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ORIGINAL ARTICLE

Population pharmacokinetics, safety and dosing optimization of voriconazole in patients with liver dysfunction: A prospective observational study

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Aims: Voriconazole is a broad-spectrum antifungal agent for the treatment of invasive fungal infections. There is limited information about the pharmacokinetics and appropriate dosage of voriconazole in patients with liver dysfunction. This study aimed to explore the relationship between voriconazole trough concentration (C_{trough}) and toxicity, identify the factors significantly associated with voriconazole pharmacokinetic parameters and propose an optimised voriconazole dosing regimen for patients with liver dysfunction.

Methods: The study prospectively enrolled 51 patients with 272 voriconazole concentrations. Receiver operating characteristic curves were used to explore the relationship between voriconazole C_{trough} and toxicity. The pharmacokinetic data was analysed with nonlinear mixed-effects method. Dosing simulations stratified by total bilirubin (TBIL, TBIL-1: TBIL < 51 μmol/L; TBIL-2: 51 μmol/L ≤ TBIL < 171 μmol/L; TBIL-3: TBIL ≥ 171 μmol/L) were performed.

Results: Receiver operating characteristic curve analysis revealed that voriconazole C_{trough} of ≤ 5.1 mg/L were associated with significantly lower the incidence of adverse events. A 1-compartment pharmacokinetic model with first-order absorption and elimination was used to describe the data. Population pharmacokinetic parameters of clearance, volume of distribution and oral bioavailability were 0.88 L/h, 148.8 L and 88.4%, respectively. Voriconazole clearance was significantly associated with TBIL and platelet count. The volume of distribution increased with body weight. Patients with TBIL-1 could be treated with a loading dose of 400 mg every 12 hours (q12h) for first day, followed by a maintenance dose of 100 mg q12h administered orally or intravenously. TBIL-2 and TBIL-3 patients could be treated with a loading dose of 200 mg q12h and maintenance doses of 50 mg q12h or 100 mg once daily and 50 mg once daily orally or intravenously, respectively.

Dan Tang and Miao Yan, contributed equally to this work

This clinical study was registered in Chinese Clinical Trial Registry (http://www.chictr.org.cn; Registration number: ChiCTR-RRC-1800015015).

The authors confirm that the principal investigators for this paper are Prof. Da-xiong Xiang and Dr Min Zhang, and that they had direct clinical responsibility for patients.

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Conclusions: Lower doses and longer dosing intervals should be considered for patients with liver dysfunction. TBIL-based dosing regimens provide a practical strategy for achieving voriconazole therapeutic range and therefore maximizing treatment outcomes.

KEYWORDS

dosing regimen, liver dysfunction, population pharmacokinetics, therapeutic drug monitoring, voriconazole

1 | INTRODUCTION

Infections are common and represent 1 of the most important reasons for progression of liver failure, development of liver-related complications and mortality in patients with liver dysfunction.[1] Invasive fungal infections can be a life-threatening complication in patients with liver dysfunction and are associated with a high morbidity and significant mortality.[2–5] Furthermore, long-term use of broad-spectrum antibiotics and glucocorticoids, invasive procedures including liver puncture, ascites drainage, indwelling catheters and haemodialysis, and multiple hospitalizations are also associated with an increased risk of invasive fungal infections[6] and are common in patients with liver dysfunction.

Voriconazole is a triazole antifungal agent that exhibits broad-spectrum activity and is used for both the prevention and treatment of invasive fungal infections.[7] Metabolism of voriconazole occurs in the liver by hepatic cytochrome P450 isoenzymes, primarily CYP2C19 and to a lesser extent CYP3A4 and CYP2C9.[8] Multiple factors are already known to be associated with variability in voriconazole pharmacokinetics, including age, weight, liver function and genetic polymorphism of the CYP2C19 enzyme.[9–12] Voriconazole exhibits complex nonlinear pharmacokinetics and has a narrow therapeutic window.[13,14] Subtherapeutic concentrations have been associated with therapeutic failure, and supratherapeutic concentrations are correlated with an increased risk of neurological, visual and hepatic toxicity.[14,15] Therapeutic drug monitoring (TDM) of voriconazole is advocated to improve treatment outcomes and minimize the risk of adverse events. As the liver plays a key role in the disposition of voriconazole including absorption, distribution, metabolism and excretion,[16] liver dysfunction can change the pharmacokinetic characteristics of voriconazole, increasing the risk of voriconazole accumulation and subsequent adverse events.

The voriconazole product information suggests that patients with mild-to-moderate liver dysfunction (Child–Pugh class A and B) should receive half of the maintenance dose after an unchanged loading dose. However, there is limited information about the pharmacokinetics and appropriate dosing of voriconazole in patients with severe liver dysfunction (Child–Pugh class C). We have previously demonstrated that the clearance of voriconazole was significantly decreased in patients with liver dysfunction[17] highlighting the necessity to optimise voriconazole dosing regimens in these patients.

What is already known about this subject

- Invasive fungal infections in patients with liver dysfunction are associated with high morbidity and significant mortality.
- Liver dysfunction can reduce the plasma clearance of drugs due to the reduction of hepatic metabolism or biliary excretion.
- It has been shown that voriconazole trough concentration directly correlates with efficacy and toxicity.

What this study adds

- This prospective observational study demonstrates that total bilirubin is an important predictor of voriconazole pharmacokinetic parameters in patients with liver dysfunction and the clearance of voriconazole was significantly decreased in patients with liver dysfunction.
- Receiver operating characteristic curve analysis confirmed that voriconazole trough concentration of ≤5.1 mg/L were associated with significantly lower the incidence of adverse events.
- Optimised dosing of voriconazole based on total bilirubin may improve treatment outcomes.

Population pharmacokinetic (PPK) analysis was used to evaluate the pharmacokinetic characteristics and identify the measurable factors of patient-related and clinical-related pharmacokinetic variabilities. Monte Carlo simulation is a valuable tool to determine dosing regimens and optimize antibacterial therapies.[18] The present study aims to: (i) explore the relationship between voriconazole trough concentration (C_{trough}) and toxicity to identify the safety C_{trough} range; (ii) develop a PPK model of voriconazole in patients with liver dysfunction; (iii) identify factors significantly associated with voriconazole pharmacokinetic parameters; and (iv) evaluate potential voriconazole dosing regimens in patients with liver dysfunction through MCS utilizing final pharmacokinetic model.

