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ORIGINAL ARTICLE

Population pharmacokinetics and exposure-response analysis of tigecycline in patients with hospital-acquired pneumonia

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Background: Tigecycline has been widely used to treat hospital-acquired pneumonia (HAP) off-label since it is effective against a wide range of multidrug-resistant bacteria. However, no recommended dosage for this indication has been evaluated, resulting in possible inadequate treatment.

Aims: The aims of this study are to establish the population pharmacokinetic (PPK) model of tigecycline in Chinese patients with HAP, as well as to evaluate the exposure-response relationship for the treatment of HAP with multidrug-resistant gram-negative bacteria.

Methods: A PPK analysis of tigecycline was conducted on pooled data from 328 blood samples obtained from 89 patients with HAP. Tigecycline plasma concentrations were measured by a two-dimensional liquid chromatographic system and the data were analysed using Phoenix NLMETM software. Exposure-response analyses for efficacy were performed based on the data from 79 HAP patients with multidrug-resistant gram-negative infections. Classification and regression tree and logistic regression analyses were employed to identify which pharmacokinetic-pharmacodynamic (PK-PD) indices and magnitudes were the significant predictors of tigecycline efficacy.

Results: A two-compartment model with zero-order absorption and first-order elimination adequately described the data. A larger body weight was associated with increased central volume of distribution and clearance ($P < .005$), and increased age, baseline creatinine concentration and aspertate aminotransferase were associated with decreased clearance ($P < .005$). The $AUC_{0\text{-}12h} \times V/MIC$ ratio, APACHEII score and combined *Pseudomonas aeruginosa* infection are the strong predictors for tigecycline clinical response. Classification and regression tree analyses indicated that the combination of APACHEII score < 24 and $AUC_{0\text{-}12h} \times V/MIC$ ratio ≥ 100 was associated with clinical success.

Conclusions: The proposed PPK model may serve as the basis for estimating tigecycline exposure for PK-PD analyses, and the PK-PD index and magnitude found in this study could be used for designing proper dosage regimens of tigecycline.

KEYWORDS
hospital-acquired pneumonia, multidrug-resistant, pharmacokinetic-pharmacodynamic, population pharmacokinetics, tigecycline

The authors confirm that the Principal Investigator for this paper is Yangang Zhou and that she had direct clinical responsibility for patients.

1 | INTRODUCTION

Hospital-acquired pneumonia (HAP) due to multidrug-resistant (MDR) gram-negative bacteria is an extreme challenge, as the MDR organisms have become resistant to most currently available antibiotics, resulting in limited treatment options.[1–3]

Tigecycline, the first antibiotic in the glycylcycline class of antimicrobial agents, has appealing in vitro activity against most MDR gram-negative bacteria.[4] Hence, although the Food and Drug Administration (FDA) only approved it for the treatment of complicated skin and skin-structure infections (cSSSI), complicated intra-abdominal infections (cIAI) and community-acquired pneumonia (CAP), tigecycline has been widely used off-label to treat HAP caused by MDR gram-negative bacteria since it became commercially available in 2010.[5] However, there is no recommended dosage for this off-label use, and the common dose of 100 mg IV once followed by 50 mg IV twice a day has been found to be insufficient to treat MDR bacteria infections based on studies.[6–8] For example, Gennaro et al found that high doses such as 100 mg every 12 hours were associated with better outcomes in the treatment of HAP due to MDR gram-negative bacteria compared with the common dose.[9] As a result, it is essential to optimize the tigecycline regimen to improve its efficacy when it is used for treating such infections.

Determination of the relationship between tigecycline in vivo exposure and clinical response is crucial for its dose adjustments and includes two critical steps: (a) development of a population pharmacokinetic (PPK) model to characterize the pharmacokinetic profile of tigecycline in the target patient population; (b) identification of the pharmacokinetic (PK)-pharmacodynamic (PD) index and magnitude associated with optimal clinical and microbiological outcomes.[10]

Several studies have established the PPK model of tigecycline, but with no consistent PK parameters, and the only study of Chinese critically ill patients reported quite low clearance of tigecycline compared with other studies.[11–14] Since this value was estimated based on a small population (10 patients), further studies were warranted to investigate the pharmacokinetic characteristics of tigecycline in Chinese patients and establish the model basis for PK-PD research.

Three previously published PK-PD studies assessed the exposure-response relationships of tigecycline efficacy in cSSSI, cIAI and CAP patients, and there was no investigation of the PK-PD character of tigecycline for the treatment of MDR gram-negative HAP. Moreover, although the investigators identified the area under the curve/minimal inhibitory concentration ($AUC_{0\text{-}24}$/MIC) thresholds of these infections using a classification and regression tree approach (CART), the $AUC_{0\text{-}24}$/MIC ratio was not a significant predictor of tigecycline clinical response in these studies.

