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GROUP PHARMACOKINETICS OF FLUCONAZOLE IN PATIENTS WITH SEVERE INFECTION

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Abstract: Objective: The aim was to investigate the population pharmacokinetics (PopPK) model of Vorticamole (VRC), identify significant covariates and corresponding dose optimization strategies in the existing clinical patient VRC PopPK model, and explore the characteristics of the existing VRC PopPK model. Methods: We searched the PubMed database for clinical PopPK studies of VRC using the nonlinear mixed-effects method from the establishment of the database to May 2025, and screened the relevant references. Results: A total of 29 studies that met the inclusion criteria were finally included. One-compartment and two-compartment models were reported in 21 and 7 studies, respectively, as the best models to describe the PopPK of VRC, and one study used a three-compartment model. More than 40 covariates were included in the screening, with the most common covariates being CYP2C19 phenotype and body weight, and ALB being a secondary covariate. The typical volume of distribution in adult and pediatric patients was similar, but the estimated clearance in pediatric patients was significantly higher than that in adult patients, and the estimated bioavailability in pediatric patients was significantly lower than that in adult patients. The typical values of voriconazole clearance and total apparent volume of distribution exhibit substantial variability, ranging from 2.29–7.35 L/h and 76–194 L, respectively. Twenty-four studies used the exponential model as the basic model to describe the inter-individual variation. Only three studies used external methods to evaluate the model. Conclusion: First, this paper emphasizes the broadness and variability of the estimated PopPK parameters of VRC and provides the covariates that affect the clearance and apparent volume of distribution in such patients. Second, external evaluation of PopPK models should be conducted, and the predictive performance of various models should be further compared to improve the extrapolation ability of the models. In addition, it is recommended to conduct Monte Carlo simulations based on the significant covariates derived from different patient groups, and to supplement PopPK models to guide the differences in clinical efficacy between dose and traditional empirical dose, track the individualized medication effects of patients guided by PopPK models, and conduct supplementary trials based on actual clinical efficacy to facilitate the more reasonable application of models in clinical practice.
Keywords: Voriconazole; Population pharmacokinetics; Exposure-response relationship

1 INTRODUCTION

Voriconazole (VRC) is a second generation triazole with broad spectrum antifungal activity [1].VRC has effective antibacterial activity against Aspergillus and Candida, as well as some clinically rare fungal pathogens [2]. It has effective activity against a wider range of clinically important fungal pathogens, including Aspergillus, Candida, Cryptococcus neoformans and some unusual organisms, such as Fusarium and Pseudobacter boydii. In 2016, the guidelines of the American Society of Infectious Diseases recommended VRC as the first choice for invasive aspergillosis and alternative therapy for candidiasis [3-4].

In recent years, many studies have studied the exposure-response relationship of VRC. The results of these studies show that low concentration may lead to higher treatment failure rate, while high concentration is related to increased toxicity. As a result, the target valley concentration range of VRC is narrow [5]. VRC is mainly metabolized by CYP2C19 isoenzymes in the human body, followed by CYP2C9 and CYP3A4 isoenzymes [6]. The CYP2C19 phenotype and its associated polymorphisms influence the metabolism of VRC by modulating enzyme expression, thereby contributing to its nonlinear pharmacokinetics. The lack of predictability in the relationship between pharmacokinetic characteristics and administered dosages may result in unpredictable pharmacological effects of VRC at standard doses, potentially leading to toxic effects [7].

The nonlinear kinetics observed for VRC partially accounts for its highly variable serum concentration. Additionally, there are substantial inter-individual and intra-individual differences in VRC pharmacokinetics, demonstrating extensive variability among different patient populations [8]. The binding affinity of VRC to proteins is moderate, approximately 60%, and its volume of distribution (Vd) ranges from 2 to 4.6 L/kg, suggesting extensive distribution both in

extracellular and intracellular compartments [9]. Although it has been observed that the pharmacokinetics of VRC exhibit relatively high inter-individual and intra-individual variability, and the therapeutic range of this compound is relatively narrow, the metabolic pathways and mechanisms of VRC have not yet been fully elucidated [10]. The third edition of the Aspergillosis Diagnosis and Treatment Guidelines in 2017 recommends that for the majority of patients receiving voriconazole for prophylaxis or treatment, the target trough concentration should be maintained at 1 - 5.5 μg/mL. For patients with severe infections, it is advisable to elevate the target trough concentration to 2 - 6 μg/mL [11]. The guideline for Individualized Use of voriconazole issued by the Chinese Pharmacological Society in 2018 recommended that the target trough concentration range of voriconazole is 0.5-5.0 μg/mL, which has good efficacy and low toxic and side effects [12]. In 2022, the Japanese Therapeutic Drug Surveillance Society's "Clinical Practice Guidelines for Voriconazole Therapeutic Drug Monitoring" suggested that the target trough concentration range for voriconazole in Asian patients should be set at 1.0–4.0 μg/mL. For non-Asian patients, the recommended trough concentration treatment range was established as 1.0–5.5 μg/mL [6]. In 2024, the European Leukemia Infection Conference updated the guidelines for antifungal prophylaxis in adults, which recommended voriconazole for the prevention of fungal infections in the range of 1.0-6.0 μg/mL [13]. The recommended concentration range of VRC is 0.5–5.0 μg/mL, as per the Chinese practice guidelines for its individualized use [12]. In conclusion, patients treated with voriconazole necessitate distinct therapeutic drug monitoring (TDM) indications, durations, and target trough concentrations, as well as individualized medication regimens to prevent drug exposure levels from exceeding the therapeutic range.

In clinical practice, TDM of VRC is recommended to enhance drug efficacy and minimize toxic and adverse effects [14]. However, the TDM method can only be applied subsequent to the initiation of treatment, and traditional TDM sampling is conducted under steady-state conditions. In practice, VRC achieves its steady-state trough concentration approximately 5 days following standard administration. Although a quasi-steady state may be attained within 24 hours post-administration, this still involves a waiting period that could potentially compromise clinical outcomes. In addition, VRC undergoes metabolism via cytochrome P450 isoenzymes, and the presence of inhibitors or inducers of these isoenzymes may alter the plasma concentration of VRC. This phenomenon also results in significant drug-drug interactions (DDIs) between VRC and co-administered medications during clinical application [15]. Therefore, the identification of factors contributing to a high degree of variation in the pharmacokinetics of VRC is crucial for determining an appropriate dosing regimen as early as possible.

In recent years, model-guided dose optimization has facilitated the advancement of individualized medicine into the quantitative decision-making phase. With the rapid evolution of quantitative pharmacological data analysis techniques, Population Pharmacokinetics (PopPK) modeling and simulation have assumed an increasingly critical role in precision medicine. By integrating PopPK models with TDM to optimize drug dosing regimens, it is possible to achieve covariate-based individualized drug administration [16]. Given the nonlinearity, significant inter- and intra-individual variability, extensive drug interactions, and relatively narrow therapeutic index of VRC, comprehending the pharmacokinetic characteristics in clinical patients receiving VRC is crucial for selecting appropriate antibiotic dosages and developing individualized treatment strategies [17]. For the development of individualized voriconazole dosing regimens, the guidelines recommend employing the PopPK method to adjust voriconazole dosing regimens when locally applicable population-based PopPK models are available [18]. In fact, over the past two decades, numerous scholars have been actively engaged in PopPK research on voriconazole. This review aims to consolidate the existing literature on VRC in clinical PopPK, thereby facilitating a comprehensive understanding of the current knowledge framework and paving the way for further research to enhance comprehension and inform optimal therapeutic dosing decisions.

2 METHODS

2.1 Methods of Retrieval

The PubMed database was systematically searched. The search time spanned from the establishment of the database to May 2025, and the search strategy was as follows: (((population pharmacokinetics) OR (PopPK) OR (nonlinear mixed-effect model) OR (PPK)) AND (voriconazole)). Search scope: All fields.

