Efficacy and Safety of Antifungal Medicines in the Treatment of Invasive Aspergillosis: A Network Meta-Analysis

Liangdong Zhu[1], Xun Yang[2], Keyu Li[1], Xiaolin Li[3] and Xia Chen[3]

[1]*Department of Respiratory and Critical Care Medicine, the First Hospital of Changsha, Changsha, China*
[2]*Department of Respiratory and Critical Care Medicine, Jiangsu Provincial People's Hospital, Chongqing Hospital, Chongqing, China*
[3]*Department of Nephrology and Rheumatology Immunology, the First Affiliated Hospital of Hunan University of Medicine, Hunan, China*

ABSTRACT

A frequentist network meta-analysis (NMA) was conducted to assess the efficacy and safety of voriconazole, posaconazole, isavuconazole, amphotericin B deoxycholate (AmB-D), and liposomal AmB (L-AmB) in the treatment of invasive aspergillosis (IA). This study searched PubMed, Cochrane Library, and Embase from the beginning till December 31, 2023. It included five randomised controlled trials (RCTs) of 1635 patients with confirmed or suspected IA. Compared to AmB-D, posaconazole (odds ratio (OR): 0.39, 95% confidence interval (CI): [0.20, 0.76]), isavuconazole (OR: 0.51, 95% CI: [0.26, 0.99]), and voriconazole (OR: 0.57, 95% CI: [0.34, 0.93]) were significantly effective in reducing all-cause mortality. Similarly, voriconazole (OR: 2.42, 95% CI: [1.48, 3.96]), posaconazole (OR: 2.34, 95% CI: [1.22, 4.50]), and isavuconazole (OR: 2.27, 95% CI: [1.13, 4.57]) also showed significantly greater efficacy in improving overall response compared to AmB-D. The area under the cumulative ranking curve (SUCRA) results showed that posaconazole was the most effective in reducing all-cause mortality, while voriconazole ranked best in overall response. In conclusion, this NMA suggests that for IA, posaconazole, isavuconazole, voriconazole, and L-AmB are all effective first-line treatment options. However, more RCTs are needed to validate these findings further.

Key Words: *Invasive aspergillosis, Posaconazole, Isavuconazole, Voriconazole, Network meta-analysis*.

How to cite this article: Zhu L, Yang X, Li K, Li X, Chen X. Efficacy and Safety of Antifungal Medicines in the Treatment of Invasive Aspergillosis: A Network Meta-Analysis. *J Coll Physicians Surg Pak* 2025; **35(09)**:1173-1179.

INTRODUCTION

Invasive aspergillosis (IA) is a severe fungal infection, predominantly impacting patients with weakened immune systems. It is closely linked to high incidence and mortality.[1,2] The risk is exceptionally high in patients with blood malignancies, neutropenia, recipients of allogeneic blood stem cells, and individuals infected with influenza or coronavirus disease 2019 (COVID-19).[1,3,4] Voriconazole has been the cornerstone of IA treatment since 2002. However, it faces challenges such as adverse reactions, drug interactions, narrow therapeutic windows, and resistance.[5,6] Compared to voriconazole, isavuconazole shows similar efficacy but offers a safer profile concerning hepatotoxicity, neurovisual toxicity, and QTc prolongation. It also features stable pharmacokinetics without the need for therapeutic drug monitoring.[7,8] Recent studies have shown that posaconazole's efficacy is comparable to that of voriconazole, with fewer adverse events, notably reduced ocular and psychiatric reactions.[9]

Correspondence to: Dr. Xia Chen, Department of Nephrology and Rheumatology Immunology, the First Affiliated Hospital of Hunan University of Medicine, Hunan, Huaihua, China
E-mail: 184895725@qq.com

Received: May 27, 2024; Revised: December 08, 2024; Accepted: December 18, 2024
DOI: https://doi.org/10.29271/jcpsp.2025.09.1173

American and European guidelines recommended voriconazole as the preferred drug for the treatment of IA, with isavuconazole and Liposomal Amphotericin B (L-AmB) as viable alternative options.[10,11] For the patients suffering from acute myeloid leukaemia or myelodysplastic syndromes, posaconazole is specifically recommended as a primary preventive measure.[12] Furthermore, during the COVID-19 and influenza pandemics, a notable increase in secondary fungal infections has been observed among critically ill patients, further complicating the treatment of those patients with respiratory distress syndrome.[13] The consensus guidelines favour voriconazole or isavuconazole for the treatment of COVID-19-related pulmonary aspergillosis.[14] However, due to the issue of potential drug interactions in critically ill COVID-19 patients, voriconazole may not be the choice.[15] In contrast, isavuconazole emerges as a viable choice due to its stable metabolism and lower toxicity profile, despite some potential interaction risks. L-AmB remains an alternative option, although its nephrotoxicity warrants careful consideration.[14,16]

Recent randomised controlled trial (RCT) results reveal that voriconazole is comparable to isavuconazole and posaconazole in treating IA.[7,9] However, directly comparative data on the relative efficacy of isavuconazole, posaconazole, and AmB in treating IA are presently lacking. In such circumstances, a network meta-analysis (NMA) proves valuable by enabling indirect comparisons of various treatment strategies. This is

achieved by synthesising RCTs with shared control groups to deduce the relative efficacy of each intervention.[17,18] This study aims to evaluate the clinical trial outcomes of voriconazole, posaconazole, isavuconazole, AmB-D, and L-AmB in the treatment of patients with IA, with the goal of providing a more substantial foundation for clinical management by examining the efficiency and safety of these medicines.

