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The revised Lund-Malmö GFR estimating equation outperforms MDRD and CKD-EPI across GFR, age and BMI intervals in a large Swedish population

Abstract

Background: The performance of creatinine-based glomerular filtration rate (GFR) estimating equations may vary in subgroups defined by GFR, age and body mass index (BMI). This study compares the performance of the Modification of Diet in Renal Disease (MDRD) study and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations with the revised Lund-Malmö equation (LM Revised), a new equation that can be expected to handle changes in GFR across the life span more accurately.

Methods: The study included 3495 examinations in 2847 adult Swedish patients referred for measurement of GFR (mGFR) 2008–2010 by plasma clearance of iothexol (median 52 mL/min/1.73 m²). Bias, precision [interquartile range (IQR)] and accuracy [percentage of estimates $\pm 10\%$ (P_{10}) and $\pm 30\%$ (P_{30}) of mGFR] were compared.

Results: The overall results of LM Revised/MDRD/CKD-EPI were: median bias 2%/8%/11%, IQR 12/14/14 mL/min/1.73 m², P_{10} 40%/35%/35% and P_{30} 84%/75%/76%. LM Revised was the most stable equation in terms of bias, precision and accuracy across mGFR, age and BMI intervals irrespective of gender. MDRD and CKD-EPI overestimated mGFR in patients with decreased kidney function, young adults and elderly. All three equations overestimated mGFR and had low accuracy in patients with BMI <20 kg/m², most pronounced among men.

Conclusions: In settings similar to the investigated cohort LM Revised should be preferred to MDRD and CKD-EPI due to its higher accuracy and more stable performance across GFR, age and BMI intervals.

Keywords: creatinine; glomerular filtration rate; kidney disease; kidney function tests; renal insufficiency.

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Introduction

During the last decade much attention in nephrology has been focused on estimating glomerular filtration rate (eGFR) using creatinine-based equations to improve the diagnosis of chronic kidney disease, a well-recognized worldwide public health problem leading to kidney failure, increased mortality and high costs [1, 2].

The four-variable Modification of Diet in Renal Disease (MDRD) Study equation [3] and the Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration equation [4], both developed during the 21st century, has been thoroughly validated and CKD-EPI is the primary choice of the 2013 international recommendation of the KDIGO (for “Kidney Disease: Improving Global Outcomes”) [1]. However, none of these two equations is optimal for all GFR ranges, patient subgroups, different nationalities and ethnicities [5–13]. Validation results may also be influenced by the chosen reference GFR measurement method [14, 15] and by the calibration of the creatinine assay as well as type of creatinine assay method [16]. Claiming traceability to isotope dilution mass spectrometry (IDMS) may not always be a guarantee for equality in calibration between laboratories [12].

An external validation from Sweden (Örebro University Hospital) indicated that the recently developed Lund-Malmö equation (LM Revised) was more accurate across subgroups than MDRD and CKD-EPI [12]. One possible explanation for this could be that LM Revised has two age terms with opposite signs (see Appendix), which opens up for a more accurate handling of expected changes in

GFR, but also in muscle mass, across the life span. There is evidence suggesting that both MDRD and CKD-EPI may overestimate GFR not only among elderly but also among young adults [10, 12]. Furthermore, the difference in the structure of the equations means that LM Revised, as opposed to MDRD and CKD-EPI, can also be applied among children [17]. However, the number of patients in subgroups defined by GFR level, age and body mass index (BMI) was limited in the previous Swedish validation, and there was also some doubts about the calibration of the used creatinine assays [12].

The aim of the present study was therefore to compare the equations in a new and larger Swedish cohort that allows for detailed subgroup evaluations. The study is based on recently calibrated IDMS-traceable enzymatic creatinine assays with concentration values close to that of a certified sample issued by Equalis AB (external quality assessment for clinical laboratory investigations in Sweden, www.equalis.se) [18].

Materials and methods

Patient samples

The present cohort, the Lund Cystatin C Standardization (LCS) cohort, was primarily established as part of an ongoing work with the international cystatin C calibrator [19]. The cohort is based on consecutive Swedish Caucasian ($\geq 99\%$) patients (≥ 18 years) referred for determination of GFR by iohexol clearance [20] at Skåne University

Hospital, Lund, from May 2008 to March 2010. During this period 3495 GFR determinations (Table 1) were performed in 2847 patients, of whom 500 patients were examined on more than one occasion. Common causes for referral were manifest or suspected diabetic nephropathy, interstitial nephritis, glomerulonephritis, nephrotic syndrome, hematuria, proteinuria, reflux nephropathy, myeloma, vasculitis, consideration of initiation of hemodialysis, evaluation of potential renal donors, control after kidney transplantation, and to dose drugs cleared by the kidneys.

