Nephrol Dial Transplant (2011) 26: 2426–2428
doi: 10.1093/ndt/gfr151
Advance Access publication 29 March 2011

A modest proposal for improving the accuracy of creatinine-based GFR estimating equations

Paul L. Hebert[1], Uday S. Nori[2], Udayan Y. Bhatt[2] and Lee A. Hebert[2]

[1]Department of Health Services, University of Washington School of Public Health and Community Medicine, Seattle, WA, USA and [2]Department of Internal Medicine, The Ohio State University Medical Center, Columbus, OH, USA

Correspondence and offprint requests to: Lee A. Hebert; E-mail: lee.hebert@osumc.edu

The most widely used creatinine-based glomerular filtration rate (GFR) estimating (e) equation (eGFR) is MDRD-4. It and its successor, CKD-EPI, do not include a term for the patient's body weight or actual body surface area (BSA). There is new and compelling evidence that, as a result, these eGFR equations are vulnerable to bias (non-random errors) that can confound their application to individuals and to group comparisons. Our 'modest proposal' is to retrofit these eGFR equations to include the patient's actual body weight (or a related term—as discussed later) and actual BSA. This editorial documents the problem incurred by these omissions, how the problem can be remedied and what should be done until it is remedied.

When MDRD-4 was devised, it was an advantage to not require body weight or BSA because clinical laboratories, which produced the creatinine measurement, did not have ready access to the patient's height or weight. They did, however, have the patient's demographics (age, race, sex), each of which influences the serum creatinine level. These demographics and the serum creatinine level became the data set for MDRD-4/CKD-EPI. Now, however, with the widespread and growing use of the electronic medical record, it would be easy to incorporate the patient's body weight and actual BSA into MDRD-4/CKD-EPI.

The MDRD-4 equation was devised to estimate actual GFR more accurately than is possible from interpretation of the serum creatinine level alone [1]. The MDRD-4 equation has become very influential. It is the basis for the K-DOQI stages of chronic kidney disease (CKD) [1], which are widely used clinically and in CKD epidemiology. Also, most clinical laboratories now automatically report MDRD-4 using a standardized creatinine measurement championed by K-DOQI.

MDRD-4's predecessor was Cockroft-Gault (CG) eGFR. CG is used widely in Europe but it never gained popularity in the USA. The disadvantages of CG are that it requires body weight, does not adjust for BSA or African ancestry and estimates creatinine clearance not GFR. Also, CG shows greater variability than MDRD-4, which has been interpreted as evidence of decreased accuracy [1]. We suggest, however, that MDRD-4 only seems more accurate than CG because, in effect, MDRD-4 has only a single variable contributing to its variance (i.e. serum creatinine), whereas CG eGFR has both serum creatinine and body weight contributing to its variance. Thus, for patients of the same age, race, sex and serum creatinine level, there is only one possible value for MDRD-4 eGFR. However, for this same set of patients, there are numerous possible correct values for their CG eGFR, depending on the individuals' body weight, as we and others have pointed out [2, 3]. The greater variability of CG compared to MDRD-4 reflects this reality. On this basis, we suggest that it is beyond question that adding a weight term and the patient's actual BSA would improve the accuracy of MDRD-4/CKD-EPI. Presently, there is a considerable effort underway to replace creatinine-based eGFR with other measures [4]. We suggest, however, that a properly retrofitted CKD-EPI may make that effort unnecessary.

Body weight is the main determinant of serum creatinine at any actual GFR. MDRD-4 attempts to adjust for lack of a body weight term by using an averaged BSA. However, BSA—even an accurately determined BSA—is not an adequate substitute for body weight. For example, a 35% difference in body weight corresponds to only a 14% difference in BSA [5].

The evidence that MDRD-4 (and by inference CKD-EPI) is biased because it does not include a body weight term or actual BSA, includes the following

The IDEAL study

IDEAL is a prospective randomized trial of early-start versus late-start dialysis in late-stage CKD [6]. IDEAL found no difference in mortality rate during 3 years of follow-up between the early-start and late-start dialysis.

