Impact of cytochrome P450 2C19 polymorphisms on the clinical efficacy and safety of voriconazole: an update systematic review and meta-analysis

Ying Zhang[1], Xu Hao[1], Kelu Hou[1], Lei Hu[1], Jingyuan Shang[1], Shiyu He[1], Changqing Yang[2], Yufei Feng[1], and Lin Huang[1]

[1]Peking University People's Hospital
[2]China Pharmaceutical University

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Abstract

Aims: To assess the impact of cytochrome P450 (CYP) 2C19 polymorphisms on the clinical efficacy and safety of voriconazole. Methods: We systematically searched PubMed, EMBASE, CENTRAL, ClinicalTrials.gov, and three Chinese databases from their inception to March 18, 2021 using a predefined search algorithm to identify relevant studies. Studies that reported voriconazole-treated patients and information on CYP2C19 polymorphisms were included. The efficacy outcome was success rate. The safety outcomes included overall adverse events, hepatotoxicity and neurotoxicity. Results: A total of 20 studies were included. Intermediate metabolizers (IMs) and Poor metabolizers (PMs) were associated with increased success rates compared with normal metabolizers (NMs) (risk ratio (RR): 1.18, 95% confidence interval (CI): 1.03˜1.34, I2=0%, p=0.02; RR: 1.28, 95%CI: 1.06˜1.54, I2=0%, p=0.01). PMs were at increased risk of overall adverse events in comparison with NMs and IMs (RR: 2.18, 95%CI: 1.35˜3.53, I2=0%, p=0.001; RR: 1.80, 95% CI: 1.23˜2.64, I2=0%, p=0.003). PMs demonstrated a trend towards an increased incidence of hepatotoxicity when compared with NMs (RR: 1.60, 95%CI: 0.94˜2.74, I2=27%, p=0.08), although there was no statistically significant difference. In addition, there was no significant association between CYP2C19 polymorphisms and neurotoxicity. Conclusions: IMs and PMs were at a significant higher success rate in comparison with NMs. PMs were significantly associated with an increased incidence of all adverse events compared with NMs and IMs. Researches are expected to further confirm these findings. Additionally, the relationship between hepatotoxicity and CYP2C19 polymorphisms deservers clinical attention.

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[1] Department of Pharmacy, Peking University People's Hospital, Beijing, 100044, China;

[2] School of Basic Medicine and Clinical Pharmacy, China Pharmaceutical University, Nanjing, 211198, China;

* Corresponding authors at: Department of Pharmacy, Peking University People's Hospital, No. 11 Xizhimen South Street, Xicheng District, Beijing 100044, China. Email: huanglin@pkuph.edu.cn; fenyufei@126.com.

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The authors declare no competing interests.

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Ying Zhang: Formal analysis, Investigation, Writing-Original draft, Visualization. **Xu Hao:** Writing-Review & editing, Visualization. **Kelu Hou:** Methodology. **Lei Hu:**Software. **Shiyu He:** Resources, Data curation. **Jingyuan Shang:** Resources, Date curation. **Changqing Yang:** Supervision.**Lin Huang:** Conceptualization, Supervision, Funding acquisition.**Yufei Feng:** Supervision, Writing- Review & editing.

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Results: A total of 20 studies were included. Intermediate metabolizers (IMs) and Poor metabolizers (PMs) were associated with increased success rates compared with normal metabolizers (NMs) (risk ratio (RR): 1.18, 95% confidence interval (CI): 1.03˜1.34, I^2=0%, p=0.02; RR: 1.28, 95%CI: 1.06˜1.54,I^2=0%, p=0.01). PMs were at increased risk of overall adverse events in comparison with NMs and IMs (RR: 2.18, 95%CI: 1.35˜3.53, I^2=0%, p=0.001; RR: 1.80, 95% CI: 1.23˜2.64,I^2=0%, p=0.003). PMs demonstrated a trend towards an increased incidence of hepatotoxicity when compared with NMs (RR: 1.60, 95%CI: 0.94˜2.74, I^2=27%, p=0.08), although there was no statistically significant difference. In addition, there was no significant association between CYP2C19 polymorphisms and neurotoxicity.

Conclusions:IMs and PMs were at a significant higher success rate in comparison with NMs. PMs were significantly associated with an increased incidence of all adverse events compared with NMs and IMs. Researches are expected to further confirm these findings. Additionally, the relationship between hepatotoxicity and CYP2C19 polymorphisms deservers clinical attention.

Introduction

Invasive fungal diseases (IFDs) are associated with a high morbidity and mortality in the immunocompromised patient [1, 2]. Voriconazole is recommended as a first-line treatment for invasive aspergillosis also as antifungal prophylaxis in high-risk patients who are undergoing hematopoietic stem cell transplantation or immunocompromised[3-6]. Given the poor prognosis of patients with IFD, failure with voriconazole treatment potentially threatens life. In addition, the management and prevention of IFD requires substantial expenditures and places a heavy burden on the healthcare system [7]. Therefore, it is necessary to ensure efficacy and safety in clinical practice.

