should be investigated because fecalith potentially is associated with colonic perforation.[3]

*Noriaki Kurita, MD, FJSIM[1,2]*
*Hirotsugu Uchihara, MD[2]*
[1]Kyoto University, Kyoto, Japan
[2]Mikamikai Yasu Hospital, Shiga, Japan
Corresponding author: kurita_n@opal.plala.or.jp

### 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

1. Muller C, Muller S, Sissoko A, Klein A, Faller B, Chantrel F. Radio-opaque fecal impaction and pseudo-occlusion in a dialyzed patient taking lanthanum carbonate. *Hemodial Int.* 2012;16:556-558.

2. Korzets A, Tsitman I, Lev N, et al. Lanthanum, constipation, bafflying X-rays and a perforated colonic diverticulum. *Clin Kidney J.* 2012;5:331-333.

3. Alaedeen DI, Cook M, Chwals WJ. Appendiceal fecalith is associated with early perforation in pediatric patients. *J Pediatr Surg.* 2008;43:889-892.

# 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 age[1] and accurate estimation of GFR is an important issue in older people. The Chronic Kidney Disease Epidemiology Collaboration creatinine equation (CKD-EPI$_{cr}$)[2] and variations including cystatin C (CKD-EPI$_{cys}$) or both creatinine and cystatin C (CKD-EPI$_{cr-cys}$)[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.[5] 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 iohexol clearance and estimated using the CKD-EPI[2,3] and BIS[5] 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 m$^2$. Plasma creatinine and iohexol 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-EPI$_{cr}$ and CKD-EPI$_{cr-cys}$ equations overestimated GFR; the CKD-EPI$_{cys}$ 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-EPI$_{cr}$ and CKD-EPI$_{cr-cys}$ equations, respectively. Although the BIS equations achieved high sensitivity for detection of GFR < 60 mL/min/1.73 m$^2$, specificity was poor compared with the CKD-EPI equations. In general, in those with GFR < 60 mL/min/1.73 m$^2$, biases tended to be mitigated, whereas for mGFR ≥ 60 mL/min/1.73 m$^2$, 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 m$^2$ and less likely to wrongly classify individuals as having GFR ≥ 60 mL/min/1.73 m$^2$. 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[5] observed significant positive bias for the CKD-EPI$_{cr}$ equation. They reported P$_{30}$ of 78% for the CKD-EPI$_{cr}$ equation, with the earlier 2008 CKD-EPI$_{cys}$ and CKD-EPI$_{cr-cys}$ equations[7] achieving P$_{30}$ values of 89% and 81%, respectively (the 2012 CKD-EPI$_{cys}$ and CKD-EPI$_{cr-cys}$ 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.[5]

We used our data from a large elderly cohort with internationally 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 m$^2$, 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.[5] 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 transferable 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.[5] 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-EPI$_{cr}$ equation.[8] BIS1 was also superior to CKD-EPI$_{cr}$ for elderly Chinese, although overall performance was disappointing (P$_{30}$ = 63%).[9] A recent evaluation of BIS2 among 95 older predominantly white Brazilians found it to be slightly more negatively biased than the CKD-EPI$_{cr-cys}$ equation, with roughly equivalent precision.[10]

