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ORIGINAL ARTICLE

Clinical application of vancomycin population pharmacokinetics model in patients with hematological diseases and neutropenia

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Abstract

To explore the clinical application of a population pharmacokinetics (PPK) model of vancomycin in patients with hematological diseases and neutropenia. Patients with hematological diseases and neutropenia were included in the PPK model study. Nonlinear mixed effect modeling approach (NONMEM) was used for model establishment. Monte Carlo simulation was carried out. A total of 74 patients were divided into model group and non-model group for clinical application research. The model group was given the initial dose of 1g q8h, and the non-model group was given 1g q12h as an empiric initial dosage. The follow-up dose adjustments were made according to the concentration results. This two-compartment model showed good stability and accuracy. The first trough concentration (C_0) and the compliance rate of the first C_0 were much higher in the model group than that in the non-model group (14.30 $\pm$ 4.73 μg/ml and 59.38% vs. 8.02 $\pm$ 2.61 μg/ml, 35.71%). Less patients needed dose adjustments and fewer adjustment times in the model group than those in the non-model group (12.50% and 0.13 $\pm$ 0.34 times vs. 50.00% and 0.61 $\pm$ 0.66 times). This suggested that for those patients who had a Creatinine clearance rate (CLCR) $\geq$ 90 ml/min/1.73 m^2, the initial dose of 1g q8h may help to reach the target C_0 (10~20 μg/ml) quickly. It also helped to reduce the times and number of patients who need dose adjustments. Our PPK model of vancomycin in patients with hematologic diseases and neutropenia can be used to shorten the time to reach the target concentration and reduce the number of dose adjustments. Clinical trial registration: Not applicable (Retrospective study).

KEYWORDS

neutropenia, population pharmacokinetics (PPK) model, vancomycin

Xiangjun Fu and Liangmo Lin contributed equally to this work.

1 | INTRODUCTION

Vancomycin is the first-line drug in the treatment of *methicillin-resistant Staphylococcus aureus* (MRSA) infection that has been clinically used for a very long time. Because of its narrow therapeutic window and obvious individual differences in pharmacokinetics, there are many guidelines and expert consensuses that guide the clinical application of vancomycin in recent years (Chen, Guan, He, & Huang, 2011; Chen & Li, 2011; Chinese Pharmacological Society, 2016; Expert Group on clinical Dosage of Vancomycin, 2012; He et al., 2021; Matsumoto et al., 2013; Rybak et al., 2020). With the development of quantitative pharmacology, numerous researches have shown clinical significance in optimizing the drug delivery scheme of vancomycin by using the population pharmacokinetics (PPK) model, which could quickly help to improve the target rate of TDM (Gao et al., 2018; Guo et al., 2021; Le et al., 2015; Liu et al., 2017; Mehrotra et al., 2012). The difference of pharmacokinetics was obvious in different pathological states and there has been an increasing interest in PPK of vancomycin in those patients (Joaguim et al., 2018). However, there are only a few model studies on adult neutropenic patients (Joaguim et al., 2018). Jarkowski had developed a two-compartment model of vancomycin in hematologic patients in 2012 (Jarkowski et al., 2012), while other reports focus on children (Lv et al., 2021).

More and more attention has been paid to the pharmacokinetics of vancomycin in patients with hematological disease. Our previous research showed that vancomycin exposure was often inadequate in this population. It is also mentioned in the guideline of vancomycin treatment drug monitoring of China revised in 2020 that neutropenic patients with fever are recommended to accept TDM, and the PPK model is helpful to realize the implementation of individualized drug delivery scheme. We had recently established a PPK model for patients with hematologic disease and neutropenia, and it showed good stability and prediction performance (Lin et al., 2021). In this paper, the clinical application of this PPK model was to set an appropriate initial dose in patients with hematological disease and neutropenia and to improve the compliance rate of the first C_0 of vancomycin at the 48th hour since reaching the target concentration in time and less dose adjustments were conducive to infection control in this special population.

