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ORIGINAL ARTICLE

Performance of creatinine-based equations to estimate glomerular filtration rate with a methodology adapted to the context of drug dosage adjustment

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Aim: The Cockcroft-Gault (CG) creatinine-based equation is still used to estimate glomerular filtration rate (eGFR) for drug dosage adjustment. Incorrect eGFR may lead to hazardous over- or underdosing.

Methods: In a cross-sectional analysis, CG was validated against measured GFR (mGFR) in 14 804 participants and compared with the Modification-of-Diet-in-Renal-Diseases (MDRD), Chronic-Kidney-Disease-Epidemiology (CKD-EPI), Lund-Malmö-Revised (LMR) and European-Kidney-Function-Consortium (EKFC) equations. Validation focused on bias, imprecision and accuracy (percentage of estimates within ±30% of mGFR, P30), overall and stratified for mGFR, age and body mass index at mGFR <60 mL/min, as well as classification in mGFR stages.

Results: The CG equation performed worse than the other equations, overall and in mGFR, age and BMI subgroups in terms of bias (systematic overestimation), imprecision and accuracy except for patients ≥65 years where bias and P30 were similar to MDRD and CKD-EPI, but worse than LMR and EKFC. In subjects with mGFR <60 mL/min and at BMI 18.5-25 kg/m^2, all equations performed similarly, and for BMI < 18.5 kg/m^2 CG and LMR had the best results though all equations had poor P30-accuracy. At BMI ≥ 25 kg/m^2 the bias of the CG increased with increasing BMI (+17.2 mL/min at BMI ≥ 40 kg/m^2). The four more recent equations also classified mGFR stages better than CG.

Conclusions: The CG equation showed poor ability to estimate GFR overall and in analyses stratified for mGFR, age and BMI. CG was inferior to correctly classify the patients in the mGFR staging compared to more recent creatinine-based equations.

KEYWORDS
chronic kidney disease, drug adjustment, glomerular filtration rate

1 | INTRODUCTION

Creatinine-based glomerular filtration rate (GFR) equations are commonly used in daily clinical practice to estimate GFR (eGFR).[1–3] eGFR is needed for dose adjustment of many drugs whose pharmacokinetics can be influenced by the level of kidney function.[4,5] Even with the emergence of new biomarkers,[6,7] the most commonly used equations in clinical practice are still those based on the measurement of serum creatinine (SCr).[1–3,8] We have recently proposed and validated a new creatinine-based equation which has the potential to estimate GFR accurately throughout the whole GFR and age range.[1] However, in the context of drug dosage adjustment, the comparison of the performance of equations requires specific methodological adaptations. First, although the Cockcroft-Gault (CG) equation is not recommended by any guidelines in nephrology, this equation is still used and considered particularly in the context of drug dosage adjustment. Of note, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) do not rule in favour of a particular equation.[9,10] Second, the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, the EMA and the FDA recommend using GFR without indexation

to body surface area (BSA) in the context of drug dosage adjustment.[9–11] Thus, measured GFR and CG must be used without BSA indexing and equations that use BSA indexation may need to be "de-indexed".[12] This requirement makes it possible to analyse the performance of eGFR equations according to body mass index (BMI) because weight is an important part of both BSA and CG equations, whereas weight is not present in other eGFR equations. Third, dosage adjustment should be applied for the vast majority of drugs, whenever GFR declines below 45 mL/min. Moreover, drug dosage is dependent on the classification of patients into the different categories of GFR, as suggested by KDIGO (categories 3a: 45-60 mL/min, 3b: 30-45 mL/min, 4: 15-30 mL/min and 5: <15 mL/min).[13] Very few studies have taken these specificities into account to compare the performance of the CG with other equations, and most studies have only compared CG with the Modification of Diet in Renal Disease (MDRD) Study equation.[14–16] In the current article, we used a large cohort of adults with measured GFR to study and compare CG performance with other equations such as the MDRD study equation[17] but also the Chronic Kidney Disease Epidemiology (CKD-EPI) equation,[2] the Lund-Malmö Revised (LMR) equation,[8] and the new European Kidney Function Consortium (EKFC) equation (EKFC being an evolution of the previous Full Age Spectrum equation).[1]

What is already known

- Estimating glomerular filtration rate (GFR) is used to adjust drug dosage.
- The Cockcroft-Gault (CG) equation is still frequently used.

