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Population Pharmacokinetics of Tigecycline for Critically Ill Patients Undergoing Continuous Renal Replacement Therapy

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Background: Tigecycline is considered one of the last resorts for treating infections caused by multidrug-resistant bacteria. Continuous renal replacement therapy (CRRT) is widely used in critically ill patients, especially those with acute kidney injury or severe infections. However, pharmacokinetic data for tigecycline in patients receiving CRRT are limited.

Methods: This was a single-center prospective clinical study with intensive sampling that included critically ill patients who received tigecycline and CRRT. A population pharmacokinetic (PPK) model was developed and evaluated by goodness-of-fit plots, bootstrap analysis, visual predictive checks, and numerical predictive checks. Pharmacokinetic/pharmacodynamic target attainment and cumulative fraction of response analyses were performed to explore the potential need for dose adjustments of tigecycline in CRRT.

Results: In total, 21 patients with 167 concentrations were included. A two-compartment model adequately described the tigecycline concentration–time points, but no covariates were found to adequately explain the viability in the pharmacokinetic parameters of tigecycline. The typical values of CL, Q, V1 and V2 were 4.42 L/h, 34.8 L/h, 30.9 L and 98.7 L, respectively. For most infections, the standard regimen of 50 mg/12 h was deemed appropriate, expect for skin and soft skin tissue infections and community-acquired pneumonia caused by *Acinetobacter baumannii* and *Klebsiella pneumoniae*, which required a dosage regimen of 100 mg/12 h or higher.

Conclusion: A tigecycline PPK model describing critically ill patients undergoing CRRT was successfully developed. The optimized dosage regimens for various infections are recommended.

Keywords: tigecycline, population pharmacokinetics, critically ill, continuous renal replacement therapy

Introduction

Tigecycline is a glycylcycline antimicrobial drug that is approved by the FDA for treating complicated intra-abdominal infections (cIAIs), skin and soft skin tissue infections (cSSSIs) and community-acquired pneumonia (CAP).[1,2] Tigecycline exhibits broad-spectrum antimicrobial activity and demonstrates potent in vitro efficacy against multidrug-resistant (MDR) bacteria, including extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae, methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant Enterococci, and multidrug-resistant *Acinetobacter baumannii*.[1] Thus, tigecycline is an alternative agent for difficult-to-treat infections in intensive care units (ICUs), especially for MDR bacterial infections that resistant to other antibiotics.[3]

Continuous renal replacement therapy (CRRT), as one of the three supportive techniques in critical care, is extensively utilized for the management of critically ill patients, especially those with severe acute kidney injury (AKI), hemodynamic instability or the need to remove inflammatory mediators.[4,5] The use of CRRT may lead to increased antibiotic clearance and reduced exposure.[6–8] Accordingly, a higher antibiotic dosage may be necessary in patients during CRRT.[9]

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Although several small-sample studies have indicated that dose adjustment of tigecycline seems unnecessary during CRRT, there are still experts who believe that it is too early to draw this conclusion.[10–13] Hence, in this prospective study, we aimed to develop a PPK model of tigecycline in critically ill patients undergoing CRRT, identify the factors influencing its pharmacokinetics, and utilize the final model to optimized tigecycline dosage regimens for different bacterial infections.

Methods

Study Design and Patient Inclusion

The detailed study protocol was published in our previous study, which complied with the Declaration of Helsinki.[14] Briefly, we included critically ill patients who were treated with intermittent intravenous tigecycline and CRRT from July 2019 to July 2023. The patients' physio-pathological data, such as age, sex, weight (WT), body mass index (BMI), infection site, pathogen status, 24-hour urine volume (UV), CRRT information, plasma tigecycline concentration, and other related laboratory test results, were collected. The exclusion criteria were as follows: (1) were < 18 years old, (2) lacked essential data, and (3) did not receive CRRT continuously during tigecycline treatment. All participants signed the informed consent form.

