

SHORT COMMUNICATION

Estimated glomerular filtration rate with and without race for drug dosing: Cystatin C vs. serum creatinine

Hyun Gi Yun¹ | Andrew J. F. Smith² | Kenneth C. DeBacker¹ | Manjunath P. Pai¹ 

¹Department of Clinical Pharmacy, College of Pharmacy, University of Michigan, Ann Arbor, Michigan, USA

²Department of Pharmacy Services, Michigan Medicine, Ann Arbor, Michigan, USA

Correspondence

Manjunath P. Pai, College of Pharmacy, University of Michigan, 428 Church Street, Ann Arbor, MI 48109, USA.
Email: amitpai@med.umich.edu

Funding information

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

The goal of this study was to use a model kidney function clearance-dependent drug (vancomycin) to understand the gain or loss of precision in dosing with use of serum creatinine (S_{cr}), serum cystatin C (S_{cys}) and race and nonrace-based equations of the estimated glomerular filtration rate (eGFR). In this study of hospitalized patients, we compared S_{cr} , S_{cys} and their combination to estimate kidney function and vancomycin clearance. The nonrace-based S_{cys} eGFR model outperformed other clearance models and improved the probability of target attainment by 15%. When S_{cys} is not available, we show that the new 2021 CKD-EPI eGFR_{cr} equation (no race factor) performs as well as the current conventional approach. This improvement in model performance does not negate the need for individualized dosing but exemplifies the need to remove race as a factor of kidney-function dose adjustment.

KEYWORDS

creatinine, creatinine clearance, cystatin C, glomerular filtration rate, vancomycin dosing

1 | INTRODUCTION

Inclusion of race to determine the estimated glomerular filtration rate (eGFR) is controversial.¹ The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) eGFR equations using serum creatinine (S_{cr}) and serum cystatin C (S_{cys}) have recently removed the race factor.² The United States Food and Drug Administration (US FDA) guidance for industry recommends eGFR or estimated creatinine clearance (eCL_{cr}) to define study inclusion criteria and drug dosing in patients with chronic kidney disease (CKD).³ The US FDA stipulates that these values be in absolute units (mL/min) and not be body surface area (BSA) indexed (mL/min/1.73 m²) values.³ Inaccuracies in kidney function estimates are detrimental to patients with active infections. Reduced therapeutic effect and a higher risk of mortality were seen in

stage 3 CKD patients enrolled in phase 3 clinical trials of newer antibiotic agents.^{4,5}

Current drug product labels have heterogeneous dosing recommendations based on eCL_{cr} or eGFR with and without BSA indexation.^{4,6} Drug dosing models almost exclusively use S_{cr} because of international assay standardization. However, S_{cr} has many limitations, leading to the consideration of serum cystatin C (S_{cys}) as a more predictive endogenous biomarker for eGFR.^{7,8} Data comparing S_{cys} to S_{cr} , including their eGFR values as surrogates of drug clearance (CL), are limited but point to an incremental advantage of S_{cys} .⁹ A direct comparison of these equations is necessary to harmonize drug dosing.⁹

The antibiotic vancomycin is routinely used in practice and serves as an excellent probe drug of the eGFR because over 80% of the dose is eliminated unchanged in the urine.¹⁰ The primary goal of this investigation was to compare S_{cr} to S_{cys} eGFR equations with and without race and BSA indexation as predictors of drug CL using vancomycin as the reference compound. Because significant heterogeneity exists in drug product labels, our secondary goal was to quantify the loss of precision when “lesser” kidney function equations are selected.

The authors confirm that the Principal Investigator for this paper is Manjunath Pai and that he had direct responsibility for maintaining patient record confidentiality for the retrospective study.

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial](https://creativecommons.org/licenses/by-nc/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2022 The Authors. *British Journal of Clinical Pharmacology* published by John Wiley & Sons Ltd on behalf of British Pharmacological Society.

2 | METHODS

A retrospective study was conducted using patient data from the Michigan Medicine health system. Local institutional review board approval was obtained prior to study initiation. Data were obtained from DataDirect, a self-service tool developed by the University of Michigan to collect patient information from the electronic medical record (Epic; Verona, WI, USA). The study timeframe was October 2010 to August 2020, and patients were included if they were 18 years of age or older, received intravenous vancomycin during an inpatient admission, had serum vancomycin concentration measurements and had both S_{cr} and S_{cys} measurements collected during the same admission. Patients were excluded if there was incomplete vancomycin dosing or concentration information or if they were supported by renal replacement therapy (including haemodialysis and continuous renal replacement therapy). RStudio (RStudio, PBC; Boston, MA, USA) was used for data manipulation.

