



# Interactive Effects of Glucocorticoids and Cytochrome P450 Polymorphisms on the Plasma Trough Concentrations of Voriconazole

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**Aims:** To explore the interactive influence of glucocorticoids and cytochrome P450 (CYP450) polymorphisms on voriconazole (VRC) plasma trough concentrations ( $C_{\min}$ ) and provide a reliable basis for reasonable application of VRC.

**Methods:** A total of 918 VRC  $C_{\min}$  from 231 patients was collected and quantified using high-performance liquid chromatography in this study. The genotypes of *CYP2C19*, *CYP3A4*, and *CYP3A5* were detected by DNA sequencing assay. The effects of different genotypes and the coadministration of glucocorticoids on VRC  $C_{\min}$  were investigated. Furthermore, the interactive effects of glucocorticoids with CYP450s on VRC  $C_{\min}$  were also analyzed.

**Results:** The median  $C_{\min}$  of oral administration was lower than that of intravenous administration (1.51 vs. 4.0 mg l<sup>-1</sup>). Coadministration of glucocorticoids (including dexamethasone, prednisone, prednisolone, and methylprednisolone) reduced the VRC  $C_{\min}$ /dose, respectively, among which dexamethasone make the median of the VRC  $C_{\min}$ /dose ratio lower. As a result, when VRC was coadministered with glucocorticoids, the proportion of VRC  $C_{\min}$ /dose in the subtherapeutic window was increased. Different CYP450 genotypes have different effects on the  $C_{\min}$ /dose of VRC. Mutations of *CYP2C19*\*2 and \*3 increased  $C_{\min}$ /dose of VRC, while *CYP2C19*\*17 and *CYP3A4* rs4646437 polymorphisms decreased  $C_{\min}$ /dose of VRC. The mutation of *CYP3A5* has no significant effect. Furthermore, *CYP2C19*\*17 mutants could strengthen the effects of glucocorticoids and decrease VRC  $C_{\min}$ /dose to a larger extent.

**Conclusion:** Our study revealed that glucocorticoids reduced the  $C_{\min}$ /dose levels of VRC and different SNPs of CYP450 have different effects on the  $C_{\min}$ /dose ratio of VRC. Glucocorticoids and *CYP2C19*\*17 mutants had a synergistic effect on reducing VRC  $C_{\min}$ /

**Abbreviations:** ADR: adverse drug reactions; C/D ratio:  $C_{\min}$ /dose ratio;  $C_{\min}$ : plasma trough concentrations; CYP450: cytochrome P450; DDIs: drug–drug interactions; IQR: interquartile difference; SD: standard deviation; TDM: therapeutic drug monitoring; VRC: voriconazole.

dose. The present results suggested that when VRC is combined with glucocorticoids, we should pay more attention to the clinical efficacy of VRC, especially when *CYP2C19*\*17 mutants exist.

**Keywords:** glucocorticoids, *CYP2C19*, *CYP3A4*, *CYP3A5*, voriconazole

## INTRODUCTION

With the increasing incidence of malignant tumors, acquired immune deficiency syndrome, and organ transplantation, the morbidity and mortality of invasive fungal infections are rising and have gradually become one of the major threats to human health in recent years (Sanguinetti et al., 2019). Voriconazole (VRC) is a second-generation triazole antifungal drug, inhibiting the activity of cytochrome P450 (CYP450)-dependent 14 $\alpha$ -sterol demethylase so that lanosterol cannot be converted into its 14 $\alpha$ -demethylated products in order to prevent ergosterol biosynthesis and change the integrity of membrane, which leads to the rupture and death of fungal cells (Naihani and Kumar, 2005). VRC has a spacious antibacterial spectrum, including *Candida*, *Cryptococcus neoformans*, *Aspergillus*, *Fusarium*, *Histoplasma*, and the other fungi (Thompson and Lewis, 2010). So far, VRC is widely used to prevent and treat invasive fungal diseases and recommended by guidelines as the first-line therapy (Ullmann et al., 2018).

In clinical application, it was gradually found that VRC had great individual differences. The steady-state trough concentrations of VRC varied greatly, which may be related with its nonlinear pharmacokinetics and many other clinical factors (Karlsson et al., 2009). Studies have shown that supratherapeutic VRC  $C_{min}$  was associated with its hepatotoxicity, nervous system disorders, and visual disturbance, while subtherapeutic VRC  $C_{min}$  may lead to treatment failures (Jin et al., 2016). It has been proven that VRC is of narrow therapeutic window (the recommended range is between 0.5–1.5 and 5–5.5 mg l<sup>-1</sup>) and therapeutic drug monitoring (TDM) (Ashbee et al., 2014) is an effective way to VRC-individualized medication (Chen et al., 2018a; Ullmann et al., 2018). As a result, it is very important to clarify the factors affecting VRC concentrations in clinical practice. It is found that intra- and inter-individual variabilities of VRC  $C_{min}$  depend on age, actual body weight, CYP450 polymorphisms including *CYP2C19*, *CYP3A4*, and *CYP3A5*, liver functions, hypoproteinemia, inflammation, and drug–drug interactions (DDIs) (Chawla et al., 2015; Gautier-Veyret et al., 2015). Among them, CYP450 polymorphisms and CYP-mediated drug interactions are important determinants of intra- and inter-individual variabilities of VRC.

Glucocorticoids such as dexamethasone, prednisone, prednisolone, and methylprednisolone are widely coadministered with VRC in patients with hematological malignancies or solid organ transplantations. Naturally, there were some studies on the effects of concomitant medication of glucocorticoids and VRC. However, the results of different researches are inconsistent. It is a hot spot of controversy whether concomitant with glucocorticoids affects VRC  $C_{min}$  and whether different glucocorticoids (ie., dexamethasone, prednisone, prednisolone, and methylprednisolone) have same

effects on VRC concentrations (Eiden et al., 2010; Dolton et al., 2012; Gautier-Veyret et al., 2015; Cojutti et al., 2016; Li et al., 2017; Blanco-Dorado et al., 2020), and the mechanism of this interaction is still unclear. In general, glucocorticoids are strong inducers of *CYP2C9*, *CYP2C11*, *CYP2C19*, *CYP3A4*, *CYP3A5*, and *CYP3A7* (Iber et al., 1997; Chen et al., 2003; Zhou et al., 2009; Dvorak and Pavek, 2010; Matsunaga et al., 2012; Matoulkova et al., 2014), which leads to a  $C_{min}$  decrease of drugs that are metabolized primarily by these CYP450s. VRC is mainly metabolized by CYP450s, thus may have DDIs with glucocorticoids. Due to the inconsistent results of previous studies, the purpose of this experiment is mainly focused on the effects of glucocorticoids on VRC  $C_{min}$ .

