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# Correlation of *CYP2C19* genotype with plasma voriconazole exposure in South-western Chinese Han patients with invasive fungal infections

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**Abstract**

The aim of this study was to investigate the correlation between *CYP2C19* genotype and dose-adjusted voriconazole (VCZ) trough concentrations ($C_0$/dose).

We analyzed the correlation between *CYP2C19*2*(681G>A), *CYP2C19*3*(636G>A), and *CYP2C19*17*(-806C>T) genetic polymorphisms and the dose-corrected pre-dose concentration ($C_0$/dose) in 106 South-western Chinese Han patients.

The frequencies of variant alleles of *CYP2C19*2*, **3*, and **17* were 29.7%, 4.25%, and 0.92%. For 49.3% of the VCZ samples, the therapeutic window between 1.5 and 5.5 μg/ml was reached. Following the first dose VCZ measurement, in subsequent samples the proportion of VCZ $C_0$ within the therapeutic window increased, suggesting effective therapeutic drug monitoring (TDM) ($P = .001$). The VCZ $C_0$ was significantly different ($P = .010$) between patients with normal metabolism (NMs), intermediate metabolism (IMs), and poor metabolism (PMs). The VZC $C_0$/dose was 12.2 (interquartile range (IQR), 8.33–18.2 $\mu g \cdot ml^{-1}/kg \cdot day^{-1}$), and 7.68 (IQR, 4.07–16.3 $\mu g \cdot ml^{-1}/kg \cdot day^{-1}$) in PMs and IMs patients, respectively, which was significantly higher than in NMs phenotype patients (4.68; IQR, 2.51–8.87 $\mu g \cdot ml^{-1}/kg \cdot day^{-1}$, $P = .008$ and $P = .014$).

This study demonstrated that the VCZ $C_0$/dose was significantly influenced by the *CYP2C19* genotype in South-western Chinese Han patients. In this patient population, more over-exposure was observed in patients with a *CYP2C19* genotype associated with poor or intermediate metabolism. *CYP2C19* genotype-based dosing combined with TDM will support individualization of VCZ dosing, and potentially will minimize toxicity and maximize therapeutic efficacy.

**Abbreviations:** ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, $C_0$/dose = dose-adjusted trough concentrations, CYP450 = cytochrome P450, GGT = gamma-glutamyl transpeptidase, IFI = invasive fungal infection, IMs = intermediate metabolizers, IQR = interquartile range, IS = internal standard, MRM = multiple reaction monitoring, NMs = normal metabolizers, PCR = polymerase chain reaction, PMs = poor metabolizers, RE = relative error, RMs = rapid metabolizers, TDM = therapeutic drug monitoring, UMs = ultra-rapid metabolizers, VCZ = voriconazole.

**Keywords:** *CYP2C19* polymorphism, invasive fungal infections, therapeutic drug monitoring, voriconazole dose-adjusted concentrations

## 1. Introduction

Voriconazole (VCZ) is a second-generation triazole antifungal drug with potent broad-spectrum activity and a strong target affinity. It is recommended by a number of guidelines for the treatment of invasive Aspergillus infections as the drug of the first choice. It is also used as prophylaxis in immunocompromised individuals.[1–3] A wide interpatient and intrapatient variability in pharmacokinetics complicate the treatment of patients in daily practice.[4,5] VCZ is extensively metabolized by hepatic cytochrome P450 (CYP) enzymes,[6] several of which are well known to be polymorphically-expressed, such as, *CYP2C19* and,[7–10] to a lesser extent, by *CYP3A4* and *CYP2C9*.[11–13]

The *CYP2C19*2*, *CYP2C19*3*, and *CYP2C19*17* alleles have a relatively high frequency in the Asian population. Two *CYP2C19* alleles, 681G>A (*CYP2C19*2*) and 636G> A (*CYP2C19*3*) genotype are associated with a poor metabolizer phenotype,[7,14] while the -806C> T (*CYP2C19*17*) gene mutation leads to ultra-rapid metabolism.[15,16] The poor metabolizer genotype is present in only about 3% to 5% of Caucasians and African–Americans, whereas this is much more frequent in the Asian population (10%–20%). The *CYP2C19*17* allele is relatively rare in the Asian population (mutation frequency < 5%), and it is estimated that in Caucasians and African–Americans this allele is about 4 times more frequent than

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in the Asian population.[17–20] In published studies on the distribution of *CYP2C19* genotypes, the Asian population has been underrepresented.