A major drawback of using voriconazole is its insufficient antifungal or higher incidence of hepatotoxic or neurotoxic events [8, 9]. The main source of variability in response to voriconazole may lie in its pharmacokinetics. Voriconazole presents extensive hepatic metabolism, predominantly by CYP2C19 [10]. The activity of

CYP2C19 shows large individual differences due to the existence of gene polymorphism [11]. There are five CYP2C19 phenotypes based on genotype that have been proposed for voriconazole by the clinical pharmacogenetics implementation consortium (CPIC) as follows: (1) normal metabolizers (NMs) (*1/*1) represents up to 50% of patients, (2) intermediate metabolizers (IMs) (*1/*2, *1/*3, *2/*17) accounts for ˜18-45% of patients, (3) poor metabolizers (PMs) (*2/*2, *3/*3, *2/*3) accounts for ˜2-15% of patients, (4) rapid metabolizers (RMs) (*1/*17) accounts for ˜2-30% of patients, (5) ultrarapid metabolizers (UMs) (*17/*17) accounts for ˜2-5% of patients [12].

As we know, the trough concentrations are associated with efficacy and toxicity of voriconazole in clinical practice [8, 9]. Recently, we have demonstrated quantitative relations between the CYP2C19 polymorphisms and voriconazole trough concentrations[13]. Accordingly, polymorphisms of the CYP2C19 have been associated with antifungal response and are supposed to predict the variability in clinical response to voriconazole [14]. However, published literatures have not consistently shown an association of CYP2C19 polymorphism with clinical response of voriconazole. The quantitative relations between the pairwise comparisons of CYP2C19 phenotypes in clinical outcome of voriconazole have been first summarized in a systematic review and meta-analysis abstracting data form 10 studies published up to January 2016[15]. The reported results showed that patients with PM phenotype had a significantly higher success rate compared with NMs, and there was no significant association between CYP2C19 polymorphisms and overall adverse events, hepatotoxicity and neurotoxicity. Notably, over the past five years, more and more studies in different countries investigated the impact of CYP2C19 polymorphisms on the clinical outcome of patients treated with voriconazole.

Therefore, we conducted an updated systematic review and meta-analysis of studies assessing the association between CYP2C19 polymorphisms and clinical outcomes of voriconazole. The aim of this study was to evaluate the nature and magnitude of the relationship of CYP2C19 polymorphisms with the efficacy and safety of voriconazole. Clarifying this relationship could have important clinical implications for future strategies in optimization of voriconazole.

Methods

Our study adhered to the PRISMA statements for reporting on systematic reviews [16].

2.1 Date sources and search strategy

We searched PubMed, EMBASE, CENTRAL, ClinicalTrials.gov, and three Chinese databases (CBM, CNKI, and WanFang) from their inception to March 18, 2021 without restrictions of language, age, or race. We applied the following search strategy: (CYP2C19 OR polymorphism OR genotype) AND (voriconazole OR Vfend). Furthermore, we searched references of available reviews for potential eligible studies.

2.2 Study selection

Two researchers independently screened titles and abstracts generated by search after removing duplicates in EndNote, and then full texts were required to explore eligible studies. Disagreements were resolved by discussion.

Prospective or retrospective studies were included if they were peer reviewed original reports or original date can be fully accessed. We considered reports that evaluated the association of genetic variants of CYP2C19 with the occurrence of efficacy and safety in patients who were taken with voriconazole. We excluded studies not reporting outcomes separately based on CYP2C19 genotypes or phenotypes.

2.3 Outcome measures

We assessed outcome measures based on the following predefined definitions: (1) given the definition of treatment/prophylaxis success inconsistent among the included studies, we used the criteria from each study, (2) overall adverse events were defined as all adverse events regardless of their causal relationship with voriconazole, (3) hepatotoxicity was defined as abnormal liver function after voriconazole initiation, (4) neurotoxicity included headache, vertigo, encephalopathy, hallucinations, confusion, or seizures.

2.4 Quality assessment

The quality of the included studies was assessed using the STRAGE recommendations for reports on genetic association studies[17]. The quality evaluation items were: (1) clear statement of objectives and hypothesis, (2) clear eligibility criteria for study participants, (3) clear definition of all variables, (4) clear definition of the outcome, (5) credible genetic testing method, (6) replicability of statistical method, (7) assessment of Hardy-Weinberg equilibrium (HWE), (8) sufficient descriptive demographic data, (9) clear report of dropout and reasons, (10) statement of outcome data. Each item was recorded as "+" or "-", depending on whether it was described in the text.