VRC is metabolized mainly by CYP450 enzymes and the effects of CYP450 polymorphisms on VRC  $C_{min}$  have been widely discussed. Among them, *CYP2C19*, *CYP3A4*, and *CYP3A5* are considered to be highly correlated with VRC metabolism (Iber et al., 1997; Chen et al., 2003; Zhou et al., 2009; Dvorak and Pavek, 2010; Matsunaga et al., 2012; Matoulkova et al., 2014). VRC is metabolized predominantly by *CYP2C19*, and variant *CYP2C19* alleles contribute to wide inter-patient variabilities of VRC serum concentrations (Moriyama et al., 2017). Recently, *CYP3A4* and *CYP3A5* polymorphisms were demonstrated to affect VRC  $C_{min}$  by some studies, while other studies identified that polymorphisms of *CYP3A4* and *CYP3A5* have no significant influences on VRC  $C_{min}$ . Hence, the effects of *CYP3A4* and *CYP3A5* polymorphisms on VRC need to be further studied (Gautier-Veyret et al., 2015; Gautier-Veyret et al., 2016). In *CYP2C19* mutational subjects, the pharmacokinetics of VRC did not change compared to *CYP2C19* wild type ones, so the influence of *CYP2C9* polymorphisms on VRC was not obvious (Geist et al., 2006). Therefore, only the influences of *CYP2C19*, *CYP3A4*, and *CYP3A5* polymorphisms on VRC concentrations were emphasized in our study. These CYP450 enzymes confirmed to affect VRC metabolism that can be induced by glucocorticoids, which indicate the potential DDIs between VRC and glucocorticoids.

Therefore, the objectives of this study are to identify the influences of four glucocorticoids (dexamethasone, prednisone, prednisolone, and methylprednisolone) on VRC  $C_{min}$ , and to further explore the effects of CYP450 polymorphisms on the interaction between glucocorticoids and VRC.

## MATERIALS AND METHODS

### Patients and Data Collection

This retrospective study was performed at the Third Xiangya Hospital of Central South University, Changsha, China. Patients

underwent TDM of VRC concentrations were recruited from January 2016 to June 2018. The inclusion criteria were that patients aged 18 years or older underwent TDM of VRC plasma concentrations at the trough level under steady state (Gautier-Veyret et al., 2015). Patients received concomitant drugs that were CYP inducers such as phenobarbital, rifampin, phenytoin, and carbamazepine or CYP inhibitors such as cimetidine and erythromycin were excluded (Yan et al., 2018). For each patient, the following data were collected: demographics (age, gender, and actual body weight), clinical data (underlying disease) and VRC therapy records (daily dosage, dosage adjustment,  $C_{min}$ , and route of administration), and concomitant medications.

The design of this research was completely conformed to the principles of the Helsinki Accords, and this study was approved by the Ethics Research Committee of the Third Xiangya Hospital of Central South University (No: 2017-S220). All subjects signed the informed consent that DNA was extracted from residual blood samples from VRC concentration analyses for laboratory testing.

## Determination of Plasma VRC Concentration

The blood samples were collected 0–30 min before administration until at least 3 days of the scheduled treatment, and all the unsteady state concentrations of VRC were removed. VRC plasma concentrations were measured by a validated high-performance liquid chromatography method (Yan et al., 2018). Briefly, samples were injected into a 2-dimensional chromatographic system. In the first step, samples were pre-separated by a perfusion chromatography column before being eluted and transferred to an analytical column. Finally, compounds were detected by a multi-channel rapid-scanning UV–VIS detector. Precision and accuracy were assessed by performing replicate analyses of quality control samples against calibration standards. Intra- and inter-assay coefficients of variation were always <5%. The plasma drug standard curve ranged from 0.1 to 20 mg l<sup>-1</sup>.

## Genotyping Assay

Genotyping was performed retrospectively on residual blood samples from VRC concentration analyses. DNA was extracted from peripheral leukocytes by the TIANamp Genomic DNA Kit (TianGen Biotech, Beijing, China). The quality and quantity of DNA were checked with the NanoDrop 2000 spectrophotometer (Thermo Scientific, Illkirch, France). The DNA samples were stored in –80°C until genotype detection. Genotyping adopted by the Sanger DNA sequencing method with an ABI3730xl-full automatic sequencing instrument (ABI Co.) from Boshang Biotechnology Co. Ltd. in Shanghai. *CYP2C19* genotyping was performed for the \*2, \*3, and \*17 alleles. Three single-nucleotide polymorphisms (SNPs) (rs35599367 and rs4646437 in *CYP3A4*, and rs776746 in *CYP3A5*) that were known commonly to affect the plasma VRC concentrations were also genotyped in the present study.

