The Challenge of GFR Assessment in Kidney Transplant Recipients

By Lesley A. Inker, Ashtar Chami, Krishna A. Agarwal, and Andrew S. Levey

In a recent issue of the *British Medical Journal*, Raynaud et al. (1) reported on the development and validation of a creatinine-based estimated glomerular filtration rate (eGFRcr) equation for use in kidney transplant recipients. There is good reason to think that eGFRcr equations developed for use in the general population, such as the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations, would have large errors in some kidney transplant patients. Following transplantation, kidney transplant recipients may have low muscle mass, reduced activity, or decreased protein intake or use medications that affect muscle mass (such as glucocorticosteroids) or that inhibit renal tubular secretion of creatinine (such as trimethoprim), all of which can lead to changes in serum creatinine independent of GFR (2, 3). GFR is used for many critical clinical decisions in kidney transplant recipients, such as detection of rejection and consideration of biopsy, or decisions regarding selection and dosage of prophylactic antimicrobials or use of contrast imaging to detect transplant complications (4, 5). As such, a comprehensive approach for assessment of GFR for patients with kidney transplants is necessary and has been missing.

The authors' equation was developed in 3622 patients from 3 French transplant centers and validated in 11,867 patients—from 8 centers in Europe, 1 center in Australia, 1 clinical center and 1 trial in the United States, and 1 international trial—who received kidney transplants between 2000 and 2021. Across the 12 validation cohorts, accuracy of the newly developed equation was variable, with percentage of estimates within 30% of measured GFR (mGFR; P_{30}) that ranged from 73% to 91%. (1 – P_{30} is a measure of large errors.) It is generally established that P_{30} >75% is acceptable for many clinical decisions and that P_{30} >90% is optimal. The variation may have been due to a differing prevalence of clinical factors mentioned above but may also have been due to methodological differences in measurement of GFR or in creatinine. In particular, the creatinine assays were variably standardized within, as well as across, cohorts—a requirement for a validated equation (6, 7). Among these cohorts, the differential accuracy compared with CKD-EPI equations was also variable, with the difference in P_{30} between the two equations ranging from 0.1% to 16% (median difference of 3.8%). The variation in the relative accuracy between the equations likely reflects methodological differences in measurement of GFR or in creatinine, as well as differences in population characteristics, rather than having a kidney transplant. Indeed, the similar performance across the equations confirms prior studies demonstrating that the CKD-EPI equations are as accurate in kidney transplant recipients as in patients with other causes of CKD and who do not have a transplant (8, 9).

Thus, in our view, these results do not change the current recommendations for a single equation to report GFR by clinical laboratories for all adults or in using that eGFR value for routine care for most kidney transplant patients. However, the question of a comprehensive approach for assessment of GFR remains open. eGFRcr is recommended as the initial test, followed by eGFR from the combination of creatinine and cystatin C (eGFRcr-cys) or mGFR as supportive tests, depending on the clinical setting (2, 7) (Figure 1). Cystatin C has not been evaluated sufficiently in kidney transplant recipients, and careful investigations are required given the possible effect of medications on level of cystatin C independent of mGFR (10, 11).

This article reminds us of the challenge of assessment of GFR in transplant patients, and we encourage continued rigorous investigation. We recommend further studies to evaluate the accuracy of eGFRcr and eGFRcr-cys equations in kidney transplant recipients with specific consideration of the clinical settings, such as medication use and health status, which can inform a holistic approach to GFR assessment. ■

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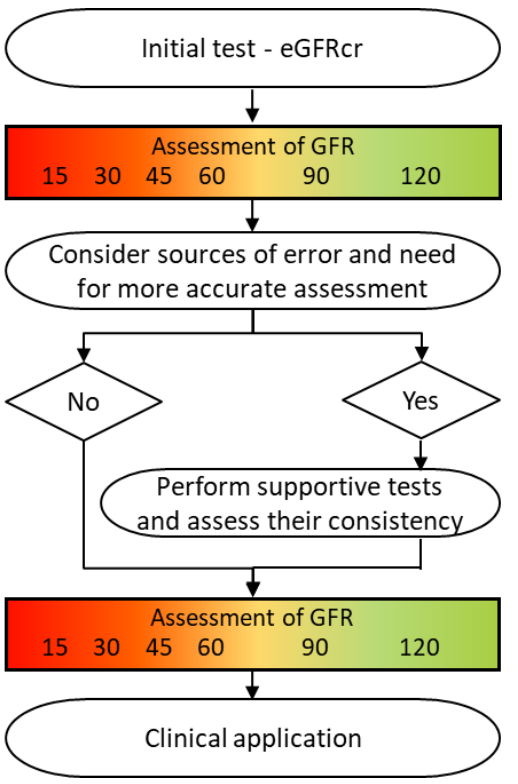
References

