Title: Comparison of Race and Non-Race Based Equations for Kidney Function Estimation in Critically Ill Thai Patients for Vancomycin Dosing

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Abstract

Empiric antibiotic dosing frequently relies on an estimate of kidney function based on age, serum creatinine (SCr), sex, and race (on occasion). New non-Race based estimated glomerular filtration rate (eGFR) equations have been published but their role to support dosing is not known. Here, we report on a population pharmacokinetic model of vancomycin that serves as a useful probe substrate of eGFR in critically ill Thai patients. Data were obtained from medical records during a 10-year period. A nonlinear mixed-effects modeling approach was conducted to estimate vancomycin parameters. Data from 208 critically ill patients (58.2% male and 36.0% septic shock) with 398 vancomycin concentrations were collected. Twenty-three covariates including 12 kidney function estimates were tested and ranked based on the model performance. The median [min, max] age, weight, and SCr was 69 [18, 97] years, 60.0 [27, 120] kg, and 1.53 [0.18, 7.15] mg/dL. The best base model was a one-compartment linear with zero-order input and proportional error model. A Thai specific eGFR equation not indexed to body surface area (BSA) model best predicted vancomycin clearance (CL). The typical value for volume of distribution and CL was 67.5 L and 1.22 L/h, respectively. A loading dose of 2000 mg followed by maintenance dose regimens based on eGFR is suggested. The Thai-GFR not indexed to BSA model best predicts vancomycin CL and dosing in the critically ill Thai population. A 5-10% absolute gain in the vancomycin probability of target attainment is expected with the use of this population specific GFR equation.

Introduction

Early effective antimicrobial therapy is a crucial strategy for lowering morbidity and mortality associated with septic shock.[1] Empirical antibiotic dosing in septic shock patients should be based on pharmacokinetic/pharmacodynamic (PK/PD) principles for improving treatment outcomes.[1] Septic shock alters antibiotic PK that can lead to subtherapeutic concentrations and also increased risk of antimicrobial toxicity. [1, 2]

Vancomycin is commonly administered empirically to septic shock patients to ensure coverage against methicillin-resistant *Staphylococcus aureus* (MRSA).[1, 3-5] Currently, an area under the curve over minimum inhibitory concentration determined by broth microdilution (AUC/MIC_{BMD}) ratio of 400-600 is recommended as the optimal PK/PD index target to sustain efficacy and minimize nephrotoxicity risk.[5] The PK of vancomycin in critically ill patients is distinct from other populations, with empirical dosing recommendations of vancomycin that suggest the need for high doses and close monitoring.[6-9]

Body weight and an estimate of kidney function is the basis for vancomycin maintenance dose selection. Estimated creatinine clearance (eCrCL) using the Cockcroft - Gault (CG) equation has consistently been identified as a covariate of vancomycin clearance (CL) in critically ill patients and is commonly used for vancomycin dose adjustment.[6, 7, 9, 10] The eCrCL in mL/minute is based on age, body weight, serum creatinine (SCr), and sex while the other estimated glomerular filtration rate (eGFR) equations including the Modification of Diet in Renal Disease (MDRD) equation and Chronic Kidney Disease–Epidemiology (CKD-EPI) equations is based on age, SCr, sex, and race and reported in mL/minute/1.73 m^2.[11, 12] The original MDRD equation for race was imprecise and so was re-expressed with a Thai racial factor correction equation to improve the kidney function estimation in the Thai population.[13] However, the relevance of this Thai race factor on drug

dosing for kidney function has not been evaluated. Recently, a new creatinine-based eGFR equation has been published to address the potential for systemic racism in medicine. While discussions have focused on black and non-black populations, less attention has been drawn to unique Asian populations such as the Thai.[14] A systematic evaluation of vancomycin CL prediction using eCrCL and eGFR equations, body surface area (BSA) indexed and unindexed values, inclusion and exclusion of race has not been performed.[15]

The objectives of this study were to rank the performance of race and non-race based equations for kidney function estimation as covariates and to evaluate the influence of covariates on PK parameters of vancomycin in Thai critically ill patients. We also quantify the marginal loss and gain with the use of alternate eGFR equations for vancomycin dosing in critically ill Thai patients.

Methods

Study Design and Study Population

This retrospective population PK study was conducted at Songklanagarind Hospital, a tertiary care university hospital located in Songkhla, Thailand. The study was approved by the human research ethics committee of Faculty of Medicine, Prince of Songkla University. Data of all patients fulfilling the inclusion criteria during August, 2011 to July, 2021 were obtained.

Thai patients greater than 18 years of age, admitted in the ICU or met critically ill patient criteria,[16] received intravenous vancomycin, and measurement of serum vancomycin concentrations during the course of vancomycin treatment were enrolled. The patients were excluded if (i) pregnant, (ii) incomplete or missing vancomycin dosing or concentration time

information, (iii) on extracorporeal membrane oxygenation, and (iv) on renal replacement therapies during vancomycin measurement.

The intravenous vancomycin orders, administration times, serum concentration, and collection times were collected. Concentrations collected ≤ 4 hours after dosing and ≤ 2 hours before dosing were defined as peak and trough values, respectively; otherwise, concentrations were classified as mid-point values. Patient demographics, vasopressors information, Sequential Organ Failure Assessment (SOFA) score, 24-hour fluid balance, pathogen and site of infection, and laboratory information on the first day of vancomycin measurement were also collected. Patients were defined as having septic shock if they had sepsis-induced hypotension, refractory to adequate fluid resuscitation and required vasopressor administration. [17]

Kidney Function Estimates

The eCLCr was based on the CG equation using total body weight (TBW), or Adjusted body weight (adjBW) in patients with a body mass index (BMI) > 23.0 kg/m^2. [18,19, 20] The eGFR was calculated by (i) 4-variable MDRD using an isotope dilution mass spectrometry (IDMS) traceable (MDRD4-IDMS) equation,[11] (ii) 2009 CKD-EPI creatinine equation, [12] (iii) 2021 CKD-EPI creatinine equation,[14] (iv) Thai eGFR equation, [13] and (v) reexpressed MDRD with Thai racial factor correction. [13] The specific equations used for these eGFR estimates are provided in Table S1. The eGFR and eCrCL for drug dosing were calculated on a single-point measurement of SCr on the first day of vancomycin measurement and were transformed into either mL/minute or BSA-indexed as mL/minute/1.73 m^2 units for all equations. Therefore, we evaluated 12 kidney function estimates from 6 equations.

