

Removing race and body surface area indexation for estimated kidney function based drug dosing: Aminoglycosides as justification of these principles

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Abstract

Study Objective: The use of race in medicine can contribute to health inequity. Updated equations for estimated glomerular filtration rate (eGFR) without race have been published. Likewise, de-indexation of eGFR to body surface area (BSA) has been recommended by regulatory guidance for drug dosing in renal impairment. Clinical data justifying these recommendations for drug dosing are sparse. We examined the gain or loss of precision in drug dosing with estimated creatinine clearance (eCLcr) and eGFR using serum creatinine (eGFRcr) with and without race and BSA indexation by evaluating the population pharmacokinetics of the aminoglycosides as a classic drug class to probe kidney function.

Design: Medical records from adult patients treated with gentamicin or tobramycin over a 13-year period were queried. Population pharmacokinetic analyses were performed using a 1-compartment base structural model. Models compared body size descriptors as covariates of the volume of distribution (V). Estimated creatinine clearance and eGFRcr using multiple contemporary equations with and without BSA indexation were tested as covariates of clearance (CL).

Main Results: The final data set included 2968 patients treated with either gentamicin (20.2%) or tobramycin (79.8%). Patients self-identified as Caucasian (82%), African-American (10%), or other. The median [5th, 95th percentile] weight and BSA were 80.5 [49.4, 136] kg and 1.94 [1.48, 2.56] m², respectively. Models of eCLcr and eGFRcr without indexation to BSA had a better model fit than eGFRcr indexed to BSA for aminoglycoside CL. The 2021 Chronic Kidney Disease Epidemiology collaboration (CKD-EPI) eGFRcr equation (no race, no BSA indexation) provided a comparable model fit to the 2009 CKD-EPI eGFRcr equation (with race, no BSA indexation) for aminoglycoside CL.

Conclusions: Race is not a relevant covariate of aminoglycoside CL. The 2021 CKD-EPI eGFR equation without race and BSA indexation is a better method for gentamicin and tobramycin CL estimation. Confirmation of these results for other drugs can support the harmonization of dosing by kidney function.

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KEYWORDS

African, black, clearance, drug development, drug dosing, kidney, precision medicine, race, regulatory, structural racism

1 | INTRODUCTION

The use of race as a categorization tool can contribute to racism and health inequity.^{1,2} Race essentialism can inadvertently reinforce the idea that biological processes such as kidney function can be explained by observable underlying human features such as skin color and hair type.¹ This is a pertinent problem in pharmacy and medicine because kidney function is routinely estimated to support drug dosing, stage kidney disease, and guide clinical decisions. Our contemporary approach relies on the translation of a single serum creatinine (Scr) measurement into estimated creatinine clearance (eCLCr) or estimated glomerular filtration rate (eGFR) using Scr (eGFRcr).³ Differences in central tendency values of Scr in different populations have contributed to the application of race as a covariate of kidney function.^{4,5} In contrast, a race factor is not necessary when other endogenous biomarkers are used for eGFR such as cystatin C (eGFRcys).⁶ Patients who self-identify as African American have a four-fold higher risk of developing kidney failure but are much less likely to receive a kidney transplant.⁷ This inequity along with a plethora of other examples led the United States House of Representatives Committee on Ways and Means to engage with 13 professional societies to re-evaluate the use of race in clinical algorithms.¹ In response to this request, a multidisciplinary task force was established in 2020 by the American Society of Nephrology and the National Kidney Foundation to address this application of race in eGFR.⁸ The task force has carefully outlined a position to exclude the use of race in diagnosing and treating kidney disease, and new eGFR equations have been published that now exclude race.⁹

As expected with any change in practice, concerns have been raised with the removal of race.^{2,10,11} The average Scr value is approximately 10%–20% higher in self-identified African Americans compared to Caucasian patients in a health system, and so the original correction factor of 1.159 in African American patients was implemented to prevent underestimation of eGFRcr.¹² Similar rationales and arguments have been made and are currently applied in Asian populations.^{13–16} Before publication of the revised 2021 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) eGFRcr equation, some institutions simply abandoned the use of the race factor without correcting the coefficients of the whole equation, which is also mathematically erroneous. As expected, the removal of a race factor could in theory reduce the eGFR computed value in African American patients and inadvertently lead to other problems.² These concerns include a risk of under dosing antibiotic and cancer chemotherapy that could lead to increased morbidity and mortality.^{2,10} Also, discontinuation or avoidance of medications such as metformin or procedures such as intravenous contrast for imaging studies could occur in African American patients with the removal of the race factor.

