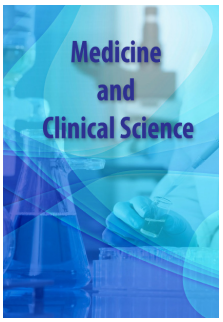
Medicine & Clinical Science

Original Article



MDRD or CKD-EPI study equations for estimating prevalence of stage 3 CKD in Moroccan population

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- Received Date: 03 Dec 2021
- Accepted Date: 15 Dec 2021
- Publication Date: 17 Dec 2021

Abstract

Background: According to the NHANES study, the prevalence of stage 3 chronic kidney disease (CKD) is increasing. The glomerular filtration rate was estimated according to the equation of the MDRD study. More recently, a new estimator has been proposed, the CKD-EPI equation, which is presumed to better perform in normal glomerular filtration rate (GFR) ranges. The aim of the study was to measure the difference in the prevalence of stage 3 CKD in the Moroccan population using equations from the MDRD or CKD-EPI study equations.

Methods: CKD screening was organized in the National Reference Laboratory (LNR) in Casablanca in Morocco. Hospitalized patients or outpatients have been included. GFR was estimated by the MDRD study equation and by the CKD-EPI equations.

Results: The population screened consisted in 29 724 people (54% of male). The prevalence of stage 3 CKD in this population using the MDRD or the CKD-EPI equations was 27.1% and 26.3%, respectively. The prevalence of stage 3 CKD is significantly higher with the MDRD study equation ($p < 0.001$).

Conclusion: Following the method used for estimating GFR, MDRD or CKD-EPI study equations, prevalence of stage 3 CKD varies in a Moroccan population. These differences are significantly important and must be confirmed and explained by additional studies using GFR measured with a reference method.

Introduction

Chronic kidney disease (CKD) has been recognized as a leading public health problem worldwide. The global estimated prevalence of CKD is 13.4% (11.7–15.1%), and patients with end-stage kidney disease (ESKD) is estimated between 4.902 and 7.083 million. [1]

The prevention of CKD (defined as estimated glomerular filtration rate (GFR) under 60 ml/min/1.73 m2) is important [2]. And the first step for efficient prevention is an early diagnosis. But the limitation of rapid diagnosis is the creatinine lack of sensitivity. In fact, the serum creatinine will rise over normal values only when 50% of GFR have already been lost [3,4].

GFR can be measured from the clearance of an exogenous marker neither secreted nor reabsorbed by the renal tubules, or estimated, using different equations, from the determination of plasma creatinine [5]. Its measurement is the most precise method for quantifying kidney function; however, there are some difficulties associated with the complexity and cost of measuring GFR. To avoid these obstacles, it is more common to use the estimation of GFR through more or less complex equations developed from the measurement of serum creatinine [6]. Historically, the first formula proposed was Gault and Cockcroft equation, then, the MDRD equation (Modification of Diet in Renal Disease) was established and even more recently the CKD-EPI (Chronic Kidney Disease Epidemiology) equation [7-9].

Numerous studies have shown, in the general population and in various sub-populations, that Cockcroft's formula has much lower performance than MDRD and CKD-EPI [8-10]. Others have underlined that MDRD equation is not precise for the estimation of GFR in healthy population and mostly when it is applied to normal creatinine values [10-12]. It is highly possible that MDRD study equation underestimates GFR and overestimate CKD prevalence in this population [10,13,14]. According to these limitations, Levey's group who is already at the

Citation: Snoussi M, Benzekri I, Sqalli M, et al. MDRD or CKD-EPI study equations for estimating prevalence of stage 3 CKD in Moroccan population . Med Clin Sci. 2021;3(4):1-6.

origin of the MDRD study equation has built a new equation from a large sample of CKD and healthy subjects. Therefore, it seems interesting to evaluate the prevalence of CKD with the MDRD equation and with the CKD-EPI equation.

Methods

A retrospective study was carried out at the National Reference Laboratory (LNR) in Casablanca. Hospitalized patients or outpatients for whom a biological assessment including at least one serum creatinine was prescribed have been included.

Serum creatinine was measured by the Isotope Dilution Mass Spectrometry (IDMS) traceable Jaffé method on the ARCHITECT ci4000 Analyzer (Abbott diagnostics). As our creatinine is IDMS traceable, the estimation of GFR was performed with the new "175" MDRD study equation and the CKD-EPI study equation [15]. (Table 1)

Table 1. *Serum creatinine (SCr; mg/dL) based equations for glomerular filtration rate (GFR) estimation*

4-variable MDRD Study equation

$GFR\ (mL/min/1.73\ m^2) = 175 \times SCr^{-1.154} \times Age^{-0.203} \times 0.742$ (if woman) × 1.21 (if black)

CKD-EPI Study equation (white subjects)

If woman:

if creatinine < 0.7 mg/dL:

$GFR\ (mL/min/1.73\ m^2) = 144 \times SCr/0.7^{-0.329} \times 0.993^{Age}$

if creatinine > 0.7 mg/dL:

$GFR\ (mL/min/1.73\ m^2) = 144 \times SCr/0.7^{-1.209} \times 0.993^{Age}$

If man:

if creatinine < 0.9 mg/dL:

