ESTIMATION OF GLOMERULAR FILTRATION RATE USING THE NEW EKFC EQUATION IN HEALTHY AND CHRONIC KIDNEY DISEASEADULT SUBJECTS FROM SUB-SAHARAN AFRICA

Abstract

Introduction: Since the publication of the first equation for estimate creatinine clearancein 1957, several other equations estimating glomerular filtration ratehave followed in succession. To date, a new equation has been published by the European Kidney Function Consortium (EKFC) in 2021, which would have the advantage of being adaptable to any type of population. In this study, we aimed to evaluate the performance of this new equation in our black African population of healthy subjects and subjects with chronic kidney disease.

Material and methods: This was a cross-sectional study involving 192 healthy subjects and 183 subjects with chronic kidney disease . Plasma iohexol clearance (mGFR) constituted the reference method used to measure glomerular filtration rate and allowed evaluation of all equation variants (EKFC crea, EKFC cys, EKFC crea-cys). Equation performance was studied by calculating the 95% CI bias, the interquartile range (25% percentile, 75% percentile) and the 30% accuracy (P30) compared with the reference method.

Results: All EKFC variants in both populations (healthy subjects and chronic kidney disease subjects) had biases below 5 ml/min/1.73 m2. Biases were therefore acceptable. On the other hand, P30s were less good in subjects with chronic kidney disease.

Conclusion: Thus, the EKFC equation performs well in the healthy population, but its evaluation in the chronic kidney disease population needs to be strengthened on the basis of larger cohorts.

Key words: EKFC, black Africans, performance

1. Introduction

Since the publication of the first equations, including Cockroft and Gault's (CG) in 1976[1]used to estimate creatinine clearance, several other equations estimating glomerular filtration rate (GFR) have followed in succession, with the aim of improving the performance of the previous equations.Thus, the equation Modification of Diet in Renal Disease study (MDRD) was born in 1999 [2] to improve the performance of the Cockroft and Gault equation.This was followed in 2009 by the Chronic Kidney Disease Epidemiology equation (CKD-Epi), which improved on the performance of the MDRD equation [3]. For a long time, these last two equations were recommended according to KDIGO (Kidney Disease Outcome Qualitiy) guidelines. However, after several studies worldwide [4,5] and even in Africa [6,7] questioned the ethno-racial factor used in these formulas as discriminatory and inappropriate respectively, the CKD-Epi 2009 equation evolved into the CKD-epi 2021 equation, which does not use an ethno-racial factor [8,9]. However, some authors, notably in Europe, found that this new equation performed less well than the previous one in European and black African populations [10, 11, 12]. Subsequently, an equation was published by the European Kidney Function Consortium (EKFC), still in 2021, which would have the advantage of adapting to any type of population, thanks to the determination of a Q variable in the equation that is specific to each population[13].This Q variable, which makes it possible to control variation linked to differences in age, sex or race, is the median value of the biomarker used to estimate the equation (Creatinine, Cystatin) in a given population [14,15]. In this study, we aimed to evaluate the performanceof this new equation in our black African population of healthy subjects and subjects with chronic kidney disease.

2. Materials and methods

2.1 Conception of study

This was a cross-sectional analytical study initiated by the Biochemistry Department of the Université Félix HouphouetBoignyd'Abidjan, Côte d'Ivoire, in collaboration with the Nephrology Departments of the CentresHospitaliersandUniversitaires de CocodyetYopougon (Abidjan, Côte d'Ivoire) for patient recruitment and the University of Liège, Belgium for Cystaine C, enzymatic creatinine and iohexol clearance determinations.

This study included 192 apparently healthy subjects taken from blood donors in Abidjan and 183 adult patients with non-dialyzed chronic kidney disease followed for at least 3 months in the Cocody and Treichville nephrology departments.Subjects with bias data greater than 2 times the IQR were excluded. All subjects gave written consent to participate in the study. Subjects with an allergy to the contrast medium were excluded from the study.

2.2. Methods

Each subject participating in the study completed a survey form, which was used to collect epidemiological and clinical data (age, sex, weight, height, Body Mass Index, medical history, treatment, etc.). Each patient had two blood samples taken from the cubital vein, the first on fasting state and the second 5 hours after intravenous injection of 5ml iohexol (Omnipaque 300®). Whole blood was collected in a tubewithout anticoagulant and centrifuged at 3500 rpm for 5 minutes. The serum collected was divided into aliquots then frozen at -20°C. The maximum retention period was 1 month.Specimens were transported between Abidjan and Liège using a specialized carrier in compliance with UN3373 [16] for determination of iohexol, cystatin C and enzymatic creatinine.

Plasma iohexol clearance (mGFR) constituted the reference method used to measure glomerular filtration rate in our study population. It was used to evaluate the EKFC equation and all its variants (EKFC crea, EKFC cys, EKFC crea-cys).

