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CLINICAL PRACTICE BASE EGFR EQUATIONS AND THEIR APPLICATIONS IN DIFFERENT CKD POPULATIONS: A NARRATIVE REVIEW

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Abstract
Every generation of medical students has learned the Cockcroft–Gault equation, which estimates the glomerular filtration rate. However, since the Modification of Diet in Renal Disease (MDRD) study equation was published in 1999, the superiority of the Cockcroft–Gault equation has been consistently debated. Recently, the Chronic Kidney Disease Epidemiology (CKD-EPI) consortium introduced a set of innovative equations for estimating the glomerular filtration rate (GFR). The MDRD and CKD-EPI equations were developed through a rigorous process, are formulated to work with standardized biomarkers of GFR (such as serum creatinine and/or serum cystatin C) and have been evaluated in various patient populations. The MDRD Study and CKD-EPI equation based on serum creatinine level have replaced the Cockcroft–Gault equation. These equations are generally considered superior and are specifically recommended by international guidelines. However, as they become more widely used, it has become evident that they are not infallible and may not provide accurate GFR estimates in certain everyday clinical situations. This review describes the development processes of the new GFR-estimating equations, and the clinical scenarios in which their applicability is questioned are discussed.

Keywords: Cystatin C, Creatinine, endogenous biomarker, kidney, chronic kidney disease.

Introduction

There is an ongoing and intense debate surrounding the methods and reasons behind estimating the glomerular filtration rate (GFR). The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) consortium should be acknowledged for its significant contributions to revitalizing the crucial field of general nephrology [1]. They breathed new life into this field by implementing a rigorous methodological framework, leading to the development of various GFR-estimating equations, all aimed at enhancing the reliability of GFR evaluation and ultimately replacing the flawed yet profoundly entrenched Cockcroft–Gault formula [2].

Like the interdependence between initial hypotheses and the formulation of a mathematical equation, GFR-estimating equations are highly sensitive to the characteristics of the population from which they are derived [3]. This sensitivity can significantly impact the equation's generalizability and raises concerns about its applicability at the individual level [4]. While previous reports from the CKD-EPI group provided reassurance regarding the suitability of the new equations for diverse populations, a substantial body of literature has emerged, specifically focusing on examining the applicability of these equations in more specific and homogeneous groups of individuals [5].

This article will begin by providing an overview of the processes that created the Cockcroft–Gault formula, the MDRD study equation, and the CKD-EPI group equations. Subsequently, we will examine and discuss the clinical scenarios where concerns about their suitability and applicability have been raised.

Prominent Biomarkers (Serum Creatinine and Cystatin C) of eGFR

Serum creatinine is the most widely known endogenous biomarker employed to estimate GFR. Although its usefulness has been acknowledged since the early 20th century [6], it comes with physiological and analytical limitations. From a physiological standpoint, two major limitations of using serum creatinine to estimate GFR are the variations in tubular secretion of creatinine and its dependence on muscle mass [7]. Furthermore, serum creatinine levels can be affected by food intake, although the exact impact of meals on serum creatinine concentration remains a topic of discussion, with estimates ranging from 10% to 100% [8].

Cystatin C is a 13,260 Da protein initially identified in cerebrospinal fluid and urine from patients with tubular disease [9]. It is a cysteine proteinase inhibitor family member, produced by all nucleated cells and encoded by a constitutively expressed gene [10]. Once filtered by the glomerulus, cystatin C is entirely reabsorbed and catabolized by the proximal tubules, making GFR the primary determinant of its plasma concentration [11]. Research on this new GFR biomarker began in 1985 with the work of Grubb et al [12]. Cystatin C is often considered superior to serum creatinine because it is believed to be less dependent on muscle mass [13]. However, this idea has been challenged, and some studies suggest that cystatin C levels may still be influenced by weight and/or muscle mass. However, this dependency on muscle mass appears to be much less significant than serum creatinine, and the normal reference values of cystatin C are not significantly influenced by ethnicity [14].

Various factors, such as thyroid disorders, tobacco consumption, HIV viral load, obesity, high doses of steroid therapy, and inflammation, can influence serum cystatin C levels beyond renal function [13-16]. While cystatin C has improved performance over serum creatinine in specific patient subgroups for detecting CKD, its superiority in general or healthy populations is unclear [17]. Several cystatin-C-based equations have been proposed, but they share two limitations: they were developed using limited sample size and lack definitive external validation, and the equations rely on cystatin C values that may not be consistently reproducible [18].

