



ORIGINAL ARTICLE

Performances of creatinine-based glomerular filtration rate estimating equations in simultaneous pancreas-kidney transplant recipients: a single center cohort study

Allyriane Dantec¹ , Luciano Selistre², Sandrine Lemoine^{3,4,5}, Fanny Buron¹, Vandra Carla de Souza², Thomas Rimmelé^{4,6}, Olivier Thauinat^{1,4,7} , Lionel Badet^{4,8}, Emmanuel Morelon^{1,4,7}, Laurence Dubourg^{3,4,9,*} & Antoine Sicard^{1,4,*}

1 Service de Transplantation, Néphrologie et Immunologie Clinique, Hôpital Edouard Herriot, Lyon, France
 2 Universidade de Caxias do Sul, Caxias do Sul, Brazil
 3 Service de Néphrologie, dialyse, hypertension et exploration fonctionnelle rénale, Hôpital Edouard Herriot, Lyon, France
 4 Université Lyon 1, Lyon, France
 5 Laboratoire CarMeN, INSERM 1060, Lyon, France
 6 Service d'anesthésie-réanimation, Hôpital Edouard-Herriot, Lyon, France
 7 Unité INSERM U1111, Lyon, France
 8 Service d'Urologie et Transplantation, Hôpital Edouard Herriot, Lyon, France
 9 UMR 5305 CNRS/UCBL, Biologie Tissulaire et Ingénierie Thérapeutique, Lyon, France

SUMMARY

Estimating glomerular filtration rate (GFR) is important for clinical management and research studies in simultaneous pancreas-kidney transplantation (SPK) recipients. No study has specifically investigated the reliability of recent creatinine-based GFR estimating equations in this singular population. We assessed the performances of CKD-EPI, MDRD, Schwartz-2009, Schwartz-Lyon, Lund-Malmo and Full Age Spectrum equations for estimating GFR after SPK. 126 patients were included. GFR was measured by a reference method (mGFR) one year after SPK and estimated with the different equations from a standardized measure of serum creatinine. Relative bias, precisions, 10% and 30% accuracies (P30) were used to determine equations reliability. Ages ranged from 29 to 58. Mean mGFR was 56.3 ± 13.3 [23.6–92.5] ml/min/1.73 m². In the whole population, P30 of the CKD-EPI and MDRD equations were 42% (38.0; 46.0) and 65% (61.5; 69) respectively. As compared to the other equations, the Schwartz-Lyon equation was significantly more accurate (P30 = 86.0% [83.5–88.0], $P < 0.01$) and less biased (1.13 [1.06–1.19], $P < 0.01$). Conclusions were similar whatever the age class (<40 or ≥40) and mGFR level (<60 or ≥60 ml/min/1.73 m²). This study suggests that the CKD-EPI and MDRD equations have poor performances in SPK recipients and that the Schwartz-Lyon equation is a reliable alternative.

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Key words

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Correspondence

Antoine Sicard MD, PhD, Hôpital Edouard Herriot, Service de Transplantation, Néphrologie et Immunologie Clinique, Pavillon P, 5 place d'Arsonval, Lyon 69003, France.
 Tel.: 04 27 85 80 20; fax: 04 72 11 02 71; e-mail: antoinesicard@yahoo.com or
 Laurence Dubourg MD, PhD, Service de Néphrologie, dialyse, hypertension et exploration fonctionnelle rénale, Hôpital Edouard Herriot, Pavillon P, 5 place d'Arsonval, Lyon 69003, France.
 Tel.: 04 27 85 80 00; fax: 04 72 11 10 25; e-mail: laurence.dubourg@chu-lyon.fr

*Equal contribution.

Introduction

Simultaneous pancreas-kidney transplantation (SPK) is considered the treatment of choice for type 1 diabetic patients with end-stage renal failure. In addition to re-establishing glucose homeostasis, SPK restores renal function. Despite excellent short-term renal outcomes [1], progressive loss of kidney function remains frequent and responsible for high morbi-mortality. An accurate monitoring of chronic kidney disease (CKD) in SPK recipients is essential to allow for specific therapeutic interventions, to guide monitoring and treatment of CKD complications, to adjust drugs dosing and to estimate prognosis [2].

