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Pharmacokinetic Changes and Influencing Factors of Polymyxin B in Different ECMO Modes

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Purpose: With the development of extracorporeal membrane oxygenation (ECMO) technology, the duration of ECMO support has gradually increased, leading to an increased risk of ECMO-related bacterial resistance. Polymyxin B (PMB) is used to treat drug-resistant bacterial infections. However, the pharmacokinetic (PK) parameters of antibiotics may change during ECMO, resulting in over- or under-exposure. This study aimed to clarify the changes in PK parameters and identify factors influencing PMB levels in patients receiving venovenous or venoarterial ECMO.

Patients and Methods: A prospective PK study was performed in 11 patients receiving ECMO with resistant bacteria. After reaching a steady state, the drug concentrations of PMB pre- and post-oxygenator were measured. Nonlinear mixed-effects modelling was used to construct a population PK model for PMB. Microbial results were assessed using repeated cultures at the end of treatment. Semiquantitative microbial culture results were used to form clearance and uncleared groups.

Results: The PMB concentrations were not significantly different between pre- and post-oxygenator. A two-compartment model best described the PK of PMB. ECMO flow rate was included as a covariate of clearance (CL). Continuous renal replacement therapy (CRRT) were included as covariates on the volume of the central compartment. The PK parameters central compartment, volume of the peripheral compartment, CL, and inter-compartmental clearance or flow rate(Q) were 20.41 L, 9.86 L, 3.75 L/h, and 3.82 L/h. 7 patients (63.64%) had two consecutive negative bacterial cultures at discharge. The $C_{ss,avg}$ shows a significant difference between clearance group (2.26±0.72) and uncleared group (1.25±0.24), $P<0.05$.

Conclusion: There were no significant differences in PMB concentrations between pre- and post-oxygenator. The PK of PMB may be altered in patients receiving CRRT-ECMO. The ECMO flow rate is strongly correlated with the CL. The $C_{ss,avg}$ is correlated with the bacterial clearance rate. In clinical practice, increasing the incidence of therapeutic drug monitoring may improve the clinical outcomes.

Plain Language Summary: The duration of ECMO support has gradually increased, leading to a heightened risk of ECMO-related bacterial resistance. PMB is used to treat drug-resistant bacterial infections. However, the PK parameters of antibiotics may change during ECMO, resulting to over- or under-exposure. CRRT in combination with ECMO may impact the PK of PMB. The ECMO flow rate is strongly correlated with CL. $C_{ss,avg}$ is correlated with the pathogen bacterial clearance rate. In clinical practice, increasing the use of therapeutic drug monitoring may improve the clinical outcomes.

Keywords: antibacterial agents, pharmacokinetic, extracorporeal membrane oxygenation, polymyxin B, continuous renal replacement therapy

Introduction

Over the past decade, extracorporeal membrane oxygenation (ECMO) technology has advanced significantly.[1] With continuous equipment upgrades and technological innovations, the duration of ECMO support has become longer.[2]

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However, this prolonged duration has concurrently led to a heightened risk of related infections,[3] especially ECMO-associated resistant bacterial infections, which have significantly impacted patient mortality.[4] According to a recent meta-analysis,[5] the incidence of hospital-acquired infections during ECMO ranges from 8.8% to 64%, with an overall incidence of 1.7–85.4 per 1000 ECMO days. Hospital-acquired infections increased the relative risk of mortality by 32%. The incidences of multidrug-resistant, extensively drug-resistant, and pan-drug-resistant bacterial strains have increased annually and are closely associated with the widespread application and extended duration of ECMO,[6] This issue has become a major research focus in recent years. However, there are no precise guidelines for the use of antibiotics during ECMO treatment.

In China, carbapenemase-producing *Klebsiella pneumoniae* (CRKP) and carbapenemase-producing *Acinetobacter baumannii* (CRAB) are the most common resistant strains. The guideline recommend treatment regimens that include polymyxin B (PMB) combined with at least one other drug.[7]

As the prevalence of carbapenem-resistant gram-negative organisms has increased, polymyxins have re-entered clinical consideration and become the first-line treatment for these infections. Polymyxins, a group of basic cyclic polypeptide antibiotics produced by *Bacillus polymyxa*, include several amino acids and fatty acids. The two main types of polymyxins are colistin (Polymyxin E) and PMB. Although colistin is widely used, its status as an inactive prodrug and individual variability have led several countries to focus on PMB.