IDEAL also assessed whether mortality rate during follow-up was related to eGFR at baseline. When the baseline eGFR was stratified according to CG adjusted for actual BSA, the proportion of deaths during follow-up was 40% in the lower range of baseline CG and 35% in the higher range of baseline CG. This mortality difference was not significant and was consistent with the study's overall outcome. However, when baseline eGFR was

stratified according to MDRD-4, a major paradox emerged. The proportion of deaths during follow-up became 29% in those in the lower range of baseline MDRD-4 and 45% in those in the higher range of baseline MDRD-4 ($P < 0.001$). This paradox was not mentioned in their publications nor was it tested statistically. We suggest that this paradox occurred because MDRD-4 could not reliably distinguish between those with a lower serum creatinine because of wasting (which should increase mortality) from those with lower serum creatinine because of higher actual GFR (which should decrease mortality) [7]. At the same time, MDRD-4 could not reliably distinguish between those with higher serum creatinine because they were relatively robust (which should decrease mortality) from those with higher serum creatinine because of lower actual GFR (which should increase mortality). This 'perfect storm' created the paradoxical and spurious mortality gap when MDRD-4 was used to stratify baseline GFR. By contrast, because CG in IDEAL included the patient's actual body weight and actual BSA, CG could more reliably estimate actual GFR. Thus, CG predicted mortality more accurately than MDRD-4.

The study of GFR decline during follow-up in the MDRD study

Recently, it was shown that during MDRD study follow-up, MDRD-4 underestimated GFR decline by 28% compared to measured GFR (mGFR, urinary iothalamate clearance) [8]. We suggest that this bias occurred because MDRD-4 overestimated actual GFR in those with lower serum creatinine level due to wasting, and becoming wasted was more common during MDRD follow-up than becoming robust. Thus, there was not an offsetting bias.

The 'rising tide' of early-start dialysis

The serum creatinine level at which patients start dialysis has decreased sharply in recent years [9]. We suggest the impetus to this 'tide' was contributed to by the MDRD-4 verbal descriptors of 'severely decreased GFR' at Stage 4 CKD and 'kidney failure' at Stage 5 CKD. Although the K-DOQI guidelines clearly state that renal replacement therapy is indicated if 'uremia' is present, apparently many nephrologists overlooked this recommendation. We suggest that the rising tide occurred primarily in relatively robust patients because MDRD-4 substantially underestimates actual GFR in these patients, as we and others have pointed out [2, 3].

The studies of eGFR and the prediction of cardiovascular risk

Recent reports show that MDRD-4 is less reliable than mGFR [4] or CG [10] in predicting cardiovascular risk. We suggest that this occurs because MDRD-4 bias underestimates cardiovascular risk in those with lower serum creatinine because of wasting and overestimates cardiovascular risk in those with higher serum creatinines because they are robust. CG and mGFR do not have this bias.

Recommendations for the weight and BSA terms

The optimum weight term is not actual body weight. That is too vulnerable to confounding, particularly by obesity. The quandary regarding the optimum body weight term for creatinine-based eGFR equations was recently reviewed [11]. The choices include ideal body weight, adjusted body weight, lean body weight, fat-free weight and others [11]. We suggest that each body weight term should be evaluated. We suggest that CKD-EPI should be used for this purpose because it has advantages over MDRD-4, CG and the 'quadratic' eGFR [12] because of its better ascertainment of the effects of age, sex and race on GFR [13].

Including actual BSA in CKD-EPI should be easy to do because the electronic medical record also contains the patient's height. Accurate adjustment for BSA is needed to compare the patient's eGFR to normative values [5].

Interim recommendations for eGFR measurement

As recently discussed, creatinine-based eGFR equations that do not include a weight term are not recommended if the person is obese or is an habitual vegetarian, habitual 'meatatarian' or has atypical muscle mass. This issue is particularly relevant if the problem is to determine whether actual GFR is normal (e.g. kidney donor evaluation). In such persons, 24-h urine creatinine clearance based on accurately collected 24-h urine is recommended [14, 15]. For others, CG adjusted for actual BSA is recommended [14]. mGFR is not recommended because of considerable intra-individual variability [16].

