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RESEARCH ARTICLE

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Extending the Lund-Malmö creatinine-based GFR equation to cystatin C – validation results from the European Kidney Function Consortium (EKFC) cohort of children and adults

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ABSTRACT

The aim of the present study was to extend the creatinine-based Lund-Malmö GFR equation for use with rescaled cystatin C (r-LMR$_{Cys}$) and validate it against measured GFR (mGFR) in the EKFC cystatin C cohort of children (n = 2,293) and adults (n = 7,727). Rescaling was obtained by dividing each biomarker by a Q-value, representing the population-specific median biomarker level among healthy individuals. Validation included median bias/precision/accuracy (percent estimates within ±30% of mGFR, P$_{30}$). Performance was compared with the EKFC-equation (EKFC$_{Cys}$), the CAPA cystatin C equation, the corresponding equations based on rescaled creatinine (r-LMR$_{Cr}$ and EKFC$_{Cr}$) and the arithmetic mean of r-LMR$_{Cr}$ and CAPA (r-LMR$_{Cr}$+CAPA), r-LMR$_{Cr}$ and r-LMR$_{Cys}$ (r-LMR$_{Mean}$), and EKFC$_{Cr}$ and EKFC$_{Cys}$ (EKFC$_{Mean}$). The overall P$_{30}$ of r-LMR$_{Cys}$ in adults was 86.2% (95% CI 85.4%-86.9%), which was 6.6 percentage points (pp; 95% CI 5.8–7.4 pp) higher than for CAPA and similar to r-LMR$_{Cr}$ (P$_{30}$ 87.4%, 95% CI 86.6%–88.1%). r-LMR$_{Cys}$ and EKFC$_{Cys}$ exhibited similar performance both overall and across subgroups of age, sex, GFR and BMI and in children. All three arithmetic mean equations had similar P$_{30}$-accuracy and generally performed better than the corresponding single-marker equations. Our results show that the Lund-Malmö GFR equation can be adapted for use with rescaled cystatin C with performance that is similar to the best-performing equations based on rescaled creatinine. The generality of the applied biomarker rescaling principle implies that the future demand for population- and biomarker-specific GFR estimating equations can be expected to decrease substantially.

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JB, UN, UB, AB, EC, NE, BOE, LDD, AG, MG, AL, ES, POS, KÅM, PD and HP are members of the European Kidney Function Consortium, which is endorsed by the European Renal Association.

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Table 1. Basic characteristics of the European Kidney Function Consortium cystatin C cohort, adults (n = 7,727) and children (n = 2,293). Descriptive measures given as median values (2.5 and 97.5 percentiles) if not stated otherwise.

	Adults (n = 7,727)	Females (n = 3,604)	Males (n = 4,123)	Children (n = 2,293)	Girls (n = 949)	Boys (n = 1,344)
Age (years)	62 (20-86)	62 (21-86)	62 (20-87)	11.9 (2.3-17.8)	11.4 (2.3-17.8)	12.1 (2.3-17.7)
Weight (kg)	76 (49-113)	68 (46-105)	82 (56-117)	40 (13-86)	39 (13-80)	41 (13-88)
Height (cm)	170 (152-188)	163 (150-176)	176 (161-190)	147 (88-185)	146 (88-177)	149 (88-188)
Body surface area (m^2)	1.87 (1.47-2.31)	1.74 (1.41-2.12)	1.98 (1.63-2.36)	1.29 (0.54-2.05)	1.26 (0.54-1.90)	1.30 (0.55-2.11)
Body mass index (kg/m^2)	26 (18-38)	26 (18-39)	27 (19-37)	18 (14-29)	18 (13-28)	18 (14-29)
Serum creatinine (μmol/L)	81 (46-343)	68 (43-284)	92 (55-395)	52 (19-155)	50 (20-153)	54 (19-155)
Serum cystatin C (mg/L)	1.06 (0.60-3.90)	1.01 (0.59-3.74)	1.13 (0.61-4.04)	0.96 (0.61-2.72)	0.92 (0.59-2.66)	0.98 (0.62-2.82)
Measured GFR (mL/min/1.73 m^2)	71 (12-120)	72 (13-116)	69 (12-122)	97 (28-169)	96 (28-169)	98 (27-168)

Introduction

The creatinine-based Lund-Malmö Revised (LMR) equation for estimated GFR (eGFR) has recently been re-expressed (r-LMR) for use with rescaled (normalized) level of serum creatinine based on population-specific Q-values representing the median value of the biomarker among healthy individuals [1, 2]. The re-expression together with the Q-values also made the equation applicable in children [3], and possibly also to other renal biomarkers such as cystatin C [4].

