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Prevalence of invasive fungal infection in critically Ill patients: a systematic review and meta-analysis

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Abstract

Background Invasive fungal infections (IFI) contribute significantly to morbidity and mortality among critically ill patients, particularly in intensive care units (ICUs). Accurate prevalence estimates are essential to inform clinical strategies. This study aimed to determine the prevalence of IFI, and assess regional and methodological variations.

Methods A systematic review and meta-analysis were conducted following PRISMA guidelines. Literature from PubMed, Scopus, Web of Science, and Cochrane Library were searched for observational studies published between 1999 and 2024. Inclusion criteria targeted studies reporting IFI prevalence in ICU populations. Data extraction and bias assessment were performed independently by two reviewers. A random-effects meta-analysis assessed pooled prevalence and heterogeneity (Cochran's Q and I2 statistics).

Results Out of 2838 screened articles, 34 studies comprising 655,169 critically ill patients met inclusion criteria. The pooled prevalence of IFI was 5% (95% CI: 3–7%). Aspergillus spp. accounted for 10% and Candida spp. for 3%. Regional prevalence ranged from 3% in high-income countries to 21% in lower-middle-income countries. Diagnostic and methodological heterogeneity were notable contributors to variability.

Conclusions IFIs represent a significant burden in ICUs, particularly in resource-limited settings. Standardized diagnostic criteria and region-specific strategies are crucial to improving patient outcomes.

Trial registration PROSPERO ID CRD42023472191.

Keywords Critically Ill Patients, Invasive fungal infection, Prevalence

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Background

Invasive fungal infections (IFIs) pose a significant challenge in clinical practice due to their high morbidity and mortality, as well as the complexity of their diagnosis. Traditionally, IFIs were primarily associated with immunocompromised patients, including those with neutropenia, hematologic malignancies, or undergoing oncologic treatment [1]. However, in recent decades, the prevalence of IFIs has increased in non-neutropenic critically ill patients, especially in intensive care units (ICUs). Globally, IFIs affect approximately 800 million people annually, with a mortality rate exceeding 1.66 million cases—comparable to tuberculosis and significantly higher than malaria [2]. Candida species and to a lesser extent, Aspergillus, are the main responsible pathogens in these settings, underscoring the clinical relevance of IFIs in ICU populations [3].

Despite their impact, accurately determining the prevalence of IFIs in critically ill patients remains a major challenge. Diagnostic limitations—often stemming from criteria originally developed for immunosuppressed populations—hamper effective identification of these infections in non-neutropenic ICU patients [4, 5]. This issue is particularly evident in cases of invasive aspergillosis, whose incidence has risen due to factors such as population aging, increased prevalence of chronic comorbidities (e.g., type 2 diabetes mellitus and chronic obstructive pulmonary disease), and the widespread use of corticosteroids [6]. Although broader diagnostic criteria have been proposed to address this shift [7], the lack of consensus makes it difficult to accurately quantify these infections in critical settings.

While there are systematic reviews addressing the prevalence of specific infections such as invasive candidiasis [8] or aspergillosis [9], comprehensive data on the overall burden of IFIs in critically ill patients remains scarce. This knowledge gap limits our understanding of the full scope of the problem and hampers the development of targeted diagnostic and therapeutic strategies for this vulnerable population.

Methods

This manuscript has been prepared in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [10].

Study protocol

Registered in PROSPERO (International prospective register of systematic reviews, NIHR), ID: CRD42023472191.

Study design

Systematic review (SR).

Eligibility criteria

All types of primary studies of cumulative ICU prevalence related to IFI in critically ill patients over 18 years of age were included, without language or date restrictions to the selection of manuscripts. Editorials, letters to the editor, narrative reviews, consensus documents, and discussions were excluded. Additionally, articles involving COVID-19 [11, 12] and pediatric patients were excluded since risk factors for these two populations are significantly different and more volatile [13–17], since they present higher susceptibility to fungal infections, which may skew the results for this systematic review.

Sources of information

The databases searched included PubMed, Scopus, Web of Science, and Cochrane Library, from inception to February 2024 (The search was conducted on February 13, 2024). Search terms included combinations of "invasive fungal infections", "intensive care unit", "prevalence", and "invasive mycosis" using Boolean operators.

Search strategies

This was carried out using the PECO components (population study [P: adult critical patients with IFI], exposure [E: none], comparator [C: none], and result [O: prevalence during UCI stay]). Sensitive searches were conducted by adapting the search strategy for each information source, considering the use of MeSH, DeCS, and Emtree terms, as well as free terms incorporated using Boolean operators (See Supplementary). A manual and cross-reference search was also carried out.

Selection process

Identified documents from each information source were managed using Rayyan® software with duplicates removed both automatically and manually. Subsequently they were screened by title and abstract by two groups of two reviewers each (MT-JM and MFG-HA), who worked independently and blinded. Disagreements between the review groups were resolved by consensus. Recruitment of articles was closed on February 13, 2024.

Data collection and analysis

For data extraction, an Excel spreadsheet was created (PC Excel, version 15·24; 2016 Microsoft Corporation). Two authors extracted data from the included studies (MT and JM) and three additional authors checked the extracted data (MFG, HA, and YYL). Disagreements between reviewers were resolved by consensus.

Variables

The variables analyzed included year of publication, geographic location (country and continent), number of cases, population size, study design, World Bank income

classification, implicated fungal species. The tables present a narrative summary of the general characteristics of all included studies. These characteristics include authors, title, journal, year of publication, region-country, design, setting, number of participants, inclusion criteria, exclusion criteria, number of centers, primary outcome, mean age, sex, definition of IFI, financing, risk of bias, severity scale, use of corticoids, use of antifungal, and prevalence.

Given the relevance of the topic and the need to obtain an added value for the prevalence of IFI, a quantitative synthesis is presented through a meta-analysis using a random effects model and a restricted maximum likelihood method was performed. Given the need to have confidence intervals for each prevalence value, in case of not having this information, the value was calculated using the Wilson formula [18].

Individual biases and quality

Methodological quality using the MInCir-Pr2 Score [19] and risk of bias classification according to the Joanna Briggs Institute (JBI) criteria. The internal validity of the primary studies was assessed using the JBI Critical Appraisal Checklist [19] assessment scale, composed of nine domains. An assessment with a score of 49% or less is classified as high risk, 50% to 69% as moderate risk, and 70% or more as low risk [20, 21].

Methods of synthesis

Before the meta-analysis, analyses were processed using a random-effects restricted maximum likelihood (REML) model. When applicable, Hartung-Knapp-Sidik-Jonkman (HKSJ or Knapp-Hartung) estimates of variance (CI) were used. A double arcsine transformation was performed using the Freeman-Tukey formula to control between-study variance. To improve comprehensibility, the results were re-transformed to prevalence after the meta-analysis.

Studies assessed as having a high risk of bias were excluded from the meta-analysis to ensure the reliability and internal validity of the synthesized evidence. High risk of bias can significantly distort effect estimates and compromise the integrity of pooled results. Including such studies may lead to over- or underestimation of intervention effects and reduce confidence in the conclusions. Therefore, only studies with low or moderate risk of bias were included to provide more accurate and trustworthy estimates of effect.

Cochran's Q test and I2 were used to assess heterogeneity. Cochran's Q test was considered statistically significant when it reached a value < 0·05. In addition, a meta-regression was performed with the following covariates: number of participants, risk of bias, geographical area, type of IFI and type of patient, to determine the source of heterogeneity.

Finally, subgroup-based sensitivity analyses were performed, correcting for heterogeneity with an I2 of 10%, a meta-analysis without including one, and corrections for the standard error of the effect size (prevalence) using the truncated Sidik-Jonkman and Knapp-Hartung methods. All analyses were performed using Stata 18 statistical software [22].

To objectively assess publication bias, the Egger's test was measured, a funnel plot was depicted, and a trim-and-fill analysis was performed. Because there is no specific instrument or methodology to measure the certainty of evidence in systematic prevalence reviews, this aspect was not evaluated.