2 | METHODS

2.1 | Patients and data collection

The prospective and observational study was conducted on liver dysfunction patients who received voriconazole between 28 February 2018 and 11 December 2018. The inclusion criteria were: (i) age ≥15 years; (ii) patients were diagnosed with liver dysfunction, such as liver failure or liver cirrhosis according to the Child–Pugh classifications; (iii) treatment or prevention of invasive fungal infections with voriconazole; and (iv) patients contributed at least 1 blood sample. The exclusion criteria were: (i) patients who were allergic or intolerant to voriconazole; (ii) pregnant or lactating patients; (iii) using potent CYP450 inducer or inhibitor such as rifampicin, isoniazid, phenytoin, carbamazepine during voriconazole treatment, but did not include proton pump inhibitors (PPIs); (iv) patients who lacked the necessary data such as genotype of CYP2C19, renal and liver function index. This study was approved by Ethics Committee of The Second XiangYa Hospital of Central South University (Changsha, China). All of the patients provided written informed consent before participating in the study.

Information of the following potential covariates was collected and analysed: age, sex, body weight (WT), platelet counts (PLT), alanine aminotransferase, aspartate aminotransferase, total bilirubin (TBIL), direct bilirubin, albumin, creatinine clearance rate, which is calculated using the Cockcroft and Gault equation,[19] international normalized ratio (INR), CYP2C19 genotype and concomitant medication (PPIs). Liver dysfunction was classified using Child–Pugh scores,[20] and Model for End-stage Liver Disease (MELD) scores.[21] The Child–Pugh score was calculated following the severity of hepatic encephalopathy, the amount of ascites, serum bilirubin, serum albumin, and prothrombin time. The MELD score according to the following formula: MELDscore = $0.957 \times \log_e(\text{creatinine, mg/dL}) + 0.378 \times \log_e(\text{bilirubin, mg/dL}) + 1.12 \times \log_e(\text{INR}) + 6.43$ *MELD score* = $0.957 \times log_e(creatinine, mg/dL) + log_e(bilirubin, mg/dL) + 1.12 \times log_e(INR) + 6.43$.

Adverse events were collected throughout voriconazole treatment, but hepatotoxicity was not assessed because it was difficult to distinguish between voriconazole-related hepatotoxicity and the patient's disease progression. The relationship of adverse events to voriconazole was determined to be definite, probable or unlikely according to Common Terminology Criteria for Adverse Events v5.0 (http://ctep.cancer.gov).

2.2 | Dosing regimen and specimen collection

Voriconazole dosing was according to the product information, where patients with mild to moderate liver dysfunction (Child–Pugh A and B) received standard loading doses (400 mg twice daily for oral or 6 mg/kg twice daily for intravenous) on the first day, followed by half the standard maintenance doses (100 mg twice daily for oral or 2 mg/kg twice daily for intravenous). Due to the limited data on the dosing of voriconazole in patients with severe liver dysfunction (Child–Pugh C), dosing of these patients was based on the clinician's experience. The subsequent doses for all patients were adjusted according to the measured voriconazole C_{trough} and the patient's clinical response to voriconazole (effective or ineffective, with or without adverse effects).

Venous blood samples (2 mL) were collected into anticoagulant tubes. Patients were randomly collected 2–3 blood samples at 0.5, 1, 1.5, 2, 4, 6, 8, 12 and 24 hours after receiving the first dose or the maintenance dose. In addition, C_{trough} samples were collected within 2 hours before any maintenance doses. All voriconazole plasma concentrations were analysed by automatic 2-dimensional liquid chromatography (Demeter Instrument Co., Ltd., Hunan, China).[17] The 2-dimensional separation conditions consisted of the following: the first-dimensional chromatographic column was FRO C18 (100 mm × 3.0 mm, 5 μm, ANAX); and the flow rate: 1.0 mL/min. The 2-dimensional chromatographic column was ASTON HD C18 (150 mm × 4.6 mm, 5 μm, ANAX). The linearity range was 0.24 to 12.04 mg/L. The intra- and interday precisions were 1.94–2.22% and 2.15–6.78%, respectively.

2.3 | DNA sequencing and CYP2C19 genetic polymorphism

Genomic DNA was extracted using commercially available EZNA SQ Blood DNA Kit II. Sanger dideoxy DNA sequencing method with ABI3730xl-full automatic sequencing instrument (ABI Co.) from Boshang Biotechnology Co. Ltd. (Shanghai, China) was used for CYP2C19 genotyping. CYP2C19 phenotypes were classified into 5 categories: ultrarapid metabolizer (UM, CYP2C19*17/*17), rapid metabolizer (RM, CYP2C19*1/*17), extensive metabolizer (EM, CYP2C19*1/*1), intermediate metabolizer (IM, CYP2C19*1/*2, CYP2C19*1/*3, CYP2C19*2/*17) and poor metabolizer (PM, CYP2C19*2/*2, CYP2C19*2/*3, CYP2C19*3/*3).[22]

2.4 | Statistical analysis

The Wilcoxon 2-sample test was used to compare voriconazole C_{trough} between the adverse event and without adverse event group. Univariate analysis was performed to assess the association between voriconazole C_{trough} and adverse events. Receiver operating characteristic (ROC) curves were used to explore the relationship between voriconazole C_{trough} and adverse events. Statistical analysis was performed with SPSS version 22.0 (IBM Corporation, Armonk, NY, USA).

2.5 | PPK analysis

The concentration–time data of voriconazole was developed using Phoenix NLME (version 8.0, Pharsight Corporation, USA).

The first-order conditional estimation method with the η-ε interaction option (FOCE ELS) was used throughout the model development.

One- and 2-compartment structural kinetic models with first-order and Michaelis–Menten elimination were evaluated to describe the pharmacokinetics of voriconazole. Finally, we comprehensively compared the objective function value (OFV), graphical goodness of fit, the evaluation of parameter estimates (including precision) and scientific and physiological plausibility to choose the best base model. The oral absorption rate constant (k_a) was fixed to a value of 1.1 h^{-1} based on the results from a previous study.[23]

The interindividual variability in voriconazole pharmacokinetic parameters was described with an exponential error model. Residual error models for voriconazole were tested as follows: the proportional error model, the additive error model and combined error model, including proportional plus additive error model.