The main components of an ECMO circuit typically include an oxygenator composed of polymethylpentene and a centrifugal pump connected via polyvinyl chloride tubing. The large surface area of the extracorporeal circuit can lead to drug absorption and significant pharmacokinetic (PK) changes, especially for lipophilic drugs and drugs with high protein binding. Several studies have indicated that drugs are consumed within the ECMO circuit, especially in the oxygenator.[8] However, due to the limitations in monitoring methods for polymyxins, most primary hospitals are unable to conduct drug monitoring and cannot empirically adjust the drug dosage. Therefore, this study investigates the PK changes in PMB in patients receiving ECMO and evaluates the impact of these changes on the final biological clearance, providing clinical recommendations for the use of PMB in patients receiving ECMO. Thereby potentially improving the prognosis of infected patients.

Materials and Methods

Ethics

The study was conducted in accordance with the Declaration of Helsinki and national and institutional standards. This study was approved by the Clinical Research Ethics Committee of First Affiliated Hospital, College of Medicine, Zhejiang University (approval number IIT20210035B-R2). Given that all patients were unconscious on admission, informed consent was obtained only from their legal guardians.

Patients

This prospective study was conducted from January to December 2021 and included patients with heart or respiratory failure who received ECMO in the intensive care unit (ICU) at the First Affiliated Hospital of Zhejiang University School of Medicine in China. All patients had infections with resistant bacteria and required the administration of PMB. PMB was administered continuously more than four times and was expected to be used for at least an additional 24 h in each patient. All patients included in this study had Severe circulatory failure or respiratory failure requires ECMO support, with a sequential organ failure assessment (SOFA) score ≥2. Exclusion criteria were: (1) age <18 years, (2) pregnant women, (3) allergic to polymyxin B. Empiric antibiotic therapy was initiated by the responsible ICU clinician after a comprehensive clinical assessment with targeted treatment adjustments guided by the microbiological test results.

ECMO and CRRT Settings

The patients were treated with either venovenous (VV) or venoarterial (VA) ECMO based on the clinical indication. The ECMO (Rotaflow; MAQUET, Hechingen, Germany) circuit was made of polyvinyl chloride tubing and a polymethylpentene membrane oxygenator (BE-PLS 2050; MAQUET). The ECMO circuit was primed with 600 mL of normal saline solution. All patients who required continuous renal replacement therapy (CRRT; Fresenius SE&Co;

Bad Homburg, Germany) for renal failure received CRRT combined with ECMO (outflow line at post-oxygenator and inflow line at pre-oxygenator).

Drug Regimens

All patients received a loading dose of 200–300 mg on the first day of PMB therapy. Then, the patients received 100–150 mg (2.5–3 mg/kg/day) PMB at the discretion of the treating physician. Each dose of PMB was dissolved in 50 mL of normal saline via 1 h of micropump infusion. After more than four doses, pre- and post-oxygenator blood samples (2–3 mL) were collected using a regular blood tube at 1, 1.5, 2, 4, 8, and 12 h after the start of the infusion. The samples were centrifuged and stored at −80°C until testing.

Drug Assay

The plasma PMB concentrations were determined using liquid chromatography-tandem mass spectrometry. Calibration curves showed acceptable linearity >0.2–10 μg/mL for PMB1 and 0.05–2.5 μg/mL for PMB2. The upper limit of quantification was extended to 20 μg/mL for PMB1 and 5.0 μg/mL for PMB2 after a four-fold dilution. The intra- and inter-day assay coefficients of variation were <10%. As PMB1 and PMB2 have similar structures, molecular weights, pharmacological activities, and PK characteristics, the plasma concentration of PMB was summed to derive the total PMB1 and PMB2 concentrations.

Population PK Modeling

The population PK parameters were determined using one- or two-compartmental models with Phoenix NLME software (v8.1; Pharsight, Mountain View, CA, USA). The PK models were estimated using a first-order conditional estimation method. The model assessment criteria included the precision of the parameter estimates (standard error), goodness-of-fit plots, and likelihood ratio test (−2 log likelihood [−2LL]). The basic parameters included the volume of central compartment distribution (V) and central compartment clearance (CL) for the one-compartment model and the volume of peripheral compartment distribution and intercompartmental clearance (Q) for the two-compartment model.

