Estimation Of Glomerular Filtration Rate: An Update

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Abstract:

Glomerular filtration rate (GFR) estimation is the fundamental component of assessment of renal function. Kidney disease: Improving global outcomes (KDIGO) guidelines define chronic kidney disease (CKD) as decline in GFR of <60 ml/min/1.73m^2 or presence of kidney damage for 3 or more months [1]. GFR can be measured indirectly as the clearance of exogenous filtration markers that are eliminated by the kidney only by glomerular filtration i-e Inulin, Iothalamate, Iohexol, 51Cr-EDTA or 99mTC-DTPA. In routine clinical practice, GFR is assessed from serum concentrations of endogenous filtration markers like Urea, creatinine or Cystatin C.

This review will discuss the different aspects of estimation of GFR and its implications.

Key Words: *Glomerular filtration rate, inulin, cysytacin C, estimation, chronic kidney disease, creatinine.*

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INTRODUCTION

Glomerular filtration rate (GFR) estimation is the fundamental component of assessment of renal function. Kidney disease: Improving global outcomes (KDIGO) guidelines define chronic kidney disease (CKD) as decline in GFR of <60 ml/min/1.73m^2 or presence of kidney damage for 3 or more months [1]. GFR can be measured indirectly as the clearance of exogenous filtration markers that are eliminated by the kidney only by glomerular filtration i-e Inulin, Iothalamate, Iohexol, 51Cr-EDTA or 99mTC-DTPA. In routine clinical practice, GFR is assessed from serum concentrations of endogenous filtration markers like Urea, creatinine or Cystatin C. However, there are many factors which affect GFR estimation by simply measuring concentration of endogenous filtration markers including

generation, renal tubular reabsorption, secretion and extra renal elimination of these markers. These factors are collectively known as non-GFR determinants [2].

GFR ESTIMATION EQUATIONS

GFR estimation equations estimate GFR from plasma levels of endogenous filtration markers and demographic and clinical variables which serve as surrogates for non-GFR determinants. They provide more reliable estimate of GFR than plasma concentration of endogenous markers alone. Estimating equations for GFR are derived in the steady state and therefore, they are more accurate in the steady state than in the non-steady state [2]. More commonly known GFR estimation equations are listed in table 1 [3].

Table 1 – Common GFR estimation equations

Name	Equations
Cockcroft-Gault formula for creatinine clearance	(140 – age) x weight x 0.85 (if female) / 72 x Serum Cr
MDRD equation (4 variable) for use with standardized serum creatinine	$175 \times \text{Scr (mg/dl)}^{-1.154} \times \text{Age}^{-0.203} \times 0.742$ (if female) $\times 1.210$ (if black)
CKD-EPI creatinine equation	$141 \min(\text{Scr}/k,1)^{\alpha} \times \max(\text{Scr}/k,1)^{1.209} \times 0.993^{\text{Age}} \times 1.018$ (if female) $\times 1.157$ (if black) Where k is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, *min* indicates the minimum of Scr/k or 1, and *max* indicates the maximum of Scr/k or 1.
CKD-EPI cystatin C equation	$133 \times \min(\text{Scys}/0.8,1)^{-0.499} \times \max(\text{Scys}/0.8,1)^{-1.328} \times 0.996^{\text{Age}} \times 0.932$ (if female) Where *min* indicates the minimum of Scys/0.8 or 1, and *max* indicates the maximum of Scys/0.8 or 1
CKD-EPI creatinine cystatin C equation	$135 \times \min(\text{SCr}/k,1)^{\alpha} \times \max(\text{SCr}/k,1)^{-0.601} \times \min(S_{cys}/0.8,1)^{-0.375} \times \min(S_{cys}/0.8,1)^{-0.711} \times 0.995^{\text{age}} \times 0.969$ (if female) $\times 1.08$ (black) Where k is 0.7 for females and 0.9 for males; α is −0.248 for females and −0.207 for males; *min* indicates the minimum of Scr/k or 1, or of Scys/0.8 or 1; and *max* indicates the maximum of Scr/k or 1, or of Scys/0.8 or 1.