The evaluation of glomerular filtration rate (GFR) is the recommended approach to monitor CKD [3]. Ideally, GFR is measured with a radioactive tracer (such as Cr-EDTA) or with an exogenous marker, such as inulin or iohexol, which are exclusively eliminated by glomerular filtration. However, for practical reasons, GFR is most often estimated from serum levels of endogenous filtration markers, like Cystatin C or plasma creatinine (PCr). Main difficulty of PCr-based GFR estimation comes from considerable inter-individual variations in PCr concentration that depends not only on GFR but also on age, sex, muscle mass, diet, nutritional state, drugs, etc. This has led to the development of several PCr-based GFR estimating equations whose performances depend upon individuals' characteristics [4].

Despite the singular characteristics of SPK recipients in terms of age, nutritional state, adipo-metabolic profile, muscle mass, diet, drugs and comorbidities, no study has specifically investigated the reliability of recent GFR estimating equations in the SPK population. As a consequence, GFR is habitually estimated in clinical practice and research studies with the Modification of Diet in Renal Disease (MDRD) [5,6] or CKD-EPI [7] equations that have been shown to perform better than alternative PCr-based equations in the overall population of solid organ transplant recipients [8,9]. However, the performances of these two equations in the specific SPK population are unknown.

The objective of the present study was to assess the performances of recent creatinine-based GFR estimating equations for evaluating GFR in SPK recipients taking into account the effect of age and level of renal function. The CKD-EPI, MDRD, Schwartz-2009, Schwartz-Lyon, Lund Malmo, Full Age Spectrum (FAS) equations were tested [5–7,10–13].

Materials and methods

Study population

Included were all adults (>18 years) who received a SPK transplantation in Lyon University Hospital (Nephrology, Clinical Immunology and Transplantation department) between June 2009 and March 2015 and had a measurement of GFR (mGFR) one year after transplantation as part of their systematic monitoring (specialized Renal Function Exploration Unit). The exclusion criteria were: (i) treatment by dialysis at the time of the study; (ii) cimetidine or trimethoprim administration, intravenous injections of albumin or diuretics before GFR measurement; (iii) GFR >160 ml/min/1.73 m². To identify the study population and collect data, information from the two departments data bases was crossed.

All the procedures were carried out in accordance with the ethical standards of the institutional and/or national research committees and of the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Precisely, an appropriate written informed consent was obtained from all the participants or their legal representatives. The consent form contained information on the procedure itself as well as on the possibility of later use of the data for research purposes.

GFR measurements

GFR measurements were performed by a trained staff with the reference standard methods (mGFR): urinary inulin ($n = 23$) or plasmatic iohexol ($n = 103$) clearance depending of the clinical status of the patient.

Renal clearance of inulin was measured using a polyfructosan-based method (Inutest, FreseniusKabi). A standard technique was used with a continuous infusion after a 30-mg/kg priming dose of polyfructosan. Water diuresis was induced by an initial 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. Three to four urine samples were collected, and a blood sample was drawn midway through each collection period. The clearance value, calculated by the usual UV/P formula, was the mean value of three to four clearance periods. The measurements of plasma and urine polyfructosan were performed using the same enzymatic method, which demonstrated very good specificity and reproducibility (within-run precision <1% and between-run precision <3.5%)[14]. The results

were expressed per 1.73 m² according to the Dubois formula: body surface area = height 0.725 × weight 0.425 × 0.007184.

Iohexol plasma clearance was performed according to a standard technique with single-bolus injection. An IV injection of 6 ml iohexol (Omnipaque 300 mg/ml; GE Healthcare SAS, Vélizy-Villacoublay, France) was administered, and blood samples were drawn from the contra lateral arm after 120, 180, and 240 min. Blood collection was performed at 120, 180, and 240 min. The GFR was calculated from the slope of plasma concentrations using a 1-compartment model corrected using the Bröchner-Mortensen formula [15]. The results were expressed per 1.73 m² according to the Dubois formula: body surface area = height 0.725 × weight 0.425 × 0.007184. The serum iohexol concentration was measured by High Performance Liquid Chromatography (HPLC) according to the method published by Cavalier *et al.* [16] which showed high analytical performances. External quality control was provided by Equalis (Uppsala, Sweden) every 3 months.

