Efficacy and safety of antifungal prophylaxis in surgical intensive care unit patients: A systematic review and meta-analysis of randomized controlled trials

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Abstract. Invasive fungal infections (IFIs) are serious complications among surgical intensive care unit (ICU) patients, leading to substantial morbidity and mortality. Antifungal prophylaxis and pre-emptive strategies are employed to reduce the risk of such infections, although their effectiveness and safety remain subjects of debate. The present systematic review and meta-analysis included randomized controlled trials evaluating antifungal prophylaxis or pre-emptive therapy in surgical ICU patients. Searches in the PubMed, Scopus, Google Scholar and Science Direct databases up to February 2025 identified 11 eligible studies. Pooled analyses demonstrated that antifungal prophylaxis significantly reduced the risk of IFIs [risk ratio (RR)=0.63; 95% CI, 0.50-0.78; P<0.0001]. While azoles were effective, polyenes and echinocandins did not show a significant effect. No significant effect on overall mortality was observed (RR=0.99; 95% CI, 0.75-1.31; P=0.9186), and there was no increased risk of severe adverse events (RR=0.98; 95% CI, 0.70-1.36) or liver dysfunction (RR=0.91; 95% CI, 0.31-2.65). The analysis did not reveal strong evidence of publication bias as evaluated by funnel plots. Overall, the results indicated that antifungal prophylaxis appeared to be effective in reducing the risk of IFIs in surgical ICU patients without elevating the risk of serious side effects. The implementation of this therapy should be targeted toward high-risk populations, considering the antifungal type, local resource availability and antimicrobial management parameters. The evidence of prophylaxis therapy in low-risk population is limited, since the majority of included studies in the present meta-analysis analyzed high-risk populations.

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Introduction

Invasive fungal infections (IFIs) are serious complications among patients admitted to surgical intensive care units (ICUs), driven by profound alterations in host microbiota and secondary immunosuppression. Surgical ICU patients face a unique constellation of predisposing factors, including broad-spectrum antibiotic use leading to dysbiosis, major surgical procedures that disrupt natural barriers, indwelling intravascular catheters that facilitate bloodstream invasion, mechanical ventilation that impairs mucociliary clearance, and immunocompromising conditions due to comorbidities or immunosuppressive therapy (1). Among the causative pathogens, *Candida* species predominate, often resulting in substantial morbidity, prolonged hospitalization, higher healthcare costs and mortality rates that remain unacceptably high despite advances in critical care (2).

IFI caused high rates of mortality in the surgical ICU. The Extended Prevalence of Infection in Intensive Care/EPIC II study, which collected data from 75 countries, reported that fungal infections accounted for 19.4% of all ICU infections, with *Candida albicans* as the most frequent species with

prevalence of 6.9 per 1,000 patients (3,4). A previous study reported a candidiasis prevalence of 3.5% among ICU patients with a mortality rate of 81.8% (5). Similarly, a study in a developing country (Indonesia) showed that *Candida* species accounted for 92.2% of ICU fungal infections, with a 50% mortality rate (6). While incidence rates differ substantially between developed and developing countries, mortality remains high, ranging from 50 to 81.8% (3-6). These findings may reflect the gap in diagnostic capabilities to detect IFI between countries, but despite that, the treatment of IFI is still a substantial issue given the high mortality rates. These figures underscore the substantial burden of IFIs in surgical ICUs and the pressing need for effective preventive strategies.

Antifungal prophylaxis has been proposed as an intervention to reduce IFI incidence in high-risk surgical ICU populations by suppressing fungal colonization, preventing invasive disease, improving clinical outcomes, and reducing the economic burden of prolonged and complex care (7). Treatment of fungal IFI often requires weeks of antifungal administration in the ICU and increases the risk of drug interactions since some commonly used agents, such as azoles, could interfere with the metabolism of other drugs (7). However, its use remains controversial due to concerns about antifungal resistance, biofilm formation, drug-related toxicity and cost implications (8-11). Randomized controlled trials (RCTs) evaluating antifungal prophylaxis in surgical ICU patients have yielded conflicting results, with certain trials demonstrating notable reductions in IFI incidence and others showing no meaningful benefit (8,9).

To date, to the best of our knowledge, no meta-analysis has specifically examined the effectiveness of antifungal prophylaxis in preventing IFIs in postoperative surgical ICU patients, regardless of the underlying diagnosis. Existing meta-analyses have largely focused on very specific population such as patients with critical illness, hematologic malignancies or hematopoietic stem cell transplantation, limiting their applicability to surgical ICU settings (2,12). A previous notable meta-analysis on fluconazole prophylaxis in critically ill surgical patients reported reduced IFI incidence but no survival advantage (12).

Given the heterogeneity and inconclusive nature of the available evidence, there is a critical need for a comprehensive systematic review and meta-analysis focused on surgical ICU patients. Such an analysis could provide a robust evidence base for clinical decision-making and policy development regarding antifungal prophylaxis in this high-risk population. The present study aimed to address this gap by analyzing data from RCTs to evaluate the efficacy and safety of antifungal prophylaxis in reducing IFI incidence and improving clinical outcomes in postoperative surgical ICU patients, thereby guiding evidence-based practice to enhance patient safety and optimize healthcare resource utilization.

Materials and methods

Study design. The current systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (13). The study protocol was prospectively registered in the International Prospective Register of Systematic Reviews with registration no. CRD420251013674 (https://www.crd.york.ac.uk/PROSPERO/view/CRD420251013674).

Literature search strategy. A comprehensive literature search was performed based on the Population, Intervention, Comparator, Outcome and Study design criteria (13). The search was conducted using PubMed (pubmed.ncbi.nlm.nih.gov), Scopus (scopus.com), Google Scholar (scholar.google.com) and ScienceDirect (www.sciencedirect.com) from database inception to February 2025. The search strategy combined Medical Subject Headings and free-text terms related to the population, intervention, comparator and outcomes, with appropriate adjustments for each database (Table SI). For the population, search terms included 'intensive care units, surgical', 'surgical intensive care unit', 'SICU', 'critically ill patients', 'postoperative patients', 'septic shock', 'multiple organ dysfunction syndrome', 'mechanical ventilation' and 'total parenteral nutrition'. For the intervention, terms such as 'antifungal agents', 'antifungal prophylaxis', 'prophylactic antifungal therapy', 'pre-emptive antifungal therapy' and 'fungal infection prevention' were applied. For comparator, terms such as 'empirical antifungal therapy' and 'placebo' were applied. For outcomes, terms such as 'mortality', 'incidence', 'adverse events' and 'length of stay' were used. The search was not restricted by language or the earliest publication date. The reference lists of all included studies and relevant reviews were screened to identify additional eligible articles.

Eligibility criteria. Studies were eligible if they enrolled patients aged ≥12 years admitted to a surgical ICU, evaluated antifungal prophylaxis or pre-emptive therapy with agents such as azoles, echinocandins or polyenes, and compared these interventions with a placebo, no prophylaxis or an alternative antifungal agent. The primary outcome of interest was the incidence of IFIs, including candidemia and invasive candidiasis. Secondary outcomes included all-cause mortality, length of ICU stay and adverse events. Only RCTs were included. Studies were excluded if they involved exclusively medical ICU patients, neonatal ICU patients or solely immunosuppressed populations, unless these formed parts of a mixed surgical ICU cohort. Observational studies, case reports, case series, narrative reviews, editorials and *in vitro* or animal studies were not considered. Studies that did not report the incidence of IFIs or relevant clinical outcomes were also excluded.

Study selection. Two authors independently screened the titles and abstracts of all retrieved references to identify potentially relevant studies. The full-text articles of these studies were then assessed for eligibility according to the inclusion and exclusion criteria (Table I). Any disagreements between the authors were resolved through discussion or consultation with a third author. The study selection process was documented in a PRISMA flow diagram, which detailed the number of records identified, screened and included, as well as the reasons for exclusion at each stage.

Data extraction and management. Data from eligible studies were extracted independently by two authors using a standardized data extraction form to ensure consistency. The

Table I. Inclusion and exclusion criteria.