Presently, there is a considerable effort underway to replace creatinine-based eGFR with other measures [4]. We suggest, however, that a properly retooled CKD-EPI may make this effort unnecessary.

Acknowledgements. Funding. National Institutes of Health ULIRR025755 CTSA, HHSN260200900049C (SPRINT), 5UO1DK48621 and HSR&D Service IIR09-049-3.

Conflict of interest statement. All of the authors declare they have no financial conflicts of interest to disclose.

References

1. Stevens LA, Coresh J, Greene T *et al.* Assessing kidney function–measured and estimated glomerular filtration rate. *N Engl J Med* 2006; 354: 2473–2483
2. Hebert LA, Nori U, Hebert PL. Measured and estimated glomerular filtration rate. *N Engl J Med* 2006; 355: 1068; author reply 1069–1070
3. Beddhu S, Samore MH, Roberts MS *et al.* Creatinine production, nutrition, and glomerular filtration rate estimation. *J Am Soc Nephrol* 2003; 14: 1000–1005
4. Spanaus KS, Kollerits B, Ritz E *et al.* Serum creatinine, cystatin C, and beta-trace protein in diagnostic staging and predicting progression

of primary nondiabetic chronic kidney disease. *Clin Chem* 2010; 56: 740–749
5. Levey AS, Kramer H. Obesity, glomerular hyperfiltration, and the surface area correction. *Am J Kidney Dis* 2010; 56: 255–258
6. Cooper BA, Branley P, Bulfone L *et al.* A randomized, controlled trial of early versus late initiation of dialysis. *N Engl J Med* 2010; 363: 609–619
7. Ix JH, de Boer IH, Wassel CL *et al.* Urinary creatinine excretion rate and mortality in persons with coronary artery disease: the Heart and Soul Study. *Circulation* 2010; 121: 1295–1303
8. Xie D, Joffe MM, Brunelli SM *et al.* A comparison of change in measured and estimated glomerular filtration rate in patients with nondiabetic kidney disease. *Clin J Am Soc Nephrol* 2008; 3: 1332–1338
9. Rosansky SJ, Clark WF, Eggers P *et al.* Initiation of dialysis at higher GFRs: is the apparent rising tide of early dialysis harmful or helpful? *Kidney Int* 2009; 76: 257–261
10. Szummer K, Lundman P, Jacobson SH *et al.* Cockcroft-Gault is better than the Modification of Diet in Renal Disease study formula at predicting outcome after a myocardial infarction: data from the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART). *Am Heart J* 2010; 159: 979–986
11. Pai MP. Estimating the glomerular filtration rate in obese adult patients for drug dosing. *Adv Chronic Kidney Dis* 2010; 17: e53–e62
12. Rule AD, Larson TS, Bergstralh EJ *et al.* Using serum creatinine to estimate glomerular filtration rate: accuracy in good health and in chronic kidney disease. *Ann Intern Med* 2004; 141: 929–937
13. Stevens LA, Claybon MA, Schmid CH *et al.* Evaluation of the Chronic Kidney Disease Epidemiology Collaboration equation for estimating the glomerular filtration rate in multiple ethnicities. *Kidney Int* 2011; 79: 555–562
14. Nori US, Pesavento TE, Hebert LA. Measured GFR has limited clinical utility. *Am J Kidney Dis* 2011; 57: 180
15. Krediet RT, Dekker FW. Can plasma creatinine levels guide initiation of dialysis. *Nat Rev Nephrol* 2010; 6: 563–564
16. Kwong YT, Stevens LA, Selvin E *et al.* Imprecision of urinary iothalamate clearance as a gold-standard measure of GFR decreases the diagnostic accuracy of kidney function estimating equations. *Am J Kidney Dis* 2010; 56: 39–49

Received for publication: 28.1.11; Accepted in revised form: 24.2.11