**TABLE 1** | Characteristics of 231 patients included in the study.

Characteristics	Patient, N (%)
Total number of patients	231
Male, n (%)	134 (58.0%)
Age (year)	51.47 ± 17.55
Weight (kg)	57.24 ± 10.98
BMI	21.39 ± 2.78
Underlying disease, n (%)	
Hematological malignancy	<b>137 (59.3%)</b>
Leukemia	93 (40.3%)
Multiple myeloma	17 (7.4%)
Lymphoma	12 (5.2%)
Aplastic anemia	7 (3.0%)
Other	8 (3.5%)
Solid organ transplantation	<b>14 (6.1%)</b>
Solid malignancy	<b>7 (3.0%)</b>
Pulmonary disease	<b>33 (14.3%)</b>
COPD	16 (6.9%)
Bronchitis	11 (4.8%)
Other	6 (5.2%)
Septic shock	<b>18 (7.8%)</b>
Liver disease	<b>7 (3.0%)</b>
Other	<b>15 (6.5%)</b>
Number of genetic tests patient	<b>159 (68.83%)</b>
Number of patient concomitant with glucocorticoids	<b>103 (44.59%)</b>

## Statistical Analysis

The statistical analyses were performed with SPSS 22.0 software (IBM SPSS, Inc., Chicago, IL, United States). The quantitative data were expressed as the mean ± standard deviation (SD), while the counting data in frequency and percentage. The Kolmogorov–Smirnov test was used for normality of measurement data. Non-normal distributed data were represented by median and interquartile difference (IQR). Nonparametric tests were used to compare non-normal distribution data (Mann–Whitney test for two groups, Kruskal–Wallis test for at least three groups, and Wilcoxon rank sum test for comparisons of paired designs). The chi-squared test was used to compare counting data. Interaction between CYP450 genotypes and glucocorticoids was analyzed by the Scheirer–Ray–Hare test.  $p < 0.05$  was considered statistically significant.

## RESULTS

### Patient Characteristics

A total of 231 patients were enrolled in this study. Of the 231 patients, 134 (58.0%) were male and 97 (42.0%) were female. The mean age and weight of patients were 51.47 ± 17.55 years and 57.24 ± 10.98 kg, respectively. The top three underlying diseases in VRC-treated patients were hematological malignancy ( $n = 137$ , 59.3%), pulmonary diseases ( $n = 33$ , 14.3%), and septic shock ( $n = 18$ , 7.8%). The most common hematological malignancies were leukemia ( $n = 93$ , 40.3%). Among 231 patients, 159 patients had genetic tests and 103 patients had the concomitant administration of glucocorticoids. The patient demographics and characteristics in this study are summarized in **Table 1**.

**TABLE 2 |** VRC plasma trough concentration included in the study.

Parameter	All (n = 918)	Oral (n = 795, 86.6%)	Intravenous (n = 123, 13.4%)	p
$C_{\min}$ (mg l <sup>-1</sup> )				<0.001
Median (IQR)	1.64 (0.90, 3.00)	1.51 (0.85, 2.60)	4.00 (2.30, 5.80)	
Range	0.04–20.4	0.04–20.4	0.08–16.17	
$C_{\min}$ level, n (%) <sup>a</sup>				<0.000
>0.5	105 (11.4%)	99 (12.5%)	6 (4.9%)	
[0.5, 5]	714 (77.8%)	639 (80.4%)	75 (61.0%)	
>5	99 (10.8%)	57 (7.2%)	42 (34.1%)	
$C_{\min}/\text{dose}$ [(mg l <sup>-1</sup> )/(mg d <sup>-1</sup> )]				<0.001
Median (IQR)	4.25 (2.25, 8.25)	3.88 (2.10, 6.93)	10.25 (5.4, 14.50)	
Range	0.08–51.0	0.08–51.0	0.40–42.50	
$C_{\min}/\text{dose}$ level, n (%) <sup>b</sup>				<0.000
<1.25	108 (11.8%)	102 (12.8%)	6 (4.9%)	
[1.25, 12.5]	702 (76.5%)	626 (78.7%)	76 (61.8%)	
>12.5	108 (11.8%)	67 (8.4%)	41 (33.3%)	

p was calculated comparing oral administration with intravenous administration by the Mann–Whitney U test or chi-squared test, accordingly.

<sup>a</sup>The therapeutic index of VRC  $C_{\min}$  is in accordance with the practice guideline for individualized medication of VRC reported by the Chinese Pharmacological Society. The lower limit of VRC  $C_{\min}$  was set above 0.5 mg d<sup>-1</sup> maintained-treatment response, and the higher limit was set as lowest concentration of hepatotoxicity.

<sup>b</sup>The therapeutic index of the VRC  $C_{\min}/\text{dose}$  ratio was calculated by VRC trough concentration divided by the most commonly used dose (400 mg d<sup>-1</sup>).

## VRC Trough Concentration Therapeutic Drug Monitoring

A total of 918 VRC plasma steady-state trough concentrations from 231 patients were included in this study. The daily dose of VRC ranges from 100 to 800 mg. VRC  $C_{\min}$  was adjusted on daily dose (for  $C_{\min}/\text{dose}$  ratio and C/D ratio) for overcoming the effect of dose (Gautier-Veyret et al., 2017; Shao et al., 2017). For example, the VRC daily dose for a patient is 400 mg d<sup>-1</sup> and the  $C_{\min}$  is 1,600 mg l<sup>-1</sup>. Thus, the  $C_{\min}/\text{dose}$  ratio of this patient is expressed as 4 mg l<sup>-1</sup>/mg d<sup>-1</sup>. As shown in **Table 2**, grading criteria of VRC  $C_{\min}$  were based on the individualized medication of VRC guidelines issued by the Chinese Pharmacological Society (Chen et al., 2018a). Similar to previous reports (Zeng et al., 2020), VRC  $C_{\min}$  were mostly the concentration of oral administration (86.6%). Meanwhile, compared with oral administration, VRC  $C_{\min}$  and the  $C_{\min}/\text{dose}$  ratio were generally higher in intravenous administration ( $p < 0.001$ ). 76.5%  $C_{\min}/\text{dose}$  were under the therapeutic window of VRC ([1.25, 12.5] mg l<sup>-1</sup>/mg d<sup>-1</sup>). Higher proportion of supratherapeutic VRC  $C_{\min}/\text{dose}$  (>12.5 mg l<sup>-1</sup>/mg d<sup>-1</sup>) and lower proportion of subtherapeutic VRC  $C_{\min}/\text{dose}$  (<1.25 mg l<sup>-1</sup>/mg d<sup>-1</sup>) were found in intravenous administration compared to oral administration (33.3% vs. 8.4% and 4.9% vs. 12.8%). These results revealed that we should pay more attention to the safety of supratherapeutic VRC  $C_{\min}$  in intravenous administration, while treatment failure results from subtherapeutic VRC  $C_{\min}$  in oral administration, respectively.