2 | MATERIAL AND METHODS

2.1 | Determination of vancomycin concentration in serum

Vancomycin concentration in serum was tested by using the Siemens automatic drug concentration analyzer Viva-E. The quantitative range was 2.0~50.0 μg/ml. The time for trough concentration (C_0) was 0.5 h before intravenous drip, and for peak concentration (C_P) was 0.5–1 h after intravenous drip. A 2 ml venous blood was collected and centrifuged at 3500 rpm. The supernatant was taken for determination.

2.2 | Establishment and validation of vancomycin PPK model in patients with hematological diseases and neutropenia

Patients in the Department of Hematology of Hainan General Hospital from 1 January 2018, to 1 January 2020, were selected as the research subjects. The inclusion criteria were as follows: 1) diagnosed with hematological diseases; 2) ≥14 years old; 3) developed neutropenia (neutrophil count, ANC $< 0.5 \times 10^9$/L) during the study; 4) received intravenous vancomycin intermittently. The exclusion criteria were: 1) <14 years old; 2) non-neutropenic state; 3) receiving any blood purification treatment; 4) incorrect samples. The body weight (BW), age, creatinine (CR), white blood cell count (WBC), ANC, hemoglobin (HGB), platelet count (PLT), serum total protein (TP), serum albumin (ALB), alanine aminotransferase (ALT), aspartate aminotransferase (AST), vancomycin dosage (mg/d), administration time (h), serum concentration (μg/ml) of the patients were collected and recorded. The above indexes were measured on the same day or within 3 days before and after the monitoring of vancomycin serum concentration. Creatinine clearance rate (CLCR) was calculated using the CKD-EPI formula developed by the US chronic kidney disease epidemiology cooperative working group. All procedures were performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. This study was approved by the Medical Ethics Department of our hospital (approval number 2018 [68]), and all patients had informed consent.

The PPK model of the neutropenic population was established by the nonlinear mixed-effects model (NONMEM). The exponential model was used to describe the variation among individuals, and the residual variation was fitted by the additive model, proportional model, and mixed model. The fitting results of different error models were compared according to the objective function value (OFV), the goodness of fit graph, and the rationality of parameters. The basic model was established based on these same approaches. In the basic model, a stepwise regression method was used to add covariates and establish the final model. When the degree of freedom $n = 1$ and the decrease of OFV was more than 3.84 after adding a certain covariate, this covariate was kept in the final model. The covariates, which included age, gender, BW, creatinine, CLCR, WBC, ANC, HGB, PLT, TP, ALB, ALT, and AST, were eliminated one by one from the final model. When the degree of freedom $n = 1$ and the increase of OFV was more than 10.83, the covariate was saved. The final model was established following this approach.

The goodness of fit (GOF) and model predictive diagnostic chart (VPC) were drawn for model-based verification. The nonparametric bootstrap method was used for internal verification. In our study, the 95% confidence interval of population parameters and the estimated values of population parameters were obtained by 1000 times bootstrap method and were compared with the estimated values of the final model parameters. In addition, patients who were not included in the model group with the same entry conditions in the same period were used for external verification. The prediction performance was judged by the prediction error (PE%) of the model.

The median relative prediction error (MDPE) was used to evaluate the model's accuracy, and the median absolute prediction error (MAPE) was used to evaluate the precision of the model. Composite indexes F_{20} and F_{30} (PE% between ± 20% and ±30% percentage) were used to evaluate the precision of the model. When MDPE ≤ ±20%, MAPE ≤ ±30%, F_{20} ≥ 35%, and F_{30} ≥ 50%, the prediction performance of the model was considered acceptable. The calculation formulas are shown in formulas (1)–(5).

$$\mathrm{PE}\% = \frac{C_{\mathrm{pred}} - C_{\mathrm{obs}}}{C_{\mathrm{obs}}} \times 100\% \quad (1)$$

$$\mathrm{MDPE}\% = \mathrm{Median}\left(\frac{C_{\mathrm{pred}} - C_{\mathrm{obs}}}{C_{\mathrm{obs}}}\right) \times 100\% \quad (2)$$

$$\mathrm{MAPE}\% = \mathrm{Median}\left(\frac{|C_{\mathrm{pred}} - C_{\mathrm{obs}}|}{C_{\mathrm{obs}}}\right) \times 100\% \quad (3)$$

$$F_{20}\% = \left(\frac{n_{|\mathrm{PE}| \le 20\%}}{n_{\mathrm{obs}}}\right) \times 100\% \quad (4)$$

$$F_{30}\% = \left(\frac{n_{|\mathrm{PE}| \le 30\%}}{n_{\mathrm{obs}}}\right) \times 100\% \quad (5)$$

2.3 | Monte Carlo simulation of PPK model

Based on the established PPK model, Monte Carlo simulation was used to simulate the steady-state trough concentration of neutropenic patients with different CLCR under different vancomycin administration schemes.