What this study adds

- Measured GFR was compared with estimated GFR equations in 14 804 participants.
- The results showed that the CG equation had the poorest performance of all estimating equations.
- For drug dosage, the CG equation should not be used, as its performance is poor.

2 | METHODS

2.1 | Design overview

Data on 18 805 patients representing 12 cohorts from Europe and the United States were available as previously described.[1] Because we focused on adults, values in subjects younger than 18 years were excluded, and 149 values were not considered because weight or height were unavailable, leaving a final cohort of 14 804 subjects. Analysis was limited to the first GFR measurement obtained per patient (if more than one was available). Data collection was planned after GFR measurement (retrospective design). Data were anonymised from the source cohorts for the analysis performed at Lund University, Sweden. All procedures involving subjects and data were in agreement with the ethical principles for medical research involving human subjects established in the World Medical Association Declaration of Helsinki. The study has been reviewed and approved by the Regional Ethical Board in Lund, Sweden (Registration No 2018/220).

2.2 | Participants

Data on GFR were collected and centralized by the European Kidney Function Consortium (EKFC), which was endorsed by the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA). Data were from participants (all nonblack) in previously published research studies as well as patients undergoing measured GFR as part of their clinical care at nephrology centres. An overview of the participating centres, the measurement methods used in these centres and the patient characteristics in the centres have been published before.[1,18,19]

2.3 | Covariates

Age, gender, height, weight and SCr were obtained from medical records. SCr was measured with assays traceable to the gold standard isotope dilution mass spectrometry (IDMS) method or was corrected to IDMS method levels (in case of the Chronic Renal Insufficiency Cohort [CRIC] Study).[20]

2.4 | Outcomes

Measured GFR was obtained using either plasma clearance (based on the decay of the plasma concentrations over time) or urinary clearance (based on urine excretion rate divided by plasma concentration) of exogenous filtration markers (iohexol, inulin, ^{51}Cr-EDTA or iothalamate), all methods with sufficient accuracy.[21,22] All results of measured GFR were nonindexed for BSA. GFR equations used for analysis are described in Supporting Information Table S1. GFR results based on MDRD, CKD-EPI, LMR and EFKC equations were de-indexed for BSA using the Du Bois equation.[12,23]

2.5 | Data and statistical analysis

2.5.1 | Performances of equations

The performances of the equations were compared with the usual metrics: median bias (ie, eGFR – mGFR) with 95% confidence

intervals (CI), imprecision (interquartile range [IQR]) and P30-accuracy (percentage of eGFR-values within ±30% of mGFR) with 95% CI. Evaluation in different subgroups was also done according to GFR (<15, [15-30[, [30-45[, [45-60[mL/min).[24] Focusing on GFR < 60 mL/min, we also performed analyses stratified by age (18-40[, [40-65[and ≥ 65 years) and BMI (<18.5, [18.5-25[, [25-30[, [30-35[, [35-40[and ≥40 kg/m^2). The target for bias is zero. Imprecision should be as low as possible. The goal for P30 was 100%, yet P30 > 75% has been considered as "sufficient for good clinical decision making" by the Kidney Disease Outcomes Quality Initiative (K/DOQI), although their goal was to reach P30 > 90%.[25,26] The EKFC equation has been partly derived from subjects included in the current analysis. Because an equation tends to perform better in the cohort used for its development, we performed a sensitivity analysis in the external validation cohort described in the seminal article, excluding subjects younger than 18 years (n = 7124) and omitting subjects who lacked information on height or weight (n = 149), leading to a final sample of 6975.

Median quantiles for bias across the age spectrum were graphically presented using fractional polynomials (linear, square and cubic). Likewise, accuracy P30 (%) was graphically presented across the age spectrum using cubic splines with two free knots and using third-degree polynomials.

2.5.2 | Classification of patients

In patients with mGFR lower than 60 mL/min (n = 4328), we calculated (percentage) and compared the ability of each equation to correctly classify subjects in the same stage as measured GFR using McNemar's test.[27] Also, we calculated the total percentage of patients who have been classified into a different CKD stage by the equation compared to mGFR, using the relevant thresholds (<15, [15-30[, [30-45[, [45-60[mL/min).[24,28] A *P* value <.05 was considered as significant.

All analyses were performed with SAS 9.4 (SAS Institute Inc., Cary, NC, USA) and Medcalc (Medcalc Software Ltd, Ostend, Belgium).

