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# Clinical outcomes of antifungal therapy on Candida pulmonary colonization in immunocompetent patients with invasive ventilation: A systematic review and meta-analysis



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| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2024-083918 |
| Article Type: | Original research |
| Date Submitted by the Author: | 03-Jan-2024 |
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| Keywords: | Meta-Analysis, Adult intensive & critical care < INTENSIVE & CRITICAL CARE, Pulmonary Disease < Lung Diseases |
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# Clinical outcomes of antifungal therapy on Candida pulmonary colonization in immunocompetent patients with invasive ventilation: A systematic review and meta-analysis

**Keywords: *Candida* colonization, pulmonary, antifungal therapy, mechanical ventilation, meta-analysis.**

## Abstract

**Objective:** This study aimed to use systematic review and meta-analysis to establish the influence of antifungal therapy on pulmonary *Candida* colonization of patients with mechanical ventilation.

**Design:** Systematic review and meta-analysis.

**Data sources:** An extensive search was undertaken on publications from inception to July 25, 2023, through PubMed, Web of Science, Medline, Embase, China National Knowledge Infrastructure, Wanfang Data and VIP Databases.

**Eligibility criteria for selecting studies:** Randomized trials, cohort studies, and case-control studies comparing the efficacy of antifungal treatment in immunocompetent patients with pulmonary *Candida* colonization after invasive ventilation.

**Data extraction and synthesis:** Two reviewers independently extracted the data and assessed the quality of studies. Dichotomous outcomes were expressed as odds ratios (OR) with 95% confidence intervals (CIs). Continuous outcomes were expressed as standard mean differences (SMD) with 95% CIs.

**Primary and secondary outcome measures:** The primary outcomes included ICU, hospital, 28-day, and 90-day mortality. The secondary outcomes included ICU length of stay, MV duration, and VAP.

**Results:** Nine high-quality studies were included. According to the data collected from these nine studies, there is no significant evidence showing a difference between the therapy group treated with antifungal drugs and the control group without antifungal drugs in clinical outcomes, including intensive care unit mortality (OR: 1.37; 95% CI, 0.84 to 2.22), hospital mortality (OR: 1.17; 95% CI, 0.57 to 2.38), 28-day mortality (OR; 0.71, 95% CI, 0.45 to 1.14), 90-day mortality (OR; 0.76, 95% CI 0.35 to 1.63), intensive care unit length of stay (SMD: -0.15; 95% CI -0.88 to 0.59), mechanical ventilation duration (SMD: 0.11; 95%CI -0.88 to 1.10), and ventilator-associated pneumonia (OR: 1.54; 95% CI 0.56 to 4.20). Subgroup analysis of different treatment types indicate that the combined effect size is stable and unaffected by different treatment types including inhalation (OR: 2.32; 95% CI 0.30 to 18.09) and intravenous (OR: 0.65; 95% CI 0.13 to 3.34).

**Conclusion:** The application of antifungal treatment did not improve clinical outcomes in patients with mechanical ventilation. We do not suggest initiating antifungal treatment in patients with *Candida* pulmonary colonization after invasive ventilation.

**Registration:** This study was registered in the International Prospective Register of Systematic Reviews, with the registration number CRD42020161138.

**Strengths and limitations of this study:** This meta-analysis has a number of outcome indicators to evaluate the effect of antifungal treatment. Subgroup analysis was conducted based on the treatment type which showed a stable result. However, in quoted and analyzed references, some studies declared whether they included patients with pre-existing pneumonia, while others did not. Second, some studies described the precise style, name, dose, and administration method of antifungal drugs, while others did not. Third, it is important to encourage future research endeavors to enhance the quality of this meta-analysis. This can be achieved by incorporating an expanded array of studies, distinguished by a larger sample size, and meticulously defined inclusion and exclusion criteria.

## 1 Introduction

*Candida* frequently exists in the normal oral cavity, upper respiratory tract, lower-intestinal tract and vagina(1). In tracheal aspirates from patients with mechanical ventilation (MV), 30% have *Candida* isolation, and nearly 50% from patients suspected to have a ventilator-associated pneumonia (VAP)(2). When respiratory *Candida* colonization is detected, it is difficult to differentiate between relatively harmless colonization and invasive infection, and leads to a therapeutic dilemma(3). Although few studies reported limited attributable ICU mortality of VAP, the death rate related to VAP can not be denied according to the mojority of previous studies(4-7). The presence of *Candida* in respiratory samples is defined as *Candida* colonization instead of infection because the appearance of *Candida* pneumonia is rare(8-10). For several years, arguments arose about whether *Candida* colonization negatively affected or simply symbolized disease severity or immunosuppression in critically ill patients(11-13). We found that the outcomes of antifungal treatment for *Candida* colonization in pulmonary tract among different studies were controversial, as some studies found that antifungal treatment is associated with lower mortality, some found that treatment made no difference in mortality, while others found that it prolonged MVduration, intensive care unit (ICU) length of stay, and hospital length of stay(8, 9, 14, 15). Therefore, we performed a systematic review and meta-analysis to establish the influence of antifungal treatment on pulmonary *Candida* colonization.

## 2 Method

### 2.1 Information sources and search strategy

This study followed the Preferred Reporting Items for Systematic Review and Meta-Analysis criteria for systematic reviews and meta-analyzes. An extensive search was undertaken on publications from inception to July 25, 2023, through PubMed, Web of Science, Medline, Embase, China National Knowledge Infrastructure, Wanfang Data and VIP Databases. The searching syntax included the following Medical Subject Headings (Mesh) and text words which are varied individually according to different databases: ventilator-associated pneumonia, *Candida*. We used the following search strategies: (ventilator-associated pneumonia OR VAP OR pneumonia, ventilator-associated OR ventilator-associated pneumonia OR ventilator-acquired pneumonia OR mechanical ventilation) AND (*Candida* OR *Candida* spp OR *Candida* colonization OR *Candida* airway colonization). There were no language restrictions on studies searching. The listed references of relevant studies were also evaluated to enlarge the search scope and ensure a complete search.

### 2.2 Inclusion criteria

Selection process of the article was performed by two researchers (LL and SS) independently, the titles and abstracts of the entries identified in the search were screened. Full text version of all articles that potentially met the eligibility criteria to make a decision. Disagreements, if any, were resolved through discussion with a third researcher (HX). Randomized trials, cohort studies, and case-control studies were included. In the included studies, the patients were adults (≥18 years old) who were diagnosed with pulmonary *Candida* colonization after invasive ventilation. Pulmonary *Candida* colonization was defined as the presence of *Candida* in bronchoalveolar lavage samples, endotracheal aspiration samples, protected brush specimens, or any positive airway secretion specimens.

### 2.3 Exclusion criteria

We excluded case reports and studies on pregnant, immunocompromised patients, or received antifungal treatment for reasons other than *Candida* colonization. Patients with candidemia or invasive candidiasis were also excluded, and the diagnostic criteria were positive results of direct detection, in which blood or tissue specimens were cultured, or indirect detection, in which surrogate markers and polymerase chain reaction assays were used(16).

### 2.4 Data collection

We screened titles and abstracts, reviewed the full text, and extracted data using an Excel sheet (Microsoft Corporation). We primarily collected the characteristics of title, author, journal, year, type, participants, inclusion or exclusion criteria, interventions, and clinical outcomes. Disagreements were resolved by discussion with a third reviewer if necessary.

### 2.5 Quality assessment

We used the Cochrane risk assessment tool to measure the risk of randomized controlled trials and the Newcastle-Ottawa Scale to measure the quality of cohort and case-control studies. Studies that scored at least six points were regarded as high-quality and included.

### 2.6 Statistical analysis

Dichotomous outcomes such as VAP, ICU mortality, hospital mortality, 28-day mortality, and 90-day mortality, were expressed as odds ratios (OR) with 95% confidence intervals (CIs). Continuous outcomes (ICU length of stay and MV duration) were expressed as standard mean differences with 95% CIs. We analyzed the data using the Inverse-Variance method with the fixed-effect model if there was no obvious heterogeneity (P>0.1), or else random-effect model if the heterogeneity was significant (P<0.1). Moreover, heterogeneity was quantified using the $I^2$ test. The interpretation of $I^2$ was guided by the Cochrane Handbook for Systematic Reviews of interventions (Version 5.2.0, updated June 2017). $I^2$ range from 0 % to 40% indicates that the heterogeneity might not be important; $I^2$ range from 30 % to 60 % may represent moderate heterogeneity; $I^2$ range from 50 % to 90 % may represent substantial heterogeneity; $I^2$ range from 75 % to 100 % indicates considerable heterogeneity. Publication bias was not assessed since there were less than 10 studies in this meta-analysis.

## 3 Results

### 3.1 Study selection

In total, 2947 records were identified. With 1246 duplicates removed and 1670 irrelevant records excluded, we assessed 31 studies for eligibility, of which 9 were included. 22 studies should not be included because of the lack of antifungal treatment, lack of supporting experimental data, lack of detection of pulmonary secretion, and occurrence in a special population (Figure 1). All patients received MV, had at least one positive culture of *Candida* in the pulmonary tract, and received different antifungal treatments.

Figure 1 Flowchart of studies identified, excluded, and included

### 3.2 Study characteristics and quality assessment

Of the nine articles included in the study, seven were retrospective cohort studies, one case-control study, and one randomized clinical trial. Two studies were conducted in North America, five in Europe, and two in Asia, giving the studies a wide geographical coverage. Other characteristics of the included studies are summarized in Supplemental Table 1, including years of accuracy, location, study style, population, number of patients, outcomes, *Candida* colonization and antifungal treatment. The columns of the quality assessment list and their corresponding points are listed in Supplemental Table 2. All included studies were assessed to be of high quality.

### 3.3 Effect of antifungal therapy on pulmonary *Candida* colonization patients' mortality

Three studies, including Ioannou 2021(2), Ong 2013(17), and Nseir 2007(18) reported ICU mortality. We found no significant difference between the therapy and control groups (OR: 1.37, 95% CI, 0.84 to 2.22). Six studies, including Du 2021(3), Ioannou 2021, Zhang 2017(19), Griffin 2016(20), Lindau 2015(21), and Albert 2014(22) reported hospital mortality. The pooled results showed no significant difference between the therapy and control groups (OR: 1.17, 95% CI, 0.57 to 2.38). Four studies, including Du 2021, Zhang 2017, VanDerGeest 2014(23), and Albert 2014, reported 28-day mortality. The results showed no significant difference between the therapy and control groups (OR: 0.71, 95% CI, 0.45 to 1.14). Three studies, Du 2021, VanDerGeest 2014, and Albert 2014, reported 90-day mortality. The results showed no significant difference between the therapy and control groups (OR: 0.76, 95% CI, 0.35 to 1.63). No indicator showed statistical significance with respect to mortality. (Figure 2)

Figure 2 (A) Forest plot for ICU mortality; (B) Forest plot for hospital mortality; (C) Forest plot for 28-day mortality; (D) Forest plot for 90-day mortality

### 3.4 Effect of antifungal therapy on pulmonary *Candida* colonization patients' ICU length of stay

Four studies, including Zhang 2017, Griffin2016, Ong 2013, and Nseir 2007, reported ICU length of stay. The results indicated non-significant results for ICU length of stay among patients receiving antifungal treatment (SMD: -0.15, 95% CI, -0.88 to 0.59), as shown in Figure 3.

Figure 3 Forest plot for ICU length of stay

### 3.5 Effect of antifungal therapy on pulmonary *Candida* colonization patients' MV duration

Three studies, including Zhang 2017, Griffin 2016, and Nseir 2007, reported the duration of MV. We did not identify a significant difference between the therapy and control groups regarding MV duration (SMD: 0.11, 95%CI, -0.88 to 1.10), as shown in Figure 4.

Figure 4 Forest plot for MV duration

### 3.6 Effect of antifungal therapy on VAP

Six studies, including Du 2021, Zhang 2017, Griffin 2016, Lindau 2015, VanDerGeest 2014, and Ong 2013, reported VAP. No significant difference was found between therapy and control groups (OR: 1.54, 95% CI, 0.56 to 4.20), as shown in Figure 5.

Figure 5 Forest plot for VAP

### 3.7 Subgroup analysis

We conducted a subgroup analysis based on effect of antifungal therapy on VAP of the included studies. The result of the subgroup analysis indicate that the combined effect size is stable and unaffected by different treatment types. As shown in Supplemental Figure 1.

Supplemental Figure 1 Forest plot for subgroup analysis of different treatment types

### 3.8 Sensitivity analysis and publication bias

A sensitivity analysis was performed by sequentially excluding one study at a time. This exclusion did not significantly impact the results, with the pooled OR ranging from 1.00 (0.51-1.96) to 2.07 (0.74-5.78) (Supplemental Figure 2). Because only 9 related studies were included in this report, approaches for detecting publication bias would have exhibited limited efficacy. Consequently, the evaluation of publication bias was not conducted.

Supplemental Figure 2 Sensitivity analysis for VAP

## 4 Discussion

In this study, we observed that antifungal therapy administered to mechanically ventilated patients with *Candida* colonization did not show a significant impact on patient outcomes, which were measured by indicators including mortality, hospital length of stay, ICU length of stay, mechanical ventilation duration, and incidence of VAP, and the result is stable when taking different treatment types into consideration. A study by Du declared that antifungal treatment was associated with a reduced risk of VAP, while an autopsy study involving 232 samples showed that although *Candida* is a common pathogen, the incidence of *Candida* pneumonia in ICU patients is extremely low(3, 9). Inconsistent with the results of the previous studies, a meta-analysis found that *Candida* pulmonary colonization probably had poorer clinical outcomes owing to longer mechanical ventilation duration, higher 28-day mortality, higher ICU mortality, and longer ICU length of stay(24). Furthermore, a study by Ioannou found that about half of the patients with *Candida* spp. isolation from their respiratory secretions were treated with antifungals. Considering the factor that patients under more critical condition could be treated with antifungals more often, a multivariate regression analysis was conducted identifying antifungal use as an independent factor associated with total hospital mortality(2). Without listing the specific articles for verification, the guideline strongly recommends that *Candida* colonization rarely requires treatment with antifungal therapy(25). Our study, may help to provide more information on this problem: whether *Candida* pulmonary colonization simply symbolizes the severity of diseases or actually have influence on outcomes(26, 27).

*Candida* colonization in the respiratory tract is related to higher inflammation and may accelerate the disease process(28, 29). A few studies used inhalation of antifungal drugs as therapy, which didn't

show significant influence on patients' outcome. This may lead to direct inhibition or damage of the alveolar-capillary membrane, resulting in an influx of surfactant-inactivating plasma proteins(17, 23). After *Candida* colonization, current increases in antifungal drug resistance in *Candida* spp. and clinical treatment failures are of concern(30). Previous history of antifungal prescription influences *Candida* species distribution and susceptibility profile to antifungal agents(31). Inadequate dose and treatment failure may contribute to high mortality(32).

Considering the various conditions, we thought that various factors cause poor clinical outcomes: antifungal treatment may have more harm than benefit in clinically ill patients. Different antifungal drugs can have varying sensitivities or resistances as well as potential toxicity or adverse effects. Inadequate dosing of antifungal drugs may also be a contributing factor. In short, further studies should be conducted to verify their influence. Considering retrospective and current studies can only provide hypotheses to prove the existence of a correlation, a prospective randomized controlled trial may be a more appropriate solution to explore the effect of antifungal treatment on patients with respiratory *Candida* colonization in combination with mechanical ventilation.

Based on the findings of this meta-analysis, the use of antifungal medication on mechanical-ventilated patients with respiratory *Candida* colonization does not appear to improve patients' clinical outcomes. No significant differences were observed in ICU mortality, hospital mortality, 28-day mortality, 90-day mortality, ICU length of stay, MV duration, and VAP associated with different treatment regimens. Further analysis of subgroups based on different treatment types confirmed these conclusions. Therefore, the use of antifungal medication is not recommended for the decolonization of mechanical-ventilated patients with respiratory *Candida* colonization.

## 5 Author Contributions

HX and HY provided article ideas and completed a literature search. LL and SS contributed to the data analysis and manuscript writing.

## 6 Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## 7 Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

## 8 Patient consent for publication

Not applicable.

## 9 Ethics approval

Not applicable.

## 10 Data Availability Statement

The raw data of this study can be obtained from corresponding author under reasonable request.

