Precision of Estimating Equations for GFR in Children with a Solitary Functioning Kidney: The KIMONO Study

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Summary

Background and objective Children with a solitary functioning kidney may develop CKD. Although widely used, equations to estimate GFR are not validated in these patients. This study sought to determine the precision of common estimating equations in the KIMONO (KIdney of MONofunctional Origin) cohort.

Design, setting, participants, & measurements Two creatinine-based (estimated GFR [eGFR]-Schwartz, urinary creatinine clearance), two cystatin C–based (eGFR-Zappitelli1, eGFR-CKiD [Chronic Kidney Disease in Children] 1), and two cystatin C/creatinine–based (eGFR-Zappitelli2, eGFR-CKiD2) estimates were compared with the gold standard GFR measured by inulin single injection (GFR-inulin) in 77 children with a solitary functioning kidney (time span of assembly, 2005–2012). Included patients were 1.5–19.8 years of age. Kidney Disease Outcomes Quality Initiative (K/DOQI) classification was compared between GFR-inulin and eGFR methods to analyze misclassification by estimating equations.

Results The eGFR-CKiD2 equation performed best in children with a solitary functioning kidney (mean bias, −0.9 ml/min per 1.73 m²; 95% and 54% of values within ±30% and ±10% of GFR-inulin, respectively). Mean bias for eGFR-Schwartz was 0.4 ml/min per 1.73 m², with 90% and 33% of values within ±30% and ±10% of GFR-inulin, respectively. For all estimates, misclassification in K/DOQI stage ranged from 22% (eGFR-Zappitelli1) to 44% (urinary creatinine clearance) of children.

Conclusions Use of a combined serum cystatin C/creatinine–based equation (eGFR-CKiD2) is recommended to monitor renal function in children with a solitary functioning kidney. When cystatin C is not routinely available, eGFR-Schwartz should be used. Misclassification in K/DOQI-stage remains a caveat for all equations.

Introduction

According to the hyperfiltration hypothesis, a reduction in renal mass results in an ongoing loss of nephrons due to changed intraglomerular hemodynamics (1–3). In the long run, glomerular hyperfiltration will lead to hypertension and (micro)albuminuria and may eventually result in a decrease in GFR.

Children with a solitary functioning kidney (SFK) are a clinically important example of renal mass reduction because they are likely to be exposed to glomerular hyperfiltration for an extended period. Although the hyperfiltration hypothesis has never been confirmed in humans, a recent study indeed demonstrated that 20%–50% of adults with an SFK from childhood required dialysis by age 30 years (4). These results prompted recent recommendations to monitor all patients with an SFK from childhood (5–7), which includes urine analysis, BP measurements, and a determination of GFR as the best overall measurement of renal function.

Unfortunately, a gold standard measurement of GFR by inulin clearance is cumbersome, costly, and therefore not commonly available (8). In daily pediatric care, equations that use creatinine to obtain an estimated GFR (eGFR) have been widely adopted by clinicians, as recommended in the Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines (9). One such equation is the “original” Schwartz formula (eGFR-Schwartz), which uses serum creatinine, height, and an empirical constant (k value). The eGFR-Schwartz was devised in the mid-1970s (10) and was recalibrated in 2009 (11). Another frequently used surrogate measure for GFR is the urinary creatinine clearance (Ccreat), which is based on timed urine collections.

Among others, a major disadvantage of GFR estimation using serum creatinine is the fact that this molecule is not only eliminated by glomerular filtration but also secreted in the proximal tubule. Because tubular secretion of creatinine varies widely and increases with declining GFR (12), the accuracy of the creatinine-based equations is limited when GFR decreases. Furthermore, serum creatinine concentrations are influenced by muscle mass (13), which may hamper the interpretation of serum values in the growing child (14). In addition, timed urine collections...
may be imprecise because of improper urine collection, in particular in children who are not yet fully toilet trained.

