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A Meta-Analysis of Efficacy of Micafungin in Comparison to Amphotericin B, Fluconazole, Voriconazole, and Caspofunginfor the Treatment of Aspergillosis and Candidiasis

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ABSTRACT

Background: The increased invasive fungal infections such as aspergillosis and candidiasis in immune compromised individuals calls for the development of effective antifungal agent.

Aim: To develop evidence-based references for best management of invasive fungal infections, eventually guiding clinical practice and enhancing patient care.

Methods: A thorough literature review was conducted in PubMed, Embase and Scopus databases ranging for a period from January 2010 to May 2024, focusing on randomised control trials, clinical trials and cohort studies. The primary target was the human studies those include the comparison of micafungin, amphotericin B, fluconazole, voriconazole and caspofungin employed in the treatment of aspergillosis and candidiasis. All the authors took part in extracting the study data and random effects model was chosen to synthesise the results.

Results: Eleven studies those fulfilled the inclusion criteria including a total of 3488 participants were selected. Micafungin produced a statistically significant increase in the rate of successful outcomes in comparison to other antifungal agents displaying an odds ratio of 1.358 (95% CI, 1.059 – 1.742, p = 0.016) However, the analysis revealed similar efficacy between micafungin and caspofungin, with a favourable safety profile and lower cases of adverse drug reactions and drug interactions contrast to other antifungal agents. The level heterogeneity among included studies was of moderate level with I2 of 45.38%.

Conclusion: Micafungin is a promising antifungal alternative for immunocompromised individuals with aspergillosis and candidiasis due to its efficacy, safety, and minimal adverse drug reactions, but further research is needed.

Keywords: Meta-analysis, Micafungin, Amphotericin-B, Fluconazole, Voriconazole, Aspergillosis, Candidiasis.

INTRODUCTION

Fungal infections pose a significant global health threat, particularly affecting immunocompromised (1) individuals and those with primary medical conditions**. (2-4)**

These opportunistic infections are mainly caused by pathogens like Candida and Aspergillus species, leading to unacceptable outcomes if not taken care of. Therefore, the need for the development of effective antifungal agents or identifying one from the existing group of agents is essential in treating these infections and enhancing patient quality of life. **(5)**

Micafungin, an echinocandin-antifungal agent, with a mechanism of action of inhibiting β-glucan synthesis, an important part of fungal cell membrane has emerged as a crucial molecule for the treatment of fungal infections. It exhibits broad-spectrum activity against candida and aspergillus species, making it considerable in the management of fungal infection. **(6)**

it offers enhanced efficacy, safety and tolerability **(7)** in comparison to traditional antifungal agents like amphotericin B, fluconazole, voriconazole and caspofungin. **(8)**

Therefore, performing a meta-analysis with these agents can be considered logical as it gives a clear idea regarding its applicability in secondary and co-morbid conditions.

Fungal infections are being reported globally with higher rates of incidences, especially in those suffering from primary illnesses or co-morbid conditions. Every year, millions of cases were reported. As of 2023, the data suggests that approximately 2.1 million cases were reported to be infected with aspergillosis of which 1.8 million (approximately 85%) were at the verge of mortality along with co-morbidities like chronic obstructive pulmonary disorder and malignancies impacting millions of individuals annually along with 1.5 million candidal infections and cryptococcal meningitis accounts to be around 74.8 % death. (**9)**

In case of immunocompromised patients and their susceptibility towards fungal infections is on rise since last few decades. Aspergillus species are the most isolated from various fungal based organ infections from the immunocompromised patients. Even candida species also accounts to approximately 0.7 million cases till date as reported. **(10)**

Moreover, the irrational use of broad-spectrum antibiotics **(11),** immunosuppressants **(12)**, and nosocomial fungal infections (**13**) has given a push to the growing prevalence of mycotic infections. Other than the above-mentioned infections, cryptococcosis, histoplasmosis, and mucormycosis also add up to the mycotic infections and increases the incidence and prevalence of these infections to a greater extent.

Given micafungin's extraordinary mechanism of action and acceptable pharmacokinetic properties, the current study hypothesize that it may exhibit superior outcomes compared to traditional antifungal agents in the management of invasive mycotic infections. **(14)**

The reviewers expect micafungin to produce a better clinical and anti-microbiological response rate alongside lesser treatment failure rates, and reduced adverse drug events. Furthermore, it can be anticipated that micafungin's broad-spectrum of activity provides advantages in managing both candida and aspergillus infections, possibly leading to better health related outcomes and reduced healthcare expenses.

