



# Worldwide prevalence of fungal coinfections among COVID-19 patients: a comprehensive systematic review and meta-analysis

Saber Soltani<sup>1,2</sup> , Milad Zandi<sup>1,2</sup> , Samireh Faramarzi<sup>3</sup> , Ramin Shahbahrami<sup>2</sup> ,  
Mohebat Vali<sup>4</sup> , Sara Akhavan Rezayat<sup>5</sup> , Reza Pakzad<sup>6,7</sup> , Pooneh Malekifar<sup>8</sup> ,  
Iraj Pakzad<sup>9</sup> , Neda Jahandoost<sup>10</sup> , Jalal Moludi<sup>11</sup>

<sup>1</sup>Department of Virology, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran

<sup>2</sup>Research Center for Clinical Virology, Tehran University of Medical Sciences, Tehran, Iran

<sup>3</sup>Razi Vaccine and Serum Research Institute, Agricultural Research, Education and Extension Organization (AREEO), Karaj, Iran

<sup>4</sup>Student Research Committee, Shiraz University of Medical Sciences, Shiraz, Iran

<sup>5</sup>Department of Management & Health Economics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran

<sup>6</sup>Department of Epidemiology, Faculty of Health, Ilam University of Medical Sciences, Ilam, Iran

<sup>7</sup>Health and Environment Research Center, Ilam University of Medical Sciences, Ilam, Iran

<sup>8</sup>Department of Epidemiology, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran

<sup>9</sup>Department of Microbiology, Faculty of Medicine, Ilam University of Medical Sciences, Ilam, Iran

<sup>10</sup>Department of Microbiology, Faculty of Science, Islamic Azad University, Sanandaj, Iran

<sup>11</sup>School of Nutrition Sciences & Food Technology, Kermanshah University of Medical Sciences, Kermanshah, Iran

## ABSTRACT

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### Corresponding author:

Reza Pakzad

Department of Epidemiology,  
Faculty of Health, Ilam University  
of Medical Sciences, Banganjab,  
6939177143 Ilam, Iran

E-mail: rezapakzad2010@yahoo.  
com

### Co-Corresponding author:

Pooneh Malekifar

Department of Epidemiology,  
School of Public Health, Tehran  
University of Medical Sciences,  
Porsina Street, 14156446

Tehran, Iran

E-mail: malekifar1989@gmail.com

Microbial coinfections can increase the morbidity and mortality rates of viral respiratory diseases. Therefore, this study aimed to determine the pooled prevalence of fungal coinfections in coronavirus disease 2019 (COVID-19) patients. Web of Science, Medline, Scopus, and Embase were searched without language restrictions to identify the related research on COVID-19 patients with fungal coinfections from December 1, 2019, to December 30, 2020. A random-effects model was used for analysis. The sample size included 2,246 patients from 8 studies. The pooled prevalence of fungal coinfections was 12.60%. The frequency of fungal subtype coinfections was 3.71% for *Aspergillus*, 2.39% for *Candida*, and 0.39% for other. The World Health Organization's Regional Office for Europe and Regional Office for Southeast Asia had the highest (23.28%) and lowest (4.53%) estimated prevalence of fungal coinfection, respectively. Our findings showed a high prevalence of fungal coinfections in COVID-19 cases, which is a likely contributor to mortality in COVID-19 patients. Early identification of fungal pathogens in the laboratory for COVID-19 patients can lead to timely treatment and prevention of further damage by this hidden infection.

**Keywords:** Coinfection; Coronavirus; COVID-19; Fungi; Meta-analysis

Saber Soltani and Milad Zandi  
contributed equally to this study  
as co-first authors.

## Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel coronavirus, is the causative agent of the recent coronavirus disease 2019 (COVID-19) pandemic [1,2], and it is mainly transmitted by respiratory droplets. The conventional method for diagnosing COVID-19 is a reverse transcription-polymerase chain reaction test [3], but other methods with similar nanotechnology-based strategies can be used for the detection of RNA viruses [4].