In addition to the use of race, eGFR equations unlike eCLCr have indexed these estimates to body surface area (BSA) of 1.73m².¹⁷ The origin and history of 1.73m² have been previously reviewed but most importantly does not reflect the United States adult population central tendency value that is closer to approximately 2 m² due to the rise in obesity.^{18,19} So, scaling to 1.73m² should theoretically underestimate the average eGFR by 15%–20%. Given that the prevalence of obesity is highest in self-identified African American adults, currently 49.9%, this indexation serves as another source of eGFR underestimation.²⁰ The United States Food and Drug Administration has recognized this scaling issue and recommended that eGFRcr and eCLCr be used in absolute and not BSA-indexed values when modeling drug clearance (CL) and establishing drug dose labeling.²¹ These changes and initiatives led us to examine the gain or loss of precision in drug dosing with eCLCr and eGFRcr with and without race and BSA indexation. We chose to tackle this question by evaluating the population pharmacokinetics (PopPK) of the aminoglycosides that serve as a classic drug class to probe kidney function.

2 | METHODS

2.1 | Ethics

This was a retrospective study conducted across the Michigan Medicine enterprise. Institutional review board approval was obtained from the University of Michigan before the collection of any patient data.

2.2 | Design and study population

Data were retrospectively obtained from “DATADIRECT”, a self-service clinical database developed and maintained by the University of Michigan. The query time frame was an approximately 13-year period between January 2009 and January 2022. Patient records were queried if the following criteria were satisfied: (i) patients greater than 18 years of age, (ii) therapy with intravenous gentamicin or tobramycin, (iii) measurement of gentamicin or tobramycin concentrations during the course of therapy, and (iv) availability of height, weight, age, Scr, and dose administration information. Data queried included patient demographics, encounters, drug orders and administration times, and laboratory information. Data were password protected and stored on a secure platform maintained by the University. Data manipulation was accomplished using the R programming language and environment. Patients were excluded if they met any of the following criteria: (i) incomplete or missing dosing information during the

first course of therapy, (ii) lack of documentation of height and weight, and (iii) renal replacement therapy (including hemodialysis and continuous renal replacement therapy).

2.3 | Alternate body size and kidney function estimates

Alternative body size scalars including ideal body weight (IBW), adjusted body weight (adjBW), lean body weight (LBW), and BSA using Mosteller's adaptation were computed as previously described.¹⁹ We also computed dosing weight (DW) that used total body weight (TBW) if less than IBW, adjBW if $TBW > 1.25 \times IBW$, and IBW if neither criteria are met.²² In addition TBW scaled as a power function $[(TBW/\text{average TBW})^\beta]$ or as a fixed power function, allometrically as $[(TBW/\text{average TBW})^{0.75}]$ were also tested. Estimates of kidney function were calculated using the Cockcroft-Gault and the 2009 and 2021 CKD-EPI eGFRcr equations.^{12,23} These eGFRcr values were also transformed and tested as BSA-deindexed values.

2.4 | Pharmacokinetic and statistical analyses

Pharmacokinetic analyses were performed using Monolix2021R1 (Monolix Suite2019R2, Antony, France: Lixoft SAS, 2019). For PopPK analysis, the stochastic approximation expectation maximization (SAEM) algorithm was used within Monolix2021R1 and individual gentamicin or tobramycin dosing and concentration time data. A 1-compartment, first-order input and linear clearance parameterized model structure was selected given repeated documentation of this model and typical measurement of two drug concentrations after dose administration. Numerous population pharmacokinetic models exist for dosing aminoglycosides that parameterize volume of distribution (V) on body weight and CL on kidney function. Our intent was not to construct a new approach to dosing aminoglycosides but rather to compare the gain and loss of precision with the new 2021 CKD-EPI eGFRcr equation models without race and BSA. Model discrimination was based on the Akaike Information Criterion (AIC), with a greater than two-point difference between models as criterion for substantial difference.²⁴ These model comparisons were performed using Sycomore2021R2 within the Monolix suite. Visual predictive checks and non-parametric distribution error checks were performed with each model run through an efficient pipeline process within Monolix2021R1.