Serum iohexol values were measured on serum obtained from a single sample collected 300 minutes (T300) after injection of 5ml iohexol by mass spectrometry (LC-MS/MS) at the University Hospital of Liège, Belgium. The measured GFR (mGFR) was calculated using the iterative method described by Jacobson[17]. Cystatin and creatinine enzyme concentrations were determined on the same serum using Cobas C501 from Roche. The mean normal values of these biomarkers in the healthy population were used as Qcrea (Male 0.98 and Female 0.76) and Qcys (Male 0.87 and Female 0.82) for GFR estimation from the EKFC equations.The estimation formula evaluated was solely the EKFC formula with its different variants (EKFC crea, EKFC cys and EKFC crea-cys)[13]

EKFC − eGFR = 107.3/[Biomarker/Q]α × [0.990(Age−40) if age >40 years],

with α=0.322 when biomarker/Q is less than 1 and α=1.132 when biomarker/Q is 1 or more

2.4.2. Statistical analysis

Normally distributed continuous variables were described as the mean +/- standard deviation. Otherwise they were described as the median and interquartile range (IQR) (P_{25} –P_{75}). The performance of the equations was studied by calculating the 95% CI bias, the interquartile range (25% percentile, 75% percentile) and the 30% accuracy (P30) in relation to the reference method (iohexol plasma clearance). The IQR measures variation in the differences between estimated GFR and measured GFR (estimated GFR minus measured GFR). The target for bias was zero, but an absolute bias of at most 5 ml/min/1,73m2 might be considered reasonable. Similarly, a 30% accuracy (P30) greater than 75% has been considered sufficient for clinical decision-making, although the target to be achieved is greater than 90% according to KDIGO guidelines [18].

3. Results

Healthy subjects had a mean age of 34 +/- 10 years, a mean BMI of 24 +/- 5 Kg/m2 and a mean mGFR of 104 +/- 17 ml/min/1.73m2.Sick subjects had a mean age of 50 +/- 13 years, a BMI of 24 +/- 5 Kg/m2 and a mean GFR of 29 +/- 13 ml/min/1.73m2 (Table1).

Table 1: Characteristics of the study population

	Age (years) Mean +/- SD	BMI (Kg/m^2) Mean +/- SD	mGFR ($ml/min/1,73m^2$) Mean +/- SD
Healthy subjects	34 (24 ; 44)	24 (19 ; 29)	104 (87 ; 121)
Subjects with chronic kidney disease	50 (37 ; 63)	24 (19 ; 29)	29 (16 ; 42)

The median serum creatinine value for men was 0.97(0.71; 1.32) mg/dl and for women was 0.75(0.53; 1.07) mg/dl in healthy subjects. While the median serumcystatin C value in men was 0.86(0.66; 1.24) mg/l, in women it was 0.79(0.63; 1.11) mg/l. In chronic kidney disease subjects, the median serum creatinine value for men was 34 (19; 51) mg/dl and for women

35(24; 51) mg/dl. While the median serumcystatin value in men was 26 +/- (18; 35) mg/l and in women 28(21; 37) mg/l. Qcrea was therefore 0.97 in men and 0.75 in women. Qcys was 0.86 in men and 0.79 in women (Table 2).

Table 2: Serum biomarker concentrations in the study population

	Biomarkers	**sexe**		**Median (Q1 ;Q3)**
Healthy subjects	**Créatinine(mg/dl)**	Men	Q crea	0,97(0,71 – 1,32)
		Women		0,75(0,53 - 1,07)
	Cystatine (mg/l)	Men	Q cys	0,86(0,66 – 1,24)
		Women		0,79(0,63 – 1,11)
Subjects with chronic kidney disease	**Créatinine (mg/dl)**	Men		34 (19 ; 51)
		Women		35 (24 ;51)
	Cystatine (mg/l)	Men		26 (18 ; 35)
		women		28 (21 ; 37)

All EKFC variants in both populations (healthy subjects and subjects with chronic kidney disease) had biases below 5 ml/min/1.73 m2. Biases were therefore acceptable. On the other hand, P30s were less good in subjects with chronic kidney disease. In both populations, EKFC cys showed the best bias and P30. The use of cystatin as a biomarker added value to the EKFC equation, particularly in subjects with chronic kidney disease. In both groups, the combination of the two biomarkers (EKFC crea-cys) showed no superiority. (Table 3).

