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Performance of CKD-EPI equation to estimate glomerular filtration rate as compared to MDRD equation in South Brazilian individuals in each stage of renal function

Abstract

Background: The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation seems to correct the overdiagnosis of chronic kidney disease (CKD) provided by Modification of Diet in Renal Disease (MDRD) equation. However, this point has not been tested in some ethnic groups. This study investigated the performance of MDRD and CKD-EPI equations in South Brazilian individuals.

Methods: This cross-sectional study included 354 individuals including healthy volunteers, diabetic and non-diabetic individuals with or without CKD. Glomerular filtration rate (GFR) was measured by the ^{51}Cr-EDTA single-injection method (^{51}Cr-GFR). Accuracy (P30), bias, and Bland-Altman agreement plots were evaluated.

Results: In the group as a whole, ^{51}Cr-GFR was 87±37 (6-187), CKD-EPI eGFR, 82±30 (6-152), and MDRD eGFR, 77±28 (6-156) mL/min/1.73 m^2 (p<0.001 for all comparisons). Analyzing the subset of individuals with ^{51}Cr-GFR <60 mL/min/1.73 m^2, P30 values were, respectively, 76% and 84% for MDRD and for CKD-EPI (p<0.001) while for ^{51}Cr-GFR ≥60 mL/min/1.73 m^2, P30 values were 57.5% for both equations (p=1.000). For MDRD and CKD-EPI, mean bias were negative for GFRs <60 (–11 vs. –12, p=0.221) and positive for values >60 (16 vs. 9, p<0.001). In multivariate analysis, absolute bias was unfavorably influenced by measured GFR >60 (for MDRD) and being diabetic or younger (for CKD-EPI).

Conclusions: CKD-EPI reduces GFR underestimation in individuals with GFRs >60, but still presents a quite low

accuracy at this GFR range. Moreover, it tends to overestimate GFR in subjects with GFRs <60 mL/min/1.73 m^2. CKD stages 1 and 2, diabetes and young age had a negative influence on the performance of the equations.

Introduction

Glomerular filtration rate (GFR) is widely accepted as the best overall measure of kidney function. Several exogenous markers have been used to provide an accurate measurement of GFR, such as inulin, ^{51}Cr-ethylediaminetetraacetic acid (^{51}Cr-EDTA), iothalamate and iohexol, but they are laborious and expensive, which precludes their use in clinical practice [1, 2]. Endogenous markers, such as serum creatinine, have many drawbacks because its concentration is largely dependent on muscle mass, which is well known to be affected by gender, age, and ethnicity, not reflecting GFR accurately [3, 4].

In 2002, the National Kidney Foundation Disease Outcomes Initiative (KDOQI) proposed a staging system to categorize chronic kidney disease (CKD), based on the level of GFR and/or evidence of kidney damage [5], that is now being widely used in adults, specifically in the 'at risk' populations. This categorization was recently refined by KDIGO, maintaining estimated GFR as a key element [6]. To estimate kidney function in routine practice, mathematical equations have been derived using serum creatinine, age, gender, race, and weight [7–10]. These efforts are justified by the need to diagnose, classify and stratify

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CKD accurately, as distinct clinical actions are recommended according to the level of GFR and CKD stage [11].

Cockcroft and Gault's equation was the first to be developed and is still used by clinicians. However, it estimates creatinine clearance instead of GFR and requires patient weight in the formula [7]. In 1999, the Modification of Diet in Renal Disease (MDRD) [8], later simplified, and more recently the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [10] equations were developed. Both require calibration of serum creatinine to a reference standard in order to decrease the errors of different assays. These new equations have proved to perform better than Cockcroft and Gault's in the estimation of GFR in a wide range of GFRs, with less bias and superior accuracy [12–14], but they still have several limitations [10, 14, 15]. The MDRD underestimates GFR in healthy individuals with normal or near normal renal function [16], and CKD-EPI equation is less accurate in patients at extremes of age and body size [14], and in patients with type 2 diabetes with GFRs >60 mL/min/1.73 m² [17, 18]. The CKD-EPI seems to be more accurate than MDRD with less bias, although precision still remains suboptimal [10, 14].

