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RESEARCH ARTICLE

DETERMINATION OF DFG IN A BLACK AFRICAN POPULATION WITH CHRONIC KIDNEY DISEASE IN 2023: COMPARISON OF THE PERFORMANCE OF 11 ESTIMATION EQUATIONS

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Abstract

Introduction: Chronic kidney disease is a public health problem. To date, several equations have been proposed for its diagnosis, but these remain relatively approximate. In Africa, in the absence of specific recommendations, these formulas are used with the consequent risk of diagnostic bias, whereas in recent years, studies carried out in Africa have questioned the relevance of the ethno-racial factor used in certain equations in a healthy population. The aim of this study was therefore to evaluate 11 equations currently in use in black African chronic kidney disease patients.

Material and Methods: This was an analytical cross-sectional study involving 183 chronically ill renal patients in whom GFR was measured by iohexol plasma clearance used as a reference and estimated by 11 current equations. The performance of the current equations was determined by calculating the median bias, interquartile range and accuracy at P30 in comparison with the reference method.

Results: EKFC equations showed the best bias and accuracy at 30%. The 2021 CKD epi equations have not proven their performance in our African population of chronic kidney disease subjects. The use of cystatin as a biomarker added value to each type of equation. Unfortunately, the 30% accuracies of all equations remain below 75% in the chronic kidney disease population.

Conclusion: The equation best suited in 2023 to our sick black African population is the EKFC equation and its variants. Although it remains the best-performing, the 30% accuracy remains below 75%.

Introduction:-

Chronic kidney disease (CKD) constitutes a public health problem due to its ongoing growth in the general population and the high cost of replacement therapies particularly in the end-stage of the disease (Legrain and Jacobs, 1999; Yao et al., 2018). In Africa, extrarenal purification and transplantation are the only treatments that are still not very accessible to our populations (Stanifer et al., 2014). Early detection of chronic kidney disease is

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therefore a vital element of management. The key biological parameter for this screening remains the estimation of glomerular filtration rate. It is used to diagnose, stage and manage CKD, prognosticate CKD-related events and mortality, and determine drug doses (Inker and Titan, 2021). For several decades now, numerous equations have been proposed for its determination, over and above the reference methods that are very costly and difficult to implement in our countries. Unfortunately, these equations are not perfect. Each of them has at least one limitation in its use, such as the age and sex of populations, the type of population (Caucasian, Afro-American, African living in Africa, African living in Europe), the nature of the endogenous biomarker, the inadequacy of ethno-racial factors, the healthy or sick nature of populations, the variability of creatinine use, etc., not giving these equations a universal character. They remain relatively approximate (Agarwal and Delanaye, 2019; Miller, 2021; Ebert et al., 2021). Over the years, these limitations have led to numerous modifications. In Africa, in the absence of specific recommendations, these formulas are used, with the consequent risks of diagnostic bias and/or late diagnosis of chronic kidney disease, whereas for some years now, several studies carried out in Africa have questioned the relevance of the ethno-racial factor used in certain equations (Sagou et al., 2016; Bukabau et al., 2019). However, this study was carried out in an apparently healthy population. Knowing that estimation equations are highly dependent on the characteristics of the populations studied, we therefore wanted in this study to evaluate all these equations currently in use in black African chronic kidney disease patients.

Materials and Methods:-

Study design

This was a cross-sectional analytical study initiated by the Biochemistry Department of the Université Félix Houphouët Boigny d'Abidjan, Côte d'Ivoire, in collaboration with the Nephrology Departments of the Centres Hospitaliers 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 assays.

The study included 183 adult patients with non-dialyzed chronic kidney disease who had been followed for at least 3 months in the Cocody and Treichville nephrology departments, and who had given written consent to participate in the study. Patients with an allergy to the contrast medium were excluded. 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. Written consent was obtained from all participants. Each patient received a free check-up and a snack.

Methods:-

Each patient taking part 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 an anticoagulant-free 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. Maximum storage time was 1 month.

Specimens were transported between Abidjan and Liège using a specialized carrier complying with UN3373 standard (Jean, 2005).

Plasma iohexol clearance (mGFR) constitutéd the reference method used to measure glomerular filtration rate in our study population. It was secondarily used to evaluate GFR estimates (eGFR) established from equations recommended by international guidelines (KDIGO). 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. Full and empty syringes as well as injection and withdrawal times were carefully recorded. The measured GFR (mGFR) was calculated using the iterative method described by Jacobsson (1983).

The biomarkers used to estimate glomerular filtration rate are enzymatic creatinine and cystatin. Their concentrations were determined on the same serum using Cobas C501® from Roche.