2.2 Inclusion and Exclusion Criteria

Studies included in this review were required to meet the following inclusion criteria: (1) the study population consisted of children, adult patients, or healthy volunteers; (2) VRC was administered as the study drug, regardless of whether it was given intravenously or orally; (3) a nonlinear mixed-effects PopPK modeling method was employed. Exclusion criteria included: (1) reviews and methodological articles; (2) laboratory-based or animal studies; (3) studies utilizing nonparametric methods.

3 RESULTS OF LITERATURE RETRIEVAL

3.1 Results of Literature Screening

After an initial search, 244 studies were retrieved from the Pubmed database. Following deduplication using Endnote

X9 software and manual screening, seven animal experiments and seven laboratory studies were excluded. Subsequently, after applying the inclusion and exclusion criteria, a total of 29 studies met the eligibility criteria, with publication years ranging from 2009 to 2025. No additional studies were identified following a review of the reference lists of the included studies. Table 1 summarizes the population characteristics of the 29 studies; the number of subjects in each study ranged from 13 to 305 (median: 95), and 21 studies (73%) included more than 50 participants. Eighteen of the studies focused on the Chinese population. There were 11 studies conducted on foreign populations, specifically in Thailand [7, 19], the United States[20, 21], the Czech Republic[9], the Netherlands [22], Japan [23], Australia [24], South Korea [25], Sweden [26], and Pakistan [27].

Table 1 Summary of Demographic Characteristics of the VRC Clinical PopPK Study

Study	country	CYP2C19 genotype (n)	Subjects /sample	Type of study	Structural model	Software	Age	Subject characteristics	Routes
Karlsson 2009[26]	Sweden	EMs:HEMs:PM=58:21:3	82/1274	perspicacity	2-CMT	NONMEM V	2-12	Paediatric patients	PO/IV
Han 2010[20]	America	NR	13	perspicacity	2-CMT	NONMEM 6.2.0	19-70	Adult lung transplant recipients	PO/IV
Han 2011[21]	America	NM:IM=11:2	13	perspicacity	1-CMT	NONMEM 6.2.0	41-67	Adult liver transplant recipient	PO/NFT
Dolton 2014[24]	Australia	NM and RM:IM and PM:UK =56:38:146	240/3352	NR	2-CMT	NONMEM 7.2	NR	Healthy adults (63) and adult patients with fungal infection (177)	PO/IV
Chen WY 2014[43]	China	NR	62/240	perspicacity	1-CMT	NONMEM VI	16-90	Critical adult patients with lung disease	IV
Muto 2015[23]	Japan	NM:PM:IM=9:2:10	39/276	NR	2-CMT	NONMEM 7	3-14	Immunocompromised children who were at high risk for systemic fungal infection	PO/IV
Li Z 2017[28]	China	RM:EM:IM:PM=2:24:25:5	56/125	retrospectivity	1-CMT	Phoenix NLME 1.4	18-60	Adult renal transplant recipients	PO/IV
Lin XB 2018[8]	China	RM:EM:IM:PM=1:44:49:12	105/342	perspicacity	1-CMT	Phoenix NLME 7.0	18-58	Adult renal transplant recipients	PO/IV
Kim 2019[25]	Korea	PM:EM:IM=48:75:70	193/1828	perspicacity	3-CMT	NONMEM 7.3	18-80	Healthy volunteers and patients	PO/IV
Chen C 2019[29]	China	CYP2C19*2:CYP2C19*3=13:5	23/121	retrospectivity	1-CMT	NONMEM 7.3.0	19-60	Haematopoietic stem cell transplant patients	PO/IV
Liu 2019[41]	China	NM:IM:PM=18:16:7	41/186	perspicacity	1-CMT	NONMEM 7.3.0	19-81	Patients with confirmed or suspected IFD haematological malignancy	PO
Tang 2019[44]	China	NR	57/166	perspicacity	1-CMT	NONMEM 7.3	27-80	Patients with liver dysfunction	PO/IV
Ren 2019[30]	China	UM:EM:IM:PM=1:61:80:18	180/NR	retrospectivity	1-CMT	Phoenix NLME 7.0	18-85	patient with cirrhosis of the liver	PO/IV
Khan-asa 2020[19]	Thailand	UM:EM:IM:PM=1:33:24:7	67/235	perspicacity	1-CMT	NONMEM	20-78	Adult haematological patients	PO
Tang 2021[38]	China	UM:EM:IM:PM=1:24:21:5	51/272	perspicacity	1-CMT	Phoenix NLME 8.0	15-89	Patients with liver dysfunction	PO/IV
Chantharit 2020[7]	Thailand	EM:IM:PM=40:36:12	106（12/60 perspicacity，		1-CMT	Phoenix 8.1	18-87	Patients with invasive Aspergillus	PO

			94/409 retrospectivity）					infections	
Lin XB 2022[40]	China	NM:IM:PM=12.11:3	26/297	perspicacity	2-CMT	Phoenix NLME 8.0	28-89	Critically ill patients with liver dysfunction	IV
Wang Jun 2021[37]	China	UM:EM:IM:PM=1:34:45:14	99/195	perspicacity	2-CMT	Phoenix NLME 8.2	0.4-13.58	Critically ill paediatric patients	IV
Wang T 2021[31]	China	NR	Cirrhosis group120/219; Non-cirrhotic group 11/83	retrospectivity	2-CMT	NONMEM 7.20	18-84	Patients with cirrhosis of the liver	PO/IV
Li SC 2021[32]	China	IM:NM:PM=32:27:16	78/427(VRC:214;VNO:213)	retrospectivity	1-CMT	Phoenix NLME8.2.0	14.0–70.0	Patients with impaired immune function	PO
Wu 2022[33]	China	EM:IM:PM=31:27:9	67/146	retrospectivity	1-CMT	NONMEM 7.4.3	5.5-14.71	Children with haematological malignancies	PO/IV
Jiang 2022[39]	China	EM:IM:PM=30:31:8	63/233	perspicacity	1-CMT	NONMEM 7.4.0	53-63	Patients with Manilfredia bluestem infections	PO/IV
Dvorackova 2023[9]	Czech Republic	NR	40/78	perspicacity	NR	Monolix Suite 2021R1	38-68	Adult lung transplant recipients	PO
Hu 2023[34]	China	NM:IM:PM=37:43:11	91/210	retrospectivity	1-CMT	NONMEM 7.5	2-14	Paediatric haematology patients	PO
Wang Jing 2023[35]	China	NR	150/438	retrospectivity	1-CMT	NONMEM 7.3.0	60-103	Elderly patients	IV
van den Born 2023[22]	Netherlands	NR	54/1060	perspicacity	1-CMT	Edsim++ 1.9.1.30	19-73	Prevention and treatment of patients with invasive fungal infections	PO/IV
Ling 2024[36]	China	NM:IM:PM=66:72:29	167/232	retrospectivity	1-CMT	NONMEM 7.3.0	16-97	Patients with invasive fungal infections	PO/IV
Wang 2025[42]	China	RM EM IM PM=1:28:39:4	72/150	perspicacity	1-CMT	NONMEM 7.3.0	77(69, 84)	COVID-19-associated pulmonary aspergillosis	IV
Akbar 2025[27]	Pakistan	NR	88/88	retrospectivity	1-CMT	NONMEM 7.4.4	3-90	Cancer patients with systemic fungal infections	IV

CMT compartment model; PO: oral administration; IV: intravenous administration; NFT: nasal feeding tube; HEMs: heterozygous extensive metabolizers; EMs: homozygous extensive metabolizers; NM: cytochrome P450 2C19 normal metabolizer; IM: cytochrome P450 2C19 interme- diate metabolizer; PM: cytochrome P450 2C19 poor metabolizer; RM: CYP2C19 rapid metabolizee; UM: ultra-rapid metabolizer

3.2 Clinical Protocol and Design

Among the included studies, 10 were retrospective in nature [27-36], 18 were prospective studies, and the remaining study adopted a mixed-methods design combining both prospective and retrospective approaches [7]. The dose of VRC was determined by the physicians in each hospital based on their clinical judgment and in accordance with the recommended dosing regimen. The route of administration across all 16 studies was either intravenous or oral; specifically, six studies utilized intravenous administration, six studies used oral administration, and one study employed oral administration via a nasogastric tube. Among the 29 PopPK models describing VRC, five studies

focused on the pediatric population [23, 26, 33-34, 37], one study was specifically designed for elderly patients [35], one study encompassed patients across all age groups [27], and the remaining studies were conducted in adult populations. The study population comprised healthy volunteers and patients receiving voriconazole for the treatment or prophylaxis of fungal infections. These individuals might also present with comorbidities such as liver dysfunction, organ transplantation, or hematologic malignancies.

