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Original Article

ORIGINAL ARTICLE

Average creatinine–urea clearance: revival of an old analytical technique?

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ABSTRACT

Background. Creatinine-based equations such as the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) are recommended for estimating glomerular filtration rate (eGFR) in clinical practice, but have reduced performance in advanced stages of chronic kidney disease. However, only rarely studies have evaluated the performance of eGFR by measuring the average of the urinary clearances of creatinine and urea ($mCl_{UN\text{-}cr}$) compared with the eGFR equations.
Methods. This cross-sectional study evaluated the usefulness of $mCl_{UN\text{-}cr}$ in a population of 855 participants who performed a GFR measurement by urinary inulin clearance. The performance of $mCl_{UN\text{-}cr}$ was compared with those of CKD-EPI 2009 and CKD-EPI 2021, considering three criteria: bias, precision and accuracy.
Results. In the whole sample, the $mCl_{UN\text{-}cr}$ performed similarly to CKD-EPI equations (2009 and 2021) [precision: 11.5 (95% CI 10.5; 12.5) vs 19.0 (95% CI 17.2; 20.1) and 19.1 (95% CI 17.4; 20.4), and accuracy P_{30}: 97.0 (95% CI 95.8; 98.0) vs 82.0 (95% CI 79.2; 84.4) and 77.2 (95% CI 74.5; 80.0)]. The CKD-EPI equations (2009 and 2021) had the best performance when mGFR was >60 mL/min/1.73 m^2. In contrast, the $mCl_{UN\text{-}cr}$ performed better than others with lowest mGFR values, more noticeable when mGFR was <60 mL/min/1.73 m^2.
Conclusions. The study described the best performance of $mCl_{UN\text{-}cr}$ at GFR levels below 60 mL/min/1.73 m^2 and a satisfactory result in the overall cohort. The findings point to a role of this tool, especially for estimating GFR in chronic kidney disease patients in developing countries, when reference measurement of GFR is not available.

Keywords: CKD-EPI equation, creatinine clearance, glomerular filtration rate, inulin, urea clearance

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INTRODUCTION

The classification of chronic kidney disease (CKD) is notably based on the glomerular filtration rate (GFR) [1–3]. In everyday practice, measurement of GFR (mGFR) by reference methods (inulin, iohexol, iothalamate, ^{51}Cr-EDTA, etc.) is difficult to perform, and CKD clinical guidelines have recommended equations to estimate GFR (eGFR) as non-invasive alternatives, especially equations based on plasma creatinine (PCr), such as the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [1–5].

The 2009 CKD-EPI equation was developed to provide a more accurate eGFR among individuals with normal or slightly reduced mGFR and is recommended to estimate GFR in adults of any age in North America, Europe and Australia, considering age, sex and ethnicity [1, 2, 6, 7]. This equation was developed using data pooled from 10 studies using iothalamate as a reference method. A new CKD-EPI equation (CKD-EPI 2021) without ethnicity was developed and considered sufficiently accurate for clinical practice, although equations that use two markers (PCr and cystatin C) are more accurate in estimating mGFR than equations with either the PCr or cystatin C level alone [8]. Besides, the CKD-EPI equation cannot be used in all patients in clinical practice, especially patients with severe chronic disease or with low muscle mass or who are undernourished, when PCr does not reflect renal function [1–5, 9].

The determination of urinary creatinine clearance (mCl_{cr}) is an alternative method of eGFR evaluation. Nevertheless, mCl_{cr} is not ideal for this purpose, partly because PCr depends on non-renal factors, such as age, gender, ethnicity, muscle mass, diet, drugs and proximal tubular secretion (10%–40%) [1, 2, 10–12]. Even with an accurate urine collection, the mCl_{cr} overestimates mGFR by 10%–40% [3, 4, 10, 12–18].

Among patients with severe CKD (stages 4–5), the urinary urea clearance (mCl_{UN}) significantly underestimated mGFR [13–16, 19]. Since mCl_{cr} significantly overestimates mGFR, some authors have proposed to calculate the average between mCl_{cr} and mCl_{UN} ($mCl_{UN\text{-}cr}$) in patients with advanced kidney disease [4, 14, 17, 19, 20]. The 2005 European Best Practices Guidelines recommended this method to estimate GFR in severe CKD stages (stages 4–5) [21]. However, remarkably, there is a scarcity of articles concerning the $mCl_{UN\text{-}cr}$ [11–14, 16–19]. Therefore, the aim of this study is to evaluate the usefulness of $mCl_{UN\text{-}cr}$ as an alternative method when reference measurement is not available, and to compare the performance of $mCl_{UN\text{-}cr}$ with those of CKD-EPI 2009, CKD-EPI 2021 and mCl_{cr}, using urinary inulin clearance as a reference method.

MATERIALS AND METHODS

Study population

This retrospective, cross-sectional study considered all 855 consecutive participants who performed a GFR measurement by urinary inulin clearance between July 2003 and July 2013 in a single university hospital (Renal and Metabolic Function Exploration Unit of Edouard Herriot Hospital, Lyon, France). Indications for assessment were: suspected or established renal dysfunction, renal risk or before kidney donation.

Patients were further divided by renal function according to the KDIGO classification as follows: stage 1 (mGFR $\geq$90 mL/min/1.73 m^2), stage 2 (60 $\leq$ mGFR $<$ 90 mL/min/1.73 m^2), stage 3A (45 $\leq$ mGFR $<$ 60 mL/min/1.73 m^2), stage 3B (30 $\leq$ mGFR $<$ 45 mL/min/1.73 m^2) and stage 4–5 (mGFR $<$30 mL/min/1.73 m^2). Stages 4 and 5 CKD were combined due to the low number of patients in each group.

