CORRESPONDENCE

Research Letter

The Impact of the New CKD-EPI Equation on GFR Estimation in the Elderly

In clinical routine, GFR is most commonly calculated using serum creatinine and GFR estimating equations. This indirect method, which includes patient's age and sex, provides a simple and rapid estimate of kidney function. The GFR result is a criterion for diagnosing chronic kidney disease (CKD) and its staging using the KDIGO definition (KDIGO, Kidney Disease: Improving Global Outcomes). A patient's CKD stage is important for assessing disease progression, selecting and dosing medication, before administering iodine-containing contrast medium, for deciding whether to commence renal replacement therapy, and before planned living kidney donation. Old age is regularly associated with multiple chronic diseases, often accompanied by the use of multiple medications (an important risk factor for nephrotoxicity), which is why proper renal function assessment is particularly important.

The commonly used creatinine-based CKD-EPI (ASR) equation (1, 2) has recently been revised (CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; ASR, age, sex, and race) because the included variable for race has been criticized for resulting in unequal treatment of black patients. Critics argued that race is not a biological but a social construct and is therefore obsolete for calculating GFR. As a result, in November 2021, the CKD-EPI equation was redeveloped using a broad database, was validated, and published as a "race free" CKD-EPI (AS) equation (3) based solely on age and sex. The new CKD-EPI (AS) equation is currently recommended for every patient in the United States, and it may be assumed that it will also be adopted in German speaking countries. But at the moment it is uncertain whether this is of any use when applied to elderly patients. The current study compares the estimate accuracy of the new CKD-EPI (AS) equation with the CKD-EPI (ASR) equation and the European Kidney Function Consortium (EKFC) equation recently developed in Europe (4).

Methods

The analysis used data from the "Berlin Initiative Study" (BIS), a population-based cohort (5). The measured GFR (mGFR) was determined in 570 BIS study participants using the invasive iohexol plasma clearance method as the gold standard. Participants were administered 5 ml of the iohexol solution, and a total of eight plasma samples were taken over a period of five hours. At the same time serum creatinine was determined using the CREA plus (Roche Diagnostics, Mannheim) assay. A detailed description of iohexol plasma clearance was published in 2012 (5).

The CKD-EPI (ASR) (1, 2), CKD-EPI (AS) (3), and EKFC (4) equations were validated externally using the mGFR. For this purpose, systematic deviation (bias, estimated GFR [eGFR] minus mGFR), precision (interquartile range), and accuracy (P30 and P10, defined as percentage of eGFR values within ±30% and ±10% of mGFR) were calculated and stratified by age (</≥80 years) and mGFR (</≥60 mL/min/1.73m²). All analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC).

TABLE

Mean bias*, P10 and P30 values for the accuracy of the eGFR equations, stratified by age and mGFR

	Bias*; IQR (pct 25; pct 75)	P10 (%), [95% CI]	P30 (%), [95% CI]
Total N = 570			
CKD-EPI (ASR)	8.4; 12.8 (1.7; 14.4)	36.0 [32.0; 39.9]	81.4 [78.2; 84.6]
CKD-EPI (AS)	13.0; 13.8 (6.0; 19.8)	21.1 [17.7; 24.4]	66.5 [62.6; 70.4]
EKFC	1.6; 11.3 (−4.0; 7.3)	49.3 [45.2; 53.4]	91.9 [89.7; 94.2]
Age ≥80 years, n = 208			
CKD-EPI (ASR)	8.3; 11.9 (1.8; 13.6)	32.7 [26.3; 39.1]	76.9 [71.1; 82.7]
CKD-EPI (AS)	13.1; 12.4 (6.5; 18.9)	17.8 [12.5; 23.0]	57.7 [50.9; 64.5]
EKFC	2.0; 10.4 (−4.0; 6.4)	45.7 [38.8; 52.5]	89.9 [85.8; 94.0]
mGFR <60mL/min/1.73 m², n = 273			
CKD-EPI (ASR)	8.8; 13.6 (1.7; 15.3)	28.6 [23.2; 34.0]	67.8 [62.2; 73.3]
CKD-EPI (AS)	12.9; 14.7 (5.5; 20.2)	18.3 [13.7; 22.9]	52.4 [46.4; 58.3]
EKFC	3.7; 11.5 (−2.3; 9.2)	37.7 [31.9; 43.5]	85.0 [80.7; 89.2]

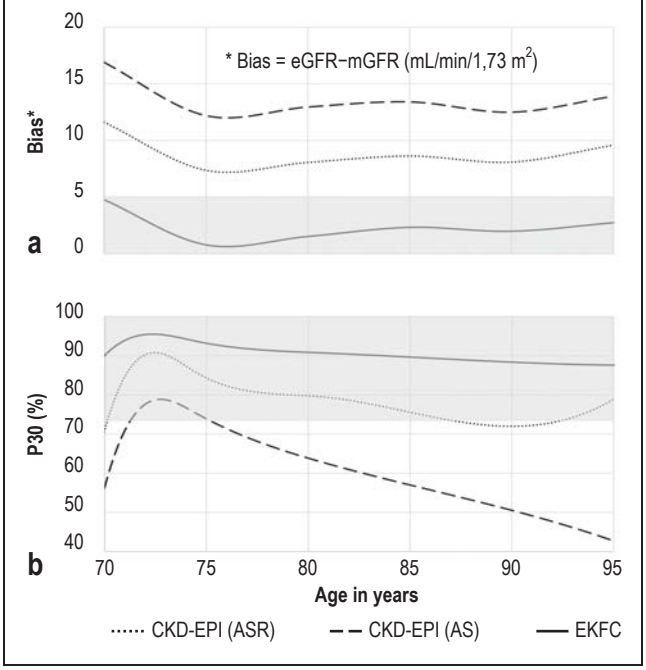
* Values in mL/min/1.73m²; for the interpretation of the systematic deviation (bias), positive values correspond to an overestimation and negative values to an underestimation of the actual GFR (bias = eGFR minus mGFR). P10 and P30 values are defined as percentage of the eGFR values within ±10% and ± 30% of the mGFR and reflect the accuracy of the GFR estimation equations.