1. Raynaud M, et al. Race-free estimated glomerular filtration rate equation in kidney transplant recipients. *BMJ* 2023; 381:e073654. doi: 10.1136/bmj-2022-073654
2. Levey AS, et al. Measured and estimated glomerular filtration rate. *Nat Rev Nephrol* 2020; 16:51–64. doi: 10.1038/s41581-019-0191-y
3. Shafi T, et al. Quantifying individual-level inaccuracy in glomerular filtration rate estimation. *Ann Intern Med* 2022; 175:1073–1082. doi: 10.7326/M22-0610
4. Rissling O, et al. High frequency of valganciclovir underdosing for cytomegalovirus prophylaxis after renal transplantation. *Clin Kidney J* 2018; 11:564–573. doi: 10.1093/ckj/sfx145
5. Sharfuddin A. Renal relevant radiology: Imaging in kidney transplantation. *Clin J Am Soc Nephrol* 2014; 9:416–429. doi: 10.2215/CJN.02960313
6. Earley A, et al. Estimating equations for glomerular filtration rate in the era of creatinine standardization. *Ann Intern Med* 2012; 156:785–795. doi: 10.7326/0003-4819-156-6-201203200-00391
7. KDIGO. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int Suppl* 2013; 3:1–150. https://kdigo.org/wp-content/uploads/2017/02/KDIGO_2012_CKD_GL.pdf
8. Stevens LA, et al. Development and validation of GFR-estimating equations using diabetes, transplant and weight. *Nephrol Dial Transplant* 2010; 25:449–457. doi: 10.1093/ndt/gfp510
9. Shaffi K, et al. Performance of creatinine-based GFR estimating equations in solid-organ transplant recipients. *Am J Kidney Dis* 2014; 63:1007–1018. doi: 10.1053/j.ajkd.2014.01.436
10. Keddis MT, et al. Creatinine-based and cystatin C-based GFR estimating equations and their non-GFR determinants in kidney transplant recipients. *Clin J Am Soc Nephrol* 2016; 11:1640–1649. doi: 10.2215/CJN.11741115
11. Hundemer GL, et al. Performance of the 2021 race-free CKD-EPI creatinine- and cystatin C-based estimated GFR equations among kidney transplant recipients. *Am J Kidney Dis* 2022; 80:462–472.e461. doi: 10.1053/j.ajkd.2022.03.014
12. Inker LA, Levey AS. Knowing your GFR—when is the number not (exactly) the number? *Kidney Int* 2019; 96:280–282. doi: 10.1016/j.kint.2019.03.026

Figure 1. Approach for GFR assessment



Our holistic approach to assessment of GFR is to use initial and supportive testing to develop a final assessment and apply it in individual decision-making. eGFRcr is the appropriate initial test. If eGFRcr is expected to be inaccurate or if a more accurate assessment is needed, then supportive tests should be measured. In the non-kidney transplant population, there is evidence that eGFRcr-cys is more accurate than eGFRcr and eGFRcys and is recommended as the second test following eGFRcr. If eGFRcr-cys is expected to be inaccurate or if an even more accurate assessment is needed, then GFR should be measured using plasma or urinary clearance of exogenous filtration markers, if available. For kidney transplant recipients, we suggest more frequent measurements of GFR for clinical decisions that rely on the level of GFR given current uncertainty about the accuracy of eGFRcr-cys (2). Adapted from Inker and Levey (12).

The challenge of GFR assessment in kidney transplant recipients

KidneyNews

Race-free kidney recipient-specific (KRS) GFR equation

Kidney transplant recipients
(Jan. 2000 to Jan. 2021)

55.9
(SD 19.7)
mL/min/1.73 m²
mean mGFR

	KRS	CKD-EPI 2021
Development **3 French cohorts** **n = 3622**	P_{30} **89.8%**	P_{30} **84.2%**
External validation **12 cohorts** ***(8 Europe, 1 Australia, 2 US [1 clinical and 1 trial], and 1 international trial)*** **n = 11,867**	P_{30} **73.0%–91.3%**	P_{30} **70.2%–88.4%**

Across the 12 validation studies, the difference in P_{30} between the two equations ranged from 0.1% to 16%.

Authors' conclusion: The new race-free KRS GFR equation was developed and validated using large, multiple international cohorts of kidney transplant recipients. The equation showed high accuracy and outperformed the race-free CKD-EPI 2021 equation that was developed in individuals with native kidneys (1). SCr, serum creatinine.

Variation in improvement in accuracy may not be due to kidney transplant per se but differences in:

1. Population characteristics
e.g., race, sex, age, BMI, etc.

2. Laboratory methods
e.g., GFR and SCr measurements

Approach to improving GFR assessment in transplant recipients: further studies needed

eGFRcr-cys

mGFR using plasma or urinary clearance

Editorial conclusion: In our view, these results do not support a change to the current recommendations for a single equation to report eGFRcr by clinical laboratories for all adults or in using the eGFRcr value for routine care for most kidney transplant recipients. Further studies are needed.

Raynaud M, et al. Race-free estimated glomerular filtration rate equation in kidney transplant recipients: Development and validation study. *BMJ* 2023; 381:e073654. doi: 10.1136/bmj-2022-073654

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