For the initial model, interindividual variability was described using an exponential error model. Intra-individual variability (residual error) was described using proportional, additive plus proportional, or log-additive models. The covariates were selected using a stepwise process. By comparing the results with the initial model, a drop of >6.635 (P=0.01) of objective function value (OFV; −2LL) during forward selection and an increase of OFV of >10.828 (P=0.001) during backward selection were used as inclusion criteria for the covariates. Subsequently, based on the scatterplot and change in OFV >-6.63, the relevant population PK parameters were introduced into the diagonal or off-diagonal elements of the variance-covariance matrix to obtain the final model.

The average steady-state concentration ($C_{ss,avg}$) was estimated as the area under the curve divided by the dosing interval (AUC0-τ). The PK parameters were analyzed using Phoenix WinNonlin software (Certara, Princeton, NJ, USA).

The adequacy of the final model was assessed using goodness of fit plots. Model performance was evaluated using a prediction-corrected visual predictive check with 1000 replicates. Additionally, the precision of the parameter estimates was assessed using bootstrap analysis with 1000 samples.

Microbiological Efficacy

Patient samples (sputum, blood, urine, stool, and abdominal drainage fluid) were collected for semiquantitative bacterial culture. The microbial results were evaluated using repeated microbial cultures at the end of treatment. According to the results of semi-quantitative microbial culture, the samples were grouped into clearance group (bacterial cultures from the infection site did not reveal the original pathogen in two consecutive tests after PMB treatment) and uncleared group (no reduction in the bacterial count or a reduction in the bacterial count but not complete clearance) groups. Compare the differences in $C_{ss,avg}$ between the two groups.

Statistical Analysis

SPSS (version 25.0; IBM, Armonk, NY, USA) was used for the statistical analysis. The continuous variables are described as the mean ± standard deviation (SD) or median and interquartile range. The categorical variables are

described as absolute number and percentage. The chi-square test, Mann–Whitney *U*-test, and *t*-test were used to detect differences between groups and samples, as appropriate. Statistical significance was set at P≤0.05.

Results

Patient Data

A total of 11 ECMO patients treated with polymyxin B were enrolled in this study (Table 1). The median age was 60 years (interquartile range: 53.50–62.50), and there were 8 male patients (72.73%). The median weight was 60 kg (interquartile range: 57.05–66.00), and the median body surface area was 1.69 m² (interquartile range: 1.68–1.79). The most common underlying chronic diseases among the patients were coronary artery disease (n=4, 36.36%), hypertension (n=4, 36.36%), and diabetes (n=3, 27.27%). The median APACHE II and SOFA scores were 14 (interquartile range: 9.50–18.00) and 10 (interquartile range: 4.00–11.50), respectively. 8 patients (72.73%) received VA-ECMO, with a median rotation speed of 3500.00 rpm (interquartile range: 3000.00–3770.00) and a median blood flow rate of 3.60 L/min (interquartile range: 3.00–3.65). The average duration of ECMO support was 16.18 days (interquartile range: 8.50–23.00).

All patients developed secondary infections, which were distributed as follows: lung infections (n=9, 81.82%), bloodstream (n=4, 36.36%), intestine (n=2, 18.18%), abdominal cavity (n=2, 18.18%), and urinary tract (n=1, 9.09%). The pathogens included CRAB (n=7, 63.64%), CRKP (n=6, 54.55%), and CRPA (n=3, 27.27%), with a PMB minimum inhibitory concentration(MIC) of 0.5 mg/L. The c-reactive protein (CRP) and procalcitonin (PCT) levels increased significantly, with a median CRP of 145.86 mg/L (interquartile range: 105.84–192.13) and a median PCT of 3.05 μg/L (interquartile range: 2.19–9.54). 7 patients (63.64%) had at least two consecutive negative pathogen cultures at the time of discharge.

Patients with a median blood urea nitrogen (BUN) of 12.37 mg/dL (interquartile range: 8.95–15.79), median serum creatinine (Scr) of 137.27 mg/dL (interquartile range: 71.00–184.50), and median creatinine clearance (CrCL) of 137.27 mL/min (interquartile range: 71.00–184.50). The median total bilirubin (TBIL) was 36.30 μmol/L (interquartile range: 19.80–52.70), median direct bilirubin (DBIL) was 19.60 μmol/L (interquartile range: 13.75–40.40), and median albumin (ALB) was 34.00 g/L (interquartile range: 30.5536.20). 8 patients received continuous VV hemodialysis (CVVHD; Ultraflux® AV1000S, Fresenius Medical Care) due to anuria.