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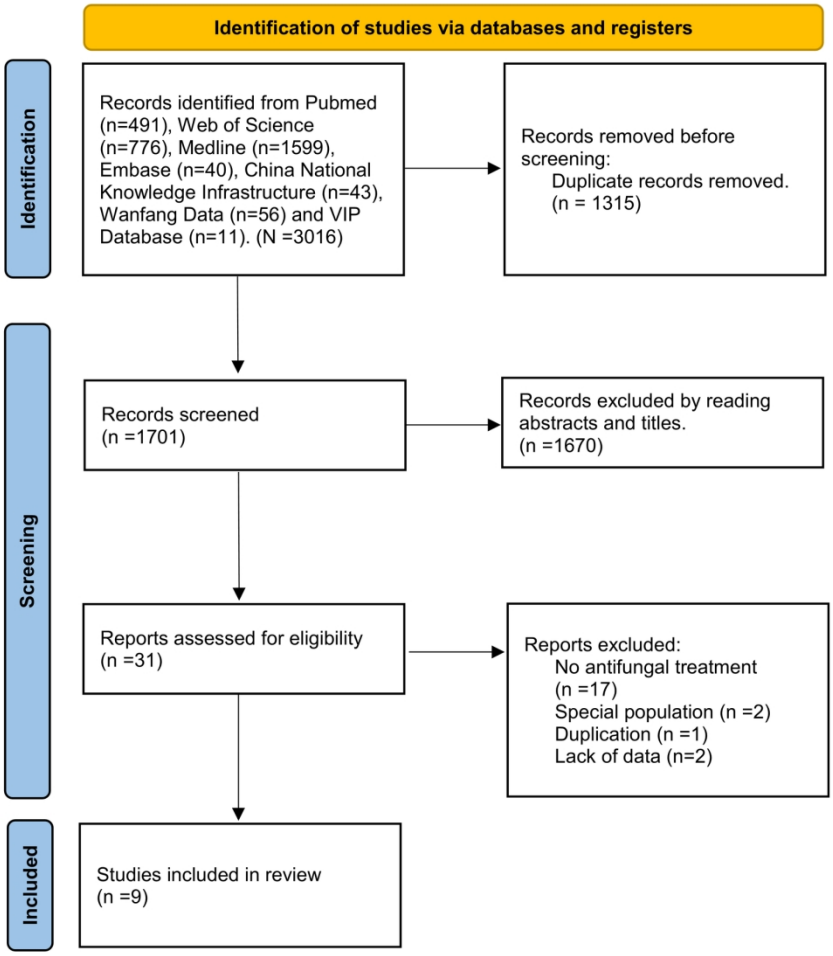


Figure 1 Flowchart of studies identified, excluded, and included

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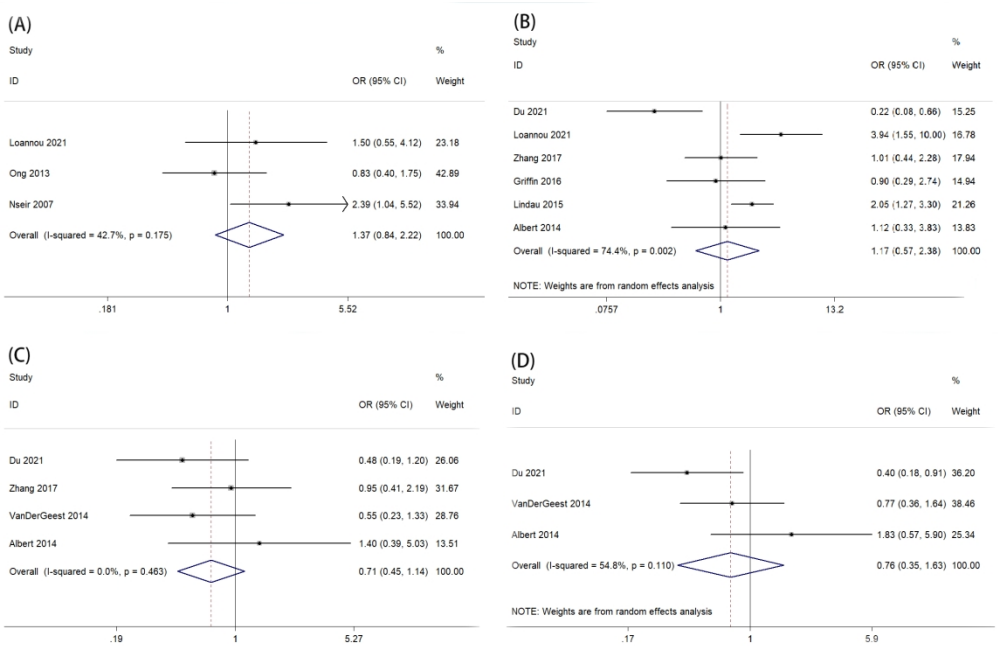


Figure 2 (A) Forest plot for ICU mortality; (B) Forest plot for hospital mortality; (C) Forest plot for 28-day mortality; (D) Forest plot for 90-day mortality

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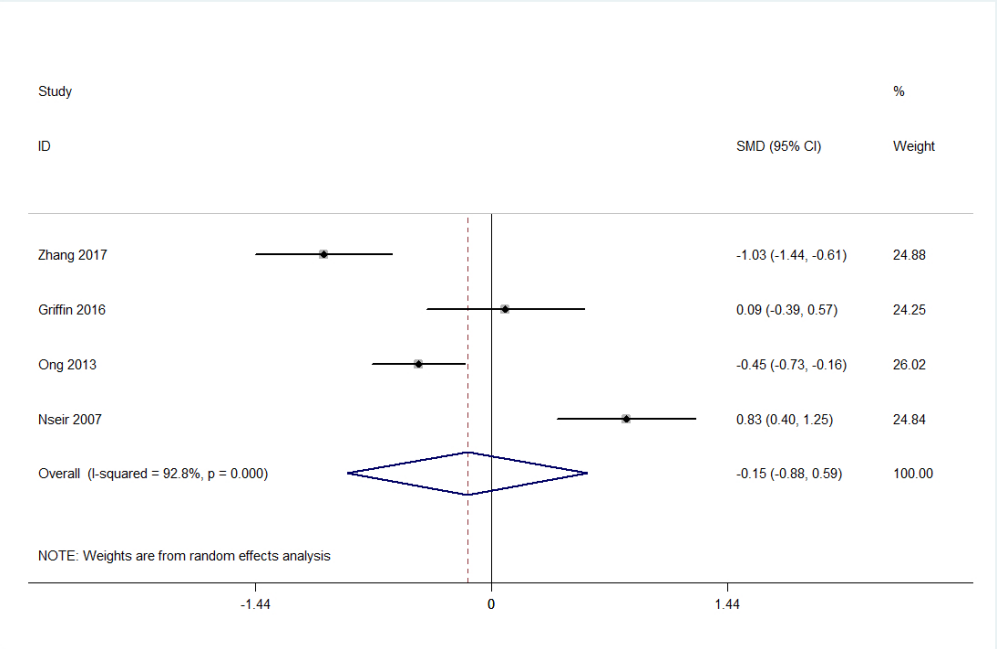


Figure 3 Forest plot for ICU length of stay

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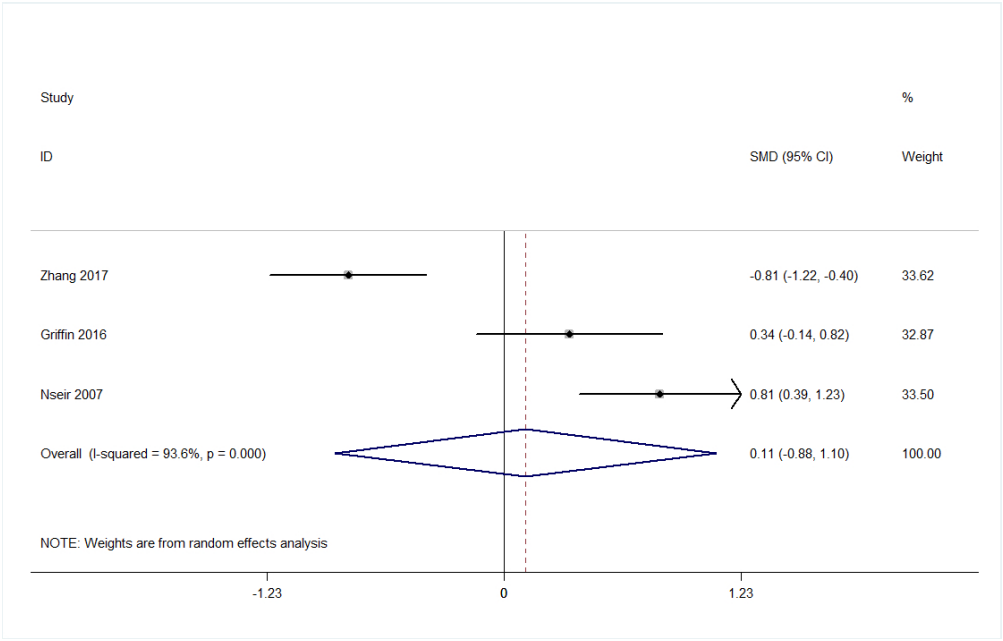


Figure 4 Forest plot for MV duration

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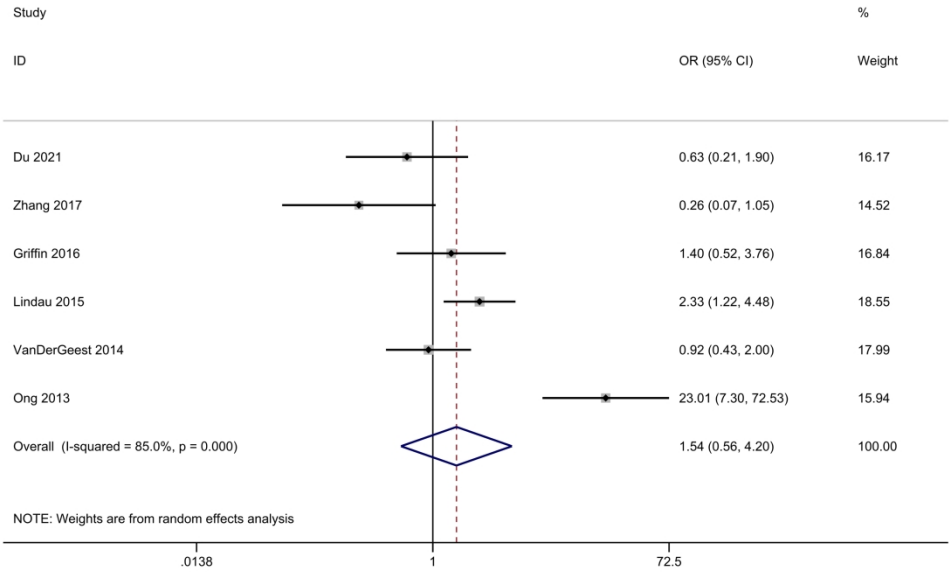


Figure 5 Forest plot for VAP

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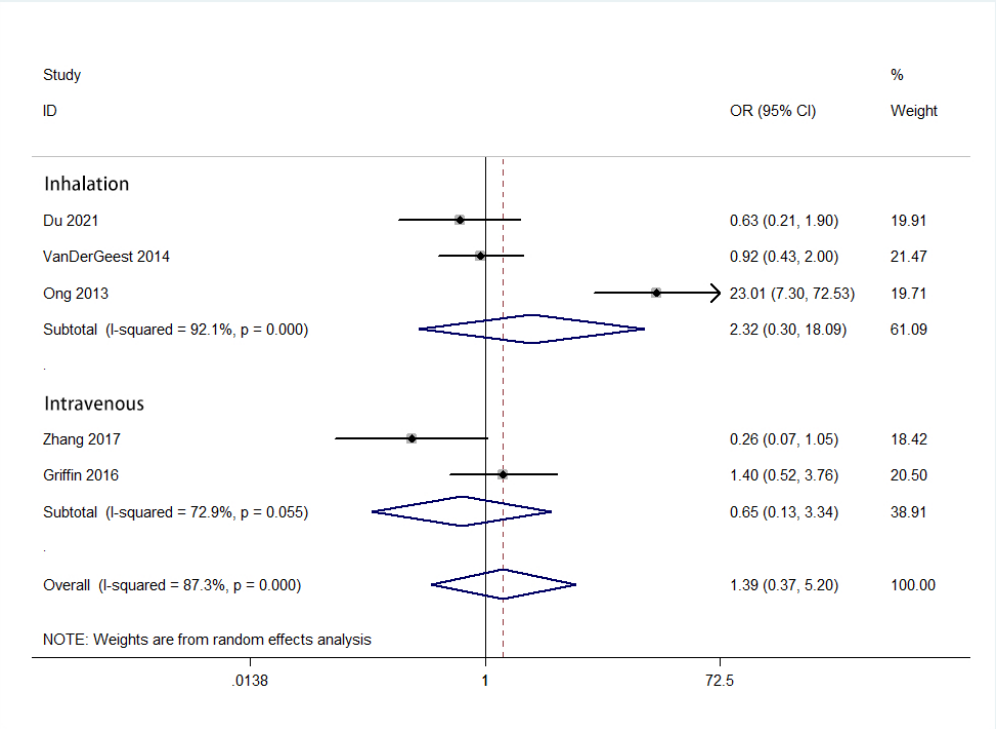


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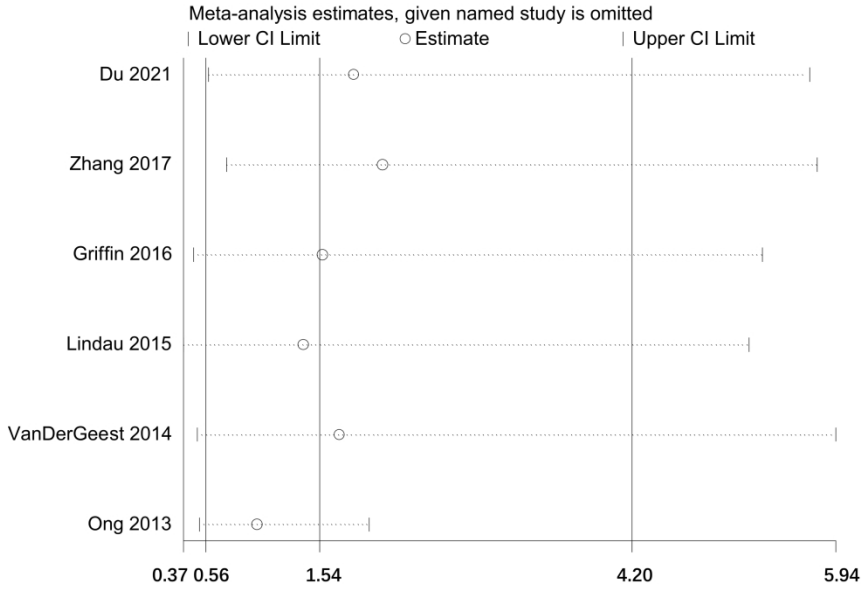


296x209mm (300 x 300 DPI)

Supplemental Table 1. Characteristics of included studies

| | Years of accrual | Country | Study style | Population | Number of patients | Outcome | Type of *Candida* isolated | *Candida* colonization | Antifungal treatment |
|---|---|---|---|---|---|---|---|---|---|
| Griffin 2016 (20) | 2011-2014 | USA | retrospective cohort | Adults | 75 | hospital mortality; ICU length of stay; MV duration; VAP (after treatment) | *Candida albicans; Candida tropicalis* | at least one bronchoalveolar lavage (+) | Intravenous fluconazole/ Echinocandin |
| Lindau 2015 (21) | 2010-2012 | Germany | retrospective cohort | Adults | 322 | hospital mortality; VAP (after treatment) | not described | at least one tracheal aspirate or bronchoalveolar lavage (+) | not described |
| VanDerGeest 2014 (23) | 2010-2011 | Netherland | retrospective cohort | Adults | 113 | 28-day mortality; 90-day mortality; VAP (after treatment) | *Candida albicans; Candida non-albicans* | culture of throat, tracheal aspirates or bronchoalveolar lavage (+ >2 | Amphotericin-B deoxycholate inhalation |
| Albert 2014 (22) | 2010-2012 | Canada | RCT | Adults | 89-60 | hospital mortality; 28-day mortality; 90-day mortality | not described | bronchoalveolar lavage or endotracheal aspirate (+) | Intravenous anidulafungin/ Fluconazole |
| Nseir 2007 (18) | 2004-2005 | France | nested case-control | Adults | 102 | ICU mortality; ICU length of stay; MV duration; | *P. aeruginosa; Candida* spp. | tracheobronchial(+) | Fluconazole |

Supplementary Material

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Zhang 2017 (19) | 2012-2016 | China | retrospective cohort | Adults APACHE II >8 | 101 | hospital mortality; 28-day mortality; ICU length of stay; MV duration; VAP (after treatment) | *Candida albicans; Candida tropicalis* | culture(+) in respiratory tract | Intravenous fluconazole/ Caspofungin |
| Ong 2013 (17) | 2008-2012 | Netherland | retrospective cohort | Adults | 333 | ICU mortality; ICU length of stay; VAP (after treatment) | not described | bronchoalveolar lavage or sputum samples (+) >2 | Nebulised amphotericin-B inhalation |
| Ioannou 2021 (2) | 2014-2016 | Greece | retrospective cohort | Adults | 90 | ICU mortality; hospital mortality; | *Candida albicans; Candida tropicalis* | tracheal aspirate, sputum or bronchoalveolar lavage(+) | Fluconazole/ Micafungin / Anidulafungin |
| Du 2021 (3) | 2012-2020 | China | retrospective cohort | Adults | 110 | hospital mortality; 28-day mortality; 90-day mortality; VAP (after treatment) | *Candida albicans; Candida non-albicans* | bronchoalveolar lavage or sputum samples (+) ⩾2 | Nebulised amphotericin-B inhalation |

Supplemental Table 2. Quality assessment of included studies

Cohort study (Newcastle-Ottawa scale)

| Study | Selection | | | | Outcome | | | Comparability of cohorts | Total score |
|---|---|---|---|---|---|---|---|---|---|
| | Representativeness of exposed cohort | Selection of the non-exposed cohort | Ascertainment of exposure | outcome of interest | Assessment of outcome | Follow-up duration | Adequacy follow cohorts | | |
| VanDerGeest 2014 (23) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 9 |
| Griffin 2016 (20) | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 2 | 7 |
| Lindau 2015 (21) | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 2 | 7 |
| Zhang 2017 (15) | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 2 | 7 |
| Ong 2013 (17) | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 2 | 7 |
| Ioannou 2021 (2) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 9 |

Supplementary Material

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Du 2021 (3) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 9 |

Case-control study (Newcastle-Ottawa scale)

| Study | Selection | | | | Exposure | | Comparability of Cases and Controls | Total score |
|---|---|---|---|---|---|---|---|---|
| | Case Definition | Representativeness | Selection of Controls | Definition of Controls | Ascertainment of Exposure | Non-Response Rate | | |
| Nseir 2007 (18) | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 8 |

Randomized controlled trial (The Cochrane risk assessment tool)

| Study | Random sequence generation | Blinding | Allocation concealment | Incomplete outcome data | Selective outcome reporting | Other bias | Total score |
|---|---|---|---|---|---|---|---|
| Albert (22) | 1 | 1 | 1 | 1 | 1 | 1 | 6 |

BMJ Open

# Clinical outcomes of antifungal therapy on Candida pulmonary colonization in immunocompetent patients with invasive ventilation: A systematic review and meta-analysis

| | |
|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2024-083918.R1 |
| Article Type: | Original research |
| Date Submitted by the Author: | 26-Aug-2024 |
| Complete List of Authors: | Li, Linqi; University of South China, The Affiliated Changsha Central Hospital; University of South China, School of Public Health<br>Su, Shan; Zhaoqing First People's Hospital, Department of Respiratory and Critical Care Medicine<br>Yang, Hongzhong ; University of South China, Department of Respiratory and Critical Care Medicine,The Affiliated Changsha Central Hospital<br>Xie, He-Bin; University of South China, The Affiliated Changsha Central Hospital; University of South China, School of Public Health |
| Primary Subject Heading: | Intensive care |
| Secondary Subject Heading: | Evidence based practice |
| Keywords: | Meta-Analysis, Adult intensive & critical care < INTENSIVE & CRITICAL CARE, Pulmonary Disease < Lung Diseases |
| | |

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# Clinical outcomes of antifungal therapy on Candida pulmonary colonization in immunocompetent patients with invasive ventilation: A systematic review and meta-analysis

**Keywords:** ***Candida*** **colonization, pulmonary, antifungal therapy, mechanical ventilation, meta-analysis.**

## Abstract

**Objective:** This study aimed to use systematic review and meta-analysis to establish the influence of antifungal therapy on pulmonary *Candida* colonization of patients with mechanical ventilation.

**Design:** Systematic review and meta-analysis.

**Data sources:** An extensive search was undertaken on publications from inception to July 25, 2023, through PubMed, Web of Science, Medline, Embase, China National Knowledge Infrastructure, Wanfang Data and VIP Databases.

**Eligibility criteria for selecting studies:** Randomized trials, cohort studies, and case-control studies comparing the efficacy of antifungal treatment in immunocompetent patients with pulmonary *Candida* colonization after invasive ventilation.