METHODOLOGY

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[19] Additionally, the study protocol was registered with PROSPERO (CRD42024510563).

A comprehensive systematic literature review was conducted to assess the efficacy and safety of voriconazole, posaconazole, isavuconazole, and AmB formulations for the treatment of IA. English-language RCT were identified through search of PubMed, Cochrane Library, and Embase published up to December 31, 2023. The search terms used were voriconazole OR posaconazole OR isavuconazole OR isavuconazonium sulfate OR amphotericin B OR liposomal amphotericin B OR AmBisome OR amphotericin B deoxycholate AND aspergillosis OR aspergillus infection OR invasive pulmonary aspergillosis OR lung aspergillosis. Additionally, to capture any studies potentially missed during electronic searches, the reference lists of all relevant articles were manually reviewed. The inclusion criteria were as follows: RCTs involving patients with suspected or confirmed IA and evaluating treatments that included comparisons with voriconazole, isavuconazole, posaconazole, L-AmB, and AmB-D. Exclusion criteria included non-RCTs, studies with missing data, duplicate publications, conference reports, and systematic reviews.

The studies were selected independently, and the data were extracted by two researchers (LZ and KL). The selection process began with the screening of potential titles and abstracts according to the predefined inclusion and exclusion criteria. The full texts of these potentially eligible studies were independently evaluated by two researchers (LZ and XL). Differences were resolved by consulting a third independent researcher (XC). From the eligible studies, the following data were extracted: first author, year of publication, follow-up time, characteristics of enrolled participants (underlying diseases and sites of infection), interventions (type, dosage, frequency, and duration), efficacy outcomes (all-cause mortality and overall response), and safety outcomes (incidence of gastrointestinal disorders and renal impairment).

The quality of the literature was assessed using the Cochrane Collaboration's tool for assessing risk of bias for systematic reviews, with the risk categorised as high, medium, or low based on seven criteria.[20,21] Two researchers (LZ and XY) independently performed the risk of bias assessment and data extraction, with any discrepancies resolved through consensus-based discussion. Efficacy was evaluated using two outcomes: all-cause mortality and overall response. Safety assessment was evaluated, using outcomes such as the incidence of gastrointestinal adverse reactions and renal impairment in participants. The mvmeta function of Stata 15.0 was used to conduct the frequentist NMA.[22] This study estimated effect sizes using a random-effects model and presented them as odds ratios (OR) with 95% confidence intervals (CI). A statistically significant difference between two interventions is considered present if the 95% CI excludes the value 1.[23,24] A two-tailed test was utilised to assess statistical significance, with the threshold set at a p-value under 0.05.[25] If a closed loop exists in the included studies, the node-splitting method will be used to assess inconsistency. If there is no statistically significant difference, the consistency model will be used for analysis. In the absence of closed loop between studies — indicating that only indirect comparisons are available — the consistency model is used by default. Since no closed loop was formed in this study, the consistency model was applied. Interventions were subsequently ranked according to the area under the cumulative ranking curve (SUCRA), with higher SUCRA values signifying a more favourable relative effect of the intervention.[26]

RESULTS

The database search yielded 3,633 records. After removing duplicates, 2,673 records were screened by title and abstract, resulting in 46 articles selected for full-text review. The analysis of these studies was based on original clinical trials, with applying different diagnostic criteria across trials. This study included five studies with 1,635 participants (Figure 1).

One clinical trial evaluated the efficacy of L-AmB vs. AmB-D in the treatment of invasive fungal disease. Among the patients studied, 77.3% were documented as highly suspected of IA.[27]

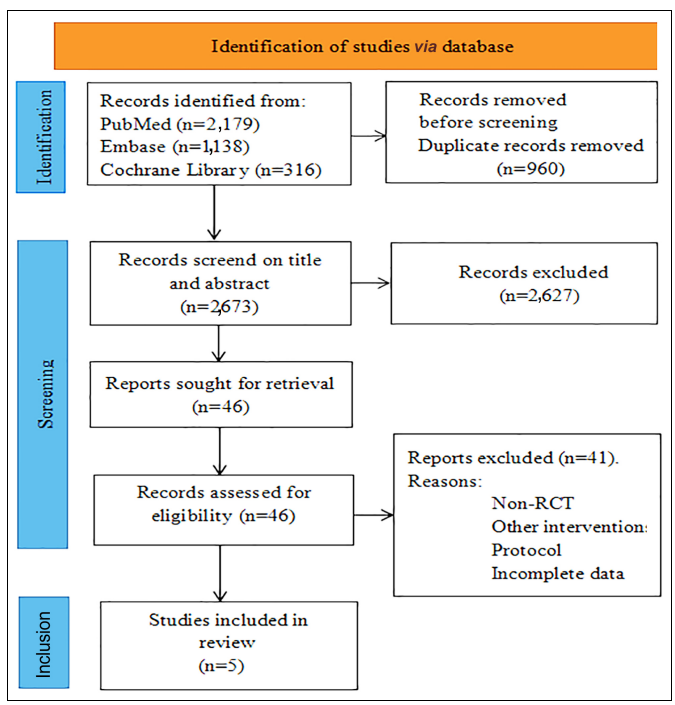

Figure 1: Flow diagram of the study selection process.

