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Estimating GFR in the Elderly—New Approaches to an Old Problem

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In the United States, 37 million adults (15%) have predialysis chronic kidney disease (CKD) defined by albuminuria (urine albumin:creatinine ratio ≥30 mg/g) or decreased estimated glomerular filtration rate (eGFR <60 ml/min per 1.73 m^2) by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[1] Nearly half (16.3 million) of those with predialysis CKD are 65 years or older. National surveys use single random measurements of kidney markers and therefore overestimate CKD prevalence by 2 to 3 percentage points, largely due to variability in albuminuria.[S1] Conversely, commonly used eGFR equations, such as the CKD-EPI or Modification of Diet in Renal Disease (MDRD), generally underestimate true glomerular filtration rate (GFR), but may overestimate it in the elderly with low muscle mass.[2] Precision of eGFR can be extremely important for appropriate patient management, where diagnosis of CKD, drug dosing, and proper health care utilization often depend on accurate estimates of kidney function. Few aspects of clinical care among older adults have stirred more controversy than the accuracy and precision of GFR obtained from estimating equations.

In this issue, Scarr *et al.*[3] assessed the performance of eGFRs by serum creatinine, cystatin C, and β2-microglobulin (β2M) as compared with measured GFR (mGFR) in older adults with and without type 1 diabetes in the Canadian Study of Longevity in Type 1 Diabetes. Seventy-five participants with type 1 diabetes and a disease duration ≥50 years were age- and sex-matched with 75 controls without diabetes, and eGFR was calculated using the MDRD; CKD-EPI, creatinine (CKD-EPIcr); CKD-EPI, cystatin C (CKD-EPIcys); CKD-EPIcr-cys; and β2M equations. GFR was also measured by the mean of 2 plasma inulin clearances. Measures of bias, precision, and accuracy were used to evaluate the performance of the eGFR equations overall and within subgroups. Bias was defined as the mean difference between eGFR and mGFR and precision was estimated from the SD of the bias. Accuracy, a marker of both bias and precision, was calculated as the percentage of eGFRs outside a 30% or 20% range of the mGFR ($1 - P_{30}$ and $1 - P_{20}$), respectively. The 95% confidence intervals around these measures were calculated using a bootstrap method. The authors observed that although no participants had mGFR <60 ml/min per 1.73 m^2, 6% of participants were classified as having eGFR <60 ml/min per 1.73 m^2 by the MDRD and CKD-EPIcr equations, 30% by CKD-EPIcys, 12% by CKD-EPIcr-cys, and 9% by β2M. All eGFRs significantly underestimated mGFR, with greater bias observed for cystatin-based equations than the other equations. Although bias was lowest for β2M (1.9 ml/min per 1.73 m^2, $P = 0.61$), this marker was also associated with the lowest precision. For all eGFR equations, negative bias was greater and accuracy was lower among participants with higher mGFR.

An unexpected finding observed by Scarr *et al.*[3] was that cystatin C did not improve eGFR performance over serum creatinine alone. Indeed, accuracy was higher for creatinine-based eGFR (MDRD 32.4%, CKD-EPIcr 37.4%) than for eGFR computed using any other markers they tested (CKD-EPIcr-cys 52.5%, β2M 52.5%, and CKD-EPIcys 69.1%, $P < 0.05$ for all comparisons). Performance metrics were similar for creatinine- or cystatin-based eGFRs, regardless of diabetes, whereas β2M eGFR showed significantly greater bias, lower precision, and lower accuracy in participants with type 1 diabetes

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than in controls. In subgroup analyses, cystatin-based eGFRs showed greater negative bias, that is, underestimation of measured GFR, and lower accuracy in older participants and in women.