The shortcomings of serum creatinine have initiated the search for new endogenous markers for CKD (15). Of these, cystatin C, a serum protein freely filtered by the glomerulus and not secreted or reabsorbed intact in the renal tubule, is the most promising (16). Serum cystatin C is independent of sex, muscle mass, and dietary intake (17) and is indeed a more precise marker for early CKD than is serum creatinine (18). This finding led to the development of eGFR formulas based on serum cystatin C in the last decade (11,19-23). For example, Schwartz et al. recently introduced a multivariate equation that uses height, sex, serum creatinine, cystatin C, and BUN (eGFR-CrCKD [Chronic Kidney Disease in Children] 2) in addition to the univariate original eGFR-Schwartz (23).

Nevertheless, all currently used estimating equations for GFR have been validated only in children with two kidneys. It is well known that the performance of estimating equations depends on the population in which the respective equation was calibrated (24). Furthermore, glomerular hyperfiltration could hypothetically lead to altered renal handling of endogenous markers. In line with this hypothesis, Tan et al. (25) showed that the serum creatinine-based eGFR equations lead to misclassification in the CKD stage in adult uninephric kidney donors (i.e., an example of SFK). Thus, it is important that common estimating equations are validated before being used in children with an SFK.

Therefore, the KIMONO (KIdney of MONofunctional Origin) study examined the precision of six common estimating equations in predicting the gold standard GFR, determined by an inulin single-injection method, in children with an SFK.

Materials and Methods
Study Patients
The study protocol adhered to the principles of the Declaration of Helsinki and was approved by the ethics committee of the VU University Medical Center. Eligible participants were all patients with an SFK known at the Pediatric Renal Center of the VU University Medical Center. Patients participated in the KIMONO study (7), a large cohort study in children with an SFK or underwent GFR estimation during the clearance study, blood was drawn for determining the precision of six common estimating equations in predicting the gold standard GFR, determined by an inulin single-injection method, in children with an SFK.

Measurements
For all study patients, height (m) and weight (kg) were measured and body mass index (kg/m²) was calculated as the weight divided by the height squared. SD scores were calculated on the basis of the Fifth Dutch Growth Study (27).

GFR was measured by the inulin single-injection method, which has been proven to be an accurate method to determine true GFR (GFR-inulin) in children (8). All patients received a single intravenous dose (5000 mg/1.73² m² of body surface area with a maximum dose of 5000 mg) of inulin (Inutest, Fresenius, Bad Homburg, Germany), which was administered within 1 minute. During administration, dedicated nurses assessed for extravasation of inulin, which did not occur in any of the patients included. Serial blood samples were obtained 10, 30, 90, and 240 minutes after injection of inulin. After sampling, blood was centrifuged at 3000 rotations per minute for 10 minutes and serum was stored at −20°C until measurement. Inulin was measured within 14 days using an enzymatic method based on the determination of fructose after acid hydrolysis of inulin as described by Jung et al. (28), with some minor modifications (29). GFR-inulin (ml/min per 1.73² m²) was calculated according to a two-compartmental model with MW/Pharm 3.5 software (Mediware, Groningen, The Netherlands), a pharmacokinetic program using a Bayesian estimate from patient and population data (8).

During the clearance study, blood was drawn for measurement of serum creatinine (mg/dl), which was determined using an enzymatic method (Modular Analytics, Roche Diagnostics, Mannheim, Germany), which is traceable to isotope dilution mass spectrometry (30). The coefficient of variation of the creatinine assay was 2.1% (mean, 1.54 mg/dl; n=21). A calibrator for automated systems (catalog no. 10759350) was used according to the manufacturer’s instructions. In 12 (16%) patients, creatinine was measured by the kinetic Jaffé method and converted to the isotope dilution mass spectrometry standard (IDMS), as described elsewhere (31). Twenty-four-hour urine was collected on the day before measurement. Parents were instructed about urine collection by a dedicated nurse and received a leaflet explaining the technique.

We obtained an extra blood sample for determination of serum cystatin C levels in all children. Immediately after sampling, blood was centrifuged and serum was stored at −20°C until measurement. Cystatin C (mg/L) was measured within one run for all samples using a particle-enhanced immunonephelometric assay (Siemens Healthcare, Marburg, Germany) on a Dade Behring Nephelometer II. The intraassay coefficients of variation of the cystatin C assay were 2.3% (mean, 0.98 mg/L; n=20) and 2.9% (mean, 2.01 mg/L; n=20), respectively. We used the commercially available calibration material PROTr CAL (no. KC770). A serum cystatin C level >0.95 mg/L was considered to be increased.