3 | RESULTS

3.1 | Study population

A total of 2968 adult patients treated with gentamicin (20.2%) or tobramycin (79.8%) were evaluated based on the inclusion and

TABLE 1 Study population demographics and kidney function estimates

Variables	Gentamicin (n = 600)	Tobramycin (n = 2368)
Male:Female	49%:51%	57.3%:42.7%
Age (years)	50 [19, 78]	54 [19, 79]
Self-Identified Race, n (%)		
African American	64 (10.7%)	232 (9.80%)
American Indian or Alaska Native	1 (0.17%)	10 (0.42%)
Asian	15 (2.50%)	37 (1.56%)
Caucasian	498 (83.0%)	1941 (82.0%)
Native Hawaiian and Other Pacific Islander	0 (0%)	2 (0.08%)
Other	11 (1.83%)	40 (1.69%)
Unknown	11 (1.83%)	106 (4.48%)
Height (cm)	170 [152, 188]	170 [152, 186]
Weight (kg)	81.0 [50.6, 134]	79.1 [49.0, 136]
Serum creatinine (mg/dl)	0.80 [0.40, 1.85]	0.80 [0.33, 2.44]
BSA (m ²)	1.95 [1.50, 2.55]	1.94 [1.48, 2.56]
Cockcroft-Gault eCLcr (ml/min)	100 [41.0, 195]	95.4 [28.9, 206]
2009 CKD-EPI eGFRcr (ml/min/1.73m ²)	96.3 [34.7, 147]	93.7 [25.1, 155]
2009 CKD-EPI eGFRcr (ml/min)	109 [43.3, 178]	104 [28.6, 180]
2021 CKD-EPI eGFRcr (ml/min/1.73m ²)	100 [37.1, 137]	97.7 [26.2, 144]
2021 CKD-EPI eGFRcr (ml/min)	110 [46.0, 169]	107 [30.1, 170]

Note: Data shown as median [5th, 95th percentiles], unless otherwise indicated.

Abbreviations: BSA, body surface area; CKD-EPI, chronic kidney disease epidemiology equation; eCLcr, estimated creatinine clearance using Cockcroft-Gault equation with dosing weight (see methods); eGFRcr, estimated glomerular filtration rate using serum creatinine.

exclusion criteria. [Table 1](#) provides a summary of the population demographics and kidney function estimates for the population. A near-equal balance of males and females was observed in the gentamicin group compared to a higher proportion of males (57.3%) in the tobramycin-treated group. The age distribution spanned young adults to the elderly in both treated groups and self-identified races matched the Michigan Medicine patient population expectations, approximately 82% Caucasian and 10% African-American. The height and weight distributions also matched current population expectations. As noted the median BSA was approximately 1.95 m², which is 13% higher than the 1.73 m² indexation. [Table 2](#) includes a comparison of Caucasian and African-American patients for this combined aminoglycoside cohort by sex (expected differences in body measurements). African-American female patients in this cohort were younger (9 years on average), and had

a higher body weight (4 kg on average), higher BSA (small difference), and higher Scr value (25% higher) compared with Caucasian female patients. Differences in the estimate of kidney function were observed by sex with the use of the 2009 CKD-EPI equation and with the 2021 CKD-EPI equation when indexed to BSA. However comparable eCLcr were observed along with eGFRcr using the 2021 CKD-EPI equation without BSA indexation by sex between these two self-identified race groups.

3.2 | Pharmacokinetic analyses

The median parameter estimates for V and CL were 23.5 L and 3.56 L/h for gentamicin and 33.9 L and 3.87 L/h for tobramycin, respectively. The interindividual variability for CL (45%–56%) was higher than that of V (30%–34%). As expected from numerous prior PopPK models, body weight was a significant predictor of V and estimates of kidney function were significant predictors of CL. Race was not a significant categorical covariate of either pharmacokinetic (PK) parameter for gentamicin or tobramycin. A [supplementary file](#) containing the correlation co-efficients and statistical analyses are included for the random effects of V and CL versus these covariates for both gentamicin and tobramycin. Given that the purpose of this assessment was to quantify the gain or loss of precision in drug dosing with eCLcr and eGFRcr with and without race and BSA indexation, we focused our analysis accordingly. The V of both gentamicin and tobramycin were modeled as power functions of weight (indexed to 80 kg). As shown in [Tables 3 and 4](#), central tendency values for these exponents (θ_1) were 0.62–0.72 for gentamicin and tobramycin, which are consistent with two-thirds power-law scaling.¹⁹ Of note, lower exponent values were estimated for models where kidney function was scaled to BSA. Likewise, CL of gentamicin and tobramycin were best scaled as