The objectives of this study were therefore (a) to establish a PPK model for tigecycline in Chinese HAP patients, (b) to examine the association between patient characteristics and individual PK parameters, (c) to investigate the relationships between tigecycline exposure and microbiological and clinical responses, and (d) to determine the appropriate PK-PD indices and magnitude for predicting tigecycline efficacy in the treatment of MDR gram-negative HAP.

What is already known about this subject?

- Tigecycline has been widely used to treat hospital-acquired pneumonia off-label since it is considerably effective against a wide range of multidrug-resistant bacteria. However, no recommended dosage for this indication has been evaluated, and the common dose of 100 mg IV once followed by 50 mg IV twice a day has been found to be insufficient to treat MDR bacteria infections. Individualized tigecycline regimens are needed to improve its efficacy.

What this study adds

- A validated population pharmacokinetic model of tigecycline in Chinese patients with HAP was established. The exposure-response relationship of tigecycline in the treatment of HAP with multidrug-resistant gram-negative bacteria was evaluated and the threshold for the PK-PD index was found.

2 | METHODS

2.1 | Study design and subjects

This was a prospective study performed between January 2017 and December 2018 in the second Xiangya Hospital of Central South University (Changsha, China), a tertiary-care teaching hospital. The study was conducted in accordance with the Declaration of Helsinki and the protocol was approved by the Research and Ethics Committee of the second Xiangya Hospital of Central South University. All subjects provided signed informed consent.

All patients aged ≥18 years old who had been diagnosed with HAP and received tigecycline treatment for >3 days were included in the PPK study. Of these, patients who received tigecycline treatment for HAP involving MDR gram-negative bacteria were enrolled in the subsequent exposure-response analysis. HAP is defined as pneumonia that occurs 48 hours or more after admission, and pneumonia was diagnosed according to the American Thoracic Society Guidelines 2005.[15] Data including demographic characteristics, medical history, comorbidities, severity scores at admission (acute physiology and chronic health evaluation II [APACHE II] score), clinical and laboratory findings, and antibiotics in addition to tigecycline were extracted from the electronic patient medical records. Baseline microorganisms were collected from the respiration samples 5 days before to 3 days after the first dose of tigecycline, and all antimicrobial susceptibility testing was conducted by using a BD Phoenix-100 automated microbiology system (Diagnostic Systems, Sparks, MD, USA).[16]

2.2 | Drug dosage and blood samples

All patients started with a 100 mg IV loading dose, followed by 50 mg in 60-minute infusions every 12 hours for at least 3 days. Blood samples (3 mL) were collected before the ninth dose of tigecycline and at 0, 3 and 8 hours after the end of infusion. The serum was separated and then frozen at −70°C until assay.

2.3 | Efficacy outcome evaluation

Efficacy was assessed using both clinical and microbiological criteria at the test-of-cure (TOC) visit (1-3 days after the last dose of tigecycline). The clinical response was determined by comparing the patient's baseline signs and symptoms of infection with those after therapy. Clinical success was defined as improvement of all signs and symptoms present at study entry by the time of the TOC, improvement or no worsening in chest X-ray, and no appearance of new signs and symptoms. Failure was defined as the occurrence of any one or more of the following circumstances: a lack of response which required additional intervention and/or additional antibacterial therapy, initial recovery followed by deterioration before the TOC visit, or death within the tigecycline treatment due to pneumonia. The microbiological efficacy was defined as the eradication (documented or presumed) of the pretreatment pathogen(s) from the post-treatment respiratory track cultures. If the clinical response was classified as a success and no material was available for culture, the pretreatment pathogen(s) was presumed to be eradicated.

2.4 | Tigecycline determination

A 300 μL sample of plasma was mixed with 900 μL of a solution of 8% perchloric acid on a vortex mixer for 30 seconds. After centrifugation at 15000*g* at room temperature for 8 min, a 200 μL aliquot of the supernatant was injected into the analytical system.

The analytical measurements of plasma samples were performed using a validated two-dimensional liquid chromatographic system, which contains two parts: the first separation system (LC1) and second separation system (LC2). LC1 consisted of a chromatography pump (LC-20ATvp, Shimadzu, Kyoto, Japan), auto sampler device (SIL-20AC, 500-μL quantitative loop, Shimadzu, Kyoto, Japan) and LC1 column ASTON SNX5 (4.6 × 50 mm, 5 μm, ANAX, Changsha, Hunan, China). LC2 consisted of a low-pressure gradient chromatography pump with four flow paths (LC-20ATvp; Shimadzu), LC2 column ASTON SCB (4.6 × 250 mm, 5 μm, ANAX), UV detector (SPD-20Avp; Shimadzu), and workstation (Lab solution ver. 5.92; Shimadzu). The detailed chromatographic parameters of the analytical method are described in the **Supporting information**.