Background of common clinical practice-based eGFR equations

Effersoe likely introduced the initial creatinine-based equation for estimating GFR in 1957 [19]. Following that, numerous other equations were proposed. However, up until 2009, the two most widely used equations were the Cockcroft–Gault equation proposed by Cockcroft and Gault in 1976 [20] and the Modification of Diet in Renal Disease (MDRD) study equation proposed by Levey et al. in 1999 [21].

Cockcroft–Gault equation

The Cockcroft–Gault equation was derived from a limited group of 249 hospitalized patients [20]. Its main advantage was its mathematical simplicity, which made it practical for bedside use with patients. However, this advantage has become less significant when computers and smartphones can easily handle complex mathematical equations [22].

The Cockcroft–Gault equation had several weaknesses, including that it estimates 24-hour creatinine clearance rather than GFR. Additionally, the development dataset comprised only Caucasian individuals, with only a small representation of women (4%). The serum creatinine measurement was accurate but not standardized, and the incorporation of 'weight' as a covariate in the equation introduced potential imprecision for individuals with abnormal body mass index (BMI) [23]. Some authors have attempted to correct the Cockcroft–Gault results by incorporating body surface area (BSA) [21], even though Cockcroft and Gault did not initially recommend this correction. However, this adjustment raises questions since weight is a crucial variable in BSA and the Cockcroft–Gault equations [22]. Furthermore, BSA indexation might be misleading for individuals with extreme BMI, such as anorexic or obese patients [24]. Despite its limitations, the Cockcroft–Gault equation has remained popular and is still utilized in specific contexts, particularly for drug-dosing recommendations [25].

MDRD equation

In 1999, Levey et al. introduced a novel creatinine based MDRD equation. This equation aimed to estimate the "true" GFR, measured by urinary clearance of iothalamate and indexed by BSA [21]. Incorporating BSA likely explains why "weight" was not considered a relevant variable in this equation [22]. Age, gender, and ethnicity were included in the equation to account for endogenous serum creatinine generation. The equation was developed based on a cohort of 1,628 American patients with CKD, where the mean GFR was 40±21 ml/min/1.73m². In this cohort, 40% of the patients were women, and 12% were African American. The MDRD study equation was later modified to use IDMS-traceable serum creatinine values [21]. Several studies have confirmed the superiority of the MDRD study equation over the Cockcroft–Gault equation. However, despite its advantages, the MDRD study equation has its limitations [26, 27].

The cohort used to develop the MDRD equation consisted of CKD patients, and the relationship between GFR and serum creatinine concentration differs between healthy individuals and those with CKD. Consequently, it was unsurprising that the MDRD study equation systematically underestimates GFR for high GFR levels (>60 ml/min/1.73m²). This underestimation, at the population level, results in an overestimation of the prevalence of stage 3 CKD (defined as estimated GFR [eGFR] <60 ml/min/1.73 m²) in the general population. Another limitation of the equation is related to serum creatinine measurement, which was conducted using a Jaffe method [21]. Given that serum creatinine is the most critical variable in the equation, the precision of the method used for its measurement directly affects the precision of the estimation [28, 29], leading to suboptimal precision for the MDRD study equation [30].

CKD-EPI creatinine equation

To address the systematic underestimation of the MDRD study equation in high GFR ranges, the CKD-EPI consortium introduced a new equation based on serum creatinine, the CKD-EPI creatinine

equation [30]. This consortium combined data from 26 cohorts, including the MDRD study cohort. GFR was measured using a reference method, and serum creatinine concentration was measured using an IDMS-traceable method. The sample size was significantly more extensive compared to previous studies on GFR estimation, with 5,504 individuals in the development dataset and 2,750 individuals in the internal validation dataset. GFR in both datasets was measured using iothalamate clearance. The equation was further validated in an external validation dataset comprising 3,896 individuals, where GFR was measured using other reference methods. Notably, many individuals in all these datasets had a measured GFR (mGFR) above 60 ml/min/1.73 m², with many being potential kidney donors. Consequently, the mean GFR in this study was higher (68 ml/min/1.73 m²) than the MDRD study population (40 ml/min/1.73 m²).