power functions of kidney function (indexed to 90 ml/min or 90 ml/min/1.73 m²). [Tables 3 and 4](#) show that CL models with kidney function in ml/min performed better than models in ml/min/1.73 m². BSA de-indexed models of eGFR performed better than eCLcr. The best model of eCLcr was based on the Cockcroft-Gault equation and use of the DW. Overall, the greatest reduction in the AIC value was observed with the use of the 2009 CKD-EPI equation (ml/min) but was indistinguishable (with two points) from the 2021 CKD-EPI equation (ml/min). Of note, the value of the exponent (θ_2) on the weighted kidney function model of CL for gentamicin increased from 0.66 to 0.86, approaching a value closest to 1.0 with the CKD-EPI 2021 equation (ml/min) implying a nearly linear relationship between the two. A similar but less pronounced trend is observable with the exponent (θ_2) on the weighted kidney function model of CL for tobramycin. Overall the interindividual variability with the use of 2021 CKD-EPI eGFRcr and weight on CL and V, respectively, were reduced by 13% and approximately 5% in absolute terms. A finding that is consistent and reasonable when interpreting PopPK models.²⁵

3.3 | Comparison of race and BSA indexation

As noted in the PopPK analyses, models that did not incorporate race performed as well as models that incorporated race (no loss of precision). However, models that evaluated kidney function in BSA deindexed values performed better than those indexed to BSA. These findings can be visualized in [Figures 1 and 2](#). [Figure 1](#) includes a scatter and linear fit plot of the model individual predicted CL of gentamicin (A) and tobramycin (B) compared to eGFR based on CKD-EPI 2021 by self-identified Caucasian and African American race. As shown, these values and relationships are essentially superimposable for these two categorical groups. Simply put, there is no

TABLE 2 Comparison of body size descriptors and kidney function estimates in self-identified African American and Caucasian patients by sex.

Variable	Male		Female	
	African American	Caucasian	African American	Caucasian
Number	141	1367	155	1072
Age (years)	53 [21, 77]	58 [21, 81]	46 [20, 70]*	55 [20, 79]
Height (cm)	178 [160, 190]	178 [163, 188]	163 [152, 172]	163 [152, 173]
Weight (kg)	83 [55.4, 136]	85 [56, 137]	80 [47, 143]*	76 [46, 126]
BSA (m ²)	2.04 [1.63, 2.61]	2.04 [1.62, 2.62]	1.90 [1.43, 2.59]*	1.84 [1.43, 2.42]
Scr (mg/dl)	1.07 [0.40, 3.0]*	0.95 [0.40, 2.78]	0.90 [0.34, 3.03]*	0.72 [0.35, 2.35]
Cockcroft-Gault eCLcr (ml/min)	85.0 [26.6, 227]	90.2 [27.7, 199]	80.6 [21.9, 186]	84.5 [24.8, 192]
CKD-EPI 2009 eGFRcr (ml/min/1.73 m ²)	91.1 [25.7, 170]*	86.5 [23.2, 146]	89.8 [21.0, 157]	89.5 [21.1, 141]
CKD-EPI 2009 eGFRcr (ml/min)	113 [30.6, 198]*	100 [27.0, 178]	102 [21.7, 200]*	92.0 [23.3, 154]
CKD-EPI 2021 eGFRcr (ml/min/1.73 m ²)	85.3 [23.3, 142]	92.2 [24.9, 141]	81.2 [19.0, 133]*	94.1 [22.7, 139]
CKD-EPI 2021 eGFRcr (ml/min)	103 [28.3, 168]	105 [29.2, 173]	90.3 [20.0, 174]	96.4 [25.1, 153]

Note: Data shown as median [5th, 95th percentiles], unless otherwise indicated.

* $p < 0.05$, comparison within sex and between self-identified race.

TABLE 3 Comparison of the base model to alternate kidney function models of gentamicin clearance.

