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The pros and cons of creatinine-based equations for estimating GFR in chronic kidney disease

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Abstract

Chronic kidney disease (CKD) is a growing clinical disorder manifested by structural and functional abnormalities, progressing to gradual kidney failure and end-stage renal disease (ESRD). CKD is characterized by decreased glomerular filtration rate, below 60 mL/min/1.73 m^2 that endure for over three months, and persistently increased albuminuria. Estimation of GFR is considered to be the most pertinent method for evaluating chronic kidney disease. Accurate assessment of GFR is therefore, essential for diagnosing and monitoring the progression of kidney disease. There have been several estimated glomerular filtration rate (eGFR) equations developed, and each one has unique properties. Clinical laboratories provide eGFR with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation or the Modification of Diet in Renal Disease (MDRD) study equation using serum creatinine according to the recommendation of the National Kidney Foundation (NKF) and American Society of Nephrology (ASN) Task Force. However, serum creatinine, is influenced by various factors including muscle mass, body weight, and gender. Since the impacts of the demographic factors, and extra-renal elimination, these equations may either underestimate or overestimate the true GFR and hence altered the clinical practice. To enable timely intervention and minimize the risk of complications, it is suggested to discover novel endogenous markers that can complement existing ones, thereby enhancing the accuracy of GFR estimation and facilitating early detection of CKD. This review highlights the need for further investigations across diverse population to improve the accuracy of GFR estimation.

Keywords: Chronic Kidney Disease; Glomerular Filtration Rate; Creatinine; Cystatin; Renal function

1. Introduction

Kidney disease is termed chronic, when the functional and structural abnormalities of the kidney are accompanied by a spectrum of physiological disorders associated with a progressive decline in glomerular filtration rate (GFR) [1]. A significant number of patients with chronic kidney disease (CKD) may progress to end-stage renal disease (ESRD), requiring renal replacement therapies. The prevalence of CKD is increasing worldwide and approximately 1 million people die globally from untreated kidney failure each year. The primary risk factors of CKD are diabetes mellitus and hypertension. Additional underlying factors are chronic glomerulonephritis, long-term anti-inflammatory drug usage, immune system disorders, polycystic kidney disease, acute renal disease as well as kidney aging [2,3] CKD is characterized by abnormal kidney function or structure that persists for over three months. This condition involves individuals, who exhibit signs of kidney damage, including eGFR<60mL/min/1.73 m^2 on more than two occasions with minimal interval of three months, deemed the most reliable measure of kidney function for identifying the existence and severity of CKD. Additional diagnostic markers are albuminuria>30mg/day, hematuria, urine sediment irregularities, electrolyte and tubular dysfunction, histological abnormalities, and history of kidney transplantation.

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Proper diagnosis and management of CKD can prevent or delay progression and reduce the development of complications, thereby preventing death associated with CKD [4]. According to Kidney Disease Improving Global Outcomes Work Group (KDIGO) criteria, CKD is categorized into five stages based on eGFR [5].

Table 1 GFR Categories in CKD

Category	eGFR	Terms	Clinical Presentations
Stage 1	≥90 mL/min/1.73m^2	Normal or high	There are some signs of kidney diseases such as blood or protein leak in urine, multiple cysts in the kidneys, single kidney
Stage 2	60-89mL/min/1.73 m^2	Mildly Reduced	Markers of kidney damage (Nephrotic and Nephritic syndrome, urinary tract disorders, hypertension due to kidney disease and urinalysis abnormalities, diabetic nephropathy
Stage 3a	45-59 mL/min/1.73m^2	Mild to moderate	Loss of renal function due to anaemia, mineral and born disorders, elevated parathyroid hormone, hypertension, lipid abnormalities, low serum albumin and albuminuria. Cardiovascular disease
Stage 3b	30-44 mL/min/1.73 m^2	Moderate to severe	
Stage 4	15–29 mL/min/1.73 m^2	Severely reduced	
Stage 5	< 15 mL/min/1.73 m^2	Kidney failure	All of the above, in addition Uremia. Dialysis or Kidney transplant may be necessary

2. Methods of Estimating GFR

GFR measurement helps to monitor the development of renal disease since the progressive decrease in GFR is associated with kidney damage. Most laboratories report eGFR based on serum creatinine, which is possible to use mathematical calculations by putting age, sex, and racial origin. Creatinine (mol.wt.113 Dalton), produced non-enzymatically from creatine of skeletal muscle, is a widely available and relatively inexpensive marker that reflects renal function. However, serum creatinine levels are affected by various factors such as age, sex, muscle mass, and certain medications, as well as different laboratories use different methods to measure serum creatinine [6]. Each of these methods gives slightly different results and the laboratory reports take account of these differences.

