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ORIGINAL RESEARCH ARTICLE

Dose Optimization of Vancomycin in Pediatric Post-Cardiac Surgery Patients: A Population Pharmacokinetic Modeling Study

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Abstract

Background and Objective Vancomycin is a glycopeptide antibiotic used for the treatment of severe gram-positive infections. Despite decades of clinical experience, optimized dosing for vancomycin in pediatric populations still warrants further investigation. Patients admitted to the pediatric intensive care unit (PICU) after cardiac surgery are often treated with vancomycin in case of (suspected) infection. However, vancomycin dosing in this population is often challenging due to fluctuations in volume status, (temporarily) compromised renal function or the use of diuretics or extracorporeal membrane oxygenation (ECMO). The main objective of this study was to describe vancomycin pharmacokinetics (PK) in pediatric cardiac surgery patients. Secondary objectives were to potentially optimize vancomycin dosing and to assess the suitability of the model to be used for model informed precision dosing (MIPD).

Methods A retrospective cohort study was performed with patients admitted to the PICU of the Leiden University Medical Center. Clinical data from post-cardiac surgery PICU patients receiving intravenous vancomycin between January 2020 and December 2023 were included in the analysis. Patients received vancomycin 10 mg/kg 4 times daily (qid), after which a trough concentration was generally sampled just before the fourth dose. Pharmacokinetic data were used to develop a population PK model by using a non-linear mixed effects modeling approach (NONMEM). In addition, potential covariates such as renal function, body weight (BW) and post-menstrual age were tested. The final model was used for vancomycin dose optimization using Monte Carlo simulations.

Results In total, 193 pediatric post-cardiac surgery patients, contributing a total of 706 vancomycin blood samples were included. The 2-compartmental population PK model best described the data. Renal function and BW were identified as significant and clinically relevant covariates on vancomycin PK. Model parameters were: elimination clearance: 4.01 L/min at 70 kg; intercompartmental clearance: 0.425 L/min at 70 kg; central volume of distribution: 56.1 L/70 kg; and peripheral volume of distribution: 21.7 L/70 kg (fixed). Dose simulations suggested a non-linear dosing algorithm, with relatively lower per kg dose for increasing BW to be optimal for our population. Furthermore, the model was considered to be suitable for the (*a posteriori*) prediction of future vancomycin serum concentrations.

Conclusion We successfully developed a population PK model for vancomycin in post-cardiac surgery children. Vancomycin PK were shown to be significantly influenced by serum creatinine and BW. Furthermore, we suggest a new vancomycin dosing regimen based on allometric scaling. The developed PK model can be used for model informed precision dosing of vancomycin in pediatric post-cardiac surgery patients.

1 Introduction

Vancomycin is a glycopeptide antibiotic used for the treatment of severe gram-positive infections [1]. Despite decades of clinical experience, optimized dosing for vancomycin in pediatric populations still warrants further investigation. This is mainly caused by the significant physiological changes that are associated with the process of maturation, critical illness and high inter-patient variability in pharmacokinetics (PK) caused by different disease states [2]. Moreover, vancomycin is characterized by a narrow therapeutic window and potential nephrotoxicity when overdosed, which necessitates close monitoring of plasma drug concentrations [3].

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Extended author information available on the last page of the article

Key Points

The population pharmacokinetics of vancomycin in post-cardiac surgery patients were successfully described using real-world data.

An allometrically scaled dosing algorithm showed to achieve optimal and homogeneous target attainment probabilities in a wide range of body weight categories.

The developed model provides a tool for model-informed precision dosing.

The area under the concentration curve over 24 h (AUC_{24}) to minimum inhibitory concentration (MIC) ratio is considered to be the optimal pharmacodynamic (PD) parameter, with a target AUC_{24}> 400 mg*h/L based on a MIC of 1 mg/L for *Staphylococcus aureus* [4, 5]. An AUC_{24} > 400 mg*h/L is considered to correspond relatively well with vancomycin trough concentrations between 10 and 15 mg/L [6, 7]. However, the use of trough concentrations for vancomycin dose individualization remains a subject of debate, due to the large inter-patient variability in vancomycin PK [5, 6].

Children who are admitted to the pediatric intensive care unit (PICU) after cardiac surgery are often treated with vancomycin in case of infection. However, vancomycin dosing in this population is often challenging due to fluctuations in volume status, impaired renal function after surgery [8–10], the use of diuretics or the use of extracorporeal membrane oxygenation (ECMO) [4, 11]. Since 80–90% of vancomycin is eliminated via glomerular filtration, alterations in renal function add to the variability in vancomycin PK [12].

In a recent review from Chung et al., the lack of population PK models in specific pediatric populations, such as dialysis patients or ICU patients was emphasized [1]. Although a total of 64 PK models for vancomycin in pediatric populations were reported, only two models described vancomycin PK in pediatric cardiac surgery patients specifically [11, 13]. Since the publication of this review, to our knowledge, only one additional report has been published on this topic [14], stressing the need of further insights in vancomycin PK in pediatric post-cardiac surgery patients.

According to the Dutch Pediatric Formulary, the recommended vancomycin dosage in patients aged > 1 month is 15 mg/kg every 6 h (i.e., a daily dose of 60 mg/kg), with variable dose corrections for renal function [15]. However, in our clinical experience, vancomycin trough concentrations in pediatric cardiac surgery patients often seem to exceed 15 mg/L when dosed according to the Dutch Pediatric Formulary. These findings led to the adoption of a local (empirical) vancomycin dosing protocol of 10 mg/kg every 6 h for pediatric cardiac surgery patients aged ≥1 month. However, an optimal vancomycin dosing protocol for this specific population is still warranted.

In addition to describing the PK of a drug within a specific population, population PK models can also enable the prediction of future drug concentrations, based on previously measured drug concentrations (priors) and covariates at that future timepoint for the individual patient. This model informed precision dosing (MIPD) approach may aid clinicians to improve the ability to predict future drug exposure and thus enable timely dose adjustments [16].

The primary objective of this study was therefore to develop a population PK model for vancomycin in pediatric cardiac surgery patients. The secondary objectives were to use the population PK model to evaluate the target attainment of the current vancomycin dosing protocols in our population, to potentially optimize vancomycin dosing protocols and to evaluate the suitability of the model for MIPD purposes.