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

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

*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-EPI$_{cr}$ ($P_2$); and of BIS2 versus CKD-EPI$_{cr-cys}$ ($P_3$). McNemar test was used to compare $P_{30}$ of BIS1 versus CKD-EPI$_{cr}$ ($P_4$); and of BIS2 versus CKD-EPI$_{cr-cys}$ ($P_5$). 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$^2$); $P_{30}$, percentage of estimates within 30% of mGFR; bias, median difference (eGFR − mGFR); precision, interquartile range of the difference; RMSE, root mean square error.
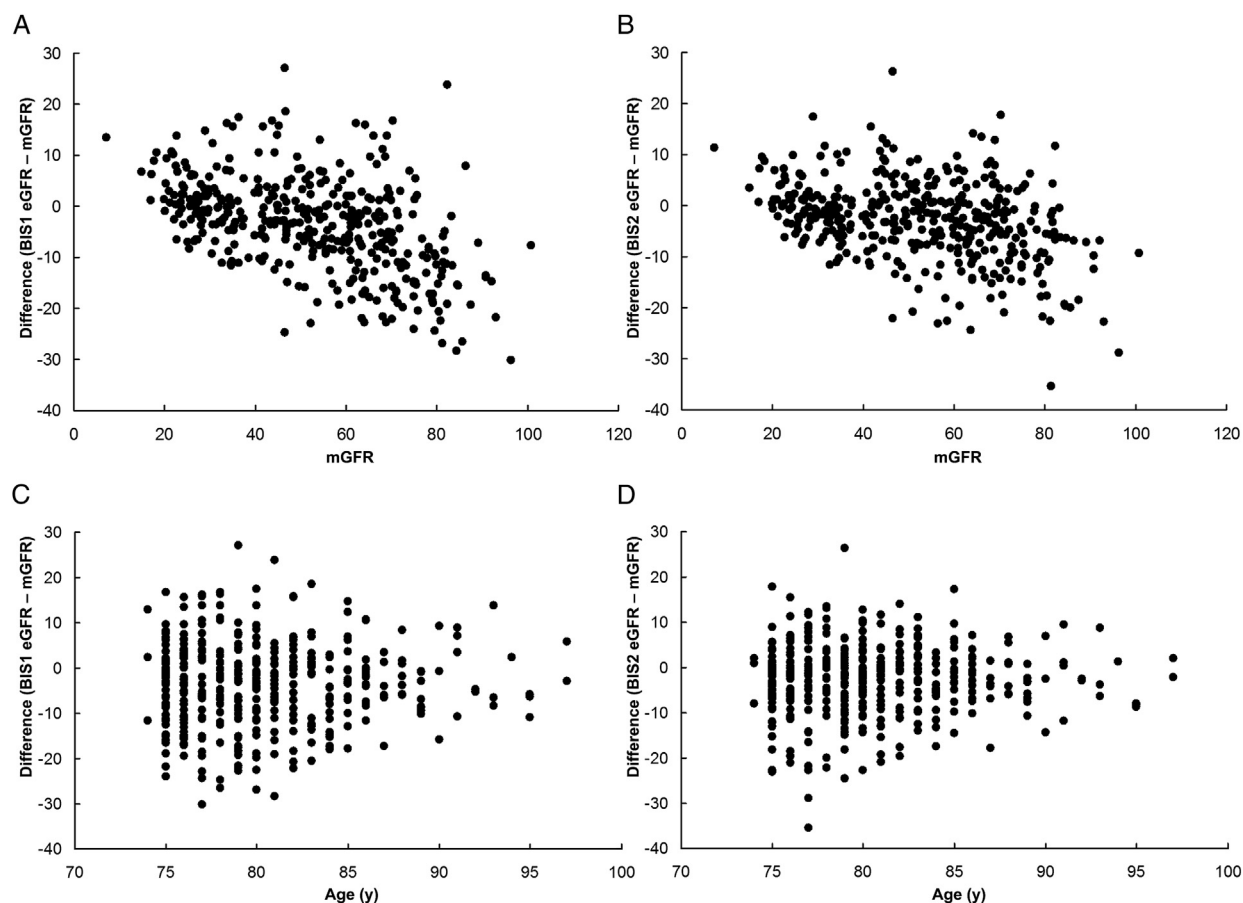
[a]Calculated on the raw GFR scale.