PMB Concentration Assay

A total of 132 blood samples were collected for the PK analysis (Figure 1). There were no significant differences in PMB concentrations between the two groups (P>0.05).

Population PK Model Development

The OFVs of the one- and two- compartmental models were 126.6 and 109.9, respectively. Based on the OFV, CV, and diagnostic scatterplots, the two-compartment model with an additive option was selected as the base model. In the covariate model building step, the ECMO rate was identified as a covariate for CL (Figure 2), and CRRT and age were identified as the covariates for V. The final PK model parameters are listed in Table 2 and the equations below:

$$CL = tvCL \times (1 + (speadECMO - 3.48\ L/min) \times dCLdspeadECMO) \times \exp(nCL)$$

$$V = tvV \times (1 + dVdCRRTO \times (if\ no\ CRRT)) \times \exp(nV)$$

The goodness-of-fit plots of the final model are shown in Figure 2. The observed concentrations were consistent with those of predicted concentration (PRED) and individual predicted Concentration (IPRED), and the plots of CWRES vs time and PRED were normally distributed. The estimated covariates and bootstrap indicate that the final model had qualified stability (Table 2). In the prediction-corrected visual predictive check (VPC) diagrams, most of the observed plots were distributed within the 95% prediction percentiles (Figure 3).

Table 1 Demographic, Clinical and Laboratory Data

Variable (N=11 patients)	Median (IQR)
Age, years	56 (48, 64)
Male, n (%)	8 (72.73%)
Female, n (%)	3 (27.27%)
Height, m	1.7 (1.65, 1.73)
Weight, kg	60 (57.05, 66.00)
BMI, kg/m2	21.26 (20.03, 23.89)
BSA, m^2	1.69 (1.68, 1.79)
Coronary heart disease, n (%)	4 (36.36%)
Hypertension, n (%)	4 (36.36%)
Diabetes, n (%)	3 (27.27%)
BUN, mg/dL	12.37 (8.95, 15.79)
Scr, mg/dL	137.27 (71.00, 184.50)
CrCL, mL/min	79.70 (33.33, 94.89)
WBC (10E9/L)	13.83 (11.58, 19.03)
HGB, g/L	68.00 (62.50, 71.00)
PLT (10E9/L)	67.00 (44.00, 117.00)
ALT, U/L	22 (17.00, 81.50)
ALB, g/L	34.00 (30.55, 36.20)
TBIL, μmol/L	36.30 (19.80, 52.70)
DBIL, μmol/L	19.60 (13.75, 40.40)
CRRT, n (%)	8 (72.73%)
PCT, μg/L	3.05 (2.19, 9.54)
CRP, mg/L	145.86 (105.84, 192.13)
APACHE II score	14 (9.50, 18.00)
SOFA score	10 (4.00, 11.50)
Infectious site, presumed or confirmed, n (%)	
Pneumonia	9 (81.82%)
Bloodstream infection	4 (36.36%)
Urinary tract infection	1 (9.09%)
Intestinal infection	2 (18.18%)
Intraabdominal	2 (18.18%)
Infectious pathogen, confirmed, n (%)	
baumannii	7 (63.64%)
Klebsiella pneumoniae	6 (54.55%)
Pseudomonas aeruginosa	3 (27.27%)
VA/VV	8/3
Duration of ECMO support, days	16.18 (8.50, 23.00)
ECMO, RPM	3500.00 (3000.00, 3770.00)
ECMO FLOW rate, LPM	3.60 (3.00, 3.65)
Duration of ventilator support	34.18 (22.00, 44.50)
Pathogenic microorganism clearance rate, n, %	6 (54.55%)

Abbreviations: ALB, albumin; ALT, alanine aminotransferase; APACHE II, acute physiology and chronic health evaluation II; AST, aspartate aminotransferase; BMI, body mass index; BSA, body surface area; CrCL, creatinine clearance; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; HGB, haemoglobin; PCT, procalcitonin; PLT, blood platelet; SCR, serum creatinine; SOFA, sequential organ failure assessment; TBIL, total bilirubin; WBC, white blood cell.