2 Methods

2.1 Study Design

A retrospective cohort study was performed with patients admitted to the PICU of the Leiden University Medical Center. This study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. The protocol for retrospective analysis was approved by the Institutional Review Board (IRB) at the Scientific Committee of the Department of Intensive Care, Medical Ethics Review Committee Leiden/The Hague/Delft (date of approval: August 15 2024, approval number: 2024-041). As retrospective data from routine clinical care were used, a waiver was granted for the requirement of informed consent by the IRB.

Data were retrospectively collected from the electronic patient database (Metavision version 6.9, Itemedical, The Netherlands). Clinical data from post-cardiac surgery PICU patients receiving intravenous vancomycin between January 2020 and December 2023 were included in the analysis. Patients were excluded when no data on vancomycin administration were available or no vancomycin serum concentrations were available.

Pharmacokinetic data extracted from the electronic patient database included: vancomycin dose, infusion duration, time and date of administration and serum vancomycin concentrations. In addition, the following clinical data were extracted: sex, age, post-menstrual age (PMA), BW, serum creatinine, serum albumin, serum urea concentrations and the use of ECMO at the time of vancomycin therapy. The final dataset was split into two similar datasets for model

development and model validation and was split at random, with 50% of the cases assigned to each dataset. Cases were included as separate individuals in the dataset when (i) vancomycin was administered during multiple pediatric ICU admissions and (ii) when a new vancomycin dose was administered > 90 hours after the last dose.

Patients started as per protocol on vancomycin 10 mg/kg four times daily (qid). This dosing scheme was based on local PICU dosing protocols. Vancomycin trough serum concentrations were generally sampled just before the fourth vancomycin dose, as part of the standard clinical routine. Additional vancomycin sampling was left to the discretion of the treating physician. Subsequent dose adjustments were aimed at vancomycin trough concentrations between 10 and 15 mg/L [17].

Vancomycin blood samples were collected in Clot Activator Tubes (CAT) and were stored at 2–8 °C until the time of analysis. A particle-enhanced turbidimetric inhibition immunoassay (Alinity C Vancomycin Reagent Kit 08P52, Abbott Laboratories, USA) was used to measure vancomycin plasma concentrations. The assay is linear across a concentration interval between 1.4 and 100 mg/L, and had a lower limit of quantification (LLOQ) of 1.4 mg/L. The LLOQ was defined as the lowest concentration at which a maximum coefficient of variation (CV%) of 20% and a maximum bias of 10% or 0.5 mg/L were met.

2.2 Population Pharmacokinetic Model Development

Pharmacokinetic data were analyzed with a nonlinear mixed effect modelling approach in NONMEM (version 7.4.4, Icon Plc, Dublin, Ireland) by using a first-order conditional estimation algorithm with interaction (FOCE-I). Based on recent data, model development was initiated with a 2-compartmental model [14]. In addition, 1-compartmental models were tested. Interindividual variability (IIV) was evaluated for each disposition parameter and was defined as: $\theta_i = \theta_{pop} * \exp(\eta_{IIV})$, where θ_i is the empirical Bayesian estimate (EBE) for individual i, θ_{pop} is the estimated population parameter value, and η_{IIV} the log normally distributed IIV specific for parameter θ_{pop}. To account for potential covariance between the structural parameters, random variability was additionally tested with a variance-covariance matrix (BLOCK()). Both proportional and combined additive-proportional error models were tested to describe the residual error. Since our data almost exclusively included trough concentrations, the peripheral volume of distribution could not be reliably estimated. Therefore, the peripheral volume of distribution was pragmatically fixed at 21.7 L at 70 kg. This population value was based on a recently published population PK model in pediatric post-cardiac surgery ICU patients [14], which, to our knowledge, is the only available 2-compartmental vancomycin population PK model for this population. Model selection was based on a significant improvement of the Objective Function Value (OFV) as reported in NONMEM ($p < 0.01$, ΔOFV of −6.63).

2.3 Covariate Analysis

Body weight was included a priori in the model as covariate on the disposition parameters, based on physiological plausibility [18]. For the clearance parameters, BW was included as: $\theta_i = \theta_{pop} * (BW/70)^{0.75}$, where θ_i is the parameter for individual i, θ_{pop} the population parameter and BW is body weight. Central volume of distribution (Vc) and peripheral volume of distribution (Vp) were allometrically scaled as: $\theta_i = \theta_{pop} * (BW/70)^{1}$.

In addition, the effect of estimated glomerular filtration rate by the Schwartz equation (eGFR) was tested on elimination clearance. The eGFR was calculated as: eGFR = (k * height)/Scr, where eGFR is the estimated glomerular filtration rate in mL/min/1.73 m^2, k is the constant 36.2 [19], height is the height of the patient in centimeters and Scr the serum creatinine concentration in µmol/L. The effect of the eGFR on elimination clearance was subsequentially defined as: $CL_i = CL_{pop} * (eGFR/120) * \theta_{eGFR,}$ where CL_i is the individual elimination clearance, CL_{pop} the population clearance parameter estimate, eGFR the estimated glomerular filtration rate as calculated by the Schwartz equation and θ_{eGFR}, the parameter that estimates the relation between eGFR and elimination clearance. Moreover, an exponential relation was tested as $CL_i = CL_{pop} * (eGFR/120)^{\theta eGFR}$.

Furthermore, a sigmoidal E_{max} model was used to evaluate the potential effect of PMA on elimination clearance: $F_{mat} = PMA^{\theta}/(TM_{50}{}^{\theta} + PMA^{\theta})$ [14], where F_{mat} is the effect of maturation on the elimination clearance, θ is the estimated slope of the maturation profile (Hill factor) and TM_{50} the PMA where 50% of the maximum maturation is reached.

Finally, the effect of ECMO was tested on elimination clearance and central volume of distribution in a linear fashion, as defined as:

$\theta_i = \theta_{pop} * (1 + \theta_{ECMO})$, where θ_{ECMO} is the estimate of the effect size of ECMO treatment on the elimination clearance.

Biological plausibility of a potential covariate was a selection criteria for the statistical assessment of covariates. Covariates were subsequently entered in the univariate statistical analysis (Chi-square, 1 df, $p < 0.05$) and subsequently, but only if applicable, in the cumulative forward inclusion ($p < 0.05$) and backward elimination ($p < 0.01$) procedure. Furthermore, covariates were retained in the model when they caused a clinically significant reduction in the unexplained IIV.

