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Efficacy and safety of isavuconazole versus voriconazole for the treatment of invasive fungal infections: a meta-analysis with trial sequential analysis

Jianzhen Weng[1], Xiaoman Du[1], Baomin Fang[1], Yanming Li[1], Lixue Huang[1] and Yang Ju[1*]

Abstract

Background Isavuconazole has been used to treat invasive fungal infections, however, it is unclear whether the efficacy of isavuconazole is superior to that of voriconazole. The purpose of this meta-analysis was to assess the efficacy and safety of isavuconazole compared to voriconazole in treating invasive fungal infections.

Methods Electronic databases, including PubMed, EMBASE, Cochrane Library, and Web of Science, were searched to identify relevant studies. Studies evaluating the effect of isavuconazole in the treatment of patients with invasive fungal infections were included. Pooled rates of overall response, all-cause mortality, drug-related adverse events (AEs), and discontinuation due to drug-related AEs were calculated.

Results Seven studies involving 890 patients were included. Meta-analysis showed that there was no significant difference between isavuconazole and voriconazole in overall response (risk ratio [RR]: 1.02, 95% confidence interval [CI]: 0.83 to 1.25, $p=0.86$) and all-cause mortality (RR: 0.95, 95% CI: 0.78 to 1.16, $p=0.61$). However, isavuconazole had a significantly lower incidence of drug-related AEs (RR: 0.70, 95% CI: 0.61 to 0.81, $p<0.001$) and discontinuation due to drug-related AEs (RR: 0.56, 95% CI: 0.39 to 0.82, $p=0.003$) compared with voriconazole. Trial sequential analysis (TSA) confirmed that the difference between isavuconazole and voriconazole in discontinuation due to drug-related AEs need further valiadation, but the results of other outcomes were conclusive.

<0.001) and discontinuation due to drug-related AEs (RR: 0.56, 95% CI: 0.39 to 0.82, $p=0.003$) compared with voriconazole. Trial sequential analysis (TSA) confirmed that the difference between isavuconazole and voriconazole in discontinuation due to drug-related AEs needs further validation, but the results of other outcomes were conclusive.

Conclusions Our findings support the use of isavuconazole as the primary therapy for invasive fungal infections. More research is needed to compare the discontinuation rates of isavuconazole and voriconazole.

Keywords Invasive fungal infections, Isavuconazole, Voriconazole, Meta-analysis, Trial sequential analysis

Introduction

Invasive fungal infections, such as invasive mucormycosis (IM) and invasive aspergillosis (IA), are life-threatening conditions [1]. *Aspergillus* and *Mucor spp.* are recognized causative agents of invasive fungal infections in a variety of high-risk and immunocompromised populations, such as transplant recipients and older individuals [2],

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accounting for a large proportion of all reported morbidity and mortality due to fungal disease [3]. The global annual incidence of IM is estimated to be over 10,000 with mortality rates of 35–96% [4], and the annual incidence of IA is 300,000 cases with and mortality rates of 30–70% [5, 6]. As a result, selecting effective treatments for invasive fungal infections is crucial for achieving successful outcomes while minimizing the risk of mortality, antifungal-related toxicity, and the development of drug resistance.

Currently, three types of antifungal agents are available for the treatment of invasive fungal infections, including polyenes, echinocandins, and triazoles [7, 8], however, each of these medications has serious drawbacks [9–11]. Polyenes have a limited role due to toxicity concerns and the need for intravenous delivery although they (e.g., amphotericin B) may be the preferred drug for invasive pulmonary mucormycosis [10]. Echinocandins are effective for treating invasive pulmonary mucormycosis and aspergillosis, however, they are usually employed as a rescue therapy or in combination with azoles and is expensive [8, 9]. Furthermore, several concerns are proposed to be related to the use of voriconazole although it may be the preferred drug for invasive pulmonary aspergillosis, such as medication interactions, pharmacokinetic variability, and toxicities [11]. Moreover, other antifungal such as fluconazole even showed ineffective in treating invasive fungal infections [7, 8].

Isavuconazole is a new triazole antifungal drug with an extensive antifungal spectrum [12]. Due to the steady rise in azole resistance and the adverse effects associated with previous azoles, Isavuconazole has emerged as an attractive candidate for the treatment of invasive fungal infections [13–17]. Isavuconazole has 98% oral bioavailability and does not require food for administration, unlike some formulations of itraconazole and posaconazole [17]. Isavuconazole shows broad tissue distribution and protein-binding ability [18], so compared with posaconazole and voriconazole, it has higher or equivalent fungicidal activity against A fumigatus, and can often show activity against isolates resistant to itraconazole, caspofungin and amphotericin B [18]. In addition, isavuconazole has lower toxicity and fewer drug interactions compared to other triazoles [19], and there is also no need for isavuconazole dosage adjustment based on age or renal function impairment [20, 21].

A recent meta-analysis [22] evaluating the role of isavuconazole in treating patients with invasive fungal infections was limited by heterogeneous control treatments, which included amphotericin B, voriconazole, and posaconazole. Furthermore, it overlooked some important outcomes such as overall response and the risk of drug-related adverse events (AEs). More importantly, due to the limited sample size of each included study, it is unclear whether definitive conclusions can be drawn. Therefore, this meta-analysis aimed to further evaluate the efficacy and safety of isavuconazole versus voriconazole in the treatment of invasive fungal infections by incorporating trial sequential analysis.

Material and methods

The current meta-analysis was conducted in accordance with the Cochrane handbook for systematic review [23], and we reported this meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist [24]. Ethical approval was not required for this meta-analysis as we collected only from published studies but not from patients.

Search strategy

We electronically searched four databases including PubMed, EMBASE, Cochrane Library and Web of Science to identify relevant studies. We constructed the search strategy using a combination of medical subject heading (MeSH) and text words. Detailed search strategies for all databases are summarized in Supplementary Table 1. In addition, we manually checked the reference lists of eligible studies and topic-related reviews to retrieve additional studies. All search strategies were limited to English literature but did not restrict publication status.