The biomarker rescaling principle was originally developed with the Full Age Spectrum (FAS) eGFR equation [5], and subsequently used in the European Kidney Function Consortium (EKFC) equation [4,6], which both have a generic formula expression based on the rescaled level of serum creatinine (sCr) or cystatin C (sCys). The rescaling is done by dividing the biomarker value of the individual with the population-specific Q-value to control for possible variations related to differences in age, sex, population and variation in analytical methods. A key advantage with this approach is that the same basic expression of the equation can be used for both children and adults [3], females and males [6] as well as in different populations [1, 7] and for different biomarkers [8].

The aim of the present study was to show the generality of the rescaling principle by extending r-LMR to cystatin C (r-LMR_{Cys}; index test). Equation performance was validated against measured GFR (mGFR; reference test) in the EKFC cystatin C cohort of children and adults.

Material and methods

The present validation of r-LMR with rescaled cystatin C was limited to White Europeans only, i.e. the combined EKFC multicentre cystatin C cohort [4, 9] with 2,293 children and 7,727 adults (≥18 years; Table 1) containing both sCr and sCys together with measured GFR, age and gender. Included subcohorts of children originated from Amsterdam (the Netherlands n = 399), Leuven (Belgium n = 106), Lund (Sweden n = 434), Lyon (France n = 259) and Stockholm (Sweden n = 1,095). Adult subcohorts originated from Berlin (Germany n = 657), Kent (United Kingdom n = 394), Lund, (Sweden n = 2,847), Lyon (France n = 914), Saint-Etienne (France n = 203), Stockholm (Sweden n = 577), Tromsö (Norway n = 1,627) and Örebro (Sweden n = 508). Patient and method characteristics have been thoroughly described previously [4, 9, 10]. Briefly clearance methods as a measure of GFR and reference test included renal clearance of inulin, chromium-51 labelled ethylene-diamine-tetra-acetic-acid (EDTA), and iohexol as well as plasma clearance of inulin, chromium-51 EDTA and iohexol, all considered acceptable as reference tests [11]. Regarding index tests all cystatin C assays were calibrated against the international reference material (ERM-DA471/IFCC) [12–14]. All creatinine assays were traceable to isotope dilution mass spectrometry (IDMS) [15] by the standard reference material (SRM) 967 (National Institute of Standards and Technology, NIST, Gaithersburg, MD, USA) [16] except for Kent, where it was measured directly with IDMS [17].

Q-values

Rescaling was obtained by dividing each biomarker by a Q-value, which represents the population-, sex- and age-specific median serum biomarker levels (cystatin C or creatinine) in healthy individuals [3, 4, 6, 9]:

Cystatin C, European males and females

$$\begin{aligned} &\text{Children } 2-17\,\text{years}: && Q = 0.83\,\text{mg/L} \\ &\text{Adults } 18-50\,\text{years}: && Q = 0.83\,\text{mg/L} \\ &\text{Adults} \geq 50\,\text{years}: && Q = 0.83 + 0.005 \times (\text{Age} - 50)\,\text{mg/L} \end{aligned} \quad (1)$$

Creatinine, European males

$$\begin{aligned} \text{Children } 2-17\,\text{years}: \; Q = \text{EXP}\,(&3.200 + 0.259 \\ &\times \text{Age} - 0.543 \times \ln(\text{Age}) \\ &- 0.00763 \times \text{Age}^2 + 0.0000790 \\ &\times \text{Age}^3)\;\mu\text{mol/L} \\ \text{Adults} \geq 18\,\text{years}: \; Q &= 80\;\mu\text{mol/L} \end{aligned} \quad (2)$$

where EXP is the natural exponential function and ln is the natural logarithm.