2.4 Internal Model Validation

Graphical methods were used to evaluate the different models and included basic goodness of fit plots, prediction corrected visual predictive checks (pcVPC) and Normalized Predicted Distribution Error (NPDE) plots. In addition, parameter robustness was tested by performing a bootstrap analysis ($n = 1000$).

2.5 External Model Validation

The model was externally validated by performing a pcVPC on the validation dataset and by assessing the NPDEs of the model when applied on the validation dataset. In addition, changes in model parameter estimates were evaluated by refitting the model parameters with the validation data. Model precision and bias were evaluated by calculating the mean prediction error (MPE) and root mean squared error (RMSE) with the following equations:

$$\text{PE}\ (\%) = \frac{C_{\text{pred,i}} - C_{\text{obs, i}}}{C_{\text{obs,i}}} \times 100\%,$$

$$\text{MPE}(\%) = \frac{\sum \text{PE}}{\text{N}},$$

$$\text{RMSE}\left(\frac{\text{mg}}{\text{L}}\right) = \sqrt{\frac{\sum (C_{\text{pred,i}} - C_{\text{obs,i}})^2}{N}},$$

where $C_{\text{pred,i}}$ and $C_{\text{obs,i}}$ represent the model predicted and observed vancomycin concentrations, respectively, and N the total number of observed concentrations. An MPE and RMSE of < 20 % and < 5 mg/L were considered to be adequate.

2.6 Dose Simulations and Optimization

Due to the critical illness in our study population, a swift antibiotic target attainment is warranted. We therefore aimed to optimize the probability of attaining an AUC_{24h} within the target range of 400–600 mg*h/L (i.e., the target range as recommended by the Dutch vancomycin TDM guidelines and the American Society of Health-System Pharmacists [5, 17]) at Day 2 after vancomycin initiation.

To first evaluate the performance of our local vancomycin dosing protocol, the current dosing regimen (i.e., 40 mg/kg divided in four doses, without loading dose) was simulated ($n = 1000$) for multiple weight and renal function categories ranging from 2 to 50 kg and from 15 to > 90 mL/min/1.73 m^2, respectively. The cut-off values for renal function were selected based on local preferences and to approximately overlap with the cut-off values as reported in the Dutch Pediatric Formulary [15].

Subsequently, a dose optimization was performed by evaluating the probability of target attainment at Day 2 with a dose range between 5 and 20 mg/kg per dose. For patients with an eGFR 15–30 mL/min/1.73 m^2, once-daily dosing schemes were simulated. Dosing intervals of 12, 8 or 6 hours were simulated for subjects within in the 30–60 mL/min/1.73 m^2, 60–90 mL/min/1.73 m^2 and eGFR > 90 mL/min/1.73 m^2 categories, respectively. In addition, since rapid target attainment was warranted for all patient groups, a loading dose of 20 mg/kg was included in the simulations [20].

2.7 Fit-for-Purpose Validation

Since the developed population PK model may be used for MIPD purposes, a fit-for-purpose validation was performed to assess the suitability of the model to predict future concentrations based on the covariate values at that moment and on vancomycin concentrations measured during a prior timepoint.

Subjects with at least three measured vancomycin concentrations were selected for the evaluation. The first two samples were used as priors to predict the third vancomycin concentration. Bias and imprecision, defined as the mean percent prediction error (MPPE) and mean absolute percentage prediction error (MAPE), were subsequently determined. In addition, percentages of the predictions within ± 10%, ± 20%, ± 30% (P10, P20 and P30) of the measured concentration were calculated. To evaluate the added value of using prior information to predict future concentrations, MPPE and MAPE values were plotted versus a situation in which either (i) no prior concentrations were available (a priori prediction, only based on population parameters and covariates), (ii) one prior concentration was available or (iii) in which two prior concentrations were available.

2.8 Software

Data preparation was performed in Microsoft Excel for Microsoft 365 MSO (Version 2208) and Rstudio version 4.2.1. The partition function from the groupdata2 (version 2.0.3) package for Rstudio was used to split the data in two similar datasets for model development and external model evaluation, respectively. In addition, NONMEM version 7.4.4. and PsN version 5.0.0. were used for the nonlinear mixed effects modelling. Rstudio version 2023.6.1.524 (Posit Software, PBC, Boston, MA) was used with R version 4.4.0. for data manipulation, graphical model evaluations and to perform simulations. The RxODE package (version 2.0.13.) [21] in combination with the PKNCA package

(version 0.10.0) were used for performing the simulations and to calculate the probability of target attainment.

3 Results

3.1 Demographics

In total, 265 cases (193 individual patients) were included in the final dataset. The development and validation datasets included 133 cased and 132 cases, respectively. As shown in Table 1, patient characteristics, especially BW, eGFR and PMA, were very similar between the development and validation datasets. A total of 19 patients needed ECMO support during the vancomycin treatment, equally distributed over both groups. No patients received intermittent hemodialysis or continuous renal replacement therapy. All patients were admitted to the PICU after cardiac surgery for a congenital heart disease. Raw vancomycin serum concentration data from the development dataset are shown in Fig. 1.

3.2 Population Pharmacokinetic Model Development

Vancomycin PKs were best described by a 2-compartmental model, with a combined additive and proportional error model. Inter-individual variability could be estimated for elimination clearance and the central volume of distribution. To account for covariance between elimination clearance and volume of distribution, IIV of both parameters was modelled as a variance-covariance matrix (BLOCK(2)).

The addition of BW as covariate reduced the unexplained IIV on elimination clearance and peripheral volume of distribution by 62% and 9.2%, respectively. Inclusion of renal function with the exponential covariate model further reduced the IIV on clearance with an additional 65%. Inclusion of PMA and ECMO treatment as covariates failed to significantly reduce the OFV or to explain a clinically relevant proportion of the IIV and were therefore not retained in the final model. A complete overview of the covariate model testing is shown in Supplementary Table 1.