Selection criteria

We introduced the PICOS acronym to guide study selection: participants (P): adult patients diagnosed with proven, probable, or possible invasive fungal infections (IFIs) primarily caused by *Aspergillus spp.*; intervention (I) and comparison (C): patients in the study group treated with isavuconazole, and patients in the control group who received voriconazole; outcome (O): studies reported at least one of overall response, all-cause mortality, drug-related AEs, or discontinuation due to study-drug-related AEs; study design (S): this meta-analysis included only comparative studies, such as randomized controlled trials (RCTs) and prospective or retrospective studies. In addition, conference abstracts with sufficient data were also considered eligible for inclusion.

Studies were judged ineligible for inclusion if they, (1) evaluated the synthetic effects of isavuconazole and other medications; (2) had an ineligible design, such as case reports, reviews, non-research letters, commentaries, or qualitative reports; (3) were experimental studies, such as animal and cell research; (4) were published in other languages than English; (5) were conference abstracts with insufficient data; or (6) were repeat reports of the same population.

Study selection

By using the EndNote X9 software, we first eliminated duplicate studies. The titles and abstracts of all articles were then independently reviewed by two authors (Weng Jianzhen and Du Xiaoman) to eliminate studies that weren't relevant. To identify which studies might meet the inclusion criteria, the two authors also read the full texts of the retained studies. The third senior author (Baomin Fang) was consulted to resolve any disagreements between the two authors regarding study selection.

Data extraction

Two authors (Weng Jianzhen and Du Xiaoman) independently extracted the following data from each study using a standardized information extraction table: basic information about the study (name of the first author, year of publication, region, study design, treatment details, and outcomes), baseline patient characteristics (sample size, gender ratio, average age of patients, type of infection, pathogens, and comorbidities), and the detailed information about the risk of bias.

Outcome definition

The current meta-analysis considered overall response and all-cause mortality as primary outcomes and drug-related AEs and discontinuation due to drug-related AEs as secondary outcomes. Overall response is crude treatment success as assessed by the Data Review Committee (DRC) at end of treatment (EOT), which is a composite of clinical, radiological, and mycological responses. All-cause mortality refers to all deaths occurring from study entry to EOT, regardless of the cause. Drug-related AEs include those reported as remotely, possibly, or probably related to the medication from the start of study treatment to EOT. Discontinuation due to drug-related AEs refers to discontinuation of treatment due to patients' intolerance to these adverse events.

Risk of bias assessment

This meta-analysis included both randomized and non-randomized studies for data analysis. Therefore, based on previous meta-analyses [22, 25], two authors (Weng Jianzhen and Du Xiaoman) independently assess the risk of bias of included studies using the Modified Downs and Black risk assessment tool [26]. This tool consists of 27 items covering reporting, external validity, internal validity-bias, internal validity-confounding (selection bias), and statistical power. The total score for risk of bias assessment ranges from 0 to 32, of which > 23 indicates low risk of bias, 16–23 indicates moderate risk of bias, and < 15 indicates high risk of bias.

Statistical analysis

We performed this meta-analysis using STATA 14.0 software (StataCorp LP, College Station, TX, USA) [27]. All outcomes were categorical variables, so we expressed estimates using risk ratio (RR) with 95% confidence interval (CI). We used Cochran's Q test and Higgins's inconsistency factor (I^2 statistics) [28] to evaluate statistical heterogeneity between studies. If significant statistical heterogeneity was found ($p < 0.1$ and $I^2 \geq 50\%$), a random-effects model was selected for meta-analysis [29]. In contrast, if there was no significant statistical heterogeneity between studies ($p \geq 0.1$ or $I^2 < 50\%$), meta-analysis was performed using a fixed-effects model [23]. We also used the leave-one-out strategy for sensitivity analysis to assess the impact of individual studies on the robustness of the pooled results. Finally, although the number of eligible studies was smaller than ten [30], we still performed Begg's and Egger's tests to assess the risk of publication bias.

Trial sequential analysis

If the sample sizes accumulated in a meta-analysis is limited, there may not be sufficient statistical power to assess treatment effects, as a meta-analysis with an extremely insufficient sample size may produce false positive or negative results [31]. In addition, as new studies are added, repeated calculation of pooled results may also lead to an increased the risk of type 1 errors in meta-analysis [32]. Therefore, this meta-analysis introduced trial sequential analysis (TSA) to assess the robustness of all pooled results. Because all outcomes are categorical variables, we specified the following parameters for TSA: type I error of 5%, type II error of 20% (corresponding to 80% statistical power), and a relative risk reduction of 15% for all outcomes. In addition, the proportion at risk in the control group and diversity were obtained from the meta-analysis.

Results

Search results

The electronic literature search retrieved 1306 studies, and 1 additional potentially eligible study was identified from a previous meta-analysis. Using EndNote software, we first removed 357 duplicate studies and registered records of 6 clinical trials. We further excluded 934 ineligible studies based on title and abstract screening. We continued to screen the full texts of the remaining 10 studies to assess their eligibility. After excluding 2 post-hoc analyses and 1 study focusing on a subset of the SECURE trial, 7 studies [21, 33–38] were ultimately

