Drug Design, Development and Therapy

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REVIEW

A Systematic Review of Population Pharmacokinetics, Safety, and Factors Influencing Trough Concentrations of Voriconazole in Asian Patients with Liver Dysfunction

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Objective: This study systematically reviews recent research on voriconazole (VRC) use in Asian patients with liver dysfunction to provide a scientific basis for individualized therapy.

Methods: A comprehensive literature search was conducted in EMBASE, PubMed, Web of Science, and the Cochrane Library for clinical studies on VRC use in Asian patients with liver dysfunction, published between January 1, 2000, and March 1, 2025. Studies meeting the inclusion and exclusion criteria were analyzed to summarize VRC safety, factors influencing trough concentrations (C_{trough}), pharmacokinetic characteristics, and advancements in dose optimization.

Results: A total of 14 studies were included, comprising 9 studies on the safety of VRC in patients with liver dysfunction, 5 studies investigating factors affecting VRC C_{trough}, and 6 studies on population pharmacokinetics (PPK) in this population. The most commonly reported adverse drug reactions (ADRs) related to VRC were hepatotoxicity, neurotoxicity, and visual impairment. ADRs typically occurred within 7 days of VRC administration. VRC C_{trough} are influenced by several factors, including liver impairment severity, CYP2C19 polymorphisms, and albumin and bilirubin levels. The PPK models assessed clearance (CL) in patients with different Child-Pugh (CP) classifications, all of which showed a significant reduction in CL among CP-C patients. Regarding the elimination half-life ($t_{1/2}$), CP-C patients exhibited a significant prolongation.

Conclusion: Therapeutic drug monitoring (TDM) and PPK studies can aid in optimizing VRC dosing, ensuring safer and more effective individualized therapy.

Keywords: voriconazole, liver dysfunction, population pharmacokinetics, safety, trough concentrations

Introduction

Invasive aspergillosis (IA) is a common, life-threatening infection in patients with severe liver dysfunction, characterized by high mortality and poor prognosis.[1,2] Voriconazole (VRC) is a broad-spectrum antifungal agent primarily metabolized by hepatic cytochrome P450 isoenzymes (CYP2C19, CYP3A4, and CYP3A5). According to previous reports, common adverse drug reactions (ADRs) to VRC included hepatotoxicity, hallucinations, visual disturbances, gastrointestinal symptoms, and skin rash in critically ill patients, pediatrics and adults.[3–5]

The Chinese Pharmacological Society (CPS) guideline recommended the therapeutic range of VRC trough concentrations (C_{trough}) was 0.5–5.0 mg/L.[6] Meta-analyses have demonstrated a significant correlation between VRC C_{trough} and ADRs. Specifically, a C_{trough} exceeding 3.0 mg/L was associated with increased hepatotoxicity, while levels above 4.0 mg/L were linked to heightened neurotoxicity.[7] The pharmacokinetics of VRC in adults are nonlinear and exhibit high inter- and intra-individual variability.[8] In addition, VRC has notable drug–drug interactions with commonly

Received: 11 July 2025
Accepted: 6 October 2025
Published: 14 October 2025

prescribed agents, including proton pump inhibitors and glucocorticoids.[9,10] Therefore, individualized VRC dosing, particularly in patients with liver dysfunction, are essential to improve efficacy while minimizing toxicity.

Recent studies have demonstrated that the Albumin–Bilirubin (ALBI) score is a novel, reliable, and objective measure of liver function,[11] whereas the Child–Pugh (CP) classification remains widely applied for assessing hepatic impairment. Current VRC instructions recommend that CP-A and CP-B patients receive an unchanged loading dose but a reduced maintenance dose (halved compared to standard dosing).[12] However, previous studies have questioned the suitability of these recommendations in patients with liver dysfunction, suggesting the need for further dose optimization.[13] Additionally, data on CP-C patients remain limited, and optimal dosing strategies for those with severe liver dysfunction have yet to be established.

To date, no systematic review has comprehensively evaluated VRC use and Pharmacokinetics/Pharmacodynamics (PK/PD) in patients with liver dysfunction. In particular, safety, pharmacokinetic characteristics, and optimal dosing strategies remain unclear, especially in Asian patients of severe hepatic impairment. Therefore, this study systematically reviews therapeutic drug monitoring (TDM) and population pharmacokinetics (PPK) analysis on VRC in Asian patients with liver dysfunction, aiming to provide scientific basis for precise dosing in this population.

Methods

Study Design

This systematic review focused on Asian patients with liver dysfunction excluding those who had undergone liver transplantation. A comprehensive literature search was conducted across multiple databases, including EMBASE, PubMed, Web of Science, and the Cochrane Library, covering publications from January 1, 2000, to March 1, 2025. The review addresses three primary objectives:

(i) Evaluating the safety of VRC in patients with liver dysfunction.

(ii) Identifying factors influencing VRC C_{trough} in this population.

(iii) Summarizing PPK models and dosing recommendations for VRC in patients with liver impairment.

Literature Search Strategy

The search strategy utilized the following terms in the databases: [(voriconazole) OR (VRC) OR (VFEND)] AND [(liver diseases) OR (hepatic insufficiency) OR (liver dysfunction) OR (liver cirrhosis) OR (liver failure) OR (chronic liver disease) OR (acute liver injury) OR (Child-Pugh) OR (MELD score) OR (ALBI score)] AND [(pharmacokinetics) OR (population pharmacokinetics) OR (PPK) OR (therapeutic drug monitoring) OR (trough concentration) OR (factors) OR (influence) OR (affect) OR (effect) OR (safety) OR (adverse drug reactions) OR (adverse events) OR (toxicity) OR (hepatotoxicity)]. Duplicate records across databases were removed using EndNote X9 software. Furthermore, the reference lists of relevant studies were manually reviewed to identify additional potentially eligible studies.