2.1. Clearance Method

Measurement of GFR is conventionally based on the renal clearance of a substance in plasma, which is calculated as the volume of plasma that completely clears the substance in a unit of time. A variety of exogenous markers such as inulin, iohexol, radio-labelled EDTA, DTPA, and iothalamate are used to measure the GFR in which the clearance of inulin is considered to be the gold standard [7]. Measured GFR (mGFR) using invasive methods are calculated based on the injection of exogenous markers. The ideal substance would be endogenous, easily filtered by the glomerulus, neither secreted nor reabsorbed by the kidney. Major endogenous markers are urea and creatinine and the widely accepted one is creatinine because of its consistent production and it is less affected by non-renal factors. Due to its low molecular weight, creatinine is freely filtered at the glomerulus and removed from the circulation; hence the concentration of creatinine in the circulation is inversely related to GFR [8]. Numerous equations such as the Cockcroft and Gault(C-G) equation, the Modification of Diet in Renal Disease (MDRD) study equation, and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation have been developed that estimate GFR using serum creatinine.

2.2. Cockcroft- Gault (C-G) Equation

In 1973, Cockcroft and Gault developed an equation to predict creatinine clearance based on age, weight, height, and serum creatinine [9]. Most recommendations for dosage adjustments in adults, particularly for medications eliminated by the kidneys, have been based on the estimated creatinine clearance provided by the C-G equation, as this was employed in earlier pharmacokinetic studies. The C-G equation was used as a proxy for GFR, when measured GFR (mGFR) values were not as available, and it was derived from measured creatinine clearance. Clinical pharmacists and other healthcare practitioners have utilized the C-G equation for adjusting medication doses in persons with reduced GFR, since publication of the C-G equation in 1976. Pharmacists are accustomed to using the C-G equation to estimate GFR as a guide for medication dose adjustments.

Table 2 Cockcroft - Gault (C-G) Equation

Original C-G Equation (1973)	**CCr = {((140–age) x weight)/ (72xScr)}x 0.85 (if female)**
C-G Equation normalized to body surface area (BSA)	GFR (males) = 1.23 × Weight (Kg)×[140-age]/ Scr (µmol/l) × 1.73/ BSA, GFR (females) = 1.03 ×Weight (Kg) × [140-age]/ Scr (µmol/l) ×1.73/BSA, where BSA (m^2) = √ [weight (Kg)× height (cm)/ 3600]
C-G Equation using ideal body weight (IBW),	IBW (males) = 51.65 + [1.85× (height-60)] IBW (females) = 48.67 + [1.65× (height-60)]

Abbreviations: CCr - Creatinine clearance in mL/minute, Scr - Serum creatinine in mg/dL, Weight in Kg, Age in years

The C-G equation was developed in an era when serum creatinine assays were not standardized is the major limitation associated with using the C-G equation. The average creatinine value has decreased by 12% compared to when the C-G equation was developed, with large variability in impact between laboratories. There has been no version of the C-G equation for use with standardized creatinine results and therefore it not recommended for clinical use. Furthermore, the original pharmacokinetic studies suggested that the Cockcroft-Gault equation is less reliable in assessing the risk of kidney damage [10]. As the average body weight is increased, the use of total body weight across the body size or weight spectrum reduces C-G accuracy.

2.3. Modification of Diet in Renal Disease (MDRD) Study Equation

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) validated and approved the Modification of Diet in Renal Disease (MDRD) Study Equation developed by Levy et al., and six factors were taken into consideration when developing the original MDRD equation in 1999. These are serum creatinine, age, sex, ethnicity, serum urea nitrogen, albumin, and urine urea nitrogen. The goal was to evaluate the acceptability, safety, and effectiveness of diet low in protein for individuals suffering from chronic kidney disease [11]. In 2000, a formula comprising four variables was proposed to simplify the clinical application, simplified MDRD equation. The variables were age, gender, ethnicity and serum creatinine. The first organization to recommend using this simplified MDRD equation in clinical practice was the Kidney Disease Outcomes Quality Initiative (KDOQI). Following the introduction of the creatinine standardization program in 2006, numerous other guidelines have recommended the new updated four variable MDRD equations [12].

Table 3 Modification of Diet in Renal Disease (MDRD) Study Equation

Original MDRD (6 Variable) Equation (1999)	(a) eGFR = 170 × $(Scr)^{-0.999}$ × $(Age)^{-0.176}$ × (0.762 if female) × (1.180 if black) × $(SUN)^{-0.170}$ × $(Alb)^{0.3}$ (b) eGFR = 198 ×$(Scr)^{-0.858}$ ×$(age)^{-0.167}$ × (0.822 if female) × (1.178 if black) ×$(SUN)^{-0.293}$× $(UUN)^{0.249}$
Simplified MDRD (4 Variable) Equation or (AbbreviatedMDRD or a MDRD) Equation (2000)	eGFR = 186 × $(Scr)^{-1.154}$ × $(Age)^{-0.203}$ × (0.742 if female) × (1.21 if black)
Updated MDRD (4 Variables) Equation (2006)	eGFR = 175 × $(Scr)^{-1.154}$ × $(Age)^{-0.203}$ × (0.742 if female) × (1.21 if black)

