

The CKD-EPI Equation for Estimating GFR from Serum Creatinine: Real Improvement or More of the Same?

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The Cockcroft-Gault equation was published in 1976 and was widely adopted for estimation of creatinine clearance from serum creatinine levels (1). The equation was developed using two steps: First, urinary creatinine excretion per body weight (UV/kg) was estimated from age in hospitalized patients; creatinine clearance was then calculated by multiplying by weight and dividing by serum creatinine (P) using the standard “UV/P” clearance formula. Not surprising, the high-risk patients who were used to develop the Cockcroft-Gault equation had lower muscle mass (creatinine excretion) than healthier individuals in the general population (2). The lack of a standardized serum creatinine assay has also been considered a problem with the Cockcroft-Gault equation, but this is not the case. Serum creatinine assay calibration has no influence on the coefficients of the Cockcroft-Gault equation, because the regression did not involve serum creatinine. Because the Cockcroft-Gault equation was developed using only white men, however, the model was not optimized to account for gender and race differences in muscle mass. Nonetheless, the Cockcroft-Gault equation is still used widely, particularly for drug dosing, for which estimates in ml/min units are desired. Because the Cockcroft-Gault equation has been used to determine recommended dosages for various medications (3), there is a consistent approach when using this equation to adjust medication dosage. However, the clinician should keep in mind that many dosing recommendations were made prior to serum creatinine standardization.

By contrast, the most widely used GFR-estimating equation today is the Modification of Diet in Renal Disease (MDRD) equation, which was published in 1999 and later simplified (4,5). This equation automatically estimates GFR from serum creatinine for most laboratories (6). This equation was developed using patients who had CKD identified by elevated serum creatinine levels and who had a fourfold higher risk for progressing to ESRD than dying first (7,8). Despite this criterion for the equation population, it has been widely advocated that estimated GFR (eGFR) be reported when <60 ml/min per 1.73 m² instead of when serum creatinine levels are elevated. Subsequently, several studies have shown that in “low-risk” pop-

ulations, 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 (9–11). This suggests that no one equation can accurately estimate GFR regardless of clinical presentation. Studies further showed that the use of an equation that is developed with mostly healthy individuals would lead to a much lower prevalence of an eGFR <60 ml/min per 1.73 m² (12–14).

Despite this problem, 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 (15). Weight, diabetes, and transplant were considered as potential variables, but the final equation uses the same variables as the MDRD equation (16). The source studies that were used for the CKD-EPI equation can be broken down into two groups: High-risk populations such as patients with clinical CKD, characterized by an average measured GFR (mGFR) <90 ml/min per 1.73 m², and low-risk populations such as potential kidney donors, characterized by an average mGFR >90 ml/min per 1.73 m². The CKD-EPI equation was developed using a sample size of 8254, 71% ($n = 5858$) of whom came from high-risk populations. The CKD-EPI equation was externally validated using a sample size of 3896, 72% ($n = 2810$) of whom came from high-risk populations. Not surprising, the CKD-EPI equation performed better in the external validation sample than did the MDRD equation that was derived using only a high-risk population (4,16); however, this validation did not address the underlying problem with the performance of GFR-estimating equations in different populations. The CKD-EPI equation authors recognized this, stating that “a single equation is unlikely to work equally well in all populations” (15). For instance, the CKD-EPI equation leads to a lower prevalence of eGFR <60 ml/min per 1.73 m² in low-risk white women than the MDRD equation (17), but when demographics in GFR-estimating equations start to model CKD risk, this comes at the cost of less optimally modeling muscle mass (2).

In this issue of *CJASN*, Michels *et al.* (18) present a validation analysis of these three equations in a series of clinical patients. Unfortunately, this study adds little insight into equation performance for several reasons: First, the study population was not defined other than as potential kidney donors combined with patients who had a mGFR for “clinical reasons,” but what

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are these clinical reasons? What was the breakdown between these two groups? Do equations perform differently in the potential kidney donors than in the other group? Without knowing the reasons for why a person is referred for a direct GFR measurement, it is difficult to interpret the study findings reported.

Second, analyses were stratified on mGFR (18). This is not valid because linear regression is asymmetric; in other words, the equation that is used to predict Y from X is not simply the inverse of the equation that is used to predict X from Y (19). Estimating equations are derived such that for any level of eGFR, $mGFR > eGFR$ will occur equally as often as $mGFR < eGFR$. Because of this, mGFR will average higher values when $mGFR > eGFR$ than when $mGFR < eGFR$. Thus, $eGFR - mGFR$ will have a negative trend with higher levels of mGFR, as shown in Figure 1 of this study (18). From a clinical perspective, it is not helpful to assess equation performance across levels of mGFR, because, if you knew mGFR, then you would not need to estimate it! Instead, equation performance should be assessed across levels of eGFR (20,21).

Third, the mean absolute difference (the authors use the term “absolute bias”) (18) between mGFR and eGFR requires a more nuanced interpretation. The mean absolute difference will increase with both equation bias and imprecision. Both the MDRD equation and CKD-EPI equation were derived to predict logarithmic mGFR because the logarithmic transformation equalizes model error (imprecision) across levels of eGFR. This is known as the *homoscedasticity* assumption of linear regression (19). It is hard to argue that the increased absolute differences between eGFR and mGFR with higher levels of mGFR is a finding, when equations are derived on a logarithmic scale specifically because of this problem. From a clinical perspective, a difference of 15 ml/min per 1.73 m² is of much greater concern between a GFR of 10 and 25 ml/min per 1.73 m² than between a GFR of 100 and 115 ml/min per 1.73 m². Logarithmic (percentage) error may better reflect meaningful differences between mGFR and eGFR.

Finally, the authors also report that older age was associated with lower absolute differences between eGFR and mGFR (18). This was more prominent with the MDRD equation than with the CKD-EPI equation and may be due to bias with how age was modeled. The MDRD equation, in particular, models the decline in muscle mass (source of creatinine) with age as being steepest in young adults when it is actually steepest in older adults (2,22). This finding may also reflect the increased model error at higher levels of GFR since younger age associates with higher GFR.

Michels *et al.* (18) conclude that the CKD-EPI equation is more accurate than the other two GFR-estimating equations in common use. This conclusion is not really germane for clinical care because it is based on equation performance in some arbitrary combination of low-risk and high-risk patients. Patients present with clinical histories, risk factors, laboratory tests, and examination findings that inform the risk for CKD. The normal decline in GFR with aging does not reflect underlying chronic parenchymal injury on renal biopsy (23). Thus, an elevated serum creatinine level representing a GFR less than

expected with normal aging is a more reasonable approach to screen for CKD than a single eGFR threshold (24). To assess disease severity after a diagnosis of CKD has been made, one can choose between the CKD-EPI equation, which loses some accuracy from the inclusion of low-risk patients, or the MDRD equation, which loses some accuracy from the statistical methods that are used to model age.

Disclosures

None.

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See related article, "Performance of the Cockcroft-Gault, MDRD, and New CKD-EPI Formulas in Relation to GFR, Age, and Body Size," on pages 1003–1009.