CKD-EPI (AS[R]), Chronic Kidney Disease – Epidemiology Collaboration (age, sex, [race]); EKFC, European Kidney Function Consortium; IQR, interquartile range; m/eGFR, measured/estimated glomerular filtration rate; pct, percentile; 95% CI, 95% confidence interval

Results

The mean age (± standard deviation) of the 570 study participants was 78.5 (±6.2) years, 57% were males, 100% were white, and the mean mGFR was 60.3 mL/min/1.73m². One quarter of the study participants had diabetes, three quarters suffered from hypertension, and one third were overweight (BMI >30 kg/m²). The mean systematic deviation (bias) was highest for the CKD-EPI (AS) equation, with an overestimation of the GFR by 13.0 mL/min/1.73m² as compared with values of 8.4 and 1.6 for the CKD-EPI (ASR) and EKFC equations, respectively (*Table*, *Figure*). In terms of accuracy, the CKD-EPI (AS) equation performed worst: The P30 value of 67% was significantly lower than for the CKD-EPI (ASR) and EKFC equations with 81% and 92%, respectively. That means that for one third the new equation overestimated or underestimated the actual GFR by more than 30% (*Table*). In the very old (≥80 years) or those with impaired

FIGURE



Bias (systematic deviation) (a) and P30 (accuracy within 30%) (b) according to age for the CKD-EPI (ASR), CKD-EPI (AS), and EKFC equations in the BIS data (n = 570)

a) The gray shaded area indicates a systematic deviation (bias) of 0–5 mL/min/1,73 m².

b) The gray shaded area indicates the part where the P30 value is more than 75 %. Bias is defined as "eGFR minus mGFR". P30 is defined as the percentage of the eGFR values within +/− 30% of mGFR and reflects the accuracy of the GFR estimation equation.

BIS, Berliner Initiative Study; CKD-EPI (AS[R]), Chronic Kidney Disease Epidemiology Collaboration (age, sex, [race]); EKFC, European Kidney Function Consortium; m/eGFR, measured/estimated glomerular filtration rate

renal function (mGFR <60), the new CKD-EPI (AS) equation performed even worse, with P30 values of 58% and 52%, respectively.

Discussion

The new CKD-EPI equation without the variable for "race" is regarded in the United States as an important step towards the equal treatment of patients. The National Kidney Foundation, as the largest patient-centered organization committed to the prevention and treatment of kidney disease, as well as the new Task Force of the American Society of Nephrology have recommended the new CKD-EPI (AS) equation for diagnosing CKD. They provide laboratory clients with information material and cover letters for the purpose of its smooth implementation in their laboratories. The justification for the changeover recommendation is also that the new equation has similar overall performance features and that there are no known potential consequences that disproportionately affect any particular group of people.

However, the present study results reveal that the new introduction of CKD-EPI (AS) in elderly patients results in both a systematic overestimation and significantly poorer GFR prediction accuracy. This is even worse in patients with a GFR <60, with a P30 of only 52%. This therefore poses a risk of medication overdose and delayed CKD diagnosis for elderly patients. Also, the introduction of the new equation would (falsely) lower CKD prevalence in the elderly population in an ad hoc way. We are aware that the BIS study population is a sample of the older white population in Germany, and so no statement can be made about the degree of confidence of the "race free" CKD-EPI equation in the older black population. We also point out with certain constraints that the BIS data were also used as part (8% of 6417) of the developmental sample (measured GFR) for the EKFC equation. We therefore recommend that European laboratories wait for further external validation of the new equation in different population and patient groups before switching to the new CKD-EPI (AS) equation in order to counteract systematic misinterpretation of renal function in routine clinical practice. Although the diagnosis of CDK is not based on GFR alone, since additional criteria such as albuminuria, anemia, impaired calcium phosphate metabolism, secondary hyperparathyroidism, and renal structure, among others, are also taken into account. Nonetheless, an optimal estimate accuracy should be targeted for indirect eGFR determination, as there is inherently a higher susceptibility to error in contrast to invasive renal function measurement (mGFR).

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Conflict of interest statement
The authors declare that are no conflict of interest exists.

Manuscript received on 16 March 2022, revised version accepted on 17 June 2022.

Translated from the original German by Dr. Grahame Larkin

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Cite this as:
Ebert N, Pottel H, van der Giet M, Kuhlmann MK, Delanaye P, Schaeffner E: The impact of the new CKD-EPI equation on GFR estimation in the elderly. Dtsch Arztebl Int 2022; 119: 694–5. DOI: 10.3238/arztebl.m2022.0258