**Figure 1.** Bias plots. Difference between (A) BIS1 and (B) BIS2 eGFR and mGFR plotted against mGFR. Both BIS equations showed increasing negative bias against mGFR at higher levels of GFR; this effect seemed more marked for the BIS1 equation: difference (BIS1 − mGFR) = −0.235(mGFR) + 8.7, $R^2$ = 0.23, $P < 0.001$; difference (BIS2 − mGFR) = −0.152(mGFR) + 5.1, $R^2$ = 0.14, $P < 0.001$. The equivalent figures for the CKD-EPI equations have been published previously.[6] Difference between (C) BIS1 and (D) BIS2 eGFR and mGFR plotted against age. There was no linear relationship between bias and age ($P > 0.05$) but increasing scatter (funnel-shaped plot) is apparent at younger ages. All data (including differences) in mL/min/1.73 m$^2$.

*Inji M. Alshaer, MRCP,[1] Hannah S. Kilbride, MRCP[1]*
*Paul E. Stevens, FRCP,[1] Gillian Eaglestone, BSc[1]*
*Sarah Knight, RGN,[1] Joanne L. Carter, PhD[1]*
*Michael P. Delaney, MD, FRCP[1]*
*Christopher K.T. Farmer, MD, FRCP[1]*
*Jean Irving, MSc,[1] Shelagh E. O'Riordan, MBBS, MRCP[1]*
*R. Neil Dalton, PhD,[2] Edmund J. Lamb, PhD, FRCPath[1]*
¹East Kent Hospitals University NHS Foundation Trust
Canterbury, United Kingdom
²Evelina Childrens Hospital, London, United Kingdom
Corresponding author: elamb@nhs.net

### 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

1. Carter JL, Stevens PE, Irving JE, Lamb EJ. Estimating glomerular filtration rate: comparison of the CKD-EPI and MDRD equations in a large UK cohort with particular emphasis on the effect of age. *QJM.* 2011;104(10):839-847.

2. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009;150(9):604-612.

3. Inker LA, Schmid CH, Tighiouart H, et al. A new equation to estimate glomerular filtration rate from standardized creatinine and cystatin C. *N Engl J Med*. 2012;367(1):20-29.

4. Kidney Disease Improving Global Outcomes. Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int Suppl*. 2013;3:1-150.

5. Schaeffner ES, Ebert N, Delanaye P, et al. Two novel equations to estimate kidney function in persons aged 70 years or older. *Ann Intern Med*. 2012;157(7):471-481.

6. Kilbride HS, Stevens PE, Eaglestone G, et al. Accuracy of the MDRD (Modification of Diet in Renal Disease) Study and CKD-EPI (CKD Epidemiology Collaboration) equations for estimation of GFR in the elderly. *Am J Kidney Dis*. 2013;61(1):57-66.

7. Stevens LA, Coresh J, Schmid CH, et al. Estimating GFR using serum cystatin C alone and in combination with serum creatinine: a pooled analysis of 3,418 individuals with CKD. *Am J Kidney Dis*. 2008;51(3):395-406.

8. Koppe L, Klich A, Dubourg L, Ecochard R, Hadj-Aissa A. Performance of creatinine-based equations compared in older patients. *J Nephrol*. 2013;26(4):716-723.

9. Liu X, Chen J, Wang C, et al. Assessment of glomerular filtration rate in elderly patients with chronic kidney disease. *Int Urol Nephrol*. 2013;45(5):1475-1482.

10. Lopes MB, Araujo LQ, Passos MT, et al. Estimation of glomerular filtration rate from serum creatinine and cystatin C in octogenarians and nonagenarians. *BMC Nephrol*. 2013;14(1):265.

## 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) equation[3] for estimating GFR unless another equation has proved more accurate in a specific population.[4] Therefore, this equation is now widely used[5]; 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.[6,7] Recently, the BIS1 equation was developed in white German participants 70 years or older[8] and validated in a 332-patient Chinese cohort[9] 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 $^{51}$Cr-EDTA was determined from 6 consecutive 30-minute clearance periods after a single intravenous bolus injection. When proper urine samples could not be obtained, $^{51}$Cr-EDTA plasma clearance was calculated, as previously described.[11] Plasma creatinine was measured with an enzymatic method and standardized to iosotope-dilution mass spectrometry. GFR was estimated with the CKD-EPI and BIS1 equations.