A well-known bedside Cockcroft-Gault equation was developed in 1976 and it provides an estimate of creatinine clearance rather than measured GFR [4]. Modification of diet in renal disease (MDRD) study equation was originally developed in 1999 based on data collected in MDRD Study and consisted of six variables including age, sex, race, serum creatinine, urea nitrogen and albumin [5]. Later it was simplified to 4 variable equation in 2000 and was re-expressed for use with standardized serum creatinine in 2006 [6]. CKD-EPI creatinine equation was developed from diverse studies including patients with and without kidney diseases, diabetes and renal transplant donors and recipients in 2009 to overcome shortcomings of MDRD study equation and can only be used with standardized serum creatinine [7]. CKD-EPI cystatin C and CKD-EPI creatinine-cystatin C equations were developed in 2008[8] and re-developed and validated in 2012 in a diverse population[9].

LIMITATIONS OF GFR ESTIMATION EQUATIONS

GFR estimation equations are limited by limitations of endogenous filtration markers on which they are based i-e serum creatinine and cystatin C [2]. These limitations are listed in table 2.

Table 2 – Limitation of serum creatinine and cystatin C for GFR estimation

	Serum creatinine	**Serum Cystatin C**
Variation in production	Increased by dietary protein intake and muscle mass	Increased by age, height, weight, male sex, inflammation, diabetes, hyper and hypothyroidism
Variation in secretion	Increased in CKD and nephrotic syndrome Reduced by trimethoprim and cimetidine	
Extra renal secretion	Increased in advanced CKD	
Measurement issues	Cefoxitin, flucytosine, bilirubin and acetoacetate can raise serum creatinine by colorimetric assay Difference in methods and equipment has been addressed by standardization of serum creatinine measurement	Variation in methods and equipment. Standard reference material has been developed

Other than limitations due to endogenous filtration markers, certain GFR estimation equations have inherent limitations due to problems during derivation and variables included in the equation. For example, Cockcroft-Gault equation provides an estimate of creatinine clearance rather than GFR [4]. In addition, it may over-estimate GFR in obese patients since weight is included in the equation. This equation was developed prior to implementation of standardized serum creatinine assays and hence cannot be used with standardized serum creatinine.

MDRD study equation was derived from predominantly white patients with non-diabetic CKD and may be less accurate in ethnicities outside USA. The main limitation to the MDRD Study equation is a systematic bias to underestimate GFR at higher levels and imprecision throughout the range [2].

WHICH GFR ESTIMATION EQUATION HAS THE BEST PERFORMANCE?

In order to assess performance of a GFR estimation equation, various performance characteristics are looked at including bias, precision and accuracy. Bias is defined as the mean difference between measured and estimated GFR. Precision describes the variability of difference around the average difference. Various metrics including standard deviation, variance and interquartile range of difference between measured and estimated GFR can summarize bias. Accuracy incorporates both precision and accuracy. Several metrics including arithmetic difference, percentage difference, mean squared root (MSE) or its square root (RMSE) or percentage of estimates within percentage of measured value like P30 can describe accuracy [2,10].

Some of the landmark studies comparing performance characteristics of various GFR estimation equations are shown in table 3[7,9,11].

In a systemic review by Early et al, CKD-EPI was found to be more accurate and less biased than MDRD study equation in patients with higher GFR (i-e eGFR > 60 ml/min/1.73 m^2). However, MDRD study equation was found to be more accurate and less biased than CKD-EPI equation in patients with lower GFR (i-e GFR < 60 ml/min/1.73 m^2) [12]. In a study by Inker et al, CKD-EPI creatinine-cystatin C equation was found to be the most accurate GFR estimation equation and it also improved the classification of measured GFR as either less than 60 ml per minute per 1.73 m^2 or greater than or equal to 60 ml per minute per 1.73 m^2 (net reclassification index, 19.4%) and correctly reclassified 16.9% of those with an estimated GFR of 45 to 59 ml per minute per 1.73 m^2 as having a GFR of 60 ml or higher per minute per 1.73 m^2 [9].

Table 3 – Studies showing comparison of GFR estimation equations [7,9,11]

Study Reference	Study Population (Validation)	GFR measurement method	GFR estimation equations compared	Bias	Precision	Accuracy (P30)
Levey et al	N=3896, mGFR=68	Urinary clearance of iothalamate or EDTA, plasma clearance of iothalamate	MDRD	5.5	18.3	80.6
			CKD-EPI creatinine	2.5	16.6	84.1*
Inker et al	N=1119, mGFR=70	Urinary clearance of EDTA, plasma clearance of iohexol	CKD-EPI creatinine	3.7	13.4	87.2
			CKD-EPI cystatin C	3.4	15.4	85.9
			CKD-EPI creatinine-cystatin C	3.9	16.4	91.8*
Stevens et al	N=5508, mGFR = 68	Urinary clearance of iothalamate	MDRD	5.8	16.4	83

- * P value <0.05

In summary, CKD-EPI creatinine cystatin C is the most accurate GFR estimation equation, whereas CKD-EPI creatinine equation is more accurate than MDRD study equation especially in patients with eGFR > 60 ml/min/1.73 m^2.