Component	Inclusion criteria	Exclusion criteria
Population	Studies with patients ≥12 years old in surgical ICUs.	Studies with non-surgical ICU patients (such as medical ICU and neonatal ICU). Studies with only immunosuppressed patients, unless part of a mixed surgical ICU population.
Intervention	Studies evaluating antifungal prophylaxis or pre-emptive therapy (fluconazole, echinocandins and amphotericin B, among others).	Studies evaluating treatment/therapy of fungal infections, not prophylaxis. Studies focusing solely on antifungal de-escalation strategies.
Comparator	Placebo or no antifungal prophylaxis. Comparisons between different antifungal agents.	NA
Outcomes	Primary: Incidence of fungal infection (such as candidemia and invasive candidiasis). Secondary: Mortality, length of stay at the ICU and adverse events.	Studies not reporting fungal infection incidence or other clinically relevant outcomes
Study design	RCTs.	Observational studies, case reports, case series, commentaries, editorials, narrative reviews, expert opinions, animal studies or *in vitro* studies.
Publication language	Any language (English and non-English).	NA

ICU, intensive care unit; RCT, randomized controlled trial; NA, not applicable.

extracted data included the following information: i) Study characteristics, such as author, year, country and setting; ii) patient demographics and clinical characteristics; ii) details of the antifungal intervention, including class, agent, dosage, route and duration; iv) comparator details; and v) outcomes, including the incidence of IFIs, mortality, length of stay at the ICU and adverse events such as liver function abnormalities, when the data were available. Discrepancies in the extracted data were resolved through consensus.

Risk of bias assessment. The risk of bias for the included RCTs was assessed using the Cochrane Risk of Bias 2.0 tool, which evaluates five domains: Bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome and bias in selection of the reported result (14). Each domain was rated as 'low risk', 'some concerns' or 'high risk' of bias. Visual summaries of the assessments were generated using the Risk-of-Bias VISualization tool (version 0.3.0.900) (15).

Data synthesis and statistical analysis. Meta-analysis was performed using RStudio and the 'meta' package version 8.2-1 (Posit Software, PBC). For dichotomous outcomes, pooled risk ratios (RRs) with 95% CIs were calculated. Heterogeneity among studies was assessed using the χ^2 test and quantified with the I^2 statistic. A random-effects model was used for all meta-analyses. Subgroup analyses were performed according to antifungal class (azole, echinocandin and polyene) and prophylaxis type (prophylactic vs. pre-emptive). Publication bias was assessed visually with funnel plots and statistically analyzed using Egger's test. A leave-one-out sensitivity analyses were conducted to evaluate the robustness of the results by excluding studies at high risk of bias. A leave-one-out sensitivity analysis was performed to evaluate the influence of each individual study on the overall pooled effect. The analysis sequentially excluded each RCT and recalculated the pooled RR to determine whether the findings were dependent on any single study. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Systematic search and study selection. The literature search identified a total of 1,578 records through database searches, with an additional 11 records identified through manual reference checks. After removing duplicates, 1,355 records remained for title and abstract screening. Of these, 1,066 records were excluded due to not meeting the eligibility criteria, leaving 289 articles for full-text assessment. Following a detailed review, 278 articles were excluded for reasons including non-RCT design, inappropriate patient population, irrelevant intervention or absence of predefined outcomes. Ultimately, 11 RCTs met the inclusion criteria and were included in the meta-analysis (9,16-25). The study selection process is presented as a PRISMA flow diagram in Fig. 1.

Quality assessment. All 11 included trials underwent risk of bias assessment using the Cochrane Risk of Bias 2.0 tool. Most trials exhibited low risk of bias across all domains, indicating good methodological rigor. Several studies showed 'some concerns' in several domains of evaluation. In total, 6 studies were evaluated as exhibiting 'some concerns' in the randomization process due to limitations in

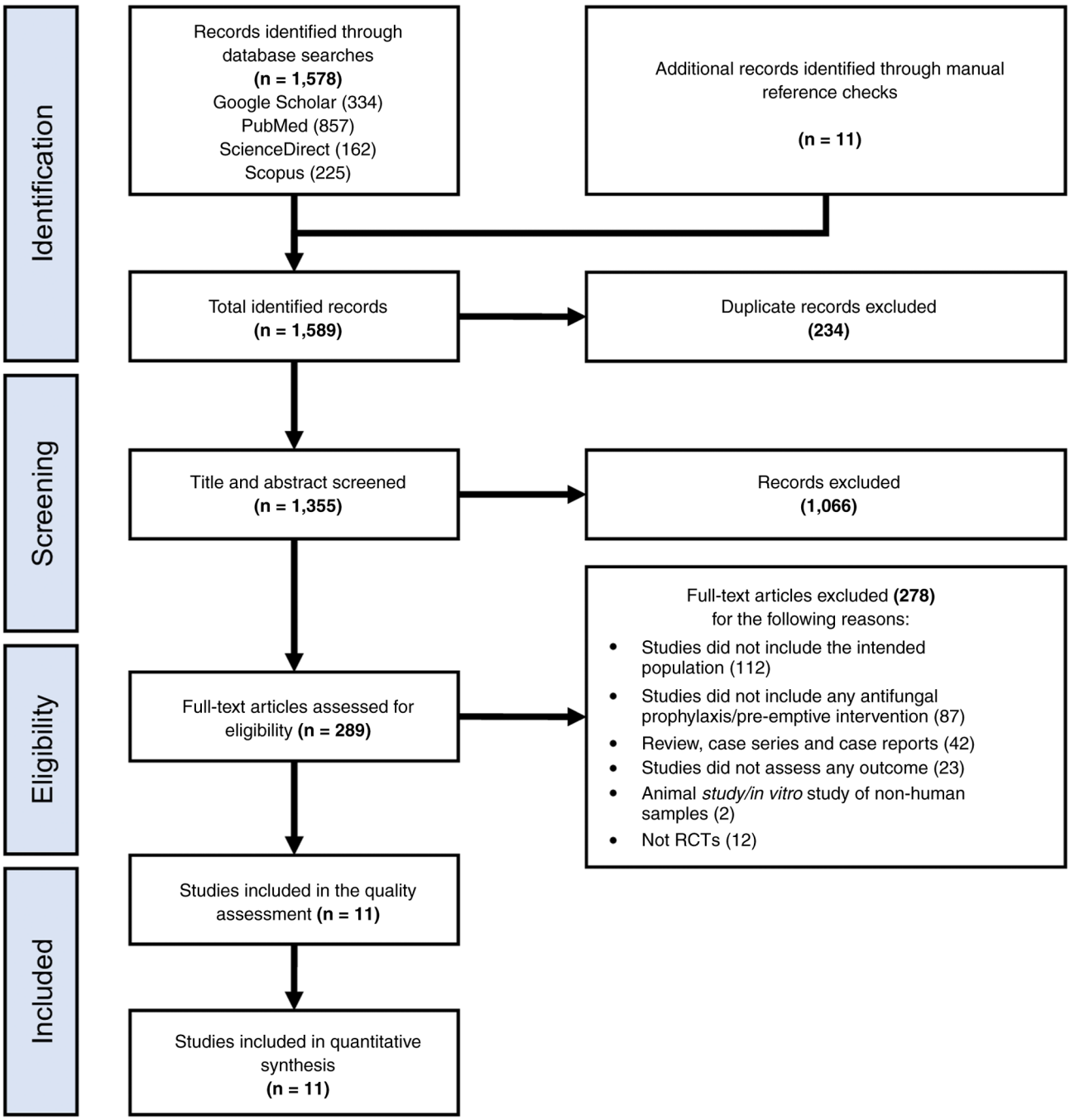

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram showing the systematic search and study selection process. RCT, randomized controlled trial.

allocation concealment or absence of blinded outcome assessment (domain 1) (16,17,20,21,24,25), 2 studies were evaluated as presenting 'some concerns' due to deviations from the intended interventions (domain 2) (19,24), 6 studies exhibited 'some concerns' regarding missing outcomes (domain 3), 1 study presented a possibility of bias in outcome measurement due to limited information of the method used to detect the fungal infection (domain 4) (19), and 3 studies showed 'some concerns' in the selection of the reported result due to limited availability of outcomes in the registered clinical trial protocol (domain 5) (9,19,20). No trial was rated as having a high risk of bias. The graphical traffic-light and summary plots in Fig. 2 provide an overview of domain-specific assessments.