Vancomycin Assays

During this 10-year study period, serum vancomycin concentrations were measured by four assays. The AxSYM (Abbott Laboratories, Abbott Park, IL, USA), VITROS Chemistry Products VANC Reagent (Ortho-Clinical Diagnostics, NY, USA), VANC2 cobas c system (Roche Diagnostics, IN, USA), and VANC3 cobas c system (Roche Diagnostics, IN, USA) with the measurement range of 2.04 – 90.65 μg/mL, 5.00 to 50.00 μg/mL, 1.7 to 80.00 μg/mL, and 4.0 – 80.0 μg/mL were used during study period. The impact of measurement method was included as a potential confounder in the covariate model development process.

Pharmacokinetic and Statistical Analyses

Data analysis processes were conducted at the College of Pharmacy, University of Michigan, Ann Arbor, MI, USA. Data management was performed by EpiData 3.1 (Odense, Denmark: EpiData Association, 2016). Pharmacokinetic analyses were performed by Monolix2020R1, and compared with Sycomore2020R1 (Antony, France: Lixoft SAS, 2021). Population parameter estimation was derived using the stochastic approximation expectation maximization (SAEM) algorithm. One-, two- and three-compartment models with zero order, linear clearance were first tested as the base model. The proportional, constant, combine1, and combine2 error model were tested to determine proper observation models of residual variability. Vancomycin parameters were estimated based on a log-normal distribution.

Once the base model was defined, the influence of covariates on vancomycin parameters were determined by stepwise forward selection approach. The 23 covariates including 12 kidney function estimates, SCr, age, sex, BSA, TBW, body mass index (BMI),

SOFA score, septic shock status, vasopressor dose as norepinephrine equivalents (NEs), 24-hour fluid balance, and vancomycin assays were evaluated for their impact on vancomycin PK parameters. Continuous covariates were normalized to the dataset median value prior to inclusion in the model for testing. The models of each covariate on vancomycin parameters were ranked based on the greatest to smallest change in Akaike Information Criterion (AIC) relative to the base model. Automatic covariate building using the Conditional Sampling use for Stepwise Approach based on Correlation tests (COSSAC) was also used to identify correlations between individual parameters and covariates for developing final model. [21]

Model discrimination was based on change in AIC (Δ AIC), precision of parameter estimates, and goodness of fit plots between models. The nonparametric bootstrap technique including 1000 bootstrap replicates was performed by R package Rsmlx (R speaks Monolix) to assess the precision of the final model parameter estimates. Group comparisons were made using Pearson's Chi squared test with results presented as frequencies with percentages, means with SDs, and medians with interquartile ranges (IQRs), respectively. Descriptive statistical analyses and graphs were produced using Stata version 17 (StataCorp LLC, College Station, TX)

Dose Regimen Optimization by Monte Carlo Simulation

The probability of target attainment (PTA) of AUC/MIC_{BMD} ratio of 400-600 served as the basis for defining optimal vancomycin dose regimen. AUC/MIC_{BMD} ratio greater than 650 indicated an increased risk of nephrotoxicity. [22] The modal vancomycin MIC is 1 mg/L at our institutions and so the AUC from time 0-24 hours (AUC_{0-24}) and 24-48 (AUC_{24-48}) hours were used to evaluate the loading dose (LD) and maintenance doses (MD), respectively. Monte Carlo Simulations (MCSs) of 1000 critically ill patients by Simulx2020R1 (Antony, France: Lixoft SAS, 2021) was conducted to estimate PK/PD index ratio and PTA of clinical effectiveness and nephrotoxicity. The LD of 1000, 1500, 2000, and 2500 mg with an infusion rate of 1000 mg/hour were simulated. Once the optimal LD was identified, MD of 750 and 1000 mg infused at 500 mg/hour after the LD every 8, 12, 24 and 48 hours as intermittent infusion (II) were simulated to predict AUC_{24-48}. The optimal time to start the MD after receiving the LD for the II regimen was also determined. Simulations of 500, 1000, 2000, 4000, and 6000 mg continuous infusion (CI) over 48 hours or approximately 10, 21, 42, 83, and 125 mg/h following the end of LD infusion were also tested.

Results

Study Population

Table 1 summarizes the population demographics, laboratory data, pathogen information, kidney function, and initial dose of vancomycin. A total of 208 critically ill patients including 75 septic shock patients were enrolled. The majority of patients were male, on a mechanical ventilator, admitted to the medical ICU, and had a BMI less than 23 kg/m^2. The median [min, max] age was 69 [18, 97] years. Norepinephrine was used in 50