Final population PK parameters were: elimination clearance, 4.01 L/h at 70 kg; central volume of distribution, 56.1 L per 70 kg; intercompartmental clearance, 0.425 L/h at 70 kg; peripheral volume of distribution, 21.7 L per 70 kg (fixed), and effect size of renal function on clearance, 0.889. Inter-individual variability (CV%) for elimination clearance and the central volume of distribution were 23.6% and 42.9%, respectively. A full overview of the model parameters and bootstrap results are shown in Table 2.

3.3 Internal Validation

The bootstrap analysis showed median parameter estimates similar to those of the final model, with the final model parameters within each 95% bootstrap confidence interval (Table 2). The basic goodness-of-fit plots (Fig. 2) showed that both population model predictions as individual model predictions were in acceptable agreement with the observed concentration data. Furthermore, the normalized prediction distribution errors were adequately normally distributed (Supplementary Fig. 1). Moreover, the pcVPC plots showed

Table 1 Demographics

	Development	Range	Validation	Range
Total number of subjects (occasions)	133		132	
Sex (male/female)	65/68		64/68	
Age (days) (median [IQR])	88 [28–202]	1–6269	115 [31–274]	1–6327
PMA (weeks) (median [IQR])	51 [43–69]	35–933	54 [44–82]	37–941
Height (cm) (median [IQR])	57 [52–68]	43–175	58 [53–68]	42–180
Body weight (kg) (median [IQR])	4.5 [3.5–7.0]	2–70	4.5 [3.5–7.5]	2–82
Serum creatinine (µmol/L) (median [IQR])	28 [20–44]	10–177	23 [17–41]	5–437
Renal function (mL/min/1.73 m^2) (median [IQR])[†]	82 [49–128]	14–256	93 [60–137]	9–325
Serum urea (mmol/L) (median [IQR])	4.4 [3.0–6.8]	1–22	5 [3.1–8.1]	1–39
Serum albumin (g/L) (median [IQR])	29 [26–34]	17–43	39 [25–34]	12–44
ECMO (*n* [%])	11		8	
Pharmacokinetic characteristics				
Initial daily dose (mg/kg) (median [IQR])[§]	40 [30–45]	7–125	40 [32–45]	9–83
Number of blood samples (*n*)	374		343	

ECMO extra corporeal membrane oxygenation, *IQR* interquartile range, *PMA* post-menstrual age

[†]Renal function as calculated by the Schwartz equation

[§]Defined as the *per kg* cumulative dose at the first day of vancomycin therapy

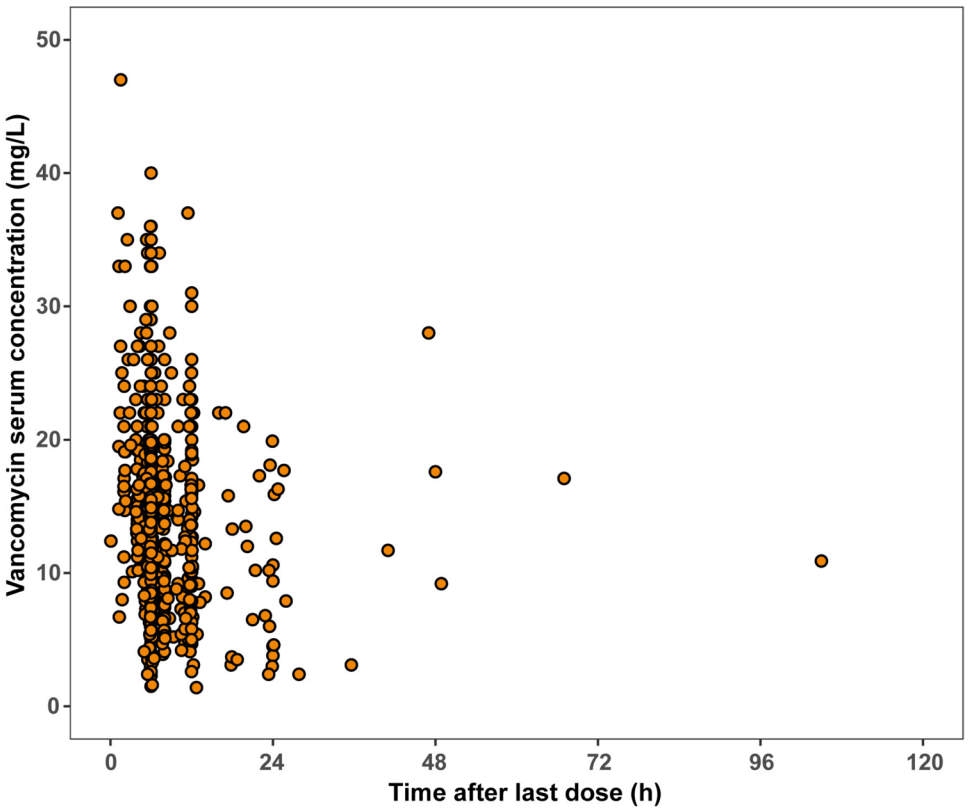

Fig. 1 Observed vancomycin serum concentration versus time after the last dose plot

Table 2 Population pharmacokinetic model parameters

	Final model			Bootstrap	
	Estimate	RSE (%)	Shrinkage (%)	Median estimate	95% CI
Final model structure					
$CL_i = \theta_{CL} \times \left(\frac{eGFR}{120}\right)^{\theta_{eGFR}} \times \left(\frac{BW}{70}\right)^{0.75}$					
$Vc_i = \theta_{Vc} \times \left(\frac{BW}{70}\right)^{1}$					
$Q_i = \theta_{Q} \times \left(\frac{BW}{70}\right)^{0.75}$					
$Vp_i = \theta_{Vp} \times \left(\frac{BW}{70}\right)^{1}$					
Population estimate					
θ_{CL} (L/h at 70 kg)	4.01	5	–	3.97	3.58–4.31
θ_{Vc} (L/70 kg)	56.1	12	–	55.1	41.0–67.6
θ_{Q} (L/h at 70 kg)	0.425	28	–	0.443	0.278–1.09
θ_{Vp} (Fixed) (L/kg)	21.7	–	–	21.7	–
Inter-individual variablity					
ω_{CL} (CV%)	23.6	8	27	23.9	19.2–28.1
ω_{Vc} (CV%)	42.9	10	45	42.9	31.9–54.0
Covariate model					
θ_{eGFR}	0.889	11	–	0.877	0.714–1.05
Error model					
Additive error (mg/L)	1.67	14	–	1.64	0.903–2.10
Proportional error (%)	17.9	9	–	17.5	13.5–21.0

BW body weight, *CL* elimination clearance, *eGFR* estimated glomerular filtration rate, as calculated by the Schwarz equation, *Q* intercompartmental clearance, *RSE* relative standard error, *Vc* central volume of distribution, *Vp* peripheral volume of distribution

that the model simulated data were generally in adequate agreement with the observed data.