Characteristics of the included studies. The characteristics of the included studies are presented in Table II. The included RCTs had cumulative sample sizes ranging between 43 and 292 patients. Geographically, the studies spanned Europe and North America with patient populations drawn from surgical ICUs following major abdominal surgery, trauma surgery, gastrointestinal perforations or complicated postoperative courses. The antifungal agents evaluated included azoles (fluconazole), echinocandins (caspofungin and micafungin) and polyenes (amphotericin B). The duration of prophylaxis varied from 5 days to 4 weeks. All trials reported IFI incidence as a primary outcome. Secondary outcomes included mortality, adverse events and liver function abnormalities.

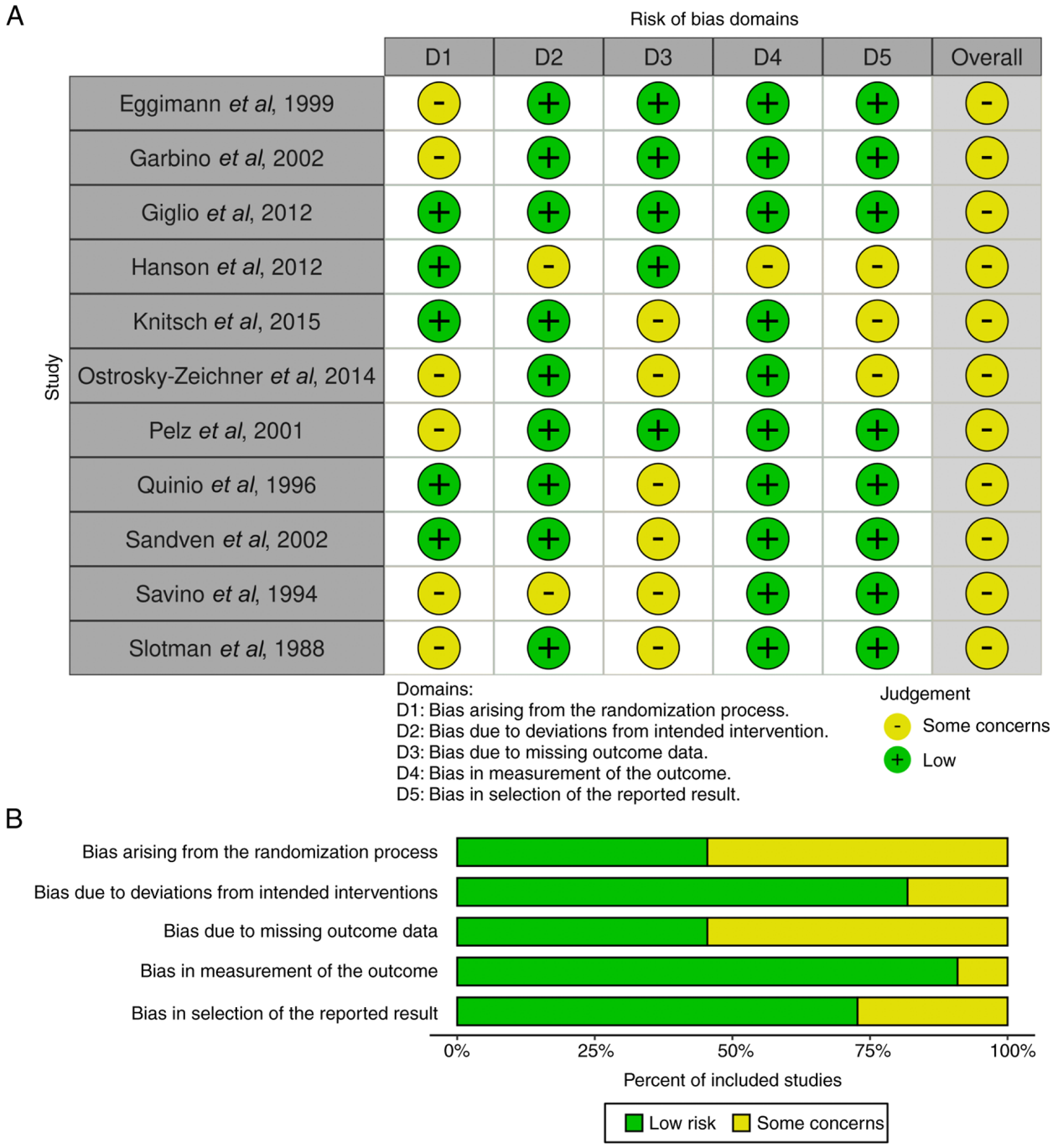

Figure 2. Risk of bias assessment of the included trials using the Cochrane Risk of Bias 2.0 tool. (A) Traffic-light plot summarizing domain-specific judgements for each trial. (B) Summary plot displaying the proportion of trials with low risk, some concerns or high risk of bias across domains. D, domain.

Effect of antifungal prophylaxis or pre-emptive therapy on fungal infection risk. Meta-analysis of all 11 trials demonstrated a statistically significant reduction in the incidence of IFIs in patients receiving antifungal prophylaxis or pre-emptive therapy compared with the controls (RR=0.63; 95% CI, 0.50-0.78; P<0.0001; Fig. 3A). Heterogeneity was low (I^2=0.0%; τ^2=0; P=0.6038), supporting the robustness of the pooled estimate. The forest plot (Fig. 3A) illustrates the consistent direction of the effect across studies. The funnel plot for this analysis (Fig. 3B) appeared symmetrical, but Egger's test showed statistical evidence of publication bias (P=0.0009).

A leave-one-out sensitivity analysis was conducted to assess the robustness of the primary pooled effect (Fig. 4). In this analysis, the study of Ostrosky-Zeichner *et al* (20) was included twice since it presented two analyses of different interventions, prophylaxis and pre-emptive strategies. The omission of each individual study sequentially did not change the effect estimate. The recalculated RRs ranged from 0.60 to 0.65 and all 95% CIs remained below 1.0 (95% CI range, 0.48-0.81), with statistically significant results, indicating a consistent protective effect. No single trial exerted a disproportionate influence on the direction or magnitude of the overall outcome. Heterogeneity remained negligible across

Table II. Characteristics of included studies.

First author/s, year	Country	Intervention category	Drug class	Intervention and dose	Control	Duration of intervention	Sample size			Surgery type	Age, years		Recorded risk factors	(Refs.)
							C	I	Total		C	I		
Eggimann *et al*, 1999	Switzerland	Prophylaxis	Azoles	Fluconazole 400 mg i.v. once a day	Placebo	Given from the admission to ICU until complete resolution of abdominal disease. If fungal infection occurs, the treatment is switched to amphotericin B.	20	23	43	GI	57.0 (33.0-78.0)	63.0 (21.0-82.0)	Diabetes, corticosteroid treatment, antibiotic therapy, parenteral nutrition, splenectomy	(16)
Garbino *et al*, 2002	Switzerland	Prophylaxis	Azoles	Fluconazole 100 mg i.v., polymyxin B (37.5 mg), neomycin (250 mg) and vanco-mycin (250 mg) syrup; six times daily for the entire treatment.	Polymy xin B (37.5 mg), neomycin (250 mg) and vancomycin (250 mg) syrup; six times daily without fluconazole	Given from the admission to ICU until a fungal infection developed, withdrawal from mechanical ventilation or suspicion of a serious adverse event.	101	103	204	GI, CV, neuronal and ortho-pedic	55.9±18.0	52.9±19.0	Diabetes, COPD CKD, neurological disorder, cancer, chronic liver failure	(17)
Giglio *et al*, 2012	Italy	Prophylaxis	Polyenes	Nystatin $2x10^6$ U/day administered three times daily via the nasogastri tube	Placebo	At least 48 h Criteria for stopping the prophylaxis are unknown.	50	49	99	GI, neuronal and trauma	58.0±19.0	54.0±22.0	Diabetes, corticosteroid treatment, neutropenia, antibiotic therapy, parenteral nutrition, CKD,central venous catheter	(18)

Table II. Continued.

