.15	42.12	55.56
Age: 13-24 months	67	11.88	23.75	13.41	29.65	12.23	22.91	13.79	24.97	80.60
Age: 2-12 years	312	2.73	32.32	0.16	31.66	6.49	33.57	0.12	31.83	79.49
Age: Females > 12 years	58	-10.00	25.65	-9.04	32.84	-6.50	23.57	-9.94	29.27	81.03
Age: Males > 12 years	80	-26.37	25.96	-29.94	34.07	-19.24	31.39	-25.68	24.36	56.25
GFR: 60 mL/min/1.73m ²	37	18.42	22.72	14.08	18.44	41.66	52.42	27.06	41.74	54.05
GFR: > 60 mL/min/1.73m ²	533	-0.14	34.62	-2.41	38.35	2.70	33.54	-2.13	33.36	75.23

* two studies were missing a BUN measurement

IQR – interquartile range, GFR glomerular filtration rate, SD – standard deviation