## Effects of Concomitant Glucocorticoids Administration on the $C_{\min}/\text{Dose}$ Ratio of VRC

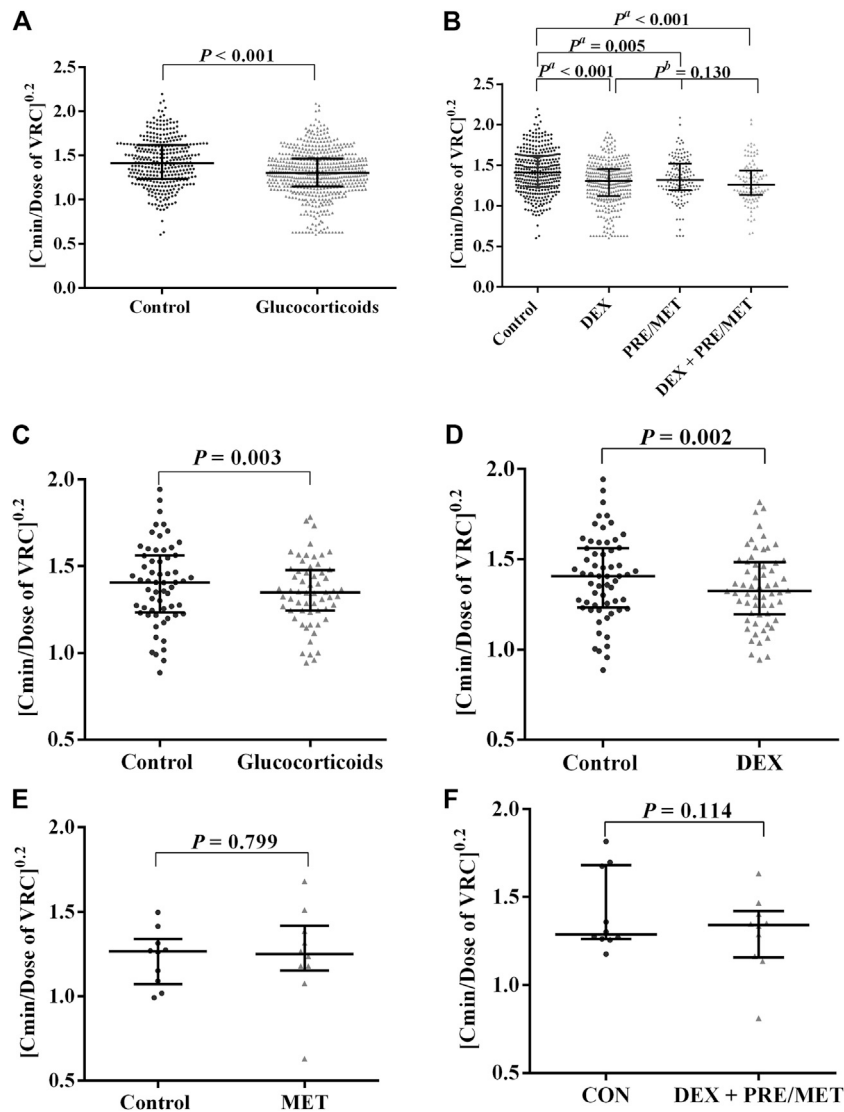
As shown in **Figure 1**, 348 VRC  $C_{\min}$  uncombined with glucocorticoids were designated as the control group and 570

VRC  $C_{\min}$  concomitant with glucocorticoids were designated as the glucocorticoids group. Compared with the control group, concomitant with glucocorticoids decreased the VRC  $C_{\min}/\text{dose}$  ratio significantly ( $p < 0.01$ , **Figure 1A**). Dexamethasone (DEX group), prednisone/prednisolone or methylprednisolone (PRE/MET group), and dexamethasone and prednisone/prednisolone/methylprednisolone (DEX + PRE/MET group) all markedly decreased the VRC  $C_{\min}/\text{dose}$  ratio statistically ( $p^c < 0.01$ , **Figure 1B**; **Supplemental Table S1**).

We further performed a paired test of the VRC  $C_{\min}/\text{dose}$  ratio with or without glucocorticoids to explore the effects of glucocorticoids on the VRC  $C_{\min}/\text{dose}$  ratio. 60 patients were monitored for VRC  $C_{\min}$  underlying comedication with or without glucocorticoids. The number of VRC  $C_{\min}$  measured in each patient ranged from 2 to 35, for a total of 507 concentrations included (see **Supplemental Table S2**). The paired test confirmed again that VRC  $C_{\min}/\text{dose}$  was reduced by glucocorticoids with statistical significance ( $p = 0.003$ , **Figure 1C**). As for the effects of different kinds of glucocorticoids on VRC, dexamethasone could decrease the median of the VRC  $C_{\min}/\text{dose}$  ratio by about 21.9% ( $p = 0.002$ , **Figure 1D**). These results verified that the combination of glucocorticoids could reduce the VRC  $C_{\min}/\text{dose}$  again.