Results

Selection of studies

A total of 2,838 studies were found. After removing duplicates, 1,816 articles were screened by reading titles and abstracts. A total of 1682 articles irrelevant to the topic were excluded and finally, after reading the full texts of 134 potentially relevant studies, 100 articles were excluded (58 did not meet selection criteria, 19 pediatric-only population, 16 irrelevant studies, 4 posters, 2 letters to the editor, 1 with COVID-19 infected population).

A total of 34 studies were included for this systematic review and prevalence meta-analysis. The study selection process is shown in the PRISMA flowchart (see Fig. 1) [10].

Characteristics of the studies

The studies included in the systematic review covered a total of 34 investigations published between 1999 and 2023 [6, 23–54]. Most studies used prospective observational designs ($n = 12$) [26, 28–32, 35, 36, 39, 42, 45, 46] or cohorts ($n = 20$, of which 4 were prospective [23–25, 41], and 16 were retrospective [6, 33, 34, 37, 40, 43, 44, 47–54], while one was a case–control trial [27], and one was a randomized controlled trial [38]. The studies were conducted in diverse regions, with North America, Europe, Asia, and Latin America standing out. France, China, the United States, and Germany were the most represented countries.

Population size varied widely across studies, from small cohorts of 53 patients [35] to databases with more than 246,000 individuals [41]. Most studies included specific populations, such as patients hospitalized in ICUs for more than 48 h, surgical patients with severe sepsis, or hematologic and oncologic patients. Some studies encompassed broader populations, such as hospitalized adults with risk factors or those infected according to multicenter databases.

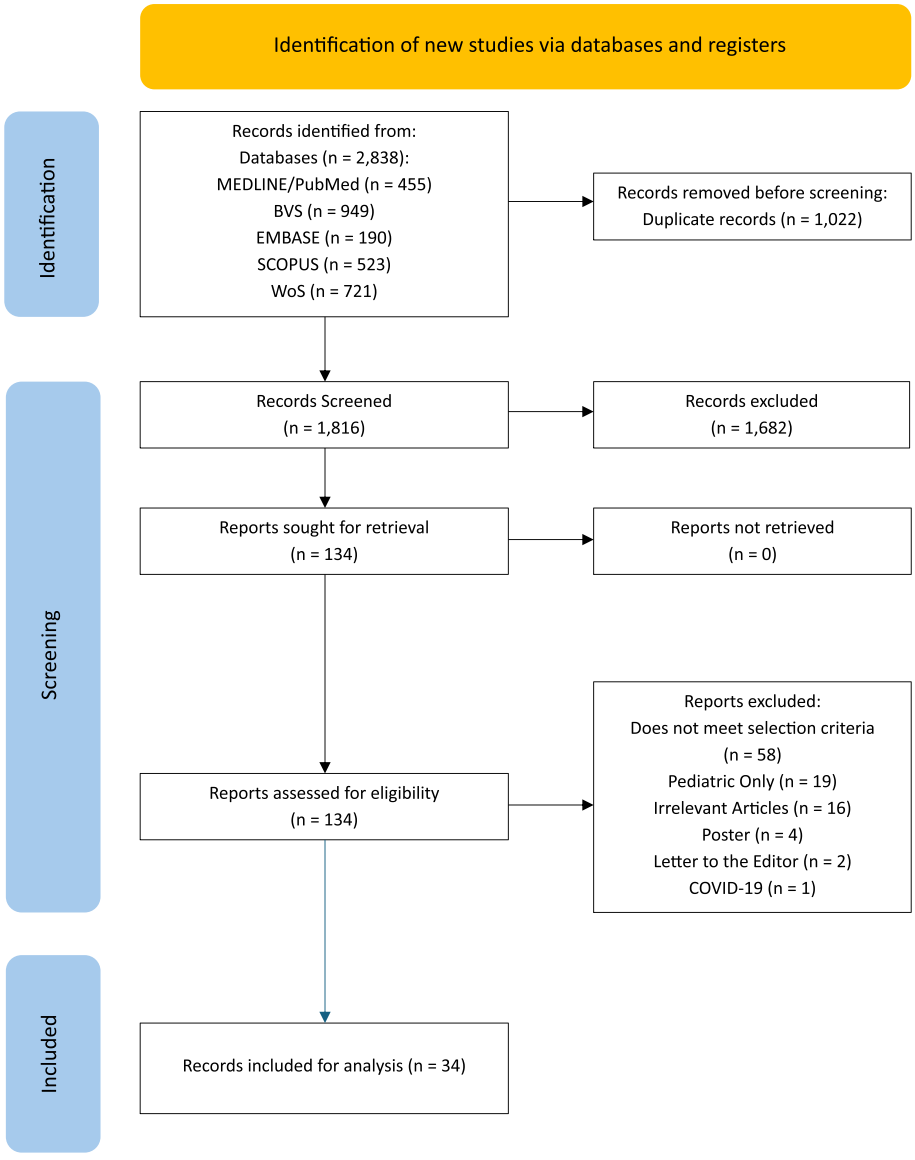

Fig. 1 PRISMA flow of information selection and exclusion

In terms of funding, ten studies received support from pharmaceutical companies [23, 28, 30, 32, 36, 39, 42, 45, 49, 52] with Pfizer standing out as the most frequent sponsor. Other studies were funded by ministries of health, government agencies or academic institutions, while six reported no funding [24, 27, 33, 43, 44, 46].

Moderate agreement was recorded in the inter-rater assessment (kappa: 0·55). The JBI Critical Appraisal Checklist assessment classified the risk of bias as low in most studies [2, 23, 24, 26–28, 30–33, 36, 38, 41, 42, 44, 47, 49, 50, 53] ($n = 20$), moderate in 11 studies [6, 25, 37, 39, 40, 43, 46, 48, 51, 52, 54] and high in three studies [29, 34, 35]. The MinClr-Pr2 score ranged from 23 to 56, reflecting variable methodological quality in the investigations included. (Supplemental Fig. 10).

Among the items on the JBI checklist, the one most frequently rated as "no" was from domain one, which pertains to the target population. In contrast, domain nine—related to the response rate—was most often rated as "unclear" (Supplemental Fig. 10). However, since all studies performed an adequate analysis to calculate prevalence, domain nine was ultimately rated as "yes" across all studies (Supplemental Fig. 11) [21].

There was considerable variability in how invasive fungal infection was defined across the studies. The majority—20 articles (57%)—relied on definitions proposed by the study authors themselves, typically combining clinical symptoms with microbiological test results [6, 23, 24, 26–34, 36, 37, 39, 41, 47, 49, 50, 54]. Six studies (18%) applied the revised EORTC/MSG 2008 criteria for invasive fungal disease [35, 42, 45, 46, 48, 53], while three

studies (9%) used the AspICU 2012 diagnostic criteria [40, 44, 51]. One study (3%) adopted the ICD-9 definition [43]. The remaining studies used a variety of other criteria, including the revised EORTC/MSG 2002 definitions [25], the AspICU 2018 criteria [52], the Vandewoude et al. criteria [45], and the EPCAN study group definition [38], as summarized in Table 1.

Characteristics of the patients

Table 2 summarizes the main characteristics of the patients included in this review, which encompassed a total of 655,169 individuals. Sample sizes varied widely, ranging from as few as 53 patients [35] to as many as 246,459 [41]. Among patients diagnosed with invasive fungal infections (IFI), the reported mean age ranged from 45.4 years (standard deviation [SD] ± 18.8) [34] to 67.5 years (SD ± 12.8) [50], while the reported median age ranged from 50.5 years (interquartile range [IQR] 42–68) [48] to 75.1 years (IQR 70.1–80.2) [54].

Male patients accounted for an average of 61.5% of the IFI population, with proportions ranging from 41.5% [28] to 81% [53]. Regarding disease severity, as measured by standardized scoring systems, the median SOFA score ranged from 5 [36, 37] to 10 [53, 54]; the mean APACHE II score ranged from 14.3 (SD ± 11.4) [45] to 27.2 (SD ± 7.2) [30]; and the median SAPS II score ranged from 40 (IQR 28–49) [48] to 59 (IQR 49–76) [53].