The following creatinine-based equations were used to calculate GFR (11):
\[
eGFR-\text{Schwartz} (\text{ml/min/1.73m}^2) = 41.3 \times \frac{\text{height (m)}}{\text{serum creatinine (mg/dl)}}
\]

and:

\[
C\text{creat} (\text{ml/min/1.73m}^2) = \frac{\text{urine creatinine (mg/dl)} \times \text{urine volume (ml)}}{\text{serum creatinine (mg/dl)} \times \text{time (hours)} \times 60} \times \frac{1.73}{\text{body surface area (m}^2)}
\]

Cystatin C-based GFR estimates were calculated according to the first Zappitelli formula (20) and the recently improved formula derived from the CKiD study cohort (23):

\[
eGFR-\text{Zappitelli1} (\text{ml/min/1.73m}^2) = 75.94 \times \left(\frac{\text{serum cystatin C (mg/l)}}{10^3}\right)^{1.17}
\]

and:

\[
eGFR-\text{CKiD1} (\text{ml/min/1.73m}^2) = 40.6 \times \left(\frac{\text{1.8}}{\text{serum cystatin C (mg/l)}}\right)^{0.93}
\]

To evaluate equations that combine both serum cystatin C and serum creatinine to estimate GFR, we also tested the second Zappitelli formula (20) and the eGFR-CKiD2 (23):

\[
eGFR-\text{Zappitelli2} (\text{ml/min/1.73m}^2) = 507.76 \times e^{0.3 \times \text{height (m)}} \times \left(\frac{\text{serum cystatin C (mg/l)}}{10^{3.5}}\right) \times \left(\frac{188.4 \times 10^{-3}}{\text{serum creatinine (mg/dl)}}\right)^{0.9}
\]

and:

\[
eGFR-\text{CKiD2} (\text{ml/min/1.73m}^2) = 39.8 \times \left(\frac{\text{height (m)}}{\text{serum creatinine (mg/dl)}}\right)^{0.456}
\]

\[
\times \left(\frac{1.8}{\text{serum cystatin C (mg/l)}}\right)^{0.418}
\]

\[
\times \left(\frac{30}{\text{blood urea nitrogen (mg/dl)}}\right)^{0.079}
\]

\[
\times \left[(1.076)^{\text{male}} \times \left(\frac{\text{height (m)}}{1.4}\right)^{0.179}\right]
\]

On the basis of the results of GFR-inulin, patients were classified according to the National Kidney Foundation–K/DOQI guidelines for CKD (9) as CKD stage 1 (GFR >90 ml/min per 1.73 m²), stage 2 (GFR, 60–89 ml/min per 1.73 m²), stage 3 (GFR, 30–59 ml/min per 1.73 m²), stage 4 (GFR, 15–29 ml/min per 1.73 m²), and stage 5 (GFR <15 ml/min per 1.73 m²).

The K/DOQI classification was compared with the respective classification obtained using the different estimating equations. We considered underestimation of CKD stage (i.e., CKD stage GFR-inulin higher than CKD stage estimating equation) as the most clinically relevant because this implies that the estimating equation would not identify progressed CKD.

**Statistical Analyses**

All analyses were performed using SPSS software, version 18.0 (Chicago, IL). Values are expressed as mean ± SD or as median (interquartile range) for continuous variables and percentages for qualitative variables. Normality of data was determined using normality plots and the Kolmogorov-Smirnov test. For continuous variables, differences between types of SFK were analyzed with the independent samples t test. In case of nonnormality, a logarithmic transformation was performed before analysis. Qualitative variables were compared using the chi-squared test.

Using Bland-Altman analysis (32), we calculated the bias (GFR-inulin – GFR-estimating equation) for all equations and determined the 95% limits of agreement (LOAs) (i.e., mean bias ± 1.96 × SD). In addition, we determined the proportions of eGFR values within ±10% and within ±30% of GFR-inulin for all estimating equations. Underestimation in CKD stage was considered as CKD-stage GFR-inulin – CKD-stage estimating equation ≥1.

Differences were considered to be statistically significant at P < 0.05 for all analyses.