(66.7%) septic shock patients with median (IQR) norepinephrine equivalents (NEs) of 0.14 (0.08, 0.41) mcg/kg/minute. Half of the patients received vancomycin as empiric therapy for bloodstream, skin- and soft-tissue, and respiratory-tract infections. Infections secondary to *Enterococcus* spp. was the primary pathogen cultured in this study with an MIC_{50} of 1 mg/L based on data from 11 isolates. Kidney function estimates were reported by eCrCL using CG equation and eGFR using 2009 CKD-EPI and Thai eGFR equation. The median (IQR) eCrCL for the population was 33.6 (15.1-56.8) mL/minute. The median (IQR) eGFR using 2009 CKD-EPI and Thai GFR was 43.5 (20.4 – 83.4) and 52.0 (30.0-80.5). The overall population kidney function estimates stratified by septic shock presence is included in Table S2. Table S3 provides a comparison of eGFR strata based on CKD staging among the Thai-GFR, the CKD-EPI 2009, and 2021 CKD-EPI equation. The 2009 and 2021 CKD-EPI equation illustrated similarity in this classification; however, a lower proportion of eGFR less than 15 mL/minute/1.73 m^2 population was observed when calculated with Thai-GFR equation. The initial dose of vancomycin was approximately 20 mg/kg. The MD was given at an intermittent infusion rate of 500 mg per hour. Most patients (n=136) received 1000 mg as the typical LD, and 22% received 2000 mg as the LD at a rate of 1000 mg per hour.

Observed Vancomycin Concentration Profile

In total, 398 vancomycin concentrations with a mean (min, max) of 1.9 (1, 7) concentrations per patient were available for population PK analysis. The lower limit of quantification (LLOQ) was observed in three samples that were imputed as LLOQ/2. The median (IQR) time to vancomycin measurement was 3.0 (1.5-6.8) days. The distribution of vancomycin concentrations for patients treated every 6-hour, every 8-hour, every 12-hour, every 24-hour, every 48-hour, every 72-hour, and every 96-hour regimens was 2 (0.5%), 17

(4.3%), 155 (38.9%), 142 (35.7%), 42 (10.6%), 14 (3.5%), and 4 (1.0%), respectively. The dosing interval for 22 (5.53%) concentrations could not be ascertained. Based on collection at time since last dose of vancomycin infusion, the vancomycin concentrations were classified to be peak (74 samples; 18.6%), mid-point (111 samples, 27.9%), and trough (193; 48.5%). Figure 1 illustrates the measured vancomycin concentration against the time since last dose categorized by dosing interval for clarity.

Pharmacokinetic Analysis

The best base model was a 1-compartment linear model with zero-order input and a proportional error model. The estimates of Vd and CL of the base model was 66.5 L and 1.48 L/hour, respectively. As expected from the sparse data per patient, a two- and three-compartment model structure did not improve AIC and had higher relative standard error (%RSE) for fixed effects. The influence of individual covariate on vancomycin PK parameters was shown in Table 2. The kidney function estimates had substantial impact on vancomycin CL. Kidney function estimates that were not indexed to BSA performed better (lower AIC) than those indexed to BSA at 1.73 m^2. The Thai GFR model (mL/minute) had the lowest AIC (Δ AIC = -205.4). Septic shock status was found to influence CL (Δ AIC = -9.9) but not impact Vd (Δ AIC = -0.3).

The automated covariate model building algorithm selected eGFR not indexed to BSA from the Thai-GFR as the covariate of CL, and age, TBW, NEs, and eGFR calculated by 2021 CKD-EPI equation as the covariates of Vd. This overly parameterized model had a high %RSE for the Vd parameter estimate and could not be supported by data contributed per patient. This led us to stepwise comparison of one covariate at a time on CL and Vd. The final model that best described vancomycin CL of our population was eGFR calculated by

Thai-GFR (mL/minute) normalized to 40 mL/minute and was used in simulation for dose regimen optimization. The 2009 CKD-EPI creatinine (mL/minute) equation and eCrCL (mL/minute) were the next best models. The 2021 CKD-EPI creatinine (mL/minute) equation will likely be incorporated by laboratories in the United States to avoid the potential for systemic racism in medicine [23], therefore, we ran dosing simulations to compare PK/PD index targets of these three alternate models to the Thai-GFR (mL/minute) equation final model.

The parameter estimates of Thai-GFR not indexed to BSA final models and bootstrap analysis are presented in Table 3. Vancomycin parameter estimates from the final model were contained within 95% CIs from 1000 bootstrap replicates. The goodness-of-fit plots showed good agreement between observed and model-predicted concentrations. The majority of population weight residual (PWRES) versus time after dose and predicted concentration lay within 2SDs, similar to the normalized prediction distribution errors (NPDE) (Figure 2 and 3). Estimated log-likelihood and information criteria, distribution of the individual parameters and visual predictive check of final PK models are presented in Table S4, Figure S1 and S2.

Dose Regimen Optimization

Parameter estimates from the Thai-GFR not indexed to BSA final models were used in simulations to predict optimal vancomycin doses for our population. MCS was conducted to identify dose regimens for each eGFR category as follows: 15-30, 30-45, 45-60, 60-90, 90-120, and 120-150 mL/minute. The $AUC_{0\text{-}24}/MIC_{BMD} \geq 400$ and ≥ 650 was used to benchmark efficacy and toxicity of the LD for each eGFR group (Table S5). Higher LDs were associated with PTAs that were likely to achieve $AUC_{0\text{-}24}/MIC_{BMD} \geq 400$, but also

exceed 650. Based on the simulations, a LD of 2000 mg of vancomycin was identified as the pragmatic option when weighing these probabilities across eGFR group.

The PTAs achieving the target of $AUC_{24\text{-}48}/MIC_{BMD}$ simulated from Thai-GFR not indexed to BSA models of MD regimens are included in Table S6. PTAs achieving $AUC_{0\text{-}24}/MIC_{BMD}$ target at various MD start time after the LD is shown in Table S7. Table 4 summarizes the suggested doses of vancomycin dose regimens for each eGFR group based on Thai-GFR compared to CG, 2009 CKD-EPI, and 2021 CKD-EPI equations.

