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Optimization of voriconazole dosage via population pharmacokinetic analysis based on the albumin–bilirubin (ALBI) score of patients with liver dysfunction

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Authorship statement

All authors contributed to the conception and design of this study. SN collected and analyzed the data and wrote the manuscript. MS revised the manuscript. YT approved the final version of the manuscript.

Abstract

Introduction

Voriconazole (VRCZ) is an antifungal agent used to treat refractory fungal infections. Its dosage is adjusted based on the individual liver function. In this study, we aimed to establish a population pharmacokinetic analysis model based on the albumin–bilirubin (ALBI) score to objectively assess the liver function using only albumin and total bilirubin levels as covariates.

Methods

In total, 126 plasma samples of 16 patients with liver dysfunction who received oral VRCZ between 2012 and 2022 were analyzed in this study. Phoenix NLME software was used for population pharmacokinetic analysis, and Monte Carlo simulations were performed to determine the optimal dosing regimen to achieve the target blood VRCZ concentration.

Results

Blood VRCZ concentration was described using a one-compartment model with lag time. In the final model, objective function was significantly decreased upon ALBI score incorporation into clearance. Monte Carlo simulations showed that the optimal dosing schedules were 100 mg twice daily, 75 mg twice daily, and 50 mg twice daily for ALBI scores of –3, –2, and –1, respectively. Notably, for an ALBI score of 0, target blood VRCZ concentration was exceeded, even a dosing regimen of 50 mg twice daily.

Conclusion

To the best of our knowledge, this study is the first to incorporate the ALBI score into a population pharmacokinetic model for VRCZ. Our simulation results suggest that the maintenance dose should be reduced based on the ALBI score. Furthermore, our findings highlight the potential use of the ALBI score for optimal drug dosage design.

Keywords: Voriconazole; Therapeutic drug monitoring; Population pharmacokinetic analysis; Albumin–bilirubin (ALBI) score

Abbreviations: ALBI: Albumin–bilirubin, ALT: alanine aminotransferase, AST: aspartate aminotransferase, CI: confidence interval, CL: clearance, CRP: C-reactive protein, CWRES: conditional weighted residuals, DV: observed values, F: bioavailability, GOF: goodness-of-fit, IPRED: individual predictions, K_a: absorption rate constant, LOESS: locally weighted scatterplot smoothing, PPK: population pharmacokinetic, PRED: population predictions, PT-INR: prothrombin time-international normalized ratio, RSE: relative standard error, TDM: Therapeutic drug monitoring, T_{lag}: lag time, V: distribution volume, VRCZ: voriconazole

1. Introduction

Voriconazole (VRCZ) is a broad-spectrum triazole antifungal agent used to treat refractory fungal infections [1, 2]. Therapeutic drug monitoring (TDM) of VRCZ is recommended in clinical settings due to the association between its blood concentration and therapeutic efficacy [3–5]. However, significant intra- and inter-individual variability is observed in VRCZ pharmacokinetics, with the optimal dose to achieve favorable therapeutic efficacy varying in each patient [6]. Moreover, VRCZ blood concentration and dosage are not proportional due to the saturation of its drug-metabolizing enzymes [7]. As excessive VRCZ exposure causes liver injury and optic neuropathy, VRCZ dosing regimen should consider the drug-metabolizing capacity of the liver of individual patients for safe and effective treatment [8, 9].

The Child–Pugh score is a conventional tool to assess the liver function [10]. The Child–Pugh score is a 1–3 point scale based on encephalopathy, ascites, total bilirubin level, albumin level, and prothrombin activity, with 5–6, 7–9, and 10–15 scores indicating classes A, B, and C, respectively. A previous study recommended reducing the maintenance dose for Child–Pugh class A or B patients to half that for a non-cirrhotic patient [11]. Yamada et al. reported that optimal blood concentration in Child–Pugh class C patients can be achieved by reducing the maintenance dose to $1/3^{rd}$ or $1/4^{th}$ that for a non-cirrhotic patient [12]. Wang et al. reported that, upon VRCZ administration at 200 mg/day, over 30% of Child–Pugh Class C patients showed trough levels ≥ 5 μg/mL, and 23.5% of patients exerted side effects, with 87.5% developing side effects within 1 week of treatment [13]. However, the Child–Pugh score does not accurately assess the liver function as the assessment of encephalopathy and ascites is subjective, incorporating factors influencing each other, such as ascites and albumin levels.