PPK Model Development

PPK modeling was performed with NONMEM 7.5.0 and PDx-Pop 5.3.1, and the results were visualized by the R program. The one- and two-compartment models with first-order eliminations were fitted to the data. The residual variability was modeled with additive, proportional, and combined error models, and the interindividual variability was modeled exponentially. The significant covariates were screened in a stepwise regression with forward inclusion (ΔOFV>3.84, p <0.05) and backward elimination (ΔOFV>10.83, p<0.001). The final model and parameter estimates were evaluated by goodness-of-fit plots, bootstrap analysis, visual predictive checks (VPCs) and numerical predictive checks (NPCs). For bootstrap analysis, a total of 1000 resampling iterations with replacement were conducted on the original dataset to create a resampled dataset to assess the uncertainty and variability associated with the estimated statistical parameters. The resulting PK parameter estimates were then compared with the original PK estimates derived from the final model. For VPCs, 1000 simulation replications were conducted to evaluate the predictive performance and adequacy of the model by comparing the observed data with simulated predictions as well as examining the quantiles of the simulated data (eg, 5th, 50th, and 95th percentiles). Complementing VPCs, NPCs were conducted to provide a quantitative assessment of the model's predictive accuracy. More detailed modeling information can be found in our previous article.[14]

Monte Carlo Simulation and Dose Regimen Evaluation

The probability of target attainment (PTA) and cumulative fraction of response (CFR) analysis were performed using Monte Carlo simulation (1000 virtual patients per group). Three dose regimens were used for simulation: 50 mg, 100 mg and 150 mg every 12 hours. The PTAs corresponding to each MIC value were derived based on the PK/PD targets for different types of infections (AUC/MIC ≥17.9 for cSSSI, ≥12.8 for CAP, and ≥6.96 for cIAI).[15–18] The CFRs, defined as the expected population PTA for a dose regimen against the whole population of microorganisms, were calculated according to the following equation:[19,20]

$$CFR = \sum_{i=1}^{n} PTA_i \times F_i$$

where PTA_i is the probability of the target attainment value for the ith MIC level (n levels in total) and F_i is the percentage of bacteria counts at that MIC level.

The MICs were extracted from the European Committee on Antimicrobial Susceptibility Testing (EUCAST) MIC distribution website (https://mic.eucast.org/search). A PTA or CFR value ≥90% was considered the optimal dosing regimen.

Results

Patient Inclusion and Characteristics

In total, 21 patients with 167 tigecycline concentrations were included in the PPK model. Table 1 shows the main demographic characteristics of the included patients.

Table 1 Demographic Characteristics of the Included Patients

No.	SEX	AGE	WT (kg)	BMI	BUN (mmol/L)	SCr (μmol/L)	ALT (U/L)	AST (U/L)	ALP (U/L)	TP (g/L)	GGT (U/L)	TBIL (μmol/L)	ALB (g/L)	UV (mL)	CRRT Information		
															CRRT type	Intensity (mL/kg/h)	Anticoagulant
1	M	62	72.6	23.7	6.42	60	150	106	64	43.2	33	99.1	30.3	6950	CVVH	28.7	Heparin
2	M	86	75	24.5	26.7	391	45	11	67	54.3	57	47.4	30.5	350	CVVH	29.3	Heparin
3	M	65	65	23.9	11.7	158	16	8	90	48.6	82	19.7	28.2	850	CVVH	31.5	Heparin
4	M	87	95	31.0	23.4	159	22	55	81	43.7	20	99.5	27.7	1000	CVVH	21.6	None
5	F	64	56	23.0	8.08	60	9	22	127	66.6	58	13.3	30.6	2800	CVVH	37.1	Heparin
6	M	42	55	20.2	17.1	257	4	13	61	50.1	23	26.7	30.2	160	CVVH	39.1	Sodium citrate
7	M	87	42	16.4	36.2	276	5	22	184	54.7	35	11.8	27.7	0	CVVH	51.2	None
8	F	66	53.5	20.9	4.91	115	13	19	101	49.3	108	90.5	25.9	1020	CVVH	37.4	Heparin
9	M	82	60	20.3	10.4	334	7	17	98	50.9	21	11.4	32.5	300	CVVH	34.7	Heparin
10	M	66	75	26.0	15.4	183	20	23	98	51.2	140	25.6	23.1	200	CVVH	28.0	Heparin
11	F	78	50.5	23.4	6.65	63	77	40	114	53.3	181	16.9	35.7	1600	CVVH	41.6	None
12	F	86	47.4	22.2	9.38	88	27	36	131	44.9	109	19.3	25.4	150	CVVH	42.2	Heparin
13	M	62	70	24.8	18.5	108	45	68	116	42.7	27	113.9	26.5	25	CVVHDF	30.0	None
14	M	22	100	30.9	33.4	469	6	15	59	52	16	18.8	27	1150	CVVH	31.0	Heparin
15	M	77	70	22.9	7.40	47	40	51	106	49.2	38	96.8	26.6	60	CVVH	29.3	Sodium citrate
16	F	71	55	22.0	7.24	64	9	29	79	56.5	51	18.9	31.5	850	CVVH	37.3	Heparin
17	M	86	75	24.5	37.3	218	47	34	69	45	16	29.3	26.3	4500	CVVH	27.3	Heparin
18	M	31	70	27.3	3.64	51	13	24	62	50.8	23	47.8	23	4000	CVVH	29.3	Sodium citrate
19	M	73	77.5	25.6	13.2	274	3	21	82	62.1	29	14.3	28.1	50	CVVH	26.5	Sodium citrate
20	M	58	100	31.6	7.78	107	12	21	122	53.8	53	63.8	30.5	1950	CVVH	21.0	Sodium citrate
21	F	73	90	37.5	14.9	144	24	29	159	55.4	137	21.6	25.5	70	CVVH	23.9	Heparin