This study aimed to investigate the distribution frequency of *CYP2C19* alleles and the correlation of *CYP2C19* polymorphisms with VCZ $C_0$/dose in South-western Chinese Han patients undergoing treatment or prophylaxis for fungal infections. A better understanding of the impact of these polymorphisms on VCZ exposure will help to achieve individualized drug dosing and will ultimately improve the clinical outcome.

## 2. Materials and methods

### 2.1. Study design and patient population

This was a retrospective cohort study of South-western Chinese Han patients aged 18 years or older treated for a probable or definite invasive fungal infection (IFI), as inpatients between April 2017 and April 2018 at West China Hospital of Sichuan University. All patients were started on standard VCZ dosing according to the package insert, consisting of a loading dose of 400 mg every 12 h for the first 24 h, followed by a maintenance dose of 200 mg twice daily. Exclusion criteria were:

1. pregnancy
2. abnormal liver function result (alanine aminotransferase or aspartate aminotransferase defined as more than 5 times the upper limit of normal; alkaline phosphatase, gamma-glutamyl transpeptidase, or total bilirubin more than 3 times the upper limit of normal)
3. a history of liver transplantation[21]
4. co-treatment with glucocorticoids or proton pump inhibitors.

The VCZ $C_0$ was measured on day 5 to 7 after VCZ initiation (ie, at steady state). In some patients after the first $C_0$ measurement, the VCZ dose was adjusted and followed by a second $C_0$ measurement when the patient reached a steady state.

From the medical records patient data were collected, including demographic information and clinical information regarding body weight, height, underlying disease, infection site, VCZ dosing, and route of administration. This study protocol was approved by the Ethics Committee of West China Hospital of Sichuan University.

### 2.2. Measurement of VCZ plasma levels

Heparinized blood was collected at steady state, just before the next VCZ dose. Plasma was collected by centrifugation at 3000 rpm for 10 min. VCZ $C_0$ were determined using a UPLC-MS/MS method developed in our laboratory. The analyses were performed using Waters Acquity Xevo TQ-S triple quadrupole mass spectrometer (Waters, USA) with an Acquity BEH C18 column (2.1 × 50 mm, 1.7 μm particle size). The mobile phase consisted of acetonitrile and PH3.0, 0.02 mol/L ammonium acetate containing 0.3% formic acid (40:60, v/v). The flow rate was 0.30 ml/min. The column temperature was 40°C and overall run time was 2 min. The detection was operated in the multiple reaction monitoring (MRM) mode. The dwell time was set to 250 ms for each MRM transition. The MRM transitions were m/z 350.4→127.16 and m/z 288.4→96.19 for VCZ and IS (200 μg/ml cyproheptadine), respectively. Sample preparation included mixing samples (100 μl) with IS(50 μl) and Methyl tert-Butyl Ether(1 ml), then vortex-mixed (20 s) and centrifuged (Eppendorf 5810R) at 12,000 rpm for 5 min, then supernatant was vacuum dried and dissolved in 150 μl of mobile phase, injected 4 μl for analyzing. This method has been fully validated and is routinely used for monitoring VCZ plasma concentrations in our hospital. No interfering peaks generated from endogenous substances were observed on the chromatograms of blank samples, indicating that the method has good specificity. The linear range of the calibration curve was from 0.5 to 1000 μg/ml. with a correlation coefficient of $(r^2) > 0.99$. We determined that the LOD and LLOQ for VCZ were 0.125 μg/ml and 0.5 μg/ml, respectively. The LLOQ level was set with a CV of 2.9% and a bias of 9.5%. The typical chromatograms of the blank plasma and plasma spiked with VCZ (at the concentration of LLOQ) and the IS were shown in Supplementary material Fig. S1, http://links.lww.com/MD/C766. We used 4 QC levels (500, 62.5, 7.8, and 1 μg/ml) sample for all method validation. The matrix effects in human plasma were all between 91.96% and 110.69% at different QC levels. The matrix effect for IS (200 μg/ml) was 91.6%. The RSD was all in the range of 10%. The extraction recovery ranged from 86.56% to 97.41% and the RSD was also all in the range of 10%. The average intra- and inter-day precision were 1.81% and 3.57%, respectively. The overall accuracy was −0.85% to 5.14% and 2.20% to 4.23% for intra- and inter-day values, respectively. There was no effect on the quantitation for plasma samples kept at room temperature for 6 h (% RE, 3.08–6.60) and the autosampler (16°C) for at least 24 h (% RE, 1.53–3.82). VCZ was also stable after 3 freeze-thaw cycles when stored at −20°C (% RE, 3.17–8.75). Similarly, the extent of drug degradation was minimal when samples were stored at −20°C for 28 days (% RE, 1.52–2.39).