All procedures were conducted in accordance with institutional ethical standards, the 2013 Helsinki Declaration and its later amendments, or with comparable ethical standards. Precisely, an appropriate informed consent was obtained from each participant or his/her legal representatives. The consent form included information on the procedure itself and on the possibility of later use of the data for research purposes.

Laboratory assessments

GFR, mCl_{cr} and mCl_{UN} measurements

The GFR was measured by renal clearance of inulin (polyfructosan, Inutest; Fresenius Kagi, Graz, Austria). A standard technique was used by a trained staff with a continuous infusion after a priming dose of 30 mg/kg of polyfructosan. Water diuresis was induced by oral administration of 5 mL/kg of water followed by 3 mL/kg every 30 min, combined with an intravenous infusion of 0.9% sodium chloride. This enabled the patients to spontaneously empty their bladder every 30 min. Patients requiring intermittent urethral catheterization were excluded from this study. Three to four urine samples were collected and a blood sample was drawn mid-way through each collection period. Plasma and urine polyfructosan, creatinine and urea measurements were performed to determine mGFR, mCl_{cr} and mCl_{UR} at the same time using the standard UV/P formula. The clearance values were obtained from the mean values of the three to four clearance periods for each of the parameters. $mCl_{UN\text{-}cr}$ was calculated as the mean of final result of mCl_{cr} and mCl_{UR}. All the mGFR results were expressed in 1.73 m^2, according to the Dubois formula: body surface area = height$^{0.725}$ $\times$ weight$^{0.425}$ $\times$ 0.007184 [22].

Polyfructosan measurements

Plasma and urine polyfructosan were measured using the same enzymatic method [20] for which we previously checked the imprecision of the assay method (within-run precision values of 0.3% and 0.7%, respectively, and between-run precision values of 3.5%, 1.6% and 2.4% at mean values of polyfructosan 117, 198 and 285 mg/L, respectively) [23].

Creatinine and urea measurements

All creatinine measurements were performed with methods traceable to the National Institute of Standards and Technology [isotope dilution mass spectrometry (IDMS)-calibrated]. From October 2003 to June 2010, plasma and urine creatinine was obtained by a kinetic colorimetric compensated Jaffé technique (Roche Modular, Meylan, France) whose results were standardized by linear regression adjustment versus the concentrations obtained by liquid chromatography mass spectrometry. The calibration equation was as follows: standardized PCr = 0.9395 $\times$ Jaffé compensated serum creatinine (in μmol/L) + 4.6964. The coefficient of correlation was 0.97. From June 2010, all plasma and urine creatinine values were obtained by an enzymatic technique (Architect c®, Abbott Diagnostics) traceable to the National Institute of Standards and Technology (NIST SRM 967 and NIST SRM 914). According to KDIGO, the two techniques are relatively similar. Plasma creatinine was expressed in µmol/L. The urea was measured by an enzymatic method and expressed in mmol/L.

GFR estimation

Concomitantly GFR was estimated in each patient by the CKD-EPI equations (2009 and 2021). According to the French recommendations (Haute Autorité de Santé), no correction factor for race and ethnicity in the CKD-EPI 2009 equation should be applied in the European population; therefore, data concerning race and ethnicity were not collected and were not available.

Statistical analysis

The study considered three criteria for performance: bias, precision and accuracy. Bias was defined as the median difference between mGFR and eGFR. Thus, a positive bias indicates an underestimation of mGFR and vice versa. Precision was defined as the interquartile range (IQR) of the differences between mGFR and eGFR. Accuracy was considered under two criteria: (i) the root mean square error (RMSE), calculated as the square root of the difference $(\log \text{mGFR} - \log \text{eGFR})^2$; (ii) the percentage of estimates within ±10% (P_{10}) and ±30% (P_{30}) of the mGFR. A $P_{30} > 90\%$ qualifies an eGFR as satisfactory for clinical interpretation [1]. Agreement was also assessed by the concordance correlation coefficient (CCC) between each eGFR and the mGFR (after logarithmic transformation of their values). The CCC is a measure of agreement that adjusts the Pearson correlation coefficient downward whenever there is a systematic bias between the methods being compared. We compared the correct classification refers to agreement between mGFR and eGFR categories of ≥90, 60–89, 45–59, 30–44 and <30 mL/min/1.73 m^2.

The 95% confidence intervals (CIs) were calculated using a bootstrap method BCa (2000 bootstraps). Median biases were compared using Mood's median test. P_{10} and P_{30} values were compared using pairwise McNemar, exact, and permutation tests as a *post hoc* to Cochran Q test. The method of Holm–Bonferroni was used to correct for multiple comparisons.

In the study, the sample size was large and the variability was narrow. Thus, small changes in any variable could lead to small *P*-values. In order to reduce random bias, the nominal *P*-value considered for statistical significance was <.005.

The analyses were performed with R for Windows, version 4.1.2 (R-Cran project, http://cran.r-project.org/).

RESULTS

The clinical characteristics of the 855 participants, are shown in Table 1. The participants' mean age (±SD) was 47.4 ± 14.4 years and 50.4% were women. The mean mGFR (±SD) was 71.3 ± 28.2 mL/min/1.73 m^2 (10–168 mL/min/1.73 m^2), and 36.5% of measurements were below 60 mL/min/1.73 m^2.

Table 1: The sociodemographic and clinical characteristics of the 855 participants.