Study Selection

Two independent reviewers screened the titles and abstracts retrieved from the databases to identify potentially relevant articles. The full texts of the selected studies were obtained and independently assessed by the same reviewers based on predefined eligibility criteria. Discrepancies were resolved through discussion, and a third reviewer was consulted when necessary. Inclusion criteria: (i) VRC was the primary drug investigated. (ii) The study population consisted of Asian individuals with liver dysfunction, including chronic liver diseases (such as cirrhosis), acute liver injury, or liver failure. (iii) The study addressed at least one of the three primary objectives outlined in the study design section. Exclusion criteria: (i) In vitro and animal studies. (ii) Reviews, commentaries, editorials, expert opinions, conference abstracts, case reports, and meta-analyses. (iii) Non-original research articles or studies not published in English. (iv) Studies involving patients who had undergone liver transplantation.

Data Extraction

Data extraction was performed by one reviewer and verified for accuracy by two independent reviewers. To facilitate this process, a data extraction table was created to systematically capture the following information: authors, publication dates,

countries of origin, funding sources, research design, sample size, and age range of participants. Additional information included underlying diseases, criteria used to assess liver dysfunction, incidence and specifics of ADRs related to VRC, target therapeutic ranges for VRC C_{trough}, dosage and administration route of VRC, methods used to measure VRC C_{trough}, significant factors influencing VRC C_{trough}, statistical methods, as well as the software and models employed in PPK studies. The pharmacokinetic parameters in patients with liver dysfunction, significant covariates affecting these parameters, and the results or conclusions from dose simulation experiments were also recorded. The literature screening process for this systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[14] Given that the included studies in the search were observational and cross-sectional in nature, their quality was assessed using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) criteria.[15] The STROBE checklist comprises 22 items, covering the title and abstract (item 1), introduction (items 2–3), methods (items 4–12), results (items 13–17), discussion (items 18–21), and other information such as funding sources (item 22). The quality of all included studies was assessed using RevMan 5.4 software.

Results

Overview of Included Literature

A total of 922 relevant articles were identified in the initial search, including 526 from EMBASE, 304 from PubMed, 83 from Web of Science, and 9 from the Cochrane Library. After applying the inclusion and exclusion criteria, 14 studies were deemed eligible for inclusion in the systematic review.[13,16–28] The study selection process is illustrated in Figure 1, and the quality assessment of the included studies is presented in Figure 2.

Safety of VRC in Patients with Liver Dysfunction

Currently, 9 studies have examined the safety of VRC in patients with liver dysfunction.[13,16–23] Among these, 2 were prospective studies,[19,21] and 7 were retrospective.[13,16–18,20,22,23] Additionally, 3 were multicenter studies,[17,18,20] while 6 were single-center studies.[13,16,19,21–23] All studies were descriptive and originated from theJapan (n = 1; 11.1%)[16] and China (n = 8; 88.9%).[13,17–23] Regarding sample sizes, 3 studies included fewer than 50 patients,[16,18,21] 2 studies enrolled 50–100 patients,[17,19] and 4 studies had more than 100 participants.[13,20,22,23] The most commonly used method for assessing liver function is the CP classification, followed by the Model for End-Stage Liver Disease (MELD) score. Regarding causality assessment, only one study applied Naranjo's scale,[13] while the others did not explicitly specify the method used.

Across the 9 studies, a total of 899 patients were analyzed, with 157 experiencing VRC-related ADRs, yielding an overall ADR incidence of 17.46%. The median incidence of VRC-related ADRs was 23.5%. The most commonly reported ADRs were hepatotoxicity, neurotoxicity, and visual impairment. ADRs typically occurred within 7 days of VRC administration Five studies reported data on VRC C_{trough} in patients with ADRs. In a study by Wang et al, the median VRC C_{trough} in ADR patients was 5.98 mg/L (range: 2.37–15.10 mg/L).[20] Another study reported VRC C_{trough} of 6.52 ± 2.83 mg/L and 4.76 ± 2.71 mg/L in two respective patient groups with ADRs.[17] In a recent publication, we reported that the median VRC C_{trough} in ADR patients was 4.00 mg/L (range: 0.77–10.01 mg/L) in patients with liver dysfunction.[13] Tang et al demonstrated through ROC curve analysis that maintaining a VRC $C_{trough} \leq 5.1$ mg/L minimized ADR incidence.[19] Additionally, Wang et al used logistic regression modeling to show that the probability of ADR occurrence was 20% when the VRC C_{trough} reached 4.52 mg/L.[18] Detailed information on the safety of VRC in patients with liver dysfunction is presented in Table 1.

Factors Influencing VRC C_{trough} in Patients with Liver Dysfunction

Five studies have investigated the factors influencing VRC C_{trough} in patients with liver dysfunction,[13,17,21,23,24] including four from China,[13,17,21,23] and one from Japan.[24] Among these, one was a multicenter study,[17] while the remaining four were single-center studies.[13,21,23,24] Three studies included over 100 cases.[13,23,24] The target therapeutic range for VRC C_{trough} varied: three studies used 1.0–5.5 mg/L,[13,21,23] one used 1.0–5.0 mg/L,[17] and another used 1.0–4.0 mg/L.[24] Regarding the measurement methods for VRC C_{trough}, one employed liquid chromatography-tandem mass spectrometry (LC-MS/MS),[13] while two studies