## The Effects of Glucocorticoids on Influencing Probability of the Therapeutic Window of VRC

Based on our results, glucocorticoids can affect VRC  $C_{\min}/\text{dose}$ . We further explored the effects of glucocorticoids on the probability of the therapeutic window of VRC. It was found that the proportion of subtherapeutic VRC  $C_{\min}/\text{dose}$  were all increased after DEX or PRE/MET or DEX + PRE/MET administrations, although only the DEX group showed statistical significance ( $p < 0.001$ , **Table 3**). The groups with



**FIGURE 1** | Effects of concomitant glucocorticoids administration on the C/D ratio of VRC. The data were non-normal distribution and expressed as median with interquartile range. The ordinate (C/D ratio of VRC) was processed to the power of 0.2. DEX was abbreviation of dexamethasone, PRE was abbreviation of prednisone or prednisolone, and MET was abbreviation of methylprednisolone. N represented the number of patients enrolled and n represented the number of VRC concentrations in the group. **(A)** showed that the C/D ratio of VRC was significantly higher in the control patients ( $n = 348$ ) than the patients receiving glucocorticoids therapy simultaneously ( $n = 570$ ) ( $p < 0.001$ ). **(B)** showed the C/D ratio of VRC in the patients accompanying different kinds of glucocorticoids compared with the control patients ( $n = 348$ ). Coadministration with DEX ( $n = 334$ ,  $p < 0.001$ ), PRE/MET ( $n = 134$ ,  $p = 0.005$ ), and DEX + PRE/MET ( $n = 102$ ,  $p < 0.001$ ) could all reduce the C/D ratio of VRC significantly, but there was no statistical difference among these three groups ( $p^b = 0.130$ ) (**Supplemental Table S1**). **(C)** showed that the C/D ratio of VRC was significantly higher in the control patients ( $n = 197$ ) than the patients receiving glucocorticoids therapy simultaneously ( $n = 310$ ) ( $N = 60$ ,  $p = 0.003$ ). **(D)** showed that the C/D ratio of VRC in the patients taking DEX ( $n = 236$ ) was significantly lower than the control patients ( $n = 197$ ) ( $N = 60$ ,  $p = 0.002$ ). **(E)** showed that the C/D ratio of VRC in the patients taking MET ( $n = 31$ ) had no statistical difference compared with the control patients ( $n = 51$ ) ( $N = 10$ ,  $p = 0.799$ ). **(F)** showed that the C/D ratio of VRC in the patients taking DEX + PRE/MET ( $n = 35$ ) had no statistical difference compared with the control patients ( $n = 37$ ) ( $N = 10$ ,  $p = 0.114$ ) (**Supplemental Table S2**).

DEX and PRE/MET decreased the percentage of supratherapeutic VRC  $C_{\min}/\text{dose}$  ( $p < 0.001$  and  $p = 0.005$ , **Table 3**). These results emphasized that combination with glucocorticoids would increase the proportion of VRC subtherapeutic concentration leading to poor treatment response. Therefore, more attention should be paid to clinical efficacy rather than the safety of VRC when combined with glucocorticoids in clinical therapy.

### Effects of CYP450 Polymorphisms on VRC

After clarifying the influences of glucocorticoids on VRC concentration, we explored whether the effects of glucocorticoids on VRC were related to CYP450s at first. We analyzed effects of *CYP2C19*, *CYP3A4*, and *CYP3A5* polymorphisms on the  $C_{\min}/\text{dose}$  ratio of VRC in 159 patients ( $N = 555$ ) (shown in **Figure 2**; **Supplemental Table S3**). Allelic mutations of *CYP2C19*\*2 (rs4244285) ( $p = 0.042$ , **Figure 2A**) and

**TABLE 3** | The effect of glucocorticoids on influencing probability of the therapeutic window of VRC.

Group	$C_{\min}$ /dose level $n$ (%)			$p^a$	$p^b$	$p^c$	$p^d$
	Subtherapeutic [ $<1.25$ ( $\text{mg l}^{-1}$ )/( $\text{mg d}^{-1}$ )]	Therapeutic [ $1.25, 12.5$ ] ( $\text{mg l}^{-1}$ )/( $\text{mg d}^{-1}$ )	Supratherapeutic [ $>12.5$ ( $\text{mg l}^{-1}$ )/( $\text{mg d}^{-1}$ )]				
Non-comedication with glucocorticoids (N = 348)	26 (7.5%)	256 (73.6%)	66 (19.0%)				
Concomitant with glucocorticoids (N = 570)							
DEX (N = 334)	55 (16.5%)	259 (77.5%)	20 (6.0%)	<b>*0.001</b>	<b>*0.001</b>	0.247	<b>*0.001</b>
PRE/MET (N = 134)	14 (10.5%)	109 (81.3%)	11 (8.2%)	<b>0.012</b>	0.356	0.077	<b>0.005</b>
DEX + PRE/MET (N = 102)	13 (12.8%)	78 (76.5%)	11 (10.8%)	0.058	0.106	0.608	0.072

DEX: dexamethasone; PRE: prednisone/prednisolone; and MET: methylprednisolone.

$p^a$  was calculated comparing the group of concomitants with DEX or PRE/MET or DEX + PRE/MET with the group of non-comedication with glucocorticoids by the chi-squared test.

$p^{b-d}$  were the values of subtherapeutic/therapeutic/supratherapeutic  $C_{\min}$ /dose level compared to the group of concomitants with DEX or PRE/MET or DEX + PRE/MET and the group of non-comedication with glucocorticoids by the chi-squared test, respectively.

*CYP2C19\*3* (rs4986893) ( $p = 0.002$ , **Figure 2B**) both increased the  $C_{\min}$ /dose ratio of VRC, while allelic mutations of *CYP2C19\*17* (rs12248560) ( $p < 0.001$ , **Figure 2C**) and *CYP3A4* (rs4646437) ( $p = 0.002$ , **Figure 2D**) could both decrease the VRC  $C_{\min}$ /dose ratio statistically, despite the large inter-individual differences. It should be noted that mutants of *CYP3A5\*3* (rs776746, **Figure 2E**) showed no statistical effects ( $p = 0.069$ ). In addition, no variant of *CYP3A4\*22* (rs 35599367) was detected in the present population. Our results suggested that allelic mutations of *CYP2C19*, *CYP3A4*, and *CYP3A5* can indeed affect VRC  $C_{\min}$ /dose, but different SNPs of CYP450 have different effects.

