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Review Article

Equations for Glomerular Filtration Rate Estimation

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Abstract

Different authorities and guidelines recommend creatinine based Glomerular Filtration Rate (GFR) estimation (eGFR) besides measurement of creatinine. In the last few years it has become routine to estimate and classify kidney function using equations based on serum creatinine. Creatinine alone is not enough detecting early stage of renal failure in Acute Kidney Injury (AKI) and Chronic Kidney Disease (CKD). A decrease in GFR precedes the onset of renal failure. Creatinine based GFR estimation equations are useful in staging of CKD, monitoring disease progression and dose adjustment in impaired renal function. Among various GFR estimation equations Cockcroft- Gault and Modification of Diet in Renal Disease (MDRD) equations are commonly used. The 2009 Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation is new and has overcome some limitations of other equations. In this article we discuss different commonly used equations.

Key words: *eGFR, CKD, MDRD*

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Introduction

The Glomerular Filtration Rate (GFR) is traditionally considered the best overall index of kidney function**.** In 2002, the National Kidney Foundation (NKF) Kidney Disease Outcome Quality Initiative (K/DOQI) clinical practice guidelines on chronic kidney disease recommends estimating the level of GFR by employing prediction equations that incorporate serum creatinine measurements.[1] This method of determining GFR was judged preferable to using serum creatinine alone or measuring creatinine clearance. Gold standard tests for measurement of renal function include the inulin clearance assay and the 125I-iodothalamate clearance assay. Unfortunately, performing these tests is difficult, and they are not available in most medical laboratories. Instead, the focus has traditionally been on serum creatinine level and on the 24 hours creatinine clearance. The National Kidney Disease Education Program (NKDEP) of the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) in United States. National Kidney Foundation (NKF) of United States and American Society of Nephrology (ASN) recommend estimating GFR (eGFR) from serum creatinine. Estimated GFR is important in assessing the excretory function of the kidneys. For example, grading of chronic renal insufficiency and dosage of drugs that are primarily excreted via urine are based on GFR (or creatinine clearance).

Methods of creatinine measurement influence GFR estimation. Several mathematical formulae have been developed to estimate GFR (eGFR) from the creatinine concentration and parameters such as the patient's age and sex. Jelliffe (1971), Mawer (1972), Jelliffe (1973), Cockcroft -Gault (1976), Hull (1981), Bjornsson (1983), Gates (1985), Levey (1999), Levey (2000)and many other equations are available. Most widely used are the Cockcroft Gault (CG) and the Modification of Diet in Renal Disease (MDRD) formulae.[7] Subsequent studies have shown that CG tends to over-estimate renal function, especially, at lower levels[4] whilst MDRD under-estimates GFR particularly at near normal levels of function. Several studies[10] have demonstrated the superiority of MDRD for screening in a variety of different populations and it is now advocated as the method of choice in the UK (Department of Health, 2005).

A new equation, the CKD-EPI (CKD Epidemiology collaboration) equation by Andrew S Levey in 2009 is better than others in terms of accuracy, less bias and applicability to all races. So the goal is to evaluate the number of commonly used equations for GFR.

Discussion

Creatinine is not a very sensitive marker at early stage of renal failure. A decrease in GFR precedes the onset of renal failure. Estimated GFR (eGFR) by different equations obviates need of GFR measurement in many cases. There are no fewer than 46 different prediction equations currently available, although the two most commonly used are the Cockcroft-Gault and the "Modification of Diet in Renal Disease" (MDRD) formulae.[2] CKD Epidemiology Collaboration (CKD EPI) formula is the latest and claimed to be better than all others, and is being used in every countries including Bangladesh.

Cockcroft-Gaultformula[3]

The first more widely spread formula used to estimate renal function is the Cockcroft-Gault formula.

$$GFR\ (ml/min) = \frac{(140 - \text{age in years}) \times \text{weight (in kg)} \times (0.85 \text{ if female})}{72 \times S.Cr\ (mg/dl)}$$

The Cockcroft and Gault formula was developed in 1973 (published in 1976), using data from 249 men aged 18-92 with creatinine clearance (C_{Cr}) from approximately 30 to 130 mL/m^2. The Cockcroft-Gault formula estimates the creatinine clearance, which is not corrected by body surface area, and thus the absolute value of the filtration rate. Due to the increased creatinine secretion, the creatinine clearance usually overestimates GFR when the GFR is low. There are several limitations to the C-G equation. The reference GFR was the 24-hours-urine creatinine clearance (C_{Cr}), so the predicted value of C-G equation is actually surrogate of creatinineclearance rate.In most of the comparative analysis performed; it is shown that the classical CG equation overestimated glomerular filtration.[4, 5] The sample size was small and all of them were male, 15% reduction was proposed for women.