Recently, the albumin–bilirubin (ALBI) score has been proposed to objectively assess the liver function based only on the albumin and total bilirubin levels [14]. The following equation is used to calculate the ALBI score: ALBI score = ($\log_{10}$ bilirubin × 0.66) + (albumin

× –0.085), where bilirubin is in μmol/L and albumin in g/L. As the ALBI score is objectively calculated using biochemical laboratory data, it is more accurate than the conventional Child–Pugh score. Therefore, ALBI score is often used to select the optimal treatment method for patients with liver cancer and predict the outcomes after liver resection in patients with hepatocellular carcinoma [15–17].

We previously analyzed the efficiency of the ALBI score in predicting the drug-metabolizing capacity of the liver and reported a strong correlation between the VRCZ maintenance dose and ALBI score [18]. Although our results indicated the possibility of applying the ALBI score for drug dosage design, the specific relationship between the ALBI score and VRCZ pharmacokinetics could not be quantitatively analyzed due to the limited sample size. Therefore, in this study, we aimed to develop a population pharmacokinetic (PPK) analysis model based on the ALBI score to design an optimal VRCZ dosing regimen.

2. Methods

2.1. Study design and patients

This single-center retrospective study was conducted at the Hokkaido University Hospital, Sapporo, Japan. Patients with liver dysfunction who received oral VRCZ between January 1, 2012 and December 31, 2022 were included in this study. Patients (1) under 18 years of age (2) who concomitantly received rifampicin, rifabutin, carbamazepine, phenytoin, letermovir, and anti-human immunodeficiency virus drugs (3) with missing laboratory data necessary for ALBI score calculation were excluded from the study. Finally, 126 plasma samples of 16 patients were analyzed in this study. This study was conducted in accordance with the Declaration of Helsinki and its amendments. The study protocol was approved by the Ethical Review Board for Life Science and Medical Research, Hokkaido University Hospital (protocol number:022-0259).

2.2. Clinical and laboratory data

Patient medical records were individually reviewed to collect clinical information, such as age, sex, clinical department, body weight, albumin, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum creatinine, and C-reactive protein (CRP) levels, prothrombin time-international normalized ratio (PT-INR), VRCZ dosage, and concomitant drugs used for treatment. Blood VRCZ concentration was measured via high-performance liquid chromatography-ultraviolet and liquid chromatography-tandem mass spectrometry, as previously described [12]. VRCZ trough samples were collected 30 min before dosing.

2.3. PPK base model

A PPK model was established using the Phoenix NLME 8.1 software. As most samples had trough concentrations, the base model was simplified to a one-compartment model with lag time. The base model is represented by Eq. 1 below.

Eq. 1: $CL_i = \theta_{CL} \times exp\,(\eta CL_i)$

$$V_i = \theta_v \times exp\,(\eta V_i)$$

where CL is clearance, and V is distribution volume.

Inter-individual variability was described using an exponential error model. Residual variability was described using a proportional error model. As VRCZ bioavailability (F) was previously shown to be almost 100% [2], F value was fixed at 1. Due to the lack of data on peak samples, absorption rate constant (K_a) and lag time (T_{lag}) were fixed to the values reported in a domestic phase III clinical study (0.654 and 0.19, respectively).

2.4. PPK final model

In the process of developing a covariate model, we selected ALBI score, albumin, total bilirubin, CRP, age, gender, and body weight as the candidate covariates that could affect the CL, and age, gender, and body weight as the candidate covariates that could affect the V. Covariates were identified via stepwise forward and backward elimination. The thresholds for objective function reduction compared to that of the base model were 6.64 for forward addition and 10.83 for backward elimination. Moreover, effects of continuous variables on pharmacokinetic parameters were described using a median-normalized proportional linear model.

2.5. PPK model evaluation and validation

Next, the PPK model was evaluated using goodness-of-fit (GOF) plots. GOF plots used for analysis included the observed values (DV) vs. population predictions (PRED), DV vs. individual predictions (IPRED), and conditional weighted residuals (CWRES) vs. PRED plots. Subsequently, effect of each patient on PPK parameters was confirmed via case-deletion diagnostics.

Robustness of the developed model was evaluated using the bootstrap method. One thousand bootstrap samples were generated, and median parameter values and 95% confidence interval (CI) were compared with the original dataset estimates.