The estimation formulas evaluated were those currently recommended by international guidelines (KDIGO), namely Modification of Diet in Renal Disease study (MDRD), Chronic Kidney Disease Epidemiology version 2009 (CKD-

EPI 2009), Chronic Kidney Disease Epidemiology version 2012 (CKD-EPI 2012), Chronic Kidney Disease Epidemiology version 2021 (CKD-EPI 2021) and European Kidney Function Consortium (EKFC) with their various variants. The Qcreatinine and Qcystatin values used in the EKFC equation were taken from a previous study in a healthy black African population (Yayo, 2018). Qcreatinine was 0.97 mg/dl for men and 0.75 mg/dl for women. Qcystatin was 0.86 mg/l for men and 0.79 mg/l for women. The performance of the different equations was compared according to the biomarker used. The added value of cystatin C in the equations was also investigated.

Data analysis

Data were presented as mean +/- standard deviation when the distribution was normal, and as median with interquartile range (IQR) corresponding to the measure of variation of the differences between the estimated GFR and the measured GFR (25th percentile or Q1; the 75th percentile or Q3), when this was not the case. Equation performance was studied by calculating the median bias with a 95% confidence interval (CI 95%), the interquartile range (IQR) and the 30% accuracy (P30) with a 95% confidence interval. The best equations are those with a bias close to 0 and the highest 30% accuracy. A median bias less than or equal to 5 ml/min/1.73m2, lower imprecision and a P30 greater than 75% have been considered sufficient for good clinical decision-making (Delanaye, 2013; K/DOQI, 2002).

Results:-

Our study population consisted of 112 men and 71 women whose general characteristics are recorded in Table 1.

The performance of the estimating equations was compared in terms of bias, imprecision or interquartile range (IQR) and accuracy 30%. In equations based on creatinine alone, only MDRD with factor, CKD-EPI 2009 with factor and EKFC had median biases below 5 ml/min/1.73m2, and these median biases were relatively identical.In contrast, all these equations had P30s below 75%. These 3 equations can be used independently when the biomarker used to estimate glomerular Filtration rate is creatinine. (Table 2) In the equations based on cystatin alone, the EKFC equation was the best, with a median bias of -0.2 ml/min/1.73m2 (-1.4; -3.7) and a P30 of 66.1% (65.2; 67.1). (Table 3)

In the combined equations, the EKFC equation was also the best, with a median bias of -4.0 ml/min/1.73m2 (-5.2; -3.3) and a P30 of 59.6% (58.7; 60.4). (Table 4)

All EKFC equations showed the best bias and accuracy 30%. The 2021 epi CKD equations have not proven their performance in our African population of chronically ill renal subjects. The use of cystatin as a biomarker added value to each type of equation.

Table 1:- General characteristics of people with chronic kidney disease.

Variables	Overall(n= 183)	Male (n=112)	Female (n=71)
1) Age (years) Mean +/- Standard deviation	51 +/- 13	52 +/- 13	50 +/- 14
Weight (Kg) Mean +/- Standard deviation	68 +/- 14	70 +/- 13	64 +/- 15
BMI (Kg/m^2) Mean +/- Standard deviation	24 +-/ 5	24 +/- 4	24 +/- 5
Body surface area (Kg/m^2) Mean +/- Standard deviation	1,8 +/- 0,2	1,8 +/- 0,2	1,7 +/- 0,2

Table 2:- Performance of creatinine-based equations in our study population.

Equations	Median bias (CI 95%)	IQR (Q1 ; Q2)	P30 (CI 95%)
MDRD with factor	-4,7 (-6,0 ; -3,4)	12,2 (-10,7 ; 1,5)	51,9 (51,0 ; 52,8)
MDRD without factor	-8,5 (-9,7 ; -7,3)	9,9 (-13,8 ; -3,9)	36,6 (35,8 ; 37,4)
CKD-epi 2009 with factor	-4,8 (-6,2 ; -3,5)	12,2 (-11,0 ; 1,2)	53,0 (52,1 ; 53,9)
CKD-epi 2009 without factor	-8,0 (-9,3 ; -6,8)	11,2 (-13,7 ; -2,5)	42,1 (41,3 ; 42,9)
CKD-epi 2021	-7,0 (-8,3 ; -5,7)	11,5 (-12,0 ; -0,5)	44,8 (44,2 ; 45,5)
EKFC	-4,6 (-5,9 ; -4,7)	12,1 (-10,5 ; 1,6)	52,5 (51,7 ; 53,2)

Table 3:- Performance of cystatin-based equations in our study population.

Equations	Media bias (CI 95%)	IQR (Q1 ; Q2)	P30 (CI 95%)
CKD-epi cys 2012	-4,7 (-6,0 ; -3,5)	11,1 (-9,2 ; 1,9)	51,4 (50,6 ; 52,1)
EKFC cys	-0,2 (-1,4 ; -3,7)	11,2 (-5,1 ; 6,1)	66,1 (65,2 ; 67,1)

Table 4:- Performance of equations based on the combination of creatinine and cystatin c in our study population.