Characteristic	Whole cohort
Participants, *n* (%)	855 (100.0)
Mean age (range), years	47.4 ± 14.4 (18.0; 83.1)
Female sex, *n* (%)	431 (50.4)
Mean weight, kg	65.9 ± 15.4
Mean height, m	1.66 ± 0.09
Mean BSA, m^2	1.73 ± 0.21
Mean BMI, kg/m^2	23.8 ± 5.0
BMI ≥30, *n* (%)	83 (9.7)
Diabetes, *n* (%)	128 (15.0)
Mean PCr, mg/dL	1.14 ± 0.50
Mean mGFR in all participants, mL/min/1.73 m^2	71.3 ± 28.2
mGFR category, *n* (%)	
<30 mL/min/1.73 m^2	51 (6.0)
30 to <44 mL/min/1.73 m^2	105 (12.3)
45 to <59 mL/min/1.73 m^2	156 (18.2)
60 to <90 mL/min/1.73 m^2	316 (36.9)
≥90 mL/min/1.73 m^2	227 (26.6)
Median albuminuria (IQR), mg/g	28.0 (8.0; 185.5)
Albuminuria, *n* (%)	
UACR <30 mg/g	667 (75.5)
UACR 30–300 mg/g	164 (18.5)
UACR >300 mg/g	24 (6.0)

Data are presented as mean ± standard deviation, median (IQR) or *n* (%).

Comparison of the performance of GFR estimating equations

In the overall population, the CKD-EPI (2009 and 2021) equations and mClcr overestimated the mGFR, whereas the mCl_{UN} underestimated it. Although bias was similar for the CKD-EPI equations and $mCl_{UN\text{-}cr}$, the precision was superior for $mCl_{UN\text{-}cr}$ [IQR (95% CI) 11.5 (10.5; 12.5), $P < .001$], as was accuracy [P_{10} and P_{30}, 48.0% (44.5; 51.2) and 97.0 (95.8; 98.0), $P < .001$] and the lower RMSE (95% CI) [0.130 (0.122; 0.146)]. In addition, $mCl_{UN\text{-}cr}$ had the only CCC greater than 0.9 [0.941 (0.933; 0.948)]. Performance of the mCl_{cr} was the worst for all metrics (Table 2). Graphically, the smallest dispersion of the points around the regression line and the closest proximity of the concordance line (45° line) are observed for $mCl_{UN\text{-}cr}$ (Fig. 1).

Table 2: Bias, precision and accuracy of the four GFR estimating equations.

Subjects and criteria	CKD-EPI 2009 equation	CKD-EPI 2021 equation	Creatinine clearance	Urea clearance	Average of creatinine and urea clearances
Population = 855					
Median bias (95% CI)	−3.7 (−4.7; −2.5)	−6.6 (−7.8; −5.5)	−14.0 (−14.0; −13.0)*	26.0 (25.0; 27.0)*	5.5 (4.5; 6.0)
IQR (95% CI)	19.0 (17.2; 20.1) *	19.1 (17.4; 20.4)*	14.0 (13.0; 15.0)*	20.0 (18.0; 21.0)*	11.5 (10.5; 12.5)
P_{10} (95% CI)	37.1 (33.8; 40.5)*	36.3 (33.1; 39.4)*	19.7 (17.2; 22.5)*	0.8 (0.02; 1.5)*	48.0 (44.5; 51.2)
P_{30} (95% CI)	82.0 (79.2; 84.4)*	77.2 (74.5; 80.0)*	66.0 (62.8; 69.2)*	20.1 (17.5; 22.9)*	97.0 (95.8; 98.0)
CCC (95% CI)	0.844 (0.824; 0.862)	0.825 (0.803; 0.844)*	0.825 (0.807; 0.841)*	0.599 (0.573; 0.624)*	0.941 (0.933; 0.948)
RMSE (95% CI)	0.234 (0.220; 0.254)	0.235 (0.221; 0.254)	0.159 (0.149; 0.171)	0.149 (0.141; 0.160)	0.130 (0.122; 0.146)
Agreement[a] (%)	59.7 (56.6; 63.2)*	59.3 (56.0; 62.5)*	54.4 (51.0; 57.8)*	9.5 (7.7; 11.6)*	70.3 (67.1; 73.3)*

Bias is defined as the median difference between mGFR and eGFR. A positive sign indicates underestimation of mGFR, and a negative sign indicates overestimation of mGFR. P_{10} and P_{30} are the proportion of eGFR within 10% and 30% of mGFR, respectively.

[a]Agreement: correct classification refers to agreement between mGFR and eGFR categories of ≥90, 60–89, 45–59, 30–44 and <30 mL/1.73 m^2.

*$P < .005$ between average clearance creatinine–urea and others eGFR.