**Results**

**Patient Characteristics**

Seventy-seven children with an SFK (26 [34%] with a congenital SFK and 51 [66%] with an acquired SFK) were included in this study (Table 1). The median age at the time of study was 14.6 (interquartile range, 10.4–17.6; range, 1.5–19.8) years (Table 2). There was a male predominance (n=48 [62%]). Mean height, weight, and body mass index SD scores were within normal ranges for both types of SFK.

**Renal Function in Children with an SFK**

Measures of renal function are displayed in Table 2. In all patients, mean GFR-inulin was 82 ± 24 (range, 23–126) ml/min per 1.73 m². Suplemental Figure 1 presents the distribution of GFR-inulin by age. There was no difference in mean GFR-inulin, eGFR-Zappitelli1, eGFR-Zappitelli2, or eGFR-CKiD1 between SFK types. This was not the case for Ccreat and eGFR-CKiD2, which showed a lower mean eGFR for children with an acquired SFK than for children with a congenital SFK. Furthermore, the acquired SFK group showed a trend toward a lower eGFR-Schwartz than the congenital SFK group (P=0.07).

Comparisons between GFR-inulin and eGFR-Schwartz, Ccreat, eGFR-CKiD1, and eGFR-CKiD2 are presented in Figures 1–4. In addition, comparisons with eGFR-Zappitelli1 and eGFR-CKiD1 are displayed in Supplemental Figures 2 and 3. The performance of all equations is demonstrated by the additional Bland-Altman plots. Furthermore, the mean bias, 95% LOAs, and accuracy for all estimating equations are shown in Table 3. On the basis of the Bland-Altman analysis, eGFR-CKiD2 had the best performance and the smallest range in 95% LOAs (mean bias, −0.9 ml/min per 1.73 m²; 95% LOA, −25.1 to 23.3 ml/min per 1.73 m²). The eGFR-CKiD2 also had the best accuracy,
with 95% of patients within ±30% and 54% within ±10% of GFR-inulin, respectively. In addition, eGFR-Schwartz was significantly more accurate than Ccreat (P=0.01).

**Classification of CKD Stage**

For all patients, CKD stage based on K/DOQI guidelines is displayed in Table 4. Twelve (16%) patients in our cohort had CKD stage ≥3 according to GFR-inulin. Table 4 also shows misclassification of CKD stage for all estimating equations. Misclassification of CKD stage ranged from 22% of patients according to eGFR-Zappitelli1 to 44% of patients according to Ccreat. Misclassification by eGFR-Schwartz occurred in 43% of patients. Underestimation of CKD stage (i.e., CKD-stage (GFR-inulin – CKD-stage estimating equation ≥1) was most frequent with Ccreat (n=27 [36%]) and least frequent with eGFR-CKiD1 (n=8 [10%]). CKD stage was underestimated in 12 (16%) children by eGFR-Schwartz and in 10 (13%) children according to eGFR-CKiD2.

On the basis of overall performance, eGFR-CKiD2 was the most accurate estimating equation and among the best-performing equations regarding correct classification of CKD stage.

**Discussion**

The KIMONO study determined the precision of six commonly used estimating equations for GFR in a large cohort of children with an SFK. Our main finding is that the improved combined serum cystatin C/creatinine/BUN-based equation by Schwartz et al. (eGFR-CKiD2) (23) is the most precise for estimating GFR in children with an SFK. On the basis of these results, we recommend the use of eGFR-CKiD2 in the clinical follow-up of GFR of children with different types of SFK. Furthermore, the widely used eGFR-Schwartz was shown to be superior to Ccreat. However, CKD stage was more frequently misclassified with
eGFR-Schwartz than with the serum cystatin C equations. Therefore, eGFR-Schwartz is a valid alternative in children with an SFK if cystatin C is not available. Finally, although the accuracy was acceptable for most estimates, misclassification of CKD stage was identified with all estimating equations. Therefore, we emphasize that misclassification is an important caveat in estimating GFR in children with an SFK.