GFR estimation

A baseline blood sample was drawn the same day before mGFR measurement for determination of serum creatinine. PCr concentration (expressed in μmol/l) was obtained with the Siemens enzymatic method (on the Dimension Vista System) traceable to National Institute of Standards and Technology creatinine Standard Reference (IDMS calibrated). Estimated GFR (eGFR) was

expressed in ml/min/1.73 m² and was calculated with CKD-EPI, MDRD, Schwartz-2009, Schwartz-Lyon, Lund Malmo, and FAS equations as described in Table 1.

Statistical analyses

Bias, precision and accuracy

The bias was defined as the mean of the eGFR/mGFR ratio. In a first step, the eGFR/mGFR ratio was modeled according to a linear mixed model with random intercept to quantify the effect of the equation type on the bias. The mean ratios according to the two equations were compared by ANOVA in the linear mixed model [17]. In a second step, two models were built: a first model that included variables “equation type” and “age class” and a second model that included an interaction between variables “equation type” and “age class”. The second model allows quantifying the change of the effect of the equation type according to age. An ANOVA was used to compare the two nested models and conclude regarding the statistical significance of the interaction. This analysis was carried out on the entire sample and on each category of renal function.

The ratio eGFR to mGFR was used instead of the difference to assess the bias and the precision of each equation. Indeed, the between-individual heterogeneity of the difference increased with the value of the GFR. The use of the ratio allowed obtaining a constant heterogeneity.

The precision was defined as the limits of agreements (2.5%; 97.5% LoA) of the eGFR/mGFR ratio.

Table 1. Equations used to estimate glomerular filtration rate (ml/min/1.73 m²).

Equation	Condition	Formula
Schwartz-lyon	Male > 13 years	eGFR = 37 × height (cm)/PCr (μmol/l)
	Female	eGFR = 33 × height (cm)/PCr (μmol/l)
Schwartz 2009 CKD-EPI	None	eGFR = 36.5 × height (cm)/PCr (μmol/l)
	Female; PCr ≤ 61.88 μmol/l	eGFR = 144 × (PCr (μmol/l)/61.88) ^{-0.329} × 0.993 ^{Age}
	Female; PCr > 61.88 μmol/l	eGFR = 144 × (PCr (μmol/l)/61.88) ^{-1.209} × 0.993 ^{Age}
	Male; PCr ≤ 79.56 μmol/l	eGFR = 141 × (PCr (μmol/l)/79.56) ^{-0.411} × 0.993 ^{Age}
MDRD	Male; PCr > 79.56 μmol/l	eGFR = 141 × (PCr (μmol/l)/79.56) ^{-1.209} × 0.993 ^{Age}
	Female	eGFR = 175 × PCr (mg/dl) ^{-1.154} × age ^{-0.203} × 0.742
Revised Lund Malmo	Male	eGFR = 175 × PCr (mg/dl) ^{-1.154} × age ^{-0.203}
	Female; PCr < 150 μmol/L	eGFR = e ^[2.50+0.0121 × (150-PCr (μmol/L)) - 0.0158 × Age + 0.438 × ln(Age)]
	Female; PCr ≥ 150 μmol/L	eGFR = e ^{[2.50-0.926 × ln(PCr (μmol/L)/150)] - 0.0158 × Age + 0.438 × ln(Age)}
	Male; PCr < 180 μmol/L	eGFR = e ^[2.56+0.00968 × (180-PCr (μmol/L)) - 0.0158 × Age + 0.438 × ln(Age)]
Full Age spectrum	Male; PCr ≥ 180 μmol/L	eGFR = e ^{[2.56-0.926 × ln(PCr (μmol/L)/180)] - 0.0158 × Age + 0.438 × ln(Age)}
	Female 20 ≤ age ≥ 40 years	eGFR = 107.3/ (SCr (μmol/L)/62)
	Female > 40 years	eGFR = 107.3/ (SCr (μmol/L)/62) × 0,988 ^(Age-40)
	Male 20 ≤ age ≥ 40 years	eGFR = 107.3/ (SCr (μmol/L)/80)
	Male > 40 years	eGFR = 107.3/ (SCr (μmol/L)/80) × 0,988 ^(Age-40)

eGFR, estimated GFR.

