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ORIGINAL RESEARCH ARTICLE

# NONMEM population pharmacokinetics and Monte Carlo dosing simulations of imipenem in critically ill patients with life-threatening severe infections during support with or without extracorporeal membrane oxygenation in an intensive care unit

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## Abstract

**Study Objectives:** The objectives of this study were (i) to determine the population pharmacokinetic (PK) of imipenem in critically ill patients with life-threatening severe infections, (ii) to investigate the impact of extracorporeal membrane oxygenation (ECMO) on the population PK of imipenem during support with ECMO compared to those without ECMO support, and (iii) to assess the probability of target attainment (PTA) for finding the optimal dosage regimens of imipenem in critically ill patients with life-threatening severe infections.

**Design:** Open-label, PK study.

**Setting:** Academic tertiary care medical center.

**Patients:** Fifty critically ill patients with or without ECMO by pooling data from previously published studiesand unpublished data from 14 patients.

**Intervention and Measurements:** The population PK of imipenem was determined using NONMEM and a Monte Carlo simulation was performed to determine the PTAs of achieving 40% and 75% exposure times during which the plasma drug concentrations remained above the MIC.

**Main Results:** The values of volume of distribution and total clearance were 30.5 L and 13.3 L/h, respectively. The ECMO circuit did not show a significant influence on the PK parameters of imipenem. For pathogens with a MIC of 4 mg/L, the PTA target of 75% fT>MIC in patients with normal renal function was achieved when the imipenem was administered by a 4-h infusion of 1 g q6h.

**Conclusion:** The ECMO circuit had little effect on enhancing the PK changes of imipenem that had already occurred in these patients. A high dosage of imipenem may be required for achieving the PK/pharmacodynamic targets against less susceptible pathogens, however, the dosage regimens in patients with renal impairment may not need to be as high as those required in patients with normal renal function.

**ClinicalTrials.gov:** NCT03858387.

KEYWORDS
critically ill patients, extracorporeal membrane oxygenation, imipenem, NONMEM, pharmacodynamics, population pharmacokinetics

## 1 | INTRODUCTION

Extracorporeal membrane oxygenation (ECMO), an advanced life-support machine, provides pulmonary and/or cardiac support for patients who have severe cardiopulmonary diseases refractory to conventional therapy.[1–3] Previous studies on the impact of ECMO in critically ill neonates have found that the ECMO circuit itself can exacerbate the already profound pathophysiological changes associated with these critical conditions, resulting in alterations of the pharmacokinetics (PK) of antibiotics.[1,2,4] In recent years, ECMO has been increasingly used for support of seriously ill adults suffering severe respiratory and/or cardiac failure.[1,5] To date, few studies have examined how this increasing use of ECMO support may be influencing the PK of coadministered drugs. Based on available PK analyses, it appears that pathophysiological changes from an ECMO circuit have little impact on PK patterns, resulting in no or minimal changes in the *V* and CL of administered drugs when compared to those changes resulting from the critical illness itself.[1,6,7] However, our previous study found that pathophysiological changes in adult patients with ECMO had a greater impact on altered PK patterns of imipenem than those occurring in patients without ECMO support.[8] Therefore, further investigations of the impact of ECMO on imipenem PK are required. The aims of this study were (i) to determine the population PK of imipenem in critically ill patients with life-threatening severe infections, (ii) to investigate the impact of ECMO on the population PK of imipenem in this patient population during support with ECMO compared to those without ECMO support, and (iii) to assess the probability of target attainment (PTA) for finding the optimal dosage regimens of imipenem in critically ill patients with life-threatening severe infections.

## 2 | MATERIALS AND METHODS

### 2.1 | Patients, study design, and blood sampling

The study was conducted on 50 critically ill patients with severe infections by pooling from two datasets.

Dataset 1: The clinical data and plasma concentrations of imipenem from 36 critically ill patients with or without ECMO support were pooled from four previous studies we conducted.[8–11]

Dataset 2: The current study also included additional data from 14 critically ill patients with severe infections admitted to the ICU of Songklanagarind Hospital between October 2018 and January 2020. All patients were ≥18 year of age and received a 1-h infusion of 0.25–0.5 g of imipenem/cilastatin q6-12 h. The imipenem PK studies were carried out during administration of the dose of imipenem after 24 h of drug administration. Blood samples (~3 ml) were obtained via a heparinized intravascular catheter by direct venipuncture at the following times: before (time zero) and 0–0.5, 0.5–2, 2–4, and 4–12 h after drug administration. The blood samples were added to a heparinized tube and centrifuged at 1000 × *g* for 10 min not later than 15 min after collection. An equal volume of stabilizing solution (0.5 M MOPS/water/ethylene glycol, 2:1:1, v/v/v) was added to each plasma sample, which was then vortexed and stored at −80°C until analysis within 1 week. The details of the patient populations and study design are summarized in Table 1.

This study was approved by the Ethics Committee of Songklanagarind Hospital, Faculty of Medicine, Prince of Songkla University (Number 60-061-14-1). Written informed consent was obtained from each patient's legally acceptable representative before enrollment.

**TABLE 1** Patient populations and study design of the 50 critically ill study patients from four previous studies and an unpublished study

| | | | Median (interquartile range) of severity of illness | |
|---|---|---|---|---|
| | **Patient population** | **Imipenem dosage regimens** | **APACHE II score** | **SOFA score** |
| Previous study 1 in 10 patients[8] | Critically ill patients with life-threatening severe infections support with ECMO | 1-h infusion, 0.5 g q6h | 24 (14.5–26.5) | 10 (9–16.25) |
| Previous study 2 in 8 patients[9] | Critically ill patients with VAP | All patients received 0.5-h infusion, 0.5 g q6h for 24 h; then 2-h infusion, 0.5 g q6h for 24 h; finally 2-h infusion, 1 g q6h for 24 h | 11 (6.75–14) | 3 (2–5) |
| Previous study 3 in 10 patients[10] | Critically ill patients with febrile neutropenia and bacteremia | Group 1: 0.5-h infusion, 0.5 g q6h<br>Group 2: 4-h infusion, 0.5 g q6h | 17 (13.5–21.25) | 4 (3–5.75) |
| Previous study 4 in 8 patients[11] | Critically ill patients with VAP | Group 1: 0.5-h infusion, 0.5 g q6h<br>Group 2: 4-h infusion, 1 g q8h | 11 (9–13) | 3 (2–3.25) |
| Unpublished study in 14 patients | Critically ill patients with sepsis | 1-h infusion, 0.25–0.5 g q6-12h | 23 (13–26.75) | 9 (3.75–13) |

Abbreviations: ECMO, extracorporeal membrane oxygenation; VAP, ventilator-associated pneumonia.

## 2.2 | Drugs and chemicals

Imipenem/cilastatin (Tienam®) used in an unpublished study was purchased from MSD, Thailand. Imipenem standard powder was purchased from the U.S. Pharmacopeia (Rockville, MD, USA) as pure powder. All the solvents were of HPLC grade.

## 2.3 | Imipenem assays

The free fractions of imipenem concentrations (not for cilastatin) were determined by reversed-phase HPLC. The samples were prepared by the method of Garcia-Capdevila et al.[12] Briefly, 250 μl of stabilizing solution was added to 250 μl of the sample. The mixture was then subjected to ultrafiltration, using an Ultrafree® MC Centrifugal Filter Unit for 10 min at 6000 × *g*. An aliquot of the sample (50 μl) was injected onto a Nova-Pak C18 column (Waters Associates). The mobile phase used 0.2 M borate buffer, pH 7.2 at a flow rate of 1 ml/min. The column effluent was monitored by a photodiode array detector (Waters 2996; Waters Associates, Milford, MA) at 300 nm. The validation tests were found to be within acceptable limits as per the 2013 U.S. Food and Drug Administration Guidance on Bioanalytical Method Validation.[13] The lower limit of quantitation (LLOQ) of imipenem was 0.25 mg/L. The intra-assay reproducibility values characterized by coefficients of variation (CVs) were 0.19%, 0.71%, and 0.11% for samples containing 0.75, 20, and 75 mg/L, respectively. The inter-assay reproducibility precision values, calculated by CVs, were 0.39%, 1.63%, and 0.23% for samples containing 0.75, 20, and 75 mg/L, respectively. A short-term stability study showed that at room temperature for samples containing 0.75 and 75 mg/L, the imipenem concentration losses were <1% for at least 1 h. A long-term stability study showed that at −80°C, the imipenem concentration losses were <5% for at least 14 days.

## 2.4 | Population pharmacokinetics analysis

The population PK model-building of imipenem was performed using NONMEM® software version 7.4 (ICON Development Solution, Ellicott City, MD, USA) along with Perl-Speaks-NONMEM version 4.9.0 (Uppsala university, Uppsala, Sweden) and Pirana software version 2.9.9 (Certara, NJ, USA). Graphical processing of the data and NONMEM output was carried out in R program version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria). The first-order conditional estimation with eta-epsilon interaction (FOCE-I) and stochastic approximation expectation maximization (SAEM) methods was examined to estimate the PK parameters. Both methods provided similar PK parameters, therefore, the FOCE-I method was chosen due to significantly shorter runtimes. Imipenem concentrations below LLOQ, which represented only 1.1% of all datasets, were imputed with LLOQ/2.

The interindividual variability (IIV) of each parameter was modeled using an exponential error model and covariance terms were estimated for any interindividual error terms displaying significant correlations. The interoccasion variability (IOV) was also tested and modeled as an additional random effects parameter. Residual variability for the pooled dataset was initially modeled by considering additive, proportional, or combined additive and proportional error models. Then, a separate residual error model for each study was investigated to account for study variability differences.

After the appropriate structural model was established, 23 clinical covariates were evaluated for their impact on PK parameters: age, gender, actual body weight, ideal body weight, adjusted body weight (ABW), body mass index, the use of ECMO support, ECMO type, ECMO flow rate, duration of ECMO, APACHE II scores, SOFA scores, creatinine clearance estimated by Cockcroft-Gault equation ($CL_{CR\text{-}CG}$), estimated glomerular filtration rate (eGFR) using the four variables from the Modification of Diet in Renal Disease study equation ($GFR_{MDRD4}$), six variables from the $GFR_{MDRD}$($GFR_{MDRD6}$) and the Chronic Kidney Disease Epidemiology Collaboration equation ($GFR_{EPI}$), acute kidney injury, mechanical ventilation support, serum albumin, fluid balance, use of inotropes, septic shock, and mean arterial blood pressure. A covariate was retained in the model if it led to significant improvement of model fit, as evaluated by a decrease in objective function value (OFV) of 3.84 ($p < 0.05$ for 1 degree of freedom [*df*]) for forward addition and an increase of OFV by 6.64 ($p < 0.01$ for 1 *df*) for a backward deletion step.

The minimum objective function value (MOFV) between nested models, and Akaike's information criterion (AIC) between a non-nested model in combination with parameter precision, and visual inspection of various goodness-of-fit plots, were considered for model selection. A non-parametric bootstrap ($n = 2000$) stratified on study was performed to evaluate the robustness of the final model and to obtain confidence intervals of all parameter estimates. The predictive performance of the final model was examined using a prediction-corrected visual predictive check (pcVPC) to compare the 5th, 50th, and 95th percentiles of the observed and simulated concentrations ($n = 2000$). The final model was also assessed by normalized prediction distribution error (NPDEs). A total of 2000 datasets were simulated using the final model parameters, and the results were summarized graphically by quantile-quantile and histogram plots. The NPDE distribution was expected to follow a normal distribution.

## 2.5 | Pharmacodynamic assessment using Monte Carlo simulations

A Monte Carlo simulations (MCS; $n = 5000$) was performed using NONMEM® version 7.4 and R program version 3.6.0 to assess the PTAs of various dosing regimens. The final population PK model was used to simulate the unbound imipenem concentration-time profiles over the first 48 h of the treatment course for various dosage regimens, duration of infusion, and $GFR_{EPI}$. For all of these regimens, the percentage of time that free drug concentrations exceeded the MIC ($fT_{>MIC}$) of each simulated condition was determined and then the probabilities of achieving $fT_{>MICs}$ of 40% and 75% were calculated.

**TABLE 2** Demographic data of the 50 critically ill study patients during support with or without Extracorporeal membrane oxygenation (ECMO)

| | Median (interquartile range) or as indicated | | |
|---|---|---|---|
| **Factor[a]** | **ECMO (*N* = 10)** | **Without ECMO (*N* = 40)** | **All patients (*N* = 50)** |
| Gender | | | |
| Male (%) | 6 (60%) | 29 (72.5%) | 35 (70%) |
| Female (%) | 4 (40%) | 11 (27.5%) | 15 (30%) |
| Age (years) | 49.00 (40.75–54.75) | 58.10 (42.05–69.60) | 56.20 (40.95–66.60) |
| Actual body weight (kg) | 62.50 (55.00–69.25) | 62.90 (51.88–70.00) | 62.90 (52.77–70.00) |
| Ideal body weight (kg) | 58.24 (51.48–67.97) | 59.15 (54.84–62.31) | 59.14 (52.83–64.35) |
| Adjusted body weight (kg) | 57.96 (54.25–66.17) | 60.67 (51.88–67.84) | 59.77 (52.08–67.88) |
| Body mass index (kg/m$^2$) | 24.72 (22.38–27.83) | 22.89 (20.04–26.35) | 23.43 (20.46–26.57) |
| $GFR_{EPI}$ | 67.43 (34.95–109.07) | 100.90 (62.48–114.49) | 98.89 (49.66–113.30) |
| Serum albumin (g/dl) | 2.25 (1.90–2.78) | 2.60 (2.38–3.40) | 2.55 (2.20–3.00) |
| Total bilirubin (mg/dl) | 1.33 (1.08–2.17) | 0.77 (0.52–1.90) | 0.87 (0.54–1.93) |
| Aspartate aminotransferase level (mg/dl) | 219.5 (57.00–1660.75) | 34.5 (18.75–59.25) | 37.5 (20.0–141.75) |
| Alanine aminotransferase level (mg/dl) | 162.5 (73.25–821.0) | 24.5 (17.75–47.25) | 35.0 (18.25–79.75) |
| Alkaline phosphatase level (U/L) | 94.5 (68.0–118.75) | 106.5 (85.0–168.25) | 102.5 (83.5–157.25) |
| The use of catecholamine infusion(s) | | | |
| Norepinephrine (%) | 7 (70%) | 8 (20%) | 15 (30%) |
| Epinephrine (%) | 3 (30%) | 1 (2.5%) | 4 (8%) |
| Dopamine (%) | 5 (50%) | 1 (2.5%) | 6 (12%) |
| Use ≥2 drugs (%) | 5 (50%) | 2 (5%) | 7 (14%) |
| The use of mechanical ventilator (%) | 10 (100%) | 25 (62.5%) | 35 (70%) |
| APACHE II scores | 30.5 (26.25–37.25) | 15.0 (11.0–22.0) | 17.5 (11.25–26.0) |
| SOFA scores | 14.0 (12.25–17.00) | 4.0 (2.0–7.0) | 5 (3.0–11.75) |
| Fluid balance 24 h (L) | 2.19 (0.87–4.21) | 0.74 (0.04–1.47) | 0.82 (0.12–1.52) |
| Source of infection | | | |
| VAP | 6 | 17 | 23 |
| HAP | – | 5 | 5 |
| CRBSI | 1 | – | 1 |
| Ruptured appendicitis | 1 | – | 1 |
| Suspected nosocomial infection | 1 | 1 | 2 |
| Aspiration pneumonia | 1 | – | 1 |
| Bacteremia | – | 11 | 11 |
| Peritonitis | – | 2 | 2 |
| Pancreatitis | – | 2 | 2 |
| UTI | – | 1 | 1 |
| Cellulitis | – | 1 | 1 |
| Isolated pathogens | | | |
| *Pseudomonas aeruginosa* | 2 | 12 | 14 |
| *Acinetobacter baumannii* | 3 | 4 | 7 |
| *Klebsiella pneumoniae* | – | 12 | 12 |
| *Moraxella catarrhalis* | – | 2 | 2 |
| *Stenotrophomonas maltophilia* | – | 2 | 2 |
| *Enterobacter cloacae* | – | 2 | 2 |
| *Escherichia coli* | – | 6 | 6 |
| Other GNB | 7 | 10 | 17 |

Abbreviations: APACHE, acute physiology and chronic health evaluation; CRBSI, catheter-related blood stream infection; fluid balance, fluid intake minus fluid output for 24 h during administration of imipenem; $GFR_{EPI}$, glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration equation; $GFR_{MDRD}$, glomerular filtration rate using the Modification of Diet in Renal Disease study equation; GNB, gram-negative bacteria; HAP, hospital-acquired pneumonia; SOFA, sepsis-related organic failure assessment; UTI, urinary tract infection; VAP, ventilator-associated pneumonia.