First author/s, year	Country	Intervention category	Drug class	Intervention and dose	Control	Duration of intervention	Sample size			Surgery type	Age, years		Recorded risk factors	(Refs.)
							C	I	Total		C	I		
Hanson *et al*, 2012	USA	Pre-emptive	Echinocandins	Anidulafungin 100 mg i.v., single dose daily	Placebo	At least 14 days.	17	47	64	GI	60.0 (22.0-82.0)	58.0 (19.0-79.0)	Diabetes, CKD, parenteral nutrition, antibiotics treatment	(19)
Knitsch *et al*, 2015	Germany	Pre-emptive	Echinocandins	Micafungin 100 mg i.v. daily	Placebo	6 weeks unless the subject experiences EOT event: Confirmed invasive candidiasis, improvement in surgical condition (as indicated by recovery of gastrointestinal function allowing enteral feeding of up to 50% of daily calorie requirement), alternative antifungal treatment or death.	124	117	241	GI	63.0±15.8	61.0±14.8	Not recorded	(9)
Ostrosky-Zeichner *et al*, 2014	USA	Pre-emptive and prophylaxis	Echinocandins	Caspofungin 70 mg i.v. loading dose, followed by 50 mg i.v. once daily	Placebo	For the duration of stay in the ICU, maximum of 28 days.	102	117	219	GI, CV and trauma	56.7±16.6	58.2±17.6	Metabolic disease, CKD, pancreatitis, neurological disorder, infection	(20)

Table II. Continued.

First author/s, year	Country	Intervention category	Drug class	Intervention and dose	Control	Duration of intervention	Sample size			Surgery type	Age, years		Recorded risk factors	(Refs.)
							C	I	Total		C	I		
Pelz *et al*, 2001	USA	Prophylaxis	Azoles	Fluconazole loading dose, 800 mg; maintenance, 400 mg p.o. or i.v. once daily	Placebo	Administered until initiation of empirical antifungals or ICU discharge.	130	130	260	Not specified	66.0 (20.0-88.0)	63.0 (18.0-92.0)	Diabetes, antibiotic use, CKD, HIV infection	(21)
Quinio *et al*, 1996	France	Prophylaxis, selective digestive decontamination	Polyenes	Colistin sulfate (polymixin E; 10 mg/ml), gentamicin (8 mg/ml) and amphotericin B (50 mg/ml) instilled through the nasogastric tube (10 ml) and nostrils (2 ml in each) four times daily; a gel with antibiotics was applied in the oropharyngeal cavity, four times daily	Placebo	Started within a day in ICU until 24 h after extubation or beginning of enteral feeding.	72	76	148	GI, thorax and head trauma	33.0±15.0	35.5±16.0	Mechanical ventilation, antibiotic use	(22)

Table II. Continued.

First author/s, year	Country	Intervention category	Drug class	Intervention and dose	Control	Duration of intervention	Sample size			Surgery type	Age, years		Recorded risk factors	(Refs.)
							C	I	Total		C	I		
Sandven *et al*, 2002	Norway	Prophylaxis	Azoles	Fluconazole 400 mg i.v. intraoperatively	Placebo	Single dose, intraoperatively	56	53	109	GI	60.0 (15.0-87.0)	68.0 (13.0-86.0)	Antibiotic use, diabetes, cancer	(23)
Savino *et al*, 1994	USA	Prophylaxis	Azoles, polyenes	Clotrimazole 10 mg three times daily or ketoconazole 200 mg daily or nystatin 2,000,000 units four times daily	Placebo	Unknown.	72	220	292	Trauma and non-trauma	54.0±19.0	Clotrimazole: 54.0±19.0; ketoconazole 57.0±18.0; nystatin: 53.0±20.0	Ventilator, antibiotic use	(24)
Slotman *et al*, 1988	USA	Prophylaxis	Azoles	Ketoconazole 200 mg p.o. daily	Placebo	21 days or until discharged from surgical ICU.	36	35	71	GI, CV, thorax, orthopedic, neuronal, genitourinary, trauma and other	58.0 (18.0-91.0)	57.0 (19.0-87.0)	Critically ill surgical patients (MODS, sepsis, AKI, major burns or malnutrition)	(25)

Age is presented as the mean ± SD or median (range). AKI, acute kidney injury; C, control; CV, cardiovascular; EOT, end of treatment; GI, gastrointestinal; I, intervention; i.v., intravenously; p.o., *per os*; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; MODS, multiple organs dysfunction syndrome; ICU, intensive care unit.

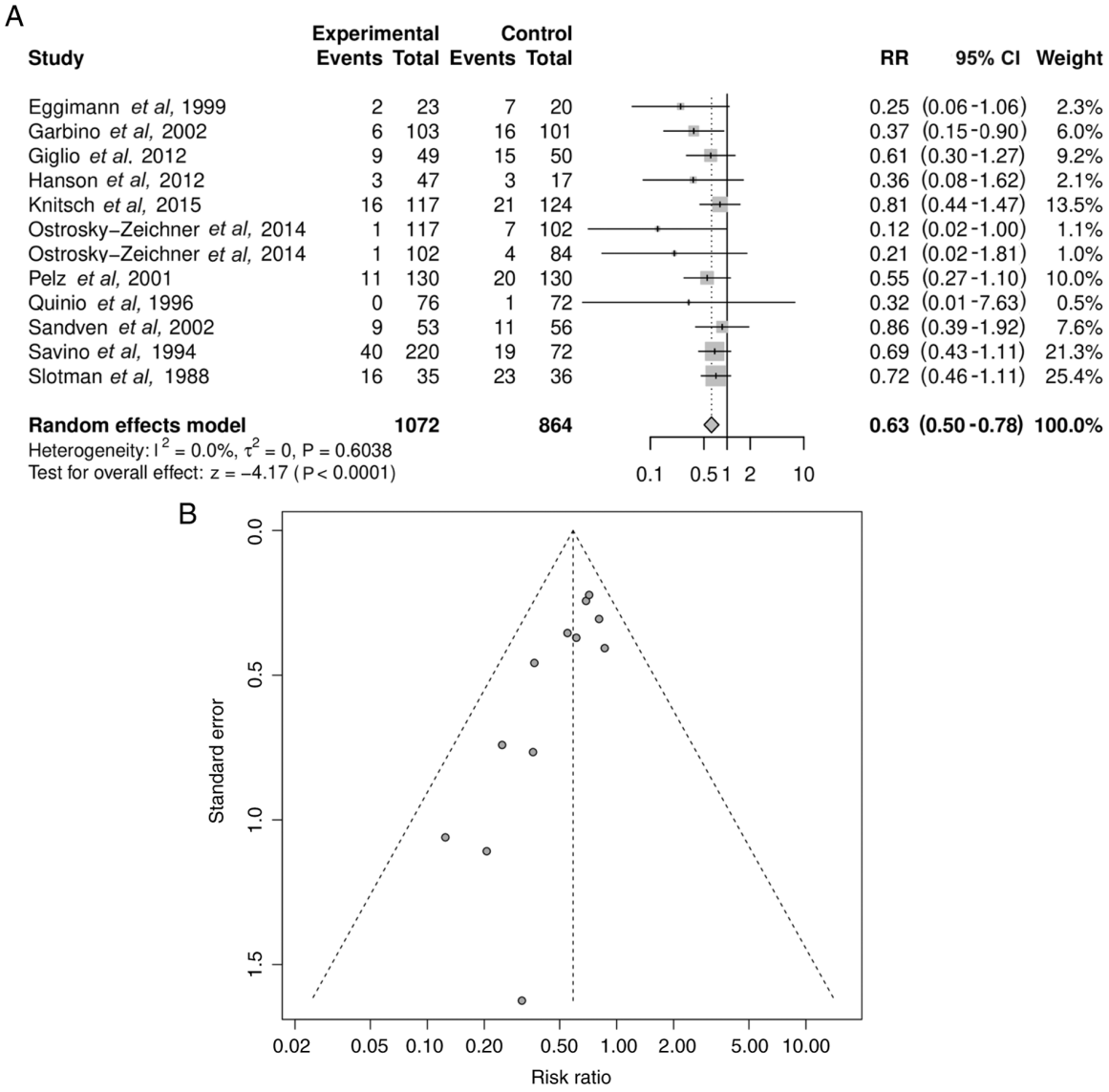

Figure 3. Effect of antifungal prophylaxis or pre-emptive therapy vs. control on the incidence of invasive fungal infections. (A) Forest plot showing the pooled relative risk estimates across 12 trials. (B) Funnel plot demonstrating symmetrical distribution, suggesting minimal publication bias. RR, risk ratio.

all iterations (I^2=0%). These findings demonstrated that the pooled effect was stable and not driven by any single study.