Creatinine, European females

$$\begin{aligned} \text{Children } 2-17\,\text{years}: \; Q = \text{EXP}(&3.080 + 0.177 \\ &\times \text{Age} - 0.223 \times \ln(\text{Age}) \\ &- 0.00596 \times \text{Age}^2 + 0.0000686 \\ &\times \text{Age}^3)\,\mu\text{mol/L} \\ \text{Adults} \geq 18\,\text{years}: \; Q &= 62\,\mu\text{mol/L} \end{aligned} \quad (3)$$

GFR estimating equations

The performance of the re-expressed LMR equation based on rescaled cystatin C (r-LMR_{Cys}) were compared with the EKFC equation ($EKFC_{Cys}$) [4] and with the Caucasian, Asian, Paediatric and Adult (CAPA) cystatin C equation [18]. The corresponding creatinine-based equations (r-LMR_{Cr} and $EKFC_{Cr}$) were included for comparison, together with the arithmetic mean of r-LMR_{Cr} and CAPA (r-LMR_{Cr}+CAPA), r-LMR_{Cr} and r-LMR_{Cys} (r-LMR_{Mean}), and $EKFC_{Cr}$ and $EKFC_{Cys}$ ($EKFC_{Mean}$). All included equations estimate GFR in mL/min/1.73 m^2.

The re-expressed Lund-Malmö Revised (r-LMR) equation for adults ≥ 18 years

$$\begin{aligned} &\text{r-LMR} = \text{EXP}[X - 0.0158\times\text{Age} + 0.438\times\ln(\text{Age})] \\ &B/Q < 2.33: \quad X = 4.3087 - 0.7623\times B/Q \\ &B/Q \geq 2.33: \quad X = 3.3145 - 0.9260\times\ln(B/Q), \end{aligned} \tag{4}$$

where B is the renal biomarker (creatinine in μmol/L or mg/dL or cystatin C in mg/L), Q represents the median biomarker level of creatinine or cystatin C, and thus, B/Q represents the rescaled (normalized) biomarker level. Note that the formulation of r-LMR used in the present study is a simplification of the original re-expressed equation [1,19] where the sex-specific coefficients have been averaged in order to establish a common equation formulation [see Supplement for details]. The performance of r-LMR in adults using the original re-expression with sex-specific coefficients was evaluated in a sensitivity analysis.

The re-expressed Lund-Malmö Revised (r-LMR) creatinine equation for children 2–17 years

The re-expression of the LMR creatinine equation for use with Q-values above can be adapted for use in children in the following way [3]:

$$\begin{aligned} &\text{r-LMR18} = \text{EXP}[X - 0.0158\times 18 + 0.438\times\ln(18)] \\ &Cr_{18}/Q_{Cr18} < 2.33: \quad X = 4.3087 - 0.7623\times Cr_{18}/Q_{Cr18} \\ &Cr_{18}/Q_{Cr18} \geq 2.33: \quad X = 3.3145 - 0.9260\times\ln(Cr_{18}/Q_{Cr18}), \end{aligned} \tag{5}$$

where Age = 18 years is used irrespectively of the actual age of the child. Q_{Cr18} represents the median creatinine level among healthy individuals at age 18 years and Cr_{18} is the anticipated creatinine level at age 18 after recalculation of the child's original creatinine level using the following creatinine growth curve equations in children (expressed in μmol/L) [3]:

$$\begin{aligned} \text{Males}: Cr_{18} = {} & \text{EXP}[\ln(sCr) + 0.259\times(18 - \text{Age}) \\ & - 0.543\times\ln(18/\text{Age}) - 0.00763\times(18^2 - \text{Age}^2) \\ & + 0.0000790\times(18^3 - \text{Age}^3)] \end{aligned} \tag{6}$$

$$\begin{aligned} \text{Females}: Cr_{18} = {} & \text{EXP}[\ln(sCr) + 0.177 \\ & \times(18 - \text{Age}) - 0.223\times\ln(18/\text{Age}) \\ & - 0.00596\times(18^2 - \text{Age}^2) + 0.0000686\times(18^3 - \text{Age}^3)] \end{aligned} \tag{7}$$

Similarly, to use the r-LMR equation with cystatin C in children, cystatin C must be recalculated into an anticipated creatinine level at age 18 (Cr_{18}*). This is done in two steps:

1. The actual cystatin C value of the child is translated into a corresponding creatinine value (sCr*) by multiplying the rescaled cystatin C value with the age-specific Q-values for creatinine of the child (Equations (2 and 3)):
$$sCr^* = (sCys/Q_{Cys})\times Q_{Cr}$$
2. The translated creatinine value (sCr*) is converted to an anticipated creatinine level at age 18 (Cr_{18}*) using the growth curve Equations (6 and 7) above.

The European Kidney Function Consortium (EKFC) equation [4,6]

$$\begin{aligned} &\text{EKFC} = 107.3\times(B/Q)^X\times[0.990^{(\text{Age}-40)}\ \text{if Age} > 40] \\ &B/Q < 1.0: X = -0.322 \\ &B/Q \geq 1.0: X = -1.132 \end{aligned} \tag{8}$$

where B is the renal biomarker (cystatin C or creatinine) and Q represents the median biomarker level as above.