2.5 Data extraction

Using a standardized form, two authors reviewed and recorded independently the author's last name and year of publication, patients' demographic characteristics (sample size, age, sex), study design, region and ethnicity, the purpose of voriconazole (treatment or prophylaxis), administration of voriconazole, outcome measures (type, number of events and total sample size according to phenotypes), method of genotype measured, CYP2C19 phenotypes. Give the similar activity and the limited sample size of RMs and UMs, we combined them into one group as UMs. Missing date for two studies[18, 19] were extracted from a previous meta-analysis[15].

2.6 Statistical analysis

We calculated risk ratio (RR) and 95% confidence intervals (CI) for summary effect based on phenotypes. Statistical significance of the summary estimates is determined by Z-tests, and $p<0.05$ indicated statistical significance. The I^2statistic was performed to measure heterogeneity among studies. WhenI^2[?]50%, a fixed-effects model was used to derived pooled estimates. Otherwise, a random-effects model was applied. For each outcome, we performed subgroup analysis according to the purpose of voriconazole and ethnicity. To explore the probable sources of heterogeneity among the studies and to assess the robustness of the pooled estimates, we conducted a sensitivity analysis by eliminating each study one by one. Publication bias among studies was assessed using Begg's test and Egger's test. Statistical analysis was performed with Microsoft excel 2019, Review Manger 5.4 and Stata version 16.0.

Result

3.1 Literature search

We identified 3140 records by the literature search (Figure 1), and 1881 remained after removal of duplicates. After screening of titles and abstracts, 36 articles were retrieved for full text assessment. Of these, 16 articles were excluded, mainly because they reported other outcomes. In addition, one study by Fu *et al* [18]beyond our search, but it was included in the previous meta-analysis, and thus we included it. Overall, 20 studies were included in the meta-analysis [14, 18-36].

3.2 Characteristics of included studies

The detailed characteristics of individual study are presented in Table 1. Years of publication ranged from 2011 to 2020. The participants were all adults. Most of these studies were carried out in Asia (China, Korea). Voriconazole was used for treatment in most studies, and for prophylaxis in three studies [23, 24, 26], as well as for treatment or prophylaxis in three studies [18, 22, 25]. Most studies followed the standard dosing of 6mg/kg (IV)/400mg (Oral) twice daily on day 1 for load and 4mg/kg (IV)/200mg (Oral) twice daily for maintenance. There were four studies with genotype-directed dosing. Two of them reported that NMs, IMs and PMs initiated voriconazole at 200 mg twice daily, whereas UMs initiated voriconazole at 300 mg twice daily[23, 26]. Two of them reported that IMs and PMs initiated voriconazole at 200 mg twice daily, whereas NMs initiated voriconazole at 400 mg twice daily [29, 31]. Thus, we excluded those non-standard dosing groups when conducted analysis. One study was performed on healthy men [28]. Only a few participants were UMs.

3.3 Quality assessment

A summary of quality of included studies is presented in Table 2. Except the HWE, all items were described in most of these studies and we graded them as relatively high quality. Two studies [18, 19] did not state outcome data in text but we could acquire them from the previous meta-analysis[15], which were acceptable for this meta-analysis.

3.4 Success rate

Eight studies explored the association of CYP2C19 phenotype with the efficacy outcome of success rate [18, 19, 26, 29, 30, 32, 33, 35]and meta-analysis results were shown in Table 3. Overall, IMs and PMs were at significant higher success rate in comparison with NMs (RR: 1.18, 95%CI: 1.03˜1.34,I^2=0%, P=0.02 and RR: 1.28, 95%CI: 1.06˜1.54, I^2=0%, p=0.01, respectively) in all studies [18, 19, 26, 30, 32, 33, 35]. There was no significant difference in comparisons between PMs and IMs (RR: 1.04, 95%CI: 0.92˜1.18,I^2=0%, p=0.54) [18, 19, 26, 29, 30, 32, 33, 35]. We were unable to analyze the difference of success rate between UMs and NMs because there was no eligible study reported the data of UMs. Sensitivity analysis on each comparison showed that results were reliable.

Results of subgroups analysis were shown in Table 3. In the treatment group and the Asians group, results were almost unchanged. There was only one study reported data in the prophylaxis and the Caucasians group, thus we didn't conduct meta-analysis [26].

3.5 Overall adverse events

The most common reported adverse reactions were visual disturbances, fever, nausea, rashes, vomiting, chills, headache, liver function test abnormal, tachycardia and hallucinations.

Thirteen studies analyzed the association of CYP2C19 phenotype with the safety outcome of overall adverse events [14, 21, 25-35]and meta-analysis results were shown in Table 4. In total, PMs were at increased risk of overall adverse events in comparison with NMs (RR:2.18, 95% CI: 1.35˜3.53,I^2=37%, p=0.001) [21, 25, 26, 28, 30, 32-35] and IMs (RR: 1.80, 95% CI: 1.23˜2.64,I^2=0%, p=0.003) [21, 25, 26, 28-35]. There were no significant differences in other comparisons. Sensitivity analysis showed the results did not alter significantly in all comparisons.