### 2.3. CYP2C19 genotyping

Genomic DNA from ethylene diamine tetra-acetic acid (EDTA) anticoagulated whole blood was isolated using a YAOJINBAO DNA purification Kit (Beijing Sino-Era Gene Tech Co. Ltd, China) according to the manufacturer's instructions. Firstly, 1.2 ml working solution and 150 μl EDTA anticoagulated whole blood was added to a sterile 1.5 ml centrifuge tube, mixed and placed at room temperature for 5 min. Then the samples were centrifuged at 700 g for 5 min, followed by discarding the supernatant. Secondly, the leukocytes were resuspended by adding 1 ml of physiological saline, then centrifuged again at 700g for 5 min, again followed by discarding the supernatant. Lastly, 50 μl Yaojinbao DNA purification reagent was added to the centrifuge tube which was enriched with white blood cells. This sample was then mixed by repeated pipetting, and placed at room temperature for 30 min. The white cell suspension was directly used for DNA analysis. *CYP2C19* genotyping for *CYP2C19*2*(rs4244285, G>A), *CYP2C19*3*(rs4986893, G>A), and *CYP2C19*17* (rs12248560, C>T) was carried out by allele-specific polymerase chain reaction combined with TaqMan double fluorescent probe detection with Fluotec 48E Trace fluorescence detector (Xi'an TianLong Science and Technology Co. Ltd). The reaction system temperature was 62°C, the standard test procedure was 55 cycles, and the total reaction time was generally within 2.5 h. The presence of the wild-type allele *CYP2C19*1* was inferred from the absence of the *2, *3, and *17 alleles.

### 2.4. CYP2C19 phenotype assignment

According to nomenclature by the Clinical Pharmacogenetics Implementation Consortium (CPIC),[22] patients with the *1/*17

genotype were classified as rapid metabolizers (RMs), and those with *17/*17 genotype were classified as ultra-rapid metabolizers (UMs). Patients with 1 copy of a *2 or a *3 allele (eg, *1/*2, *1/*3, *2/*17) were assigned the intermediate metabolizer (IMs) phenotype, and carriers of 2 copies (eg, *2/*2, *2/*3) were assigned the poor metabolizer (PMs) phenotype. The normal metabolizer (NMs) phenotype was assigned by default to patients without a *2, *3, or *17 allele.

### 2.5. Statistical analysis

The demographic details and the ratios of VCZ concentrations and doses were expressed as median (IQR). Statistical analysis used Kruskal–Wallis 1 way ANOVA test or a Mann–Whitney *U* test and Pearson chi-square test, and a Dunn-Bonferroni test for post hoc comparisons. Categorical variables are reported as frequencies and percentages. All statistical tests were 2-tailed and a *P* value less than .05 was deemed significant. The analysis was performed with SPSS (Statistical Package for the Social Sciences, version 19.0).

## 3. Results

### 3.1. Baseline characteristics

A total of 106 patients were enrolled. From all patients, a first VCZ trough concentration drawn at steady state was obtained, and from 46 patients also a second sample was collected. The patient characteristics are summarized in Table 1. Over half of the patients were male (n = 68, 64.2%). The average age of patients in this study was 49.7 ± 16.6 years. Mean (SD) body mass index (BMI) was 21.7 ± 3.48 kg/m$^2$. The underlying diseases mainly included fungal pneumonia (n = 40, 37.7%) and kidney transplantation (n = 25, 23.6%). The main infection site was pulmonary (80.2%). VCZ was administered by oral route in most patients (66%).