When CLCR was 30, 60, 90, 120 ml/min/1.73 m^2, respectively, the following drug delivery schemes (including 1g q12h, 1g q8h, 0.5g q8h, 0.5g q6h) were simulated. One thousand sets of simulation data were generated for each combination of the dosing scheme and CLCR. If the vancomycin trough concentration was maintained at 10~20 μg/ml, it was considered that the scheme was feasible with this CLCR.

2.4 | Clinical application of PPK model

Patients with hematologic disease and neutropenia who had a CLCR ≥ 90 ml/min/1.73 m^2 were selected as the research subjects and were treated by intravenous vancomycin. The patients were randomly divided into two groups: the model administration group and the non-model administration group. The age, height, weight, CLCR, the first C_0, medication days of vancomycin, dose adjustment times, the compliance rate of the first C_0, the proportion of patients who received dose adjustments and in the two groups were compared.

2.5 | Statistical analysis

NONMEM (icon development solutions, USA, version 7.3) software was used for model establishment and simulation. Perl speak NONMEM (PSN version 3.4.2) was used for model validation. R software (version 2.12.0) was used for statistical testing and drawing, and SPSS 19.0 was used for data analysis.

3 | RESULTS

3.1 | Basic information of patients

A total of 77 patients, including 42 males and 35 females, were included in this PPK model study. One hundred nine trough concentrations and 43 peak concentrations were monitored. The primary diseases were 34 cases of acute myeloid leukemia, 16 cases of acute lymphoblastic leukemia, 10 cases of lymphoma, 5 cases of aplastic anemia, 5 cases of myelodysplastic syndrome, 4 cases of chronic myeloid leukemia, 2 cases of multiple myeloma, and 1 case of chronic monocytic leukemia. A total of 26 patients were included in the external validation. The basic information of patients was shown in Table 1. The vancomycin administration protocol were: 80.74% of the patients were given 1g q12h, 7.34% were given 1g q8h, 8.26% were given 0.5g q6h, while 1.83% and 1.83% for 0.5g q8h and 0.5g qd. The administration protocol was shown in Table 2.

3.2 | The final PPK model and verification results

3.2.1 | The final PPK model

One compartment model and a two-compartment model were used to fit the data. The OFV of the two-compartment model was lower than that of the one-compartment model. After considering the rationality of the objective function value, the goodness of fit graph, and parameters, the two-compartment model was finally used as the basic model. The mixed model was used to describe the variation among individuals, and the OFV was 532.06. The estimated values of CL, V_1, Q, and V_2 were 6.43 L/h, 18.9 L, 19.5 L/h, and 37.1 L/h, respectively. Inter-individual variation of CL (ω^2CL) was 0.0615, and the inter-individual variation of V_1 ($\omega^2 V_1$) was 0.126. The stepwise regression method and stepwise elimination method were used to screen the covariates. Only CLCR was retained so that the final model was obtained. The formula for the final model was as follows:

$$\mathrm{CL} = 6.84^{*}(\mathrm{BW}/70)^{0.75^{*}}\ (\mathrm{CLCR}/116)0.895^{*}\exp\ (\eta_1) \quad (6)$$

CL was the clearance rate, 6.84 in formula (6) was the typical value of Cl, BW was the bodyweight of patients. η_1 represented the difference between the patient clearance rate and the typical value of the population.

$$V_1 = 20.5^{*}(\mathrm{BW}/70)^{*}\exp(\eta_2) \quad (7)$$

V_1 was the distribution volume of the central ventricle, and 20.5 in formula (7) was the typical value of V_1. η_2 represented the

TABLE 1 The basic information of enrolled patients for model establishment and validation