Subgroup analysis revealed that the results in groups treatment and Asians were not significantly changed. However, in the subgroup of Caucasians, there were a limited number of studies (2˜4) and no significant differences were found in all comparisons (Table 4). For the subgroup of prophylaxis, there was only one study reported data that five patients experienced a grade 3 adverse events (one IMs, one NMs, and two UMs) [26].

3.6 Hepatotoxicity

Eight studies investigated the association of CYP2C19 phenotype with the safety outcome of hepatotoxicity [20-24, 34-36] and meta-analysis results were shown in Table 5. Our meta-analysis exhibited no statistically significant differences at all comparisons. However, the PMs showed a toward of higher risk of hepatotoxicity than NMs in all studies (RR: 1.60, 95%CI: 0.94˜2.74,I^2=27%, p=0.08) [20-23, 34-36]. Sensitivity analysis showed the results did not alter significantly in all comparisons, but, the result of the comparison between PMs and NMs (RR: 2.38, 95%CI: 1.25˜4.52,I^2=0%, p=0.008) became statistically significant after excluding study by Kim *et al*[35].

Subgroup analysis revealed that the results were not significantly changed in all subgroups. (Table 5)

3.7 Neurotoxicity

Four studies investigated the association of CYP2C19 phenotype with the safety outcome of neurotoxicity [21, 23, 24, 35] and meta-analysis results were shown in Table 6. Our meta-analysis exhibited no statistically significant differences for all comparisons in all studies and all subgroups. Sensitivity analysis showed the results were not altered essentially.

Subgroup analysis revealed that the results were not significantly changed in all subgroups. (Table 6)

3.8 Publication bias

Given the limited number of studies, we only performed publication bias at the comparison between IMs and PMs for safety outcome of overall adverse events (11 studies). No evidence of publication bias was observed by Begg's test (p=1.8805) and Egger's test (p=0.2510).

Discussion

Our update meta-analysis included a total of 20 studies of different countries. The meta-analysis suggested that the success rate and overall adverse events were strongly influenced by CYP2C19 polymorphisms. There was no significant association between CYP2C19 polymorphisms and hepatotoxicity or neurotoxicity. The meta-analysis showed that IMs and PMs were at a significant higher success rate in comparison with NMs. PMs were significantly associated with an increased incidence of all adverse events compared with NMs and IMs. In addition, PMs were more likely to experience hepatotoxicity than NMs, although there were no statistically significant differences.

Our findings reinforced a significant association between the CYP2C19 polymorphism and success rate of voriconazole. We found that PMs had a higher success rate than NMs, which was consistent with a previous meta-analysis by Li *et al* published in 2016 (n=4 studies, RR: 1.31, 95%CI: 1.04˜1.67,I^2=0%, p=0.02) [15]. Notably, the result of our meta-analysis indicated that IMs also had a higher success rate than NMs, which was in line with the higher voriconazole concentrations observed in PMs and IMs compared with NMs[13]. The above findings suggested that NMs might need to increase the standard dose of voriconazole. The magnitude of these results remained essentially unaltered in subgroups of the treatment and Asians. Owing to the scarce data, subgroups analysis could not be performed at subgroups of the prophylaxis and Caucasians.

PMs had a significant higher risk of the overall adverse events than NMs and IMs in the meta-analysis. Notably, when the analysis was stratified by ethnicity, the statistically significant difference disappeared in Caucasians. However, in subgroup of Asians, PMs remained at increased risk of the overall adverse events compared with NMs and IMs, suggesting that PMs might be relatively important for Asians and subsequently susceptible to adverse events while taking voriconazole. In addition, the significant difference remained in the subgroup of the treatment. Given the limited studies focusing on the subgroups of prophylaxis, the relationship of overall adverse events between PMs and NMs warrants further evaluation.

The meta-analysis suggested that there was no statistically significant association of the CYP2C19 phenotype with hepatotoxicity, which was in line with the results of a previous meta-analysis. Besides, the conclusion of several original researches did not support a link between the CYP2C19 phenotype status and hepatotoxicity [37-39]. However, it should be noted that PMs showed a trend towards a higher risk of hepatotoxicity compared with NMs. In addition, when we excluded study by Kim *et al* [35] in the process of sensitivity analysis, the result became statistically significant. This may be due to the current use of therapeutic drug monitoring (TDM) minimized their connection in this study. The lack of significance did not rule out the existence of a true causal relationship between hepatotoxicity and CYP2C19 phenotype status. More large trials are required to clarify the association.