**Table 1**

**Demographic and clinical characteristics of the study subjects (N = 106).**

| Characteristics | Number of patients; (mean) (%) |
|---|---|
| Sex | |
| Male | 68 (64.2%) |
| Female | 38 (35.9%) |
| Age (year), median (range) | 49.5 (39.5, 62.3) |
| Body weight (Kg), median (range) | 57.8 (50.0, 65.0) |
| Height (m), median (range) | 1.65 (1.60, 1.70) |
| BMI, median (range) | 21.2 (19.3, 23.7) |
| Underlying disease | |
| Kidney transplantation | 25 (23.6%) |
| Chronic renal failure | 4 (3.8%) |
| Hematological disorder | 12 (11.3%) |
| Fungal pneumonia | 40 (37.7%) |
| septic shock | 6 (5.7%) |
| other | 19 (17.9%) |
| Infection site | |
| Pulmonary | 85 (80.2%) |
| Extra Pulmonary | 21 (19.8%) |
| Route of administration | |
| Intravenous | 36 (34%) |
| Oral | 70 (66%) |

BMI = body mass index.

### 3.2. CYP2C19 genotyping predicted phenotype and VCZ exposure

The *CYP2C19* genotype was determined in all 106 patients. The numbers and frequencies of variant alleles of *CYP2C19* are displayed in Table 2. The wild-type allele *CYP2C19*1* was observed most frequently (138/212, 65.1%) followed by the *CYP2C19*2* allele (63/212, 29.7%) and the *CYP2C19*3* allele (9/212, 4.25%), while the *CYP2C19*17* allele was detected only twice (Table 3). Based on the *CYP2C19* genotype 14 patients (11 homozygous *2/*2 and 3 heterozygous *2/*3) were predicted to be PMs (incidence 13.2%). For 44/106 (41.5%) patients the predicted phenotype was IMs (Table 4).

The VCZ $C_0$ and $C_0$/dose have significantly associated with the *CYP2C19*2* (rs4244285) polymorphism ($P = .009$, $P = .002$; Table 2). The median $C_0$/dose for patients with the *CYP2C19*2* AA genotype was 13.7 μg·ml$^{-1}$/kg·day$^{-1}$, which was significantly higher than for patients with the GG genotype 5.08 μg·ml$^{-1}$/kg·day$^{-1}$ ($P = .005$; Table 2). The median $C_0$/dose level for patients with the *CYP2C19*3* GA genotype (9.43 μg·ml$^{-1}$/kg·day$^{-1}$) was numerically higher than for those with the GG homozygous wild-type (5.78 μg·ml$^{-1}$/kg·day$^{-1}$) genotype but this difference did not reach statistical significance ($P = .289$; Table 2). The median $C_0$/dose for patients with the *CYP2C19*17* CT genotype (1.03 μg·ml$^{-1}$/kg·day$^{-1}$) was significantly lower than for patients with the CC homozygous wild-type genotype (6.18 μg·ml$^{-1}$/kg·day$^{-1}$, $P = .037$; Table 2). The VCZ $C_0$ were

**Table 2**

**Association between *CYP2C19* polymorphisms with VCZ $C_0$ and $C_0$/dose.**

| *CYP2C19* polymorphism | n (%) | $C_0$ (μg·ml$^{-1}$) median (IQR) | *P* value | $C_0$/dose (μg·ml$^{-1}$/kg·day$^{-1}$) median (IQR) | *P* value |
|---|---|---|---|---|---|
| *CYP2C19*2* (rs4244285) 681G>A | | | | | |
| GG | 55 (51.9%) | 2.03 (0.94, 3.76) | — | 5.08 (2.55, 9.68) | — |
| GA | 40 (37.7%) | 3.05 (1.20, 5.31) | .129* | 7.68 (3.01, 16.3) | .081* |
| AA | 11 (10.4%) | 5.13 (2.83, 7.67) | .017* | 13.7 (8.75, 19.2) | .005* |
| *P* value | | .009† | | .002† | |
| *CYP2C19*3* (rs4986893) 636G>A | | | | | |
| GG | 97 (91.5%) | 2.31 (1.06, 5.01) | | 5.78 (2.65, 13.0) | |
| GA | 9 (8.5%) | 3.04 (1.92, 5.07) | .646* | 9.43 (5.23, 15.6) | .289* |
| *CYP2C19*17* (rs12248560) -806C>T | | | | | |
| CC | 104 (98.1%) | 2.39 (1.11, 5.07) | | 6.18 (2.78, 13.3) | |
| CT | 2 (1.89%) | 0.39 (—,—) | .045* | 1.03 (—,—) | .037* |

IQR = interquartile range.