Groups	Modeling patients	Non-modeling patients	*p*
Age (y)	43.28 ± 15.88 (17, 83)	40.15 ± 16.20 (20, 68)	0.908
Height (cm)	162.57 ± 9.52 (148.00, 185.00)	161.78 ± 9.66 (153.00, 172.00)	0.747
Body weight (kg)	56.84 ± 11.09 (33.00, 83.50)	58.26 ± 8.39 (49.00, 76.00))	0.956
BMI (kg/m^2)	21.52 ± 3.63 (14.67, 31.87)	22.24 ± 3.11 (16.04, 28.38)	0.418
Creatinine (μmol/L)	53.66 ± 18.36 (23.00, 125.00)	56.54 ± 18.19 (26.00, 112.00)	0.504
CLCR (ml/min/1.73 m^2)	118.78 ± 22.69 (45.60, 163.80)	118.92 ± 21.57 (59.00, 164.70)	0.456
WBC (10^9/L)	2.37 ± 8.37 (0.01, 66.74)	1.11 ± 2.01 (0.16, 45.63)	0.153
ANC (10^9/L)	0.19 ± 0.36 (0.00, 0.49)	0.18 ± 0.45 (0.00, 0.48)	0.849
HGB (g/L)	66.71 ± 17.01 (34.00, 128.00)	64.69 ± 13.58 (35.00, 119.00)	0.403
PLT (10^9/L)	26.75 ± 23.68 (1.00, 138.00)	27.42 ± 21.71 (3.00, 106.00)	0.751
ALT (10^9/L)	40.03 ± 86.97 (3.60, 568.40)	58.66 ± 76.87 (6.20, 501.60)	0.260
AST (10^9/L)	21.82 ± 29.08 (3.10, 223.50)	26.79 ± 32.26 (6.40, 212.30)	0.228
TP (g/L)	59.08 ± 8.41 (34.20, 78.10)	59.19 ± 9.67 (41.2, 71.90)	0.243
ALB (g/L)	32.23 ± 6.34 (17.90, 59.40)	30.93 ± 5.75 (16.81, 56.10)	0.994

TABLE 2 Information of concentration and administration protocol of vancomycin

Item	$x \pm s$	Min	Max
C_0 (μg/ml)	9.07 ± 5.47	2.30	34.00
C_p (μg/ml)	32.03 ± 10.45	10.60	56.70
Daily dose of vancomycin (g/d)	2.05 ± 0.32	0.50	3.00
Infusion rate (mg/h)	894.83 ± 283.72	250.00	1000.00

Note: C_0, the trough concentration; C_p, the peak concentration.

TABLE 3 The parameter and an estimated value of parameter variation of the final model

Parameter	Estimated value	RSE (%)	95% CI
CL (L/h)	6.84	4.5	(6.234, 7.446)
V_1 (L)	20.5	17.3	(13.562, 27.438)
Q (L/h)	15.2	23.4	(8.242, 22.158)
V_2 (L)	50	27.2	(23.344, 76.656)
θ_{CLCR_CL}	0.895	14.3	(0.644, 1.146)
η_1 (%)	17.8	15	–
η_2 (%)	33	35.8	–

difference between the apparent distribution volume of patients and the typical value of the population.

$$Q = 15.2^{*}(\mathrm{BW}/70)^{0.75*}\exp(\eta_3) \quad (8)$$

Q was the clearance rate between rooms, 15.2 in formula (8) was the typical value of Q, η_3 represented the difference between the parameters of patients' IVT and the typical values of the population.

$$V_2 = 50^{*}(\mathrm{BW}/70)^{*}\exp(\eta_4) \quad (9)$$

V_2 was the distribution volume of the peripheral ventricle. In formula (9), 50 was the typical value of V_2, η_4 represented the difference between the distribution volume of the peripheral ventricle and the typical value of the population.

The parameters of the final model are shown in Table 3.

3.2.2 | Model validation

The goodness of fit map (GOF) was drawn, including scatter plot of basic model observations (DV) and population predicted values (PRED), scatter plot of DV and individual predictive value (IPRED), scatter plot of DV and conditional weight residuals (CWRES), scatter plot of DV and time. According to DV and PRED scatter plots, the coincidence degree of the trend line and reference line was high; the distribution of scatter plot of predicted value and conditional weight residual and scatter plot of predicted value and time were symmetrical, and there was no obvious trend change, which indicated that the final model had a good predictive ability. The final model GOF and predictive diagnosis diagram are shown in Figures 1 and 2.