As expected, the lower eGFR groups should receive lower doses and longer dosing intervals to maintain PK/PD efficacy and safety targets. The PTAs to were comparable for intermittent and continuous infusion regimens based on the expected daily dose. A statistically significant difference in PTAs to achieve $AUC_{24\text{-}48}/MIC_{BMD}$ of 400-600 was noted when the Thai-GFR equation model was compared to the other alternate kidney function models (*p*-value <0.05). This difference was greatest when compared to eCrCL, where an approximately 10% absolute difference in PTA is expected. In contrast a 5-7% difference in PTA is expected when comparing Thai-GFR to the two alternate CKD-EPI models.

Discussion

Bacterial infections are common in critically ill patients requiring the administration of antibiotic therapy in more than half of admitted patients.[24] Serious infections can lead to septic shock in 5.9% to 16.1% of ICU admissions with a high (40%) probability of mortality.[25, 26] Rapid initiation of effective antimicrobial therapy is therefore a crucial strategy for lowering morbidity and mortality associated with septic shock. Fluid resuscitation and vasopressors

are also administered alongside antimicrobials to manage hypotension. Previous studies have suggested patients with septic shock can have a higher vancomycin Vd and altered CL that may be augmented early on or reduced due to acute kidney injury (AKI). As expected, these temporal shifts in physiology and pharmacokinetics are complex to capture. Most population PK of vancomycin models have linked kidney function estimates to CL and body weight to Vd. In this analysis, we focused on identifying the optimal kidney function estimation equation to predict vancomycin CL by specifically comparing race to non-race based equations. As a secondary aim, we tested the potential of other critical care patient factors as covariates of Vd.

Our analyses show in relative terms that covariates had a smaller effect on the interindividual variability of Vd compared to CL. While weight is often used to predict Vd, we show that this covariate does not improve the model. In contrast, the model for CL is substantially improved by eGFR and in standard units (mL/minute) compared to BSA scaled values (mL/minute/1.73 m^2). We show that the race-based factors Thai-GFR equation is the best model to predict vancomycin CL in our Thai critically ill patients. As a reference model, Thai-GFR had 8.6, 9.7, and 17.9 point differences in AIC to 2009 CKD-EPI, CG and 2021 CKD-EPI equations resulting in distinct probabilities of PTAs of vancomycin in this simulated study. As with previous vancomycin population PK models, pragmatic dosing regimens are predicted to achieve the AUC/MIC_{BMD} target in 40-50% of cases with II. This reinforces the need for therapeutic drug monitoring to achieve the optimal exposure target. Our approach is relatively unique in the literature given that we compared the “best” model to potential alternatives that fit conventional approaches. A 5-10% difference in the PTA is expected and needs clinical confirmation. This expected improvement is based on comparisons of PTAs at the same dosage regimen using different equations for kidney function. It’s possible that the optimal dosage regimen may be different if a different equation of kidney function was used

during simulation and clinical confirmation is needed to evaluate which regimen is ultimately optimal. While race is a social construct, our findings suggest that there may be a loss of precision when the population origin is not factored. While we did not test genetic ancestry, our population is expected to more homogenous than that of other multicultural societies.

As noted, the purpose of our analysis was to clarify the distinction between race and non-race based eGFR functions. We did not intend to generate a new vancomycin population PK model but rather use this drug as a test case. Regardless, our model is consistent with the literature. Heffernan and colleagues most recently evaluated the PK of vancomycin in 27 patients with sepsis and septic shock. [6] This analysis included sample collections at 1 hour post infusion and within 30 minutes of the next dose. The evaluated population was a median (IQR) 37 (26-49.3) years and 75 (65.5-84.8) kg. This analysis only identified eCrCL (Jelliffe equation) as a covariate of CL and did not identify any covariates of Vd. Similar to most models, the final population model only accounted for 43.9% of the interindividual variability. Similar to our findings, these investigators did not identify a relationship between weight or illness severity on vancomycin PK. A similar small study (n=16) with more intensively sampled study (peak, two random, trough concentrations) of obese patients in sepsis and septic shock was recently reported. This population had a median weight of 113 kg and 62 years of age. This model also identified no covariate relationship of weight to Vd and only eCrCL was predictive of vancomycin CL. [27] As a final point of reproducibility, Katip and colleagues also show through intensive sampled and non-compartmental analysis in 12 septic shock patients that Vd does not increase. [7] Our study includes a larger sample size and a population median age of 69 years and 60 kg and confirms these findings in contradiction to clinical convention.

Our study suffers from the limitations expected from a retrospective analysis, lengthy data collection period, and reliance on multiple assay methods to quantify vancomycin. Our data could not support development of a time-varying Vd or CL model. So, our prediction of LD and MD assume no change over time in Vd and CL. Central to this limitation is the recognition that eGFR and eCrCL equations are based on the assumption of homeostasis in creatinine production and elimination that allows for translation of a single steady-state measurement of serum creatinine to CL. This assumption may be false in many patients with acute infections. [15] Studies have shown that alternate kinetic functions of eGFR such as the Chen model and Chiou model are better than time-invariant models of vancomycin CL. [15, 30, 31] We did not have the data available to us in this study to explore this major point. This key limitation is also not addressed in drug development when building population PK models in patients with critical illness and is a major caveat that impacts interpretation of kidney function based dose adjustment in this population. [28, 29] Our simulations are also based on infusing vancomycin MD at 500 mg/hour that is half the typical rate of that in the US. We acknowledge these limitations with the rigor and detailed disclosure of our analysis. Our approach and findings are relevant to drug development because they add granularity on the impact of race and non-race based eGFR on drug dosing considerations. Future studies should assess the marginal cost associated with a 5-10% difference in PTA or work to build consensus on what is clinically meaningful. While our findings remain to be reproduced for other drug products that are adjusted for kidney function, our approach provides a valuable template to tease out these differences. Additional work in this domain is encouraged to demonstrate that elimination of the race factors does not negatively harm drug dosing decisions. These works will support international harmonization on kidney function estimation for both CKD staging and drug dosing, and aid global drug development.