Additionally, one trial compared the efficacy of voriconazole with AmB-D in treating IA, while another study examined the effects of regular doses (3 mg/kg/d) *vs.* high doses (10 mg/kg/d) of L-AmB.[5,28] Furthermore, two other trials compared the treatment effects of isavuconazole with voriconazole and posaconazole with voriconazole.[7,9] For outcome measures, two studies assessed all-cause mortality and clinical response at 42 days.[7,9] Four studies evaluated treatment outcomes at 12 weeks (84 days).[5,7,9,28] One RCT assessed efficacy 14 days after treatment completion.[27] The comprehensive analysis of the RCTs showed high consistency in infection sites and underlying disease types, with the lungs being the most frequently infected site and haematological malignancies being the most common underlying disease. The basic characteristics of the included RCT and the summarised data are presented in Table I and Table II, respectively.

Regarding the risk of bias, the assessment indicated that the randomisation was appropriate in all studies, with a low risk. However, one study employed an open-label design without blinding or concealment, thereby posing a risk of bias.[27] In contrast, another study, although it employed blinding for treatment allocation, lacked blinding in other aspects.

Table I: Basic characteristics of included studies.

Studies	Underlying diseases	Treatment arms	Medicine regimens	Sites of infection
Leenders *et al*.[27]	ANLL/MDS, ALL, chronic leukaemia	L-AmB	5 mg/kg/d	56% pulmonary, 44% unreported
		AmB-D	1 mg/kg/d	65% pulmonary, 35% unreported
Herbrecht *et al*.[5]	AML, HSCT, ALL, SOT Other haematologic malignancies	Voriconazole	Day 1: IV 6 mg/kg BID; thereafter, IV 4 mg/kg or oral 200 mg BID	85.4% pulmonary, 5.6% sinus 3.5% cerebral
		AmB-D	1.0-1.5 mg/kg/d	88% pulmonary, 5.3% sinus 3.8% cerebral
Cornely *et al*.[28]	Haematologic malignancies, HSCT	L-AmB	3 mg/kg/d	91.6% pulmonary
		L-AmB#	10 mg/kg/d	89.4% pulmonary
Maertens *et al*.[7]	AML, ALL, Lymphoma, MDS, CLL, AA, CML Chronic obstructive pulmonary disease	Isavuconazole	Day 1 and 2: IV 200 mg TID; thereafter, IV or oral 200 mg QD	81% pulmonary 8% pulmonary and other organs
	Hodgkin's disease and multiple myeloma	Voriconazole	Day 1: IV 6 mg/kg BID; thereafter, IV 4 mg/kg or oral 200 mg BID	83% pulmonary 12% pulmonary and other organs
Maertens *et al*.[9]	Prolonged neutropenia, HSCT treated with T-cell immunosuppressants	Posaconazole	Day 1: IV or oral 300 mg BID; thereafter, 300 mg QD	79.9% pulmonary, 1% sinus 16.7% multiple sites
	Prolonged use of corticosteroids inherited severe immunodeficiency	Voriconazole	Day 1: IV 6 mg/kg or oral 300 mg BID; thereafter, IV 4 mg/kg or oral 200 mg BID	80.1% pulmonary, 2.4% sinus 15.7% multiple sites

ANLL: Acute non-lymphocytic leukaemia; MDS: myelodysplastic syndromes; ALL: acute lymphoblastic leukaemia; AML: Acute myeloid leukaemia; HSCT: Haematopoietic stem cell transplantation; SOT: Solid organ transplantation; CLL: Chronic lymphocytic leukaemia; AA: Aplastic anemia; CML: Chronic myeloid leukaemia; L-AmB: Liposomal amphotericin B; AmB-D: Amphotericin B deoxycholate; IV: Intravenous; BID: Twice daily; QD: Once daily; TID: Three times daily; #Various dosage levels.

Table II: Summarised available data.

Studies	Treatment arms	Number of patients (n)	All-cause mortality (n) (Populations, time point)	Overall response (n)	Gastrointestinal disorders (n) (Populations)	Renal impairment (n)	Other time points Completion of therapy
Leenders *et al*.[27]	L-AmB	32	7 (CE, EOT)	21 (CE, EOT)	0 (NA)	6(NA)	14 days
	AmB-D	34	13 (CE, EOT)	19 (CE, EOT)	1 (NA)	22 (NA)	
	AmB-D	133	56 (ITT, 12 weeks)	42 (mITT, 12 weeks)	1 (RID)	19 (RID)	
Herbrecht *et al*.[5]	Voriconazole	144	42 (ITT, 12 weeks)	76 (mITT, 12 weeks)	4 (RID)	2 (RID)	12 weeks
Cornely *et al*.[28]	L-AmB	107	30 (mITT, 12 weeks)	53 (ITT,12 weeks)	12 (ITT)	17 (ITT)	EOT, 12 weeks
	L-AmB#	94	39 (mITT, 12 weeks)	43 (ITT, 12 weeks)	30 (ITT)	23 (ITT)	
Maertens *et al*.[7]	Isavuconazole	258	48 (ITT, 42 days)	50 (mITT, EOT)	174 (ITT)	55 (ITT)	EOT, 42 days, 84 days
	Voriconazole	258	52 (ITT, 42 days)	47 (mITT, EOT)	180 (ITT)	58 (ITT)	
Maertens *et al*.[9]	Posaconazole	288	44 (ITT, 42 days)	73 (FAS, 42 days)	23 (ITT)	4 (ITT)	42 days, 84 days
	Voriconazole	287	59 (ITT, 42 days)	78 (FAS, 42 days)	25 (ITT)	3 (ITT)	

L-AmB: Liposomal amphotericin B; AmB-D: Amphotericin B deoxycholate; CE: Clinically evaluable population; EOT: End of treatment; ITT: Intent-to-treat population; mITT: Modified intent-to-treat population; FAS: Full analysis set; RID: Received initial medicines population; NA: Not available; #Various dosage levels.