The Bootstrap method was used to verify the final model. Repeated sampling 1000 times from the original data was performed in order to generate multiple sets of Bootstrap data. Then fitted the Bootstrap data and estimated the model parameters, summarized all the results of successful operation, and compared those with the final model parameters. There was no significant difference between the final model parameters and bootstrap median, and the success rate of convergence was 90%, indicating that the model was reliable. The validation results were shown in Table 4.

The external validation results were: MDPE = −4.68%, MAPE = 18.74%, F_{20} = 52.27%, F_{30} = 68.18%, which showed that the prediction performance of the model was good.

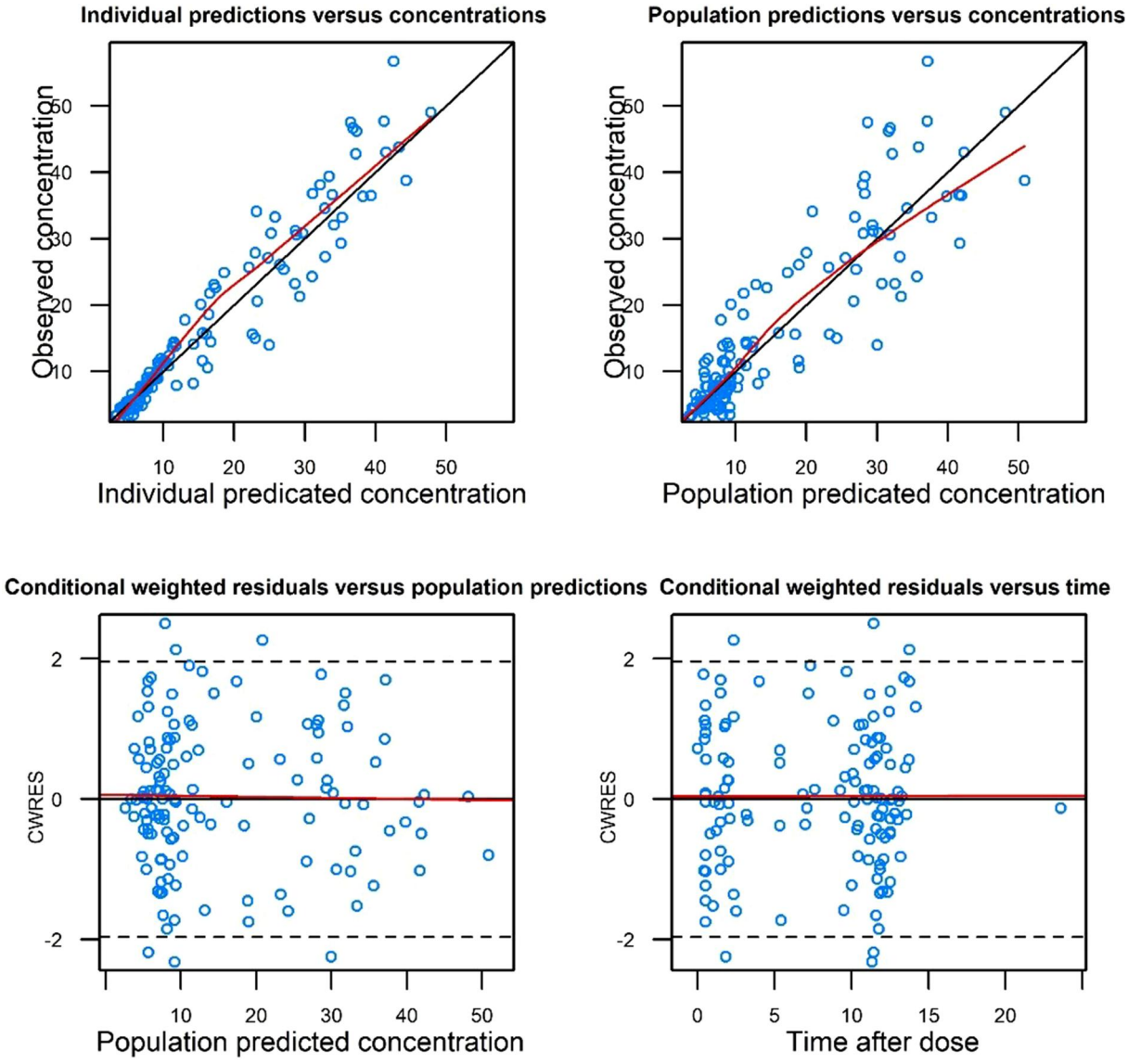

FIGURE 1 Goodness-of-fit plots of final

3.3 | Results of Monte Carlo simulation

According to Monte Carlo simulation, the predicted trough concentration of vancomycin in neutropenic patients with different CLCR under different administration regimens is shown in Figure 3. When CLCR was 30 ml/min/1.73 m^2, the recommended dosage regimen of vancomycin was 0.5g q8h; when CLCR was 60 ml/min/1.73 m^2, the recommended dosage regimen was 1g q12h, 0.5g q6h or 0.5g q8h; when CLCR was ≥90 ml/min/1.73 m^2, vancomycin 1g q8h could reach a satisfactory trough concentration of 10~20 μg/ml for the 48th hour (the first C_0).

3.4 | Clinical application results of the PPK model

As the CLCR of neutropenia patients was generally high (Fu et al., 2020; Hirai et al., 2016) and the results obtained from Monte Carlo simulation, the CLCR ≥ 90 ml/min/1.73 m^2 was taken as the entry condition. A total of 74 adult patients with hematological diseases and neutropenia, including 45 males and 29 females, were included for the clinical study. Among them, 32 were in the model group, and 42 were in the non-model group. All of them had a CLCR ≥90 ml/min/1.73 m^2. The age, height, weight, CLCR and medication days showed no difference between those two groups. The model group was given an initial dose of 1g q8h