Estimating Glomerular Filtration Rate in Kidney Transplantation: Is the New Chronic Kidney Disease Epidemiology Collaboration Equation Any Better?

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BACKGROUND: The new Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was developed to address the systematic underestimation of the glomerular filtration rate (GFR) by the Modification of Diet in Renal Disease (MDRD) Study equation in patients with a relatively well-preserved kidney function. The performance of the new equation for kidney transplant recipients (KTRs) is unknown.

METHODS: We used the plasma clearance of 99mTc–diethylenetriamine pentaacetic acid to measure the GFR in a cohort of 207 stable KTRs and estimated the GFR with the new CKD-EPI equation.

RESULTS: The mean bias for the CKD-EPI equation of –4.5 mL·min⁻¹·(1.73 m²)⁻¹ was lower than that of the 4-variable MDRD Study equation; however, the 2 equations showed similar variation of individual biases around the mean or median bias, so that only modest improvement was seen in the overall percentage of GFR estimates within 30% of the measured GFR (84% vs 77% for the CKD-EPI vs MDRD Study equations, respectively). In the cohort with a GFR >60 mL·min⁻¹·(1.73 m²)⁻¹ (n = 98), the CKD-EPI bias was much less than that of the MDRD Study equation [–7.4 mL·min⁻¹·(1.73 m²)⁻¹ vs –14.3 mL·min⁻¹·(1.73 m²)⁻¹], and an accuracy of ±30% was seen for 89% of GFR estimates, compared with 77% with the MDRD Study equation. The variation of the individual biases around the mean bias remained substantial [SD = 13.7 mL·min⁻¹·(1.73 m²)⁻¹].

CONCLUSIONS: The CKD-EPI equation shows improved estimation ability, and we recommend that it replace the MDRD Study equation as the currently preferred creatinine-based estimating equation for KTRs. The precision of GFR estimates obtained with the CKD-EPI equation remains suboptimal, however, and we recommend that research on other markers of GFR, such as cystatin C and β-trace protein, be pursued.

The serum creatinine concentration remains the most common measure of graft function in kidney transplantation; however, it is affected by a variety of factors independent of the glomerular filtration rate (GFR), thus limiting its predictive ability. Various creatinine-based equations have been developed in an attempt to improve the estimation of GFR from the serum creatinine concentration. In kidney transplantation, the equations most commonly used are the Modification of Diet in Renal Disease (MDRD) Study equation, the Cockcroft–Gault equation, and the Nankivell equation (see Table 1 in the Data Supplement that accompanies the online version of this Brief Communication at http://www.clinchem.org/content/vol56/issue3). Only the Nankivell equation was derived from kidney transplant recipients (KTRs). Because these equations for estimating GFR have low accuracy and poor precision, none are ideal for use in the kidney transplant population.

One of the most important shortcomings of the MDRD Study equations has been the systematic underestimation of GFR in patients with a relatively well-preserved kidney function. We and others have shown this shortcoming also to hold true in KTRs. The new Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation proposed recently by Levey and colleagues introduces a “correction” or spline term for patients with low creatinine values. Four percent of the CKD-EPI derivation cohort consisted of organ transplant recipients. The equation showed improved performance compared with the 4-variable MDRD Study equation, primarily in nontransplantation patients with high GFR values. Performance data for the subgroup with kidney transplants were not provided. The current study sought to determine the performance of the novel CKD-EPI equation in a population of stable adult KTRs.

5 Nonstandard abbreviations: GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; KTR, kidney transplant recipient; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; 99mTc–DTPA, 99mTc–diethylenetriamine pentaacetic acid; IDMS, isotope dilution mass spectrometry.
Materials and Methods

STUDY POPULATION
Adult KTRs who had stable graft function followed at the Ottawa Hospital for >6 months were eligible for this study. The Ottawa Hospital Research Ethics Board approved the study.

LABORATORY ASSESSMENT
The plasma clearance of $^{99m}$Tc–diethylenetriamine pentaacetic acid ($^{99m}$Tc-DTPA) was used to measure GFR, as previously described (8). On the day of $^{99m}$Tc-DTPA GFR measurement, serum creatinine was measured by means of the modified Jaffé reaction on a Beckman Coulter LX20 PRO Clinical System and with the manufacturer’s reagents. The CV for serum creatinine was 4.9% at 0.6 mg/dL (55 μmol/L), 1.7% at 1.7 mg/dL (150 μmol/L), and 1.3% at 6.8 mg/dL (600 μmol/L).