WHICH GFR ESTIATMION EQUATION HAS THE BEST PROGNOSTIC VALUE?

An important question is that other than accuracy, which GFR estimation equation can best predict

Table 4 – GFR estimation equations in patients with cirrhosis [24-26]

	New GFR estimation equations in patients with cirrhosis
eGFR equation by Cholongitas	163 − [creatinine × (19.6)] − [cysC × (11.8)] – [age × (0.86)]
Royal Free Hospital GFR	45.9 × (creatinine$^{-0.836}$) × (urea$^{-0.229}$) × (international normalized ratio$^{-0.113}$) × (age$^{-0.129}$)
eGFR equation by Mindikoglu	105.49 * (serum creatinine$^{-0.712}$) * (serum cystatin C$^{-0.285}$) * (0.993^{age}) * (0.864^{female}) * (1.014$^{African-American}$) (Use 1 if female or African-American, otherwise 0)

the risk of death, cardiovascular event or end stage renal disease. In a meta-analysis of data of 1.1 million adults, 34.7% of participants with eGFR 45-59 ml/min/1.73 m^2 by MDRD study equation were classified to higher eGFR of 60-89 ml/min/1.73 m^2 by CKD-EPI equation and these patients had lower rates of death, cardiovascular event and end stage renal disease (ESRD). So creatinine based CKD-EPI equation resulted in fewer patients with CKD and more accurately categorized the risk of mortality and ESRD than did MDRD study equation [13]. In another study, compared with GFR estimated using the MDRD equation, GFR estimated using the CKD-EPI equation added more predictive power to the risk of heart failure in diabetic patients along with the other risk factors. Also, CKD-EPI equation provided more accurate heart failure risk stratification than MDRD equation [14]

In a subsequent study of 16 cohorts, across all eGFR categories, the reclassification of the eGFR to a higher value with cystatin C based CKD-EPI equation (alone or combined cystatin C creatinine equation), as compared with creatinine, was associated with a reduced risk of death, cardiovascular mortality and end stage renal disease, and reclassification to a lower eGFR was associated with an increased risk [15]. In a study by Blanco et al of 350 subjects with Non- ST elevation MI, cystatin C based GFR CKD-EPI equations were found to be independent predictor of mortality compared to CKD-EPI creatinine equation [16].

In summary, cystatin based CKD-EPI equations have better prognostic value compared to CKD-EPI creatinine equation, which by its self has superior prognostic value compared to MDRD study equation.

RECOMMENDATIONS BY KDIGO GUIDELINES

A brief summary of KDIGO 2012 guidelines for evaluation and management of chronic kidney disease concerning GFR estimation is listed below [1]

- Measure serum creatinine or Cystatin C using an assay with calibration traceable to international standard reference material.
- Report $eGFR_{creat}$ in adults using the 2009 CKD-EPI creatinine equation.
- Report $eGFR_{cys}$ and $eGFR_{creat-cys}$ in adults using the 2012 CKD-EPI cystatin C and 2012 CKD-EPI creatinine-cystatin C equations, respectively.
- Measure cystatin C in adults with $eGFR_{creat}$ 45-59 ml/min/1.73m^2 who do not have markers of kidney damage if confirmation of CKD is required
    - If $eGFR_{cys}$/$eGFR_{creat-cys}$ is also < 60 ml/min/1.73 m^2 then diagnosis of CKD is confirmed.
    - If $eGFR_{cys}$/$eGFR_{creat-cys}$ is >60 ml/min/1.73 m^2 then diagnosis of CKD is not confirmed.
- Measure GFR using an exogenous filtration marker under circumstances where more accurate ascertainment of GFR will impact on treatment decisions (i-e organ donation, dosing of toxic drugs etc.)