[a]*N*, number of patients.

The PTA of ≥90% was considered to be optimal in critically ill patients with severe infections.

## 3 | RESULTS

The demographic data of the 50 patients from the five studies are shown in Table 2. A total of 534 sample concentrations were used for the population PK analysis. A two-compartment model with first-order elimination best described the pooled imipenem concentration-time profiles. The IIV was able to be estimated in all parameters, but the IIV on Q was very low, and therefore, it was fixed to zero. Since there was a significant correlation between IIV on CL, $V_{C,}$ and $V_P$, covariance terms were incorporated which resulted in a substantial improvement of the model fit (ΔAIC = −24.2). Because the plasma concentrations in the second study were available for multiple doses, the IOVs were taken into account. The only IOV found to be statistically significant was the IOV on $V_C$ (ΔMOFV = −39.4). The magnitude of the IOV on $V_C$ was moderate (coefficient of variation 33.2%), which suggests that the $V_C$ within an individual may change over time. However, the percentage of shrinkage (SHR) and relative standard error (RSE) estimates of this parameter were high (SHR 77.3% and RSE 65.7%), therefore, it was not included in further model development. Residual variability was described using a combined proportional plus additive error model. Subsequently, the residual variability model was modified by adding separate error terms for each study; this modified model resulted in a better fit model. The details of model development are provided in Appendixes 1 and 2. After completing the covariate testing, all estimated renal functions were the significant covariates describing the CL of imipenem and the $GFR_{EPI}$ was the best improvement of the model fit, whereas ABW was the only significant covariate explaining the $V_C$ of imipenem. The use of ECMO support, ECMO type, ECMO flow rate, and duration of ECMO did not show significant influences on the PK parameters of imipenem (Figure 1). The final parameter estimates along with their precisions are summarized in Table 3. All model parameters were estimated with acceptable precision and the parameters obtained from the final model were generally similar and contained within 95% CIs from 2000 bootstrap runs, indicating the robustness of the model. The goodness-of-fit plots showed good agreement between observed and model-predicted concentrations (Figure 2). A majority of the conditional weighted residuals (CWRES) lay within 2 SDs and were symmetrically distributed around zero. The pcVPC plot (Figure 3) shows that the 5th, 50th, and 95th percentiles of observed data were within the 95% prediction intervals, indicating good predictive performance of the final model. Furthermore, the NPDE distribution and histogram (Figure 4) comply well with the theoretical *N* (0,1) distribution and density. With regard to overall plots, the fit of this model seemed reasonably good with no apparent visual biases.

The PTAs for various dosage regimens of imipenem for achieving 40% $fT_{>MIC}$ and 75% $fT_{>MIC}$ in patients with various ranges of GFR are shown in Table 4 and Appendix 3. For the PTAs of achieving 40% $T_{>MIC}$ in patients with GFR of 60–120 ml/min, the imipenem dosages of a 4-h infusion of 0.5 g q8h for a MIC of 2 mg/L and a 4-h infusion of 1 g q8h for a MIC of 4 mg/L were 97.1% and 97.2%, respectively. For the PTAs of achieving 75% $T_{>MIC}$ in patients with GFR of 60–120 ml/min, the imipenem dosages of a 4-h infusion of 0.5 g q6h for a MIC of 2 mg/L and a 4-h infusion of 1 g q6h for a MIC of 4 mg/L were 92.7% and 91%, respectively.

## 4 | DISCUSSION

In this study, the ECMO circuit had little effect on enhancing the PK changes of imipenem that had already occurred in critically ill

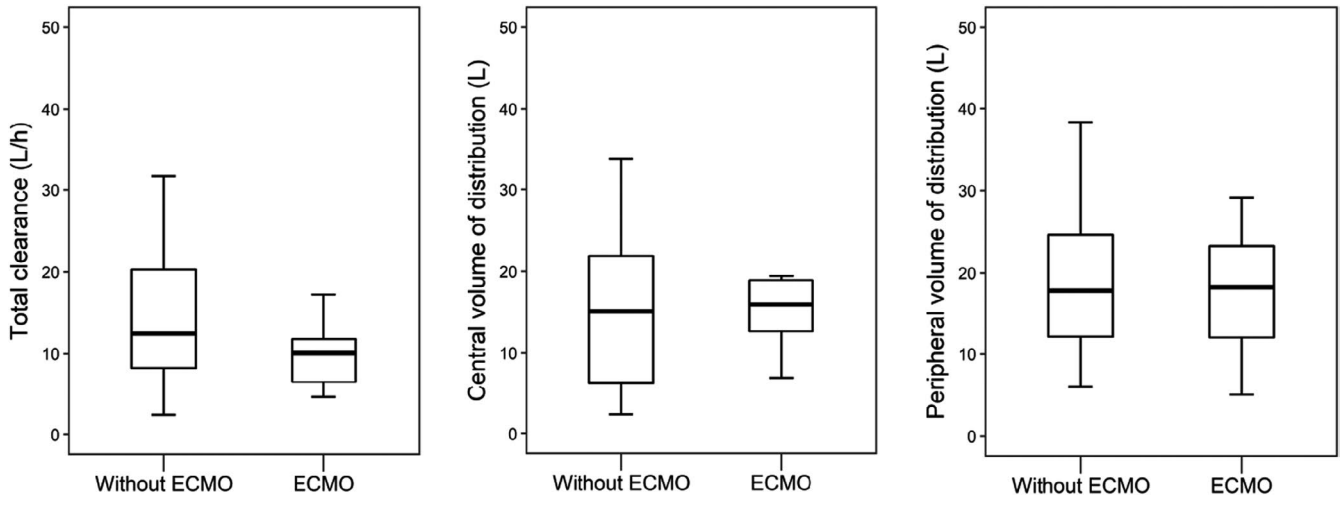


**FIGURE 1** The population pharmacokinetic parameters of imipenem in critically ill patients with life-threatening severe infections during support with or without extracorporeal membrane oxygenation (ECMO). The horizontal lines in the box-whiskers plots are the medians; the lower and upper boundaries of the box indicate the 25th and 75th percentiles, respectively. Vertical lines (whiskers) indicate 1.5× IQR below the 25th and above the 75th percentiles

**TABLE 3** Population pharmacokinetic parameters of imipenem from the base and final models[a]

| | Base model (MOFV = 1186.4) | | Final model[b] (MOFV = 1022.3) | | | |
|---|---|---|---|---|---|---|
| **Parameter** | **Estimate** | **%RSE** | **Estimate** | **%RSE** | **%SHR** | **Median (95% CI)** |
| Fixed-effect parameter | | | | | | |
| CL (L/h) | 11.8 | 9.5 | 13.3 | 7.3 | | 13.3 (11.7, 15.1) |
| $\theta_1$ | | | 0.112 | 11.8 | | 0.113 (0.088, 0.139) |
| $V_C$ (L) | 15.0 | 12.4 | 13.6 | 11.0 | | 13.6 (10.9, 16.4) |
| $\theta_2$ | | | −0.348 | 26.8 | | −0.337 (−0.52, −0.135) |
| $V_P$ (L) | 15.4 | 12.4 | 16.9 | 10.6 | | 17.0 (13.7, 20.7) |
| Q (L/h) | 19.4 | 20.6 | 24.3 | 17.4 | | 24.2 (16.7, 33.7) |
| Interindividual variability (IIV) | | | | | | |
| IIV on CL (%CV) | 66.6 | 17.2 | 51.0 | 17.7 | 0.1 | 50.2 (41.1, 58.7) |
| IIV on $V_C$ (%CV) | 75.0 | 23.1 | 66.9 | 23.0 | 6.5 | 65.6 (52.6, 82.1) |
| IIV on $V_P$ (%CV) | 60.3 | 23.1 | 56.0 | 22.9 | 12.5 | 55.1 (42.2, 67.3) |
| Covariance between CL and $V_C$ | | | 0.253 | 23.8 | – | 0.249 (0.144, 0.377) |
| Covariance between CL and $V_P$ | | | 0.166 | 29.2 | – | 0.161 (0.073, 0.270) |
| Covariance between $V_C$ and $V_P$ | | | 0.202 | 34.9 | – | 0.199 (0.066, 0.349) |
| Residual variability | | | | | | |
| Additive (mg/L) | 0.186 | 39.8 | 0.216 | 31.2 | 11.0 | 0.217 (0.145, 0.288) |
| Proportional error (%) | 19.7 | 21.0 | – | – | – | – |
| Proportional error for study 1 (%) | | | 10.6 | 26.6 | 12.6 | 10.6 (7.7, 13.4) |
| Proportional error for study 2 (%) | | | 17.4 | 33.2 | 11.7 | 17.2 (10.6, 23.0) |
| Proportional error for study 3 (%) | | | 25.6 | 21.8 | 5.0 | 25.6 (19.9, 30.7) |
| Proportional error for study 4 (%) | | | 10.2 | 28.8 | 13.8 | 10.0 (7.0, 12.9) |
| Proportional error for study 5 (%) | | | 18.3 | 42.5 | 22.0 | 18.1 (10.3, 25.3) |

Abbreviations: %CV, percentage of coefficient of variation; ABW, adjusted body weight; CI, confidence interval; CL, total clearance; $GFR_{EPI}$, glomerular filtration rate calculated by Chronic Kidney Disease Epidemiology Collaboration equation; MOFV, minimum objective function value; Q, intercompartment clearance; SHR, shrinkage; $V_C$, central volume of distribution; $V_P$, peripheral volume of distribution; $\theta_1$, slope estimate reflecting the influence of $GFR_{EPI}$ on CL; $\theta_2$, slope estimate reflecting the influence of BW on $V_C$.

[a]%RSE, percentage of relative standard error.

[b]The final PK model parameter: $CL(L/h) = 13.3 + \theta_1 \times (GFR_{EPI} - 89)$

$V_C(L) = 13.8 + \theta_2 \times (ABW - 60)$.

patients with severe infections. A high dosage of imipenem may be required for achieving the PK/PD target against less susceptible pathogens in critically ill patients with severe infections.

Although ECMO has been increasingly used for lifesaving support in patients with potentially reversible respiratory and/or cardiac failure for several years, an in-depth understanding of the complex changes in the PK of administered drugs in these cases is still needed for designing the optimal dosing regimens. Several previous PK investigations found that ECMO affected the altered PK of drugs in several ways.[1,2,4,14] First, the interaction between the ECMO circuit and the drug can cause an alteration of the PK of several drugs used in these patients, and subsequently, affect therapeutic plasma concentrations and the achievement of PD targets. Direct drug extraction by the ECMO circuit is a well-recognized effect on the PK alteration across all patient populations that depends on both the circuit factors and the physicochemical properties of the drug.[1,4,14] The degree of sequestration of a drug can be affected by several circuit factors such as oxygenator materials, the type of circuit tubing, circuit age, and composition of the priming solution.[1,14,15] The physicochemical properties of any given drug, including molecular weight, pKa, and degree of ionization, plasma protein binding, and lipophilicity, can also affect the extent of the interaction of the drug with the ECMO circuit.[1,14] Several previous *ex vivo* studies have demonstrated that the degree of lipophilicity and protein binding is significant factors affecting the extent of drug extraction when subjected to an ECMO circuit.[1,14] Imipenem is a hydrophilic β-lactam antibiotic with a relatively low *V* at steady state and low protein binding of less than 10% to 20%.[16,17] Therefore, the degree of drug extraction of imipenem

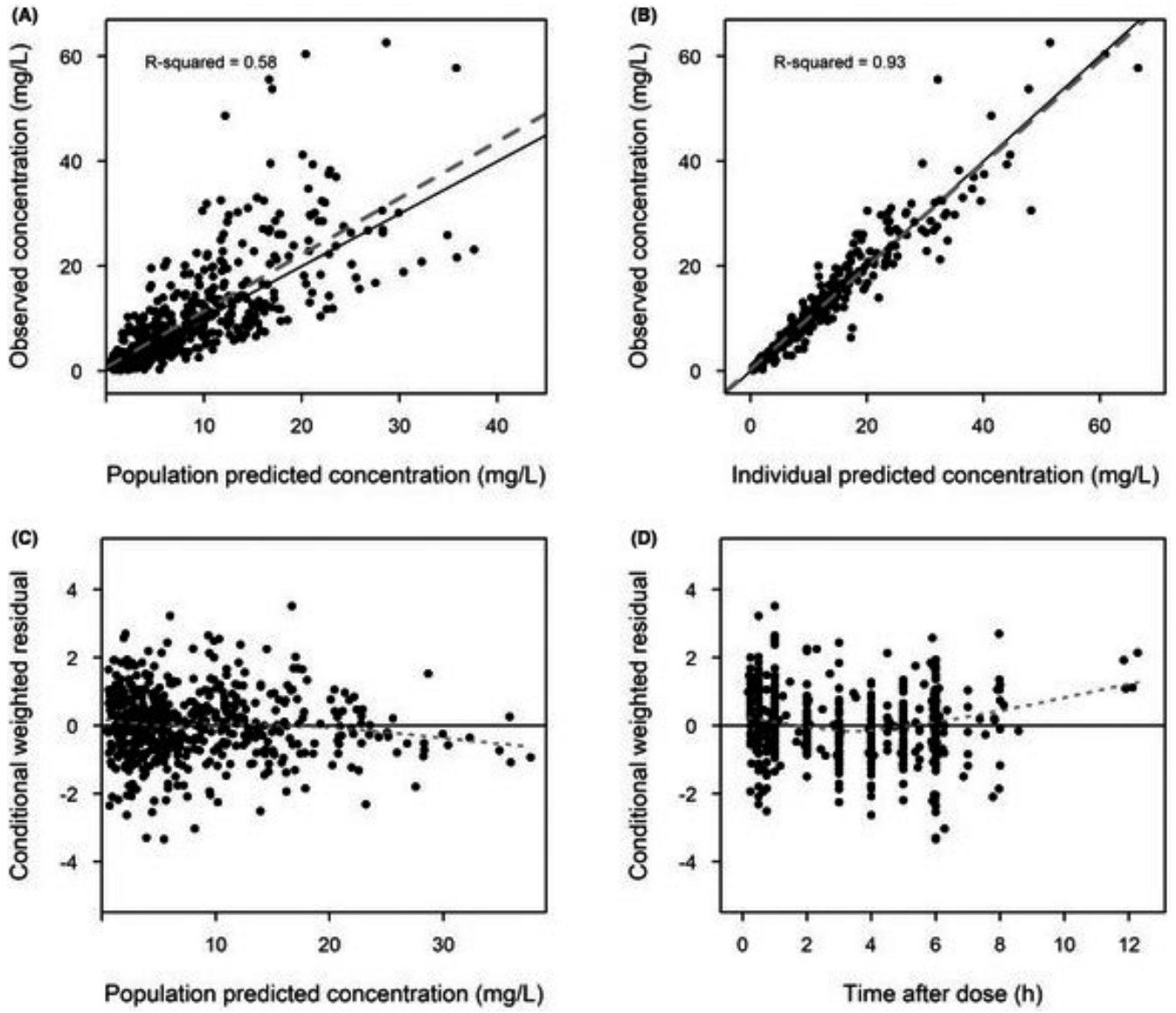


**FIGURE 2** The goodness-of-fit plots of the final imipenem pharmacokinetic model. (A) Observed concentration versus population predicted concentration; (B) observed concentration versus individual predicted concentration; (C) conditional weighted residual versus population predicted concentration; (D) conditional weighted residual versus time after dose. Solid lines represent the line of identity, the dashed line is the linear regression line, and the dotted line is the locally weighted smoothing line to indicate trends

by an ECMO circuit may not be high compared to highly lipophilic and highly protein-bound antimicrobial agents. Second, hemodilution from the large volume of exogenous blood, blood products, and crystalloid fluid required to prime the circuit flows of the ECMO result in increased *V*s of all administered drugs.[1,4,14] This effect has a greater impact on hydrophilic drugs with a low *V* than lipophilic drugs with a high *V* that are distributed widely to the tissues. However, the association between the hemodilution effect from an ECMO circuit and an enlarged *V* has mostly been investigated in neonates, resulting in difficulties extrapolating the data for use in critically ill adults due to significant differences in physiological conditions and composition of body fluids.[1,2,4] Therefore, the hemodilution effect from the priming solution of the ECMO circuit may have different effects in adults. Third, ECMO affects various organ systems due to hypoxia and hypoperfusion, resulting in decreased renal clearance of imipenem in patients receiving ECMO.[1,4,14]