Microbial coinfections can increase the mortality rate of COVID-19 patients and lead to prolonged hospitalizations [5]. In particular, fungal coinfections pose a significant threat to COVID-19 patients [6]. Studies have indicated that the detection of fungal coinfections in patients infected with COVID-19 can be difficult and creates a challenging situation when deciding on the proper treatment for these patients; furthermore, fungal coinfections can remain undetectable even after death, thereby skewing estimates of mortality rates [7]. The clinical and radiological features of viral respiratory diseases, such as COVID-19, are similar to those of respiratory diseases caused by fungal pathogens, creating another challenge in diagnosing fungal coinfections [8]. The limited sensitivity of fungal pathogen detection tests is a real problem in identifying fungal pathogens, as exemplified by reports that approximately 50% of *Candida* infections are not detectable by blood culture [9]. Various studies have noted that coinfections with fungi such as *Aspergillus* and *Candida* can increase mortality rates, especially in critically ill patients [10] such as those hospitalized in critical care wards with COVID-19. Therefore, the prevalence of fungal coinfections in COVID-19 patients should be routinely monitored [10]. In the context of monitoring different types of coinfections among COVID-19 patients, this study aims to identify the prevalence of fungal coinfection. Our goal is to provide evidence that will be valuable for identifying coinfections in COVID-19 patients and help clinicians to provide suitable treatments, especially in the early stages of the disease.

## Materials and Methods

This study was registered in the International Prospective Register of Systemic Reviews (CRD42021240030, [https://www.crd.york.ac.uk/prospero/display\\_record.php?RecordID=240030](https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=240030)) [11]. All required steps of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) protocol were conducted (Suppl. 1). We applied the keywords: COVID-19, coronavirus, SARS-CoV-2 infection, SARS-CoV-2, polymicrobial infection, fungal AND coinfections, fungal

AND secondary infections, and mixed infections for all included studies.

### Literature Search

An in-depth search without language restrictions was performed to find related articles in Web of Science, Medline, Scopus, and Embase. Other databases such as MedRxiv and Social Science Research Network (SSRN) were also reviewed to enhance the accuracy of the search and to obtain any other associated articles. The search period was December 1, 2019, to December 30, 2020. We used Medical Subject Headings (MeSH) keywords for searching the databases. The patient, intervention, comparison, outcome (PICO) framework was applied in this article, as described below for Medline, following the suggestion made by Salvador-Olivan et al. [12]: population/patient: COVID-19 patients; intervention/exposure: none; comparison: none; outcome: fungal coinfection.

The search strategy (Box 1) and keywords used for database searches (Box 2) are available in Suppl. 2.

In addition, we used Google Scholar to explore the gray literature, had a mycologist identify important research, and manually searched reference lists to find related articles. All extracted articles were exported to Endnote ver. X6 and duplicate articles were removed. The screening process was conducted in 3 phases. Articles were first reviewed by title, then by abstract, and finally the full texts were reviewed. To gain access to articles with data that were not publicly available, emails were sent to the corresponding authors. Articles with no response from the corresponding author were excluded. Two independent raters reviewed the 3 phases independently. A third evaluator resolved any inter-rater discrepancies. Study selection processes were conducted based on blinding and task separation. The kappa coefficient for the inter-rater agreement was 94%.

### Inclusion and Exclusion Criteria

Epidemiological research assessing the prevalence of fungal coinfections among COVID-19 cases was recorded without restriction. We excluded case-control studies, clinical trials, and review studies. We also excluded case reports and case series studies with sample sizes less than 10.

### Data Extraction

The author's name, type of study, year of the study, country, sample size, subjects' age and sex, the number of subjects, and fungal species were recorded from the eligible articles. Patients confirmed to have COVID-19 and fungal coinfection were included in the study.

### Variable Definition

We classified the fungal coinfections based on transmission mode and clinical features. The World Health Organization (WHO) regional classification, which included the Regional Office for Africa, the Regional Office for the Americas, the Regional Office for the Eastern Mediterranean, the Regional Office for Europe, the Regional Office for Southeast Asia, and the Regional Office for the Western Pacific, was used to categorize the countries.

### Quality Assessment

The quality of the studies was evaluated using the Newcastle-Ottawa Scale [13]. Two researchers independently assessed the articles and, for each study, an overall score was determined. The studies were classified as very good, good, satisfactory, and unsatisfactory [14].