3.3 PopPK Analysis

Table 2 provides a summary of the model characteristics for the included studies. As shown in Table 2, 19 studies utilized NONMEM modeling along with associated parameter analysis, 8 studies employed Phoenix®NLME modeling, 1 study adopted Monolix Suite modeling, and 1 study applied Edsim++ modeling. Twenty-one literatures were included in the CYP2C19 genotyping data [7-8, 19, 21, 23-26, 28-30, 32-34, 36-42]. Most of the individual variability in the base model was attributed to the exponential error model, while the individual variability in the final model was primarily driven by residual variation combined with the exponential error model. For covariate screening of the model, all studies employed the stepwise method for forward inclusion and backward elimination. In the context of model verification and evaluation, the majority of studies adopt the goodness-of-fit plot method (GOF) to assess the adequacy of the final model fit, the nonparametric Bootstrap method to evaluate the robustness and reliability of the final model, and the visual predictive check (VPC) to assess the predictive performance of the model [38]. Several models were assessed both graphically and statistically through the utilization of normalized prediction distribution errors (NPDEs)[33, 37]. A total of five studies established the absorption rate constant as a fixed value [7, 29, 33, 37, 38], four studies used lag times to balance the delayed absorption of the model [21, 23-25].

Table 2 Summary of Covariate Characteristics of the VRC Clinical PopPK Model

Study	Combination of drugs	Covariates tested	Significant covariate	Residual model	Pharmacokinetic parameters
Karlsson 2009[26]	CYP2C19 inhibitors, CYP2C9 inhibitors, CYP3A4 inhibitors and CYP450 inducers	Age, Sex, Weight, Height, Race, Scr, AST, ALT, ALP, GGT, ALB, TBIL, and Total Protein Levels	CYP2C19 genotype and alanine aminotransferase levels	BSV: exponential error model; WSV NR	CL=4.28×(DBIL /2.6)−0.4 L/h; Vc=93.4 L; Vc (L/kg)=0.807; Q=0.609; Vp=2.17; Ka(h-1)=0.849; F= 44.6%
Han 2010[20]	NR	Diagnosis, age, weight, race, sex, days post-transplant, and pre-transplant, post-transplant, and same-day laboratory biochemical characteristics	Cystic fibrosis, postoperative time and body weight	BSV: exponential error model; WSV combinatorial error model	F=45.9%; CL=3.45L/h、Vc=54.7L; Vp=143L
Han 2011[21]	Pantoprazole, alanine transaminase	Age, sex, weight, body mass index, liver and kidney function and CYP2C19 genotype	ALT and pantoprazole	BSV&WSV Additive error models, proportional error models, combinatorial error models and exponential error models	CL/F=7.92 L/h Vd/F=248 L
Dolton 2014[24]	PPIs, phenytoin, rifampicin, short-term ritonavir and glucocorticosteroids	Body weight, age, sex and CYP2C19 genotype	Combined use of phenytoin or rifampicin, St John's wort, methylprednisolone, dexamethasone and prednisone , CYP2C19 phenotypes for EM/ HUM	BSV exponential error model; WSV Proportional error models, additive error models and combinatorial error models	Ka=0.53h−1; Lag time=0.162h F=94.2%; Vc=27.1 L; Vp=127 L; Q=35.1L/h; Vmax=43.9 mg/h; Km =3.33 mg/L
Chen WY 2014[43]	Azithromycin, methylprednisolone, omeprazole, glutathione, levofloxacin	Age, sex, weight, BUN, CRP, UA, CLCR, ALB, ALT, AST, ALP, GGT, TBIL, DBIL, TG, CHO, TBA	DBIL	BSV exponential error model; WSV constant coefficient model	CL=4.28 L/h; V=93.4 L
Muto 2015[23]	NR	Age, sex, weight, body mass index, CYP2C19 genotype	Age and weight	BSV exponential error model; WSV additive error model	CL (liters/h/70 kgc)= 6.16; F=73%; V2 (liters/70

					kg)= 79.0; V3 (liters/70 kg)= 103; Q (liters/h/70 kgc)=25.4
Li Z 2017[28]	Glucocorticoids and PPIs	Age, sex, weight, blood, liver and renal function indices, time since transplantation, CYP2C19 genotype	AST and CYP2C19 genotypes	BSV exponential error model; WSV proportional error model	CL=4.76 L/h; V=22.47 L
Lin XB 2018[8]	Tacrolimus, cyclosporine; omeprazole, esomeprazole, pantoprazole, lansoprazole and methylprednisolone	Age,weight,WBC,HGB,PLT, ALT,AST,ALB,TBIL,DBIL, Scr,CYP2C19 genotype, POT	CYP2C19 genotypes, POT, weight	BSV exponential error model; WSV additive error model	θV=169.27; θCL=2.88; θF=58%
Kim 2019[25]	PPIs and glucocorticoids	Age, sex, weight, CYP2C19 genotype, AST, ALT, Scr, eGFR	CYP2C19 genotypes, weight, Hepatic insufficiency (≥grade 3)	BSV exponential error model WSV Additive error models, proportional error models and joint additive and proportional error models	V2:35.7;CL:45.3 V3:58.9;Q2:10.9 V4:25.4;Q3:54.6 Ka:1.23 F1=87.6%; lag time 0.237 h
Chen C 2019[29]	MMF, acyclovir and SMZ dosage forms, dosage amounts, dosing intervals, duration of administration	Sex, age, weight and WBC, RBC, MCV, NEUT, PLT, lymphocytes, monocytes, AST, ALT, ALB, total protein, ALP, GGT, TBIL, CR and BUN	CYP2C19*2 genotype and MMF co-administration	BSV NR; WSV proportional error model	F=89.5%; FIX;CL=9.52 L/h;V=155 L;Ka (h-1)=1.1 FIX
Liu 2019[41]	CYP2C19 inhibitor, inducer	Age, sex, weight, ALP, AST, ALT, TBIL, total protein, ALB, BUN, Scr, HGB levels	CYP2C19 genotypes, Age	BSV exponential error model; WSV joint additive and proportional error models	CL=4.18 L/h，V=88.9 L，Ka=0.729h−1
Tang 2019[44]	PPI	Age, sex, weight, HGB, PLT, ALT, AST, ALB, TBIL, DBIL, BUN, UA, INR, CLCR, CYP2C19 genotype	PLT	BSV exponential error model; WSV Additive error model, proportional error model, exponential error model	CL=0.58 L/h，Vd=134 L，F=80.8%
Ren 2019[30]	PPI	VRC dose, frequency and duration of use, age, sex, weight, CLCR, PL, Scr, PT, ALT, AST, ALP, TBIL, GGT, ALB, HGB, CRP, Child-Pugh classification (A, B, C)	CYP2C19 genotypes and Child-Pugh classification、BW	BSV exponential error model; WSV proportional error model	CL=1.45 L/h; V=132.12 L
Khan-asa 2020[19]	PPIs,sulfamethoxazole /metronidazole, glucocorticoids	Age, sex, diagnosis, weight, source of fungal infection, WBC, NEUT, HGB, MCV, PLT, BUN, Scr, AST, ALT, ALP, DB, TB, ALB, Glo, CYP2C19 genotype	Alb and omeprazole ≥40 mg/day	BSV exponential error model; WSV Additive error model	CL/F(oral cavity)=3.43 L/h V/F=47.6 L; Ka=1.1 h−1
Tang 2021[38]	PPIs	Age, sex, weight, PLT, ALT, AST, TBIL, DBIL, ALB, CLCR, INR	PLT、TBIL	BSV exponential error model; WSV proportional error model	CL=0.88 L/h; V=148.8 L; F=88.4%; CL=18.0%; V=12.0%; ka (h−1) =1.1(fix)
Chanthar it 2020[7]	glucocorticoids、PPIs	Age, sex, weight, underlying disease, site of infection, time of blood collection, underlying disease, AST, ALT, ALB, GGT, CYP2C19 genotypes, sepsis	ALB、GGT	BSV exponential error model; WSV Combinations of additive, proportional and (additive + proportional) modelsl	CL=7.32L/h ; V=417.91L; ka (h−1) =1.1(fix)
Lin XB 2022[40]	PPIs	Age, weight, inflammatory markers, Child-Pugh category, CYP2C19 genotype, APACHE II score,	weight、Child-Pugh category	BSV exponential error model; WSV Combinations of additive, proportional	CL (CP-A/B)=2.33 L/h; CL(CP-C)=1.29