The eCL_{cr} was computed using the Cockcroft-Gault (CG) equation with dosing weight (DW); the DW was based on the principle for use of total body weight (TBW) if $TBW < \text{ideal body weight (IBW)}$ or adjusted body weight if $TBW > 1.25 \times \text{IBW}$, or IBW neither condition is met.¹¹ The $eGFR_{cr}$ was estimated using the Modification of Diet in Renal Disease and CKD-EPI equations.^{12,13} The $eGFR$ was also estimated using the modified CKD-EPI that incorporated S_{cys} and both S_{cr} and S_{cys} .^{14,15} These kidney function estimates were adjusted for body surface area to yield units in mL/min.³

Pharmacokinetic (PK) analyses were performed using Monolix and Sycomore (MonolixSuite 2020R1; Lixoft SAS, Antony, France). For population PK analysis, the stochastic approximation expectation maximization algorithm was used within Monolix 2020R1 along with individual vancomycin dosing and concentration-time data. A one-compartment, zero-order input and linear clearance parameterized model was used as the base model and was subsequently modified by testing each demographic and kidney function estimate as a covariate of clearance. This was performed on a stepwise basis by testing each potential covariate independently. The typical values for volume of distribution and CL were estimated using the auto-initiation function in Monolix and matched clinical expectations.

Model discrimination was based on the Akaike information criterion (AIC), the goodness-of-fit plots and changes to the residual standard error between models. Models were ranked based on the greatest to the smallest change in AIC relative to the base model. For vancomycin dose regimen simulations, Monte Carlo simulations ($n = 1000$) were performed with the best performing model and were stratified by $eGFR$ groups (5-14, 15-29, 30-44, 45-59, 60-74, 75-89, 90-119 and 120-180 mL/min). Vancomycin doses of 750 to 1500 mg (250 mg increments) at 8-, 12-, 24- and 48-h intervals over a week were simulated and the probability of achieving an AUC_{24} of 400-600 h-mg/L was computed. The typical AUC_{24} in clinical practice is informed after the third or fourth dose. For fair comparisons across $eGFR$ strata, the AUC_{24} at steady state was defined as a value computed between 120 and 144 h that allowed for administration of at least three doses in the lowest $eGFR$ group (5-14 mL/min). Longer

What is already known about this subject

- Drug dosing adjustment based on estimated kidney function is based on serum creatinine (S_{cr}) with equations that include or exclude race as a covariate.
- Alternate kidney function equations that use serum cystatin C (S_{cys}) do not include race as a covariate but have not been applied for drug dosing.
- Removal of race-based equations in clinical pharmacology is an important element to dismantling structural racism due to the improper attribution of human phenotype to this social construct.

What this study adds

- Race is not a useful covariate of kidney function for drug clearance estimation.
- Equations that use S_{cys} outperform those that use S_{cr} to estimate the clearance of the model kidney function-dependent drug vancomycin.
- Vancomycin dosing based on nonrace-based equations of kidney function are more likely to achieve the probability of target attainment than race-based equations.

dosing intervals risk low exposures early in the dosing regimen and so the use of loading doses was also tested. Multiple iterations were tested to identify the optimal pragmatic vancomycin regimen with the “best” $eGFR$ model. This dosing nomogram was then tested to compute the PTA for “lesser” kidney models given that S_{cys} may not be available in some institutions.

3 | RESULTS

Eighty-two patients were included in the analysis, with the following values reported as median (5th percentile, 95th percentile). Fifty per cent were male, 81.7% were Caucasian, aged 54.5 (18, 79) years, weight 69.4 [42.0, 113] kg and height 1.65 (1.40, 1.85) m. The median baseline S_{cr} and S_{cys} values were 1.17 (0.34, 3.19) mg/dL and 2.40 (0.64, 4.02) mg/L, respectively. The patients received a median of three vancomycin doses, and therapeutic drug monitoring included a good distribution of trough measurements (48%) and mid-concentration (random) or peak measurements (52%) (Supporting Information Figure S1).

A one-compartment model provided the optimal structural model fit, and discrimination of covariates of CL through the stepwise model-building process is reported here. As shown in Table 1, weight and race did not improve the model relative to age, sex and height.

The inclusion of S_{cys} as a single covariate had the largest reduction in AIC (-81.3 points) compared to S_{cr} (-26.6 points), including eCL_{cr} estimated by the CG equation and S_{cr} -based eGFR equations.^{2,11-15} Supporting Information Table S1 includes detailed comparisons of 10 versions of the CKD-EPI equations using S_{cr} , S_{cys} and the combination of S_{cr} - S_{cys} in absolute and BSA indexed units with and without race. eGFR translated into absolute units (no BSA) had significantly lower AIC values (8.9 to 17.4 points lower) than BSA-indexed eGFR values (Supporting Information Table S1). For reference, a greater than a 2-point difference in AIC values is considered sufficiently discriminatory of one model over the other. The 2012 CKD-EPI eGFR_{cys} equation demonstrated the most improvement over the base model