In critically ill patients not receiving ECMO, pathophysiological changes occurring in life-threatening severe infections and multiple comorbidities can also cause an alteration of PK patterns for antimicrobial agents.[18–20] In the initial hyperdynamic state of severe infections, a high cardiac output and increased renal blood flow, as well as the use of inotropes during the management of septic shock, result in enhancement of renal clearance of antimicrobial agents, whereas in late-stage disease, decreased renal clearance due to end-organ dysfunction can be observed with severe infections.[18–20]

The two-compartment model was the best model for describing the concentration-time profile of imipenem, which was consistent

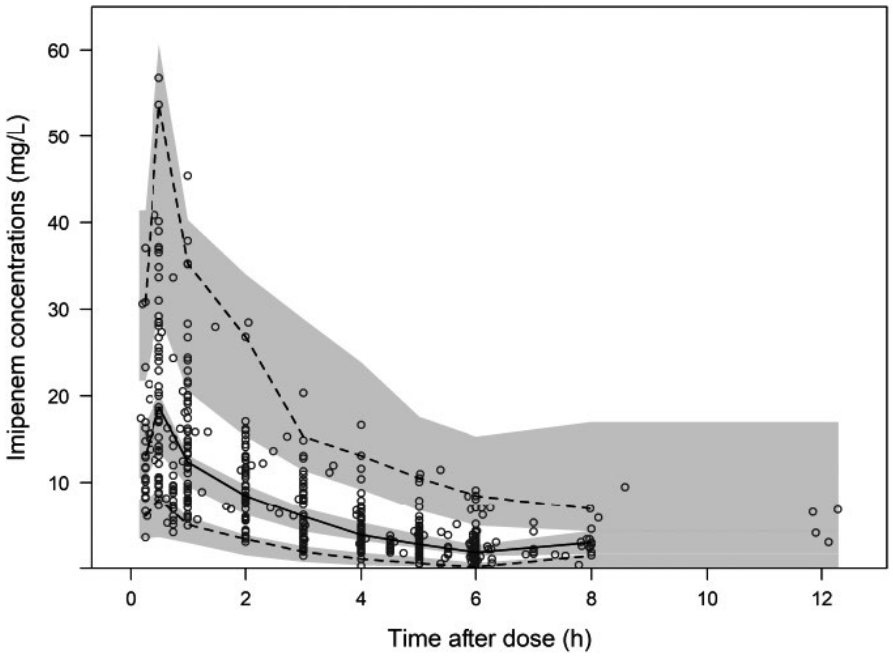


**FIGURE 3** Prediction-corrected visual predictive check (pcVPC) of the final population pharmacokinetic model. Open circles are observed concentrations. The solid line represents the 50th percentiles of the observations, and dashed lines represent the 5th and 95th percentiles of the observations. The shaded areas are the 95% confidence intervals around the 5th, 50th, and 95th percentiles of the predicted data

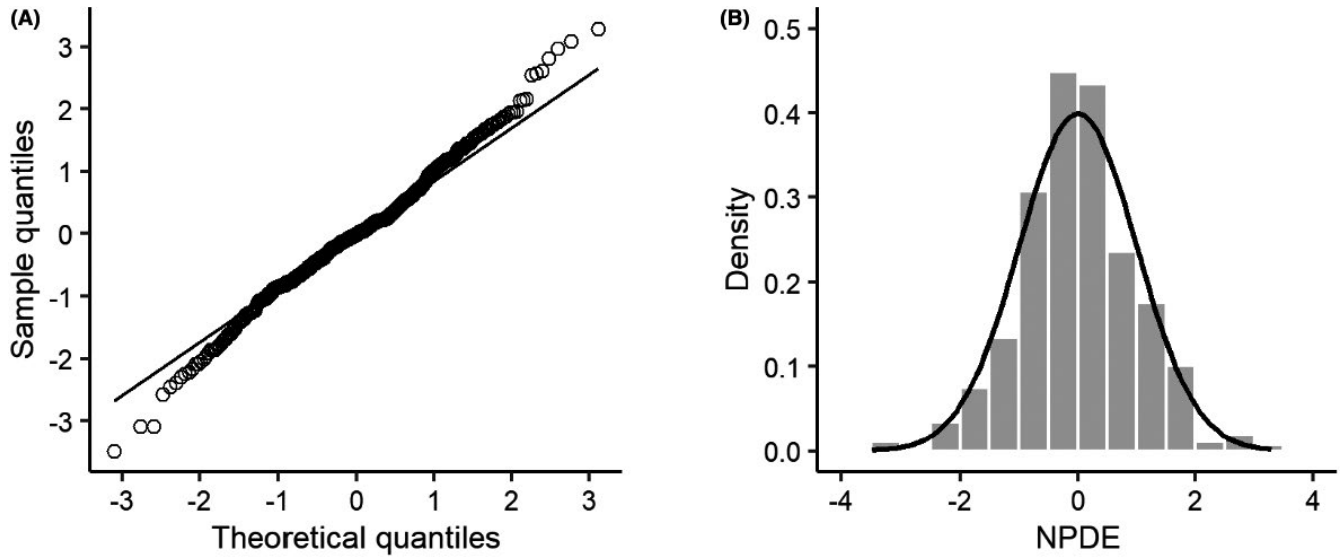


**FIGURE 4** Normalized prediction distribution error (NPDE) analysis ($n$ = 2000). (A) Quantile-quantile plot of the NPDE distribution versus the expected standard normal distribution. (B) Histogram of the NPDE distribution with the standard normal distribution overlaid (solid line)

with the results of previous population PK studies.[10,11] The ECMO circuit in our study had less impact on enhancing the alteration of PK parameters of imipenem, although it seemed that the patients with ECMO had greater baseline pathophysiologic derangements and severities of illness such as renal and liver impairment, lower serum albumin, higher fluid balance, higher use of catecholamine infusions, and higher APACHE II and SOFA scores compared to the patients without ECMO. These results may be explained by noting that, from the covariates analysis, patients with ECMO had less variability in PK changes than patients without ECMO and the study was conducted in adult patients treated with imipenem, in which this agent had a low degree of drug extraction by the ECMO. Further prospective large well-defined clinical trials with controlled data are required to investigate the impact of the ECMO on PK changes and optimal imipenem dosage regimens. The $V$ of imipenem in our study was consistent with the values obtained from a previous study that also evaluated imipenem population PK in critically ill patients with or without ECMO, although the CL was greater than the values obtained from a previous study,[21] which may be due to the higher GFR of our patients. The previous population PK study in critically ill patients with ECMO (19.43%) and without ECMO (80.57%) showed that the $CL_{CR\text{-}CG}$ and ECMO affected the CL of imipenem, resulting in decreased achievement of PTA in patients with ECMO compared to patients without ECMO, and increased achievement of PTA with the decline of $CL_{CR\text{-}CG}$; body weight had only a small influence on the CL of imipenem.[21] In the same study, more patients with ECMO (27%)

**TABLE 4** Probability of target attainment (PTA) for imipenem regimens achieving 40% $fT_{>MIC}$ and 75% $fT_{>MIC}$ at various glomerular filtration rates (GFR) in 50 critically ill patients with life-threatening severe infections

| | | Probability of attaining the following $\%fT_{>MIC}$ | | | | | |
|---|---|---|---|---|---|---|---|
| | | GFR 15–29.9 ml/min | | GFR 30–59.9 ml/min | | GFR 60–120 ml/min | |
| Dosage regimen | MIC (mg/L) | 40% | 75% | 40% | 75% | 40% | 75% |
| 0.5 g q12h, 1-h inf | 0.5 | 100 | 99.1 | 99.9 | 91.6 | 97.9 | 55.0 |
| | 1 | 99.9 | 94.5 | 98.5 | 73.3 | 85.2 | 27.5 |
| | 2 | 97.9 | 75.0 | 89.1 | 41.5 | 55.5 | 8.4 |
| | 4 | 79.9 | 36.1 | 56.7 | 12.7 | 19.9 | 1.1 |
| | 8 | 35.3 | 7.0 | 16.2 | 1.4 | 2.0 | 0.0 |
| 0.5 g q12h, 4-h inf | 0.5 | 100 | 100 | 100 | 97.6 | 99.9 | 75.6 |
| | 1 | 100 | 98.1 | 99.9 | 87.9 | 97.4 | 43.7 |
| | 2 | 99.3 | 86.5 | 96.5 | 59.3 | 77.7 | 14.7 |
| | 4 | 87.3 | 48.1 | 71.3 | 20.4 | 32.4 | 2.4 |
| | 8 | 40.5 | 10.2 | 21.4 | 2.3 | 4.34 | 0.1 |
| 0.5 g q8h, 1-h inf | 0.5 | 100 | 100 | 100 | 99.5 | 99.9 | 89.7 |
| | 1 | 100 | 99.7 | 99.9 | 96.4 | 98.0 | 68.2 |
| | 2 | 99.9 | 95.7 | 98.6 | 81.3 | 85.8 | 36.1 |
| | 4 | 95.4 | 74.6 | 84.6 | 45.7 | 49.7 | 10.2 |
| | 8 | 65.2 | 31.6 | 41.9 | 11.2 | 12.9 | 1.0 |
| 0.5 g q8h, 4-h inf | 0.5 | 100 | 100 | 100 | 100 | 100 | 99.0 |
| | 1 | 100 | 100 | 100 | 99.5 | 100 | 91.6 |
| | 2 | 100 | 99.0 | 99.8 | 93.8 | 97.1 | 66.5 |
| | 4 | 97.5 | 85.9 | 90.7 | 63.8 | 70.2 | 25.3 |
| | 8 | 70.3 | 41.6 | 48.3 | 18.8 | 19.6 | 3.3 |
| 0.5 g q6h, 1-h inf | 0.5 | 100 | 100 | 100 | 99.9 | 100 | 98.3 |
| | 1 | 100 | 99.9 | 100 | 99.4 | 99.7 | 90.5 |
| | 2 | 100 | 99.3 | 99.6 | 94.6 | 95.4 | 66.4 |
| | 4 | 98.8 | 91.5 | 94.2 | 71.5 | 71.5 | 29.2 |
| | 8 | 83.5 | 57.5 | 63.0 | 29.4 | 29.0 | 5.5 |
| 0.5 g q6h, 4-h inf | 0.5 | 100 | 100 | 100 | 100 | 100 | 100 |
| | 1 | 100 | 100 | 100 | 100 | 100 | 99.5 |
| | 2 | 100 | 99.9 | 100 | 99.0 | 99.3 | 92.7 |
| | 4 | 99.4 | 96.4 | 96.5 | 86.3 | 85.3 | 59.3 |
| | 8 | 86.2 | 67.4 | 67.7 | 45.0 | 37.6 | 15.8 |
| 1 g q8h, 1-h inf | 0.5 | 100 | 100 | 100 | 99.9 | 100 | 97.0 |
| | 1 | 100 | 100 | 100 | 99.5 | 99.8 | 89.0 |
| | 2 | 100 | 99.6 | 100 | 95.7 | 98.1 | 68.4 |
| | 4 | 99.8 | 96.0 | 98.2 | 80.0 | 86.0 | 37.6 |
| | 8 | 95.2 | 74.4 | 81.9 | 42.8 | 50.5 | 10.4 |
| 1 g q8h, 4-h inf | 0.5 | 100 | 100 | 100 | 100 | 100 | 99.9 |
| | 1 | 100 | 100 | 100 | 100 | 100 | 98.6 |
| | 2 | 100 | 99.0 | 100 | 99.5 | 99.9 | 91.3 |
| | 4 | 97.5 | 86.1 | 99.7 | 93.1 | 97.2 | 65.5 |
| | 8 | 70.4 | 41.8 | 90.6 | 62.8 | 70.4 | 26.1 |

(Continues)

**TABLE 4** (Continued)

| | | Probability of attaining the following $\%fT_{>MIC}$ | | | | | |
|---|---|---|---|---|---|---|---|
| | | GFR 15–29.9 ml/min | | GFR 30–59.9 ml/min | | GFR 60–120 ml/min | |
| **Dosage regimen** | **MIC (mg/L)** | **40%** | **75%** | **40%** | **75%** | **40%** | **75%** |
| 1 g q6h, 1-h inf | 0.5 | 100 | 100 | 100 | 100 | 100 | 99.5 |
| | 1 | 100 | 100 | 100 | 99.9 | 100 | 97.2 |
| | 2 | 100 | 100 | 100 | 99.3 | 99.4 | 89.1 |
| | 4 | 99.9 | 99.2 | 99.7 | 93.7 | 94.5 | 66.3 |
| | 8 | 98.8 | 91.5 | 93.4 | 70.0 | 73.1 | 29.9 |
| 1 g q6h, 4-h inf | 0.5 | 100 | 100 | 100 | 100 | 100 | 100 |
| | 1 | 100 | 100 | 100 | 100 | 100 | 99.9 |
| | 2 | 100 | 100 | 100 | 100 | 100 | 99.4 |
| | 4 | 100 | 100 | 99.9 | 99.1 | 99.1 | 91.0 |
| | 8 | 99.4 | 96.3 | 96.6 | 86.6 | 83.5 | 58.0 |

Abbreviation: inf, infusion.

received continuous renal replacement therapy than non-ECMO patients (21%) which was one of the reasons why the CL of imipenem was higher in patients with ECMO.[21]