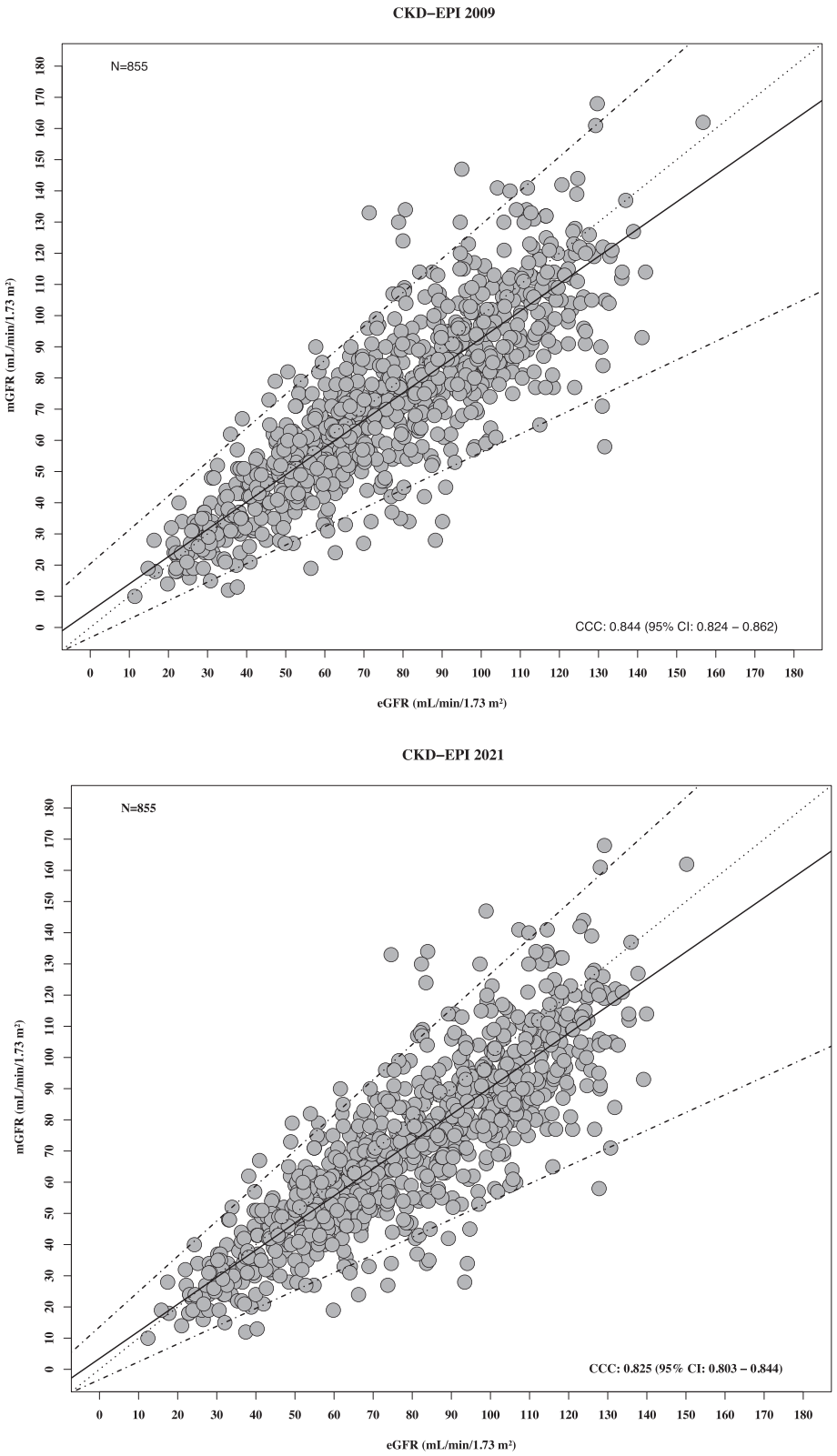
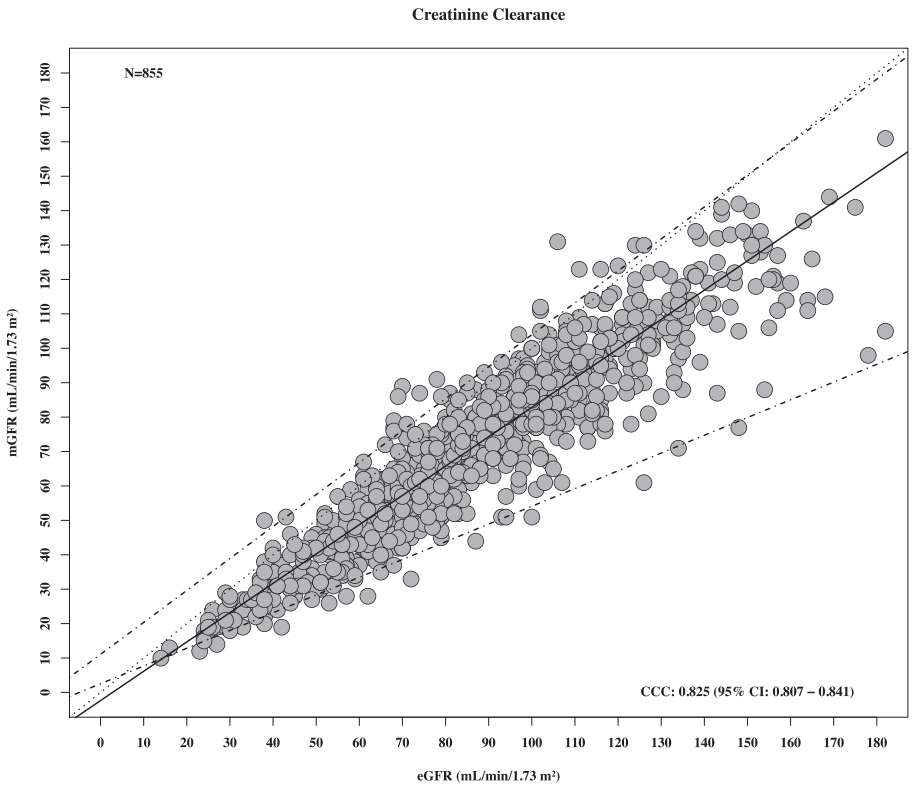


Figure 1: Scatterplots showing, for each estimated GFR versus the measured GFR (in mL/min/1.73 m^2). The plain line represents the line regression. The dashed lines represent the 95% confidence limits. The dotted lines represent the perfect concordance.