The CKD-EPI creatinine equation has a different mathematical structure compared to the MDRD study equation, and different exponents are applied to serum creatinine based on its concentration. Additionally, the choice of exponent varies according to gender, and the threshold of serum creatinine concentration that determines the choice of the exponent also varies. While the exponent for higher serum creatinine values is comparable to the one used in the MDRD equation (-1.209 versus -1.154, respectively), the exponent for lower serum creatinine values (indicating higher eGFRs) is much lower (-0.329).

The CKD-EPI creatinine equation demonstrated superior performance in the seminal study compared to the MDRD study equation. For instance, in the external validation dataset, the median difference between estimated GFR (eGFR) and measured GFR (mGFR) - a measure of bias - was -5.5 ml/min/1.73 m² for the MDRD equation. In comparison, the CKD-EPI creatinine equation was -2.5 ml/min/1.73 m². The respective interquartile ranges measuring precision were 18.3 ml/min/1.73 m² for the MDRD equation and 16.6 ml/min/1.73 m² for the CKD-EPI creatinine equation. Additionally, the percentages of GFR estimates falling within 30% of mGFR - an accuracy indicator - were 81% for the MDRD equation and 84% for the CKD-EPI creatinine equation.

Notably, the new CKD-EPI equation significantly improved its performance for individuals with a GFR greater than 60 ml/min/1.73 m². In this group, the median differences between estimated and measured GFR were -10.6 ml/min/1.73 m² for the MDRD equation and -3.5 ml/min/1.73 m² for the CKD-EPI creatinine equation. The interquartile ranges for these equations were 25.7 ml/min/1.73 m² and 24.2 ml/min/1.73 m², respectively, and the percentages of GFR estimates within 30% of mGFR were 85% for the MDRD equation and 88% for the CKD-EPI creatinine equation.

The significant improvement in the performance of the CKD-EPI creatinine equation compared to the MDRD study equation was mainly due to a reduction in bias. At the same time, precision showed little to no improvement. In epidemiological studies, the enhanced performance of the CKD-EPI creatinine equation was quickly confirmed [30-33]. However, at the individual level, where the estimator's precision is more critical than systematic bias, the superiority of the CKD-EPI creatinine equation (in terms of accuracy within 30% of mGFR) is less evident. All researchers have not consistently supported it [34, 35]. Murata et al. conducted a study comparing the accuracy of the MDRD and CKD-EPI creatinine equations in estimating GFR in 5,238 patients from the Mayo Clinic, categorized into five subgroups: potential kidney donors, kidney donors after nephrectomy, native CKD patients, kidney transplant recipients, and recipients of other organs. The results confirmed that in kidney donors before and after donation, the CKD-EPI creatinine equation underestimated mGFR to a lesser extent than the MDRD equation. However, in the three other patient groups, particularly those with eGFR below 90 ml/min/1.73m², the performance of the CKD-EPI equation was not superior and even showed a slight trend towards overestimation [34]. This overestimation in CKD patients might be the trade-off for improved performance at higher GFR levels.

Applicability of eGFR equations in different clinical settings

Kidney transplant recipients

Several studies have compared different creatinine-based equations in kidney transplant recipients and have consistently found that the novel GFR-estimating equations (the MDRD and CKD-EPI equations) outperform the traditional Cockcroft–Gault formula. In these comparisons, GFR was measured using reference methods, and serum creatinine was measured with an IDMS-traceable method [36, 37]. However, the overall performance of the MDRD and CKD-EPI creatinine equations is generally worse in kidney transplant patients than in non-transplant patients. Most of the studies, except one, have reported an accuracy within 30% of mGFR (percentage of GFR estimates within 30% of measured GFR) of less than or equal to 80% [38].

Interestingly, while the CKD-EPI creatinine equation has performed better than the MDRD study equation in non-transplant patients, this superiority has not been consistently observed in kidney transplant recipients. While some researchers have found the CKD-EPI creatinine equation superior in this population, most studies have not shown such a clear advantage [39].Considering the disappointing results with creatinine-based equations in kidney transplant recipients, the potential usefulness of cystatin C as an alternative marker for GFR estimation should be considered. Studies on cystatin-C-based equations in kidney transplant recipients have generally performed better than the MDRD study equation. Still, there has been significant heterogeneity in the results, primarily due to the lack of standardized cystatin C measurements [40].

