Evaluation of imipenem pharmacokinetic/pharmacodynamic parameters and the impact on antimicrobial outcomes in critically ill patients

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Abstract

Aims: Imipenem is a widely used antibiotic for the treatment of critically ill patients with severe infections. Here, we present a translational pharmacokinetic/pharmacodynamic mathematical model to assess fT>MIC and evaluate the clinical outcomes of imipenem treatment in critically ill patients. Methods: Critically ill patients with severe infections were included in our study. Blood samples at different time points were collected after imipenem plasma concentration reached a steady state in vivo. A one-compartment model was used for pharmacokinetic profiles. PK/PD parameters were calculated separately with or without a mathematical model. Clinical results were mainly defined as the microbiological results. The resolution of fever and the decrease in PCT and WBC levels were also considered. Results: A total of 54 patients were enrolled in our study. The fT>MIC calculated by the mathematical model was 67.26±39.96%, and the fT>MIC was 73.75±23.11% without the model. The PK/PD parameters calculated between the two groups were not significantly different. Regarding clinical outcomes, 35 (64.3%) patients were defined as having clinical success. The fT>MIC was 83.33±12.90% in the clinical success group and 59.42±19.11% in the clinical failure group. The fT>MIC was significantly different between the two groups (p=0.022). Based on the regimens, the PCT level decreased to at least 20% of the peak level and the WBC level decreased during the first 3 days when patients' fT>MIC was greater than 70%. Conclusion: The pharmacokinetic mathematical model may be used for PK/PD parameter evaluation. To treat critically ill patients, achieving fT>MIC greater than 70% may be necessary.

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Principal Investigator statement: The authors confirm that the Principal Investigator for this paper is Pengmei Li and that she had direct clinical responsibility for patients.

Running head: Imipenem PK/PD parameters in ICU patients

WHAT IS ALREADY KNOWN ABOUT THE SUBJECT :

$f\ T_{>MIC}$ is the best pharmacokinetic/pharmacodynamic index correlating with clinical efficacy for imipenem. The $f\ T_{>MIC}$of imipenem could not be calculated and the therapeutic ranges for clinically ill patients in

Chinese population have not been established.

WHAT THIS STUDY ADDS:

- A translational pharmacokinetic/pharmacodynamic mathematical model to assess $f\ T_{>MIC}$ was established in Chinese critically ill patients in this study.
- Based on regimens, maintaining an adequate drug concentration of imipenem above the MIC 70% of the dosing interval may achieve a better clinical result in critically ill patients.

ABSTRACT :

Aims : Imipenem is a widely used antibiotic for the treatment of critically ill patients with severe infections. Here, we present a translational pharmacokinetic/pharmacodynamic mathematical model to assess$f\ T_{>MIC}$ and evaluate the clinical outcomes of imipenem treatment in critically ill patients.

Methods : Critically ill patients with severe infections were included in our study. Blood samples at different time points were collected after imipenem plasma concentration reached a steady state*in vivo* . A one-compartment model was used for pharmacokinetic profiles. PK/PD parameters were calculated separately with or without a mathematical model. Clinical results were mainly defined as the microbiological results. The resolution of fever and the decrease in PCT and WBC levels were also considered.

Results : A total of 54 patients were enrolled in our study. The$f\ T_{>MIC}$ calculated by the mathematical model was 67.26±39.96%, and the$f\ T_{>MIC}$ was 73.75±23.11% without the model. The PK/PD parameters calculated between the two groups were not significantly different. Regarding clinical outcomes, 35 (64.3%) patients were defined as having clinical success. The $f\ T_{>MIC}$ was 83.33±12.90% in the clinical success group and 59.42±19.11% in the clinical failure group. The $f\ T_{>MIC}$was significantly different between the two groups (p=0.022). Based on the regimens, the PCT level decreased to at least 20% of the peak level and the WBC level decreased during the first 3 days when patients'$f\ T_{>MIC}$ was greater than 70%.