Participants had a mean age of $75.9 \pm 4.4$ years; mean mGFR was $40.6 \pm 16.8$ mL/min/1.73 m$^2$ and decreased with age (Table 1). As defined by GFR < 60 mL/min/1.73 m$^2$ and/or by albuminuria or other kidney disease marker, 95% of patients had CKD. In the entire population, median biases and overall accuracy ($P_{30}$) of the CKD-EPI and BIS1 equations did not differ, although the BIS1 equation had a lower RMSE value (Table 2). In age subgroup analysis, median biases of the CKD-EPI and BIS1 equations did not vary with age. Conversely, median bias of the BIS1 equation, unlike that of the CKD-EPI equation, significantly varied with GFR ($P < 0.001$; Table 2; Fig S1).

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

| | All (N = 609) | 70-75 y (n = 283) | 75-80 y (n = 203) | 80-85 y (n = 99) | 85-90 y (n = 24) |
|---|---|---|---|---|---|
| Male sex | 399 (66) | 184 (65) | 136 (67) | 62 (63) | 17 (71) |
| African origin | 29 (4.8) | 15 (5.3) | 11 (5.4) | 2 (2.0) | 1 (4.2) |
| Age (y) | 75.9 ± 4.4 | 72.2 ± 1.4 | 77.0 ± 1.3 | 81.8 ± 1.4 | 86.6 ± 1.6 |
| Body mass index (kg/m$^2$) | 27.6 ± 4.9 | 27.5 ± 5.2 | 28.1 ± 4.9 | 27.4 ± 4.1 | 25.4 ± 3.6 |
| Body surface area (m$^2$) | 1.82 ± 0.22 | 1.83 ± 0.21 | 1.81 ± 0.22 | 1.83 ± 0.19 | 1.74 ± 0.27 |
| Weight (kg) | 73.3 ± 14.8 | 74.3 ± 15.7 | 73.5 ± 14.7 | 71.7 ± 11.8 | 65.9 ± 13.5 |
| Serum creatinine (mg/dL) | 1.75 ± 0.76 | 1.69 ± 0.78 | 1.78 ± 0.74 | 1.74 ± 0.61 | 2.15 ± 1.18 |
| mGFR (mL/min/1.73 m$^2$)[a] | 40.6 ± 16.8 | 44.1 ± 18.5 | 38.9 ± 15.6 | 36.7 ± 12.3 | 29.3 ± 10.3 |
| eGFR$_{CKD-EPI}$ (mL/min/1.73 m$^2$)[a] | 41.1 ± 17.9 | 44.5 ± 19.6 | 39.3 ± 16.5 | 37.0 ± 14.0 | 31.8 ± 13.8 |
| eGFR$_{BIS1}$ (mL/min/1.73 m$^2$)[a] | 39.9 ± 13.3 | 43.4 ± 14.6 | 38.2 ± 11.8 | 35.5 ± 9.6 | 30.6 ± 9.9 |
| mGFR ≥ 60 mL/min/1.73 m$^2$ | 79 (13) | 55 (19) | 18 (9) | 6 (6) | 0 (0) |
| 30 ≤ mGFR < 60 mL/min/1.73 m$^2$ | 359 (59) | 162 (58) | 123 (60) | 63 (64) | 11 (46) |
| mGFR < 30 mL/min/1.73 m$^2$ | 171 (28) | 66 (23) | 62 (31) | 30 (30) | 13 (54) |

*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)$^{1/2}$. eGFR$_{CKD-EPI}$ = 141 × min(Scr/κ, 1)$^α$ × max(Scr/κ, 1)$^{-1.209}$ × 0.993$^{Age}$ × 1.018 [if female] × 1.159 [if black], κ is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min is the minimum of Scr/κ or 1; max is the maximum of Scr/κ or 1. eGFR$_{BIS1}$ = 3,736 × Scr$^{-0.87}$ × Age$^{0.95}$ × 0.82 (if female).

[a]$P < 0.001$, one-way ANOVA for age group.