2.6 | Role of the funding source

Professor J. Björk has funding from the Swedish Research Council (VR) to conduct large-scale epidemiological studies linked with registered data from healthcare (Vetenskapsrådet; grant no. 2019-00198). This funding source was at no time involved in the design, analysis, presentation or interpretation of the results from the present study.

3 | RESULTS

The characteristics of the study participants are summarized in Supporting Information Table S2. Further details on each cohort can be found in Supporting Information Appendix Table S3. The mean ± SD age was 55.1 ± 18.9 years, mean measured GFR was 78.8 ± 34.2 mL/min and 49.5% were female. The performance of the five equations in the whole study population (n = 14 804) is shown in Supporting Information Table S4 and illustrated in Supporting Information Appendix Figure S1A,B. In comparison to more recent equations, the performance of the CG equation to estimate was worse than for all other equations in terms of bias (with the largest and systematic overestimation) (Supporting Information Appendix Figure S1A), imprecision (with the highest IQR) and accuracy (with the poorest P30) (Supporting Information Appendix Figure S1B). Among the recent equations, the overall performances of the EFKC and LMR equations were similar and better than that of the MDRD and CKD-EPI equations. The analysis stratified by mGFR (below 60 mL/min) is shown in Table 1 and Figure 1A,B, demonstrating the same results. The CG equation performed systematically worse in terms of bias (Figure 1A), precision and P30 (Figure 1B). Once again, both EFKC and LMR performed better than MDRD and CKD-EPI. In patients with mGFR < 60 mL/min, a subanalysis according to age and BMI is summarized in Table 2-3 and Figure 2. The same ranking among equations can be made in participants younger than 65 years. In older individuals, both bias (but not precision) and P30 of the CG equation were similar to the MDRD and CKD-EPI equations, but all had worse performance than LMR and EKFC equations. In patients with BMI higher than 25 kg/m^2, the performance of the CG was also worse, especially in terms of bias, which increased with increasing BMI. In patients with BMI between 18.5 and 25 kg/m^2, all equations presented with a similar performance. In patients with low BMI (<18.5 kg/m^2), both CG and LMR equations had the best results, but all equations shared a relatively poor performance (with P30 of 58.8% and 57.3% for CG and LMR equations, respectively).

As a sensitivity analysis, the same analysis was repeated in the external validation dataset only (see Supporting Information Tables S5 and S6 for the whole external cohort population and stratified by age, mGFR and BMI, respectively). The results and conclusions were not different from the whole cohort.

In comparison with measured GFR under 60 mL/min, subjects were correctly classified in the KDIGO categories in 43.5%, 49.8%, 48.1%, 54.0% and 52.9% with the CG, MDRD, CKD-EPI, LMR and EKFC equations, respectively. LMR was slightly better than EKFC. EKFC and LMR were significantly better than MDRD and CKD-EPI. All four equations also performed better than the CG. The difference in categorization between measured and estimated GFR was one stage (eg, stage 3a or 4 with eGFR and 3b with mGFR) in 46.1%, 43.1%, 43.7%, 40.6% and 41.1% with the CG, MDRD, CKD-EPI, LMR and EKFC equations, respectively. Errors of one stage were less frequent in LMR and EFKC compared to MDRD and CKD-EPI. Errors of one stage were less frequent with all four eGFR equations compared to CG. The difference in categorization between measured and estimated GFR was two stages (eg, stage 2 or 4 with eGFR and 3b with mGFR) in 9.3%, 6.2%, 7.2%, 5.0% and 5.4% with the CG, MDRD, CKD-EPI, LMR and EKFC equations, respectively. Errors of two stages

TABLE 1 Performance of different equations in subgroups according to measured GFR