The method was validated in terms of its selectivity, accuracy, within- and between-run precision, recovery, linearity, sensitivity, and stability. The calibration curve equations was $Y = 80.694X - 1683.7$, ($r = 0.9999$) in the range of 49.68-2649.6 ng/mL, and the Low Limit of Detection (LLOD) of tigecycline was 35 ng/mL. The extraction recoveries were 93.1 ± 2.5% low quality control (QC), 95.7 ± 3.1% (middle QC), and 98.1 ± 2.4% (high QC). The intraday and interday accuracies ranged from 94.3% to 103.8%, and coefficients of variation (CVs) were between 1.0% and 8.3%. The detailed procedure of the method validation is described in the **Supporting information.**

2.5 | Population PK model and calculation of exposure and PK-PD index

Nonlinear mixed effect modelling was performed by using Phoenix NLME software (Version 8.1, Certara L.P. Princeton, NJ, USA) to estimate the population means and the variances of pharmacokinetic parameters, as well as to identify the factors influencing the parameters. The following estimated PK parameters were involved in this model: apparent volume of distribution for the central (V) and peripheral (V_2) compartments, central compartment clearance (CL) and intercompartmental clearance (CL_2). To determine the population PK parameters and estimate their variabilities, the first-order conditional estimation with extended least squares (FOCE-ELS) method was used. Different PK models (two- or three-compartment models) were evaluated based on the objective function value (OFV) and statistical significance was set at $P < .05$. Exponential models were used to count the interindividual variability (IIV) of the pharmacokinetic parameters, which were assumed to have normal distributions with a mean of 0 and variances ω^2. Residual variability was assessed by comparing the proportional, additive and combined error models.

The covariates considered for the modelling included age, gender, body weight (Wt) and levels of alanine aminotransferase (ALT), aspertate aminotransferase (AST), serum creatinine (Cr), total bilirubin (TBiL), direct bilirubin (DbiL) and albumin (ALB). A reduction in OFVs of >3.841 ($P < .05$) was considered to be statistically significant for the inclusion of one additional parameter in the forward inclusion steps and a decrease in OFV of >7.879 ($P < .005$) was considered to be statistically significant in the backward elimination steps. The validity of the population PK model was assessed by goodness-of-fit plots, including observed (OBS) *vs* individual predicted concentrations (IPRED), observed (OBS) *vs* population predicted concentrations (PRED), conditional weighted residuals (CWRES) *vs* independent variable (IVAR) and CWRES *vs* population predicted concentration (PRED), as well as CV in the estimated parameters.

The visual predictive check (VPC) and nonparametric bootstrap analysis were applied to evaluate the PK model. For VPC, 1000 data sets were simulated using the final model parameters, and the 90% confidence intervals of the 5th, 50th and 95th percentiles of the simulated concentrations were visually compared with the actual observed data. The results of the bootstrap analyses (median, 95% CI) were compared with the estimated values of the parameters obtained from the final model. A total of 1000 bootstrap pseudo-sample evaluations were performed.

Calculation of exposure and PK-PD index: $AUC_{0\text{-}12h}$, $AUC_{0\text{-}12h} \times V$ and the ratio of the $AUC_{0\text{-}12h}$, $AUC_{0\text{-}12h} \times V$ to the MIC

($AUC_{0\text{-}12h}$/MIC and $AUC_{0\text{-}12h}$ × V/MIC). The 12 hours area under the concentration-time curve ($AUC_{0\text{-}12h}$) at steady state was calculated according to Equation (1):

$$AUC_{0-12h} = dose/CL \quad (1)$$

where 'dose' is the dose of tigecycline (50 mg) and CL is the typical value of elimination generated from the population PK analysis. For those patients with more than one baseline pathogen, the $AUC_{0\text{-}12h}$/MIC and $AUC_{0\text{-}12h}$ × V/MIC ratio evaluations were based on the pathogen with the highest MIC value.

2.6 | PK-PD analysis for efficacy

Exposure-response analyses for efficacy involved the evaluation of clinical response (success *vs* failure) and microbiological response (eradication *vs* persistence). Exploratory analyses of clinical and microbiological responses were conducted to identify the relationships between these response and exposure measurements, patient demographic characteristics and comorbidities; univariable and multivariable logistic regression analyses with $P < .05$ were used to determine whether these variables were the statistically significant predictors of clinical or microbiological responses.

The threshold values for PK-PD parameters distinguishing patients with impressive differences in response were evaluated using classification and regression tree (CART) analysis.

The logistic regression was conducted by SPSS 20.0, and R 3.6.1 was utilized to perform the CART analysis.

3 | RESULTS

3.1 | Population pharmacokinetic parameters

The PPK model was developed based on 328 serum tigecycline concentrations obtained from 89 patients. Since tigecycline is mostly used in critically ill patients with MDR bacterial infection in China, all of the patients in this study came from medical or surgical intensive care units (ICU). Patient characteristics are summarized in Table 1. A two-compartment model with zero-order absorption and first-order elimination adequately describes the data, and a proportional model was selected for the residual variability.