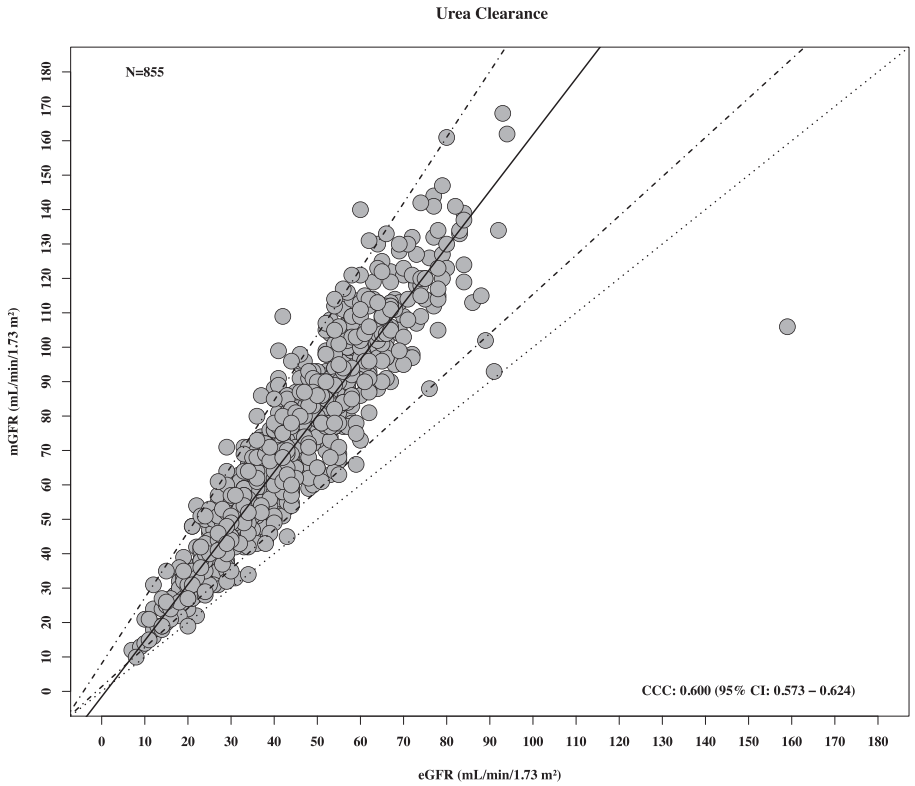


Figure 1: Continued.

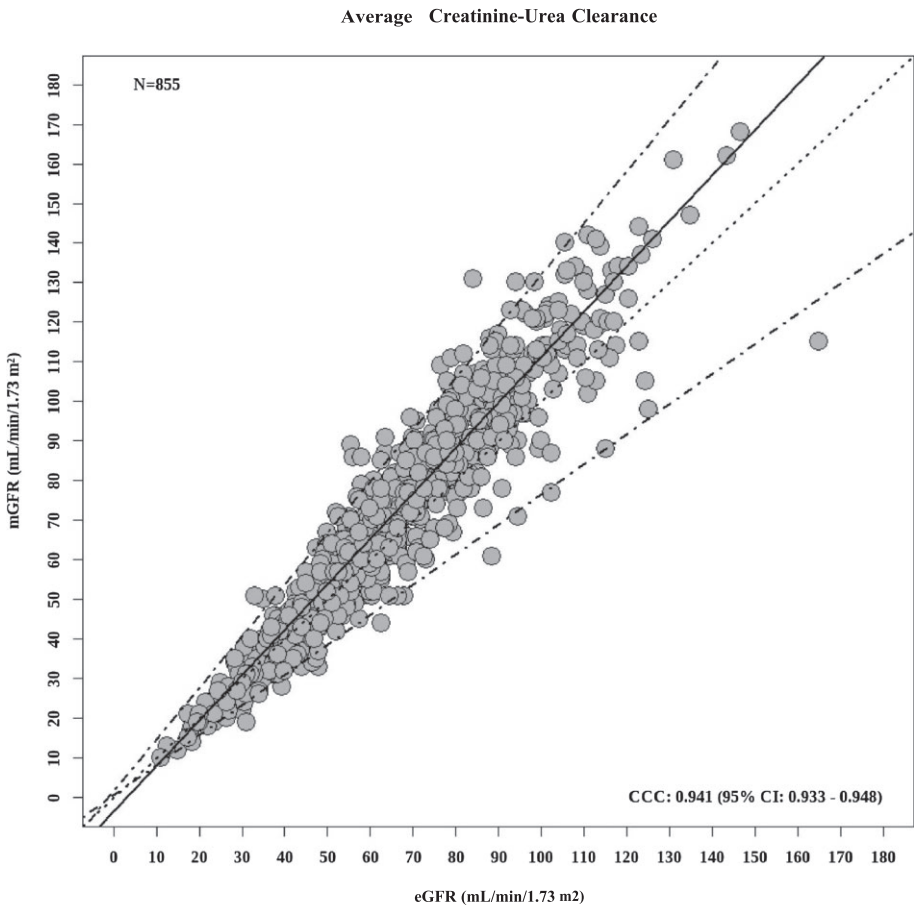


Figure 1: Continued.

Agreement according to the KDIGO classification

The overall correct classification for mGFR categories of ≥90, 60–89, 45–59, 30–44 and <30 mL/min/1.73 m^2 was better for $mCl_{UN\text{-}cr}$ [70.3% (67.1; 73.3)] than the other eGFR equations (Table 2).

At mGFR ≥90 mL/min/1.73 m^2, the CKD-EPI equations (2009 and 2021) performed better than mCl_{cr}, mCl_{UN} and $mCl_{UN\text{-}cr}$, regarding bias [1.0 (−1.5; 3.5) and −2.5 (−5.0; −0.7)] and accuracy P_{30} [94.3 (90.8; 97.0) and 94.3 (91.2; 97.4)], but had less precision than $mCl_{UN\text{-}cr}$ [IQR 21.5 (17.0; 25.0) and 20.0 (16.5; 24.0) versus 11.5 (9.5; 13.5)]. The $mCl_{UN\text{-}cr}$ had the best precision with the smallest value of IQR whatever the mGFR category (Table 3).