		SOFA score		and (additive + proportional) modelsl	L/h; Vc=51.64L; Vp=110.89 L; Q (L/h) =36.45
Wang Jun 2021[37]	Concomitant drugs (not specified)	Age, sex, weight, height, BSA, ALT, AST,TBIL, ALB, BUN, Scr, UA, eGFR, CRP, IL-6, CYP2C19 genotypes	weight、CYP2C19 genotypes、omeprazole	BSV exponential error model; WSV proportional error model	V1=22.79L; V2=61.28L; Q=13.71L·h-1; Vmax=18.13L·h-1; Km=1.15 h-1(fixed)
Wang T 2021[31]	CYP2C19 inhibitors and inducers	Time of administration, dose, route, demographics, type of cirrhosis, Child-Pugh classification and MELD end-stage liver disease model	Child-Pugh category、weight	BSV exponential error model; WSV proportional error model	CL（non-LC）=7.59 L/h; CL (CP-A/B)=1.86 L/h; CL (CP-C)=0.93 L/h; Vc=100.8 L; Vp=55.2 L; F=91.6%;
Li SC 2021[32]	PPIs、GLU	Age, sex, weight, height, TBIL, DBIL, IBIL, TBA, ALT, AST, ALP, GGT, TP, ALB, GLB, BUN, UA, SCR, BSA	CYP2C19 genotypes	BSV exponential error model; WSV WSV Proportional error models, additive error models and combinatorial error models	ka=1.1/h;F=89.5 %;V (L)=207.29;CL(L/h)=1.91
Wu 2022[33]	PPIs、GLU	Age, sex, weight, BSA, WBC, NEUT, HGB, PLT, TBIL, AST, ALT, GGT, ALB, ALP, Scr, CYSC, Ccr	ALB、CYP2C19genotypes	BSV exponential error model; WSV Proportional error models, additive error models and combinatorial error models	CL=2.29 L/h，V=76 L; F=90.2%; Ka= 1.19h-1(fixed)
Jiang 2022[39]	PPI	Sex, age, weight, height, underlying disease (HIV), VRC medication information (date, dose, time of administration, interval), WBC, HGB, PLT, NEUT, ALT, AST, ALB, TP, TBIL, GGT, urea, CRP	CRP	BSV exponential error model; WSV additive and proportional model	CL=4.34 L/h，V=97.4 L，K=1.1 h-1，F=95.1%
Dvorackova 2023[9]	tacrolimus, Glu (prednisone), gastric pH-raising drugs (famotidine or proton pump inhibitors) and CYP450 inhibitors (azithromycin)	Age, sex, height, Scr, ALT, AST, GGT, eGFR	Age	BSV&WSV Proportional error model	Vd/F=964.46 L; CL/F=32.26 L/h; Ka=0.59h-1
Hu 2023[34]	NR	Race, IFIs, CYP2C19 genotypes, diagnosis, dose, duration of therapy, route of administration, co-administration of medications, TDM results, hepatic and renal function markers	CYP2C19 genotypes	BSV&WSV exponential error model	CL=7.35 L/h、Vc=376 L、F=52.2%、K=1.19h-1
Wang J 2023[35]	Dose, dosing interval, duration of administration, dexamethasone, fluconazole, itraconazole, methylprednisolone, omeprazole, pantoprazole, phenytoin, prednisolone, rabeprazole, rifampicin	Age, sex, weight, ALB, ALT, ALP, APoA, APoB, AST, CRP, CLCR, DBIL, eGFR, GGT, GLO, HGB, PLT, TBIL, TP, WBC	ALB、γ-GGT、DBIL	BSV exponential error model; WSV WSV proportional error models, additive error models and combinatorial error models	CL=3.22 L/h，V=194 L

van den Born 2023[22]	NR	Weight, CRP, ALT, AST, TBIL, ALP, GGT	CRP	BSV&WSV proportional error models, additive error models	V=145 L，Km=5.7 mg/L，Vmax=86.4 mg/h，F=83%
Ling J 2024[36]	PPIs;glucocorticoids	Age, gender, body weight, the CYP2C19 genotypes, CRP, ALB,ALT, AST,TBIL, HGB, PLT, Scr, UA,	CL age,ALB, gender, CRP, CYP2C19 genotypes; V body weight.	BSV exponential error model; WSV Index Additive Portfolio error models	CL=3.83 L/h，V=134 L/h，F=96.5%
Wang 2025[42]	paxlovid, azvudine, clopidogrel, PPIs, CCBs,Glu	Sex, age, weigh, ALT, AST, ALP, GGT, TBIL, DBIL, ALB, GLO, WBC, NEUT, HGB, HCT, PLT, APoA, APoB, GLU, INR, Scr, CRP, CLCR, eGFR, CRRT	CL CRRT、CRP、GGT、AST、PLT	BSV exponential error model; WSV additive error models	CL/F=3.17 L/h，V/F=135 L
Akbar 2025[27]	NR	Age, weight, sex, AST,ALT,ALP,Type of cancer (primary diagnosis) and type of fungal infection	CL CLCR、cancer (primary diagnosis)	BSV exponential error model; WSV proportional error model	CL=6.17 L/h，V=55.9 L

AST aspartate transaminase; ALT alanine aminotransferase; ALP alkaline phosphatase; ALB albumin; TBIL total bilirubin; BUN blood nitrogen; UA uric acid; CLCR creatinine clearance; GGT γ- glutamyltransferase; DBIL direct bilirubin; TG triglycerides; CHO Total cholesterol; TBA Total bile acids; WBC white blood cells; HGB hemoglobin; PLT platelet count ; Scr serum creatinine; POT postoperative time; RBC Red blood cells; MCV Red blood cell volume; NEUT Neutrophils; INR International normalized ratio; PT Prothrombin time; BSA body surface area (calculated according to Mosteller formula); eGFR glomerular filtration rate (calculated according to CKP-EPI formula); IL-6 interleukin-6; TP total protein; BUN blood urea nitrogen; CYSC cystatin C; Ccr endogenous creatinine clearance; APoA apolipoprotein A; APoB apolipoprotein B; GLo globulin; NR not reported; MMF mycophenolate mofetil; SMZ Sulfamethoxazole; GLUs glucocorticoids.

