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ORIGINAL RESEARCH

Therapeutic Monitoring of Polymyxin B in Critically Ill Patients with Carbapenem-Resistant Organisms: Evaluation Based on Steady-State Trough and Peak Concentrations

Jun Yang[1,*], Yunpei Zhao[1,*], Linli Xie[1,*], Yu Gan[1], Mingjie Yu[2], Ge Yang[1], Yongchuan Chen[1]

[1]Department of Pharmacy, The First Affiliated Hospital of Army Medical University, Chongqing, People's Republic of China; [2]Department of Pharmacy, The First Affiliated Hospital of Chongqing Medical University, Chongqing, People's Republic of China

*These authors contributed equally to this work

Correspondence: Yongchuan Chen, Department of Pharmacy, the First Affiliated Hospital of Army Medical University, Chongqing, People's Republic of China, Email zwmcyc@tmmu.edu.cn

Objective: In critically ill patients with carbapenem-resistant organisms (CRO) infections, optimizing polymyxin B (PMB) exposure is crucial for survival. This prospective single-center study was conducted to assess the factors influencing the steady-state trough ($C_{trough,ss}$) and peak concentrations ($C_{peak,ss}$) of PMB, as well as the relationship between the steady-state 24-hour area under the concentration-time curve ($AUC_{ss,24h}$) of PMB, estimated from $C_{trough,ss}$ and $C_{peak,ss}$ and clinical efficacy.

Methods: Plasma PMB concentrations were measured using liquid chromatography-tandem mass spectrometry. The first-order elimination kinetic equation was used to compute $AUC_{ss,24h}$ based on $C_{trough,ss}$ and $C_{peak,ss}$ with the therapeutic window of PMB defined as $AUC_{ss,24h}$ ranging from 50 to 100 $mg \cdot h \cdot L^{-1}$. Clinical effectiveness was defined as a composite of symptom improvement, inflammatory response reduction and stable oxygenation.

Results: A total of 140 critically ill patients were enrolled, yielding 155 paired measurements for $C_{trough,ss}$ and $C_{peak,ss}$ from which 155 $AUC_{ss,24h}$ values were calculated. PMB therapy was efficacious in 52.14% of cases, with 42.58% (66/155) having an AUC_{ss} of 50–100 $mg \cdot h \cdot L^{-1}$ within 24h. Creatinine clearance (CrCL) and sepsis are both linked to low $C_{trough,ss}$ levels. Maintenance dose and haemoglobin (HGB) had positive relationships with $C_{peak,ss}$ but sepsis and APACHE II scores were negatively correlated. Higher $AUC_{ss,24h}$ and maintenance of $AUC_{ss,24h}$ within the therapeutic window were identified as favourable factors for clinical efficacy. However, advanced age, elevated blood urea nitrogen (BUN) and alkaline phosphatase (ALP) levels, and sepsis were risk factors.

Conclusion: The PMB $AUC_{ss,24h}$ estimated from $C_{trough,ss}$ and $C_{peak,ss}$ was closely correlated with clinical efficacy. The two-point sampling strategy based on steady-state trough and peak concentrations is applicable for therapeutic monitoring of PMB in critically ill patients.

Keywords: polymyxin B, critical illness, steady-state concentration, carbapenem-resistant organisms, therapeutic monitoring

Introduction

Carbapenem-resistant organisms (CRO), characterized by high mortality rates, transmissibility, and a globally worsening resistance landscape, have been designated by the World Health Organization (WHO) as pathogens of the highest critical priority, requiring urgent intervention.[1–3] Their extensive resistance to commonly used antimicrobial agents significantly increases their risk of treatment failure and mortality. Polymyxin B (PMB), exhibiting potent activity against the vast majority of CRO isolates, has emerged as a critical therapeutic agent for CRO infections.[4,5] Critically ill patients represent a high-risk population for CRO infections due to factors such as immunosuppression, broad-spectrum antimicrobial exposure, and frequent invasive procedures.[6,7] Furthermore, the complex pathophysiology in this population – often

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including multi-organ dysfunction, hypoalbuminemia, hemodynamic instability, and the application of supportive therapies like continuous renal replacement therapy (CRRT) or extracorporeal membrane oxygenation (ECMO) – significantly alters the pharmacokinetic (PK) profile of antimicrobial agents.[8,9] Maintaining effective drug exposure within target PK/pharmacodynamic (PD) parameters is crucial for improving clinical outcomes in critically ill patients.[9,10]

Polymyxin B is vital for combating CRO infections, yet its clinical utility is significantly limited by challenges in balancing efficacy and safety. It also carries substantial nephrotoxic risks: acute kidney injury (AKI) incidence ranges from 15%–60%,[11] exhibiting both dose-dependent and cumulative toxicity. Crucially, the concentration range required for antibacterial efficacy overlaps with AKI-inducing concentrations, resulting in a narrow therapeutic window. Consequently, guidelines[12–14] recommend therapeutic drug monitoring (TDM) for this agent and a target steady-state 24-hour area under the concentration-time curve ($AUC_{ss,24h}$) range of 50–100 $mg{\cdot}h{\cdot}L^{-1}$ for PMB when the minimum inhibitory concentration (MIC) of the pathogen is ≤ 2 $mg{\cdot}L^{-1}$ (susceptible breakpoint). The population pharmacokinetic (PPK) model-based Bayesian forecasting approach is a commonly employed method for estimating $AUC_{ss,24h}$. However, its reliance on complex modelling computations, stringent requirements for precise sampling timepoints, and need for specialized personnel often hinder its ability to meet the time-sensitive demands of managing severe infections in critically ill patients and limit its practical implementation in this setting.

As a potential simplification, guidelines[12] recommend a first-order elimination kinetic equation method based on steady-state trough ($C_{trough,ss}$) and peak ($C_{peak,ss}$) concentrations. This "two-point sampling strategy" requires only blood samples collected before dose ($C_{trough,ss}$) and immediately after the end of infusion ($C_{peak,ss}$), offering operational simplicity that is better suited to the critical care environment. However, the clinical validation of this simplified approach faces two key challenges: (1) the lack of direct evidence linking the estimated $AUC_{ss,24h}$ to clinical efficacy, and (2) insufficient systematic elucidation of the key factors influencing $C_{trough,ss}$ and $C_{peak,ss}$ within the complex pathophysiological state of critically ill patients. These limitations constrain the utility of this strategy in guiding individualized PMB dosing.