**Data extraction and synthesis:** Two reviewers independently extracted the data and assessed the quality of studies. Dichotomous outcomes were expressed as odds ratios (OR) with 95% confidence intervals (CIs). Continuous outcomes were expressed as standardized mean differences (SMD) with 95% CIs.

**Primary and secondary outcome measures:** The primary outcomes included intensive care unit (ICU), hospital, 28-day, and 90-day mortality. The secondary outcomes included ICU length of stay, mechanical ventilation (MV) duration, and ventilator-associated pneumonia (VAP).

**Results:** Nine high-quality studies were included. According to the data collected from these nine studies, there is no significant evidence showing a difference between the therapy group treated with antifungal drugs and the control group without antifungal drugs in clinical outcomes, including intensive care unit mortality (OR: 1.37; 95% CI, 0.84 to 2.22), hospital mortality (OR: 1.17; 95% CI, 0.57 to 2.38), 28-day mortality (OR; 0.71, 95% CI, 0.45 to 1.14), 90-day mortality (OR; 0.76, 95% CI 0.35 to 1.63), intensive care unit length of stay (SMD: -0.15; 95% CI -0.88 to 0.59), mechanical ventilation duration (SMD: 0.11; 95%CI -0.88 to 1.10), and ventilator-associated pneumonia (OR: 1.54; 95% CI 0.56 to 4.20). Subgroup analysis of different treatment types indicates that the combined effect size is stable and unaffected by different treatment types including inhalation (OR: 2.32; 95% CI 0.30 to 18.09) and intravenous (OR: 0.65; 95% CI 0.13 to 3.34).

**Conclusion:** The application of antifungal treatment did not improve clinical outcomes in patients with mechanical ventilation. We do not suggest initiating antifungal treatment in patients with *Candida* pulmonary colonization after invasive ventilation.

**Registration:** This study was registered in the International Prospective Register of Systematic Reviews, with the registration number CRD42020161138.

**Strengths and limitations of this study:**

1. This study included a number of outcome indicators to assess the effectiveness of antifungal treatment, with subgroup analyses performed based on the type of treatment administered.

2. Most studies included are retrospective studies, raising potential concerns regarding their external validity.

3. Some studies described the precise style, name, dose, and administration method of antifungal drugs, while others did not.

4. This study is limited by the number of studies included, especially when it comes to single outcomes such as ICU mortality.

5. Most studies included were cohort studies instead of random contral trials, which provide stronger evidence.

## 1 Introduction

*Candida* frequently exists in the normal oral cavity, upper respiratory tract, lower-intestinal tract and vagina(1). In tracheal aspirates from patients with MV, 30% have *Candida* isolation, and nearly 50% from patients suspected to have a VAP(2, 3). When respiratory *Candida* colonization is detected, it is difficult to differentiate between relatively harmless colonization and invasive infection, and leads to a therapeutic dilemma(4). Although few studies reported limited attributable ICU mortality of VAP, the death rate related to VAP cannot be denied according to the majority of previous studies(5-8). The incidence of VAP frequently extends hospital stay, elevates the economic burden, and raises the mortality rate(9). The presence of *Candida* in respiratory samples is defined as *Candida* colonization instead of infection because the appearance of *Candida* pneumonia is rare(10-13). For several years, arguments have arisen about whether *Candida* colonization negatively affects or simply indicates disease severity or immunosuppression in critically ill patients(14-16). We found that the outcomes of antifungal treatment for *Candida* colonization in pulmonary tract among different studies were controversial, as some studies found that antifungal treatment was associated with lower mortality, some found that treatment made no difference in mortality, while others found that it prolonged MV duration, intensive care unit (ICU) length of stay, and hospital length of stay(10, 11, 17, 18). Therefore, we performed a systematic review and meta-analysis to establish the influence of antifungal treatment on pulmonary *Candida* colonization.

## 2 Method

### 2.1 Information sources and search strategy

This study followed the Preferred Reporting Items for Systematic Review and Meta-Analysis criteria for systematic reviews and meta-analyzes. An extensive search was undertaken on publications from inception to July 25, 2023, through PubMed, Web of Science, Medline, Embase, China National Knowledge Infrastructure, Wanfang Data and VIP Databases. The searching syntax included the following Medical Subject Headings (MeSH) and text words which are varied individually according to different databases: ventilator-associated pneumonia, *Candida*. We used the following search

strategies: (ventilator-associated pneumonia OR VAP OR pneumonia, ventilator-associated OR ventilator-associated pneumonia OR ventilator-acquired pneumonia OR mechanical ventilation) AND (*Candida* OR *Candida* spp OR *Candida* colonization OR *Candida* airway colonization). There were no language restrictions on studies searching. The listed references of relevant studies were also evaluated to enlarge the search scope and ensure a complete search. Selection process of the article was performed by two researchers (LL and SS) independently. The titles and abstracts of the entries identified in the search were screened. Full text version of all articles that potentially met the eligibility criteria was reviewed to make a decision. Disagreements, if any, were resolved through discussion with a third researcher (HX).

### 2.2 Inclusion criteria

Randomized trials, cohort studies, and case-control studies were included while selecting. In the included studies, the patients were adults (≥18 years old) who were diagnosed with pulmonary *Candida* colonization after invasive ventilation. Pulmonary *Candida* colonization was defined as the presence of *Candida* in bronchoalveolar lavage samples, endotracheal aspiration samples, protected brush specimens, or any positive airway secretion specimens.

### 2.3 Exclusion criteria

We excluded case reports and studies on pregnant, immunocompromised patients, or those who received antifungal treatment for reasons other than *Candida* colonization. Patients with candidemia or invasive candidiasis were also excluded, and the diagnostic criteria were positive results of direct detection, in which blood or tissue specimens were cultured, or indirect detection, in which surrogate markers and polymerase chain reaction assays were used(19).

### 2.4 Data collection

We screened titles and abstracts, reviewed the full text, and extracted data using an Excel sheet (Microsoft Corporation). We primarily collected the characteristics of title, author, journal, year, type, participants, inclusion or exclusion criteria, interventions, and clinical outcomes. Clinical outcomes included 28-day mortality, 90-day mortality, ICU mortality, hospital mortality, ICU length of stay, MV duration, and VAP. Disagreements were resolved by discussion with a third reviewer if necessary.

### 2.5 Quality assessment

We used the Cochrane risk assessment tool to measure the risk of randomized controlled trials and the Newcastle-Ottawa Scale to measure the quality of cohort and case-control studies(20). Studies that scored at least six points were regarded as high-quality and included.

### 2.6 Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

### 2.7 Statistical analysis

Statistical analysis was performed by Stata software (Version 16.0). Dichotomous outcomes such as VAP, ICU mortality, hospital mortality, 28-day mortality, and 90-day mortality, were expressed as OR with 95% CIs. Continuous outcomes (ICU length of stay and MV duration) were expressed as

SMD with 95% CIs. We analyzed the data using the Inverse-Variance method with the fixed-effect model if there was no obvious heterogeneity ($P$>0.1), or else random-effect model if the heterogeneity was significant ($P$<0.1). Moreover, heterogeneity was quantified using the $I^2$ test. The interpretation of $I^2$ was guided by the Cochrane Handbook for Systematic Reviews of interventions (Version 5.2.0, updated June 2017). Sensitivity analyses was conducted by excluding one study at a time from the analysis to assess the stability of the results. Publication bias was not assessed since there were fewer than 10 studies in this meta-analysis.

## 3 Results

### 3.1 Study selection

In total, 2947 records were identified. With 1246 duplicates removed and 1670 irrelevant records excluded, we assessed 31 studies for eligibility, of which 9 were included. 22 studies were excluded because of the lack of antifungal treatment, lack of supporting experimental data, lack of detection of pulmonary secretion, and occurrence in a special population (Figure 1). All patients received MV, had at least one positive culture of *Candida* in the pulmonary tract, and received different antifungal treatments.

Figure 1 Flowchart of studies identified, excluded, and included

### 3.2 Study characteristics and quality assessment

Of the nine articles included in the study, seven were retrospective cohort studies, one case-control study, and one randomized clinical trial. Two studies were conducted in North America, five in Europe, and two in Asia, giving the studies a wide geographical coverage. Other characteristics of the included studies are summarized in Supplemental Table 1, including years of accuracy, location, study design, population, number of patients, outcomes, *Candida* colonization and antifungal treatment. The columns of the quality assessment list and their corresponding points are listed in Supplemental Table 2. All included studies were assessed to be of high quality.

### 3.3 Effect of antifungal therapy on pulmonary *Candida* colonization patients' mortality

Three studies, including Ioannou 2021(2), Ong 2013(21), and Nseir 2007(22) reported ICU mortality. We found no significant difference between the therapy and control groups (OR: 1.37, 95% CI, 0.84 to 2.22). Six studies, including Du 2021(4), Ioannou 2021, Zhang 2017(23), Griffin 2016(24), Lindau 2015(25), and Albert 2014(26) reported hospital mortality. The pooled results showed no significant difference between the therapy and control groups (OR: 1.17, 95% CI, 0.57 to 2.38). Four studies, including Du 2021, Zhang 2017, VanDerGeest 2014(27), and Albert 2014, reported 28-day mortality. The results showed no significant difference between the therapy and control groups (OR: 0.71, 95% CI, 0.45 to 1.14). Three studies, Du 2021, VanDerGeest 2014, and Albert 2014, reported 90-day mortality. The results showed no significant difference between the therapy and control groups (OR: 0.76, 95% CI, 0.35 to 1.63). No indicator showed statistical significance with respect to mortality. (Figure 2)

Figure 2 (A) Forest plot for ICU mortality; (B) Forest plot for hospital mortality; (C) Forest plot for 28-day mortality; (D) Forest plot for 90-day mortality

### 3.4 Effect of antifungal therapy on pulmonary *Candida* colonization patients' ICU length of stay

Four studies, including Zhang 2017, Griffin2016, Ong 2013, and Nseir 2007, reported ICU length of stay. The results indicated non-significant differences for ICU length of stay among patients receiving antifungal treatment (SMD: -0.15, 95% CI, -0.88 to 0.59), as shown in Figure 3.

Figure 3 Forest plot for ICU length of stay

### 3.5 Effect of antifungal therapy on pulmonary *Candida* colonization patients' MV duration

Three studies, including Zhang 2017, Griffin 2016, and Nseir 2007, reported the duration of MV. We did not identify a significant difference between the therapy and control groups regarding MV duration (SMD: 0.11, 95%CI, -0.88 to 1.10), as shown in Figure 4.

Figure 4 Forest plot for MV duration

### 3.6 Effect of antifungal therapy on VAP

Six studies, including Du 2021, Zhang 2017, Griffin 2016, Lindau 2015, VanDerGeest 2014, and Ong 2013, reported VAP. No significant difference was found between therapy and control groups (OR: 1.54, 95% CI, 0.56 to 4.20), as shown in Figure 5.

Figure 5 Forest plot for VAP

### 3.7 Subgroup analysis

We conducted a subgroup analysis based on the effect of antifungal therapy on VAP of the included studies. The result of the subgroup analysis indicate that the combined effect size is stable and unaffected by different treatment types. As shown in Supplemental Figure 1.

Supplemental Figure 1 Forest plot for subgroup analysis of different treatment types

### 3.8 Sensitivity analysis and publication bias

A sensitivity analysis was performed by sequentially excluding one study at a time. This exclusion did not significantly impact the results, with the pooled OR ranging from 1.00 (0.51-1.96) to 2.07 (0.74-5.78) (Supplemental Figure 2). Because only 9 related studies were included in this report, approaches for detecting publication bias would have exhibited limited efficacy. Consequently, the evaluation of publication bias was not conducted.

Supplemental Figure 2 Sensitivity analysis for VAP

## 4 Discussion

In this study, we observed that antifungal therapy administered to mechanically ventilated patients with *Candida* colonization did not show a significant impact on patient outcomes, which were measured by indicators including mortality, hospital length of stay, ICU length of stay, mechanical ventilation duration, and incidence of VAP, and the result is stable when taking different treatment types into consideration. A study by Du declared that antifungal treatment was associated with a reduced risk of VAP, while an autopsy study involving 232 samples showed that although *Candida* is a common pathogen, the incidence of *Candida* pneumonia in ICU patients is extremely low(4, 11). Inconsistent with the results of the previous studies, a meta-analysis found that *Candida* pulmonary colonization probably had poorer clinical outcomes owing to longer mechanical ventilation duration, higher 28-day mortality, higher ICU mortality, and longer ICU length of stay(28). Furthermore, a

study by Ioannou found that about half of the patients with *Candida* spp. isolation from their respiratory secretions were treated with antifungals. Considering the factor that patients under more critical condition could be treated with antifungals more often, a multivariate regression analysis was conducted identifying antifungal use as an independent factor associated with total hospital mortality(2). Without listing the specific articles for verification, the guideline strongly recommends that *Candida* colonization rarely requires treatment with antifungal therapy(29). Our study, may help to provide more information on this problem: whether *Candida* pulmonary colonization simply symbolizes the severity of diseases or actually has influence on outcomes(30, 31).

*Candida* colonization in the respiratory tract is related to higher inflammation and may accelerate the disease process(32, 33). A few studies used inhalation of antifungal drugs as therapy, which did not show significant influence on patients' outcomes. This may lead to direct inhibition or damage of the alveolar-capillary membrane, resulting in an influx of surfactant-inactivating plasma proteins(21, 27). After *Candida* colonization, current increases in antifungal drug resistance in *Candida* spp. and clinical treatment failures are of concern(34). Previous history of antifungal prescription influences *Candida* species distribution and susceptibility profile to antifungal agents(35). Inadequate dose and treatment failure may contribute to high mortality(36).

Considering the various conditions, we thought that various factors cause poor clinical outcomes: antifungal treatment may have more harm than benefit in clinically ill patients. Different antifungal drugs can have varying sensitivities or resistances as well as potential toxicity or adverse effects. Inadequate dosing of antifungal drugs may also be a contributing factor. Although the analysis of this study showed that antifungal treatment did not improve patients' clinical outcomes, the sample size of included studies were limited and the 95% confidence intervals were wide. Further studies should be conducted to verify their influence. Considering retrospective and current studies can only provide hypotheses to support the existence of a correlation, a prospective randomized controlled trial might be a more appropriate solution to explore the effect of antifungal treatment on patients with respiratory *Candida* colonization in combination with mechanical ventilation.

Based on the findings of this meta-analysis, the use of antifungal medication on mechanical-ventilated patients with respiratory *Candida* colonization does not appear to improve patients' clinical outcomes. No significant differences were observed in ICU mortality, hospital mortality, 28-day mortality, 90-day mortality, ICU length of stay, MV duration, and VAP associated with different treatment regimens. Further analysis of subgroups based on different treatment types confirmed these conclusions. Therefore, the use of antifungal medication is not recommended for the decolonization of mechanical-ventilated patients with respiratory *Candida* colonization.

The strength of this study is that it included a number of outcome indicators to assess the effectiveness of antifungal treatment, with subgroup analyses performed based on the type of treatment administered. However it encountered several limitations. Most studies included are retrospective studies, raising potential concerns regarding their external validity. Additionally, some studies described the precise style, name, dose, and administration method of antifungal drugs, while others did not. Furthermore, this study is limited by the number of studies included, especially when it comes to single outcomes such as ICU mortality. Moreover, most studies included were cohort studies instead of random contral trials, which provide stronger evidence.

## 5 Author Contributions

HX and HY provided article ideas and completed a literature search. LL and SS contributed to the data analysis and manuscript writing. HX is the guarantor.

## 6 Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## 7 Patient consent for publication

Not applicable.

## 8 Ethics approval

Not applicable.

## 9 Data Availability Statement

The raw data of this study can be obtained from corresponding author under reasonable request.

## 10 Funding

This study was funded by Changsha Municipal Health Committee (No.KJ-B2023032).

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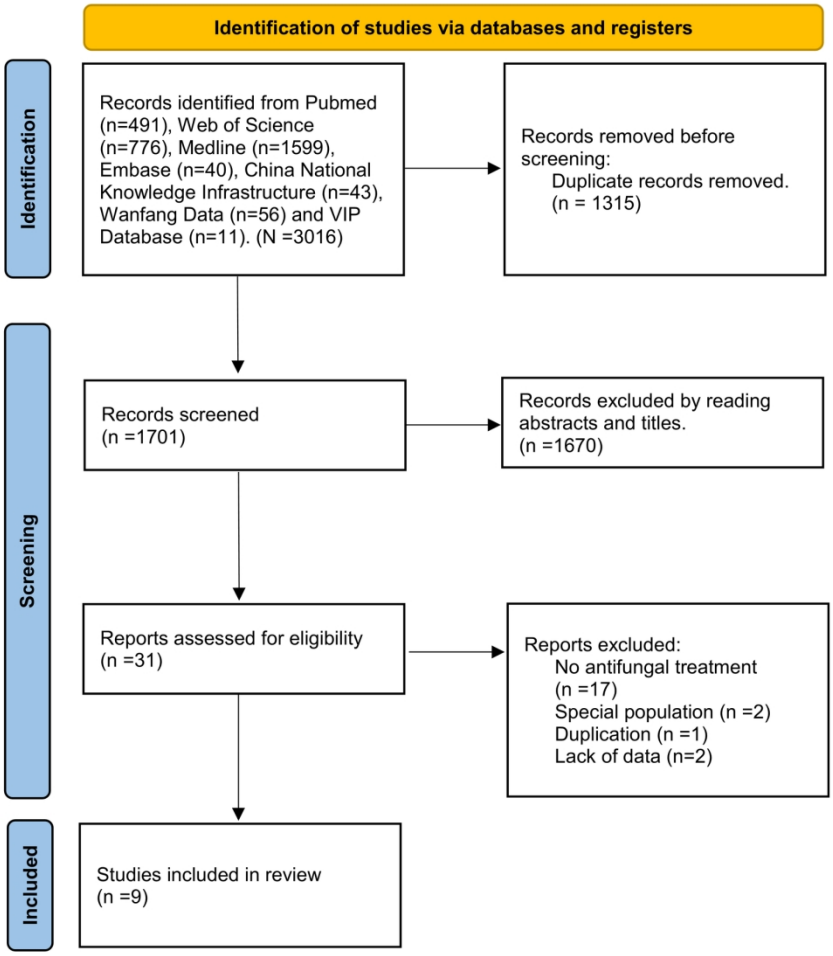



Figure 1 Flowchart of studies identified, excluded, and included

163x169mm (300 x 300 DPI)