The Caucasian, Asian, Pediatric and Adult (CAPA) cystatin C equation [18]

$$\text{CAPA} = 130\times sCys^{-1,069}\times\text{Age}^{-0,117} - 7 \tag{9}$$

Statistical evaluation

All statistical evaluations were conducted using IBM SPSS Statistics (version 25; IBM Corp.), STATA (version 14.2; StataCorp) and Microsoft Excel (Microsoft Corporation, Redmond, WA, USA). The analysis focused on bias, precision, and accuracy of the GFR estimating equations regarded as index test [20]. Bias was assessed as the median of estimated minus measured GFR (eGFR – mGFR) and precision as the interquartile range (IQR) of the differences eGFR – mGFR. Accuracy was assessed from the absolute error |eGFR – mGFR| and expressed in mL/min/1.73 m^2 and as the percentage of estimates within ±10% and ±30% of mGFR (P_{10} and P_{30}). P_{30} accuracy of at least 75% has been considered sufficient "for good clinical decision-making" by the National Kidney Foundation but the benchmark is to reach P_{30} > 90% [21]. In children main results were presented stratified by mGFR below and above 75 mL/min/1.73 m^2 as abnormal GFR in children has been regarded to start below this threshold [22].

Bias and accuracy (P_{30}) were for adults evaluated in subgroups defined by sex, mGFR (<30, 30–44, 45–59, 60–89 and ≥90 mL/min/1.73 m^2), age (18–39, 40–64 and ≥65 years) and body mass index (BMI <18.5, 18.5–24, 25–29, 30–34, 35–39 and ≥40 kg/m^2; adults only). In children bias and accuracy (P_{30}) were evaluated further in subgroups defined by sex, mGFR (<75 and ≥75 mL/min/1.73 m^2) and age (2.0–7.9, 8.0–12.9 and 13.0–17.9 years). Non-parametric and asymptotic 95% confidence intervals

Table 2. Adult European Kidney Function Consortium cystatin C cohort ($n = 7,727$). Bias, precision and accuracy (95% confidence intervals) of GFR estimating equations.

Equations	Creatinine		Cystatin C			Creatinine and cystatin C		
	r-LMR$_{Cr}$	EKFC$_{Cr}$	r-LMR$_{Cys}$	CAPA	EKFC$_{Cys}$	r-LMR$_{Cr}$ + CAPA	r-LMR$_{Mean}$	EKFC$_{Mean}$
Bias	-1.6	0.8	-2.6	0.3	0.0	-0.3	-1.9	0.5
	(-1.9; -1.4)	(0.6; 1.1)	(-2.8; -2.3)	(-0.6; 0.0)	(-0.4; 0.3)	(-0.5; 0.0)	(-2.2; -1.7)	(0.3;0.8)
IQR	14.3	14.5	14.9	18.3	14.4	12.6	12.2	12.0
Absolute error	7.3	7.2	7.4	9.1	7.1	6.3	6.0	6.0
	(7.0; 7.5)	(7.0; 7.4)	(7.2; 7.6)	(8.8; 9.4)	(6.9; 7.3)	(6.2; 6.5)	(5.8; 6.2)	(5.9;6.2)
P$_{10}$ accuracy	41.9	43.2	40.1	33.1	41.7	47.2	48.2	48.9
	(40.8; 43.0)	(42.1; 44.3)	(39.0; 41.2)	(32.1; 34.2)	(40.6; 42.8)	(46.1; 48.3)	(47.1; 49.4)	(47.8;50.0)
P$_{30}$ accuracy	87.4	85.5	86.2	79.6	86.2	91.0	91.5	90.3
	(86.6; 88.1)	(84.8; 86.3)	(85.4; 86.9)	(78.7; 80.5)	(85.4; 87.0)	(90.4; 91.7)	(90.8; 92.1)	(89.7;91.0)