MDRD (Modification of Diet in Renal Disease) study equation[6, 7]

The MDRD (Modification of Diet in Renal Disease) Study equation was developed in 1999 using data from 1,628 patients with CKD with GFR from approximately 5 to 90 ml/min/1.73 m^2. It estimates GFR adjusted for body surface area and is more accurate than measured creatinine clearance from 24-hours urine collections or estimated by the Cockcroft and Gault formula. The formula was developed from the MDRD study, which consisted of non-transplanted CKD-patients with non-diabetic renal disease.

The abbreviated, or four-variable equation includes age, sex, creatinine, and race (black or not black). Adding more variables (albumin, urea) adds little to accuracy.

4 variable MDRD equation:

$$eGFR = 186 \times (SCr)^{-1.154} \times (age)^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if black})$$

6 variable MDRD equation:

$GFR=170x(SCr)^{-0.999}x\ (age)^{-0.176}\ x[0.762\ if\ female]x\ [1.180\ if\ black]\ x\ BUN^{-0.170}\ x\ Albumin^{+0.318}$

The MDRD equation was re-expressed in 2006. The new equation is adjusted to a standardized creatinine calibration which gives approximately 5% lower values of the S-Cr.[8, 9]

Re-expressed MDRD equation

$GFR = 175\ x\ (Standardized\ S\text{-}Cr)^{-1.154}\ x\ (age)^{-0.203}\ x\ (0.742\ if\ female)\ x\ (1.210\ if\ African\ American)$

For individuals of African or Caribbean descent the eGFR value obtained should be multiplied by a factor of 1.2 to reflect a greater inherent muscle mass. All other races are to use the basic formula provided. The MDRD does not require the input of height or weight variables and avoids inaccuracies introduced through these measures. It also has been standardized to a 1.73 m^2 body surface area (BSA) which is the normal average for young adults. Adjusting the formula for BSA allows comparisons of an individual's result with age/sex/race appropriate norms. In doing so it also provides a convenient means to compare an individual's renal function to defined stages of CKD.

The MDRD formula is not considered applicable to individuals age <18 years, those with rapidly changing kidney function such as individuals experiencing acute renal failure, pregnant females, oedematous states such as Congestive Heart Failure(CHF), individuals with muscle wasting diseases-rhabdomyolysis, recent trauma, amputees, paraplegics, quadriplegics, malnourished individuals and those at both extremes of body size (BMI). In the above circumstances, a 24 hours creatinine clearance is acknowledged to provide a better estimate of the GFR. MDRD study equation has been derived based on GFR measured using an accepted method (urinary clearance of 125I-iothalamate or traceable to an isotope dilution mass spectrometry (IDMS) reference method, hence, it estimates GFR rather than creatinine clearance.

Several studies have shown that in "low-risk" populations, such as living kidney donors or individuals with early diabetes, the MDRD equation systematically underestimated GFR, particularly in patients with high-normal serum creatinine levels.[10,11] One caveat is that the MDRD formula tends to provide falsely low estimates in young healthy individuals (especially well muscled males).[12] In fact, some authorities suggest routine reporting of specific eGFR values >60 ml/min/1.73 m^2 is not recommended.[13] Again, this issue arises as the MDRD has not been validated for screening in healthy normal individuals. Its use should be restricted to screening those at risk of CKD and those with known CKD to gauge severity and ascertain prognosis.[14] Rule AD found the MDRD equation underestimated GFR by 6.2% in patients with chronic kidney disease and by 29% in healthy persons.[11]

Many studies have compared the performance of the two equations to measured GFR. In some of these studies, the MDRD Study equation was more accurate than the Cockcroft and Gault equation. Other studies demonstrated similar performance. The Cockcroft and Gault equation appears to be less accurate than the MDRD Study equation, specifically in older and obese people.[15]

The Mayo Clinic's Quadratic Equation

The Mayo clinic quadratic equation is a new equation developed by Rule AD and Larson TS et.al. at the Mayo Clinic, a tertiary-care medical centre based on the results of iothalamate clearance in both 320 patients with chronic kidney diseases and 580 healthy subjects evaluated for kidney donation .