There were no significant differences in association of CYP2C19 polymorphisms with neurotoxicity. The neurotoxicity such as hallucinations, headache, and dizziness are central nervous system disorders. Voriconazole is lipophilic, demonstrates a large volume of distribution (4.61L/kg) and is able to penetrate the blood-brain barrier. Lutsar *et al* [40] reported that the median ratio of cerebrospinal fluid to plasma concentration of voriconazole was 0.46 in immunocompetent patients, and the voriconazole concentrations of brain/plasma ratios were 2˜3 in healthy adults [41], which might have contributed to neurotoxicity. The lack of significance did not rule out the existence of a true causal relationship between neurotoxicity and CYP2C19 phenotype status. Apart from genetic polymorphisms, several other factors such as concomitant medications and patients' pathophysiological status might also contribute to clinical outcomes [42, 43]. More large trials are required to clarify the association of CYP2C19 polymorphisms with neurotoxicity.

To our knowledge, the meta-analysis assessing the association of CYP2C19 polymorphisms with efficacy and safety of voriconazole was the largest assessment to date. Our findings corroborated and extended the results of previous small meta-analysis. However, our meta-analysis had some limitations that should be mentioned. First, heterogeneity existed in criteria of treatment success, which means comparisons were indirect. Second, included studies varied in some aspects, such as comorbidities, infectious pathogen, site of infection, concomitant medicines and method of genotyping, which could be effect modifiers. Third, six studies located in Asia only detected alleles CYP2C19*2 and CYP2C19*3, and thus patients carrying CYP2C19*17 were classified to NMs who are assigned by default if CYP2C19*2, CYP2C19*3 and CYP2C19*17 are not detected. However, the frequency of CYP2C19*17 is present very low in Asian population (0.15˜0.44%) [44]. Clearly, studies including an adequate number of all four CYP2C19 alleles are needed to explore its relationship with the efficacy and safety of voriconazole.

Conclusions

In summary, the update meta-analysis supported CYP2C19 polymorphisms were related with clinical outcomes. Compared with NMs, IMs and PMs had significantly higher success rates. Additionally, PMs were significantly associated with an increased incidence of all adverse events compared with NMs and IMs. Therefore, there is a likelihood to guide personalized treatment with voriconazole based on CYP2C19 polymorphisms. Additionally, hepatotoxicity is a common adverse event in patients taking voriconazole and our study suggested that the relationship between hepatotoxicity and CYP2C19 polymorphisms deserves clinical attention. Researches are expected to further confirm these findings.

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Table 1 Characteristics of included studies

Study	Sample size	Age (year)	Male (%)	Study design	Region/ethnicity	Purpose of voriconazole	Dosing	Outcome	Alleles	Method of genotype measured	CYP2C19 phenotype	CYP2C19 phenotype	CYP2C19 phenotype
											NMs	IMs	PMs
[a]Li 2020[32]	14	57.66±12.54	64	Prospective	China/East Asian	treatment	iv loading dose: 6mg/kg (q12h); maintenance dose: 4mg/kg (q12h)	Success rate Overall adverse events	*2 *3 *17	RT-PCR	20	9	9
Li-I 2019[34]	11	61.13±17.76	63	Retrospective	China/East Asian	treatment	iv 200mg (q12h); po 100-300mg (bid)	Overall adverse events Hepatotoxicity	*2 *3	PCR-chip hybridization	5	9	2
Li-U 2019[33]	15	41.9±28.12	9	Prospective	China/East Asian	treatment	Adult iv/po loading dose 400mg (q12h), maintenance dose 200mg (q12h); Child 4mg/kg (q12h)	Success rate Overall adverse events	*2 *3	PCR-chip hybridization	27	12	3

Study	Sample size	Age (year)	Male (%)	Study design	Region/ethnicity	Purpose of voriconazole	Dosing	Outcome	Alleles	Method of genotype measured	CYP2C19 phenotype	CYP2C19 phenotype	CYP2C19 phenotype
Wang 2018[20]	141	60±20	67	Retrospective	China/East Asian	treatment	according to package insert	Hepatotoxicity	*2 *3 *17	NR	62	62	17
Sienkiewicz 2018[24]	30	52(median)	63	Prospective	Poland/European	prophylaxis	according to package insert	Neurotoxicity Hepatotoxicity	*1 *2 *17	PCR-RFLP	4	15	/
Song 2019[36]	25	57.04±18.66 50.30+-19.45(DILI case)	36(control)	Prospective	China/East Asian	treatment	iv loading dose 6mg/kg (bid), maintenance dose 4mg/kg (bid); po loading dose 400mg (bid), maintenance dose 200mg (bid)	Hepatotoxicity	*2 *3	gene chip hybrid	13	21	4
Wang 2016[22]	63	56-85	70	Prospective	China/East Asian	treatment/ prophylaxis	according to package insert	Hepatotoxicity	*2 *3 *17	Sequenom MassARRAY	31	24	8

