Strengths and limitations of estimated and measured GFR

Andrew S. Levey, Josef Coresh, Hocine Tighiouart, Tom Greene and Lesley A. Inker

Evaluation of glomerular filtration rate (GFR) is central to medical practice, research and public health. As investigators who developed the Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations for estimation of GFR, and as leaders of national and international guideline committees and workshops on the use of estimated GFR (eGFR), we take issue with the conclusions of Porrini et al. stated in their Perspectives article (Porrini, E. et al. Estimated GFR: time for a critical appraisal. *Nat. Rev. Nephrol.* **15**, 177–190 (2019)[1]), which discusses the reliability of eGFR equations. These authors conclude that "eGFR is an unreliable tool to assess renal function in health and disease, as well as in clinical practice and research". Instead of eGFR, they recommend more frequent use of measured GFR (mGFR). We agree that eGFR may be imprecise; using the most accurate eGFR equations, the proportion of eGFR values that are within 30% of mGFR values (P_{30}) generally does not exceed 90%, which is the performance goal for eGFR[2,3]. We also agree that more frequent use of mGFR is desirable, and we applaud the work of Porrini et al. in implementing plasma clearance of iohexol in research studies. However, we regard their conclusions as flawed for several reasons.

First, their analysis includes studies that did not standardize assays for creatinine or cystatin C, leading to unpredictable bias in eGFR values based on levels of creatinine ($eGFR_{cr}$), cystatin C ($eGFR_{cys}$) or both ($eGFR_{cr-cys}$), and to unreliable estimates of the accuracy of these equations. This flaw can only be avoided by limiting the analysis to studies that used standardized assays and equations developed or re-expressed for use with standardized assays[4].

Second, they underestimate error in mGFR compared with 'true' GFR[5], which contributes substantially to the errors reported in comparisons between eGFR and mGFR in both cross-sectional and longitudinal studies. A systematic review by Soveri and colleagues[6] demonstrated bias and imprecision in all current mGFR methods compared to the classical method of inulin clearance described by Homer Smith; P_{30} often did not exceed 90%. Even the classical inulin clearance method is imprecise, with a coefficient of variation (CV) for repeated measures of approximately 7%[7]. The smallest reported CVs using other mGFR methods are approximately 5–15%, generally with higher values for urinary clearance than plasma clearance methods[8–14]. Critically, for an unbiased mGFR method, a CV for repeated measures of 10% would be equivalent to approximately 90% of mGFR within 15% of true GFR (P_{15} of 90%).

Third, they propose an alternative performance goal for eGFR of P_{10} > 90% compared with mGFR (90% of eGFR values within 10% of mGFR values). This goal is unrealistic, as it is not attainable for repeated measurements of mGFR using many methods.

Fourth, they fail to consider that clinical decision-making in most settings includes multiple factors in addition to eGFR[15,16]. For many clinical decisions, a P_{30} for $eGFR_{cr}$ compared with mGFR of 80–90% is adequate. If more accurate assessment is required, $eGFR_{cys}$, $eGFR_{cr-cys}$ or mGFR are recommended as confirmatory tests, depending on their availability and the level of accuracy required for clinical decision-making.

In contrast to Porrini and colleagues, we conclude that both mGFR and eGFR have strengths and limitations and both can be improved. We recommend that clinicians, researchers and public health officials understand these strengths and limitations for wise use of both mGFR and eGFR.

There is a reply to this letter by Porrini, E. et al. *Nat. Rev. Nephrol.* https://doi.org/10.1038/s41581-019-0214-8 (2019).

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