* *P* value was analyzed by Dunn-Bonferroni test for post hoc comparisons. Comparison with wild-type allele GG or CC.

† *P* value was analyzed by Kruskal–Wallis 1 way ANOVA test.

**Table 3**

**Association between *CYP2C19* genotype with VCZ $C_0$ and $C_0$ /dose.**

| *CYP2C19* genotype | N(%) (N = 106) | $C_0$ (μg·ml$^{-1}$) median (IQR) | *P* value | $C_0$/dose (μg. ml$^{-1}$/kg. day$^{-1}$) median (IQR) | *P* value |
|---|---|---|---|---|---|
| *1/*1 | 48 (45.3%) | 1.87 (0.80, 3.68) | — | 4.68 (2.51, 8.87) | — |
| *1/*2 | 36 (34.0%) | 3.32 (1.63, 5.80) | .136* | 7.67 (4.07, 16.5) | .075* |
| *1/*3 | 6 (5.66%) | 3.12 (2.10, 7.81) | 1.000* | 12.9 (5.26,19.5) | .340* |
| *2/*17 | 2 (1.89%) | 0.39 (—,—) | – | 1.03 (—,—) | – |
| *2/*2 | 11 (10.4%) | 5.13 (2.83, 7.67) | .053* | 13.7 (8.75, 19.2) | .011* |
| *2/*3 | 3 (2.83%) | 1.77 (—,—) | – | 8.85 (—,—) | – |
| *P* value | | .003† | | .001† | |

IQR = interquartile range.

* *P* value was analyzed by Dunn-Bonferroni test for post hoc comparisons. Comparison with *1/*1 genotype.

† *P* value was analyzed by Kruskal–Wallis 1 way ANOVA test.

**Table 4**

**Association between *CYP2C19* predicted phenotype and VCZ exposure.**

| *CYP2C19* phenotype | N (%) (N = 106) | $C_0$ (μg·ml$^{-1}$) median (IQR) | *P* value | $C_0$/dose (μg. ml$^{-1}$/kg. day$^{-1}$) median (IQR) | *P* value |
|---|---|---|---|---|---|
| NM | 48 (45.3%) | 1.87 (0.80, 3.68) | — | 4.68 (2.51, 8.87) | — |
| IM | 44 (41.5%) | 3.12 (1.63, 5.80) | .034* | 7.68 (4.07, 16.3) | .014* |
| PM | 14 (13.2%) | 4.22 (1.77, 7.27) | .041* | 12.2 (8.33, 18.2) | .008* |
| *P*-value | | .010† | | .002† | |

IM = intermediate metabolizer, IQR = interquartile range, NM = normal metabolizer, PM = poor metabolizer.

NM: CYP2C19 *1/*1; IM: CYP2C19 *1/*2, CYP2C19 *1/*3, and CYP2C19 *2/*17; PM: CYP2C19 *2/*2, CYP2C19 *2/*3.

* *P* value was analyzed by Dunn-Bonferroni test for post hoc comparisons. Comparison with NM phenotype.

† *P* value was analyzed by a Kruskal–Wallis 1 way ANOVA test.

similar in patients with the *CYP2C19**2 and *CYP2C19**3 genotypes (Table 2).

VCZ $C_0$ and $C_0$/dose were highly correlated with the *CYP2C19* genotype. There were significant differences between the different *CYP2C19* genotype groups (Table 3). The median $C_0$/dose for patients with the *CYP2C19**2/*2 genotype (13.7 μg·ml$^{-1}$/kg·day$^{-1}$) was significantly higher than in patients with the *CYP2C19**1/*1 genotype (4.68 μg·ml$^{-1}$/kg·day$^{-1}$; $P = .011$) (Table 3). However, the median $C_0$/dose for patients with the *CYP2C19**1/*2 and *1/*3 genotypes (7.67 resp 12.9 μg·ml$^{-1}$/kg·day$^{-1}$) was not significantly higher than in patients with the *CYP2C19**1/*1 genotype (4.68 μg·ml$^{-1}$/kg·day$^{-1}$, $P = .075$ and $P = .340$) (Table 3). In IMs patients with the *CYP2C19**1/*2, *1/*3, and *2/*17 genotypes the $C_0$/dose level was 7.68 μg·ml$^{-1}$/kg·day$^{-1}$ (IQR, 4.07—16.3 μg·ml$^{-1}$/kg·day$^{-1}$), and significantly higher than those of patients with the NMs phenotype (4.68; IQR, 2.51—8.87 μg·ml$^{-1}$/kg·day$^{-1}$, $P = .014$; Table 4 and Fig. 1B). In comparison, in PMs with the *CYP2C19**2/*2 and *2/*3 genotypes the $C_0$/dose level was 12.2 μg·ml$^{-1}$/kg·day$^{-1}$ (IQR, 8.33—18.2 μg·ml$^{-1}$/kg·day$^{-1}$), which was significantly higher than for NMs (4.68; IQR, 2.51—8.87 μg·ml$^{-1}$/kg·day$^{-1}$, $P = .008$; Table 4 and Fig. 1B).