Conclusion : The pharmacokinetic mathematical model may be used for PK/PD parameter evaluation. To treat critically ill patients, achieving $f\ T_{>MIC}$ greater than 70% may be necessary.

KEY WORDS : Imipenem; PK/PD; antimicrobial; critically ill patients

INTRODUCTION

Imipenem is a leading antibiotic of the carbapenem family with a broad antibacterial spectrum against gram-positive, gram-negative and anaerobic bacteria[1]. This drug is frequently used in the treatment of critically ill patients with severe infections because of its wide spectrum of antimicrobial activity. Imipenem is a β-lactam and exhibits time-dependent bactericidal activity; the free plasma concentration above the minimum concentration of pathogens ($f\ T_{>MIC}$) is the best pharmacokinetic/pharmacodynamic index correlating with clinical efficacy[2].

Early and aggressive antibiotic therapy is very important in the treatment of critically ill patients with serious infections. However, appropriate antibiotic dosing and regimens in critically ill patients are challenging tasks. For critically ill patients, the rapidly changing physiology (e.g., organ dysfunction) might lead to markedly altered antibiotic PK and PD[3]. Augmented renal clearance (ARC), low plasma proteins and hypervolemia distributions affect the metabolism of imipenem *in vivo* . The susceptibility of bacteria may decrease because of inappropriate PK/PD profiles, and drug resistance may occur[4,5].

Clinicians are increasingly employing therapeutic drug monitoring (TDM) of β-lactam antibiotics to ensure adequate antibiotic exposure[6]. Imipenem is a hydrophilic molecule that is rapidly distributed to most tissues.$f\ T_{>MIC}$ with a target fractional time greater than 40% is the best PD parameter correlated with clinical efficacy[7,8]. However, for clinically ill patients, the changing physiology might lead to subtherapeutic plasma concentrations, and the target$f\ T_{>MIC}$ (greater than 40%) will not be suitable.

In previous studies, a $f\ T_{>MIC}$ of 100% or a $f\ T_{>5\ MIC}$ to 100% may be necessary[9]. Continuous or prolonged infusions were selected to increase efficacy. However, for dose regimen optimization, the most

popular method was using population PK/PD simulation[10]. This approach comprises integrating prior information and evaluating the PK of antibiotic regimens in small numbers. The$f$ $T_{>MIC}$ was calculated for a specific population, and therapeutic ranges for clinically ill patients have not been established.

In this research, we determined the$f$ $T_{>MIC}$ of imipenem by pharmacokinetic parameters and simulated a mathematical model. The PK model incorporates the limited sampling concentration, and the PK/PD profiles will be verified. We also examined the clinical outcomes of clinically ill patients undergoing imipenem TDM during therapy for bacterial infections and evaluated the best$f$ $T_{>MIC}$ level for critically ill patients.

METHODS

2.1 Patient selection

We conducted a prospective open-label trial between September 2018 and August 2019 in the intensive care unit of the hospital. This study was conducted with approval from the Ethics Research Committee of the hospital. A total of 101 patients were selected for our study. Patients older than 18 years and younger than 80 years with severe infection were included. Some patients were excluded from our study based on exclusion criteria such as (i) expected death within 48 h or stay in the ICU shorter than 3 days; (ii) severe renal function impairment (CL_{CR}<10 mL/min or renal replacement therapy); (iv) allergy to imipenem; and (v) CRRT. The patient selection procedure is shown in Fig 1.

Imipenem dosing regimens

Ultimately, 54 patients were selected for our research. All the participants were empirically treated with imipenem intravenously based on their physiological condition. The therapy began within 24 h of the microbiological sample collection. The dosing regimen was 500 mg every 8 h with a 1 h infusion. The treatment was not altered for the first 48 h of the regimen to ensure that the concentration of imipenem reached a steady level *in vivo* .

2.3 Data collected

For each patient, the standard clinical data were collected at baseline, including age, gender, simplified acute physiology score (SAPS2) (from admission and baseline data) and sepsis-related organ failure assessment (SOFA) score. WBC count, PCT and clinical outcomes were recorded during the ICU stay.