Model	Base Model	Cockcroft-Gault eCLcr (ml/min)	2009 CKD-EPI eGFRcr (ml/min/1.73 m ²)	2009 CKD-EPI eGFRcr (ml/min)	2021 CKD-EPI eGFRcr (ml/min/1.73 m ²)	2021 CKD-EPI eGFRcr (ml/min)
Race Factor	NA	No	Yes	Yes	No	No
BSA Indexed	NA	No	Yes	No	Yes	No
AIC	3999.99	3667.32	3682.32	3609.16	3690.59	3609.53
Delta AIC	0	-332.67	-317.67	-390.83	-309.40	-390.46
Fixed effects value (%RSE)						
V _{pop} (L)	23.54 (2.56)	23.51 (2.39)	24.19 (2.48)	23.55 (2.35)	23.88 (2.42)	23.83 (2.34)
θ ₁ - V		0.62 (12.7)	0.49 (16.8)	0.72 (10.8)	0.5 (16.0)	0.72 (10.8)
CL _{pop} (L/h)	3.56 (2.24)	3.38 (1.81)	3.64 (1.84)	3.28 (1.77)	3.59 (1.83)	3.22 (1.80)
θ ₂ - CL		0.66 (5.17)	0.74 (5.41)	0.81 (4.65)	0.79 (5.34)	0.86 (4.68)
Standard deviation of the random effects value (%RSE)						
Ω - V	0.30 (10.1)	0.27 (10.7)	0.29 (9.74)	0.26 (10.9)	0.27 (10.6)	0.25 (11.6)
Ω - CL	0.45 (3.73)	0.33 (4.27)	0.34 (4.27)	0.32 (4.36)	0.34 (4.25)	0.32 (4.34)
Error model parameters value (%RSE)						
Additive	0.17 (9.92)	0.16 (10.1)	0.14 (11.3)	0.15 (10.5)	0.15 (10.5)	0.14 (10.8)
Proportional	0.25 (5.74)	0.25 (5.29)	0.26 (5.13)	0.25 (5.14)	0.25 (5.23)	0.26 (5.04)

Abbreviations: AIC, Akaike Information Criteria; BSA, body surface area; CKD-EPI, chronic kidney disease epidemiology equation; CL_{pop}, population estimate of clearance; eCLcr, estimated creatinine clearance using Cockcroft-Gault equation with dosing weight (see methods); eGFRcr, estimated glomerular filtration rate using serum creatinine; NA, not applicable; V_{pop}, population estimate of volume of distribution.

$V = V_{pop} \times (\text{Weight}/80)^{0.1} + \text{error}$, weight in kg.

$CL = CL_{pop} \times ([\text{eCLcr or eGFRcr}]/90)^{0.2} + \text{error}$, kidney function in ml/min or ml/min/1.73 m².

TABLE 4 Comparison of base model to alternate kidney function models of tobramycin clearance

Model	Base model	Cockcroft-Gault eCLcr (ml/min)	2009 CKD-EPI eGFRcr (ml/min/1.73 m ²)	2009 CKD-EPI eGFRcr (ml/min)	2021 CKD-EPI eGFRcr (ml/min/1.73 m ²)	2021 CKD-EPI eGFRcr (ml/min)
Race factor	NA	No	Yes	Yes	No	No
BSA indexed	NA	No	Yes	No	Yes	No
AIC	22888.8	21586.26	21668.73	21505.08	21667.57	21505.31
Delta AIC	0	-1302.54	-1220.07	-1383.72	-1221.23	-1383.49
Fixed effects value (%RSE)						
V _{pop} (L)	33.94 (1.13)	34.05 (1.03)	34.14 (1.04)	33.96 (1.03)	34.20 (1.04)	33.95 (1.03)
θ ₁ - V		0.62 (5.34)	0.58 (5.77)	0.64 (5.17)	0.59 (5.64)	0.63 (5.27)
CL _{pop} (L/h)	3.87 (1.30)	4.20 (1.07)	4.44 (1.15)	4.13 (1.05)	4.40 (1.14)	4.07 (1.05)
θ ₂ - CL		0.63 (2.67)	0.63 (2.95)	0.67 (2.68)	0.66 (2.95)	0.70 (2.69)
Standard deviation of the random effects value (%RSE)						
Ω - V	0.34 (3.44)	0.29 (3.87)	0.30 (3.84)	0.29 (3.87)	0.29 (3.89)	0.29 (3.84)
Ω - CL	0.56 (1.74)	0.44 (1.88)	0.45 (1.86)	0.43 (1.89)	0.45 (1.86)	0.43 (1.88)
Error model parameters value (%RSE)						
Additive	0.056 (7.83)	0.055 (7.67)	0.056 (7.69)	0.055 (7.67)	0.055 (7.78)	0.055 (7.66)
Proportional	0.32 (1.64)	0.31 (1.58)	0.31 (1.59)	0.31 (1.58)	0.31 (1.59)	0.31 (1.59)