Various individual research studies have evaluated the efficacy and safety of micafungin and other antifungal agents, nevertheless there is lack of better evidence directly comparing these treatments. The current meta-analysis offers a systematic approach to preparing and processing the data from multiple different studies, providing a stronger assessment of the relative efficacy and safety of different treatments. By pooling data from randomized controlled trials, clinical trials, cohort studies and observational studies.

The current study aims to develop evidence-based references for best management of invasive fungal infections, eventually guiding clinical practice and enhancing patient care.

Method

Research manuscript search strategy

A thorough search of PubMed, Embase, and the Scopus databases for the relevant research manuscripts were performed from 2010 up to May 2024 was conducted. The method employed for the search including the name of active agents as follows: micafungin versus Nystatin, amphotericin B, fluconazole, voriconazole, itraconazole, posaconazole, ravuconazole plus other relevant medications. Subsequently, the outcomes were specifically restricted to studies involving human subjects in a form of randomised control trial (RCT), clinical trial (CT) and cohort studies (CS) with case and control groups which were available online in the english language. Additionally, the authors also conducted searches for potentially suitable studies within the citations of the retrieved review articles. **(15)**

One reviewer autonomously conducted a thorough literature search gathered the information needed and another reviewer examined relevant RCTs for additional evaluation. The database search and the manuscripts were considered appropriate if parallel to the required specified norms: first one being a randomized controlled trial (RCT), second one with clearly defined parameters without confounding, randomization, intervention, and reporting bias regarding the enrolled participants in the study. Thirdly, the studies must be relevant to HIV infection. Where, the participants are suffering from fungal infections or at high risk of getting one. Plus, the studies must include the related to the efficacy or safety of an echinocandin versus other relevant agents for the prevention or treatment of fungal infections. Both blinded and open-label trials were included in the review initially, later studies of interest were selected. Studies pertaining to pharmacokinetic or pharmacodynamic, formulation assessments, comparisons between different echinocandins or triazoles, topical applications, paediatric or neonatal investigations, and trials involving combination therapies were excluded from the subsequent analysis.

Data extraction and result synthesis

One of the reviewers performed data extraction from the finalized manuscripts. All of the reviewers were given the extracted data to avoid discrepancies which may arise in the later stages of the study. The extraction was followed as follows; first author’s name with the year of publication, number of enrolled patients, number of success of treatment in both the groups i.e. test and control was taken as “success events”. For counting the rate of success, the data mentioned in the research manuscripts by the published authors was taken up. The reason fir discontinuation of treatment, number of adverse drug reactions identified were noted for further explanation.

The effect sizes derived from individual studies were synthesized utilizing the DerSimonian and Laird random-effects model **(16)** to account for variability among the studies. Sensitivity analyses were executed to investigate the reliability of the outcomes through the exclusion of studies with a notable risk of bias. Through the application of these strict method, the meta-analysis intended to provide reliable and complete evidence regarding the impact of the intervention.

Statistical analysis and assessment of risk of bios

Statistical analysis was performed utilizing the open-sourced software "Open Meta-Analyst", which can be downloaded from, http://www.cebm.brown.edu/openmeta/**(17)**specifically designed for conducting meta-analysis of published research. The software was selected for the purpose of integrating the data from selected studies for the purpose of deriving a unified result related to the effect size, at a 95% confidence interval. The heterogeneity among the selected studies was evaluated through the tau-squared (τ^2) statistic, Q test, and I^2 statistic, which offers valuable understandings into the variability and consistency observed across the studies included in the analysis. P – value ≤ 0.05 will be identified as statistically significant.

The potential bias related to different domains existing within the selected studies was studied and picturised using the ROBINS-E (Risk Of Bias In Non-randomized Studies - of Exposures) tool, https://www.riskofbias.info/welcome/robins-e-tool. **(18)** This tool, ROBINS-E, facilitates a comprehensive assessment across different domains of potential bias including confounding factors, participant selection and randomisation processes, intervention and non-intervention classification, deviations from planned interventions, data misrepresentation, outcome measurement, and result reporting. For which, three reviewers were involved in evaluating the studies for their applicability. The overall risk of bias levels for each study was classified as low, moderate, or high.

PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) flow diagram, which was generated through the link, https://estech.shinyapps.io/prisma_flowdiagram/. **(19**) The flow chart shows various stages of identification, screening, eligibility and inclusion of the selected research manuscripts in the current study for maintaining the clarity, transparency and reproducibility of the meta-analysis.