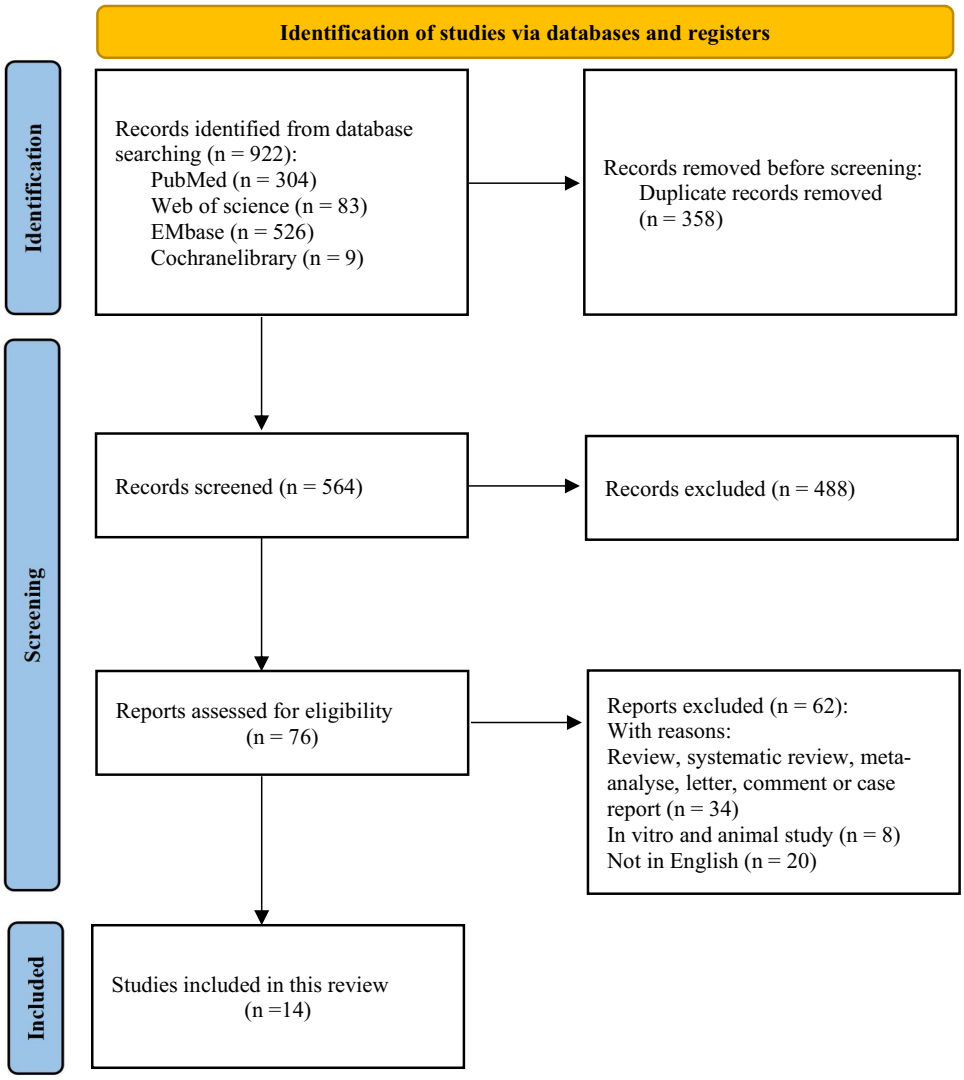

Figure 1 The flowchart of articles selection.

utilized high-performance liquid chromatography (HPLC).[17,24] Two studies utilized two-dimensional HPLC.[21,23] Steady-state VRC C_{trough} were utilized in all studies.

Four studies applied multiple linear regression analysis to identify factors affecting VRC C_{trough} in patients with liver dysfunction.[13,17,21,23] Among genetic factors, CYP2C19 polymorphisms were reported to influence VRC C_{trough}, while no associations were found with CYP3A4 or CYP3A5 polymorphisms. Non-genetic factors included age, sex, dosage, administration route, concomitant medications, CP class, ALBI classification, MELD score, and inflammatory markers such as C-reactive protein (CRP). Additionally, other laboratory markers, including albumin (ALB), total bilirubin (TBil), direct bilirubin (DBil), blood urea nitrogen (BUN), serum creatinine (Scr), platelet count (PLT), lymphocyte count (LYM), prothrombin activity (PTA), and international normalized ratio (INR), were also identified as factors influencing VRC C_{trough}. Detailed information on these influencing factors is presented in Table 2.

PPK Models and Dose Recommendations of VRC in Patients with Liver Dysfunction

Currently, six studies have reported PPK models for VRC in patients with liver dysfunction, all conducted in China.[19,20,25–28] Of these, three were prospective studies,[26–28] and three were retrospective.[19,20,25] One study was multicenter,[20] while the remaining five were conducted at single centers.[19,25–28] Two studies included more than 100 participants.[20,25] Three studies employed a one-compartment pharmacokinetic model,[19,25,27] two used a two-