	CG	MDRD	CKD-EPI	LMR	EKFC
mGFR<60 mL/min n = 4328					
Median bias (95% CI)	6.1 (5.7; 6.5)	3.9 (3.5; 4.2)	4.4 (4.0; 4.7)	1.5 (1.2; 1.8)	2.9 (2.6; 3.2)
Imprecision	14.8	13.2	14.3	12.0	12.4
P30 (%) (95% CI)	59.4 (57.9; 60.9)	67.3 (65.9; 68.7)	64.9 (63.5; 66.3)	73.8 (72.5; 75.1)	70.3 (68.9; 71.7)
mGFR [45-60[mL/min n = 1490					
Median bias (95% CI)	7.0 (6.1; 7.9)	5.1 (4.3; 6.0)	4.4 (6.4; 8.1)	1.5 (1.9; 3.3)	2.9 (2.8; 4.4)
Imprecision	20.3	18.6	20.6	16.4	17.2
P30 (%) (95% CI)	67.1 (64.7; 69.5)	73.2 (70.9; 75.4)	67.1 (64.7; 69.5)	78.4 (76.3; 80.5)	76.6 (74.4; 78.7)
mGFR [30-45[mL/min n = 1299					
Median bias (95% CI)	6.5 (5.5; 7.2)	4.3 (3.5; 5.0)	5.3 (4.4; 5.8)	0.9 (0.1; 1.7)	3.1 (2.4; 3.8)
Imprecision	16.4	13.8	15.0	14.7	13.5
P30 (%) (95% CI)	63.5 (60.9; 66.1)	68.8 (66.3; 71.3)	67.2 (4.7; 69.8)	72.5 (70.1;74.9)	71.7 (69.2;74.1)
mGFR [15-30[mL/min n = 1207					
Median bias (95% CI)	6.0 (5.4; 6.5)	3.5 (2.9; 4.0)	3.0 (2.5; 3.6)	0.7 (0.3; 1.4)	2.7 (2.2; 3.2)
Imprecision	11.1	9.9	10.3	7.9	9.6
P30 (%) (95% CI)	49.5 (46.7; 52.4)	62.1 (59.4; 64.9)	61.9 (59.1; 64.6)	72.8 (70.3; 75.3)	64.7 (62.0; 67.4)
mGFR <15 mL/min n = 332					
Median bias (95% CI)	4.2 (3.4; 4.7)	2.3 (1.8; 3.2)	1.8 (1.1; 2.3)	2.2 (1.8; 2.5)	2.0 (1.6; 2.5)
Imprecision	6.6	6.2	6.4	5.0	6.2
P30 (%) (95% CI)	44.6 (39.2; 49.4)	536 (48.3;59.0)	56.6 (51.3;61.9)	62.0 (56.8; 67.3)	57.2 (51.9; 62.5)

Note: Bias (estimated GFR − measured GFR) and imprecision (interquartile range) expressed in mL/min.
Abbreviations: CG, Cockcroft-Gault; CKD-EPI, Chronic Kidney Disease Epidemiology; CI, confidence interval; EKFC, European Kidney Function Consortium; LMR, Lund Malmö Revised; MDRD, Modification of Diet in Renal Diseases; mGFR, measured glomerular filtration rate; P30, percentage of estimated GFR within ±30% of measured GFR.

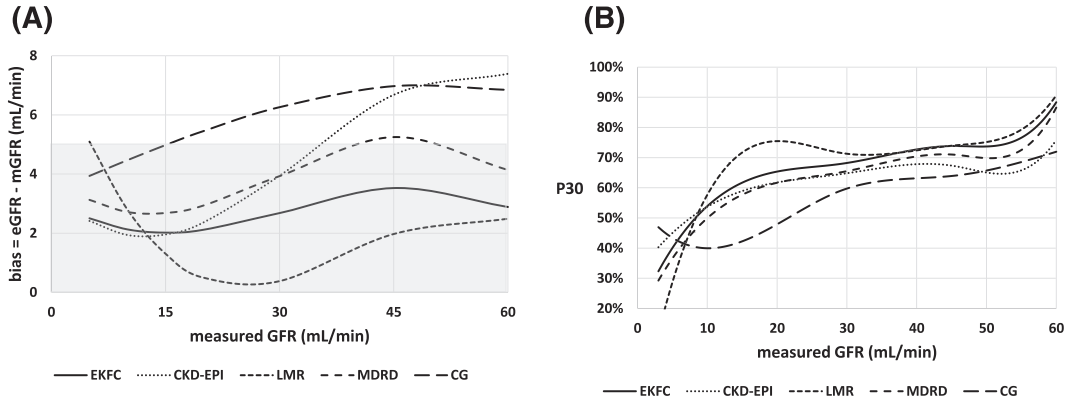

FIGURE 1 (A) Bias = eGFR − mGFR against measured GFR for the Cockcroft-Gault (CG), Modification of Diet in Renal Diseases (MDRD), Chronic Kidney Disease Epidemiology (CKD-EPI), Lund Malmö Revised (LMR) and European Kidney Function Consortium (EKFC) equations in patients with mGFR <60 mL/min. Positive bias indicates overestimation; negative bias indicates underestimation. The grey zone corresponds to a bias of ± 5 mL/min. (B) P30 against measured GFR for the CG, MDRD, CKD-EPI, LMR and EKFC equations in patients with mGFR < 60 mL/min (n = 4328)