2.4 Blood sampling and analytical method

Blood sample collection

The patients were divided into two groups. The first group contained 42 patients. Blood samples were collected from the first group at 5 h and 7.5 h after the sixth dosing. A total of 84 concentration data points were collected. The other group contained 12 patients. Blood samples were obtained at 0, 0.5, 1, 2, 4, 6, 8, and 12 h after the sixth dosing. A total of 96 concentration data points were collected from the second group.

Imipenem analysis method

All blood samples were placed into EDTA-coated tubes. The plasma and blood cells were separated within 2 h. Samples were centrifuged at 3000 rpm for 10 min at 4°C and stored at -80°C until further use. A selective and sensitive ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) method was established and validated for the simultaneous quantification of imipenem in human plasma. Liquid–liquid extraction using 400 μL of acetonitrile was used to extract imipenem and the internal standard (IS; Meropenem-d6) from 200 μL of human plasma. The analytes were chromatographically separated using an Acquity UPLC BEH C18 column (50×2.1 mm, 1.8 μm) with 0.1% FA in acetonitrile and 2 mM ammonium acetate in water. The mobile phase was produced with a composition of 50% water to 50% acetonitrile containing 0.1% FA and delivered at a flow rate of 0.2 mL/min. The total run time was 6 min. Mass detection was performed using a Waters Xevo TQ-S triple-quadrupole mass spectrometer in positive

electrospray ionization mode. The mass transitions selected were m/z 300.0-171.0 and m/z 390.1-147.0 to quantify RST and IS, respectively.

2.5 fT>MIC assessment

A one-compartment model was used to evaluate the pharmacokinetic profiles and metabolic processes of imipenem. The pharmacodynamic parameter f $T_{>MIC}$ could be derived by pharmacokinetic formulas as follows:

(1) Derive imipenem concentration at an infusion time after multiple infusions.

When Tin <t[?]τ , the steady state concentration can be assessed by formula (1):

$C = \frac{\text{Dose}}{\text{kV}T_{\text{in}}} \bullet \frac{1-e^{-k\bullet Tin}}{1-e^{-k\bullet\tau}} \bullet e^{-k(t-Tin)}(1)$

where Tin is the time of infusion; C, the plasma concentration;t , the time after-dose; τ , dosing interval; k , the elimination rate constant; and V , apparent distribution volume.

When 0[?]t[?]Tin , the imipenem plasma concentration at time t after the Mth dosage was the summed concentration from the first dosage to the Nth dosage. The concentration at time t after the Mth dosage can be calculated by (2)(3)(4):

$C = \frac{\text{Dose}}{\text{kV}T_{\text{in}}} \bullet \left(1 - e^{-k\bullet t}\right) + C1 + C2 \cdots + C_N(2)$

$Cn = Cmax \bullet e^{-k(n\tau - Tin + t)}$ (3)

Then,

$C = \frac{\text{Dose}}{\text{kV}T_{\text{in}}} \bullet \left(1 - e^{-k\bullet t}\right) + \frac{\text{Dose}}{\text{kV}T_{\text{in}}} \bullet \left(1 - e^{-k\bullet Tin}\right) \bullet e^{-kt} \bullet e^{k\bullet Tin} \sum_{n=1}^{N} e^{-nk\tau}(4)$

where M is the number of times doses were given and N is the number of times doses were given after steady state was reached.

In formula (4), $1+\sum_{n=1}^{N} e^{-\nu\varkappa\tau} = \frac{1-e^{-nk\bullet\tau}}{1-e^{-k\bullet\tau}}$

When n-[?], then $e^{-nk\bullet\tau}$-0

Therefore, we conclude the following:

$\sum_{n=1}^{N} e^{-nk\tau} = \frac{e^{-k\tau}}{1-e^{-k\tau}}(5)$

Applying formula (5) to (4), the concentration at the time of infusion at steady state could be assessed by formula (6):

$C = \frac{\text{Dose}}{\text{kV}T_{\text{in}}} \bullet \left(1 - e^{-k\bullet t}\right) + \frac{\text{Dose}}{\text{kV}T_{\text{in}}} \bullet \left(e^{k\bullet Tin} - 1\right) \bullet e^{-kt} \bullet \frac{e^{-k\bullet\tau}}{1-e^{-k\bullet\tau}}(6)$

(2) Calculate$f$$\mathbf{T_{>MIC}}$after multiple infusions.

