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Do we need another equation to estimate GFR from serum creatinine in renal allograft recipients?

Andrew D. Rule and **Timothy S. Larson**
Mayo Clinic, Rochester, MN, USA

Andrew D. Rule: rule.andrew@mayo.edu; Timothy S. Larson:

Sir,

We read with interest the study by Pöge *et al*. evaluating a refit version of the MDRD equation and the Mayo Clinic Quadratic equation to improve estimation of GFR in renal allograft recipients [1]. As pointed out by Poge *et al*., these two equations were not developed using a standardized assay for serum creatinine. Because the same creatinine assay was used to develop these two equations, it still could be shown that differences in the source population can lead to different equations [2]. However, we recognize that it has been difficult to determine to what extent the Mayo Clinic Quadratic and MDRD equations perform differently due to assay calibration versus the source population. A confirmed conversion factor between a standardized assay (i.e. traceable to isotope dilution mass spectroscopy) and the Mayo Clinic assay used to develop these equations may be helpful. Since the Mayo Clinic assay used an uncompensated rate-Jaffe method, the following calibration correction based on assay differences reported in the literature could be used [3]:

Literature calibration

$$\text{Creatinine}_{\text{IDMS}} = 0.95 \times (\text{Creatinine}_{\text{Mayo Clinic}} - 0.23\ \text{mg/dl}).$$

Recently, indirect calibration was reported using historical College of American Pathologists Survey Data on 45 samples sent to the Mayo Clinic and 253 frozen College of American Pathologists samples in the MDRD study [4]:

Indirect calibration

$$\text{Creatinine}_{\text{IDMS}} = 0.906 \times (1.098 \times \text{Creatinine}_{\text{Mayo Clinic}} - 0.216\ \text{mg/dl}).$$

More recently, direct calibration was performed using the Cleveland Clinic Roche Enzymatic assay on frozen samples from 144 patients who also had same-day creatinine levels on the Mayo Clinic assay.

Conflict of interest statement. None declared.

Direct calibration

$$\text{Creatinine}_{\text{IDMS}} = 1.092 \times \text{Creatinine}_{\text{Mayo Clinic}} - 0.265 \text{ mg/dl}.$$

Applying these calibrations to the upper limit of normal for serum creatinine (97.5th percentile in healthy white men and in healthy white women) [5] highlights the differences in these calibration approaches (see Table 1).

A more important issue may be whether creatinine assay calibration is even adequate to draw inferences about equation performance between populations. Using standardized assays, there was a 0.04 mg/dl rise in creatinine levels over a 10-year period among young adults without diabetes or hypertension that suggested small residual differences in calibration may still bias comparisons between populations [6]. There also may be calibration differences between measured GFR by an iothalamate urinary clearance compared to a ^{99m}Tc-DTPA plasma clearance. To compare renal allograft recipients and native kidney disease patients (the population used to derive the MDRD equation), we would argue that, optimally, both populations need to be sampled using the same creatinine and GFR assays. Using this approach, we did not find a statistically significant difference (2.5%, 95% CI: −3.5–9.0%) in measured GFR between transplant recipients and native kidney disease patients at the same serum creatinine level. We did find less correlation between creatinine and measured GFR in transplant recipients ($r^2 = 0.671$) than native kidney disease patients ($r^2 = 0.770$), suggesting there is less precision with GFR estimates among transplant recipients compared to native kidney disease patients [7]. To improve precision, additional variables in creatinine-based equations are needed to better model the non-GFR variability (muscle mass, dietary protein and tubular secretion) than is accomplished with demographics (age, sex and race) alone. For now, we concur that measured GFR has a role in renal allograft recipients, particularly for monitoring disease progression [8].

Reply

Sir,

We thank A. Rule and T. Larson for their stimulating comment that provides two additional equations to transform creatinine traceable to the isotope dilution mass spectroscopy into the creatinine of the Mayo Clinic assay.

Since we felt that a direct and indirect approach possibly could improve the performance of the so-called Mayo Clinic Quadratic equation (reference) and the refitted MDRD formula (reference), we re-calculated correlation, bias, precision and accuracy of both equations in our cohort.

However, as outlined in Table 1, we could not demonstrate significant advantages as compared to the literature-based conversion primarily applied in our recently published paper irrespective of the approach to calibrate the creatinine. Thus, neither directly nor indirectly calibrated creatinine improved the performance of the equations to estimate GFR.

These disappointing results may be related to the fact that the differences between the IDMS traceable creatinine and the Mayo clinic assay were smaller using the direct and indirect transformation. Consequently, the conversion method used in the publication (reference) resulted in higher creatinine values.

Our results basically indicate an overestimation of the Mayo Clinic Quadratic equation. The 'new' creatinine values were lower, and consecutively, GFR estimation there-fore augments this overestimation and will yield a lower performance. Thus, indeed a further note of caution may be mandatory with respect to patient characteristics of different or mixed populations, e.g. native kidney disease patients and transplant recipients when inferences about equation performances are drawn between varying patient populations. Hence, we agree with Rule and Larson that additional factors like differences in GFR determination (DTPA versus iothalamate) potentially may lead to biased results when measured GFR and estimated GFR are used to monitor disease progression in various patient cohorts with differing diseases.

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Ume Pöge

Rainer P. Woitas

Department of internal medicine

University of Bonn

Siegmund Freud Str. 25

Bonn 53105

Germany

E-mail: dr.poege@nephrologie-bonn.de; rainer.woitas@ ukb.uni-bonn.de

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Table 1

Impact of different calibration methods on the upper limit of normal for creatinine

Calibration method	Healthy white men (97.5th percentile)		Healthy white women (97.5th percentile)	
Original Mayo Clinic value	1.4 mg/dl	(123 μmol/l)	1.2 mg/dl	(98 μmol/l)
Literature calibration	1.11 mg/dl	(98 μmol/l)	0.92 mg/dl	(81 μmol/l)
Indirect calibration	1.20 mg/dl	(106 μmol/l)	1.00 mg/dl	(88 μmol/l)
Direct calibration	1.26 mg/dl	(111 μmol/l)	1.05 mg/dl	(92 μmol/l)