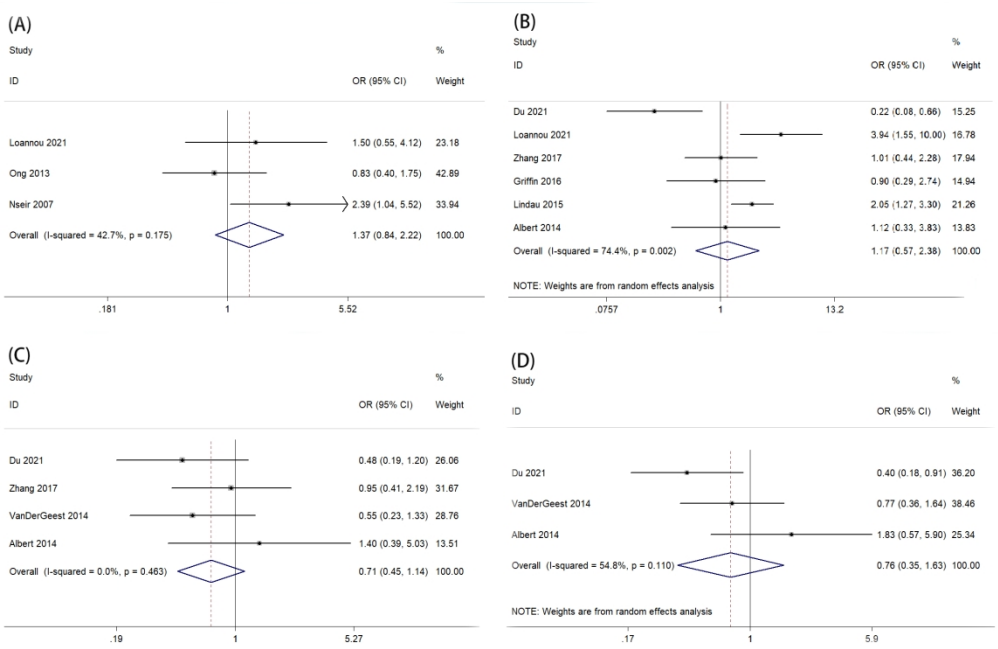



Figure 2 (A) Forest plot for ICU mortality; (B) Forest plot for hospital mortality; (C) Forest plot for 28-day mortality; (D) Forest plot for 90-day mortality

569x373mm (96 x 96 DPI)

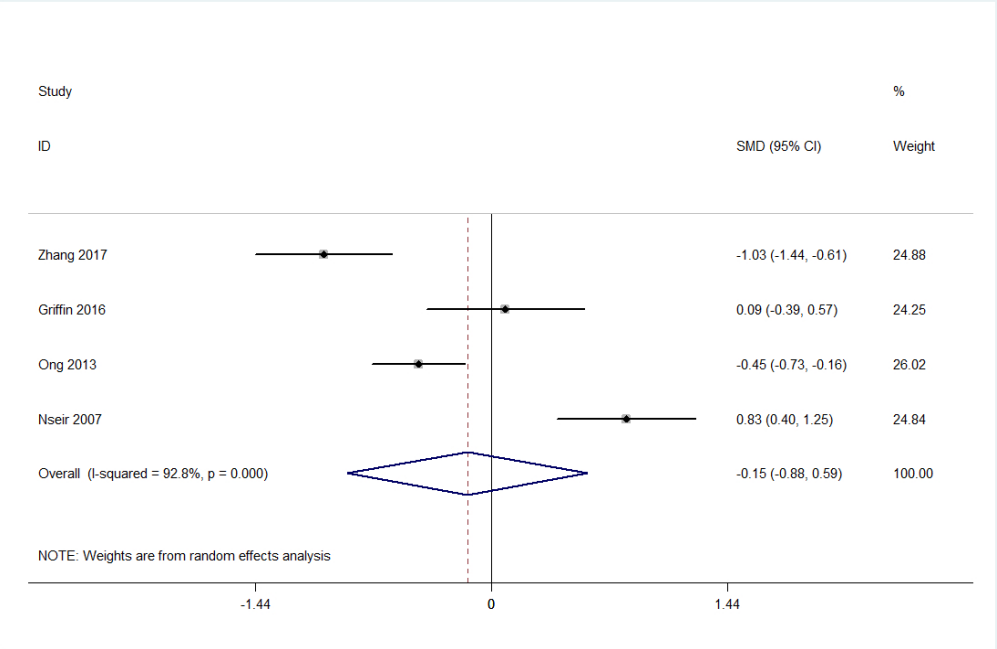



Figure 3 Forest plot for ICU length of stay

386x251mm (72 x 72 DPI)

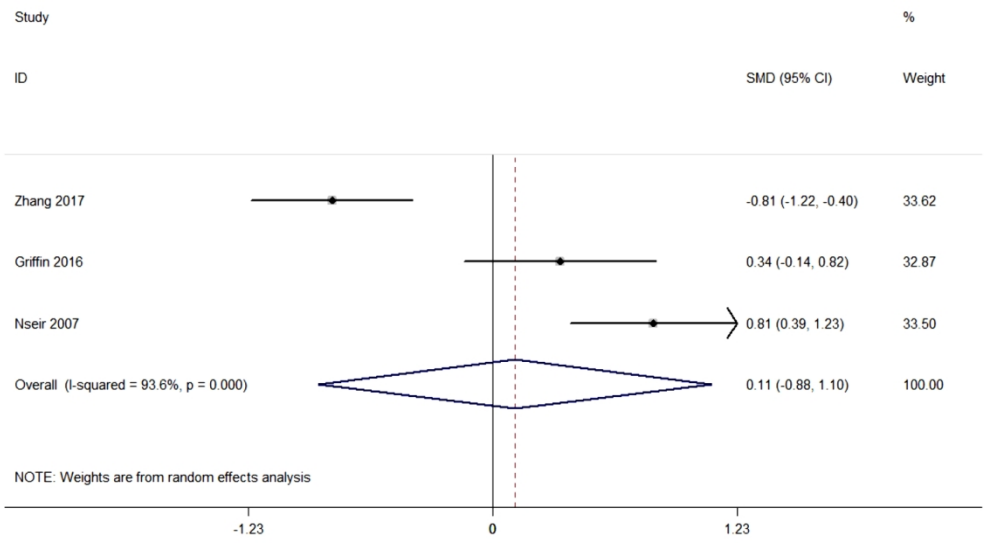



Figure 4 Forest plot for MV duration

554x316mm (72 x 72 DPI)

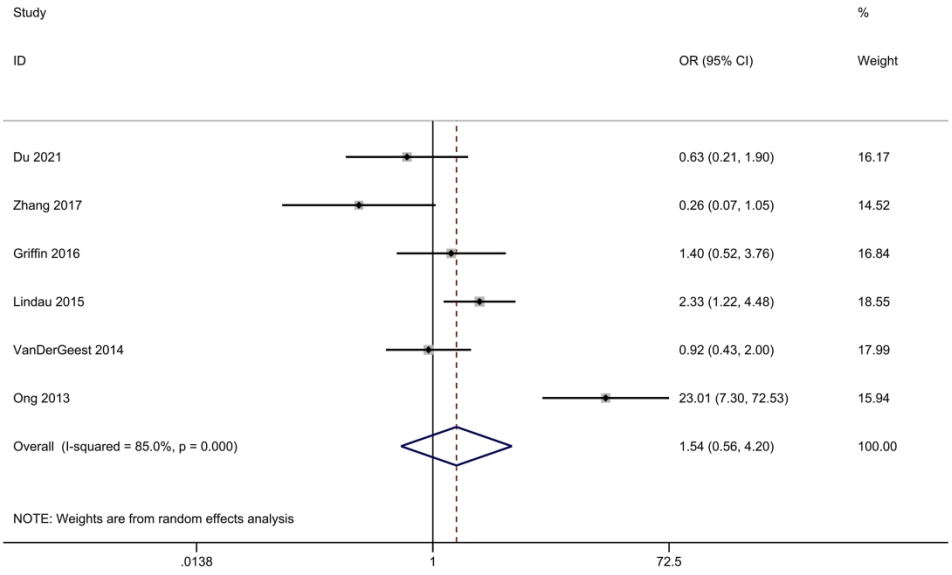



Figure 5 Forest plot for VAP

272x186mm (300 x 300 DPI)

Supplemental Table 1. Characteristics of included studies

| | Years of accrual | Country | Study style | Population | Patients' gender | Outcome | Type of *Candida* isolated | *Candida* colonization | Antifungal treatment |
|---|---|---|---|---|---|---|---|---|---|
| Griffin 2016 (24) | 2011-2014 | USA | retrospective cohort | Adults | Male: 48<br>Female: 27 | hospital mortality; ICU length of stay; MV duration; VAP (after treatment) | *Candida albicans; Candida tropicalis* | at least one bronchoalveolar lavage (+) | Intravenous fluconazole/ Echinocandin |
| Lindau 2015 (25) | 2010-2012 | Germany | retrospective cohort | Adults | Male: 245<br>Female: 77 | hospital mortality; VAP (after treatment) | not described | at least one tracheal aspirates or bronchoalveolar lavage (+) | not described |
| VanDerGeest 2014 (27) | 2010-2011 | Netherland | retrospective cohort | Adults | Male: 71<br>Female: 42 | 28-day mortality; 90-day mortality; VAP (after treatment) | *Candida albicans; Candida non-albicans* | cultures of throat, tracheal aspirates or bronchoalveolar lavage (+) >2 | Amphotericin-B deoxycholate inhalation |
| Albert 2014 (26) | 2010-2012 | Canada | Random control trails | Adults | Male: 63<br>Female: 25 | hospital mortality; 28-day mortality; 90-day mortality | not described | bronchoalveolar lavage or endotracheal aspirate (+) | Intravenous anidulafungin/ Fluconazole |
| Nseir 2007 (22) | 2004-2005 | France | nested case-control | Adults | Male: 42<br>Female: 60 | ICU mortality; ICU length of stay; MV duration; | *P. aeruginosa; Candida* spp. | tracheobronchial(+) | Fluconazole |

Supplementary Material

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Zhang 2017 (23) | 2012-2016 | China | retrospective cohort | Adults APACHE II >8 | Male: 64<br>Female: 37 | hospital mortality; 28-day mortality; ICU length of stay; MV duration; VAP (after treatment) | *Candida albicans; Candida tropicalis* | cultured (+) in respiratory tract | Intravenous fluconazole/ Caspofungin |
| Ong 2013 (21) | 2008-2012 | Netherland | retrospective cohort | Adults | Male: 232<br>Female: 101 | ICU mortality; ICU length of stay; VAP (after treatment) | not described | bronchoalveolar lavage/sputum samples (+) >2 | Nebulised amphotericin-B inhalation |
| Ioannou 2021 (2) | 2014-2016 | Greece | retrospective cohort | Adults | Male: 67<br>Female: 23 | ICU mortality; hospital mortality; | *Candida albicans; Candida tropicalis* | tracheal aspirate, sputum or bronchoalveolar lavage (+) | Fluconazole/ Micafungin / Anidulafungin |
| Du 2021 (4) | 2012-2020 | China | retrospective cohort | Adults | Male: 55<br>Female: 55 | hospital mortality; 28-day mortality; 90-day mortality; VAP (after treatment) | *Candida albicans; Candida non-albicans* | bronchoalveolar lavage or sputum samples (+) ⩾2 | Nebulised amphotericin-B inhalation |

Supplemental Table 2. Quality assessment of included studies

Cohort study (Newcastle-Ottawa scale)

| Study | Selection | | | | Outcome | | | Comparability of cohorts | Total score |
|---|---|---|---|---|---|---|---|---|---|
| | Representativeness of exposed cohort | Selection of the non-exposed cohort | Ascertainment of exposure | outcome of interest | Assessment of outcome | Follow-up duration | Adequacy of follow cohorts | | |
| VanDerGeest 2014 (27) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 9 |
| Griffin 2016 (24) | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 2 | 7 |
| Lindau 2015 (25) | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 2 | 7 |
| Zhang 2017 (23) | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 2 | 7 |
| Ong 2013 (21) | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 2 | 7 |
| Ioannou 2021 (2) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 9 |

Supplementary Material

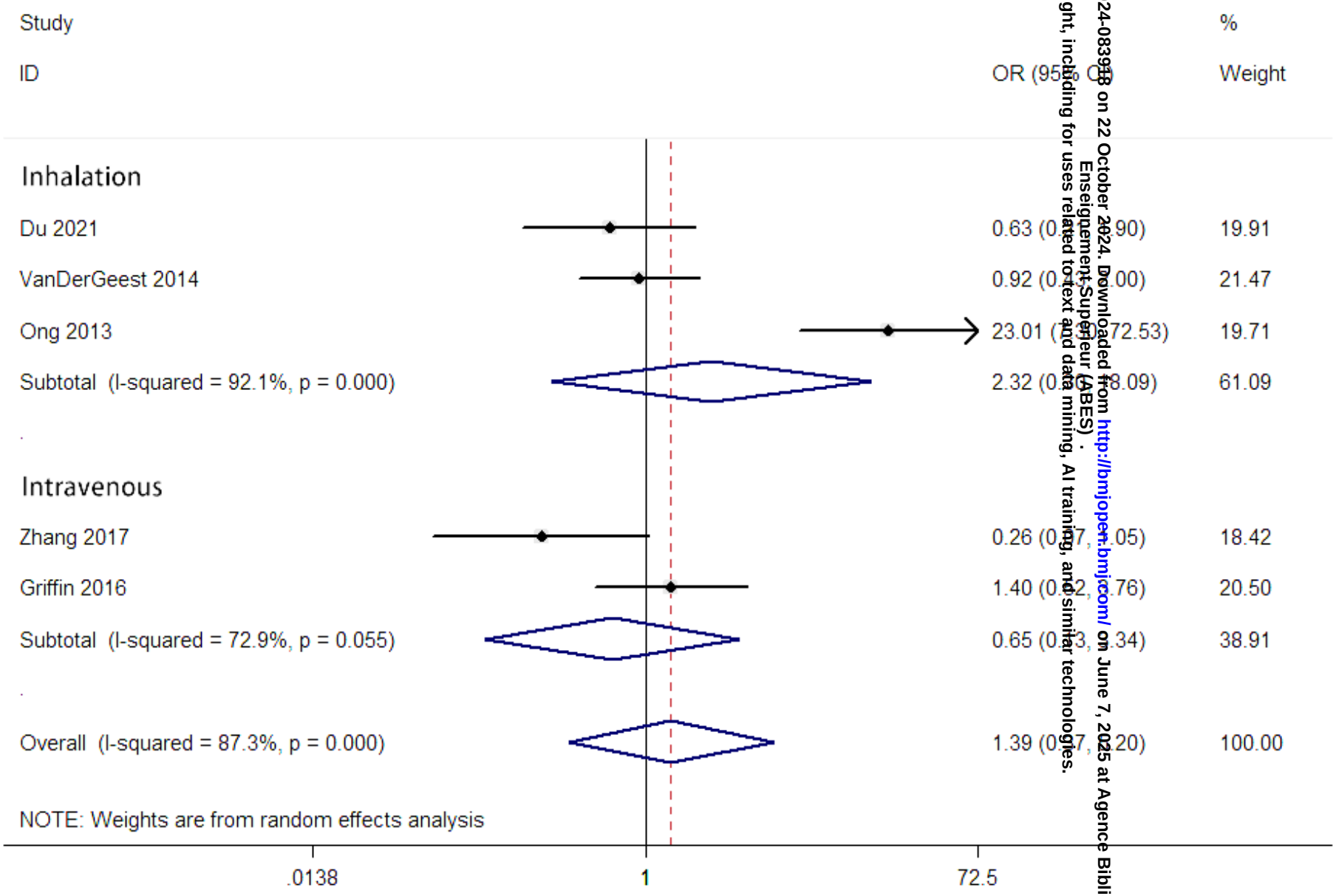
| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Du 2021 (4) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 9 |

Case-control study (Newcastle-Ottawa scale)

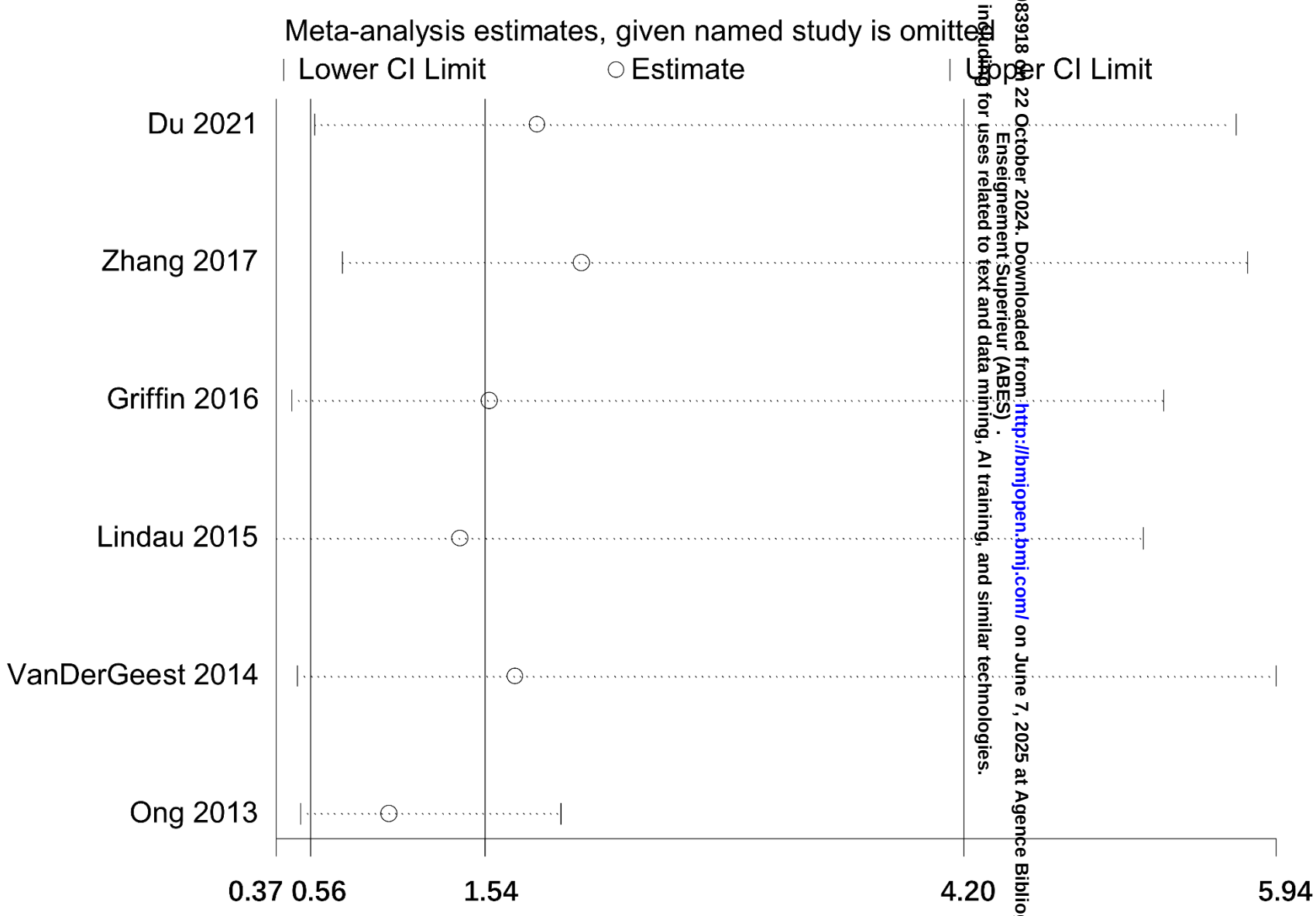
| Study | Selection | | | | Exposure | | Comparability of Cases and Controls | Total score |
|---|---|---|---|---|---|---|---|---|
| | Case Definition | Representativeness | Selection of Controls | Definition of Controls | Ascertainment of Exposure | Non-Response Rate | | |
| Nseir 2007 (22) | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 8 |