Microbiological Efficacy

7 patients (63.64%) had two consecutive negative bacterial cultures at the time of discharge. The $C_{ss,avg}$ shows a significant difference between clearance group (2.26±0.72) and uncleared group (1.25±0.24), P<0.05 (Figure 4).

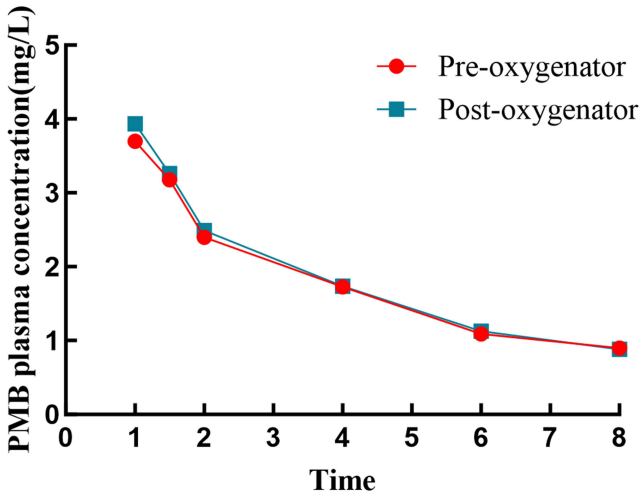

Figure 1 Polymyxin B concentrations between Pre-oxygenator and Post-oxygenator. Pre-oxygenator, before oxygenation by ECMO; Postoxygenator, after oxygenation by ECMO.

Discussion

With the widespread use of ECMO technology, the duration of ECMO support has increased. This is particularly true for patients with heart failure following myocardial infarction, who are awaiting heart or lung transplantation. Compared with traditional short-term perioperative VA-ECMO, prolonged ECMO significantly increases the risk of infection.[9] CRAB, CRKP, and CRPA are among the most common resistant bacteria during ECMO.[10] In our study, the median duration of ECMO support in patients with ECMO-associated resistant bacterial infections was 16.18 days, which is consistent with previous reports.[2]

A previous study[11] reported that the introduction of ECMO may significantly alter the PK of drugs via circuit sequestration, increased volume of distribution, or changes in CL. In addition, the oxygenator significantly affects drug sequestration,[12,13] especially for lipophilic drugs.[14] This study is the first to directly compare the concentration changes of PMB between pre- and post-oxygenator sites; no significant differences were found within the therapeutic range, which aligns with the findings of Surovoy et al.[15] However, the PK parameters of PMB sulfate exhibited considerable variability among different populations. Some studies have reported a CL of 1.16 L/h and a Vd of only 19.7L for PMB in ECMO patients, which is significantly lower than previous studies in sepsis patients.[16] These results are consistent with those of previous studies.[17] Therefore, the PK changes of PMB in patients receiving ECMO remain highly controversial. Due to the instability of VA-ECMO conditions, reports regarding PMB therapy during VA-ECMO are rare. As a result, clinical practice often refers to data from VV-ECMO, despite significant hemodynamic differences between the two modes. The PK/PD changes in both modes were explored in this study, where 72.73% of the patients received VA-ECMO, which is more representative of clinical practice.[1]

Several studies have indicated that creatinine clearance has a more significant impact on PK than ECMO flow.[15,18] However, patients with acute kidney injury (AKI) receiving ECMO often undergo CRRT, which affects creatinine clearance, making it difficult to use as an objective reference. According to Pi et al[19] in the absence of ECMO, there is a significant difference in the $AUC_{0\text{-}12}$ for PMB between the patients receiving CRRT and those who do not. Due to the complexity of ECMO, current studies often focus on ECMO and CRRT separately, though this differs significantly from actual clinical settings. The population PK results of this study suggest that the covariate CRRT is significantly correlated with the central compartment and that patients receiving CRRT-ECMO had significantly increased the central compartment. This is the first study to use CRRT as a covariate of ECMO for PMB. Similar results have been reported in studies regarding other drugs,[10] in which CRRT in the CVVHD mode was significantly correlated with drug PK. In clinical practice, CRRT and ECMO can be connected in series or in parallel, which may affect the results of this study. Therefore, further research is needed to better understand the effects of CRRT on drug PK in ECMO patients.