2.6. PPK model simulations

VRCZ dosing schedule was fixed at twice daily, every 12 h, and the steady-state trough concentration was simulated for each ALBI score at 100, 150, and 200 mg/day. Patients are classified into grade 1 (≤ −2.60), 2 (−2.59 to −1.39), or 3 (> −1.39) based on the ALBI score [14]. ALBI scores in the simulations were set at –3, –2, and –1 as representative values for each grade. Severe cases with an ALBI score of 0 were also simulated. The number of Monte Carlo simulations was set to 1000, and target trough concentration was set to 1–4 μg/mL based on a

183 previous report [4].

184

185 ## 3. Results

186 ### 3.1. Patient characteristics

187 Patient characteristics are shown in Table 1. In this study, the median patient age was
188 56.5 (51.75–64.75) years, with a male to female ratio of 1:1. Thirteen patients were admitted to
189 the department of gastroenterological surgery and three to the department of hematology. Seven
190 patients were classified into Child–Pugh class A, one into class B, and eight into class C. ALBI
191 score distribution for each Child–Pugh class is shown in Fig. 1. ALBI scores were distributed
192 in the range of –2 to –3 in Child–Pugh class A patients and 0.5 to –1.5 in Child–Pugh class C
193 patients.

194

195 ### 3.2. PPK analysis

196 Blood VRCZ concentration was modeled using a one-compartment model with lag
197 time. In the process of developing a base model, a one-compartment model and a nonlinear
198 pharmacokinetic model were compared. The objective function values were comparable
199 between the two models (371.0 and 369.7, respectively), but the nonlinear pharmacokinetic
200 model had two more parameters than the one-compartment model. In addition, the shrinkage
201 of michaelis constant and maximal velocity associated with CL were 23.4% and 44.9%,
202 respectively in non-linear pharmacokinetic models, which might not adequately estimate inter-
203 individual variability, so the one-compartment model is used in this report. In the one-
204 compartment model, the shrinkage of CL is 7.2%, confirming that the inter-individual
205 variability is properly estimated. For the intra-individual variation model, the proportional,
206 absolute, and combined error models were compared, and the proportional error model was
207 found to be the most appropriate. Analysis assuming covariance of CL and V showed no
208 significant decrease in the objective function. Estimated values of these parameters in the base

model were CL = 3.72 (L/h) and V = 174.08 (L).

In the covariate model, when incorporating the factors one by one, those that showed a significant decrease in the objective function are shown in Table 2. The model incorporating CRP was considered an inappropriate model because decrease in inter-individual variation in CL was not observed. Both models incorporating albumin and total bilirubin showed a decrease in inter-individual variation in CL, but these models showed no good correlation with CL compared with the model incorporating the ALBI score (Supplementary Fig. 1). Based on these results, the model incorporating ALBI score into CL was used in this study. As the inter-individual variability of V was small, suggesting its improper estimation, the final model was represented by Eq. 2, excluding the inter-individual variability of V. PPK parameters are listed in Table 3.

Eq. 2: $$CL_i = \theta_{CL} \times \left(1 + (ALBI_i - ALBI_{median}) \times \theta_{ALBI_CL}\right) \times exp\,(\eta CL_i)$$

$$V_i = \theta_v$$

3.3. Model evaluation and validation

The DV vs. PRED plot was evenly distributed around Y = X (Fig. 2a). The DV vs. IPRED plot showed good linearity (Fig. 2b). Conditional weighted residuals (CWRES) vs. PRED plot was evenly distributed around 0 and did not exceed the ±3 range (Fig. 2c). Case-deletion diagnostics revealed no significant differences in the effects on PPK parameters among the patients (Supplementary Fig. 2). Furthermore, original dataset estimates were within 95% CI for each parameter tested by the bootstrap method (Table 3). Notably, bootstrap sampling was performed 1000 times, and all analyses were successfully completed.

3.4. Dosage simulation

Based on the population model, dosing simulation was performed 1000 times to predict

the optimal dose to achieve the target VRCZ trough concentration (1–4 μg/mL; Fig. 3). As VRCZ exhibits non-linear pharmacokinetics, optimal dosing schedule was set so that the maximum values of the box plots did not exceed 4 μg/mL, with 100 mg twice daily (200 mg/day), 75 mg twice daily (150 mg/day), and 50 mg twice daily (100 mg/day) for ALBI scores of –3, –2, and –1, respectively. For an ALBI score of 0, the maximum value of the box plot exceeded the target blood VRCZ concentration, even when administered at 50 mg twice daily.