eGFR = estimated glomerular filtration rate, mGFR = measured glomerular filtration rate.
Median bias (eGFR-mGFR), precision (IQR, interquartile range) and accuracy in terms of absolute error |eGFR - mGFR| expressed in mL/min/1.73 m^2, and P$_{10}$ and P$_{30}$ accuracy expressed in percentage of GFR estimates within ±10% and ±30% of measured GFR.
CAPA = Caucasian, Asian, Pediatric and Adult cystatin C equation, EKFC$_{Cr}$ and EKFC$_{Cys}$= European Kidney Function Consortium equation based on rescaled creatinine and cystatin C values, EKFC$_{Mean}$ = arithmetic mean of EKFC$_{Cr}$ and EKFC$_{Cys}$, r-LMR$_{Cr}$ and r-LMR$_{Cys}$ = re-expressed Lund-Malmö revised equation based on rescaled creatinine and cystatin C values and nonsex-specific coefficients, r-LMR$_{Cr}$ + CAPA = arithmetic mean of r-LMR$_{Cr}$ and CAPA, r-LMR$_{Mean}$ = arithmetic mean of r-LMR$_{Cr}$ and r-LMR$_{Cys}$.

(CI) were calculated for the main results as measures of the statistical uncertainty in medians and proportions (P$_{10}$ and P$_{30}$). We used McNemar's exact test and corresponding 95% CIs for pairwise comparisons of P$_{30}$ across different equations for the main results.

Results

Adults

The r-LMR$_{Cys}$ and EKFC$_{Cys}$ equations had generally similar performance overall with regard to bias, precision, and accuracy (Table 2), irrespective of sex (Table S1). The overall P$_{30}$ of r-LMR$_{Cys}$ was 86.2% (95% CI 85.4-86.9), which was 6.6 percentage points (pp, 95% CI 5.8–7.4 pp, $p < 0.001$) higher than for CAPA. The increased accuracy of r-LMR$_{Cys}$ and EKFC$_{Cys}$ was explained by improved precision (lower IQR) compared with CAPA. The r-LMR$_{Cys}$ and EKFC$_{Cys}$ equations performed as well as the two corresponding creatinine-based equations, r-LMR$_{Cr}$ and EKFC$_{Cr}$, (Table 2). All three arithmetic mean equations, r-LMR$_{Cr}$+CAPA, r-LMR$_{Mean}$ and EKFC$_{Mean}$, had similar P$_{30}$-accuracy overall and performed better than the corresponding single-marker equations (Table 2).

Stratifying by mGFR, the superior performance of r-LMR$_{Cys}$ and EKFC$_{Cys}$ compared with CAPA was evident above but not below 60 mL/min/1.73 m^2 (Figure 1(A,B), Table S2). At mGFR < 30 mL/min/1.73 m^2, none of the single-marker equations reached the P$_{30}$-threshold of 75% for satisfactory accuracy, and also EKFC$_{Mean}$ among the arithmetic mean equations was below this threshold ($n = 1,134$; Table S2). At mGFR ≥ 90 mL/min/1.73 m^2 ($n = 1,990$), in particular r-LMR but also EKFC was negatively biased irrespectively of biomarker. CAPA had low bias at mGFR ≥ 90 mL/min/1.73 m^2 but still lower P$_{30}$, 84.1% (95% CI 82.5–85.7), than the other single-marker equations.

All equations were generally somewhat less accurate in older adults ≥ 65 years ($n = 3,206$) but still had P$_{30}$ ≥ 80% (Table S3). When stratifying for BMI, lower accuracy was noted for all equations at BMI < 18.5 kg/m^2 ($n = 216$) and BMI ≥ 40 kg/m^2 ($n = 127$; Table S4).

In all main analyses of the adult cohort the same r-LMR-equation expression was used for males and females. Using sex-specific coefficients instead did not generally improve equation performance in adults (Table S5).

Children

The r-LMR$_{Cys}$ and EKFC$_{Cys}$ equations had generally similar performance with regard to bias, precision, and accuracy (Table 3), irrespective of sex (Table S6) and age (Table S7). The difference in accuracy between r-LMR$_{Cys}$ and CAPA was more evident below than above 75 mL/min/1.73 m^2 (Figure 1(C,D)). Hence, the difference in P$_{30}$-accuracy between the two equations was 4.2 pp (95% 1.1–7.3 pp, $p = 0.01$) and 2.1 pp (95% CI 1.1–4.1, $p = 0.04$) below and above mGFR 75 mL/min/1.73 m^2, respectively. r-LMR$_{Cys}$ and EKFC$_{Cys}$ were more accurate overall than the creatinine-based equations at mGFR < 75 mL/min/1.73 m^2 ($n = 503$) but were more negatively biased and less accurate than their counterparts at mGFR ≥ 75 mL/min/1.73 m^2 ($n = 1790$; Table 3). All three arithmetic mean equations, r-LMR$_{Cr}$+CAPA, r-LMR$_{Mean}$ and EKFC$_{Mean}$, had similar P$_{30}$-accuracy and generally performed better than the corresponding single-marker equations.

