should be investigated because fecolith potentially is associated with colonic perforation.

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Acknowledgements

We thank Drs Yuki Tanaka and Masato Wakabayashi for patient care and Mr Seitaro Isobe for managing medical information retrieval.

Financial Disclosure: The authors declare that they have no relevant financial interests.

Supplementary Material

Item S1: Fecalith formation in the cecum.

Note: The supplementary material accompanying this article (http://dx.doi.org/10.1053/j.ajkd.2014.01.424) is available at www.ajkd.org

References


Originally published online March 6, 2014. © 2014 by the National Kidney Foundation, Inc. http://dx.doi.org/10.1053/j.ajkd.2014.01.424

RESEARCH LETTERS

External Validation of the Berlin Equations for Estimation of GFR in the Elderly

To the Editor:

Chronic kidney disease prevalence increases markedly with age1 and accurate estimation of GFR is an important issue in older people. The Chronic Kidney Disease Epidemiology Collaboration creatinine equation (CKD-EPIcys)2 and variations including cystatin C (CKD-EPIcys)3 or both creatinine and cystatin C (CKD-EPIcr-cys)3 have been recommended for estimating GFR.4 Recently, the Berlin Initiative Study (BIS) reported 2 GFR equations specifically developed in older people: BIS1, which uses creatinine, and BIS2, which uses both creatinine and cystatin C.2 Here, we compare how the BIS and CKD-EPI equations perform in a large cohort of older people.

The methods have been described previously (Item S1).6 GFR was measured in 394 white people 74 years or older by plasma iothexol clearance and estimated using the CKD-EPI2,3 and BIS6 equations. Median age was 80 (range, 74-97) years; 48% were men, 19% had diabetes, and 55% had hypertension. Median mGFR was 53.4 (7.2-100.9) mL/min/1.73 m2. Plasma creatinine and iothexol were measured simultaneously using isotope-dilution mass spectrometry. Serum cystatin C was measured by immunoassay. Data were analyzed using Analyse-it and Stata, version 12.0.

The BIS equations underestimated and the CKD-EPIcys, and CKD-EPIcr-cys, equations overestimated GFR; the CKD-EPIcys equation was unbiased (Table 1). Both BIS equations showed increasing negative bias against mGFR at higher GFRs (Fig 1). The BIS1 and BIS2 equations were more accurate (higher $P_{30}$) than the CKD-EPIcys and CKD-EPIcr-cys equations, respectively. Although the BIS equations achieved high sensitivity for detection of GFR < 60 mL/min/1.73 m2, specificity was poor compared with the CKD-EPI equations. In general, in those with GFR < 60 mL/min/1.73 m2, biases tended to be mitigated, whereas for mGFR ≥ 60 mL/min/1.73 m2, the respective biases for all equations were exaggerated (Table S1). Similar trends in equation performance were seen whether individuals were older or younger than 80 years (Table S2). Misclassification errors were consistent with the biases of the equations: the negatively biased BIS equations were more likely to wrongly classify individuals as having GFR < 60 mL/min/1.73 m2 and less likely to wrongly classify individuals as having GFR ≥ 60 mL/min/1.73 m2. For all equations, misclassification errors appeared worse for individuals younger than 80 years (Fig 1).

Whereas we previously reported reasonable overall performance of the CKD-EPI equations among the elderly,6 Schaeffner et al observed significant positive bias for the CKD-EPIcys equation. They reported $P_{30}$ of 78% for the CKD-EPIcys equation, with the earlier 2008 CKD-EPIcys and CKD-EPIcr-cys equations’ achieving $P_{30}$ values of 89% and 81%, respectively (the 2012 CKD-EPIcys and CKD-EPIcr-cys equations were not studied). In their analysis, the BIS1 and BIS2 equations were unbiased against mGFR and achieved $P_{30}$ values of 95% and 96%, respectively.2 We used our data from a large elderly cohort with international standardized creatinine and cystatin C measurements together with reference GFR assessment to independently validate the BIS equations. Although the BIS equations were negatively biased compared to mGFR, especially in those with GFR ≥ 60 mL/min/1.73 m2, they demonstrated good precision and $P_{30}$ values. Total misclassification errors did not differ markedly between the BIS and CKD-EPI equations and were similar to those originally reported.2 Misclassification errors for all equations appeared lower for equations incorporating cystatin C.

Of some concern, misclassification errors were higher among individuals younger than 80 years. The BIS equations also had increasing negative bias at higher GFRs. Both these factors could suggest that the equations are unlikely to be readily translatable to younger populations with more preserved kidney function.