4. **Discussion**

VRCZ is a broad-spectrum triazole antifungal agent used to treat refractory fungal infections; its dosage should be adjusted based on the individual liver function. Wang et al. and Lin et al. developed a PPK model incorporating the Child–Pugh score as a covariate for patients with cirrhosis [19–21]. However, Child–Pugh score is a severity classification of liver cirrhosis and an ordinal variable; therefore, it does not accurately assess the liver function. In contrast, ALBI score is calculated as a continuous variable based only on the albumin and total bilirubin levels; therefore, it predicts the liver function better than the Child–Pugh score in patients with liver cancer [14–16]. This study aimed to establish a PPK analysis model incorporating the ALBI score to design an optimal dosing regimen for patients with liver dysfunction.

Blood VRCZ concentration was represented by a one-compartment model with lag time. CYP2C19, CYP2C9, and CYP3A4 are involved in VRCZ metabolism, and saturation of these metabolic enzymes results in non-linear pharmacokinetics [22, 23]. However, in this study, the Michaelis–Menten model did not show a significant reduction in the objective function. Therefore, non-linear pharmacokinetics were not observed in the population analyzed in this study. Here, VRCZ maintenance dose was reduced to approximately 100 mg/day for all Child–Pugh class C patients based on a previous report [12], which possibly prevented the saturation of the metabolizing enzyme. Fig. 3a shows the simulation results of VRCZ administration at a dose of 100 mg twice daily (200 mg/day). Notably, trough concentration can be higher when

pharmacokinetic exhibits non-linearity; therefore, VRCZ should be administered at an even lower dose in clinical settings.

In the covariate model, ALBI score, albumin and total bilirubin were determined as significant covariates. However, using albumin and total bilirubin individually to predict CL has clinical risks because these can vary independently due to various non-hepatic conditions such as sepsis, hemolysis, or nutritional status. In this study, the ALBI score was incorporated into the final model for its clinical utility. On the other hand, body weight was not determined as a significant covariate. This is possibly because patients with severe liver dysfunction, such as those classified into Child–Pugh class C, develop refractory ascites, and actual weight may not accurately reflect the drug distribution volume in each patient. Therefore, it is more appropriate to use the ideal body weight instead of the actual body weight when designing dosing schedules for patients with severe liver dysfunction. Previous studies have reported that CRP and blood VRCZ concentrations are positively correlated [24, 25]. This is because high CRP levels induce interleukin-6 expression, resulting in CYP2C19 downregulation [26, 27]. In a population model analysis of VRCZ in healthy subjects, CRP was reported as a covariate with a significant effect on VRCZ pharmacokinetics [28]. Notably, previous studies have not indicated CRP as a significant covariate for patients with cirrhosis, similar to the findings of this study [19–21]. Drug-metabolizing capacity is significantly reduced due to the decreased number of hepatocytes in patients with liver cirrhosis. Therefore, effect of gene induction on inflammatory response is relatively small and possibly masked by liver dysfunction in these patients.

Simulation results showed that the optimal dosing schedules were 100 mg twice daily (200 mg/day), 75 mg twice daily (150 mg/day), and 50 mg twice daily (100 mg/day) for ALBI scores of –3, –2, and –1, respectively. However, when the ALBI score was 0, the maximum value of the box plot exceeded the target blood concentration even when administered at 50 mg twice daily, suggesting the need for further dose reduction. Additionally, variability in blood

concentrations was greater when the ALBI score was 0, suggesting the need for more frequent TDM and dosage adjustments for each patient. Previous studies have also recommended VRCZ dose reduction for patients with hepatic dysfunction [29, 30]. Wang et al. conducted simulations using a PPK model in patients with cirrhosis and reported 150 mg/day for Child–Pugh class A and B and 100 mg/day for class C as the recommended dosage [19]. In this study, ALBI score distribution ranged from –2 to –3 in Child–Pugh Class A patients, and simulation results suggested 200 mg/day as the acceptable schedule for patients with an ALBI score of –3 (Figs. 1 and 3). For Child–Pugh Class C patients, ALBI score distribution ranged from –1 to 0, and 100 mg/day was appropriate for patients with an ALBI score of –1, whereas 100 mg/day may lead to an overdose in patients with an ALBI score of 0 (Figs. 1 and 3). This study suggests that incorporating the ALBI score over the Child–Pugh score into a PPK model enables a more accurate dosing design.