In terms of comorbidities, the prevalence of diabetes mellitus ranged from 8% to 44.7%, arterial hypertension from 9.1% to 91.8%, and lung diseases from 1.5% to 83.3%. Chronic kidney failure was reported in 2% to 52% of IFI patients, and cancer in 2% to 50% [30, 31, 33, 44, 49–51, 53], excluding studies exclusively involving oncologic populations, where cancer prevalence was 100% [35, 39, 47].

Finally, prior corticosteroid use before ICU admission was reported in 3% to 69% of patients across several studies [28, 32, 40, 44–47, 53, 54].

Regarding the focus of fungal infections, the most commonly reported sites were respiratory, blood, and intra-abdominal. Antifungal treatment was primarily centered on fluconazole, which was used in 13 studies [6, 24, 25, 27, 30, 31, 36, 37, 48–50, 53], with reported usage ranging from 3.8% and 97.6%. Voriconazole was reported in 11 studies [6, 27, 30, 31, 35, 40, 44, 49, 50, 53], with usage ranging from 1% to 73.5%. Caspofungin was used in eight studies [6, 27, 30, 31, 36, 40, 49], with a reported range of 2% and 86·4%. Amphotericin B was administered in 12 studies [6, 24, 25, 27, 31, 35, 37, 40, 44, 49, 53], with usage ranging from 0.3% and 69.2%. Additionally, the use of other antifungal agents was documented in 7 studies [6, 25, 31, 35, 49, 50, 53], with the highest proportion observed in the study by Zhang et al. (2022), reporting use in 38.4% of cases [6]; (See Supplementary Table 1).

During ICU stay, several key interventions were reported across studies. Vasopressor support was documented in six studies [39, 40, 44, 51, 53, 54] with usage ranging from 35.8% and 88.9%. Mechanical ventilation was reported in 16 studies [6, 25, 30–33, 36, 39, 40, 44–46, 49, 51, 53, 54], with a minimum usage of 47.5% [45]. The presence of a central venous catheter was reported in 12 studies [24, 25, 28, 30–33, 36, 41, 47, 53, 54], with a minimum prevalence of 77.4%, and in four studies, all patients had a catheter [24, 33, 36, 47].

Corticosteroid use during hospitalization was reported in 8 studies [24, 25, 27, 28, 33, 35, 36, 40], ranging from a minimum of 9.1% [27] to a maximum of 95.4% [36]. The duration of mechanical ventilation ranged from a median of 14 days (IQR 9—31) [44] to 35 days (IQR 24.3—54) . Median ICU length of stay varied from 9 days (IQR 5—17) [39] to 29 days (IQR 18—49) [41], while the longest reported median hospital stay was 37 days (IQR 22—66) [49].

Hospital mortality was reported in 8 studies [6, 28, 31, 39, 44, 47, 51], ranging from 15.8% [47] to 81.8% . ICU mortality, reported in 20 studies [24, 25, 27, 30–32, 34, 36, 37, 39–42, 44–47, 51–53], ranged widely—from a minimum of 13.6% [36] to 100% [46] (see Supplementary Table 2).

Prevalence of IFI

The overall pooled prevalence of invasive fungal infection (IFI) was 5% (95% CI: 3–7%) with high heterogeneity ($I2 = 99.9\%$, $\tau 2 = 0.09$, $p < 0.001$) (see Fig. 2; Table 3). Among specific pathogens, aspergillosis was the most frequently reported, with a prevalence of 10% (95% CI: 5–18%, $I2 = 95.1\%$), followed by candidiasis at 3% (95% CI: 1–5%, $I2 = 99.9\%$) and infections caused by other fungal species at 5% (95% CI: 1–5%, $I2 = 99.9\%$) (see Supplementary Material).

In the continent-level analysis, the highest prevalence of invasive fungal infection was observed in South America at 15% (95% CI: 3–32%; $I2 = 96.9\%$), followed by Africa with 16% (95% CI: 11–23%) based on a single study. Asia reported a prevalence of 10% (95% CI: 2–24%; $I2 = 99.9\%$), North America 4% (95% CI: 1–9%; $I2 = 99.5\%$), and Europe 3% (95% CI: 2–5%; $I2 = 99.8\%$) (see Supplementary Data).

When stratified by country income level, the prevalence was 3% (95% CI: 2–5%) in high-income countries, 6% (95% CI: 1–15%) in upper-middle-income countries, and 21% (95% CI: 14–29%) in lower-middle-income countries. The overall global prevalence remained at 5% (95% CI: 3–7%).

Risk of bias between studies

When assuming low heterogeneity ($I2 = 10\%$), the changes in prevalence estimates were clinically negligible.

Table 1 Characteristics of the Included Studies

Author	Year	Type of study	Country	Study period	Total population	Population	Definition of IFI	N° Centers	Financing	Risk of bias	Min-Clr
Rangel	1999	Prospective cohort	United States	October 1993 to November 1995	4276	More than 48 h in ICU	The isolation of any Candida species from the bloodstream in two or more culture samples. *	6	Pfizer Educational Grant	Lower risk	30
Dimopoulos	2007	Prospective cohort	Greece	February 2000 to January 2002	1627	More than 48 h in ICU	Candidemia was defined by at least one positive blood culture for Candida spp.*	1	N/R	Lower risk	30
Xie	2008	Prospective cohort	China	December 2004 to November 2005	318	Adult surgical patients with severe sepsis	Revised Definitions of Invasive Fungal Disease EORTC/MSG 2002	10	National Natural Science Foundation of China and the New Century Excellent Talents Program	Moderate	39

Table 1 (continued)

Author	Year	Type of study	Country	Study period	Total population	Population	Definition of IFI	N° Centers	Financing	Risk of bias	Min-Clr
Magill	2009	Prospective observational	United States	January 2003 to August 2003	235	Adults, more than 72 h in ICU	Invasive Candidiasis is defined as meeting 2 criteria for systemic inflammatory response syndrome and one of the following criteria: (1) at least 1 positive blood test for yeast species; (2) at least 1 fungus-positive culture obtained during a sterile procedure at a normally sterile site on the body; or (3) positive histopathology or autopsy examination revealing invasion of tissue by fungal forms. *	1	Johns Hopkins University School of Medicine Center for General Clinical Research	Lower risk	51
Pratikaki	2009	Cases and controls	Greece	August 2004 to January 2006	855	More than 48 h in ICU	Candidemia was defined as a positive blood culture for Candida. *	1	N/R	Lower risk	39

Table 1 (continued)

Author	Year	Type of study	Country	Study period	Total population	Population	Definition of IFI	N° Centers	Financing	Risk of bias	Min-Clr
Ajenjo	2011	Prospective observational	Chile	October 2001 to August 2003	231	Adults with risk factors	Invasive candidiasis is defined as: 1.- Candidemia defined as the presence of at least one positive blood culture for yeasts; 2.- Disseminated invasive candidiasis defined as the clinical picture characterized by a febrile syndrome without a focus and without response to broad-spectrum antimicrobials, in a patient with at least one risk factor and isolation of yeasts in at least two sites, excluding oral cavity and stools; 3.- Local invasive candidiasis \defined by the presence of a sterile site culture positive for yeasts. *	1	Pfizer Chile	Lower risk	36
Kett	2011	Prospective observational	Worldwide	May 2007 to July 2007	7330	Infected (EPIC II database)	Candida bloodstream infection was defined as Candida positive blood culture. *	1265	There was no funding	High risk	31

Table 1 (continued)

Author	Year	Type of study	Country	Study period	Total population	Population	Definition of IFI	N° Centers	Financing	Risk of bias	Min-Clr
Guo	2013	Prospective observational	China	November 2009 to April 2011	96,060	Adults	One of the following diagnostic criteria: 1. direct histopathological, cytopathological, or microscopic confirmation of yeast cells in a specimen obtained by needle aspiration or biopsy from a normally sterile site (other than mucous membranes); 2.- at least one peripheral blood culture positive for Candida; and 3.- positive culture of Candida from a sample obtained by sterile technique from a normally sterile site (e.g., cerebrospinal fluid, pleural, peritoneal or peritoneal abscess). *	67	Merck Sharp & Dohme China	Lower risk	43
Harrison	2013	Prospective observational	United Kingdom	July 2009 to March 2011	60,778	Adults	Blood culture or a sample from a normally sterile site that shows yeast/mold cells in a microbiological or histopathological report. *	96	Health Technology Assessment Programme of the National Institute for Health Research in the United Kingdom	Lower risk	52