### 3.3. Achievement of VCZ target $C_0$ levels among different *CYP2C19* phenotypes

Of initial 106 first VCZ $C_0$ samples, 39.6% reached the therapeutic window (between 1.5 and 5.5 μg/ml). A subtherapeutic $C_0$ level was observed in 34.9% of cases, whereas the $C_0$ was above 5.5 μg/ml in 25.5% of cases (Table 5). The prevalence of sub-therapeutic, therapeutic and toxic VCZ trough concentrations in wild-type and non-wild type was clearly different (Table 5; $P = .001$). There were also significant differences between the 3 metabolic phenotype groups (Table 5; $P = .005$).

### 3.4. First VCZ sample vs subsequent VCZ sample

For this analysis, the 106 initial VCZ $C_0$ samples were compared with the 46 subsequent samples. The proportion of samples

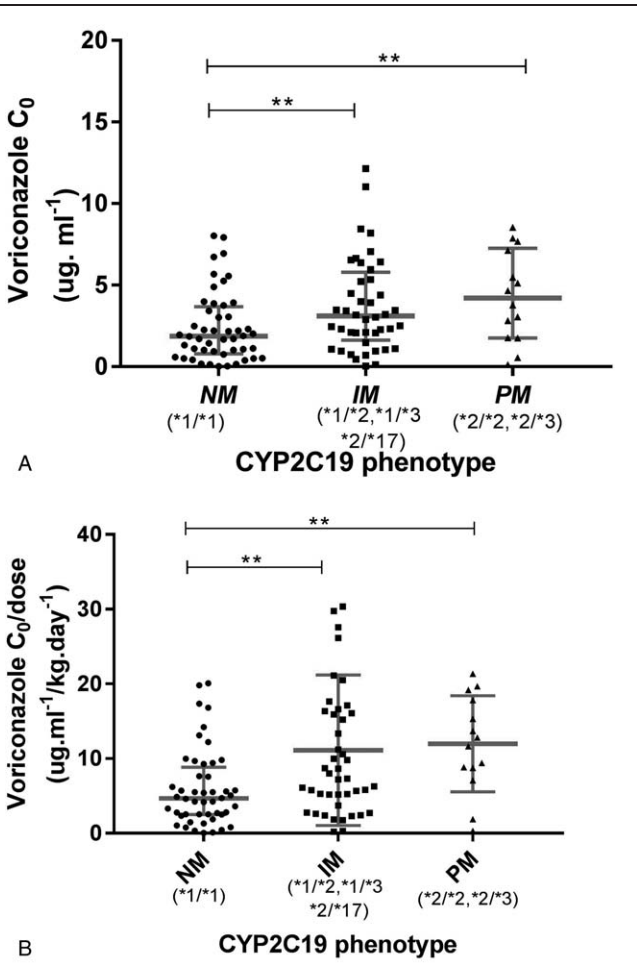


**Figure 1.** Association between predicted *CYP2C19* phenotypes and plasma voriconazole concentration (μg/ml). (A) Distribution of voriconazole trough concentrations ($C_0$); (B) dose-adjusted trough concentrations ($C_0$/dose). ** $P < .05$. IM: intermediate metabolizer, NM: normal metabolizer, PM: poor metabolizer.