This study has several limitations. First, almost all blood samples exhibited trough concentrations, making it difficult to estimate the time course-related parameters (K_a and T_{lag}). Second, sample size analyzed in this study was small and possibly insufficient to optimize the VRCZ dosing schedule. Additionally, this study included more samples of Child–Pugh class C patients than Child–Pugh class A/B patients, as TDM is frequently performed in Child–Pugh class C patients (Supplementary Table 1). Case-deletion diagnostics suggested that patients with frequent TDM did not significantly influence the PPK parameters (Supplementary Fig. 2). Furthermore, genetic polymorphism of CYP2C19, a major VRCZ-metabolizing enzyme in the liver, was not assessed in this study. Kubota et al. reported that approximately 20% of the Japanese population are poor CYP2C19 metabolizers [31]. Moreover, VRCZ pharmacokinetics are strongly affected by the CYP2C19 genotype [32–34]. Previous meta-analysis showed that trough concentrations were significantly higher in CYP2C19 poor metabolizers compared with extensive metabolizers (mean difference, 1.22 mg/L; 95 % CI, 0.72-1.71; $P < 0.0001$) [35]. On the other hand, there was no significant difference in the maintenance dose of VRCZ between

intermediate metabolizers and extensive metabolizers for CYP2C19 [35]. Since a reduction in the maintenance dose is essential to achieve target blood levels for patients with liver cirrhosis, the effect of genetic polymorphisms may be relatively small compared with the effect of hepatic dysfunction. In addition, previous studies showed that CYP2C19 phenotype (intermediate metabolizer/poor metabolizer versus extensive metabolizer) had no significant effect on the PPK model of VRCZ in liver cirrhotic patients [20], suggesting that the effect of CYP2C19 polymorphisms in liver cirrhotic patients may be limited.

5. Conclusion

To the best of our knowledge, this study is the first to incorporate the ALBI score into a PPK model for VRCZ. Our results highlight the applicability of the ALBI score to drug dosage design. However, further multicenter studies are necessary to verify the external validity of our model.

Conflict of interest

The authors declare no conflict of interests.

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Figure captions

Fig. 1 Violin plots of baseline albumin–bilirubin (ALBI) score distribution for each Child–Pugh class. ALBI, albumin–bilirubin

Fig. 2 Goodness-of-fit (GOF) plots for the final model. (a) Observed concentration (DV) vs. population predictions (PRED). (b) DV vs. individual predictions (IPRED). (c) Conditional weighted residuals (CWRES) vs. PRED. Blue line indicates the locally weighted scatterplot smoothing (LOESS) curve for the overall residual, and red line indicates the unilateral LOESS curve for the residual.

Fig. 3 Monte Carlo simulation of voriconazole (VRCZ) trough concentrations at steady state. Steady state VRCZ trough levels at ALBI scores of –3, –2, –1, and 0 were simulated using our established population pharmacokinetic model. Dosing schedules were set to (a) 100 mg twice daily (200 mg/day), (b) 75 mg twice daily (150 mg/day), and (c) 50 mg twice daily (100 mg/day). Box plots show the 25^{th}, 50^{th}, and 75^{th} percentiles; whiskers show the minimum and maximum values at the 25^{th} and 75^{th} percentiles plus 1.5-times the interquartile range. Dots indicate the outliers. Gray shading indicates the target VRCZ trough concentration (1–4 μg/mL). ALBI, albumin–bilirubin