Potential demographic and biochemical covariates were evaluated by visual inspection of covariates possible relationships with pharmacokinetic parameters included in the model. For continuous covariates, a linear, piece-wise, exponential and power parameter–covariate relations were tested. Categorical covariates were linearly included. Then, a covariate model in a stepwise forward–inclusion and backward–elimination procedure were carried out. A covariate was considered to be significant when inclusion of the covariate resulted in a decrease in the OFV of >6.64 (P < .01) and elimination of the covariate resulted in an increase in the OFV of >10.83 (P < .001).

Goodness-of-fit plots were used to evaluate the adequacy of fitting. The bootstrap method was used to assess the robustness and stability of the final model. One thousand individuals from the original data were performed. All of the model parameters were estimated, and their median and 2.5th and 97.5th percentiles were calculated. That was stable if the 95% confidence interval (CI) for the parameter estimates derived from the 1000 bootstrap runs encompassed the original final parameter estimate.

Visual predictive check (VPC) was used to assess the predictive performance of the model. VPC is a simulation-based method of model validation, which does not consider the uncertainty of the estimated parameters. The 95% CIs for the 10th, 50th, and 90th percentiles of the simulated concentrations were calculated, and compared with the observed concentrations.

2.6 | MCS

One thousand individuals receiving the dosing regimens including loading doses of 200, 300 and 400 mg every 12 hours (q12h), and maintenance doses of 50, 100, 150 and 200 mg once daily (qd) or q12h orally or intravenously were simulated by the final model. The dosing regimens were simulated for 30-days and stratified by TBIL (TBIL-1: TBIL < 51 μmol/L; TBIL-2: 51 μmol/L ≤ TBIL < 171 μmol/L; TBIL-3: TBIL ≥ 171 μmol/L) were performed. The voriconazole C_{trough} range of 0.5–5.0 mg/L, which was recommended in the Chinese Practice Guideline for Individualized Medication of voriconazole,[24] was used as the acceptable range. The probability of target attainment (PTA) for the C_{trough} range was examined for each of the different dosing regimens.

3 | RESULTS

3.1 | Patients' characteristics

Fifty-one patients with a total of 272 voriconazole plasma concentrations were included in this study. The demographics and clinical information of the patients are summarized in Table 1. Patients with Child–Pugh grade C or MELD score >15 scored up >70% of all patients. There was a significant variation in the voriconazole plasma concentrations, with a median concentration of 3.4 mg/L and a range of 0.26–14.08 mg/L. There were 190 plasma C_{trough}, and 82 plasma concentrations collected within the 24 hours after intravenous or oral administration. There were 4 types of CYP2C19 genotypes in the present study, 1 UM patients (CYP2C19*17*17), 24 EM patients (CYP2C19*1*1), 21 IM patients (CYP2C19*1*2, CYP2C19*1*3) and 5 PM patients (CYP2C19*2*2, CYP2C19*2*3). The genotypes were divided into 3 groups (UM/EM, IM and PM) for the purposes of PPK model development.

3.2 | Voriconazole concentrations and adverse events

Adverse events were reported in 20 patients (39.2%) during voriconazole therapy. These included dizziness, hallucinations and visual disturbance such as altered colour discrimination, blurred vision and photophobia. The median duration from voriconazole initiation to onset of adverse events was 2 days (range, 1–12 days). The median voriconazole concentration at the time of these adverse events was significantly higher than in patients without adverse events (6.5 mg/L *vs* 2.3 mg/L, P < .0001). An ROC curve analysis confirmed voriconazole C_{trough} to be a significant predictor of adverse events, with a voriconazole C_{trough} of ≤5.1 mg/L found to minimize the incidence of adverse events (Figure 1).

3.3 | PPK analysis

A 1-compartment pharmacokinetic model with first-order oral absorption and elimination adequately describes the data. Interindividual variability of the parameters was best fitted to an exponential equation, and residual error was best characterized by a proportional error model.

The analysis identified the PLT and TBIL as the most significant covariates for clearance (CL) and WT as a significant covariate for

TABLE 1 Demographics and clinical information of the study patients (n = 51)

Characteristic	Value [a]
Sex (male/female), *n*	43/8
Age (y)	46.4 ± 12.8 (47,15–89)
Weight (kg)	60.0 ± 13.1 (58,36–99)
PLT count (10^9/L)	85.4 ± 70.8 (65,20–450)
ALT (U/L)	59.4 ± 70.7 (39.5,5.7–48.6)
AST (U/L)	106.5 ± 98.5 (78.3,15.5–737)
ALB (g/L)	32.6 ± 4.9 (32.4,23.3–49.3)
TBIL (μmol/L)	300.6 ± 178.4 (314,7.8–729)
DBIL (μmol/L)	205.1 ± 124.0 (217.4,3.4–545.2)
BUN (mmol/L)	7.3 ± 5.8 (5.4,1.3–33.7)
CLcr (mL/min)[b]	100.6 ± 45.1 (94.5,17.3–231)
INR	2.38 ± 1.2 (2.1,0.9–5.9)
PT (second)	25.6 ± 9.9 (23.2,11.8–53.9)
PTA (%)	42.9 ± 24.0 (35,13–117)
C_{trough} (mg/L)	3.9 ± 2.5 (3.4,0.26–14.08)
Concomitant medication (PPI)	n (%) of patients
Omeprazole	8 (15.7%)
Esomeprazole	9 (17.6%)
Pantoprazole	6 (11.8%)
Lansoprazole	16 (31.4%)
Genotype distribution frequency	
Ultrarapid metabolizer (UM)	1 (2.0%)
Extensive metabolizer (EM)	24 (47.1%)
Intermediate metabolizer (IM)	21 (41.1%)
Poor metabolizer (PM)	5 (9.8%)
Child–Pugh class (A:B:C)	4:11:36
MELD score	22.4 ± 10.7(23.8, 1–45.5)

PLT count, platelets count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; TBIL, total bilirubin; DBIL, direct bilirubin; BUN, blood urea nitrogen; CLcr, creatinine clearance rate; INR, international normalized ratio; PT, Prothrombin time; PTA, prothrombin time activity; PPI, proton pump inhibitors;

[a]Results for continuous covariates are presented as mean ± SD [median, range], and results for categorical covariates are presented as frequency (percentage).