The Kidney Disease: Improving Global Outcomes guidelines[S2] recommend that GFR estimates based on cystatin C be used to confirm the presence of CKD in adults with eGFRcr of 45 to 59 ml/min per 1.73 m^2 but without evidence of kidney damage, or in patients in whom an accurate determination of GFR is required and measurement of GFR with an exogenous marker is not feasible. This recommendation heeded ongoing controversy over the application of an arbitrary and isolated threshold of GFR to define CKD. An eGFRcys or eGFRcr-cys below 60 ml/min per 1.73 m^2 would confirm the presence of CKD diagnosed by a creatinine-based equation, whereas a value above this cutoff would refute this diagnosis. The rationale for this practice was based on a significant body of literature indicating that cystatin C improved accuracy of GFR estimation and had greater predictive power for clinical outcomes, including end-stage kidney disease, mortality, and cardiovascular disease events, leading to better CKD classification than creatinine-based eGFR. The guideline made no specific suggestions or recommendations for use of these markers in the elderly. However, because serum cystatin C is less dependent on muscle mass than serum creatinine and is virtually completely cleared from the circulation by glomerular filtration with subsequent proximal tubular uptake and degradation, it is generally considered as an ideal alternate marker of kidney function, particularly in older individuals. How then do we explain the findings by Scarr *et al.*?[3]

Several factors need to be considered when addressing this question. First, significant interlaboratory variability in serum creatinine measurement persists even after the introduction of isotope dilution mass spectrometry standardization.[4] Studies analyzing patient samples across the range of serum creatinine concentrations find that Jaffe assays, as used by Scarr *et al.*,[3] yield higher creatinine values than enzymatic assays, leading to a more frequent diagnosis of CKD. In one study in which serum creatinine concentration was measured by both methods in the same samples,[4] 60% of eGFRs based on creatinine measured by the Jaffe method yielded eGFR values <60 ml/min per 1.73 m^2, whereas only 39% of eGFRs based on creatinine measured by the enzymatic method did so. In addition, serum concentrations of bilirubin >0.5 mg/dl or of glucose >90 mg/dl were shown to increase interlaboratory variability and differences between Jaffe and enzymatic results, particularly when the creatinine concentration is low, as in elderly persons with low muscle mass. And cystatin C concentrations also vary substantially between assays despite claims of calibration traceability to the ERM-DA471/IFCC reference material.[5]

Second, a non-normal distribution of the differences between eGFR methods may adversely affect performance comparisons.[6,S3] If the differences are not normally distributed, transformation of the original data may be helpful, or nonparametric tests with confidence limits computed using bootstrap procedures that account for non-normality should be considered.

Third, eGFR equations (like all estimating equations) perform best in the cohorts from which they are developed. To date, few studies have explored the performance of eGFRs in elderly individuals of diverse racial/ethnic background and a wide spectrum of kidney function, and even fewer include frail and hospitalized patients, in whom these estimates are least reliable but most needed. Newer equations developed specifically for this age category, such as the Berlin Initiative Study creatinine equation, the Berlin Initiative Study creatinine and cystatin C equation,[S4] or the Full Age Spectrum equation,[7] appear to offer better accuracy than either MDRD or CKD-EPI, but these equations have not been externally validated. Even as newer equations are improving on previous ones, the applicability of a single equation to all situations may ultimately require a trade-off between the cost of the filtration markers and the accuracy and precision of the estimate. Foreseeable alternatives are novel, rapid, and affordable methods of GFR measurement in humans. Transcutaneous GFR measurements using exogenous fluorescent marker fluorescein isothiocyanate–sinistrin have been studied in animal models, allowing GFR assessment in real time without serial blood or urine sampling.[8] Fluorescence technologies in humans are being developed using 2-compartment GFR measurements that allow rapid direct quantification of GFR and renal reserve. GFR measurement by iohexol clearance using dried capillary blood spots may also be a useful option when an accurate measurement is required.[9]

The findings reported by Scarr *et al.*,[3] and the inconsistencies they and others have noted among studies of eGFR performance generally, remind us of the many challenges associated with estimating and interpreting GFR in elderly persons and in other high-risk groups in whom precise and accurate estimates of kidney function are increasingly needed for

optimal clinical management. Identifying appropriate filtration markers and estimating equations for these important subgroups first requires that we address inconsistencies across studies caused by differences in study design; statistical approach; laboratory assays; and specimen collection, handling, and storage. Perhaps through standardized reporting requirements for eGFR performance comparisons, we can more confidently identify the best approaches for evaluating kidney function in these groups. The study by Scarr *et al*.[3] moves us closer to that goal.

DISCLOSURE

The authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary References.

Supplementary material is linked to the online version of the paper at www.kireports.org.

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