Previous studies evaluating the performance of prediction equations have focused on comparison of individuals with and without CKD, suggesting that the new CKD-EPI equation tends to correct the overdiagnosis of CKD provided by MDRD equation [19]. However, this point has not been tested in some ethnic groups. Furthermore, an unsolved question is whether this performance differs taking into account gender, age, weight, and presence of diabetes [14, 18, 20]. Therefore, the aim of the present study was to investigate, in South Brazilian individuals, the performance of MDRD and CKD-EPI equations compared with ⁵¹Cr-EDTA GFR, analyzing healthy volunteers, and patients with CKD and/or diabetes stratified by level of kidney function.

Materials and methods

This cross-sectional study analyzed individuals aged ≥18 years, including healthy volunteers recruited from the community and hospital staff, type 2 diabetic subjects with or without kidney disease and non-diabetic individuals with CKD, between January 2007 and October 2011. A subset of the diabetic patients [18] and the healthy volunteers [21] were previously examined in separated cohorts.

Volunteers were defined as healthy when they reported no personal or familial history of kidney disease, diabetes and hypertension; when blood pressure levels were <140×90 mm Hg; when fasting plasma glucose was <100 mg/dL; when measured GFR was >60 mL/min/1.73 m² and there was no hematuria or proteinuria in urinalysis. CKD in the present study was defined [5] as a GFR <60 mL/min/1.73 m² as measured by ⁵¹Cr-EDTA, not taking into account the presence or absence of albuminuria. Exclusion criteria for patients with CKD were an acute change in renal function, defined by a 25% increase in baseline serum creatinine in three measurements, or the immediate need of renal replacement therapy (dialysis or transplantation). This study was approved by the Ethics Committee of Hospital de Clínicas de Porto Alegre (HCPA), Brazil and all the patients signed a written informed consent.

Data collected included age, gender, ethnicity, etiology of CKD, height, weight, body surface area (BSA) (m²) and body mass index (BMI=weight/height², kg/m²). CKD was classified in five stages according to K-DOQI staging system [5].

GFR was measured by ⁵¹Cr-EDTA single-injection method, and the procedure is described below, following the British Nuclear Medicine Society Guidelines [22]. We employed a dose of 5.55 MBq of ⁵¹Cr-EDTA, and blood samples were collected from the opposite arm, 2, 3 and 4 h post-injection. Plasma samples were counted with appropriate standards and blanks for background in a well counter. A logarithm of the plasma activity was plotted as a function of time and the apparent zero time plasma activity determined by extrapolation of the linear part of the curve. A constant correction factor of 0.87 was made for the missing AUC due to the fast exponential, therefore, GFR=volume of distribution×0.693×0.87×1000/t1/2, according to Chantler [23], and expressed as mL/min/1.73 m². BSA was calculated according to Gehan and George formula: $0.0235 \times [(100 \times height)^{0.42246}] \times (weight^{0.51456})$ [24]. The mean intra-individual coefficient of variation of GFR at our laboratory is 12% [25].

Serum creatinine was measured by a Jaffe reaction (Modular P Roche Diagnostic, Mannheim, Germany) traceable to isotope dilution mass spectrometry (ID-MS). The CKD-EPI equation was calculated as: GFR (mL/min/1.73 m²)=141×min (serum creatinine/k, 1)$^{\alpha}$×max (serum creatinine/k, 1)$^{-1.209}$×0.993^{Age}×1.018 (if female)×1.159 (if black), where k is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min indicates minimum serum creatinine/k or 1, and max indicates maximum serum creatinine/k or 1 [10]. MDRD equation was calculated as: GFR (mL/min/1.73 m²)=175×(serum creatinine)$^{-1.154}$×(age)$^{-0.203}$×(0.742 for women)×(1.210 for black subjects) [26]. Proteinuria was measured by urinary total protein to creatinine ratio (colorimetric Pyrogallol Red and Jaffe reaction, respectively), and normal values established at <0.20. Albuminuria was measured by immunoturbidimetry.

Statistical analysis

Bias was calculated as the mean difference between measured and estimated GFR, and absolute bias was determined by the Inverse Gaussian probability distribution. Absolute bias measures the magnitude of bias without the negative and positive signals, allowing a more meaningful quantitative interpretation of the bias size. Absolute bias was determined within strata of age, gender, ethnicity, BMI, diabetes mellitus and measured GFR.