Therefore, this study aimed to: (1) prospectively collect $C_{trough,ss}$ and $C_{peak,ss}$ samples from critically ill patients receiving PMB, calculate $AUC_{ss,24h}$ using the first-order elimination equation, and systematically evaluate its correlation with clinical efficacy to validate the pharmacodynamic predictive value of the two-point sampling strategy; and (2) conduct an in-depth analysis of the key factors influencing PMB $C_{trough,ss}$ and $C_{peak,ss}$ in critically ill patients to elucidate the sources of inter-individual exposure variability. This study establishes a theoretical foundation for optimizing PMB dosing regimens and mitigating toxicity risks, thereby enabling streamlined TDM that enhances medication safety and clinical efficiency in ICU settings, ultimately supporting the rational clinical use of PMB in this vulnerable population.

Materials and Methods

Study Design

This single-center prospective study was conducted at the Department of Critical Care Medicine, the First Affiliated Hospital of Army Medical University, from August 2021 to July 2024. All enrolled patients or legally authorized representatives provided written informed consent. The inclusion criteria were as follows: 1) patients aged $\geq$ 18 years, 2) patients confirmed to have CRO infection by etiological testing and receiving intravenous PMB therapy, and 3) patients who received at least four consecutive doses of PMB or a loading dose followed by at least three consecutive maintenance doses. The exclusion criteria were as follows: 1) patients with incomplete clinical data, 2) patients with a hospital stay of less than 7 days, and 3) patients who had received polymyxin E before PMB administration.

PMB Sampling, Detection, and Clinical Data Collection

After at least 4 intravenous maintenance doses (or 3 loading doses) of PMB, blood samples were collected within 15 minutes before (steady-state trough) and after (steady-state peak) the next infusion.[12] The PMB concentrations were quantified using a previously validated HPLC-MS/MS method.[15]

Clinical data extracted from hospital electronic medical records included basic information (sex, age, height, weight, primary diagnosis, comorbidities, and hospital stay duration), biochemical parameters (liver/kidney function, blood routine, inflammatory markers, and coagulation indices), PMB administration details (duration, dosage, and sampling time), and other supportive therapies (CRRT and ECMO).

Estimation of AUC and Definition

The $AUC_{ss,24h}$ ranging from 50 to 100 $mg{\cdot}h{\cdot}L^{-1}$ was defined within the therapeutic window.[12–14] The formulas for estimating AUC are provided in Equations.[1–3,12]

$$k_e = \frac{\ln C_{peak,ss} - \ln C_{trough,ss}}{\tau - \text{Infusion}} \tag{1}$$

$$C_{soi'} = \frac{C_{peak,ss}}{e^{-k_e \cdot \text{Infusion}}} \tag{2}$$

$$AUC = \frac{C_{soi'} - C_{trough,ss}}{k_e} \times n \tag{3}$$

Note: Infusion, infusion duration; τ, dosing interval; C_{soi}, exploratory concentration at the start of administration based on the assumption of one-compartment linear elimination pharmacokinetics; k_e elimination constant; n, number of administrations within 24h.

Clinical efficacy was assessed using medical records (discharge summaries, diagnoses, test reports, etc). Clinical Effectiveness (CE) was defined as a composite of resolved/improved symptoms (temperature < 38 °C), ≥30% reduction in peripheral white blood cell count or C-reactive protein level, and stable PaO_2/FiO_2 ratio. For bacteremia patients, microbiological cure (no growth of initial isolates in post-treatment blood cultures) was mandatory. Non-effectiveness (NE) was defined as not meeting all criteria.[14,16] Nephrotoxicity was evaluated using the KDIGO criteria.[17] AKI was defined as a ≥0.3 $mg{\cdot}dL^{-1}$ (26.5 $\mu mol{\cdot}L^{-1}$) increase in serum creatinine (SCr) over two consecutive measurements during PMB therapy, with a 50% rise from baseline.

Statistical Analysis

Data were analyzed using the SPSS software (version 26.0, IBM) and R (version 4.4.0). Continuous variables with a normal distribution were described as mean ± standard deviation and compared by means of the *t*-test, while those with a non-normal distribution were presented as median (interquartile range), and compared through the Mann–Whitney *U*-test. Categorical data were expressed as percentages (%) and were compared using the chi-square test or Fisher's exact test. Univariate screening ($P < 0.10$) identified candidate variables for multivariate analysis. Forward stepwise selection (likelihood ratio; with a significance level of 0.10 for entry/removal) determined independent predictors of $C_{trough,ss}/C_{peak,ss}$ using multiple linear regression. Backward elimination (removal $P > 0.10$) selected clinical efficacy predictors via logistic regression. Statistical significance was set at $P < 0.05$.

Results

Patient Characteristics

Blood samples were collected from 166 critically ill patients who had undergone PMB. Seven patients were excluded due to sampling before reaching steady state, five for concurrent nebulized colistin administration during treatment, four for mismatched collection of $C_{trough,ss}$ and $C_{peak,ss}$ and ten for incomplete sampling of either $C_{trough,ss}$ or $C_{peak,ss}$. Ultimately, 140 patients with 310 measurable concentrations were included, including 13 patients who underwent repeated concentration measurements. The flow of the study is shown in Figure 1.