Subgroup analysis: Prophylaxis vs. pre-emptive therapy. When stratified by strategy, prophylaxis significantly reduced IFI risk but pre-emptive therapy did not. Prophylaxis yielded a pooled RR of 0.62 (95% CI, 0.49-0.79; P=0.0001) with non-significant heterogeneity (I^2=0.0%; τ^2=0; P=0.6944), while pre-emptive therapy showed a pooled RR of 0.47 (95% CI, 0.17-1.27; P=0.1378) with moderate but non-significant heterogeneity (I^2=44.7%; τ^2=0.3677; P=0.1637) (Fig. 5A and B). The funnel plots for each subgroup (Fig. 5C and D) generally demonstrated symmetrical distribution, but there was a significant publication bias among publications analyzed in Fig. 5D as assessed by Egger's test (Fig. 5C, P=0.1138; Fig. 5D, P=0.0236).

Subgroup analysis stratified by antifungal class. Azole prophylaxis was associated with a significant reduction in IFI risk (RR=0.62; 95% CI, 0.48-0.80; P=0.0002) and low heterogeneity (I^2=0.0%; τ^2=0; P=0.6002) (Fig. 6A). By contrast, echinocandin prophylaxis (RR=0.44; 95% CI, 0.18-1.04; P=0.0614) with heterogeneity of I^2=35.6% (τ^2=0.2923; P=0.1983) (Fig. 6B) and polyene prophylaxis (RR=0.71; 95% CI, 0.46-1.12; P=0.1407) with heterogeneity of I^2=0.0% (τ^2=0; P=0.7402) (Fig. 6C) were not significantly associated with protection from IFI risk. In this analysis, the study of Ostrosky-Zeichner *et al* (20) was included twice since it presented analyses of two different interventions, prophylaxis and pre-emptive strategies. This analysis also separated the study of Savino *et al* (24) since by three different types of intervention, clotrimazole, ketoconazole and nystatin. The funnel plots for azoles (Egger's test P=0.0615), echinocandins (Egger's test P=0.0207) and polyenes (Egger's test P=0.4220) (Fig. 7A-C) were symmetrical, indicating no strong evidence of publication bias except for the studies that investigated echinocandins.

Effect on mortality. In total, 6 trials reported all-cause mortality. Pooled analysis revealed no significant difference in the mortality risk between the antifungal prophylaxis

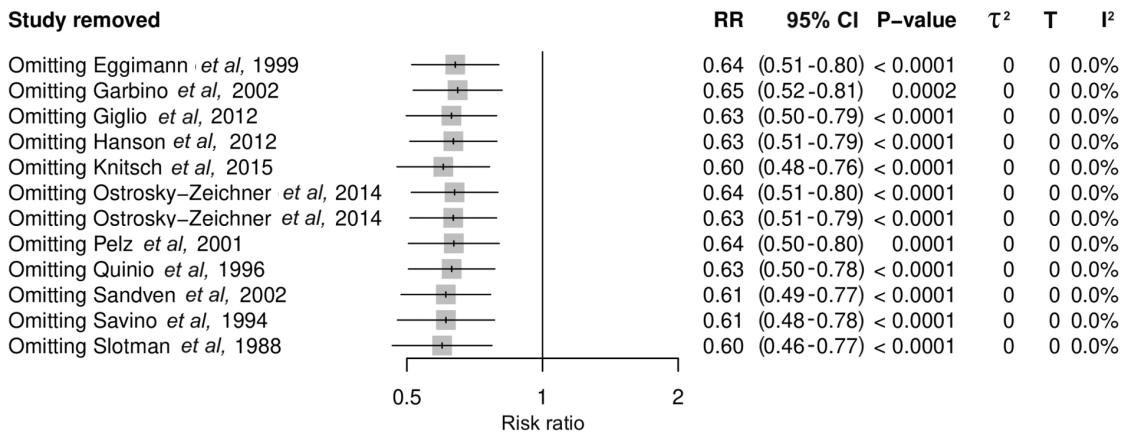

Figure 4. Leave-one-out sensitivity analysis demonstrating study influence on the pooled treatment effect. Each line represents the recalculated relative risk after removing one study from the analysis. The pooled estimates remained narrowly distributed (RR range, 0.56-0.61) with CIs consistently <1.0, confirming that no single trial disproportionately influenced the findings. RR, risk ratio.

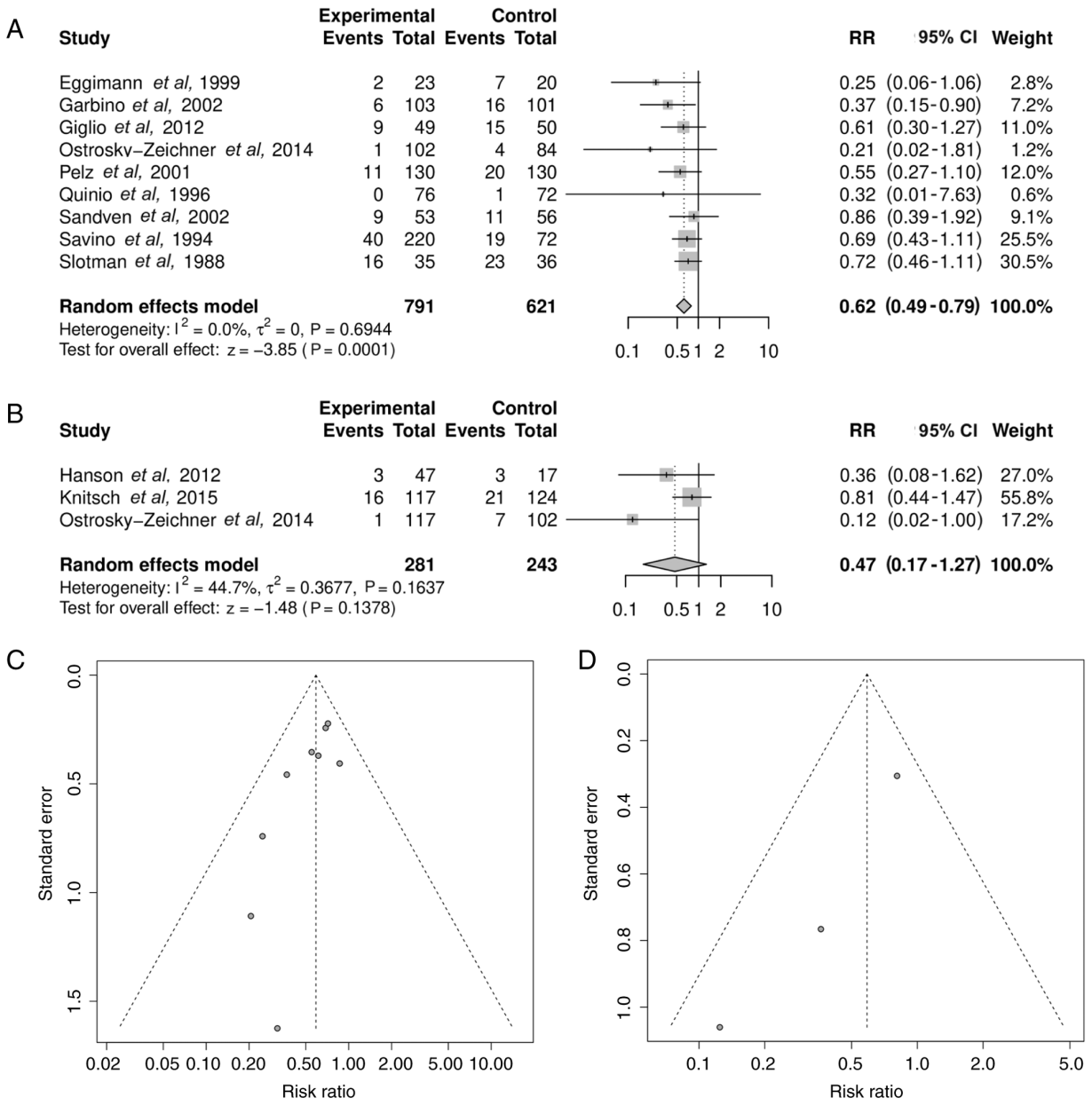

Figure 5. Subgroup analysis by intervention strategy. (A) Forest plot for prophylaxis trials. (B) Forest plot for pre-emptive therapy trials. (C) Funnel plot for prophylaxis. (D) Funnel plot for pre-emptive therapy. RR, risk ratio.