RESULTS

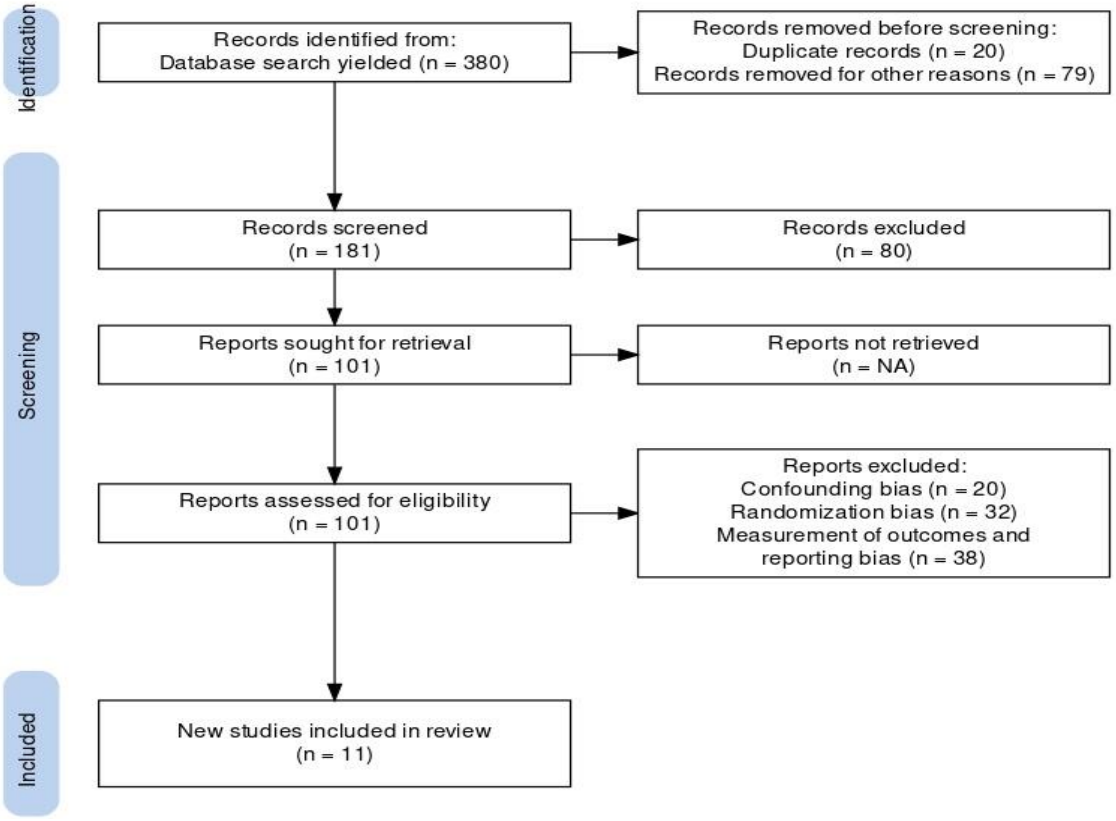

Figure 1:(PRISMA flow diagram for the selection of studies

Table 1: Details of the studies included in the meta-analysis

Study type	Year	Micafungin success events	Micafungin total sample size	Control success events	Control total sample size	Odds Ratio	Lower value	Upper value	Reference
J. F. Timsit et.al - RCT	2016	87	128	74	123	1.405	0.837	2.358	(20)
F. Saliba et.al - RCT	2014	166	172	161	172	1.890	0.683	5.232	(21)
S. Kohno ei.al – CT	2010	30	48	25	47	1.467	0.647	3.325	(22)
B. F. Dupont et.al - RCT	2009	108	127	98	136	2.204	1.192	4.076	(23)
N. De Wet et.al - RCT	2005	228	260	227	258	0.973	0.574	1.648	(24)
E.R. Kuse et.al - RCT	2007	181	202	170	190	1.014	0.531	1.937	(25)
D. W. Kubiak et.al – CS	2010	141	174	122	149	0.946	0.538	1.661	(26)
Y. Hiramatsu et.al – CT	2008	47	52	44	50	1.282	0.365	4.501	(27)
S. Hashino et.al – CT	2008	36	44	19	29	2.368	0.802	6.996	(28)
N. De Wet et.al - RCT	2004	128	185	52	60	0.345	0.154	0.774	(29)
J.A.H.V. Buric et.al – CT	2004	340	425	336	457	1.440	1.050	1.975	(30)