Table 1 (continued)

Author	Year	Type of study	Country	Study period	Total population	Population	Definition of IFI	N° Centers	Financing	Risk of bias	Min-Clr
Montagna	2013	Prospective observational	Italy	February 2007 to August 2008	5561	Adults	Yeast IFI was defined as the recovery of yeast from a blood culture or other normally sterile site. Fungaemia was considered to be catheter-related if a culture of the catheter tip shed the same isolated yeast into the bloodstream. Persistent fungemia was defined as persistence of positive blood cultures for 2 days from the time of the first positive blood culture. Mold IFI was defined as the isolation of filamentous fungi (e.g., Aspergillus, Fusarium, Mucormycetes) from a normally sterile or non-sterile body site, along with suggestive clinical manifestations and instrumental test findings. *	18	Pfizer Italy	Lower risk	44

Table 1 (continued)

Author	Year	Type of study	Country	Study period	Total population	Population	Definition of IFI	N° Centers	Financing	Risk of bias	Min-Clr
Serrano	2013	Retrospective Descriptive Cohort	Spain	January 2007 to December 2010	4276	Adults, Nonneutropenic	Candidemia and isolates in sterile liquids were considered representative of IFI. *	1	N/R	Lower risk	32
Marzaban	2014	Retrospective cohort	Egypt	2011 to 2013	140	Post liver transplant	Culture is the standard criterion for the diagnosis of IFI, as long as the specimens come from sterile sites. *	1	There was no funding	High risk	26
Rocchi	2014	Prospective observational	France	January 2010 to May 2012	53	Hematologic	European Organization for Research and Treatment of Cancer Standard Definition (EORTC 2008)	1	There was no funding	High risk	37
Aguilar	2015	Prospective observational	Spain	January 2012 to December 2013	1149	Adults, more than 10 days in ICU	The definition of Invasive Candidiasis was the recovery of yeast from a blood culture or other normally sterile site. Candidemia was thought to be catheter-related if a culture of the catheter tip shed the same isolated yeast into the bloodstream. *	1	Pfizer Spain	Lower risk	26
Gill	2015	Retrospective observational	Paraguay	2013	1034	Adults	Positive cultures for systemic or deep mycoses. *	1	There was no funding	Moderate	27

Table 1 (continued)

Author	Year	Type of study	Country	Study period	Total population	Population	Definition of IFI	N° Centers	Financing	Risk of bias	Min-Clr
Jensen	2015	Randomized controlled trial	Denmark	September 2006 to February 2009	1200	Adults, Infected	Definition of the EPCAN study group	9	Copenhagen HIV Programme Danish Research Agency for the Hvidovre University Hospital	Lower risk	56
Azoulay	2016	Prospective observational	France and Belgium	January 2010 to May 2011	737	Hematological and oncological	Candidemia was defined as the recovery of any Candida species from at least one blood culture. *	17	French Ministry of Health French Society of Critical Care Pfizer France	Moderate	47
Contou	2016	Retrospective cohort	France	January 2006 to December 2015	423	Adults, Moderate-to-severe ARDS with IMV for 48 h	AspICU 2012 Diagnostic Criteria	1	There was no funding	Moderate	37
Baldesi	2017	Prospective cohort	France	January 2004 to June 2013	246,459	Adults, more than 48 h in ICU	ICU-acquired candidemia was defined by at least one blood culture taken after more than 48 h of ICU stay and positive for Candida spp; A positive catheter culture was required to define catheter-related candidemia. *	163	French Ministry of Health and French National Public Health Agency	Lower risk	39
Arsenijević	2018	Prospective observational	Serbia	November 2014 to December 2015	7437	Infected	Revised Definitions of Invasive Fungal Disease EORTC/MSG 2008	15	Ministry of Education, Science and Technology of the Republic of Serbia Pfizer	Lower risk	33
Cavayas	2018	Retrospective cohort	Canada	January 2006 to September 2016	19,697	Adult, ECMO	As defined by ICD-9 or any positive fungal culture. *	300	N/R	Moderate	38

Table 1 (continued)

Author	Year	Type of study	Country	Study period	Total population	Population	Definition of IFI	N° Centers	Financing	Risk of bias	Min-Clr
Schauwvlieghe	2018	Retrospective cohort	Belgium and the Netherlands	January 2009 to June 2016	432	Adults, H1N1 pneumonia	AspICU 2012 Diagnostic Criteria	7	N/R	Lower risk	39
Chakrabarti	2019	Prospective observational	India	April 2016 to September 2017	41,879	Proven/Probable Mould-Infected	Revised Definitions of Invasive Fungal Disease EORTC/MSG 2008, Definition by Vandewoude et al. and Definition by Bulpa et al	11	Merck Sharp and Dohme	Lower risk	42
Lahmer	2019	Prospective observational	Germany	April 2016 to April 2018	84	With a diagnosis of liver cirrhosis	Revised Definitions of Invasive Fungal Disease EORTC/MSG 2008	1	N/R	Moderate	34

Table 1 (continued)

Author	Year	Type of study	Country	Study period	Total population	Population	Definition of IFI	N° Centers	Financing	Risk of bias	Min-Clr
Xia	2019	Retrospective cohort	China	January 2010 to October 2014	229	Surgical Oncology	Invasive candidiasis was defined as patients with clinical signs of infection (at the discretion of the treating physician) and met at least 1 of the following 3 diagnostic criteria. Direct histopathological, cytopathological, or microscopic confirmation of yeast cells in a specimen obtained by needle aspiration or biopsy from a normally sterile site (other than mucous membranes). 2.- At least one peripheral blood culture positive for Candida. 3.- A positive culture of Candida from a specimen obtained by sterile technique from a normally sterile site (e.g., cerebrospinal fluid, pleural, peritoneal or peritoneal abscess). *	1	Tianjin Medical University and the Science and Technology Funds of the Tianjin Health Bureau	Lower risk	37

Table 1 (continued)

Author	Year	Type of study	Country	Study period	Total population	Population	Definition of IFI	N° Centers	Financing	Risk of bias	Min-Clr
Maurel	2020	Retrospective cohort	France and Belgium	January 2010 to December 2015	8503	Adults, Burned	Revised Definitions of Invasive Fungal Disease EORTC/MSG 2008	10	SPILF-CMIT research group	Moderate	25
Schroeder	2020	Retrospective cohort	Germany	October 2008 to July 2017	75,741	Confirmed BSI	Candidemia defined as positive blood cultures for Candida spp. *	1	Pfizer Germany	Lower risk	37
Ulrych	2020	Retrospective cohort	Czech Republic	January 2013 to December 2016	3487	Surgical	Intra-abdominal candidiasis was classified as patients with clinical evidence of intra-abdominal infection and isolation of Candida species in a sample collected from an intra-abdominal site or abdominal drains that were placed < 24 h. *	1	Ministry of Health of the Czech Republic	Lower risk	23
Waldeck	2020	Retrospective cohort	Switzerland	December 2017 to April 2018	81	Adults, H1N1 pneumonia	AspICU 2012 Diagnostic Criteria	2	There was no funding	Moderate	28
Coste	2021	Retrospective Cohort	France	September 2009 to April 2018	524	H1N1 pneumonia	AspICU 2018 Diagnostic Criteria	5	Novartis, Pfizer, Gilead, Merck, Sharp and Dohme	Moderate	39
Larcher	2021	Retrospective cohort	France	January 2006 to December 2019	6900	Onco-hematological and post-kidney transplantation	Revised Definitions of Invasive Fungal Disease EORTC/MSG 2008	1	There was no funding	Lower risk	28

Table 1 (continued)