directly, while the non-model group was given 1g q12h based on the experience as usual. The dosage regimen was adjusted after monitoring the concentration. At the 48th hour of administration, serum samples were collected 30 min before the next administration to monitor the first C_0 with 10~20 μg/ml being the target concentration. In the model group the first C_0 was 14.30 ± 4.73 μg/ml; dose adjustment times and the proportion of patients who received dose adjustments were 0.13 ± 0.34 times and 12.50%; the compliance rate of the first C_0 was 59.38%. In the non-model group the first C_0 was 8.02 ± 2.61 μg/ml;

dose adjustment times and the proportion of patients who received dose adjustments were 0.61 ± 0.66 times and 50.00%; the compliance rate of the first C_0 was 35.71%.

Mann–Whitney U test and *Chi-square test* showed that the first C_0 and the compliance rate of the first C_0 were higher than the non-model group. Thus it needed fewer times and less patients for dose adjustments. These results suggested that for patients with hematological diseases and neutropenia CLCR ≥ 90 ml/min/1.73 m^2, the initial dose of 1g q8h could be more appropriate to quickly reach the target C_0. The clinical application results were shown in Table 5.

3.5 | Introduction of a typical case

A 50-year-old female patient weighing 47 kg, with a CLCR of 128.6 ml/min/1.73 m^2 was diagnosed with acute myeloid leukemia. She developed neutropenia with fever after chemotherapy and was diagnosed with *Streptococcus bovis* infection in the blood. From 18 February 2021, she received 1g q12h of vancomycin. The first concentration of vancomycin was 6.0 μg/ml 48 h after the prescription. PPK model was used to predict that the concentration of 1 g q8h after adjustment was 11.8 μg/ml, and the real measured concentration was 10.2 μg/ml. The prediction error was 13.56%. A week later, the blood culture showed that the pathogen was negative. If the patient had received 1g q8h at the first dose, this would have helped to quickly reach the target blood concentration and control the infection.