Accuracy was defined at two levels: P10, the percentage of eGFR values within the 10% percent limits above and below the mGFR and P30, the percentage of eGFR values within the 30% percent limits above and below the mGFR.

The 95% confidence intervals (CIs) of the eGFR/mGFR ratio, P10 and P30 values were calculated using the bootstrap method (2000 bootstraps) [18].

The comparisons of the 10% and 30% accuracies between the equations were done with the Cochran Q tests with pairwise McNemar permutation tests as a post-hoc.

The method of Holm-Bonferroni was used to correct all multiple comparisons.

Bland and Altman and regression graphs

Bland and Altman and regression graphs were built using the mGFR values on the *x*-axis because the mGFR (i.e., clearance) is considered as the gold standard method for GFR measurement [19].

The analyses were performed with R for Windows, version 3.1.1 (R-Cran project, <http://cran.r-project.org/>). The nominal *P*-value used to conclude to a statistical significance was <0.05.

Results

Characteristics of the study population

Over the study period, 126 SPK recipients fulfilled the inclusion criteria and were enrolled in the study. All of them were transplanted for instable type 1 diabetes with diabetic nephropathy. Table 2 shows the characteristics of the study population at time of GFR measurement. Seventy two (57.1%) patients were men and 54 (42.8%) patients were women. All of them were Caucasians. Mean age was 43.6 ± 7.9 . Mean weight was 64.1 ± 10.8 kg (female: 57.9 ± 7.8 kg; males: 68.8 ± 10.4 kg). Height was 168.1 ± 9.1 cm (female: 160.9 ± 6 cm; males: 173.5 ± 7 cm). Mean BMI was 22.7 ± 3.3 kg/m². 5.6% of patients were underweight (BMI < 18.5 kg/m²), 73.8% were in the normal range (BMI 18.5–25 kg/m²), 15% were overweight (BMI 25–30 kg/m²) and 5.6% were obese (BMI ≥ 30 kg/m²).

Values of mGFR and distribution

Mean mGFR was 56.3 ± 13.3 ml/min/1.73 m². Within the mGFR range of 23.6–92.5 ml/min/1.73 m², 73 participants (57.9%) had values <60, and 53 (42.1%)

Table 2. Characteristics of the study population (*n* = 126) at time of GFR measurement.

Sex (Male)	72 (57.1)
Age (year)	43.6 \pm 7.9
Weight (kg)	64.1 \pm 10.8
Female	57.9 \pm 7.8
Male	68.8 \pm 10.4
Height (cm)	168.1 \pm 9.1
Female	160.9 \pm 6
Male	173.5 \pm 7
BMI (kg/m ²)	22.7 \pm 3.3
<18.5 kg/m ²	7 (5.6)
≥ 18.5 –25 kg/m ²	93 (73.8)
≥ 25 –30 kg/m ²	19 (15)
≥ 30 kg/m ²	7 (5.6)
Body surface area, m ²	1.7 \pm 0.2
Urine albumine/urine creatinine (mg/mmol)	9.7 \pm 37.9
<3 (mg/mmol)	87 (69.1)
3–30 (mg/mmol)	30 (23.8)
>30 (mg/mmol)	9 (7.1)
PCr (μ mol/l)	99.7 \pm 29.3
mGFR (ml/min/1.73 m ²)	56.3 \pm 13.3
<60 ml/min/m ²	73 (57.9)
≥ 60 ml/min/m ²	53 (42.1)

Values are expressed as mean \pm SD or *n* (%).