Accuracy was calculated as the percentage of estimates within 15% (P15) and 30% (P30) of measured GFR, and the differences between the two equations were established by the McNemar-Bowker test. Precision was measured as one standard deviation (SD) of bias. The agreement between measured GFR and equations was evaluated using Bland-Altman plots, with the calculation of agreement limits (bias±2 SD) and confidence intervals (CI) [27]; 200 individuals is the recommended sample size, giving a 95% CI of about 24% of SD [28]. Data were summarized as mean±SD or median and interquartile range.

Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) to identify CKD were calculated.

Agreement between measured and estimated GFR according to CKD stage was calculated by quadratic weighted κ, establishing as excellent agreement values >0.75, fair to good between 0.40 and 0.75, and poor when <0.40. The effect of independent variables on absolute bias and accuracy (P30 ≥30%) of the two equations was determined by the log-γ and logistic regression, respectively. Data were processed and analyzed using SPSS for Windows, version 18.0 (Chicago, IL, USA). The level of significance was set at p<0.05.

Results

This cross-sectional study included 354 adult individuals that had GFR measured by the ^{51}Cr-EDTA method. Clinical characteristics of the study population were shown in Table 1. In the group as a whole, ^{51}Cr-GFR was 87±37 (6-187), CKD-EPI-GFR, 82±30 (6-152), and MDRD-GFR, 77±28 (6-156) mL/min/1.73 m^2 (p<0.001 for all comparisons).

Overall, the CKD-EPI and MDRD equations systematically underestimated measured GFR in the normal levels, and no agreement was found between measured and estimated GFR (p<0.001). Overall, the mean bias of MDRD and CKD-EPI were 10±25 and 5±23, respectively (p=0.001), P15 were higher for the CKD-EPI formula (p=0.007), but for P30 the difference between the two equations did not reach statistical significance (p=0.057), as shown in Table 2. Sensitivity, specificity, PPV and NPV of MDRD and CKD-EPI for the detection of CKD did not differ as well, but the area under the curve for correctly estimating GFR level was significantly higher for CKD-EPI (Table 2).

Figure 1 shows GFR classification according to KDIGO stages. The prevalence of GFR <60 mL/min/1.73 m^2 was found in 80 (22.6%) patients by ^{51}Cr-EDTA, 81 (22.9%) by CKD-EPI (p=0.648, vs. ^{51}Cr-EDTA), and 88 (25.6%) by

Table 1 Clinical characteristics of the study population.

Clinical data (n=354)	
Age, years	53±17 (18–92)
Female gender	196 (55)
White	306 (86)
Healthy volunteers	140 (39)
Diabetes mellitus	130 (37)
Chronic kidney disease	80 (23)
Hypertensive nephrosclerosis	25 (31)
Chronic glomerulonephritis	22 (27)
Diabetic nephropathy	16 (20)
Other	17 (22)
Body surface area, m^2	1.85±0.21
Body mass index, kg/m^2	27±5 (16–45)
Measured GFR, mL/min/1.73 m^2	87±37 (6–187)

Data expressed as mean±SD (range) or number of cases (%). GFR, glomerular filtration rate.

Table 2 Bias, accuracy, sensitivity and specificity of MDRD and CKD-EPI equations to diagnose chronic kidney disease (GFR <60 mL/min/1.73 m^2) in the 354 individuals.

	MDRD	CKD-EPI	p-Value
eGFR	77±28	82±30	<0.001
P15	37% (130/354)	44% (156/354)	0.007
P30	72% (254/354)	78% (276/354)	0.057
Bias	10±25	5±23	0.001
Absolute bias	20±17	17±15	<0.001
Sensitivity	75% (60/80)	75% (60/80)	1.000
Specificity	89% (245/274)	92% (252/274)	0.303
PPV	67% (60/89)	73% (60/82)	0.411
NPV	92% (245/265)	93% (252/272)	0.932
AUC (CI 95%)	0.904	0.919	0.011
	(0.862–0.945)	(0.883–0.956)	