When the free plasma concentration equals the MIC,f $T_{>MIC}$ is the D-value of t_{e_MIC} (in elimination time) and t_{in_MIC} (in infusion time).

Take $e^{-kt}$from (6),

$e^{-kt} = \frac{1-e^{-k\tau}}{e^{k\bullet(Tin-\tau)}-1} \bullet \left(\frac{ckV\bullet Tin}{\text{Dose}} - 1\right)(7)$

The formula for elimination time was:

$e^{-kt} = \frac{1-e^{-k\tau}}{e^{k\bullet Tin}-1} \bullet \frac{ckV\bullet Tin}{\text{Dose}}(8)$

Take (7)/(8),

$e^{k(te\_MIC - t\text{in}\_MIC)} = \frac{e^{k\text{Tin}}-1}{e^{k\bullet(Tin-\tau)}-1} \bullet \left(1 - \frac{\text{Dose}}{\text{fu}\bullet\text{MIC}\bullet kV\bullet Tin}\right)(9)$

f $T_{>MIC}$ can be assessed by the following formula:

$$\mathrm{fT_{>MIC}}=\frac{1}{k}\bullet ln\frac{(e^{\mathrm{kTin}}-1)\bullet(1-\frac{fu\bullet \mathrm{Dose}}{\mathrm{MIC}\bullet kV\bullet Tin})}{e^{k\bullet(Tin-\tau)}-1} \quad (10)$$

(3) Perform simulations

In our research, the fu of imipenem was set to 0.8. The formulas were organized in Microsoft Excel software. According to formulas (1) and (6), the imipenem concentration may be assessed after we set the$k$ and V values. The input parameter values included imipenem concentration (at 5 h and 7.5 h), MIC, Tin , τ and dosage. The correlation between C_r and C_a was evaluated (C_r, imipenem concentration detected by UPLC-MS/MS; C_a, imipenem concentration assessed by software). The k and V values may change when the objective function value (OFV) is set to the minimum value. The drug concentration curve was observed, and the result was used when C_r and C_a values coincided. We can obtain $f\ T_{>MIC}$ from the software.

2.6 Outcome assessment

Microbiological success was chosen as the major outcome in our study. We defined microbiological success as a [?]10^3 cfu/mL quantitative culture decrease in bacterial count three days after the initial treatment. The clinical outcomes were evaluated by investigators on days 5, 14, and 28. A clinical success was defined as a decrease in PCT and WBC levels in the first 5 days and the resolution of fever or clinical symptoms. We consider that if clinical outcome was not achieved until day 5, the patient was defined as a clinical failure case. Microbiological success was detected by blood or sputum samples and drug resistance analysis on days 10-14. We also evaluated the 28-day mortality on days 28-30 and the time of stay in the ICU.

2.7 Statistical analysis

One-way analysis of variance (ANOVA) was used to statistically analyse our results. Fisher's exact test was used for precise analyses. Two sided p-values were used and analyses were accepted when $p<0.05$. Statistical analyses were performed using SPSS 19.0 software. Pharmacokinetic parameters were calculated with Kinetica 5.1 software.

RESULTS

3.1 Basic patient information

Patients were divided into two groups. In the model group,$f\ T_{>MIC}$ was calculated by mathematical formulas using Microsoft Excel software. The basic patient information is presented in Table 1. There were no significant differences detected in terms of age, sex, BMI, medical history, or aetiology. The Cr, ALB, AST, and ALT levels between the groups were not significantly different.