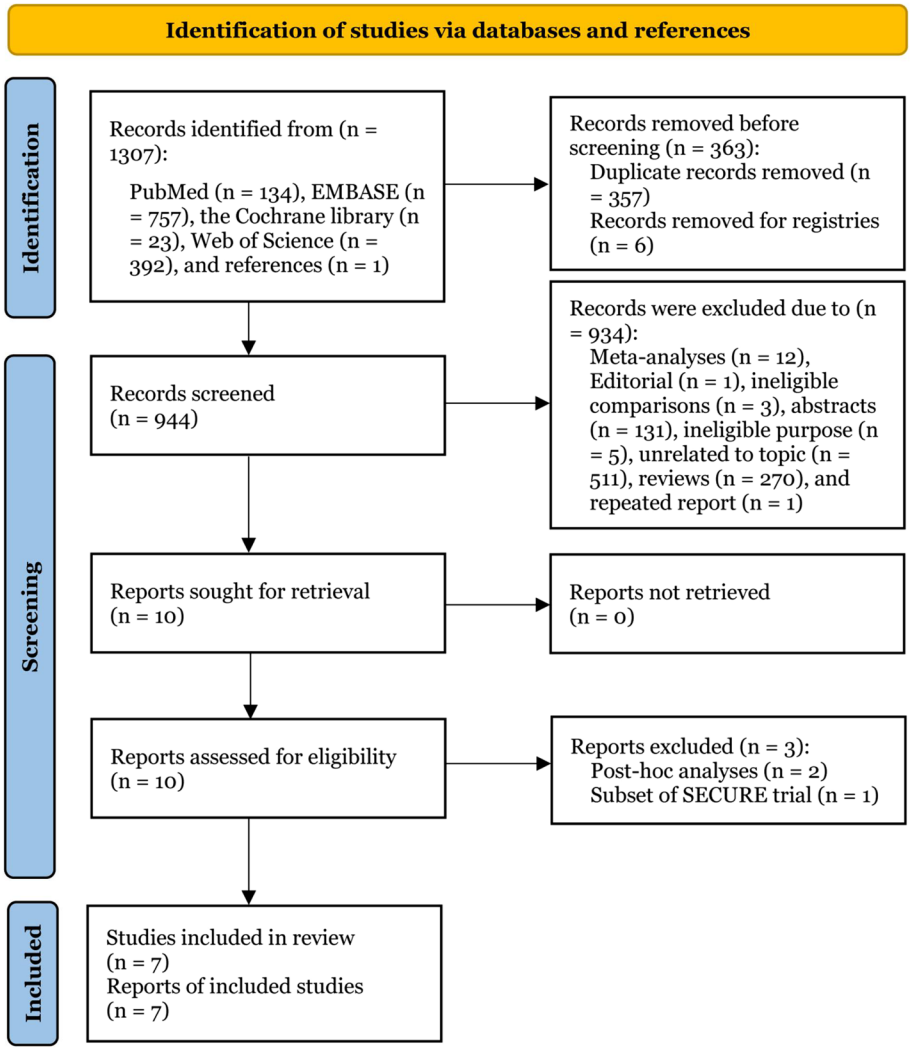

Fig. 1 PRISMA flow diagram of study selection

included in this meta-analysis. We present the detailed process of study screening in Fig. 1.

Characteristics of included studies

All studies were published between 2016 and 2023. Four studies recruited participants in the United States [34, 35, 37, 38], one study recruited participates in the United Kingdom [33], one study recruited participates in Japan [36], and one study recruited participates globally [21]. Two studies were conducted at multi-centers and five studies were conducted at single centers. A total of 442 participants received isavuconazole and 428 participants received voriconazole. We summarized the detailed basic characteristics of the seven eligible studies in Table 1 and record the baseline patient characteristics of included in the seven studies in Table 2.

Risk of bias assessment

Detailed scores for the risk of bias assessment of all eligible studies are recorded in Table 1. Specifically, the scores for individual studies ranged from 17 to 27, with six studies having a moderate risk of bias and only one study having a low risk of bias. Most studies were assessed as having a moderate risk of bias due to their retrospective design [33–35, 37, 38], while only one study was considered to have a low risk of bias because of its double-blinded design [21]. Another RCT was deemed to be at moderate risk of bias due to its open-label design [36].

Meta-analysis of overall response

Four studies involving 476 patients evaluated the difference in overall response between isavuconazole versus voriconazole, with overall responses of 44.84% and 41.07% in the isavuconazole and voriconazole groups,

Table 1 Characteristics of seven eligible studies included in the present meta-analysis

Study	Region	Study design	Infection type	Pathogen	Outcomes (ISAV *vs.* VRCA)				Score for risk of bias
					Overall response	All-cause mortality	Discontinuation	AEs	
Maertens et al., 2016 [21]	Global	RCT in MC	Fungal infections	Aspergillus, Mucor	50 *vs.* 47	81 *vs.* 87	21 *vs.*35	109 *vs.* 155	27
Cheng et al., 2018 [35]	United States	RSC in SC	Aspergillosis	Aspergillus	9 *vs.* 12	n/a	1 *vs.* 8	n/a	17
Bongomin et al., 2019 [33]	United Kingdom	RSC in SC	Aspergillosis	Aspergillus	n/a	n/a	8 *vs.* 10	12 *vs.* 18	20
Stull et al., 2019 [37]	United States	RSC in SC	Aspergillosis, mucorymycosis	Aspergillus, Mucor	n/a	6 *vs.* 9	0 *vs.* 1	n/a	19
van Matre et al., 2019 [38]	United States	RSC in SC	Fungal infections	Aspergillus, Mucor	n/a	15 *vs.* 16	n/a	2 *vs.* 5	20
Cheng et al., 2020 [34]	United States	RSC in SC	Aspergillosis	Aspergillus	13 *vs.* 16	14 *vs.* 13	1 *vs.* 7	n/a	18
Kohno et al., 2023 [36]	Japan	RCT in MC	Fungal infections	Aspergillus, Mucor, Cryptococcus	41 *vs.* 17	1 *vs.* 0	7 *vs.* 4	32 *vs.* 23	21

ISAV Isavuconazole, *VRCZ* Voriconazole, *RSC* Retrospective cohort, *RCT* Randomized controlled trial, *SC* Single-center, *MC* Multicenter, *n/a* not available

respectively. No significant statistical heterogeneity was detected between studies ($p=0.59$, $I^2=0.0\%$), so we conducted a meta-analysis using the fixed-effects model. As shown in Fig. 2a, there was no significant difference in overall response between isavuconazole versus voriconazole (RR = 1.02, 95% CI: 0.83 to 1.25, $p=0.86$). Furthermore, as shown in Fig. 2b, although the cumulative sample size did not reach the required sample size ($n=1086$), the Z-curve was located in the infertile area. Therefore, we can draw a definitive conclusion that isavuconazole is significantly higher than voriconazole in terms of overall response.