The main PK/pharmacodynamics (PD) index of β-lactams that is best associated with therapeutic antimicrobial activity is $\%fT_{>MIC}$[22,23] and the target required for achieving the optimal antimicrobial activity of imipenem in life-threatening severe infections should be close to 100% $fT_{>MIC}$.[24–26] A study evaluating treatment of bacteremia with meropenem in patients with febrile neutropenia found that the optimal clinical response was achieved when % $fT_{>MIC}$ was 75% of the dosing interval.[27] The MCS findings of our study indicated that the PTAs for achieving 40% $fT_{>MIC}$ and 75% $fT_{>MIC}$ of the 4-h prolonged infusion regimen of imipenem were greater than those of the 1-h infusion regimens. Another study found that imipenem, the drug with the greatest instability among the β-lactams, remained 90% stable for 3 h and 30 min at 25°C but became degraded by up to 25% within 24 h at 25°C and up to 60%–70% within 24 h at 37°C.[28] Therefore, instability of imipenem is considered to be a limitation for administration of this agent by continuous infusion, especially in tropical countries. We suggest that a prolonged infusion is a more effective strategy for achieving optimal PD exposure for pathogens with higher MICs than dose escalation. In this study, we found that for achieving the PTA targets of 75% $fT_{>MIC}$ in patients with GFR of 60–120 ml/min, imipenem dosage regimens of 4-h infusions of 0.5 g q6h and 1 g q6h were required for coverage of pathogens with MICs of 2 and 4 mg/L, respectively. These results indicate that high dosage regimens are required for coverage of less susceptible pathogens in this patient population. Augmented renal clearance in critically ill patients has been found to be associated with subtherapeutic initial β-lactam concentrations.[25] Higher-than-standard dosage regimens of imipenem may be required for achieving the PTA targets against less susceptible pathogens with MIC of 4 mg/L. Moreover, in patients with a GFR of 15–29.9 ml/min, PTAs (90%) achieving 75% $fT_{>MIC}$ for a MIC of 2 mg/L were observed when imipenem was administered by 1-h or 4-h infusions of 0.5 g q8h and the dosage of 1-h or 4-h infusion of 0.5 g q6h for a MIC of 4 mg/L, thus the achievement of the PTA targets of imipenem at low GFRs of 15–29.9 ml/min was greater than those with higher GFRs of 30–59.9 and 60–120 ml/min at the same daily dosage. The standard dosage regimen appears to be well tolerated with few adverse events.[16,17] However, manufacturers' instructions for imipenem include a warning that central nervous system (CNS) side effects have been reported, especially in patients with CNS disorders and/or compromised renal functions. Therefore, imipenem should be used with caution in these patients.

This study had a few limitations that have to be considered. First, the results of our study should be extrapolated only cautiously in the general population because of the effect of the low body weight of our patients on *V* and CL. Second, the small number of patients supported with ECMO could be considered a potential limitation, and further large well-designed clinical trials are required to investigate the impact of ECMO on the PK patterns of imipenem in this patient population to confirm these findings.

In conclusion, the effect of a critical illness in patients with life-threatening severe infections can cause alterations of the PK patterns of imipenem, but the ECMO had little effect on enhancing the PK changes of imipenem that had already occurred in our patients during support with ECMO compared to patients without ECMO support. High dosages of imipenem may be required for achieving the PK/PD targets against less susceptible pathogens in critically ill patients with severe infections, however, the dosage regimens in patients with renal impairment may be less than those required in patients with normal renal function.

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## CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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## REFERENCES


1. Sherwin J, Heath T, Watt K. Pharmacokinetics and dosing of anti-infective drugs in patients on extracorporeal membrane oxygenation: a review of the current literature. *Clin Ther*. 2016;38(9):1976-1994.
2. Honoré PM, Jacobs R, Spapen HD. Antimicrobial dosing during extracorporeal membrane oxygenation. In: Vincent JL, ed. *Annual Update in Intensive Care and Emergency Medicine*. New York: Springer; 2014:43-53.
3. Ratnani I, Tuazon D, Zainab A, Uddin F. The role and impact of extracorporeal membrane oxygenation in critical care. *Methodist Debakey Cardiovasc J*. 2018;14(2):110-119.
4. Shekar K, Fraser JF, Smith MT, Roberts JA. Pharmacokinetic changes in patients receiving extracorporeal membrane oxygenation. *J Crit Care*. 2012;27(6): 741.e9-741.e18.
5. Mosier JM, Kelsey M, Raz Y, et al. Extracorporeal membrane oxygenation (ECMO) for critically ill adults in the emergency department: history, current applications, and future direction. *Crit Care*. 2015;19:431.
6. Donadello K, Antonucci E, Cristallini S, et al. β-Lactam pharmacokinetics during extracorporeal membrane oxygenation therapy: a case-control study. *Int J Antimicrob Agents*. 2015;45(3):278-282.
7. Shekar K, Fraser JF, Taccone FS, et al. The combined effects of extracorporeal membrane oxygenation and renal replacement therapy on meropenem pharmacokinetics: a matched cohort study. *Crit Care*. 2014;18(6):565.
8. Jaruratanasirikul S, Vattanavanit V, Wongpoowarak W, Nawakitrangsan M, Samaeng M. Pharmacokinetics and Monte Carlo dosing simulations of imipenem in critically ill patients with life-threatening severe infections during support with extracorporeal membrane oxygenation. *Eur J Drug Metab Pharmacokinet*. 2020;45(6):735-747.
9. Jaruratanasirikul S, Sudsai T. Comparison of the pharmacodynamics of imipenem in patients with ventilator-associated pneumonia following administration by 2 or 0.5 h infusion. *J Antimicrob Chemother*. 2009;63(3):560-563.
10. Jaruratanasirikul S, Wongpoowarak W, Jullangkoon M, Samaeng M. Population pharmacokinetics and dosing simulations of imipenem in serious bacteraemia in immunocompromised patients with febrile neutropenia. *J Pharmacol Sci*. 2015;127(2):164-169.
11. Jaruratanasirikul S, Wongpoowarak W, Nawakitrangsan M, Thengyai S, Samaeng M. Population pharmacokinetics and Monte Carlo dosing simulations of imipenem in patients with ventilator-associated pneumonia. *Lung Breath J*. 2017;1(1):1-4.
12. Garcia-Capdevila L, López-Calull C, Arroyo C, et al. Determination of imipenem in plasma by high-performance liquid chromatography for pharmacokinetic studies in patients. *J Chromatogr B*. 1997;692(1):127-132.
13. U.S. Food and Drug Administration. U.S. Department of Health and Human Services. Draft guidance for industry: bioanalytical method validation 2013. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidance/UCM368107.pdf
14. Cheng V, Abdul-Aziz MH, Roberts JA, Shekar K. Optimising drug dosing in patients receiving extracorporeal membrane oxygenation. *J Thorac Dis*. 2018;10(Suppl 5):S629-S641.
15. Park J, Shin DA, Lee S, et al. Investigation of key circuit constituents affecting drug sequestration during extracorporeal membrane oxygenation treatment. *ASAIO J*. 2017;63(3):293-298.
16. Rodlof AC, Goldstein EJC, Torres A. Two decades of imipenem therapy. *J Antimicrob Chemother*. 2006;58(5):916-929.
17. Balfour JA, Bryson HM, Brogden RN. Imipenem/Cilastatin: an update of its antibacterial activity, pharmacokinetics and therapeutic efficacy in the treatment of serious infections. *Drugs*. 1996;51(1):99-136.
18. van der Poll T, Wiersinga WJ. Sepsis and septic shock. In: Bennett JE, Dolin R, Blaser MJ, editors. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. Philadelphia: Churchill Livingstone Elsevier; 2020: 990-1008.e3.
19. Taccone FS, Hites M, Beumier M, Scolletta S, Jacobs F. Appropriate antibiotic dosage levels in the treatment of severe sepsis and septic shock. *Curr Infect Dis Rep*. 2011;13(5):406-415.
20. Varghese JM, Roberts JA, Lipman J. Antimicrobial pharmacokinetic and pharmacodynamic issues in the critically ill with severe sepsis and septic shock. *Crit Care Clin*. 2011;27(1):19-34.
21. Chen W, Zhang D, Lian W, et al. Imipenem population pharmacokinetics: therapeutic drug monitoring data collected in critically ill patients with or without extracorporeal membrane oxygenation. *Antimicrob Agents Chemother*. 2020;64(6):e00385-20.
22. Craig WA. Interrelationship between pharmacokinetics and pharmacodynamics in determining dosage regimens for broadspectrum cephalosporins. *Diagn Microbiol Infect Dis*. 1995;22(1-2):89-96.
23. Vogelman B, Gudmundsson S, Leggett J, Turnidge J, Ebert S, Craig WA. Correlation of antimicrobial pharmacokinetic parameters with therapeutic efficacy in an animal model. *J Infect Dis*. 1988;158(4):831-847.
24. Taccone FS, Laterre PF, Dugernier T, et al. Insufficient β-lactam concentrations in the early phase of severe sepsis and septic shock. *Crit Care*. 2010;14(4):R126.
25. Udy AA, Varghese JM, Altukroni M, et al. Subtherapeutic initial β-lactam concentrations in select critically ill patients: association between augmented renal clearance and low trough drug concentrations. *Chest*. 2012;142(1):30-39.
26. Drusano GL. Prevention of resistance: a goal for dose selection for antimicrobial agents. *Clin Infect Dis*. 2003;36(Suppl 1):S42-S50.
27. Ariano RE, Nyhlén A, Donnelly JP, Sitar DS, Harding GKM, Zelenitsky SA. Pharmacokinetics and pharmacodynamics of meropenem in febrile neutropenic patients with bacteremia. *Ann Pharmacother*. 2005;39(1):32-38.
28. Viaene E, Chanteux H, Servais H, Mingeot-Leclercq MP, Tulkens PM. Comparative stability studies of antipseudomonal betalactams for potential administration through portable elastomeric pumps (home therapy for cystic fibrosis patients) and motor-operated syringes (intensive care units). *Antimicrob Agents Chemother*. 2020;46(8):2327-2332.


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## APPENDIX 1

### THE RESIDUAL ERROR MODEL DEVELOPMENT

The current study performed population pharmacokinetic analyses using data pooled from five different studies. The concentration-time profiles of each study are displayed in Figure A1. The residual variability for the pooled datasets was initially modeled by considering additive, proportional, or combined additive plus proportional error models. All imipenem concentrations from the five studies were quantified in the same laboratory using the same measurement procedure but determined by a different analyser. Moreover, the pooled datasets were quite heterogeneous, and it was anticipated that the residual error might not be consistent across studies (as shown in Figure A1). Therefore, separate residual variance terms for each study were further investigated to account for study variability differences.

**The combined additive plus proportional error model best described the residual variability of the pooled dataset. After covariate analysis, revisions were made to the final model (Model 1). The residual variance terms were modified by adding separate error terms for each study (Model 2). This model resulted in a 65.5-unit decrease in the Akaike information criterion (AIC). This result suggested that separate residual variance terms greatly improved the model fit. Unfortunately, the relative standard error of additive component for each study was high and not able to be precisely estimated (Table A1). Therefore, a further model modification was made by fixing these additive components to zero or using a single additive component for all studies (Models 3–5). It was found that a combined single additive plus separate proportional error term for each study (Model 5) showed the most significant reduction in AIC (Table A1).**

## APPENDIX 2

### THE COVARIATE MODEL BUILDING PROCESS

#### Method

After the appropriate structural model was established, candidate covariates were investigated for their impact on all parameters using a stepwise covariate modeling approach. The correlation analysis between covariates was first performed before covariate screening to avoid the simultaneous incorporation of colinear variables into the model.

Various function forms were used to relate the effects of covariates to PK parameters, as described below:

*For categorical covariates*

$$\text{Proportioal shift model:}\quad \theta_i = \theta_{pop} \times (1 + \theta_{cov} \cdot (Cov - Cov_{median}))$$

*For continuous covariates*

$$\text{Linear function form:}\quad \theta_i = \theta_{pop} + \theta_{cov} \cdot (Cov - Cov_{median})$$

$$\text{Power function form:}\quad \theta_i = \theta_{pop} \times \left(\frac{Cov}{Cov_{median}}\right)^{\theta_{cov}}$$

$$\text{Exponential function form:}\quad \theta_i = \theta_{pop} \cdot e^{\theta_{cov} \times (cov - cov_{median})}$$

where $\theta_i$ is the individual PK parameter for subject $i$th, $\theta_{pop}$ is the typical value or population mean of the PK parameter, $\theta_{cov}$ is the covariate coefficient, Cov is the specific covariate value, $Cov_{median}$ is the median or mean value of the covariate.

The potential covariates were statistically tested for their impact on the PK parameter using a stepwise covariate modeling approach. The covariates were kept in the model if they were biologically plausible and their inclusion led to the significant improvement of model fit, as evaluated by a decrease of at least 3.84 units of OFV ($p < 0.05$ for 1 degree of freedom [$df$]) for forward inclusion and an increase of at least 6.64 units of OFV ($p < 0.01$ for 1 $df$) for backward elimination.

#### Results

The correlation matrix between covariates is displayed in Figure B1. Based on information in Table B1, the effect of $GFR_{EPI}$ on the total clearance (CL) using linear function form was added to the base model following forward addition step 1. After that, the effects of adjusted body weight (ABW) on $V_C$ and mechanical ventilator support (MCV) on CL were added to the model (Tables B2 and B3). After including $GFR_{EPI}$, ABW, and MCV into the model, no other covariates significantly affected the PK parameters (Table B4).

After completion of the forward selection step, the full multivariable model was evaluated. Since there were significant correlations between IIV on CL, $V_{C,}$ and $V_P$, a full variance-covariance matrix was incorporated, which resulted in a substantial improvement of the model fit.

$$OFV_{base} - OFV_{base,covariance} = -24.2\,\text{units}$$

$$OFV_{full\text{-}covariates} - OFV_{full\text{-}covariates,\,covariance} = -40.0\,\text{units}$$

Therefore, the full variance-covariance matrix was retained in the model.

**In the backward deletion process, removal of $GFR_{EPI}$ or ABW resulted in an increase of OFV greater than 6.64. Therefore, these covariates were retained in the final model. The details of the backward deletion step are displayed in Tables B5 and B6.**

Therefore, $GFR_{EPI}$ and adjusted body weight were retained in the final model.