Randomized controlled trial (The Cochrane risk assessment tool)

| Study | Random sequence generation | Blinding | Allocation concealment | Incomplete outcome data | Selective outcome reporting | Other bias | Total score |
|---|---|---|---|---|---|---|---|
| Albert (26) | 1 | 1 | 1 | 1 | 1 | 1 | 6 |




Supplemental Figure 1 Forest plot for subgroup analysis of different treatment types




Supplemental Figure 2 Sensitivity analysis for VAP

# PRISMA 2020 Checklist

| Section and Topic | Item # | Checklist item | Location where item is reported |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review. | L1 |
| **ABSTRACT** | | | |
| Abstract | 2 | See the PRISMA 2020 for Abstracts checklist. | L75 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of existing knowledge. | L55 |
| Objectives | 4 | Provide an explicit statement of the objective(s) or question(s) the review addresses. | L71 |
| **METHODS** | | | |
| Eligibility criteria | 5 | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. | L90 |
| Information sources | 6 | Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted. | L76 |
| Search strategy | 7 | Present the full search strategies for all databases, registers and websites, including any filters and limits used. | L81 |
| Selection process | 8 | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process. | L85 |
| Data collection process | 9 | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. | L85 |
| Data items | 10a | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect. | L109 |
| | 10b | List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information. | L108 |
| Study risk of bias assessment | 11 | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process. | L113 |
| Effect measures | 12 | Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results. | L121 |
| Synthesis methods | 13a | Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)). | L114 |
| | 13b | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. | L106 |
| | 13c | Describe any methods used to tabulate or visually display results of individual studies and syntheses. | L120 |
| | 13d | Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used. | L120 |
| | 13e | Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression). | L181 |
| | 13f | Describe any sensitivity analyses conducted to assess robustness of the synthesized results. | L131 |
| Reporting bias assessment | 14 | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). | L133 |
| Certainty | 15 | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. | L131 |

# PRISMA 2020 Checklist

| Section and Topic | Item # | Checklist item | Location where item is reported |
|---|---|---|---|
| assessment | | | |
| **RESULTS** | | | |
| Study selection | 16a | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram. | Figure1 |
| | 16b | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded. | Figure1 |
| Study characteristics | 17 | Cite each included study and present its characteristics. | Supplemental Table 1 |
| Risk of bias in studies | 18 | Present assessments of risk of bias for each included study. | Supplemental Table 2 |
| Results of individual studies | 19 | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots. | Figure2-5 |
| Results of syntheses | 20a | For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies. | Supplemental Table 2 |
| | 20b | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. | L134 |
| | 20c | Present results of all investigations of possible causes of heterogeneity among study results. | NA |
| | 20d | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results. | L186 |
| Reporting biases | 21 | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed. | NA |
| Certainty of evidence | 22 | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed. | NA |
| **DISCUSSION** | | | |
| Discussion | 23a | Provide a general interpretation of the results in the context of other evidence. | L194 |
| | 23b | Discuss any limitations of the evidence included in the review. | L36 |
| | 23c | Discuss any limitations of the review processes used. | L36 |
| | 23d | Discuss implications of the results for practice, policy, and future research. | L224 |
| **OTHER INFORMATION** | | | |
| Registration and protocol | 24a | Provide registration information for the review, including register name and registration number, or state that the review was not registered. | L34 |
| | 24b | Indicate where the review protocol can be accessed, or state that a protocol was not prepared. | NA |
| | 24c | Describe and explain any amendments to information provided at registration or in the protocol. | NA |
| Support | 25 | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review. | L252 |
| Competing interests | 26 | Declare any competing interests of review authors. | L240 |
| Availability of data, code and other materials | 27 | Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review. | L250 |

# PRISMA 2020 Checklist

*From:* Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

**Search:**

(ventilator-associated pneumonia OR VAP OR pneumonia, ventilator-associated OR ventilator-associated pneumonia OR ventilator-acquired pneumonia OR mechanical ventilation) AND (Candida OR Candida spp OR Candida colonization OR Candida airway colonization)

**Details:**

("pneumonia, ventilator associated"[MeSH Terms] OR ("pneumonia"[All Fields] AND "ventilator-associated"[All Fields]) OR "ventilator-associated pneumonia"[All Fields] OR ("ventilator"[All Fields] AND "associated"[All Fields] AND "pneumonia"[All Fields]) OR "ventilator associated pneumonia"[All Fields] OR "VAP"[All Fields] OR (("pneumonia"[MeSH Terms] OR "pneumonia"[All Fields] OR "pneumonias"[All Fields] OR "pneumoniae"[All Fields] OR "pneumoniae s"[All Fields]) AND "ventilator-associated"[All Fields]) OR ("pneumonia, ventilator associated"[MeSH Terms] OR ("pneumonia"[All Fields] AND "ventilator-associated"[All Fields]) OR "ventilator-associated pneumonia"[All Fields] OR ("ventilator"[All Fields] AND "associated"[All Fields] AND "pneumonia"[All Fields]) OR "ventilator associated pneumonia"[All Fields]) OR ("pneumonia, ventilator associated"[MeSH Terms] OR ("pneumonia"[All Fields] AND "ventilator-associated"[All Fields]) OR "ventilator-associated pneumonia"[All Fields] OR ("ventilator"[All Fields] AND "acquired"[All Fields] AND "pneumonia"[All Fields]) OR "ventilator acquired pneumonia"[All Fields]) OR ("respiration, artificial"[MeSH Terms] OR ("respiration"[All Fields] AND "artificial"[All Fields]) OR "artificial respiration"[All Fields] OR ("mechanical"[All Fields] AND "ventilation"[All Fields]) OR "mechanical ventilation"[All Fields])) AND ("candida"[MeSH Terms] OR "candida"[All Fields] OR "candidae"[All Fields] OR "candidas"[All Fields] OR (("candida"[MeSH Terms] OR "candida"[All Fields] OR "candidae"[All Fields] OR "candidas"[All Fields]) AND ("sci public policy"[Journal] OR "spp"[All Fields])) OR (("candida"[MeSH Terms] OR "candida"[All Fields] OR "candidae"[All Fields] OR "candidas"[All Fields]) AND ("colonisation"[All Fields] OR "colonisations"[All Fields] OR "colonise"[All Fields] OR "colonised"[All Fields] OR "coloniser"[All Fields] OR "colonisers"[All Fields] OR "colonises"[All Fields] OR "colonising"[All Fields] OR "colonization"[All Fields] OR "colonizations"[All Fields] OR "colonize"[All Fields] OR "colonized"[All Fields] OR "colonizer"[All Fields] OR "colonizers"[All Fields] OR "colonizes"[All Fields] OR "colonizing"[All Fields])) OR (("candida"[MeSH Terms] OR "candida"[All Fields] OR "candidae"[All Fields] OR "candidas"[All Fields]) AND ("airway"[All Fields] OR "airway s"[All Fields] OR "airways"[All Fields]) AND ("colonisation"[All Fields] OR "colonisations"[All Fields] OR "colonise"[All Fields] OR "colonised"[All Fields] OR "coloniser"[All Fields] OR "colonisers"[All Fields] OR "colonises"[All Fields] OR "colonising"[All Fields] OR "colonization"[All Fields] OR "colonizations"[All Fields] OR "colonize"[All Fields] OR "colonized"[All Fields] OR "colonizer"[All Fields] OR "colonizers"[All Fields] OR "colonizes"[All Fields] OR "colonizing"[All Fields])))

**Translations:**

ventilator-associated pneumonia: "pneumonia, ventilator-associated"[MeSH Terms] OR ("pneumonia"[All Fields] AND "ventilator-associated"[All Fields]) OR "ventilator-associated pneumonia"[All Fields] OR ("ventilator"[All Fields] AND "associated"[All Fields] AND "pneumonia"[All Fields]) OR "ventilator associated pneumonia"[All Fields]

pneumonia: "pneumonia"[MeSH Terms] OR "pneumonia"[All Fields] OR "pneumonias"[All Fields] OR "pneumoniae"[All Fields] OR "pneumoniae's"[All Fields]

ventilator-associated pneumonia: "pneumonia, ventilator-associated"[MeSH Terms] OR ("pneumonia"[All Fields] AND "ventilator-associated"[All Fields]) OR "ventilator-associated pneumonia"[All Fields] OR ("ventilator"[All Fields] AND "associated"[All Fields] AND "pneumonia"[All Fields]) OR "ventilator associated pneumonia"[All Fields]

ventilator-acquired pneumonia: "pneumonia, ventilator-associated"[MeSH Terms] OR ("pneumonia"[All Fields] AND "ventilator-associated"[All Fields]) OR "ventilator-associated pneumonia"[All Fields] OR ("ventilator"[All Fields] AND "acquired"[All Fields] AND "pneumonia"[All Fields]) OR "ventilator acquired pneumonia"[All Fields]

mechanical ventilation: "respiration, artificial"[MeSH Terms] OR ("respiration"[All Fields] AND "artificial"[All Fields]) OR "artificial respiration"[All Fields] OR ("mechanical"[All Fields] AND "ventilation"[All Fields]) OR "mechanical ventilation"[All Fields]

Candida: "candida"[MeSH Terms] OR "candida"[All Fields] OR "candidae"[All Fields] OR "candidas"[All Fields]

Candida: "candida"[MeSH Terms] OR "candida"[All Fields] OR "candidae"[All Fields] OR "candidas"[All Fields]

spp: "Sci Public Policy"[Journal:__jid0417663] OR "spp"[All Fields]

Candida: "candida"[MeSH Terms] OR "candida"[All Fields] OR "candidae"[All Fields] OR "candidas"[All Fields]

colonization: "colonisation"[All Fields] OR "colonisations"[All Fields] OR "colonise"[All Fields] OR "colonised"[All Fields] OR "coloniser"[All Fields] OR "colonisers"[All Fields] OR "colonises"[All Fields] OR "colonising"[All Fields] OR "colonization"[All Fields] OR "colonizations"[All Fields] OR "colonize"[All Fields] OR "colonized"[All Fields] OR "colonizer"[All Fields] OR "colonizers"[All Fields] OR "colonizes"[All Fields] OR "colonizing"[All Fields]

Candida: "candida"[MeSH Terms] OR "candida"[All Fields] OR "candidae"[All Fields] OR "candidas"[All Fields]

airway: "airway"[All Fields] OR "airway's"[All Fields] OR "airways"[All Fields]

colonization: "colonisation"[All Fields] OR "colonisations"[All Fields] OR "colonise"[All Fields] OR "colonised"[All Fields] OR "coloniser"[All Fields] OR "colonisers"[All Fields] OR "colonises"[All Fields] OR "colonising"[All Fields] OR "colonization"[All Fields] OR "colonizations"[All Fields] OR "colonize"[All Fields] OR "colonized"[All Fields] OR "colonizer"[All Fields] OR "colonizers"[All Fields] OR "colonizes"[All Fields] OR "colonizing"[All Fields]

BMJ Open

# Clinical outcomes of antifungal therapy on Candida pulmonary colonization in immunocompetent patients with invasive ventilation: A systematic review and meta-analysis

| | |
|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2024-083918.R2 |
| Article Type: | Original research |
| Date Submitted by the Author: | 27-Sep-2024 |
| Complete List of Authors: | Li, Linqi; University of South China, The Affiliated Changsha Central Hospital; University of South China, School of Public Health<br>Su, Shan; Zhaoqing First People's Hospital, Department of Respiratory and Critical Care Medicine<br>Yang, Hongzhong ; University of South China, Department of Respiratory and Critical Care Medicine,The Affiliated Changsha Central Hospital<br>Xie, He-Bin; University of South China, The Affiliated Changsha Central Hospital; University of South China, School of Public Health |
| Primary Subject Heading: | Intensive care |
| Secondary Subject Heading: | Evidence based practice |
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# Clinical outcomes of antifungal therapy on Candida pulmonary colonization in immunocompetent patients with invasive ventilation: A systematic review and meta-analysis

**Keywords:** ***Candida*** **colonization, pulmonary, antifungal therapy, mechanical ventilation, meta-analysis.**

## Abstract

**Objective:** This study aimed to use systematic review and meta-analysis to establish the influence of antifungal therapy on pulmonary *Candida* colonization of patients with mechanical ventilation.

**Design:** Systematic review and meta-analysis.

**Data sources:** An extensive search was undertaken on publications from inception to July 25, 2023, through PubMed, Web of Science, Medline, Embase, China National Knowledge Infrastructure, Wanfang Data and VIP Databases.

**Eligibility criteria for selecting studies:** Randomized trials, cohort studies, and case-control studies comparing the efficacy of antifungal treatment in immunocompetent patients with pulmonary *Candida* colonization after invasive ventilation.

**Data extraction and synthesis:** Two reviewers independently extracted the data and assessed the quality of studies. Dichotomous outcomes were expressed as odds ratios (OR) with 95% confidence intervals (CIs). Continuous outcomes were expressed as standardized mean differences (SMD) with 95% CIs.

**Primary and secondary outcome measures:** The primary outcomes included intensive care unit (ICU), hospital, 28-day, and 90-day mortality. The secondary outcomes included ICU length of stay, mechanical ventilation (MV) duration, and ventilator-associated pneumonia (VAP).

**Results:** Nine high-quality studies were included. According to the data collected from these nine studies, there is no significant evidence showing a difference between the therapy group treated with antifungal drugs and the control group without antifungal drugs in clinical outcomes, including intensive care unit mortality (OR: 1.37; 95% CI, 0.84 to 2.22), hospital mortality (OR: 1.17; 95% CI, 0.57 to 2.38), 28-day mortality (OR; 0.71, 95% CI, 0.45 to 1.14), 90-day mortality (OR; 0.76, 95% CI 0.35 to 1.63), intensive care unit length of stay (SMD: -0.15; 95% CI -0.88 to 0.59), mechanical ventilation duration (SMD: 0.11; 95%CI -0.88 to 1.10), and ventilator-associated pneumonia (OR: 1.54; 95% CI 0.56 to 4.20). Subgroup analysis of different treatment types indicates that the combined effect size is stable and unaffected by different treatment types including inhalation (OR: 2.32; 95% CI 0.30 to 18.09) and intravenous (OR: 0.65; 95% CI 0.13 to 3.34).

**Conclusion:** The application of antifungal treatment did not improve clinical outcomes in patients with mechanical ventilation. We do not suggest initiating antifungal treatment in patients with *Candida* pulmonary colonization after invasive ventilation.

**Registration:** This study was registered in the International Prospective Register of Systematic Reviews, with the registration number CRD42020161138.

**Strengths and limitations of this study:**

1. This study included a number of outcome indicators to assess the effectiveness of antifungal treatment, with subgroup analyses performed based on the type of treatment administered.

2. Most studies included are retrospective studies, raising potential concerns regarding their external validity.

3. Some studies described the precise style, name, dose, and administration method of antifungal drugs, while others did not.

4. This study is limited by the number of studies included, especially when it comes to single outcomes such as ICU mortality.

5. Most studies included were cohort studies instead of random contral trials, which provide stronger evidence.

## 1 Introduction

*Candida* frequently exists in the normal oral cavity, upper respiratory tract, lower-intestinal tract and vagina[1]. In tracheal aspirates from patients with mechanical ventilation (MV), 30% have *Candida* isolation, and nearly 50% from patients suspected to have a ventilator-associated pneumonia (VAP)[2, 3]. When respiratory *Candida* colonization is detected, it is difficult to differentiate between relatively harmless colonization and invasive infection, and leads to a therapeutic dilemma[4]. Although few studies reported limited attributable intensive care unit (ICU) mortality of VAP, the death rate related to VAP cannot be denied according to the majority of previous studies[5-8]. The incidence of VAP frequently extends hospital stay, elevates the economic burden, and raises the mortality rate[9]. The presence of *Candida* in respiratory samples is defined as *Candida* colonization instead of infection because the appearance of *Candida* pneumonia is rare[10-13]. For several years, arguments have arisen about whether *Candida* colonization negatively affects or simply indicates disease severity or immunosuppression in critically ill patients[14-16]. We found that the outcomes of antifungal treatment for *Candida* colonization in pulmonary tract among different studies were controversial, as some studies found that antifungal treatment was associated with lower mortality, some found that treatment made no difference in mortality, while others found that it prolonged MV duration, ICU length of stay, and hospital length of stay[10, 11, 17, 18]. Therefore, we performed a systematic review and meta-analysis to establish the influence of antifungal treatment on pulmonary *Candida* colonization.

## 2 Method

### 2.1 Information sources and search strategy

This study followed the Preferred Reporting Items for Systematic Review and Meta-Analysis criteria for systematic reviews and meta-analyzes[19]. An extensive search was undertaken on publications from inception to July 25, 2023, through PubMed, Web of Science, Medline, Embase, China National Knowledge Infrastructure, Wanfang Data and VIP Databases. The searching syntax included the following Medical Subject Headings (MeSH) and text words which are varied

individually according to different databases: ventilator-associated pneumonia, *Candida*. We used the following search strategies in all of the databases above: (ventilator-associated pneumonia OR VAP OR pneumonia, ventilator-associated OR ventilator-associated pneumonia OR ventilator-acquired pneumonia OR mechanical ventilation) AND (*Candida* OR *Candida* spp OR *Candida* colonization OR *Candida* airway colonization). There were no language restrictions on studies searching. The listed references of relevant studies were also evaluated to enlarge the search scope and ensure a complete search. Full search strategy of pubmed database is provided in the supplemental material. Selection process of the article was performed by two researchers (LL and SS) independently. The titles and abstracts of the entries identified in the search were screened. Full text version of all articles that potentially met the eligibility criteria was reviewed to make a decision. Disagreements, if any, were resolved through discussion with a third researcher (HX).