After a stepwise screening procedure, Wt on V and CL, as well as age, Cr and AST on CL were identified as the significant covariates. The final models are expressed in Equations (2) and (3):

$$V(L) = 105.9 \times (Wt/60)^{2.235} \times \exp(\eta V) \quad (2)$$

$$CL(L/h) = 23.1 \times (age/61)^{(-0.388)} \times (Cr/73.4)^{(-0.296)} \times (AST/34.5)^{(-0.174)} \times (Wt/60)^{2.271} \times \exp(\eta CL) \quad (3)$$

TABLE 1 Characteristics of 89 patients included in the PPK model

Characterisic	Value[a]
Gender	
Male	55 (61.8%)
Female	34 (38.2%)
Age (year), median, range	61 (18-89)
Wt (kg), median, range	60 (35-80)
Cr (μmol/L), median, range	74.8(19.7-563.1)
CRRT, (no/yes) (number)	10/79
AST, U/L, median, range	34.5 (9.3-2626)
ALT, U/L, median, range	22.8 (1.2-874.1)
TBiL, μmol/L, median, range	11.2 (3.8-163.5)
DBiL, μmol/L, median, range	6.4 (1.7-130.7)
Albumin concentration, g/L, median, range	32.7 (20.3-54.5)
Clinical condition	
APACHEII score	15 (5-48)
Mechanical ventilation	53 (59.6%)
Comorbidities	
Stroke	27 (30.3%)
Chronic pulmonary disease	14 (15.7%)
Hypertension	13 (14.6%)
Diabetes mellitus	5 (5.6%)
Renal insufficiency	23 (25.8%)
Sepsis	14 (15.7%)
Trauma	6 (6.7%)
Malignance	8 (9.0%)
Multiple organ failure	6 (6.7%)
Combinational therapy (n = 79)	
Amikacin	4 (5.1%)
Polymycin B	3 (3.8%)
Meropenem	16 (20.3%)
Cefoperazone-sulbactam	56 (70.8%)

Abbreviations: ALT, alanine aminotransferase; AST, aspertate aminotransferase; Cr, serum creatinine; CRRT, continuous renal replacement therapy; DBiL, direct bilirubin; TBiL, total bilirubin; Wt, body weight.

[a]Categorical data are number (%) of subjects, continuous data are expressed as median (range).

The PK parameter estimates of the final model are listed in Table 2. The typical population CL, CL_2, V and V_2 values were 23.1 L/h, 31.9 L/h, 105.9 L and 124.9 L, respectively. The OFV of the final model decreased by 76.1 (3808.4 *vs* 3732.3), and the IIV of V and CL were reduced by 4.1% and 19.1%, respectively, as the significant covariates were taken into account.

Goodness-of-fit plots of the final model are presented in Figure 1. The individual and population predictions versus observed concentrations are relatively symmetrically distributed around the line of

TABLE 2 Parameter estimates of tigecycline from the final models

	Final model			Bootstrap	
Parameter	Estimate	CV (%)	95% CI	Median	95% CI
Pharmacokinetic parameters					
V	105.9	12.1	80.6-131.1	103.8	66.5-140.6
V_2	124.9	13.9	90.9-159.0	126.6	93.9-169.9
CL	23.1	4.93	20.8-25.3	23.0	20.5-25.4
CL_2	31.9	16.0	21.9-41.9	32.3	18.7-53
V-Wt	-0.174	−28.2	−0.270-−0.077	−0.180	−0.273-0.072
CL-AGE	2.235	30.4	0.898-3.571	2.220	0.65-4.016
CL-Wt	−0.388	−32.0	−0.633-−0.144	−0.399	−0.713-0.14
CL-Cr	−0.296	−19.4	−0.409-−0.183	−0.283	−0.403-0.167
CL-AST	2.271	14.0	1.644-2.899	2.236	1.434-3.117
Interindividual variability					
V	58.7	36.7			
CL	39.1	17.1			
Residual variability (%)					
σ_{prop}	27.8	5.8	24.6-30.9	27.2	22.1-32.6

Abbreviations: AGE, age; AST, aspertate aminotransferase; CI, confidence interval; Cr, serum creatinine; CV, coefficient of variation; σ_{prop}, standard deviation of proportional residual random error; Wt, body weight.