Abbreviations: M, male; F, female; WT, body weight; BMI, body mass index; BUN, blood urea nitrogen; SCr, serum creatinine; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; TP, total protein; GGT, γ-glutamyl transpeptidase; TBIL, total bilirubin; ALB, albumin; UV, 24-hour urine volume; CVVH, continuous veno-venous hemofiltration;CVVHDF, continuous veno-venous hemodiafiltration.

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PPK Model Development and Model Evaluation

The tigecycline concentration data could be well illustrated by a two-compartment model with first-order elimination (2425.331 and 2188.14 for the Akaike information criterion in one and two compartments, respectively). An exponential model and a proportional model were used to describe the interindividual variability and residual variability, respectively. The final PPK model and parameter estimates are shown in Table 2, and the key progression of covariate screening is shown in Table S1. We found that the inclusion of AST in the peripheral volume distribution led to a decrease in the OFV of 13.719. However, its inclusion had no impact on the PTA or CFR outcomes. Consequently, we ultimately decided to remove it from the final model.

The final model was evaluated by goodness-of-fit plots (Figure 1), VPCs (Figure 2), 1000 bootstrap analyses (Table 2) and NPCs (Table 3), which showed that the model had good robustness and acceptable predictive performance.

Simulation and Dosing Regimen Optimization

The PTAs and CFRs for the different dosages of tigecycline and the MIC distributions are shown in Figures 3 and 4 and Tables S2 and S3, respectively. The simulation results showed that for cSSSI, when the MIC was 1 mg/L, the PTAs of the standard and double-dose regimens (50 mg/12 h and 100 mg/12 h) were 58.2% and 98.1%, respectively, while for CAP, the PTA values were 85.0% and 99.9%, respectively. For cIAI, the PTAs were 82.4% and 99.7% at an MIC of 2 mg/L. The CFR results showed that all regimens exhibited a CFR > 90% for cIAI infection. In contrast, for cSSSI, the standard dosage regimens were 72.9% and 80.1% for *Acinetobacter baumannii* and *Klebsiella pneumoniae* infections, respectively. Similarly, for CAP, the CFR values at the 50 mg/12 h dose were 81.8% and 87.3% for these two pathogens, respectively.

Discussion

To our knowledge, this study was the only extensive sampled prospective study on the tigecycline pharmacokinetics exclusively in critically ill patients undergoing CRRT. Most notably, despite the use of an adequate base model, we were unable to identify any significant covariates influencing tigecycline pharmacokinetics. This surprising result highlights the complexity of drug deposition and excretion in critically ill patients receiving CRRT. Physicians and pharmacists worldwide could benefit from understanding the pharmacokinetics of tigecycline in these patients. Moreover, this study provided the optimized dosage regimens for common indications of tigecycline based on model simulation, which

Table 2 Distribution Characteristics of CRRT or Non-CRRT Final Model Estimation Parameters and Bootstrap Analysis