ANALYSIS
GFR was estimated with the 4-variable MDRD Study equation (3), the reexpressed MDRD Study equation (11), and the CKD-EPI equation (10) (see Table 1 in the online Data Supplement). For the 4-variable MDRD Study equation, creatinine values were calibrated with the Cleveland Clinic (11, 12). In brief, 50 Ottawa Hospital samples (creatinine concentration range, 53–354 μmol/L) were sent to the Cleveland Clinic laboratory. The calibrated creatinine concentration was calculated as follows: 1.076 × (Ottawa Hospital serum creatinine) − 7.35 μmol/L. For the reexpressed MDRD Study and CKD-EPI equations, creatinine values were adjusted to the isotope dilution mass spectrometry (IDMS) standard (11, 13). Fifty Ottawa Hospital samples (range, 35–500 μmol/L) were analyzed with the “old” calibrators (not referenced to IDMS) and then reanalyzed with set points obtained from the instrument manufacturers that would give IDMS-compatible results. The following regression equation was obtained: IDMS creatinine = 0.990 × (Ottawa Hospital serum creatinine) − 6.02 μmol/L.

The performance of the prediction equations was determined by calculating the bias, precision, and accuracy as recommended (14). Bias was calculated by subtracting the measured GFR value from the estimated GFR; thus, a negative bias indicates that the prediction equation underestimates the GFR. Precision, a measure of the dispersion of the individual biases around the median or mean bias, was defined as the interquartile range (the difference between the 75th and 25th percentiles) of the median bias and as the SD of the mean bias (10, 14). Accuracy, which reflects both bias and precision, was defined as the percentage of GFR estimates lying within 30% of the measured GFR values (14). The analysis was repeated after stratifying patients by a measured GFR cutoff of 60 mL·min$^{-1}$·(1.73 m$^2$)$^{-1}$. Differences in equation bias and accuracy were assessed with a paired t-test or a McNemar test as appropriate.

Results

Table 2 in the online Data Supplement shows the baseline characteristics of the study population (n = 207). The majority (92%) were white, 64% were male, and 19% were taking trimethoprim-sulfamethoxazole. The mean (SD) measured GFR was 58 (22) mL·min$^{-1}$·(1.73 m$^2$)$^{-1}$. All 5 stages of chronic kidney disease are represented (14).

EQUATION PERFORMANCE
Table 1 shows the performance of the estimation equations in the whole cohort and in the 2 subgroups. Overall, the mean bias for the new equation was much lower [−4.5 mL·min$^{-1}$·(1.73 m$^2$)$^{-1}$] than for the 4-variable MDRD Study equation and the reexpressed MDRD Study equation [−9.3 mL·min$^{-1}$·(1.73 m$^2$)$^{-1}$ and −8.0 mL·min$^{-1}$·(1.73 m$^2$)$^{-1}$, respectively; P < 0.001 for both comparisons]. There were no significant differences between the equations in precision (the dispersion of the individual biases around the mean or median bias). The percentage of estimated GFRs within 30% of the measured GFR was significantly higher with the CKD-EPI equation than with the 4-variable MDRD Study equation (84% vs 77%; P = 0.02), but not compared with the reexpressed MDRD Study equation (84% vs 79%; P = 0.07).

In the lower-GFR subgroup, the CKD-EPI mean bias was only −1.9 mL·min$^{-1}$·(1.73 m$^2$)$^{-1}$, which was significantly less than that of the 4-variable MDRD Study equation and the reexpressed MDRD Study equation [−4.9 mL·min$^{-1}$·(1.73 m$^2$)$^{-1}$ and −3.8 mL·min$^{-1}$·(1.73 m$^2$)$^{-1}$, respectively; P < 0.0001 for both comparisons]. The accuracy within 30% obtained with the CKD-EPI equation was not significantly higher than that obtained with the 4-variable MDRD Study equation (79% vs 78%; P = 0.8) or the reexpressed MDRD Study equation (79% vs 80%; P = 0.76).

As expected, the CKD-EPI mean bias obtained in the higher-GFR cohort [−7.4 mL·min$^{-1}$·(1.73 m$^2$)$^{-1}$] was significantly lower than that obtained with the 4-variable MDRD Study equation and with the reexpressed MDRD Study equation [−14.3 mL·min$^{-1}$·(1.73 m$^2$)$^{-1}$ and −12.6 mL·min$^{-1}$·(1.73 m$^2$)$^{-1}$, respectively; P < 0.0001 for both comparisons]. In this cohort, the accuracy within 30% obtained with the CKD-EPI equation was significantly higher than that obtained with the 4-variable MDRD Study equation (89% vs 77%; P = 0.003) and with the reexpressed...
was similar to that of the original study cohort has been observed in the CKD-EPI external validation bias and accuracy in the high-GFR group parallel what the new CKD-EPI equation in KTRs. The improved accuracy, precision was worse compared to the MDRD Study equation (89% vs 79%; P = 0.008). Despite the improved accuracy, precision was worse compared with the lower-GFR subgroup, and there were no differences between the prediction equations.