The $P_{30}$ values we observed for the BIS equations were slightly lower than those originally reported.3 It is common for equations to perform less well outside the cohorts in which they were developed for reasons including case-mix and study design, although there are strong similarities between the present study and that of the BIS group. There have been few other published evaluations. A study of French white individuals older than 70 years found the BIS1 equation to perform better than the CKD-EPIcys equation.7 BIS1 was also superior to CKD-EPIcys for older Chinese, although overall performance was disappointing ($P_{30} = 63$%).7 A recent evaluation of BIS2 among 95 older predominantly white Brazilians found it to be slightly more negatively biased than the CKD-EPIcr-cys equation, with roughly equivalent precision.8

In conclusion, we have demonstrated good performance of the BIS equations in an independent external validation cohort including a large number of older people drawn from secondary care and the community and with comorbidity and pharmacotherapy typical of such populations in the Western world. Whether their advantages may outweigh the practical difficulties of using different equations in different age groups remains open to question.
Table 1. Performance of the GFR Estimating Equations Compared to Measured GFR

<table>
<thead>
<tr>
<th></th>
<th>eGFR</th>
<th>Bias (95% CI)</th>
<th>Precision (95% CI)</th>
<th>Accuracy: P30 (95% CI)</th>
<th>Accuracy: RMSE* (95% CI)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Wrongly Considered to Have GFR &lt; 60</th>
<th>Wrongly Considered to Have GFR ≥ 60</th>
<th>Total Misclassified</th>
</tr>
</thead>
<tbody>
<tr>
<td>BIS1</td>
<td>49.5 [16.1 to 106.0]</td>
<td>-3.6 (-4.5 to -2.7)  ( P_1 &lt; 0.001, P_2 &lt; 0.001 )</td>
<td>11.3 (9.8 to 12.8)</td>
<td>88 (84 to 91)  ( P_4 = 0.01 )</td>
<td>10.0 (9.2 to 10.7)</td>
<td>95.3</td>
<td>63.8</td>
<td>58 (14.7)</td>
<td>11 (2.8)</td>
<td>69 (17.5)</td>
</tr>
<tr>
<td>BIS2</td>
<td>51.5 [16.6 to 94.0]</td>
<td>-2.7 (-3.3 to -2.0)  ( P_1 &lt; 0.001, P_3 &lt; 0.001 )</td>
<td>8.5 (7.4 to 9.6)</td>
<td>94 (91 to 96)  ( P_5 &lt; 0.001 )</td>
<td>8.3 (7.5 to 9.0)</td>
<td>97.0</td>
<td>71.9</td>
<td>45 (11.4)</td>
<td>7 (1.8)</td>
<td>52 (13.2)</td>
</tr>
<tr>
<td>CKD-EPIcr</td>
<td>57.0 [12.0 to 98.2]</td>
<td>2.3 (1.3 to 3.4)  ( P_1 &lt; 0.001 )</td>
<td>13.1 (11.7 to 14.6)</td>
<td>83 (79 to 87)  ( P_6 &lt; 0.001 )</td>
<td>10.9 (10.0 to 11.7)</td>
<td>83.7</td>
<td>86.9</td>
<td>21 (5.3)</td>
<td>38 (9.6)</td>
<td>59 (14.5)</td>
</tr>
<tr>
<td>CKD-EPIcys</td>
<td>55.2 [13.6 to 98.7]</td>
<td>-0.1 (-1.1 to 1.0)  ( P_1 = 0.9 )</td>
<td>14.2 (12.5 to 15.9)</td>
<td>86 (82 to 89)  ( P_7 &lt; 0.001 )</td>
<td>10.5 (9.6 to 11.4)</td>
<td>88.9</td>
<td>85.6</td>
<td>23 (5.8)</td>
<td>26 (6.6)</td>
<td>49 (12.4)</td>
</tr>
<tr>
<td>CKD-EPIcr-cys</td>
<td>56.1 [12.5 to 102.1]</td>
<td>1.2 (0.2 to 2.2)  ( P_1 = 0.02 )</td>
<td>12.7 (11.5 to 13.9)</td>
<td>86 (82 to 90)  ( P_8 &lt; 0.001 )</td>
<td>9.8 (9.0 to 10.5)</td>
<td>87.2</td>
<td>87.5</td>
<td>20 (5.1)</td>
<td>30 (7.6)</td>
<td>50 (12.7)</td>
</tr>
</tbody>
</table>

Note: Unless otherwise indicated, values shown as median [range] or number (percentage). Wilcoxon matched pairs signed rank test was used to compare the bias of each of the GFR estimates versus mGFR \( (P_1) \); of BIS1 versus CKD-EPIcr \( (P_2) \); and of BIS2 versus CKD-EPIcr-cys \( (P_3) \). McNemar test was used to compare P30 of BIS1 versus CKD-EPIcr \( (P_4) \); and of BIS2 versus CKD-EPIcr-cys \( (P_5) \). Some data for the CKD-EPI equation have been published previously\(^6\) but are shown here for comparison.