[b]According to Cockcroft–Gault formulation.

volume of distribution (V). The typical value of CL, V and oral bioavailability (F) of voriconazole obtained in the final model are 0.88 L/h, 148.8 L and 88.4%, respectively. The terminal elimination half-life ($t_{1/2}$) was 117.2 hours, and the time for voriconazole to reach steady state is about 30 days. The interindividual variability of CL and V in final model were 18.0% and 12.0%, respectively. Compared to the base model (CL: 68.3%, V: 15.3%), the interindividual variability of CL and V significantly decreased in the final model. The interindividual variability of F is fixed as 0 due to the large of shrinkage for F. The final model included the following equations: CL(L/h) = 0.88 × (PLT/65) ^ 0.32 × (TBIL/314) ^ (−0.57) × exp(ηCL); V (L) = 148.8 × (WT/58) ^ 1.43 × exp(ηV); F = 88.4%. The final model parameters and the result of bootstrap are summarized in Table 2.

Goodness-of-fit plots from the basic and final models presenting the correlations between population-predicted concentrations and individual-predicted *vs* observed concentrations of voriconazole are shown in Figure 2. The figure showed improvement in the final model fit had been improved compared to the base model. There was no structural bias in the plot of population-predicted and individual-predicted concentrations *vs* observed concentrations. The conditional weighted residuals of population-predicted concentrations and time for voriconazole are shown in Figure 3. The conditional weighted residuals random distribution was around zero for voriconazole. The distribution was symmetrical distribution and no concentration- or time-related trends were observed for voriconazole. Most points were within an acceptable range (−2 to 2).

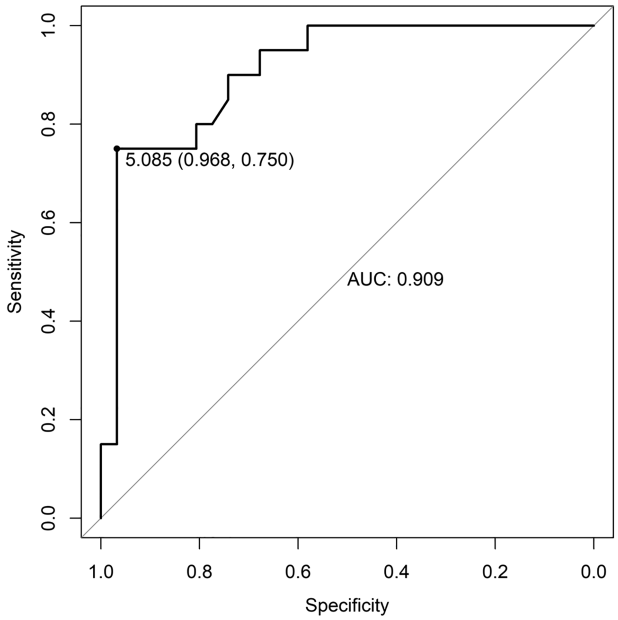

FIGURE 1 Receiver operating characteristic curves for predicting adverse events from voriconazole concentration. AUC, area under the curve

The bootstrap (n = 1000) results are summarized in Table 2. The bootstrap analysis showed that 961 out of 1000 run converged successfully. The parameter estimates of the final model were similar to those of the bootstrap, suggested good robustness and stability of the final model. The parameters of the final model were within the 95% CI obtained from bootstrap replications, indicating that the estimates for the pharmacokinetic parameters in the final model were accurate and that the model was stable.

The VPC results for the final model are shown in Figure 4. Most of the 10th, 50th and 90th percentiles of observed data fell within the 95% CI of the corresponding percentiles of predictions. The results indicated that the final model have a good predictive performance.

3.4 | MCS

The elimination of voriconazole was markedly prolonged (typical value of CL: 0.88 L/h) in patients with liver dysfunction. The $t_{1/2}$ is 117.2 hours, calculated by the CL and V, which means that voriconazole concentration reaches the steady state about 30 days later. Furthermore, fungal infection treatment usually takes 1 month or more. Therefore, the dosing regimens were simulated at 30-days for treatment. Simulations of oral or intravenous administration did not demonstrated a significant difference. The probability of C_{trough} target attainment after intravenous and oral administration for 30 days of standard unadjusted dosing regimen of voriconazole for patients without liver dysfunction (loading dose: 400 mg q12h, maintenance dose: 200 mg q12h) are shown in Table 3. The maximum PTA of all group was <50%. Apart from TBIL-1 patients, there was 90% overexposure in the other groups. The results for the recommended dosing regimen of voriconazole for patients with mild to moderate liver dysfunction (Child–Pugh A and B; loading dose: 400 mg q12h, maintenance dose: 100 mg q12h) are shown in Table 4. The PTA for patients with TBIL-1 was 91.7 and 85.2%, administered orally and intravenously respectively. It indicated that dosing regimen with a loading dose of 400 mg q12h for 2 doses, followed by a maintenance dose of 100 mg q12h administered intravenously or orally for patients with TBIL-1 was suitable.

TABLE 2 Population pharmacokinetic parameter estimates from the final model and bootstrap validation

	Basic model		Final model		Bootstrap	
Parameter	Estimate	CV%	Estimate	CV%	Median	95%CI
CL (L/h)	1.07	13.0%	0.88	10.5%	0.90	0.74–1.10
V (L)	141.4	8.1%	148.8	7.5%	148.8	129.3–172.9
k_a (h^{-1})	1.1(fix)	-	1.1(fix)	-	1.1(fix)	-
F (%)	86.4	7.5%	88.4	7.5%	89.9	78.1–99.9
PLT on CL	-	-	0.32	21.2%	0.31	0.075–0.52
TBIL on CL	-	-	-0.57	−12.6%	−0.57	−0.72 to 0.44
WT on V	-	-	1.43	18.0%	1.42	0.86–1.96
Interindividual variability						
ηCL	68.3%	25.8%	18.0%	45.3%	17.6%	0.043–0.32
ηV	15.3%	22.9%	12.0%	45.6%	10.9%	0.02–0.19
Residual variability						
Proportional error	21.8%	10.3%	19.4%	10.0%	19.3%	0.15–0.24

CL, clearance of the central compartment; V, volume of distribution for the central compartment; k_a, first-order absorption rate constant; F, bioavailability; PLT, platelets; TBIL, total bilirubin; WT, body weight; η, interindividual variability; CV, coefficient of variation, calculated as 100* standard errors/parameter value; CI: confidence interval, 2.5th and 97.5th percentile of the ranked bootstrap parameter estimates.