AUC, area under the curve, calculated by receiver operating characteristics curve; eGFR, estimated glomerular filtration rate (mL/min/1.73 m^2); NPV, negative predictive value; PPV, positive predictive value for the diagnosis of CKD.
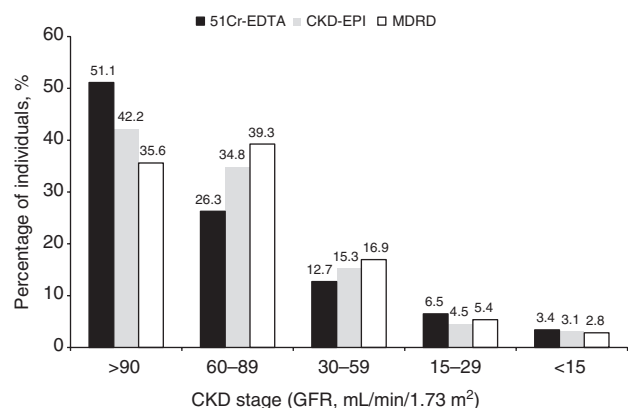
Figure 1 Prevalence of CKD stages according to measured and estimated GFR by MDRD and CKD-EPI equations.
MDRD vs. ^{51}Cr-EDTA, p<0.001; CKD-EPI vs. ^{51}Cr-EDTA, p=0.009 (McNemar-Bowker test).

MDRD (p=0.038, vs. ^{51}Cr-EDTA). Both equations overestimated GFR between 30–89 mL/min/1.73 m^2 and underestimated values >90 mL/min/1.73 m^2, but concordance with ^{51}Cr-EDTA to classify CKD in stages 4 and 5 was fairly good with close values in this GFR range (<30 mL/min/1.73 m^2).

The analysis of agreement between ^{51}Cr-EDTA and each equation to measure GFR as <60 mL/min/1.73 m^2 (CKD stages 3–5) was good for both MDRD: κ=0.76 (95% CI 0.70–0.81; p<0.001) and CKD-EPI: κ=0.79 (95% CI 0.74–0.84; p<0.001). To diagnose CKD stages 1 and 2 (GFR ≥60 mL/min/1.73 m^2) the level of agreement was poor for MDRD [κ=0.34 (95% CI 0.27–0.42); p=0.34] and fair to good for CKD-EPI [κ=0.43 (95% CI 0.36–0.51),
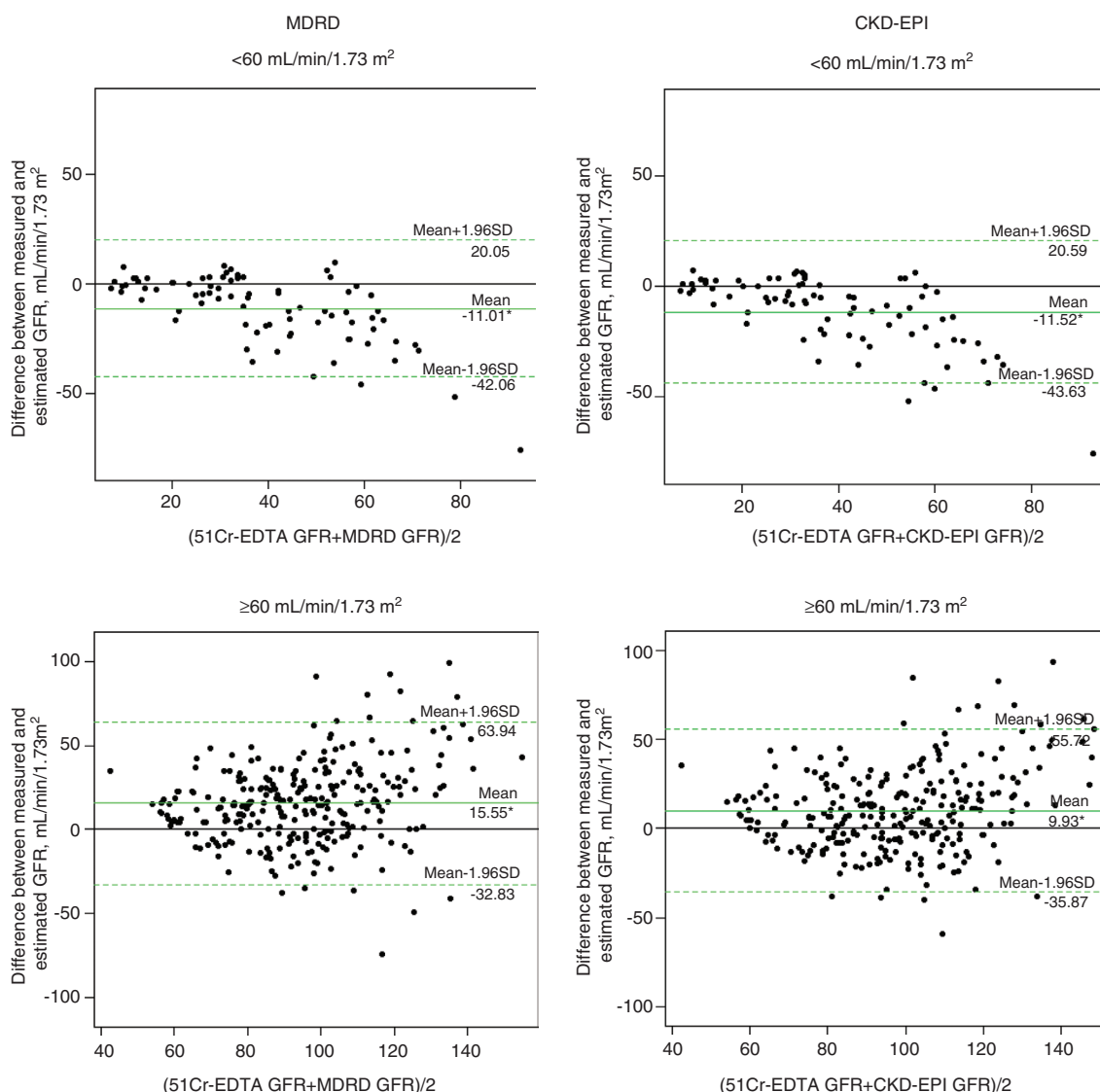
Figure 2 Agreement determined by the Bland-Altman method between MDRD and CKD-EPI equations with measured ^{51}Cr-GFR, according to level of GFR <60 mL/min/1.73 m[2] or ≥60 mL/min/1.73 m[2].