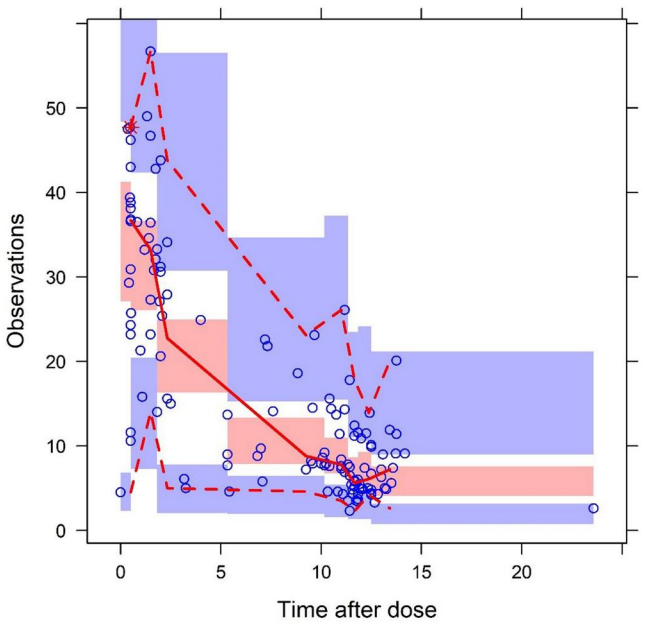

FIGURE 2 Visual predictive checks of the final model

4 | DISCUSSION

The phenomenon of insufficient concentration of vancomycin is commonly found in patients with hematological diseases. Kergueris reported that the vancomycin elimination rate, which is constant in patients with neutropenia, was higher than that in the general population and had no significant correlation with serum creatinine and urine volume in such patients (Kergueris et al., 1994). Michiel B. Haeseker's study revealed that the clearance rate of vancomycin in patients with neutropenia was significantly higher than that in patients without neutropenia (CL = 67 ± 26 ml/min vs. CL = 50 ± 22 ml/min). They suggested that the average dose of vancomycin should be increased by one-third in neutropenic patients (Haeseker et al., 2014). Choi et al. used multiple logistic regression, which showed that neutropenia was the main cause of insufficient vancomycin exposure (OR = 1.75, $p = 0.029$) (Choi et al., 2017). Our previous study revealed that the incidence of acute renal hyperfunction (ARC) in patients with hematologic diseases was 37.88%, while that in patients without hematologic diseases was only 21.56% ($p = 0.001$) (Fu et al., 2020). Patients with neutropenia often have a severe infection and high mortality, thus requiring timely anti-infection treatment (Chinese Society of Hematology. Chinese Medical Association, 2020; Zhang et al., 2018). Therefore, it is very important to make individual medication plans for vancomycin in this population.

In a meta-analysis conducted by Wang et al., which included 100 vancomycin PPK models, the median value of clearance (CL) in the PPK model for adults, the elderly, and children was 3.47 (0.0272~9.3200) L/h, 2.45 (2.025~4.230) L/h, and 1.20 (0.004~25.200) L/h, respectively (Wang et al., 2020). The estimated CL value of neutropenia patients in this study was 6.84 L/h, which was higher than that reported above. As shown by the results, such patients had a higher vancomycin clearance rate. According to the PPK model and Monte Carlo simulation, ARC is defined as

TABLE 4 The typical value of population and validation results of Bootstrap

	Final model		Bootstrap	
Parameter	Estimated value	95% CI	Median	95% CI
CL (L/h)	6.84	(6.221, 7.459)	6.62	(5.801, 7.211)
V_1 (L)	20.5	(13.777, 27.223)	21.00	(12.545, 33.884)
Q (L/h)	15.2	(8.142, 22.276)	14.17	(8.339, 32.719)
V_2 (L)	50	(22.168, 77.832)	51.36	(31.139, 184.524)
θ_{CLCR_CL}	0.895	(0.642, 1.148)	0.93	(0.633, 1.388)