ESTIMATING GFR IN SPECIAL POPULATION

CHRONIC LIVER DISEASE

GFR estimation based on serum creatinine may not be reliable in patients with chronic liver disease as multiple factors including reduced muscle mass, malnutrition, high bilirubin and low serum albumin may affect serum creatinine measurement in these patients [17]. Serum Cystatin C may be a more sensitive marker than serum creatinine in detecting patients with reduced eGFR , however studies addressing its superiority over serum creatinine in patients with cirrhosis have shown conflicting results [18,19]. Recently, studies of CKD-EPI cystatin C based equations in patients with cirrhosis have shown more promising results. In a study of 202 patients with cirrhosis, cystatin C based CKD-EPI GFR estimation equation was found to have superior accuracy (P30 83.2%) compared to that of 42.6%, 58.4% and 56.4% for MDRD4, MDRD6 and CKD-EPI creatinine eGFR equations respectively [20]. In a study of 72 subjects with cirrhosis, CKD-EPI creatinine cystatin C equation was found to be more accurate than other equations including creatinine clearance, cock-croft gault, MDRD and CKD-EPI equations based on measurement of either serum creatinine or cystatin C alone [21]. This finding was confirmed in another study of 50 patients, which showed that CKD EPI creatinine-cystatin C equation has the least bias compared to other creatinine based eGFR equations [22]. GFR estimation by CKD-EPI Cystatin C equation was significantly associated with death (HR 1.24, 95% CI 1.02-1.50) in patients with cirrhosis, whereas no such association was found with MDRD or other CKD-EPI equations [23].

Other researchers have developed new eGFR equations with better performance characteristics in patients with cirrhosis. Mindikoglu eGFR equation was found to be more accurate than CKD-EPI cystatin C based equations [22]. A subsequent equation developed by Cholongitas et al. showed lower bias but similar precision and accuracy compared to Mindikoglu eGFR equation [24]. These equations are shown in table 4 [24 – 26]. Other than Mindikoglu eGFR equation, the remaining two equations have not been validated in independent population.

In summary, cystatin based CKD-EPI eGFR equations especially CKD-EPI creatinine-cystatin C equation appears to be more dependable in assessing kidney function in patients with chronic liver disease. The newer eGFR estimation equation seems to have even better performance characteristics but they will like need validation in independent patient population.

OBESE PATIENTS

GFR estimation equations were primarily derived from non-obese patients so validation of these equations in obese patients has been the subject of various studies. Cockcroft-Gault equation is well known to over-estimate GFR in obese patients since body weight is incorporate in its formula. Several studies have compared both CKD-EPI creatinine and MDRD equations in obese patients as a subgroup analysis. In a study by Stevens et al., CKD EPI equation has a lower bias in 951 patients with BMI > 30 kg/m^2 ,but precision and accuracy were not specified which limits interpretation of results [27]. Other studies have found no difference in accuracy between CKD EPI

and MDRD equation in obese sub- groups [28 - 30]. However, these studies were limited due to analysis of obese patients as sub-groups and inclusion of patients with only moderate obesity. A subsequent study of 209 obese CKD patients confirmed that CKD-EPI creatinine equation has a good accuracy (P30 was 78% for measured GFR and 84% for measured GFR indexed for ideal body weight) and a low bias (0.29, 95% CI -1.7 to 2.3). The bias was least if measured GFR was indexed for ideal body weight rather than real body weight. But no comparison with MDRD study equation was made in this study [31]. However, a French study of 366 obese patients showed that MDRD equation had a lower bias (+1.9±14.3 vs. +4.6±14.7 ml/min/1.73 m^2) and better accuracy (P30 80% vs. 76%) than CKD-EPI equation, though difference in accuracy was not significant in patients with measured GFR > 60 ml/min/1.73 m^2 [32].

Cystatin C can be elevated in obese patients so it' s utility alone or in an eGFR estimation equation has been questioned in obese population. But recent studies have shown superiority of cystatin based CKD-EPI GFR equations compared to CKD -EPI creatinine equations in obese patients. In severely obese 36 bariatric surgery patients, CKD-EPI creatinine cystatin C equation provided the most accurate estimate of GFR (P30 over 80%) among the three CKD EPI equations [33]. Similarly, Lemoine et al showed that de-indexed cystatin based CKD-EPI equations outperform CKD-EPI creatinine equation in 166 obese CKD patients especially in women and those with BMI > 35 kg/m^2 [34].