Plasma concentration of creatinine, weight, height, age and gender were recorded at the time of the GFR examination. The blood samples were collected in Li-Heparinate tubes (Vacutainer system, Becton-Dickinson Inc., Franklin Lakes, NJ, USA). All procedures involving subjects and data were in agreement with the ethical principles for medical research involving human subjects established in the Helsinki Declaration of 1975, as revised in 2000. Samples and patient data were treated anonymously in all analyses.

Determination of iohexol clearance

GFR was measured (mGFR) as plasma clearance of iohexol using a single plasma sample technique, which is considered as reliable as using multisampling [21]. Five mL iohexol (Omnipaque 300 mg I/mL, GE Healthcare, Oslo, Norway) was administered intravenously in an antecubital vein. One plasma sample was drawn at varying times depending on the expected GFR [22, 23] estimated by the Cockcroft-Gault equation [24]; 3–4 h at eGFR >50 mL/min, 6–8 h at eGFR 20–50 mL/min and 22–30 h at eGFR <20 mL/min. The exact times of administration and blood sampling were documented. Plasma iohexol concentrations were determined by high-pressure liquid chromatography [25]. The total analytical coefficient of variation (CV) of the iohexol method was 2.2% for a control sample with an assigned value of 32 mg iohexol/L and 1.9% for a control sample with an assigned value of 63 mg iohexol/L.

Table 1 Patient characteristics of the Lund Cystatin C Standardization cohort of 3495 examinations (2847 patients; 1380 women and 1467 men).

Variables	All (n=3495)	Women (n=1647)	Men (n=1848)
Age, years	63 (21–86)	63 (24–86)	63 (19–86)
Total body weight, kg	77 (48–115)	68 (45–107)	83 (57–119)
Height, cm	170 (152–190)	164 (150–176)	176 (162–193)
Body surface area, m ²	1.88 (1.47–2.34)	1.75 (1.41–2.15)	1.99 (1.64–2.39)
Body mass index, kg/m ²	26 (18–39)	25 (18–40)	26 (19–37)
Plasma creatinine, μ mol/L	102 (46–465)	80 (42–365)	123 (55–505)
Measured GFR, mL/min/1.73 m ²	52 (10–115)	59 (11–116)	46 (9–114)
Measured GFR, number, %			
<30 mL/min/1.73 m ²	920 (26)	355 (22)	565 (31)
30–59 mL/min/1.73 m ²	1077 (31)	480 (29)	597 (32)
60–89 mL/min/1.73 m ²	987 (28)	533 (32)	454 (25)
≥ 90 mL/min/1.73 m ²	511 (15)	279 (17)	232 (13)
Estimated GFR, mL/min/1.73 m ²			
LM Revised	57 (11–110)	63 (12–111)	51 (10–110)
MDRD	57 (10–138)	64 (11–137)	53 (10–138)
CKD-EPI	60 (10–126)	68 (11–122)	54 (9–127)

Descriptive measures are given as median values (2.5 and 97.5 percentiles), if not stated otherwise.

The method described by Jacobsson [26] was used to calculate GFR from the iohexol concentration (see Appendix). Final GFR was normalized to 1.73 m² body surface area (BSA) using the equation of Dubois and Dubois (see Appendix) [27].

Determination of plasma creatinine

To minimize creatinine assay variations with time, as it will add to the total imprecision of the equations, and to use the most recent calibration against a certified standard, all 3495 blood samples were frozen at -70°C for later analysis. All samples were sent for analysis to the Department of Clinical Chemistry, Uppsala University Hospital, Sweden, as they had the capacity of analyzing a large number (up to 700) of tests per day on a single instrument. The same creatinine reagent batch was used for all tests. Plasma concentrations of creatinine were determined by an enzymatic colorimetric assay on an Architect Ci8200 analyzer (Abbott Laboratories, Abbott Park, IL, USA). The method is traceable to primary reference material with values assigned by IDMS (National Institute of Standards and Technology, SRM 967). The total CV for the creatinine method was 1.2% at 92 µmol/L and 0.9% at 346 µmol/L.