3.2 Pharmacokinetic and pharmacodynamic parameters assessed

In the model group, the concentrations of imipenem at 5 h and 7.5 h after the sixth dosing were 5.18±2.99 and 2.64±1.82 μg/ml, respectively. The $f\ T_{>MIC}$ calculated by the formula was 67.26±39.96%, and the $f\ T_{>4\ MIC}$was 53.93±14.19%. In the non-model group, the concentrations of imipenem were 6.77±3.84 and 2.19±0.85 μg/ml at the 5 h and 7.5 h time points, respectively. The $f\ T_{>MIC}$ and$f\ T_{>4\ MIC}$ were 73.75±23.11% and 41.38±11.25%, respectively. The pharmacokinetic parameters of the two groups are presented in Table 2.

In our research, the pharmacokinetic and pharmacodynamic parameters between the two groups were not significantly different. The plasma concentration curves of the two groups are shown in Fig 2. The detected imipenem concentration and the simulated concentration curves fit very well. The results showed that the pharmacokinetic mathematical formula can be used with modelling software to evaluate the imipenem PK/PD profiles in patients.

3.3 Clinical outcomes of different$f\mathbf{T_{>MIC}}$

We calculated $f\ T_{>MIC}$ of all the patients using modelling software. In our research, three patients achieved 100% $f\ T_{>MIC}$ and 57.1% of participants were below 70% $f\ T_{>MIC}$. Two patients were below 40% $f\ T_{>MIC}$.

There were 35 (64.3%) patients who were defined as having clinical success and 19 (35.2%) patients who were defined as having clinical failure. The $f\ T_{>MIC}$ was 73.33±22.90% in the success group and 59.42±19.11% in the failure group. The $f\ T_{>MIC}$ was significantly different between the two groups (p=0.022). The$f\ T_{>4\ MIC}$ also showed a significant difference between the success and failure groups (p=0.031). The results were shown in Table 3.

The levels of WBC and PCT were considered necessary for clinical regimens. The WBC and PCT levels changed during the antibiotic treatment, especially during the first 5 days. Based on data from the regimens, the PCT level decreased to at least 20% of the peak level or below 0.5 ng/ml when patients'$f\ T_{>MIC}$was greater than 70% or $f\ T_{>4\ MIC}$was greater than 50%. The WBC level decreased during the first 3 days and reached steady regimen values when$f\ T_{>MIC}$ was greater than 70% or$f\ T_{>4\ MIC}$ was greater than 50%. These results indicated that adjusted$f\ T_{>MIC}$higher than 70% or $f\ T_{>4\ MIC}$ higher than 50% may result in a better clinical outcome. These results are shown in Fig 3.

DISCUSSION

In this research, a pharmacokinetic model was established using Microsoft Excel software. The calculations in the software were based on pharmacokinetic formulas, and the PK/PD parameters were simulated. Compared to the multipoint sampling method, the PK profiles simulated by software can reflect the metabolism of imipenem *in vivo* .$f\ T_{>MIC}$ of imipenem in critically ill Chinese patients was assessed by software in this study. Approximately 64.3% of patients were defined as having clinical success. All the patients' $f\ T_{>MIC}$ values were higher than 70% in the success group and showed a significant difference from the failure group (p=0.022). The levels of WBC and PCT decreased quickly during the first 3 and 5 days when$f\ T_{>MIC}$ was greater than 70%, and the patients may obtain better clinical outcomes, especially with critical infections.

$f\ T_{>MIC}$ is the best pharmacokinetic/pharmacodynamic index correlating with imipenem clinical outcomes[11]. Although a significant association between PD exposure and microbiological or clinical outcomes was not found for imipenem, changing the infusion regimens and obtaining a proper $f\ T_{>MIC}$ is especially necessary for the treatment of critically ill patients[4]. In previous studies, most imipenem pharmacokinetic characteristics were assessed by a Monte Carlo model. Some PD parameters, such as $f\ T_{>MIC}$or f AUC/MIC, were assessed by a population PK model[12,13]. The PPK model involved imipenem free plasma concentrations and simulated the dosage regiment property. These PPK models refer to specialist patients, and we could not obtain the exact PD parameters individually. We could also not use these PPK models to evaluate the clinical efficacy of imipenem because of the particular physiology in critically ill patients. Camille[14]studied a PPK model in severe infection patients to evaluate the best dosage regimens. The pharmacokinetic parameters changed sensitively in the distribution of body fluids, and the PPK model can only be used for VAP and non-renal failure patients. In our study, we established pharmacokinetic formula software to calculate$f\ T_{>MIC}$ and PK parameters. Only two blood samples were needed in our research. Compared to the multiple sampling method, the simulated PK/PD parameters can reflect the metabolism of imipenem. We can use this pharmacokinetic software to calculate the imipenem PD parameters and guide the clinical outcomes on an individual basis.