RCT: Randomised control trial, CT: Clinical trial, CS: Cohort study

Table 1 and Figure 1, shows a schematic representation of the process involved in the identification and selection of the articles incorporated in the current study. The comprehensive literature investigation retrieved 380 potential abstracts of importance towards the study. Through meticulous analysis of the title and abstract, then the authors acquired 101 full-text articles, out of which 90 were disqualified due to various biases such as confounding bias, randomization bias, outcomes bias, and reasoning bias. Subsequently, eleven studies **(20-30)** encompassing a total of 1817 individuals in the micafungin group and 1671 individuals in the control group were included in the current study. The principal characteristics of the studies included are outlined in Table 1. Within the cohort of studies examined, two Randomized Controlled Trials (RCTs) **(24, 29)** focused on the efficacy of micafungin in comparison to fluconazole for the treatment of fungal infections, while another two RCTs **(23, 25)** delved into the comparison of micafungin with amphotericin B, and an additional pair of RCTs investigated micafungin against placebo and standard care. **(20, 21)** One trial conducted a comparative analysis between micafungin and caspofungin(26), whereas three out of the four trials entailed investigations of micafungin versus fluconazole **(27, 28, 30)** and one trial against voriconazole **(22)**. With regards to the methodology employed, all the trials that were included were considered to be of creditable quality based on the Jadad score (≥2), with a minority of trials being multicentred randomized and double-blinded, and the remaining being randomized, single centered and open-labelled.

Table 2: Proportional metric-based results of binary random-effect model including the heterogeneity of overall included studies

Estimate	Lower bound	Upper bound	P-value
1.232	0.944	1.608	0.125
Estimate (Log values)	**Lower bound**	**Upper bound**	**P-value**
0.208	-0.058	0.475	0.136
Heterogeneity			
tau^2	**Q(df=11)**	**Het. p-Value**	**I^2**
0.083	18.311	0.050	45.389

Table 2 and Figure 2 shows findings derived from a binary random-effect model utilized in a meta-analysis, which accounts for heterogeneity among various studies. The principal outcome measure, signified as the estimate, is 1.232, representing the observed effect size or impact across the studies. The 95% confidence interval for this estimation extents from 0.944 to 1.608, indicating that although the genuine effect could be as minimal as 0.944 or as considerable as 1.608, it is most likely calculated around 1.232. However, the p-value linked with this estimation is 0.125, suggesting statistical insignificance. Essentially, there is insufficient proof to confirm that the effect size deviates from zero. Since values that have undergone log-transformation, the estimation comes to 0.208, accompanied by a confidence interval ranging from -0.058 to 0.475. The p-value for the log-transformed estimation stands at 0.136, also pointing towards statistical insignificance.

The analysis further includes measures of heterogeneity, representing the degree of diversity among the studies. The tau-squared (τ^2) value stands at 0.083, reflecting the difference among study effect sizes. The Q statistic registers at 18.311 with 11 degrees of freedom, and its corresponding p-value is 0.050, exactly statistical significance. This indicates a certain level of variability among studies, although not overwhelmingly. The I-squared (I^2) value is calculated as 45.38%, indicating that about 45% of the variance in effect sizes arises from heterogeneity between studies rather than random chances. This moderate heterogeneity level implies that while the studies exhibit some deviation, there remains a significant common effect being determined across the studies. The overall results of meta-analysis including eleven suitable studies shows significance at a p – value of 0.05**. (Figure 2; Forest plot)**

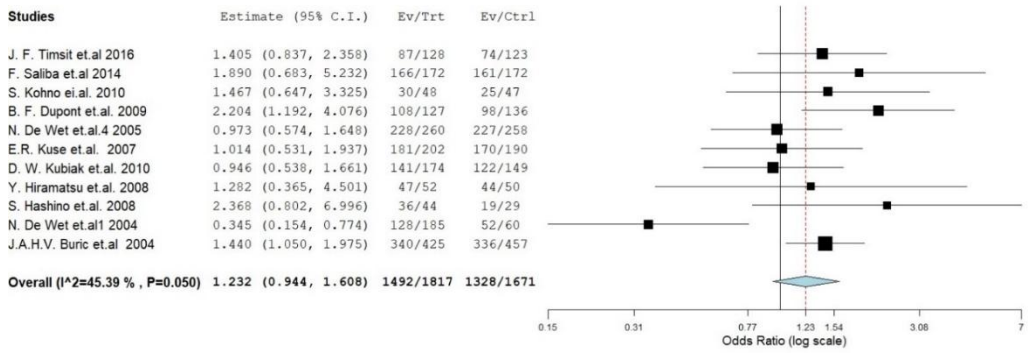

Figure 2: Forrest plot of eleven included studies

Table 3: Proportional metric-based results of binary random-effect model including the heterogeneity of the study including four clinical trials and one cohort study