### 2.2 Inclusion criteria

Randomized trials, cohort studies, and case-control studies were included while selecting. In the included studies, the patients were adults (≥18 years old) who were diagnosed with pulmonary *Candida* colonization after invasive ventilation. Pulmonary *Candida* colonization was defined as the presence of *Candida* in bronchoalveolar lavage samples, endotracheal aspiration samples, protected brush specimens, or any positive airway secretion specimens.

### 2.3 Exclusion criteria

We excluded case reports and studies on pregnant, immunocompromised patients, or those who received antifungal treatment for reasons other than *Candida* colonization. Patients with candidemia or invasive candidiasis were also excluded, and the diagnostic criteria were positive results of direct detection, in which blood or tissue specimens were cultured, or indirect detection, in which surrogate markers and polymerase chain reaction assays were used[20].

### 2.4 Data collection

We screened titles and abstracts, reviewed the full text, and extracted data using an Excel sheet (Microsoft Corporation). We primarily collected the characteristics of title, author, journal, year, type, participants, inclusion or exclusion criteria, interventions, and clinical outcomes. Clinical outcomes included 28-day mortality, 90-day mortality, ICU mortality, hospital mortality, ICU length of stay, MV duration, and VAP. Disagreements were resolved by discussion with a third reviewer if necessary.

### 2.5 Quality assessment

We used the Cochrane risk assessment tool to measure the risk of randomized controlled trials and the Newcastle-Ottawa Scale to measure the quality of cohort and case-control studies[21]. Studies that scored at least six points were regarded as high-quality and included.

### 2.6 Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

### 2.7 Statistical analysis

Statistical analysis was performed by Stata software (Version 16.0). Dichotomous outcomes such as VAP, ICU mortality, hospital mortality, 28-day mortality, and 90-day mortality, were expressed as odds ratios (OR) with 95% confidence intervals (CIs). Continuous outcomes (ICU length of stay and MV duration) were expressed as standardized mean differences (SMD) with 95% CIs. We analyzed the data using the Inverse-Variance method with the fixed-effect model if there was no obvious heterogeneity ($P$>0.1), or else random-effect model if the heterogeneity was significant ($P$<0.1). Moreover, heterogeneity was quantified using the $I^2$ test. The interpretation of $I^2$ was guided by the Cochrane Handbook for Systematic Reviews of interventions (Version 5.2.0, updated June 2017). Sensitivity analyses was conducted by excluding one study at a time from the analysis to assess the stability of the results. Subgroup analyses were performed on the effect of antifungal therapy. Publication bias was not assessed since there were fewer than 10 studies in this meta-analysis.

## 3 Results

### 3.1 Study selection

In total, 2947 records were identified. With 1246 duplicates removed and 1670 irrelevant records excluded, we assessed 31 studies for eligibility, of which 9 were included. 22 studies were excluded because of the lack of antifungal treatment, lack of supporting experimental data, lack of detection of pulmonary secretion, and occurrence in a special population (Figure 1). All patients received MV, had at least one positive culture of *Candida* in the pulmonary tract, and received different antifungal treatments.

Figure 1 Flowchart of studies identified, excluded, and included

### 3.2 Study characteristics and quality assessment

Of the nine articles included in the study, seven were retrospective cohort studies, one case-control study, and one randomized clinical trial. Two studies were conducted in North America, five in Europe, and two in Asia, giving the studies a wide geographical coverage. Other characteristics of the included studies are summarized in Supplemental Table 1, including years of accuracy, location, study design, population, number of patients, outcomes, *Candida* colonization and antifungal treatment. The columns of the quality assessment list and their corresponding points are listed in Supplemental Table 2. All included studies were assessed to be of high quality.

### 3.3 Effect of antifungal therapy on pulmonary *Candida* colonization patients' mortality

Three studies, including Ioannou 2021[2], Ong 2013[22], and Nseir 2007[23] reported ICU mortality. We found no significant difference between the therapy and control groups (OR: 1.37, 95% CI, 0.84 to 2.22). Six studies, including Du 2021[4], Ioannou 2021, Zhang 2017[24], Griffin 2016[25], Lindau 2015[26], and Albert 2014[27] reported hospital mortality. The pooled results showed no significant difference between the therapy and control groups (OR: 1.17, 95% CI, 0.57 to 2.38). Four studies, including Du 2021, Zhang 2017, VanDerGeest 2014[28], and Albert 2014, reported 28-day mortality. The results showed no significant difference between the therapy and control groups (OR: 0.71, 95% CI, 0.45 to 1.14). Three studies, Du 2021, VanDerGeest 2014, and Albert 2014, reported 90-day mortality. The results showed no significant difference between the therapy and control groups (OR: 0.76, 95% CI, 0.35 to 1.63). No indicator showed statistical significance with respect to mortality. (Figure 2)

Figure 2 (A) Forest plot for ICU mortality; (B) Forest plot for hospital mortality; (C) Forest plot for 28-day mortality; (D) Forest plot for 90-day mortality

### 3.4 Effect of antifungal therapy on pulmonary *Candida* colonization patients' ICU length of stay

Four studies, including Zhang 2017, Griffin2016, Ong 2013, and Nseir 2007, reported ICU length of stay. The results indicated non-significant differences for ICU length of stay among patients receiving antifungal treatment (SMD: -0.15, 95% CI, -0.88 to 0.59), as shown in Figure 3.

Figure 3 Forest plot for ICU length of stay

### 3.5 Effect of antifungal therapy on pulmonary *Candida* colonization patients' MV duration

Three studies, including Zhang 2017, Griffin 2016, and Nseir 2007, reported the duration of MV. We did not identify a significant difference between the therapy and control groups regarding MV duration (SMD: 0.11, 95%CI, -0.88 to 1.10), as shown in Figure 4.

Figure 4 Forest plot for MV duration

### 3.6 Effect of antifungal therapy on VAP

Six studies, including Du 2021, Zhang 2017, Griffin 2016, Lindau 2015, VanDerGeest 2014, and Ong 2013, reported VAP. No significant difference was found between therapy and control groups (OR: 1.54, 95% CI, 0.56 to 4.20), as shown in Figure 5.

Figure 5 Forest plot for VAP

### 3.7 Subgroup analysis

We conducted a subgroup analysis based on the effect of antifungal therapy on VAP of the included studies. The result of the subgroup analysis indicate that the combined effect size is stable and unaffected by different treatment types. As shown in Supplemental Figure 1.

Supplemental Figure 1 Forest plot for subgroup analysis of different treatment types

### 3.8 Sensitivity analysis and publication bias

A sensitivity analysis was performed by sequentially excluding one study at a time. This exclusion did not significantly impact the results, with the pooled OR ranging from 1.00 (0.51-1.96) to 2.07 (0.74-5.78) (Supplemental Figure 2). Because only 9 related studies were included in this report, approaches for detecting publication bias would have exhibited limited efficacy. Consequently, the evaluation of publication bias was not conducted.

Supplemental Figure 2 Sensitivity analysis for VAP

## 4 Discussion

In this study, we observed that antifungal therapy administered to mechanically ventilated patients with *Candida* colonization did not show a significant impact on patient outcomes, which were measured by indicators including mortality, hospital length of stay, ICU length of stay, mechanical ventilation duration, and incidence of VAP, and the result is stable when taking different treatment

types into consideration. A study by Du declared that antifungal treatment was associated with a reduced risk of VAP, while an autopsy study involving 232 samples showed that although *Candida* is a common pathogen, the incidence of *Candida* pneumonia in ICU patients is extremely low[4, 11]. Inconsistent with the results of the previous studies, a meta-analysis found that *Candida* pulmonary colonization probably had poorer clinical outcomes owing to longer mechanical ventilation duration, higher 28-day mortality, higher ICU mortality, and longer ICU length of stay[29]. Furthermore, a study by Ioannou found that about half of the patients with *Candida* spp. isolation from their respiratory secretions were treated with antifungals. Considering the factor that patients under more critical condition could be treated with antifungals more often, a multivariate regression analysis was conducted identifying antifungal use as an independent factor associated with total hospital mortality[2]. Without listing the specific articles for verification, the guideline strongly recommends that *Candida* colonization rarely requires treatment with antifungal therapy[30]. Our study, may help to provide more information on this problem: whether *Candida* pulmonary colonization simply symbolizes the severity of diseases or actually has influence on outcomes[31, 32].

*Candida* colonization in the respiratory tract is related to higher inflammation and may accelerate the disease process[33, 34]. A few studies used inhalation of antifungal drugs as therapy, which did not show significant influence on patients' outcomes. This may lead to direct inhibition or damage of the alveolar-capillary membrane, resulting in an influx of surfactant-inactivating plasma proteins[22, 28]. After *Candida* colonization, current increases in antifungal drug resistance in *Candida* spp. and clinical treatment failures are of concern[35]. Previous history of antifungal prescription influences *Candida* species distribution and susceptibility profile to antifungal agents[36]. Inadequate dose and treatment failure may contribute to high mortality[37].

Considering the various conditions, we thought that various factors cause poor clinical outcomes: antifungal treatment may have more harm than benefit in clinically ill patients. Different antifungal drugs can have varying sensitivities or resistances as well as potential toxicity or adverse effects. Inadequate dosing of antifungal drugs may also be a contributing factor. Although the analysis of this study showed that antifungal treatment did not improve patients' clinical outcomes, the sample size of included studies were limited and the 95% confidence intervals were wide. Further studies should be conducted to verify their influence. Considering retrospective and current studies can only provide hypotheses to support the existence of a correlation, a prospective randomized controlled trial might be a more appropriate solution to explore the effect of antifungal treatment on patients with respiratory *Candida* colonization in combination with mechanical ventilation.

Based on the findings of this meta-analysis, the use of antifungal medication on mechanical-ventilated patients with respiratory *Candida* colonization does not appear to improve patients' clinical outcomes. No significant differences were observed in ICU mortality, hospital mortality, 28-day mortality, 90-day mortality, ICU length of stay, MV duration, and VAP associated with different treatment regimens. Further analysis of subgroups based on different treatment types confirmed these conclusions. Therefore, the use of antifungal medication is not recommended for the decolonization of mechanical-ventilated patients with respiratory *Candida* colonization.

The strength of this study is that it included a number of outcome indicators to assess the effectiveness of antifungal treatment, with subgroup analyses performed based on the type of treatment administered. However it encountered several limitations. Most studies included are retrospective studies, raising potential concerns regarding their external validity. Additionally, some studies described the precise style, name, dose, and administration method of antifungal drugs, while others did not. Furthermore, this study is limited by the number of studies included, especially when

it comes to single outcomes such as ICU mortality. Moreover, most studies included were cohort studies instead of random contral trials, which provide stronger evidence.

## 5 Author Contributions

HX and HY provided article ideas and completed a literature search. LL and SS contributed to the data analysis and manuscript writing. HX is the guarantor.

## 6 Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## 7 Patient consent for publication

Not applicable.

## 8 Ethics approval

Not applicable.

## 9 Data Availability Statement

The raw data of this study can be obtained from corresponding author under reasonable request.

## 10 Funding

This study was funded by Changsha Municipal Health Committee (No.KJ-B2023032).

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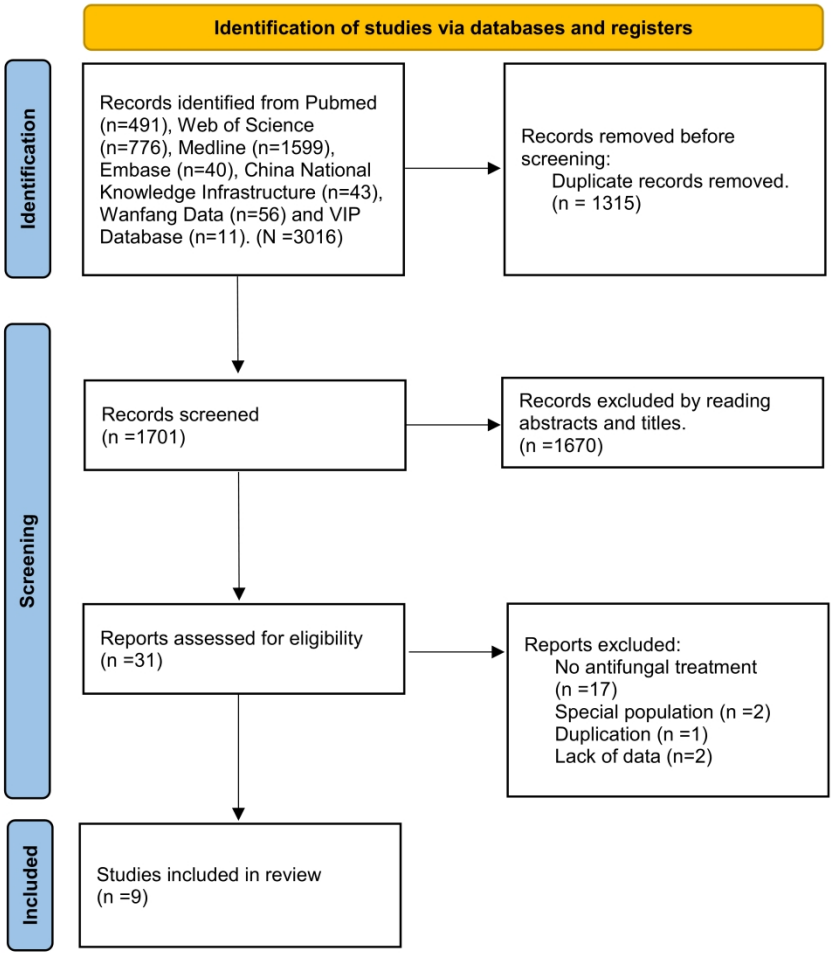


Figure 1 Flowchart of studies identified, excluded, and included

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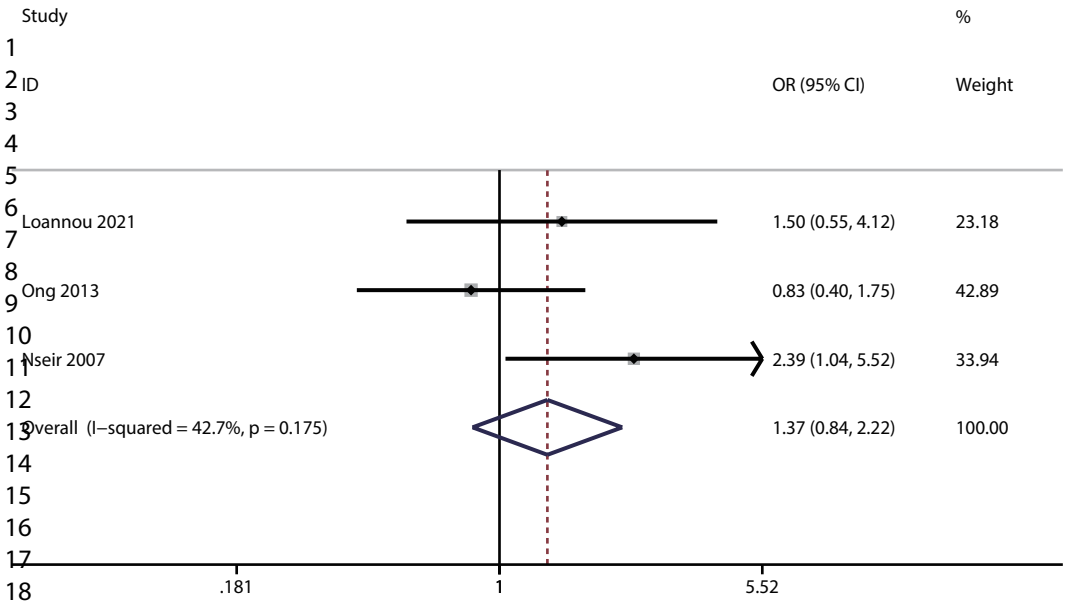


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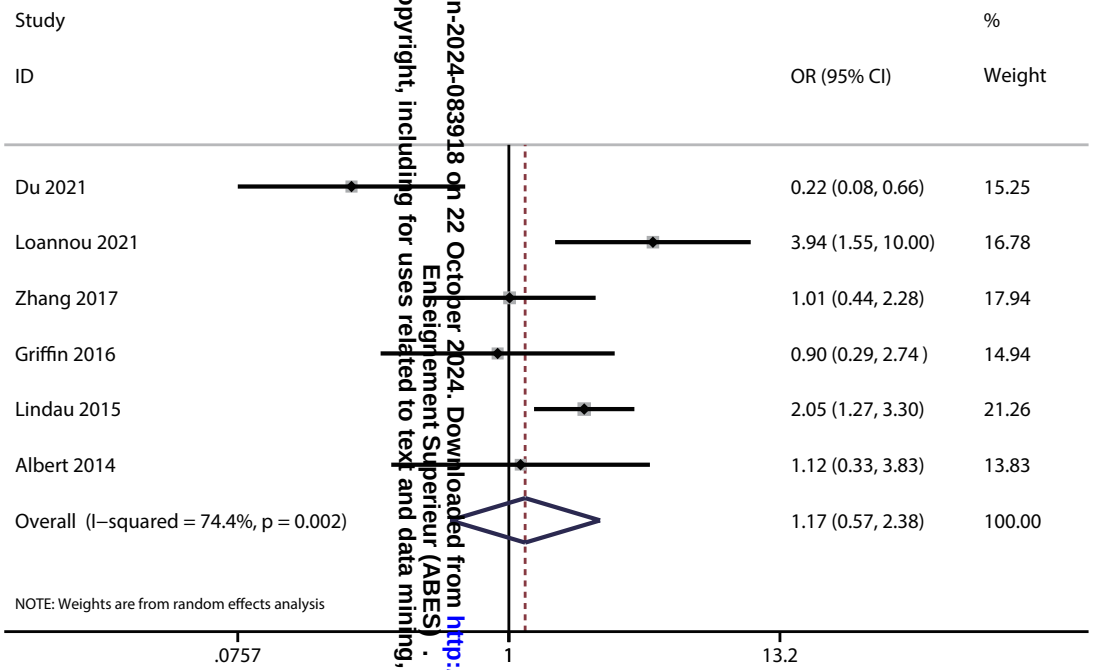