BMI, body mass index; PCr, plasma creatinine; mGFR, measured glomerular filtration rate.

had values ≥ 60 ml/min/1.73 m². Figure 1 shows the distribution of mGFR values in the study population.

Formula performances

Figure 2 shows the Bland and Altman and the regression graphs for each formula (Figure 2a and b respectively). Bias, precision, 10% and 30% accuracies for each formula are given and compared in Table 3. In the whole population, the Schwartz-Lyon equation estimated GFR with a significantly lower bias than the other equations (relative bias: 1.13, 95% CI: [1.06; 1.19] ml/min/1.73 m², *P* < 0.01). This equation also had significantly better 10% (P10: 39.0, 95% CI: [35.5; 42.0], *P* < 0.01) and 30% accuracies (P30: 86.0, 95% CI: [83.5; 88.0], *P* < 0.01) than all the other equations. The linear mixed-effects model showed that there was no effect of the GFR measurement method (i.e. iohexol plasma clearance or inulin renal clearance) on bias, accuracy and limits of agreements values of each equation and their comparisons (*P* = 0.6, not shown).

When analyzing the equations performances according to age class (<40 or ≥ 40 years old) and mGFR level

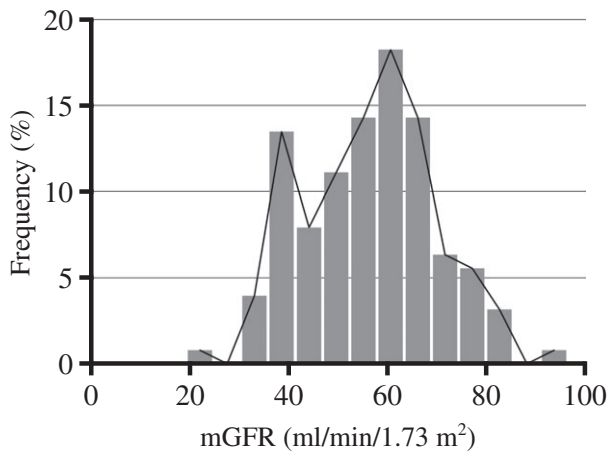


Figure 1 Distribution of mGFR values in the study population.

(<60 or ≥ 60 ml/min/1.73 m²), conclusions were similar (Table 3). The Schwartz-Lyon equation performed significantly better than CKD-EPI, MDRD, Schwartz-2009, Lund Malmo, FAS, and FAS-height equations regarding bias and accuracy whatever the age class and mGFR level (Table 3).

Discussion

Simultaneous pancreas-kidney is associated with excellent short term renal outcomes [1]. However, many factors, foremost among which are the allo-immune response and calcineurin inhibitors, cause damages to the kidney allograft and lead to renal failure. The latter is an important cause of morbi-mortality in SPK recipients. Patients therefore undergo a regular assessment of their kidney allograft function that guides therapeutic interventions, monitoring of CKD complications, adjustment of drugs dosing and prognosis evaluation [2]. Most of the teams caring for SPK patients perform this monitoring in clinical practice and research studies by using the CKD-EPI or the MDRD equations which are commonly recommended in other populations including the solid organ transplant population. Saeed Kamran Shaffi *et al.* [8] recently compared the performances of the CKD-EPI and MDRD equations to alternative equations in a population of 3622 solid organ transplant recipients constructed from five previous key studies. The authors found that P30% for the CKD-EPI and MDRD equations was 78.9% for both. Both equations performed better than or as well as the alternative equations in the whole population and in most subgroups, including the type of transplanted organ. However, the study included only 26 pancreas-only transplant recipients and the SPK subgroup could

not be analysed. In the present study, we compared the CKD-EPI and MDRD equations to four alternative equations in 126 SPK recipients. We found that the CKD-EPI and MDRD equations failed to estimate GFR with good performances (P30%: 42% (38.0; 46.0) and 65% (61.5; 69) respectively), which leads us to recommend not to use these equations in SPK recipients. The Schwartz-Lyon equation significantly outperformed all the other equations and had performances close to the KDOQI recommendations (P30 = 86.0% [83.5–88.0]) [20]. We therefore recommend using this equation in SPK recipients for both clinical management and research studies.