$GFR\ (mL/min/1.73\ m^2) = 141 \times SCr/0.9^{-0.411} \times 0.993^{Age}$

if creatinine > 0.9 mg/dL:

$GFR\ (mL/min/1.73\ m^2) = 141 \times SCr/0.9^{-1.209} \times 0.993^{Age}$

All results are expressed as mean ± SD. We have calculated and compared the percentage of patients with stage 3 CKD or worse obtained with the two equations, but also the coefficients of correlation between the different equations. Agreement between equations to discriminate GFR over and less than 60 mL/min/1.73 m2 has been evaluated by Kappa statistics. The results of GFR estimated by the MDRD and the CKD-EPI equations have also been compared by Bland and Altman analysis [16]. Arbitrarily, in these analyses, we chose the MDRD equation results as the referent. Bias between equations was defined as the mean of the differences. The SD around the mean reflected the dispersion and the precision of the equations. $p < 0.05$ was considered as significant. Also, we have evaluated if difference between equations might be correlated to variables such as age, sex, creatinine or estimated GFR levels. We also repeated Bland and Altman analysis in subgroups according to sex.

Results

During the study period, 29 724 people were screened (54% male and 46% women). Clinical and biological characteristics of the global population are shown in Table 2.

Table 2. *Clinical and biological description of the population (n = 29724).*

N= 29724	Mean	SD	Range
Age (years)	56	19	3-92
Creatinine (mg/L)	13	16	4-161
MDRD study (mL/min/1.73m^2)	80	36	3-198
CKD-EPI study (mL/min/1.73^2)	81	35	3-153

By paired samples t-test, the estimated GFR by the MDRD and the CKD-EPI equations were different from each other ($p < 0.0001$). Prevalence of stage 3 CKD when GFR was estimated by the MDRD equation study was 27.1% (n = 8042). This prevalence was significantly higher than the prevalence obtained with the CKD-EPI equation which was 26.3% (n = 7821). However, Kappa statistics showed very good agreement between the two equations ($\kappa = 0.8$).

Results given by the two equations were highly correlated ($p < 0.0001$)($r = 0,93$).

The Bland and Altman analysis results are summarized in Figure 1.

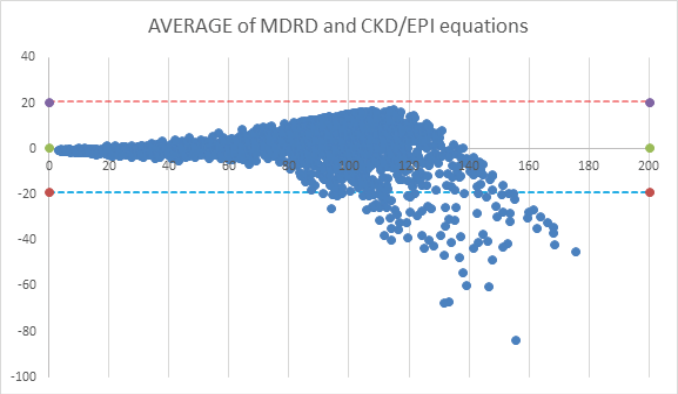

Figure 1. *Bland and Altman analysis between the MDRD study equation and the new CKD-EPI equations.*

The continuous line represents the mean difference between estimated GFRs, whereas the dashed lines represent the limits of agreement (mean difference ± 2SD). All values are expressed in mL/min/1.73 m^2.

The mean difference between the MDRD and the CKD-EPI equations was 0.9 ± 10.1 mL/min/1.73 m^2.

Two subgroups' analyses were conducted following sex and estimated GFR. If we restricted analysis to estimated GFR under 60 mL/min/1.73 m2 with the MDRD equation (n = 8042), the paired samples t-test still showed significant difference between the estimated GFR by the MDRD and the CKD-EPI study equations ($p < 0.0001$). And, this is still the case when results over 60 mL/ min/1.73 m^2 were analyzed (n = 21682).

Clinical and biological values were different between men and women, as it was illustrated in Table 3.

But the mean results of the CKD-EPI equation were not different between men and women. Kappa statistics showed very good agreement between the two equations, and

Table 3: *Clinical and biological description of the population according to gender.*

N= 29724	Men	Women	Difference
Age (years)	58 ± 18	53 ± 20	P < 0.001
Creatinine (mg/dL)	16 ± 20	11 ± 11	P < 0.001
MDRD study (mL/min/1.73m^2)	80 ± 37	81 ± 34	P < 0.001
CKD-EPI study (mL/min/1.73^2)	78 ± 35	84 ± 34	P < 0.001

agreement seemed slightly better for men than for women (κ = 0.9 and 0.7, respectively). In the same way, prevalence of stage 3 CKD in men was 28.7% and 28.4% with the MDRD and the CKD-EPI equations, respectively (non-significant difference). In women, prevalence of stage 3 CKD was 25.1% and 23.9% with the MDRD and the CKD-EPI equations, respectively (significant difference).