Abbreviations: AIC, Akaike Information Criteria; BSA, body surface area; CKD-EPI, chronic kidney disease epidemiology equation; CL_{pop}, population estimate of clearance; eCLcr, estimated creatinine clearance using Cockcroft-Gault equation with dosing weight (see methods); eGFRcr, estimated glomerular filtration rate using serum creatinine; NA, not applicable; V_{pop}, population estimate of volume of distribution.

$V = V_{pop} \times (\text{Weight}/80)^{0.1} + \text{error}$, weight in kg.

$CL = CL_{pop} \times ([\text{eCLcr or eGFRcr}]/90)^{0.2} + \text{error}$, kidney function in ml/min or ml/min/1.73 m².

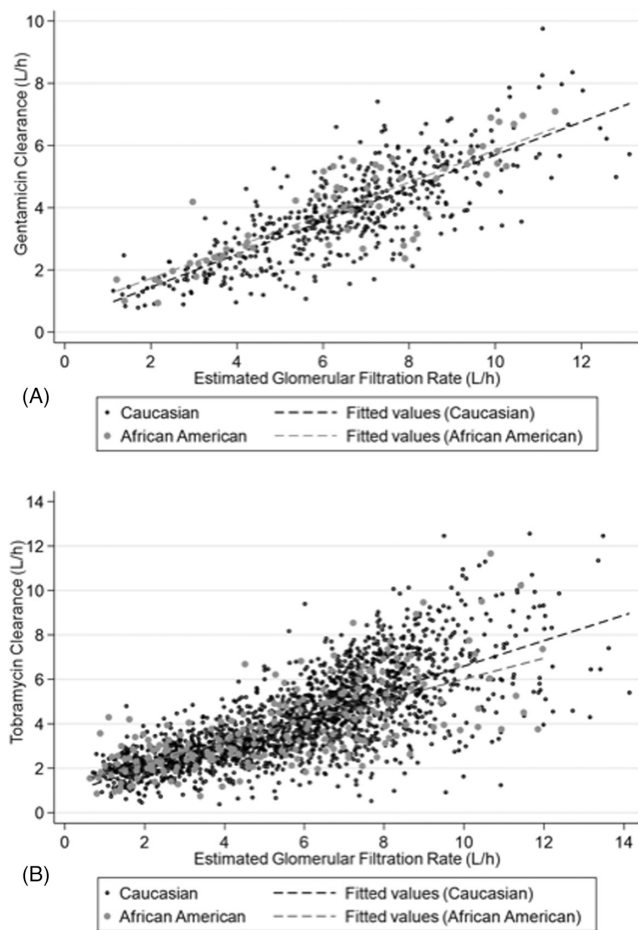


FIGURE 1 Scatter and linear fit plot of the final model predicted gentamicin (A) and tobramycin (B) clearance compared to the estimated glomerular filtration rate in self-identified Caucasian and African-American patients. Estimated glomerular filtration rate based on the 2021 Chronic Kidney Disease Epidemiology collaboration equation with serum creatinine.

difference in gentamicin or tobramycin CL in self-identified African Americans compared to Caucasians.

Figure 2 includes the scatter and linear fit plot of the individual model predicted CL for gentamicin and tobramycin compared to eGFRcr in BSA-indexed and non-indexed values. The individual model predictions in this illustration are on the base model (no-covariates) to better illustrate independent relationships. Indexation of values to 1.73m^2 leads to eGFRcr truncation and so weakens the linear relationship to CL. However as shown by Figure 2, the R^2 of eGFRcr to aminoglycoside CL is in the 0.35 to 0.38 range that is consistent with prior studies.^{26,27} Put in context, kidney function estimates account for less than half of the interindividual variability for a class of compounds that are predominantly eliminated unchanged in urine.