Parameter	Non-CRRT*	CRRT		
		Final Model	Bootstrap Analysis	
	Estimate [RSE (%)]	Estimate [RSE (%)]	Median Estimate [RSE (%)]	95% CI
CL (L/h)	3.09 (26.3)	4.22 (10.4)	4.27 (9.51)	3.47–5.07
V1 (L)	32.1 (8.38)	30.9 (15.9)	31.6 (16.7)	22.4–43.1
Q (L/h)	39.7 (5.79)	34.8 (8.94)	35.0 (9.25)	29.4–42.3
V2 (L)	113 (4.61)	98.7 (11.8)	98.5 (10.9)	78.4–120
Inter-individual variability				
ω_{CL} (%)	27.0 (15.0)	22.4 (31.6)	20.7 (33.0)	9.93–36.3
ω_{V1} (%)	72.5 (13.9)	55.2 (25.4)	52.7 (25.3)	28.4–81.0
Residual variability				
σ (%)	2.02 (13.8)	1.58 (15.7)	1.52 (15.0)	1.11–1.98

Notes: * Parameters of non-CRRT patients were derivate from Su et al, *Front Pharm*. 2024, 15: 1342954.
Abbreviations: CRRT, continuous renal replacement therapy; CL, typical value of apparent clearance; V1, central volume of distribution; Q, inter-compartmental clearance; V2, peripheral volume of distribution; ω_{CL}, fixed-effect parameter of CL; ω_{V1}, fixed-effect parameter of V1; σ, residual variability for proportional error; RSE, residual standard error; CI, confidence interval.