Conclusions

Models of eGFR are better than eCrCL as predictors of vancomycin CL. The race-based Thai-GFR model performs best when the eGFR value is in mL/minute and not indexed to BSA. Both race and non-race based models of eGFR generate comparable dosing regimens for this representative kidney function adjusted compound. Body weight may not serve as a reliable covariate of vancomycin Vd in critically ill patients in this study and confirms several recent findings. A fixed loading dose followed by maintenance doses of vancomycin by eGFR are suggested by our model.

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Conflicts of Interest

None

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Data Sharing Statement

Data sharing of representative datasets and analysis code can be made available upon request of the corresponding author (sirima@pharmacy.psu.ac.th).

Supplemental Information

Table S1 to Table S10, Figures S1 and S2

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Table 1. Demographic, Anthropometric, and Laboratory Variables of Study Population

Variable	N (%) or median (IQR)		
	Overall (n = 208)	Septic shock (n = 75)	Without shock (n = 133)
Sex (male)	121 (58.2)	41 (54.7)	80 (60.2)
Age (years)	69.0 (54.0 – 78.0)	69.0 (54.5 – 77.5)	69.0 (54.0 – 78.0)
Hight (cm)	162.5 (154.0 – 170.0)	163.0 (153.0 – 167.5)	162.0 (155.0 – 170.0)
TBW (kg)	60.0 (50.0 – 67.6)	58.4 (50.0 – 68.3)	60.0 (50.0 – 66.0)
BMI (kg/m^2)	22.5 (19.6 – 24.4)	22.6 (20.4 – 26.2)	22.5 (19.4 – 24.2)
<18.5 kg/m^2	36 (17.3)	12 (16.0)	24 (18.0)
18.5-22.9 kg/m^2	86 (41.3)	29 (38.7)	57 (42.9)
23-30 kg/m^2	73 (35.1)	27 (36.0)	46 (34.6)
≥30 kg/m^2	13 (6.3)	7 (9.3)	6 (4.5)
BSA (m^2)	1.6 (1.5 – 1.8)	1.6 (1.5 – 1.8)	1.6 (1.5 – 1.8)
Setting			
Medical ICU (%)	124 (59.6)	51 (68.0)	73 (54.9)
Surgical ICU (%)	78 (37.5)	23 (30.7)	55 (41.4)

Other (%)	6 (2.9)	1 (1.3)	5 (3.8)
Mechanical ventilation (%)	165 (79.3)	68 (90.7)	97 (72.9)
NEs (mcg/kg/min) [a]	n/a	0.14 (0.08, 0.41)	n/a
SOFA score	6 (4 – 11)	12 (9 - 15)	4 (3 – 6)
Albumin (g/dL) [b]	2.60 (2.10 – 3.00)	2.40 (1.90 – 2.90)	2.70 (2.30 – 3.10)
Lactate (mmol/L) [b]	2.05 (1.23 – 3.78)	2.80 (1.58 – 4.83)	1.45 (1.20 – 2.25)
24-hour fluid balance (mL)	802.50 (-91.25 - 1753.50)	1935.00 (924.00 - 2752.00)	400.00 (-285.00 - 1105.00)
Indication of vancomycin			
Empirical therapy (%)	115 (55.3)	56 (74.7)	59 (44.4)
Pathogen specific therapy (%)	93 (44.7)	19 (25.3)	74 (55.6)
E.faecium	45 (48.4)	12 (63.2)	33 (44.6)
MRSA	19 (20.4)	3 (15.8)	16 (21.6)
MRSE	12 (12.9)	1 (5.3)	11 (14.9)
E.faecalis	5 (5.4)	0 (0)	5 (6.8)
Corynebacterium spp.	3 (3.2)	1 (5.3)	2 (2.7)
S.hemolyticus	3 (3.2)	1 (5.3)	2 (2.7)

Other	6 (6.5)	1 (5.3)	5 (6.8)
Site of infection			
Blood stream infection	53 (25.5)	20 (26.7)	33 (24.8)
Skin and soft tissue infection	39 (18.8)	14 (18.7)	25 (18.8)
Respiratory tract infection	35 (16.8)	17 (22.7)	18 (13.5)
Intraabdominal infections	23 (11.1)	7 (9.3)	16 (12.0)
Urinary tract infection	23 (11.1)	7 (9.3)	16 (12.0)
Central nervous system infection	20 (9.6)	1 (1.3)	19 (14.3)
Infective endocarditis	13 (6.3)	9 (12.0)	4 (3.0)
Bone or joint infection	2 (1.1)	0 (0)	2 (1.5)
MIC (mg/L)			
Total specimen	11	5	6
MIC_{50} (min-max)	1 (0.02-2)	1 (0.02-2)	1 (0.5-1.5)
BUN (mg/dL) [b]	37.40 (20.8 – 60.0)	31.29 (17.3 – 47.3)	31.00 (16.0 – 52.8)
SCr (mg/dL) [b]	1.53 (0.89-2.65)	1.85 (1.43 – 3.14)	1.27 (0.74-2.33)

eGFR (mL/minute/1.73m^2)			
2009 CKD-EPI	43.5 (20.4 – 83.4)	30.9 (17.1-48.5)	51.4 (23.1-98.4)
Thai-GFR	52.0 (30.0-80.5)	39.4 (27.9-56.6)	58.7 (33.2-108.1)
eCrCL (mL/minute)	33.6 (15.1-56.8)	24.7 (14.2-43.8)	37.4 (17.3-71.3)
Initial dose of vancomycin (mg)	1000 (1000-1500)	1000 (1000-2000)	1000 (1000-1500)
Initial dose of vancomycin (mg/kg)	20.0 (15.6-27.4)	21.7 (15.3-30.3)	19.6 (15.6-25)