Over the last decades, a considerable amount of studies has aimed at assessing the validity of PCr-based GFR-predicting equations, but only one, performed in 1995 in 33 patients, has specifically searched for the most reliable equation in SPK recipients, without using a standardized procedure of creatinine measurement [21]. As a consequence, there is currently no reliable recommendation regarding the equation to use in this population. This is somehow surprising because SPK recipients are widely considered as a very specific population in which many parameters affect muscle mass and thus PCr level and GFR estimation. A long history of glucose homeostasis dysregulation indeed leads inevitably to profound metabolic perturbations that adversely affect the skeletal muscle, a process named diabetic myopathy [22,23]. In addition, SPK recipients often have singular dietary habits, malabsorption due to diabetic autonomic neuropathy and sensory-motor disorders due to diabetic peripheral neuropathy [22]. These disorders, which are poorly reversible after SPK, strongly influence the patients muscle mass. The latter may also vary because of corticosteroids or increased catabolism caused by infections after transplantation. All together, these factors influence PCr-based GFR estimation and certainly explain the low performances of the MDRD and CKD-EPI equations in the SPK population as compared with the general population of CKD patients [5–7,24]. Clinicians have to keep this in mind and must be aware that the estimation of renal function is not reliable with the CKD-EPI and MDRD equations.

Of interest is the reason why the Schwartz-Lyon equation performed better than the other equations. When comparing the characteristics of the SPK population and those of the populations used to build the different formula, no clinical or biological parameter was found to account for the reason why the Schwartz-Lyon equation performs better than the other equations. In particular