Discussion

Epidemiological studies in different Western countries have recently shown that prevalence of CKD, defined as GFR under 60 mL/min/1.73 m^2, is about 10% in the global population [17,18]. The MDRD study equation using a calibrated serum creatinine was used for these data [19,20]. Obviously, the use of this equation can be criticized. It has been demonstrated that this equation tends to strongly underestimate GFR in patients with normal or near normal creatinine values [10,13,14,21]. According to these limitations, the Levey's group has proposed a new equation which is thought to be better in the higher GFR range (over 60 ml/min/1.73 m^2). Therefore, the new CKD-EPI equations are different following the creatinine value (7 mg/L for women and 9 mg/L for men). This change seems logical because the relationship between GFR and creatinine is different in healthy subjects compared to subjects with CKD. The better accuracy of the new equation is also explained by the authors because of the inclusion of healthy subjects in the equation's development study.

Using the CKD-EPI equations, the prevalence of stage 3 CKD in our population is significantly lower than if the MDRD study equation is used (26.3% versus 27.1%). Over 29 724 patients screened, 238 (0.8%) were classified as having stage 3 CKD with the MDRD study equation compared to the CKD-EPI study equation. These data are not negligible from an epidemiological point of view. This observation has also been made in other international studies, as in Belgium where prevalence of stage 3 CKD varies strongly following the method used for estimating GFR, MDRD or CKDEPI study equations [22].

Also, another study conducted in populations from 40 countries of Asia, Europe, North America and South America, Middle East, and Oceania showed that the CKD-EPI equation classified fewer individuals as having CKD than the MDRD study equation [23].

Analysis of subgroups by sex shows a difference between the two equations. This difference seems to be a little greater in women compared to men. This is not explained by GFR level or age, as women have a higher average GFR and are younger.

This difference could be explained by the lower cut-off chosen in women for the CKD-EPI equations. Since the relationship between creatinine and GFR is exponential, it makes sense that the differences between the two equations are greater in women. Nevertheless, further studies are needed to explain such discrepancies as it is highly likely that one of the two equations is more accurate in women.

In the NHANES study, Levey et al also compared the prevalence of CKD. The authors found that the prevalence of CKD in the NHANES study was 9.9% with the CKD-EPI equation and 10.8% with the MDRD study equations [24]. The difference in prevalence is almost equivalent in our study. In the MDRD equation, a constant exponent is applied to age (age-0.203) while age is an exponent in the CKD-EPI equation (0.993age). Even though the performance of the MDRD equation in the older population is controversial [25,26], the one of the CKD-EPI equations has not been studied (only 3% of patients aged 70 to 75 years were included in the development of the CKD-EPI equations study).

First, it would make sense for the equations to vary with age, as the relationship between creatinine levels is heavily influenced by age. Second, there is a lack of data regarding elderly patients (over 70 years) who are underrepresented in the CKD-EPI study. Third, the way in which factor 175 was obtained in MDRD equation to make IDMS results traceable has been criticized [12,13]. This criticism is also valid for the CKD-EPI equation because serum creatinine measurements had been measured with the Jaffé method. Thus, one might think that the factors used in the CKD-EPI equations (144 for women and 141 for men) are too low, leading to a systematic overestimation of the prevalence of CKD. Finally, the main criticism of the CKD-EPI equations is its lack of improved accuracy in estimating the GFR. Indeed, in Levey's study, in subjects with a GFR greater than 60 ml/min/1.73 m2, the bias with the measured GFR is improved when using the CKD-EPI equations compared to the MDRD equation, however, the accuracy of the CKD-EPI equation seems slightly lower than those of the MDRD. So, if the GFR estimation by equation CKD-EPI has an improved systematic bias, this equation does not improve the accuracy of the estimate. This seems logical because bias is, by nature, systematic and accuracy is random and is mostly related to the accuracy of creatinine measurement.

There are some limitations to our study. First, the main limitation is related to the fact that we did not measure the GFR with a reference method. Even if we have arguments to assert that the MDRD equations overestimate the prevalence of CKD, this must be verified using a reference method. Our data highlight potential discrepancies between the results of epidemiological studies when the equations of the MDRD or CKD-EPI study are used. Epidemiological studies on kidney function in the global population are still awaited. Our population is not representative of the entire Moroccan population (as only volunteer patients were included) our stage 3 CKD prevalence results should not be considered for epidemiological studies. Thirdly, we do not have data on ethnicity. As the ethnicity factor varies between equations, this could be a source of bias. Moreover, the ethnic factor used was the Caucasian one, but it is not explained that this factor can be used for the Moroccan population. A new ethnic factor should probably be developed for the Moroccan population. Fourth, as in several epidemiological studies, our subjects were tested only once, although the definition of CKD implies that two or three tests should be performed over a three-month period.

Conclusion

The present study highlighted some observed differences in the prevalence of stage 3 CKD in the Moroccan population according to the method used to estimate the GFR. Some arguments disfavor the use of the MDRD equation in epidemiological studies, but the CKD-EPI equations also have some criticisms. Epidemiological studies of different populations using GFR measurements with a reference method are also needed to confirm and explain these discrepancies.

Competing interests

The authors declare that they have no competing interests.

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