Original Research Article

ESTIMATION OF GLOMERULAR FILTRATION RATE USING THE NEW EKFC EQUATION IN HEALTHY AND SICK ADULT SUBJECTS FROM SUB-SAHARAN AFRICA

Abstract

Introduction: Since the publication of the first equation for estimating Glomerular Filtration Rate (GFR) in 1957, several other equations have 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. We therefore evaluated the performance of this equation in our black African population, made up of healthy subjects and subjects with chronic kidney disease.

Material and methods : This was a cross -sectional study involving 202 healthy subjects and 208 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: In healthy subjects, EKFC crea, EKFCcys and EKFC crea-cys had respective biases of -1.7 (-4.2 ;0.9), 2.4 (-0.1 ; 5.0) and -6.1 (-8.3 ; -3.8) and P30s of 87%, 91%, 93%. In diseased subjects, EKFC crea, EKFC cys and EKFC crea-cys had respective biases of -0.6 (-2.6; 1.4), 1.0 (-0.6 ;2.7), -2.6 (-4.1 ;-1.0) and P30s of 50%, 62%, 56%. The performance of the EKFC equation was therefore good in healthy subjects and less good in sick subjects, even though the biases were closer to 0.

Conclusion : Thus, the EKFC equation performs well in the healthy population, but its evaluation in the sick 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 equation for estimating Glomerular Filtration Rate, Cockroft and Gault in 1957, several other equations have followed in succession with the aim of improving the performance of the previous equations. Thus, the MDRD equation (Modification of Diet in Renal Disease study) was born in 1999 to improve the performance of the Cockroft and Gault equation. This was followed in 2009 by the CKD-Epi (Chronic Kidney Disease Epidemiology) equation, which improved on the performance of the MDRD equation. For a long time, these last two equations were recommended according to KDIGO (Kidney Disease Outcome Qualitiy) guidelines. However, after several studies worldwide [1,2] and even in Africa [3,4] 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 [5,6]. However, some authors, notably in Europe, found that this new equation performed less well than the previous one in European and black African populations [7,8,9]. 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. This Q variable, which makes it possible to control variation linked to differences in age, sex or race, is the average normal

value of the biomarker used to estimate the equation (Creatinine, Cystatin) in a given population [10,11,12]. In this study, we therefore evaluated the performance of this new equation in our black African population of healthy subjects and subjects with chronic kidney disease.

2. Materials and methods

2.1 Study design

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

2.2 Inclusion & exclusion criteria

This study included 202 apparently healthy subjects taken from blood donors in Abidjan and 208 adult patients with non-dialyzed chronic kidney disease followed for at least 3 months in the Cocody and Treichville nephrology departments.

All subjects gave written consent to participate in the study. Subjects with an allergy to the contrast medium were excluded from the study.

2.3 Ethical approval & informed 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.

2.4. Methods

2.4.1.Pre-analytical phase

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 elbow, the first on an empty stomach and the second 5 hours after intravenous injection of 5ml iohexol (Omnipaque 300®). Whole blood was collected in a dry tube and centrifuged at 3500 rpm for 5 minutes. The serum collected was divided into aliquots. These were stored at -20°C for subsequent determination of iohexol, cystatin C and enzymatic creatinine.

2.4.2. Determination of iohexol clearance

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.

2.4.3. Determination of cystatin C and enzymatic creatinine

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.

2.4.4. Determination of estimated GFR using the EKFC equation

The estimation formula evaluated was solely the EKFC formula with its different variants (EKFC crea, EKFC cys and EKFC crea-cys).

2.4.5. Statistical analysis

Results are expressed as mean +/- standard deviation. 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 variant of the EKFC equation with a bias closer to 0 is less biased and more accurate. 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 [13].

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)	BMI (Kg/m^2)	mGFR ($ml/min/1,73m^2$)
	Mean +/- SD	Mean +/- SD	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 mean creatinine value for men was 0.98 +/- 0.15 mg/dl and for women was 0.76 +/- 0.15 mg/dl in healthy subjects . While the mean cystatin C value in men was 0.87 +/- 0.15 mg/l, in women it was 0.82 +/- 0.14 mg/l. In sick subjects, the mean creatinine value for men was 42 +/- 32 mg/dl and for women 46 +/- 43 mg/dl. While the mean cystatin value in men was 27 +/- 13 mg/l and in women 30 +/- 13 mg/l. Qcrea was therefore 0.98 in men and 0.76 in women. Qcys was 0.87 in men and 0.82 in women (Table 2).