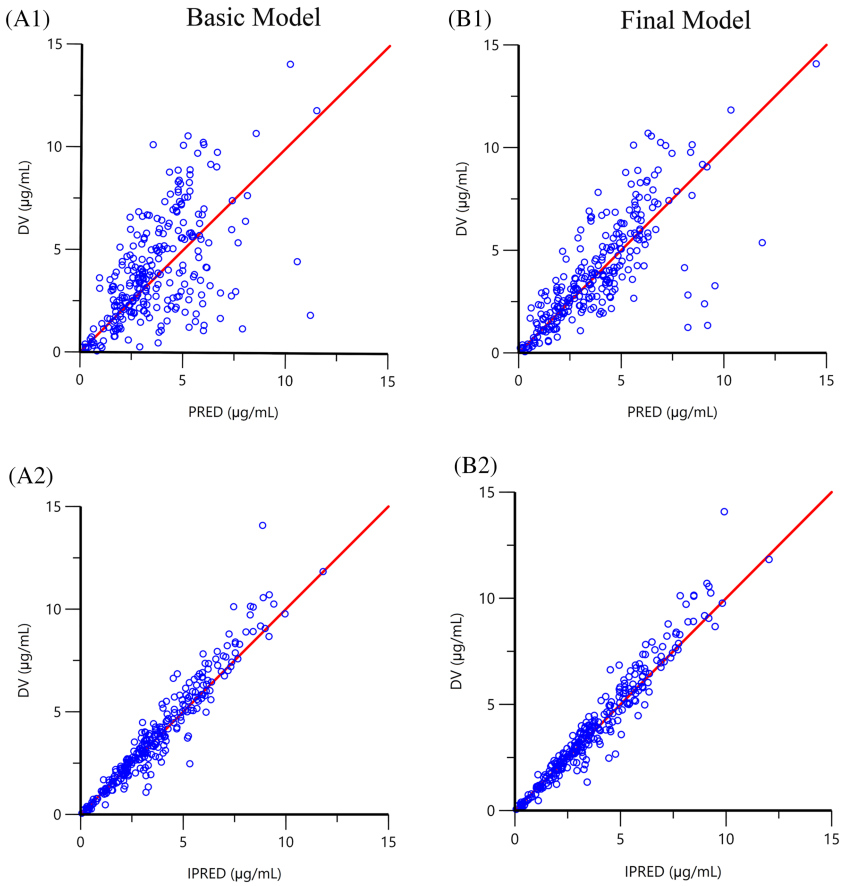

FIGURE 2 Diagnostic goodness-of-fit plots for basic model (A1, A2) and final model (B1, B2). A1 and B1, observed voriconazole plasma concentrations *vs* population-predicted (PRED) concentrations; A2 and B2, observed voriconazole plasma concentrations *vs* individual-predicted (IPRED) concentrations; the lines are the lines of unity y = x. DV, dependent variable

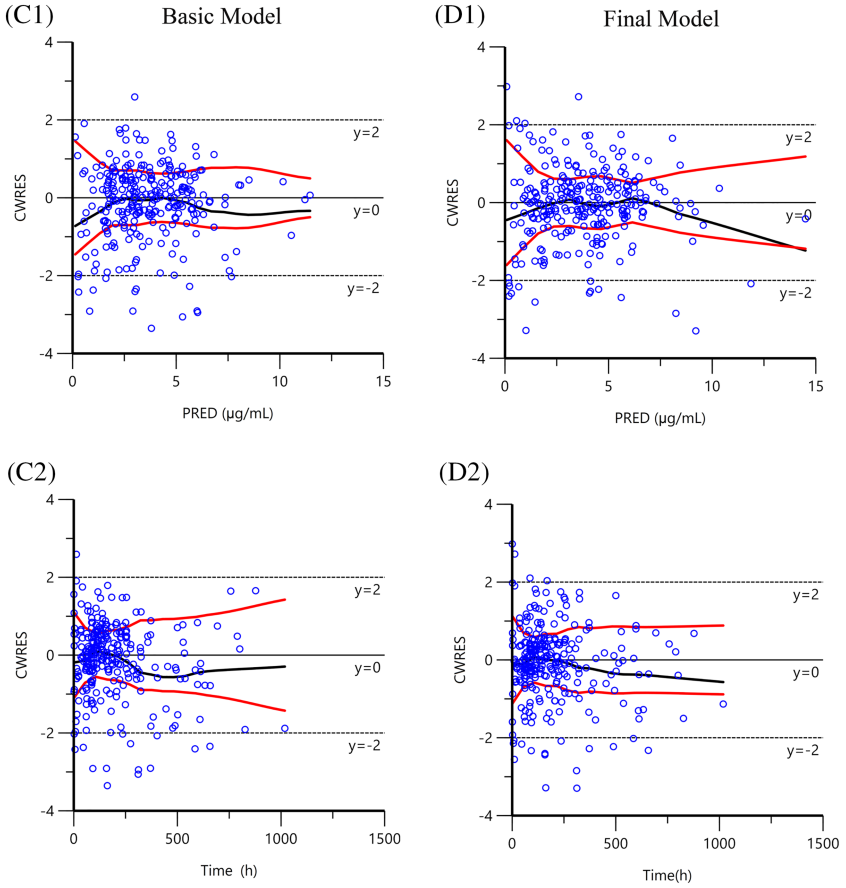

FIGURE 3 Diagnostic goodness-of-fit plots for basic model (C1, C2) and final model (D1, D2). C1 and D1, conditional weighted residuals (CWRES) *vs* population-predicted (PRED) concentrations; C2 and D2, conditional weighted residuals *vs* time. The black curve is the locally weighted scatterplot smoothing (loess) curve of the overall residual; the red curve is the unilateral loess curve of the residual