Author	Year	Type of study	Country	Study period	Total population	Population	Definition of IFI	N° Centers	Financing	Risk of bias	Min-Clr
Poth	2022	Retrospective	Germany	1 January 2013 to 30 April 2021	646	ECMO	Vandewoude et al. criteria for invasive aspergillosis or positive culture for candida except for tracheal aspirates and urine. *	1	There was no funding	Lower risk	32
Zhang	2022	Retrospective cohort	United States	2008 to 2019	50,048	Adults, under 89 years of age	Positive culture for fungal species in a deep site. *	1	Aerospace Medical Health Technology Scientific Foundation	Moderate	38
Dong	2023	Retrospective cohort	United States	2008 to 2019 and 2001 to 2008	6739	Adults, 65 years of age and older	Invasive candidiasis was defined as the detection of Candida spp. in blood, peritoneal fluid, or other sterile sites from the second day after admission to the ICU until discharge. However, samples such as urine, sputum or bronchial lavage were not considered sources of invasive candidiasis. *	1	The Guangdong Natural Science Foundation	Moderate	50

AspICU A Clinical Algorithm for Diagnosing Invasive Pulmonary Aspergillosis in Critically Ill Patients, *BAL* Bronchoalveolar Lavage, *CMIT* The University College of Infectious and Tropical Diseases, *ECMO* Extracorporeal Membrane Oxygenation, *EORTC/IFIG* European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group, *EPCAN* Candidiasis Prevalence Study, *EPIC* European Prospective Investigation into Cancer and Nutrition, *ICD-9* International Classification of Diseases, Ninth Revision, *IFI* Invasive Fungal Infection, *NIAID/MSG* National Institute of Allergy and Infectious Diseases Mycosis Study Group, *N/R* Not Reported, *ARDS* Acute Respiratory Distress Syndrome, *SPILF* The French-Language Society of Infectious Pathology, *SPP* Species of, *ICU* Intensive Care Unit, *HIV* human immunodeficiency virus, *IMV* Invasive mechanical ventilation

* Definition determined by the authors

Sensitivity analyses using standard error adjustment methods—Sidik-Jonkman and truncated Knapp-Hartung—showed no significant differences in the estimated prevalence. Additionally, a leave-one-out analysis, in which each study was removed sequentially, yielded prevalence estimates ranging from 2.6% to 6.7%, without substantially altering the overall pooled prevalence (see Table 4).

Egger's test obtained a $p < 0.001$. The funnel plot also demonstrated asymmetry, with several studies falling

Table 2 Characteristics of the population with IFI

Author	Population (N)	IFI (N)	Age (SD) (IQR)	Male N (%)	Severity Scale (SD) (IQR)	Comorbidities N (%)	Previous cortico-steroids N (%)
Rangel 1999 [16]	4276	42	N/R	N/R	N/R	N/R	N/R
Dimopoulos 2007 [17]	1627	24	51 (43,5–54)	14 (58)	CI: SOFA 8 (± 1) APACHE II 24 (± 3) No IC: SOFA 6 (± 2) APACHE II 20 (± 3)	DM 5 (20.8)	N/R
Xie 2008 [18]	318	90	65 (50–76,2)	57 (63,3)	N/R	N/R	N/R
Magill 2009 [19]	235	12	N/R	N/R	N/R	N/R	N/R
Pratikaki 2009 [20]	855	33	57 (± 18)	21 (64)	SOFA 9 (± 3.9) APACHE II 20.7 (± 9)	MD 8 (24.2)	N/R
Ajenjo 2011 [21]	231	53	67 (17–92)	22 (41,5)	N/R	N/R	11 (20,7)
Kett 2011 [22]	7330	99	N/R	N/R	N/R	N/R	N/R
Guo 2013 [23]	96,060	306	61.5 (± 20)	210 (68,2)	SOFA 11.1 (± 3.4) APACHE II 27.2 (± 7.2)	MD 67 (21.9) Pneumopathy 35 (11.4) CKD 33 (10.8) Cancer 60 (19.6) CI 246 (80.4)	N/R
Harrison 2013 [8]	66,778	383	62 (49–73)	183 (47,8)	N/R	MD: 56 (14.6) Pneumopathy 6 (1.5) CKD 8 (2) Cancer 11 (2.8) CI 30 (7.83)	N/R
Montagna 2013 [24]	5561	105	60 (44,5–71)	67 (63,8)	SOFA 7 (6–8)	MD: 16 (15.2) Pneumopathy 12 (11.4)	25 (23,8)
Serrano 2013 [49]	4276	20	61.7 (± 14.4)	11 (55)	SOFA 8 (4.5–9.7) APACHE II 21.8 (± 5)	HTN 6 (30) DM 2 (10) Pneumopathy 8 (40) Cancer 1 (5) CI 19 (95)	N/R
Marzaban 2014 [26]	140	23	45.4 (± 18.8)	18 (78,3)	N/R	N/R	N/R
Rocchi 2014 [27]	53	14	55 (31–56)	8 (57,2)	N/R	Cancer 14 (100)	N/R
Aguilar 2015 [28]	1149	22	66 (53,7–74,2)	16 (72,7)	SOFA 5 (3–6,2)	MD 7 (31.8) CKD 3 (13.6) Cancer 7 (31.8)	N/R
Gill 2015 [29]	1034	85	54 (± 14)	45 (53)	SOFA 5 (4–8) APACHE II 14 (11–16)	HTN 78 (91.8) MD 38 (44.7) CKD 11 (12.9)	N/R
Jensen 2015 [30]	1200	74	67 (58–76)	N/R	N/R	N/R	N/R
Azoulay 2016 [31]	737	78	58 (48–64)	46 (59)	N/R	Cancer 78 (100)	N/R
Contou 2016 [32]	423	35	62 (49–72)	24 (69)	SAPS II 51 (34–68)	MD 6 (17) Pneumopathy 4 (11) CKD 1 (3) CI 17 (48.5)	1 (3)
Baldesi 2017 [33]	246,459	851	65 (54–75)	533 (62,6)	SAPS II 53 (42–67)	CI 43 (5.1)	N/R
Arsenijević 2018 [34]	7437	26	59 (21–83)	N/R	N/R	N/R	N/R
Cavayas 2018 [35]	19,697	2129	48.5 (± 15.7)	1264 (59,7)	N/R	N/R	N/R
Schauwvlieghe 2018 [36]	432	83	60 (± 12)	56 (67)	APACHE II 25 (± 9)	MD 10 (12) Pneumopathy 13 (16) CKD 16 (19) Cancer 26 (32) CI 57 (68),5)	46 (56)
Chakrabarti 2019 [37]	41,879	398	45.6 (± 21.9)	254 (64)	APACHE II 14.3 (± 11.4)	MD 115 (28.9) Pneumopathy 68 (17.1) CKD 48 (12.1)	190 (47,7)

Table 2 (continued)

Author	Population (N)	IFI (N)	Age (SD) (IQR)	Male N (%)	Severity Scale (SD) (IQR)	Comorbidities N (%)	Previous corticosteroids N (%)
Lahmer 2019 [38]	80	12	59 (±8)	9 (75)	SOFA 14 (±4) APACHE II 26 (±8)	MD 1 (8) Pneumopathy 1 (8) CI 12 (100)	2 (16)
Xia 2019 [39]	229	19	63 (54–74)	10 (52,6)	APACHE II 16 (13–19)	HTN 6 (31.6) DM 3 (15.8) Pneumopathy 1 (5.3) CKD 2 (10.5) Cancer 19 (100)	2 (10,5)
Maurel 2020 [40]	194	94	50,5 (42–68)	58 (62)	SAPS II 40 (28–49)	N/R	N/R
Schroeder 2020 [41]	75,741	391	65 (56–74)	240 (61)	SAPS II 44 (35–53) SOFA 8 (5–11)	MD 99 (25) Pneumopathy 57 (15) CKD 205 (52) Cancer 139 (36) CI 28 (7)	N/R
Ulrych 2020 [42]	3487	64	67.5 (±12.8)	30 (46,8)	SOFA 4.1 (±3.9)	Cancer 32 (50)	N/R
Waldeck 2020 [43]	81	9	58 (57–64)	6 (66)	SAPS II 44 (39–66)	MD 3 (33.3) Pneumopathy 2 (22.2) Cancer 1 (11.1) CI 8 (89)	N/R
Coste 2021 [44]	524	10	N/R	N/R	N/R	N/R	N/R
Larcher 2021 [45]	6900	26	58,5 (48–49)	21 (81)	SAPS II 59 (49–76) SOFA 10 (8–13)	MD 6 (23) CKD 4 (15) Cancer 15 (58) CI 11 (42)	18 (69)
Poth 2022 [46]	368	22	57.34 (±9.55)	13 (59,1)	SAPS II 47.9 (±11.7) SOFA 9 (7–10)	HTN 2 (9.1) MD 5 (22.7) Pneumopathy 4 (18.2) CKD 1 (4.5) Cancer 2 (9.1) CI 4 (18.2)	N/R
Zhang 2022 [47]	50,048	1981	59.61 (±15.37)	1075 (54,3)	N/R	N/R	N/R
Dong 2023 [48]	6739	134	75,1 (70,1–80,2)	79 (59)	SAPS II 44 (36–56) SOFA 10 (6–13)	MD 37 (27.6) Pneumopathy 26 (19.4)	22 (16,4)