Table 2: Serum biomarker concentrations in the study population

	Biomarkers	**sexe**	**Mean +/- SD**	**Median (Q1 ;Q3)**
Healthy subjects	**Créatinine(mg/dl)**	Men	0,98+/-0,15	0,97(0,71 – 1,32)
		Women Q crea	0,76+/-0,15	0,75(0,53 - 1,07)
	Cystatine (mg/l)	Men	0,87 +/- 0,15	0,86(0,66 – 1,24)
		Women Q cys	0,82 +/- 0,14	0,79(0,63 – 1,11)
Subjects with	**Créatinine (mg/dl)**	Men	42 +/- 32	34 (19 ;51)

chronic kidney disease	**Cystatine (mg/l)**	Women	46 +/- 43	35 (24 ;51)
		Men	27 +/- 13	26 (18 ; 35)
		women	30 +/-13	28 (21 ;37)

Concerning the EKFC equation, in healthy subjects, EKFC crea, EKFCcys and EKFC crea-cys had respective biases of -1.7 (-4.2 ;0.9), 2.4 (-0.1 ; 5.0) and -6.1 (-8.3 ; -3.8) and P30s of 87%, 91%, 93%. The performance of the EKFC equation was therefore good in healthy subjects. In sick subjects, EKFC crea, EKFC cys and EKFC crea-cys had respective biases of -0.6 (-2.6; 1.4), 1.0 (-0.6 ;2.7), -2.6 (-4.1 ;-1.0) and P30s of 50%, 62%, 56%. The P30s were therefore worse in sick subjects, even though the biases were closer to 0. In both populations, EKFC crea and EKFC cys had almost similar biases, but with 30% higher accuracies for EKFC cys. The use of cystatin as a biomarker added value to the EKFC equation, particularly in sick subjects. In both groups, the combination of the two biomarkers (EKFC crea-cys) had a higher bias (Table 3).

Table 3: Performance of EKFC variants according to population type

	Equations	**Bias (95% CI)**	**IQR (Q1; Q3)**	**Exactitude 30%**
Healthy subjects	EKFC crea	-1,7 (-4,2 ; 0,9)	23,1 (-13,5 ; 9,6)	87
	EKFC cys	2,4 (-0,1; 5,0)	21,3 (-8,1 ; 13,2)	91
	EKFC crea/cys	-6,1 (-8,3 ; -3,8)	17,9 (-14,2 ; 3,7)	93
Subjects with	EKFC crea	-0,6 (-2,6 ; 1,4)	15,8 (-9,5 ; 6,3)	50

chronic kidney disease	EKFC cys	1,0 (-0,6 ; 2,7)	13,3 (-6,1 ; 7,2)	62
	EKFC crea/cys	-2,6 (-4,1; -1,0)	11,5 (-8,8 ; 2,7)	56

4. Discussion

Several formulas used in current clinical practice have been developed to estimate GFR. In 2021, Pottel et al. 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 sick black African population. In both groups, the biases of the EKFC variants were close to 0, and EKFCcys and EKFC crea were equivalent. This 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 [14,15,16,17]. 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 [17].

In our study, P30s were good in healthy subjects, at 87%, 91% and 93% respectively for crea EKFC, cys EKFC and combined EKFC. On the other hand, they were less good in sick subjects, with P30s of 50%, 62% and 56% respectively for crea EKFC, cys EKFC and combined EKFC. This decline in performance in the sick 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 [18], 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%) [19]. 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) [20,21] and the CKD-epi equation is known for its lack of ability to classify subjects according to CKD stage [20,22]. It is therefore important to conduct further, more in-depth studies in sick 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 [17]. 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 [23]. 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 sick subjects, since in healthy subjects the P30 of EKFC crea is greater than 75%, whereas in sick subjects it remains well below 75%.

5. Conclusion

The EKFC equation performed well in the healthy population, but the p30s were relatively low in the diseased 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 sick population, to enable evaluation of the equation in each stage of chronic kidney disease.

10. References

1. Eneanya ND, Boulware LE, Tsai J et al. Healthinequities and the inappropriate use of race in nephrology. Nat RevNephrol2022;18:84–94. https://doi.org/10.1038/s41581-021-00501-8

2. Eneanya ND, Yang W, Reese PP. Reconsidering the consequences of using race to estimatekidneyfunction. JAMA 2019;322:113–4. https://doi.org/10.1001/jama.2019.5774

3. Yayo SE, Aye M, Konan JL, et al. Inadequacy of the ethnic factor for the estimation of the glomerular filtration rate in the general black-Africanpopulation:results in Ivory Coast. NephrolTher. 2016;12(6):454–459. doi: 10.1016/j.nephro.2016.03.006. [PubMed] [CrossRef] [Google Scholar]

4. Bukabau JB, Sumaili EK, Cavalier E, et al. Performance of glomerular filtration rate estimation equations in Congolesehealthyadults: the inopportunity of the ethnic correction. PLoS One. 2018;13(3):e0193384. doi:10.1371/journal.pone.0193384. Published 2018 Mar 2. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

5. Delgado C, Baweja M, Crews DC et al. A Unifyingapproach for GFR estimation:recommendations of the NKF-ASN task force on reassessing the inclusion of race in diagnosingkidneydisease. J Am Soc Nephrol2021;32:2994–3015. https://doi.org/10.1681/ASN.2021070988

6. Miller WG, Kaufman HW, Levey AS, et al. National KidneyFoundationLaboratory Engagement Working Group recommendations for implementing the CKD-EPI 2021 race-free equations for estimatedglomerular filtration rate:practical guidance for clinicallaboratories. Clin Chem2022;68:511–20. https://doi.org/10.1093/clinchem/hvab278

7. Inker LA, Eneanya ND, Coresh J et al. New creatinine- and cystatin C–basedequations to estimate GFR without race. N Engl J Med 2021;385:1737–49. h 48.