BMI, body mass index; BSA, body surface area; BUN, blood urea nitrogen; eCrCL, estimated creatinine clearance using Cockcroft-Gault equation; eGFR, estimated glomerular filtration rate using 2009 Chronic Kidney Disease Epidemiology creatinine equation and Thai-glomerular filtration rate equations; ICU, intensive care unit; IQR, interquartile range; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; MRSE, methicillin-resistant *Staphylococcus epidermidis;* NEs, norepinephrine equivalents; SCr, serum creatinine; SOFA, Sequential Organ Failure Assessment; TBW, total body weight

[a] Norepinephrine equivalents = norepinephrine dose in mcg/kg/min + epinephrine dose in mcg/kg/min + dopamine dose in mcg/kg/min divided by 100

[b] Normal ranges: albumin, 3.5-5.2 g/dL; lactate, 0.5-1.6 mmol/L; BUN, 6-20 mg/dL; SCr, 0.67-1.17 mg/dL

Table 2. Covariate Ranking based on the Akaike Information Criterion (AIC) for Vancomycin Clearance and Volume of Distribution Relative to the Base Model

Covariates on CL	AIC	Δ AIC	Covariates on Vd	AIC	Δ AIC
Base model	2985.5		Base model	2985.5	
Thai GFR (mL/minute)	2780.0	-205.4	2021 CKD-EPI (mL/minute)	2975.1	-10.4
2009 CKD-EPI (mL/minute)	2788.7	-196.8	2009 CKD-EPI (mL/minute)	2977.6	-7.9
eCrCL (mL/minute)	2789.8	-195.7	2021 CKD-EPI (mL/minute/1.73 m^2)	2977.6	-7.9
MDRD4-IDMS (mL/minute)	2796.3	-189.2			
MDRD with Thai racial factor correction (mL/minute)	2796.5	-188.9	MDRD with Thai racial factor correction (mL/minute)	2978.7	-6.8
2021 CKD-EPI (mL/minute)	2798.0	-187.5	MDRD4-IDMS (mL/minute)	2978.9	-6.6
Thai GFR (mL/minute/1.73 m^2)	2798.2	-187.3	Thai GFR (mL/minute)	2979.5	-6.0
eCrCL (mL/minute/1.73 m^2)	2806.6	-178.9	2009 CKD-EPI (mL/minute/1.73 m^2)	2980.4	-5.1

Covariates on CL	AIC	Δ AIC	Covariates on Vd	AIC	Δ AIC
2009 CKD-EPI (mL/minute/1.73 m^2)	2807.6	-177.9	NEs	2980.5	-5.0
			Sex	2980.6	-4.8
2021 CKD-EPI (mL/minute/1.73 m^2)	2814.6	-170.9	MDRD with Thai racial factor correction (mL/minute/1.73 m^2)	2981.5	-4.0
MDRD with Thai racial factor correction (mL/minute/1.73 m^2)	2817.4	-168.1	SCr	2981.5	-4.0
MDRD4-IDMS (mL/minute/1.73 m^2)	2817.5	-168.0	SOFA score	2982.5	-3.0
SCr	2852.6	-132.9	Thai GFR (mL/minute/1.73 m^2)	2982.8	-2.7
Age	2947.5	-38.0	MDRD4-IDMS (mL/minute/1.73 m^2)	2983.1	-2.4
SOFA score	2955.4	-30.1	eCrCL (mL/minute)	2983.2	-2.3
Septic shock	2975.6	-9.9	TBW	2983.8	-1.7
NEs	2978.9	-6.6	Age	2984.0	-1.5
BSA	2979.4	-6.1	eCrCL (mL/minute/1.73 m^2)	2984.1	-1.3

Covariates on CL	AIC	∆ AIC	Covariates on Vd	AIC	∆ AIC
TBW	2981.9	-3.6	24-hour fluid balance	2984.6	-0.9
Sex	2983.2	-2.2	Septic shock	2985.2	-0.3
24-hour fluid balance	2986.2	0.7	BSA	2985.9	0.4
BMI	2988.0	2.6	BMI	2986.8	1.3
Vancomycin assays	2991.4	5.9	Vancomycin assays	2987.7	2.2

2009 CKD-EPI, 2009 Chronic Kidney Disease Epidemiology creatinine equation; 2021 CKD-EPI, 2021 Chronic Kidney Disease Epidemiology creatinine equation; AIC, Akaike information criterion which is ∆ AIC was difference of AIC to base model, BMI, body surface area; BSA, body mass index; CL, clearance of vancomycin; eCrCL, estimated creatinine clearance calculated by Cockcroft - Gault (CG) equation; MDRD4-IDMS, 4-variable Modification of Diet in Renal Disease using an isotope dilution mass spectrometry (IDMS) traceable equation; MDRD with Thai racial factor correction, reexpressed Modification of Diet in Renal Disease with Thai racial factor correction; NEs, norepinephrine equivalents; SCr, serum creatinine; SOFA, Sequential Organ Failure Assessment; TBW, total body weight; Thai-GFR, Thai-glomerular filtration rate equations, Vd, volume of distribution of vancomycin

Table 3. Pharmacokinetic Parameters of Final Vancomycin Population Model and Bootstrap

	Final Model [a]		Bootstrap of Final Model	
	Estimate	%RSE	Estimate	95%CI
Fixed-effect parameter				
CL (L/h)	1.22	4.46	1.23	1.09 - 1.33
Vd (L)	67.46	4.63	66.51	61.05 - 75.66
$\theta 1$	1.01	5.61	1.00	0.90 – 1.15
Interindividual variability (IIV)				
IIV on CL	0.41	6.97	0.39	0.24 - 0.49
IIV on Vd	0.38	11.1	0.41	0.34 - 0.48
Residual variability				
Proportional	0.21	5.32	0.21	0.16 – 0.27