The CKD-EPI equations (2009 and 2021) had better performance than mCl_{cr}, mCl_{UR} and $mCl_{UN\text{-}cr}$ when mGFR was >60 mL/min/1.73 m^2. In contrast, the $mCl_{UN\text{-}cr}$ performed better than the other four with lowest mGFR values, more noticeable when mGFR <60 mL/min/1.73 m^2 (Table 3).

The performance of the equations was similar considering the gender of the participants (Table 4).

DISCUSSION

The present study compared the performance of mClcr, $mCl_{UN\text{-}cr}$ and CKD-EPI equations (2009 and 2021) using urinary inulin clearance as the reference method and reported the following main findings: (i) satisfactory performance of $mCl_{UN\text{-}cr}$ compared with mClcr and CKD-EPI equations in the overall cohort; (ii) best performance of CKD-EPI equations when when mGFR is >60 mL/min/1.73 m^2; (iii) best performance of $mCl_{UN\text{-}cr}$ when mGFR is <60 mL/min/1.73 m^2; and (iv) similarity between the CKD-EPI equations 2009 and 2021.

Previous studies have already highlighted the global lack of precision of the eGFR equations [1, 2, 7]. However, only few articles have compared the performance of $mCl_{UN\text{-}cr}$ and eGFR equations, although urea and PCr measurements are well-established laboratory tests [12, 20]. The $mCl_{UN\text{-}cr}$has been used in studies on the contribution of residual GFR to adequacy of dialysis treatment as suggested by the European Best Practices Guidelines [21]. This tool is recommended for patients who are in in the late stages of renal failure. Urea clearance significantly underestimates the GFR. Since the mCl_{cr} overestimates this function, one alternative could be to average both the PCr and urea clearances that may give a more accurate eGFR than either clearance by itself [5, 20, 24]. Our study is the first to show a superior performance of $mCl_{UN\text{-}cr}$ over CKD-EPI equations and mCl_{cr} when compared with the clearance of inulin in patient with moderate and advanced CKD (mean GFR 71.3 mL/min/1.73 m^2). On the contrary, the utility of $mCl_{UN\text{-}cr}$ was not demonstrated by Thye *et al*. in 81 subjects with preserved renal function (mean mGFR 123.66 mL/min/1.73 m^2) [25].

The 2009 CKD-EPI equation is reasonably accurate for following changes in GFR over time, and is recommended for estimating GFR in adults of any age in North America, Europe and Australia [1, 2, 5, 6]. It was developed in a North American and European population with a wide age range and a mean mGFR of 68.0 mL/min/1.73 m^2 [6]. Our analyses showed that the

Table 3: Bias, precision and accuracy of the four GFR estimating equations.

Subjects and criteria	CKD-EPI 2009 equation	CKD-EPI 2021 equation	Creatinine clearance	Urea clearance	Average of creatinine and urea clearances
mGFR ≥90 mL/min/1.73 m^2 ($N = 227$)					
Median bias (95% CI)	1.0 (−1.5; 3.5)	−2.5 (−5.0; −0.7)	−17.0 (−18.0; −14.0)	43.0 (41.0; 45.0)	13.5 (12.5; 14.5)
IQR (95% CI)	21.5 (17.0; 25.0)	20.0 (16.5; 24.0)	18.0 (15.0; 20.0)	13.5 (12.0; 15.0)	11.5 (9.5; 13.5)
P_{10} (95% CI)	49.7 (43.2; 56.4)*	52.0 (45.8; 58.2)*	33.9 (28.2; 40.0)*	0.5 (0.0; 1.5)*	35.2 (29.1; 41.4)
P_{30} (95% CI)	94.3 (90.8; 97.0)*	94.3 (91.2; 97.4)*	88.1 (83.7; 92.7)	6.7 (3.5; 9.7)*	98.2 (96.5; 99.6)
mGFR 60–89 mL/min/1.73 m^2 ($N = 316$)					
Median bias (95% CI)	−4.0 (−5.8; −2.0)	−8.0 (−9.3; −5.1)	−14.0 (−15.0; −13.0)*	28.0 (27.0; 29.0)*	7.0 (6.0; 7.5)
IQR (95% CI)	21.0 (19.0; 23.0)	21.5 (19.0; 23.0)	14.0 (12.0; 16.0)	8.0 (7.0; 10.0)	9.0 (8.0; 10.0)
P_{10} (95% CI)	39.6 (34.2; 45.0)*	36.0 (31.0; 42.0)*	21.5(17.1; 26.3)*	0.0 (0.0; 1.0)*	47.5 (41.8; 52.5)
P_{30} (95% CI)	86.1 (82.0; 90.0)*	81.0 (76.6; 85.1)*	74.4 (69.6; 78.8)*	14.9 (11.1; 19.0)*	97.8 (96.0; 99.0)
mGFR 45–59 mL/min/1.73 m^2 ($N = 156$)					
Median bias (95% CI)	−6.0 (−8.5; −3.5)	−8.8 (−11.5; −6.5)	−15.0 (−16.0; −13.0)*	6.0 (5.0; 8.0)	2.0 (1.0; 3.0)
IQR (95% CI)	17.0 (14.5; 21.0)	17.0 (15.0; 21.0)	9.0 (4.5; 13.5)	6.0 (5.0; 8.0)	7.0 (5.5; 9.0)
P_{10} (95% CI)	27.0 (20.0; 34.0)*	27.5 (20.5; 34.6)*	24.5 (21.0; 28.0)*	0.6 (0.0; 1.9)*	62.2 (54.5; 70.0)
P_{30} (95% CI)	74.5 (67.0; 80.8)*	66.7 (59.0; 74.3)*	50.6 (43.0; 58.3)*	26.3 (19.2; 33.3)*	98.1 (95.5; 100.0)
mGFR 30–44 mL/min/1.73 m^2 ($N = 105$)					
Median bias (95% CI)	−5.0 (−8.5; −2.4)	−7.5 (−10.5; −4.5)*	14.0 (12.0; 17.0)	−12.0 (−13.0; −12.0)*	1.0 (−0.5; 2.0)
IQR (95% CI)	13.0 (10.5; 18.0)	14.0 (11.0; 18.5)	13.0 (11.0; 14.0)	6.0 (4.0; 7.0)	7.5 (5.0; 8.0)
P_{10} (95% CI)	23.8 (16.2; 32.4)*	24.8 (17.2; 33.3)*	6.7 (2.9; 11.4)*	2.9 (0.0; 6.7)*	55.2 (45.7; 64.8)
P_{30} (95% CI)	68.6 (60.0; 77.0)*	60.0 (50.5; 68.6)*	36.2 (26.7; 45.7)*	35.2 (26.7; 44.8)*	95.3 (90.5; 99.0)
mGFR <30 mL/min/1.73 m^2 ($N = 51$)					
Median bias (95% CI)	−6.0 (−10.0; −3.5)	−7.0 (−12.0; −5.0)*	−9.0 (−12.0; −8.0)	−7.0 (−7.0; −6.0)	−1.5 (−2.5; −0.5)
IQR (95% CI)	14.0 (8.0; 21.0)	14.0 (8.5; 20.5)	6.0 (4.0; 10.0)	3.0 (2.5; 5.5)	4.0 (2.5; 6.0)
P_{10} (95% CI)	23.5 (11.8; 35.3)	17.6 (8.0; 29.4)	5.9 (0.0; 13.8)	3.9 (0.0; 9.8)	51.0 (37.3; 64.7)
P_{30} (95% CI)	51.0 (37.3; 64.7)	45.0 (31.3; 58.9)	23.5 (11.8; 35.3)	62.7 (49.0; 76.5)	86.3 (76.7; 94.1)