The cohort was predominantly male (111/140, 79.29%) with a mean APACHE II score of 26.61. Severe infections (71/140, 50.71%) constituted the most common primary diagnosis and sepsis was presented in 75 patients (53.57%). In the CE group (n=73), the primary CRO included carbapenem-resistant *Acinetobacter baumannii* (CRAB, n=54), carbapenem-resistant *Klebsiella pneumoniae* (CRKP, n=39), and carbapenem-resistant *Pseudomonas aeruginosa*

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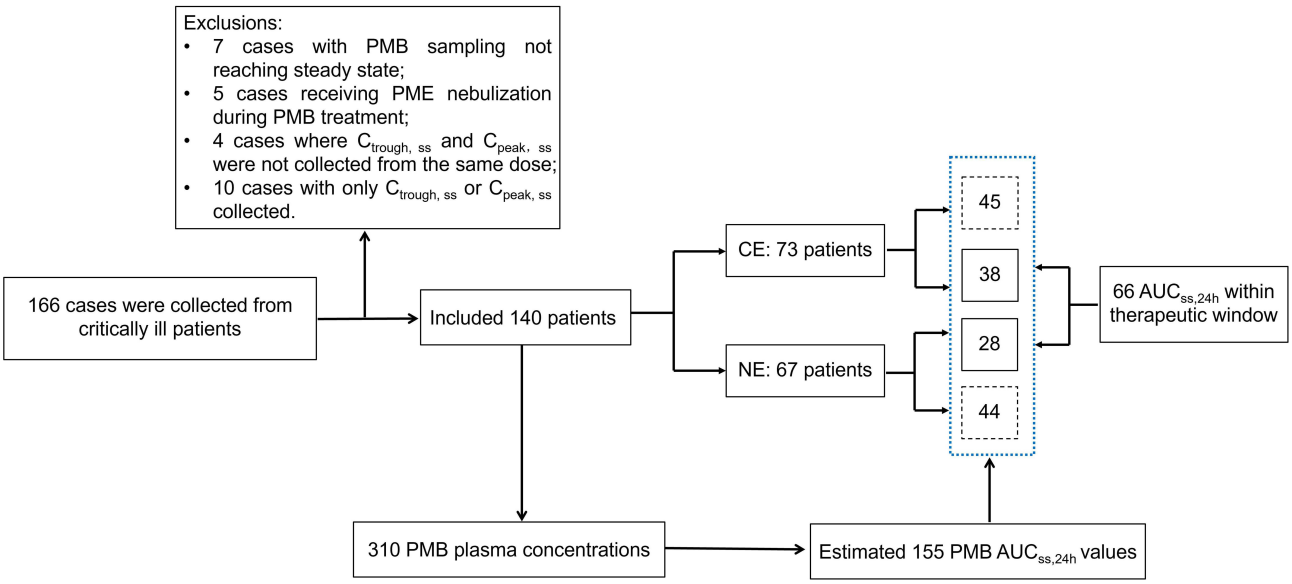

Figure 1 Participant enrollment flow diagram detailing screening, exclusion, and final cohort allocation.

(CRPA, n=18). CRO comprised of CRAB (n=55), CRKP (n=40), and CRPA (n=11) in the NE group (n = 67). PMB MIC values in the CE group were ≤0.5 $mg{\cdot}L^{-1}$ (49/73, 67.12%), 1 $mg{\cdot}L^{-1}$ (13/73, 17.81%), and 2 $mg{\cdot}L^{-1}$ (11/73, 15.07%); in the NE group, values were ≤0.5 $mg{\cdot}L^{-1}$ (47/67, 70.15%), 1 $mg{\cdot}L^{-1}$ (n=14, 20.90%), 2 $mg{\cdot}L^{-1}$ (n=4, 5.97%), 4 $mg{\cdot}L^{-1}$ (n=2, 2.99%), and 16 $mg{\cdot}L^{-1}$ (n=4, 5.97%) (P=0.046). When MIC exceeded 2 $mg{\cdot}L^{-1}$, NE occurred in all patients regardless of pathogen type. Among patients with an MIC of 4 $mg{\cdot}L^{-1}$, the pathogens identified were CRPA (n=1) and CRAB (n=2); among those with an MIC of 16 $mg{\cdot}L^{-1}$, pathogens included CRPA (n=1), CRKP (n=3), and CRAB (n=2). Three patients had polymicrobial infections: two were infected with both CRAB and CRKP, and one with both CRAB and CRPA. CRAB predominated (n=4), followed by CRKP (n=3, all with an MIC of 16 $mg{\cdot}L^{-1}$). Notably, CRPA infections with an MIC of ≥4 $mg{\cdot}L^{-1}$ consistently led to treatment failure, underscoring the critical impact of antimicrobial resistance on clinical efficacy.

The mean PMB maintenance dose was 1.25 $mg{\cdot}kg^{-1}$. Median steady-state concentrations were: $C_{trough,ss}$ 1.70 $mg{\cdot}L^{-1}$, $C_{peak,ss}$ 5.26 $mg{\cdot}L^{-1}$, and $AUC_{ss,24h}$ was 79.92 $mg{\cdot}h{\cdot}L^{-1}$. β-lactams were the most frequently co-administered antibiotics (115/140, 82.14%). Significant differences (P<0.05) between the CE and NE groups were observed in terms of age, weight, APACHE II score, $AUC_{ss,24h}$, blood urea nitrogen (BUN), creatinine clearance (CrCL), estimated glomerular filtration rate (eGFR), alkaline phosphatase (ALP), albumin (ALB), white blood cell count (WBC), platelet count (PLT), neutrophil count (Neu), sepsis, multiple organ dysfunction syndrome (MODS), and MIC distribution. Detailed characteristics are shown in Table 1.

Factors Influencing $C_{trough,ss}$ and $C_{peak,ss}$

Univariate analysis identified significant determinants of PMB $C_{trough,ss}$ including sepsis, fibrinogen, procalcitonin (PCT), Neu, ALP, alanine aminotransferase (ALT), eGFR, CrCL, SCr, BUN, age, and sex (P<0.05; Figure 2A). Subsequently, multivariate linear regression (Table 2) established two independent predictors. CrCL demonstrated an inverse association with $C_{trough,ss}$ (β = −0.40, 95% CI: −0.013 to −0.006; P<0.001), whereas sepsis was associated with significantly lower concentrations (β = −0.32, 95% CI: −1.36 to −0.53; P<0.001).