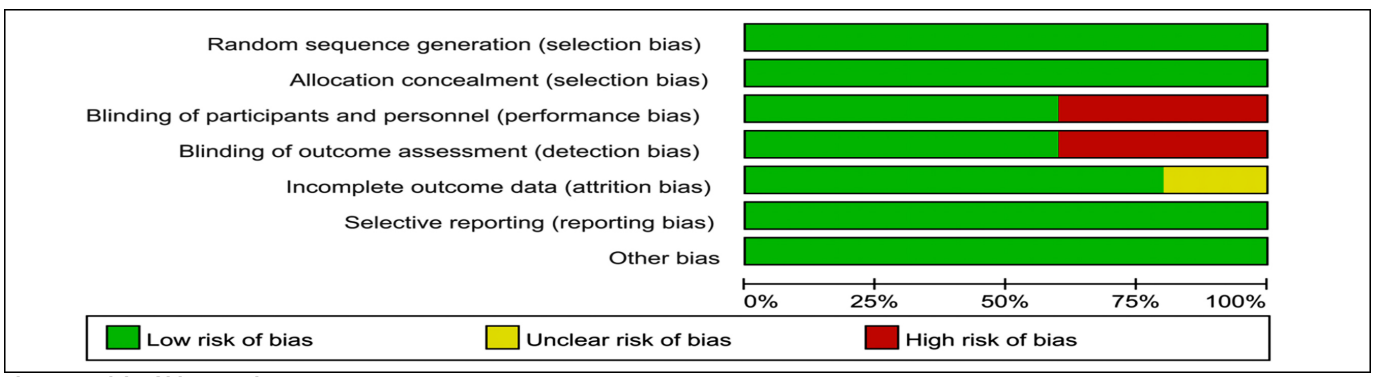

Figure 2: Risk of bias graph.

A	All-cause mortality					
Overall response	Posaconazole	0.87 (0.24,3.11)	0.77 (0.42,1.42)	0.70 (0.45,1.07)	0.48 (0.12,1.94)	0.39 (0.20,0.76)
	1.55 (0.47,5.11)	L-AmB (3-5mg/kg/d)	0.88 (0.25,3.15)	0.80 (0.24,2.64)	0.55 (0.31,0.99)	0.45 (0.15,1.34)
	1.03 (0.53,1.99)	0.66 (0.20,2.24)	Isavuconazole	0.91 (0.58,1.40)	0.62 (0.15,2.53)	0.51 (0.26,0.99)
	0.97 (0.63,1.49)	0.62 (0.21,1.89)	0.94 (0.57,1.54)	Voriconazole	0.69 (0.18,2.61)	0.57 (0.34,0.93)
	1.81 (0.49,6.73)	1.16 (0.67,2.03)	1.75 (0.46,6.68)	1.87 (0.54,6.47)	L-AmB (10mg/kg/d)	0.82 (0.24,2.83)
	2.34 (1.22,4.50)	1.51 (0.56,4.08)	2.27 (1.13,4.57)	2.42 (1.48,3.96)	1.29 (0.41,4.05)	AmB-D

B	Gastrointestinal disorders					
Renal impairment	Isavuconazole	1.01 (0.50,2.03)	0.92 (0.63,1.33)	10.47 (0.20,535.28)	3.29 (0.06,180.14)	3.56 (0.38,33.25)
	0.71 (0.15,3.38)	Posaconazole	0.91 (0.50,1.64)	10.35 (0.20,543.80)	3.26 (0.06,182.92)	3.52 (0.36,34.46)
	0.94 (0.62,1.43)	1.33 (0.30,6.01)	Voriconazole	11.38 (0.23,572.23)	3.58 (0.07,192.63)	3.87 (0.43,35.05)
	0.45 (0.07,2.83)	0.64 (0.06,6.61)	0.48 (0.08,2.86)	L-AmB (3-5mg/kg/d)	0.31 (0.15,0.65)	0.34 (0.01,8.61)
	0.30 (0.04,2.13)	0.42 (0.04,4.85)	0.32 (0.05,2.16)	0.66 (0.33,1.32)	L-AmB (10mg/kg/d)	1.08 (0.04,29.70)
	0.09 (0.02,0.40)	0.12 (0.01,1.00)	0.09 (0.02,0.40)	0.19 (0.07,0.52)	0.29 (0.08,0.97)	AmB-D

Figure 3: League table. (A) Data below the diagonal display OR and 95% CI for overall response. An OR value greater than one indicates that the treatment on the top is more effective. Data above the diagonal display the value of OR and 95% CI for all-cause mortality. An OR value less than one indicates that the treatment on the left is more effective. (B) Data below the diagonal display the value of OR and 95% CI for renal impairment. An OR value less than one indicates that the treatment on the top is more effective. Data above the diagonal display the value of OR and 95% CI for gastrointestinal disorders. An OR value greater than one indicates that the treatment on the left is more effective. *L-AmB: Liposomal amphotericin B; AmB-D: Amphotericin B deoxycholate*.