Imipenem is used effectively as a therapy for severe infections by strains such as *Klebsiella* , *Escherichia coli* , and*Enterobacter* that are found in the ICU. A clear and compelling rationale suggests that when plasma drug concentrations are above the MIC for 40% of the dosing interval, imipenem dosing regimens may achieve favourable target attainment in patients[15]. However, for life-threatening severe infections in immunocompromised hosts, the$f\ T_{>MIC}$ target required for sufficient bactericidal effects is increased to almost 100%[16-18]. Dulhunty[19]*et al* assessed a trial in a randomized double-blind controlled method and indicated that increasing the$f\ T_{>MIC}$ of carbapenem to 82% may achieve a better clinical result compared with 22% in continuous infusion. Sutep Jaruratanasirikul[20] *et al*suggest that a recommendation for high dosages of imipenem should be required and that plasma concentrations of imipenem 100% $T_{>MIC}$ for MICs of 2 and 4 mg/L are necessary for treatment of highly resistant microorganisms in life-threatening severe infections. In our study, the free plasma concentration of imipenem above the MIC 70% of the dosing interval produced significant differences in clinical outcomes between the clinical improvement and clinical failure

groups. Pathophysiological changes in critically ill patients with severe infections had a greater impact on pharmacokinetic patterns of imipenem. Therefore, maintaining an adequate drug concentration to achieve af $T_{>MIC}$ greater than 70% may be a target for effective antimicrobial therapy in this patient population.

In our study, the changes in PCT levels refer to an important index in the clinical outcome evaluation. The international guidelines recommend PCT as a necessary and important laboratory marker for antibiotic stewardship strategies[21]. Procalcitonin-directed protocols for clinicians may be effective for the antibiotic treatment of clinically ill patients. Pierre[22] *et al* . assessed a cohort study including 180 patients who appropriately received empirical antibiotic therapy. The results showed that the patients' overall survival was significantly associated with the decreased level of PCT between D2 and D3. Andreas Hohn[23] *et al* . studied procalcitonin-guided antibiotic treatment in critically ill patients. Their results showed that using PCT protocols may effectively direct antibiotic treatment[24]. In our research, the PCT levels of patients were collected during the first five days after imipenem infusion. The decreasing PCT levels were a better reflection of clinical antibiotic efficacy.

CONCLUSION

In conclusion, a PK model of imipenem for$f$ $T_{>MIC}$ calculations was established in critically ill patients in this study. The imipenem PK/PD profiles in the model group were not significantly different from those in the non-model group. The PK model could be used for imipenem PK/PD evaluation. In clinical outcomes, maintaining an adequate drug concentration of imipenem above the MIC 70% of the dosing interval may achieve a better clinical result in critically ill patients.

COMPETING INTERESTS

The authors declare that they have no conflict of interest.

CONTRIBUTORS

DZ: analysed data and wrote the manuscript., WQC, WYX, WQ and WXX: contributed to the development, interpretation of results. XLZ and PML revision of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the PI. The data are not publicly available due to ongoing studies.