For $C_{peak,ss}$ univariate analysis revealed significant determinants, including the APACHE II score, sepsis, MODS, CRRT, fibrinogen, interleukin-6 (IL-6), haematocrit (HCT), haemoglobin (HGB), total bilirubin (TBIL), total protein, and daily maintenance dose (mg/kg) (P<0.05; Figure 2B). In the corresponding multivariate model (Table 3), maintenance dose exhibited the strongest positive association (β = 0.35, 95% CI: 1.84–4.30; P<0.001), whereas sepsis independently predicted reduced concentrations (β = −0.21, 95% CI: −1.92 to −0.31; P=0.007). Additionally, higher HGB levels were

Table 1 Characteristics of the Study Cohort: Demographic and Laboratory Parameters (n=140)

Characteristic	Overall (n=140)	Clinical Effectiveness (n=73)	Non-Effectiveness (n=67)	P-value
Age, years	60 (51–75)	58 (47–69)	64.65 ± 20.75	0.01
Sex				0.69
Male	111 (79.29%)	57 (78.08%)	54 (80.60%)	
Female	29 (20.71%)	16 (21.92%)	13 (19.40%)	
Weight, kg	62 (56–74)	65 (60–75)	62.32 ± 11.62	0.03
APACHE II score	26.81 ± 10.04	24.07 ± 9.64	29.97 ± 9.62	<0.001
Primary diagnosis				
Severe infection	71 (50.71%)	30 (41.10%)	41 (61.19%)	
Malignancy	18 (12.86%)	8 (10.96%)	10 (14.93%)	
Major trauma	15 (10.71%)	9 (12.33%)	6 (8.96%)	
Acute cardiovascular event	15 (10.71%)	11 (15.07%)	4 (5.97%)	
Severe pancreatitis	12 (8.57%)	6 (8.22%)	6 (8.96%)	
Gastrointestinal bleeding	6 (4.29%)	6 (8.22%)	–	
Other	3 (2.14%)	3 (4.10%)	–	
Comorbidities				
CRRT	42 (30.00%)	18 (24.66%)	24 (35.82%)	0.15
AKI	35 (25.00%)	14 (19.18%)	21 (31.34%)	0.10
Nebulized administration	83 (59.29%)	41 (56.16%)	42 (62.69%)	0.43
Sepsis	75 (53.57%)	29 (39.73%)	46 (68.66%)	<0.001
MODS	47 (33.57%)	15 (20.55%)	32 (47.76%)	<0.001
ARDS	28 (20.00%)	13 (17.81%)	15 (22.39%)	0.50
Polymyxin B therapy				
Maintenance dose, $mg \cdot kg^{-1}$	1.25 ± 0.32	1.24 ± 0.31	1.27 ± 0.29	0.51
Treatment duration, days	11 (8–17)	11 (9–17)	12 (8–18)	0.43
$C_{trough,ss}$ $mg \cdot L^{-1}$	1.70 (0.77–2.84)	1.71 (0.89–3.04)	1.58 (0.67–2.73)	0.21
$C_{peak,ss}$ $mg \cdot L^{-1}$	5.26 (3.69–7.27)	5.82 (4.08–7.85)	5.25 ± 2.61	0.07
$AUC_{ss,24h}$ $mg \cdot h \cdot L^{-1}$	79.92 (55.92–126.48)	84.00 (63.12–133.92)	73.92 (49.44–115.20)	0.04
Concomitant antibiotics				
β-Lactams	115 (82.14%)	60 (82.19%)	55 (82.09%)	0.98
Glycopeptides	19 (13.57%)	10 (13.70%)	9 (13.43%)	0.99
Tigecycline	9 (6.43%)	4 (5.48%)	5 (7.46%)	0.74
Quinolones	6 (4.29%)	4 (5.48%)	2 (2.98%)	0.68
Tetracyclines	11 (7.86%)	8 (10.96%)	3 (4.48%)	0.20
Linezolid	13 (9.29%)	4 (5.48%)	9 (13.43%)	0.11
Aminoglycosides	7 (5.00%)	3 (4.11%)	4 (5.97%)	0.71
Fosfomycin	3 (2.14%)	2 (2.74%)	1 (1.49%)	0.99
Trimethoprim-sulfamethoxazole	2 (1.43%)	–	2 (2.98%)	
Laboratory parameters				
BUN, $mmol \cdot L^{-1}$	12.18 (8.06–19.34)	9.96 (6.50–16.59)	15.83 (8.90–22.24)	<0.0001
SCr, $\mu mol \cdot L^{-1}$	79.70 (51.60–158.90)	77.80 (51.60–127.10)	87.15 (58.01–178.95)	0.08
CrCL, $mL \cdot min^{-1}$	80.60 (54.20–80.60)	88.98 (46.15–131.65)	50.20 (31.98–104.25)	0.002
eGFR, $mL \cdot min^{-1} \cdot 1.73m^{-2}$	80.74 (39.63–129.71)	90.28 (48.05–134.66)	73.60 (31.44–115.42)	0.01
ALT, $IU \cdot L^{-1}$	32.7 (15.7–65.2)	41.50 (17.00–66.40)	28.90 (12.78–56.73)	0.14
AST, $IU \cdot L^{-1}$	50.00 (31.90–85.30)	48.40 (30.50–77.80)	50.75 (32.40–87.68)	0.38
ALP, $IU \cdot L^{-1}$	122.00 (83.00–177.00)	115.10 (81.00–144.00)	147.00 (87.40–231.00)	0.01
GGT, $IU \cdot L^{-1}$	78.10 (40.00–152.30)	115.10 (81.00–144.00)	77.30 (38.40–148.60)	0.98
TP, $g \cdot L^{-1}$	33.60 (30.60–36.00)	61.52 ± 6.62	59.29 ± 9.33	0.08
ALB, $g \cdot L^{-1}$	17.40 (11.50–39.30)	34.10 ± 4.15	32.85 (29.43–35.08)	0.03
TBIL, $\mu mol \cdot L^{-1}$	17.40 (11.50–39.30)	16.40 (11.60–26.60)	21.28 (11.13–59.90)	0.06
HGB, $g \cdot L^{-1}$	83.00 (75.00–93.00)	85.20 ± 14.05	81.50 (74.00–90.50)	0.27

(*Continued*)

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Table 1 (Continued).