P_{10}, percentage of estimated GFRs that lay within range (measured GFR – 10% of measured GFR; measured GFR + 10% of measured GFR); P_{30}, percentage of estimated GFRs that lay within range (measured GFR – 30% of measured GFR; measured GFR + 30% of measured GFR).
*$P < .001$ between average clearance creatinine–urea and others eGFR.

CKD-EPI equation has a good performance (P_{30} = 82.0%) in our population and the recently published 2021 CKD-EPI equation, without ethnicity, was not statistically or clinically superior to the 2009 CKD-EPI equation (P_{30} 77.2%), although ethnicity was not available in our data.

The CKD-EPI equations (2009 and 2021), as previously shown, are less biased and more accurate than mCl_{cr} in the study population. In fact, the mCl_{cr} alone is an inaccurate method for the measurement of GFR because it overestimates the GFR as a consequence of the PCr tubular secretion, notably in CKD class 4–5 [1, 3, 11, 13–15, 19]. Also, there are two major errors that can limit the accuracy of the mCl_{cr}: an inaccurate urine collection and increasing creatinine secretion. An alternative to increase the reliability of the urine sample would be to estimate the completeness of the collection, monitoring the creatinine excretion by weight. In adults, daily creatinine excretion should be 20–25 mg/kg lean body weight in men and 15–20 mg/kg lean body weight in women [26]. Kim *et al.* showed that with progressive decline of GFR the mCl_{cr} tends to become proportionately higher than the corresponding inulin clearance [27]. Zhang *et al.* propose that measurement error provides an alternative explanation for the ratio of mClcr/mGFR gets larger at lower mGFR levels [28].

The mCI_{UN} alone is rarely used for kidney function because it underestimates the mGFR [13–16]. A high protein diet, tissue breakdown, major gastrointestinal haemorrhage and corticosteroid therapy can lead to an increase in the urea whereas a low protein diet and liver disease can lead to a reduction. A 40%–50% of filtered urea may be reabsorbed by the tubules, while the proportion is reduced in advanced renal failure [11, 13–15, 17, 18, 24]. When kidney function declines, the degree of this underestimation decreases and the mCl_{UN} approximates the mGFR. The explanation for this is that during the course of renal disease, the number of functioning nephrons declines. The capacity to reabsorb water is impaired and the fraction of urea reabsorbed also diminishes [11, 13, 15, 16]. Besides, the technique reliability also depends on proper urine collection.

Although the study showed that the $mCl_{UN\text{-}cr}$ method could play a role in estimating GFR in late stages of kidney disease, there is still a limitation of urinary collection. Alternatively, some authors have described shorter periods of urinary collection with acceptable performance to estimate GFR. Okuda *et al.* evaluated the usefulness of the $mCl_{UN\text{-}cr}$ examined over a 1-h urine collection period in children, compared with urinary inulin clearance [29]. In addition, Uemura *et al.* compared urinary inulin clearance with 2-h and 24-h urine collection mCl_{cr}. They found that 24-h mCl_{cr} was approximately 80% of 2-h mCl_{cr}, and overestimated GFR approximately 1.3-fold, while the 2-h mCl_{cr} overestimated GFR approximately 1.5-fold [30].