Only one study has investigated the utility of serum cystatin C as a filtration marker in kidney transplantation, and it proposed an external validation using standardized cystatin C values. In this study, the CKD-EPI cystatin C and combined equations performed better than the CKD-EPI creatinine equation [41]. However, more confirmatory studies are needed before cystatin C and cystatin-C-derived equations can be definitively recommended in transplant recipients, especially considering that the CKD-EPI creatinine equation might not be the best comparator in this specific population.

Elderly

Estimating GFR in older adults is crucial yet challenging due to the physiological decline in GFR with age and the higher risk of CKD in older individuals. However, the MDRD and CKD-EPI cohorts had relatively low proportions of elderly subjects, specifically those over 70 years old [42]. This lack of representation led some authors to continue recommending the use of the Cockcroft–Gault equation [43].

Cystatin C holds promise as an alternative GFR estimation marker for the elderly population due to its reduced dependence on muscle mass. However, normal reference values for cystatin C are higher in healthy individuals over 60 years, possibly influenced by the natural decline in GFR with age. Recent studies have investigated GFR estimation in older people. In one study comparing the performance of the Cockcroft–Gault, MDRD, and CKD-EPI creatinine equations in CKD patients over 65 years old, the Cockcroft–Gault equation showed the worst performance, potentially due to imperfect age modeling in the equation. The MDRD and CKD-EPI creatinine equations showed similar performance in this CKD population [5, 44, 45].

Another study of individuals with a median age of 80 years found that the creatinine-based equations had similar accuracy in the elderly compared to younger individuals (around 80-85% of estimates within 30% of mGFR). The CKD-EPI creatinine equation performed slightly better than the MDRD equation for high GFR levels. The addition of cystatin-C-based equations showed limited improvement, particularly when compared with the MDRD equation and mainly in individuals with mGFR greater than 60 ml/min/1.73 m^2. A third study focused on Caucasian individuals over 70 years old and proposed two new equations based on serum creatinine and

cystatin C. The internal validation results showed impressive levels of accuracy, with the BIS1 equation at 95% accuracy and the BIS2 equation at 96%. However, external validation studies in diverse populations must confirm these promising results [5].

In conclusion, estimating GFR in the elderly is challenging. While the CKD-EPI creatinine equation has improved performance over the MDRD equation, the overall accuracy of creatinine-based equations in older adults is comparable to that in younger individuals. The potential utility of cystatin C as an alternative marker requires further validation, especially in non-Caucasian populations, to assess its performance relative to existing equations, particularly in elderly patients.

Hospitalized patients

The majority of patients cared for by nephrologists, especially in developed countries, are frail, elderly, or hospitalized individuals [46-48]. These patients pose challenges for GFR estimation, as serum creatinine as a GFR marker is likely less reliable in such cases. However, limited studies have examined GFR estimation in these patient populations. One study by Poggio et al. measured GFR in 107 sick hospitalized patients with CKD and found that all creatinine-based equations significantly overestimated GFR. Low serum creatinine values were mainly attributed to sarcopenia rather than reduced GFR in this context. A similar overestimation of GFR has been observed in patients with conditions such as anorexia and cirrhosis [49-51].

In terms of the potential usefulness of cystatin C in hospitalized patients, Segarra et al. demonstrated in a study of 3,114 hospitalized patients that cystatin-C-derived equations were more accurate than the CKD-EPI creatinine equation in estimating GFR measured by iohexol clearance, particularly in patients with malnutrition, extensive reduction of body surface area (BSA), or loss of muscle mass. However, these results must be further validated using standardized cystatin C values. There are two other clinical situations worth mentioning that are somewhat like hospitalized patients. First, in patients with end-stage renal disease (GFR <15 ml/min/1.73 m^2), differences in creatinine levels often reflect changes in muscle mass rather than GFR, leading to significant inaccuracies in serum creatinine-based equations for assessing residual renal function [52]. Secondly, patients with nephrotic syndrome have shown substantial overestimation of mGFR by serum creatinine-based equations, suggesting that these equations may not be reliable in this population [53, 54]. The potential utility of cystatin C-based estimation in these specific situations remains unknown and requires further investigation.