Abbreviations and definitions: CI, confidence interval; e/mGFR, estimated/measured glomerular filtration rate (in mL/min/1.73 m\(^2\)); P30, percentage of estimates within 30% of mGFR; bias, median difference (eGFR - mGFR); precision, interquartile range of the difference; RMSE, root mean square error.

*Calculated on the raw GFR scale.
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Acknowledgements

We thank the staff of Clinical Biochemistry and The Kent Kidney Care Centre, East Kent Hospitals University NHS Foundation Trust for cooperation and help. The study received statistical advice at the proposal stage from Drs A. Laurence and E. Bassett of the Institute of Mathematics, Statistics and Actuarial Science, University of Kent. Mr Paul Bassett (Statsconsultancy Ltd) helped with the data analysis.

Support: We acknowledge the support of the National Institute for Health Research (NIHR), which commissioned this independent research through the Comprehensive Clinical Research Network (Research for Patient Benefit Programme, grant PB-PG-0107-12073). The views expressed are those of the authors and not necessarily those of the National Health Service, the NIHR, or the Department of Health.

Financial Disclosure: The authors declare that they have no other relevant financial interests.

Supplementary Material

Table S1: Performance of the GFR estimating equations vs mGFR, stratified by GFR.
Table S2: Performance of the GFR estimating equations vs mGFR, stratified by age and GFR.
Item S1: Detailed methods and analysis.
Note: The supplementary material accompanying this article (http://dx.doi.org/10.1053/j.ajkd.2014.01.013) is available at www.ajkd.org

References


Received September 17, 2013. Accepted in revised form January 1, 2014. Originally published online February 14, 2014. © 2014 by the National Kidney Foundation, Inc. http://dx.doi.org/10.1053/j.ajkd.2014.01.013

External Validation of the BIS (Berlin Initiative Study)-1 GFR Estimating Equation in the Elderly

To the Editor:

Evaluating glomerular filtration rate (GFR) in the elderly is key to the diagnosis and management of CKD, which is highly prevalent in this population.1 Accurate GFR assessment is particularly important for drug dose adaptation.2 The most recent KDIGO guideline recommended using the CKD Epidemiology Collaboration (CKD-EPI) equation3 for estimating GFR unless another equation has proved more accurate in a specific population.4 Therefore, this equation is now widely used; however, it was not specifically designed for elderly patients and there were only 219 patients older than 70 years in the development cohort. The precision of GFR estimation remains an issue in the elderly.5-7 Recently, the BIS1 equation was developed in white German patients 70 years or older1 and validated in a 332-patient Chinese cohort9 and 224 white patients.10 The BIS1 equation must be externally validated in large cohorts including CKD patients before it can be routinely implemented. We evaluated the performance of the BIS1 equation (vs the CKD-EPI equation) in a large cohort of elderly patients.

Between January 2007 and September 2013, data from all patients referred to Bichat and Tenon hospitals for GFR measurement and 70 years or older were collected. Kidney transplant recipients were excluded. Patients gave their consent for scientific use of anonymous data. Data from 486 of the 609 patients are part of a previous publication before the BIS1 equation was available.7 Urinary clearance of 51Cr-EDTA was determined from 6 consecutive 30-minute clearance periods after a single intravenous bolus injection. When proper urine samples could not be obtained, 51Cr-EDTA plasma clearance was calculated, as previously described.11 Plasma creatinine was measured with an enzymatic method and standardized to isotope-dilution mass spectrometry. GFR was estimated with the CKD-EPI and BIS1 equations.