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Table 1. Patients' basic information of different groups

Basic information		Model	Non-model	p
Age(years)		64.2±23.8	55.3±13.9	0.214
Male	Yes	31	7	0.285
Total body weight(kg)		67.3±11.9	58.2±8.8	0.617
Cr(umol/L)		77,5±34.3	101.0±40.8	0.75
ALB(g/L)		31.3±3.1	42.5±6.1	0.499
ALT(IU/l)		27.8±11.2	33.5±12.9	0.711
AST(IU/l)		32.7±10.3	29.1±9.5	0.749
Admission category, n(%)				
medical	Yes	37(88.1)	9(75.0)	0.437
surgical	Yes	5(11.9)	2(16.7)	0.588
Main reason for hosipital or ICU, n(%)				
pulmonary infection	Yes	39(92.8)	10(83.3)	0.394
urinary infection	Yes	3(7.1)	0	–
acute pancreatitis	Yes	1(2.3)	0	–
Acute peritonitis	Yes	1(2.3)	0	–
Comorbidity,n(%)				
Severe pneumonia	Yes	13(30.9)	7(58.3)	0.779
Viral pneumonia	Yes	4(9.5)	0	–
interstitial lung disease	Yes	9(21.4)	0	–
COPD	Yes	2(4.7)	10(83.3)	0.843
ARDS	Yes	3(7.1)	0	–
Bacteremia	Yes	6(14.3)	2(16.7)	0.472
Septic shock	Yes	6(14.3)	0	–
Etiologic results,n(%)				
A.baumannii	Yes	13(30.9)	2(16.7)	0.211
P.aeruginosa	Yes	12(28.5)	1(3.5)	0.372
Burkholderiacepacia	Yes	8(19.0)	6(50)	0.591
E. coli	Yes	5(11.9)	5(41.7)	0.291
E. cloacae	Yes	2(4.7)	0	–
E. aerogenes	Yes	2(4.7)	0	–
Klebsiella spp.	Yes	4(9.5)	0	–
Haemophilus spp.	Yes	1(2.4)	0	–

Table 2. The pharmacokinetic parameters of the two groups.

Parameter	Model	Non-model	p
5 hour Con. (μg/ml)	5.18±2.99	6.77±3.84	0.217
7.5 hour Con. (μg/ml)	2.64±1.82	2.19±0.85	0.331
Ka	0.27±0.11	0.44±0.21	0.745

Parameter	Model	Non-model	p
V(L)	63.15±33.70	75.33±41.25	0.218
C_{max}(ug/ml)	18.81±14.6	24.01±10.2	0.394
$t_{1/2}$(h)	2.64±1.86	1.54±0.77	0.177
$MRT_{0\text{-}24}$(h)	4.53±1.87	2.28±1.55	0.521
CL/Z(L/g*h)	212.07±112.30	113.25±78.05	0.388
$AUC_{0\text{-}24}$(ngh/ml)	78.83±54.78	88.42±37.11	0.29
fT>MIC	67.26±39.96	73.75±23.11	0.088
fT>4MIC	53.93±14.19	41.38±11.25	0.094

Table 3. Different parameters of clinical groups

	Overall population	Clinical anti-infection Failure	Clinical anti-infection success	P
5 hour Con. (μg/ml)	5.98±3.11	5.68±2.97	6.01±2.77	0.513
7.5 hour Con. (μg/ml)	2.42±1.17	2.45±1.83	2.71±1.90	0.244
fAUC/MIC	83.63±27.95	80.11±31.04	82.17±29.15	0.719
fT>MIC	75.06±21.77	59.42±19.11	83.33±12.90	0.022*
fT>4MIC	47.66±13.17	30.29±11.25	55.71±17.24	0.031*
WBC *10*g/L	13.11±9.07	16.77±7.90	7.96±1.50	0.001*
PCT (μg/ml)	7.33±10.25	5.05±7.75	1.12±1.63	0.001*