Characteristic	Overall (n=140)	Clinical Effectiveness (n=73)	Non-Effectiveness (n=67)	P-value
WBC, $\times10^9\cdot L^{-1}$	9.93 (6.54–14.04)	8.48 (5.90–11.50)	11.62 (8.81–16.39)	<0.0001
PLT, $\times10^9\cdot L^{-1}$	171.00 (84.00–268.00)	200.00 (113.00–311.00)	144.50 (55.25–240.75)	0.007
HCT, %	25.50 ± 4.67	26.59 ± 4.48	24.85 (22.43–28.13)	0.19
Neu, $\times10^9\cdot L^{-1}$	7.81 (5.15–11.07)	6.90 (4.27–9.67)	9.33 (6.44–14.07)	<0.0001
IL-6, $ng\cdot L^{-1}$	58.54 (24.16–141.40)	52.32 (20.98–103.50)	121.50 (50.20–246.30)	0.01
INR	1.17 (1.07–1.31)	1.14 (1.05–1.23)	1.22 (1.09–1.38)	0.004
APTT, s	33.60 (29.50–41.80)	31.90 (28.30–36.70)	38.45 (32.48–48.25)	<0.0001
TT, s	17.80 (16.70–20.60)	17.70 (16.70–19.50)	18.15 (16.70–21.18)	0.19
Fib, $g\cdot L^{-1}$	3.86 (2.67–5.10)	3.88 (2.73–5.07)	3.82 (2.62–5.10)	0.98

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; CRRT, Continuous renal replacement therapy; AKI, Acute kidney injury; MODS, Multiple organ dysfunction syndrome; ARDS, Acute respiratory distress syndrome; $C_{trough,ss}$, Steady-state trough concentration; $C_{peak,ss}$, Steady-state peak concentration; $AUC_{ss,24h}$, Area under the concentration-time curve over 24 hours at steady state; BUN, Blood urea nitrogen; SCr, Serum creatinine; CrCL, Creatinine clearance (calculated by Cockcroft-Gault formula); eGFR, Estimated glomerular filtration rate; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; ALP, Alkaline phosphatase; GGT, Gamma-Glutamyl Transferase; TP, Total protein; ALB, Albumin; TBIL, Total bilirubin; HGB, Hemoglobin; WBC, White blood cell count; PLT, Platelet count; HCT, Hematocrit; Neu, Neutrophil count; IL-6, Interleukin-6; INR, International normalized ratio; APTT, Activated partial thromboplastin time; TT, Thrombin Time; Fib, Fibrinogen; CE, Clinical effectiveness group (n=73); NE, Non-effectiveness group (n=67).

significantly associated with increased exposure (β = 0.20, 95% CI: 0.012–0.061; P=0.004), while elevated APACHE II scores were inversely correlated with $C_{peak,ss}$ (β = −0.19, 95% CI: −0.091 − −0.011; P=0.013).

Association Between PMB $AUC_{ss,24h}$ and Clinical Efficacy

Univariate analysis identified significant associations with clinical efficacy (P<0.05), including APACHE II score, sepsis, MODS, APTT, IL-6, Neu, WBC, TBIL, ALP, eGFR, CrCL, BUN, $AUC_{ss,24h}$, body weight, and age (Figure 3). Multivariate

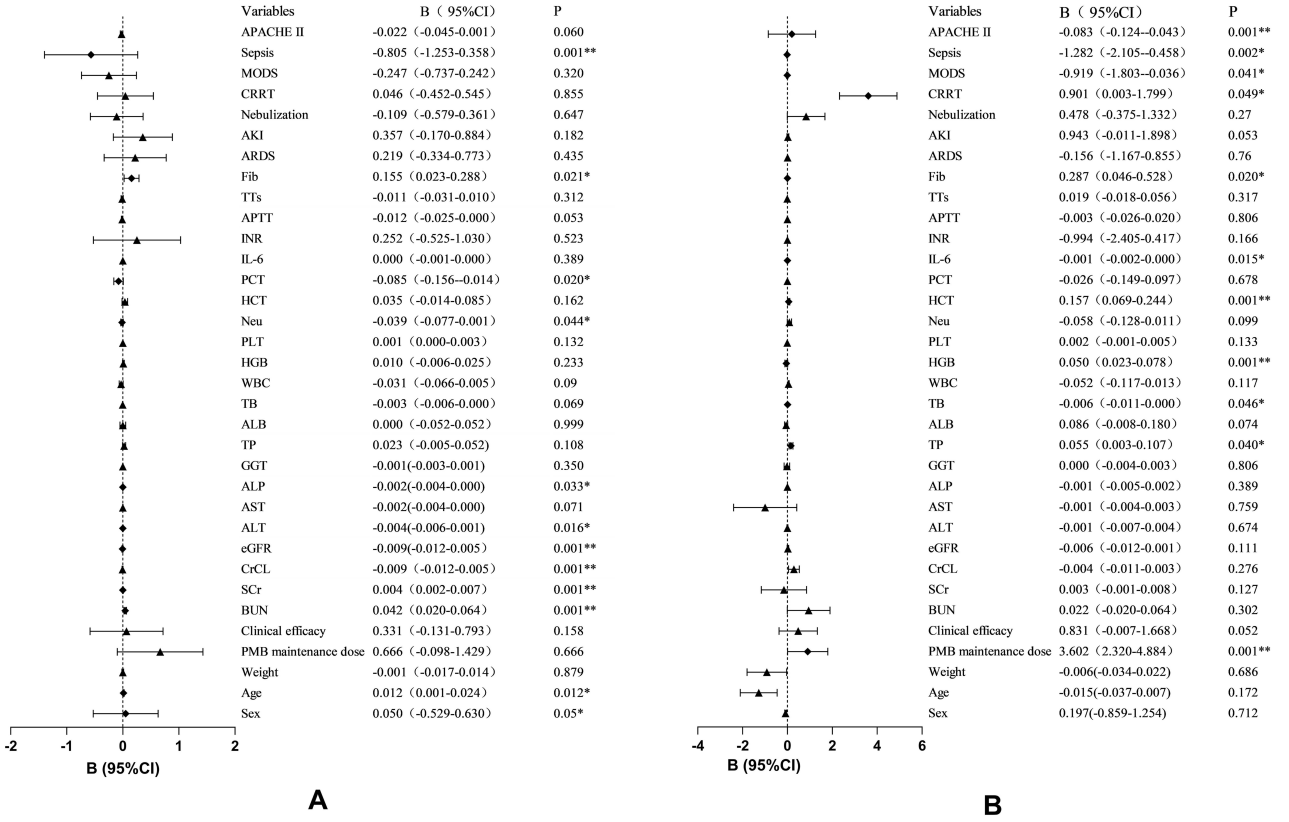

Figure 2 Univariate regression analysis of $C_{trough,ss}$ (**A**) and $C_{peak,ss}$ (**B**) determinants. *P<0.05; **P<0.001.