Meta-analysis of all-cause mortality

Five studies involving 764 patients evaluated the difference in all-cause mortality between isavuconazole versus voriconazole, with mortality of 29.85% and 33.60% in the isavuconazole and voriconazole groups, respectively. No significant statistical heterogeneity was detected between studies ($p=0.73$, $I^2=0.0\%$), so we conducted a meta-analysis using the fixed-effects model. As shown in Fig. 3a, there was no significant difference in all-cause mortality between isavuconazole versus voriconazole (RR = 0.95, 95% CI: 0.78 to 1.16, $p=0.61$). Furthermore, as shown in Fig. 3b, although the cumulative sample size did not reach the required sample size ($n=1467$), the Z-curve was located in the infertile area. Therefore, we can draw a definitive conclusion that isavuconazole is comparable to voriconazole in terms of all-cause mortality.

Meta-analysis of drug-related AEs

Four studies involving 703 patients evaluated the difference in the incidence of drug-related AEs between isavuconazole versus voriconazole, with an incidence of 42.82% and 58.94% in the isavuconazole and voriconazole groups, respectively. No significant statistical heterogeneity was detected between studies ($p=0.92$, $I^2=0.0\%$), so we conducted a meta-analysis using the fixed-effects model. As shown in Fig. 4a, isavuconazole was associated with significantly lower incidence of drug-related AEs compared with voriconazole (RR = 0.70, 95% CI: 0.61 to 0.81, $p<0.001$). Furthermore, as shown in Fig. 4b, the cumulative sample size was larger than the required sample size ($n=563$), and the Z-curve crossed both conventional and trial sequential beneficial monitoring boundaries. Based on this finding, we can draw a definitive conclusion that isavuconazole is significantly lower than voriconazole in terms of drug-related AEs.

Meta-analysis of discontinuation due to drug-related AEs

Six studies involving 803 patients evaluated the difference in the discontinuation rate due to drug-related AEs between isavuconazole versus voriconazole, with a discontinuation rate of 9.31% and 16.46% in the isavuconazole and voriconazole groups, respectively. No significant statistical heterogeneity was detected between studies ($p=0.40$, $I^2=3.0\%$), so we conducted a meta-analysis using the fixed-effects model. As shown in Fig. 5a, isavuconazole was associated with significantly

Table 2 Baseline characteristics of the patients of studies included in the meta-analysis

Study	No. of patients, n		Male, n		Average age, years		Comorbidities	Details of treatments	
	ISAV	VRCZ	ISAV	VRCZ	ISAV	VRCZ		ISAV	VRCZ
Maertens et al., 2016 [21]	258	258	145	163	51.1	51.2	Acute myeloid leukemia, lymphoma, acute lymphoblastic leukemia, Myelodysplastic syndrome, chronic lymphocytic leukemia, aplastic anemia, chronic myeloid leukemia, multiple myeloma, COPD, Hodgkin's disease, diabetes	200 mg, once every 5 h with a total of six doses, then 200 mg once daily	12 mg/kg on day 1, 8 mg/kg on day 2 or 400 mg/day from day 3
Cheng et al., 2018 [35]	29	36	n/a	n/a	n/a	n/a	hematological malignancy, hematopoietic-cell transplantation, solid organ transplantation	n/a	n/a
Bongomin et al., 2019 [33]	20	21	14	12	65.0	66.0	COPD, tuberculosis, Pulmonary sarcoidosis, Lung cancer, asthma, community-acquired pneumonia, asbestosis, bronchiectasis	200 mg, once every 5 h with a total of six doses, then 200 mg once daily	n/a
Stull et al., 2019 [37]	22	20	n/a	n/a	n/a	n/a	Myeloid leukemia, hematopoietic stem cell transplantation, diabetes, solid-organ transplantation	n/a	n/a
van Matre et al., 2019 [38]	33	34	17	20	58.8	56.9	n/a	n/a	n/a
Cheng et al., 2020 [34]	28	32	11	20	59.0	64.0	Hematological malignancy, hematopoietic stem cell transplantation, diabetes, solid-organ transplantation, solid malignancy, others	200 mg, once every 5 h with a total of six doses, then 200 mg once daily	400 mg/day
Kohno et al., 2023 [36]	52	27	46	23	66.0	68.1	COPD, bronchiectasis	200 mg, once every 5 h with a total of six doses, then 200 mg once daily	12 mg/kg on day 1, 8 mg/kg on day 2 or 400 mg/day from day 3

ISAV Isavuconazole, *VRCZ* Voriconazole, *COPD* Chronic obstructive pulmonary disease, *n/a* not available