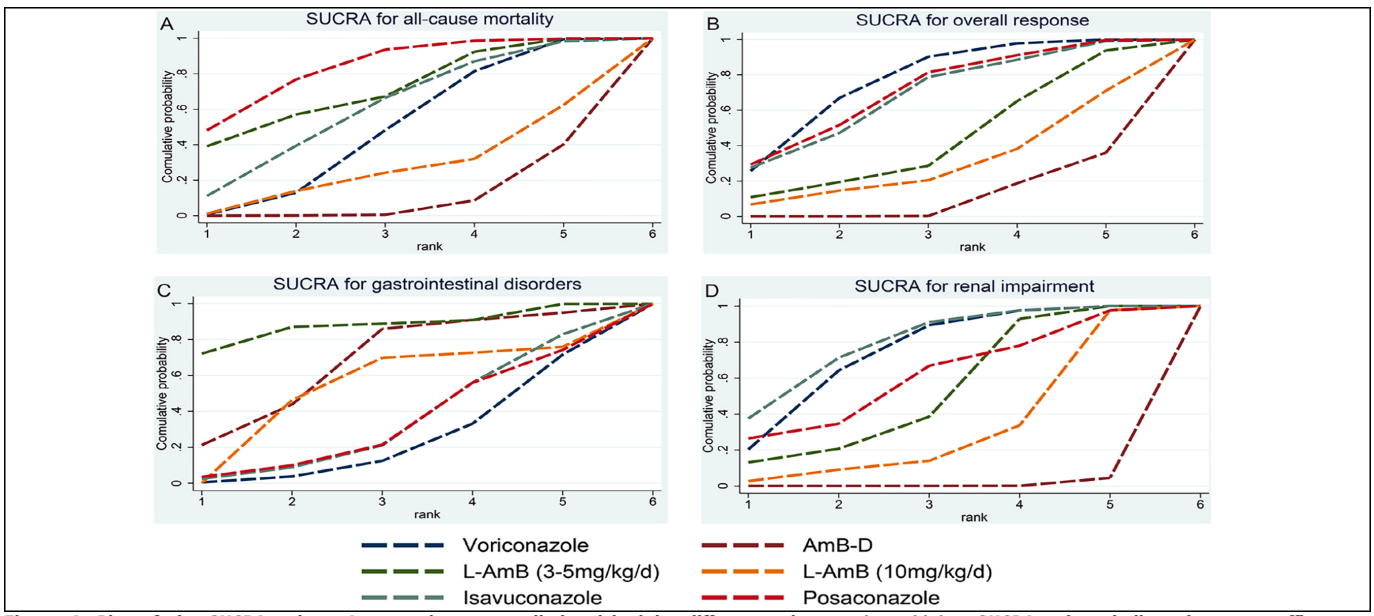

Figure 4: Plot of the SUCRA values. Interventions were distinguished by different colours, where higher SUCRA values indicated greater efficacy or safety. *SUCRA: Surface under the cumulative ranking curve; L-AmB: Liposomal amphotericin B; AmB-D: Amphotericin B deoxycholate.*

Moreover, the baseline characteristics of this study were reported based on a modified intention-to-treat population, potentially concealing a bias due to incomplete outcome data.[5] No risk of bias from unreported data was detected in the studies, and no additional biases were identified (Figure 2). The network league comparing different treatment approaches is presented in Figure 3. Compared to AmB-D, posaconazole (OR: 0.39, 95% CI [0.20, 0.76]), isavuconazole (OR: 0.51, 95% CI [0.26, 0.99]), and voriconazole (OR: 0.57, 95% CI [0.34, 0.93]) significantly reduced all-cause mortality. Similarly, compared to 10 mg/kg/d of L-AmB, 3-5 mg/kg/d of L-AmB (OR: 0.55, 95% CI [0.31, 0.99]) also showed better outcomes in all-cause mortality (Figure 3A). The SUCRA cumulative probability rankogram for the IA treatment strategy network is illustrated in Figure 4. The SUCRA analysis showed that posaconazole (83.4%) was the most effective among the interventions in decreasing all-cause mortality, followed by 3-5 mg/kg/d of L-AmB (71.1%), isavu-

conazole (60.5%), voriconazole (48.5%), 10 mg/kg/d of L-AmB (26.7%), and AmB-D (9.8%). Thus, posaconazole demonstrated superiority in reducing all-cause mortality compared to the other antifungal medications.

In assessing overall response, the results showed that compared to AmB-D, voriconazole (OR: 2.42, 95% CI [1.48, 3.96]), posaconazole (OR: 2.34, 95% CI [1.22, 4.50]), and isavuconazole (OR: 2.27, 95% CI [1.13, 4.57]) demonstrated significant improvement in efficacy (Figure 3A). The SUCRA 5 results further indicated that voriconazole (76.2%) had the optimal effect in overall response, followed by posaconazole (70.7%), isavuconazole (68.3%), 3-5 mg/kg/d of L-AmB (43.6%), 10 mg/kg/d of L-AmB (30.3%), and AmB-D (11.0%) (Figure 4).