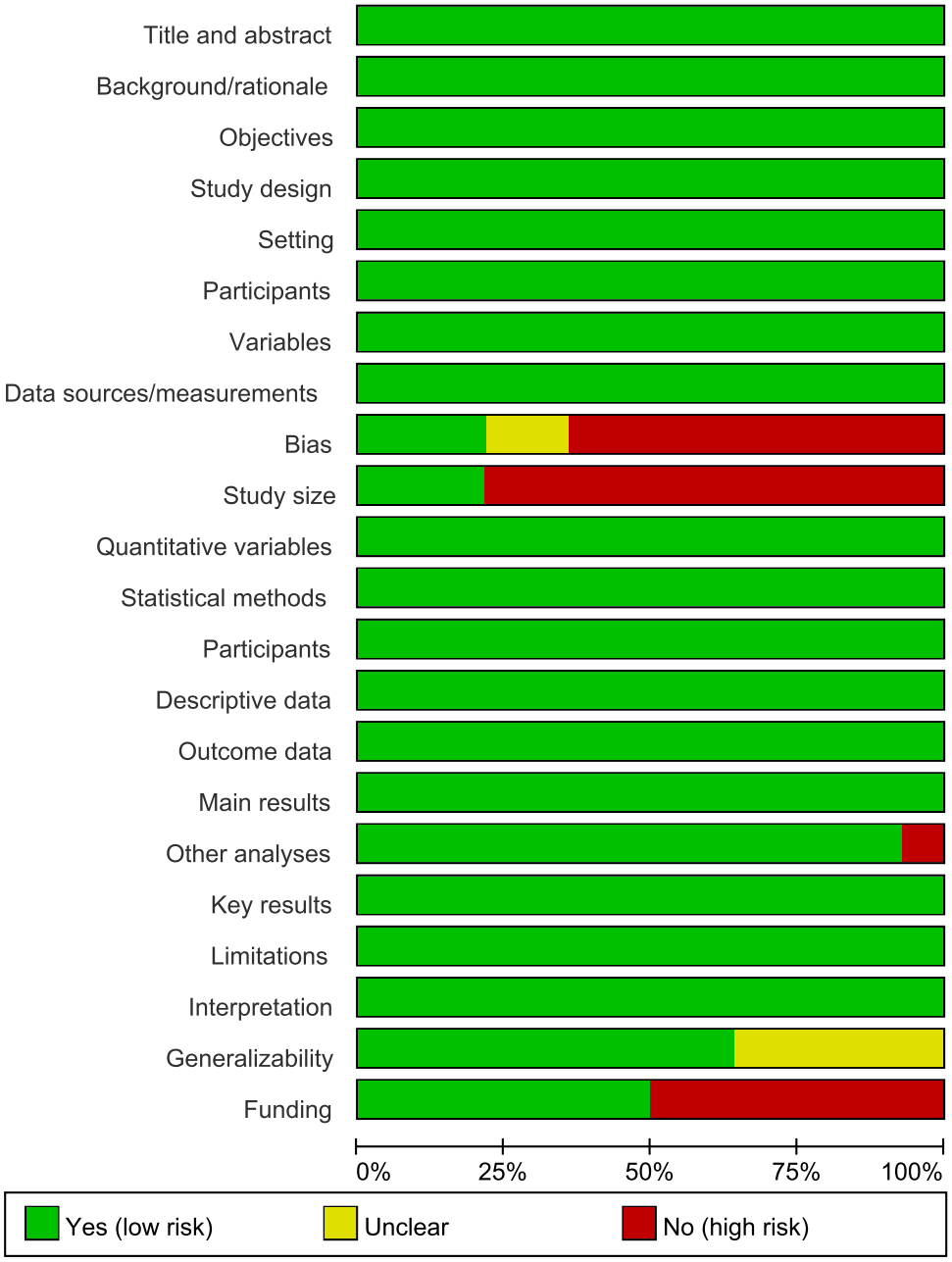

Figure 2 Risk of bias for each study included in the systematic review (adherence to STROBE recommendations).

compartment model,[20,28] and one used non-compartmental analysis.[26] Two studies focused on patients in the intensive care unit as their study population.[26,28]

Three PPK models assessed clearance (CL) in patients with different CP classifications, all of which showed a significant reduction in CL among CP-C patients. For example, Lin et al reported CL values of 3.31 L/h, 2.54 L/h, and 2.04 L/h for CP-A, CP-B, and CP-C patients, respectively.[26] In another study, Lin et al reported median CL values of 2.50 L/h, 2.30 L/h, and 1.45 L/h for CP-A, CP-B, and CP-C patients, respectively.[28] Wang et al observed CL values of 7.59 L/h, 1.86 L/h, and 0.93 L/h in non-cirrhotic, CP-A/B, and CP-C patients, respectively.[20] Regarding the elimination half-life ($t_1/_2$), CP-C patients exhibited a significant prolongation. Lin et al reported $t_1/_2$ values for VRC in intensive care unit patients with CP-A, B, and C liver dysfunction as 24.4 h, 29.1 h, and 60.7 h, respectively.[26] In terms of bioavailability (F), three studies reported F values were 80.8%,[19] 88.4%,[27] and 91.6%,[20] respectively. Significant