### Statistical Analysis

We performed the statistical analysis with Stata ver. 14.0 (StataCorp., College Station, TX, USA). We also extracted the number of COVID-19 infection cases, the prevalence of COVID-19 with fungal coinfection, and the fungal species. The Cochran Q test was used to identify heterogeneity as quantified by the  $I^2$  index, with  $I^2 > 0.7$  indicating high heterogeneity. “Metaprop” commands were applied in a forest plot to estimate the pooled prevalence with a 95% confidence interval (CI). A random-effects model was used to estimate the pooled prevalence [15–20]. Meta-regression analysis was used to evaluate the effect of the WHO region, sample size, and age on heterogeneity. The “metabias” command was used to evaluate publication bias. We adjusted the prevalence rate with the “metatrim” command, using the trim-and-fill method if there was publication bias. Statistical significance was indicated by a  $p < 0.05$ .

## Results

Medline, Scopus, Web of Science, and Embase searches resulted in 1,010 studies, and 41 articles were obtained from other sources. After removing duplicate papers, 510 studies remained. During the first round of screening, 301 studies were excluded, 114 studies were excluded in the second round, and 87 studies were excluded in the third round, leaving 8 studies [21–28] with a sample size of 2,246 cases. Figure 1 shows the selection process flow chart. The different features of the studies are illustrated in Table 1 and more details about coinfections by fungal type are available in Table S1 [21–28]. The European area had the highest number of studies on this subject ( $n=4$ ) and Southeast Asia provided the lowest number of studies ( $n=1$ ). All studies

were published in 2020. Four case series, 1 cohort study, 1 letter to the editor, and 1 cross-sectional study were included in our research.

### Pooled Prevalence of Fungal Coinfections in COVID-19 Patients

Table 1 shows the prevalence of fungal coinfections in the included studies [21–28]. Figure 2 illustrates the prevalence of fungal coinfections in a forest plot [21–28]. Hughes et al. [24] reported the lowest prevalence of fungal coinfections (prevalence, 0.36%; 95% CI, 0.07–1.05) in the United Kingdom and Intra et al. [25], in a study conducted in Italy, reported the highest prevalence of fungal coinfections (prevalence, 31.15%; 95% CI, 19.90–44.29). Figure 2 shows the estimated pooled prevalence of fungal coinfections (prevalence, 12.60%; 95% CI, 7.84–17.36;  $I^2$ , 96.1%;  $p < 0.001$ ). For every 1,000 people infected with COVID-19, 78 to 173 experienced fungal coinfections.