The Mayo quadratic equation was further shown to have similar diagnostic performance to the MDRD equation in diabetic patients; in contrast to MDRD equation, the Mayo quadratic equation does not underestimate normal GFR in diabetic subjects.[16]

CKD-EPI Formula

The CKD Epidemiology Collaboration (CKD-EPI) equation was published in 2009 and intended to be more generalizable across various clinical settings than the MDRD equation. It has developed from a large database of participants in research studies and patients from clinical populations with diverse characteristics including those with or without kidney disease, diabetes and history of organ transplantation to overcome limitations of the MDRD study equation. CKD-EPI produces higher eGFR values in the high eGFR range (>60 ml/min/1.73 m2), and lower eGFR values in the lowest range.[17] Weight, diabetes, and transplant were considered as potential variables, but the final equation uses the same variables as the MDRD equation.[18] By CKD-EPI equation median estimated GFR was 9.5 ml/min/ 1.73 m^2 higher, which decreases the prevalence estimate for chronic kidney disease by 1.6% (11.5% vs. 13.1% using the MDRD Study equation) in US population.

The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula developed is represented as the equation below, in which the values of the constants of *a*, *b*, and *c* vary on the basis of race, sex, and serum creatinine.

$$\mathbf{GFR} = a \times (\text{serum creatinine}/b)^{c} \times (0.993)^{\text{age}}$$

The variable *a* takes on the following values on the basis of race and sex:

- Black
  - Women = 166
  - Men = 163
- White/other
  - Women = 144
  - Men = 141

The variable *b* takes on the following values on the basis of sex:

- Women = 0.7
- Men = 0.9

The variable *c* takes on the following values on the basis of sex and creatinine measurement:

- Women
  - Serum creatinine ≤ 0.7 mg/dL = -0.329
  - Serum creatinine> 0.7 mg/dL = -1.209
- Men
  - Serum creatinine ≤ 0.9 mg/dL = -0.411
  - Serum creatinine> 0.9 mg/dL = -1.209

Authors concluded: The CKD-EPI creatinine equation is more accurate than the MDRD. Study equation and could replace it for routine clinical use. The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend that clinical laboratories report eGFR in all adults using CKD-EPI creatinine equations, or using other equations if shown to be superior to CKD-EPI equation in that population.[19]

Schwartz's Formula

Schwartz and colleagues[20]originally published a formula to estimate glomerular filtration rate (GFR) in children in 1976, the same year that Cockcroft and Gault published what became the canonical estimation formula for creatinine clearance in adults.

Original Schwartz Formula

GFR (mL/min/1.73 m^2) = k× (Height) / Serum Creatinine

k = Constant

o k = 0.33 in Preemie Infants

o k = 0.45 in Term infants to 1 year old

o k = 0.55 in Children and adolescent girls

o k = 0.65 in Adolescent males (Not females because of the presumed increase in male muscle mass. The constant remains 0 .55 for females.) Height in cm,Serum Creatinine in mg/dl.

A recent report by Schwartz and coworkers has described improved equations for estimating GFR in children [21]. The equations were developed with data collected from 349 children 1–16 years of age with GFRs of approximately20–90 ml/min/1.73 m^2 who were enrolled in the Chronic Kidney Disease in Children (CKiD) study. Like the original equation, the revised equationis based on height and creatinine measurements, but the new equation uses creatinine as measured by an enzymatic method with calibration traceable to an isotope dilution mass spectrometry (IDMS) reference measurement procedure. This updated Schwartz equation has not been validated for use with methods based on the Jaffe (alkaline picrate) reaction.

Revised Schwartz's Equation:

GFR (mL/min/1.73 m^2) = (0.41 × Height in cm) / Creatinine in mg/dL

Conclusion

Pursuit for correcting GFR is continuing. GFR estimating equations using serum Cystatin C, ßTP (ß Trace Protein), $ß_2$M ($ß_2$Microglobulin) has been developed. Until now CKD EPI equation is best recommended for estimating GFR based on creatinine measurement. Application based soft wares for estimation of GFR are available for smart devices. Clinical laboratories and doctors should routinely use creatinine based eGFR besides other tests of kidney function.

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