https://doi.org/10.2147/DDDT.S553073

https://doi.org/10.2147/DDDT.S553073

Table 1 Summary of ADRs Associated with VRC in Patients with Liver Dysfunction

Country, Study Design	Patient Characteristics, Liver Function Assessments	No. of Samples (Male/Female)	Age (Years) or Age Group	VRC Dose (Administration Route)	The Incidence of ADRs (No. of Patients)	The Details of ADRs	The VRC C_{trough} in Patients with ADRs	The Median Time from VRC Administration to the Onset of the ADRs	First Author and Year
Japan, retrospective study	CP-C cirrhosis, CP class	6 (3/3)	61.0 (55.5, 64.0) [a]	50-600 [b] mg qd on day 1, followed by 50–200 [b] mg qd.	0	/	/	/	Yamada T 2018[16]
China, multicenter and retrospective study	CP-B and CP-C cirrhosis, MELD score	78 (63/15), including group A:34 (28/6) and group B: 44 (35/9)	22-82 [b]	Group A: 400mg qd (PO: IV: sequential regimen 20:9:5). Group B: 400mg qd on day 1, followed by 200mg qd (PO: IV: sequential regimen 39:2:3).	20.5% (n = 16)	Group A: 9 patients, including hallucinations (n = 3), neurological disturbance (n = 2), rash (n = 1), acute renal failure (n = 2), and vomiting (n = 1). Group B: 7 patients, including neurological disturbance (n = 5), hallucinations (n = 1), and rash (n = 1).	Group A: 6.52 ± 2.83 [c] mg/L. Group B: 4.76 ± 2.71 [c] mg/L.	Group A: 6 (1–12) [d] days Group B: 4 (3–10) [d] days	Wang T 2018[17]
China, multicenter and retrospective study	CP-C cirrhosis, CP class	34 (25/9), including group A:19 (14/5) and group B: 15 (11/4)	22-82 [b]	Group A: 400mg qd on day 1, followed by 100 mg q12h (PO: IV: sequential regimen 17:0:2). Group B: 400mg qd on day 1, followed by 200 mg qd (PO: IV: sequential regimen 9:5:1).	23.5% (n = 8)	Group A: 4 patients, including rash, dizziness, tremor, and encephalopathy. Group B: 4 patients, including hallucination, rash, encephalopathy, and consciousness disturbance.	Logistic regression analysis showed the estimated probability of an ADR at a VRC C_{trough} of 4.52 mg/L was 20%.	4 (2– 10) [d] days	Wang T 2018[18]
China, prospective study	Liver dysfunction, CP class and MELD score	51 (43/8)	46.4 ± 12.8 [c]	CP-A/B: instruction dose. CP-C: decided by the doctors.	39.2% (n = 20)	Including hallucinations, dizziness and visual disturbance, such as colour discrimination, blurred vision, and photophobia.	VRC C_{trough} ≤ 5.1 mg/L was found to minimize the incidence of ADRs.	2 (1–12) [d] days	Tang D 2020[19]
China, retrospective and two centers study	LC, CP class and MELD score	120 (95/25)	50.5 ± 13.2 [c]	400 mg (6 mg/kg) or 200 mg (4 mg/kg) q12h on day 1,followed by 100–600 [b] mg qd.	24.2% (n = 29)	Neurotoxicity (n = 12), visual disturbances (n = 6), hallucination (n = 3), rash (n = 3), nausea and vomit (n = 2), hypokalemia (n = 2), and nephrotoxicity (n = 1).	5.98 (2.37–15.10) [d] mg/L.	6 (2–15) [d] days	Wang T 2021[20]
China, prospective study	CP-C cirrhosis, CP class	43 (39/4)	49.35 ± 11.65 [c]	100-400 [b] mg qd (PO: IV: sequential regimen 15:23:5)	46.5% (n = 20)	Including dizziness, hallucinations and visual disturbance, such as altered color discrimination, blurred vision, and photophobia.	/	2 (1–12) [d] days	Zhao Y 2021[21]
China, retrospective study	Liver dysfunction, CP class	308 (191/117)	<60 (n = 188), ≥60 (n = 120)	CP-A/B: 200mg qd (n=158), 400mg qd (n=38). CP-C: 200mg qd (n=84), 400mg qd (n=28). (all patients were administered intravenously)	10.4% (n = 32)	Encephalopathy (n = 6), consciousness disturbance (n = 5), dizziness (n = 4), tremor (n = 4), hallucination (n = 3).	/	/	Cai X 2023[22]
China, retrospective study	Liver dysfunction, CP class and MELD score	157 (133/24)	48.73 ± 12.438 [c]	CP-A/B: instruction dose or TBil-based dosing. CP-C: decided by the doctors.	1.3% (n = 2)	/	/	/	Zhao Y 2024[23]
China, retrospective study	Liver dysfunction, CP class	102 (67/35)	65.5 (24–100) [d]	CP-A/B: instruction dose. CP-C: decided by the doctors. (PO: IV: sequential regimen 19:80:3).	29.4% (n = 30)	Exacerbated liver damage (n = 21), mental abnormalities (n = 5), visual impairment (n = 2), gastrointestinal reactions (n = 1), and rash (n = 1).	4.00 (0.77–10.01) [d] mg/L.	7.5 (2–29) [d] days	Hu L 2024[13]

Notes: Data were expressed as [a] median (interquartile range), [b] range, [c] $\bar{x} \pm s$, [d] median (range). "/" Representing no data.

Abbreviations: VRC, voriconazole; C_{trough}, trough concentration; MELD, Model for End Stage Liver Disease; CP, Child–Pugh; LC, liver cirrhosis; IV, intravenous; PO, Oral; ADR, adverse drug reaction.

Table 2 Summary of Studies Exploring the Factors Affecting the VRC C_{trough} in Patients with Liver Dysfunction

Country, Study Design	Patient Population	No. of Samples	Age (Years)	VRC Therapeutic Target Range (mg/L)	Measurement of VRC C_{trough} (Steady State or non-Steady State Concentration)	Analytical Methods and Factors Affecting the VRC C_{trough}	First Author and Year
China, multicenter and retrospective study	CP-B and CP-C cirrhosis	78	22-82 [a]	1.0–5.0	HPLC (steady state)	Univariate analysis: TBIL, ALB, INR, MELD score, and co-medication with CYP2C19 inhibitors. Multivariable linear regression model: INR and co-medication with CYP2C19 inhibitors.	Wang T 2018[17]
China, prospective study	CP-C cirrhosis	43	49.35 ± 11.65 [b]	1.0–5.5	2D-HPLC (steady state)	Multivariate bivariate correlation analysis: sex, CYP2C19 genotype, daily dose, PTA, INR, PLT, and MELD score. Multiple linear regression model: sex, daily dose, PTA and CYP2C19 genotype.	Zhao Y 2021[21]
Japan, retrospective study	LC	159	/	1.0–4.0	HPLC (steady state)	Univariate analysis: ALBI score.	Nashimoto S 2023[24]
China, retrospective study	Liver dysfunction	157	48.73 ± 12.438 [b]	1.0–5.5	2D-HPLC (steady state)	Spearman correlation analysis: daily dose, DBil, LYM counts and percentage, PLT, BUN and Scr levels. Multiple linear regression analysis: daily dose, LYM counts and Scr levels.	Zhao Y 2024[23]
China, retrospective study	Liver dysfunction	102	65.5 (24–100) [c]	1.0–5.5	LC-MS/MS (steady state)	Multiple linear regression analysis: age ≥ 70 years, CP class, CRP concentration and DBil levels.	Hu L 2024[13]

Notes: Data were expressed as [a] range. [b] $\overline{x} \pm s$. [c] median (range). "/" Representing no data.