To investigate variation in the creatinine assays between laboratories, the plasma creatinine assays performed in Uppsala were compared with the analysis of the same samples (3259 available for comparison) made at the time of the measurement of iohexol clearance in Lund. Plasma concentrations of creatinine in Lund were determined by an enzymatic colorimetric assay on a Hitachi Modular P analyzer (Roche Diagnostics, Mannheim, Germany) and with an IDMS-traceable calibrator (National Institute of Standards and Technology, SRM 967). The CV was 1.7% at 70 µmol/L and 1.4% at 600 µmol/L.

Statistical evaluation of GFR equations

The three evaluated equations, LM Revised, MDRD and CKD-EPI, are presented in the Appendix. All statistical evaluations were conducted using SPSS release 20.0.0 (IBM Corp., NY, USA) and Microsoft Excel, focussing on bias, precision and accuracy [28]. Bias was defined as the median of the individual differences between eGFR and mGFR, expressed in mL/min/1.73 m² (median difference) and in percent relative to mGFR (median percentage difference). We denoted bias ≥10% in any direction as marked bias since median percentage difference of <10% of mGFR has been considered clinically acceptable [29]. Precision was assessed as the interquartile range (IQR) of the differences eGFR-mGFR and expressed in mL/min/1.73 m².

Accuracy was assessed from the absolute difference |eGFR-mGFR| and expressed in percent of mGFR. From these absolute percentage differences the accuracy was summarized by the median, i.e., a measure of how large the percentage error in eGFR is on average, and the percentage of estimates within 10% (labeled P₁₀) and 30% (labeled P₃₀) of mGFR. P₃₀ of at least 75% has been considered “sufficient for good clinical decision-making” [30]. The proportion of overestimations >+30% and underestimations <-30% was also evaluated.

Non-parametric and asymptotic 95% confidence intervals (CI) were calculated as measures of the statistical uncertainty in medians and proportions (P₁₀ and P₃₀) of the overall results, respectively. CIs

for IQR were estimated using bootstrap methods with 1000 replications [31]. We used McNemar’s exact test for pairwise comparisons of P₃₀.

Bias and accuracy (P₃₀) were evaluated in subgroups defined by mGFR (<30, 30–59, 60–89 and ≥90 mL/min/1.73 m²), age (18–29, 30–39, 40–49, 50–59, 60–69, 70–79 and ≥80 years), BMI (<20, 20–24, 25–29, 30–34, 35–39 and ≥40 kg/m²) and gender.

Detailed evaluations of the GFR-equations were based on the creatinine assays performed in Uppsala. In addition, the overall percentage bias and P₃₀ accuracy of the three eGFR-equations based on the creatinine assays in Uppsala were compared with the analysis of the same samples made at the time of the measurement of iohexol clearance in Lund.

Results

Variation in creatinine assays

The comparison of the creatinine methods in Lund and Uppsala resulted in the regression equation:

$$y(\text{creat. Lund})=1.01x(\text{creat. Uppsala})+0.56 (R^2=0.9927),$$

indicating no important systematic difference between the two assays. The reproducibility CV of the creatinine methods across the two laboratories was 4.9%, or expressed in eGFR: 5.2% for LM Revised, 5.4% for CKD-EPI and 12.3% for MDRD.

Overall equation performance

LM Revised had the smallest bias and highest precision resulting in the highest overall P₃₀ of the three equations (Table 2), 83.7%, i.e., 8.4 percentage points higher than MDRD (95% CI 7.1%–9.6%; p<0.001) and 8.0 percentage points higher than CKD-EPI (95% CI 6.9%–9.2%; p<0.001). CKD-EPI was the only equation that showed marked bias, 11% overestimation in median. Calculating eGFR based on the creatinine analyses from Lund instead of Uppsala had no important impact on bias, precision or accuracy (Table 2).

Limiting the results to the first examination in each patient, thereby decreasing the sample size from 3495 to 2847 examinations resulted in a marginal, roughly one percentage point increase in P₃₀; LM Revised 85.0% (95% CI 83.7%–86.3%), MDRD 76.2% (95% CI 74.6%–77.7%) and CKD-EPI 77.0% (95% CI 75.4%–78.5%) (see Supplemental data, Table 1, which accompanies the article at <http://www.degruyter.com/view/j/cclm.2014.52.issue-6/issue-files/cclm.2014.52.issue-6.xml>).

Table 2 Bias, precision and accuracy calculated from the differences between estimated and measured GFR for the LM Revised, MDRD and CKD-EPI equations based on plasma creatinine samples analyzed at Uppsala University Hospital (n=3495 examinations) from the Lund Cystatin C Standardization cohort. Some results are also given based on the same plasma creatinine samples analyzed at Skåne University Hospital in Lund at the time of iohexol clearance measurements (n=3259 available for comparison).

