Reply to ‘Strengths and limitations of estimated and measured GFR’

Esteban Porrini, Piero Ruggerenti, Sergio Luis-Lima, Fabiola Carrara, Alejandro Jiménez, Aiko P. J. de Vries, Armando Torres, Flavio Gaspari and Giuseppe Remuzzi

We would like to thank Levey and colleagues for their correspondence on our Perspectives article (Porrini, E. et al. Estimated GFR: time for a critical appraisal. *Nat. Rev. Nephrol.* **15**, 177–190 (2019)¹), which argues that our conclusion that estimated glomerular filtration rate (eGFR) is not a reliable tool for assessment of renal function is flawed (Levey, A. et al. Strengths and limitations of estimated and measured GFR. *Nat. Rev. Nephrol.* <https://doi.org/10.1038/s41581-019-0213-9> (2019)²). Here, we provide a response to the points made in their correspondence.

First, they suggest that the inclusion of studies that did not use standardized assays for creatinine or cystatin C in our analysis led to unreliable estimates of the accuracy of eGFR equations. However, poor correlations between creatinine levels and measured GFR (mGFR) have been observed with creatinine measurements obtained using both standardized and nonstandardized assays¹. Stevens et al.³ reported comparable percentage of eGFR values that are within $\pm 30\%$ of mGFR values (P_{30}) for eGFRs based on creatinine levels measured in the same samples using either standardized or nonstandardized assays (80% and 83%, respectively). Additional studies that used either nonstandardized^{4–7} or standardized^{8–10} creatinine assays showed comparable P_{30} values for eGFR. Assay standardization therefore clearly does not improve the performance of eGFR formulas.

Second, they argue that we underestimated error in mGFR compared with “true GFR”. To our knowledge, it is not possible to define ‘true GFR’, and no rationale exists to suggest that inulin clearance is the ‘gold standard’ for GFR measurement. To which method was the clearance of inulin compared to establish it as the gold standard? This is unknown. Also, inulin clearance is not a perfect method for measuring GFR because inulin undergoes both renal and extrarenal clearance, which might lead to overestimation of GFR¹¹. Thus, the level of error in mGFR compared with ‘true GFR’ is supposition rather than fact. By contrast, error in eGFR compared with mGFR is real, wide and frequent; a fact that has been largely overlooked.

The systematic review by Soveri et al.¹² that analysed diverse methods used to measure GFR is a landmark publication. However, the authors compared studies using a single point with others using multiple points to measure GFR. This approach is not correct because accuracy and precision increase with the numbers of points taken. Their overall analysis that combines different studies must therefore be examined in detail and with caution. In fact, the plasma clearance of iothexol seems to be comparable to the plasma clearance of inulin when multiple blood samples are taken for the analysis of GFR^{13,14}. Moreover, Soveri et al.¹² conclude that “there is enough evidence to consider the renal clearance of iothalamate and renal or plasma clearances of EDTA and the plasma clearance of iothexol as reliable alternatives to the inulin clearance”.

Third, we fully agree with Levey and colleagues that a performance goal for eGFR equations of $P_{10} > 90\%$ (that is, 90% of eGFR values within 10% of mGFR values) is unrealistic given that the average error of eGFR equations is as wide as $\pm 30\%$, or even larger. However, methods of evaluating formulas that estimate GFR must be adapted to the needs of patients and not to the evident limitations of eGFR equations. The error in eGFR that we tolerate in nephrology would be unacceptable in other areas of medicine. How many patients with hypertension would be diagnosed as normotensive (or vice versa) if we used a sphygmomanometer with an error of 30–50%?

Fourth, a P_{30} of 80–90%, which Levey and colleagues consider to be acceptable for many clinical decisions, means that most eGFR values differ from mGFR values by $\pm 30\%$. It is difficult to accept that such variation, which would equate to ± 20 –30 ml/min/1.73 m² in a patient with a mGFR of 60 ml/min/1.73 m², will not have consequences in the clinic (Supplementary Fig. 1). Indeed, there is evidence that this level of error in eGFR has important consequences including overdosing or underdosing of toxic drugs¹⁵, erroneous classification of chronic kidney disease (CKD) stages¹⁰, accepting kidney donors with low GFR and rejecting potential donors with

adequate kidney function¹⁶. Unfortunately, use of cystatin C rather than creatinine or a combination of cystatin C and creatinine to estimate GFR does not improve the accuracy of eGFR values, as discussed in our Perspectives article^{1,9,10}. The consequences of this lack of precision and accuracy of eGFR equations in the clinic must not be overlooked.

In contrast to Levey and colleagues, we think there is enough evidence to conclude that in specific clinical conditions, the error in eGFR values obtained using any of the current formulas is unacceptable as it could have severe consequences.

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Competing interests

The authors declare no competing interests.

Supplementary information

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