4 RESULTS

4.1 Patients with Fungal Infections

During infection or inflammation, drug-metabolizing enzymes, including CYP450 isoenzymes, exhibit decreased expression at the transcriptional level, leading to reduced metabolism of voriconazole (VRC). Additionally, the C-reactive protein (CRP) level and the concomitant use of proton pump inhibitors (PPIs) were identified as significant covariates for optimizing the initial voriconazole dose in the population pharmacokinetic (PopPK) study conducted by Jiang et al [39], the maximum daily dose of PPI should not exceed 40 mg. In this study, when CRP ≤ 96 mg/L in patients with F. marneffei using VRC, the recommended loading dose is 250 mg/12 h, and the maintenance dose is 100 mg/12 h. When CRP > 96 mg/L, the recommended loading dose is 200 mg/12 h, and the maintenance dose is 75 mg/12 h [39]. In the PopPK model of Aspergillus patients established by Chantharit et al [7] ,serum albumin (ALB) and γ-glutamyl transpeptidase (GGT) were significantly correlated with VRC clearance, and patients in the ALB>30 g/L group needed higher doses to achieve a target concentration similar to that in the ALB≤30 g/L group. Meanwhile, nutritional status was considered to be unexplored. Based on the review of 22 previous PopPK models of VRC, Van Den Born et al [22] selected one of the one-compartment models to establish the PopPK model in patients with fungal infection, and found that CRP significantly affected Vmax. However, the inclusion of CRP increased the coefficient of variation of Vmax CV% from 52% to 99%. It is possible that this study mainly included retrospective data and the high heterogeneity reduced the reliability of the model. Based on the review of previous 22-item VRC PopPK model, although Van Den Born et al. 's model further verified Chantharit et al ' s guess that CRP may affect VRC exposure, more comprehensive data should be used in the future to improve the accuracy of the model.

In critically ill patients with pulmonary fungal infection, Chen et al [43] found that direct bilirubin (DBIL) was significantly correlated with CL after investigating the related factors affecting VRC metabolism. If DBIL was higher than 1 times the average level, CL of VRC decreased by 24.21%. This study suggests that the range of VRC therapy in critically ill patients is between 1.5 and 4.0 μg/mL, which is narrower than that in normal patients. Therefore, it is recommended that the initial loading dose be followed by ivgtt of 150 mg or 200 mg q12h, and 150 mg bid for patients with mild to moderate infection or prophylactic treatment. Ling et al [36] conducted a retrospective analysis of invasive fungal infection patients with different CRP levels combined with CYP2C19 genotype polymorphism, in which the group of patients with CRP over 200 mg/L was compared with the group of patients with CRP below 10 mg/L. The percentage of CYP2C19 NM and IM patients reaching therapeutic trough concentration increased from 20.10% and 41.10% to 26.65% and 14.06%, while the percentage of patients reaching toxic range increased from 20.10% and 41.10% to 73.34% and 85.94%, respectively. The level of inflammation combined with genotype seems to be beneficial for adjusting VRC dosing regimens. Moreover, Wang et al [42] evaluated the PK characteristics of voriconazole in patients with COVID-19 related pulmonary aspergillosis and found that CRRT and CRP both affected the CL of voriconazole. For every 150 mg/L increase in CRP, the CL of voriconazole decreased by 50%. Dosing regimens were

optimized according to whether patients were receiving CRRT, with recommended doses of 2 mg/kg q12h for those not receiving CRRT and 4 mg/kg q12h for those receiving CRRT to ensure a therapeutic range of 2-5 μg/mL.

4.2 Transplant Patients and Immunodeficient Patients

In renal transplant patients, the PopPK model of Li et al [28] showed that AST and CYP2C19 genotype had a significant effect on CL, and the trough concentration of VRC was significantly higher in CYP2C19 intermediate metabolic phenotype (IM) than in extensive metabolic phenotype (NM). This is consistent with the prospective PopPK study of Lin et al [8] in renal transplant patients, CYP2C19 genotype has a significant effect on CL, and the VRC trough concentration of the poor metabolic group (PM) is significantly higher than that of the IM and NM phenotypes. The study combined with the time after transplantation to give the estimated dosing regimen for PM, IM and NM genotypes, respectively. See Table 3 for details. Han et al [20] found in lung transplant patients that the bioavailability of VRC in patients with pulmonary fibrosis was significantly lower than that in patients without fibrosis, and that pulmonary fibrosis, time after transplantation, and body weight were factors affecting VRC clearance. However, this study suggests correction bias in population predictions only at low concentrations, which also suggests that patient variables only partially explain the variability in VRC pharmacokinetics in lung transplant patients. Han et al. identified pantoprazole, race, and ALT as parameters influencing VRC pharmacokinetics in liver transplant patients, and the model was externally validated using a retrospectively collected random sample. [21].

Table 3 Summary of CYP2C19 Genotype-Guided VRC Dosing Regimens

CYP2C19 genotype dosing regimen	PM	IM	EM/NM
Lin XB 2018[8](renal transplant recipients)	150 mg bid ivgtt/250mg bid po	200 mg bid ivgtt350mg bid po	300 mg bid ivgtt
LI SC 2021[32]（immunocompromised patients）	225 mg bid/150 mg tid	275 mg bid/175 mg tid	325 mg bid/200 mg tid
Hu Lin 2023[34]（paediatric hematological diseases patients ）	6 mg/kg bid po /5 mg/kg bid ivgtt	9 mg/kg bid po / 5mg/kg bid ivgtt	9 mg/kg bid po / 8mg/kg bid ivgtt
Kim 2019[25]（healthy volunteers and patient）	Loading dose 400mg bid po, maintenance dose 100mg bid po	Loading dose 400mg bid po, maintenance dose 200mg bid po	Loading dose 400mg bid po, maintenance dose 400mg bid po
Liu Yang 2019[41]（elderly patients）	50mg bid po	100mg bid po	\
Ren 2019[30] (patients with A. fumigatus infections)	\	\	Child-Pugh class A and B,75 mg bid ivgtt/Child-Pugh class C，100 mg qd ivgtt

Note: bid: twice daily; po: oral;ivgtt: intravenous drip; qd: once daily; q12h: every 12 hours; q8h: every 8 hours; LD: loading dose; MD: maintenance dose; Child-Pugh: liver function class

In the PopPK of lung transplant patients established by Eliska et al [9], CL of VRC decreased by 0.021 L/h with increasing patient age. In immunocompromised patients, only Li et al [32] retrospectively established the PopPK model and estimated the dosing regimen for NM, IM, and PM genotypes by weighing the relationship between toxicity and efficacy, but the study included only trough concentrations due to retrospective analysis. It is difficult to estimate the evaluation of VRC and its metabolites, such as n-oxide metabolites, during the absorption and distribution periods [32]. Wang et al [31] conducted a PopPK study on patients with liver cirrhosis and found that 69.0% of VRC-related Adverse Events (AEs) occurred within the first week after VRC treatment, indicating that accurate initial dose or blood concentration monitoring of VRC should be carried out as soon as possible to avoid adverse reactions.

VRC is used as a first-line agent to prevent and treat IFIs in allogeneic hematopoietic stem cell transplant recipients [45]. Chen et al [29] conducted PopPK modeling based on the retrospective blood drug concentration data of patients with hematopoietic stem cell transplantation, and the model showed that mycophenolate mofetil and CYP2C19* 2 polymorphism showed a significant effect on CL, with a positive correlation between mycophenolate mofetil and a negative correlation between CYP2C19* 2. In order to discuss the pharmacokinetic changes of VRC in patients with allogeneic hematopoietic stem cell recipients, Suetsugu et al [45] conducted a retrospective PopPK analysis of VRC trough concentrations and found that the combination of letemovir and methylprednisolone increased Vmax of VRC, thereby reducing plasma VRC trough concentrations. Therefore, when lemovir and methylprednisolone are administered simultaneously, the daily dose of VRC needs to be increased to obtain the optimal VRC trough concentration.