Children

The issue of estimating GFR in children has been extensively studied. As expected, all creatinine-based equations derived from adults are inaccurate in children and adolescents. Unlike serum creatinine, cystatin C concentrations in children are minimally affected by muscle mass. The normal reference values for cystatin C remain consistent between the ages of 2 years and 18 years, which is advantageous in clinical practice [55, 56]

Over the years, several creatinine-based, cystatin-C-based, or combined equations have been proposed for estimating GFR in children. One of the most popular creatinine-based equations for this purpose is the Schwartz equation, particularly the 2009 version. Based on serum creatinine and height, this equation was developed using IDMS and enzymatic methods and validated against a reference method (iohexol clearance) [57]. In a study by Schwartz et al. 2012, the researchers further investigated GFR estimation in children from the chronic kidney disease in Children (CKiD) study. They compared the performance of various equations based on cystatin C, serum creatinine, height, gender, and blood urea nitrogen. The accuracy (percentage of estimates within 30% of mGFR) of the equations ranged from 80% for the cystatin C-based equation to 91% for the combined equations. The high accuracy was likely due to the homogeneity of the population (children with CKD) and the precision of the biological assays used [58].

However, these new Schwartz equations need external validation, especially in children without CKD. Additionally, as standardized cystatin C was not used in the study, there is potential for further improvement in the equations' performance and generalizability.

Ethnicity

The potential differences in muscle mass and tubular secretion of creatinine across different ethnicities have been extensively discussed, particularly in Caucasian and African American individuals. The MDRD study group was the first to propose an ethnic coefficient for African American individuals. Although the validity of this coefficient is well accepted for African Americans with CKD, some researchers have questioned its accuracy in healthy individuals. Evidence suggests that the coefficient might be too high when applied to healthy African American individuals, leading to an underestimation of the prevalence of CKD in the general African American population. This could explain the epidemiological paradox observed in African Americans, where the prevalence of stage 3 CKD is lower despite a higher proportion of end-stage renal disease cases [21, 59-61]

It is important to note that the African American ethnic coefficient is unlikely to apply to other black populations in regions like Africa, Europe, the Caribbean, or Australia. The situation becomes even more complex and confusing in Asian populations, as studies in China and Japan have produced different coefficients. It is unclear whether these differences reflect ethnic variations or are influenced by methodological discrepancies in measuring GFR and serum creatinine [62-64].

On the other hand, cystatin C is less affected by ethnic variation than creatinine. No ethnic correction has been considered for cystatin-C-based equations [65]. However, the performance of the new standardized cystatin-C-based equation and combined equations still needs to be validated in multi-ethnic studies to assess their accuracy across different ethnic groups.

Conclusion

Current international guidelines unequivocally recommend the CKD-EPI creatinine equation as the preferred method for estimating GFR. There is little debate that, at this point, the CKD-EPI creatinine equation is the most reliable estimator available, particularly from an epidemiological perspective when compared to the Cockcroft–Gault equation. However, it is essential for nephrologists, as specialized physicians, to be aware of the limitations of the CKD-EPI creatinine equation when using it to estimate GFR at the individual level.

The CKD-EPI equations were developed based on cohorts of selected patients with and without CKD, possibly excluding the most frail and sick individuals. Moreover, many patients with normal GFR included in the CKD-EPI datasets were potential living kidney donors, which may not fully represent the general population or completely healthy individuals. Although there are several clinical situations where the applicability of the CKD-EPI creatinine equation is questionable, this limitation is not unique to this equation. Still, it can be extended to all creatinine based GFR equations. As a result, alternative options should be considered.

Most importantly, direct measurement of "true" GFR is considered the best solution when GFR-estimating equations do not apply to specific populations. Therefore, it may be time to reevaluate the role of so-called reference methods of GFR measurements. Descriptions of these methods as fastidious and burdensome may have been valid for historic urinary clearance of inulin. Still, newer approaches, such as plasma clearance of contrast agents, are now available and easier to implement. While some researchers have pointed out analytical weaknesses and lack of concordance among different reference markers, suggesting they should not be used as gold standards, others argue that GFR-estimating equations should be validated based on their ability to predict patients' outcomes, not "true" GFR. However, the authors disagree with this epidemiological perspective, emphasizing

the need to address analytical issues with the same rigour applied to developing and validating GFR-estimating equations. They propose international guidelines to redefine the utility and utilization of GFR-measuring methods as a more sensible approach rather than discarding reference methods altogether.

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