Abbreviations: Scr - Standardized serum creatinine in mg/dL, Age in Years, SUN - Serum Urea Nitrogen in mg/dL Alb-Serum Albumin in g/dL, UUN - Urine Urea Nitrogen in g/dL

For adults, the MDRD study equation provides a therapeutically relevant estimate of GFR up to 90mL/min/1.73 m^2. As per the MDRD study equation, the eGFR is <60mL/min/1.73 m^2 in approximately 10% of the US population having stage-3 CKD [13]. Advantage of the MDRD study equation is that it was developed with: (i) GFR measured directly by urine clearance, (ii) participants were African American and European Americans, and (iii) validation in a large (n>500) independent group of individuals [14]. This equation is more accurate when compared with the C-G formula as well as creatinine clearance determined from 24-hour urine collection, which estimates 5% lower values for serum creatinine concentration [15].

The major drawbacks of the MDRD Study equation include a lack of precision and a consistent tendency to underestimate measured GFR (bias) at elevated values. In the pooled database, the equation exhibited minimal bias for GFR estimates below 60 ml/min per 1.73 m^2 across various demographic and clinical subgroups. Conversely, for GFR estimates of 60 ml/min per 1.73 m^2 or higher, the bias was more pronounced, with significant variability observed

among different subgroups. Additionally, there was a notable lack of precision and systemic underestimation, especially for GFR values exceeding 90 ml/min per 1.73 m^2 [16]. Research has indicated inconsistent findings regarding the efficacy of the MDRD Study equation, influenced by factors such as age, sex, diabetes status, transplant history, or body mass index (BMI) [17,18]. These discrepancies may stem from variations in GFR measurement techniques, differences in creatinine calibration, or the inclusion of participants with higher GFR levels in certain studies. Nonetheless, the majority of laboratories were reporting GFR using the MDRD equation, which is frequently inappropriate for kidney disease assays.

2.4. CKD- EPI Creatinine equation (2009)

In 2009, Levy et al. developed and validated a novel creatinine-based equation and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) approved the study that would be as accurate as the MDRD Study equation at GFR< 60 ml/min/1.73 m^2 and more accurate at higher GFR [19]. The formula uses serum creatinine, age, gender, and race to estimate GFR for individuals eighteen years of age and older and it is in conventional and SI units.

The CKD-EPI creatinine (2009) equation is more accurate than the widely used MDRD study equation, specifically at GFR≥60mL/min/1.73m^2. The higher accuracy circumvents certain limitations of the MDRD Study equation and enhances clinical decision-making in patients with decreased renal function. It has important ramifications for public health and clinical practice as well. The CKD-EPI equation has a lower bias, leading to more accurate estimates of the distribution of eGFR and the burden of chronic kidney disease in the population. In particular, lower bias should reduce the rate of false positive diagnoses of CKD stages. According to Stevens LA et al. the CKD-EPI equation demonstrated 91% and 87% sensitivity and specificity for estimated GFR less than 60mL/min/1.73 m^2 and the MDRD Study equation demonstrated 95% and 82% sensitivity and specificity respectively [20]. Concordance of estimated and measured GFR stages was 69% for the CKD-EPI equation and 64% for the MDRD Study equation (p< 0.001) indicating the estimated GFR with the CKD-EPI equation, primarily caused the reduction in bias.

A study in the Korean General Population comparing the MDRD and CKD-EPI equations reported that the CKD-EPI equation estimated the GFR with less bias and provided more precision than the MDRD study equation at GFR ≥60 mL/min/1.73m^2, approved the Fifth Korea National Health and Nutrition Examination Survey (KNHANES V-1). The prevalence of the CKD stages 1, 2, and 3 in the Korean general population were 47.56, 49.23, and 3.07%, respectively, for the MDRD study equation; and were 68.48, 28.89, and 2.49%, respectively for the CKD-EPI equation. The median biases of the MDRD study and CKD-EPI equations among Asians at GFR<60mL/min/1.73m^2 were 2.4 and 1.5mL/min/1.73m^2 respectively. At GFR≥60mL/min/1.73m^2, the corresponding biases were 5.3 and 0.9 mL/min/1.73m^2, respectively [21].

The weakness of the study is that there were relatively few participants who were older than seventy years of age or members of racial minorities other than Black who are at higher risk for CKD. Similar to the MDRD Study equation, the CKD-EPI equation includes age, race, and sex for GFR determinants of serum creatinine. These variables are related to muscle mass, which is the main determinant of creatinine formation. Therefore, care should be taken when administering any creatinine-based equation to a person with abnormally high or low muscle mass. Moreover, the study lacks complete information on the type of diabetes, immunosuppressive transplant agents, muscle mass measurements, and other medical diseases and drugs. The imprecision of GFR estimates indicates that the prevalence is lower in White people and women but higher in men, Black people, and the elderly population [22]. The Black participants had higher mean serum creatinine concentrations relative to measured GFR while using the 2009 CKD-EPI creatinine equation, which has a term for race with the validation data sets, resulting in a differential race bias [23]. The CKD-EPI equation is more complex than the MDRD Study equation. However, GFR calculations based on serum creatinine will remain in use in clinical practice for the foreseeable future since serum creatinine is now essential for the clinical evaluation of renal function.