TABLE 2 Performance of different equations in patients with mGFR < 60 mL/min according to age

Age [18-40[years n = 567	**CG**	**MDRD**	**CKD-EPI**	**LMR**	**EKFC**
Median bias (95% CI)	16.7 (15.4; 18.0)	7.2 (5.7; 9.3)	13.5 (11.6; 15.9)	5.9 (4.4; 7.1)	8.7 (7.4; 10.2)
Imprecision	17.2	16.7	20.0	15.9	15.7
P30 (%) (95% CI)	35.1 (31.2; 39.0)	61.6 (57.6; 65.6)	46.4 (42.3; 50.5)	65.6 (61.7; 69.5)	57.5 (53.4; 61.6)
Age [40-65[years n = 1077					
Median bias (95% CI)	10.0 (9.1; 11.2)	2.0 (1.3; 2.8)	3.8 (3.2; 5.3)	2.3 (1.7; 3.4)	4.6 (3.8; 5.6)
Imprecision	15.1	13.6	14.8	13.5	14.0
P30 (%) (95% CI)	47.8 (44.8; 50.8)	70.1 (67.4; 72.8)	65.7 (62.9; 68.6)	70.5 (67.7; 73.2)	66.7 (63.9; 69.5)
Age ≥65 years n = 2684					
Median bias (95% CI)	3.0 (2.6; 3.4)	4.0 (3.6; 4.4)	3.4 (2.9; 3.8)	0.6 (0.2; 1.0)	1.6 (1.2; 2.0)
Imprecision	11.7	12.2	12.1	10.6	10.9
P30 (%) (95% CI)	69.2 (67.4; 70.9)	67.4 (65.6; 69.1)	68.4 (66.7; 70.2)	76.9 (75.3; 78.5)	74.5 (72.8; 76.1)

Note: Bias (estimated GFR − measured GFR) and imprecision (interquartile range) expressed in mL/min.
Abbreviations: BMI, body mass index; CG, Cockcroft-Gault; CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology; EKFC, European Kidney Function Consortium; LMR, Lund Malmö Revised; MDRD, Modification of Diet in Renal Diseases; mGFR, measured glomerular filtration rate; P30, percentage of estimated GFR within ±30% of measured GFR.

TABLE 3 Performance of different equations in patients with mGFR <60 mL/min according to body mass index