The strengths of the study were: (i) the wide ranges in age (18–83 years) and GFR levels (10–168 mL/min/1.73 m^2); (ii) the IDMS standardization of PCr measurements according to international recommendations; (iii) the performance of the equations compared with a gold standard (inulin) for GFR measurement; and (iv) the use of rigorous statistical techniques based on a large population. The limitations were: (i) the study populations included few non-Caucasian patients and thus it could not assess the effect of ethnicity for 2009 CKD-EPI equation; and (ii) the data collection was retrospective and the $mCl_{UN\text{-}cr}$ versus mGFR should be clarified in a prospective study.

Table 4: Bias, precision and accuracy of the four GFR estimating equations.

Subjects and criteria	CKD-EPI 2009 equation	CKD-EPI 2021 equation	Creatinine clearance	Urea clearance	Average of creatinine and urea clearances
Males ($n = 424$)					
Median bias (95% CI)	−4.6 (−6.4; −3.7)	−8.2 (−9.4; −6.6)	−15.0 (−16.0; −14.0)*	25.0 (23.0; 26.0)*	4.0 (3.5; 5.5)
IQR (95% CI)	18.0 (16.5; 21.0)*	19.0 (16.8; 21.4)*	14.0 (13.0; 16.0)*	21.0 (18.0; 23.0)*	11.5 (10.0; 13.0)
P_{10} (95% CI)	35.8 (31.6; 40.5)*	34.9 (30.7; 39.6)*	17.7 (13.9; 21.5)*	1.2 (0.2; 2.4)*	50.7 (46.0; 55.4)
P_{30} (95% CI)	80.0 (76.2; 83.7)*	73.8 (69.6; 78.1)*	62.3 (57.5; 67.0)*	25.5 (21.5; 29.7)*	96.4 (94.6; 98.1)
CCC (95% CI)	0.843 (0.814; 0.868)	0.821 (0.790; 0.849)*	0.821 (0.794; 0.844)*	0.624 (0.587; 0.658)*	0.945 (0.935; 0.954)
RMSE (95% CI)	0.235 (0.215; 0.260)	0.235 (0.216; 0.260)	0.160 (0.148; 0.182)	0.154 (0.142; 0.175)	0.136 (0.123; 0.163)
Agreement[a] (%)	58.5 (53.8; 63.2)*	57.8 (52.8; 62.5)*	53.8 (48.4; 57.8)*	11.8 (8.9; 14.8)*	70.5 (66.3; 75.0)*
Females ($n = 431$)					
Median bias (95% CI)	−2.0 (−3.7; −0.7)	−4.6 (−6.3; −2.9)	−14.0 (−15.0; −12.0)*	27.0 (26.0; 28.0)*	6.0 (5.5; 7.5)
IQR (95% CI)	17.5 (15.8; 20.7)*	18.4 (15.8; 21.4)*	13.0 (11.0; 14.5)*	18.0 (16.0; 20.0)*	11.5 (10.5; 13.0)
P_{10} (95% CI)	38.3 (33.8; 42.9)*	37.6 (33.0; 42.2)*	14.8 (11.6; 18.1)*	0.4 (0.0; 1.7)*	45.2 (40.6; 50.0)
P_{30} (95% CI)	83.7 (80.3; 87.0)*	80.5 (76.8; 84.2)*	69.6 (65.0; 73.8)*	14.8 (11.8; 18.3)*	97.5 (95.8; 98.8)
CCC (95% CI)	0.845 (0.816; 0.869)*	0.829 (0.798; 0.855)*	0.830 (0.804; 0.852)*	0.575 (0.538; 0.610)*	0.936 (0.925; 0.946)
RMSE (95% CI)	0.232 (0.211; 0.261)	0.232 (0.211; 0.260)	0.156 (0.144; 0.172)	0.142 (0.132; 0.154)	0.122 (0.111; 0.134)
Agreement[a] (%)	61.0 (56.4; 65.7)*	60.7 (56.1; 65.4)*	55.7 (51.0; 60.6)*	7.5 (5.1; 10.0)*	70.0 (65.7; 74.3)*

Bias is defined as the median difference between mGFR and eGFR. A positive sign indicates underestimation of mGFR, and a negative sign indicates overestimation of mGFR. P_{10} and P_{30} are the proportion of eGFR within 10 and 30% of mGFR, respectively.

[a]Agreement: correct classification refers to agreement between mGFR and eGFR categories of ≥90, 60–89, 45–59, 30–44 and <30 mL/1.73 m^2.

*$P < .005$ between average clearance creatinine–urea and others eGFR.

This study shows that there is a role for the $mCl_{UN\text{-}cr}$ in evaluating advanced CKD when the nephrologist wants more precision than the eGFR equations (CKD-EPI) and the reference measurement of GFR is not available. From another perspective, the use of $mCl_{UN\text{-}cr}$ requires no additional laboratory costs (e.g. exogenous marker) and is easy to use, and so is an interesting option especially in developing countries.

AUTHORS' CONTRIBUTIONS

L.S. designed the study, and performed data analysis and statistical considerations. L.D.-D. designed the study, participated in the recruitment of patients and contributed data interpretation. V.S. contributed to conceptualization and design of the study, and wrote the first draft and the final version of the manuscript, which was critically read by L.D.-D., C.N. L.J. and S.L. participated in the recruitment of patients. C.N. evaluated data and critically supervised the final version of the manuscript. All authors revised and approved the final version of the manuscript.

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DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available on request from the corresponding author.

CONFLICT OF INTEREST STATEMENT

L.J. reports consultancy agreements with AstraZeneca, Baxter, Vifor, Fresenius, Hemotech and Sanofi. All remaining authors have nothing to disclose.

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