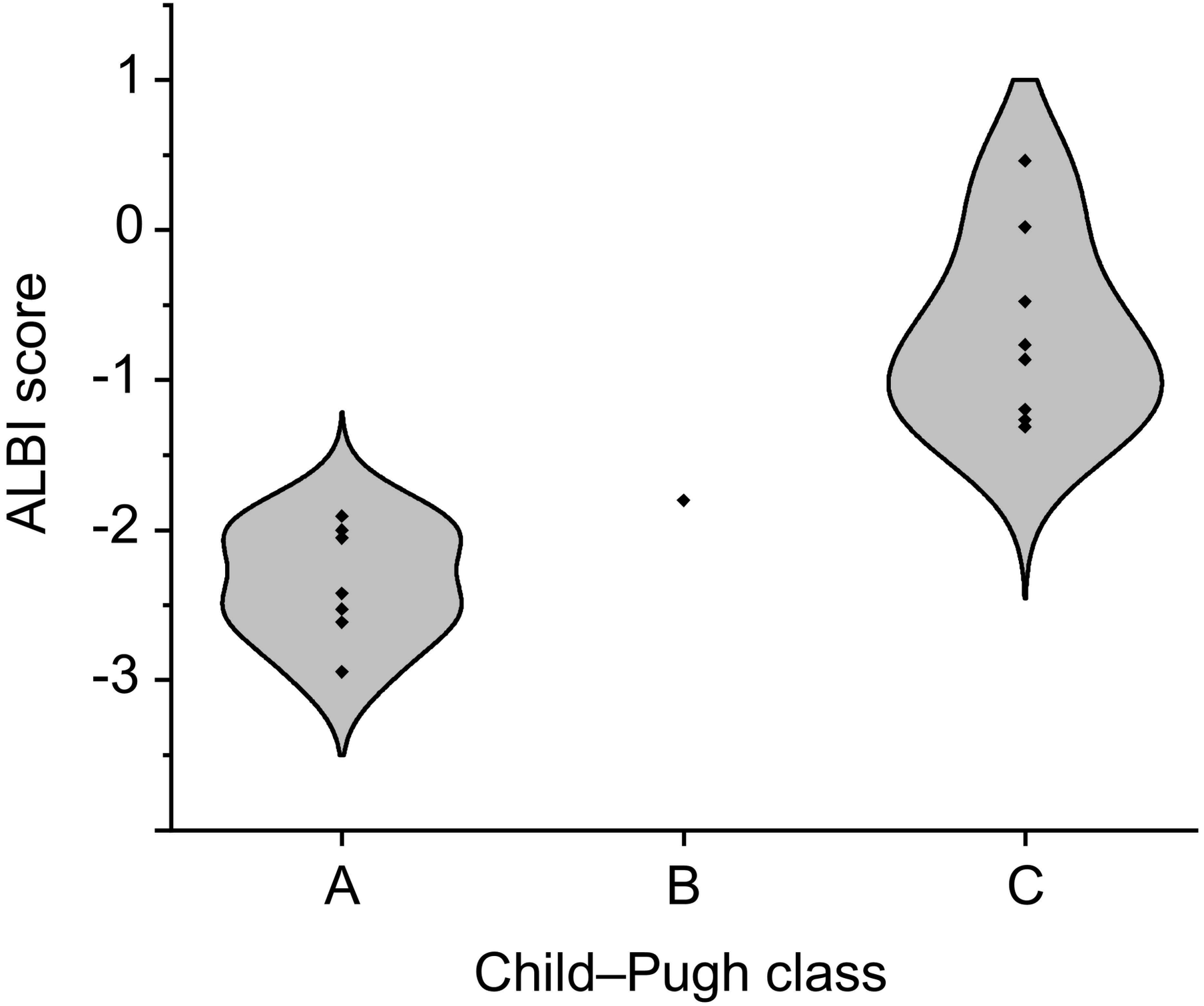
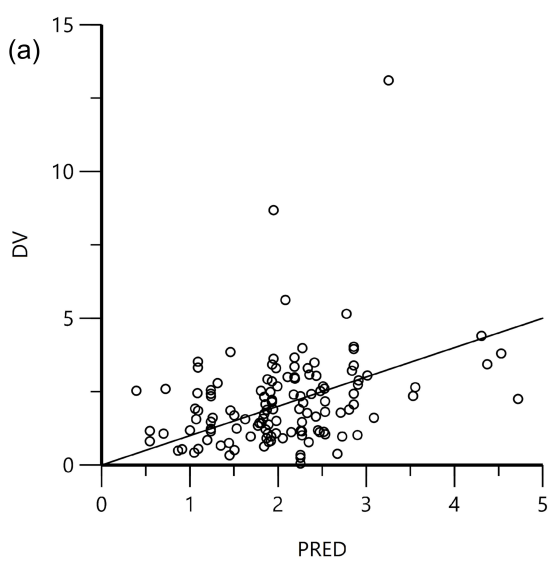