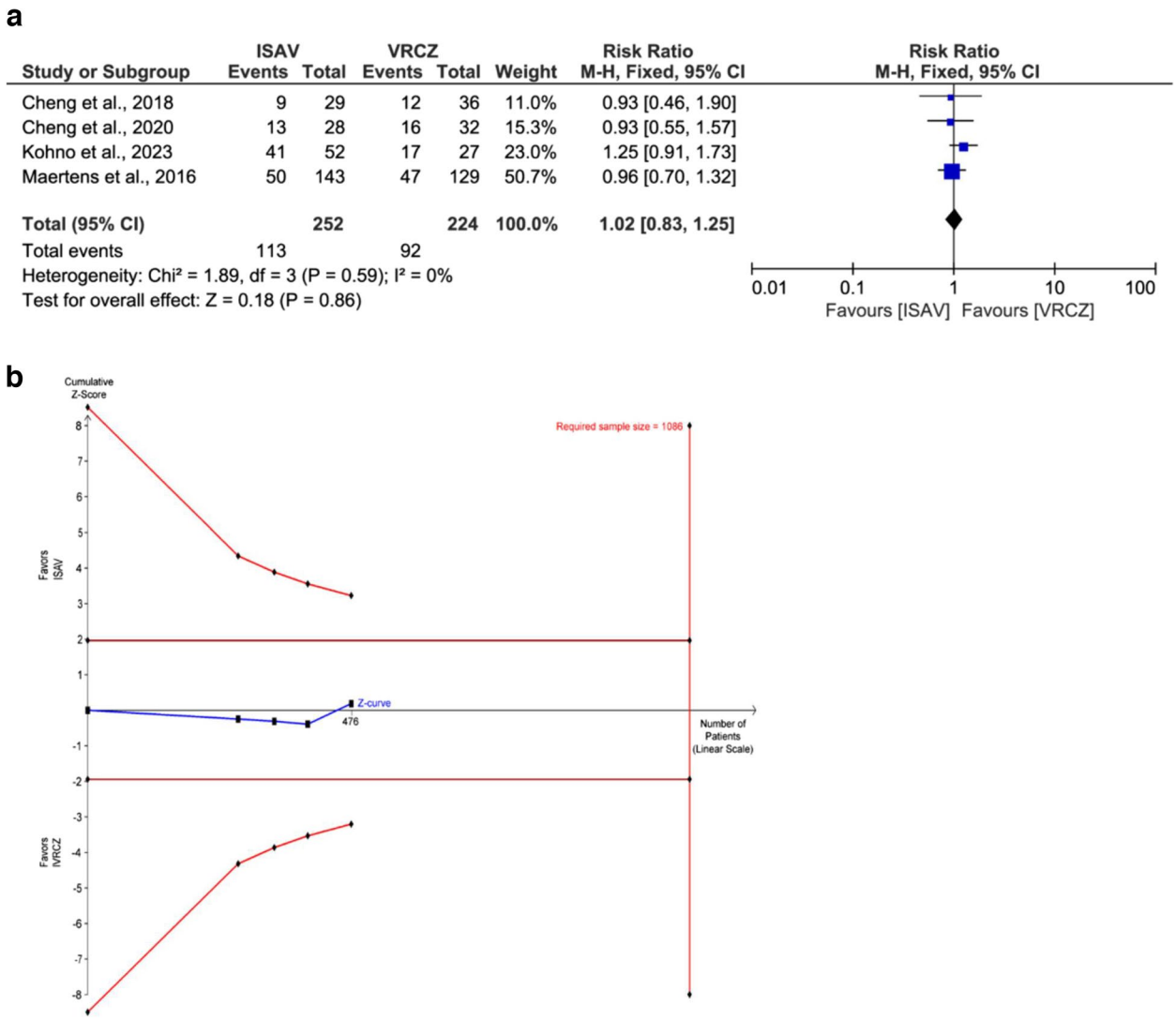

Fig. 2 Meta-analysis (**a**) and trial sequential analysis (**b**) showing difference in overall response between isavuconazole and voriconazole

lower discontinuation rate due to drug-related AEs compared with voriconazole (RR = 0.56, 95% CI: 0.39to 0.82, $p = 0.003$). Furthermore, as shown in Fig. 5b, the Z-curve crossed the conventional beneficial monitoring boundary but did not cross the trial sequential beneficial monitoring boundary. More importantly, the cumulative sample size was much smaller than the required sample size ($n = 3661$), indicating that no definitive conclusion could be drawn. Therefore, the difference in discontinuation rate due to drug-related AEs between isavuconazole and voriconazole should be evaluated in more studies.

Sensitivity analysis

As shown in Supplementary Figs. 1 to 4, sensitivity analyses indicated that the pooled results for all outcomes did not change significantly after omitting one study at a time, thus suggesting that the pooled results were not adversely affected by the variations across studies.

Publication bias

Begg's test showed that there was no publication bias for all outcomes, and the *p* values for overall response, all-cause mortality, incidence of drug-related AEs, and discontinuation rate due to drug-related AEs were 0.734, 0.806, 0.308, and 0.452, respectively. Furthermore, the results of Egger's test consistently showed no publication bias in the meta-analysis of overall response, all-cause mortality, incidence of drug-related AEs, and