Study	Sample size	Age (year)	Male (%)	Study design	Region/ethnicity	Purpose of voriconazole	Dosing	Outcome	Alleles	Method of genotype measured	CYP2C19 phenotype	CYP2C19 phenotype	CYP2C19 phenotype
Blanco 2020[25]	78	68 (19-93)	55	Prospective	Spain/European	treatment/prophylaxis	iv maintenance dose 200mg (bid); iv loading dose 5.90±0.73mg/kg (bid), maintenance dose 3.79±0.79mg/kg (bid)	Overall adverse events	*2, *3, *4, *5, *6, *7, *8, *10, *17.	real-time PCR with Taqman probes and Open Array technology	34	20	1
[b]Niu 2018[29]	30	71.15±14.53	33	Prospective	China/East Asian	treatment	iv loading dose 400mg (q12h); maintenance dose: NM 400mg; IM and PM 200mg (q12h)	Success rate Overall adverse events	*2 *3 *17	PCR-RFLP	10	18	12

Study	Sample size	Age (year)	Male (%)	Study design	Region/ethnicity	Purpose of voriconazole	Dosing	Outcome	Alleles	Method of genotype measured	CYP2C19 phenotype	CYP2C19 phenotype	CYP2C19 phenotype
[b]Zuo 2020[31]	78	NR	NR	Prospective	China/East Asian	treatment	iv loading dose 400mg (q12h); maintenance dose: NM 400mg; IM and M200mg (q12h)	Overall adverse events	*2 *3 *17	NA	25	47	31
[b]Hicks 2020[23]	127	64 (19-81)	52	Prospective	USA/North America	prophylaxis	po NM, IM, and PM 200mg (q12h); UM 300mg (q12h)	Neurotoxicity Hepatotoxicity	*2 *3 *17	Luminex xTAG CYP2C19 Kit version 3	64	56	7
[b]Patel 2020[26]	50	54.0±14.6	62	Prospective	USA/North America	prophylaxis	po NM, IM, and PM 200mg (q12h); UM 300mg (q12h)	Success rate Overall adverse events	*2 *3 *17	TaqMan Drug Metabolism Genotyping Assays	24	23	3

Study	Sample size	Age (year)	Male (%)	Study design	Region/ethnicity	Purpose of voriconazole	Dosing	Outcome	Alleles	Method of genotype measured	CYP2C19 phenotype	CYP2C19 phenotype	CYP2C19 phenotype
Berge 2011[27]	24	26±7	46	Retrospective	France/European	treatment	iv loading dose 6mg/kg (q12h); maintenance dose: adjusted for administration route and body weight	Overall adverse events	*2 *17	real-time polymerase chain reaction	7	10	
Kim 2011[21]	19	19-37	48	Prospective	Korea/East Asian	treatment	iv loading dose 6mg/kg (q12h); maintenance dose 4mg/kg (q12h)	Overall adverse events Hepatotoxicity Neurotoxicity	*2 *3	RFLP	6	17	2

Study	Sample size	Age (year)	Male (%)	Study design	Region/ethnicity	Purpose of voriconazole	Dosing	Outcome	Alleles	Method of genotype measured	CYP2C19 phenotype	CYP2C19 phenotype	CYP2C19 phenotype
[a]Kim 2013[35]	65	53±12	52	Prospective	Korea/East Asian	treatment	iv loading dose 6mg/kg (bid); maintenance dose 4mg/kg (bid) or po 200mg (bid)	Success rate Overall adverse events Hepatotoxicity Neurotoxicity	*2 *3 *17	multiplex polymerase chain reaction	39	50	15
Wang 2014[19]	144	60.6±13.5	67	Retrospective	China/East Asian	treatment	according to package insert	Success rate	*2 *3 *17	NR	62	62	17
Liang 2015[30]	42	60.2±14.9	65	Retrospective	China/East Asian	treatment	iv loading dose 300mg (q12h); maintenance dose 200mg (q12h)	Success rate Overall adverse events	2 *3	PCR	7	30	12
Trubiano 2015[14]	19	64 (median)	63	Prospective	Australia/Oceanian	treatment	iv loading dose 6mg/kg (q12h); maintenance dose 4mg/kg (q12h)	Overall adverse events	*1 *2 *3 *17	PCR and RFLP	8	5	/

Study	Sample size	Age (year)	Male (%)	Study design	Region/ethnicity	Purpose of voriconazole	Dosing	Outcome	Alleles	Method of genotype measured	CYP2C19 phenotype	CYP2C19 phenotype	CYP2C19 phenotype
Lee 2012[28]	18	20-50	100	Prospective	Korea/Asian	trial	200mg po bid	Overall adverse events	*2 *3 *17	TaqMan allelic discrimination assays	6	6	6
Fu 2013[18]	10	22-83	67	Prospective	China/East Asian	treatment/prophylaxis	200-400mg	Success rate	*2 *3	NR	2	7	3