3.4 External Validation

The normalized prediction distribution errors were shown to generally be adequately normally distributed (Supplementary Fig. 2). Moreover, the pcVPC plots showed that the model simulated data were generally in adequate agreement with the observed data from the validation dataset. An MPE value of 0.81% and an RMSE of 2.60 mg/L indicated that the model was able to predict vancomycin concentrations in the external cohort with acceptable bias and precision. An overview of the re-estimated model parameters based on the validation dataset are shown in Supplementary Table 2 (Fig. 3).

3.5 Dose Simulations and Optimization

Model simulations with the current dosing protocol showed low to very low target attainment probabilities at Day 2 for most categories. The highest target attainment probabilities were found in patients with a BW between 2–9 kg and an eGFR between 60–90 mL/min, and for patients with a BW between 10–40 kg and an eGFR > 90 mL/min. A full overview of the simulated target attainment probabilities with the local dosing protocol is shown in Table 3.

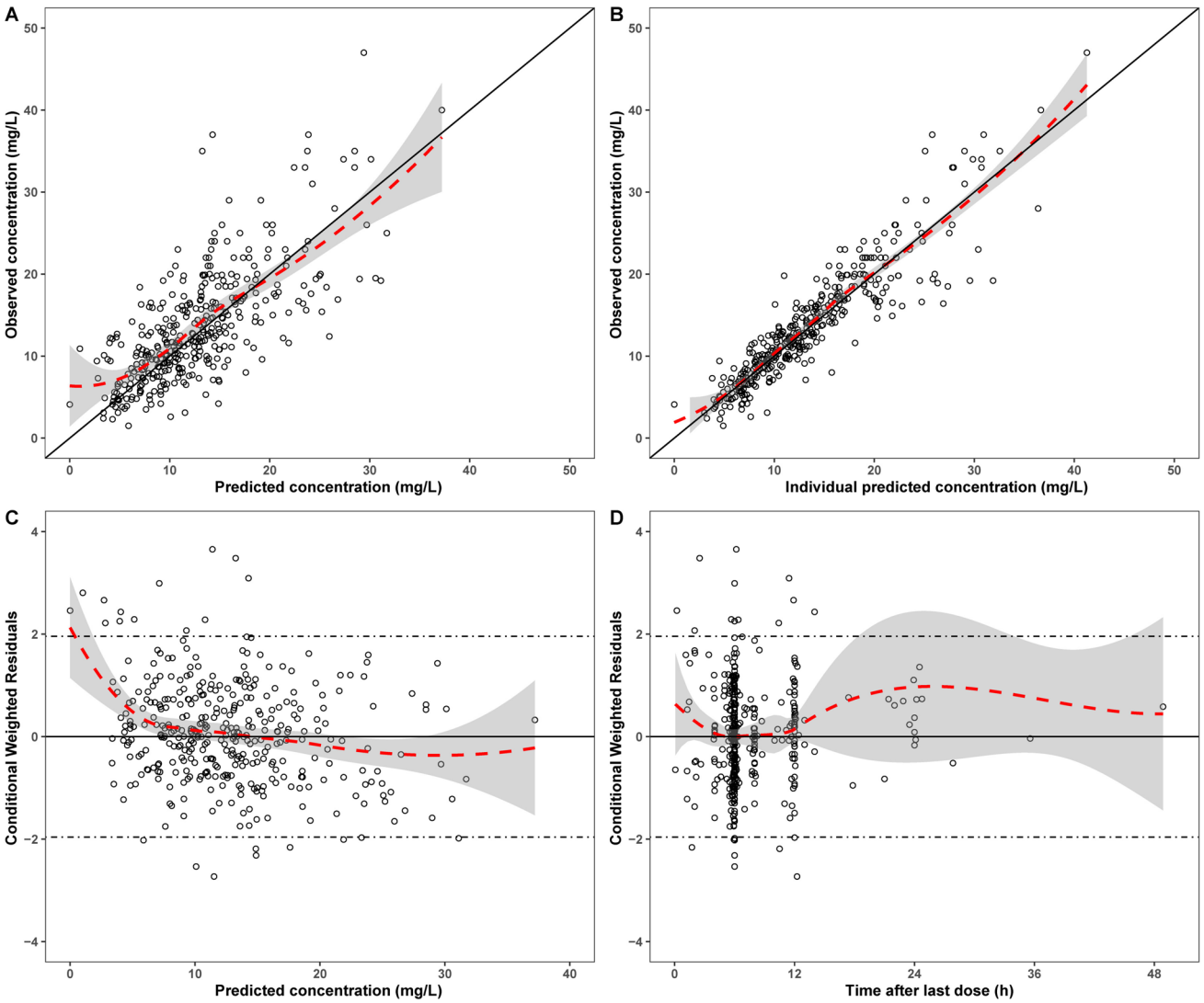

Fig. 2 Basic goodness of fit plots from the internal validation. **A** Observed vancomycin concentrations versus predicted concentrations. **B** Observed vancomycin concentrations versus individual predicted concentrations. **C** Conditional weighted residuals versus predicted concentrations. **D** Conditional weighted residuals versus time after last dose. The local polynomial regression (LOESS) fitting and 95 % confidence intervals (CIs) are shown by the dashed red lines and grey shaded areas, respectively