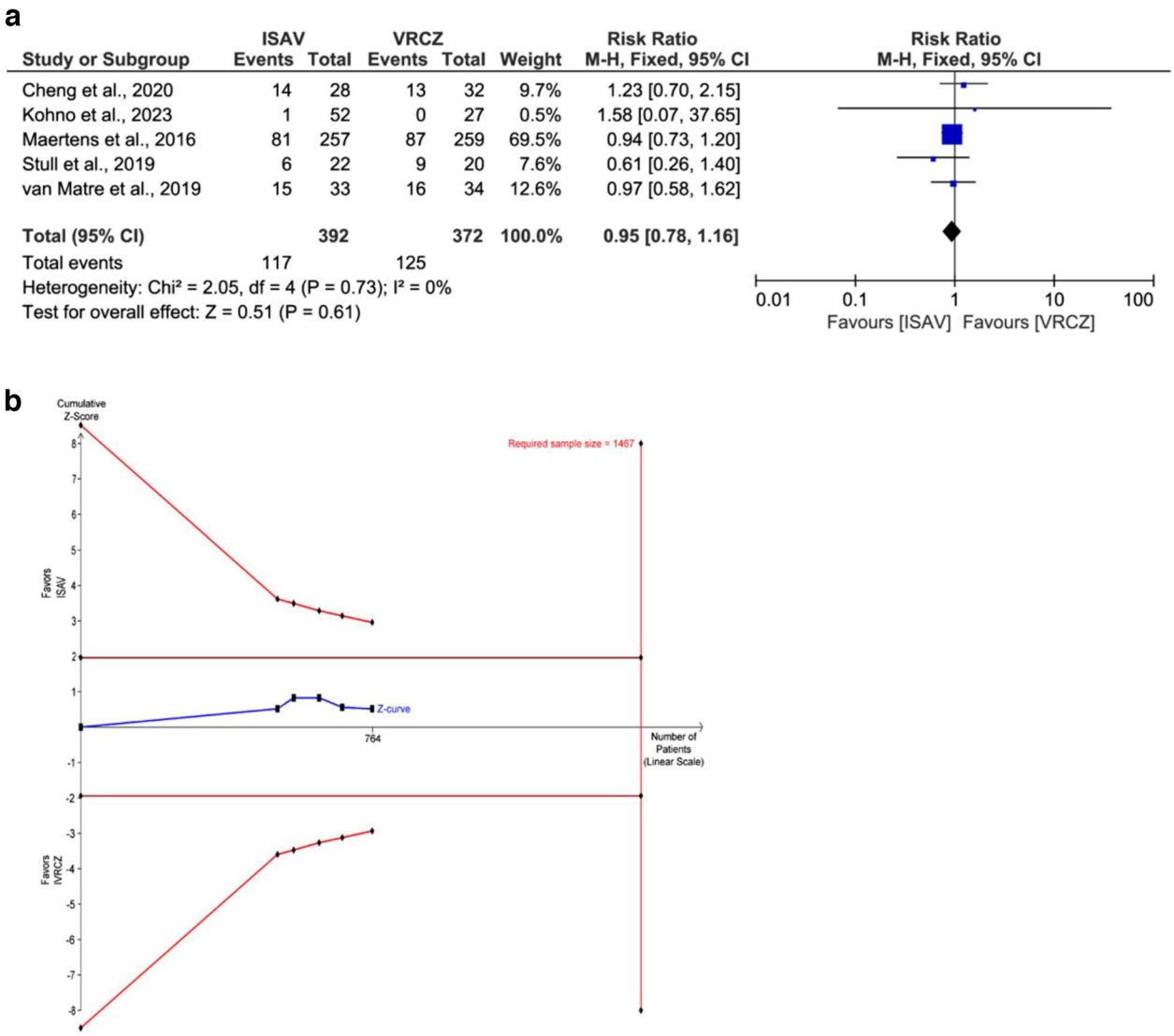

Fig. 3 Meta-analysis (**a**) and trial sequential analysis (**b**) showing difference in all-cause mortality between isavuconazole and voriconazole

discontinuation rate due to drug-related AEs, with a corresponding *p* value of 0.538, 0.954, 0.170, and 0.185.

Discussion

This study used meta-analytic technique to systematically evaluate the comparative efficacy and safety of isavuconazole versus voriconazole for the treatment of invasive fungal infections. Pooled results showed that isavuconazole is not inferior to voriconazole in terms of overall response and all-cause mortality. However, isavuconazole is associated with significantly lower rate of drug-related AEs and a lower discontinuation rate due to drug-related AEs compared with voriconazole.

As a new broad-spectrum triazole antifungal drug, having an efficacy that is not inferior to existing drugs is essential in determining whether isavuconazole should be approved for the treatment of invasive fungal infections. Four studies [21, 34–36] out of seven included studies consistently reported that isavuconazole had a comparable overall response to voriconazole. Nevertheless, three studies [34–36] recruited only extremely limited numbers of participants to make this finding, thus requiring us to interpret these results with caution. Similarly, although five eligible studies [21, 34, 36–38] consistently supported no difference in all-cause mortality between isavuconazole and voriconazole, four studies [34, 36–38] also recruited only very limited numbers of participants, increasing the risk of generating false negative results. Although the current meta-analysis reported consistent findings with eligible studies, a greater cumulative sample