Discussion

Recently, it was shown how the biomarker rescaling principle can be used to generalize the EKFC estimation equation intended for one biomarker (creatinine) to another biomarker (cystatin C) by developing biomarker-specific Q-values [4]. The present study shows that the Lund-Malmö revised equation, originally developed for estimating GFR based on serum creatinine in adults [23], may also be used to estimate GFR based on serum cystatin C in both adults and children. This is achieved by using the biomarker rescaling principle and applying population-, sex- and age-specific Q-values [4, 9]. Similar rescaling should be possible to apply also for other GFR estimating equations and other biomarkers such as beta trace protein [8]. The rescaling makes the biomarker-GFR relationship less complex, which comes with many advantages for the GFR equations: (i) applicable and continuous for all

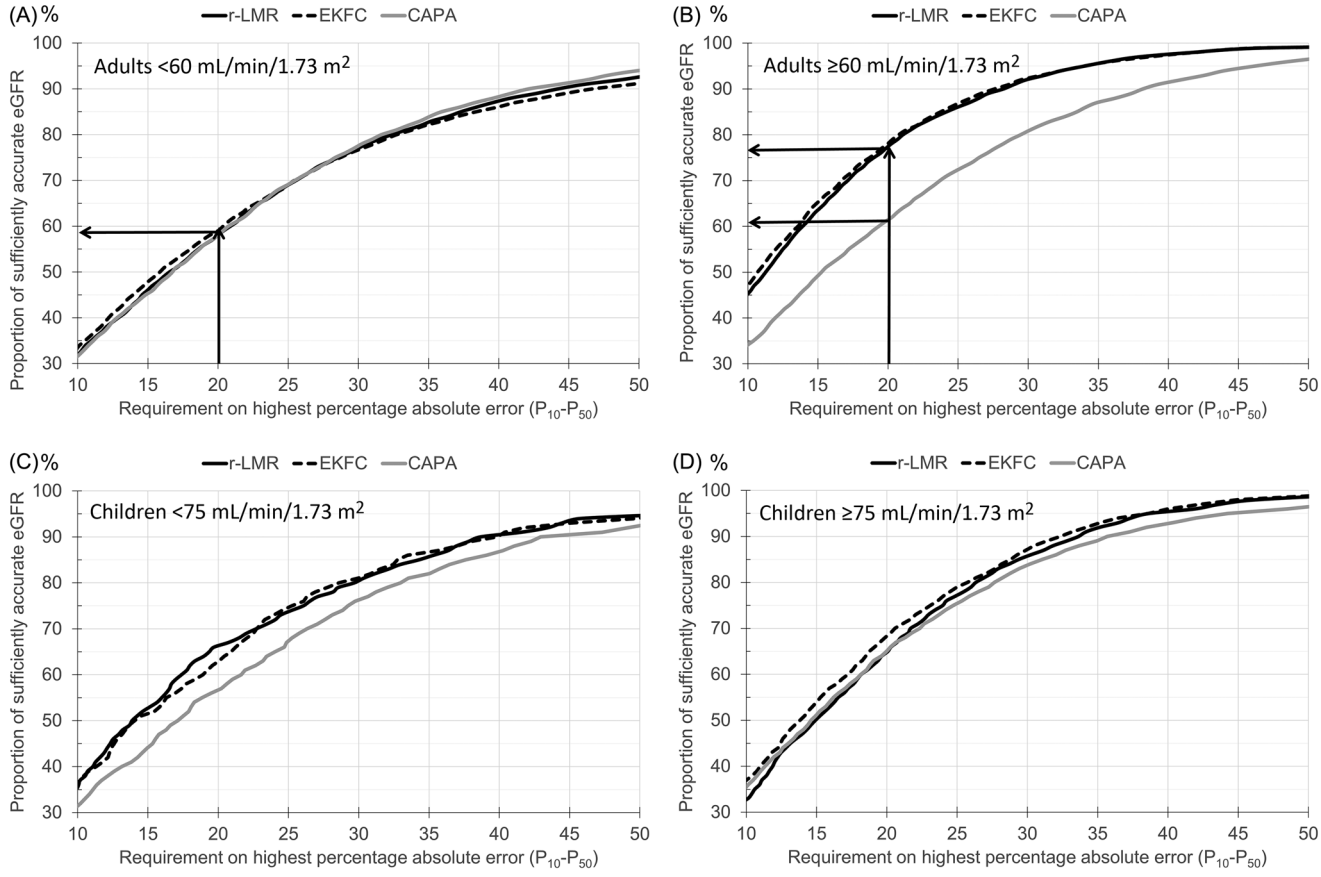

Figure 1. The proportion of patients with sufficiently accurate estimated GFR (y-axis) at different requirements on highest percentage absolute error (x-axis), that is, from 10% to 50% (P_{10}–P_{50}) in relation to measured glomerular filtration rate (mGFR). (A) adults with mGFR <60, (B) adults with mGFR ≥60, (C) children with mGFR <75 and (D) children with mGFR ≥75 mL/min/1.73 m^2 comparing r-LMR and EKFC using rescaled cystatin C with the CAPA cystatin C equations. As examples indicated by the arrows, P_{20} was about 58% for all three equations in (A) and ranged between 61% (CAPA) and 76% (r-LMR and EKFC) in (B).