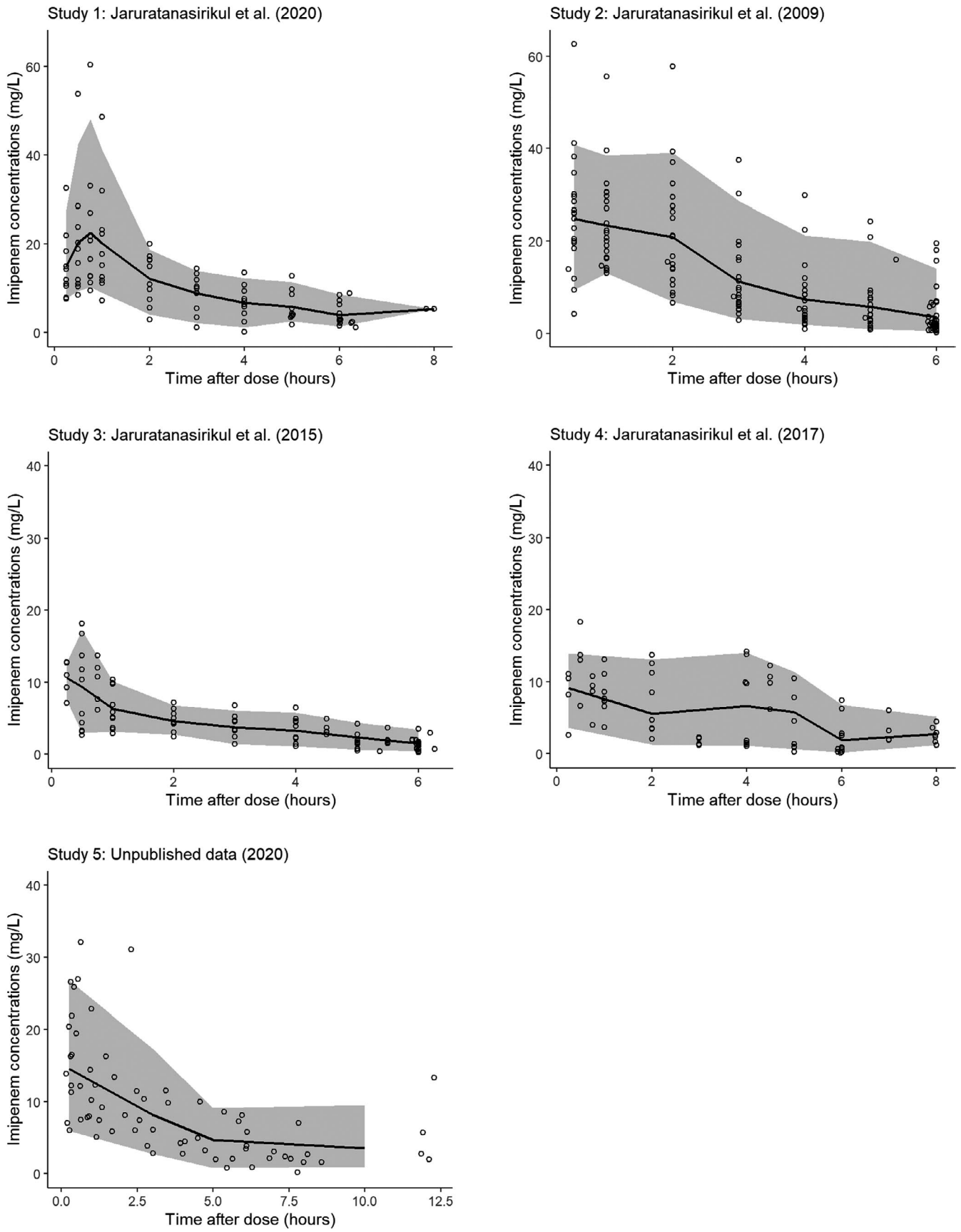


**FIGURE A1** The imipenem concentration-time profiles of the 5 pooled datasets. The solid lines are the average concentrations, and the shaded areas represent the 95% confidence intervals of the observed data

**TABLE A1** Population pharmacokinetic parameters of the final model using different residual error models

| | Estimate (%RSE) | | | | |
|---|---|---|---|---|---|
| **Parameter** | **Model 1** | **Model 2** | **Model 3** | **Model 4** | **Model 5** |
| OFV | 1098.5 | 1019.0 | 1047.6 | 1065.6 | 1022.3 |
| AIC | 1126.5 | 1061.0 | 1087.6 | 1101.6 | 1058.3 |
| ΔAIC | | −65.5 | −38.9 | −24.9 | −68.2 |
| Fixed-effect parameter | | | | | |
| CL (L/h) | 13.3 (7.7%) | 13.3 (7.7%) | 13.3 (7.5%) | 13.3 (7.8%) | 13.3 (7.3%) |
| $\theta_1$ | 0.11 (12.2%) | 0.11 (12.1%) | 0.11 (11.9%) | 0.11 (12.3%) | 0.11 (11.8%) |
| $V_C$ (L) | 15.2 (10.9%) | 13.8 (10.9%) | 14.0 (11.9%) | 14.9 (10.9%) | 13.6 (11.0%) |
| $\theta_2$ | −0.34 (26.6%) | −0.35 (27.0%) | −0.35 (27.5%) | −0.35 (26.3%) | −0.35 (26.8%) |
| $V_P$ (L) | 16.1 (12.5%) | 17.0 (10.3%) | 16.6 (11.6%) | 16.2 (13.0%) | 16.9 (10.6%) |
| Q (L/h) | 17.7 (27.3%) | 23.7 (15.6%) | 22.6 (19.8%) | 19.7 (22.4%) | 24.3 (17.4%) |
| Interindividual variability (%CV) | | | | | |
| $\omega_{CL}$ | 60.0 (17.5%) | 50.9 (18.0%) | 50.8 (17.7%) | 50.4 (18.2%) | 51.0 (17.7%) |
| $\omega_{Vc}$ | 62.8 (19.6%) | 66.5 (22.1%) | 65.3 (23.5%) | 62.8 (22.1%) | 66.9 (23.0%) |
| $\omega_{Vp}$ | 55.1 (25.2%) | 55.6 (23.2%) | 57.4 (22.2%) | 61.2 (23.4%) | 56.0 (22.9%) |
| Covariance CL and $V_C$ | 0.25 (22.1%) | 0.25 (23.6%) | 0.25 (23.8%) | 0.24 (23.4%) | 0.25 (23.8%) |
| Covariance CL and $V_P$ | 0.18 (29.7%) | 0.17 (27.7%) | 0.16 (32.0%) | 0.16 (34.2%) | 0.17 (29.2%) |
| Covariance $V_C$ and $V_P$ | 0.25 (31.0%) | 0.21 (34.4%) | 0.20 (34.7%) | 0.21 (32.6%) | 0.20 (34.9%) |
| Residual variability | | | | | |
| $\sigma_{prop}$ (%) | 19.7 (21.1%) | – | – | – | – |
| $\sigma_{add}$ (mg/L) | 0.2 (36.7%) | – | – | – | 0.22 (31.6%) |
| $\sigma_{prop,\ study1}$ (%) | – | 10.0 (34.1%) | 14.1 (44.8%) | 14.2 (44.7%) | 10.6 (26.6%) |
| $\sigma_{prop,\ study2}$ (%) | – | 16.9 (34.6%) | 16.9 (33.9%) | 16.6 (33.6%) | 17.4 (33.2%) |
| $\sigma_{prop,\ study3}$ (%) | – | 26.4 (19.5%) | 26.4 (19.7%) | 26.3 (19.8%) | 25.6 (21.8%) |
| $\sigma_{prop,\ study4}$ (%) | – | 10.6 (31.7%) | 10.6 (31.9%) | 14.9 (22.5%) | 10.2 (28.8%) |
| $\sigma_{prop,\ study5}$ (%) | – | 18.2 (41.4%) | 18.2 (40.5%) | 22.2 (35.8%) | 18.3 (42.5%) |
| $\sigma_{add,\ study1}$ (mg/L) | – | 0.33 (127%) | 0 (Fixed) | 0 (Fixed) | – |
| $\sigma_{add,\ study2}$ (mg/L) | – | 0.24 (51.1%) | 0.24 (48.8%) | 0.24 (53.7%) | – |
| $\sigma_{add,\ study3}$ (mg/L) | – | 0 (Fixed) | 0 (Fixed) | 0 (Fixed) | – |
| $\sigma_{add,\ study4}$ (mg/L) | – | 0.20 (56.6%) | 0.19 (58.1%) | 0 (Fixed) | – |
| $\sigma_{add,\ study5}$ (mg/L) | – | 0.27 (42.6%) | 0.26 (64.7%) | 0 (Fixed) | – |

Abbreviations: ΔAIC, value compared with Model 1; AIC, Akaike's information criterion; CL, total clearance; OFV, objective function value; Q, intercompartment clearance; RSE, percentage of relative standard error; $V_C$, central volume of distribution; $V_P$, peripheral volume of distribution; $\theta_1$, slope estimate reflecting the influence of $GFR_{EPI}$ on CL; $\theta_2$, slope estimate reflecting the influence of BW on $V_C$; $\sigma_{add}$, additional residual error; $\sigma_{prop}$, proportional residual error; $\omega_{CL}$, Interindividual variability on CL; $\omega_{Vc}$, interindividual variability on $V_C$; $\omega_{Vp}$, interindividual variability on $V_P$.

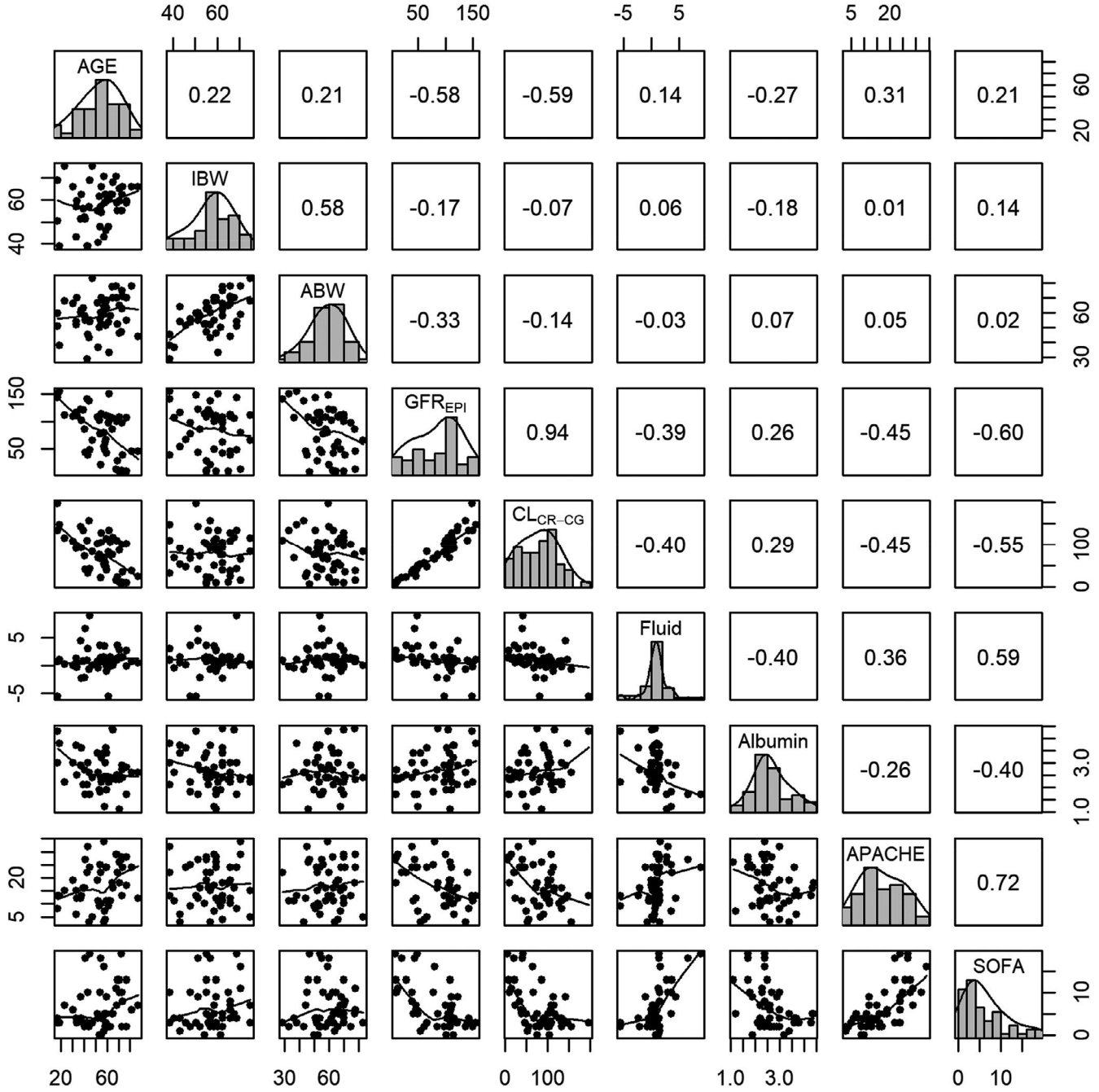


**FIGURE B1** The scatterplot correlation matrix and histogram of covariates. The correlation coefficients between paired covariates are displayed above the diagonal. IBW, ideal body weight; ABW, adjusted body weight; $GFR_{EPI}$, glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration equation; $CL_{CR\text{-}CG}$, creatinine clearance estimated by the Cockcroft-Gault equation; APACHE, acute physiology and chronic health evaluation; SOFA, sepsis-related organic failure assessment.

**TABLE B1** The covariate forward addition step 1 results

| No. | PK parameter | Covariate | Function form | OFV | ΔOFV | Sig[a] |
|---|---|---|---|---|---|---|
| | | Base Model | – | 1186.4 | | |
| 1 | CL | $CL_{CR\text{-}CG}$ (ml/min) | Linear | 1161.5 | −24.9 | Yes |
| 2 | CL | $CL_{CR\text{-}CG}$ (ml/min) | Power | 1161.1 | −25.3 | Yes |
| 3 | CL | $CL_{CR\text{-}CG}$ (ml/min) | Exponential | 1164.4 | −22.0 | Yes |
| 4 | CL | $GFR_{MDRD4}$ (ml/min/1.73 $m^2$) | Linear | 1161.3 | −25.1 | Yes |
| 5 | CL | $GFR_{MDRD4}$ (ml/min/1.73 $m^2$) | Power | 1160.0 | −26.4 | Yes |
| 6 | CL | $GFR_{MDRD4}$ (ml/min/1.73 $m^2$) | Exponential | 1165.3 | −21.1 | Yes |
| 7 | CL | $GFR_{MDRD6}$ (ml/min/1.73 $m^2$) | Linear | 1157.3 | −29.1 | Yes |
| 8 | CL | $GFR_{MDRD6}$ (ml/min/1.73 $m^2$) | Power | 1157.2 | −29.2 | Yes |
| 9 | CL | $GFR_{MDRD6}$ (ml/min/1.73 $m^2$) | Exponential | 1161.9 | −24.5 | Yes |
| 10 | CL | $GFR_{EPI}$ (ml/min/1.73 $m^2$) | Linear | 1157.2 | −29.2 | Yes |
| 11 | CL | $GFR_{EPI}$ (ml/min/1.73 $m^2$) | Power | 1159.2 | −27.2 | Yes |
| 12 | CL | $GFR_{EPI}$ (ml/min/1.73 $m^2$) | Exponential | 1157.6 | −28.8 | Yes |
| 13 | CL | Age (years) | Linear | 1175.4 | −11.0 | Yes |
| 14 | CL | Age (years) | Power | 1180.0 | −6.4 | Yes |
| 15 | CL | Age (years) | Exponential | 1176.9 | −9.5 | Yes |
| 16 | CL | Gender (male/female) | Proportional | 1179.6 | −6.8 | Yes |
| 17 | CL | Actual body weight (kg) | Linear | 1181.7 | −4.7 | Yes |
| 18 | CL | Actual body weight (kg) | Power | 1183.5 | −2.9 | No |
| 19 | CL | Actual body weight (kg) | Exponential | 1183.9 | −2.5 | No |
| 20 | CL | Ideal body weight (kg) | Linear | 1181.4 | −5.0 | Yes |
| 21 | CL | Ideal body weight (kg) | Power | 1182.1 | −4.3 | Yes |
| 22 | CL | Ideal body weight (kg) | Exponential | 1181.7 | −4.7 | Yes |
| 23 | CL | Adjusted body weight (kg) | Linear | 1181.7 | −4.7 | Yes |
| 24 | CL | Adjusted body weight (kg) | Power | 1182.1 | −4.3 | Yes |
| 25 | CL | Adjusted body weight (kg) | Exponential | 1181.9 | −4.5 | Yes |
| 26 | CL | Body mass index (kg/$m^2$) | Linear | 1185.9 | −0.5 | No |
| 27 | CL | Body mass index (kg/$m^2$) | Power | 1185.4 | −1.0 | No |
| 28 | CL | Body mass index (kg/$m^2$) | Exponential | 1185.8 | −0.6 | No |
| 29 | CL | The use of ECMO support (yes/no) | Proportional | 1185.7 | −0.7 | No |
| 30 | CL | ECMO type (VV/VA) | Proportional | 1186.2 | −0.2 | No |
| 31 | CL | ECMO flow rate (L/min) | Linear | 1186.2 | −0.2 | No |
| 32 | CL | Duration of ECMO (h) | Linear | 1184.8 | −1.6 | No |
| 33 | CL | APACHE II scores | Linear | 1183.8 | −2.6 | No |
| 34 | CL | APACHE II scores | Power | 1185.7 | −0.7 | No |
| 35 | CL | APACHE II scores | Exponential | 1184.3 | −2.1 | No |
| 36 | CL | SOFA scores | Linear | 1174.3 | −12.1 | Yes |
| 37 | CL | SOFA scores | Exponential | 1174.2 | −12.2 | Yes |
| 38 | CL | Acute kidney injury (yes/no) | Proportional | 1176.3 | −10.1 | Yes |
| 39 | CL | Mechanical ventilator (yes/no) | Proportional | 1171.0 | −15.4 | Yes |
| 40 | CL | Serum albumin (g/dl) | Linear | 1182.1 | −4.3 | Yes |
| 41 | CL | Serum albumin (g/dl) | Power | 1182.3 | −4.1 | Yes |
| 42 | CL | Serum albumin (g/dl) | Exponential | 1181.9 | −4.5 | Yes |
| 43 | CL | Fluid balance (L) | Linear | 1182.5 | −3.9 | Yes |
| 44 | CL | Fluid balance (L) | Exponential | 1181.0 | - 5.4 | Yes |