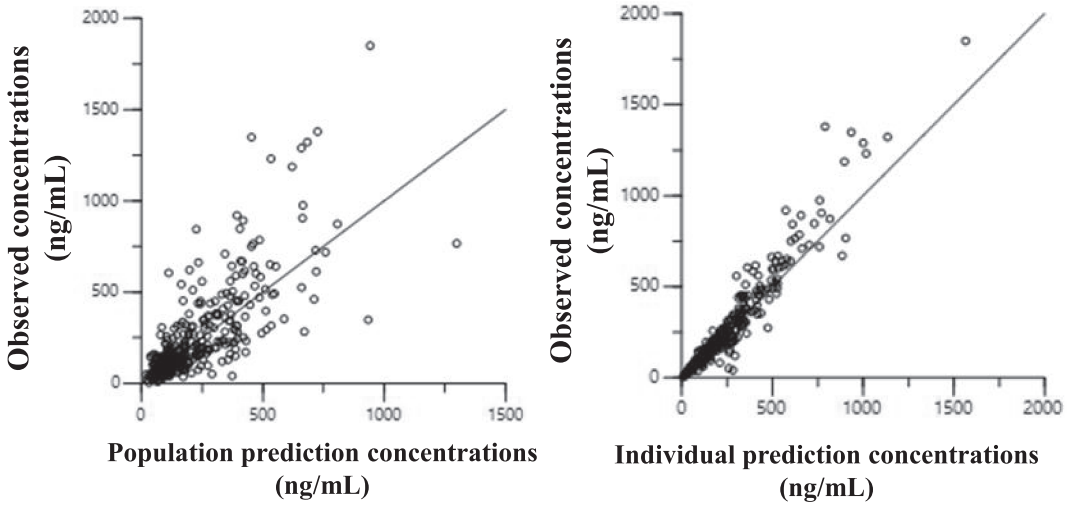

FIGURE 1 Observed concentrations versus population predicted concentrations (left) or individual predicted concentrations (right) in the final model. The solid line is diagonal

identity. The CWRES of predicted concentrations of the final model are more uniform and most of the variables are within the range of −2 to 2 (Figure 2). The VPC showed that the simulation-based 90% confidence intervals covered the corresponding 5th, 50th and 95th percentiles of the observed concentration, which indicated that the central tendency of the data was recaptured very well (Figure 3). The summary of parameter estimates from the 1000 bootstrap procedure is also presented in Table 2. No difference >5% in the parameter estimates was observed compared with the corresponding values in the final model, and the symmetric 95% CIs were also congruent with the 95% bootstrap percentile CIs.

3.2 | PK-PD analysis for efficacy

3.2.1 | Data

Among the 89 patients included in the PPK analysis, there were 83 patients with positive bacterial cultures that were evaluable for clinical and microbiological outcomes and had the covariates data required for estimating the pharmacokinetic parameters. Four of these were excluded because of short tigecycline treatment duration (<7 days), thus a total of 79 patients were included in the final exposure-response analysis.

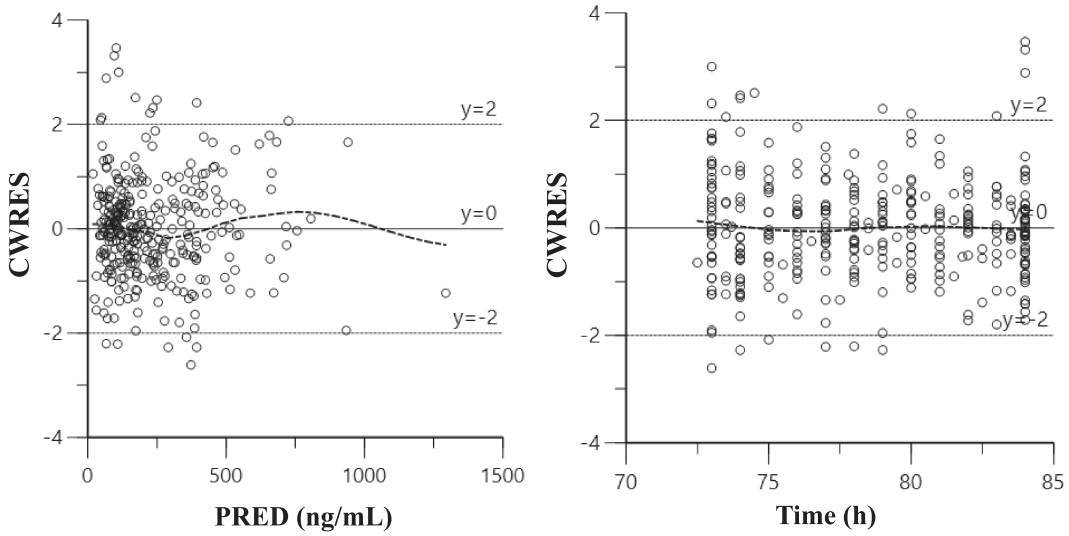

FIGURE 2 Conditional weighted residuals (CWRES) versus population predicted concentrations (PRED) (left) and time (right) in the final model