2.5. CKD-EPI Creatinine-Cystatin Equation (2012)

This is a version of the CKD–EPI Creatinine (2009) equation that considers the level of serum cystatin C. Cystatin C is a low molecular weight protein (13.3 k Da) generated by all nucleated cells. Due to its small size and positive charge, it passes the glomerular membrane easily with a sieving coefficient of 0.84. The cystatin C levels are independent on age, gender, ethnicity, diet, and muscle mass and are superior to the other biomarkers that are now available in a wide variety of patient populations, particularly diabetic patients [24]. It provides more accurate results for patients with unusual diets or extreme muscle mass.

The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) approved the study conducted by Lesly AI et al. under the cooperative agreement with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

They developed equations for cystatin C alone and in combination with creatinine in 5352 individuals from a range of populations by using cross-sectional analysis. These participants were randomly divided into distinct data sets for internal validation (1830) and development (3522) and also included 5 other studies with 1119 participants for external validation.

In the validation data set, the creatinine–cystatin C equation performed better than that using either creatinine or cystatin C alone. The creatinine equation and the cystatin C equation exhibited a median difference between measured and estimated GFR of 3.7 and 3.4 mL/min/1.73m^2 respectively, whereas the combined equation had a median difference of 3.9 mL/min/1.73 m^2. There was comparable bias in all three equations but precision was improved with the combined equation (inter-quartile range of the difference, 13.4 vs. 15.4 and 16.4 ml per minute per 1.73 m^{2,} respectively) and the and the results were more accurate [25].

The equation that combines creatinine and cystatin C provides the most precise and accurate estimate of GFR across the range of GFRs and in subgroups based on demographic and clinical characteristics. This improvement holds true even among participants with a body-mass index of less than 20, a subgroup in which creatinine-based GFR estimates are known to be less accurate. The errors due to the non GFR determinants of creatinine and cystatin C are independent and smaller in an equation that uses both markers than in an equation that uses only one marker. Possible reasons for the continued imprecision are the residual contribution of non GFR determinants of each marker, as well as physiologic variation in GFR and error in measurement of GFR. It may be useful to consider more widespread use of GFR estimates based on cystatin C, either alone or in combination with creatinine. The combination of creatinine and cystatin C provides more precise GFR estimates, which may be useful as a confirmatory test for the diagnosis of chronic kidney disease in patients with a decreased GFR as estimated from creatinine.

There are several cohort studies have created broader interest in cystatin C as a clinical test of kidney function. These studies have had immediate impact on the 2012 KDIGO (Kidney Disease: Improving Global Outcomes) clinical practice guideline relating to the assessment and management of kidney disease. Researchers have identified the potential of cystatin C as an alternative filtration marker to overcome known limitations of serum creatinine. The relationship of serum cystatin C to measured GFR appears to be influenced less by demographic characteristics and health status than creatinine. Many patients with renal dysfunction had high serum cystatin C levels at the time when serum creatinine was still in the normal range. Hence serum cystatin C is considered as a better marker of GFR than serum creatinine. Studies have reported that the CKD-EPI-2012 creatinine- cystatin equation was more precise and accurate in hypertensive patients with higher GFR [26]. Researchers have evaluated the validity of the proposed equations in the elderly population and considered it might be the better equation for confirmation and classification of the elderly CKD patients [27]. The combined eGFR creatinine-cystatin should be used to determine the optimal GFR estimate for a particular clinical reason. Grubb et al. identified cystatin C as a GFR marker and they created an algorithm for calculating GFR based on cystatin C [28]. Most studies have found that serum cystatin C is a more accurate measure of renal function than serum creatinine since patients with renal dysfunction had high serum cystatin C levels at the time when serum creatinine was still in the normal range. Contrary to creatinine-based GFR estimation models, the cystatin C equation eliminates the need for disputed racial or sexual coefficients [29].

The major limitation of the equation is that none of the data sets came from populations of patients with reduced muscle mass or malnutrition. There were essentially no racial or ethnic minorities in the development data set and there were very few blacks in the validation data set. The equation has not been evaluated in large segments of the population, such as nonblack/non-white ethnicities and elderly persons. Kidney transplant patients were not included in this analysis, since there are differences between transplant recipients and other patients with chronic kidney disease [30]. Moreover, cystatin C is more expensive to run, with the implications for public health expenditure also being examined.