p=0.033]. However, their 95% CIs overlap and statistically it means that they did not differ.

The limits of agreement of Bland-Altman plots were similar between MDRD and CKD-EPI equations for GFRs above and below 60 mL/min/1.73 m[2] (Figure 2). However, even underestimating GFR at higher values, the mean difference of CKD-EPI measurements was lower than for MDRD (9.9 vs. 15.5 mL/min/1.73 m[2], respectively).

Table 3 shows the clinical characteristics and performance of the equations according to the presence or absence of CKD as determined by ^{51}Cr-EDTA. Overall, age was higher in patients with CKD (p<0.001), and diabetes mellitus was more prevalent in non-CKD because our

sample included a high proportion of diabetic individuals with normal or near normal GFRs. Bias of MDRD was higher than that of CKD-EPI in patients with eGFR ≥60 mL/min/1.73 m[2] (16±24 vs. 9±22, p<0.001). P15 of CKD-EPI were higher in non-CKD compared to CKD patients (p=0.005) but did not differ for MDRD (p=0.292). P30 was higher for both MDRD (p=0.001) and CKD-EPI (p<0.001) equations in non-CKD patients. Comparing P15 and P30 values of MDRD and CKD-EPI in each strata of GFR (CKD and non-CKD), we found that P15 and P30 of the equations did not differ for GFRs <60 mL/min/1.73 m[2], but for GFRs ≥60 mL/min/1.73 m[2] both P15 (p=0.003) and P30 (p<0.001) were significantly higher for the CKD-EPI equation (Table 3).

Table 3 Clinical parameters, bias and accuracy of MDRD and CKD-EPI equations according to the presence or absence of CKD (GFR <60 mL/min/1.73 m²).