## Effects of CYP450 Polymorphisms on Glucocorticoids Reduced the $C_{\min}$ /Dose Ratio and Probability of the Therapeutic Window of VRC

We further explored the interactions between glucocorticoids and CYP450 polymorphisms on the  $C_{\min}$ /dose ratio of VRC. Exception for *CYP2C19\*1\*3* and *CYP2C19\*3\*3*, comedication with glucocorticoids reduced the  $C_{\min}$ /dose ratio of VRC significantly at each genotype compared with non-comedication groups ( $p < 0.05$ , **Table 4**). These results further confirmed that comedication with glucocorticoids could reduce the VRC  $C_{\min}$ /dose ratio. As shown in **Table 4**, mutants of *CYP2C19\*17* ( $p < 0.001$ ) and *CYP3A5\*3* ( $p = 0.039$ ) could reduce the  $C_{\min}$ /dose of VRC, while mutant of *CYP2C19\*3* ( $p = 0.003$ ) could increase the  $C_{\min}$ /dose of VRC significantly in comedication with the glucocorticoids group. The above results indicated that the effects of CYP450 polymorphisms on VRC  $C_{\min}$  were inconsistent and complex and the effects of DDIs between glucocorticoids and VRC played a major role in VRC  $C_{\min}$  instead of CYP450 polymorphisms. Thus, more attention should be paid to the effects of DDIs between glucocorticoids and VRC rather than genetic polymorphisms when VRC was used.

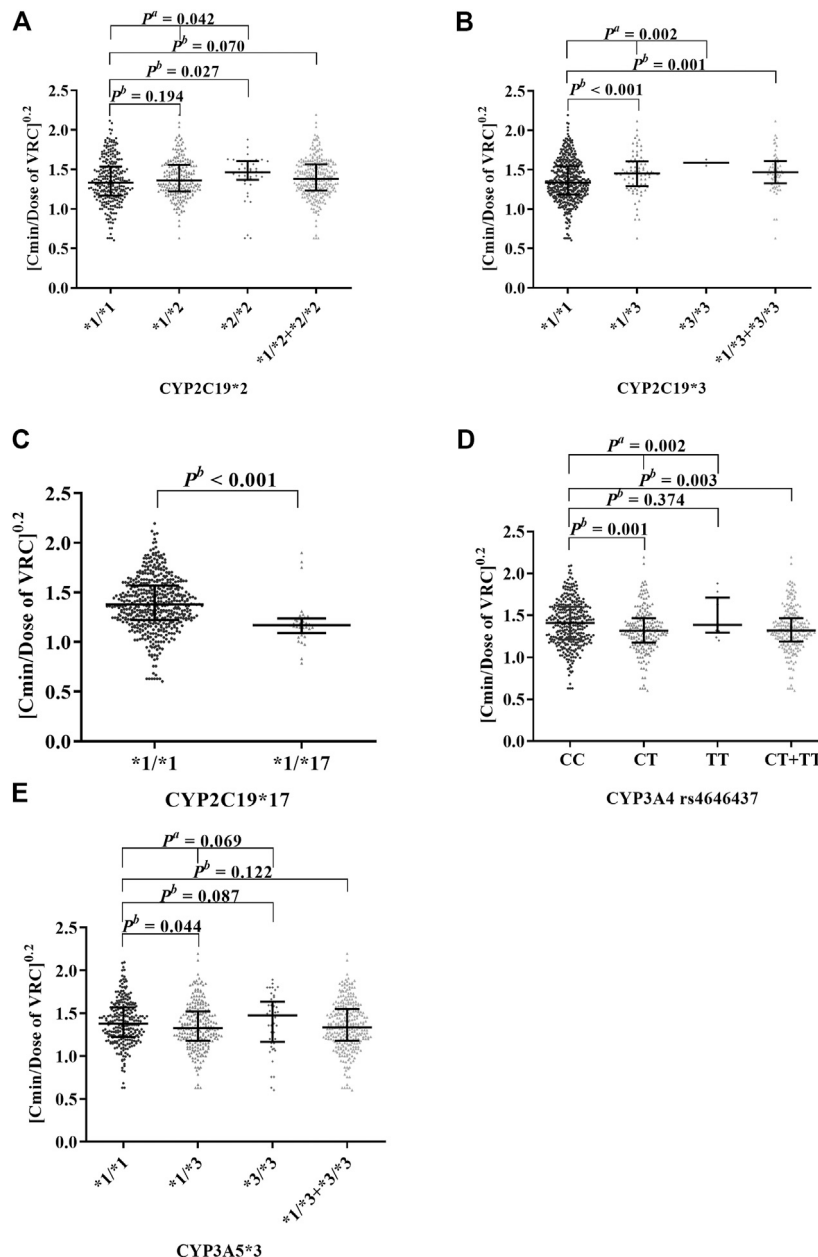
Moreover, the two-factor nonparametric analysis of variances further suggested that only *CYP2C19\*17* genotypes had a significant interaction with glucocorticoids ( $p = 0.037$ , **Table 4**), which meant glucocorticoids had a more noteworthy

effect on reducing the VRC  $C_{\min}$ /dose ratio in patients with *CYP2C19\*1\*17* genotype. Whereas, *CYP2C19\*2* mutation could increase the proportion of VRC  $C_{\min}$  in the therapeutic window under comedication with glucocorticoids statistically ( $p = 0.030$ , **Supplemental Table S4**), and *CYP3A4* mutant decreased the proportion of VRC  $C_{\min}$  in the supratherapeutic window ( $p = 0.033$ , **Supplemental Table S4**).

## DISCUSSIONS

VRC is widely used in hematology, ICU, pneumology, and some other departments. The samples in our study were mainly collected from the hematology department. VRC is a first-line regimen in clinical preventions and treatments of invasive *Aspergillus* infections recommended by the guidelines of the European Society of Clinical Microbiology and Infectious Diseases. In practical application, VRC is often inevitably coadministered with corticosteroids, proton pump inhibitors (PPIs), immunosuppressants, and other drugs, which lead to large individual differences. As a result, TDM-directed dose adjustment of VRC was recommended by guidelines (Moriyama et al., 2017). Although the proportion of the therapeutic VRC  $C_{\min}$ /dose ratio was higher in the present study than the previous literature (Cabral-Galeano et al., 2015; Zhou et al., 2020), there was still 22.2% (204 of 918) of VRC  $C_{\min}$  in the subtherapeutic or supratherapeutic window. Therefore, it has great significance to clarify the influencing factors of VRC concentrations and conduct TDM detection for VRC. VRC can be administered orally or intravenously. Oral administration of VRC is more convenient and the bioavailability of VRC is over 90% because VRC can be absorbed quickly and thoroughly (Purkins et al., 2003; Theuretzbacher et al., 2006). Thus, VRC was mostly administered orally in clinical practice, which was consistent with the characteristics of our data and previous reports (Zeng et al., 2020).