Variables	LM Revised	MDRD	CKD-EPI
Bias			
Median difference, mL/min/1.73 m ² (95% CI) ^a	0.7 (0.3–1.0)	3.3 (2.9–3.8)	4.8 (4.3–5.3)
Median percentage difference (95% CI) ^a	1.6 (0.8–2.6)	7.9 (6.8–8.9)	10.8 (9.9–11.6)
Lund creatinine assays	0.4 (–0.2–1.2)	6.3 (5.2–7.2)	9.1 (8.4–10.1)
Precision			
IQR of differences, mL/min/1.73 m ² (95% CI) ^a	12.1 (11.6–12.7)	14.1 (13.3–14.7)	14.4 (13.9–15.1)
Lund creatinine assays	11.7 (11.3–12.3)	13.6 (11.1–14.2)	13.9 (1.3–14.5)
Accuracy, percent (95% CI)			
Median absolute percentage difference ^a	13.0 (11.9–14.1)	15.3 (14.1–16.5)	15.6 (14.4–16.8)
P ₁₀ ^a	40.1 (38.4–41.6)	35.5 (33.8–37.0)	34.8 (33.1–36.3)
P ₃₀ ^a	83.7 (82.4–84.8)	75.3 (73.9–76.7)	75.6 (74.2–77.0)
Lund creatinine assays	84.5 (83.3–85.8)	77.9 (76.5–79.3)	77.5 (76.1–79.0)

CI, confidence interval; IQR, interquartile range. P₁₀ and P₃₀ refer to percentage of GFR estimates within 10% and 30%, respectively, of measured GFR. ^aResults based on plasma creatinine assays at Uppsala University Hospital (n=3495 examinations).

Stratification for GFR

LM Revised did not exhibit any marked bias ($\geq 10\%$) at any mGFR interval, while MDRD overestimated renal function markedly at mGFR intervals <30 and CKD-EPI at mGFR intervals <90 mL/min/1.73 m², respectively (Figure 1). For all three equations the vast majority of percentage errors that exceeded 30% of mGFR were overestimations (Figure 2).

LM Revised was also more precise in terms of IQR, and more accurate in terms of median absolute percentage difference, than the two other equations at all mGFR intervals <90 mL/min/1.73 m² (Supplemental data, Table 2). At mGFR intervals ≥ 90 mL/min/1.73 m² CKD-EPI was the

most precise equation and had the lowest absolute percentage error.

At mGFR <30 mL/min/1.73 m² the bias and imprecision of MDRD and CKD-EPI caused about ten percentage points lower P₃₀ (95% CI 8–13 percentage points lower; $p < 0.001$) compared with LM Revised (Figure 2). LM Revised also had a P₃₀ that was equal or superior to MDRD and CKD-EPI at all mGFR intervals ≥ 30 mL/min/1.73 m². Restricting the results to the first examination in each patient did not alter bias or accuracy noticeably at any GFR interval (Supplemental data, Table 1).

Stratification for age

LM Revised demonstrated no marked bias at any age interval and the P₃₀ accuracy ranged between 80% and 87% (Table 3). MDRD and CKD-EPI overestimated mGFR among both young adults and in older age groups, and was less precise than LM Revised in all age groups, with lower accuracy as a result (Supplemental data, Table 3).

Stratification for gender and BMI

Both women and men discerned the same pattern of bias and accuracy for the three equations overall and when stratified for mGFR and age (not in tables). At BMI <20 kg/m² all three equations were imprecise and overestimated GFR with poor P₃₀ as a result, a pattern most pronounced among men and for MDRD and CKD-EPI (Table 4 and Supplemental data, Table 4). At all other BMI intervals LM

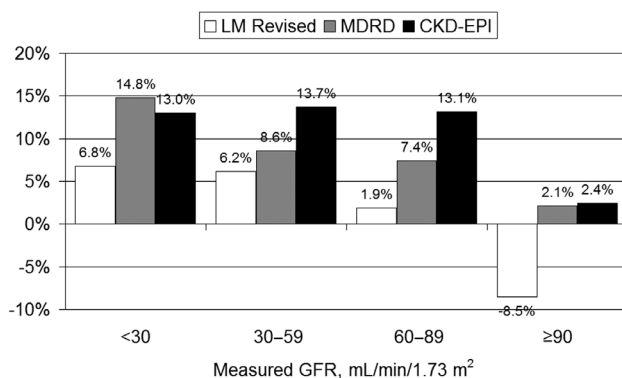


Figure 1 Bias, i.e., prediction error in percent of measured GFR [$100 \times (eGFR - mGFR) / mGFR$] summarized by the median, for LM Revised, MDRD and CKD-EPI.