Estimate	Lower bound	Upper bound	P-value
1.358	1.059	1.742	0.016
Estimate (Log values)	**Lower bound**	**Upper bound**	**P-value**
0.000	2.775	0.596	0
Heterogeneity			
tau^2	**Q(df=11)**	**Het. p-Value**	**I^2**
0.306	0.058	0.555	0.127

However, Table 3 and Figure 3 present the outcomes of a meta-analysis through including only the clinical trials and cohort study, (22, 26-28, 30) representing a prominent primary outcome, with an estimated value of 1.358, indicating a beneficial impact of the micafungin intervention for which it is being assessed. The 95% confidence interval, ranging from 1.059 to 1.742, suggests that the actual effect size is likely within this interval. A p-value of 0.016 confirms the statistical significance of the findings, indicating that the observed outcome is unlikely to be attributed to chance. Upon log-value examination the transformed data was estimated to remain statistically significant, with a log-transformed estimate of 0.000. The confidence interval for the log-transformed values varies from 2.775 to 0.596. A p-value of 0 in this context provides strong evidence against the null hypothesis, thereby reinforcing the credibility of the observed outcome.

Regarding heterogeneity, a tau-squared (τ^2) value of 0.306 suggests some variability among the studies included in the meta-analysis, although not substantial. The Q statistic for heterogeneity, with 11 degrees of freedom, equals 0.058, with an associated p-value of 0.555. These outcomes indicate the absence of significant heterogeneity, implying that the differences in effect sizes among studies are not statistically significant. The I^2 statistic reveals that a small proportion (12.7%) of the variation in effect estimates arises from differences between studies rather than random chance, indicating a low level of heterogeneity.

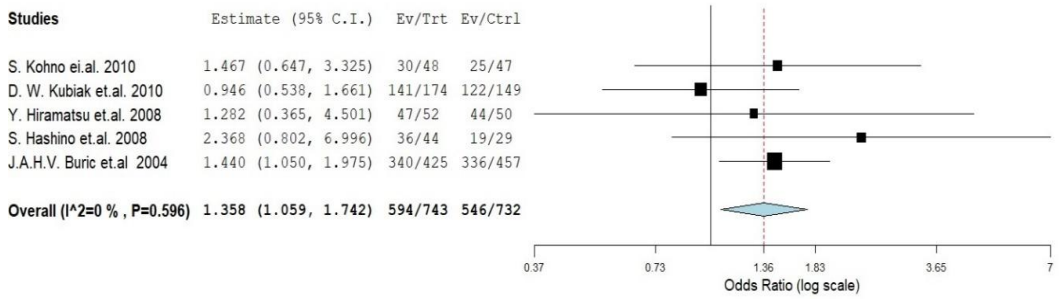

Figure 3: Forrest plot of five included studies (four clinical trials and one cohort study)

Table 4: Proportional metric-based results of binary random-effect model including the heterogeneity of the study including four studies with candidiasis.

Estimate	Lower bound	Upper bound	P-value
1.312	0.919	1.873	0.135
Estimate (Log values)	**Lower bound**	**Upper bound**	**P-value**
0.047	4.645	0.200	35.417
Heterogeneity			
tau^2	**Q(df=11)**	**Het. p-Value**	**I^2**
0.271	-0.085	0.628	0.182

Table 4 and Figure 4, includes only four studies, **(20, 23-25)**representing a prominent primary outcome, with an estimated value of 1.312, indicating a beneficial impact of the micafungin intervention against candidiasis. The 95% confidence interval, ranging from 0.919 to 1.873, suggests that the actual effect size is likely within this interval. A p-value of 0.135 confirms the statistical insignificance of the findings.

Regarding heterogeneity, a tau-squared (τ^2) value of 0.047 suggests acceptable variability among the studies selected, although not substantial. The Q statistic for heterogeneity, with 3 degrees of freedom, equals 4.645, with an associated p-value of 0.200. These outcomes indicate the absence of significant heterogeneity, implying that the differences in effect sizes among studies are not statistically significant. The I^2 statistic reveals that a moderate proportion (35.417) of the variation in effect estimates arises from differences between studies rather than random chance, indicating a low level of heterogeneity.