(Continues)

TABLE B1 (Continued)

| No. | PK parameter | Covariate | Function form | OFV | ΔOFV | Sig[a] |
|---|---|---|---|---|---|---|
| 45 | CL | Use of inotropes | Linear | 1181.4 | −5.0 | Yes |
| 46 | CL | Septic shock (yes/no) | Proportional | 1181.8 | −4.6 | Yes |
| 47 | CL | Mean arterial pressure (mmHg) | Linear | 1186.3 | −0.1 | No |
| 48 | CL | Mean arterial pressure (mmHg) | Power | 1186.4 | 0.0 | No |
| 49 | CL | Mean arterial pressure (mmHg) | Exponential | 1186.3 | −0.1 | No |
| 50 | $V_C$ | Age (years) | Linear | 1186.2 | −0.2 | No |
| 51 | $V_C$ | Age (years) | Power | 1186.3 | −0.1 | No |
| 52 | $V_C$ | Age (years) | Exponential | 1186.2 | −0.2 | No |
| 53 | $V_C$ | Gender (male/female) | Proportional | 1183.3 | −3.1 | No |
| 54 | $V_C$ | Actual body weight (kg) | Linear | 1180.3 | −6.1 | Yes |
| 55 | $V_C$ | Actual body weight (kg) | Power | 1180.5 | −5.9 | Yes |
| 56 | $V_C$ | Actual body weight (kg) | Exponential | 1180.3 | −6.1 | Yes |
| 57 | $V_C$ | Ideal body weight (kg) | Linear | 1183.1 | −3.3 | No |
| 58 | $V_C$ | Ideal body weight (kg) | Power | 1183.7 | −2.7 | No |
| 59 | $V_C$ | Ideal body weight (kg) | Exponential | 1183.3 | −3.1 | No |
| 60 | $V_C$ | Adjusted body weight (kg) | Linear | 1176.2 | −10.2 | Yes |
| 61 | $V_C$ | Adjusted body weight (kg) | Power | 1177.9 | −8.5 | Yes |
| 62 | $V_C$ | Adjusted body weight (kg) | Exponential | 1177.1 | −9.3 | Yes |
| 63 | $V_C$ | Body mass index (kg/m$^2$) | Linear | 1184.3 | −2.1 | No |
| 64 | $V_C$ | Body mass index (kg/m$^2$) | Power | 1182.9 | −3.5 | No |
| 65 | $V_C$ | Body mass index (kg/m$^2$) | Exponential | 1183.7 | −2.7 | No |
| 66 | $V_C$ | The use of ECMO support (yes/no) | Proportional | 1186.3 | −0.1 | No |
| 67 | $V_C$ | ECMO type (VV/VA) | Proportional | 1185.6 | −0.8 | No |
| 68 | $V_C$ | ECMO flow rate (L/min) | Linear | 1186.2 | −0.2 | No |
| 69 | $V_C$ | Duration of ECMO (h) | Linear | 1186.4 | 0.0 | No |
| 70 | $V_C$ | APACHE II scores | Linear | 1180.7 | −5.7 | Yes |
| 71 | $V_C$ | APACHE II scores | Power | 1180.7 | −5.7 | Yes |
| 72 | $V_C$ | APACHE II scores | Exponential | 1181.2 | −5.2 | Yes |
| 73 | $V_C$ | SOFA scores | Linear | 1184.8 | −1.6 | No |
| 74 | $V_C$ | SOFA scores | Exponential | 1184.7 | −1.7 | No |
| 75 | $V_C$ | Mechanical ventilator (yes/no) | Proportional | 1183.0 | −3.4 | No |
| 76 | $V_C$ | Serum albumin (g/dl) | Linear | 1186.1 | −0.3 | No |
| 77 | $V_C$ | Serum albumin (g/dl) | Power | 1186.2 | −0.2 | No |
| 78 | $V_C$ | Serum albumin (g/dl) | Exponential | 1186.1 | −0.3 | No |
| 79 | $V_C$ | Fluid balance (L) | Linear | 1186.4 | 0.0 | No |
| 80 | $V_C$ | Fluid balance (L) | Exponential | 1186.2 | −0.2 | No |
| 81 | $V_C$ | Use of inotropes (yes/no) | Linear | 1183.2 | −3.2 | No |
| 82 | $V_C$ | Septic shock (yes/no) | Proportional | 1183.4 | −3.0 | No |
| 83 | $V_C$ | Mean arterial pressure (mmHg) | Linear | 1185.0 | −1.4 | No |
| 84 | $V_C$ | Mean arterial pressure (mmHg) | Power | 1184.2 | −2.2 | No |
| 85 | $V_C$ | Mean arterial pressure (mmHg) | Exponential | 1184.7 | −1.7 | No |
| 86 | $V_P$ | Age (years) | Linear | 1185.8 | −0.6 | No |
| 87 | $V_P$ | Age (years) | Power | 1185.6 | −0.8 | No |
| 88 | $V_P$ | Age (years) | Exponential | 1185.8 | −0.6 | No |
| 89 | $V_P$ | Gender (male/female) | Proportional | 1185.0 | −1.4 | No |

(Continues)

TABLE B1 (Continued)

| No. | PK parameter | Covariate | Function form | OFV | ΔOFV | Sig[a] |
|---|---|---|---|---|---|---|
| 90 | $V_P$ | Actual body weight (kg) | Linear | 1185.7 | −0.7 | No |
| 91 | $V_P$ | Actual body weight (kg) | Power | 1185.7 | −0.7 | No |
| 92 | $V_P$ | Actual body weight (kg) | Exponential | 1185.7 | −0.7 | No |
| 93 | $V_P$ | Ideal body weight (kg) | Linear | 1186.3 | −0.1 | No |
| 94 | $V_P$ | Ideal body weight (kg) | Power | 1186.2 | −0.2 | No |
| 95 | $V_P$ | Ideal body weight (kg) | Exponential | 1186.3 | −0.1 | No |
| 96 | $V_P$ | Adjusted body weight (kg) | Linear | 1186.0 | −0.4 | No |
| 97 | $V_P$ | Adjusted body weight (kg) | Power | 1186.0 | −0.4 | No |
| 98 | $V_P$ | Adjusted body weight (kg) | Exponential | 1186.0 | −0.4 | No |
| 99 | $V_P$ | Body mass index (kg/m$^2$) | Linear | 1185.4 | −1.0 | No |
| 100 | $V_P$ | Body mass index (kg/m$^2$) | Power | 1185.4 | −1.0 | No |
| 101 | $V_P$ | Body mass index (kg/m$^2$) | Exponential | 1185.4 | −1.0 | No |
| 102 | $V_P$ | The use of ECMO support (yes/no) | Proportional | 1185.9 | −0.5 | No |
| 103 | $V_P$ | ECMO type (VV/VA) | Proportional | 1184.7 | −1.7 | No |
| 104 | $V_P$ | ECMO flow rate (L/min) | Linear | 1186.4 | 0.0 | No |
| 105 | $V_P$ | Duration of ECMO (h) | Linear | 1186.4 | 0.0 | No |
| 106 | $V_P$ | APACHE II scores | Linear | 1179.5 | −6.9 | Yes |
| 107 | $V_P$ | APACHE II scores | Power | 1180.2 | −6.2 | Yes |
| 108 | $V_P$ | APACHE II scores | Exponential | 1179.6 | −6.8 | Yes |
| 109 | $V_P$ | SOFA scores | Linear | 1183.0 | −3.4 | No |
| 110 | $V_P$ | SOFA scores | Exponential | 1183.0 | −3.4 | No |
| 111 | $V_P$ | Mechanical ventilator (yes/no) | Proportional | 1185.1 | −1.3 | No |
| 112 | $V_P$ | Serum albumin (g/dl) | Linear | 1184.8 | −1.6 | No |
| 113 | $V_P$ | Serum albumin (g/dl) | Power | 1185.1 | −1.3 | No |
| 114 | $V_P$ | Serum albumin (g/dl) | Exponential | 1184.7 | −1.7 | No |
| 115 | $V_P$ | Fluid balance (L) | Linear | 1186.2 | −0.2 | No |
| 116 | $V_P$ | Fluid balance (L) | Exponential | 1186.2 | −0.2 | No |
| 117 | $V_P$ | Use of inotropes (yes/no) | Linear | 1184.4 | −2.0 | No |
| 118 | $V_P$ | Septic shock (yes/no) | Proportional | 1183.7 | −2.7 | No |
| 119 | $V_P$ | Mean arterial pressure (mmHg) | Linear | 1184.7 | −1.7 | No |
| 120 | $V_P$ | Mean arterial pressure (mmHg) | Power | 1184.0 | −2.4 | No |
| 121 | $V_P$ | Mean arterial pressure (mmHg) | Exponential | 1184.4 | −2.0 | No |

Abbreviations: APACHE, acute physiology and chronic health evaluation; CL, total clearance; $CL_{CR\text{-}CG}$, creatinine clearance estimated by the Cockcroft-Gault equation; ECMO, extracorporeal membrane oxygenation; $GFR_{EPI}$, glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration equation; $GFR_{MDRD4}$, glomerular filtration rate using the Modification of Diet in Renal Disease study equation; $GFR_{MDRD6}$, six variables from the $GFR_{MDRD}$; OFV, objective function value; SOFA, sepsis-related organic failure assessment; $V_C$, central volume of distribution; $V_P$, peripheral volume of distribution.

[a]OFV decrease at least 3.84 ($p$ value < 0.05, $\chi^2$, $df$ = 1).

TABLE B2 The covariate forward addition step 2 results

| No. | PK parameter | Covariate | Function form | OFV | ΔOFV | Sig[a] |
|---|---|---|---|---|---|---|
| | | Base model with the inclusion of $GFR_{EPI}$ on CL | – | 1157.2 | | |
| 1 | CL | Age (years) | Linear | 1156.7 | −0.5 | No |
| 2 | CL | Age (years) | Power | 1157.2 | 0 | No |
| 3 | CL | Age (years) | Exponential | 1156.8 | −0.4 | No |
| 4 | CL | Gender (male/female) | Proportional | 1153.7 | −3.5 | No |
| 5 | CL | Actual body weight (kg) | Linear | 1156.5 | −0.7 | No |
| 6 | CL | Actual body weight (kg) | Power | 1156.6 | −0.6 | No |
| 7 | CL | Actual body weight (kg) | Exponential | 1156.5 | −0.7 | No |
| 8 | CL | Ideal body weight (kg) | Linear | 1152.7 | −4.5 | Yes |
| 9 | CL | Ideal body weight (kg) | Power | 1153.8 | −3.4 | No |
| 10 | CL | Ideal body weight (kg) | Exponential | 1153.2 | −4.0 | Yes |
| 11 | CL | Adjusted body weight (kg) | Linear | 1155.7 | −1.5 | No |
| 12 | CL | Adjusted body weight (kg) | Power | 1155.9 | −1.3 | No |
| 13 | CL | Adjusted body weight (kg) | Exponential | 1155.8 | −1.4 | No |
| 14 | CL | Body mass index ($kg/m^2$) | Linear | 1157.2 | 0 | No |
| 15 | CL | Body mass index ($kg/m^2$) | Power | 1157.2 | 0 | No |
| 16 | CL | Body mass index ($kg/m^2$) | Exponential | 1157.2 | 0 | No |
| 17 | CL | The use of ECMO support (yes/no) | Proportional | 1157.1 | −0.1 | No |
| 18 | CL | ECMO type (VV/VA) | Proportional | 1156.9 | −0.3 | No |
| 19 | CL | ECMO flow rate (L/min) | Linear | 1157.2 | 0 | No |
| 20 | CL | Duration of ECMO (h) | Linear | 1156.8 | −0.4 | No |
| 21 | CL | APACHE II scores | Linear | 1155.9 | −1.3 | No |
| 22 | CL | APACHE II scores | Power | 1155.7 | −1.5 | No |
| 23 | CL | APACHE II scores | Exponential | 1156.1 | −1.1 | No |
| 24 | CL | SOFA scores | Linear | 1156.7 | −0.5 | No |
| 25 | CL | SOFA scores | Exponential | 1156.7 | −0.5 | No |
| 26 | CL | Mechanical ventilator (yes/no) | Proportional | 1147.6 | −9.6 | Yes |
| 27 | CL | Serum albumin (g/dl) | Linear | 1155.6 | −1.6 | No |
| 28 | CL | Serum albumin (g/dl) | Power | 1155.5 | −1.7 | No |
| 29 | CL | Serum albumin (g/dl) | Exponential | 1155.6 | −1.6 | No |
| 30 | CL | Fluid balance (L) | Linear | 1156.7 | −0.5 | No |
| 31 | CL | Fluid balance (L) | Exponential | 1156.5 | −0.7 | No |
| 32 | CL | Use of inotropes (yes/no) | Proportional | 1154.0 | −3.2 | No |
| 33 | CL | Septic shock (yes/no) | Proportional | 1157.2 | 0 | No |
| 34 | CL | Mean arterial pressure (mmHg) | Linear | 1157.0 | −0.2 | No |
| 35 | CL | Mean arterial pressure (mmHg) | Power | 1156.8 | −0.4 | No |
| 36 | CL | Mean arterial pressure (mmHg) | Exponential | 1157.0 | −0.2 | No |
| 37 | $V_C$ | Age (years) | Linear | 1156.9 | −0.3 | No |
| 38 | $V_C$ | Age (years) | Power | 1157.1 | −0.1 | No |
| 39 | $V_C$ | Age (years) | Exponential | 1157.0 | −0.2 | No |
| 40 | $V_C$ | Gender (male/female) | Proportional | 1154.0 | −3.2 | No |
| 41 | $V_C$ | Actual body weight (kg) | Linear | 1150.9 | −6.3 | Yes |
| 42 | $V_C$ | Actual body weight (kg) | Power | 1151.0 | −6.2 | Yes |
| 43 | $V_C$ | Actual body weight (kg) | Exponential | 1150.9 | −6.3 | Yes |
| 44 | $V_C$ | Ideal body weight (kg) | Linear | 1153.8 | −3.4 | No |