Table 3: Performance of EKFC variants according to population type

	Equations	Bias median (95% CI)	IQR (Q1; Q3)	Exactitude 30%
Healthy subjects	EKFC crea	-0,8(-3,5 ; 1,9)	25,2 (-14,4 ; 10,8)	79
	EKFC cys	-0,4 (-2,4 ; 1,6)	17,6 (-7,6 ; 12,0)	82
	EKFC crea/cys	-4,8(-6,8 ; -2,9)	17,6 (-13,1 ; 4,5)	84
Subjects with chronic kidney disease	EKFC crea	-4,6 (-5,9 ; -4,7)	11,4 (-11,0 ; 1,6)	52
	EKFC cys	-0,2 (-1,4 ; -3,7)	11,2 (-5,1 ; 6,1)	66
	EKFC crea/cys	-4,0 (-5,2; -3,3)	10,4 (-8,4 ; 2,0)	60

4. Discussion

Several formulas used in current clinical practice have been developed to estimate GFR. In 2021, Pottel et al. [13] developed and validated the EKFC equation, which is a modified GFR estimation equation based on creatinine and cystatin C and covering the whole age spectrum. Our study evaluated this EKFC equation with its different variants in our healthy and chronic kidney disease black African population.In both groups, the biases of the EKFC variants were acceptable. The EKFCcys and EKFC crea variants were equivalent in healthy subjects, but the EKFCcys was significantly better in subjects with chronic kidney disease. Equivalence between the EKFC crea and EKFC cys equations has been reported in several other studies, which showed that the EKFC cys equation was similar to the EKFC crea equation in terms of GFR estimation [19, 20, 21], but the superiority of EKFCcys in the patient may be explained

by the fact that cystatin is a more stable parameter and less influenced by population specificity [22].In our study, however, the combined EKFC had a relatively higher bias than the other variants. We therefore did not find the particular improvement in the EKFC crea-cys equation described by Pottel et al in 2023, who found that the EKFC equation was much better when combining these two biomarkers [22].

In our study, P30s were good in healthy subjects, at 79%, 82% and 84% respectively for crea EKFC, cys EKFC and combined EKFC. On the other hand, they were less good in sick subjects, with P30s of 52%, 66% and 60% respectively for crea EKFC, cys EKFC and combined EKFC. This decline in performance in the chronic kidney disease population was also described in the Asian population, where in the subgroup of patients with GFR<= 60 ml/min/1.73m2, P30 was 68.1%, while in the GFR > 60 ml/min/1.73 m2 group, P30 was 95.7%. Although overall, the performance of the EKFC equation remains acceptable [23], the results are not conclusive.

In Delanaye's study, evaluating the EKFC equation in 4 different populations, including black Africa (508 black Africans), the P30 was much higher than in our study (P30: 80.9%) [24]. However, in this study, the mean GFR in this African population was 86 +/- 12 ml/min/1.73m2 (GFR > 60 ml/min/1.73m2), compared with 29 +/- 13 ml/min/1.73m2 (GFR < 60 ml/min/1.73m2) in our study. The black African cohort used to assess renal function in this study had relatively less advanced CKD than our study. As seen in the EKFC equation, most GFR estimation equations have difficulty reconciling these two groups (GFR <= 60 ml/min/1.73m2 and GFR > 60 ml/min/1.73m2). Indeed, the MDRD equation is known to systematically underestimate high GFRs (> 60 ml/min/1.73m2) [25,26] and the CKD-epi equation is known for its lack of ability to classify subjects according to CKD stage [25,27]. It is therefore important to conduct further, more in-depth studies in chronic kidney disease patients with larger, sufficient cohorts to evaluate the EKFC equation by CKD stage.

Furthermore, P30s in both groups were lower when using creatinine as a biomarker. Could this be due to the high variability of creatinine? Indeed, Pottel found in his 2023 study that there were clear differences between black and white patients, and between men and women, with regard to serum creatinine levels. Therefore, to obtain the most accurate (unbiased) estimate of GFR based on serum creatinine, population- and demographically-specific adjustments to creatinine levels are required. Whereas, such population-specific adjustments are not necessary for cytatin C and the EKFCcys equation can be used without including race and gender [22]. However, this variability in creatinine would be the purpose of using the Q variable in the EKFC equation, which is supposed, thanks to this population-specific Q variable, to control variation linked to differences in age, sex or race [28]. And this is what we have done in our study, using Qs specific to our population. There may be other factors to take into account, particularly in chronic kidney disease subjects, since in healthy subjects the P30 of EKFC crea is greater than 75%, whereas in chronic kidney disease subjects it remains well below 75%.

5. Conclusion

The EKFC equation performed well in the healthy population, but the p30s were relatively low in thechronic kidney disease population. Its evaluation in the diseased population needs to be strengthened on the basis of larger cohorts. In addition, a comparison with other equations in use is necessary to determine the equation best suited to our black African population.

6. Limitations of our Study

We would have preferred to have a larger cohort, especially in the chronic kidney disease population, to enable evaluation of the equation in each stage of chronic kidney disease.

Ethical Approval and Consent

This study was approved by the Comité National d'Ethique et de la Recherche (CNER) of the Ministry of Health and Public Hygiene of the Republic of Côte d'Ivoire under number 138-22 /MSHP/CNESVS-km. A free and informed consent form was obtained from all participants. Each patient received a free check-up and a snack.

10. References

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