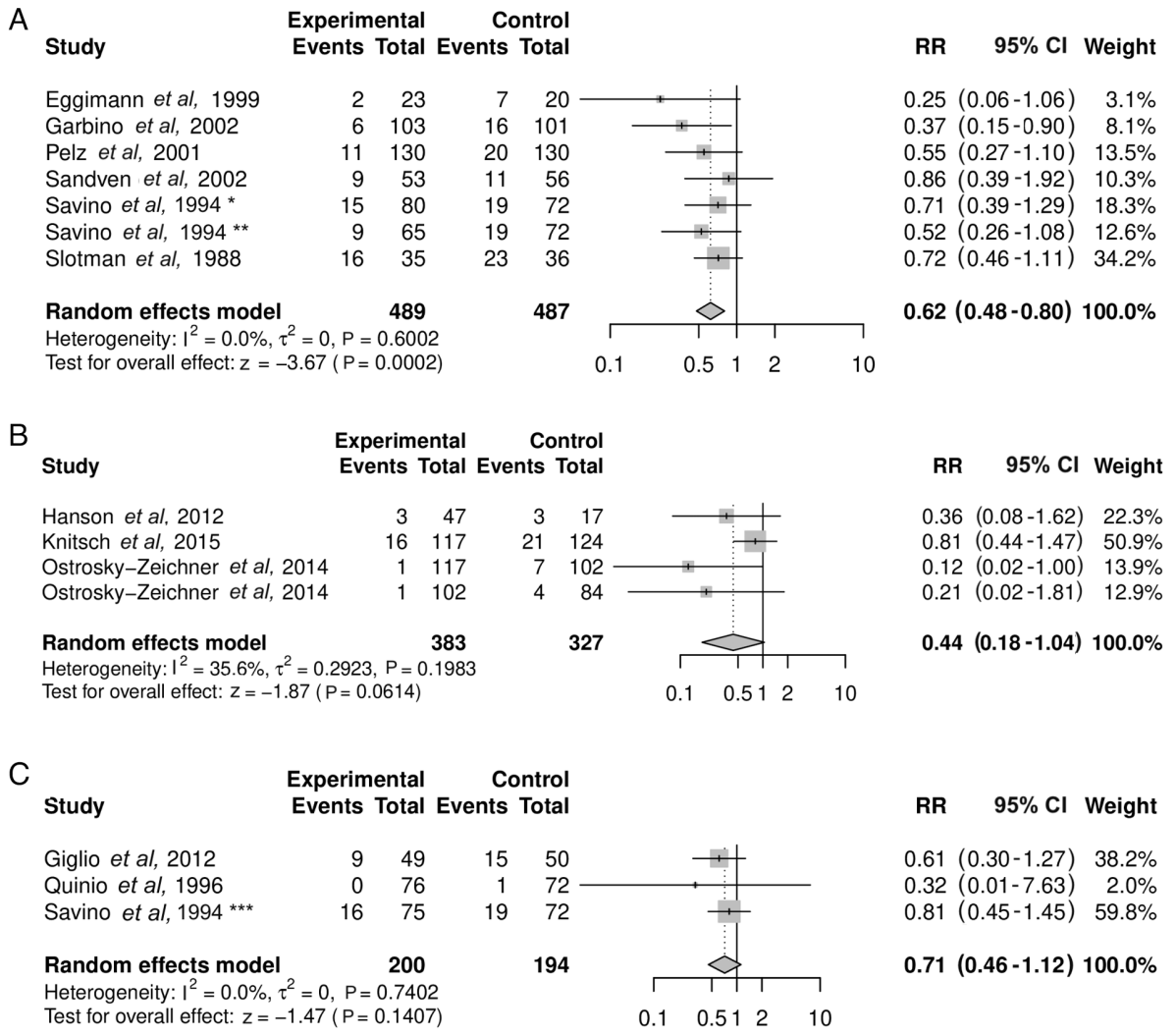

Figure 6. Subgroup analysis by antifungal class. (A) Forest plot for azoles. The study by Savino *et al*, 1994 is analyzed twice since it contains two different intervention groups, clotrimazole (*) and ketoconazole (**). (B) Forest plot for echinocandins. (C) Forest plot for polyenes. The study by Savino *et al*, 1994 is represented in this plot with the nystatin group (***). RR, risk ratio.

and control groups (RR=0.99; 95% CI, 0.75-1.31; P=0.9186) with low heterogeneity (I^2=0.0%; τ^2=0; P=0.6028) (Fig. 8A). The funnel plot for mortality (Fig. 8B) was symmetrical (Egger's test P=0.0563).

Severe adverse events and liver function abnormalities. In total, 3 trials reported severe adverse events. Pooled analysis revealed no significant association between antifungal prophylaxis and the risk of severe adverse events (RR=0.98; 95% CI, 0.70-1.36; P=0.8839) with heterogeneity of I^2=0.0% (τ^2=0; P=0.9254) (Fig. 9A). In total, 3 trials reported liver function outcomes. The pooled RR for liver dysfunction was 0.91 (95% CI, 0.31-2.65; P=0.8619) with heterogeneity of I^2=55.1% (τ^2=0.4761; P=0.1076) (Fig. 9B). The corresponding funnel plots (Fig. 9C and D) showed a balanced distribution (Egger's test P=0.8266 and 0.8852, respectively), suggesting no major publication bias.

Discussion

The present systematic review and meta-analysis demonstrated that antifungal prophylaxis (especially when administered as prophylaxis but not as a pre-emptive strategy) significantly reduced the risk of fungal infections in surgical ICU patients without increasing the risk of severe adverse events or hepatotoxicity. Across 11 RCTs, azoles were effective, while polyenes and echinocandins did not confer a significant benefit. Despite the reduction in IFI risk, no mortality benefit was observed.

The relative risk reduction in fungal infection incidence is clinically meaningful and mirrors outcomes reported in populations with hematologic malignancies and transplantations (1,26,27). Surgical ICU patients face multiple predisposing factors, including gastrointestinal surgery, central venous catheters, parenteral nutrition, prolonged ventilation and broad-spectrum antibiotics administration, which increase the susceptibility to IFIs (12,26,28). The present findings suggest that targeted prophylaxis offers substantial protection in this context.

Although prophylaxis was effective, pre-emptive therapy did not reduce the IFI risk. This difference may be attributed to earlier intervention, as pre-emptive approaches often depend on the presence of biomarkers such as β-D-glucan or galactomannan, which may allow limited fungal proliferation

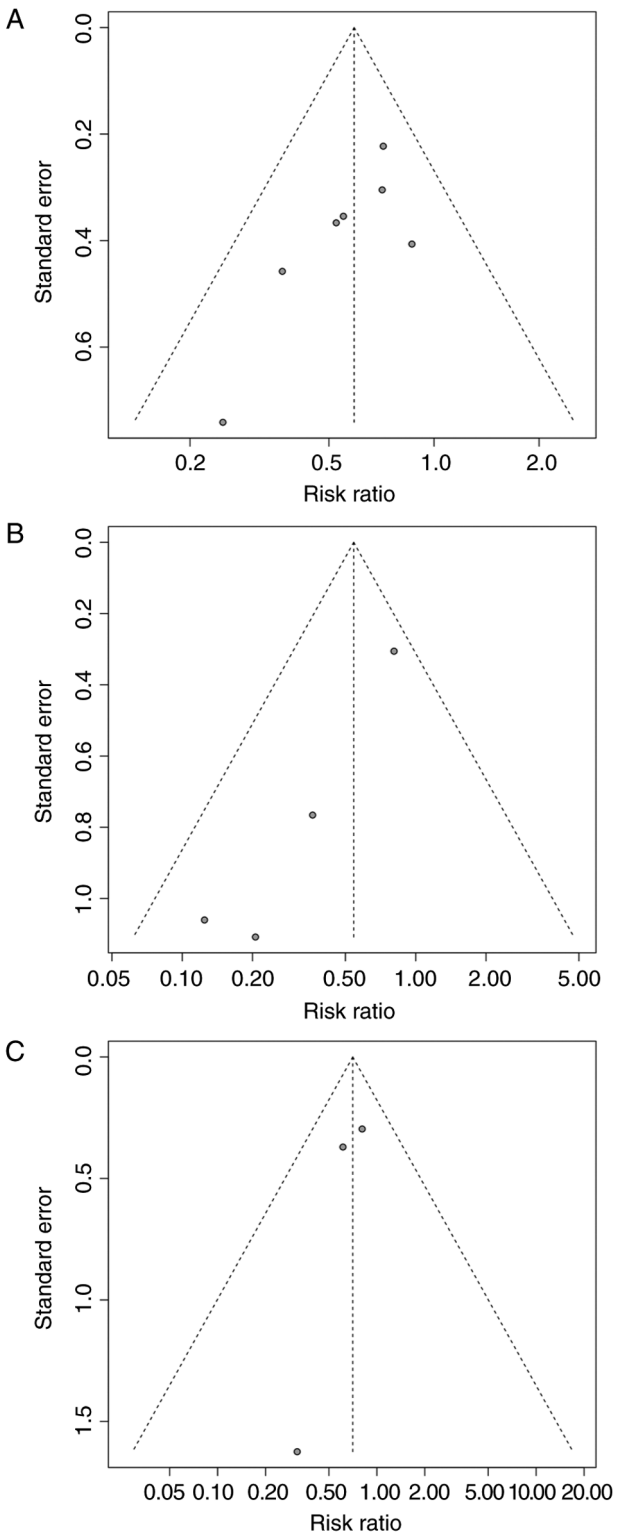

Figure 7. Funnel plots for studies stratified by antifungal class. (A) Azoles, (B) echinocandins and (C) polyenes.