For safety assessment, compared to 10 mg/kg/d of L-AmB, 3-5 mg/kg/d of L-AmB (OR: 0.31, 95% CI [0.15, 0.65]) significantly reduced gastrointestinal disorders (Figure 3B). The SUCRA values further showed that 3-5 mg/kg/d of L-AmB (87.8%) performed best in reducing gastrointestinal disorders, followed by AmB-D (67.4%), 10mg/kg/d of L-AmB (53.0%), isavuconazole (34.3%), posaconazole (33.1%), and voriconazole (24.4%) (Figure 4). In evaluating renal impairment, compared to AmB-D, isavuconazole (OR: 0.09, 95% CI [0.02, 0.40]), voriconazole (OR: 0.09, 95% CI: 0.02-0.40), and 3-5 mg/kg/d of L-AmB (OR: 0.19, 95% CI [0.07, 0.52]) significantly reduced the risk of renal impairment (Figure 3B). The SUCRA values concluded that isavuconazole (79.5%) had the lowest likelihood of reducing renal impairment, followed by voriconazole (74.3%), posaconazole (60.7%), 3-5 mg/kg/d of L-AmB (53.0%), 10 mg/kg/d of L-AmB (31.5%), with AmB-D (1%) having the highest risk of renal impairment (Figure 4).

DISCUSSION

This NMA assessed the efficacy and safety of posaconazole, isavuconazole, voriconazole, L-AmB, and AmB-D in the treatment of IA. In this study, posaconazole emerged as the most effective in reducing all-cause mortality, while voriconazole proved superior performence in enhancing overall response. Compared to AmB-D, isavuconazole, posaconazole, and voriconazole demonstrated superior efficacy in all-cause mortality and overall response. However, when these medicines were compared with different doses of L-AmB, the study found no significant statistical differences in all-cause mortality and overall response. A dose of 3-5 mg/kg per day of L-AmB was significantly more effective in reducing the incidence of gastrointestinal disorders than 10 mg/kg per day of L-AmB. Additionally, compared to AmB-D, isavuconazole, voriconazole, and L-AmB at 3-5 mg/kg per day significantly reduced the incidence of renal impairment.

Polyene medications, once the primary choice for IA treatment, have now limited use due to their significant renal toxicity and reliance on intravenous administration.[29,30] Voriconazole, endorsed as the preferred therapeutic agent in international medical guidelines, is processed by cytochrome P450 (CYP450) enzymes, including CYP2C19 and CYP3A4, which may result in extensive medicine interactions.[31,32] Additionally, genetic polymorphism in CYP2C19 may result in significant pharmacokinetic variability among patients.[33,34] Therefore, combining CYP2C19 genotyping with therapeutic medicine monitoring is recommended for personalised medication. Isavuconazole stands out due to its predictable linear pharmacokinetics, lower interpatient variability, and posaconazole's heightened sensitivity to certain resistant fungi.[31,35] Although voriconazole is known for its narrow therapeutic window and potential for adverse events at elevated serum levels, this study found that it was second only to isavuconazole in reducing the risk of renal impairment, with the highest risk associated with AmB-D.

Selecting the primary efficacy endpoint as all-cause mortality at day 42 in the included studies was based on its ability to provide the most objective, highly repeatable, and closest approximation to true attributable mortality.[7,36] In one study, day-42 mortality was found to be 19% in the group treated with isavuconazole and 20% in the group treated with voriconazole.[7] This suggests comparable therapeutic efficacy between the two medicines. In another comparison, the all-cause mortality was 15% in the posaconazole group and 21% in the voriconazole group.[9] The consistent mortality rate for voriconazole across studies suggests that posaconazole offers a mortality benefit by day 42 compared to isavuconazole, aligning with the current findings. The NMA by Herbrecht indicated that the efficacy of isavuconazole in IA treatment surpasses AmB-D and is comparable to L-AmB and voriconazole.[37] However, this study suggests that isavuconazole, posaconazole, voriconazole, and L-AmB are comparably effective in treating IA and are all viable first-line treatments.

This NMA exhibits significant limitations. A constrained number of RCTs fit the analysis criteria. Moreover, variations in diagnostic criteria and treatment evaluation timeline across clinical reports may compromise result comparability. Furthermore, rapid advancements in medical technology for underlying diseases could lead to efficacy variances in antimicrobial medicines, potentially skewing all-cause mortality comparisons among different studies. Most importantly, this NMA included patients with IA, with a specific focus on those with haematological malignancies. This focus may limit the generalisability of the findings to other patient populations, as patients with haematological malignancies often exhibit distinct risk factors and treatment responses compared to individuals with other types of immunocompromised conditions. Despite these challenges, this analysis, grounded in high-quality RCTs and an adequate sample size, offers a dependable foundation for gauging the relative efficacy of various antimicrobial medicines. The observed consistency between overall clinical response and all-cause

mortality further validates the current analysis, closely matching the outcomes of all included RCTs.

CONCLUSION

This study suggested that for the treatment of IA, posaconazole, isavuconazole, voriconazole, and L-AmB are all effective first-line treatment medicines. However, more RCTs are needed to validate these findings. To optimise treatment outcomes, selecting the appropriate antifungal medication should involve a comprehensive consideration of the drug's efficacy, safety, and the patient's specific conditions, along with potential drug interactions for personalised management.

FUNDING:
This work was funded by the Natural Science Foundation of Hunan Province, China (Grant No. 2024JJ9593).