2.6. CKD – EPI Creatinine Equation 2021

Inker et al. modified the 2009 CKD-EPI creatinine equation by removing the racial component which was found to overestimate GFR, especially in Black patients. The researchers pooled the data from multiple studies to develop and validate the new equation. The 2021 CKD-EPI creatinine equation was found accurate, with 85% of eGFR being within 30% of measured GFR for Blacks and non-Blacks. Improved precision of the CKD-EPI creatinine 2021 equation has significant insinuation for both clinical practice and public health, clinical laboratories in the United States recommended to use it because race is not taken into account in the equation [31]. One of the goals for the 2021 CKD-EPI eGFR creatinine was to develop one equation for the overall population, and not report two separate values. This approach better represents the diversity present across all patients and within the social constructs of race.

The two organizations, the National Kidney Foundation and the American Society of Nephrology (NKF-ASN), applauded the choice and recommended the new equation for estimating GFR [32]. The recommendations from the Task Force are summarized: (1) Implementation of the equation without the race variable for adults whom have normal kidney function because it does not include race in the calculation and reporting, includes diversity in its development, and has acceptable performance characteristics and potential consequences that do not disproportionately affect any one group of individuals. (2) Research on GFR estimation with new endogenous filtration markers and on interventions to eliminate race and ethnic disparities should be encouraged and funded. An investment in science is needed for newer approaches that generate accurate, unbiased, and precise GFR measurement and estimation without the inclusion of race, and that promotes health equity and do not generate disparate care. (3) The equations included a diverse development population, consisting of 40% Black participants, did not include a variable for race group in development of the equations, nor in the equations, had acceptable performance characteristics in all groups, and the potential consequences of their use are not anticipated to disproportionately affect any one group of individuals. The Task Force recommended immediately replacing older eGFRcreatinine equations (MDRD Study and CKD-EPI 2009) with the new CKD-EPI 2021 equation.

The major drawbacks of the equation including age and sex and excluding race, underestimates the eGFR in Blacks and overestimated eGFR in non-Blacks. Since non-Black people represent a diverse range of communities, including Asians, it is crucial to evaluate how the eGFR equation transition affects the incidence of renal disease in Asian populations. A bias of up to 30% would result in a reported eGFR ranging from 42mL/min/1.73m^2 to 78mL/min/1.73m^2; leading to significantly different clinical interpretations of renal function [33]. Moreover, muscle mass and other demographic factors have an independent effect on GFR while using creatinine as the marker. When using any creatinine-based formula for individuals who have unusually high or low muscle mass, care should be taken. Although precision improves, bias remains subpar, particularly at higher estimated GFR.

2.7. CKD-EPI Creatinine-Cystatin Equation (2021)

Inker et al. developed the new eGFR creatinine-cystatin equation (2021), without race using data from two development data sets: 10 studies (8254 participants, 31.5% Black) for serum creatinine and 13 studies (5352 participants, 39.7% Black) for both serum creatinine and cystatin C. In a validation data set of 12 studies (4050 participants, 14.3% Black), they compared the accuracy of new eGFR equations to measured GFR and projected the prevalence of chronic kidney disease and GFR stages of U.S. adults, using current and new equations. In the validation data set, the current creatinine equation that uses age, sex, and race, overestimated measured GFR in Blacks (median, 3.7 ml per minute per 1.73 m^2 of body-surface area; 95% confidence interval [CI], 1.8 to 5.4) and to a lesser degree in non-Blacks (median, 0.5 ml per minute per 1.73 m^2; 95% CI, 0.0 to 0.9). When the adjustment for Black race was omitted from the current eGFR equation, measured GFR in Blacks was underestimated (median, 7.1 ml per minute per 1.73 m^2; 95% CI, 5.9 to 8.8). A new equation using age and sex and omitting race underestimated measured GFR in Blacks (median, 3.6 ml per minute per 1.73 m^2; 95% CI, 1.8 to 5.5) and overestimated measured GFR in non-Blacks (median, 3.9 ml per minute per 1.73 m^2; 95% CI, 3.4 to 4.4). For all equations, 85% or more of the eGFRs for Blacks and non-Blacks were within 30% of measured GFR. New creatinine–cystatin C equations without race were more accurate than new creatinine equations, with smaller differences between race groups. As compared with the current creatinine equation, the new creatinine equations, but not the new creatinine–cystatin C equations, increased population estimates of CKD prevalence among Blacks and yielded similar or lower prevalence among non-Blacks. The new eGFR creatinine-cystatin equation (age and sex without race) had a smaller bias in Black participants, while other equations such as eGFR creatinine (2021) or eGFR creatinine-cystatin (2012), showed greater bias in Black participants [34].

The NKF-ASN Task Force suggested using the 2021CKD-EPI creatinine-cystatin equation, since it does not include a variable for race group. The eGFR equations for creatinine alone and in combination with cystatin C (eGFR creatinine-cystatin), which was solely corrected for age and gender, were verified by the CKD-EPI Consortium. The Organ Procurement Transplantation Network (OPTN) and the Leadership of the United States Pathology and Laboratory Society have both accepted it and unanimously agreed to apply the new race-neutral formula [35]. The new eGFRcr-cys 2021 equation minimized inaccuracy for different race groups, differences in eGFR between race groups, and differences in estimated CKD prevalence. More frequent use of eGFRcr-cys may improve the accuracy of CKD diagnosis and GFR staging while eliminating the use of race in GFR estimating equations. The addition of race as a variable did not improve the performance of the cystatin C–based equation in the black sub group. Given the difficulties in assigning race and the lack of information about race in laboratory and administrative databases, a GFR estimating equation that does not require race may be more generalizable across populations and could greatly facilitate the use of estimated GFR in clinical practice, research, and public health programs. This equation is more accurate and led to smaller differences between Black participants and non-Black participants than new equations without race with either creatinine or cystatin C alone.