before therapy begins (9,19,20). These results align with the 2025 guideline by the European Confederation of Medical Mycology, International Society of Human and Animal Mycology (ISHAM) and American Society for Microbiology (ASM) for the diagnosis and management of candidiasis (29). The guideline advised in favor of prophylaxis for surgical ICU patients with high-risk factors, such as anastomotic leaks, necrotizing pancreatitis or multifocal *Candida* colonization, while noting that pre-emptive strategies remain less validated outside controlled settings (29).

While the findings of the present meta-analysis demonstrated a clinically meaningful reduction in IFI risk, it is important to interpret this benefit in the context of the broader ecological implications of antifungal exposure. Beyond individual patient outcomes, widespread or prolonged antifungal use may alter the local microbial flora by selecting for resistant fungal strains, disrupting commensal microbiota and increasing the likelihood of future breakthrough infections with reduced treatment responsiveness (30,31). Prolonged prophylaxis has been associated with shifts in local epidemiology, including increased colonization and infection by non-*albicans Candida* species with reduced azole susceptibility (27,32). Thus, although prophylaxis may be valuable in selected high-risk surgical ICU patients, its implementation should remain management-driven and supported by local surveillance data to mitigate the long-term risk of resistance and preserve the efficacy of antifungals.

Cost considerations are also relevant, especially in low- and middle-income countries where access to treatments and diagnostic capacity may be limited. When targeted to high-risk surgical ICU patients, prophylaxis may remain cost-effective by preventing IFIs and associated ICU resource utilization, but broader indiscriminate use may not provide the same value. A previous systematic review has also suggested that prophylaxis treatment potentially brings cost benefits to ICU patients with high-risk factors for IFIs (33). Compared with a previous meta-analysis that focused primarily on fluconazole and did not evaluate pre-emptive approaches or echinocandin use, the present study offers a more updated and comprehensive assessment and better reflects current therapeutic options (12).

According to the present study, azoles, particularly fluconazole, showed consistent efficacy in reducing IFI risk, reinforcing their role as frontline prophylactic agents where local resistance rates are low (16,17,21,23). Although the limited number of included studies could not demonstrate the effectiveness of echinocandins in the present meta-analysis, echinocandins may also be beneficial and relevant in the context of rising azole resistance; however, their high cost limits routine prophylactic use (7,33). In our study, polyenes did not exhibit a clear benefit. These findings are consistent with those of previous studies supporting the effectiveness of azoles in preventing candidemia in abdominal surgical patients (26,34). ISHAM and ASM also recommend fluconazole administration in selected high-risk patients but caution should be taken against its widespread use due to concerns of resistance to species such as *Candida glabrata* and *Candida krusei* (29). Echinocandins remain primarily recommended for the treatment of IFI (29), although the present analysis suggests that they may have prophylactic potential. Therefore, further and more comprehensive studies are needed to establish whether it is beneficial to start echinocandins earlier in patients that have a high risk of IFI.

The results of the present meta-analysis revealed no mortality benefit of the use of antifungal prophylaxis or pre-emptive therapy. This is unsurprising, given the multifactorial causes of death in critically ill patients, including bacterial sepsis, multi-organ failure and postoperative

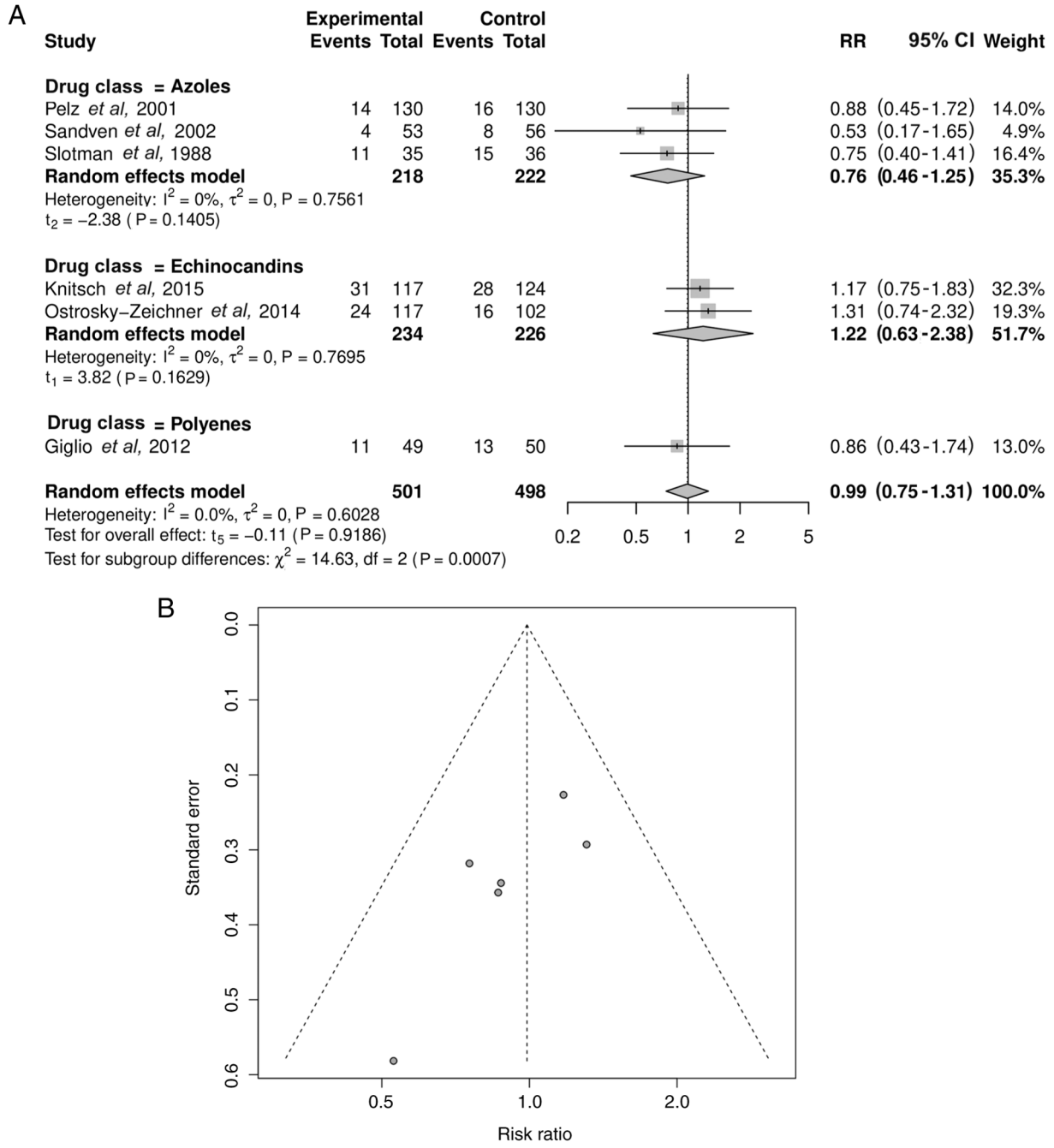

Figure 8. Effect of antifungal prophylaxis on all-cause mortality. (A) Forest plot and (B) funnel plot indicating symmetry and lack of publication bias. df, degrees of freedom; RR, risk ratio.

complications (35,36). Breakthrough infections in control arms, when diagnosed and treated promptly, may also result in minimized survival differences (35,36). Furthermore, most RCTs were underpowered for mortality outcomes. The 2025 guideline by ISHAM and ASM similarly emphasizes that prophylaxis is unlikely to improve overall survival in ICU populations, where mortality reflects a broad interplay of comorbid conditions (29).