Table 2 Multivariate Regression Analysis of Factors Influencing $C_{trough,ss}$

Determinant	β	B (95% CI)	P-value
CrCL	−0.40	−0.009 (−0.013 to −0.006)	<0.0001
Sepsis	−0.32	−0.95 (−1.36 to −0.53)	<0.0001
Constant		3.30 (8.76 to 124.64)	<0.0001

Abbreviation: CrCL, Creatinine clearance (calculated by Cockcroft-Gault formula).

Table 3 Multivariate Regression Analysis of Factors Influencing $C_{peak,ss}$

Determinant	β	B (95% CI)	P-value
PMB maintenance dose (mg/kg)	0.35	3.07 (1.84 to 4.30)	<0.001
Sepsis	−0.21	−1.12 (−1.92 to −0.31)	0.007
HGB, $g \cdot L^{-1}$	0.20	0.036 (0.012 to 0.061)	0.004
APACHE II score	−0.19	−0.051 (−0.091 to −0.011)	0.013

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; HGB, Hemoglobin.

logistic regression established six independent predictors (Table 4): $AUC_{ss,24h}$ target attainment demonstrated the strongest protective effect (OR=5.21, 95% CI:1.63–15.44; P=0.0009), with continuous $AUC_{ss,24h}$ exposure significantly enhancing treatment efficacy (OR=2.18, 95% CI:1.22–3.70; P=0.01). Conversely, sepsis (OR=0.31, 95% CI:0.14–0.69; P=0.006), elevated BUN level (OR=0.91), advanced age (OR=0.97), and increased ALP level (OR=0.99) were independent risk factors. Bootstrap internal validation confirmed the model stability, with all predictors exhibiting 95% confidence intervals, excluding zero (coefficient of variation <8%), which indicated statistically significant effects and robust reliability (Table 5).

Discussion

This study systematically identified the determinants of PMB $C_{trough,ss}/C_{peak,ss}$ thereby advancing our understanding of exposure variability. We further confirmed that the $AUC_{ss,24h}$ estimated using a simplified two-point (trough/peak) method correlated significantly with clinical efficacy (P<0.05). Compared with PPK modelling or trapezoidal methods requiring intensive sampling, this approach reduces the sampling burden while maintaining feasibility in critical care, highlighting its potential for optimizing PMB TDM.

Our study analyzed the independent factors influencing PMB $C_{trough,ss}$ including CrCL and sepsis, and $C_{peak,ss}$ including maintenance dose, sepsis, HGB, and APACHE II scores in critically ill patients. Significant interindividual variability existed in the renal clearance of PMB, with CrCL identified as a key covariate substantially influencing PMB pharmacokinetic parameters.[15,18–22] Based on these findings, CrCL may potentially influence $C_{trough,ss.}$ Sepsis was significantly associated with both $C_{trough,ss}$ and $C_{peak,ss}$ likely due to increased vascular permeability and downregulated drug-metabolizing enzymes in critically ill patients.[23,24] Notably, this study prospectively identified HGB as a novel determinant of $C_{peak,ss}$—beyond established factors (CrCL, maintenance dose, and APACHE II score[25–27]). Concomitant renal dysfunction such as a AKI may further decrease HGB levels and directly alter renal clearance,[28] consequently affecting PMB $C_{peak,ss.}$ Another possible mechanism we speculated that may involve electrostatic binding of PMB by HGB, expanding volume of distribution and reducing free drug fraction, this increased total plasma peak concentrations while potentially impairing antimicrobial activity,[29,30] an effect amplified by massive HGB release in critical illness. However, the specific relationship between HGB levels and PMB concentrations requires further elucidation.

Few studies have evaluated PMB efficacy determinants with direct plasma concentration measurements, which were critical for defining antibacterial activity.[31] Our data showed that age, $AUC_{ss,24h}$, $AUC_{ss,24h}$ target attainment (50–100 $mg \cdot h \cdot L^{-1}$), BUN, ALP, and sepsis independently influenced the outcomes. Higher $AUC_{ss,24h}$ and target attainment were correlated with favorable efficacy, while advanced age, elevated BUN/ALP, and sepsis were independent risk factors for poor outcomes.

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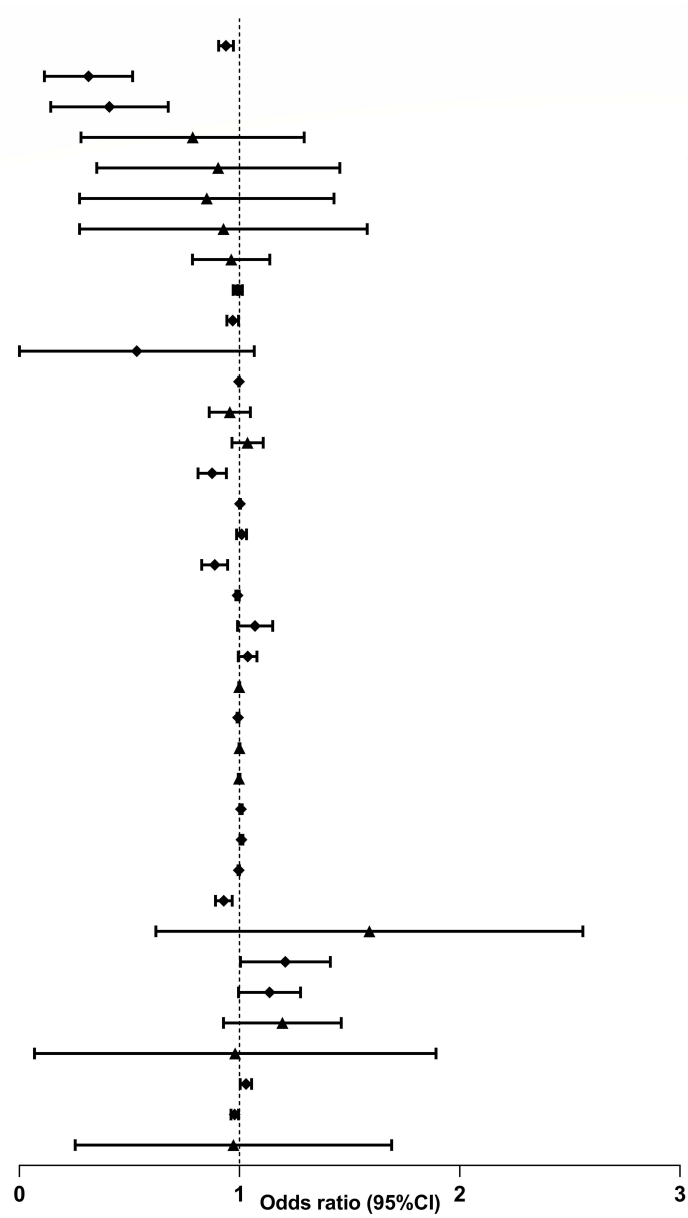