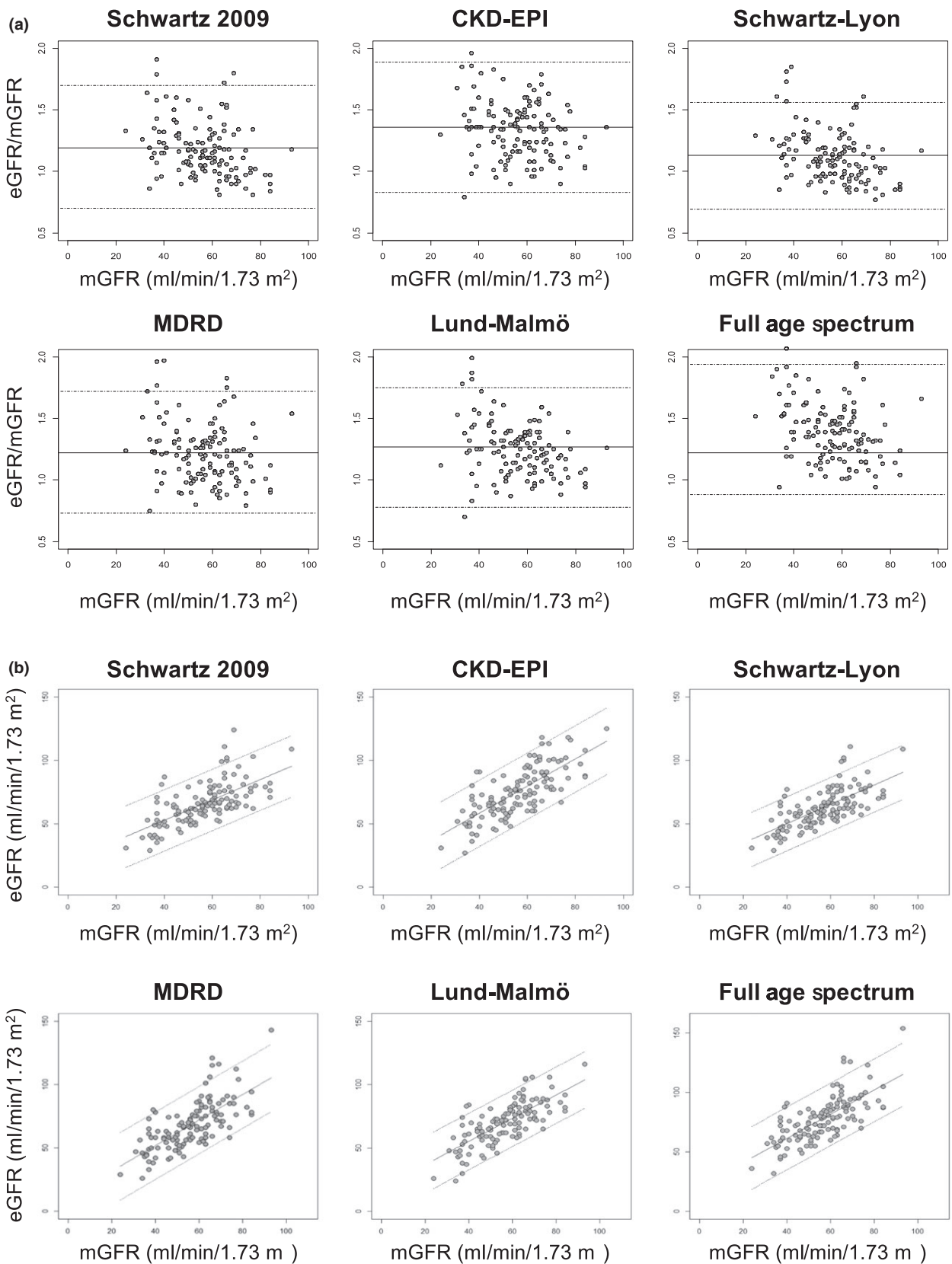


Figure 2 Bland and Altman (a) and regression graphs (b) for the CKD-EPI, Schwartz-2009, MDRD, Lund-Malmö, Schwartz-Lyon and Full Age Spectrum (FAS) formula.

Table 3. Bias, precision and accuracy of the different equations in the whole population and according to age class and mGFR level.