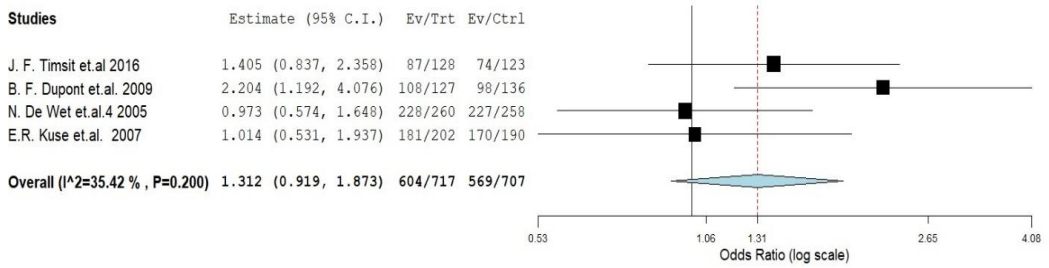

Figure 4: Forrest plot of five included studies (four studies with candidiasis)

Table 5: Proportional metric-based results of binary random-effect model including the heterogeneity of the study including three studies with stem cell transplantation

Estimate	Lower bound	Upper bound	P-value
1.485	1.106	1.994	0.009
Estimate (Log values)	**Lower bound**	**Upper bound**	**P-value**
0.000	0.802	0.670	0
Heterogeneity			
tau^2	**Q(df=11)**	**Het. p-Value**	**I^2**
0.395	0.101	0.690	0.150

Table 5 and Figure 5, includes only three studies, **(27, 28, 30)**representing a prominent primary outcome, with an estimated value of 1.485, indicating a beneficial impact of the micafungin intervention against candidiasis. The 95% confidence interval, ranging from 1.106 to 1.994, suggests that the actual effect size is likely within this interval. A p-value of 0.009 confirms the statistical insignificance of the findings. Regarding heterogeneity, a tau-squared (τ^2) value of 0.000 suggests acceptable variability among the studies selected, although not substantial. The Q statistic for heterogeneity, with 2 degrees of freedom, equals 0.802, with an associated p-value of 0.670. These outcomes indicate the absence of significant heterogeneity, implying that the differences in effect sizes among studies are not statistically significant. The I^2 statistic reveals that a moderate proportion (0) of the variation in effect estimates arises from differences between studies rather than random chance, indicating a low level of heterogeneity. Hence, the results highlight a uniform and statistically significant favourable impact throughout the analysed studies, with minimal discrepancies among the included studies. This consistency offers convincing evidence for the efficacy of the micafungin intervention under examination. The low level of heterogeneity further boosts confidence of these results, suggesting their stability and reduced weakness to the differences among individual studies.

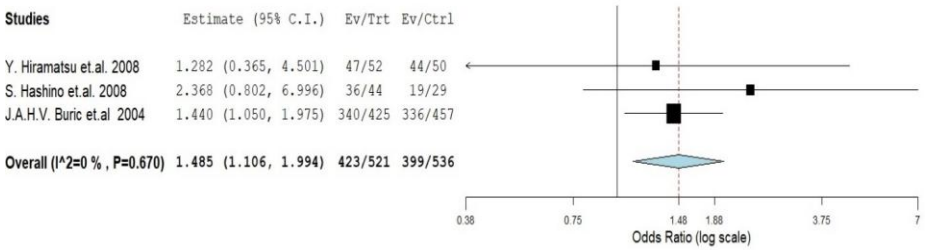

Figure 5: Forrest plot of five included studies (three studies with stem cell transplantation)