4 | DISCUSSION

Use of race in medical algorithms such as kidney function estimation can contribute to health inequity and incorrect scientific attribution

of a physiologic function to a social construct.²⁸ We have generally accepted corrections for eGFRcr by race due to measured differences in Scr in populations that we infer to be muscle mass and diet-related.^{5,29} As an example, we have surmised that a broadly (60% of global population) categorized groups of individuals such as “Asians” have lower Scr values than Caucasians, who have lower Scr values than African American patients.^{30,31} Although this central tendency difference in Scr is measurable on a population level in some groups it is obviously not reliable on an individual patient basis.⁵ In the current study this statistical difference in Scr central tendency was observed in African American females compared to Caucasian females but not in the comparison of males. However, these differences will not be seen when estimation is performed using the Cockcroft-Gault equation or the newly revised 2021 CKD-EPI equation that eliminates race when deindexed to BSA (not true if indexed).

As expected, the removal of this race factor and readjustment of existing equations can have the theoretical effect of misclassifying other populations. The United States has a declining Caucasian population and an increase in the number of individuals who self-identify as two or more races.³² So can the removal of the race factor negatively impact our estimation of drug doses in the predominant population when using the revised 2021 CKD-EPI eGFRcr equation? To address this question, we evaluated gentamicin and tobramycin because they have limited plasma protein binding, no known metabolism, and are eliminated unchanged (>90%) in urine, and so serve as exceptional probes of the GFR.³³ Our analyses show that the estimates of gentamicin and tobramycin CL across eGFRcr are not different in self-identified Caucasians compared to African Americans. Most importantly, estimated kidney function can only account for a portion of the interindividual variability of aminoglycoside CL. As illustrated, we have R^2 values that are between 0.35–0.38 for the relationship of aminoglycoside CL to eGFRcr. When incorporating weight and kidney function in population PK models, we show a 13% reduction in the standard deviation of the random effect (interindividual variability).

These findings are consistent for many drugs that are eliminated unchanged in urine. For example, a recent population PK model of gabapentin showed that weight and kidney function accounted for 15% of the interindividual variability of the apparent CL (CL/F).³⁴ As a consequence, the selection of one eGFRcr or eCLcr equation over the other is often perceived to be of minor consequence to pharmacometricians. This is also the reasoning behind language in guidance to industry to use a “contemporary equation” rather than a specific equation.²¹ Again, while this approach is mathematically sound from a population level, it presents real-world challenges to clinical pharmacists who are engaged in drug dosing decisions.³⁵ As noted in several works, significant discordance exists in product labels and institutional practice when making estimated kidney function based dose adjustments. Our analysis cannot address this larger need for harmonization between eCLcr and eGFRcr equations, which must occur through consensus. Our bias is that the 2021 CKD-EPI eGFRcr equation should be advanced because it is based on standardized Scr measurements, a large contemporary population, relies on an exogenous standard (iohexol), and eliminates race as a factor.⁹ This