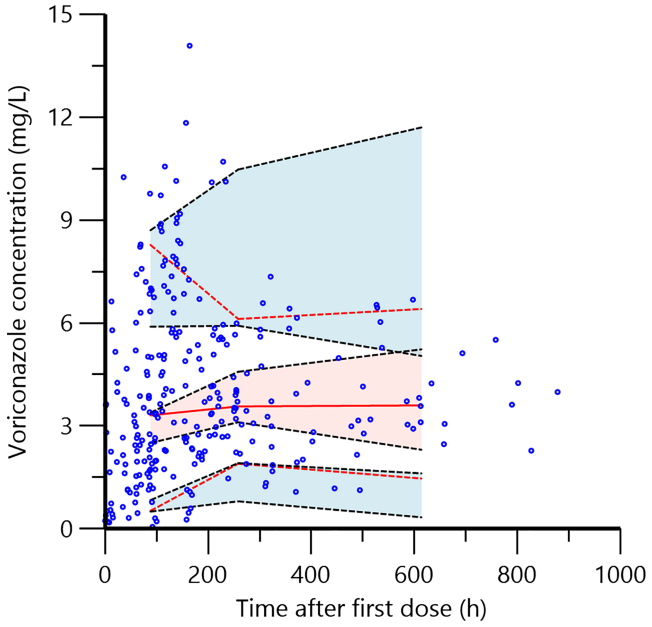

FIGURE 4 Visual predictive check of the final model. The observed concentrations of voriconazole are shown as blue circles. Red solid and dashed lines represent the 50th, 10th and 90th percentile of the observed concentrations, respectively. The shaded areas are the 95% CI for the model-predicted 90th, 50th and 10th percentiles

For patients with TBIL-2 and TBIL-3, we simulated the achievement of C_{trough} after oral and intravenous administration with different loading doses (400, 300 and 200 mg q12h) in order to determine the loading dose, the results are shown in Table 5. An oral and intravenous loading dose of 200 mg q12h demonstrated the highest PTA (>90%). Utilizing this loading dose, different maintenance doses and dosing intervals were simulated to determine the optimal maintenance dose. The PTA of the examined maintenance doses are shown in Table 6. The simulations demonstrated that a maintenance dose of 50 mg q12h or 100 mg qd orally or intravenously for TBIL-2 patients, and a maintenance dose of 50 mg qd orally or intravenously for TBIL-3 patients were optimal. The simulated 30-day median voriconazole C_{trough} *vs* time profiles based on the optimal intravenous or oral dosing regimen are shown in Figure 5. The results showed that the median voriconazole C_{trough} in all patients were within the acceptable concentration range (0.5–5.0 mg/L), and the distribution of C_{trough} was centralized between 2 and 4 mg/L.

4 | DISCUSSION

This study prospectively investigated 51 patients with liver dysfunction to develop a PPK model. The results of this analysis showed that a 1-compartment pharmacokinetic model with first-order absorption and elimination was able to describe voriconazole pharmacokinetics in patients with liver dysfunction, which is consistent with our previous retrospective studies, and it is also similar to studies by Pascual et al.[23] and Wang et al.[25] who investigated voriconazole pharmacokinetics in patients with IFIs. However, a premarketing study[13] on the pharmacokinetics, safety and tolerability of voriconazole showed that voriconazole exhibits nonlinear elimination and the study was

TABLE 3 Probability of C_{trough} attainment after intravenous administration for 30 days in doses of normal liver function patients (loading dose: 400 mg every 12 h, maintenance dose: 200 mg every 12 h)

	Probability of C_{trough} attainment					
	Intravenous administration			Oral administration		
Group of TBIL	<0.5 mg/L	0.5–5.0 mg/L	>5.0 mg/L	<0.5 mg/L	0.5–5.0 mg/L	>5.0 mg/L
TBIL-1	0.0%	37.2%	62.8%	0.0%	48.4%	51.6%
TBIL-2	0.0%	8.1%	91.9%	0.0%	13.1%	86.9%
TBIL-3	0.0%	2.7%	97.3%	0.0%	3.9%	96.1%

TABLE 4 Probability of C_{trough} attainment after intravenous or oral administration for 30 days according to the recommended dosing regimen (loading dose: 400 mg every 12 h, maintenance dose: 100 mg every 12 h) of voriconazole instructions for mild to moderate patients with liver dysfunction

	Probability of C_{trough} attainment					
	Intravenous administration			Oral administration		
Group of TBIL	<0.5 mg/L	0.5–5.0 mg/L	>5.0 mg/L	<0.5 mg/L	0.5–5.0 mg/L	>5.0 mg/L
TBIL-1	0.0%	85.2%	14.8%	0.0%	91.7%	8.3%
TBIL-2	0.1%	45.0%	55.0%	0.0%	56.6%	43.4%
TBIL-3	0.0%	9.8%	90.2%	0.0%	16.2%	83.8%

TBIL, total bilirubin;
TBIL-1, TBIL <51 μmol/L; TBIL-2, 51 μmol/L ≤ TBIL < 171 μmol/L; TBIL-3, TBIL ≥ 171 μmol/L

TABLE 5 Probability of C_{trough} attainment after oral or intravenous administration at different loading doses in TBIL-2 and TBIL-3 patients

		Probability of C_{trough} attainment					
		Intravenous administration			Oral administration		
Loading doses	Group of TBIL	<0.5 mg/L	0.5–5.0 mg/L	>5.0 mg/L	<0.5 mg/L	0.5–5.0 mg/L	>5.0 mg/L
400 mg q12h	TBIL-2	0.0%	64.2%	35.8%	0.0%	77.5%	22.5%
	TBIL-3	0.0%	53.2%	46.8%	0.0%	68.1%	31.9%
300 mg q12h	TBIL-2	0.0%	91.7%	8.3%	0.0%	96.6%	3.4%
	TBIL-3	0.0%	83.4%	16.6%	0.0%	91.0%	9.0%
200 mg q12h	TBIL-2	0.0%	99.8%	0.2%	0.0%	100%	0.0%
	TBIL-3	0.0%	98.8%	1.2%	0.0%	99.7%	0.3%

q12h, every 12 hours; TBIL, total bilirubin;
TBIL-1, TBIL <51 μmol/L; TBIL-2, 51 μmol/L ≤ TBIL < 171 μmol/L; TBIL-3, TBIL ≥ 171 μmol/L

TABLE 6 Probability of C_{trough} attainment after oral and intravenous administration at different maintenance doses in TBIL-2 and TBIL-3 patients based on a loading dose of 200 mg every 12 hours