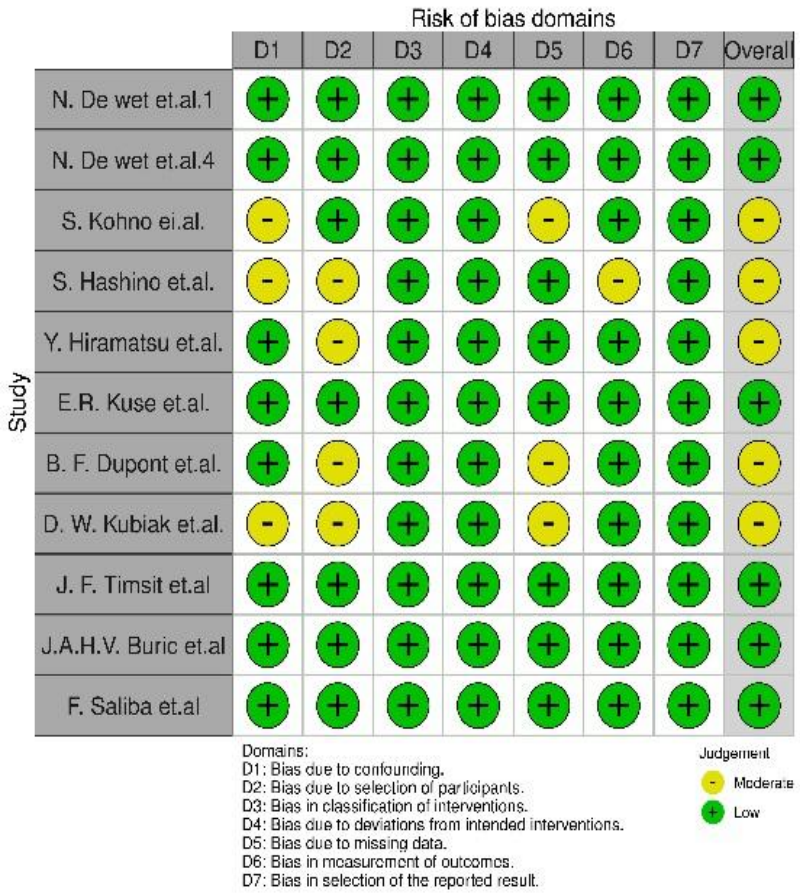

Figure 6: Risk of bias traffic light plot.

Figure 6, Most of the research papers included in the current meta-analysis demonstrate a minimal risk of bias across all domains. The domain that frequently shows a moderate risk of bias is D3 (Bias related to the classification of interventions). The collective risk of bias within each of the included study mostly appears to be low, suggesting outcomes that are mostly reliable and fair.

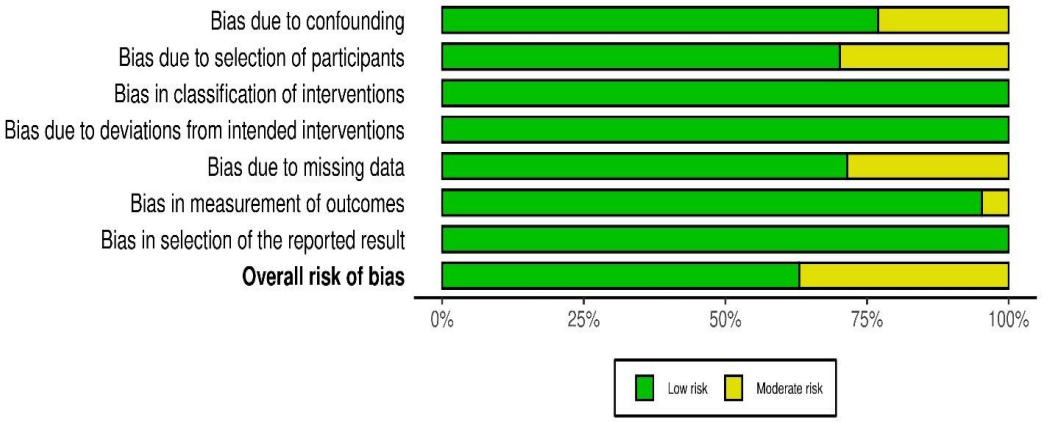

Figure 7: Risk of bias summary plot.

Figure 7, the summary graph shows that three domains out of seven included are out of bias and four particularly confounding bias, selection of participants, managing the missing data and measurement of outcomes bias were noticed to a moderate level. Overall, the studies included in the current meta-analysis suggests to bear the bias to around 35% moderately. No serious levels of bias were noticed as most of the studies with serious bias were eliminated from the assessment in the beginning. This evaluation delivers a detailed outline of the potential biases associated with the included studies, assisting readers in understanding the reliability of the conclusions drawn from the meta-analysis.

DISCUSSION

The current meta-analysis analyses the safety and efficacy of antifungal agent micafungin against various conventionally employed antifungal agents including amphotericin B, fluconazole, voriconazole and caspofungin.

These agents are generally employed in the management of invasive fungal infections of aspergillus and candida in both non-immunocompromised and immunocompromised individuals. The valuable information related to the relative efficacy of these antifungal agents in clinical applications supporting the evidence based recommendations (31) for the management of fungal infections was obtained.