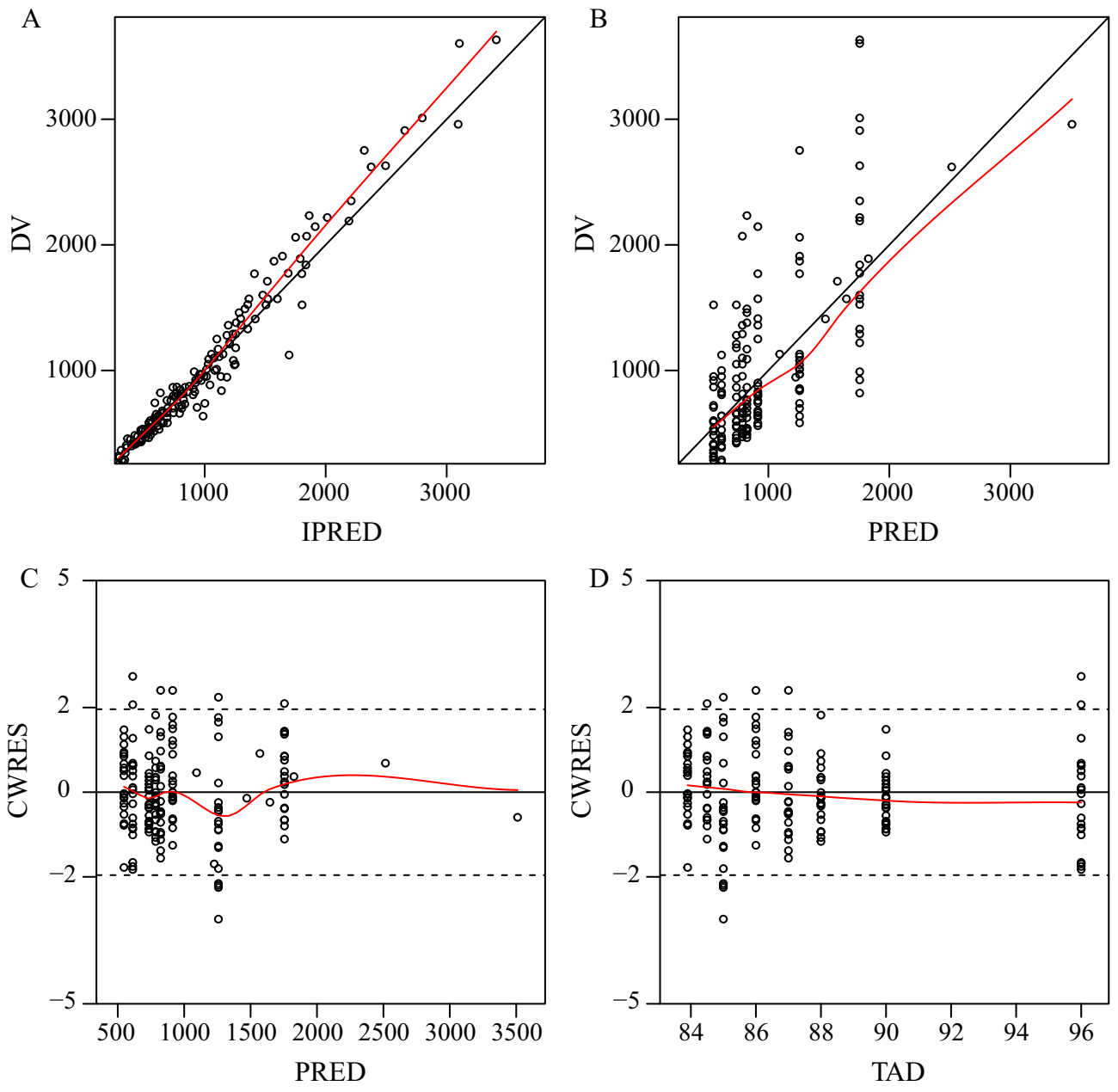

Figure 1 Goodness-of-fit plots for the final PPK model. (**A**) Observed tigecycline concentrations (DV) versus individual predictions (IPRED); (**B**) DV versus population predictions (PRED); (**C**) Conditional weighted residuals (CWRES) versus PRED; (**D**) CWRES versus time after dose (TAD).

emphasized the need for individualized dosing strategies, the importance of therapeutic drug monitoring, and the necessity for further research to enhance clinical outcomes.

Currently, data on the pharmacokinetics of tigecycline during CRRT are insufficient. To the best of our knowledge, only two population pharmacokinetic studies have been conducted in patients undergoing CRRT with tigecycline.[12,21] A population pharmacokinetics study on critically ill patients with IAIs conducted by Broeker incorporated bilirubin as a significant covariate for clearance.[12] However, only 11 patients were enrolled in this study, and 6 of whom had liver failure, cirrhosis, or liver transplantation. Conversely, another study on the population pharmacokinetics of high-dose tigecycline in sepsis or septic shock patients did not identify any significant covariates, which included 31 patients who underwent CRRT and 6 patients who did not underwent CRRT.[21] In our study, the various infections enrolled, aligning more closely with clinical characteristics.

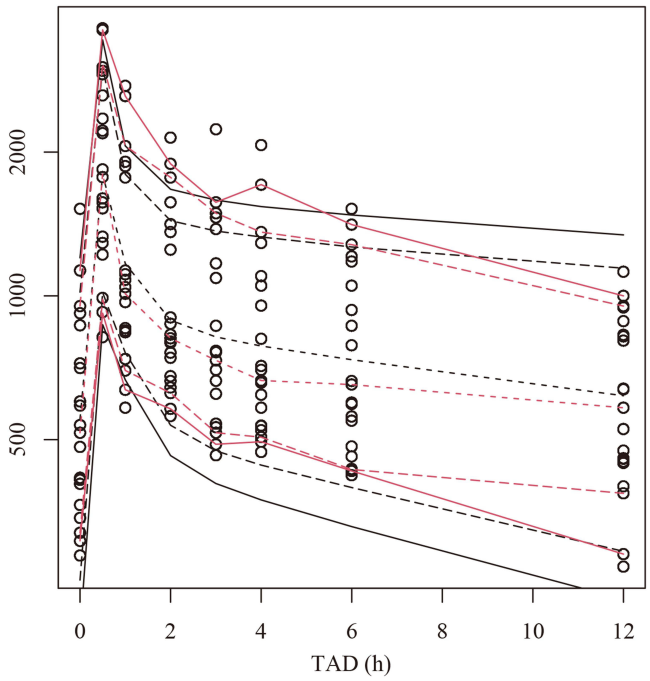

Figure 2 Visual predictive check (VPC) plots for the plasma tigecycline concentration. The Y-axis is the logarithm of the concentration. The open circles represent the observed concentrations. The hollow circles represent the observations. Observed (red lines) and predicted (black lines) 5th, 10th, 50th, 90th and 95th percentiles.