Abbreviations: VRC, voriconazole; C_{trough}, trough concentration; CRP, c-reactive protein; BUN, blood urea nitrogen; Scr, serum creatinine; DBil, direct bilirubin; PLT, platelet; LYM, lymphocyte; PTA, prothrombin time activity; ALBI, albumin–bilirubin; CP, Child–Pugh; LC, liver cirrhosis; HPLC, high performance liquid chromatography; 2D-HPLC, two-dimensional high performance liquid chromatography; LC-MS/MS, liquid chromatography–tandem mass spectrometry.

covariates influencing CL included CP classification, CYP2C19 phenotype, TBil, PLT, AST, and INR. Covariates significantly affecting $t_1/_2$ included AST, TBil, and INR. Body weight was identified as a significant factor influencing the volume of distribution.

Four studies have proposed specific dose adjustment strategies for patients with liver dysfunction based on dose simulation experiments.[20,25,27,28] For example, Tang et al recommended adjusting the VRC dosage according to TBil levels.[27] Ren et al suggested reducing the VRC dose to 100 mg once daily (qd) for patients with moderate to severe cirrhosis.[25] Wang T et al advised lowering the VRC dose to one-fourth for CP-C patients and to one-third for CP-A/B patients compared to the standard recommended dose.[20] Lin XB et al proposed reducing the intravenous loading dose of VRC to 5 mg/kg every 12 h (q12h) in critically ill patients.[28] Detailed PPK data and recommended VRC dosages for patients with liver dysfunction are summarized in Table 3.

Discussion

Safety of VRC in Patients with Liver Dysfunction

The most common ADRs related to VRC include hepatotoxicity, neurotoxicity, and visual disturbances. The mechanism underlying VRC-induced liver injury remains unclear, and no specific biomarkers are currently available for its prediction or diagnosis. Some studies suggested that VRC-induced hepatotoxicity was associated with oxidative stress, which disrupted cellular function and affected energy metabolism, the urea cycle, and nucleoside metabolism.[29] Additionally, impaired fatty acid oxidation and reduced bile acid excretion may contribute to VRC-induced liver injury.[30] Central nervous system (CNS) toxicity occurs because VRC can penetrate the vitreous humor, aqueous humor, and cerebrospinal fluid via the blood-eye and blood-brain barriers, leading to retinal changes and CNS disturbances. These effects can manifest as visual impairment, hallucinations, altered consciousness, and headaches. A retrospective study reported that patients with a VRC C_{trough} > 4.85 mg/L had a higher risk of CNS toxicity.[31] Similarly, Liu et al documented three cases of visual impairment and hallucinations occurring within one week of VRC initiation.[32] Their review of case reports since 2014 found that the onset of these symptoms was independent of the administration route. A single-center, double-blind, randomized, placebo-controlled, parallel-group study indicated that VRC-induced visual impairment was non-progressive and reversible during treatment.[33] However, its exact pathological mechanism remains unclear. Further research is needed to elucidate their underlying mechanisms.

Most VRC-related ADRs occur within the first 7 days of treatment. Therefore, early TDM and timely dosage adjustments may help reduce the incidence of these ADRs. The consensus from Japanese Society of Chemotherapy and the Japanese Society of Therapeutic Drug Monitoring (JSC/JSTDM) suggests that due to the higher prevalence of CYP2C19 poor metabolizers in the Asian population, the incidence of ADRs is higher in Asians compared to non-Asians.[34] Consequently, the recommended VRC dosage and target therapeutic ranges may differ between these populations. Tang et al found that maintaining a VRC C_{trough} of ≤ 5.1 mg/L was significantly associated with a lower incidence of adverse events.[19] However, most studies currently use a target therapeutic range of 1.0–5.5 mg/L for VRC C_{trough},[13,23] which may not be suitable for patients with liver dysfunction. Further research is needed to establish an optimal target range for VRC C_{trough} in this population.

Factors Influencing VRC C_{trough} in Patients with Liver Dysfunction

Multiple factors influence the C_{trough} of VRC in patients with liver dysfunction. To date, only CYP2C19 polymorphisms have been reported as influencing VRC C_{trough} in this population. However, the potential impact of polymorphisms in other metabolic enzymes, such as CYP3A4, CYP3A5, and flavin-containing monooxygenase 3 (FMO-3), remains unexplored. Among non-genetic factors, key determinants of VRC C_{trough} in liver dysfunction include CP classification and ALBI grading, which is based on ALB and bilirubin levels. These findings indicate that varying degrees of liver impairment significantly affect VRC C_{trough}. Therefore, in patients with severe liver dysfunction, the risks and benefits of VRC treatment should be carefully weighed, with the treatment being accompanied by rigorous monitoring of both liver function and C_{trough}.

Most studies assessing liver function utilize the CP classification, while a few rely on the MELD score. However, the CP classification is primarily used for patients with cirrhosis and depends on subjective indicators such as ascites and

Table 3 Summary of Studies on PPK Analysis and Current Recommendations of VRC Optimal Dosing Regimen in Patients with Liver Dysfunction