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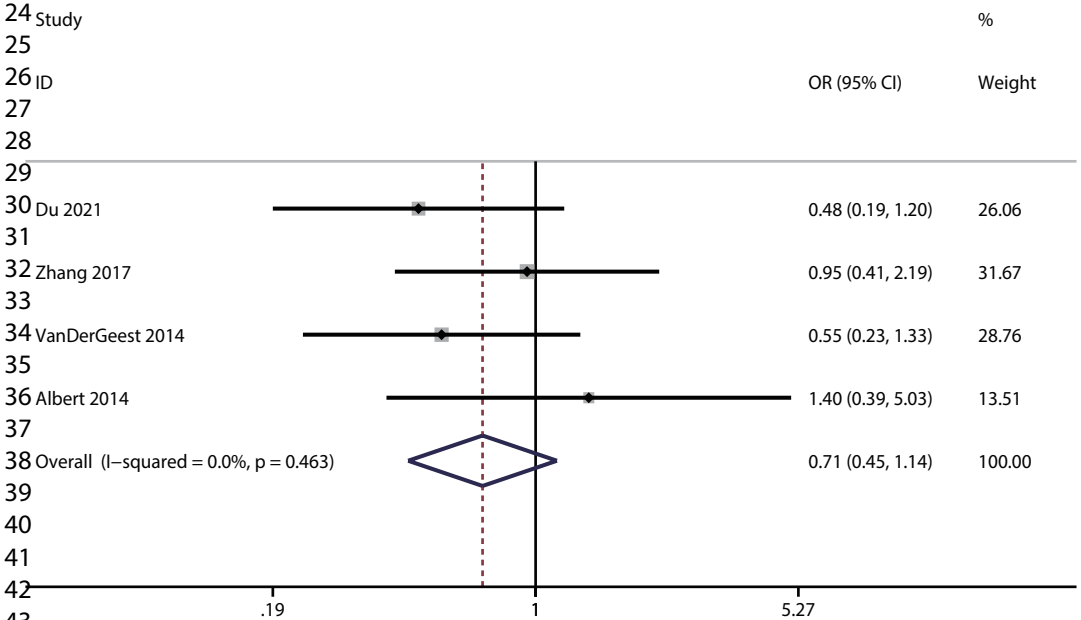


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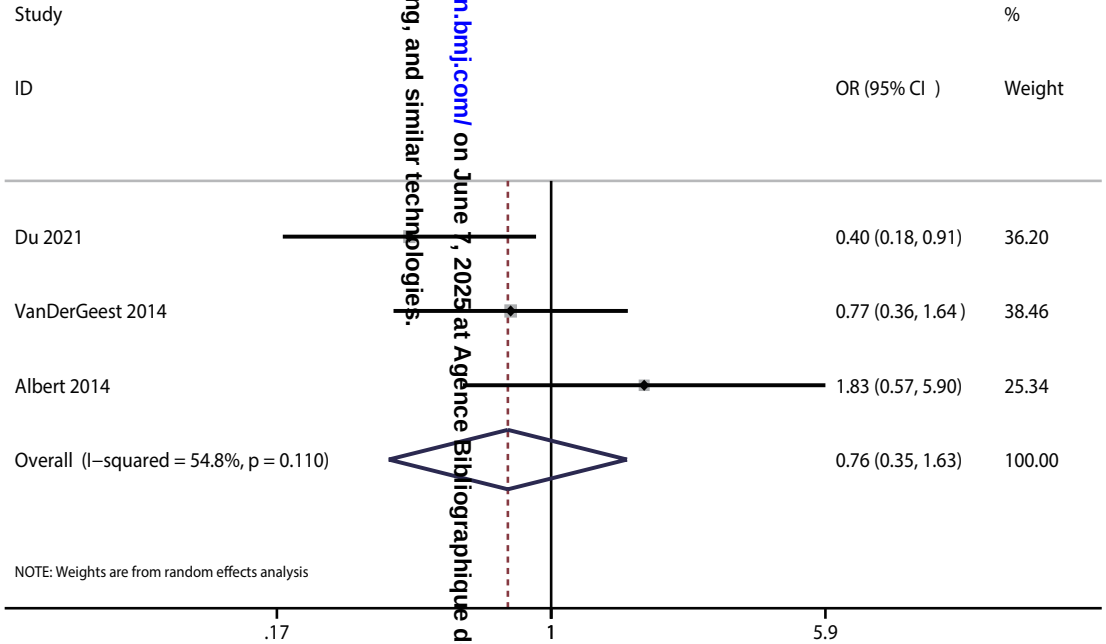
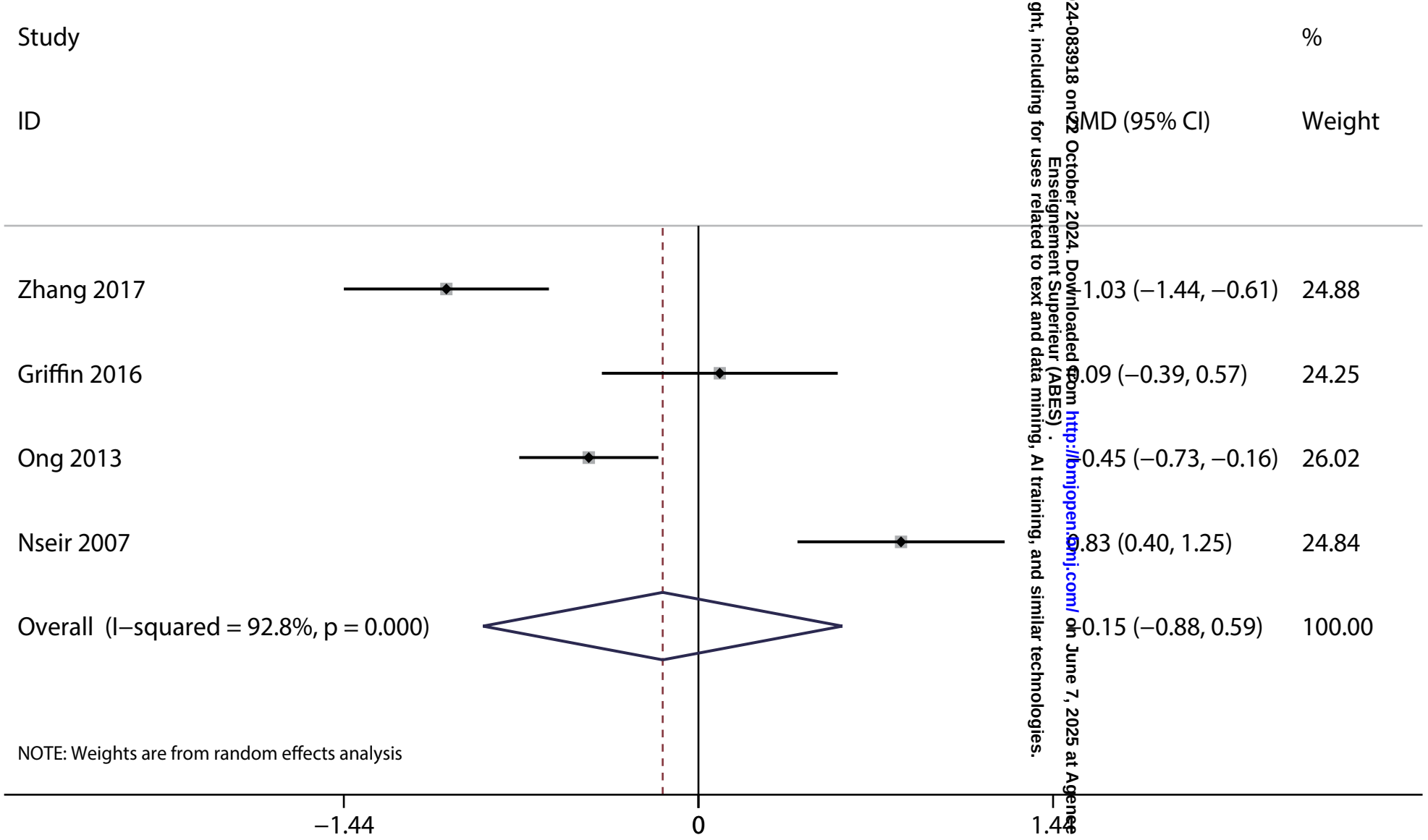
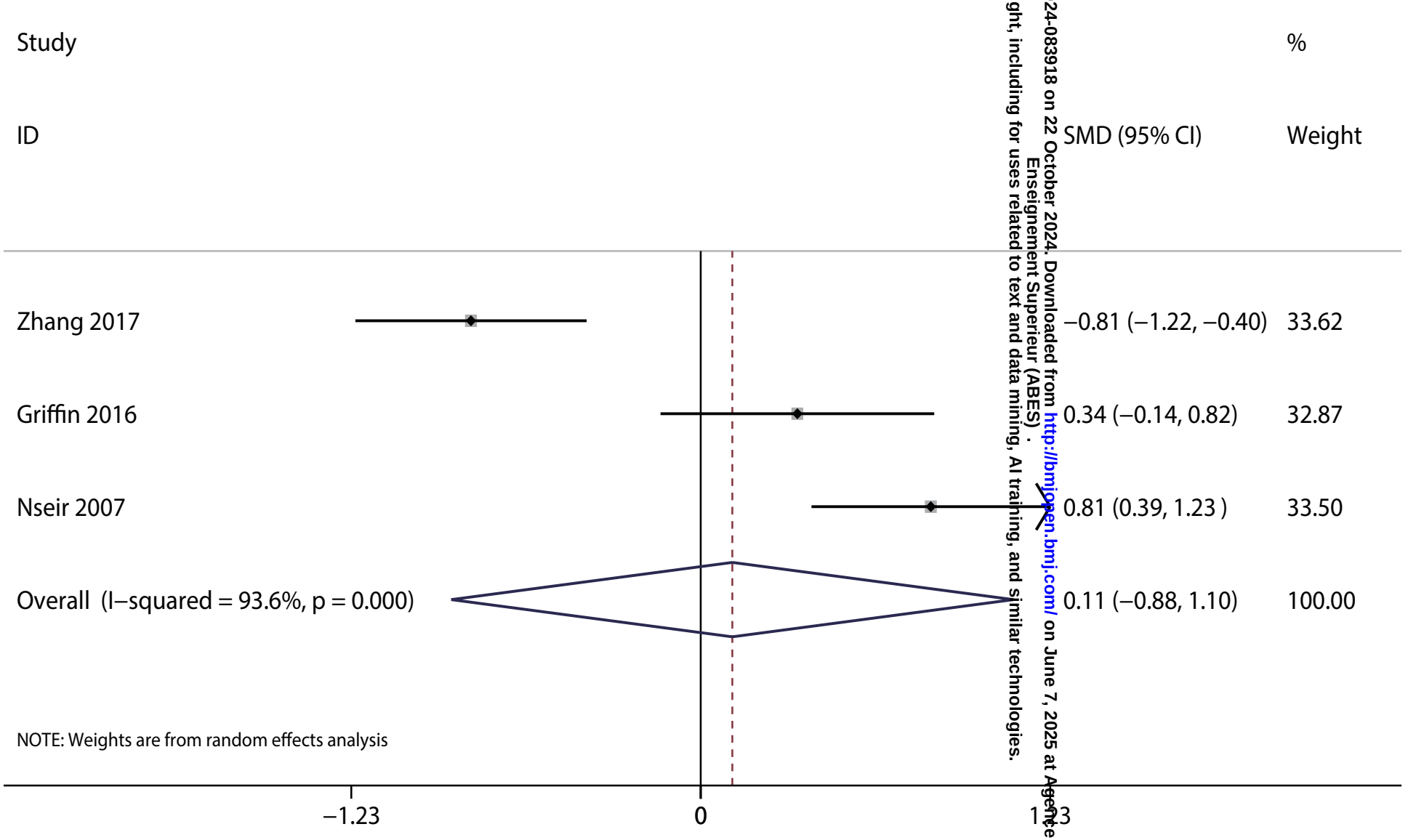
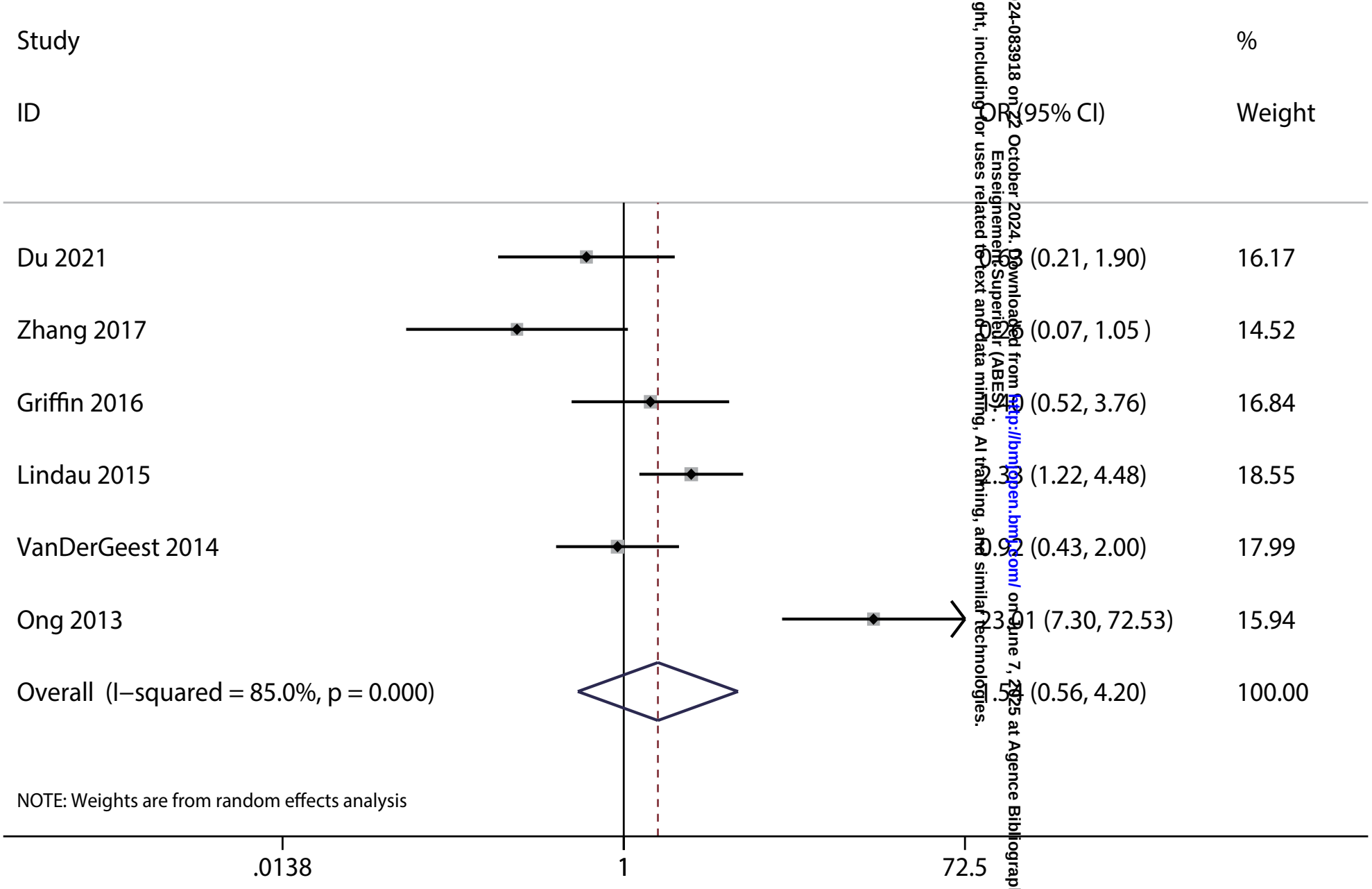








Supplemental Table 1. Characteristics of included studies

| | Years of accrual | Country | Study style | Population | Patients' gender | Outcome | Type of *Candida* isolated | *Candida* colonization | Antifungal treatment |
|---|---|---|---|---|---|---|---|---|---|
| Griffin 2016 (24) | 2011-2014 | USA | retrospective cohort | Adults | Male: 48<br>Female: 27 | hospital mortality; ICU length of stay; MV duration; VAP (after treatment) | *Candida albicans; Candida tropicalis* | at least one bronchoalveolar lavage (+) | Intravenous fluconazole/ Echinocandin |
| Lindau 2015 (25) | 2010-2012 | Germany | retrospective cohort | Adults | Male: 245<br>Female: 77 | hospital mortality; VAP (after treatment) | not described | at least one tracheal aspirates or bronchoalveolar lavage (+) | not described |
| VanDerGeest 2014 (27) | 2010-2011 | Netherland | retrospective cohort | Adults | Male: 71<br>Female: 42 | 28-day mortality; 90-day mortality; VAP (after treatment) | *Candida albicans; Candida non-albicans* | cultures of throat, tracheal aspirates or bronchoalveolar lavage (+) >2 | Amphotericin-B deoxycholate inhalation |
| Albert 2014 (26) | 2010-2012 | Canada | Random control trails | Adults | Male: 63<br>Female: 25 | hospital mortality; 28-day mortality; 90-day mortality | not described | bronchoalveolar lavage or endotracheal aspirate (+) | Intravenous anidulafungin/ Fluconazole |
| Nseir 2007 (22) | 2004-2005 | France | nested case-control | Adults | Male: 42<br>Female: 60 | ICU mortality; ICU length of stay; MV duration; | *P. aeruginosa; Candida* spp. | tracheobronchial(+) | Fluconazole |

Supplementary Material

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Zhang 2017 (23) | 2012-2016 | China | retrospective cohort | Adults APACHE II >8 | Male: 64<br>Female: 37 | hospital mortality; 28-day mortality; ICU length of stay; MV duration; VAP (after treatment) | *Candida albicans; Candida tropicalis* | cultured (+) in respiratory tract | Intravenous fluconazole/ Caspofungin |
| Ong 2013 (21) | 2008-2012 | Netherland | retrospective cohort | Adults | Male: 232<br>Female: 101 | ICU mortality; ICU length of stay; VAP (after treatment) | not described | bronchoalveolar lavage/sputum samples (+) >2 | Nebulised amphotericin-B inhalation |
| Ioannou 2021 (2) | 2014-2016 | Greece | retrospective cohort | Adults | Male: 67<br>Female: 23 | ICU mortality; hospital mortality; | *Candida albicans; Candida tropicalis* | tracheal aspirate, sputum or bronchoalveolar lavage (+) | Fluconazole/ Micafungin / Anidulafungin |
| Du 2021 (4) | 2012-2020 | China | retrospective cohort | Adults | Male: 55<br>Female: 55 | hospital mortality; 28-day mortality; 90-day mortality; VAP (after treatment) | *Candida albicans; Candida non-albicans* | bronchoalveolar lavage or sputum samples (+) ⩾2 | Nebulised amphotericin-B inhalation |

Supplemental Table 2. Quality assessment of included studies

Cohort study (Newcastle-Ottawa scale)

| Study | Selection | | | | Outcome | | | Comparability of cohorts | Total score |
|---|---|---|---|---|---|---|---|---|---|
| | Representativeness of exposed cohort | Selection of the non-exposed cohort | Ascertainment of exposure | outcome of interest | Assessment of outcome | Follow-up duration | Adequacy of follow cohorts | | |
| VanDerGeest 2014 (27) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 9 |
| Griffin 2016 (24) | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 2 | 7 |
| Lindau 2015 (25) | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 2 | 7 |
| Zhang 2017 (23) | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 2 | 7 |
| Ong 2013 (21) | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 2 | 7 |
| Ioannou 2021 (2) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 9 |