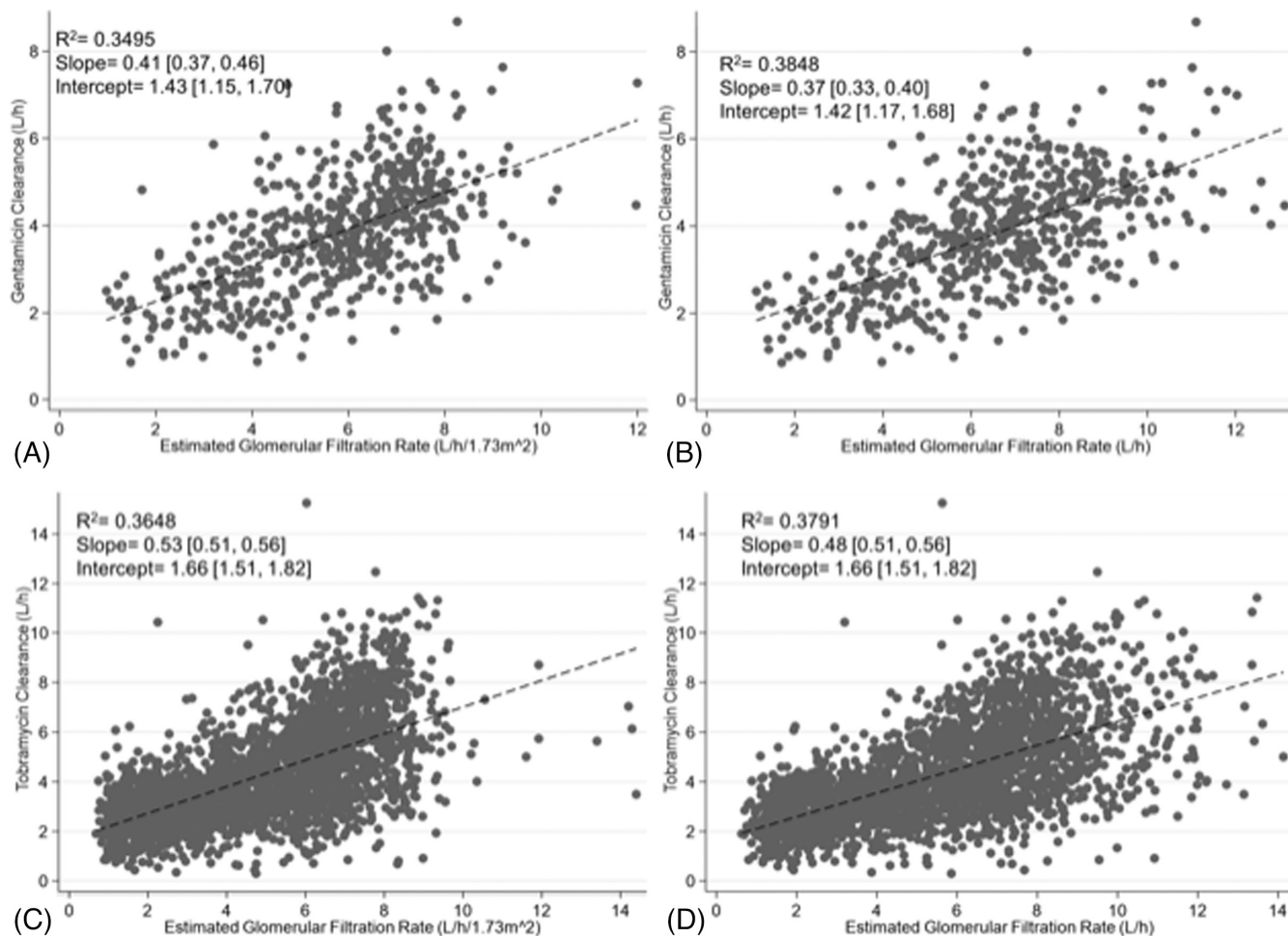


FIGURE 2 Scatter and linear fit plot of the base model predicted gentamicin (A and B) and tobramycin (C and D) clearance compared to the estimated glomerular filtration rate in absolute and body surface area indexed units. Estimated glomerular filtration rate based on the 2021 Chronic Kidney Disease Epidemiology collaboration equation with serum creatinine.

bias recognizes the difficulty of measuring GFR or using eGFR_{cys} because this more informative biomarker is not readily available or incorporated in drug development. Our analysis shows that future adoption of non-race based CKD-EPI eGFR_{cys} method without BSA indexation does not lead to a substantial loss in the precision of aminoglycoside CL. The inference is that this finding will be reproducible with other drugs that require dose adjustments for kidney function.

Our analyses are limited by the retrospective nature of data collection. We are not able to account for other potential confounders such as severity of illness and comorbidities such as diabetes, liver disease, and frailty. Our intent was also not to build a new PopPK model or method for dosing aminoglycosides. Instead, we used this tool to support comparisons of key contemporary methods of eGFR_{cys} and eCL_{cys}. Prospective enrollment and generation of such a large dataset would require a multi-institutional approach, would be expensive to do, and not generate results in a timely manner. Validation of our findings is also feasible by other independent research groups because of the routine use of therapeutic drug monitoring of these agents and access to electronic health records. This affords rigor and reproducibility to move this model forward.

5 | CONCLUSIONS

Our study does not support race as a relevant covariate either alone or in equations that estimate GFR for determining aminoglycoside CL. The 2021 CKD-EPI eGFR_{cys} equation (no race) offers similar precision to the 2009 CKD-EPI eGFR_{cys} equation (with race) for the estimation of gentamicin and tobramycin CL estimates. Use of kidney function values in ml/min is better than indexation to ml/min/1.73m² when estimating CL for drug dosing. The 2021 CKD-EPI eGFR_{cys} equation without race and BSA indexation should be evaluated as a potential standard model for drug dosing across kidney function in drug development.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

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

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