CI, confidence interval; CL, clearance of vancomycin; RSE, relative standard error; Thai-GFR, Thai-glomerular filtration rate equations; Vd, volume of distribution of vancomycin; $\theta 1$ reflecting the influence of estimated glomerular filtration rate (eGFR) on CL

[a] Final model: $CL = 1.22 \times (eGFR/40)^{1.01} \times e^{\eta i}$ where eGFR calculated by Thai-GFR equation not indexed to BSA (mL/minute) and η_i represents the random effects

Table 4. Comparison of the Probability of Target Attainment ($AUC_{24\text{-}48}/MIC_{BMD}$ 400 to 600) by Kidney Function Equation for Each Estimated Glomerular Filtration Rate (eGFR) Group and Intermittent Infusion Dose or Continuous Infusion Rate

eGFR (mL/minute)	Suggested MD Regimens [a]	PTAs to achieve $AUC_{24\text{-}48}/MIC_{BMD}$ 400-600 (%)						
		Thai-GFR	2009 CKD-EPI	*p*-value [b]	2021 CKD-EPI	*p*-value [b]	eCrCL	*p*-value [b]
15-29	1000 mg Q48H	52.8	42.7	0.000	43.0	0.000	35.7	0.000
	10 mg/h	46.1	48.2	0.347	49.9	0.089	47.2	0.622
30-44	750 mg Q24H	45.3	51.5	0.006	49.2	0.081	48.0	0.226
	10 mg/h	50.0	40.5	0.000	40.2	0.000	32.2	0.000
45-59	750 mg Q24H	51.7	42.3	0.000	42.5	0.000	36.5	0.000
	21 mg/h	48.4	38.3	0.000	40.2	0.000	30.9	0.000

60-89	1000 mg Q24H	44.7	35.3	0.000	36.2	0.000	30.1	0.000
	42 mg/h	46.2	42.6	0.105	43.0	0.150	39.0	0.001
90-119	750 mg Q12H	43.5	38.4	0.020	38.7	0.029	34.9	0.000
	42 mg/h	34.6	27.1	0.000	29.2	0.010	23.1	0.000
120-150	1000 mg Q12H	43.2	42.0	0.587	39.6	0.102	39.7	0.112
	83 mg/h	41.0	37.5	0.109	37.7	0.131	36.7	0.049

$AUC_{24\text{-}48}/MIC_{BMD}$, area under the curve during 24 to 48 hours over minimum inhibitory concentration determined by broth microdilution ratio; CI, continuous infusion; CKD-EPI, Chronic Kidney Disease Epidemiology creatinine equation; eCrCL, estimated creatinine clearance calculated by Cockcroft-Gault (CG) equation; II, intermittent infusion; MD, maintenance dose; PTAs, probability of target attainments assuming a vancomycin MIC_{BMD} of 1 mg/L; Thai-GFR, Thai-glomerular filtration rate equations

[a] *Intermittent infusion regimens*: after the loading dose (LD) of 2000 mg is infused, the first maintenance dose should be administered as follows: 24-48 hours after LD for every 48-

hour regimen; 12-24 hours after LD for every 24-hour regimen; and 8-12 hours after LD for every 12-hour regimen

Continuous infusion regimens: the maintenance doses are suggested to initial at the end of 2000 mg loading dose infusion

[b] Pearson's Chi squared test

Figure 1. Observed vancomycin concentrations as peak, mid-point, and trough values by dosing interval from time to last dose.