NMs: normal metabolizers (CYP2C19*1/*1); IMs: intermediate metabolizers (CYP2C19*1/*2, CYP2C19*1/*3, CYP2C19*2/*17); PMs: poor metabolizers (CYP2C19*2/*2, CYP2C19*3/*3, CYP2C19*2/*3); UMs: ultra-rapid metabolizers (CYP2C19*1/*17, CYP2C19*17/*17); NR: not reported; NA: not available; "/" means no data.

a: in this study, patient with CYP2C19*1/*1, CYP2C19*1/*17 genotype was assigned as NMs groups.

b: the initial dosage regimen was different between CYP2C19 phenotype status.

Table 2 Genetic quality assessment of included studies

study	Clear statement of objectives and hypothesis	Clear eligibility criteria for study participants	Clear c
Li 2020[32]	+	+	+
Li-I 2019[34]	+	-	+
Li-U 2019[33]	+	+	+
Wang 2018[20]	+	+	+
Sienkiewicz 2018[24]	+	-	+
Song 2019[36]	+	+	+
Wang 2016[22]	+	+	+
Blanco 2020[25]	+	+	+
Niu 2018[29]	+	+	+
Zuo 2020[31]	+	+	+
Hicks 2020[23]	+	+	+
Patel 2020[26]	+	+	+
Berge 2011[27]	+	+	+
Kim 2011[21]	+	+	+
Kim 2013[35]	+	+	+
Wang 2014[19]	+	+	+
Liang 2015[30]	+	+	+
Trubiano 2015[14]	+	+	+
Lee 2012[28]	+	+	+
Fu 2013[18]	+	+	+

"+" detailed description, "-"no description

Table 3 Results of meta-analysis of success rate

Table 3 Results of meta-analysis of success rate

Success rate	Success rate	Success rate	Comparison	IMs vs NMs	PMs vs NMs
All	All	All	n	7	7
			RR(95%CI)	**1.18 [1.03, 1.34]**	**1.28 [1.06, 1.54]**
			Heterogeneity(I^2)	0	0
			Z tests (P)	0.02	0.01
			Refs.	18, 19, 26, 30, 32, 33, 35	18, 19, 26, 30, 32, 33
Subgroups	Purpose of voriconazole	Treatment	n	5	5
			RR(95%CI)	**1.18 [1.02, 1.38]**	**1.35 [1.11, 1.65]**
			Heterogeneity(I^2)	0	0
			Z tests (P)	0.03	0.003
			Refs.	19, 30, 32, 33, 35	19, 30, 32, 33, 35
		Prophylaxis	n	1	1
			Refs.	26	26
	Ethnicity	Asians	n	6	6
			RR(95%CI)	**1.18 [1.02, 1.36]**	**1.31 [1.08, 1.59]**
			Heterogeneity(I^2)	0	0
			Z tests (P)	0.03	0.006
			Refs.	18, 19, 30, 32, 33, 35	18, 19, 30, 32, 33, 35
		Caucasians	n	1	1
			Refs.	26	26

NMs: normal metabolizers (CYP2C19*1/*1); IMs: intermediate metabolizers (CYP2C19*1/*2, CYP2C19*1/*3, CYP2C19*2/*17); PMs: poor metabolizers (CYP2C19*2/*2, CYP2C19*3/*3, CYP2C19*2/*3); UMs: ultra-rapid metabolizers (CYP2C19*1/*17, CYP2C19*17/*17); "/" means no data.

Table 4 Results of meta-analysis of overall adverse events

Overall adverse events	Overall adverse events	Overall adverse events	comparison	IMs vs NMs
All	All	All	n	11
			RR(95%CI)	1.22 [0.87, 1.73]
			Heterogeneity(I^2)	0
			Z tests (P)	0.25
			Refs.	14, 21, 25, 26, 27, 28, 30, 3
Subgroups	Purpose of voriconazole	Treatment	n	8
			RR(95%CI)	1.24 [0.85, 1.80]
			Heterogeneity(I^2)	0
			Z tests (P)	0.26
			Refs.	14, 21, 27, 30, 32, 33, 34, 3
		Prophylaxis	n	1
			Refs.	26
	Ethnicity	Asians	n	7
			RR(95%CI)	1.32 [0.85, 2.05]
			Heterogeneity(I^2)	0
			Z tests (P)	0.21
			Refs.	21, 28, 30, 32, 33, 34, 35
		Caucasians	n	4
			RR(95%CI)	1.05 [0.61, 1.83]
			Heterogeneity(I^2)	0

Overall adverse events	Overall adverse events	Overall adverse events	comparison	IMs vs NMs
			Z tests (P)	0.85
			Refs.	14, 25, 26, 27

NMs: normal metabolizers (CYP2C19*1/*1); IMs: intermediate metabolizers (CYP2C19*1/*2, CYP2C19*1/*3, CYP2C19*2/*17); PMs: poor metabolizers (CYP2C19*2/*2, CYP2C19*3/*3, CYP2C19*2/*3); UMs: ultra-rapid metabolizers (CYP2C19*1/*17, CYP2C19*17/*17); "/" means no data.