outside the pseudo-95% CI. To further explore whether this asymmetry was attributable to publication bias or to between-study heterogeneity, a Trim-and-Fill analysis was performed. This method did not impute any missing studies, which may indicate that the asymmetry is not primarily due to unpublished negative studies, but rather to substantial heterogeneity in study design, diagnostic criteria, and population characteristics across the included studies.

Meta regression

In the random-effects meta-regression, the only statistically significant association was with the covariate number of participants ($p = 0.03$), indicating that studies with larger samples tended to report smaller effects. The residual between-study variance (τ2) after adjusting for sample size was 0.76, and the residual heterogeneity (I2) was 99.87%, suggesting high unexplained heterogeneity remained.

The remaining covariates assessed (risk of bias, geographical area, type of IFI, and type of patient) showed non-significant associations.

Discussion

To our knowledge, this is the first systematic review and meta-analysis to comprehensively evaluate the prevalence of invasive fungal infections (IFIs) across a broad spectrum of critically ill ICU populations, thereby providing a more inclusive assessment of IFI burden in the ICU setting.

Although the overall prevalence of IFI was relatively low at 5%, the clinical burden should not be underestimated due to the high associated mortality [59]. Primary studies report associated mortality rate of 40 to 70% [40, 52, 53] representing a major health issue and significant hospital costs.

Although critically ill patients in many cases do not meet the classic"host"criteria to develop an IFI as defined

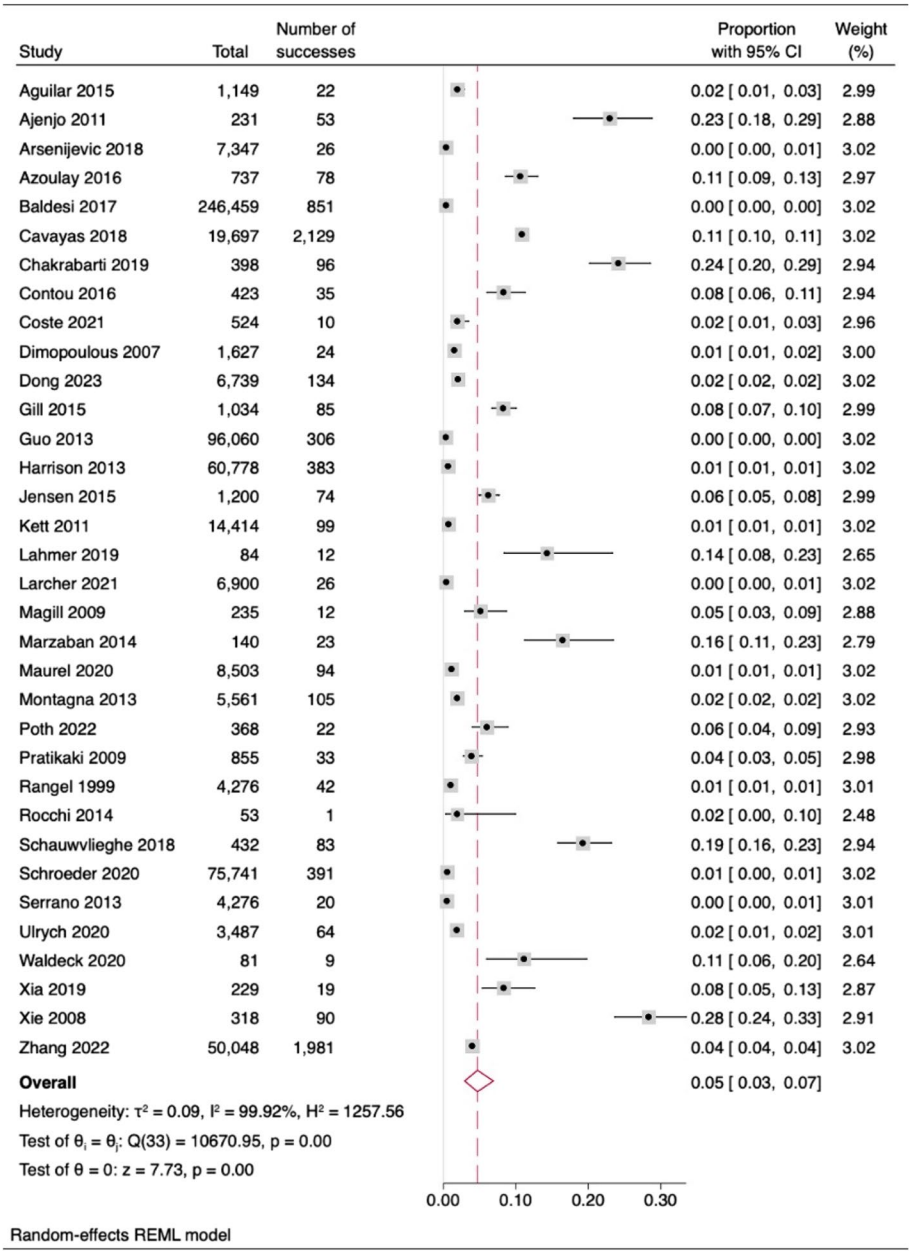

Fig. 2 Forest Plot of the global prevalence of IFI

by oncology or transplant guidelines, they do however, frequently experience functional immune alterations, including dysregulated innate and adaptive immune responses. These changes render ICU patients vulnerable to opportunistic fungal infections, supporting their inclusion in risk stratification strategies [49].

We observed significant regional variation in IFI prevalence. The lowest prevalence (3%) was found in high-income countries, while the highest (21%) occurred in lower-middle-income regions. This disparity may reflect differences in diagnostic capacity, resource availability, and underlying fungal epidemiology. Similar findings have been documented by Allegranzi [53] et al., who emphasized the role of systemic limitations in infection control and delayed diagnosis in low-resource settings.

Prevalence estimates also varied across continents: 3% in Europe, 4% in North America, 10% in Asia, and 15% in South America. The higher rates in South America likely stem from limited access to diagnostic technologies, delays in antifungal treatment, and overall weaker surveillance infrastructure. These challenges collectively contribute to both increased prevalence and worse outcomes [6, 25].