The limitations are that categorization of race into two groups does not adequately represent the diversity within and among racial groups, some of the included studies that were used in the development of the equations are old, and none were in representative populations. The Black participants are small in number than non-Black participants in the validation set, so the accuracy may be less precise in Black persons, and had an insufficient representation of racial and ethnic groups other than Black and White. The studies involved only ambulatory adult population without serious coexisting conditions and most of the patients in the study were White population. The sample size was moderate, and only a small number of patients had a GFR of less than 30mL/min/1.73 m^2. The equation that included age and sex and excluded race, underestimated the eGFR in Black people whereas overestimated in non-Black people.

Table 4 CKD-EPI Equation (Chronic Kidney Disease Epidemiology Collaboration Equation)

CKD-EPI Creatinine equation (2009) *	$eGFR = 141 \times \min(Scr/k, 1)^{\alpha} \times \max(Scr/k, 1)^{-1.209} \times 0.993^{Age} \times a \times b$
CKD-EPI Creatinine - Cystatin Equation (2012) **	$eGFR = 135 \times \min(Scr/k, 1)^{\alpha} \times \max(Scr/k, 1)^{-0.601} \times \min(Scys/0.8, 1)^{-0.375} \times \max(Scys/0.8,1)^{-0.711} \times 0.995^{Age} \times a \times b$
CKD – EPI Creatinine Equation (2021) ***	$eGFR = 142 \times \min(Scr/k,1)^{\alpha} \times \max(Scr/k,1)^{-1.200} \times 0.9938^{Age} \times 1.012$ (if female)
CKD-EPI Creatinine- Cystatin Equation (2021) ****	$eGFRcr\text{-}cys = 135 \times \min(S\ cr/\kappa, 1)^{\alpha} \times \max(S\ cr/\kappa, 1)^{-0.544} \times \min(S\ cys/0.8, 1)^{-0.323} \times \max(S\ cys/0.8, 1)^{-0.778} \times 0.9961^{Age} \times 0.963$ [if female]

Abbreviations: * α - Coefficient dependent on sex: -0.329 for females, -0.411 for males; k - Coefficient dependent on sex: 0.7 for females, 0.9 for males; a - Coefficient dependent on sex: 1.018 for females, 1 for males; b - Coefficient dependent on race: 1.159 for black, 1 for others, Scr - Serum creatinine in mg/dL. ** α - Coefficient dependent on sex: -0.248 for females, -0.207 for males; k - Coefficient dependent on sex: 0.7 for females, 0.9 for males; a - Coefficient dependent on sex: 1.969 for females, 1 for males; b - Coefficient dependent on race: 1.08 for black, 1 for other; Scr - serum creatinine in mg/dL; and Scys - Serum cystatin C in mg/L. *** Scr - Serum creatinine in mg/dL, k- 0.7 if female or 0.9 if male; α- - 0.241 if female or -0.302 if male, min is the minimum and max is the maximum. ****S cr - Serum creatinine in mg/dL κ - 0.7 (females) or 0.9 (males) α - -0.219 (females) or -0.144 (males) min (Scr/κ, 1) - Minimum of S cr/κ or 1.0, max (Scr/κ, 1) - Maximum of S cr/κ or 1.0, Scys- Serum cystatin C in mg/L, Age - Years

2.8. eGFR Equations- FAS and Xiangya

2.8.1. eGFR FAS:

The CKD-EPI equation based on serum creatinine developed in 2009 and recommended by the 2012 KDIGO guideline for assessing GFR was not ideal in the Chinese healthy population due to few sample study of Asians and a certain number of patients with chronic kidney disease in the development dataset **[**36**].** In 2016, Pottel et al. developed a full-age-spectrum (FAS) equation recruiting 6,870 healthy European subjects, which had continuity throughout the age spectrum and avoided conversion for estimation equations between different age groups [37].