4.3 Patients with Organ Dysfunction

In patients with liver dysfunction, the PopPK model of Tang et al [38] showed that total bilirubin (TBIL) was an important predictor of VRC pharmacokinetic parameters, and platelet count (PLT) was significantly correlated with VRC pharmacokinetic parameters. Since CL of VRC is significantly reduced in patients with hepatic insufficiency, dose reduction and prolonged dosing interval should be considered for such patient [38]. For patients with cirrhosis, Ren et al

[30] demonstrated that Child-Pugh class B or C and CYP2C19 genotype are significant factors influencing voriconazole clearance. This finding underscores the importance of utilizing comprehensive liver function indices to evaluate the dosing regimen. These results are consistent with the retrospective PopPK study conducted by Wang et al [31] in cirrhotic patients, which indicated that cirrhosis may exert a greater influence on voriconazole PK parameters than CYP2C19 gene polymorphisms. Lin et al [40] established a PopPK model for patients with hepatic insufficiency, and the results proved that the weight was positively correlated with the volume of distribution (V) of VRC, and Child-Pugh classification had a significant effect on CL. In this study, the recommended intravenous VRC maintenance dose regimen was 100 mg q12h or 200 mg q24h for patients with C-P A/B and 50 mg q12h or 100 mg q24h for patients with C-P C. In addition, the combined use of inflammation and PPIs was also not identified as a significant covariate in Lin's study [40], including the effect of hypoproteinemia on VRC pharmacokinetics in patients with liver disease requiring further investigation.

Khan-Asa et al [19] conducted a PopPK study of VRC in adult patients with hematological diseases. The results indicated that ALB levels and omeprazole doses ≥40 mg/day significantly influenced the clearance-to-fraction absorbed ratio (CL/F). Specifically, patients with lower ALB levels should be prescribed a reduced dose of VRC compared to those with normal ALB levels. Furthermore, caution is advised when administering VRC to patients with hypoalbuminemia who are concurrently receiving omeprazole at doses ≥40 mg/day. Meanwhile, Liu et al [41] developed a PopPK model for VRC in Chinese adult patients with hematological malignancies. Their findings demonstrated that age and CYP2C19 phenotype significantly influenced the CL of VRC, suggesting that genetic testing is essential for elderly Asian patients. Additionally, Akbar et al [27] investigated covariates affecting the pharmacokinetics of intravenous VRC in Pakistani cancer patients. They identified that variations in cancer type and CLCR resulted in differences in VRC clearance. However, further research is warranted to determine how cancer type can guide VRC dosing strategies for individual patients.

4.4 Patients with Special Populations

Wang et al [35] conducted a PopPK study in elderly patients, and the covariate analysis of the model revealed that ALB, γ-glutamyl transpeptidase(γ-GGT), and DBIL significantly influenced the CL of VRC. This study represents the first effort to externally and systematically assess the predictive performance of the PopPK model for VRC in the elderly population. Resztak et al [14] demonstrated that interindividual PK variability is more pronounced in children compared to adults, attributed to their higher weight-standardized clearance and enhanced whole-body and first-pass metabolism. This finding aligns with the study by Karlsson et al [26], who reported that the liver mass to body mass ratio is greater in children than in adults. Consequently, they recommended an intravenous dose of 7 mg/kg twice daily or an oral dose of 200 mg twice daily for patients aged 2-12 years. Additionally, the clearance rate of VRC is significantly higher in children under 12 years old, and its oral bioavailability in children is lower than in adults, reaching only 62%. These observations underscore that age is a critical factor influencing VRC plasma exposure [14].

Hu et al [34] established a PopPK model of VRC in children with hematological IFIs, and the results showed that the oral bioavailability of VRC was only 52%, which was lower than 96% of adults, which was similar to the value of 66% obtained by Walsh et al [46] in children aged 2-12 years. At the same time, this study suggests that the presence of CYP3A4 in the intestine may accelerate the metabolism of oral VRC, which is worthy of further confirmation. This study suggests that CYP2C19 phenotype can be used to guide the adjustment of VRC trough concentration dose in pediatric patients with IFIs. Wu et al [33] established a PopPK model of VRC in Chinese children with hematological malignancies, and the study confirmed that body weight was more suitable than age when allometric model was considered, and the final model showed that body weight, CYP2C19 phenotype and ALB had a significant impact on VRC clearance. Similarly, Takahashi et al [47] investigated the genetic and covariate associations of PK variability among VRC individuals and showed that PK variability among VRC individuals in the age range from 7 months to 20 years is best described by weight function allometric scaling and CYP2C19 phenotype. The study model of adult hematological malignancies by Liu et al [41] showed that age and CYP2C19 genotype were important covariates, while the study model of children by Wu et al [33] showed that weight was more suitable for guiding drug administration than age.

As it is well known that developmental factors play an important role in VRC metabolism in children, Wang J et al [37] developed a PopPK model of intravenous VRC in critically ill children, tested six candidate models to describe differences in the growth and clearance processes of allopathy, and suggested that it was necessary to adjust the dosing regimen according to CYP2C19 genotype. Muto et al [23] established a PopPK model for children with weakened immunity, which tried to identify the effects of new covariates such as CYP2C19 genotype, gender and liver function parameters on other PK parameters of VRC, but failed. CYP2C19 genotype does not seem to be a basis for adjusting the dose for Japanese children. Moreover, no trend was observed by graphical evaluation, and final age and weight were considered as significant covariates in this model. Bioavailability was in the range of 65±20.64 in the four pediatric patients included in this study [23, 26, 33, 34], the bioavailability of 12 items in adult patients ranged from 83.34±15.57 [8, 20-22, 25, 29, 31, 32, 36, 38, 39, 44].

5 GENOTYPE POLYMORPHISM

More and more studies have shown that CYP2C19 genotype is closely related to the therapeutic plasma concentration

difference of VRC. Studies have shown that the proportion of CYP2C19 generation PM phenotype is the highest in the Asian population, about 23%, while the European phenotype is about 7% [14]. Therefore, it is necessary for Asian patients to undergo genetic testing [41]. Of the 29 studies included in this review, only 8 studies did not include CYP2C19 genotype. In adult lung transplant patients [9, 20]、in patients with liver dysfunction [44]、in elderly patients [35]、in patients with cirrhosis [31]、in immunocompromised patients [23]、in patients with cancer [27]、and in patients with a fungal infection [22].

Kim et al [25] established a PopPK model including CYP2C19 phenotype in a group of healthy volunteers and patient populations, and CYP2C19 phenotype, body weight and liver function indicators were considered as significant covariates. This study showed that EM subjects were more likely to reach subtherapeutic concentrations (73.9%) and PM subjects were more likely to reach highly toxic concentrations (48.3%), suggesting that VRC dosing should be adjusted according to CYP2C19 phenotype. Hu et al [34] suggested that low oral bioavailability, high CL and high proportion of CYP2C19 NM were responsible for low VRC trough concentrations. Therefore, it is important to focus on the problem of low VRC trough concentration levels in NMs. Ling et al [36] retrospectively analyzed the effect of inflammation on VRC pharmacokinetics in patients with different CYP2C19 genotypes, and indicated that patients with NM and IM complicated with inflammation should be closely monitored when given VRC.