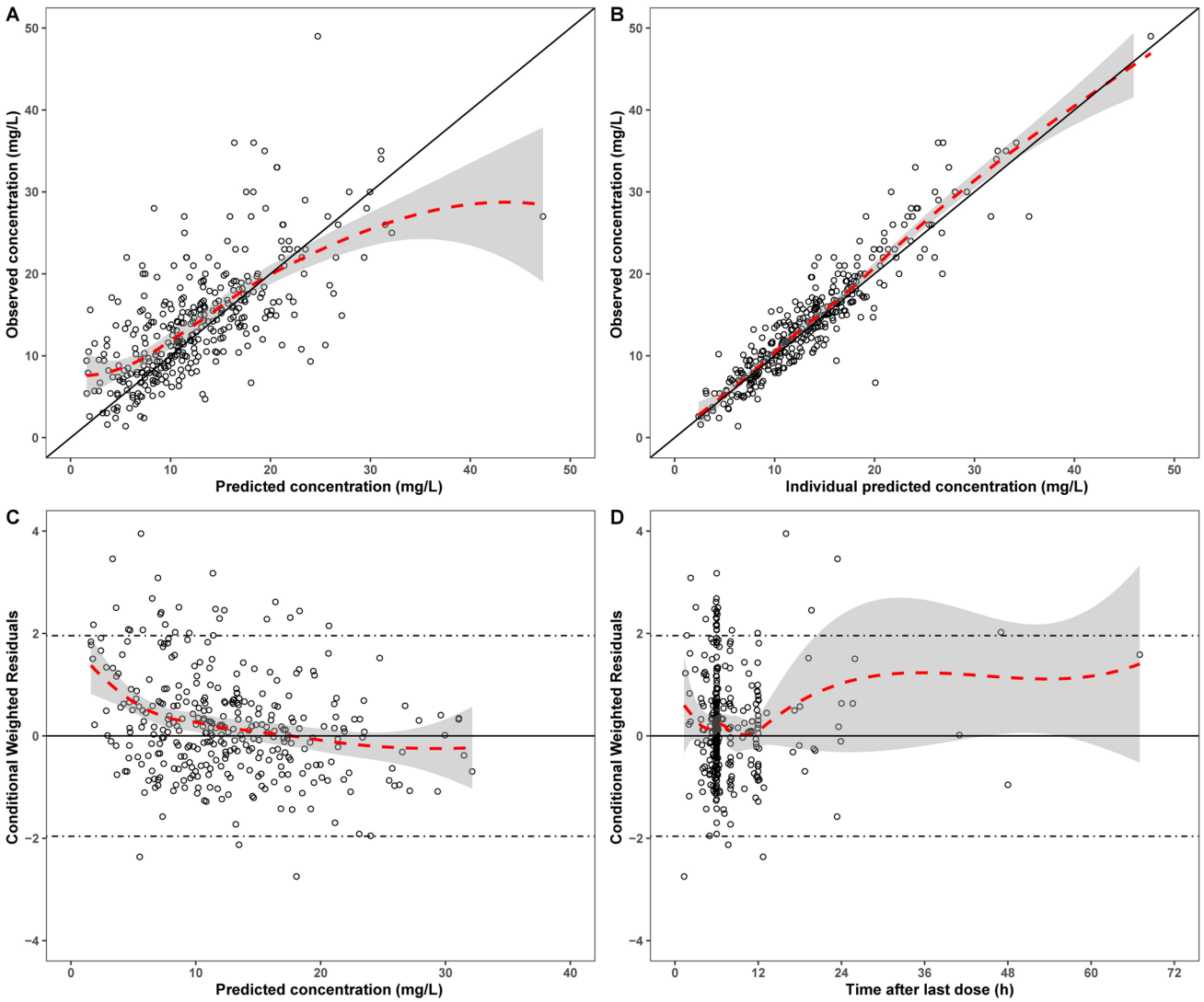

Fig. 3 Basic goodness-of-fit plots from the external validation. **A** Observed vancomycin concentrations versus predicted concentrations. **B** Observed vancomycin concentrations versus individual predicted concentrations. **C** Conditional weighted residuals versus predicted concentrations. **D** Conditional weighted residuals versus time after last dose. The local polynomial regression (LOESS) fitting and 95% confidence intervals (CIs) are shown by the dashed red lines and grey shaded areas, respectively

An overview of the optimized dosing algorithm to reach a target AUC_{24h} of 400–600 mg*h/L is shown In Table 4. Optimized daily doses for the higher BW groups were relatively lower than the optimized doses for patients with a lower BW. Simulations therefore suggested a non-linear relation between BW and optimal vancomycin dose and the use of a 20 mg/kg loading dose.

3.6 Fit-for-Purpose Evaluation

The fit-for-purpose evaluation showed that the model was able to predict future concentrations with an acceptable bias (MPPE) of 6.6% (95% CI −0.65 to 13.8%) when using

Table 3 Simulation based target attainment probabilities with the current local dosing protocol

Body weight (kg)	Estimated glomerular filtration rate (mL/min/1.73 m^2)			
	15–30	30–60	60–90	> 90
2–5	2%	40%	64%	24%
5–9	2%	21%	68%	51%
10–15	2%	11%	54%	66%
15–20	0%	8%	42%	67%
20–30	1%	5%	29%	66%
30–40	1%	4%	24%	60%
40–50	0%	2%	17%	49%

Table 4 Optimal dosing and target attainment based on body weight and renal function

Body weight (kg)	Estimated glomerular filtration rate (mL/min/1.73 m^2) (dosing interval)			
	15–30 (24 h)	30–60 (12 h)	60–90 (8 h)	> 90 (6 h)
2–5	18 mg/kg [70%]	14 mg/kg [69%]	15 mg/kg [66%]	14 mg/kg [65%]
5–9	16 mg/kg [68%]	13 mg/kg [69%]	12 mg/kg [70%]	12 mg/kg [67%]
10–15	14 mg/kg [70%]	11 mg/kg [69%]	10 mg/kg [67%]	10 mg/kg [66%]
15–20	13 mg/kg [70%]	10 mg/kg [71%]	10 mg/kg [70%]	10 mg/kg [66%]
20–30	13 mg/kg [66%]	9 mg/kg [70%]	9 mg/kg [68%]	9 mg/kg [68%]
30–40	13 mg/kg [64%]	8 mg/kg [68%]	8 mg/kg [68%]	9 mg/kg [66%]

Optimized dosing in mg/kg *per dose* after a loading dose of 20 mg/kg

Target attainment probabilities are shown between brackets

two prior vancomycin serum concentrations. Imprecision (MAPE) was 23.6% (95% CI 17.8–29.5%) with 33.6%, 60.3% and 75% of the predictions within 10%, 20% and 30% of the observations. The effects of adding prior information to the model are visualized in Fig. 4.