Results are stratified for measured GFR (plasma clearance of iohexol) and based on the creatinine samples analyzed at Uppsala University Hospital (n=3495 examinations).

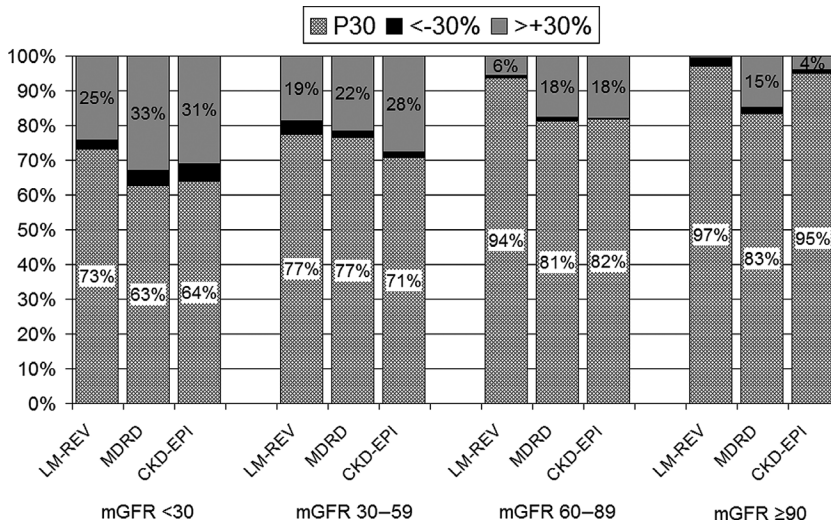


Figure 2 Proportion of prediction errors (eGFR–mGFR) for LM Revised, MDRD and CKD-EPI that did not exceed 30% of measured GFR (P₃₀). Proportions of prediction errors exceeding 30% of measured GFR (>+30%) or falling below minus 30% of measured GFR (<-30%) are also illustrated. Results are stratified for measured GFR (plasma clearance of iohexol) and based on the creatinine samples analyzed at Uppsala University Hospital (n=3495 examinations).

Revised discerned no marked bias with equal or superior P₃₀ compared with MDRD and CKD-EPI in both women and men. Both MDRD and CKD-EPI showed substandard accuracy in men with BMI ≥35 kg/m².

Discussion

Principal findings

The overall accuracy of LM Revised was superior to the MDRD and CKD-EPI equations in the present LCS cohort with an overall P₃₀ of 84%, eight percentage points higher than for MDRD and CKD-EPI. The performance of LM Revised was also more stable in terms of bias and accuracy

across mGFR, age and BMI intervals. CKD-EPI, advocated as the equation of choice by KDIGO [1], was less accurate compared with LM Revised except when mGFR ≥90 mL/min/1.73 m². Both MDRD and CKD-EPI showed substandard accuracy (P₃₀ <75%) at mGFR below 30 mL/min/1.73 m². Inaccuracy was also noted for CKD-EPI in young adults, for MDRD in elderly, for all three equations at BMI below 20 kg/m² and for both MDRD and CKD-EPI in men at BMI ≥35 kg/m².

Strengths and limitations of the study

A major strength of this study was the large sample size with a substantial variability in mGFR, age and BMI. Another strength was the fact that the results, based on

Table 3 Comparison of LM Revised, MDRD and CKD-EPI equations in estimating GFR in various age intervals based on plasma creatinine samples analyzed at Uppsala University Hospital (n=3495 examinations) from the Lund Cystatin C Standardization cohort.

Age intervals, years (Number/percentage of patients in each interval)	Median measured GFR, mL/min/1.73 m ²	Bias, median percentage difference			P ₃₀ , percentage ^a		
		LM Revised	MDRD	CKD-EPI	LM Revised	MDRD	CKD-EPI
18–29 (194/6%)	85	4	12	22	87	72	65
30–39 (266/8%)	76	3	3	14	83	80	73
40–49 (414/12%)	68	1	-1	7	88	84	81
50–59 (594/17%)	61	2	3	10	85	80	78
60–69 (929/27%)	53	3	9	11	82	74	76
70–79 (756/22%)	37	1	13	10	83	72	75
≥80 (342/10%)	26	-3	16	9	80	66	75

^aP₃₀ refers to percentage of GFR estimates within 30% of measured GFR.