2.8.2. eGFR Xiangya

Xiangya equation was developed based on a multi-ethnic Chinese population in 2019, considering the influence of race on the accuracy of FAS equations [38]. Lue Wei et al. investigated the application of the CKD-EPI, FAS, and Xiangya equations for the estimation of eGFR in the Chinese healthy individuals and noticed the eGFR trend with aging and examined the rate of decrease in each age group using general linear regression analysis [39]. Estimated GFR_{FAS} remains steady in the population between the ages of 18 and 39 and decreased by the age of 40 years and above. When compared to men, the eGFR level of females was higher after adulthood, but their aging process was faster [40]. Additionally, 40 years old was found to be the lowest infection point of falling GFR with aging by Pottel et al. in a meta-analysis [41]. In the meantime, the eGFR level determined by the Xiangya equation was lower, particularly in younger adults. The discrepancies in GFR trends with age could potentially impact the precision of the Xiangya equation, leading to notable disparities between Xiangya and the other two equations among individuals in good health. After the age of 18, the eGFR by CKD-EPI and the Xiangya equation began to decrease. In healthy individuals, the trend of eGFR with aging was different by CKD-EPI, FAS, and Xiangya equations. It would be necessary to take these equations or age-related differences into consideration when assessing kidney function in the Chinese population.

The drawback is that these equations produce diverse and non-comparable values. The FAS and Xiangya equations are not frequently used in clinical practice because there is insufficient data to support them as well as guideline recommendations. Few studies have examined the age-related trend in eGFR by using the aforementioned equations in the healthy population to date. Additional research may yield specific guidelines for clinical practice for assessing kidney function. The assessment is expensive and intricate to be performed frequently on healthy people. Furthermore, no Black patients were included.

2.9. EKFC -Creatinine Equation

In 2021, Pottel et al. developed and validated the new creatinine-based European Kidney Function Consortium (EKFC) equation by combining the features of the FAS and CKD-EPI equations, which can be applied to the full spectrum of age and renal function [42]. This equation is an advancement of the FAS equation. They reported that the overall bias of the EKFC equation was lower than that of the 2009 CKD-EPI equation for Europeans, whereas the bias was greater for Americans according to Levey et al [43].

Tae-Dong et al. assessed the EKFC equations efficacy in the Korean population, investigated 1,654 Korean patients who were 18 years and above, and compared them with the CKD-EPI equations of 2009 and 2021. The eGFR is calculated, and among the three eGFR equations assessed, the EKFC equation showed the least bias, however, the bias of the 2021 CKD-EPI equation was significantly greater than the 2009 CKD-EPI equation in Koreans. The prevalence of CKD varied among the Korean population, according to the eGFR equations. There was a noticeable difference in the proportion between the CKD-EPI and the EKFC equations among the population [44]. For example, the proportion of the CKD stage 3 eGFR category was 3.4% for the 2009 CKD-EPI equation, 2.6% for the 2021 CKD-EPI equation, and 5.1% for the EKFC equation. Li Zhaoa et al. evaluated the GFR CKD-EPI and GFR EKFC in CKD patients and assessed the diagnostic performance of the two equations, and a comparison was made with the standard technique for determining measured GFR (mGFR). With a correlation coefficient of 0.95 and a regression equation of GFR_{EKFC} =mGFR×0.87, they found a substantial association between GFR_{EKFC} and mGFR. The median bias of the EKFC equation was larger in the eGFR>60 mL/min/1.73 m^2 subgroup than in the eGFR ≤ 60 mL/min/1.73 m^2 subgroup and it was higher than that of the CKD EPI equation [45].

There are few studies on creatinine-based GFR_{EKFC} equations, mostly limited to White populations is the major disadvantage. Although the EKFC equation performance in Koreans investigated the clinical impact in the prevalence of CKD in the Korean general population, the sample size was not sufficient and the study included adult CKD patients, its accuracy in child populations has not been established, Furthermore, external validation studies are needed to verify the clinical application of the EKFC equation. The performance of the e GFR equations can be affected by a number of factors, such as the characteristics of the participants, the methods used to estimate m GFR, and the uncertainty in the measurement of serum creatinine concentration.

Table 5 eGFR FAS, eGFR Xiangya and EKFC -Creatinine Equation

$eGFR_{FAS:}$ (2016)	eGFR=107.3/(Scr/QScr) (for 2≤age≤40 years), eGFR=107.3/(Scr/QScr) × 0.988(age−40) (for age>40 years)
$eGFR_{Xiangya}$ (2019)	eGFR= 2374.78× $Scr^{-0.54753}$× $age^{-0.25011}$× (0.85 26126 if female).
EKFC -Creatinine Equation (2021)	107.3 × (Scr/Q) -0.322 (2-40 years), Scr/Q <1 107.3 × (Scr/Q) -1.132 (2-40 years), Scr/Q ≥ 1 107.3 × (Scr/Q) -0.322× 0.990 age-40 (> 40 years) Scr/Q< 1 107.3 × (Scr/Q) -1.322 × 0.990 age-40 (> 40 years) Scr/Q≥ 1

Abbreviations : Scr- Serum creatinine, (female: QScr=0.70 mg/dL; male: QScr=0.90 mg/dL), Age- Years Q value calculations for ages between 2 and 25 years: Males: (Q) = 3.200 + 0.259 × Age - 0.543 × (Age) - 0.00763 ×Age2 + 0.0000790 ×Age3 Females: (Q) ¼=3.080 + 0.177 × Age - 0.223× (Age) - 0.00596 × Age2 + 0.0000686×Age3 Q value calculations for ages greater than 25 years: Males: Q = 80 µmol/L (0.90 mg/dL), Females: Q = 62 µmol/L (0.70 mg/dL).