The VRC  $C_{\min}$  can be affected by numerous factors, among which CYP450 polymorphisms and DDIs can cause greater individual differences of VRC. It was reported that the pharmacokinetic values (AUC and  $C_{\max}$ ) of VRC were changed to various degrees when combined with several PPIs (Qi et al., 2017). Coadministration



**FIGURE 2** | Effects of cytochrome P450 polymorphisms on the C/D ratio of VRC. The data were non-normal distribution and expressed as median with interquartile range. The ordinate (C/D ratio of VRC) was processed to the power of 0.2. Data showed in **Supplemental Table S3**. **(A)** showed that the comparison between *CYP2C19*\*1/\*1 ( $n = 286$ ), *CYP2C19*\*1/\*2 ( $n = 228$ ), and *CYP2C19*\*2/\*2 ( $n = 41$ ) was significant ( $p^a = 0.042$ ). **(B)** showed that the *CYP2C19*\*1/\*3 + *CYP2C19*\*3/\*3 ( $n = 83$ ) can increase the C/D ratio of VRC significantly compared to *CYP2C19*\*1/\*1 ( $n = 472$ ,  $p^b = 0.001$ ). **(C)** showed that the *CYP2C19*\*1/\*17 ( $n = 35$ ) can reduce the C/D ratio of VRC significantly compared to *CYP2C19*\*1/\*1 ( $n = 520$ ,  $P^b < 0.001$ ). **(D)** showed that the comparison between *CYP3A4* genotype CC ( $n = 338$ ) and CT + TT ( $n = 217$ ) had statistical differences ( $P^b = 0.003$ ). **(E)** showed that the comparison between *CYP3A5*\*1/\*1 ( $n = 267$ ), *CYP3A5*\*1/\*3 ( $n = 240$ ), and *CYP3A5*\*3/\*3 ( $n = 48$ ) was insignificant ( $P^a = 0.069$ ).

of rifampicin was found to appreciably reduce VRC concentrations (Dolton et al., 2012). Since the combination of glucocorticoids and VRC is very common in clinical practice, the DDIs of VRC was focused on glucocorticoids in our research.

Although VRC could be metabolized by various CYP450 enzymes induced by corticosteroid (Li et al., 2017), the specific

interference effect of glucocorticoids on the concentration and pharmacokinetics of VRC is still controversial (Dolton et al., 2012; Gautier-Veyret et al., 2015; Li et al., 2017; Imataki et al., 2018; Blanco-Dorado et al., 2020). Hence, the effects of glucocorticoid type and dosage on VRC remains to be further studied. Our results showed that combination with

**TABLE 4** | Effects of candidate SNPs on  $C_{\min}$ /dose of VRC in comedication or non-comedication with glucocorticoids.

Key haplotype	SNPs	Genotype	N	Comedication with glucocorticoids (N = 319)		$p^a$	Non-comedication with glucocorticoids (N = 236)		$p^a$	$p^b$	$p^c$	
				N	$C_{\min}$ /dose [(mg l <sup>-1</sup> )/(mg d <sup>-1</sup> )], median (IQR)		N	$C_{\min}$ /dose [(mg l <sup>-1</sup> )/(mg d <sup>-1</sup> )], median (IQR)				
CYP2C19*2	rs4244285					0.052			0.572		0.798	
CYP2C19*1/*1		GG	286	161	3.50 (1.91, 6.63)		125	5.67 (2.54, 13.63)				<b>*0.001</b>
CYP2C19*1/*2 + CYP2C19*2/*2		GA + AA	269	158	4.38 (2.48, 10.89)		111	6.50 (3.30, 11.00)				<b>*0.001</b>
CYP2C19*3	rs4986893					<b>0.003</b>			0.106		0.578	
CYP2C19*1/*1		GG	472	275	3.68 (2.08, 6.75)		197	5.67 (2.76, 11.98)				<b>0.003</b>
CYP2C19*1/*3 + CYP2C19*3/*3		GA + AA	83	44	6.24 (3.55, 8.56)		39	7.20 (4.17, 13.13)				0.106
CYP2C19*17	rs12248560					<b>*0.001</b>			0.713		<b>0.037</b>	
CYP2C19*1/*1		CC	520	293	4.25 (2.50, 7.43)		227	6.40 (2.90, 11.75)				<b>*0.001</b>
CYP2C19*1/*17		CT	35	26	1.99 (1.29, 2.37)		9	3.38 (2.76, 17.88)				<b>0.001</b>
CYP3A4	rs4646437					0.054			0.400		0.608	
—		CC	338	170	4.55 (2.25, 8.52)		168	7.00 (2.96, 12.09)				<b>*0.001</b>
—		CT + TT	217	149	3.75 (2.15, 5.63)		68	5.28 (2.58, 12.13)				<b>0.002</b>
CYP3A5*3	rs776746					<b>0.039</b>			0.610		0.159	
CYP3A5*1/*1		GG	267	144	4.53 (2.40, 7.24)		123	5.74 (2.91, 11.00)				<b>0.015</b>
CYP3A5*1/*3 + CYP3A5*3/*3		AG + AA	288	175	3.67 (1.86, 6.75)		113	6.90 (2.76, 13.25)				<b>*0.001</b>

<sup>a</sup> $p$  was calculated comparing the mutant type with the wild type by the Mann–Whitney U test.

<sup>b</sup> $p$  was calculated comparing between comedication with glucocorticoids and non-comedication with glucocorticoids in the same genotype by the Mann–Whitney U test.