**Table 5**

**Frequency of level of first VCZ trough plasma concentration in different *CYP2C19* phenotypes (N, %).**

| | *CYP2C19* phenotype | *CYP2C19* metabolic phenotype | Frequency of VCZ trough plasma concentration (μg/ml) | | | |
|---|---|---|---|---|---|---|
| | | | Sub-therapeutic (<1.5) | Therapeutic (1.5—5.5) | Toxic (>5.5) | Total |
| | Wild-type | NM | 24 (50.0%) | 19 (39.6%) | 5 (10.4%) | 48 (100%) |
| | Non-wild type | IM | 11 (25.0%) | 18 (40.9%) | 15 (34.1%) | 44 (100%) |
| | | PM | 2 (14.3%) | 5 (35.7%) | 7 (50.0%) | 14 (100%) |
| Total | | | 37 (34.9%) | 42 (39.6%) | 27 (25.5%) | 106 (100%) |
| *P* value | .001* | .005† | | | | |

IM = intermediate metabolizer, NM = normal metabolizer, PM = poor metabolizer, VCZ = voriconazole.

*P* value was analyzed by Pearson Chi-square test.

* Compared the wild-type and non-wild type.

† Compared the NM, IM, and PM metabolic phenotype.

within the therapeutic window was significantly lower in the analysis of the first sample than in that of the subsequent samples (39.6% vs 71.7%) (Fig. 2).

## 4. Discussion

This pharmacogenetic study was performed in a South-western Chinese Han patient population and as a result, the *CYP2C19*2*, and the *CYP2C19*3* allele were present in a relatively high frequency. Mikus Gerd et al reported 23% to 25%, 5% and 1% to 4% as the allele frequencies for *CYP2C19*2*, **3*, and **17* in Asians.[19]These data are in line with the frequencies of the variant alleles of *CYP2C19*2*, **3*, and **17* in our study (29.7%, 4.25%, and 0.92%). The increased function *CYP2C19*17* allele results in enhanced transcription and increased enzyme activity for some substrates, and is rare in Chinese patients. In contrast, the more frequent *CYP2C19*2* and **3* mutations are associated with higher concentration-to-dose ratios than the wild-type *CYP2C19*1* (Fig. 1B). However, due to the much smaller sample size for *CYP2C19*3* GA, the median $C_0$/dose level for patients with *CYP2C19*3* GA genotype compared with GG homozygous wild-type did not reach statistical significance (Table 2). Also, previous studies demonstrated elevated VCZ plasma concentrations in *CYP2C19* IMs and PMs compared to NMs.[9,15,16,23] In our study, VCZ $C_0$/dose in *CYP2C19* IMs and PMs were found to be 1.64 and 2.61 times higher as compared to NMs (Table 4; Fig. 1). An important difference between the South-western Chinese Han population and the Caucasian population is that the allele frequency of *CYP2C19*17* in the Caucasian population is high, and that in Caucasian patients rapid metabolism of VCZ and underexposure to VCZ are more important problems than in South-western Chinese Han patients, where over-exposure due to poor or intermediate metabolism is more frequent.[24]

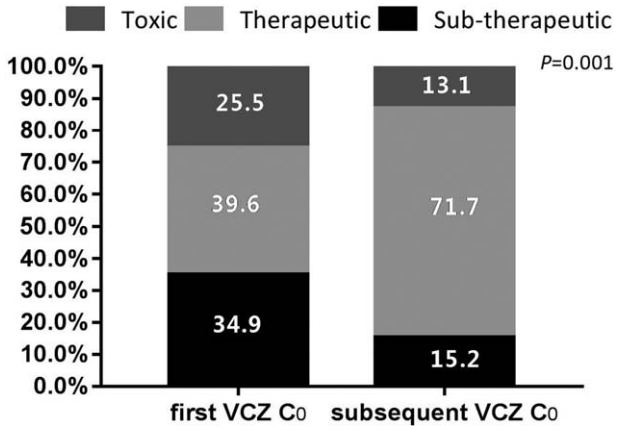


**Figure 2.** Proportion of first and subsequent samples with sub-therapeutic, therapeutic, and toxic voriconazole $C_0$ levels.