Table 3. Pediatric European Kidney Function Consortium cystatin C cohort (n = 2,293) stratified for measured GFR. Bias, precision, accuracy (95% confidence intervals) of GFR estimating equations.

Equations	Creatinine		Cystatin C			Creatinine and cystatin C		
	r-LMR$_{Cr}$	EKFC$_{Cr}$	r-LMR$_{Cys}$	CAPA	EKFC$_{Cys}$	r-LMR$_{Cr}$ + CAPA	r-LMR$_{Mean}$	EKFC$_{Mean}$
mGFR <75 mL/min/1.73 m^2 (n = 503)								
Bias	4.2	3.9	-0.3	1.0	0.1	2.7	1.6	2.2
	(2.9; 5.0)	(3.0; 5.2)	(-1.8; 0.8)	(-0.3; 2.3)	(-1.3; 1.3)	(1.6; 4.0)	(0.6; 2.7)	(1.3; 3.6)
IQR	16.5	18.6	13.6	17.2	13.9	13.9	12.9	13.4
Absolute error	7.9	7.5	6.9	8.3	7.0	6.7	6.0	6.3
	(6.8; 8.9)	(6.7; 8.6)	(6.3; 7.6)	(7.2; 9.3)	(6.2; 7.8)	(5.9; 7.6)	(5.5; 6.8)	(5.5; 6.9)
P_{10} accuracy	35.0	32.2	35.4	31.4	36.6	38.6	41.6	41.7
	(30.8; 39.2)	(28.1; 36.3)	(31.2; 39.6)	(27.4; 35.5)	(32.4; 40.8)	(34.3; 42.8)	(37.2; 45.9)	(37.4; 46.1)
P_{30} accuracy	74.2	72.0	80.5	76.3	81.1	81.3	85.5	81.7
	(70.3; 78.0)	(68.0; 75.9)	(77.1; 84.0)	(72.6; 80.1)	(77.7; 84.5)	(77.9; 84.7)	(82.4; 88.6)	(78.3; 85.1)
mGFR ≥75 mL/min/1.73 m^2 (n = 1,790)								
Bias	-7.9	-4.1	-14.0	-1.5	-11.0	-3.5	-10.3	-6.7
	(-8.5; -6.9)	(-5.4; -3.0)	(-15.2; -13.2)	(-2.9; -0.2)	(-11.9; -9.9)	(-4.5; -2.8)	(-11.0; -9.4)	(-7.6; -6.0)
IQR	24.2	25.8	23.8	31.7	25.2	21.0	21.3	22.4
Absolute error	13.1	12.8	15.2	15.6	14.4	10.7	12.4	11.3
	(12.0; 14.0)	(12.2; 13.6)	(14.2; 16.3)	(14.9; 16.6)	(13.5; 15.3)	(9.9; 11.3)	(11.5; 13.1)	(10.5; 11.9)
P_{10} accuracy	41.2	41.9	32.8	35.5	37.0	48.9	42.1	45.1
	(38.9; 43.5)	(39.6; 44.2)	(30.6; 35.0)	(33.3; 37.7)	(34.7; 39.2)	(46.6; 51.3)	(39.8; 44.4)	(42.8; 47.4)
P_{30} accuracy	89.1	88.9	85.7	83.6	87.4	93.6	91.6	92.8
	(87.7; 90.5)	(87.5; 90.4)	(84.1; 87.3)	(81.9; 85.3)	(85.8; 88.9)	(92.5; 94.8)	(90.3; 92.9)	(91.7; 94.0)