Table 4 Comparison of LM Revised, MDRD and CKD-EPI equations in estimating GFR in various BMI intervals based on plasma creatinine samples analyzed at Uppsala University Hospital in women (n=1647 examinations) and in men (n=1848 examinations) from the Lund Cystatin C Standardization cohort.

BMI intervals, kg/m ² (Number of women/ men in each interval)	Median measured GFR, mL/min/1.73 m ²	Bias, median percentage difference			P ₃₀ ^a percentage ^a		
		LM Revised	MDRD	CKD-EPI	LM Revised	MDRD	CKD-EPI
		Women/men	Women/men	Women/men	Women/men	Women/men	Women/men
<20 (134/71)	55/58	10/22	19/33	20/39	72/59	66/39	65/37
20–24 (581/520)	66/52	1/4	6/12	11/15	87/82	76/71	78/73
25–29 (527/828)	60/46	-1/-1	5/6	7/8	88/84	81/78	81/77
30–34 (249/311)	52/44	0/2	3/7	8/8	84/83	78/76	76/77
35–39 (107/97)	51/35	6/9	7/13	11/16	81/80	75/69	74/69
≥40 (49/21)	33/31	0/1	2/3	6/8	78/76	78/71	78/71

^aP₃₀ refers to percentage of GFR estimates within 30% of measured GFR.

the re-analysis of plasma creatinine assays in Uppsala at a later occasion, were in accordance with the results based on plasma creatinine analyzed at the time of the GFR measurements in Lund. This verifies a similar calibration of the creatinine methods between two University Hospitals located in different regions of Sweden and over a 4-year time period.

A major limitation was that data were restricted to patients referred for GFR measurements, and the generalizability of the findings to clinical settings where GFR are seldom measured is therefore uncertain, e.g., primary care, geriatric and hospitalized patients. Data did not allow for separate validation in additional subgroups such as diabetics, organ donors, organ transplant patients, oncology patients or other ethnicities than Caucasians. A further limitation is that the present validation of LM Revised has to be regarded as internal since it is based on the same reference GFR method and a similar population from the same hospital as that used to develop the equation.

Results in relation to previous studies

All three equations yielded on average 8–10 percentage points higher estimates vis-à-vis mGFR in the present cohort compared with a previous Swedish external validation, where the same GFR measurement method, single sample of plasma clearance of iohexol, was used [12]. This may be explained by the fact that the median value of creatinine assays in Sweden in relation to a certified reference measurement procedure value has decreased gradually between 2003 and 2011 [18]. The median values of the creatinine results from both laboratories used in the present study (Lund and Uppsala) were close to the reference measurement value in external quality assessments during the relevant time period. During the same time interlaboratory

variation coefficient from measurements of the certified creatinine sample had decreased from previously 10% to 5% in Swedish laboratories according to Equalis AB [18]. Thus, the results of the present study, suggesting no marked bias for LM Revised at any mGFR level, are likely to be more representative than previous validations for the current creatinine calibration, at least in Sweden.

The P₃₀ figures close to 75% for both CKD-EPI and MDRD in the present study are in contrast with the original results of CKD-EPI where P₃₀ was 84% compared with 81% for the MDRD equation [4]. Differences in creatinine calibrations between North America and Europe cannot be ruled out as an explanation for the transatlantic differences in performance of MDRD and CKD-EPI. Both the MDRD and CKD-EPI equations have been developed from plasma creatinine samples measured mostly with the Jaffe assay, i.e., non-enzymatic methods, and traceability to IDMS standard has been obtained indirectly or a posteriori [32]. It should also be noted that the North American equations were established using renal clearance of iothalamate as reference, whereas single sample of plasma clearance of iohexol was used when LM Revised was developed. This could be another explanation for differences in eGFR between the equations.

LM Revised was the only equation with P₃₀ accuracy approaching 75% at mGFR <30 mL/min/1.73 m², while MDRD and CKD-EPI showed marked bias and insufficient accuracy at this mGFR interval. Similar findings have been reported in two previous regional Swedish studies [10, 12] and in an analysis of more than 2000 patients with mGFR <30 mL/min/1.73 m² from the national Swedish Renal Registry [33]. One explanation for these discrepant findings may be that LM Revised was developed with the goal to improve estimations at low mGFR levels [34], whereas the goal of developing CKD-EPI was to improve estimations at mGFR >60 mL/min/1.73 m² [4].