			Probability of C_{trough} attainment					
			Intravenous administration			Oral administration		
Group of TBIL	Dosing intervals	Maintenance doses	<0.5 mg/L	0.5–5.0 mg/L	>5.0 mg/L	<0.5 mg/L	0.5–5.0 mg/L	>5.0 mg/L
TBIL-2	q12h	200 mg	0.0%	11.7%	88.3%	0.0%	15.9%	84.1%
		150 mg	0.0%	22.9%	77.1%	0.0%	30.8%	69.2%
		100 mg	0.0%	53.2%	46.8%	0.0%	63.6%	36.4%
		50 mg	0.0%	95.2%	4.8%	0.1%	97.8%	2.1%
	qd	200 mg	0.0%	59.7%	40.3%	0.0%	69.6%	30.4%
		150 mg	0.0%	80.7%	19.3%	0.0%	87.3%	12.7%
		100 mg	0.2%	95.9%	3.9%	0.3%	97.8%	1.9%
		50 mg	2.3%	97.6%	0.0%	4.0%	96.0%	0.0%
TBIL-3	q12h	200 mg	0.0%	6.2%	93.8%	0.0%	7.6%	92.4%
		150 mg	0.0%	9.2%	90.8%	0.0%	11.7%	88.3%
		100 mg	0.0%	17.4%	82.6%	0.0%	24.0%	76.0%
		50 mg	0.0%	65.3%	34.7%	0.0%	76.2%	23.8%
	qd	200 mg	0.0%	20.9%	79.1%	0.0%	27.2%	72.8%
		150 mg	0.0%	37.2%	62.8%	0.0%	47.2%	52.8%
		100 mg	0.0%	70.1%	29.9%	0.0%	80.5%	19.5%
		50 mg	0.0%	98.7%	1.3%	0.1%	99.6%	0.4%

q12h, every 12 hours; qd, once a day; TBIL, total bilirubin;
TBIL-1, TBIL <51 μmol/L; TBIL-2, 51 μmol/L ≤ TBIL < 171 μmol/L; TBIL-3, TBIL ≥ 171 μmol/L

conducted on healthy male volunteers. Farkas et al.[26] compared the accuracy and precision of 3 different structural PPK models: the linear, mixed linear and nonlinear models respectively to predict future voriconazole concentrations. The results showed that while simulations with the linear model was found to be slightly more accurate and similarly precise, the small difference in accuracy was probably negligible from the clinical point of view, making all 3 approaches appropriate for use in a voriconazole TDM program. Therefore, the choice of structural model should be combined with data characteristics and model selection principles to select the best model.

The estimated values of the pharmacokinetic parameters CL, V and F of voriconazole in patients with liver dysfunction (0.88 L/h, 148.8 L and 88.4%, respectively) are similar to our previous findings[17] (0.56 L/h, 134 L and 80.8%, respectively). A dose escalation study[13] in healthy subjects found that voriconazole CL was 8.1–20 L/h, and V was 124–160 L. The pharmacokinetic studies of voriconazole in renal transplant recipients[12] and lung transplant recipients[27] showed that voriconazole CL was 2.88 and 3.45 L/h, respectively. The V of voriconazole was 169.3 L and 197.7 L, respectively. In addition, the CL of voriconazole in patients with invasive fungal infections by

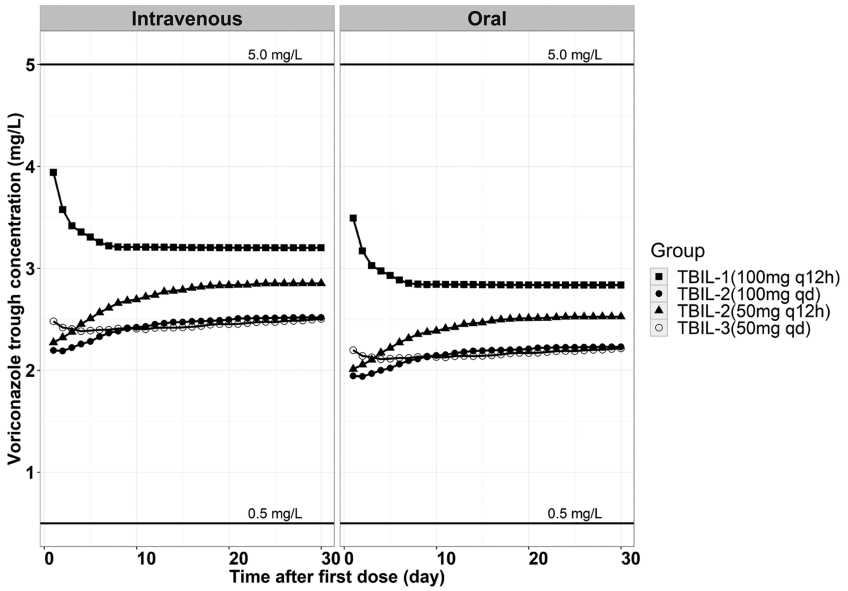

FIGURE 5 The median voriconazole C_{trough} *vs* time profiles for 30 days based on the optimal intravenous (right) or oral (left) dosing regimen. The loading doses of TBIL-1, TBIL-2 and TBIL-3 patients were 400 mg q12h, 200 mg q12h and 200 mg q12h for first day, respectively. The maintenance doses of TBIL-1, TBIL-2 and TBIL-3 patients were 100 mg q12h (squares), 50 mg q12h (filled dots) or 100 mg qd (triangles) and 50 mg qd (hollow dots), respectively. q12h, every 12 hours; qd, once a day; TBIL, total bilirubin

Pascual et al.[23] and Wang et al.[25] was 5.2 L/h and 6.95 L/h, the V was 92 L and 200 L, respectively. This indicated that compared with patients without liver disease and healthy subjects, voriconazole showed a significant decrease in CL in patients with liver dysfunction, but the V was not significantly different in the presence of liver disease.

TBIL was shown to be an important covariate affecting the CL of voriconazole in this study. The final model demonstrated that high TBIL values were significantly correlated with decreased CL. Voriconazole is mainly metabolized by cytochrome P450 enzymes in the liver (98%) and then excreted through the kidney and bile, with <2% of a dose of voriconazole is excreted into the urine as unchanged voriconazole.[28] In liver disease, a reduction in absolute liver cell mass or a decreased in metabolic enzyme activity may lead to impaired drug metabolism,[16] which causes a large amount of voriconazole to accumulate in the body. Therefore, voriconazole CL is significantly decreased for patients with liver dysfunction. The PLT was found to be significantly associated with CL in the present study, similar to our previous studies.[17] The reduction of PLT counts is very common in patients with cirrhosis and is correlated with severity of liver function. WT had a significant effect on V, and was positively correlated with V.