Table 3 Prevalence of IFI

Author/Year	Type of Population	Type of IFI	Population	IFI	Candida N (%)	Candida Albicans N (%)	Candida no Albicans N (%)	Aspergilus N (%)	Other N (%)	Prevalence % (CI)
Rangel 1999 [16]	Adults, more than 48 h in ICU	Candida Bloodstream Infections	4276	42	42 (100)	20 (48)	22 (52)	N/R	N/R	0,98 (0,68–1,28)
Dimopoulos 2007 [17]	Adults, more than 48 h in ICU	Candidemia	1627	24	24 (100)	15 (62,5)	9 (37,5)	N/R	N/R	1,48 (0,89–2,07)
Pugliese, et al. 2007 [55]	Post Solid Organ Transplant	General IFI	278	46	45 (97,8)	33 (71)	12 (26)	1 (2,17)	N/R	16,55 (12,18–20,83)
Xie 2008 [18]	Surgical	General IFI	318	90	93 (93)	58 (58)	35 (35)	3 (3)	Other unspecified 4 (4)	28,30 (23,35–33,25)
Magill 2009 [19]	Adults, more than 72 h in ICU	General IFI	235	12	11 (91,7)	6 (50)	5 (41,6)	1 (8,3)	N/R	5,11 (2,29–7,93)
Pratikaki 2009 [20]	Adults, more than 48 h in ICU	Candidemia	855	33	33 (100)	11 (33,3)	22 (66,7)	N/R	N/R	3,86 (2,57–5,15)
Ajenjo 2011 [21]	Adults with risk factors	Invasive Candidiasis	231	53	53 (100)	32 (60,4)	21 (39,6)	N/R	N/R	22,94 17,52–29,36)
Kett 2011 [22]	Infected (EPIC II database)	Candida Bloodstream Infections	7330	99	N/R	N/R	N/R	N/R	N/R	1,35 (1.09–1.61)
Wauter, et al. 2012 [56]	H1N1 pneumonia	Invasive pulmonary aspergillosis	40	9	N/R	N/R	N/R	9 (100)	N/R	22,50 (9.56–35–44)
Guo 2013 [23]	Adults	Invasive Candidiasis	96,060	306	143 (100)	102 (41,8)	131 (56,7)	N/R	N/R	0,32 (0.28–0.36)
Harrison 2013 [8]	Adults	General IFI	66,778	383	359 (93,7)	235 (61,3)	110 (28,7)	7 (1,8)	Geotrichum 1 (0.35) Saccharomyces 2 (0.7) Pneumocystis J. 1 (0.35) Missing species 13 (3)	0,57 (0.51–0.63)
Montagna 2013 [24]	Adults	General IFI	5561	105	92 (87,6)	37 (35,2)	55 (59,8)	12 (11,4)	Scedosporium a 1 (0.95)	1,89 (1.53–2–25)
Serrano 2013 [49]	Nonneutropenic	General IFI	4276	20	24	16 (80)	8 (40)	3 (15)	N/R	0,47 (0.26–0.68)
Marzaban 2014 [26]	Post liver transplant	General IFI	140	23	17 (73,9)	N/R	N/R	6 (26,1)	N/R	16,43 (10.29–22.57)
Rocchi 2014 [27]	Hematologic	Invasive pulmonary aspergillosis	53	14	N/R	N/R	N/R	14 (100)	N/R	26,42 (14.55–38.29)
Aguilar 2015 [28]	Adults, more than 10 days in ICU	Invasive Candidiasis	1149	22	22 (100)	13 (59,1)	9 (40,9)	N/R	N/R	1,91 (1.12–2.7)
Gill 2015 [29]	Adults	General IFI	1034	85	84 (98,8)	12 (14,1)	28 (32,9)	1 (1,18)	Candida spp 44 (51.76)	8,22 (6.55–8.89)
Jensen 2015 [30]	Infected	Invasive Candidiasis	1200	74	74 (100)	47 (63,5)	27 (36,5)	N/R	N/R	6,17 (4.81–7.53)
Azoulay 2016 [31]	Hematological and oncological	General IFI	737	78	13 (16,6)	N/R	N/R	54 (69,2)	Pneumocystis J. 13 (16,6) Fusarium 3 (3,8)	10,58 (8.36–12.8)
Contou 2016 [32]	Moderate-to-severe ARDS with IMV for 48 h	Invasive pulmonary aspergillosis	423	35	N/R	N/R	N/R	35 (100)	N/R	8,27 (5.65–10.89)
Baldesi 2017 [33]	Adults, more than 48 h in ICU	ICU-acquired candidemia	246,459	851	851 (100)	522 (61,4)	329 (38,6)	N/R	N/R	0,35 (0.33–0.37)

Table 3 (continued)

Author/Year	Type of Population	Type of IFI	Population	IFI	Candida N (%)	Candida Albicans N (%)	Candida no Albicans N (%)	Aspergilus N (%)	Other N (%)	Prevalence % (CI)
Arsenijević 2018 [34]	Adults	Candida Bloodstream Infections	7437	26	26 (100)	12 (46)	14 (54)	N/R	N/R	0,35 (0.22–0.48)
Cavayas 2018 [35]	ECMO	General IFI	19,697	2129	1907 (89,6)	N/R	N/R	272 (12,7)	Blastomycosis 17 (0.8) Other fungi 33 (1.55)	10,81 (10.38–11.24)
Schauwvlieghe 2018 [36]	H1N1 pneumonia	Invasive pulmonary aspergillosis	432	83	N/R	N/R	N/R	83 (100)	N/R	19,21 (15.5–22.92)
Chakrabarti 2019 [37]	Adults	invasive mold infections	41,879	398	N/R	N/R	N/R	142 (35,7)	Mucorales 25 (13,2) Rhizopus spp 19 (10) Iso. multiples 17 (8,9) Fasarium spp 4 (2,1) Apophysomyces v. 2 (1) Pythium insidious 1 (0,5)	0,95 (0.86–1.04)
Mansour, et al. 2019 [57]	Respiratory pathologies	Pulmonary IFI	80	34	13 (38,2)	N/R	N/R	15 (44,1)	Candida + Aspergillus 6 (17.6)	42,50 (31.67–53.33)
Xia 2019 [39]	Surgical Oncology	Invasive Candidiasis	229	19	19 (100)	10 (52,6)	9 (47,3)	N/R	N/R	8,30 (4.73–11.87)
Maurel 2020 [40]	Burned	General IFI	8503	94	77 (70)	45 (41)	32 (29)	8 (7)	Trichosporon 2 (1.8) Mucorale 16 (14.5) Fusarium 6 (5.5) Scedosporium 1 (0.9)	1,11 (0.89–1.33)
Loughlin, et al. 2020 [58]	Ventilator-associated pneumonia	Invasive pulmonary aspergillosis	194	24	N/R	N/R	N/R	24 (100)	N/R	12,37 (7.74–17)
Schroeder 2020 [41]	Adults	Candidemia	75,741	391	374 (100)	238 (60,9)	136 (39,1)	N/R	N/R	0,52 (0.47–0.57)
Ulrych 2020 [42]	Surgical	Intra-abdominal candidiasis	3487	64	67 (95,7)	35 (50)	32 (45,7)	N/R	Saccharomyces 3 (4,3)	1,84 (1.39–2.29)
Waldeck 2020 [43]	H1N1 pneumonia	Invasive pulmonary aspergillosis	81	9	N/R	N/R	N/R	9 (100)	N/R	11,11 (4.27–17.95)
Coste 2021 [44]	H1N1 pneumonia	Invasive pulmonary aspergillosis	524	10	N/R	N/R	N/R	10 (100)	N/R	1,91 (0.74–3.08)
Larcher 2021 [45]	Oncohematological and post-kidney transplantation	Emerging invasive fungal infections	6900	26	N/R	N/R	N/R	N/R	Mucormycosis 13 (50) Other IFI 13 (50) Rhizopus sp 9 (35) Saprochaete 5 (23) Lichtheimia c. 2 (8) Fusarium sp 2 (8) Scedosporium a 2 (8) Rhizomucor pusillus 1 (4) Mucor circinelloides 1 (4) Trichosporon asahii 1 (4) Chaetomium c. 1 (4) Saccharomyces c. 1 (4)	0,38 (0.23–0.53)
Poth 2022 [46]	ECMO	General IFI	368	22	20 (90,7)	15 (68,2)	5 (22,5)	2 (9,1)	N/R	5,98 (3.56–8.4)

Table 3 (continued)

Author/Year	Type of Population	Type of IFI	Population	IFI	Candida N (%)	Candida Albicans N (%)	Candida no Albicans N (%)	Aspergilus N (%)	Other N (%)	Prevalence % (CI)
Zhang 2022 [47]	Adults, under 89 years of age	General IFI	50,048	1981	1438 (72,6)	655 (33,1)	783 (39,52)	378 (19,1)	Other: 165 (8,3) includes: Pneumocystis J. 62 (3,1) Cryptosporidium p. 8 (0,4) Cryptococcus n. 28 (1,41) etc	3,96 (3.79–4.13)
Dong 2023 [48]	Adults, 65 years of age and older	Invasive Candidiasis	6739	134	134 (100)	94 (70,1)	40 (29,9)	N/R	N/R	1,99 (1.66–2.32)