The typical PK parameter value of clearance, intercompartment clearance, central and peripheral volumes of distribution (4.22 L/h, 34.8 L/h, 30.9 L and 98.7 L, respectively) observed in our cohort of patients undergoing CRRT was similar with the previously reported value (3.09 L/h, 39.7 L/h, 32.1 L and 113 L, respectively) in critically ill non-CRRT patients from our published study.[14] However, these values significantly differ from those reported in other studies, such as Broeker's findings of approximately 18.3 L/h, 56.4 L/h, 58.7 L and 154 L for relevant tigecycline pharmacokinetic parameters in CRRT patients.[12] This observed discrepancy may be attributed to the inclusion of different patient populations, distinct pathophysiological conditions among patients, and variations in CRRT patterns. These findings indicate the substantial variability of tigecycline in CRRT patients and emphasize the important role of TDM for tigecycline in this specific population. In this study, we evaluated multiple potential covariates and observed that the AST could significantly affect the distribution of peripheral volumes. However, subsequent analysis revealed that changes in AST had minimal impact on the PTA and CFR, indicating that the changes in AST might be statistically significant but not clinically significant. Therefore, we decided to exclude this covariate from the final model. In addition, the pharmacokinetic parameters of tigecycline may also be affected by the specific setting of CRRT.[11] A prospective study demonstrated that the type of CRRT had different effects on

Table 3 The Numerical Predictive Check (NPC) of the Final Population Pharmacokinetic Model

PI	Points Below PI (Count)	Points Below PI (%)	95% CI (%)	Points Above PI (Count)	Points Above PI (%)	95% CI (%)
0%	101	60.5	32.3–66.5	66	39.5	33.5–67.7
20%	86	51.5	23.4–56.9	52	31.1	24.0–55.7
40%	58	34.7	14.4–46.7	50	29.9	15.6–44.9
50%	47	28.1	10.8–40.1	43	25.7	11.4–38.9
60%	37	22.2	7.19–34.1	39	23.4	7.78–32.3
80%	9	5.39	1.80–20.4	28	16.8	1.80–19.8
90%	3	1.80	0–12.6	16	9.58	0–13.2
95%	1	0.60	0–8.38	10	5.99	0–8.98

Abbreviations: PI, prediction interval; CI, confidence interval.