The concept that estimating equations might be imprecise for patients with an SFK compared with healthy two-kidney individuals has been supported by several authors (13,25,33). Tan et al. reported that serum creatinine–based GFR estimates in adults within 86 months after living-kidney donation commonly led to misclassification of CKD stage, especially in patients older than age 55 years (25). According to their results, Tan et al. submit that the practice of predicting GFR from eGFR in living donors should be abandoned (25). Pierrat et al. have compared common estimating equations with GFR measured by continuous intravenous infusion of inulin in 30 children with an acquired SFK (13). They found an overestimation of approximately 20 ml/min per 1.73 m² with the original Schwartz formula (14), which is based on age and sex. Contrary to our results, Ccreat in that study did not yield this difference. Unfortunately, the authors did not perform separate correlation analysis for patients with an SFK and did not provide additional Bland-Altman plots, thereby impeding comparison with our results. The present study shows that the recalibrated eGFR-Schwartz accurately estimates GFR for most patients with an SFK. Ccreat, however, overestimates GFR and leads to underestimation of CKD stage. Bland-Altman analysis demonstrates that Ccreat overestimates GFR in individuals with a GFR exceeding approximately 80 ml/min per 1.73 m². We did not observe this in the other equations containing serum creatinine, which implies that incorrect urine collection is the most likely explanation for our finding. Because this problem is widely recognized and underlined in the K/DOQI guidelines (9), we discourage the use of Ccreat to monitor GFR in patients with an SFK.
Wasilewska et al. determined serum cystatin C levels in 36 children with a congenital SFK and no other urinary tract defects (34). Compared with a healthy control group, they found increased serum cystatin C levels in children with an SFK older than age 12 years, whereas the original Schwartz formula yielded normal results. In their cohort, the proportion of SFK patients with an increased serum cystatin C level was similar to that in our study (44% vs. 35%, respectively). Recently, Peco-Antić et al. demonstrated that serum cystatin C is a good predictor of renal functional reserve capacity in children with a congenital SFK and normal renal function (35).

In our study, equations based on the combination of serum cystatin C and serum creatinine are the most precise estimates for GFR in children with an SFK. This is in accordance with data on children and adults with two kidneys (36,37). All these results indicate that cystatin C is a promising "early" marker for CKD in children with an SFK. Nevertheless, differences in calibration of various cystatin C assays hamper the universal use of serum cystatin C as renal marker at the moment. We therefore chose the improved CKID and Zappitelli equations for comparison in our study because they had been derived using the Dade Behring nephelometric cystatin C assay. After an initiative by the International Federation of Clinical Chemistry, a uniform calibrator for cystatin C has been developed, which will probably improve the implementation of cystatin C as a marker for pediatric CKD (38). In this light, it would also be interesting to compare cystatin C with novel markers for CKD in patients with an SFK, such as fibroblast growth factor 23, osteopontin, and symmetric dimethylarginine (39,40).

Significant differences between the original reports and this study should be addressed. First, although the GFR in Zappitelli and colleagues’ population was similar to that in our patients with an SFK (mean GFR, 74 ml/min per 1.73 m²) (20), the patients studied by Schwartz et al. had a much lower GFR (41–43 ml/min per 1.73 m²) (11,23).
Because it is well known that the performance of GFR estimation equations is influenced by patient (i.e., GFR in the calibration population vs. application population) and laboratory characteristics (41), the good performance of eGFR-Schwartz as well as the eGFR-CKiD equations in our SFK population is noteworthy.

The most striking difference lies in the gold standard GFR measurement. The Zappitelli equations were calibrated using a constant-infusion iothalamate clearance (20), whereas the updated equations by Schwartz used a single-injection iohexol clearance (11,23). We have used the inulin single-injection method, which has been shown to be accurate for determining true GFR in children and adults (8,42). Inulin was measured by an enzymatic method, which has a lower sensitivity than mass spectrometry measurement and could be biased by cross-reactions with other serum metabolites, such as glucose. Single-injection GFR measurements are hampered by the need for full equilibration of the tracer in the extracellular space after injection, which has to be separated from the decline in concentration reflecting glomerular filtration. This problem is particularly observed at low GFR, where late sampling is essential (43). Indeed, van Rossum et al. demonstrated that the inulin single-injection method used in the present study overestimated GFR by 9.7 ml/min per 1.73 m² compared with continuous infusion inulin clearance (44).

