Errors in the Assessment of Estimated Glomerular Filtration Rate

To the Editor:

The article by Grubb et al. (1) is an important contribution to the developing field of clinical chemistry and medicine. However, we believe that several factors possibly detract from it. First, the application of the Modification of Diet in Renal Disease (MDRD) formulae (2,3) in children is inappropriate, as those equations are not applicable to this age group. As a result, the scales of the axes in Figs. 1 and 3 in the article (1) are inappropriate from the adult viewpoint. This makes graphical interpretation of the adult data more difficult—the data for children and adults should have been separated graphically and statistically.

Second, Grubb et al. (1) used a population different from the population studied by Levey and coworkers (2,3): i.e., relatively normal vs abnormal, respectively. The intent of the MDRD formulae is as a screen for patients at risk for end-stage renal disease and not as a screen for the general population.

Third, the cystatin C–based equation involving the factor 83.93 does not appear to be linear, as none of the ~27 data points above an iohexol clearance of ~110 mL/min in Fig. 3A (1) seems to have a positive percentage error. Although errors in this range of glomerular filtration rate (GFR) may not be critical, it does beg the question concerning the derivation, and thus the validity, of the cystatin C–based equation throughout the whole GFR range. The authors state that they built “linear regression models based on log-transformed plasma clearance of iohexol [in mL·min⁻¹·(1.73 m²)⁻¹] and cystatin C concentrations (in mg/L) because these transformations produced roughly symmetrically distributed regression residuals homogeneous variance’ (1). As a result, we wonder whether the model put to use is actually the optimal model and whether it is mathematically justifiable. The formulae developed by both groups (1–3) were developed by empirical means with no attempt to apply an appropriate mathematical model. Empirical models are acceptable as rough sketches of relationships, but one should not depend on them for making precise clinical decisions. Empirical models, especially those built with log-transformed data, are weak because of their capacity to propagate errors.

The reports by Grubb et al. (1) and Levey and coworkers (2,3) represent the beginnings of the process to develop a simple laboratory method to identify patients at greater risk for renal failure, but we must caution clinicians not to believe that the estimates are infallible or to apply great clinical weight to their results. For example, 20% of patients had predicted cystatin C–based GFR values that differed more than 30% from the measured GFR values (1). A significant number of patients will have a measured GFR of 60 mL·min⁻¹·(1.73 m²)⁻¹, but one-fifth of them will have an estimated GFR >78 or <42 mL·min⁻¹·(1.73 m²)⁻¹. This is very important from both a wider population and an individual point of view, as it will have major influence on the selection of diagnostic tests as well as on the selection of therapeutic agents for the treatment of patients. Before the laboratory community adopts estimated GFR as an approach to identifying patients at risk, we should ensure that a modern approach to model building is applied.

Finally, there are issues concerning the comparison of the various equations. The population used in the derivation of the cystatin C–based equation appears to be the same population used in the comparison study (1). If this is the case, then the cystatin C comparison data are not independent and will lead to overestimation of the accuracy of the cystatin C–based equation. Even if this is not the case, because the cystatin C–based equation was calibrated with iohexol clearance (1) and the MDRD formulae were calibrated with iothalamate (2,3), any study comparing the equations with iohexol clearance should favor the cystatin C equation. The alternative reference methods to the gold standard inulin clearance are similar but not the same.

Despite the above, the differences in the data above the age of 50 years in Fig. 1 in the article by Grubb et al. (1) raise some interesting questions: is the MDRD equation more likely to have a significant positive bias in patients >50 years of age than the cystatin C–based equation, and if so, why?

References


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