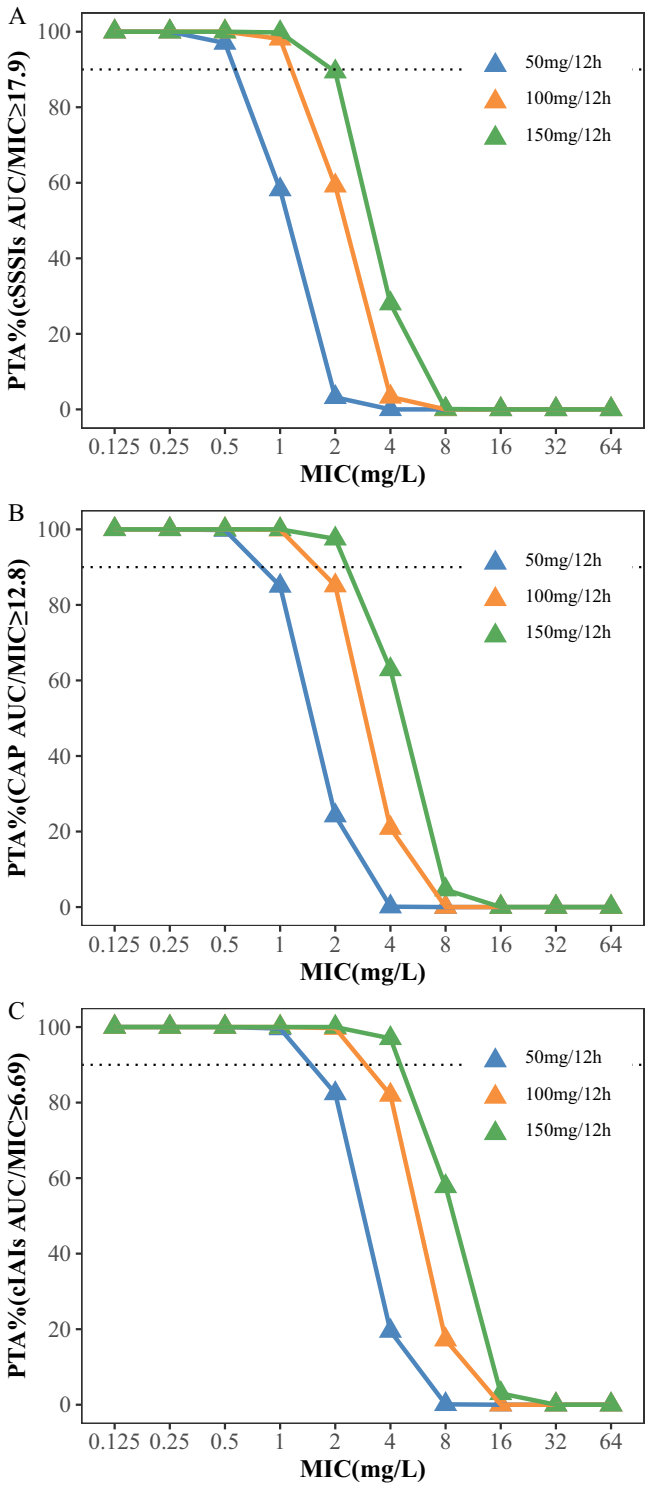

Figure 3 Probability of target attainment (PTA) for different dosage regimens of tigecycline for PK/PD targets with AUC/MIC ≥ 17.9 (**A**), 12.8 (**B**) and 6.96 (**C**). The dashed lines indicate a PTA of 90%.

tigecycline clearance, with CL of 2.71 L/h for CVVHDF and 1.69 L/h for CVVHD.[12] This discrepancy may arise from the differing saturation coefficients of tigecycline in the two modes of CRRT. Broeker et al determined that CVVHD exhibited an average saturation coefficient of 0.79, while CVVHDF demonstrated a higher average saturation coefficient of 0.90.[12] Despite these findings, they still believed that the tigecycline dose would not require adjustment during CRRT due to a total