	GFR <60 mL/min/1.73 m² (n=80)	GFR ≥60 mL/min/1.73 m² (n=274)	p-Value[a]
Measured GFR	33±15	102±25	<0.001
eGFR-MDRD[b]	44±24	86±20	<0.001
eGFR-CKD-EPI	45±25	92±20	<0.001
Age, years	64±18	50±15	<0.001
Gender, male	43 (54)	115 (42)	0.062
Ethnicity (white)	71 (89)	235 (86)	0.493
BSA, m²	1.81±0.21	1.86±0.20	0.070
BMI, kg/m²	26.4±4.8	27.7±5.1	0.051
Diabetes	21 (26)	107 (39)	0.036
Bias MDRD[c]	−11±15	16±24	<0.001
Bias CKD-EPI	−12±16	9±22	<0.001
P15 MDRD[d]	31.3%	38.3%	0.292
P15 CKD-EPI	30.0%	48.2%	0.005
P30 MDRD[e]	57.5%	76%	0.001
P30 CKD-EPI	57.5%	84%	<0.001

BMI, body mass index; BSA, body surface area; GFR, glomerular filtration rate (mL/min/1.73 m²). [a]Independent samples test: CKD vs. non-CKD; [b,c,d,e]Paired samples test (MDRD vs. CKD-EPI); [e]eGFR ≥60: p<0.001 and eGFR <60: p=0.221; [c]Bias: CKD: p=0.261 and non-CKD: p<0.001; [d]P15: CKD: p=1.000 and non-CKD: p=0.003; [e]P30: CKD: p=1.000 and non-CKD: p<0.001.

For MDRD and CKD-EPI, respectively, absolute bias was higher in individuals <50 years as compared to ≥50 years (24 vs. 15, p=0.001; 18 vs. 13, p=0.011), in diabetic patients, but only for CKD-EPI (16 vs. 12, p=0.005), and for those with GFRs ≥60 vs. <60 mL/min/1.73 m² (MDRD: 18 vs. 7, p<0.001; CKD-EPI: 14 vs. 7, p<0.001).

The effect of independent variables on absolute bias and P30 was determined by multivariate models that included only variables with statistical significance in the univariate analysis. For MDRD, eGFR ≥60 mL/min/1.73 m², diabetes and age <50 years increased absolute bias 1.44 times (95% CI 1.13–1.83; p=0.003), 1.37 times (95% CI 1.09–1.72; p=0.006) and 1.52 times (95% CI 1.21–1.91; p<0.001), respectively. Thus, average absolute bias of MDRD was 44%, 37% and 52% higher in these categories. For CKD-EPI, diabetes and age <50 years increased absolute bias 1.57 times (95% CI 1.26–1.98; p<0.001) and 1.50 times (95% CI 1.20–1.88; p<0.001), respectively. Absolute bias of CKD-EPI was not influenced by the level of GFR (≥60 or <60 mL/min/1.73 m²).

In logistic regression analysis adjusted for age, the numbers represent the odds ratio of P30 being equal to or higher than 30%. For MDRD, GFR ≥60 mL/min/1.73 m² had an odds ratio of 2.31 (95% CI 1.31–4.05; p=0.004). For CKD-EPI, eGFR ≥60 mL/min/1.73 m² and diabetes had an odds ratio of 5.93 (95% CI 3.06–11.46; p<0.001) and 2.93 (95% CI 1.58–5.42; p=0.001), respectively.

Discussion

This study explores the performance of two widely used equations – CKD-EPI and MDRD – to estimate GFR based on standardized serum creatinine in a South Brazilian population. It was observed that CKD-EPI produced less GFR underestimation in individuals with GFRs >60, but still presented a quite low accuracy at this GFR range. Moreover, it tended to overestimate GFR in subjects with GFRs <60 mL/min/1.73 m². Diabetes and young age had a negative influence on the performance of the equations.

The southernmost state of Rio Grande do Sul in Brazil received an expressive number of European immigrants during the colonization period, resulting in a mixed ethnic pattern, with predominance of Germans, Italians, Portuguese, Spanish, along with native Indians and blacks, the last coming from a different region of the African continent than those settled in USA [29, 30]. This has produced a unique miscegenation, whose effect on creatinine production and hence on the performance of estimated GFR formulas has not been tested [31]. Yet, the main results of the study confirmed other reports showing a poor performance of both equations when GFR is >60 mL/min, tending to underestimate true renal function when GFR is >90 mL/min. However, both equations overestimated GFRs <90 mL/min, yielding a disappointing PPV for CKD (GFR <60 mL/min) between 67% and 73%. Accuracy was

influenced by the level of measured GFR as well, being lower with higher rates.