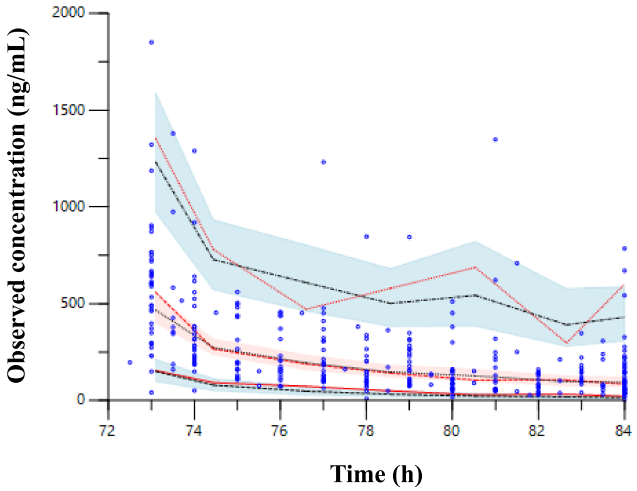

FIGURE 3 Visual predictive check (VPC) of the final PPK model. The red and black lines represent the 5th, 50th and 95th quantiles of the observed and predicted concentration, and the shaded area represents the simulation-based 90% confidence intervals

All these patients had positive sputum cultures for MDR *Acinetobacter baumannii* (MDRAB) or carbapenem-resistant Klebsiella (CRKP). Table 3 provides a summary of pathogens included in the PK-PD analyses. Monomicrobial infections occurred in 44.3% (35/79) of patients, 45.6% (36/79) had two pathogens and 10.1% (8/79) had three organisms. The mean $AUC_{0\text{-}12h}$/MIC and $AUC_{0\text{-}12h}$ × V/MIC ratios were 1.2 (SD, 0.68) and 123.8 (SD, 63.1), respectively.

3.2.2 | Clinical response

The clinical success rate was 51.9% (41/79), and the 30-day all-cause mortality was 24.1% (19/79). Univariate analysis indicated that the

TABLE 3 Baseline pathogens from sputum culture

Organisms	No. of observations	MIC range (mg/L)
MDRAB	55	1-4
CRKP	36	2-4
Pseudomonas aeruginosa	24	N/A
Stenotrophomonas maltophilia	6	0.25-2

CRKP, carbapenem-resistant Klebsiella; MDRAB, MDR *Acinetobacter baumannii*; N/A, not applicable.

$AUC_{0\text{-}12h}$ × V/MIC ratio, V, APACHEII score and combined *Pseudomonas aeruginosa* (PA) infection were the significant predictors for clinical response. When these variables were included in a multivariate logistic regression model, the independent predictors for clinical resolution were $AUC_{0\text{-}12h}$ × V/MIC ratio, APACHEII and combined PA infection (Table 4). Although $AUC_{0\text{-}12h}$/MIC ratio as a continuous variable was not a significant predictor of response, it was also assessed for threshold by using CART as it was a recommended index in the previous studies.

The $AUC_{0\text{-}12h}$/MIC threshold values of 0.75 and 1.5 for clinical resolution were identified using CART analysis (Figure 4A) in which the patients were divided into three groups. The $AUC_{0\text{-}12h}$/MIC ≥ 1.5 and $AUC_{0\text{-}12h}$/MIC < 0.75 groups were associated with clinical resolution, whereas the 0.75 < $AUC_{0\text{-}12h}$/MIC < 1.5 group indicated clinical failure. The results demonstrated that $AUC_{0\text{-}12h}$/MIC is not an appropriate predictor for clinical efficacy of tigecycline.

The $AUC_{0\text{-}12h}$ × V/MIC threshold value of 100 was found to be predictive of clinical resolution, and the accuracy of clinical resolution prediction was 79.7% (63/79), as shown in Figure 4B. The CART technique was also used to analyse the thresholds for all of the three significant predictors for clinical resolution: $AUC_{0\text{-}12h}$ × V/MIC ratio, APACHEII score and combined PA infection. The results showed that

TABLE 4 Univariate and multivariate logistic regression analysis for clinical response

	Univariate logistic regression				Multivariate logistic regression	
Variable	Success (n = 41)	Failure (n = 38)	OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
APACHEII score	12.8 (4.9)	21.3 (9.6)	0.84 (0.77-0.92)	<0.0001	0.74 (0.62-0.87)	<0.0001
Combined PA infection	6 (14.6%)	18 (47.4%)	5.25 (1.79-15.38)	0.002	14.31 (2.36-86.60)	0.004
$AUC_{0\text{-}12h} \times V/MIC$	150.9 (57.5)	94.5 (55.9)	1.02 (1.01-1.03)	<0.0001	1.04 (1.01-1.06)	0.001
V	139.0 (55.5)	88.1 (33.2)	1.03 (1.01-1.04)	<0.0001	1.01 (0.99-1.04)	0.199

Abbreviations: CI confidence interval; OR, odds ratio; PA, *Pseudomonas aeruginosa*.
[a]Categorical data are number (%) of subjects, continuous data are expressed as mean (standard deviation).