The present and previous validation studies suggest that the performance of creatinine-based equations among elderly vary substantially across CKD-stages, populations and clinical conditions [10, 12, 35–38]. A detailed analysis conducted by Swedish Council on Health Technology Assessment (SBU) suggests that it is not the age as such, but rather the decreased GFR, that makes the accuracy of creatinine-based equations lower among elderly (see figure 3.2.12 in reference [18]). The simplistic handling of age in MDRD and CKD-EPI may explain why these two equations tended to overestimate mGFR in both tails of the age distribution not only in the present but also in previous Swedish validations [10, 12]. LM Revised has a more elaborated handling of age that could explain its stable performance across age groups. For a given plasma concentration of creatinine, estimated GFR based on LM Revised decreases with 14% from age 70 to 85 years old, compared with 10% for CKD-EPI and only 4% for MDRD (cf. figure 4 in Nyman et al. [10]). Thus, one likely explanation why MDRD is inappropriate for monitoring of kidney function among elderly is that it does not capture the age-related decline in muscles mass and creatinine generation. CKD-EPI was developed in a cohort with a low proportion of patients above 80 years old (<1% vs. 10% in the present validation cohort), which raises concern about its applicability among elderly. Previous validation studies of CKD-EPI among elderly have yielded mixed results with some studies showing overestimations [35, 36], whereas no or marginal bias has been reported in other studies [37, 38]. A novel creatinine-based equation tailor-made for a general population at least 70 years of age, the Berlin Initiative Study 1 (BIS1) equation, has been shown to outperform CKD-EPI among elderly [35, 36]. However, the BIS1 equation showed insufficient accuracy when applied to patients ≥ 70 years old in the present cohort ($P_{30}=70\%$, median bias +11%, $n=1098$; not in results). One possible explanation for the discrepant findings could be that our cohort has a larger proportion with severe CKD than the general population of elderly in the BIS study.

LM Revised, MDRD and CKD-EPI demonstrated considerable overestimation of mGFR in patients with $BMI < 20 \text{ kg/m}^2$, more pronounced in men than in women. Similar overestimation among underweight patients was noted for MDRD and CKD-EPI in the two previous Swedish validations, whereas LM Revised was only evaluated in one of these studies and was unbiased [10, 12]. In the CKD-EPI development cohort ($n=5504$) MDRD caused no marked bias in patients with $BMI < 20 \text{ kg/m}^2$ though the P_{30} accuracy was only 74%. No stratification for gender was reported [39]. In a large Spanish study of

hospitalized patients CKD-EPI overestimated renal function among malnourished patients with a P_{30} reduced to 70% compared with 82% among all patients [11]. One way to improve eGFR based on creatinine among underweight patients may be to use an equation that includes estimated lean body mass (eLBM) based on height and weight such as the “Lund-Malmö equation with lean body mass” (LM-eLBM) [40]. No marked bias and P_{30} -values $> 80\%$ was observed for both men and women with $BMI < 20 \text{ kg/m}^2$ when this equation was applied in the present cohort (not in results). LM-eLBM also performed as accurate as LM Revised when stratified for GFR and age intervals and with an overall P_{30} accuracy of 84%.

Both MDRD and CKD-EPI was inaccurate in men with $BMI \geq 35 \text{ kg/m}^2$. Bouquegneau et al. recently reported an increasing bias in a European population with BMI above 30 kg/m^2 for both MDRD and CKD-EPI though the P_{30} figures were still above 75%, i.e., 80% and 76%, respectively [41]. The authors suggested that such overestimations of mGFR may result from exaggerated correction of the distribution volume of creatinine when indexing to extreme BSA levels. Instead it has been proposed that GFR should be indexed against total body water [42]. Measuring GFR instead of estimating GFR may still be preferable in very low and very high BMI.

Implications and issues for further research

For patients in CKD stage 3–5 ($GFR < 60 \text{ mL/min/1.73 m}^2$) the proportion of estimation errors exceeding 30% of mGFR were predominantly overestimations for all equations. Such overestimation may result in lack of sensitivity of eGFR equations to detect CKD, which may have serious consequences for patients due to risk of undertreatment of the renal dysfunction or overdosing of drugs and radiographic contrast media excreted by the kidneys that may result in toxic effects. It seems unlikely that the accuracy at lower mGFR levels can be increased much further using creatinine-based equations alone. However, combining eGFR-estimates based on creatinine and cystatin C has the potential to improve performance overall as well as in subgroups, e.g., CKD, underweight patients and elderly, where eGFR equations based on creatinine alone performs poorly [35, 43–45]. The introduction of an international cystatin C calibrator [19] now makes it possible to finally develop cystatin C equations that, combined with equations using standardized enzymatic creatinine methods, may reach the 10-year-old KDOQI benchmark with a P_{30} accuracy of at least 90% [13, 30], and be independent of the assays used.