2.10. e GFR Equations: C MDRD and Ma Equation

The Chinese-adapted MDRD equation (C-MDRD), was developed in 2006 and shown to perform better in the Chinese individuals than other MDRD equations [46]. Ma equation was developed in 2007 and is based on creatinine and cystatin C data from the Chinese population [47]. It was discovered that the Ma equation outperformed the C-MDRD equation, particularly in the early identification of chronic kidney disease [48]. Two Chinese equation studies, the C-MDRD equation, and the Ma equation, were based on CKD patients, with eGFR always playing a role in screening the patients.

The major limitation of the study is that it is restricted to the Chinese population, and all the participants were recruited from the hospital, very few people in the population were in perfect health. There are only a few participants with significantly decreased muscle mass or malnutrition. Additionally, neither Black nor other Asian populations are studied.

2.11. e GFR Equations in children

2.11.1. Schwartz Equation

The original Schwartz eGFR formula was created in the mid-1970s to estimate GFR in the pediatric population. In 2009, Schwartz et al. introduced an updated eGFR formula using data from a cohort of children in the Chronic Kidney Disease (CKiD) study. This model is suitable for children aged 1 to 16 years. The linear regression analyses generated a model that incorporates height, serum creatinine, cystatin C, blood urea nitrogen (BUN), and gender [49]. Due to the complexity of this formula, a "bedside" version was created that only necessitates height and creatinine levels. The equation is, eGFR = k x (height/serum creatinine), where k is 0.45 in infants (<1 year), 0.55 in 1–12-year-olds and adolescent girls, 0.7 in adolescent boys, 0.413 in CKiD (children with chronic kidney disease), 36.5 in males aged above 13 years, and 32.5 in others.

The revised eGFR equation in 2009 is effective, especially with enzymatic serum creatinine measurement. In a cohort of 168 CKiD patients followed for one year, this formula demonstrated favourable results when compared to previously established equations for paediatric populations. It offers a reliable approximation of the estimated GFR equation. Further research involving children with elevated GFR levels is essential to confirm the applicability of these equations for screening all children for chronic kidney disease.

Table 6 C MDRD, Ma Equation and Schwartz Equation

C-MDRD Equation (2006)	$175 \times Scr^{-1.234} \times age^{-0.179} (\times 0.79$ if female)
Ma Equation (2007)	$169 \times Scr^{-0.608} \times Scys^{-0.63} \times age^{-0.157} (\times 0.83$ if female)
Schwartz Equation (2009)	$eGFR=39.1[height/creatinine]^{0.516}$ $X[1.8/cystatinC]^{0.294}$ $[30/BUN]^{0.169}$ $[1.099]^{male}$ $[height/1.4]^{0.188}$ eGFR = k x (height/serum creatinine) *

Abbeviations: Scr- Serum creatinine, Scys- Serum cystatin, age- years, BUN- Blood Urea Nitrogen * height in cm, and creatinine in mg/dL, k = 0.45 in infants (<1 year), k= 0.55 in 1–12-year-olds and adolescent girls, k= 0.7 in adolescent boys, k= 0.413 in CKiD (children with chronic kidney disease), k = 36.5 in males aged above 13 years and k= 32.5 in others.

The primary limitation of the Schwartz equations for estimating eGFR in children with normal kidney function is that they tend to underestimate the real GFR. This equation should be utilized with a stable creatinine level, as it becomes unreliable when there are rapid fluctuations in serum creatinine. Additionally, it is not applicable for children who have diminished muscle mass, have undergone amputations, experienced cachexia, or using creatine supplements. The eGFR derived from the Schwartz formula tends to overestimate GFR in patients suffering from renal disease. The performance of all creatinine-based formulas is inadequate with significant GFR overestimation, mainly in subjects with mGFR > 75 mL/min/1.73 m^2. Conversely, cystatin C-based or combined formulas have acceptable performance in patients of paediatric nephrology [50]. The extent of overestimation of GFR using the Schwartz formula exhibited an inverse relationship with the level of renal function. Further research involving children with higher GFR values is necessary to confirm the applicability of these formulas for screening all paediatric patients for chronic kidney disease.

3. Conclusion

Clinical laboratories estimate GFR using serum creatinine by the recommendations of the Kidney Disease Outcomes Quality Initiative (KDOQI) and the National Institute for Health and Care Excellence (NICE). Several equations based on creatinine have developed and it is important to note that these equations may either underestimate or overestimate the true GFR in CKD. Accurate assessment of GFR is essential for evaluating the severity and progression of CKD. It is necessary to establish a new equation of diagnostic procedures with external validity for the general population. Hence this review suggests that there may still be a need to identify additional optimal endogenous markers for GFR estimation.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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