Table 3. Performance of estimating equations compared with GFR based on inulin single-injection method in children with a solitary functioning kidney

<table>
<thead>
<tr>
<th>Equation</th>
<th>Mean Bias (ml/min per 1.73 m²)</th>
<th>95% Limits of Agreement (ml/min per 1.73 m²)</th>
<th>Proportion of eGFR within ±30% of GFR-Inulin (%)</th>
<th>Proportion of eGFR within ±10% of GFR-Inulin (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR-Schwartz</td>
<td>0.4</td>
<td>−35.2 to 36.1</td>
<td>90</td>
<td>33</td>
</tr>
<tr>
<td>Ccreat</td>
<td>−29.9</td>
<td>−96.5 to 36.7</td>
<td>55</td>
<td>14</td>
</tr>
<tr>
<td>eGFR-Zappitelli1</td>
<td>−1.2</td>
<td>−32.9 to 30.5</td>
<td>87</td>
<td>46</td>
</tr>
<tr>
<td>eGFR-Zappitelli2</td>
<td>−2.8</td>
<td>−32.6 to 26.7</td>
<td>90</td>
<td>44</td>
</tr>
<tr>
<td>eGFR-CKiD1</td>
<td>2.3</td>
<td>−27.1 to 31.6</td>
<td>94</td>
<td>46</td>
</tr>
<tr>
<td>eGFR-CKiD2</td>
<td>−0.9</td>
<td>−25.1 to 23.3</td>
<td>95</td>
<td>55</td>
</tr>
</tbody>
</table>

GFR-inulin, GFR based on inulin single-injection method; eGFR-Schwartz, estimated GFR based on serum creatinine; Ccreat, urinary creatinine clearance; eGFR-Zappitelli1, estimated GFR based on serum cystatin C; eGFR-Zappitelli2, estimated GFR based on serum cystatin C and creatinine; eGFR-CKiD1 [Chronic Kidney Disease in Children] 1, estimated GFR based on serum cystatin C; eGFR-CKiD2, estimated GFR based on serum cystatin C, creatinine, and BUN.

Table 4. CKD stage based on Kidney Disease Outcomes Quality Initiative guidelines for GFR-inulin and estimating equations in children with a solitary functioning kidney

<table>
<thead>
<tr>
<th>Equation</th>
<th>CKD Stage</th>
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<tbody>
<tr>
<td></td>
<td>Stage 1 (&gt;90 ml/min per 1.73 m²)</td>
</tr>
<tr>
<td>----------------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td>GFR-inulin</td>
<td>33 (43)</td>
</tr>
<tr>
<td>eGFR-Schwartz</td>
<td>26 (34)</td>
</tr>
<tr>
<td>Ccreat</td>
<td>51 (66)</td>
</tr>
<tr>
<td>eGFR-Zappitelli1</td>
<td>34 (44)</td>
</tr>
<tr>
<td>eGFR-Zappitelli2</td>
<td>32 (42)</td>
</tr>
<tr>
<td>eGFR-CKiD1</td>
<td>21 (27)</td>
</tr>
<tr>
<td>eGFR-CKiD2</td>
<td>32 (42)</td>
</tr>
</tbody>
</table>

Data are presented as number of patients (%). Misclassification is defined as the proportion of patients with an unequal CKD stage between GFR-inulin and the estimating equation. GFR-inulin, GFR based on inulin single-injection method; eGFR-Schwartz, estimated GFR based on serum creatinine; Ccreat, urinary creatinine clearance; eGFR-Zappitelli1, estimated GFR based on serum cystatin C; eGFR-Zappitelli2, estimated GFR based on serum cystatin C and creatinine; eGFR-CKiD1 [Chronic Kidney Disease in Children] 1, estimated GFR based on serum cystatin C; eGFR-CKiD2, estimated GFR based on serum cystatin C, creatinine, and BUN.
C measurement is not available, eGFR-Schwartz is an acceptable alternative and more precise than creatinine clearance, which should be abandoned. Nevertheless, we emphasize that misclassification of CKD stage remains a pitfall in estimating GFR of children with an SFK and that these patients require a gold standard GFR measurement if knowledge about the exact GFR is clinically indicated.

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Disclosures

None.

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