According to Table 3, the recommended dose of EM/NM in patients with normal extensive metabolism is generally higher than that in patients with intermediate metabolism IM phenotype and poor metabolism PM phenotype, and the appropriate dose and frequency are in the range of 300 mg bid to 400 mg bid. 75 mg bid ivgtt is recommended for patients with mild-to-moderate liver injury, and 100 mg qd ivgtt is recommended for patients with severe liver injury. However, the dosing regimen guided by CYP2C19 phenotype still has challenges in real life [24], because genotype information is usually difficult to obtain in clinical practice, and may be obtained after the patient has been treated. Liu et al [48] proposed that CYP2C19 gene polymorphism should be genotyped for drug administration, and it does not seem to be necessary to consider the effects of CYP2C9, CYP3A4 and FMO3 polymorphisms on the pharmacokinetics of voriconazole. In fact, this is in contrast to the study by Gautier-Veyret et al [49], who demonstrated in a retrospective study that the CYP3A4*22 polymorphism (rs35599367) significantly affected voriconazole trough concentrations in 29 patients undergoing allogeneic HSCT. In addition, two retrospective studies in China found that SNPS located in the intron region of CYP3A4 (rs4646437) were associated with higher VRC levels [50, 51]. Data on genetic variants in CYP3A4 affecting plasma concentrations of VRC are limited and need to be confirmed in independent and larger cohorts of patients treated with voriconazole.

6 SUMMARY OF SIGNIFICANT COVARIATES

By summarizing the significant covariates in the PopPK model of VRC, Table 4 was obtained. Most of the methods for covariate screening in this review were stepwise covariate modeling, and a few were log-likelihood methods. Among the 21 studies, the CYP2C19 genotype was identified as a significant covariate in 13 studies [8, 24-26, 28-30, 32-34, 37, 41].In conclusion, CYP2C19 phenotype is considered to have a significant effect on the pharmacokinetic parameters of VRC in many PopPK models, and it is expected to be an important basis for guiding the individualized treatment of VRC. Body weight was identified as a significant covariate in 8 studies [8, 23, 25, 30, 31, 36, 37, 40], indicating the potential to guide the clinical use of VRC according to patient weight, Albumin was accepted as a significant covariate in 5 studies[7, 26, 33, 35, 36], followed by age [9, 23, 36, 41]、γ -GGT [7, 21, 35, 42]and CRP[22, 36, 39, 42] were each identified as a significant covariate in 4 studies. Most of the significant covariates affecting VRC clearance were indicators of liver function, which can reduce plasma clearance of drugs due to reduced liver metabolism or biliary excretion [38].

Table 4 Significant Covariates Included in the Studies Reviewed

Study	Significant covariate
Kim 2019[25]、Dolton 2014[24]、Chen 2019[29]、Liu 2019[41]、WangJ 2021[37]、Wu 2022[33]、Li 2017[28]、Ren 2019[30]、Hu 2023[34]、LiSC 2021[32]、Karlsson 2009[26]、Lin XB 2018[8]、Ling J 2024[36]	CYP2C19 phenotype
Kim 2019[25]、Lin 2022[40]、WangJ 2021[37]、Ren 2019[30]、WangT 2021[31]、Muto 2015[23]、Lin XB 2018[8]、Ling J 2024[36]	Weight
Wu 2022[33]、Wang 2023[35]、Chantharit 2020[7]、Ling J2024[36]、Karlsson 2009[26]	ALB
Dvorackova 2023[9]、Liu 2019[41]、Muto 2015[23]、Ling J 2024[36]	Age
Wang 2023[35]、Han 2011[21]、Chantharit 2020[7]、Wang 2025[42]	γ -GGT
Jiang 2023[39]、van den Born 2023[22]、Ling J 2024[36]、Wang 2025[42]	CRP
Lin 2022[40]、Ren 2019[30]、WangT 2021[31]	Child-Pugh classification
Tang 2019[44]、Tang Dan 2021[38]、Wang 2025[42]	PLT
Wang 2023[35]、Chen WY 2014[43]	DBIL
Karlsson 2009[26]、Wang 2025[42]	ALT
Kim 2019[25]	Liver insufficiency (≥ grade 3)
Dolton 2014[24]	Glu

Ling J 2024[36]	Gender
Chen 2019[29]	MMF
WangJ 2021[37]	Omeprazole
Khan-asa 2020[19]	Omeprazole≥40 mg/Day
Li 2017[28]	AST
Akbar 2025[27]	CLCR
Han 2011[21]	Pantoprazole
Tang Dan 2021[38]	TBIL
Wang 2025[42]	CRRT
Akbar 2025[27]	Cancer (primary diagnosis)

7 DRUG-DRUG INTERACTIONS IN THE VRC

The common concomitant drugs of voriconazole include PPIs and glucocorticoids. It is not clear whether the changes of voriconazole plasma concentration are affected by DDIs. Currently, it has been suggested that the exposure of voriconazole in plasma may be related to the type and dose of PPIs. Only three studies [19, 21, 37]， in this review included PPI as a significant covariate affecting VRC clearance or apparent volume of distribution. The Khan-asa study in the Thai population suggests that voriconazole should be used with caution or appropriately reduced dose in patients with hypoalbuminemia who are treated with omeprazole ≥40mg/day [19]。 Hna et al [21] suggested that co-administration of pantoprazole may affect the PK of VRC, but further correlation studies are lacking. Wang [37] in a study of critically ill pediatric patients, suggested that when omeprazole was not used, patients in the PM and IM groups required doses of 6 mg/kg and 8 mg/kg21 q12h, respectively, while patients in the EM group required doses of 9 mg/kg q12h. However, due to the limited sample size, the recommendations are for reference only and further clinical practice is needed. The study of Dolton et al [24] in healthy people showed that the combination of phenytoin, rifampin, St. John's's extract, methylprednisolone, dexamethasone and prednisone was associated with a significant increase in Vmax of the VRC, possibly because the exposure of the VRC was reduced to varying degrees by such drugs. Especially in patients with CYP2C19 phenotype EM/HUM, while short-term use of ritonavir can reduce Vmax, especially in patients with CYP2C19 phenotype PM/HEM. Therefore, glucocorticoids were included as a significant covariate in the study by Dolton et al [24]. In addition, DDIs between VRC and immunosuppressive agents in Hiv-Infected patients were not evaluated because antiretroviral therapy was not initiated during VRC induction therapy.

8 DISCUSSION

VRC is a widely used antifungal agent in IFIs patients with life-threatening infections caused by Aspergillus and Candida [52]. Although VRC is an established drug in clinical practice and is included in the World Health Organization Core List of Essential Medicines for adults and children[53], the relative importance of its different pathways and metabolic enzymes involved is still not fully elucidated. The dose optimization of VRC has always been a hot topic in clinical practice due to the nonlinearity of its pharmacokinetics, high inter-individual and intra-individual variability, large drug interactions, and relatively narrow therapeutic range [54]。

This study reviews the research on VRC in various clinical patients at home and abroad that includes it. In China, the PopPK of VRC has been preliminarily studied in patients with liver dysfunction, patients undergoing hematopoietic stem cell transplantation, patients with hematological malignancies, critically ill children, patients undergoing kidney transplantation, elderly patients, patients with impaired immune function, and patients with pulmonary infections. However, among them, the studies on patients with impaired immune function, patients with liver cirrhosis, etc. were all retrospective studies. The included data in these studies were all trough concentration data, which could not be used to characterize the absorption phase. It might not be possible to fully capture the distribution and elimination characteristics of VRC, thereby posing challenges to the estimation of its pharmacokinetics. Therefore, in such patients, The accuracy of parameter estimation and covariate detection still needs to be confirmed by developing large-sample prospective studies [32, 35]. The PopPK of VRC abroad has been preliminarily studied in transplant patients, adult patients with hematological diseases, pediatric patients and patients with invasive fungal infections.