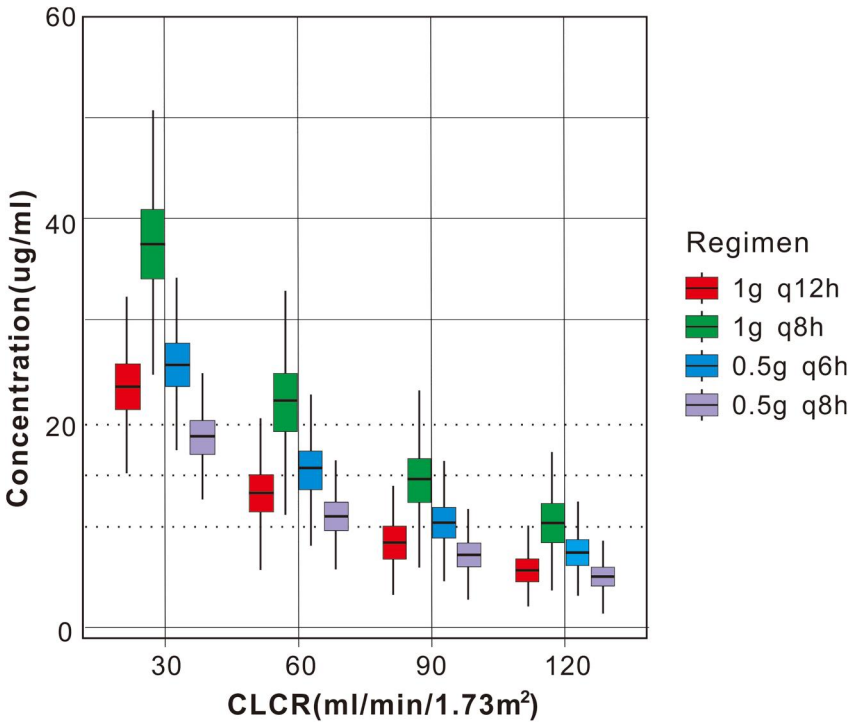

FIGURE 3 Trough concentrations of patients with different creatinine clearance under different dosage regimens

TABLE 5 Information and comparison results of the model group and non-model group

	Model group (n = 32)	Non-model group (n = 42)	p	X^2
Initial dose (g/d)	3.0	2.0	–	–
Age (y)	44.81 ± 14.22 (25, 68)	43.05 ± 13.66 (18, 69)	0.639	–
Height (cm)	162.68 ± 8.25 (150, 175)	163.33 ± 9.28 (146, 180)	0.760	–
Weight (kg)	56.57 ± 9.40 (38.0, 72.0)	56.43 ± 9.56 (48.0, 73.5)	0.947	–
CLCR (ml/min/1.73 m^2)	125.46 ± 17.57 (92.2, 164.8)	119.63 ± 18.62 (93.6, 167.3)	0.374	–
The first C_0 (μg/ml)	14.30 ± 4.73 (6.8, 23.1)	8.02 ± 2.61 (3.0, 12.9)	0.000	–
Medication days (d)	10.39 ± 4.41 (4, 24)	12.14 ± 7.32 (3, 44)	0.254	-
Dose adjustment times (n)	0.13 ± 0.34 (0, 1)	0.61 ± 0.66 (0, 2)	0.000	–
Compliance rate of the first C_0 (%, n/n)	59.38% (19/32)	35.71% (15/42)	0.043	4.094
Patients received dose adjustments (%, n/n)	12.50% (4/32)	50.00% (21/42)	0.001	11.417

CLCR ≥ 130 ml/min/1.73 m^2 (Hirai et al., 2016). When the CLCR of neutrophil deficiency patients was ≥90 ml/min/1.73 m^2, an initial dose of 1g q8h helped to achieve sufficient drug exposure quickly. The CLCR value was lower than the definition of ARC, which should be considered in clinical practice. After long-term chemotherapy and other treatment, patients with hematological malignancies tend to lose weight gradually, which may affect the detection of serum creatinine. How to eliminate these effects needs to be further studied. In general, establishing the PPK model in line with the characteristics of patients with neutropenia has certain significance for optimizing the clinical application of vancomycin. The clinical application research of the model established in this study needs to be further researched to accumulate sufficient experience and promote the individualized application of vancomycin.

5 | CONCLUSION

PPK models of vancomycin in adult patients with hematologic diseases and neutropenia are few. The established model is an important tool for setting the initial dose in patients with hematological disease and neutropenia and ClCr > 90 ml/min/1.73 m^2.

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care patients based on NONMEM model and population pharmacokinetics; grant number 20A200280).

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

CONSENT FOR PUBLICATION

Not applicable.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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