Country, Study Design	Patient Population	No. of Samples (Male/Female)	Age (Years)	VRC Therapeutic Target Range (mg/L)	Software	Model	VRC Pharmacokinetic Parameters	Significant Covariates	Dose Recommendations	First Author Year
China, retrospective study	LC	180 (137/43)	51.1 ± 12.9 [a]	*f*AUC/MIC ≥ 25	Phoenix NLME	A one-compartment model	CL 1.45 L/h, *V* 132.12 L.	CYP2C19 phenotype and CP class was correlated with CL. WT was correlated with *V*.	For EMs: 75 mg q12h in mild to moderate LC, 100 mg qd in moderate to severe LC.	Ren QX 2019[25]
China, retrospective study	Liver dysfunction	57 (48/9)	48.31 ± 11.95 [a]	/	NONMEM	A one-compartment model	CL 0.58 L/h, V_d 134 L, *F* 80.8%.	PLT was correlated with CL.	/	Tang D 2019[19]
China, prospective study	Liver dysfunction in the ICU	12 (9/3)	51 (33–72) [b]	2.0–6.0	WinNonlin	A non-compartmental analysis	$t_{1/2}$ and CL in CP-A, B, and C were 24.4 h and 3.31 L/h, 29.1 h and 2.54 L/h, 60.7h and 2.04 L/h.	INR was correlated with $t_{1/2}$. AST and TBIL was correlated with $AUC_{0-12.}$ WT was correlated with V_{ss}.	/	Lin XB 2020[26]
China, prospective study	Liver dysfunction	51 (43/8)	46.4 ± 12.8 [a]	0.5–5.0	Phoenix NLME	A one-compartment model	CL 0.88 L/h, *V* 148.8 L, *F* 88.4%.	TBIL and PLT was correlated with CL.	For patients with TBIL-1: 400 mg q12h on day 1, followed by 100 mg q12h. For patients with TBIL-2 and TBIL-3: 200 mg q12h on day 1, followed by 50 mg q12h or 100 mg qd and 50 mg qd.	Tang D 2021[27]
China, retrospective and two centers study	LC	120 (95/25)	50.5 ± 13.2 [a]	1.0–5.0	NONMEM	A two-compartment model	CL in non-cirrhotic, CP-A/B and CP-C patients was 7.59, 1.86, and 0.93 L/h. V_c and V_p was 100.8 and 55.2 L. *F* was 91.6%.	CP class was correlated with CL. WT was correlated with V_c.	Reduced to 1/4 for CP-C and 1/3 for CP-A/B compared to instruction dose.	Wang T 2021[20]
China, prospective study	Critically ill patients with liver dysfunction in the ICU	26 (22/4)	55.5 (28.0–89.0) [b]	2.0–6.0	Phoenix NLME	A two-compartment model	The median CL of CP-A/B/C patients was 2.50, 2.30 and 1.45 L/h.	WT was correlated with V_c and V_p. CP class was correlated with CL.	The intravenous loading dose reduced to 5 mg/kg q12h.	Lin XB 2022[28]

Notes: Data were expressed as [a] $\bar{x} \pm s$. [b] median (range). "/" Representing no data.

Abbreviations: VRC, voriconazole; PPK, population pharmacokinetics; EMs, extensive metabolizers; WT, weight; TBil, total bilirubin; AST, aspartate transaminase; INR, international normalized ratio; PLT, platelet; ICU, intensive care unit; LC, liver cirrhosis; CP, Child–Pugh; q12h, every 12 h; qd, once daily; CL, clearance; $t_{1/2}$, half-life; AUC_{0-12}, area under the curve; V_{ss}, steady-state volume of distribution; *F*, bioavailability; *V*, volume of distribution; V_c, central distribution volume; V_p, peripheral distribution volume.

hepatic encephalopathy, which can lead to inaccurate assessments. Furthermore, some studies do not exclusively focus on cirrhosis, and the MELD score is mainly employed to prioritize liver transplantation. Thus, both CP and MELD scoring systems have limitations in evaluating liver function severity. Recent studies have found a correlation between VRC C_{trough} and the ALBI grading.[24] Unlike CP classification, ALBI grading eliminates subjective factors like ascites and hepatic encephalopathy, providing a more objective assessment of liver function by quantitatively analyzing bilirubin and ALB levels. Additionally, ALBI grading is applicable to both cirrhotic and non-cirrhotic patients, making it a more broadly applicable tool for evaluating liver function in VRC research. Recent evidence also suggested that ALBI grading may serve as a predictor for VRC-induced liver toxicity.[35] At present, VRC dosing recommendations are based on CP class. However, future research may explore the potential for optimizing VRC doses based on ALBI grading.

Patients with liver dysfunction often exhibit hypoalbuminemia and hyperbilirubinemia. Our previous research has demonstrated that VRC C_{trough} is correlated with both ALB and DBil levels.[13] Additionally, a study by Tang et al identified TBil as a significant predictor of VRC pharmacokinetic parameters in these patients, suggesting that optimizing VRC dosage based on TBil levels could enhance treatment outcomes.[27] However, current guidelines do not recommend adjusting VRC dosage according to ALB levels. Our study also identified other factors influencing VRC C_{trough}, such as the effect of the inflammatory marker CRP.[13] Elevated CRP levels have been associated with an increased risk of excessive VRC exposure and ADRs.[36] Therefore, when determining the appropriate VRC dosage for patients with liver dysfunction, it is essential to consider their inflammatory status.[37] Moreover, compared to other populations, patients with liver dysfunction present additional unique factors, such as PT, INR, and PLT. These factors suggest that individualized VRC dosing should take into account coagulation function and blood routine parameters. Further investigation into the impact of other potential factors on VRC pharmacokinetics in patients with liver dysfunction is warranted. Current research on the factors influencing VRC C_{trough} in patients with liver dysfunction has largely been exploratory. Relatively few studies have investigated how identified influencing factors can be applied to clinical TDM decision-making. Consequently, the clinical applicability of these findings cannot yet be summarized and currently serves only as a reference point for future research. Further studies are warranted to determine how these significant factors, particularly emerging factors such as CRP and ALBI grading can be applied to optimize VRC dosing strategies.