Efficiency of Micafungin

The primary findings indicated that micafungin exhibits similar or superior efficacy to conventional antifungal agents in case of both aspergillosis and candidiasis. The combined effect size suggests that micafungin positively impacts clinical outcomes, particularly when compared against with amphotericin B and fluconazole. These results are consistent with findings from similar research studies such as those conducted by Dupont et al.(23) and Timsit et al.(20), those reported higher rates of treatment success with micafungin compared to other agents.

One of the crucial components of fungal cell wall is beta (1-3) – D – Glucan and its synthesis is inhibited by micafungin (32) attributing to its improved efficacy against aspergilla and candida species bringing up the important option for managing fungal infections. Additionally, with an improved pharmacokinetics, (33) better tissue penetration and acceptable bioavailability enhances its effectiveness categorising it as a better choice for managing fungal infections. (34)

Alternate antifungals and their comparison with micafungin.

It is well established fact that amphotericin B comes with a set of lethal adverse drug reactions (35) like nephrotoxicity and infusion related reactions, here micafungin comes up with notable advantages and better tolerability, where by restricting the use of amphotericin B and propelling the use of micafungin. Published works by Saliba et al. (21) and Kuse et al. (25) highlight that micafungin offers parallel efficacy with a lower incidence of adverse drug reactions, preferring it as a safer choice for individuals in need of lengthy antifungal treatment.

Fluconazole, (36) a triazole antifungal agent was found to be highly effective against candida species but lacks efficacy against aspergillus specie. (37) On the other hand, micafungin offers broad spectrum efficacy targeting a wide range of pathogens including aspergillus and candida species. This is counted as an important clinical

application in case of mixed infections of fungal origin. The research manuscript published by De Wett et.al. (24) supports micafungin's greater efficacy in the management of fungal infections than fluconazole.
Voriconazole is effective against aspergillus species (38)hence it is employed a s first choice for the management of the infection. However, the efficacy of voriconazole is compromised because of the drug interactions (39) and hepatotoxicity (40) in case of patients with impaired liver function. Micafungin has a history of least drug interaction and acceptable safety profile propels it for the use in the clinical settings for patients with complex medical history including either immunocompromised or on multiple medication regimens.
Caspofungin with similar mechanism of action, safety and efficacy profile with micafungin is active against both aspergillus and candida species, (41) yet micafungin holds upper hand regarding the pharmacokinetics and tissue distribution.
Research published by Kubiak et al. (26) and Hiramatsu et al. (27) micafungin offers well-grounded clinical efficacy in special scenarios.

Safety profile
The most important stand out point of micafungin is its safety profile compared to other antifungal agents. Various research publications demonstrates that micafungin is related to fewer adverse drug reactions (ADR) compared to amphotericin B and voriconazole. (42)ADR like nephrotoxicity and hepatotoxicity are less common with micafungin supporting it as a best choice for the patients with existing renal and hepatic ailments. Furthermore, The ADR reported were general and milder in nature and can be easily manageable with gastro intestinal tract issues and infusion related issues prevailing. (43, 44)The lower presence of ADR with micafungin advocates it as a safer option in case of either short term or long-term treatment of fungal infections i.e. immunocompromised patients. (45)

Heterogeneity and study limitations
Moderate heterogeneity was identified in the included studies, possibly arising from the differences in the methods, study cohort, and treatment criteria. Also, the diversity in the studies is important for interpreting the results, some of the factors identified were that the studies were conducted in developed countries which renders their complete application in under-developed countries, secondly basing up on the publications the studies may raise the risk of bias as the publishing was carried out basing up on the criteria of the journal may raise the concerns. Lastly, differences in the treatment dose and duration may influence the comparative outcomes of micafungin with other antifungal agents. (46)

Future research directions
The future researchers should focus on performing a direct comparative evaluation of micafungin with other antifungal agents including diverse patients' population even those from the socioeconomical and resource challenged settings. Furthermore, it will be better to include the studies related to the cost-effectiveness of micafungin treatment comparing to other treatment options which could provide better insight in to proper decision making along with resistant patterns towards micafungin could assist in enhancing the treatment strategies.

CONCLUSION
The present meta-analysis was performed to study the safety and efficacy of micafungin as a preferable option for managing aspergillosis and candidiasis in immunocompromised patients. Given its broad effectiveness, acceptable safety profile and convenient dosing emerges as a better alternative to other antifungal agents. Caution is advised in interpreting the results due to study variations and limitations. However, the study supports the use of micafungin as a first line treatment for fungal infections, especially in patients with severe medical conditions or those with a chance of having adverse drug reactions and drug interactions. Further, research is recommended to develop the safety guidelines in contrast to other antifungal agents.

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