Supplementary Material

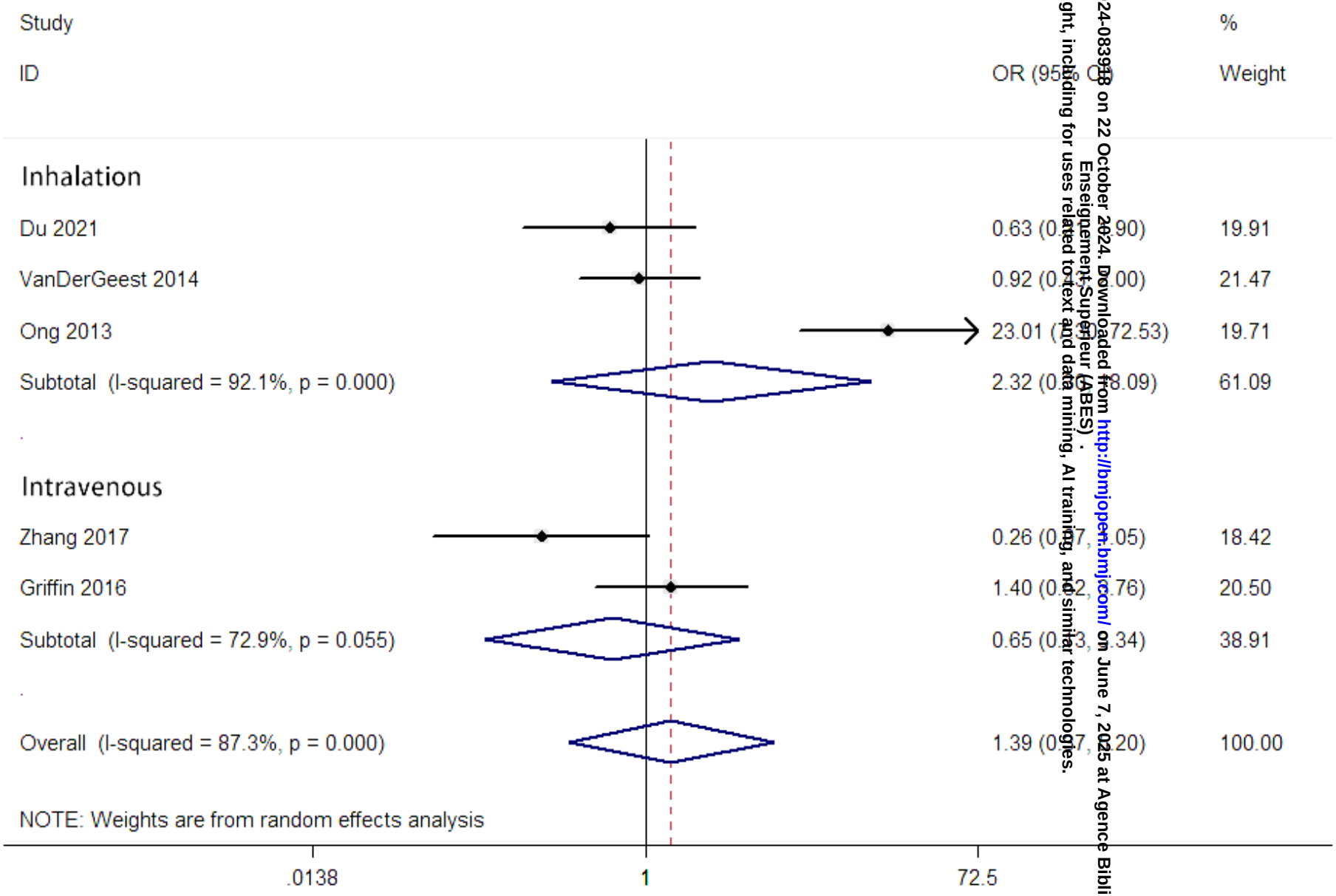
| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Du 2021 (4) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 9 |

Case-control study (Newcastle-Ottawa scale)

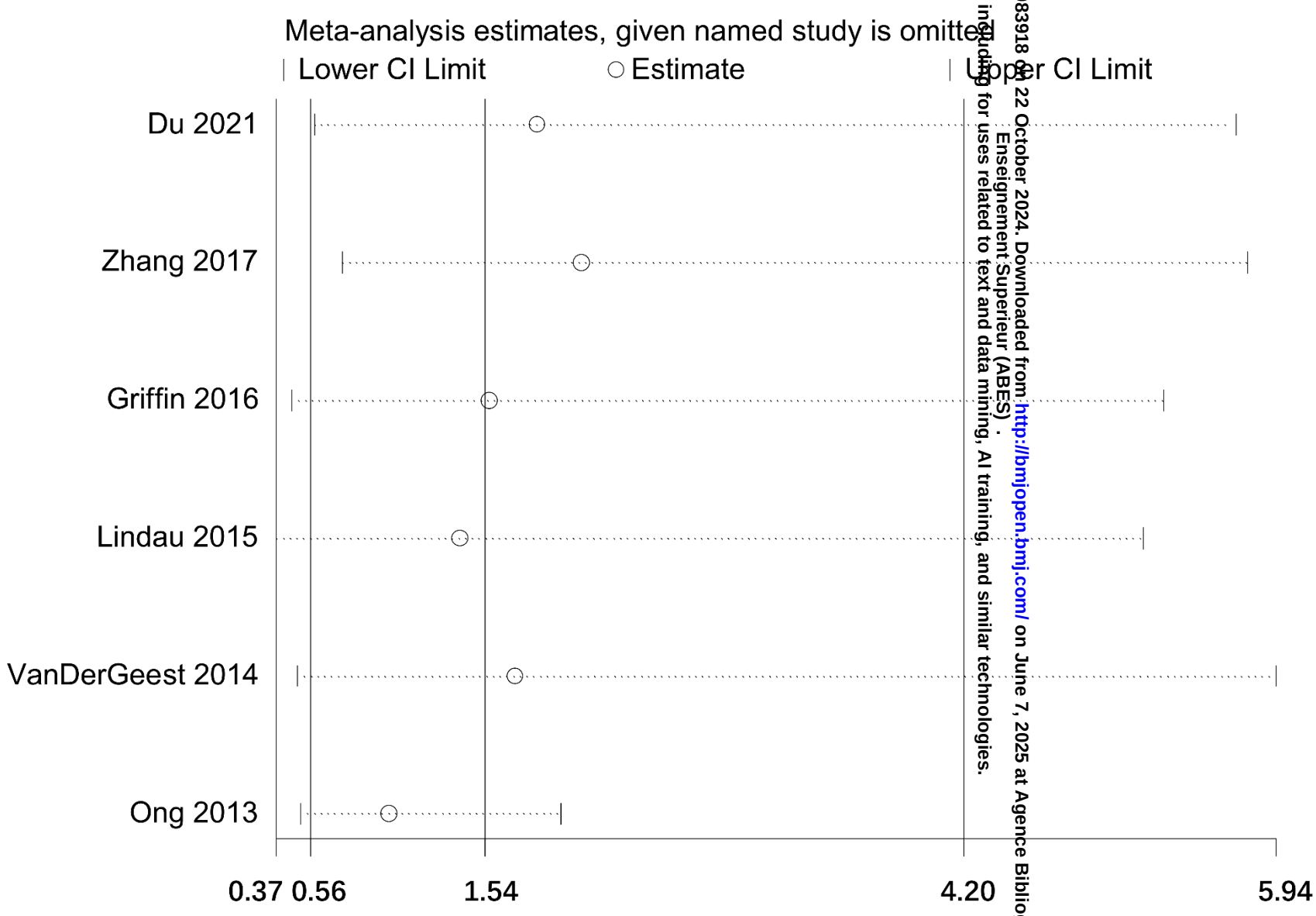
| Study | Selection | | | | Exposure | | Comparability of Cases and Controls | Total score |
|---|---|---|---|---|---|---|---|---|
| | Case Definition | Representativeness | Selection of Controls | Definition of Controls | Ascertainment of Exposure | Non-Response Rate | | |
| Nseir 2007 (22) | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 8 |

Randomized controlled trial (The Cochrane risk assessment tool)

| Study | Random sequence generation | Blinding | Allocation concealment | Incomplete outcome data | Selective outcome reporting | Other bias | Total score |
|---|---|---|---|---|---|---|---|
| Albert (26) | 1 | 1 | 1 | 1 | 1 | 1 | 6 |




Supplemental Figure 1 Forest plot for subgroup analysis of different treatment types




Supplemental Figure 2 Sensitivity analysis for VAP

# PRISMA 2020 Checklist

| Section and Topic | Item # | Checklist item | Location where item is reported |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review. | L1 |
| **ABSTRACT** | | | |
| Abstract | 2 | See the PRISMA 2020 for Abstracts checklist. | L75 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of existing knowledge. | L55 |
| Objectives | 4 | Provide an explicit statement of the objective(s) or question(s) the review addresses. | L71 |
| **METHODS** | | | |
| Eligibility criteria | 5 | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. | L90 |
| Information sources | 6 | Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted. | L76 |
| Search strategy | 7 | Present the full search strategies for all databases, registers and websites, including any filters and limits used. | L81 |
| Selection process | 8 | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process. | L85 |
| Data collection process | 9 | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. | L85 |
| Data items | 10a | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect. | L109 |
| | 10b | List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information. | L108 |
| Study risk of bias assessment | 11 | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process. | L113 |
| Effect measures | 12 | Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results. | L121 |
| Synthesis methods | 13a | Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)). | L114 |
| | 13b | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. | L106 |
| | 13c | Describe any methods used to tabulate or visually display results of individual studies and syntheses. | L120 |
| | 13d | Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used. | L120 |
| | 13e | Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression). | L181 |
| | 13f | Describe any sensitivity analyses conducted to assess robustness of the synthesized results. | L131 |
| Reporting bias assessment | 14 | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). | L133 |
| Certainty | 15 | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. | L131 |

# PRISMA 2020 Checklist

| Section and Topic | Item # | Checklist item | Location where item is reported |
|---|---|---|---|
| assessment | | | |
| **RESULTS** | | | |
| Study selection | 16a | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram. | Figure1 |
| | 16b | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded. | Figure1 |
| Study characteristics | 17 | Cite each included study and present its characteristics. | Supplemental Table 1 |
| Risk of bias in studies | 18 | Present assessments of risk of bias for each included study. | Supplemental Table 2 |
| Results of individual studies | 19 | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots. | Figure2-5 |
| Results of syntheses | 20a | For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies. | Supplemental Table 2 |
| | 20b | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. | L134 |
| | 20c | Present results of all investigations of possible causes of heterogeneity among study results. | NA |
| | 20d | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results. | L186 |
| Reporting biases | 21 | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed. | NA |
| Certainty of evidence | 22 | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed. | NA |
| **DISCUSSION** | | | |
| Discussion | 23a | Provide a general interpretation of the results in the context of other evidence. | L194 |
| | 23b | Discuss any limitations of the evidence included in the review. | L36 |
| | 23c | Discuss any limitations of the review processes used. | L36 |
| | 23d | Discuss implications of the results for practice, policy, and future research. | L224 |
| **OTHER INFORMATION** | | | |
| Registration and protocol | 24a | Provide registration information for the review, including register name and registration number, or state that the review was not registered. | L34 |
| | 24b | Indicate where the review protocol can be accessed, or state that a protocol was not prepared. | NA |
| | 24c | Describe and explain any amendments to information provided at registration or in the protocol. | NA |
| Support | 25 | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review. | L252 |
| Competing interests | 26 | Declare any competing interests of review authors. | L240 |
| Availability of data, code and other materials | 27 | Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review. | L250 |

# PRISMA 2020 Checklist

*From:* Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

**Search:**

(ventilator-associated pneumonia OR VAP OR pneumonia, ventilator-associated OR ventilator-associated pneumonia OR ventilator-acquired pneumonia OR mechanical ventilation) AND (Candida OR Candida spp OR Candida colonization OR Candida airway colonization)

**Details:**

("pneumonia, ventilator associated"[MeSH Terms] OR ("pneumonia"[All Fields] AND "ventilator-associated"[All Fields]) OR "ventilator-associated pneumonia"[All Fields] OR ("ventilator"[All Fields] AND "associated"[All Fields] AND "pneumonia"[All Fields]) OR "ventilator associated pneumonia"[All Fields] OR "VAP"[All Fields] OR (("pneumonia"[MeSH Terms] OR "pneumonia"[All Fields] OR "pneumonias"[All Fields] OR "pneumoniae"[All Fields] OR "pneumoniae s"[All Fields]) AND "ventilator-associated"[All Fields]) OR ("pneumonia, ventilator associated"[MeSH Terms] OR ("pneumonia"[All Fields] AND "ventilator-associated"[All Fields]) OR "ventilator-associated pneumonia"[All Fields] OR ("ventilator"[All Fields] AND "associated"[All Fields] AND "pneumonia"[All Fields]) OR "ventilator associated pneumonia"[All Fields]) OR ("pneumonia, ventilator associated"[MeSH Terms] OR ("pneumonia"[All Fields] AND "ventilator-associated"[All Fields]) OR "ventilator-associated pneumonia"[All Fields] OR ("ventilator"[All Fields] AND "acquired"[All Fields] AND "pneumonia"[All Fields]) OR "ventilator acquired pneumonia"[All Fields]) OR ("respiration, artificial"[MeSH Terms] OR ("respiration"[All Fields] AND "artificial"[All Fields]) OR "artificial respiration"[All Fields] OR ("mechanical"[All Fields] AND "ventilation"[All Fields]) OR "mechanical ventilation"[All Fields])) AND ("candida"[MeSH Terms] OR "candida"[All Fields] OR "candidae"[All Fields] OR "candidas"[All Fields] OR (("candida"[MeSH Terms] OR "candida"[All Fields] OR "candidae"[All Fields] OR "candidas"[All Fields]) AND ("sci public policy"[Journal] OR "spp"[All Fields])) OR (("candida"[MeSH Terms] OR "candida"[All Fields] OR "candidae"[All Fields] OR "candidas"[All Fields]) AND ("colonisation"[All Fields] OR "colonisations"[All Fields] OR "colonise"[All Fields] OR "colonised"[All Fields] OR "coloniser"[All Fields] OR "colonisers"[All Fields] OR "colonises"[All Fields] OR "colonising"[All Fields] OR "colonization"[All Fields] OR "colonizations"[All Fields] OR "colonize"[All Fields] OR "colonized"[All Fields] OR "colonizer"[All Fields] OR "colonizers"[All Fields] OR "colonizes"[All Fields] OR "colonizing"[All Fields])) OR (("candida"[MeSH Terms] OR "candida"[All Fields] OR "candidae"[All Fields] OR "candidas"[All Fields]) AND ("airway"[All Fields] OR "airway s"[All Fields] OR "airways"[All Fields]) AND ("colonisation"[All Fields] OR "colonisations"[All Fields] OR "colonise"[All Fields] OR "colonised"[All Fields] OR "coloniser"[All Fields] OR "colonisers"[All Fields] OR "colonises"[All Fields] OR "colonising"[All Fields] OR "colonization"[All Fields] OR "colonizations"[All Fields] OR "colonize"[All Fields] OR "colonized"[All Fields] OR "colonizer"[All Fields] OR "colonizers"[All Fields] OR "colonizes"[All Fields] OR "colonizing"[All Fields])))

**Translations:**

ventilator-associated pneumonia: "pneumonia, ventilator-associated"[MeSH Terms] OR ("pneumonia"[All Fields] AND "ventilator-associated"[All Fields]) OR "ventilator-associated pneumonia"[All Fields] OR ("ventilator"[All Fields] AND "associated"[All Fields] AND "pneumonia"[All Fields]) OR "ventilator associated pneumonia"[All Fields]

pneumonia: "pneumonia"[MeSH Terms] OR "pneumonia"[All Fields] OR "pneumonias"[All Fields] OR "pneumoniae"[All Fields] OR "pneumoniae's"[All Fields]

ventilator-associated pneumonia: "pneumonia, ventilator-associated"[MeSH Terms] OR ("pneumonia"[All Fields] AND "ventilator-associated"[All Fields]) OR "ventilator-associated pneumonia"[All Fields] OR ("ventilator"[All Fields] AND "associated"[All Fields] AND "pneumonia"[All Fields]) OR "ventilator associated pneumonia"[All Fields]

ventilator-acquired pneumonia: "pneumonia, ventilator-associated"[MeSH Terms] OR ("pneumonia"[All Fields] AND "ventilator-associated"[All Fields]) OR "ventilator-associated pneumonia"[All Fields] OR ("ventilator"[All Fields] AND "acquired"[All Fields] AND "pneumonia"[All Fields]) OR "ventilator acquired pneumonia"[All Fields]

mechanical ventilation: "respiration, artificial"[MeSH Terms] OR ("respiration"[All Fields] AND "artificial"[All Fields]) OR "artificial respiration"[All Fields] OR ("mechanical"[All Fields] AND "ventilation"[All Fields]) OR "mechanical ventilation"[All Fields]

Candida: "candida"[MeSH Terms] OR "candida"[All Fields] OR "candidae"[All Fields] OR "candidas"[All Fields]

Candida: "candida"[MeSH Terms] OR "candida"[All Fields] OR "candidae"[All Fields] OR "candidas"[All Fields]

spp: "Sci Public Policy"[Journal:__jid0417663] OR "spp"[All Fields]

Candida: "candida"[MeSH Terms] OR "candida"[All Fields] OR "candidae"[All Fields] OR "candidas"[All Fields]

colonization: "colonisation"[All Fields] OR "colonisations"[All Fields] OR "colonise"[All Fields] OR "colonised"[All Fields] OR "coloniser"[All Fields] OR "colonisers"[All Fields] OR "colonises"[All Fields] OR "colonising"[All Fields] OR "colonization"[All Fields] OR "colonizations"[All Fields] OR "colonize"[All Fields] OR "colonized"[All Fields] OR "colonizer"[All Fields] OR "colonizers"[All Fields] OR "colonizes"[All Fields] OR "colonizing"[All Fields]

Candida: "candida"[MeSH Terms] OR "candida"[All Fields] OR "candidae"[All Fields] OR "candidas"[All Fields]

airway: "airway"[All Fields] OR "airway's"[All Fields] OR "airways"[All Fields]

colonization: "colonisation"[All Fields] OR "colonisations"[All Fields] OR "colonise"[All Fields] OR "colonised"[All Fields] OR "coloniser"[All Fields] OR "colonisers"[All Fields] OR "colonises"[All Fields] OR "colonising"[All Fields] OR "colonization"[All Fields] OR "colonizations"[All Fields] OR "colonize"[All Fields] OR "colonized"[All Fields] OR "colonizer"[All Fields] OR "colonizers"[All Fields] OR "colonizes"[All Fields] OR "colonizing"[All Fields]