(Continues)

TABLE B2 (Continued)

| No. | PK parameter | Covariate | Function form | OFV | ΔOFV | Sig[a] |
|---|---|---|---|---|---|---|
| 45 | $V_C$ | Ideal body weight (kg) | Power | 1154.4 | −2.8 | No |
| 46 | $V_C$ | Ideal body weight (kg) | Exponential | 1154.1 | −3.1 | No |
| 47 | $V_C$ | Adjusted body weight (kg) | Linear | 1146.7 | −10.5 | Yes |
| 48 | $V_C$ | Adjusted body weight (kg) | Power | 1148.4 | −8.8 | Yes |
| 49 | $V_C$ | Adjusted body weight (kg) | Exponential | 1147.6 | −9.6 | Yes |
| 50 | $V_C$ | Body mass index (kg/m$^2$) | Linear | 1154.9 | −2.3 | No |
| 51 | $V_C$ | Body mass index (kg/m$^2$) | Power | 1157.2 | 0 | No |
| 52 | $V_C$ | Body mass index (kg/m$^2$) | Exponential | 1154.3 | −2.9 | No |
| 53 | $V_C$ | The use of ECMO support (yes/no) | Proportional | 1157.1 | −0.1 | No |
| 54 | $V_C$ | ECMO type (VV/VA) | Proportional | 1156.3 | −0.9 | No |
| 55 | $V_C$ | ECMO flow rate (L/min) | Linear | 1157.0 | −0.2 | No |
| 56 | $V_C$ | Duration of ECMO (h) | Linear | 1157.1 | −0.1 | No |
| 57 | $V_C$ | APACHE II scores | Linear | 1151.6 | −5.6 | Yes |
| 58 | $V_C$ | APACHE II scores | Power | 1151.6 | −5.6 | Yes |
| 59 | $V_C$ | APACHE II scores | Exponential | 1152.0 | −5.2 | Yes |
| 60 | $V_C$ | SOFA scores | Linear | 1155.6 | −1.6 | No |
| 61 | $V_C$ | SOFA scores | Exponential | 1155.5 | −1.7 | No |
| 62 | $V_C$ | Mechanical ventilator (yes/no) | Proportional | 1153.7 | −3.5 | No |
| 63 | $V_C$ | Serum albumin (g/dl) | Linear | 1156.9 | −0.3 | No |
| 64 | $V_C$ | Serum albumin (g/dl) | Power | 1157.2 | 0.0 | No |
| 65 | $V_C$ | Serum albumin (g/dl) | Exponential | 1156.9 | −0.3 | No |
| 66 | $V_C$ | Fluid balance (L) | Linear | 1157.1 | −0.1 | No |
| 67 | $V_C$ | Fluid balance (L) | Exponential | 1157.1 | −0.1 | No |
| 68 | $V_C$ | Use of inotropes (yes/no) | Proportional | 1154.0 | −3.2 | No |
| 69 | $V_C$ | Septic shock (yes/no) | Proportional | 1154.2 | −3.0 | No |
| 70 | $V_C$ | Mean arterial pressure (mmHg) | Linear | 1155.8 | −1.4 | No |
| 71 | $V_C$ | Mean arterial pressure (mmHg) | Power | 1154.9 | −2.3 | No |
| 72 | $V_C$ | Mean arterial pressure (mmHg) | Exponential | 1155.4 | −1.8 | No |
| 73 | $V_P$ | Age (years) | Linear | 1156.6 | −0.6 | No |
| 74 | $V_P$ | Age (years) | Power | 1156.4 | −0.8 | No |
| 75 | $V_P$ | Age (years) | Exponential | 1156.6 | −0.6 | No |
| 76 | $V_P$ | Gender (male/female) | Proportional | 1155.8 | −1.4 | No |
| 77 | $V_P$ | Actual body weight (kg) | Linear | 1156.4 | −0.8 | No |
| 78 | $V_P$ | Actual body weight (kg) | Power | 1156.7 | −0.5 | No |
| 79 | $V_P$ | Actual body weight (kg) | Exponential | 1156.4 | −0.8 | No |
| 80 | $V_P$ | Ideal body weight (kg) | Linear | 1157.0 | −0.2 | No |
| 81 | $V_P$ | Ideal body weight (kg) | Power | 1157.0 | −0.2 | No |
| 82 | $V_P$ | Ideal body weight (kg) | Exponential | 1157.0 | −0.2 | No |
| 83 | $V_P$ | Adjusted body weight (kg) | Linear | 1156.7 | −0.5 | No |
| 84 | $V_P$ | Adjusted body weight (kg) | Power | 1156.6 | −0.6 | No |
| 85 | $V_P$ | Adjusted body weight (kg) | Exponential | 1156.7 | −0.5 | No |
| 86 | $V_P$ | Body mass index (kg/m$^2$) | Linear | 1156.1 | −1.1 | No |
| 87 | $V_P$ | Body mass index (kg/m$^2$) | Power | 1156.1 | −1.1 | No |
| 88 | $V_P$ | Body mass index (kg/m$^2$) | Exponential | 1156.1 | −1.1 | No |
| 89 | $V_P$ | The use of ECMO support (yes/no) | Proportional | 1156.6 | −0.6 | No |

(Continues)

TABLE B2 (Continued)

| No. | PK parameter | Covariate | Function form | OFV | ΔOFV | Sig[a] |
|---|---|---|---|---|---|---|
| 90 | $V_P$ | ECMO type (VV/VA) | Proportional | 1155.5 | −1.7 | No |
| 91 | $V_P$ | ECMO flow rate (L/min) | Linear | 1157.1 | −0.1 | No |
| 92 | $V_P$ | Duration of ECMO (h) | Linear | 1157.1 | −0.1 | No |
| 93 | $V_P$ | APACHE II scores | Linear | 1150.5 | −6.7 | Yes |
| 94 | $V_P$ | APACHE II scores | Power | 1151.2 | −6.0 | Yes |
| 95 | $V_P$ | APACHE II scores | Exponential | 1150.6 | −6.6 | Yes |
| 96 | $V_P$ | SOFA scores | Linear | 1153.9 | −3.3 | No |
| 97 | $V_P$ | SOFA scores | Exponential | 1153.9 | −3.3 | No |
| 98 | $V_P$ | Mechanical ventilator (yes/no) | Proportional | 1155.8 | −1.4 | No |
| 99 | $V_P$ | Serum albumin (g/dl) | Linear | 1155.6 | −1.6 | No |
| 100 | $V_P$ | Serum albumin (g/dl) | Power | 1155.3 | −1.9 | No |
| 101 | $V_P$ | Serum albumin (g/dl) | Exponential | 1155.4 | −1.8 | No |
| 102 | $V_P$ | Fluid balance (L) | Linear | 1157.0 | −0.2 | No |
| 103 | $V_P$ | Fluid balance (L) | Exponential | 1156.9 | −0.3 | No |
| 104 | $V_P$ | Use of inotropes (yes/no) | Proportional | 1155.3 | −1.9 | No |
| 105 | $V_P$ | Septic shock (yes/no) | Proportional | 1154.7 | −2.5 | No |
| 106 | $V_P$ | Mean arterial pressure (mmHg) | Linear | 1155.5 | −1.7 | No |
| 107 | $V_P$ | Mean arterial pressure (mmHg) | Power | 1154.8 | −2.4 | No |
| 108 | $V_P$ | Mean arterial pressure (mmHg) | Exponential | 1155.2 | −2.0 | No |

Abbreviations: APACHE, acute physiology and chronic health evaluation; CL, total clearance; ECMO, extracorporeal membrane oxygenation; $GFR_{EPI}$, glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration equation; OFV, objective function value; Sig, significant; SOFA, sepsis-related organic failure assessment;$V_C$, central volume of distribution; $V_P$, peripheral volume of distribution.

[a]OFV decrease at least 3.84 ($p$ value < 0.05, $\chi^2$, $df$ = 1).

**TABLE B3** The covariate forward addition step 3 results

| No. | PK parameter | Covariate | Function form | OFV | ΔOFV | Sig[a] |
|---|---|---|---|---|---|---|
| | | Base model with inclusion of<br>- $GFR_{EPI}$ on CL<br>- Adjusted body weight on $V_C$ | - | 1146.7 | | |
| 1 | CL | Age (years) | Linear | 1146.7 | 0 | No |
| 2 | CL | Age (years) | Power | 1146.7 | 0 | No |
| 3 | CL | Age (years) | Exponential | 1146.3 | −0.4 | No |
| 4 | CL | Gender (male/female) | Proportional | 1143.2 | −3.5 | No |
| 5 | CL | Actual body weight (kg) | Linear | 1145.9 | −0.8 | No |
| 6 | CL | Actual body weight (kg) | Power | 1146.1 | −0.6 | No |
| 7 | CL | Actual body weight (kg) | Exponential | 1146.0 | −0.7 | No |
| 8 | CL | Ideal body weight (kg) | Linear | 1142.1 | −4.6 | Yes |
| 9 | CL | Ideal body weight (kg) | Power | 1143.2 | −3.5 | No |
| 10 | CL | Ideal body weight (kg) | Exponential | 1142.5 | −4.2 | Yes |
| 11 | CL | Adjusted body weight (kg) | Linear | 1145.1 | −1.6 | No |
| 12 | CL | Adjusted body weight (kg) | Power | 1145.3 | −1.4 | No |
| 13 | CL | Adjusted body weight (kg) | Exponential | 1145.2 | −1.5 | No |
| 14 | CL | Body mass index ($kg/m^2$) | Linear | 1146.7 | 0 | No |
| 15 | CL | Body mass index ($kg/m^2$) | Power | 1146.7 | 0 | No |
| 16 | CL | Body mass index ($kg/m^2$) | Exponential | 1146.7 | 0 | No |
| 17 | CL | The use of ECMO support (yes/no) | Proportional | 1146.6 | −0.1 | No |
| 18 | CL | ECMO type (VV/VA) | Proportional | 1146.4 | −0.3 | No |
| 19 | CL | ECMO flow rate (L/min) | Linear | 1146.7 | 0 | No |
| 20 | CL | Duration of ECMO (h) | Linear | 1146.4 | −0.3 | No |
| 21 | CL | Mechanical ventilator (yes/no) | Proportional | 1137.2 | −9.5 | Yes |
| 22 | CL | Serum albumin (g/dl) | Linear | 1145.2 | −1.5 | No |
| 23 | CL | Serum albumin (g/dl) | Power | 1145.1 | −1.6 | No |
| 24 | CL | Serum albumin (g/dl) | Exponential | 1145.2 | −1.5 | No |
| 25 | CL | Fluid balance (L) | Linear | 1146.2 | −0.5 | No |
| 26 | CL | Fluid balance (L) | Exponential | 1146.1 | −0.6 | No |
| 27 | CL | Use of inotropes (yes/no) | Proportional | 1146.5 | −0.2 | No |
| 28 | CL | Septic shock (yes/no) | Proportional | 1146.7 | 0 | No |
| 29 | CL | Mean arterial pressure (mmHg) | Linear | 1146.5 | −0.2 | No |
| 30 | CL | Mean arterial pressure (mmHg) | Power | 1146.3 | −0.4 | No |
| 31 | CL | Mean arterial pressure (mmHg) | Exponential | 1146.5 | −0.2 | No |
| 32 | $V_C$ | Age (years) | Linear | 1146.6 | −0.1 | No |
| 33 | $V_C$ | Age (years) | Power | 1146.5 | −0.2 | No |
| 34 | $V_C$ | Age (years) | Exponential | 1146.6 | −0.1 | No |
| 35 | $V_C$ | Gender (male/female) | Proportional | 1146.4 | −0.3 | No |
| 36 | $V_C$ | The use of ECMO support (yes/no) | Proportional | 1146.5 | −0.2 | No |
| 37 | $V_C$ | ECMO type (VV/VA) | Proportional | 1146.4 | −0.3 | No |
| 38 | $V_C$ | ECMO flow rate (L/min) | Linear | 1146.3 | −0.4 | No |
| 39 | $V_C$ | Duration of ECMO (hours) | Linear | 1146.7 | 0.0 | No |
| 40 | $V_C$ | Mechanical ventilator (yes/no) | Proportional | 1144.1 | −2.6 | No |
| 41 | $V_C$ | Serum albumin (g/dl) | Linear | 1146.5 | −0.2 | No |
| 42 | $V_C$ | Serum albumin (g/dl) | Power | 1146.7 | 0.0 | No |
| 43 | $V_C$ | Serum albumin (g/dl) | Exponential | 1146.5 | −0.2 | No |

(Continues)

TABLE B3 (Continued)

| No. | PK parameter | Covariate | Function form | OFV | ΔOFV | Sig[a] |
|---|---|---|---|---|---|---|
| 44 | $V_C$ | Fluid balance (L) | Linear | 1146.7 | 0.0 | No |
| 45 | $V_C$ | Fluid balance (L) | Exponential | 1146.7 | 0.0 | No |
| 46 | $V_C$ | Use of inotropes (yes/no) | Proportional | 1145.6 | −1.1 | No |
| 47 | $V_C$ | Septic shock (yes/no) | Proportional | 1145.6 | −1.1 | No |
| 48 | $V_C$ | Mean arterial pressure (mmHg) | Linear | 1146.7 | 0.0 | No |
| 49 | $V_C$ | Mean arterial pressure (mmHg) | Power | 1146.7 | 0.0 | No |
| 50 | $V_C$ | Mean arterial pressure (mmHg) | Exponential | 1146.7 | 0.0 | No |
| 51 | $V_P$ | Age (years) | Linear | 1146.1 | −0.6 | No |
| 52 | $V_P$ | Age (years) | Power | 1145.9 | −0.8 | No |
| 53 | $V_P$ | Age (years) | Exponential | 1146.1 | −0.6 | No |
| 54 | $V_P$ | Gender (male/female) | Proportional | 1145.1 | −1.6 | No |
| 55 | $V_P$ | Actual body weight (kg) | Linear | 1146.1 | −0.6 | No |
| 56 | $V_P$ | Actual body weight (kg) | Power | 1146.1 | −0.6 | No |
| 57 | $V_P$ | Actual body weight (kg) | Exponential | 1146.1 | −0.6 | No |
| 58 | $V_P$ | Ideal body weight (kg) | Linear | 1146.5 | −0.2 | No |
| 59 | $V_P$ | Ideal body weight (kg) | Power | 1146.4 | −0.3 | No |
| 60 | $V_P$ | Ideal body weight (kg) | Exponential | 1146.5 | −0.2 | No |
| 61 | $V_P$ | Adjusted body weight (kg) | Linear | 1146.4 | −0.3 | No |
| 62 | $V_P$ | Adjusted body weight (kg) | Power | 1146.4 | −0.3 | No |
| 63 | $V_P$ | Adjusted body weight (kg) | Exponential | 1146.4 | −0.3 | No |
| 64 | $V_P$ | Body mass index (kg/m$^2$) | Linear | 1145.8 | −0.9 | No |
| 65 | $V_P$ | Body mass index (kg/m$^2$) | Power | 1145.8 | −0.9 | No |
| 66 | $V_P$ | Body mass index (kg/m$^2$) | Exponential | 1145.8 | −0.9 | No |
| 67 | $V_P$ | The use of ECMO support (yes/no) | Proportional | 1146.2 | −0.5 | No |
| 68 | $V_P$ | ECMO type (VV/VA) | Proportional | 1145.0 | −1.7 | No |
| 69 | $V_P$ | ECMO flow rate (L/min) | Linear | 1146.7 | 0.0 | No |
| 70 | $V_P$ | Duration of ECMO (h) | Linear | 1146.7 | 0.0 | No |
| 71 | $V_P$ | Mechanical ventilator (yes/no) | Proportional | 1145.3 | −1.4 | No |
| 72 | $V_P$ | Serum albumin (g/dl) | Linear | 1145.2 | −1.5 | No |
| 73 | $V_P$ | Serum albumin (g/dl) | Power | 1144.8 | −1.9 | No |
| 74 | $V_P$ | Serum albumin (g/dl) | Exponential | 1145.0 | −1.7 | No |
| 75 | $V_P$ | Fluid balance (L) | Linear | 1146.5 | −0.2 | No |
| 76 | $V_P$ | Fluid balance (L) | Exponential | 1146.5 | −0.2 | No |
| 77 | $V_P$ | Use of inotropes (yes/no) | Proportional | 1144.8 | −1.9 | No |
| 78 | $V_P$ | Septic shock (yes/no) | Proportional | 1144.3 | −2.4 | No |
| 79 | $V_P$ | Mean arterial pressure (mmHg) | Linear | 1145.2 | −1.5 | No |
| 80 | $V_P$ | Mean arterial pressure (mmHg) | Power | 1144.6 | −2.1 | No |
| 81 | $V_P$ | Mean arterial pressure (mmHg) | Exponential | 1144.9 | −1.8 | No |