TABLE 1 Comparison of pharmacokinetic models with physical characteristics and kidney function biomarkers and estimates tested as a covariate of clearance

Model	AIC	Δ AIC
Base model	1498.6	0
Weight	1501.3	+2.7
Race	1499.6	+1.0
Height	1495.2	-3.4
Sex	1479.9	-18.7
S_{cr}	1472.0	-26.6
Age	1471.1	-27.5
CG (mL/min)	1464.1	-34.5
MDRD (mL/min/1.73 m ⁻²)	1464.3	-34.3
MDRD (mL/min)	1457.4	-41.2
S_{cys}	1417.3	-81.3

Abbreviations: AIC, Akaike information criterion; CG, Cockcroft-Gault; MDRD, Modification of Diet in Renal Disease; S_{cr} , serum creatinine; S_{cys} , serum cystatin C; Δ AIC, difference in AIC between covariate model and the base model.

with a change in AIC of 97 points (Supporting Information Table S1). Model diagnostics are provided in Supporting Information Figures S1-S4 to compare the base to the final model (2012 CKD-EPI eGFR_{cys}). Using this final model in Monte Carlo simulations, the probability of target attainment for achieving a vancomycin AUC₂₄/MIC (assuming MIC = 1 mg/L) of 400 to 600 was 71% to 74% across pragmatic regimens of eGFR strata (Table 2). Supporting Information Figure S5 illustrates the distributions of simulated concentration-time profiles ($n = 1000$) for this dosing regimen with this final model.

The 2012 CKD-EPI eGFR_{cys} equation does not include a race-based factor, and so the next "best" model based on this analysis if the race is excluded and only S_{cr} is measured would be the new 2021 CKD-EPI eGFR_{cr} equation (no BSA or race) (Supporting Information Table S1). Using the same eGFR strata, the PTA for these vancomycin regimens would be 54-67%. Likewise, using the conventional eCL_{cr} method based on the CG equation is expected to yield a PTA of 58-65% across these regimens (Table 2). Taken together, the availability of S_{cys} and use of the 2012 CKD-EPI eGFR_{cys} equation are predicted to improve the PTA by a median (min, max) absolute difference of 15% (4%, 19%) compared to the 2021 CKD-EPI eGFR_{cr} equation.

4 | DISCUSSION

Currently, S_{cr} -based methods of estimating kidney function remain the standard, as reflected in the recent US FDA guidance for establishing dosing recommendations in renal impairment.³ Increasing evidence supports S_{cys} as a better predictor of kidney function and drug CL compared to S_{cr} . In this analysis, a population pharmacokinetic model that used the CKD-EPI equation and incorporated S_{cys} best-predicted vancomycin CL among a cohort of 82 hospitalized patients. The final eGFR_{cys} model performed better than eCL_{cr} , eGFR_{cr} and eGFR_{cr-cys} models with and without race as a factor.

TABLE 2 Probability of target attainment by estimated glomerular filtration rate strata based on pragmatic dose and frequency of administration considerations using three nonrace-based equations for estimation of kidney function

eGFR (mL/min)	Vancomycin dosing regimen	Probability of target attainment (PTA) (%)		
		2012 CKD-EPI eGFR _{cys}	2021 CKD-EPI eGFR _{cr}	1976 CG eCL_{cr}
5-14	1000 mg loading dose, 750 mg every 48 h	71	67	65
15-29	750 mg every 24 h	73	66	62
30-44	1000 mg every 24 h	74	65	58
45-59	1500 mg every 24 h	73	58	59
60-74	1000 mg every 12 h	73	55	59
75-89	1250 mg every 12 h	73	54	58
90-119	1500 mg every 12 h	72	56	58
120-180	1500 mg every 8 h	71	56	58

Note: The best performing model pharmacokinetic model was used to simulate vancomycin clearance across the spectrum of renal function. The probability of attaining AUC₂₄/MIC 400-600 over a week was estimated.

Abbreviations: CG, Cockcroft-Gault; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eCL_{cr} , estimated creatinine clearance; eGFR, estimated glomerular filtration rate (derivatives incorporating serum creatinine [eGFR_{cr}] or cystatin C [eGFR_{cys}] were estimated).

This study is not without limitations surrounding generalizability. It is a single-centre, retrospective study, which may be biased by uncontrolled confounders or circumstances unique to this institution and patient population. Data collection was narrowed to patients' laboratory values and vancomycin dosing regimens. Information about patients' clinical status, acuity, infection and outcomes could not be accounted for. While this is a limitation, our results reveal a high likelihood of improvement using S_{cys} compared to S_{cr} in practice. A head-to-head comparison of a S_{cys} -based and S_{cr} -based dosing algorithm for antibiotics such as vancomycin is necessary to confirm our findings. Adopting the use of S_{cys} and 2012 CKD-EPI $eGFR_{cys}$ also reduces the potential for race-based equation bias and may add value to the dosing considerations of other agents.¹⁴ The use of the 2021 CKD-EPI $eGFR_{cr}$ equation (no BSA) that excludes race as a factor does not reduce the precision of vancomycin dosing compared to the conventional eCL_{cr} standard if only S_{cr} is available.² Extending our findings to other key drugs that require dose adjustment in patients with abnormal kidney function is necessary to support clinical implementation and patient outcomes.