Participants had a mean age of 75.9 ± 4.4 years; mean mGFR was 40.6 ± 16.8 mL/min/1.73 m² and decreased with age (Table 1). As defined by GFR < 60 mL/min/1.73 m² and/or by albuminuria or other kidney disease marker, 95% of patients had CKD. In the entire population, median biases and overall accuracy (P < 0.001; Table 2; Fig S1). Between January 2007 and September 2013, data from all patients referred to Bichat and Tenon hospitals for GFR measurement and 70 years or older were collected. Kidney transplant recipients were excluded. Patients gave their consent for scientific use of anonymous data. Data from 486 of the 609 patients are part of a previous publication before the BIS1 equation was available.7 Urinary clearance of 51Cr-EDTA was determined from 6 consecutive 30-minute clearance periods after a single intravenous bolus injection. When proper urine samples could not be obtained, 51Cr-EDTA plasma clearance was calculated, as previously described.11 Plasma creatinine was measured with an enzymatic method and standardized to isotope-dilution mass spectrometry. GFR was estimated with the CKD-EPI and BIS1 equations.

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All equations developed to estimate creatinine clearance or GFR have incorporated age with different mathematical models. However, because their development cohorts included few old patients,

Table 1. Baseline Characteristics of Patients

<table>
<thead>
<tr>
<th></th>
<th>All (N = 609)</th>
<th>70-75 y (n = 283)</th>
<th>75-80 y (n = 203)</th>
<th>80-85 y (n = 99)</th>
<th>85-90 y (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African origin</td>
<td>29 (4.8)</td>
<td>15 (5.3)</td>
<td>11 (5.4)</td>
<td>2 (2.0)</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>75.9 ± 4.4</td>
<td>72.2 ± 1.4</td>
<td>77.0 ± 1.3</td>
<td>81.8 ± 1.4</td>
<td>86.6 ± 1.6</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27.6 ± 4.9</td>
<td>27.5 ± 5.2</td>
<td>28.1 ± 4.9</td>
<td>27.4 ± 4.1</td>
<td>25.4 ± 3.6</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.82 ± 0.22</td>
<td>1.83 ± 0.21</td>
<td>1.81 ± 0.22</td>
<td>1.83 ± 0.19</td>
<td>1.74 ± 0.27</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>73.3 ± 14.8</td>
<td>74.3 ± 15.7</td>
<td>73.5 ± 14.7</td>
<td>71.7 ± 11.8</td>
<td>65.9 ± 13.5</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>1.75 ± 0.76</td>
<td>1.69 ± 0.78</td>
<td>1.78 ± 0.74</td>
<td>1.74 ± 0.61</td>
<td>2.15 ± 1.18</td>
</tr>
<tr>
<td>mGFR (mL/min/1.73 m²)</td>
<td>40.6 ± 16.8</td>
<td>44.1 ± 18.5</td>
<td>39.8 ± 15.6</td>
<td>36.7 ± 12.3</td>
<td>29.3 ± 10.3</td>
</tr>
<tr>
<td>eGFRCKD-EPI (mL/min/1.73 m²)</td>
<td>41.1 ± 17.9</td>
<td>44.5 ± 19.6</td>
<td>39.3 ± 16.5</td>
<td>37.0 ± 14.0</td>
<td>31.8 ± 13.8</td>
</tr>
<tr>
<td>eGFRBIS1 (mL/min/1.73 m²)</td>
<td>39.9 ± 13.3</td>
<td>43.4 ± 14.6</td>
<td>38.2 ± 11.8</td>
<td>35.5 ± 9.6</td>
<td>30.6 ± 9.9</td>
</tr>
<tr>
<td>mGFR &lt; 60 mL/min/1.73 m²</td>
<td>79 (13)</td>
<td>55 (19)</td>
<td>18 (9)</td>
<td>6 (6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>30 &lt; mGFR &lt; 60 mL/min/1.73 m²</td>
<td>359 (59)</td>
<td>162 (58)</td>
<td>123 (60)</td>
<td>63 (64)</td>
<td>11 (46)</td>
</tr>
<tr>
<td>mGFR &lt; 30 mL/min/1.73 m²</td>
<td>171 (28)</td>
<td>66 (23)</td>
<td>62 (31)</td>
<td>30 (30)</td>
<td>13 (54)</td>
</tr>
</tbody>
</table>

Note: Data are expressed as mean ± SD or number (percentage). Patients not of African origin were white. BSA was calculated as (weight in kg) × (height in cm/3,600)0.725. eGFRCKD-EPI = 141 × min(Scr/1, 1)1.094 × 0.996 × 1.018 (if female) × 1.159 (if black); k is 0.7 for females and 0.9 for males, x = 0.269 for females and 0.411 for males, min is the minimum of Scr/k or 1; max is the maximum of Scr/k or 1. eGFRBIS1 = 3.736 × Scr−0.417 × Age0.269 × 0.82 (if female).

*P < 0.001, one-way ANOVA for age group.