Abbreviations: APACHE, acute physiology and chronic health evaluation; CL, total clearance; ECMO, extracorporeal membrane oxygenation; $GFR_{EPI}$, glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration equation; OFV, objective function value; Sig, significant; SOFA, sepsis-related organic failure assessment; $V_C$, central volume of distribution; $V_P$, peripheral volume of distribution.

[a]OFV decrease at least 3.84 ($p$ value < 0.05, $\chi^2$, $df$ = 1).

**TABLE B4** The covariate forward addition step 4 results

| No. | PK | Covariate | Function form | OFV | ΔOFV | Sig[a] |
|---|---|---|---|---|---|---|
| | | Base model with inclusion of<br>- $GFR_{EPI}$ on CL<br>- Adjusted body weight on $V_C$<br>- Mechanical ventilator support on CL | - | 1137.2 | | |
| 1 | CL | Age (years) | Linear | 1137.1 | −0.1 | No |
| 2 | CL | Age (years) | Power | 1136.4 | −0.8 | No |
| 3 | CL | Age (years) | Exponential | 1135.6 | −1.6 | No |
| 4 | CL | Gender (male/female) | Proportional | 1134.8 | −2.4 | No |
| 5 | CL | Actual body weight (kg) | Linear | 1135.6 | −1.6 | No |
| 6 | CL | Actual body weight (kg) | Power | 1136.0 | −1.2 | No |
| 7 | CL | Actual body weight (kg) | Exponential | 1135.7 | −1.5 | No |
| 8 | CL | Ideal body weight (kg) | Linear | 1134.8 | −2.4 | No |
| 9 | CL | Ideal body weight (kg) | Power | 1135.7 | −1.5 | No |
| 10 | CL | Ideal body weight (kg) | Exponential | 1135.2 | −2.0 | No |
| 11 | CL | Adjusted body weight (kg) | Linear | 1135.6 | −1.6 | No |
| 12 | CL | Adjusted body weight (kg) | Power | 1135.7 | −1.5 | No |
| 13 | CL | Adjusted body weight (kg) | Exponential | 1135.6 | −1.6 | No |
| 14 | CL | Body mass index ($kg/m^2$) | Linear | 1136.8 | −0.4 | No |
| 15 | CL | Body mass index ($kg/m^2$) | Power | 1136.8 | −0.4 | No |
| 16 | CL | Body mass index ($kg/m^2$) | Exponential | 1136.8 | −0.4 | No |
| 17 | CL | The use of ECMO support (yes/no) | Proportional | 1136.8 | −0.4 | No |
| 18 | CL | ECMO type (VV/VA) | Proportional | 1137.1 | −0.1 | No |
| 19 | CL | ECMO flow rate (L/min) | Linear | 1136.6 | −0.6 | No |
| 20 | CL | Duration of ECMO (h) | Linear | 1137.2 | 0.0 | No |
| 21 | CL | Serum albumin (g/dl) | Linear | 1137.1 | −0.1 | No |
| 22 | CL | Serum albumin (g/dl) | Power | 1137.1 | −0.1 | No |
| 23 | CL | Serum albumin (g/dl) | Exponential | 1137.1 | −0.1 | No |
| 24 | CL | Fluid balance (L) | Linear | 1137.1 | −0.1 | No |
| 25 | CL | Fluid balance (L) | Exponential | 1137.1 | −0.1 | No |
| 26 | CL | Use of inotropes (yes/no) | Proportional | 1137.1 | −0.1 | No |
| 27 | CL | Septic shock (yes/no) | Proportional | 1136.6 | −0.6 | No |
| 28 | CL | Mean arterial pressure (mmHg) | Linear | 1136.2 | −1.0 | No |
| 29 | CL | Mean arterial pressure (mmHg) | Power | 1135.6 | −1.6 | No |
| 30 | CL | Mean arterial pressure (mmHg) | Exponential | 1136.1 | −1.1 | No |
| 31 | $V_C$ | Age (years) | Linear | 1137.1 | −0.1 | No |
| 32 | $V_C$ | Age (years) | Power | 1137.0 | −0.2 | No |
| 33 | $V_C$ | Age (years) | Exponential | 1137.1 | −0.1 | No |
| 34 | $V_C$ | Gender (male/female) | Proportional | 1136.9 | −0.3 | No |
| 35 | $V_C$ | The use of ECMO support (yes/no) | Proportional | 1137.0 | −0.2 | No |
| 36 | $V_C$ | ECMO type (VV/VA) | Proportional | 1136.9 | −0.3 | No |
| 37 | $V_C$ | ECMO flow rate (L/min) | Linear | 1136.8 | −0.4 | No |
| 38 | $V_C$ | Duration of ECMO (h) | Linear | 1137.2 | 0.0 | No |
| 39 | $V_C$ | Serum albumin (g/dl) | Linear | 1137.0 | −0.2 | No |
| 40 | $V_C$ | Serum albumin (g/dl) | Power | 1137.0 | −0.2 | No |
| 41 | $V_C$ | Serum albumin (g/dl) | Exponential | 1137.0 | −0.2 | No |
| 42 | $V_C$ | Fluid balance (L) | Linear | 1137.2 | 0.0 | No |

(Continues)

TABLE B4 (Continued)

| No. | PK | Covariate | Function form | OFV | ΔOFV | Sig[a] |
|---|---|---|---|---|---|---|
| 43 | $V_C$ | Fluid balance (L) | Exponential | 1137.2 | 0.0 | No |
| 44 | $V_C$ | Use of inotropes (yes/no) | Proportional | 1135.3 | −1.9 | No |
| 45 | $V_C$ | Septic shock (yes/no) | Proportional | 1136.1 | −1.1 | No |
| 46 | $V_C$ | Mean arterial pressure (mmHg) | Linear | 1137.2 | 0.0 | No |
| 47 | $V_C$ | Mean arterial pressure (mmHg) | Power | 1137.1 | −0.1 | No |
| 48 | $V_C$ | Mean arterial pressure (mmHg) | Exponential | 1137.2 | 0.0 | No |
| 49 | $V_P$ | Age (years) | Linear | 1136.6 | −0.6 | No |
| 50 | $V_P$ | Age (years) | Power | 1136.4 | −0.8 | No |
| 51 | $V_P$ | Age (years) | Exponential | 1136.6 | −0.6 | No |
| 52 | $V_P$ | Gender (male/female) | Proportional | 1135.6 | −1.6 | No |
| 53 | $V_P$ | Actual body weight (kg) | Linear | 1136.6 | −0.6 | No |
| 54 | $V_P$ | Actual body weight (kg) | Power | 1137.2 | 0.0 | No |
| 55 | $V_P$ | Actual body weight (kg) | Exponential | 1136.9 | −0.3 | No |
| 56 | $V_P$ | Ideal body weight (kg) | Linear | 1137.0 | −0.2 | No |
| 57 | $V_P$ | Ideal body weight (kg) | Power | 1136.9 | −0.3 | No |
| 58 | $V_P$ | Ideal body weight (kg) | Exponential | 1137.0 | −0.2 | No |
| 59 | $V_P$ | Adjusted body weight (kg) | Linear | 1136.9 | −0.3 | No |
| 60 | $V_P$ | Adjusted body weight (kg) | Power | 1137.2 | 0.0 | No |
| 61 | $V_P$ | Adjusted body weight (kg) | Exponential | 1136.9 | −0.3 | No |
| 62 | $V_P$ | Body mass index (kg/m$^2$) | Linear | 1136.4 | −0.8 | No |
| 63 | $V_P$ | Body mass index (kg/m$^2$) | Power | 1136.3 | −0.9 | No |
| 64 | $V_P$ | Body mass index (kg/m$^2$) | Exponential | 1136.4 | −0.8 | No |
| 65 | $V_P$ | The use of ECMO support (yes/no) | Proportional | 1136.6 | −0.6 | No |
| 66 | $V_P$ | ECMO type (VV/VA) | Proportional | 1135.5 | −1.7 | No |
| 67 | $V_P$ | ECMO flow rate (L/min) | Linear | 1137.1 | −0.1 | No |
| 68 | $V_P$ | Duration of ECMO (h) | Linear | 1137.1 | −0.1 | No |
| 69 | $V_P$ | Serum albumin (g/dl) | Linear | 1135.7 | −1.5 | No |
| 70 | $V_P$ | Serum albumin (g/dl) | Power | 1135.4 | −1.8 | No |
| 71 | $V_P$ | Serum albumin (g/dl) | Exponential | 1135.6 | −1.6 | No |
| 72 | $V_P$ | Fluid balance (L) | Linear | 1137.0 | −0.2 | No |
| 73 | $V_P$ | Fluid balance (L) | Exponential | 1137.0 | −0.2 | No |
| 74 | $V_P$ | Use of inotropes (yes/no) | Proportional | 1135.5 | −1.7 | No |
| 75 | $V_P$ | Septic shock (yes/no) | Proportional | 1134.9 | −2.3 | No |
| 76 | $V_P$ | Mean arterial pressure (mmHg) | Linear | 1135.8 | −1.4 | No |
| 77 | $V_P$ | Mean arterial pressure (mmHg) | Power | 1135.1 | −2.1 | No |
| 78 | $V_P$ | Mean arterial pressure (mmHg) | Exponential | 1135.5 | −1.7 | No |

Abbreviations: CL, total clearance; ECMO, extracorporeal membrane oxygenation; $GFR_{EPI}$, glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration equation; OFV, objective function value; Sig, significant; $V_C$, central volume of distribution; $V_P$, peripheral volume of distribution.

[a]OFV decrease at least 3.84 ($p$ value < 0.05, $\chi^2$, $df$ = 1).

**TABLE B5** The results of stepwise backward deletion step 1

| No | Model | OFV | ΔOFV | Sig[a] |
|---|---|---|---|---|
| | A full model including covariance terms between CL, $V_C$, $V_P$, and including 3 covariates:<br>- $GFR_{EPI}$ on CL<br>- Adjusted body weight on $V_C$<br>- Mechanical ventilator support on CL | 1092.5 | | |
| 1 | Remove $GFR_{EPI}$ on CL | 1137.0 | +44.5 | Yes |
| 2 | Remove adjusted body weight on $V_C$ | 1104.8 | +12.3 | Yes |
| 3 | Remove mechanical ventilator support on CL | 1098.5 | +6.0 | No |

Abbreviations: CL, total clearance; $GFR_{EPI}$, glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration equation; OFV, objective function value; Sig, significant; $V_C$, central volume of distribution; $V_P$, peripheral volume of distribution.

[a]OFV decrease at least 3.84 ($p$ value < 0.05, $\chi^2$, $df$ = 1).

**TABLE B6** The results of stepwise backward deletion step 2

| No | Model | OFV | ΔOFV | Sig[a] |
|---|---|---|---|---|
| | A full model including covariance terms between CL, $V_C$, $V_P$, and including 2 covariates:<br>- $GFR_{EPI}$ on CL<br>- Adjusted body weight on $V_C$ | 1098.5 | | |
| 1 | Remove $eGFR_{EPI}$ on CL | 1148.8 | +50.3 | Yes |
| 2 | Remove adjusted body weight on $V_C$ | 1111.2 | +12.7 | Yes |

Abbreviations: CL, total clearance; $GFR_{EPI}$, glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration equation; OFV, objective function value; Sig, significant; $V_C$, central volume of distribution; $V_P$, peripheral volume of distribution.

[a]OFV increase at least 6.64 ($p$-value < 0.01, $\chi^2$, $df$ = 1).

## APPENDIX 3

Probability of target attainment (PTA) for imipenem regimens achieving 40% $fT_{>MIC}$ and 75% $fT_{>MIC}$ at GFR 120.1 – 180 ml/min in 50 critically ill patients with life-threatening severe infections

| Dosage regimen | MIC (mg/L) | Probability of attaining the following $\%fT_{>MIC}$ 40% | 75% |
|---|---|---|---|
| 0.5 g q6h, 1-h inf | 0.5 | 99.9 | 85.8 |
| | 1 | 96.2 | 59.5 |
| | 2 | 77.7 | 24.8 |
| | 4 | 38.1 | 4.8 |
| | 8 | 7.3 | 0.4 |
| 0.5 g q6h, 4-h inf | 0.5 | 100 | 99.9 |
| | 1 | 99.9 | 94.4 |
| | 2 | 95.2 | 69.1 |
| | 4 | 61.5 | 24.7 |
| | 8 | 14.3 | 2.7 |
| 1 g q6h, 1-h inf | 0.5 | 100 | 96.5 |
| | 1 | 99.5 | 85.1 |
| | 2 | 96.0 | 59.4 |
| | 4 | 77.2 | 26.3 |
| | 8 | 39.2 | 6.1 |
| 1 g q6h, 4-h inf | 0.5 | 100 | 100 |
| | 1 | 100 | 99.6 |
| | 2 | 99.9 | 94.9 |
| | 4 | 95.7 | 69.2 |
| | 8 | 63.0 | 24.7 |
| 1.5 g q6h, 1-h inf | 0.5 | 100 | 98.8 |
| | 1 | 100 | 93.3 |
| | 2 | 98.8 | 75.3 |
| | 4 | 91.3 | 45.0 |
| | 8 | 63.4 | 14.8 |
| 1.5 g q6h, 4-h inf | 0.5 | 100 | 100 |
| | 1 | 100 | 99.9 |
| | 2 | 100 | 98.8 |
| | 4 | 99.4 | 87.5 |
| | 8 | 86.8 | 50.7 |

Abbreviation: inf, infusion.