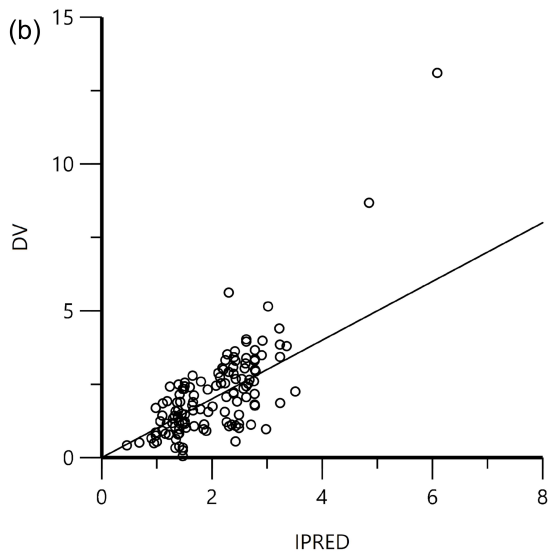
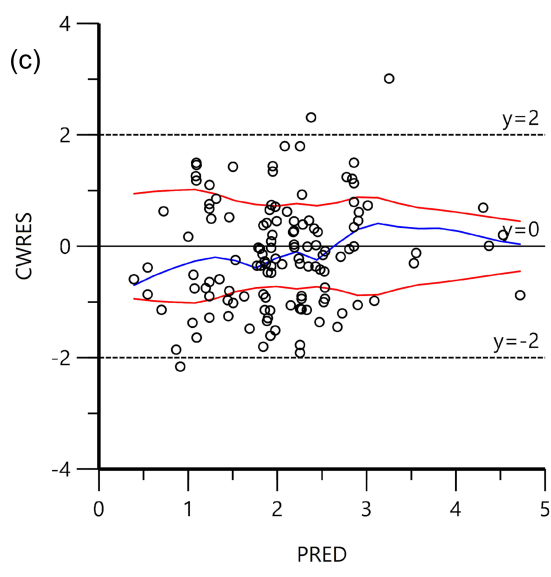