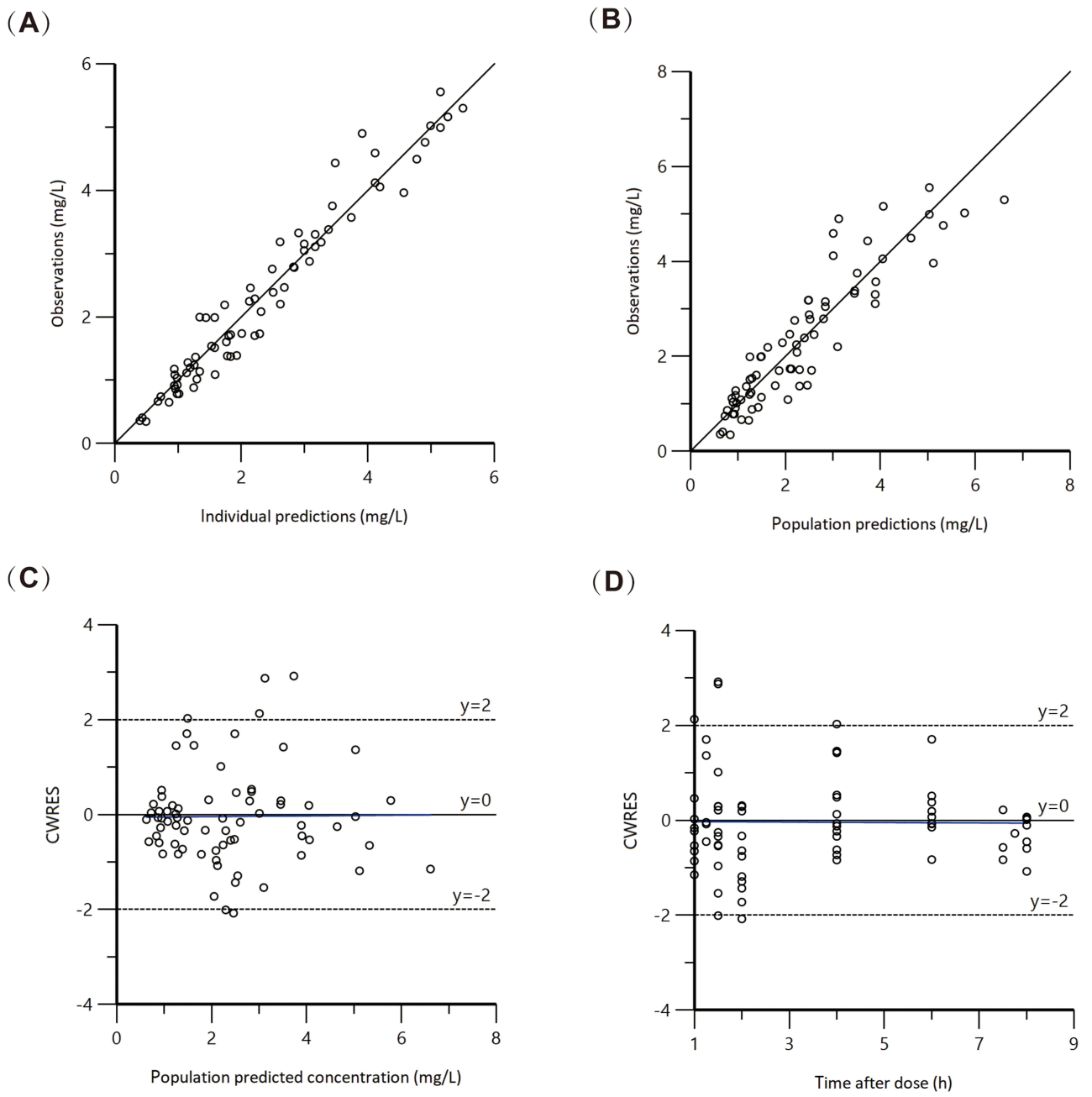

Figure 2 Goodness-of-fit plots for the final population pharmacokinetic model of PMB. (**A**) Observed versus individual predicted concentrations (DV vs IPRED); (**B**) Observed versus population predicted concentration (DV vs PRED); (**C**) Conditional weighted residuals versus population predicted concentrations (CWRES vs PRED); (**D**) Conditional weighted residuals versus time after dose (CWRES vs TAD); The reds lines in panels (**C** and **D**) represent smoothed regression lines.