BMI < 18.5 kg/m^2 n = 262	**CG**	**MDRD**	**CKD-EPI**	**LMR**	**EKFC**
Median bias (95% CI)	7.5 (6.1; 9.5)	11.2 (9.5;12.4)	15.8 (12.7; 17.4)	8.8 (6.8; 11.0)	10.8 (9.1; 12.9)
Imprecision	13.9	16.9	20.1	14.8	15.9
P30 (%) (95% CI)	58.8 (52.8; 64.7)	49.2 (43.2; 55.3)	36.6 (30.8; 42.5)	57.3 (51.3; 63.2)	50.0 (43.9; 56.1)
BMI [18.5-25[kg/m^2 n = 1713					
Median bias (95% CI)	3.9 (3.3; 4.6)	4.6 (4.0; 5.1)	5.6 (5.0; 6.0)	2.1 (1.7; 2.4)	3.6 (3.1;4.2)
Imprecision	14.9	13.0	15.0	12.4	12.7
P30 (%) (95% CI)	65.6 (63.4; 67.9)	66.1 (63.9; 68.4)	63.1 (60.8; 65.4)	72.9 (70.8; 75.0)	68.7 (66.5; 70.8)
BMI [25-30[kg/m^2 n = 1415					
Median bias (95% CI)	5.2 (4.7; 6.0)	3.0 (2.3; 3.5)	3.0 (2.5; 3.6)	0.4 (−0.1; 0.9)	1.9 (1.5; 2.4)
Imprecision	12.8	11.7	12.2	10.7	11.0
P30 (%) (95% CI)	62.0 (59.5; 64.6)	71.0 (68.7; 73.4)	69.8 (67.4; 72.1)	77.5 (75.4; 79.7)	74.6 (72.4; 76.9)
BMI [30-35[kg/m^2 n = 643					
Median bias (95% CI)	8.5 (7.7; 9.5)	2.7 (1.9; 3.7)	2.5 (1.4; 3.5)	0.2 (−0.6; 1.1)	1.7 (0.8; 2.5)
Imprecision	14.1	12.3	12.3	11.0	11.1
P30 (%) (95% CI)	50.1 (46.2; 53.9)	68.7 (65.2; 72.3)	69.1 (65.5; 72.6)	76.2 (72.9; 79.5)	73.9 (70.5; 77.3)
BMI [35-40[kg/m^2 n = 203					
Median bias (95% CI)	15.4 (13.6; 17.4)	3.4 (1.3; 4.9)	3.7 (2.0; 5.4)	1.3 (−0.1; 3.2)	3.0 (1.2; 5.3)
Imprecision	17.9	14.4	14.5	13.4	12.9
P30 (%) (95% CI)	33.5 (27.0; 40.0)	68.5 (62.1; 74.9)	68.0 (61.6; 74.4)	73.8 (67.3; 79.5)	70.3 (63.1; 75.8)
BMI ≥40 kg/m^2 n = 92					
Median bias (95% CI)	17.2 (14.2; 21.0)	−0.5 (−2.8; 1.9)	0.1 (−2.4; 2.9)	−1.4 (−3.5; 0.2)	−0.1 (−2.4; 2.1)
Imprecision	19.3	13.7	14.9	13.7	14.9
P30 (%) (95% CI)	27.2 (18.1; 36.3)	69.6 (60.2; 79.0)	67.4 (57.8; 77.0)	65.2 (55.5; 74.9)	69.6 (60.2; 79.0)

Bias (estimated GFR − measured GFR) and imprecision (interquartile range) expressed in mL/min.
BMI, body mass index; CG, Cockcroft-Gault; CKD-EPI, Chronic Kidney Disease Epidemiology; CI, confidence interval; EKFC, European Kidney Function Consortium; LMR, Lund Malmö Revised; MDRD, Modification of Diet in Renal Diseases; mGFR, measured glomerular filtration rate; P30, percentage of estimated GFR within ±30% of measured GFR.