When we compared both equations, CKD-EPI performed better, with values closer to the measured GFR, with less bias and a better area under ROC curve. Despite the low accuracy of both equations, it was even lower for MDRD (close to statistical significance), due to significant lower P30 for individuals with GFR <60 mL/min/1.73 m². Also, for subjects with GFR >60 mL/min/1.73 m² bias with CKD-EPI was lower than with MDRD. In fact, when controlled for diabetes and age, bias of the CKD-EPI equation was not influenced by the level of GFR.

Our data showed that in the range of values >60 mL/min/1.73 m² the absolute bias of MDRD increased, but not of CKD-EPI. For GFRs <60 mL/min/1.73 m², relative bias and accuracy of the two equations did not differ, as well as the proportion of patients classified in stages 3–5. Overall, these results are in line with other reports [10, 14, 32, 33]. Quoting Delanaye, at best the CKD-EPI equation might be considered as an evolution but not a revolution [34]. Misclassification is an important issue in clinical practice and to healthcare policy, having an impact on investigations, treatment decisions, drug dosages, follow-up and monitoring of patient functional evolution, and preparation to renal replacement therapy.

Diabetes and age had an unfavorable influence on bias for both equations. We have previously demonstrated that both MDRD and CKD-EPI equations pronouncedly underestimate GFR in diabetic individuals [18], a finding confirmed by other authors [17]. The effect of hyperglycemia upon creatinine measurement is a well-known phenomenon, especially with the Jaffe method, and this probably influenced the results, increasing creatinine levels and consequently decreasing GFR estimation [35]. Creatinine measurement with enzymatic methods tends to improve, although not fully correcting, this limitation [36].

In the present study, both equations – MDRD and CKD-EPI – largely underestimated GFR in the subset of the 10% hyperfiltering subjects. This finding confirms previous observations, especially regarding diabetic patients [18, 37]. According to Gaspari, changes in tubular handling and interferences in serum creatinine measurement, such as that promoted by hyperglycemia, might explain the underestimation of GFR [37].

Our study demonstrated a negative influence of young age in the performance of CKD-EPI equation. However, younger subjects had the higher GFRs, and, therefore, age could be just acting as a confounding factor for the real impact of increased GFR itself. In the elderly, large cohorts of older patients with CKD suggested that except for Cockcroft and Gault, all equations perform similarly, with

estimates that are not perfect, but rather satisfactory [38]. A study aiming specifically to analyze this issue, evaluated individuals >70 years and concluded that the CKD-EPI equation appeared less biased and was more accurate than the MDRD Study equation, and that GFR estimation was as satisfactory in older people of European ancestry as it has been reported to be in younger individuals [39]. However, serum creatinine may be misleading in elderly individuals and thus influence the equations. In this regard, novel equations have been developed, such as the BIS1 (creatinine-based) and BIS2 (creatinine- and cystatin C-based), which were validated in a German community-based population. The BIS-2, followed by the BIS-1, performed better in patients aged 70 years or older for assessing renal function in CKD stages 1–3 compared to the other equations [40].

CKD-EPI equation had a worse performance than MDRD in only one variable: P30 in black individuals. It is not defined yet if eGFR correction for African-American individuals should be generalized for populations of different ethnic origins (e.g., Afro-descendants from other regions) [41]. We re-analyzed our data in a separate set of 48 individuals with African origin without correction for race, in both equations. For those with eGFR ≥60 mL/min/1.73 m² the values of P15, P30 and bias worsened, and for those with eGFR <60 mL/min/1.73 m² there was a reduction in overestimation, increasing P15 and P30 and reducing bias. This subject should be investigated in another study, with a larger sample of individuals with African ancestry.

A putative limitation of our study is that when estimating GFR from ⁵¹Cr-EDTA through slope-intercept techniques, sampling is restricted to the second phase of the clearance, with the need for correcting the systematic errors. The linear Chantler equation uses a constant multiplicative correction factor to adjust the GFR values [23]. Fleming [42] demonstrated that the Chantler's equation gave a systematic overestimation of GFR, and the error increased with GFR with 30% overestimation at 180 mL/min/1.73 m², but these values are above those found in the present paper.

In conclusion, the CKD-EPI equation reduced GFR underestimation in individuals with higher GFRs, but tended to overestimate the values at lower ranges. The imprecision of both MDRD and CKD-EPI to predict eGFR should be taken into account when diagnosing and staging CKD because this has a negative impact in clinical management and health costs.

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