Table 5 Results of meta-analysis of hepatotoxicity

Hepatotoxicity	Hepatotoxicity	Hepatotoxicity	Hepatotoxicity	comparison	IMs vs NMs
All	All	All	All	n	8
				RR(95%CI)	1.19 [0.80, 1.77]
				Heterogeneity(I^2)	0
				Z tests (P)	0.4
				Refs.	20, 21, 22, 23, 24, 34,
Subgroups	Purpose of voriconazole	Treatment	n	n	5
			RR(95%CI)	RR(95%CI)	1.27 [0.79, 2.02]
			Heterogeneity(I^2)	Heterogeneity(I^2)	0
			Z tests (P)	Z tests (P)	0.32
			Refs.	Refs.	20, 21, 34, 35, 36
		Prophylaxis	n	n	2
			RR(95%CI)	RR(95%CI)	0.63 [0.22, 1.78]
			Heterogeneity(I^2)	Heterogeneity(I^2)	0
			Z tests (P)	Z tests (P)	0.38
			Refs.	Refs.	23, 24
	Ethnicity	Asians	n	n	6
			RR(95%CI)	RR(95%CI)	1.35 [0.87, 2.09]
			Heterogeneity(I^2)	Heterogeneity(I^2)	0
			Z tests (P)	Z tests (P)	0.18
			Refs.	Refs.	20, 21, 22, 34, 35, 36
		Caucasians	n	n	2
			RR(95%CI)	RR(95%CI)	0.63 [0.22, 1.78]
			Heterogeneity(I^2)	Heterogeneity(I^2)	0
			Z tests (P)	Z tests (P)	0.38
			Refs.	Refs.	23, 24

NMs: normal metabolizers (CYP2C19*1/*1); IMs: intermediate metabolizers (CYP2C19*1/*2, CYP2C19*1/*3, CYP2C19*2/*17); PMs: poor metabolizers (CYP2C19*2/*2, CYP2C19*3/*3, CYP2C19*2/*3); UMs: ultra-rapid metabolizers (CYP2C19*1/*17, CYP2C19*17/*17); "/" means no data.

Table 6 Results of meta-analysis of neurotoxicity

Neurotoxicity	Neurotoxicity	Neurotoxicity	comparisons	IMs vs NMs	PMs vs NMs	UMs vs
All	All	All	n	4	3	1
			RR(95%CI)	0.67[0.34, 1.34]	1.28 [0.39, 4.20]	/
			Heterogeneity(I^2)	0	0	/
			Z tests (P)	0.26	0.68	/
			Refs.	21, 23, 24, 35	21, 23, 35	24

Neurotoxicity	Neurotoxicity	Neurotoxicity	comparisons	IMs vs NMs	PMs vs NMs	UMs vs
Subgroups	Purpose of voriconazole	Treatment	n	2	2	0
			RR(95%CI)	0.69[0.13, 3.74]	2.51 [0.47, 13.37]	/
			Heterogeneity(I^2)	0	0	/
			Z tests (P)	0.66	0.28	/
			Refs.	21, 35	21, 35	/
		Prophylaxis	n	2	1	1
			RR(95%CI)	0.83 [0.21, 3.33]	/	/
			Heterogeneity(I^2)	53	/	/
			Z tests (P)	0.8	/	/
			Refs.	23, 24	23	24
	Ethnicity	Asians	n	2	2	0
			RR(95%CI)	0.69[0.13, 3.74]	2.51 [0.47, 13.37]	/
			Heterogeneity(I^2)	0	0	/
			Z tests (P)	0.66	0.28	/
			Refs.	21, 35	21, 35	/
		Caucasians	n	2	1	1
			RR(95%CI)	0.83 [0.21, 3.33]	/	/
			Heterogeneity(I^2)	53	/	/
			Z tests (P)	0.8	/	/
			Refs.	24, 24	23	24

NMs: normal metabolizers (CYP2C19*1/*1); IMs: intermediate metabolizers (CYP2C19*1/*2, CYP2C19*1/*3, CYP2C19*2/*17); PMs: poor metabolizers (CYP2C19*2/*2, CYP2C19*3/*3, CYP2C19*2/*3); UMs: ultra-rapid metabolizers (CYP2C19*1/*17, CYP2C19*17/*17); "/" means no data.

Figure legends

Figure 1. Flow chart of eligible studies.