4 Discussion

Data on the PK of vancomycin in pediatric post-cardiac surgery patients are extremely limited [1]. The population of pediatric post-cardiac surgery patients is characterized by a large heterogenicity due to differences in diagnosis, performed surgical procedure, renal function or the drugs co-administered during PICU admittance. Population PK modeling is a useful method to help describe and predict the PK variations in pre-defined patient populations and may aid with the dose optimization in this vulnerable population. We therefore developed a population PK model for vancomycin in post-cardiac surgery PICU patients. Subsequent simulations with the model indicated that the current dosing regimens based on a linear relation between dose and BW might not be optimal for this population. We therefore propose a new dosing algorithm, based on allometric dosing rather than on linear (per kg) dosing over all BW categories. Moreover, the model was shown to be suitable for MIPD purposes.

As reported in the recent papers of Chung et al. and Shimamoto et al. [1, 14], vancomycin PK in pediatric ICU patients are generally best described by 2-compartmental models [1, 14]. However, few studies are currently published on vancomycin PK in pediatric post-cardiac surgery

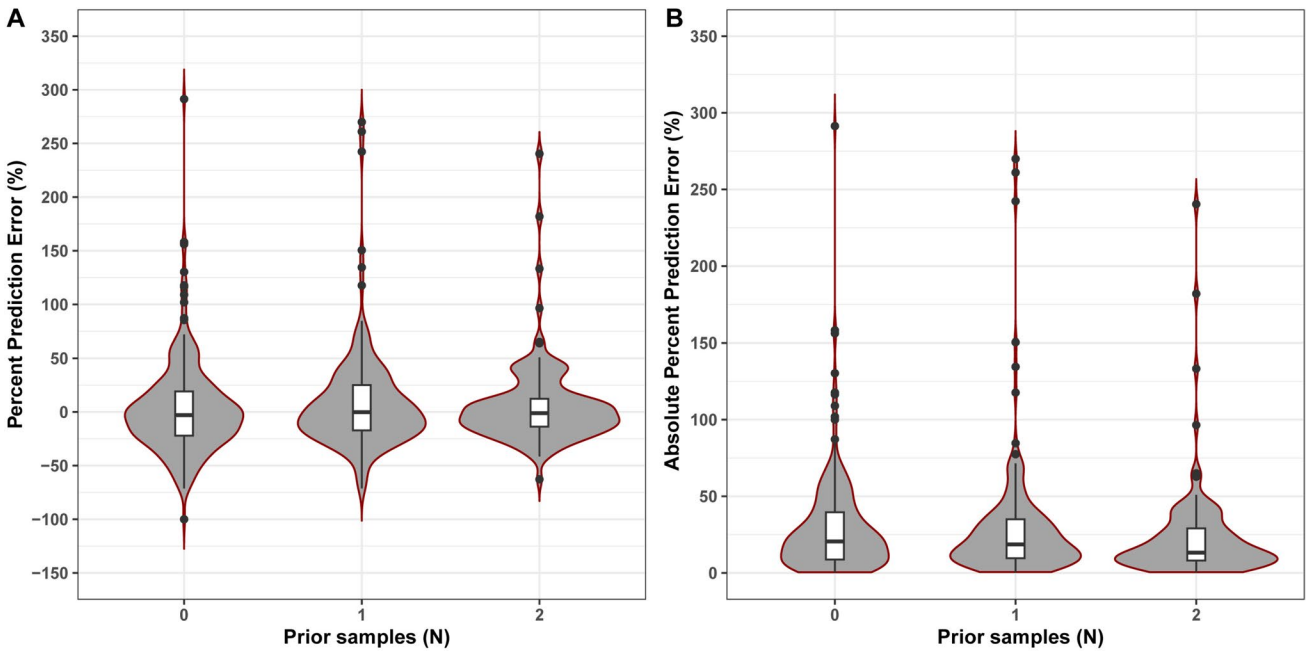

Fig. 4 Violin plot showing **A** bias, defined as percent prediction error and **B** imprecision, defined as absolute percent prediction error. Results are shown in case of no prior samples, one prior sample, or two prior samples

populations [11, 14]. In accordance to the studies in pediatric post-cardiac surgery patients, the current model showed substantial effects of BW and renal function on vancomycin PK. However, in contrast to the studies of Moffet et al. and Shimamoto et al., no significant effect of PMA was observed. This difference may be explained by a combination of sparse sampling in our dataset and the relatively small variability in PMA in our population compared to the population reported by Shimamoto et al (median [IQR]: 51.0 weeks [43.2–69.1] in the current population vs 55.2 [43.5–107.1] in the population reported by Shimamoto et al). Moreover, while full renal maturation is reached at an age of around 2 years [14], the majority of the patients in our population were aged < one year. This might have contributed to the lack of a PMA effect in our model.

It is currently debated if ECMO therapy influences vancomycin PK [4, 22, 23]. In the current study, we were unable to show a significant impact of ECMO on vancomycin PK. Although this may have partly resulted from the small number of ECMO cases in our cohort (11 and 8 cases in the development and validation datasets, respectively), our findings are in line with the results from a recent multicenter study that investigated the influence of ECMO on commonly used drugs in critically ill adult patients [24]. Moreover, since highly protein bound and lipophilic drugs are assumed to be the most influenced by ECMO [25, 26], the effect of ECMO on the PK of the hydrophilic and low protein-bound (30–55%) vancomycin [17] might be clinically insignificant.

Serum creatinine was shown to significantly explain observed variability in elimination clearance. Considering that up to 80% of a vancomycin dose is excreted by glomerular filtration during the first 24 h after administration, a significant effect of serum creatinine on clearance was to be expected [12]. Serum creatinine explained approximately 63% (relative reduction) of the clearance variability in our model, which emphasizes the need for dose adjustments based on renal function. These findings were in line with a recently reported systematic review, which stated that 60% of the published 2-compartmental models in critically ill pediatric populations included serum creatinine as a covariate [1].