*p<0.05

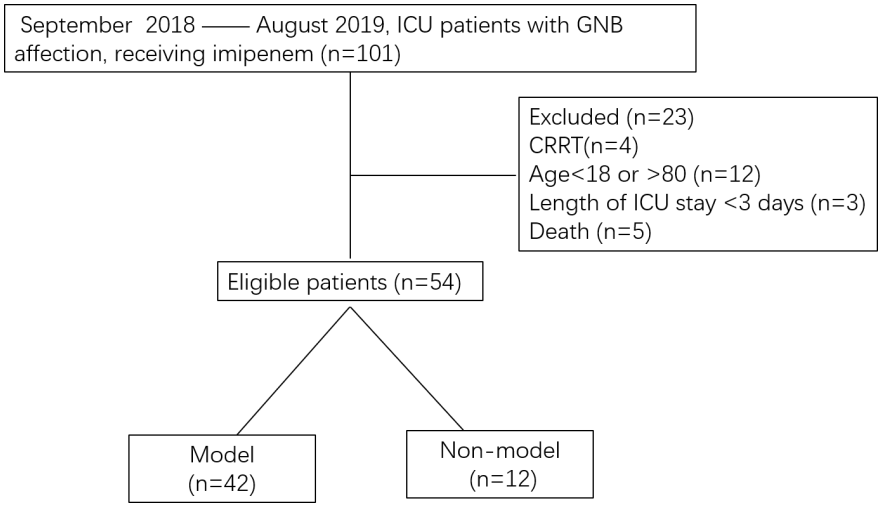

Fig.1 Patients selection.

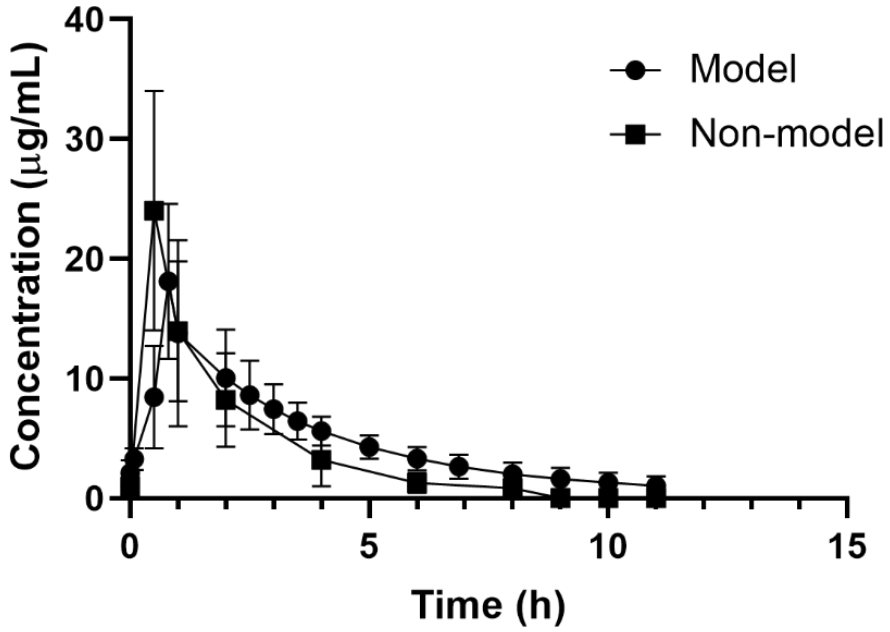

Fig.2 The two groups plasma concentration curves.

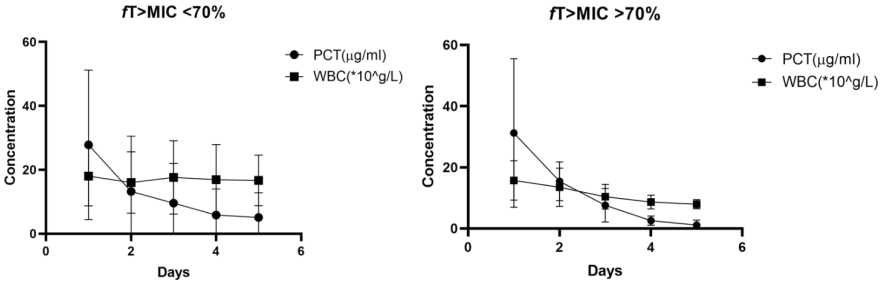

Fig. 3 The clinical outcomes of different f T>MIC in the first 5 days.

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