eGFR = estimated glomerular filtration rate, mGFR = measured glomerular filtration rate.
Median bias (eGFR-mGFR), precision (IQR, interquartile range) and accuracy in terms of absolute error |eGFR - mGFR| expressed in mL/min/1.73 m^2, and P_{10} and P_{30} accuracy expressed in percentage of GFR estimates within ±10% and ±30% of measured GFR.
CAPA = Caucasian, Asian, Pediatric and Adult cystatin C equation, EKFC$_{Cr}$ and EKFC$_{Cys}$ = European Kidney Function Consortium equation based on rescaled creatinine and cystatin C values, EKFC$_{Mean}$ = arithmetic mean of EKFC$_{Cr}$ and EKFC$_{Cys}$, r-LMR$_{Cr}$ and r-LMR$_{Cys}$ = re-expressed Lund-Malmö revised equation based on rescaled creatinine and cystatin C values and nonsex-specific coefficients, r-LMR$_{Cr}$ + CAPA = arithmetic mean of r-LMR$_{Cr}$ and CAPA, r-LMR$_{Mean}$ = arithmetic mean of r-LMR$_{Cr}$ and r-LMR$_{Cys}$.

ages, (ii) applicable to males and females, (iii) applicable for different populations including different ethnicities [4, 7, 24], (iv) applicable for different biomarkers and v) more stable performance in comparison with equations not based on rescaled biomarkers [4, 6]. To further improve the accuracy of the Q-values, accounting for methodological differences between laboratories or changes within the laboratory may be important, even when routine methods are standardized and traceable to IDMS measurements.

The CAPA equation was developed in 2014 with the explicit goal to provide a simplistic formula expression for eGFR based on only two variables, cystatin C standardized to the new international calibrator and age [18]. While validation studies in both adults and children have generally exhibited satisfactory performance of CAPA [25–30] the present study shows that simplicity leads to lower precision and thereby lower accuracy, in adults especially at higher mGFR levels, than if more complex formula expressions such as EKFC and r-LMR are used. More complex equations also make the accuracy of eGFR based on creatinine and cystatin C similar overall. As an example, while r-LMR_{Cr} exhibited noticeably higher P_{30}-accuracy in adults in the present study than CAPA (7.7 pp difference, 95% CI 6.6–8.9), the difference vs. r-LMR_{Cys} was considerably smaller (1.2 pp, 95% CI 0.3–2.1).

The performance of EKFC and r-LMR were in the present study generally similar, both in adults and children, across subgroups and irrespective of biomarker. If anything, the results for adults suggest that the r-LMR equations are somewhat more accurate at GFR-levels below 30 mL/min/1.73 m^2, while the EKFC equations exhibit some superiority at GFR-levels above 90 mL/min/1.73 m^2, which is a finding that is consistent with how these two equations were originally developed [6, 23].

In conclusion, the present study shows how the creatinine-based Lund-Malmö GFR equation can be adapted for use with cystatin C, and with satisfactory performance in both adults and children, irrespectively of sex, age and GFR level. The generality of the applied biomarker rescaling principle implies that the future demand for population- and biomarker-specific GFR estimating equations can be expected to decrease substantially.

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Author contributions

J.B. and U.N. conceived the study, conducted the statistical analyses and drafted the article. All other authors contributed with data, analysis and interpretation of data, provided intellectual content of critical importance to the work described, revising the article and have accepted responsibility for the entire content of this manuscript and approved its submission.

Ethical approval

All procedures involving subjects and data agreed with the ethical principles for medical research involving human subjects established in the World Medical Association Declaration of Helsinki. The study was based on the EKFC cohort that was reviewed and originally approved by the Regional Ethical Board in Lund, Sweden (reg no. 2018/220) with amendments subsequently reviewed and approved by the Swedish Ethical Review Authority (reg no. 2021-04177). Data were anonymized from the source cohort for the analysis performed at Lund University, Sweden.

Informed consent

For this type of retrospective study, all extracted data were fully anonymous without any personal information, why informed consent was not required according to the original regional ethical board approval in Lund, Sweden, and the subsequent amendment approved by the Swedish Ethical Review Authority.

Disclosure statement

Pierre Delanaye is a consultant for Nephrolyx (Berlin, Germany). All other authors state no conflict of interest.

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