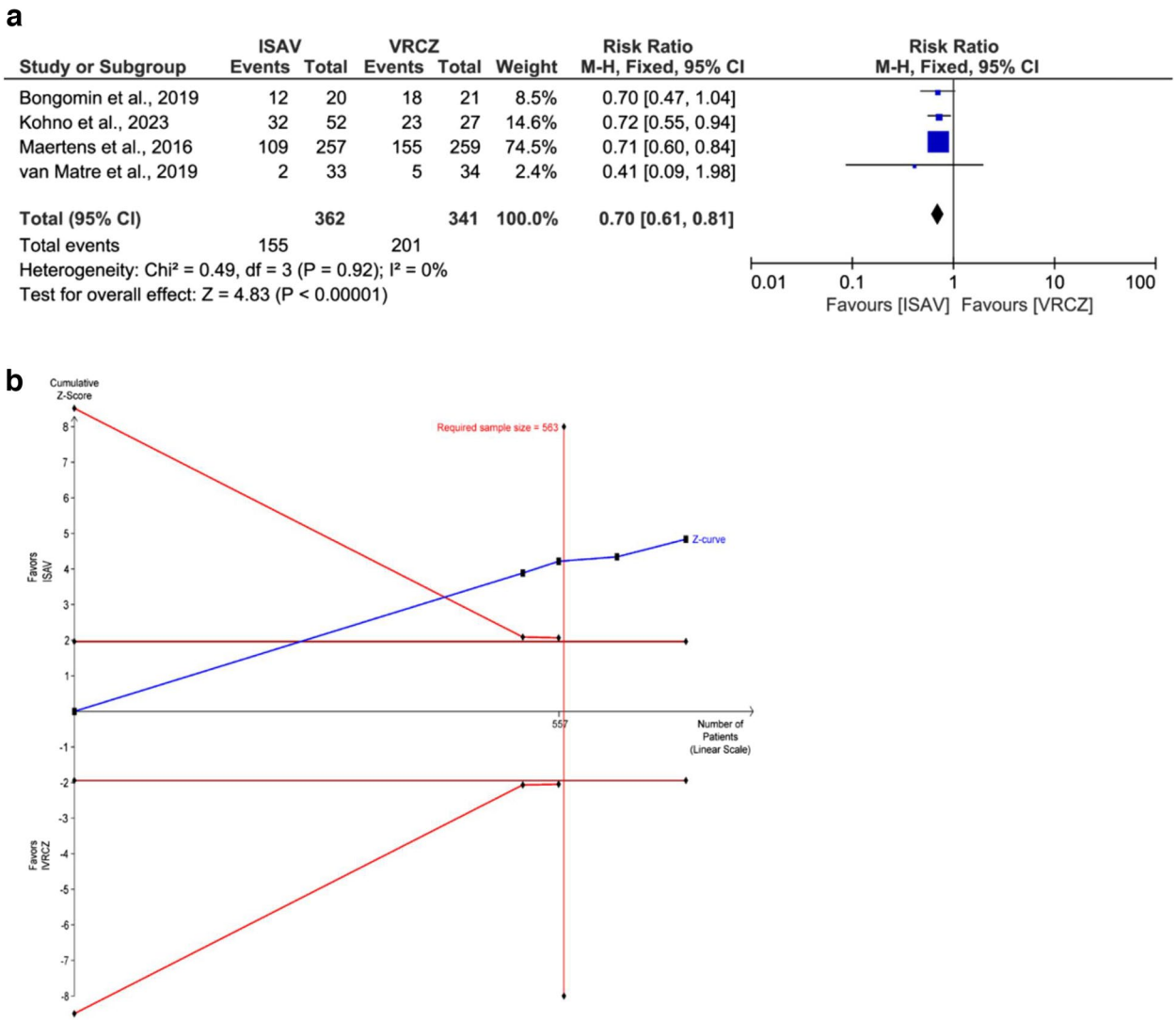

Fig. 4 Meta-analysis (**a**) and trial sequential analysis (**b**) showing difference in the incidence of drug-related treatment-emergent adverse events between isavuconazole and voriconazole

size would significantly increase the statistical power to detect the true difference between isavuconazole and voriconazole in overall response and all-cause mortality [27]. Notably, the results of the TSA confirmed the reliability of our findings regarding these two outcomes, conclusively indicating that isavuconazole is at least inferior to not voriconazole for the treatment of invasive fungal infections.

Assessing the incidence of drug-related AEs is also critical to unraveling the safety profile of isavuconazole [39]. The current meta-analysis found that, compared with voriconazole, isavuconazole was associated with significantly fewer drug-related AEs, which is consistent with two RCTs [21, 36] included in this meta-analysis. Although two other studies [33, 38] reported comparable drug-related AEs between isavuconazole and voriconazole, we must emphasize the potential negative impact of retrospective design and insufficient sample size on the results. In fact, hepatotoxicity is recognized a well-known AE related to isavuconazole, which is considered to be well tolerated [12], further supporting the satisfactory safety profile of isavuconazole. More importantly, the results of the TSA confirmed that the finding of drug-related AEs is conclusive, suggesting that the safety profile of isavuconazole is superior to that of voriconazole.

Our meta-analysis also revealed that isavuconazole is superior to voriconazole in terms of discontinuation due to drug-related AEs. Isavuconazole exposure has