The ECMO flow rate is a crucial parameter in patients receiving ECMO as it determines the running speed of the drug throughout the circuit, similar to the role of cardiac output in hemodynamics.[20] In previous studies regarding the PK/PD of drugs in ECMO patients, the ECMO flow rate has not been considered an important factor, especially in PMB studies. This is the first study to use the ECMO flow rate as a covariate in PMB research. The results suggest a statistically significant correlation between the ECMO flow rate and CL, which is a novel finding. Although such findings have rarely been reported in studies of other drugs, no studies have yet explained the underlying mechanisms.

PIEZO1,[21] a mechanosensitive ion channel protein, plays a key role in regulating blood flow, cell morphology, and mechanical signaling. It has been studied in ECMO patients, as blood flow significantly affects systemic circulation.[22]

Table 2 Parameters Estimates, Bootstrap Medians, and Confidence Intervals for PMB

Parameter	Final Model		Bootstrap of Final Model	
	Estimate, Mean	CV, %	Estimate, Median	95% CI
tvV, L	20.41	17.1	20.47	12.82–27.89
tvV_p, L	9.86	53.4	10.34	4.06–24.34
tvCL, L/h	3.75	6.98	3.74	1.59–4.34
tvQ, L/h	3.82	42.1	4.19	1.83–10.49
dVdCRRT0	−0.525	−19.1	−0.553	−0.769-(−0.207)
dCLdspeedECMO	−0.321	−13.9	−0.315	−0.710–0.00120
Inter-individual variability				
ω^2V	0.062	–	0.058	–
ω^2CL	0.038	–	0.049	–
Residual variability (σ)				
stdev0	0.361	12.0	0.351	0.256–0.447

Abbreviations: CV%, percent confidence of variation; CI, confidence interval; tvV, typical value of central compartment distribution; tvV_p, typical value of peripheral compartment distribution; tvCL, typical value of central compartment clearance; tvQ, typical value of intercompartmental clearance; dVdage, fixed parameter coefficient of age (year) to V; dVdCRRT0, fixed parameter coefficient of CRRT to V; dCLdspeadECMO, fixed parameter coefficient of spead of ECMO (L/min); ωV, variance of inter-individual variability for V; ωCL, variance of inter-individual variability for CL; stdev0, standard deviation.

Increased ECMO flow also increases shear force.[23] PIEZO1 is expressed in endothelial cells and plays a key role in sensing blood flow shear force, affecting vascular tension and diameter regulation, ultimately regulating blood pressure. Based on this principle, changes in the shear force caused by ECMO blood flow may affect the apparent volume of