Conclusions

In settings similar to the LCS cohort LM Revised should be preferred to MDRD and CKD-EPI in estimating GFR due to its superior accuracy and more stable performance across GFR, age and BMI intervals irrespective of gender. However, the generalizability of the findings to clinical settings such as primary care, geriatric and hospitalized patients where GFR are seldom measured is uncertain.

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Appendix

Calculation of iohexol clearance (=measured GFR)

GFR was calculated from the iohexol concentration with corrections for lack of complete uniform distribution and non-immediate mixing. Initial GFR was calculated as follows:

$$\text{GFR}_{\text{initial}} \text{ (mL/min)} = [1/(t/V + 0.0016)] \times \ln[Q_{\text{tot}}/(V \times C_t)]$$

where t =time interval between injection and sampling (min), \ln =natural logarithm, Q_{tot} =injected amount of iohexol (mg), C_t =iohexol concentration (mg/mL) at time (t) after injection and V =distribution volume (mL) calculated as a function of body weight (kilogram) [46]:

$$\text{Men: } 166 \times \text{weight} + 2490$$

$$\text{Women: } 95 \times \text{weight} + 6170$$

To correct for lack of complete uniform distribution of iohexol the correction factor (m) for distribution volume was calculated [26]:

$$m = 0.991 - 0.00122 \times \text{GFR}_{\text{initial}}$$

The corrected distribution volume ($V^* = V/m$) was used calculate the final GFR:

$$\text{GFR}_{\text{final}} \text{ (mL/min)} = [1/(t/V^* + 0.0016)] \times \ln[Q_{\text{tot}}/(V^* \times C_t)]$$

Conflict of interest statement

Authors' conflict of interest disclosure: The authors stated that there are no conflicts of interest regarding the publication of this article.

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Body surface area equation of Dubois and Dubois [27].

$$\text{BSA} = 0.007184 \times (\text{weight in kg})^{0.425} \times (\text{height in cm})^{0.725}$$

Equations for estimating GFR

In all equations for estimating GFR given below plasma creatinine (pCr) is expressed in $\mu\text{mol/L}$ (to convert pCr in mg/dL to $\mu\text{mol/L}$, multiply by 88.4), age in years, height in cm, weight in kg and estimated GFR in mL/min/1.73 m² body surface area. \ln =natural logarithm.

Revised Lund-Malmö Study equation (LM Revised) [34]

$$e^{X - 0.0158 \times \text{Age} + 0.438 \times \ln(\text{Age})}$$

$$\text{Female pCr} < 150 \mu\text{mol/L: } X = 2.50 + 0.0121 \times (150 - \text{pCr})$$

$$\text{Female pCr} \geq 150 \mu\text{mol/L: } X = 2.50 - 0.926 \times \ln(\text{pCr}/150)$$

$$\text{Male pCr} < 180 \mu\text{mol/L: } X = 2.56 + 0.00968 \times (180 - \text{pCr})$$

$$\text{Male pCr} \geq 180 \mu\text{mol/L: } X = 2.56 - 0.926 \times \ln(\text{pCr}/180)$$

CKD-EPI Study equation for Caucasians [4]

$$\text{Female pCr} \leq 62 \mu\text{mol/L: } 144 \times (\text{pCr}/62)^{-0.329} \times 0.993^{\text{Age}}$$

$$\text{Female pCr} > 62 \mu\text{mol/L: } 144 \times (\text{pCr}/62)^{-1.209} \times 0.993^{\text{Age}}$$

$$\text{Male pCr} \leq 80 \mu\text{mol/L: } 141 \times (\text{pCr}/80)^{-0.411} \times 0.993^{\text{Age}}$$

$$\text{Male pCr} > 80 \mu\text{mol/L: } 141 \times (\text{pCr}/80)^{-1.209} \times 0.993^{\text{Age}}$$

MDRD Study equation for caucasians based on IDMS-traceable creatinine assays [3]

$$175 \times (\text{pCr}/88.4)^{-1.154} \times \text{Age}^{-0.203} \times 0.742 \text{ (if female)}$$

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