Applicability of estimating glomerular filtration rate equations in pediatric patients: comparison with a measured glomerular filtration rate by iohexol clearance

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Estimating glomerular filtration rate (eGFR) has become popular in clinical medicine as an alternative to measured GFR (mGFR), but there are few studies comparing them in clinical practice. We determined mGFR by iohexol clearance in 81 consecutive children in routine practice and calculated eGFR from 14 standard equations using serum creatinine, cystatin C, and urea nitrogen that were collected at the time of the mGFR procedure. Nonparametric Wilcoxon test, Spearman correlation, Bland-Altman analysis, bias (median difference), and accuracy (P_{15}, P_{30}) were used to compare mGFR with eGFR. For the entire study group, the mGFR was 77.9 ± 38.8 mL/min/1.73 m^2. Eight of the 14 estimating equations demonstrated values without a significant difference from the mGFR value and demonstrated a lower bias in Bland-Altman analysis. Three of these 8 equations based on a combination of creatinine and cystatin C (Schwartz et al. New equations to estimate GFR in children with CKD. J Am Soc Nephrol 2009;20:629–37; Schwartz et al. Improved equations estimating GFR in children with chronic kidney disease using an immunonephelometric determination of cystatin C. Kidney Int 2012;82:445–53; Chehade et al. New combined serum creatinine and cystatin C quadratic formula for GFR assessment in children. Clin J Am Soc Nephrol 2014;9:54–63) had the highest accuracy with approximately 60% of P_{15} and 80% of P_{30}. In 10 patients with a single kidney, 7 with kidney transplant, and 11 additional children with short stature, values of the 3 equations had low bias and no significant difference when compared with mGFR. In conclusion, the 3 equations that used cystatin C, creatinine, and growth parameters performed in a superior manner over univariate equations based on either creatinine or cystatin C and also had good applicability in specific pediatric patients with single kidneys, those with a kidney transplant, and short stature. Thus, we suggest that eGFR calculations in pediatric clinical practice use only a multivariate equation. (Translational Research 2015;165:437–445)

Abbreviations: BUN = blood urea nitrogen; eGFR = estimated glomerular filtration rate; mGFR = measured glomerular filtration rate; Scr = serum creatinine; Scys = serum cystatin C

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AT A GLANCE COMMENTARY

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Background

There are many estimating glomerular filtration rate (GFR) equations used in clinical practice. The bedside CKiD formula, based on creatinine only, is the most widely used formula in children. However, recent studies mainly in adults demonstrated that a combination of creatinine and cystatin C has superior performance. Few studies have evaluated estimating GFR equations in pediatric patients.

Translational Significance

This study translated the field of laboratory medicine for determining kidney function in children into an improved standard of clinical practice, by calculating the accuracy of multiple estimating equations through careful analysis of correlations' accuracy. When applied in 2 special populations, we found 3 equations to remain robust when compared with measured GFR.

INTRODUCTION

The glomerular filtration rate (GFR) is considered the best overall index of kidney function in health and disease. Thus, accurate measured GFR (mGFR) plays an important role in the clinical management of various diseases, both intrinsic to the kidney and with other diseases in which altered kidney function may influence the use of therapeutic agents, for example. More than 80% of clinical laboratories now report an estimating GFR (eGFR) when serum creatinine (Scr) is measured.[1] However, in recent years there are many studies that have shown that eGFR equations using additional markers of filtration, such as cystatin C, are superior to conventional equations based on Scr alone.[2,3] These equations were tested mainly in adult patients with chronic kidney disease (CKD), whereas only a few studies have evaluated performance of eGFR equations in pediatric CKD outside a research setting.

The most popular equation currently used in children is the 2009 Schwartz formula, which is based on Scr.[4] Despite standardization of Scr assays, eGFR remains relatively imprecise owing to variation in non-GFR determinants of Scr.[5] This equation does not differentiate between gender, despite the known gender difference in linear height and Scr concentrations, beginning in early adolescence. Thus, such anthropometric disparities result in a considerable variation in muscle mass and may be a dominant factor in eGFR differences.[6] Some studies in children have demonstrated that the inclusion of serum cystatin C (Scys) in the estimating equation increases the correlation with the mGFR than Scr alone.[7,8]

We compared 14 published eGFR equations against a gold standard mathematical model for mGFR from iohexol blood clearance[9] to guide clinicians in optimal eGFR determinations in a diverse group of children with possible kidney dysfunction. We hypothesized that the complex equation using gender, height, Scr, and Scys may be highly predictive of mGFR.

METHODS

Study design and data. This study was conducted at the Ann and Robert H. Lurie Children's Hospital of Chicago, Illinois (Lurie Children's), from November 2012 to January 2014. We used a single cross-sectional data set from 81 consecutive outpatients in which iohexol-based mGFR was calculated, based on the model used by Schwartz et al from the Chronic Kidney Disease in Children (CKiD) study,[9] and for which we are a participating center. At the time of the patient's mGFR study, additional data collected included Scr, Scys, blood urea nitrogen, visit date, anthropometrics, and demographics. We calculated height-for-age *Z*-score according to the United States Centers for Disease Control standards of recumbent length *Z*-scores, birth to 24 months, and stature *Z*-scores, 2–20 years in centimeters, by gender and age.[10] Fourteen eGFR equations were included and their respective values for 81 patients were compared against the mGFRs. This retrospective study was approved by the Lurie Children's Hospital of Chicago Institutional Review Board.

Laboratory analyses. We measured iohexol in serum by a validated liquid chromatography tandem mass spectroscopy method from 4 serial blood samples collected at 10, 30, 120, and 300 minutes postiohexol injection with the clearance calculated using the concentration of iohexol as a function of time in 2 curves (fast and slow plasma disappearance).[9] Scr was measured using an isotope-dilution mass spectrometry (IDMS)-traceable enzymatic method on the Roche Cobas 6000, following the Food and Drug Administration cleared procedure for Roche or Hitachi Cobas C systems. Blood urea nitrogen and cystatin C were analyzed in serum on the Roche Cobas 6000, following the Food and Drug Administration cleared procedures for Roche or Hitachi Cobas C systems. The cystatin C method on the Roche Cobas 6000 uses an automated particle-enhanced immunoturbidimetric assay (PETIA).