Variables	OR (95%CI)	P
APACHEII	0.938（0.905-0.972）	0.001**
Sepsis	0.272（0.139-0.532）	0.001**
MODS	0.351 (0.176-0.7）	0.003*
CRRT	0.678 (0.344-1.339）	0.263
Nebulization	0.791 (0.416-1.503）	0.474
AKI	0.721 (0.35-1.483）	0.374
ARDS	0.773 (0.364-1.643）	0.503
Fib	0.951 (0.792-1.143）	0.592
TTs	0.992 (0.971-1.013）	0.435
APTT	0.969 (0.943-0.996）	0.022*
INR	0.356 (0.112-1.133）	0.08
IL-6	0.998 (0.996-0.999）	0.01*
PCT	0.953 (0.864-1.051）	0.336
HCT	1.035 (0.966-1.108）	0.334
Neu	0.874 (0.813-0.941）	0.0001**
PLT	1 (1.004-0.052）	0.052
HGB	1.009 (0.987-1.032）	0.409
WBC	0.886 (0.829-0.947）	0.001**
TB	0.991 (0.984-0.999）	0.021*
ALB	1.069 (0.992-1.151）	0.081
TP	1.036 (0.995-1.08）	0.084
GGT	0.999 (0.996-1.001）	0.293
ALP	0.993 (0.989-0.998）	0.003*
AST	1 (0.997-1.002）	0.767
ALT	0.998 (0.994-1.002）	0.4
eGFR	1.006 (1.001-1.012）	0.025*
CrCL	1.008 (1.002-1.015）	0.005*
SCr	0.997 (0.993-1）	0.07
BUN	0.928 (0.891-967）	0.0001**
$AUC_{24h,ss}$ meets the target	1.393（0.734-2.643）	0.1
$AUC_{24h,ss}$	1.197 (1.01-1.418）	0.038*
$C_{peak,ss}$	1.13 (0.998-1.28）	0.054
$C_{trough,ss}$	1.175 (0.938-1.471）	0.16
PMB maintenance dose	0.698 (0.243-2）	0.503
Weight	1.029 (1.003-1.055）	0.031*
Age	0.978 (0.961-0.995）	0.01*
Sex	0.796 (0.359-1.763）	0.573

Figure 3 Univariate logistic regression analysis of factors influencing clinical efficacy. *P<0.05; **P<0.001.

The CE/NE groups differed significantly (P<0.05) in age, body weight, APACHE II score, $AUC_{ss,24h}$, renal function (BUN, CrCL, eGFR), inflammation (WBC, Neu, IL-6), coagulation (APTT, INR), sepsis, and MODS. In patients with renal insufficiency, reduced PMB clearance caused drug accumulation, aligning with its known PK profile.[32] Elevated failure rates among patients with sepsis, MODS, or heightened inflammatory markers were consistent with prior reports.[33–35]

We confirmed $AUC_{ss,24h}$ (estimated via steady-state peak-trough kinetics) as an independent predictor of clinical efficacy; a higher $AUC_{ss,24h}$ correlated with better outcomes, consistent with concentration-dependent activity of PMB. $AUC_{ss,24h}$ within the 50–100 $mg \cdot h \cdot L^{-1}$ window significantly improved efficacy (OR=5.21, 95% CI 1.63–15.44), validating its role as the primary PD parameter for PMB exposure assessment. Importantly, both $AUC_{ss,24h}$ and target attainment emerged as key efficacy determinants, reinforcing $fAUC_{ss,24h}$/MIC as a critical pharmacodynamic parameter.[13,14]

While our findings directly support implementing simplified PMB TDM in critically ill populations through dose adjustments maintaining two-point sampling-estimated $AUC_{ss,24h}$ within 50–100 $mg \cdot h \cdot L^{-1}$—a pragmatic strategy for resource-limited

Table 4 Predictors of Clinical Efficacy in Multivariate Logistic Regression Analysis

Predictor	β	OR (95% CI)	P-value
Age (per year)	−0.028	0.97 (0.94–0.99)	0.008
$AUC_{ss,24h}$	0.38	2.18 (1.22–3.70)	0.01
BUN,mmol·L^{-1}	−0.089	0.91 (0.87–0.95)	<0.001
ALP,IU·L^{-1}	−0.0087	0.99 (0.98–0.999)	0.0016
Sepsis	−1.18	0.31 (0.14–0.69)	0.006
$AUC_{ss,24h}$ Target Attainment	1.56	5.21 (1.63–15.44)	0.0009
Constant	3.00	33.05 (8.76–124.64)	0.002

Abbreviations: $AUC_{ss,24h}$, Area under the concentration-time curve over 24 hours at steady state; BUN, Blood urea nitrogen; ALP, Alkaline phosphatase.