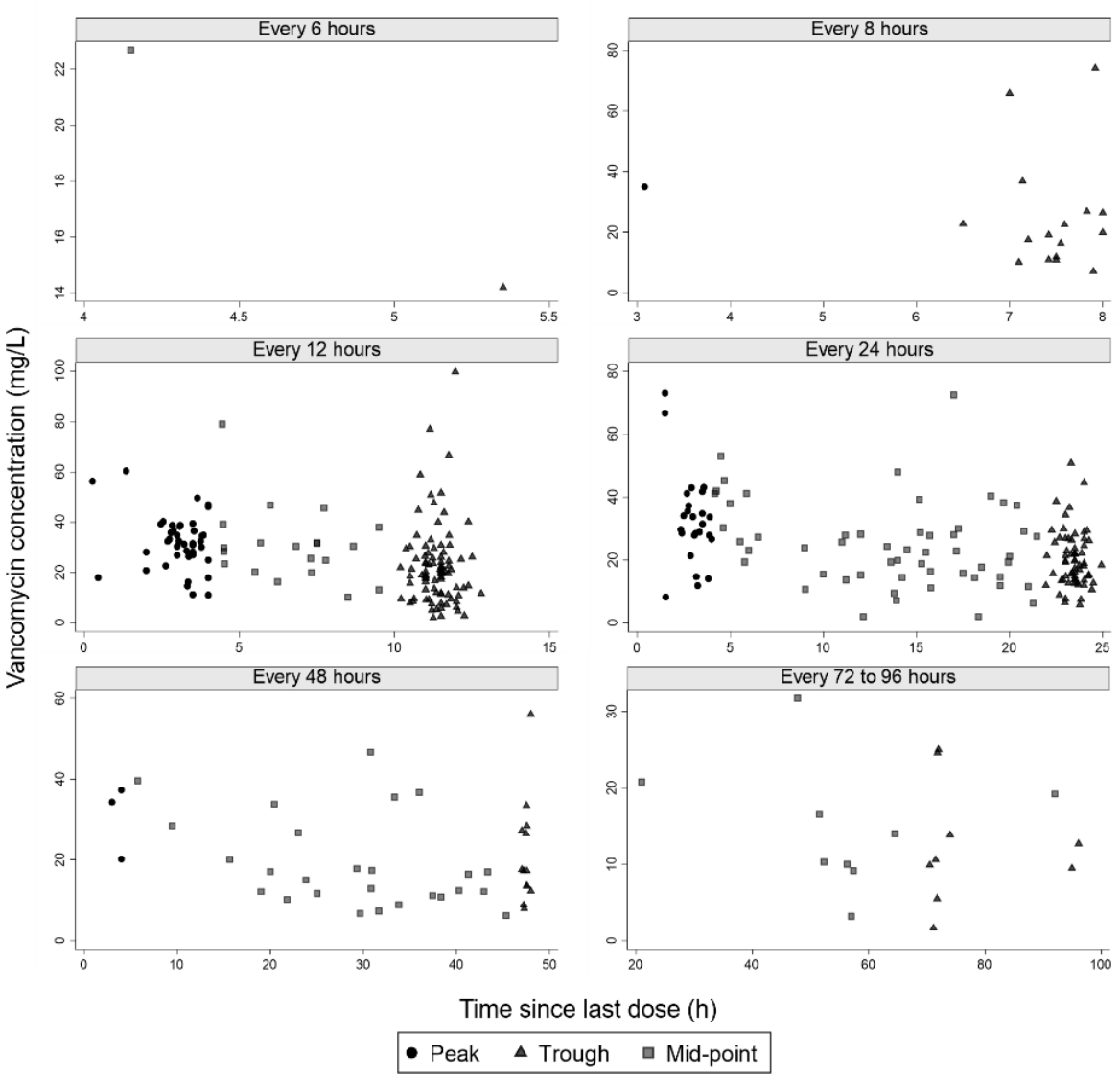

Figure 2. The goodness-of-fit plots of the Thai-GFR equation final vancomycin model. (A) observed concentration versus population predicted concentration; (B) observed concentration versus individual predicted concentration; (C) population weighted residuals versus time after dose; and (D) population weighted residuals versus population predicted concentration.

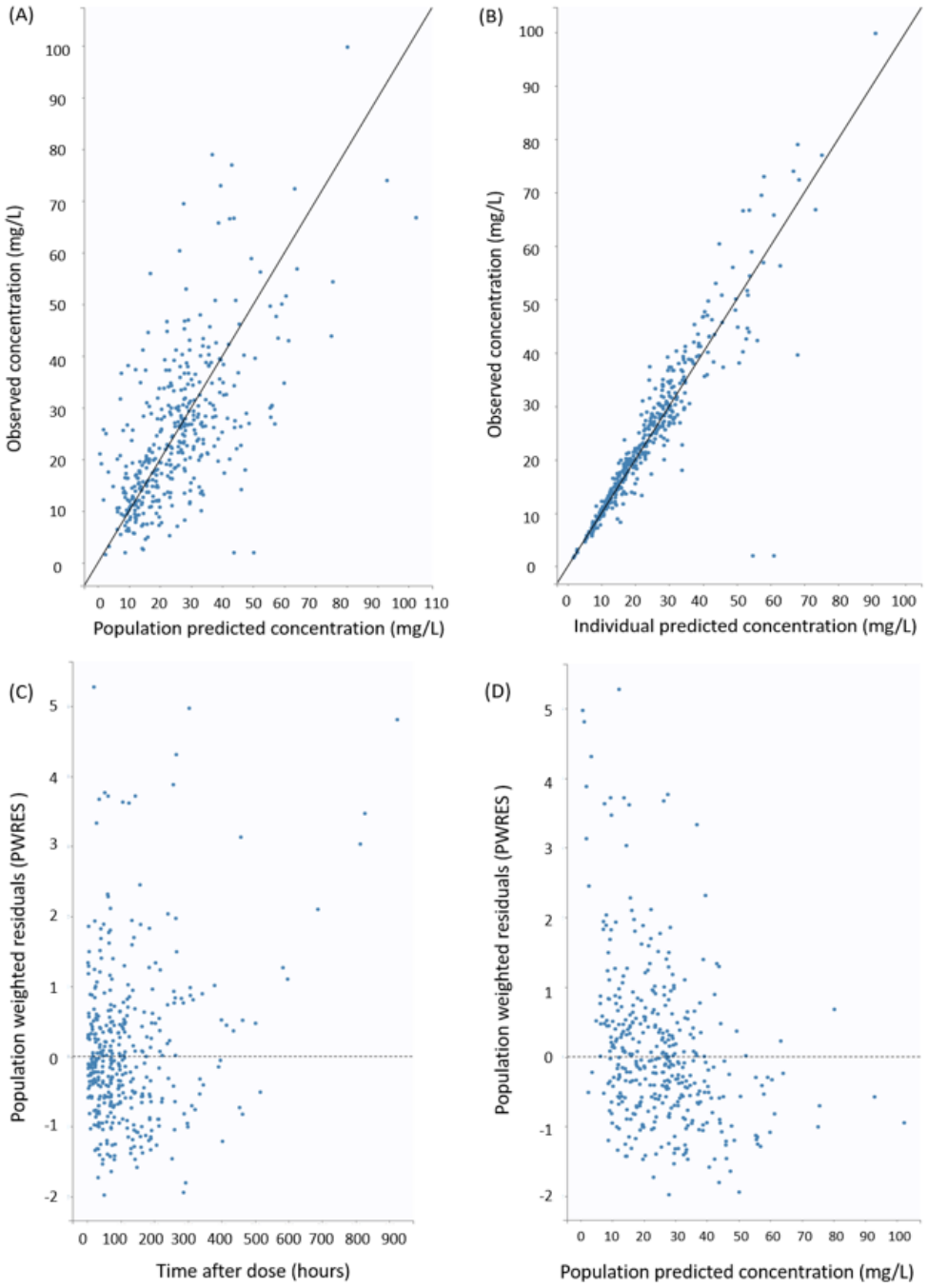

Figure 3. Histogram of the normalized prediction distribution errors (NPDE) of Thai-GFR equation final vancomycin model with the theoretical distribution (dash line).