There are numerous reports on the relationship between the efficacy of VCZ and its plasma concentration. The currently recommended ranges of therapeutic concentrations vary somewhat but are mostly in the range of 1 to 4 μg/ml,[9,10] 2 to 6 μg/ml,[16,25,26] or 1 to 5.5 μg/ml.[3,27,28] In a population of solid organ transplant recipients, there were fewer IFIs at troughs of >1.5 μg/ml.[29] A specific target range for VCZ trough concentrations for the Chinese patients has not been defined. In our study, we chose the reference range between 1.5 and 5.5 μg/ml for both treatment and prophylaxis. In the *CYP2C19* PMs and IMs group, the proportion of patients reaching VCZ concentrations above the therapeutic range was higher as compared to the NMs (50.0% and 34.1% vs 10.4%, Table 5). Also, other studies have reported that PMs and IMs patients will more often reach (too) high VCZ concentrations, as compared to NMs patients. This overexposure is also associated with more adverse effects such as neurotoxicity and hepatotoxicity.[6,18,29] In addition, we found that therapeutic drug monitoring (TDM) can significantly increase the proportion of patients with a VCZ $C_0$ within the therapeutic window (71.7% vs 39.6%, Fig. 2). While genotype can help to choose the best starting dose, TDM can further refine the best next dose and thus optimize efficacy and reduce toxicity.

Contradictory studies on the impact of the *CYP2C19*2/*17* genotype on VCZ pharmacokinetics have been published. It has been suggested that this genotype would result in a poor metabolizer phenotype, with higher VCZ serum levels and more adverse drug reactions.[30] Weiss et al, however, reported that VCZ pharmacokinetics were similar between patients carrying the *CYP2C19*2/*17* genotype and those with the *CYP2C19*1/*17* genotype.[31] In contrast, Chung et al classified patients with the *CYP2C19*2/*17* variant as IMs.[32] The CPIC Guideline[10,22] also classified this diplotype as IMs, but they stressed that more data are needed to confirm this provisional classification. In our study, we initially defined patients with this genotype as IMs according to the CPIC guidelines. Based on our data, with lower VCZ concentrations compared to other genotype IMs patients, so we guess that the *CYP2C19*2/*17* genotype is more likely to result in RMs in Asian patients, it seems that depending on ethnicity the phenotype of *CYP2C19*2/*17* variant is either RM (Asian patients) or IM (Caucasian patients), but again more data were needed to verify this finding.

Shao et al suggested that for VCZ dose individualization besides *CYP2C19* genotype also gene polymorphisms in *CYP3A4*, and non-genetic factors such as BMI and age should be taken into account.[12] In our study, we did find a significant correlation between age and VCZ concentration in NM phenotype patients ($P < .05$, Supplementary material Table S1, http://links.lww.com/MD/C766). Since the study was a retrospective study, we were unable to obtain *CYP3A4* data and failed to verify the above results. We also analyzed the effect of different routes of administration on the concentration of VCZ and found that oral and intravenous administration had no significant effect on the VCZ concentration ($P > .05$, Supplementary material Table S2, http://links.lww.com/MD/C766). This result was in agreement with the recommendation to use the same dose for oral and intravenous drip mentioned in the VCZ drug label.

Our study also has some limitations. First, it was a single center study and a relatively small number of patients was included. Consequently, the *CYP2C19*17* allele variant was only present in 2 patients. Also, our series of patients contained a small number of PMs (14/106, 13.2%) patients. Second, the focus of our study was on the influence of genetic polymorphisms in the *CYP2C19* gene on VCZ pharmacokinetics, but the clinical outcome was not evaluated.

## 5. Conclusion

The VCZ $C_0$/dose and the *CYP2C19* genotype were significantly correlated in a population of South-western Chinese Han patients. *CYP2C19* genotype explains part of the wide inter-individual variability in VCZ pharmacokinetics. In South-western Chinese Han patients more often suffer from over-exposure due to the presence of *CYP2C19* genotypes associated with poor or intermediate metabolism. *CYP2C19* genotype-based dosing combined with TDM will support individualization of VCZ dosing, and potentially will minimize toxicity and maximize therapeutic efficacy.

## Author contributions

Lan-Lan Wang and Yun-Ying Shi conceived and designed the study. Qiang Miao and Jiang-Tao Tang conducted the research, performed the data analysis and wrote the manuscript. Ya-Mei Li, Yang-Juan Bai, and Yuan-Gao Zou contributed to performing the experiments, acquiring data and played an important role in interpreting the results. Teun van Gelder revised the manuscript with constructive discussions. All authors contributed equally to the drafting of this manuscript.

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