Table 5 Bootstrap Validation results of the Final Logistic Regression Model

Predictor	Original β	SE	95% CI Lower	95% CI Upper
Age	−0.028	0.016	−0.062	−0.0007
$AUC_{ss,24h}$	0.380	0.160	0.160	0.670
BUN, mmol·L^{-1}	−0.089	0.027	−0.160	−0.052
ALP,IU·L^{-1}	−0.0087	0.0030	−0.0160	−0.0045
Sepsis	−1.180	0.510	−2.400	−0.330
$AUC_{ss,24h}$ Target Attainment	1.560	0.550	0.740	2.920
Constant	3.000	1.450	0.890	6.610

Abbreviations: $AUC_{ss,24h}$, Area under the concentration-time curve over 24 hours at steady state; BUN, Blood urea nitrogen; ALP, Alkaline phosphatase.

settings—it should be noted that our study did not establish a connection between AKI and $AUC_{ss,24h}$. In contrast, Yang et al[14] demonstrated that $AUC_{ss,24h}$ >100 mg·h·L^{-1} predicted AKI development and Stage 3 AKI patients exhibited higher $AUC_{ss,24h}$ than stage 1, establishing PMB pharmacokinetic exposure as a key modulator of AKI development. Nevertheless, guidelines[13] do not recommend dose adjustment based on renal function, which potentially compromises therapeutic efficacy. Elias et al[36] and Liu et al[27] both found that patients receiving higher-dose PMB exhibited reduced in-hospital mortality despite developing moderate-to-severe AKI, indicated that maintaining higher dosing regimens may improve clinical outcomes even in the presence of AKI. While prior studies have reported increased PMB clearance and reduced $AUC_{ss,24h}$ in CRRT patients,[37,38] our subgroup analysis showed no significant difference in $AUC_{ss,24h}$ target attainment between the CRRT and non-CRRT groups (34.0% vs 35.1%, P=0.896). This may reflect the high protein binding of PMB (≈90%) and its large molecular weight (1200 Da), resulting in low CRRT clearance (<15%),[39,40] which was insufficient to alter the dose requirements for target attainment. Including CRRT patients (35.3% of the cohort) enhanced the generalizability to real-world severely infected populations and validated the therapeutic window across different renal function statuses.

Our study also found that sepsis was an independent risk factor associated with clinical failure. Patients with sepsis were more susceptible to secondary infections because of immunocompromised. Meanwhile, sepsis was often accompanied by multiple organ dysfunction or failure, such as liver and kidney dysfunction, which influenced drug metabolism and excretion.[19]

Several limitations in the current study need to be considered. First of all, this study relied on data collected from a single center of critically ill patients, and there may be some bias. Secondly, AKI is an adverse reaction with a high incidence in PMB; however, our study failed to establish a connection between AKI and $AUC_{ss,24h}$. Thirdly, although this study enhanced the clinical representativeness by retaining CRRT patients (35.3%), the CRRT subgroup was difficult to analyze the subtle effects of different filtration patterns on PMB clearance. Lastly, our analysis focused on total plasma PMB concentrations, which may obscure exposure-response relationships due to variable protein binding rates in critically ill patients.

Conclusion

In summary, we identified key determinants of PMB $C_{trough,ss}$ and $C_{peak,ss}$ and prospectively established HGB as a novel predictor of $C_{peak,ss}$, distinct from known covariates. Also, this study reported for the first time that the association between $AUC_{ss,24h}$ estimated via two-point sampling and clinical efficacy in critically ill adults. Optimizing PMB dosing by adjusting $AUC_{ss,24h}$ to maintain levels within the target range (50–100 $mg \cdot h \cdot L^{-1}$) ensures therapeutic exposure. This provides a simplified, actionable approach to enhance efficacy in cases where $AUC_{ss,24h}$ is subtherapeutic. Furthermore, sepsis severity and renal function markers jointly modulate PMB exposure and clinical outcomes, necessitating their integration into dosing strategies for critically ill adults. Future research requires large-scale, multicenter validation trials to establish the general applicability of the two-point sampling method and further exploration of its pharmacokinetic extension value in special populations is also warranted.

Abbreviations

AKI, Acute kidney injury; GGT, Gamma-glutamyl transferase; ALB, Albumin; HCT, Hematocrit; ALT, Alanine Aminotransferase; HGB, Hemoglobin; APACHE II, Acute Physiology and Chronic Health Evaluation II; IL-6, Interleukin-6; APTT, Activated partial thromboplastin time; INR, International normalized ratio; ARDS, Acute respiratory distress syndrome; MIC, Minimum Inhibitory Concentration; AST Aspartate aminotransferase; MODS, Multiple organ dysfunction syndrome; $AUC_{ss,24h}$ Concentration-time curve at steady state over 24 hours; NE, Non-effectiveness; BUN, Blood urea nitrogen; Neu, Neutrophils; CE, Clinical effectiveness; PCT, Procalcitonin; CI, Confidence Interval; PK/PD, pharmacokinetics/pharmacodynamics; $C_{peak,ss}$ Steady-state peak concentration; PLT, Platelet count; CRAB, Carbapenem-resistant *Acinetobacter baumannii*; PMB, Polymyxin B; CrCL, Creatinine Clearance; PPK, Population Pharmacokinetics; CRRT, Continuous renal replacement therapy; SCr, Serum creatinine; CRO, Carbapenem-resistant organisms; TB, Total bilirubin; CRKP, Carbapenem-resistant *Klebsiella pneumoniae*; TDM, Therapeutic Drug Monitoring; CRPA, Carbapenem-resistant *Pseudomonas aeruginosa*; TP, Total protein; $C_{trough,\ ss}$ Steady-state trough concentration; TT, Thrombin time; eGFR, Estimated glomerular filtration rate; Fib, Fibrinogen; WBC, White Blood Cell; UPLC-MS/MS, Ultra-performance liquid chromatography-tandem mass spectrometry.

Data Accessibility

Study datasets contain confidential patient information and, thus, cannot be publicly shared by institutional policies. De-identified data are available from the corresponding author upon formal request, contingent on ethics approval and signed data use agreements.

Ethical Compliance

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki; the study protocol received approval from the Ethics Committee of the First Affiliated Hospital of the Army Medical University (Approval No. (A) KY2021064, on 28 July 2021). Written informed consent was obtained from all participants after detailed explanation of the study procedures, risks, and benefits; all personal identifiers were removed or pseudonymized to ensure participant confidentiality.

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Disclosure

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial or nonfinancial interests in the subject matter discussed in this manuscript.

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