Equations	Median bias (CI 95%)	IQR (Q1 ; Q2)	P30 (CI 95%)
CKD-EPI comb 2012	-7,1 (-8,3 ; -6,0)	10,3 (-12,0 ; -1,7)	47,0 (46,3 ; 47,7)
CKD-EPI comb 2021	-5,7 (-6,9 ; -4,4)	10,9 (-10,9 ; 0)	47,0 (46,3 ; 47,7)
EKFC comb	-4,0 (-5,2 ; -3,3)	10,4 (-8,4 ; 2,0)	59,6 (58,7 ; 60,4)

Discussion:-

Equations for estimating GFR have undergone numerous modifications over the years, with the aim of finding an equation more suitable for any population in the world. These have included the Cockroft and Gault equation (1976), MDRD in 1999 (Levey et al., 1999), CKD epi in 2009 (Levey et al., 2009), CKD epi AS in 2021 (Delgado et al., 2021; Miller et al., 2022) and the EKFC equation in 2021 (Pottel et al., 2008; 2017; 2021). Unfortunately, the universality of these different equations has not been proven. In Africa, several studies have shown the inadequacy of the ethno-racial factor in certain equations in a healthy population (Sagou et al., 2016; Bukabau et al., 2019) . In the absence of specific recommendations in Africa, these equations are used leading to biases in the management of chronic kidney disease . Thus, our work consisted in evaluating these different equations in a sick West African population by comparing their performance through the calculation of median bias, imprecision and accuracy at 30% (P30) from GFR measurement by a reference method namely iohexol plasma clearance. Our work shows that the EKFC equations outperform all other equations in our African population of chronic kidney patients. This superiority was described in the study by Pottel et al (2023), which showed that the EKFC estimation equations in general (EKFC cys, EKFC crea-cys, EKFc crea) outperformed the parallel CKD-Epi equations, and in the study published by Delanaye et al. (2023b) comparing the EKFC 2021 equations to the CKD EPI 2021 equation with cohorts of white and black European populations, Brazilians and Africans. In addition, a study carried out in an Asian population showed that the overall performance of the EKFC equation was acceptable in this population (Zhao et al., 2023). This performance of the EKFC equations would be due to the prior determination in each population of a Q value that corresponds to the median creatinine value in a given population because is specific to each population (Pottel et al., 2008; 2017). Thus, for the estimation of the EKFC creat equation in our sick population, we used the mean creatinine values pre-established by Yayo (2018) which was 0.97 for men and 0.75 for women. Furthermore, in our study, the EKFCcys equation presented the best bias (-0.2 ml/min/1.73m2) and the best accuracy 30% (66.1%). This did not agree with Pottel et al in 202310, who instead showed identical accuracy and precision between EKFCcys andEKFCcreat, and even better performance when they were coupled (EKFC cys/creat).

The CKD-epi 2021 equation showed no particular gain over the CKD-epi 2009 and MDRD equations. This lack of added value was also reported by Delanaye et al. (2023a) and could be explained by the fact that in the CDK-EPI

2021 equation, the vast majority of the black populations included in its development came from the USA (Delanaye et al., 2023a). In our study, the old CKD-EPI 2009 and MDRD equations, used with the ethno-racial factor, performed almost identically to the EKFC crea equation. So these old equations aren't completely bad . Indeed, it is known that the cohort of the MDRD equation was a CKD cohort with a large majority of patients with a GFR , 60ml/min/1.73m2 and the CKD epi equation in a general population . Indeed, this ethnic factor was determined from African-American subjects, the vast majority of whom came from the African-American Study of Hypertension and Kidney Disease (AASK) and had a decreased GFR (Lewis et al., 2001). In contrast, the use of these equations was much better without ethno-racial factors in the healthy population (Sagou et al., 2016). Furthermore, the use of cystatin C in the various equations showed an added value in terms of performance, especially when used alone. Indeed, it has been shown that cystatin C is a marker known to be more stable than creatinine, as it is less affected by muscle mass and diet (Steven et al., 2009; Tangry et al., 2011). Thus, the introduction of cystatin C into GFR estimation formulas has the advantage of being less subject to race hence the absence of an ethnic factor in cystatin-based equations (Inker et al., 2012). It is important to emphasize that in our study, no equation had a P30 greater than 75% in our African population of chronic kidney disease subjects. They are therefore very far from the objective to be reached, which is to have a P30 greater than 90%. This underscores the need for further studies to obtain an equation that can bring as many people as possible into agreement.

Conclusion:-

In our African patient population, the EKFC equation with its variants performed best in our black African population of chronic kidney patients. Unfortunately, none of these equations presented an accuracy 30% higher than 75% in this population. There is still work to be done before we can find a formula better suited to our population.

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None.

Conflict of Interest
None.

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