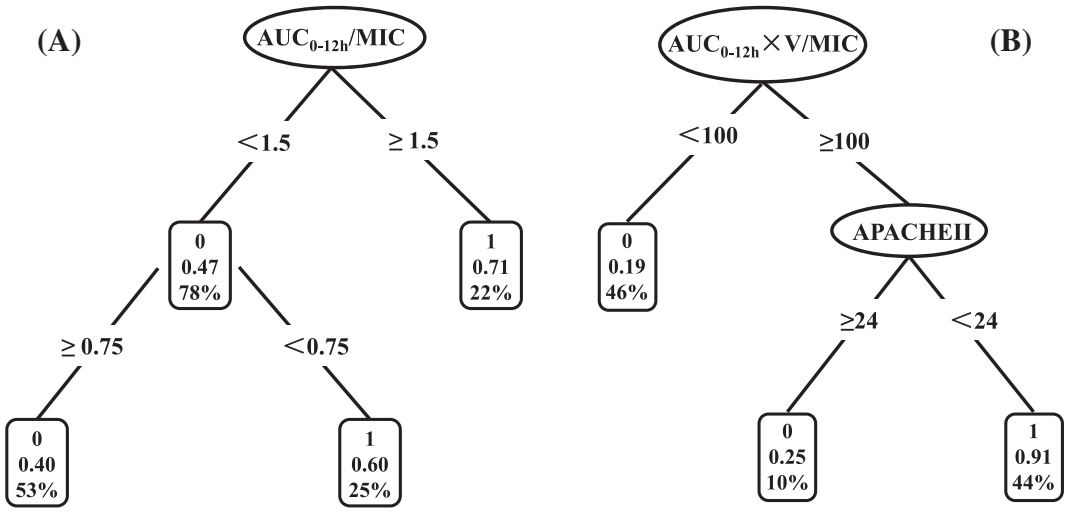

FIGURE 4 CART analysis for thresholds of the clinical response. 1, clinical success; 0, clinical failure. (A) $AUC_{0\text{-}12h}$/MIC. (B) Combined $AUC_{0\text{-}12h} \times V/MIC$ and APACHEII score

the patients with $AUC_{0\text{-}12h} \times V/MIC$ ratio ≥ 100 as well as APACHEII score <24 were more likely to achieve clinical success, whereas patients with $AUC_{0\text{-}12h} \times V/MIC$ ratio <100, $AUC_{0\text{-}12h} \times V/MIC$ ratio ≥100 and APACHEII score ≥24 were more likely to result in clinical failure (Figure 4B). The accuracy of this model prediction was 86.1% (68/79), indicating an adequate model fit. Therefore, $AUC_{0\text{-}12h} \times V/MIC \geq 100$ is a reasonable threshold value for predicting tigecycline efficacy.

3.2.3 | Microbiological response

The microbiological eradication rate was 20.2% (16/79) and univariable analysis showed that the $AUC_{0\text{-}12h} \times V/MIC$ ratio was a significant predictor for microbiological response. However, no predictable threshold of $AUC_{0\text{-}12h} \times V/MIC$ for microbiological resolution was identified using CART analysis (data not shown).

4 | DISCUSSION

This study developed a PPK model of tigecycline for Chinese critically ill patients with HAP infections. To the best of our knowledge, this is the first study that has investigated the association between tigecycline exposure and clinical responses in HAP patients with MDR gram-negative bacteria.

A two-compartment model with zero-order input and first-order linear elimination adequately describes tigecycline concentration-time data, which was consistent with previous studies.[12–14] The estimated mean value of clearance (23.1 L/h) was similar to the published studies, but the mean V_{ss} (229.9 L) was smaller than the value estimated by Rubino et al (398 L) and Van Wart et al (759 L).[12,13] The large difference between the volumes of distribution could be because of the pathophysiological changes in the critically ill patients in this study, which was consistent with the previous PPK model in sepsis patients (249.9 L).[14] We also found that in two patients who passed away the day after we collect the samples, the plasma concentrations were extremely high and the V_{ss} were very low, therefore it seems that the circulation is very unstable in critically ill patients, which might influence the distribution of the medication.

The covariate analysis identified Wt, age, Cr and AST as the significant predictors of CL in the final PPK model. Although Wt, age and Cr were identified as the covariates of CL in the previous report,[11–13] our results identified hepatic function marker as a covariate for the first time, which might be caused by the hepatic clearance of tigecycline. However, since AST was also influenced by many other

factors, how it affects the clearance of tigecycline according to the limited data is not yet clear, and further research with larger numbers of samples is needed to investigate the in vivo process of tigecycline. In this model, there was a significant association between Wt and volume of distribution for the central compartment (V) in which the significant individual variation was observed. Hence, the tigecycline regimen might need to be adjusted based on the corresponding Wt.