Age, CYP2C19 genotype and PPI were not found to affect significantly the pharmacokinetic parameters of voriconazole, which is consistent with our previous analysis.[17] A prospective study of voriconazole by Wang et al.[25] has shown that age has a significant effect on voriconazole CL, the median voriconazole plasma concentrations in elderly (age ≥65 years) have been 80–90% higher than those in younger patients. Another prospective study of lung transplant recipients[29] found a correlation between age and initial voriconazole C_{trough}: older patients (age ≥60 y) are more likely to have a higher initial C_{trough}. In older patients, the hepatic mass, volume and blood flow, renal excretion and total body water were reduced, which resulted in lower CL.[30–32] However, this study did not find age to have a significant effect on the pharmacokinetic parameters of voriconazole. Many studies[33–36] in patients without liver disease have showed that PM patients have higher voriconazole plasma concentration compared with EM and IM patients. However, CYP2C19 polymorphisms and PPI (CYP2C19 enzyme inhibitors) seem to have no effect on the pharmacokinetic parameters of voriconazole in this study. Ohnishi et al.[37] have reported that in 31 patients with chronic liver disease (9 with chronic hepatitis, 22 with cirrhosis comprising 20 Child–Pugh type A, 1 type B, 1 type C), patients with PM polymorphisms have higher omeprazole hydroxylation indexes (a metabolite of CYP2C19 enzyme) than those with EM and IM polymorphisms, but only 2 Child–Pugh B and C patients were included. In patients with moderate to severe liver dysfunction, whether gene polymorphism is still an important factor affecting CYP2C19 enzyme activity is worthy of further investigation.

At present, the product information for voriconazole suggests that the standard loading dose should be used but the maintenance dosing should be halved in patients with mild-to-moderate liver disease (Child–Pugh class A and B); however, no dose recommendations in severe liver dysfunction patients are provided. A multicentre, retrospective clinical study found that the recommended dose and halved maintenance dose might be inappropriate in patients with Child–Pugh class B and C cirrhosis.[38,39] It has been reported in a retrospective study[40] that oral voriconazole maintenance doses in patients with Child–Pugh class C should be reduced to approximately 1/3 that of patients with normal liver function, while another clinical study for acute-on-chronic liver failure (ACLF) patients[4] has proposed that voriconazole concentration can be maintained a reasonable range (1–5 mg/L) with a loading dose of 200 mg twice daily and a maintenance dose of 100 mg once daily of voriconazole dosing regimen. However, both of these studies are retrospective analyses with small sample sizes (6 cases of cirrhosis C grade and 20 cases of chronic acute liver failure, respectively), so the voriconazole dosing regimen for patients with liver dysfunction still needs further verification.

In the current study, TBIL-based simulations after intravenous and oral voriconazole were performed using voriconazole C_{trough} (0.5–5.0 mg/L) as a target with the combination of MCS to optimize voriconazole dosing regimen. The dosing regimen was divided into 3 groups (TBIL-1 group: TBIL < 51 μmol/L; TBIL-2 group: 51 μmol/L ≤ TBIL < 171 μmol/L; TBIL-3 group: TBIL ≥ 171 μmol/L) according to TBIL level. The cut-off value of TBIL (51 μmol/L and 171 μmol/L) was determined according to the upper limit of TBIL for Child–Pugh score and the diagnostic criteria of liver failure, respectively. The results showed that there was no significant difference in the PTA after voriconazole intravenous and oral administration. The dosing regimen for patients with normal liver function (loading dose: 400 mg q12h; maintenance dose: 200 mg q12h) is probably inappropriate for patients with liver dysfunction, and is associated with a high risk of toxicity (51.6–97.3% probability of toxicity). Patients with TBIL-1 can be treated with loading dose of 400 mg q12h for 2 doses followed by maintenance dose of 100 mg q12h intravenously or orally, which is the dosing regimen of patients with mild-to-moderate liver disease (Child–Pugh Class A and B) in the medication label of voriconazole, but it is not suitable for patients with TBIL-2 and TBIL-3. For patients with TBIL-2 and TBIL-3, the PTA of voriconazole within 30 days is >90% when TBIL-2 and TBIL-3 patients can be treated with maintenance doses of 50 mg q12h or 100 mg qd and 50 mg qd orally or intravenous, respectively. Meanwhile, the steady-state time (about 30 days) of voriconazole was markedly prolonged in patients with liver dysfunction, a loading dose of 200 mg q12h orally or intravenously must be given to rapidly achieve the voriconazole acceptable concentration range.

This study found that adverse events have generally occurred at higher voriconazole concentrations, and ROC curve analysis revealed a significant association between voriconazole C_{trough} and toxicity, with voriconazole C_{trough} of ≤5.1 mg/L found to minimize the incidence of adverse events, which was similar to the studies by Dolton et al.[41,42] and Troke et al.[43]

There are several limitations to the present study. Firstly, this study has a small sample size and it is a single-centre study. Secondly, this study did not find the CYP2C19 genotype to have a significant effect on the pharmacokinetic parameters of voriconazole, possibly due to the small number of patients with PM and UM polymorphisms included. Thus, the results need further validation in future clinical studies.

5 | CONCLUSIONS

This study suggests that the TBIL, PLT and WT are significantly associated with voriconazole pharmacokinetic parameters. TBIL is a critical factor leading to large pharmacokinetic variation of voriconazole. Using MCS to optimize the dosing regimen in patients with liver dysfunction based on our PPK model and TBIL stratification, we demonstrated that lower doses and longer administration intervals should be considered for patients with liver dysfunction. This is helpful for clinicians making decisions about voriconazole dosing regimens, especially to determine efficient initial dosing strategies and in primary hospitals where TDM is not available.

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AUTHORS' CONTRIBUTIONS

D.T. participated in the DNA extraction and detection, data collection, drafting of the manuscript, and conducted the population pharmacokinetics analyses. M.Y. designed the study protocol and participated in the manuscript preparation and editing. B.-L.S. performed the statistical analyses, graphic production, interpretation of data and drafting of the manuscript. Y.Z. was involved in revising this article. Y.-W.X. participated in data extraction and patient chart review. F.W. helped with the blood sampling and concentration analysis. W.L. and B.Z. managed the study database. X.C. and J.-J.Z. helped critical revision of the manuscript for intellectual content and study supervision. Y.T., W.W., Y.J. and G.G. helped the medical management of study patients. M.Z. and D.-X.X. was the study leader for voriconazole and contributed to the planning and conduct of the clinical studies. All authors read and approved the final manuscript.

COMPETING INTERESTS

There are no competing interests to declare.

DATA AVAILABILITY STATEMENT

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

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