<sup>c</sup> $p$  was calculated comparing interaction between SNPs and glucocorticoids on the VRC C/D ratio by the Scheirer–Ray–Hare test.

glucocorticoids could significantly reduce VRC  $C_{\min}$ /dose by both paired and unpaired tests. We further analyzed the effects of different kinds of glucocorticoids on VRC. Though the effect of dexamethasone in reducing VRC  $C_{\min}$ /dose was more obvious, there was no difference in the effect of different kinds of glucocorticoids, which was inconsistent with literature reports (Dolton et al., 2012; Li et al., 2017). In paired tests, we found that only the effect of dexamethasone on VRC  $C_{\min}$ /dose was significant, other types of glucocorticoids showed no statistical difference or cannot be analyzed because of the small sample size. In addition, glucocorticoids also decreased the proportion of VRC supratherapeutic  $C_{\min}$ /dose and increased the ratio of VRC subtherapeutic  $C_{\min}$ /dose, indicating that more attention should be paid to clinical efficacy rather than the safety of VRC when combined with glucocorticoids. On the whole, we verified glucocorticoids can reduce VRC  $C_{\min}$ /dose.

Since that glucocorticoids are inducers of CYP450 enzymes and VRC is mainly metabolized through CYP450 enzymes, we further investigated whether CYP450s are involved in the influence of glucocorticoids on VRC. VRC is metabolized by CYP2C19, CYP3A4, and CYP3A5 enzymes and polymorphisms of CYP450 affect VRC concentration by changing the CYP450s enzymatic activity (He et al., 2015; Lin et al., 2018). Our results further confirmed the argument that allelic mutations of CYP2C19\*2 and \*3 made a higher  $C_{\min}$ /dose ratio of VRC, while the allelic mutations of CYP2C19\*17 and CYP3A4 produced a lower  $C_{\min}$ /dose ratio of VRC (He et al., 2015; Moriyama et al., 2017). The effect of CYP3A5\*3 on the VRC  $C_{\min}$ /dose ratio was slight and not significant which we speculated, the reason may be that CYP3A5 was not the main metabolic enzyme of VRC (Moriyama et al., 2017).

In order to explore the synergistic effects of glucocorticoids and CYP450 polymorphisms, we conducted two-factor nonparametric interaction analysis by the Scheirer–Ray–Hare test. The results showed that CYP2C19\*17 was the only allele interacting with glucocorticoids. The effect of CYP2C19\*17 on the reduction of concentration was strengthened by glucocorticoids, which suggested that there is a synergistic effect between CYP2C19\*17 gene mutation and glucocorticoids. Mutations in CYP2C19\*2, \*3, and CYP3A4 led to decreased enzyme activity, which was opposite to the effect of glucocorticoids on the activity of CYP2C19 and CYP3A4, so the overall effects on VRC  $C_{\min}$ /dose of these two factors were counterweighed. The CYP3A5\*3 mutant caused a decrease in the VRC  $C_{\min}$ /dose ratio when combined with glucocorticoids, while the effect was opposite in non-comedication with the glucocorticoids group. We speculate the reason was that the mutation of CYP3A5\*3 reduced the activity of hepatic microsomal enzyme CYP3A5 (Moriyama et al., 2017), thus reducing glucocorticoids metabolism and increasing glucocorticoids plasma concentration, leading to greater influence on VRC concentration when CYP3A5\*3 mutated. The above results reminded us that other confounding factors (such as DDIs) rather than the genotype should be emphasized. Regardless of SNP mutations, coadministration with glucocorticoids could reduce the  $C_{\min}$ /dose ratio of VRC. However, when glucocorticoids were not used in combination with VRC, CYP450 mutations did not produce a statistically significant impact on the VRC  $C_{\min}$ /dose ratio. Therefore, it was suggested that the influence on the VRC  $C_{\min}$ /dose ratio of glucocorticoids was more illustrious than that of gene polymorphisms. Therefore, we recommend TDM rather than gene detection for routine clinical application (Moriyama et al., 2017).



Limitations still exist in this research. This is a retrospective study. The sample size of different glucocorticoids was dissimilar. In the paring analysis of glucocorticoids in VRC concentration, the available sample size of prednisone/prednisolone was too small to be analyzed. What is more, there are other factors that need to be considered in clinical practice, and the effect of glucocorticoids on VRC was influenced by other combination drugs or clinical factors. We did not analyze the combined effects of multiple drugs' coadministration on VRC concentration which needs to be further explored. Moreover, our results showed that the effects of glucocorticoids on VRC cannot be fully explained by CYP450 polymorphisms, and other possible mechanisms such as inflammation need further investigation. In the rat septic shock mode, glucocorticoids can relieve inflammation and reduce C-reactive protein and procalcitonin (Li et al., 2019). Researchers have found that the inflammatory state could increase the plasma concentration of VRC through metabolic reduction in immunocompromised patients (Naito et al., 2015). Whether the effect of glucocorticoids on the concentration of VRC is related to the inflammatory state or is more closely related to the CYP450 genotypes deserves further study.

## CONCLUSION

In conclusion, our study confirmed that glucocorticoids reduced the  $C_{min}/dose$  level of VRC despite the SNPs of *CYP2C19* \*2, \*3, \*17, *CYP3A4*, and *CYP3A5*. Glucocorticoids and *CYP2C19*\*17 polymorphisms had a synergistic effect on reducing the VRC  $C_{min}/dose$  ratio. The results indicated us that when combined with glucocorticoids, we should pay attention to the possibility of invalidation of VRC, especially when *CYP2C19*\*17 mutation exists.

## DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and

accession number(s) can be found in the article/**Supplementary Material**.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Research Committee of the Third Xiangya Hospital of Central South University. The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

Y-LX and S-JJ had full access to the conception and design of the study. S-YH, QX, and ZY collected the clinical data. P-HH measured VRC plasma concentrations. K-QG, Y-LX, and S-JJ wrote the first draft of the manuscript. RG and X-CZ contributed to revising and proofreading the manuscript. All authors contributed and approved the submitted version of the manuscript.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fphar.2021.666296/full#supplementary-material>

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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