**Discussion**

This study is the first to examine the performance of the new CKD-EPI equation in KTRs. The improved bias and accuracy in the high-GFR group parallel what has been observed in the CKD-EPI external validation cohort (10). The suboptimal precision in our analysis was similar to that of the original study (10) and likely reflects the non-GFR determinants of serum creatinine that are not adequately captured by the variables contained within the equations. The absolute differences in bias and precision between the CKD-EPI validation cohort and our study are likely due to a variety of causes, including inherent differences in patient populations, the use of medications in KTRs that affect creatinine secretion (such as trimethoprim-sulfamethoxazole, 19% of this cohort), and potential differences in GFR measurement and creatinine calibration, despite rigorous efforts to minimize such differences.

The strengths of this study include appropriate serum creatinine calibration and the use of a reference-standard technique to measure GFR. A major limitation of our analysis was the lack of black patients, as well as other ethnic groups.

The new CKD-EPI equation represents a modest improvement over the 4-variable and reexpressed MDRD Study equations. The overall improvement in bias and accuracy will improve GFR estimation in the kidney transplant population, especially patients in the higher GFR range. Precision remains suboptimal, however, and as with other creatinine-based equations, this feature will limit the value of the CKD-EPI equation for monitoring changes in kidney function over time.

Serum creatinine remains the most widely used laboratory test in clinical practice for monitoring kidney function, and thus GFR estimates based on creatinine concentration will continue to be used until better endogenous markers become readily available. Because the CKD-EPI equation represents an improvement over the MDRD Study equation, we recommend that it be preferentially used when estimating the GFR in KTRs. This recommendation, however, does not preclude the continued search for better predictors of GFR, such as cystatin C, β-trace protein, or combinations of these analytes (15–17). Although the CKD-EPI equation currently yields the most accurate creatinine-based estimate of GFR in the context of kidney transplantation, it is still not sufficient when a precise estimate of GFR is required, such as in the setting of a clinical trial (18).

**Table 1. Bias, precision, and accuracy of GFR prediction equations.a**

<table>
<thead>
<tr>
<th>Equation</th>
<th>Median bias</th>
<th>Precision (IQR)</th>
<th>Mean bias</th>
<th>Precision (SD)</th>
<th>Accuracy within 30% (95% CI), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole cohort (n = 207)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-Variable MDRD Study</td>
<td>−8.2</td>
<td>14.5</td>
<td>−9.3</td>
<td>12.1</td>
<td>77 (71–82)</td>
</tr>
<tr>
<td>Reexpressed MDRD Study</td>
<td>−7.4</td>
<td>14.4</td>
<td>−8.0</td>
<td>12.1</td>
<td>79 (73–84)</td>
</tr>
<tr>
<td>CKD-EPI</td>
<td>−5.2</td>
<td>15.7</td>
<td>−4.5</td>
<td>12.6</td>
<td>84 (78–88)</td>
</tr>
<tr>
<td>GFR &lt;60 mL·min⁻¹·(1.73 m²)⁻¹ (n = 109)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-Variable MDRD Study</td>
<td>−4.8</td>
<td>11.8</td>
<td>−4.9</td>
<td>9.0</td>
<td>78 (69–85)</td>
</tr>
<tr>
<td>Reexpressed MDRD Study</td>
<td>−4.0</td>
<td>11.6</td>
<td>−3.8</td>
<td>9.1</td>
<td>80 (71–86)</td>
</tr>
<tr>
<td>CKD-EPI</td>
<td>−2.1</td>
<td>12.3</td>
<td>−1.9</td>
<td>11.1</td>
<td>79 (70–85)</td>
</tr>
<tr>
<td>GFR &gt;60 mL·min⁻¹·(1.73 m²)⁻¹ (n = 98)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>4-Variable MDRD Study</td>
<td>−15.4</td>
<td>15.7</td>
<td>−14.3</td>
<td>13.2</td>
<td>77 (67–84)</td>
</tr>
<tr>
<td>Reexpressed MDRD Study</td>
<td>−14.0</td>
<td>15.8</td>
<td>−12.6</td>
<td>13.3</td>
<td>79 (69–86)</td>
</tr>
<tr>
<td>CKD-EPI</td>
<td>−8.2</td>
<td>17.9</td>
<td>−7.4</td>
<td>13.7</td>
<td>89 (81–94)</td>
</tr>
</tbody>
</table>

a Bias was defined as the difference between the estimated and measured (with 99mTc-DTPA) GFR values (i.e., estimated GFR − measured GFR). Precision (variation in the individual biases around the mean or median bias) was defined as the interquartile range (IQR) for the median bias and as the SD for the mean bias. Both precision and bias are expressed as mL·min⁻¹·(1.73 m²)⁻¹. Values for accuracy, which was defined as the percentage of estimates that were within 30% of the measured GFR, are presented with the 95% CI.

**Author Contributions:** All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

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References