COMPETING INTERESTS

All the authors declared no competing interests.

DATA AVAILABILITY STATEMENT

Data are available on request from the authors.

ORCID

Manjunath P. Pai  <https://orcid.org/0000-0001-7119-5034>

REFERENCES

- Delgado C, Baweja M, Crews DC, et al. A unifying approach for GFR estimation: recommendations of the NKF-ASN Task Force on reassessing the inclusion of race in diagnosing kidney disease. *Am J Kidney Dis.* 2022;79(2):268-288.e1. doi:10.1053/j.ajkd.2021.08.003
- Inker LA, Eneanya ND, Coresh J, et al. New creatinine- and cystatin C-based equations to estimate GFR without race. *N Engl J Med.* 2021; 385(19):1737-1749. doi:10.1056/NEJMoa2102953
- US Food and Drug Administration. Pharmacokinetics in patients with impaired renal function—study design, data analysis, and impact on dosing and labeling. September 3, 2020. Accessed April 12, 2022. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pharmacokinetics-patients-impaired-renal-function-study-design-data-analysis-and-impact-dosing-and>
- Crass RL, Pai MP. Estimating renal function in drug development: time to take the fork in the road. *J Clin Pharmacol.* 2019;59(2):159-167. doi:10.1002/jcph.1314
- Bidell MR, Lodise TP. Suboptimal clinical response rates with newer antibiotics among patients with moderate renal impairment: review of the literature and potential pharmacokinetic and pharmacodynamic considerations for observed findings. *Pharmacotherapy.* 2018;38(12): 1205-1215. doi:10.1002/phar.2184
- Dowling TC, Matzke GR, Murphy JE, Burckart GJ. Evaluation of renal drug dosing: prescribing information and clinical pharmacist approaches. *Pharmacotherapy.* 2010;30(8):776-786. doi:10.1592/phco.30.8.776
- Delanaye P, Cavalier E, Pottel H. Serum creatinine: Not so simple! *Nephron.* 2017;136(4):302-308. doi:10.1159/000469669
- Onopiuk A, Tokarzewicz A, Gorodkiewicz E. Cystatin C: a kidney function biomarker. *Adv Clin Chem.* 2015;68:57-69. doi:10.1016/bs.acc.2014.11.007
- Barreto EF, Rule AD, Murad MH, et al. Prediction of the renal elimination of drugs with cystatin C vs creatinine: a systematic review. *Mayo Clin Proc.* 2019;94(3):500-514. doi:10.1016/j.mayocp.2018.08.002
- Rybak MJ. The pharmacokinetic and pharmacodynamic properties of vancomycin. *Clin Infect Dis.* 2006;42(Suppl 1):S35-S39. doi:10.1086/491712
- Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron.* 1976;16(1):31-41. doi:10.1159/000180580
- Levey AS, Coresh J, Greene T, et al. Using standardized serum creatinine values in the Modification of Diet in Renal Disease study equation for estimating glomerular filtration rate [published correction appears in *Ann Intern Med.* 2008 Oct 7;149(7):519] [published correction appears in *Ann Intern Med.* 2021 Apr;174(4):584]. *Ann Intern Med.* 2006;145(4):247-254. doi:10.7326/0003-4819-145-4-200608150-00004
- Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate [published correction appears in *Ann Intern Med.* 2011 Sep 20;155(6):408]. *Ann Intern Med.* 2009;150(9):604-612. doi:10.7326/0003-4819-150-9-200905050-00006
- Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C [published correction appears in *N Engl J Med.* 2012 Aug 16;367(7):681] [published correction appears in *N Engl J Med.* 2012 Nov 22;367(21):2060]. *N Engl J Med.* 2012;367(1):20-29. doi:10.1056/NEJMoa1114248
- Inker LA, Eckfeldt J, Levey AS, et al. Expressing the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) cystatin C equations for estimating GFR with standardized serum cystatin C values. *Am J Kidney Dis.* 2011;58(4):682-684. doi:10.1053/j.ajkd.2011.05.019

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Yun HG, Smith AJF, DeBacker KC, Pai MP. Estimated glomerular filtration rate with and without race for drug dosing: Cystatin C vs. serum creatinine. *Br J Clin Pharmacol.* 2023;89(3):1207-1210. doi:10.1111/bcp.15592