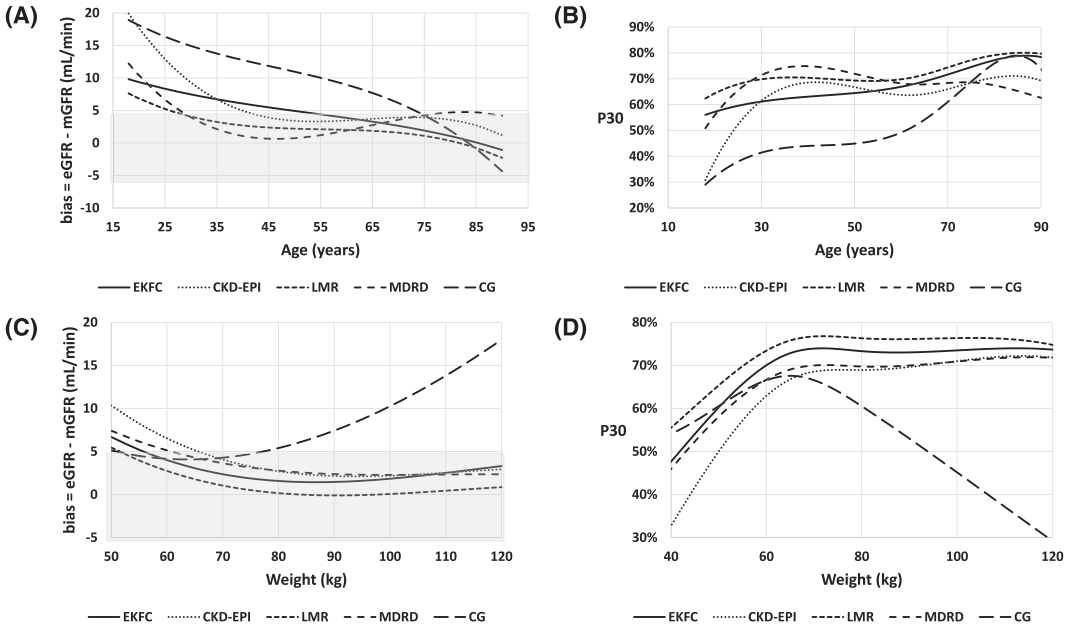

FIGURE 2 (A) Bias = eGFR – mGFR against age for the Cockcroft-Gault (CG), Modification of Diet in Renal Diseases (MDRD), Chronic Kidney Disease Epidemiology (CKD-EPI), Lund Malmö Revised (LMR) and European Kidney Function Consortium (EKFC) equations in patients with mGFR < 60 mL/min. Positive bias indicates overestimation; negative bias indicates underestimation. The grey zone corresponds to a bias of ± 5 mL/min. (B) P30 against age for the CG, MDRD, CKD-EPI, LMR and EKFC equations in patients with mGFR < 60 mL/min. (C) Bias = eGFR – mGFR against weight for the CG, MDRD, CKD-EPI, LMR and EKFC equations in patients with mGFR < 60 mL/min. Positive bias indicates overestimation; negative bias indicates underestimation. The grey zone corresponds to a bias of ± 5 mL/min. (D) P30 against weight for the CG, MDRD, CKD-EPI, LMR and EKFC equations in patients with mGFR < 60 mL/min (n = 4328)

were less frequent in LMR and EFKC compared to MDRD and to CKD-EPI. Errors of two stages were less frequent with all four equations compared to CG.

4 | DISCUSSION

The main objective of this study was to evaluate the performance of the CG equation to estimate GFR in comparison with four more recent creatinine-based equations.[1–3,29] Originally, the methodology was adapted with regard to drug dosage adjustment, ie, GFR was expressed in mL/min and we focused on GFR < 60 mL/min.[9–12] We showed that the CG equation had the worst performance compared to all other equations to estimate GFR: CG had the largest bias (with a systematic overestimation, especially in the high BMI range[30,31]), the lowest precision and the poorest accuracy. Also, the CG equation was associated with a higher number of errors (and larger errors) in terms of GFR classification of patients.[27] Among the other equations, both EKFC and LMR performed significantly better than MDRD and CKD-EPI, even if the difference in performance between these equations was much lower than the difference observed between CG and all the others. The inferiority of the CG equation compared to the others was confirmed in most subanalyses, ie, according to GFR, age and BMI. The poor performance of CG has been described in the past but either the methodology was not adapted to drug dosage adjustment or the comparison was only with the MDRD study equation.[14–16]

In patients older than 65 years, CG performed as well as the MDRD and CKD-EPI equations. The relatively good performance of CG in the elderly is also described in other cohorts,[14,32,33] however we show here that both LMR and EKFC do significantly better in this population.[1,34] Regarding the performance of CG, it was slightly better for patients with low or very low BMI. One can hypothesize that patients in these BMI ranges have abnormally low muscle mass.[35] In these patients, serum creatinine (in the denominator in CG) is falsely low, which results in overestimation of GFR. In the CG equation, this overestimation due to serum creatinine is counterbalanced by the variable weight (in the numerator) which is, by definition, low in this population. Weight is not directly present in recent equations. Having said that, it remains difficult to recommend CG in a population of very lean individuals as its overall performance remains very poor.[29,35] Consequently, measuring GFR, or using cystatin C-based estimation, are probably to be recommended in such a population.[36,37]

In terms of GFR estimation and patient categorization, we thus confirm the superiority of MDRD and CKD-EPI equations over CG, this superiority being still more obvious when EKFC and LMR are considered for comparison.[14,15,38] In our cohort, this is especially illustrated by errors of more than two stages (eg, stage 2 or 4 with eGFR and 3b with mGFR), which are two times more frequent with CG than with LMR or EKFC.