In addition to renal function, BW was shown to explain a substantial amount of the IIV. Clearances were allometrically scaled to BW, indicating that the increase in clearance per kg BW tends to become smaller at the higher BW ranges. Since the optimal maintenance dose depends on elimination clearance, this would suggest that especially low BW patients (i.e., younger patients) would need relatively higher per kg vancomycin doses compared to pediatric patients with a higher BW. Interestingly, most dose recommendations and dose optimization studies recommended vancomycin dosing on a linear scale, defined as mg vancomycin per kg BW [7, 13, 14, 27, 28]. Based on the assumption of a non-linear relation between BW and clearance, this suggests that pediatric patients in higher weight classes might be at risk of being overdosed. Especially in pediatric populations, characterized by a large variability in BW, allometric dosing seems more rational than linear based dosing algorithms.

As expected, our dose simulations suggested a clear non-linear relationship between the per kg dose to attain the target AUC and the total BW. Although our local vancomycin dosing protocol showed to perform reasonably well for the "median" (i.e., BW between 2–5 kg and an eGFR between 60–90 mL/min/1.73 m^2) post-cardiac surgery patients on our PICU, target attainment in patients outside this group were substantially lower. Compared to our local dosing protocol, the newly developed and allometrically scaled dosing protocol maximized the probability of target attainment for a wide range of patients, minimizing the risk for under- or overdosing. However, despite the dose optimization, it is expected that up to ~35% of some patient categories will fail to attain the target AUC_{24h} at Day 2. The target attainment probabilities as found in the current study were shown to be similar to the target attainment probabilities reported by Shimamoto et al, who reported a linear per kg dosing algorithm, with stratification based on renal function and patient age [14]. This similarity in target attainment probabilities between both studies highlights the importance of TDM, which can be explained by the relatively high IIV.

The fit-for-purpose suitability evaluation showed that the model was able to predict future concentrations and with acceptable bias. Although imprecision was relatively high (23.6%), 75% of the predictions remained at < 30% within the observed concentrations when using two prior serum concentrations, indicating that *a posteriori* model predictions were sufficiently precise to be used for MIPD purposes. Moreover, taking the remaining unexplained IIV of 23.6% and 42.9% (for clearance and peripheral volume of distribution, respectively) into consideration, an imprecision of ±25% can be considered to be acceptable. To achieve a rapid target attainment, early sampling (i.e., obtaining a trough concentration after the first dose) might be considered for the *a posteriori* prediction future steady state concentrations, enabling timely dose adjustments if needed.

The developed population PK model was based on a sparse dataset since trough concentration-based vancomycin TDM is the current standard of care in our center. Due to the retrospective character of the study, most vancomycin serum concentrations concerned trough concentrations, with additional randomly sampled concentrations in some subjects. It might be an important limitation of this study that sparse data were used for the development of the population PK model. However, despite the limited number of peak concentrations and samples drawn during the elimination phase of vancomycin, our data were sufficiently informative to describe the data with 2-compartmental model. However,

the lack of information due to the sparse sampled character of our data, necessitated the fixation of the peripheral volume of distribution parameter estimate. Although more densely sampled data will be more likely to adequately estimate the peripheral volume of distribution, RSE values were generally low, indicating adequate parameter estimate robustness.

In addition, to account for potential inter-occasion variability, cases were included as separate individuals in the dataset, when vancomycin was administered > 90 h after the last dose or when vancomycin was administered during separate PICU admissions. Since cases were allocated at random to either the development dataset or the validation dataset, separate cases from a single individual patient might be assigned to each of the datasets. Theoretically this might affect the reliability of the external validation set; however, in our clinical experience, patient characteristics are highly variable during longer PICU admissions or between separate PICU admissions and can therefore be seen in another patient. We therefore did not consider it to be problematic that several cases from a single individual were assigned to both the development and validation datasets.

Lastly, we used the bedside Schwartz equation [19] to estimate the renal function for all included patients, regardless of age. Despite that this equation is not validated for neonates and preterms and the use of serum creatinine might not be the optimal marker to estimate renal function for these specific age groups due to physiological changes [29], we consider the use of the bedside Schwartz equation to be more clinically feasible compared to other more invasive methods [29].

The strength of the current study was that we were able to both develop and thoroughly validate (i.e., internally and externally) a population PK model for vancomycin in pediatric post-cardiac surgery ICU patients. More importantly, the developed model was used to optimize vancomycin dosing over multiple ages and renal function categories, increasing the likelihood of a rapid and spot-on target attainment, further limiting the risk for toxicity and improving efficacy. Moreover, fit-for-purpose testing showed that the model was suitable to be used for Bayesian forecasting, enabling timely dose adjustments, based on previously sampled vancomycin concentrations. Future studies may be directed to the clinical implementation of the dose recommendations as proposed in the current study and to the implementation of the developed model for MIPD in the clinic.

5 Conclusion

We successfully developed a population PK model for vancomycin in pediatric post-cardiac surgery patients. Vancomycin PK were shown to be significantly influenced by serum creatinine and BW. Furthermore, we suggested a new vancomycin dosing regimen, including a loading dose, based on an allometric scaling and renal function. Allometric dosing showed improved target attainments compared to the more conventional linear dosing. Moreover, the developed model was shown to be suitable for MIPD purposes.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40262-024-01463-3.

Declarations

Ethics This study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. The protocol was approved by the Institutional Review Board (IRB) at the Scientific Committee of the Department of Intensive Care, Medical Ethics Review Committee Leiden/Den Haag/Delft.

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Competing Interest Related to This Work No disclosures are applicable for this work. No authors have any conflicts to declare.

Institutional Review Board Statement As retrospective data from routine clinical care were used, a waiver was granted for the requirement of informed consent by the IRB (date of approval: August 15th 2024, approval number: 2024-041). Furthermore, a waiver for the requirement for informed consent was granted.

Consent to Participate The protocol was approved by the Institutional Review Board (IRB) at the Scientific Committee of the Department of Intensive Care, Medical Ethics Review Committee Leiden/Den Haag/Delft.

Data Availability Data are available on reasonable request from the authors.

Code Availability Code available in the supplemental material.

Author Contributions Conception and design: D.J.A.R. Moes and P.P. Roeleveld. Acquisition of data D.J.A.R. Moes, D.J.E. Wannet, J. Kamp, P.P. Roeleveld . Analysis and interpretation of data: All authors. Writing, review, and/or revision of the manuscript: All authors. Final approval of manuscript: All authors.

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