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
LZ, XY, KL, XL, XC: Contributed to data analysis, writing, and reading of the article.
LZ, XY, XC: Conceived and designed the study, reviewed the quality of data, extracted and analysed the data.
All authors approved the final version of the manuscript to be published.

REFERENCES

1. Echeverria-Esnal D, Martin-Ontiyuelo C, Navarrete-Rouco ME, Barcelo-Vidal J, Conde-Estevez D, Carballo N, *et al*. Pharmacological management of antifungal agents in pulmonary aspergillosis: An updated review. *Expert Rev Anti Infect Ther* 2022; **20(2)**:179-97. doi: 10.1080/14787210.2021.1962292.
2. Cadena J, Thompson GR, 3rd, Patterson TF. Aspergillosis: Epidemiology, diagnosis, and treatment. *Infect Dis Clin North Am* 2021; **35(2)**:415-34. doi: 10.1016/j.idc.2021.03.008.
3. Verweij PE, Rijnders BJA, Bruggemann RJM, Azoulay E, Bassetti M, Blot S, *et al*. Review of influenza-associated pulmonary aspergillosis in ICU patients and proposal for a case definition: An expert opinion. *Intensive Care Med* 2020; **46(8)**:1524-35. doi: 10.1007/s00134-020-06091-6.
4. Alexander BD, Lamoth F, Heussel CP, Prokop CS, Desai SR, Morrissey CO, *et al*. Guidance on imaging for invasive pulmonary aspergillosis and mucormycosis: From the imaging working group for the revision and update of the consensus definitions of fungal disease from the EORTC/MSGERC. *Clin Infect Dis* 2021; **72(Suppl 2)**:S79-88. doi: 10.1093/cid/ciaa1855.
5. Herbrecht R, Denning DW, Patterson TF, Bennett JE, Greene RE, Oestmann JW, *et al*. Voriconazole *versus* amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med* 2002; **347(6)**:408-15. doi: 10.1056/NEJMoa020191.
6. Sivasubramanian G, Chandrasekar PH. Efficacy and safety of Isavuconazole for the treatment of invasive Aspergillus infection - An update of the literature. *Expert Opin Pharmacother* 2022; **23(5)**:543-9. doi: 10.1080/14656566.2022.2032645.
7. Maertens JA, Raad II, Marr KA, Patterson TF, Kontoyiannis DP, Cornely OA, *et al*. Isavuconazole *versus* voriconazole for primary treatment of invasive mould disease caused by Aspergillus and other filamentous fungi (SECURE): A phase 3, randomised-controlled, non-inferiority trial. *Lancet* 2016; **387(10020)**:760-9. doi: 10.1016/s0140-6736(15)01159-9.
8. Lamoth F, Calandra T. Pulmonary aspergillosis: Diagnosis and treatment. *Eur Respir Rev* 2022; **31(166)**:220114. doi: 10.1183/16000617.0114-2022.
9. Maertens JA, Rahav G, Lee DG, Ponce-de-Leon A, Ramirez Sanchez IC, Klimko N, *et al*. Posaconazole *versus* voriconazole for primary treatment of invasive aspergillosis: A phase 3, randomised, controlled, non-inferiority trial. *Lancet* 2021; **397(10273)**:499-509. doi: 10.1016/s0140-6736(21)00219-1.
10. Patterson TF, Thompson GR 3rd, Denning DW, Fishman JA, Hadley S, Herbrecht R, *et al*. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the infectious diseases society of America. *Clin Infect Dis* 2016; **63(4)**:e1-60. doi: 10.1093/cid/ciw326.
11. Ullmann AJ, Aguado JM, Arikan-Akdagli S, Denning DW, Groll AH, Lagrou K, *et al*. Diagnosis and management of Aspergillus diseases: Executive summary of the 2017 ESCMID-ECMM-ERS guideline. *Clin Microbiol Infect* 2018; **24 (Suppl 1)**:e1-38. doi: 10.1016/j.cmi.2018.01.002.
12. Groll AH, Pana D, Lanternier F, Mesini A, Ammann RA, Averbuch D, *et al*. 8th European conference on infections in leukaemia: 2020 guidelines for the diagnosis, prevention, and treatment of invasive fungal diseases in paediatric patients with cancer or post-haematopoietic cell transplantation. *Lancet Oncol* 2021; **22(6)**:e254-69. doi: 10.1016/s1470-2045(20)30723-3.
13. Gioia F, Walti LN, Orchanian-Cheff A, Husain S. Risk factors for COVID-19-associated pulmonary aspergillosis: A systematic review and meta-analysis. *Lancet Respir Med* 2024; **12(3)**:207-16. doi: 10.1016/s2213-2600(23)00408-3.
14. Koehler P, Bassetti M, Chakrabarti A, Chen SCA, Colombo AL, Hoenigl M, *et al*. Defining and managing COVID-19-associated pulmonary aspergillosis: The 2020 ECMM/ISHAM consensus criteria for research and clinical guidance. *Lancet Infect Dis* 2021; **21(6)**:e149-62. doi: 10.1016/s1473-3099(20)30847-1.
15. Huang SF, Ying-Jung Wu A, Shin-Jung Lee S, Huang YS, Lee CY, Yang TL, *et al*. COVID-19 associated mold infections: Review of COVID-19 associated pulmonary aspergillosis and mucormycosis. *J Microbiol Immunol Infect* 2023; **56(3)**: 442-54. doi: 10.1016/j.jmii.2022.12.004.
16. Gangneux JP, Dannaoui E, Fekkar A, Luyt CE, Botterel F, De Prost N, *et al*. Fungal infections in mechanically ventilated patients with COVID-19 during the first wave: The French multicenter MYCOVID study. *Lancet Respir Med* 2022; **10(2)**:180-90. doi: 10.1016/s2213-2600(21)00442-2.
17. Salanti G, Higgins JP, Ades AE, Ioannidis JP. Evaluation of networks of randomized trials. *Stat Methods Med Res* 2008; **17(3)**:279-301. doi: 10.1177/0962280207080643.
18. Mavridis D. Network meta-analysis in a nutshell. *Evid Based Ment Health* 2019; **22(3)**:100-1. doi: 10.1136/ebmental-2019-300104.

19. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, *et al*. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: Checklist and explanations. *Ann Intern Med* 2015; **162(11)**:777-84. doi: 10.7326/m14-2385.
20. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, *et al*. The cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; **343**:d5928. doi: 10.1136/bmj.d5928.
21. Hrobjartsson A, Boutron I, Turner L, Altman DG, Moher D. Assessing risk of bias in randomised clinical trials included in Cochrane reviews: The why is easy, the how is a challenge. *Cochrane Database Syst Rev* 2013; **2013(4)**:Ed000058. doi: 10.1002/14651858.ed000058.
22. Chaimani A, Higgins JP, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STATA. *PloS One* 2013; **8(10)**:e76654. doi: 10.1371/journal.pone.0076654.
23. DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. *Contemp Clin Trials* 2015; **45(Pt A)**:139-45. doi: 10.1016/j.cct.2015.09.002.
24. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* 2014; **14**:135. doi: 10.1186/1471-2288-14-135.
25. Kwak S. Are only p-values less than 0.05 significant? A p-value greater than 0.05 is also significant! *J Lipid Atherosler* 2023; **12(2)**:89-95. doi: 10.12997/jla.2023.12.2.89.
26. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol* 2011; **64(2)**:163-71. doi: 10.1016/j.jclinepi.2010.03.016.
27. Leenders AC, Daenen S, Jansen RL, Hop WC, Lowenberg B, Wijermans PW, *et al*. Liposomal amphotericin B compared with amphotericin B deoxycholate in the treatment of documented and suspected neutropenia-associated invasive fungal infections. *Br J Haematol* 1998; **103(1)**:205-12. doi: 10.1046/j.1365-2141.1998.00944.x.
28. Cornely OA, Maertens J, Bresnik M, Ebrahimi R, Ullmann AJ, Bouza E, *et al*. Liposomal amphotericin B as initial therapy for invasive mold infection: A randomised trial comparing a high-loading dose regimen with standard dosing (AmBiLoad trial). *Clin Infect Dis* 2007; **44(10)**:1289-97. doi: 10.1086/514341.
29. Boyer J, Feys S, Zsifkovits I, Hoenigl M, Egger M. Treatment of invasive aspergillosis: How it's going, Where It's heading. *Mycopathol* 2023; **188(5)**:667-81. doi: 10.1007/s11046-023-00727-z.
30. Johnson MD. Antifungals in Clinical Use and the Pipeline. *Infect Dis Clin North Am* 2021; **35(2)**:341-71. doi: 10.1016/j.idc.2021.03.005.
31. Perez-Cantero A, Lopez-Fernandez L, Guarro J, Capilla J. Azole resistance mechanisms in Aspergillus: Update and recent advances. *Int J Antimicrob Agents* 2020; **55(1)**:105807. doi: 10.1016/j.ijantimicag.2019.09.011.
32. Biswas M, Shobana J, Jinda P, Sukasem C. Azole antifungals and inter-individual differences in drug metabolism: the role of pharmacogenomics and precision medicine. *Expert Opin Drug Metabol Toxicol* 2023; **19(3)**:165-74. doi: 10.1080/17425255.2023.2203860.
33. Mikus G, Scholz IM, Weiss J. Pharmacogenomics of the triazole antifungal agent voriconazole. *Pharmacogenomics* 2011; **12(6)**:861-72. doi: 10.2217/pgs.11.18.
34. Zonios D, Yamazaki H, Murayama N, Natarajan V, Palmore T, Childs R, *et al*. Voriconazole metabolism, toxicity, and the effect of cytochrome P450 2C19 genotype. *J Infect Dis* 2014; **209(12)**:1941-8. doi: 10.1093/infdis/jiu017.
35. Shu Y, Shi Y, Yang Y, Dong Z, Yi Q, Shi H. Progress of triazole antifungal agent posaconazole in individualized therapy. *J Clin Pharm Ther* 2022; **47(12)**:1966-81. doi: 10.1111/jcpt.13821.
36. Marty FM, Ostrosky-Zeichner L, Cornely OA, Mullane KM, Perfect JR, Thompson GR 3rd, *et al*. Isavuconazole treatment for mucormycosis: A single-arm open-label trial and case-control analysis. *Lancet Infect Dis* 2016; **16(7)**:828-37. doi: 10.1016/s1473-3099(16)00071-2.
37. Herbrecht R, Kuessner D, Pooley N, Posthumus J, Escrig C. Systematic review and network meta-analysis of clinical outcomes associated with isavuconazole *versus* relevant comparators for patients with invasive aspergillosis. *Curr Med Res Opin* 2018; **34(12)**:2187-95. doi: 10.1080/03007995.2018.1502659.