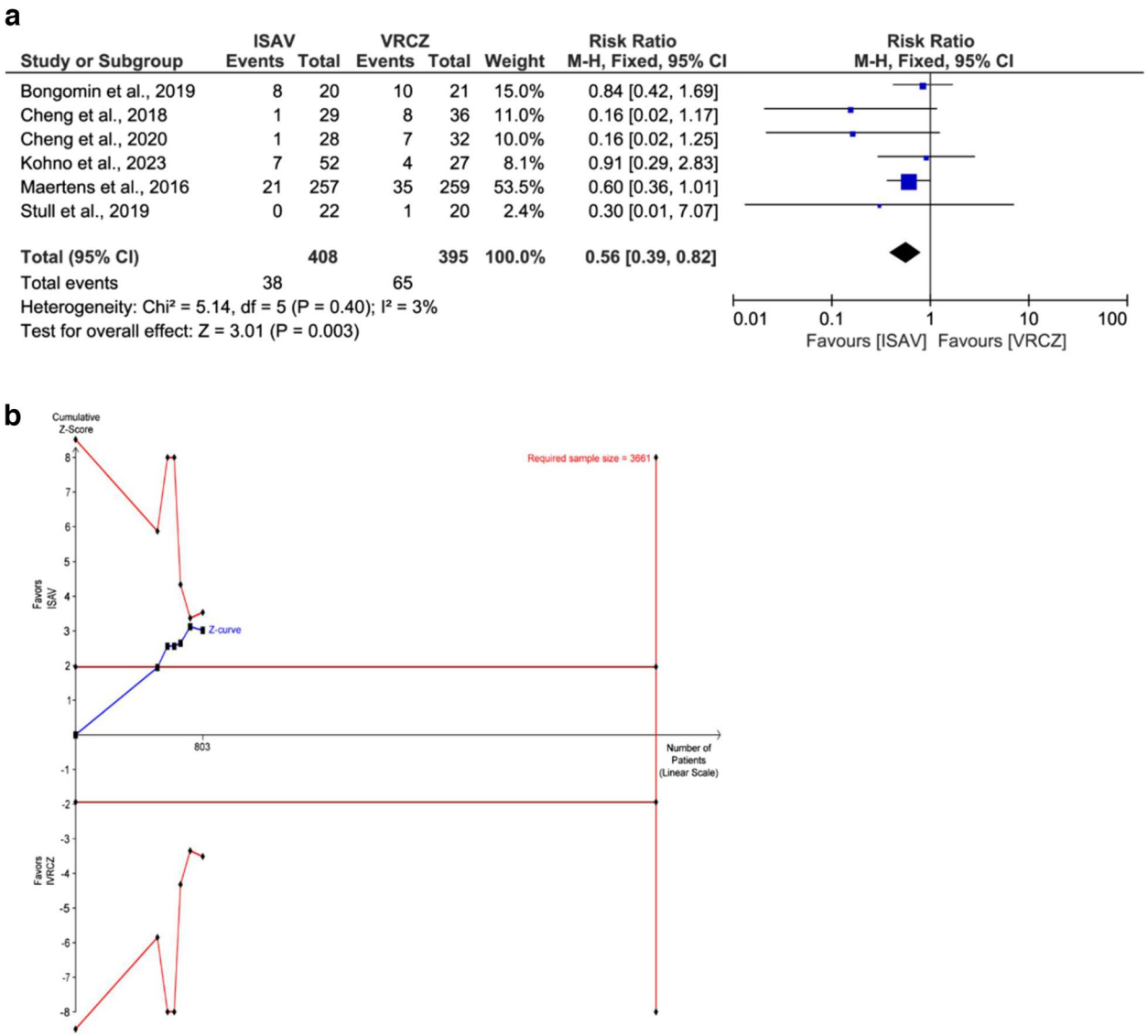

Fig. 5 Meta-analysis (**a**) and trial sequential analysis (**b**) showing difference in the rate of discontinuation due to drug-related adverse events between isavuconazole and voriconazole

been found to be less variable than voriconazole exposure and is well tolerated by patients who are unable to continue voriconazole treatment due to AEs [40]. Additionally, it was discovered that isavuconazole has a lower intra-individual coefficient of variation than voriconazole when both medications are administered sequentially to the same patients [41]. All these factors may help explain why isavuconazole has a lower discontinuation rate than voriconazole; however, we still recommend further studies to clarify whether adjusting the patients' doses might improve the rate of discontinuation [22].

Up to date, one meta-analysis [22] has evaluated the comparative efficacy and safety of isavuconazole versus other antifungal agents for the treatment and prophylaxis of invasive fungal infections. However, this meta-analysis simply combined other antifungal agents as controls, thereby significantly increasing the risk of false-negative results. However, our meta-analysis used voriconazole as the sole control, thus enhancing the reliability of estimates for all outcomes. In addition, the previous meta-analysis did not evaluate some important outcomes, such as overall response and the incidence of overall drug-related AEs, which further compromised its value. More importantly, compared to the previous meta-analysis, our meta-analysis introduced the TSA strategy to definitively conclude that isavuconazole was comparable to

voriconazole in terms of overall response and all-cause mortality but had lower risk of drug-related AEs than voriconazole. Additionally, the result of the TSA revealed that more studies are required to evaluate the differences in discontinuation between isavuconazole and voriconazole. All this information could not be obtained from the previous meta-analysis.

We must acknowledge that our meta-analysis has some limitations. First and foremost, although seven studies were included in the final data analysis, six studies (85.7%) had a limited number of participants. There is no doubt that insufficient information can lead to an overestimation or underestimation of treatment effects. However, our meta-analysis improves statistical power by accumulating the sample sizes of individual studies. More importantly, we introduce the TSA to confirm the results for most outcomes. Second, although significant statistical heterogeneity was not detected across studies, we should not overlook the variations in comorbidities, dosages of medications, and treatment duration between studies. Undoubtedly, these variations may introduce bias that could negatively affect the robustness of pooled results. However, it was impossible to conduct subgroup analysis to eliminate the impact of these factors on our findings due to insufficient data. However, it is also important to recognize that these variations actually enhance the generalizability of our findings. Third, only two RCTs met our inclusion criteria, while the other five studies were retrospective. We must acknowledge that retrospective studies may be biased by confounding factors compared to RCTs [42]. Therefore, treatment effects estimated from a meta-analysis combining RCTs and retrospective studies will inevitably be biased. However, when studies are insufficient, this is the best way to comprehensively assess the efficacy and safety of a treatment [42]. Fourth, although voriconazole is an antifungal agent with a broad spectrum of activity, it is naturally resistant to Mucor and Rhizopus. Among the seven included studies, four studies recruited patients who suffering from invasive fungal infections caused by Mucor, thereby inevitably biasing the therapeutic effect of isavuconazole. Finally, risk of bias assessments revealed that just one study was classified as having a low risk of bias, while the other six were rated as having moderate risk. The inclusion of predominantly retrospective studies with moderate bias risk limits the overall quality of evidence supporting the conclusions drawn from this meta-analysis. Therefore, the findings should be interpreted with caution, recognizing that the presence of bias may influence the reliability and generalizability of the results. This highlights the need for further high-quality RCTs to strengthen the evidence base in this area.

Conclusions

Based on the currently available data, we conclude that isavuconazole has similar efficacy to voriconazole but with fewer adverse events. Furthermore, more studies are needed to compare the discontinuation rates of isavuconazole and voriconazole, as a no definitive conclusion can be drawn. Despite this, our findings support the use of isavuconazole as the primary therapy for invasive fungal infections.

Abbreviations

IM	Invasive mucormycosis
AEs	Adverse events
MeSH	Medical subject heading
DRC	Data Review Committee
EOT	End of treatment
TSA	Trial sequential analysis

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-025-10627-w.

Supplementary Material 1.

Supplementary Material 2.

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None.

Authors' contributions

Conception and design: Jianzhen Weng; Administrative support: Yang Ju, Baomin Fang, Yanming Li; Collection and assembly of data: Jianzhen Weng, Xiaoman Du; Data analysis and interpretation: Jianzhen Weng, Xiaoman Du, Lixue Huang; Manuscript writing: All authors; Final approval of manuscript: All authors.

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Data availability

All data generated or analysed during this study are included in this published article and its supplementary information files.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable. This study did not involve human participants.

Competing interests

The authors declare no competing interests.

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