The lack of a demonstrable mortality benefit in the present meta-analysis should be interpreted in the context of the underlying complexity of critical illness. Most trials were not statistically powered to detect differences in mortality, used IFI incidence as the primary endpoint and enrolled relatively small cohorts with limited follow-up (16,17,19,22,23). Taken together, these factors make it biologically plausible that antifungal prophylaxis substantially reduces IFI incidence without translating into a measurable mortality advantage at the trial level.

The safety outcomes were favorable, with no increase in serious adverse events or hepatotoxicity. This supports selective prophylaxis in well-defined risk groups, providing that safety monitoring is maintained. Nevertheless, the potential for antifungal resistance remains a critical concern.

Clinically, the present results support prophylaxis for surgical ICU patients at high risk, for example, those with complicated abdominal surgery, necrotizing pancreatitis or

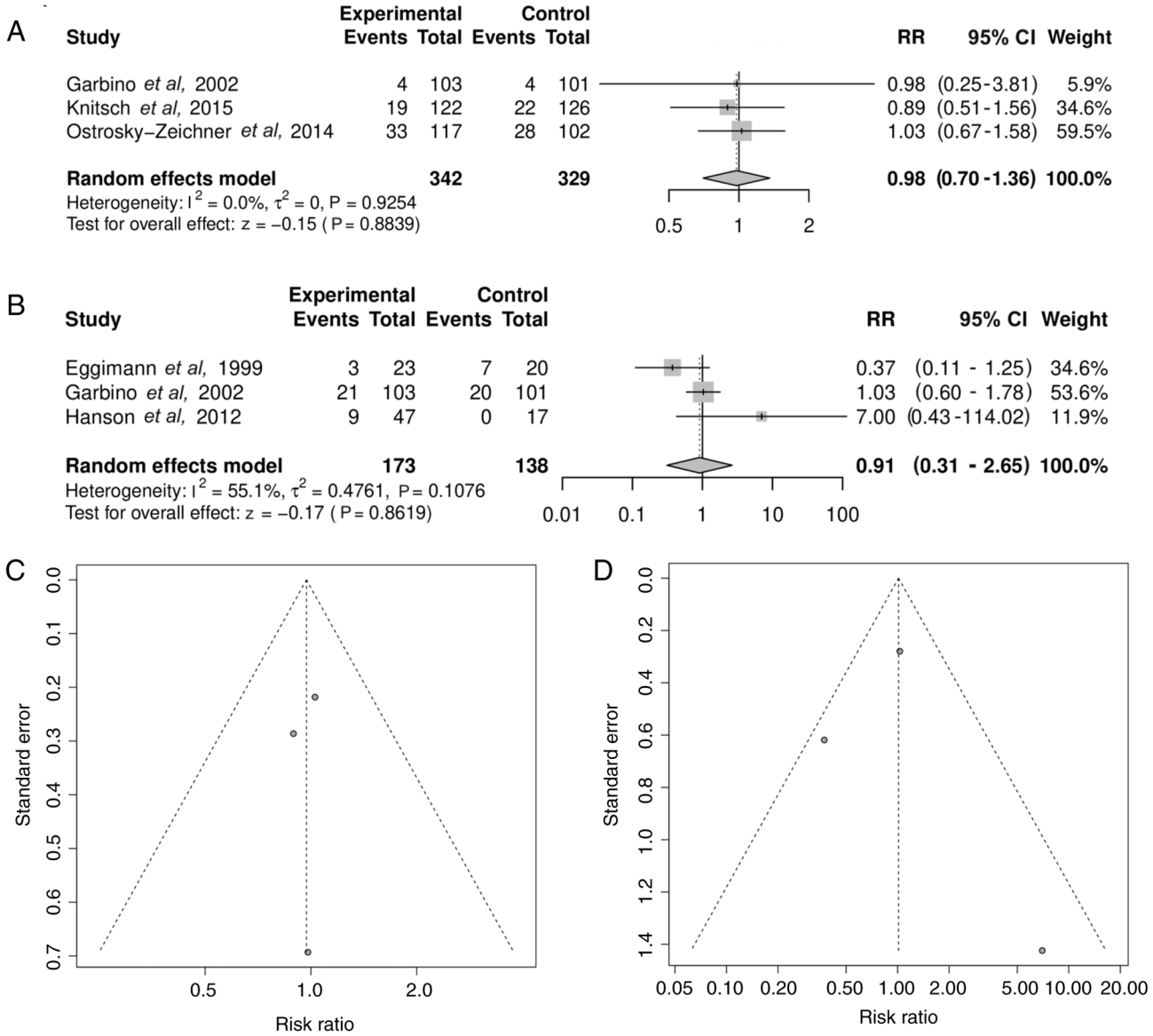

Figure 9. Effect of antifungal prophylaxis on severe adverse events. (A) Forest plot for severe adverse events. (B) Forest plot for liver function abnormalities. (C) Funnel plot for severe adverse events. (D) Funnel plot for liver function abnormalities. RR, risk ratio.

septic shock requiring parenteral nutrition and central venous access. Prophylaxis appears more dependable than pre-emptive strategy in resource-limited settings where diagnostics are constrained.

The present study has a number of strengths: Inclusion of only RCTs, rigorous risk of bias assessment, low heterogeneity, and clinically meaningful subgroup analyses based on antifungal class and strategy. To the best of our knowledge, this is the first meta-analysis focused solely on surgical ICU patients, rather than combined ICU populations. This distinction is clinically meaningful, as surgical patients differ in baseline risk, exposure to invasive procedures and epidemiology of fungal colonization, making the findings of the present study more directly applicable to real-world decision-making in perioperative critical care. However, certain limitations should be acknowledged. The number of echinocandin and polyene trials was small, limiting statistical precision. All included studies were conducted in high-income countries, restricting applicability to low- and middle-income settings with differing epidemiology, diagnostic capacity and management infrastructure. Important outcomes, such as the length of stay at the ICU, cost-effectiveness and long-term resistance were not reported in the included studies. Finally, although publication bias was not apparent, undetected negative studies cannot be excluded.

Future research should focus on large, multicenter RCTs that directly compare antifungal classes, employ standardized mortality endpoints, and evaluate cost-effectiveness. Trials in low- and middle-income countries are particularly needed to establish generalizability. Studies on biomarker-guided pre-emptive strategies may clarify their role, especially in resource-constrained environments. Integrating prophylaxis trials into management frameworks and infection prevention programs will enhance their real-world utility.

In conclusion, the present meta-analysis indicated that antifungal prophylaxis reduced the incidence risk of IFIs in high-risk surgical ICU patients without increasing the risk of severe adverse events. Although no survival benefit was

demonstrated, the prevention of fungal infections justifies the use of antifungal prophylaxis in carefully selected patients. Implementation should remain targeted, guided by local resistance patterns and embedded within antifungal management programs to balance efficacy with the long-term risk of resistance.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

INK conceived the present study, and was involved in the methodology (designed the protocol and research plan), systematic search, data curation and formal analysis, writing the original draft and study supervision. MAE was involved in data extraction, methodology (designed the protocol and research plan), formal analysis and reviewing and editing the manuscript. ED was involved in quality assessment, formal analysis and reviewing and editing the manuscript. IR performed data extraction, statistical analysis and visualization of the forest plots. AMW was involved in the literature search, data curation and reviewing and editing the manuscript. EBK performed formal analysis, study supervision, wrote the original manuscript and critically revised the manuscript. DDCHR performed statistical analysis, interpreted the results, and reviewed and edited the manuscript. EA was involved in methodology (designed the protocol and research plan), data authentication, formal analysis, providing resources, writing the original manuscript and revising the manuscript. PDE conceived the present study, and was involved in the methodology, systematic search, reviewing and editing the manuscript, as well as study supervision. INK, MAE and EBK confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools (Superhuman Platform, Inc.) were used to improve the readability and language of the manuscript.

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