This study found a significant relationship between $AUC_{0\text{-}12h} \times V/MIC$ and tigecycline clinical response, and the corresponding PK-PD target of $AUC_{0\text{-}12h} \times V/MIC \geq 100$. The reasons for choosing $AUC_{0\text{-}12h} \times V/MIC$ ratio instead of $AUC_{0\text{-}12h}/MIC$ were (a) $AUC_{0\text{-}12h}/MIC$ was not a significant predictor for clinical response either as a continuous covariate or analysed by the CART threshold and (b) as tigecycline spreads widely in tissues with a large volume of distribution, the plasma concentration (AUC) might not be able to reflect the exposure and tissue concentration of tigecycline correctly. By testing along with the apparent volume of distribution, we are able to predict tigecycline exposure in the whole body more precisely, and receive a more reliable predictor for the clinical response, which was confirmed by our results.

We also found that in the logistic regression analysis, the APACHEII score and combined with PA infection were the significant predictors for clinical resolution. The CART analysis demonstrated that the APACHEII score and the $AUC_{0\text{-}12h} \times V/MIC$ ratio as a combined index provided a more predictive model compared with the model including the PK-PD index alone (prediction accuracy 86.1% *vs* 79.7%). These results indicate that the pathophysiological state of the patients is of vital importance as well as the antibiotic exposure, which is in accordance with previous studies,[14,17,18] and in the circumstance of this study, higher tigecycline dosage might be needed in critically ill patients.

The positive microbiological response rate was lower than the clinical efficiency in this study. This may be because tigecycline is a bacteriostatic agent, and higher concentration may be needed to eradicate the bacteria in a short time. This could be the reason that even though the $AUC_{0\text{-}12h} \times V/MIC$ ratio was the significant predictor for the microbiological response, a threshold could not be established since only a few patients achieve the required higher concentration in the study.

At present, antibiotics are categorized into three classes according to their pharmacodynamic features against bacteria: time-dependent with short post-antibiotic effect (PAE), time-dependent with long PAE and concentration-dependent. Antibiotics in the same group usually use uniform PK-PD indices to predict their anti-infective effects.[19] However, since the pharmacokinetic characteristics of antibiotics in vivo are very complex and different from each other, it may not be appropriate to describe each category of antibiotic using the same PK-PD indices just on account of having a similar pattern of bactericidal activities. Tigecycline is a time-dependent antibiotic with long PAE, and the AUC/MIC ratio is recommended as the PK-PD index to predict its anti-infective effect.[20] Three previous PK-PD studies on tigecycline in the treatment of CAP, cSSSI and cIAI, however, failed to identify a relationship between the PK-PD indices ($fAUC_{0\text{-}24}/MIC$ or $AUC_{0\text{-}24}/MIC$ ratio) and tigecycline efficacy.[21–23] Although two of them found the AUC/MIC thresholds for the response by using CART analysis, this can only be used to predict the microbiologic effect in patients with homogeneous pathogen. These results were consistent with our study which means that the AUC/MIC ratio might not be an appropriate PK-PD index for tigecycline because of its widespread distribution in vivo, and also suggests that individualized PK-PD indices based on the characteristics of each antibiotic may be needed in antibiotic PK-PD studies.

There were limitations in this study. First, it was a single-centre study in which tigecycline was used to treat multiresistant gram-negative bacteria HAP in ICU. The results may not be generalized to other infections and other medical units. Second, the sample size was limited, thus the ability to evaluating the impact of covariates on the PPK parameters was restricted.

5 | CONCLUSION

In conclusion, a validated PPK model of tigecycline in Chinese patients with HAP was developed. The covariates of Wt, age, Cr and AST were associated with the IIV in the pharmacokinetic parameters. The study described the relationship between tigecycline exposure and the clinical response in patients with HAP and demonstrated that the $AUC_{0\text{-}12} \times V/MIC$ ratio was the most appropriate PK-PD index for predicting tigecycline clinical efficacy, and that a $AUC_{0\text{-}12h} \times V/MIC$ threshold of 100 is recommended in the treatment of HAP with multidrug resistance bacteria. These results provide important information to optimize the tigecycline regime, and suggest that individual PK-PD indexes might be needed instead of a uniform index in future research.

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COMPETING INTERESTS

None of the authors have conflicting interests that interfere with the integrity of the content of the article.

CONTRIBUTORS

Y.Z. supervised and participated in the entire procedure, reviewed the data and drafted the manuscript. P.X., H.Y. and D.X. conducted the TOC visit, evaluated the tigecycline efficacy and collected the blood samples. H.L. contributed to the conception of the work. F.W. and B.Z. helped with tigecycline determination. W.L. established the PPK model. H.L.B. analysed the data and revised the manuscript.

DATA AVAILABILITY STATEMENT

The data used to support the findings of this study are available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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