There are several plausible reasons why CG is inferior to the more recent eGFR equations. First, *sensu stricto*, CG is supposed to estimate

creatinine clearance (which is a less precise GFR measure because of errors in urine collection and tubular secretion of creatinine) whereas the four other equations have been developed from "true" GFR measurements.[3,21,39] Second, serum creatinine in the CG equation was not IDMS traceable, as most creatinine assays are now.[20,40] Third, there are several methodologic limitations in the CG study (including its simplistic mathematical model, low sample of development and lack of female subjects). From a strict "nephrological" point of view, we therefore question why the CG is still used in clinical research and practice to estimate GFR in the context of drug dosage adjustment. Different factors may explain why CG is still used. Several guidelines for drug dosage adaption have been established with the CG equation (or creatinine clearance). Also, adverse events with drugs are particularly frequent in the frail elderly.[41] In this specific population combining low BMI and old age, CG will typically yield a lower GFR result than MDRD and CKD-EPI, which may lead to safer drug dosage. This point explains why CG is still often preferred in the geriatric context. This argument is spurious, however, because if it is true at the population level, it is not automatically true for the individual (eg, if older adults are obese, CG results will be higher than other equations).[39,42] Moreover, one might also consider the risk of underdosing important drugs in elderly people.

Our study has several limitations. First, our population was mostly European. The race factor in MDRD and CKD-EPI has recently been extensively questioned.[43,44] As a reminder, no black subjects were included in the seminal CG article. Dedicated studies in patients of African ancestry are urgently needed to assess the performance of the CG equation compared to more recent estimating equations. Second, the EKFC equations were developed from the identical large cohort (in whole or in part). However, the results were similar when the analysis was restricted to the external validation dataset. An external validation performed by independent investigators would further strengthen our results. Third, the performance of new equations like LMR and EKFC is close to 87% (P30 accuracy), not far from the recommended target by the Kidney Disease Outcomes Quality Initiative.[45] However, there is insufficient performance in subgroups and in specific patients and situations (eg, for drug dosage adjustment of drugs with narrow therapeutic window, the use of measured GFR must be considered). Fourth, the performance of equations has been studied against different methods of measuring GFR. All these methods are recognized methods[33] but some differences could persist and explain at least in part the results in estimating GFR. Finally, our study remains cross-sectional. Our results could pave the way for a prospective study with patients randomized for drug dosage (based on CG in one group and EKFC or LMR in the other group) with efficacy and safety endpoints definitively answering the question of which equation is the best for drug dosage adjustment.

In conclusion, the older CG equation which is still used for drug dosing purpose is the worst performing equation to estimate GFR and to correctly classify patients in the GFR staging system, in comparison to modern creatinine-based equations. Among these modern equations, EKFC and LMR performed better than CKD-EPI and MDRD equations.

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COMPETING INTERESTS

The results presented in this paper have not been published previously in whole or part. U. Nyman has received lecture fees from GE Healthcare AB. M. Courbebaisse has received grant support from BIOPAL, USA. N. Dalton is a Director of and minority shareholder in a University/NHS spin-out company, SpOtOn Clinical Diagnostics, and has grant support from NHS Health Technology Assessment and the Juvenile Diabetes Research Foundation. N. Ebert has received lecture fees from Siemens Healthineer and Roche Diagnostics. B.O. Eriksen has received lecture fees from Sanofi-Aventis. N. Kamar has received consulting fees or paid advisory boards, lecture fees and travel support from the following companies: Abbvie, Amgen, Astellas, Chiesi, Fresenius Medical Care, Gilead, Merck Sharp and Dohme, Neovii, Novartis, Roche, Sanofi and Shire. C. Legendre received consulting fees or paid advisory boards from CSL Behring and Novartis, and lecture fees from Sandoz. E. Schaeffner has received lecture fees from Siemens Healthineers and Fresenius Kabi. All remaining authors declared no competing interests.

CONTRIBUTORS

Conception of the study: P.D., H.P., J.B., U.N. Analysis and interpretation of data: P.D., H.P., J.B., U.N. Collection of data: J.B., M.C., L.C., N.E., B.O.E., R.N.D., L.D., F.G., C.G., A.G., L.J., M.H., N.K., E.J.L., C.L., K.L., C.M., T.M., L.R., A.D.R., E.S., P.O.S., U.B., K.A.M., L.S., A.A., A.L., A.B., U.N. Drafting of the article: P.D., H.P., J.B., U.N. All authors critically reviewed the manuscript, have accepted responsibility for the entire content of this manuscript and approved its submission.

DATA AVAILABILITY STATEMENT

The EKFC dataset used in the present study is hosted by the Lund University Population Research Platform. Legal and ethical restrictions prevent public sharing of the dataset. Data can be made available for collaborations upon request to interested researchers but would generally require a new ethical permission and the permission of each of the data-owners. You can find contact information for the data host at https://www.lupop.lu.se/.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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