In summary, CKD-EPI creatinine and MDRD equations appear to have comparable accuracy, while cystatin C based CKD EPI equations especially CKD-EPI creatinine-cystatin C may be the most accurate GFR estimation equation in patients with obesity similar to what has been found in general population.

ELDERLY POPULATION

In a study by Kilbride HS, CKD-EPI creatinine based equation was less biased and more accurate than MDRD equation in patients 74 years or older, though none of the equations reached ideal P30 [35]. In a study by Matsushita et al, CKD-EPI creatinine based equation more accurately classified patients into correct GFR stages than did MDRD study equation in subgroup of patients > 65 years [13]. Similarly, another meta-analysis of similar cohorts showed that CKD-EPI creatinine-cystatin C and cystatin C equations reclassified patients with CKD more accurately than did CKD-EPI creatinine in general population and in sub-group with ages > 65 years [15].

Table 5 – Berlin initiative study equations in elderly population [38]

	BERLIN INITIATIVE STUDY EQUATION
BIS 1	$3736 \times \text{creatinine}^{-0.87} \times \text{age}^{-0.95} \times 0.82$ (if female)
BIS 2	$767 \times \text{cystatin C}^{-0.61} \times \text{creatinine}^{-0.40} \times \text{age}^{-0.57} \times 0.87$ (if female)

Two novel equations were developed to estimate GFR in elderly patients aged 70 years or older in a study by Shaeffner ES at el. These two equations, Berlin initiative study equations (BIS) 1 and 2 are shown in table 5. BIS2 has the smallest bias (50.4%) and has smallest misclassification rate (11.6%) compared to other equations including cock-craft gault, MDRD, CKD-EPI creatinine and CKD-EPI cystatin C equations [36]. In a subsequent study by Lopes et al, CKD EPI creatinine-cystatin C equation and BIS creatinine-cystatin C equations showed better accuracy (85% and 83% respectively) compared to other equations [37]. In a larger study of 805 elderly patients, Japanese, BIS and Caucasian and Asian pediatric and adult subjects (CAPA) equations were not superior to CKD-EPI equation and among CKD-EPI equations, CKD-EPI creatinine-cystatin C equation had better performance compared to other equations [38]. CKD-EPI creatinine-cystatin C and CKD-EPI cystatin C equations were found to best predict mortality and cardiovascular events in elderly patients compared to BIS, MDRD and CKD-EPI creatinine equations [39].

In summary, CKD EPI creatinine-cystatin C equations appears to be accurate in elderly population, while BIS equations especially BIS2 equation is an acceptable alternative.

PAKISTANI POPULATION

A study was done in 581 patients of age 40 years or above from randomly selected low to middle income communities in Karachi. Among 581, 40 patients were enrolled from renal clinic who had serum creatinine > 2.0 mg/dl. GFR was measured by urinary clearance of inulin. Compared to MDRD study equation, CKD-EPI creatinine equation was more accurate (P30 – 76.1% vs. 68%) especially in patients with eGFR >90 ml/min/1.73 m^2. A modified CKD-EPI$_{PK}$ ($0.686 \times eGFR_{CKD\text{-}EPI}^{1.059}$) has even improved accuracy (P30 81.6%). Of note, accuracy of CKD-EPI, CKD-EPI$_{pk}$ and MDRD study equation was comparable among patients with eGFR <90 ml/min/1.73 m^2 [40].

Other than Pakistani population, CKD-EPI equation has been found to be valid in other Asian populations including Chinese, Thai, Japanese, Taiwanese and Arabic population [41].

SUMMARY

CKD-EPI creatinine is more accurate than MDRD study equation. CKD-EPI creatinine-cystatin C equation is the most accurate GFR estimation equation. GFR estimation based on Cystatin C (CKD-EPI cystatin C or CKD-EPI creatinine-cystatin C best predicts the risk of mortality, cardiovascular mortality and ESRD. CKD-EPI creatinine has better risk prediction than MDRD study equation. KDIGO guidelines recommend GFR estimation using CKD EPI equation for serum creatinine and/or both serum creatinine and cystatin C (if available). Cystatin C based GFR estimation is recommended to confirm the diagnosis of CKD if eGFR by CKD-EPI creatinine is between 45-60 ml/min/1.73m^2 and there are no markers of kidney damage. In Pakistani population, CKD-EPI creatinine is more accurate than MDRD study equation and CKD-EPI$_{PK}$ improves the accuracy of GFR estimation.

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