Fig. 1


(a)
15
10
5
0
DV
0
1
2
3
4
5
PRED


(b)
15
10
5
0
DV
0
2
4
6
8
IPRED


(c)
4
2
0
-2
-4
CWRES
y=2
y=0
y=-2
0
1
2
3
4
5
PRED

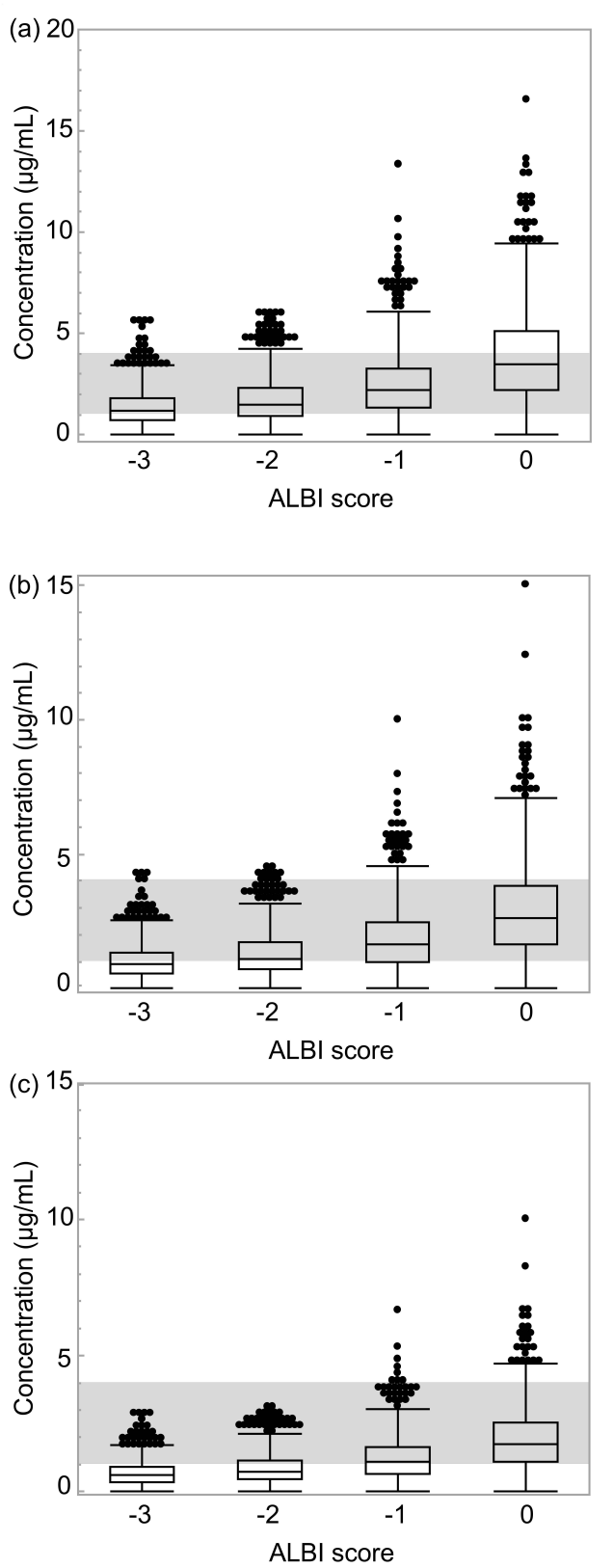

(a)
Concentration (μg/mL)
20
15
10
5
0
-3
-2
-1
0
ALBI score
(b)
Concentration (μg/mL)
15
10
5
0
-3
-2
-1
0
ALBI score
(c)
Concentration (μg/mL)
15
10
5
0
-3
-2
-1
0
ALBI score

Fig. 3

Tables

Table 1 Baseline characteristics of voriconazole (VRCZ) administered patients (n=16)

Parameters	Value
Age (years) [#]	56.5 (51.75–64.75)
Male / female [†]	8/8
Body weight (kg) [#]	57.5 (46.9–60.1)
Child-Pugh class A/B/C[ǂ]	7/1/8
ALBI score[#]	-1.56 (-2.14 – -0.84)
Albumin (g/dL) [#]	3.1 (2.9–3.4)
Total bilirubin (mg/dL) [#]	3.1 (0.62–17.68)
AST(IU/L)[#]	39.5 (22.5–66.0)
ALT(IU/L)[#]	21.5 (14.5–44.5)
PT-INR [#]	1.36 (1.17–1.66)
Serum creatinine (mg/dL) [#]	0.99 (0.695–1.403)
CRP (mg/dL) [#]	1.99 (0.31–2.79)
Diagnosis and treatment department	
Gastroenterological surgery/hematology[†]	13/3

[#]Data are expressed as the median (interquartile range); [†]Data are expressed as n/n; [ǂ]Data are expressed as n/n/n.

ALBI, albumin–bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; PT-INR, prothrombin time-international normalized ratio; CRP, C-reactive protein; VRCZ, voriconazole.

Table 2 Comparison of objective function and inter-individual variation of CL values for each covariate model

Model tested	OBJ	ωCL
Base model	370.96	54.2%
Model incorporating CRP into CL	345.39	53.7%
Model incorporating albumin into CL	353.38	45.9%
Model incorporating total bilirubin into CL	356.77	45.3%
Model incorporating ALBI score into CL	354.38	43.3%

OBJ, objective function value; CRP, C-reactive protein; CL, clearance; ALBI, albumin–bilirubin

Table 3 Population pharmacokinetic parameter estimates for the final model and bootstrap analysis results.

	Final model			Bootstrap		
	Estimate	RSE (%)	Shrinkage (%)	Median	2.5% CI	97.5% CI
Parameters						
θ_V (L)	149.89	20.08	NA	153.32	110.84	236.19
θ_{CL} (L/hr)	3.95	13.13	NA	3.92	2.60	5.66
Effect of ALBI score on θ_{CL} (θ_{ALBI_CL})	-0.29	-14.89	NA	-0.29	-0.46	-0.17
Inter-individual variability						
ω_{CL}	43.3%	34.9	9.2	41.4%	21.9%	56.2%
Residual error						
σ	46.1%	12.5	4.9	45.7%	34.3%	57.1%

ALBI, albumin–bilirubin; CI, confidence interval; CL, clearance; F, bioavailability; K_a, absorption rate constant; NA, not applicable; RSE, relative standard error; T_{lag}, lag time; V, distribution volume.