PPK Models and Dose Recommendations of VRC in Patients with Liver Dysfunction

Currently, only four studies have reported dose recommendations for VRC in patients with liver dysfunction. Some studies have found that the $t_1/_2$ of VRC is significantly prolonged and its CL rate notably reduced, especially in patients with severe liver dysfunction. Tang et al proposed a VRC dose adjustment scheme based on varying levels of TBil through prospective PPK research.[27] This dosing strategy has been recognized and recommended by the JSC/JSTDM consensus. However, it is important to note that the study population in this research was exclusively Chinese. Since most of the included studies were conducted in Chinese populations, it is important to consider the impact of ethnic variability, such as differences in the prevalence of CYP2C19 polymorphisms when extrapolating the findings. As a result, the generalizability of these PPK results to non-Asian populations may be limited. Currently, there are no large-scale, multi-ethnic studies on VRC, underscoring the need for future research to explore appropriate dose adjustments for different ethnic groups within this patient population.

Recommendations for the Use of VRC in Patients with Liver Dysfunction in Guidelines and Consensus

Currently, guidelines and consensus on the use of VRC in patients with liver dysfunction is provided by the Clinical Pharmacogenetics Implementation Consortium (CPIC),[38] the CPS,[6] and the JSC/JSTDM.[34] In addition to the drug instructions, the JSC/JSTDM consensus proposed specific dosage adjustments for patients with cirrhosis and hyperbilirubinemia. The CPIC guidelines emphasized the need for dose adjustments in patients with mild to moderate liver dysfunction but did not provide detailed VRC dosage recommendations. For patients with severe liver dysfunction, CPIC guidelines suggested considering alternative antifungal agents to avoid the potential toxic effects of VRC. The CPS

Table 4 Therapeutic Recommendations for the Use of VRC in Patients with Liver Dysfunction in the Drug Instructions and Guidelines

Guideline or Consensus	Publication Year	Target Populations	Recommendations for the Use of VRC	Evidence Grading
VRC label information[12]	Updated October 30, 2024	CP-A/B	Load dose: standard dose. Maintenance dose: halved.	/
		CP-C	No recommendations because no research on the application of VRC in this population.	/
		Patients with liver function impairment	Must closely monitor the toxicity of the drug when using VRC.	/
CPIC Guideline[38]	2017	Mild to moderate hepatic impairment	A dose adjustment for VRC is recommended.	/
		Significant hepatic impairment	Selection of an alternative antifungal agent due to the risk of VRC hepatotoxicity.	/
CPS Guideline[6]	2018	In severe hepatic dysfunction	VRC is not suggested as first-line treatment. After balancing the benefits and harms, VRC can be used for these patients under rigorous TDM and hepatic function monitoring	2D, Conditional recommendation, very low quality of evidence.
JSC/JSTDM Consensus[34]	2022	CP-A/B	A loading dose of 5–6 mg/kg q12h on the first day followed by half of the standard daily maintenance dose.	II, General recommendation with moderate evidence for efficacy with clinical benefit.
		In patients with hyperbilirubinemia	(i) TBil levels 3–10 mg/dL: a loading dose of 200 mg q12h on the first day followed by maintenance doses of 50 mg q12h. (ii) TBil levels ≥10 mg/dL: a loading dose of 100 mg qd followed by 50 mg qd.	IIIA, Suggestion to encourage use by expert opinion without sufficient evidence.

Note: "/" Representing no data.

Abbreviations: VRC, voriconazole; CPIC, Clinical Pharmacogenetics Implementation Consortium; CPS, Chinese Pharmacological Society; JSC/JSTDM, Japanese Society of Chemotherapy and the Japanese Society of Therapeutic Drug Monitoring; TDM, therapeutic drug monitoring; TBil, total bilirubin; CP, Child–Pugh; q12h, every 12 h; qd, once daily.

https://doi.org/10.2147/DDDT.S553073

guidelines also stated that VRC was not recommended as a first-line treatment in patients with severe liver dysfunction. If necessary, VRC use may be considered, but only after carefully weighing the potential benefits and risks, and under close monitoring of C_{trough} and liver function. Therefore, further PPK studies are needed to investigate optimal dosing strategies for patients with varying degrees of liver function. A summary of the specific dosing recommendations from these guidelines and consensus is provided in Table 4.

Limitations

Most of the studies included in this systematic review were single-center and retrospective in design, with limited sample sizes. The included studies vary significantly in type, patient characteristics, and the definition standards of ADRs, which limits the comparability of the data. Additionally, the recommended VRC dosages proposed by different studies vary greatly, and there is a lack of consensus based evidence, further affecting the reliability of the conclusions. Most of the existing PPK models lack external validation, and relevant external validation data should be supplemented. Furthermore, the majority of the study population was of Asian descent, potentially limiting the generalizability of the findings to other ethnic groups. Due to the potential early impact of transplant rejection and ischemia–reperfusion injury on liver function in liver transplant recipients, including this population may lead to an overestimation of VRC-associated hepatotoxicity. In contrast, during the later post-transplant period, liver function often returns to normal, and these patients may no longer present with hepatic dysfunction. However, the reviewed literature did not clearly indicate which patients were in the early post-transplant phase. Therefore, liver transplant recipients were excluded from this study. Future research should consider analyzing liver transplant recipients as a separate subgroup, rather than combining them with patients experiencing other types of liver dysfunction.

Conclusion

The incidence of VRC-related ADRs is relatively high in Asian patients with liver dysfunction. VRC C_{trough} are influenced by several factors, including the severity of liver impairment, CYP2C19 polymorphisms, and ALB and bilirubin levels. Therefore, the use of VRC in this population requires close monitoring of both C_{trough} and liver function, particularly in patients with severe liver dysfunction. Individualized VRC dosing, guided by TDM and PPK, is essential for optimizing patient outcomes in clinical practice. To improve the efficacy and safety of VRC in patients with liver dysfunction, large-scale, multi-center, and multi-ethnic prospective studies are needed to establish optimal dosing strategies.

Funding

This study was supported by the Natural Science Foundation of Hunan Province (2024JJ8227), the Scientific Research Project of Hunan Provincial Health Commission (W20243243) and the Scientific Research Project of Changsha Municipal Health Commission (KJ-B2023042).

Disclosure

The authors declare that they have no competing of interests.

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