Equation	P < 0.05*				
	^a CKD-EPI	^b Schwartz-2009	^c MDRD	^d LM	^e FAS
Whole population					
Relative bias (95% CI)	1.13 (1.06; 1.19)	1.19 (1.13; 1.25)	1.22 (1.16; 1.29)	1.26 (1.20; 1.33)	1.41 (1.36; 1.46)
Precision (2.5; 97.5% LoA)	(0.69; 1.56)	(0.70; 1.68)	(0.73; 1.72)	(0.78; 1.75)	(0.98; 1.94)
P10 (95% CI)	39.0 (35.5; 42.0)	29.0 (23.0; 35.0)	28.0 (24.0; 31.0)	24.0 (21.0; 26.0)	12.0 (9.5; 14.0)
P30 (95% CI)	86.0 (83.5; 88.0)	74.0 (70.5; 77.5)	65 (61.5; 69)	60.5 (57.0; 63.5)	37.5 (34.0; 40.5)
Age <40 years old					
Relative bias (95% CI)	1.11 (1.06; 1.17)	1.18 (1.12; 1.25)	1.24 (1.18; 1.30)	1.30 (1.24; 1.36)	1.46 (1.39; 1.52)
Precision (2.5; 97.5% LoA)	(0.73; 1.50)	(0.74; 1.63)	(0.81; 1.67)	(0.88; 1.71)	(0.98; 1.94)
P10 (95% CI)	37.0 (32.0; 40.5)	29.0 (23.0; 35.0)	23.0 (17.5; 28.0)	15.5 (13.0; 19.0)	4.0 (2.0; 6.5)
P30 (95% CI)	83.0 (79.0; 86.0)	77.0 (72.2; 82.5)	64.5 (58.5; 70.5)	49.0 (44.0; 53.0)	30.0 (24.0; 34.0)
Age ≥40 years old					
Relative bias (95% CI)	1.14 (1.08; 1.19)	1.19 (1.13; 1.25)	1.21 (1.15; 1.27)	1.25 (1.19; 1.30)	1.38 (1.31; 1.44)
Precision (2.5; 97.5% LoA)	(0.68; 1.60)	(0.67; 1.71)	(0.68; 1.75)	(0.73; 1.76)	(0.83; 1.93)
P10 (95% CI)	42.0 (37.0; 47.0)	36.0 (31.0; 41.0)	31.0 (26.0; 35.5)	27.0 (23.0; 31.0)	17.0 (13.0; 20.0)
P30 (95% CI)	82.0 (79.0; 85.0)	72.0 (67.5; 76.0)	65.5 (60.5; 70.0)	61.5 (57.0; 65.0)	42.5 (38.0; 46.5)
mGFR < 60 ml/min/1.73 m²					
Relative bias (95% CI)	1.18 (1.13; 1.24)	1.25 (1.19; 1.31)	1.25 (1.19; 1.31)	1.32 (1.25; 1.38)	1.46 (1.40; 1.53)
Precision (2.5; 97.5% LoA)	(0.74; 1.62)	(0.75; 1.76)	(0.74; 1.75)	(0.78; 1.86)	(0.92; 2.01)
P10 (95% CI)	37.0 (32.0; 40.5)	25.5 (20.0; 30.0)	25.5 (20.5; 30.0)	15.5 (12.0; 19.5)	5.5 (3.5; 8.0)
P30 (95% CI)	83.0 (80.0; 86.0)	67.5 (62.5; 72.5)	62.0 (57.0; 67.0)	49.5 (44.5; 53.5)	29.5 (25.0; 33.5)
mGFR ≥60 ml/min/1.73 m²					
Relative bias (95% CI)	1.06 (1.01; 1.11)	1.11 (1.06; 1.17)	1.19 (1.12; 1.25)	1.20 (1.15; 1.25)	1.34 (1.27; 1.40)
Precision (2.5; 97.5% LoA)	(0.67; 1.45)	(0.68; 1.55)	(0.71; 1.67)	(0.68; 1.71)	(0.86; 1.81)
P10 (95% CI)	42.0 (37.0; 47.0)	43.5 (38.0; 49.5)	30.0 (25.5; 36.5)	34.5 (30.0; 40.0)	20.0 (16.0; 24.0)
P30 (95% CI)	89.0 (85.5; 92.0)	82.0 (77.0; 86.5)	69.0 (63.5; 74.5)	74.5 (70.0; 78.5)	47.5 (42.5; 52.0)

CI, confidence interval; FAS, Full Age Spectrum. Relative bias: mean of eGFR/mGFR ratio. LoA: limits of agreement. P10 and P30: within 10% and 30% limits above and below the mGFR.

*Comparison of the Schwartz-Lyon equation with: ^aCKD-EPI equation, ^bSchwartz 2009 equation, ^cMDRD equation, ^dLMR equation, ^eFAS equation.

age, sex or weight of the study population did not explain why the Schwartz-Lyon equation had better performances (not shown). The use of age, sex and race as surrogates of muscle mass, age being a central component, may be less relevant than the use of height. The Schwartz-Lyon equation indeed only uses the height as muscle mass determinant. The choice of height rather than age makes sense in SPK recipients who are most often young to middle-age adults. Muscle mass remains constant until middle-age adulthood and, before it begins to decrease, is more closely related to height than to age [25,26].

The present study has some limitations. First, the study population included few non-white participants and could not assess the effect of ethnicity. Second, the performance of eGFR equations in participants with mGFR < 30 ml/min/1.73 m² could not be independently examined because of the small number of participants with severe CKD.

In conclusion, we observed in that cohort of SPK patients that the CKD-EPI and MDRD equations had low performances for estimating GFR. The Schwartz-Lyon equation was more reliable and had performances close to the recommendations.

Authorship

AD, LS, SL, EM, LD, AS: participated in study design. AD, LD, AS: participated in data collection. AD, LS, SL, LD, AS: participated in data analysis. AD, LS, AS: participated in writing the first draft of the manuscript and figures. AD, LS, SL, FB, VCS, TR, OT, LB, EM, LD, AS: participated in scientific discussion, manuscript corrections and final manuscript construction.

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Conflict of interest

None declared.

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