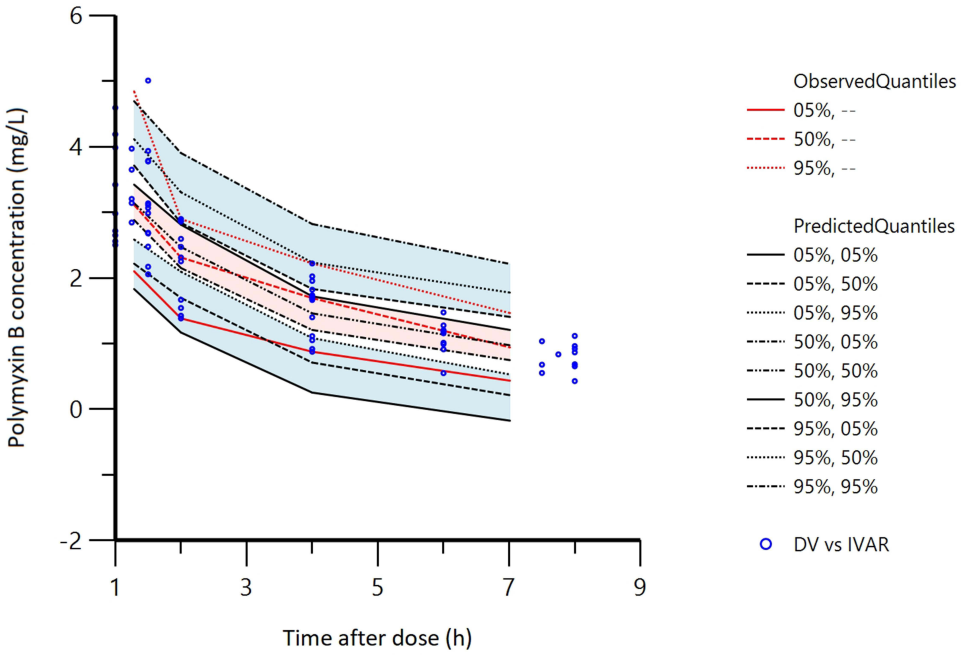

Figure 3 Prediction-corrected visual predictive check of the final model. Prediction corrected-visual predictive check of the final model. Red lines represent the 5th, 50th, and 95th percentiles of the observed concentrations; the shaded areas represent the 90% confidence intervals of the 5th, 50th, and 95th percentiles of the simulated concentrations, respectively; the dots represent the prediction-corrected observation concentration.
Abbreviations: DV, observed dependent variable; IVAR, independent variable.

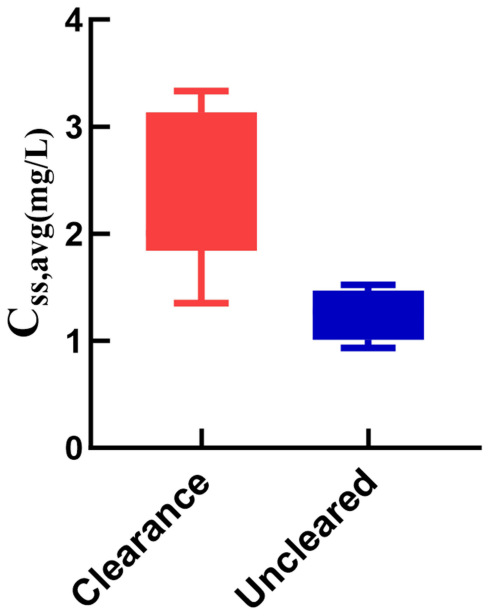

Figure 4 $C_{ss,avg}$ and bacterial clearance.
Abbreviations: $C_{ss,avg}$, average steady-state plasma concentration of colistin.

distribution, which may explain the observed correlation between ECMO flow rate and distribution volume in this study. However, the mechanism remains unclear. A future study regarding PIEZO1 at different ECMO flow rates is necessary. These findings may have implications for the pharmacokinetics of all drugs administered to ECMO patients.

The AUC and $C_{ss,avg}$ are important parameters with different meanings and uses in PK analysis and PD evaluation.[24] $C_{ss,avg}$ reflects the long-term steady-state drug concentration and is crucial for assessing the stability of drug levels under constant dosing.[25] In this study, all drug concentration samples were obtained after the drug concentration reached a steady state, rendering $C_{ss,avg}$ a more reliable indicator. For microbiological efficacy evaluation, bacterial clearance was defined as two consecutive negative cultures. In this study, the pathogen clearance rate was 63.64%, and the $C_{ss,avg}$ shows a significant difference between the two group, similar to findings in non-ECMO patients.[25] In the uncleared group, we found that the ECMO rotational speed of the patients was less than 3500 rpm, and all of them used CRRT. Given that the dosing regimen was consistent across groups, this may explain the lower $C_{ss,avg}$ observed in the uncleared group. This finding requires further investigation.

This study has several limitations. First, the sample size was small and from a single center, which may have affected the results. Future studies should include a larger sample size with a consistent treatment dosage. A control group, and the determination of PMB concentration at additional sites. As this study was prospective, the impact of CRRT and ECMO flow rate on PK could not be predicted; therefore, these factors were not grouped separately. Future studies should examine these factors in greater detail based on the current results.

Given that most medical institutions cannot monitor the PK/PD of PMB, this study provides suggestions for adjusting drug concentrations in patients receiving ECMO.

Conclusion

There were no significant differences in PMB concentrations between pre- and post-oxygenator. The PK of PMB may be altered in patients receiving CRRT-ECMO. The ECMO flow rate is strongly correlated with the clearance. The $C_{ss,avg}$ is correlated with the bacterial clearance rate. In clinical practice, increasing the incidence of therapeutic drug monitoring may improve the clinical outcomes.

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reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no conflict of interest to disclose.

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