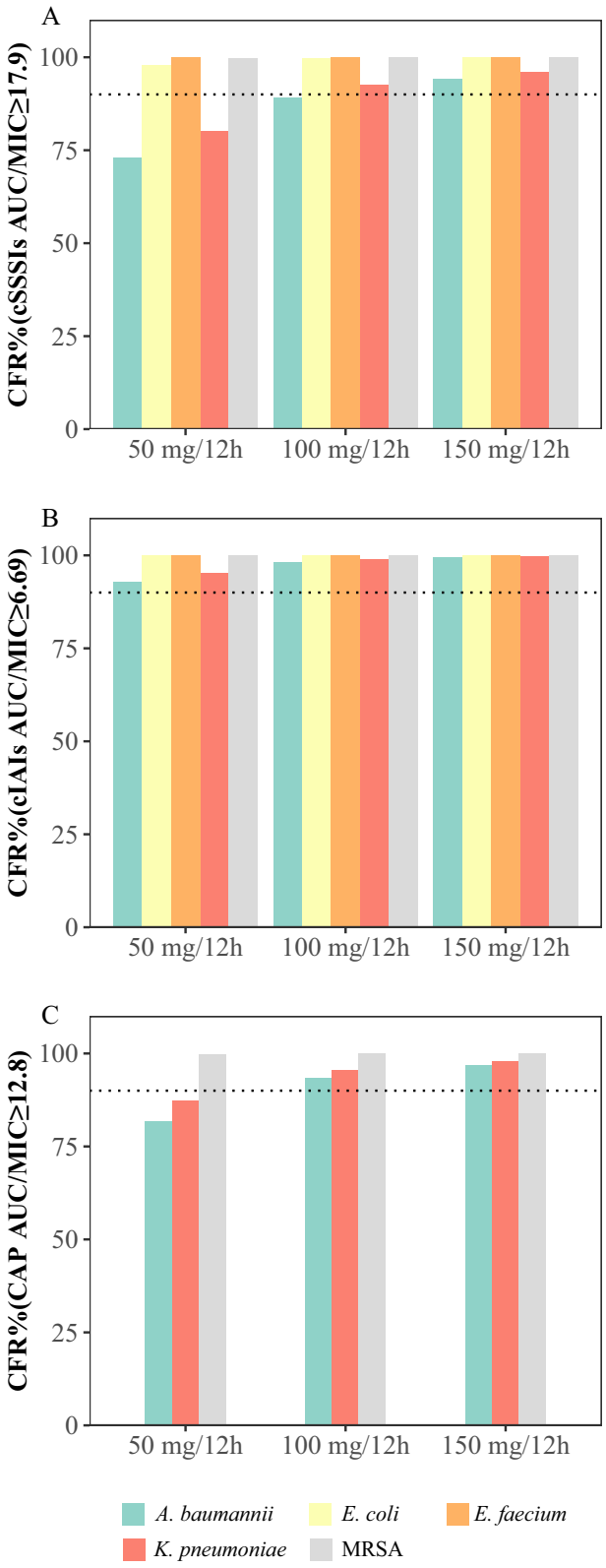

Figure 4 Cumulative fraction of response (CFR) for different dosage regimens of tigecycline for PK/PD targets with AUC/MIC ≥ 17.9 (**A**), 12.8 (**B**) and 6.96 (**C**). The MICs were determined based on the European Committee on Antimicrobial Susceptibility Testing (EUCAST) MIC distribution website. The dashed lines indicate a PTA of 90%.
Abbreviations: *A. baumannii, Acinetobacter baumannii; E. faecium, Enterococcus faecium; E. coli, Escherichia coli; K. pneumoniae, Klebsiella pneumoniae*; MRSA, methicillin-resistant *Staphylococcus aureus*.

clearance of 18.3 L/h. However, this result was derived from a small population (3 patients with CVVHDF and 8 patients with CVVHD). Moreover, the adsorption rate of tigecycline varies across different membranes. Tigecycline could be significantly adsorbed on polyethyleneimine-treated polyacrylonitrile membranes (over 90% of the administered dose), while it was less adsorbed on polysulfone filter membranes (up to 10%).[22] In addition, tigecycline exhibits atypical nonlinear PPB behavior and can be affected by divalent metal ions, such as regional citrate anticoagulation (RCA).[11,23] Thus, we also assessed the types and intensity of CRRT and the types of anticoagulants used. Regrettably, none of these factors had a significant impact on tigecycline pharmacokinetics. The insufficient sample size in our study may have contributed to this outcome, as only one individual underwent CVVHDF.

Our study therefore also assessed the probability of reaching the three PK/PD targets for various dose regimens. The findings revealed that standard dosing may be sufficient for the majority of patients with infections. Conversely, for patients with SSSIs or CAP caused by *Acinetobacter baumannii* and *Klebsiella pneumoniae*, the CFRs of the recommended dose regimens were less than 90%, necessitating higher tigecycline doses, such as 100 mg/12 h, or other available therapies to achieve optimal therapeutic efficacy.[24–26] High-dose tigecycline therapy has been demonstrated to reduce all-cause mortality and improve microbial and clinical efficiency.[27] Compared to monotherapy, tigecycline combination therapy has more advantages and may be a better choice for advanced-aged or severely ill patients.[28,29]

This study has several limitations. This model lacks external validation. The parameter settings for CRRT are not comprehensively recorded, making it challenging to accurately assess the actual intensity of CRRT. Consequently, this complicates the evaluation of how CRRT intensity influences the pharmacokinetics of tigecycline. Patients received CVVHDF was limited, and the impact of CRRT modality needs further data. Additionally, the most available data were derived from small cohorts, and it is imperative to conduct large-sample and well-designed randomized studies to ascertain the impact of the CRRT setting on the pharmacokinetics of tigecycline.

Conclusions

This single-center prospective study provided valuable population pharmacokinetic evidence for tigecycline in critically ill patients receiving CRRT. The pharmacokinetics of tigecycline in this population were well described by a two-compartment model. A dosage regimen of 50 mg every 12 h was suitable for most infected patients, while 100 mg every 12 h or higher dosage was needed for CAP and cSSSI caused by *Acinetobacter baumannii* and *Klebsiella pneumoniae*.

Data Sharing Statement

The data are contained within the article or supplementary material. Further requirements can be requested from the corresponding author.

Institutional Review Board Statement

The study was approved by the ethics committee of Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University (reference number KEYAN20190108-9) and complied with the Declaration of Helsinki.

Informed Consent Statement

Written informed consent was obtained from the patient or his/her representative before enrollment.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically 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.

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Disclosure

The authors report no conflicts of interest in this work.

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