VRC is mainly metabolized by CYP2C19 P450 enzyme. The proportion of homozygous fast metabolizer enzyme in Asian population (35%) is lower than that in Caucasian population (75%), so the plasma concentration of VRC in Asian population is generally higher than that in Caucasian population. In China, there is still a lack of research on CYP2C19 genotype in the modeling of PopPK in patients with liver dysfunction, elderly patients, and critically ill patients with pulmonary diseases, which needs further research in the future. In addition, the efficacy, safety, and economics of CYP2C19 genetic testing prior to VRC use have not been demonstrated [18]. In this study, a total of 21 studies included CYP2C19 genotype polymorphism as a model covariate, of which 13 studies included it as the final significant covariate in the model, indicating that it was of great significance for optimizing VRC in the guidance of precise drug delivery in clinical practice. It can be seen from this study that patients with NM, IM and PM phenotypes are more common than patients with UM and RM phenotypes in CYP2C19 genotype polymorphism in the Chinese population, and the ratio is about 3:3:1. Therefore, PM phenotype is less than NM phenotype and IM phenotype. In this review, several studies [38, 39] found that there was no significant difference in voriconazole PTA obtained through intravenous and oral routes, which may suggest that oral and intravenous administration can be alternated based on the patient's own gut nutrition assessment.

Invasive fungal disease poses a significant threat to immunocompromised patients, especially those with pediatric hematologic disorders or those receiving hematopoietic stem cell therapy [34]. In recent years, inflammation level and other clinical indicators such as CRP have also been considered to be related to individual PK differences of voriconazole in several PopPK models, but the specific dose and administration regimen need to be further verified. In organ transplant and immunodeficient patients treated with VRC, the time after transplantation and the degree of body recovery lead to gradual changes in the metabolism and excretion of VRC, which may affect the pharmacokinetics of VRC. The PopPK study of VRC in HSCT patients should also be studied prospectively in pediatric patients. There have been reports of using mechanistic models to simultaneously evaluate the PopPK properties of VRC and its n-oxide metabolite, but the effect of VNO on VRC can only partially explain the nonlinear pharmacokinetics of VRC, and VRC metabolite evaluation needs to be further studied [32].

In patients with organ dysfunction receiving VRC, especially those with liver dysfunction, the changes of transaminase and bilirubin should be monitored to control the individualized dosing of VRC. In patients with hematologic diseases, age and genotype are considered to be significant indicators that have a chance to guide the administration of drugs in such patients. Invasive aspergillosis (IA) is the most common IFIs in such patients, which is characterized by high morbidity and mortality [55], the European Conference on Infectious Leukemia (ECIL) and IDSA guidelines currently recommend VRC and itsuonazole as the first choice for the treatment of IA in patients with hematological malignancies, with the same level of recommendation (in the IDSA guidelines, VRC has a slightly higher recommendation level than itsuonazole) [4, 56]. In patients with liver dysfunction, liver function classification has been identified as a significant covariate affecting the pharmacokinetic variation of VRC in many studies, and Child-Pugh classification has been recommended for individualized treatment of VRC. Inflammatory markers, albumin and other factors are rarely validated as significant covariates in such patients.

In the special population of patients receiving VRC treatment, the body function of children continues to improve with age, and the metabolism of drugs also changes. So far, the toxicity targets of this group have not been verified, and the PopPK model of patients under 2 years old needs to be further established [16]. In this review, body weight was recommended by most PopPK models as an important indicator for VRC administration in children. However, it has been pointed out that because ontogenetic differences in VRC metabolic enzymes seem to lead to higher first-pass effects in children compared with adults, the dose required in children is much higher than in adults, even when body weight is considered [10]. The bioavailability of VRC in children (65±20.64) was also significantly lower than that in adults (83.34±15.57). In addition, the neonatal population is still at risk of underdosing and overdosing of VRC, and CYP2C19 genotype is also recommended for consideration in pediatric patients.

Multiple studies in this review have shown that standardized VRC dosing regimens are insufficient to achieve target therapeutic exposures in a variety of clinical Settings [29, 33, 57]. Optimizing the drug delivery strategy based on PopPK model combined with TDM can improve the VRC to achieve appropriate PK/PD indicators, optimize its precise drug delivery, and control its blood drug concentration within the therapeutic window [16]. Not only that, PopPK has important advantages in clinical practice, especially in pediatric patients, where PopPK is able to take advantage of opportunistic blood sampling. In this review, 3 pediatric studies [33, 34, 37] used residual blood after routine biochemical tests to determine PopPK, which provided new ideas for the study of POPPK in children with VRC.

In addition, model predictability must be assessed before use of model-informed precision dosing (MIPD). PopPK model evaluation methods are divided into basic internal evaluation, advanced internal evaluation, and external model evaluation. In fact, external evaluation of the model has proven to be one of the most rigorous methods for model testing and is necessary for the use of patient dose personalization in clinical Settings [58]. Only 3 reviews included in this study [21, 35, 57] made external validation of the model. The external validation is to use random samples of clinical patients not used for model construction as the model validation group, and to optimize the established PopPK model using the Bayesian feedback method, which is considered to be the most rigorous validation method, and the optimized final model helps to provide accurate and precise concentration prediction for specific patient groups [21]. In addition, there is a lack of research on the comparison of dose adjustment based on PopPK method and empirical dose adjustment at home and abroad, which is one of the directions that needs to be continued to be studied in the future.

In this review study, CYP450 metabolic enzymes and alleles serve as a critical foundation for individualized voriconazole dosing. However, there remain certain technical limitations and insufficient information in determining the actual genetic phenotype of patients to guide voriconazole (VRC) dosing. Currently, research on VRC in real-world clinical patients has broadly encompassed most drug users, and the population pharmacokinetic (PopPK) model plays a central role in guiding personalized VRC treatment. Nevertheless, in this review, only a subset of patients underwent simulation of the dosing regimen and external validation of the model based on significant covariates. Few studies have selected an independent cohort of patients to verify the simulated dosing regimen and evaluate its implementation, which warrants further investigation with larger sample sizes in future studies. Several limitations need to be considered. First, the limitation of this study to English literature may have led to the unintentional exclusion of relevant studies published in other languages, thus limiting the opportunity for comparative analyses within the same geographic region. Second, only parametric PPK models were included in this study, and non-parametric PPK models were excluded because the parameters of the non-parametric model were difficult to bridge to the parametric model

9 CONCLUSION

The implementation of a model repository that includes parameterized PopPK models within the VRC demonstrates

significant potential for advancing the field of MIPD. This review provides an in-depth analysis of relevant information on the population pharmacokinetics of VRC, serving as a valuable reference for both clinicians and researchers. For clinicians, this review emphasizes key predictors that can be utilized to optimize VRC dosing strategies. For researchers, it is recommended to conduct PopPK analyses on datasets collected over extended periods post-treatment initiation, enabling the detection of any potential temporal changes in pharmacokinetic parameters. A more detailed stratification and comprehensive investigation into the population pharmacokinetics of special populations warrant further exploration. In the future, when constructing PopPK models for VRC in specific patient populations, external validation of the model and comparison of its predictive performance are essential to ensure clinical applicability. Most studies have identified significant covariates of VRC in patients with varying physiological and pathological conditions; however, simulations based on these covariates for personalized dosing regimens remain underexplored. Monte Carlo simulation is proposed as a method to evaluate covariate effects derived from diverse patient groups. Additionally, it is recommended to assess the clinical efficacy differences between doses guided by PopPK models and traditional empirical doses, track the individualized medication effects of PopPK models, and conduct supplementary trials integrated with real-world clinical outcomes to enhance the rational use of these models in practice.

COMPETING INTERESTS

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AUTHORS' CONTRIBUTIONS

Min Luo, Liu Shi was responsible for reviewing, searching, screening the literature and checking the format of the review; Lu Yao was responsible for extracting the pharmacokinetic parameters and summarizing them into a table to write the review; Lei Gong, Bao Fu, Yan Chen and Tao Chen was responsible for checking and suggesting changes. All authors contributed to the design of the manuscript and discussed the typesetting of the manuscript.

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