ICU Intensive Care Unit, *CI* Confidence Interval, *IFI* Invasive fungal infection, *ARDS* Acute respiratory distress syndrome, *IMV* Invasive mechanical ventilation, *ECMO* Extracorporeal membrane oxygenation, *N/R* Not reported, *EPIC* The widespread prevalence of infections in intensive care

Table 4 Meta-analysis: leaving one out

Omitted Study	Proportion	95% CI
Aguilar 2015 [28]	0.05	0.03–0.07
Ajenjo 2011 [21]	0.04	0.03–0.07
Arsenijevic 2018 [34]	0.05	0.03–0.07
Azoulay 2016 [31]	0.05	0.03–0.07
Baldesi 2017 [33]	0.05	0.03–0.07
Cavayas 2018 [35]	0.05	0.03–0.07
Chakrabarti 2019 [37]	0.04	0.03–0.06
Contou 2016 [32]	0.05	0.03–0.07
Coste 2021 [44]	0.05	0.03–0.07
Dimopoulous 2007 [17]	0.05	0.03–0.07
Dong 2023 [48]	0.05	0.03–0.07
Gill 2015 [29]	0.05	0.03–0.07
Guo 2013 [23]	0.05	0.03–0.07
Harrison 2013 [8]	0.05	0.03–0.07
Jensen 2015 [30]	0.05	0.03–0.07
Kett 2011 [22]	0.05	0.03–0.07
Lahmer 2019 [38]	0.05	0.03–0.07
Larcher 2021 [45]	0.05	0.03–0.07
Magill 2009 [19]	0.05	0.03–0.07
Marzaban 2014 [26]	0.04	0.03–0.07
Maurel 2020 [40]	0.05	0.03–0.07
Montagna 2013 [24]	0.05	0.03–0.07
Poth 2022 [46]	0.05	0.03–0.07
Pratikaki 2009 [20]	0.05	0.03–0.07
Rangel 1999 [16]	0.05	0.03–0.07
Rocchi 2014 [27]	0.05	0.03–0.07
Schauwvlieghe 2018 [36]	0.04	0.03–0.07
Schroeder 2020 [41]	0.05	0.03–0.07
Serrano 2013 [49]	0.05	0.03–0.07
Ulrych 2020 [42]	0.05	0.03–0.07
Waldeck 2020 [43]	0.05	0.03–0.07
Xia 2019 [39]	0.05	0.03–0.07
Xie 2008 [18]	0.04	0.03–0.06
Zhang 2022 [47]	0.05	0.03–0.07

Regarding fungal species, invasive aspergillosis emerged as the most frequently reported IFI in our review, with a pooled prevalence of 10%, followed by invasive candidiasis at 3%. This pattern contrasts with historical trends favoring candidiasis and highlights the growing recognition of Aspergillus spp. in non-neutropenic critically ill patients. The increased burden is likely influenced by the rise in conditions such as viral ARDS (notably from influenza and SARS-CoV-2), COPD, systemic corticosteroid use, solid tumors, and use of immunomodulatory therapies like ibrutinib [54, 59].

A key strength of this meta-analysis is its provision of consolidated, globally relevant prevalence estimates. These findings highlight the need for increased clinical awareness and improved diagnostic strategies in ICUs, particularly in settings with limited resources. The implementation of standardized diagnostic criteria and regionally adapted surveillance protocols could enhance early detection and improve outcomes.

Limitations

This study has several important limitations. First, high statistical heterogeneity was observed across the included studies. A major contributor to this heterogeneity was the variability in IFI definitions. Some studies relied on microbiological evidence alone (e.g., positive blood cultures for Candida spp.), while others applied composite criteria such as EORTC/MSG or the AspICU algorithm, incorporating clinical, radiologic, and microbiological components. These inconsistencies may result in misclassification, thereby affecting the accuracy of the pooled prevalence.

Nevertheless, the statistically significant Egger's test warrants caution, as it suggests the potential presence of small-study effects or selective reporting. However, it is important to note that a significant Egger's test often reflects substantial between-study heterogeneity—rather than true publication bias—particularly when studies vary widely in design, population characteristics, and

regional prevalence. These findings highlight the need to interpret the pooled prevalence with an understanding of the underlying methodological variability and resource disparities across studies, which may introduce inherent biases into the available literature.

Second, the diagnostic tools and practices used across studies varied significantly. The diagnosis of IFI remains challenging due to its nonspecific clinical presentation, low sensitivity of serum biomarkers, and delays in culture-based identification. Furthermore, invasive procedures like bronchoalveolar lavage or tissue biopsy are often required but not always feasible, especially in unstable ICU patients or in low-resource settings. These limitations increase the likelihood of under-diagnosis and under-reporting, particularly in lower-income regions.

Third, microbiological data alone may not reliably distinguish colonization from true invasive disease. In the absence of confirmatory diagnostic tools, reliance on culture results can lead to overestimation of prevalence, especially in studies lacking access to advanced diagnostics such as galactomannan or β-D-glucan testing.

Fourth, the generalizability of our findings is limited by the geographical distribution of studies. The majority originated from high- and upper-middle-income countries, with only two studies representing lower-middle-income settings. This limits the external validity and hinders our ability to draw strong conclusions about global trends or to inform guidelines applicable to resource-constrained regions.

Lastly, some populations, such as pediatric patients and those with COVID-19, were underrepresented or excluded, which restricts the applicability of our findings to these important subgroups.

Conclusions

The current systematic review and meta-analysis showed that IFI has a low prevalence in the general population with extremely high heterogeneity. Given the substantial heterogeneity across studies (as indicated by the I2 statistic and the wide variability in individual effect sizes), the pooled prevalence estimate should be interpreted with caution. This heterogeneity suggests that the underlying populations or methodologies differ significantly, limiting the generalizability and robustness of the overall estimate. In addition, there is variability in criteria for defining IFI, which implies unifying concepts for decision-making in the hospital setting, thus reducing the error of not differentiating between colonization and fungal infection and obtaining real data. Consequently, the global prevalence reported should be interpreted with caution and further context-specific analyses are warranted.

Abbreviations

IFI	Invasive Fungal Infection
ICU	Intensive Care Unit
CI	Confidence Interval at α = 0.05
RoB	Risk of Bias
PC	Personal Computer
MInCir-Pr2 Scale	Metodología de Investigación en Cirugía—Prognosis Studies Assessment 2nd Version
JBI	Joanna Briggs Institute
COVID-19	Severe acute respiratory syndrome 2, SARS-CoV-2 Virus, Coronavirus Disease of 2019
EORTC/MSG	European Organization for Research and Treatment of Cancer and the Mycoses Study Group
EPCAN	European Primary Care AIDS Network
SD	Standard Deviation
SOFA	Sequential Organ Failure Assessment
APACHE	Acute Physiology and Chronic Health Evaluation
IQR	Interquartile Range
AsplCU	Acute Severity and Physiological ICU criteria
ARDS	Berlin Definition of Acute Respiratory Distress Syndrome
COPD	Chronic Obstructive Pulmonary Disease
BAL	Bronchoalveolar Lavage Fluid

Supplementary Information

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Supplementary Material 1.

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Clinical trial number

Not applicable.

Authors' contributions

Authors' contributions: LF, MT, JM, MFG designed and conducted the independent literature search and eligibility review. MT, JM, MFG, HA, YY extracted data from included studies. The Joanna Briggs Institute Criteria to assess risk of bias was conducted independently by YY and HA, with MFG as an independent third reviewer in case of conflicts. The statistical analysis was coded and reported by LF, DC, and YY. The first draft of the manuscript was written by MT, JM, CP, and MFG. All authors were involved in commenting, reviewing and approval of the final manuscript.

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Data availability

Data is provided within the manuscript or supplementary information files.

Declarations

Ethics approval and consent to participate

Ethics approval and consent to participate were not required as no patient information was collected or analyzed.

Consent of publication

Not applicable as no patient data was used.

Competing interests

The authors declare no competing interests.

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