DOI: 10.1056/NEJMoa2102953

8. Miller W.G. Perspective on new equations for estimatingglomerular filtration rate. Clin Chem2021;3:1–3. https://doi.org/10.1093/clinchem/hvab029

9. Delanaye P, Vidal-Petiot E, Björk J et al. Performance of creatinine-basedequations to estimateglomerular filtration rate in White and Black populations in Europe, Brazil, and Africa. Nephrol Dial Transplant 2023;38:106–18. https://doi.org/10.1093/ndt/gfac241ttps://doi.org/10.1056/NEJMoa2102953

10. Pottel H, Björk J, Courbebaisse M et al. Development and validation of a modified full agespectrumcreatinine-basedequation to estimateglomerular filtration rate. A cross-sectional analysis of pooled data. Ann Intern Med 2021;174:183–91. https://doi.org/10.7326/M20-4366

11. Pottel H, Vrydags N, Mahieu B et al. Establishingage/sexrelatedserumcreatininereferenceintervalsfromhospitallaboratory data

based on differentstatisticalmethods. Clin Chim Acta 2008;396:49–55. https://doi.org/10.1016/j.cca.2008.06.017

12. Pottel H, Dubourg L, Schaeffner E et al. The diagnostic value of rescaledrenalbiomarkersserumcreatinine and serumcystatin C and theirrelationshipwithmeasuredglomerular filtration rate. Clin Chim Acta 2017;471:164–70. https://doi.org/10.1016/j.cca.2017.06.005

13. National KidneyFoundation. K/DOQI clinical practice guidelines for chronickidneydisease:evaluation, classification, and stratification. Am J Kidney Dis 2002;39:Suppl 1:S1-S266.

14. Inker LA, Schmid CH, Tighiouart H, et al. Estimatingglomerular filtration rate fromserumcreatinine and cystatin C. N Engl J Med 2012;367:20-29. DOI: 10.1056/NEJMoa1114248

15. Rule AD, Bergstralh EJ, Slezak JM, Bergert J, Larson TS. Glomerular filtration rate estimated by cystatin C amongdifferentclinicalpresentations. Kidney Int 2006;69:399-405. https://doi.org/10.1038/sj.ki.5000073

16. Hsu C-Y, Yang W, Parikh RV, et al. Race, geneticancestry, and estimatingkidneyfunction in CKD. N Engl J Med 2021;385:1750-1760. DOI: 10.1056/NEJMoa2103753

17. Pottel H, Björk J, Rule AD, et al. Cystatin C–basedequation to estimate GFR without the inclusion of race and sex N Engl J Med, 388 (4) (2023), pp. 333-343, 10.1056/NEJMoa2203769

18. Li Zhao, Huan-li Li, Hui-jing Liu, Jin Ma, Wei Liu, Jian-min Huang Validation of the EKFC equation for glomerular filtration rate estimation and comparisonwith the Asian-modified CKD-EPI equation in Chinesechronickidneydisease patients in an externalstudy. Renal Failure. 2023; 45(1) https://doi.org/10.1080/0886022X.2022.2150217

19. Pierre Delanaye P, Vidal-Petiot E, Björk J, Ebert N, Eriksen B. Performance of creatinine-basedequations to estimateglomerular filtration rate in White and Black populations in Europe, Brazil and Africa, NephrologyDialysis Transplantation. 2023; 38 (1): 106–118 https://doi.org/10.1093/ndt/gfac241

20. Delanaye P, Mariat C, Moranne O, Cavalier E, Flamant M. Estimation of glomerular filtration rate in2012:whatadded value for the new CKD-EPI equation? Nephrology and Therapeutics. 2012; 8(4): 199-205 https://doi.org/10.1016/j.nephro.2012.03.002

21. Poggio ED, Wang X, Greene T, Van Lente F, Hall PM. Performance of the modification of diet in renaldisease and Cockcroft-Gault equations in the estimation of GFR in health and in chronickidneydisease. J Am Soc Nephrol JASN. 2005; 16(2): 459‐ 66. https://doi.org/10.1681/asn.2004060447

22. Delanaye P, Cavalier E, Mariat C, Maillard N, Krzesinski J-M. MDRD or CKD-EPI studyequations for estimatingprevalence of stage 3 CKD in epidemiologicalstudies:whichdifference? Is thisdifferencerelevant? BMC Nephrol. 2010;11: 8.

23. DelanayeP, Cavalier E, Pottel H, Stehlé T. New and old GFR equations: aEuropean perspective. ClinicalKidney Journal. 2023; 16 (9):1375–1383, https://doi.org/10.1093/ckj/sfad039