### Pooled Prevalence of Fungal Coinfections Based on Different Subgroups

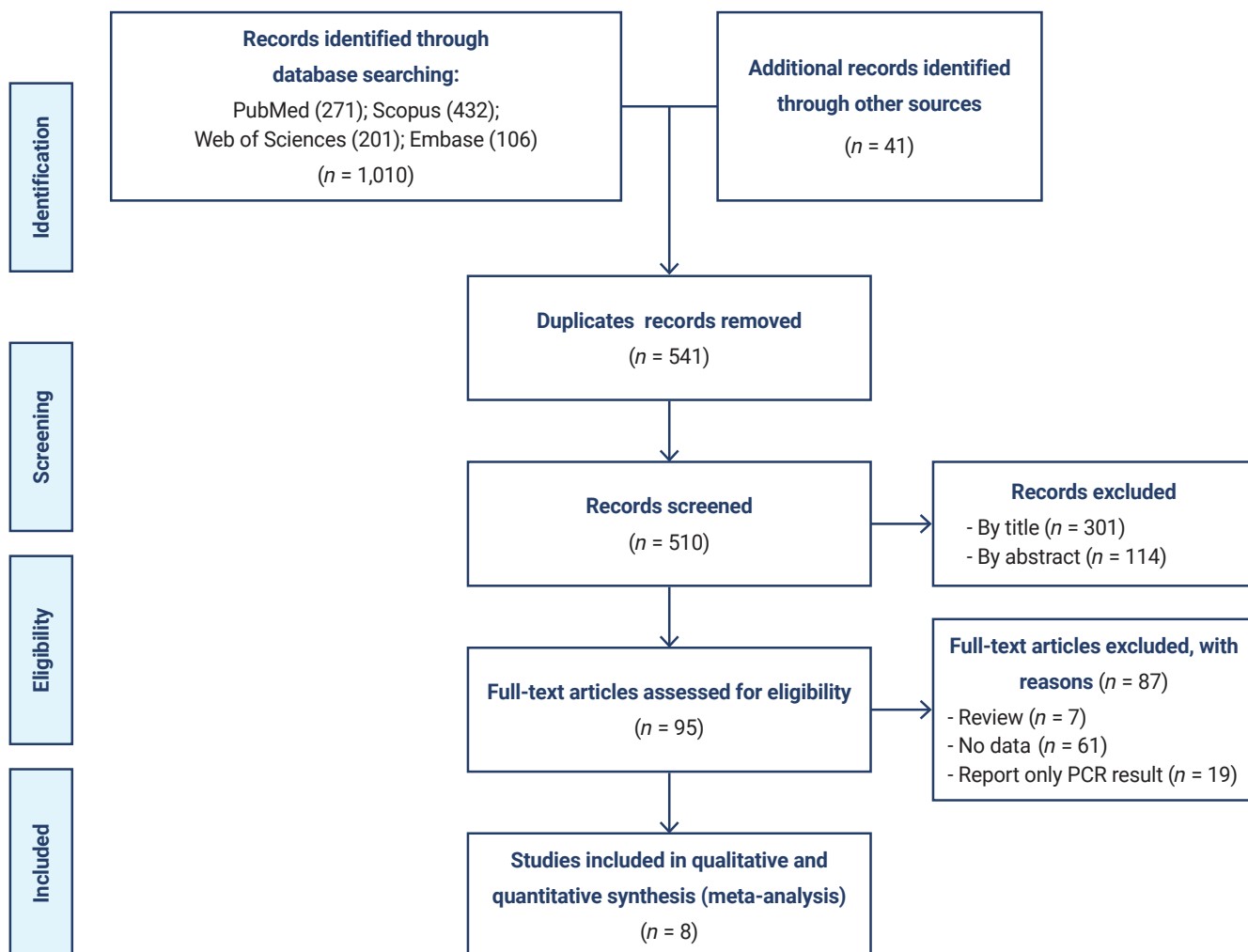
Figure 3 provides prevalence data on fungal coinfections according in detail. The most frequent genus among fungal coinfections was *Aspergillus* (pooled prevalence, 3.71%; 95% CI, 0.54–9.11), with other taxa being the least frequent (pooled prevalence, 0.39%; 95% CI, 0.01–2.15). The pooled prevalence of *Candida* was 2.39% (95% CI, 0.92–4.42). The highest and lowest pooled prevalence of fungal coinfections occurred in the Regional Office for Europe and Regional Office for Southeast Asia regions, with 23.28% (95% CI, 1.67–58.41) and 4.53% (95% CI, 3.01–6.52), respectively. The pooled prevalence for the Regional Office for the Western Pacific is presented in Figure 3.

### Heterogeneity and Meta-Regression

Significant heterogeneity was found among the studies, as shown in Table 2 ( $p < 0.001$ ). The  $I^2$  index for total fungal coinfections and different species was 85%. Meta-regression showed that the WHO region size (coefficient,  $-0.0118$ ;  $p=0.924$ ), sample size (coefficient,  $-0.001$ ;  $p=0.132$ ), age (coefficient,  $-0.0171$ ;  $p=0.110$ ) and quality score (coefficient,  $0.001$ ;  $p=0.297$ ) had no significant effect on the heterogeneity of the studies (Figure 4).

### Publication Bias

The Egger test showed no significant publication bias in the present meta-analysis.



**Figure 1.** Study flowchart based on the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guideline. PCR, polymerase chain reaction.

**Table 1.** Characteristics of studies included in the meta-analysis

Study	Country	Design	Publication year	Mean age (y)	Sample size	Fungal coinfection prevalence (%) (95% CI)
Zhu et al. [21]	China	Retrospective case series	2020	-	257	23.35 (18.31–29.00)
Agrifoglio et al. [22]	Spain	Letter to the editor	2020	58.7	139	10.79 (6.17–17.17)
Chowdhary et al. [23]	India	Cross-sectional	2020	-	596	2.52 (1.41–4.11)
Hughes et al. [24]	United Kingdom	Retrospective case series	2020	69.5	836	0.36 (0.07–1.05)
Intra et al. [25]	Italy	Retrospective case series	2020	-	61	31.15 (19.90–44.29)
Segrelles-Calvo et al. [26]	Spain	Cohort	2021	59.6	215	22.79 (17.36–28.99)
Wang et al. [27]	China	Retrospective case series	2020	73	104	7.69 (3.38–14.60)
Zhang et al. [28]	China	Retrospective cohort	2020	64.76	38	15.79 (6.02–31.25)

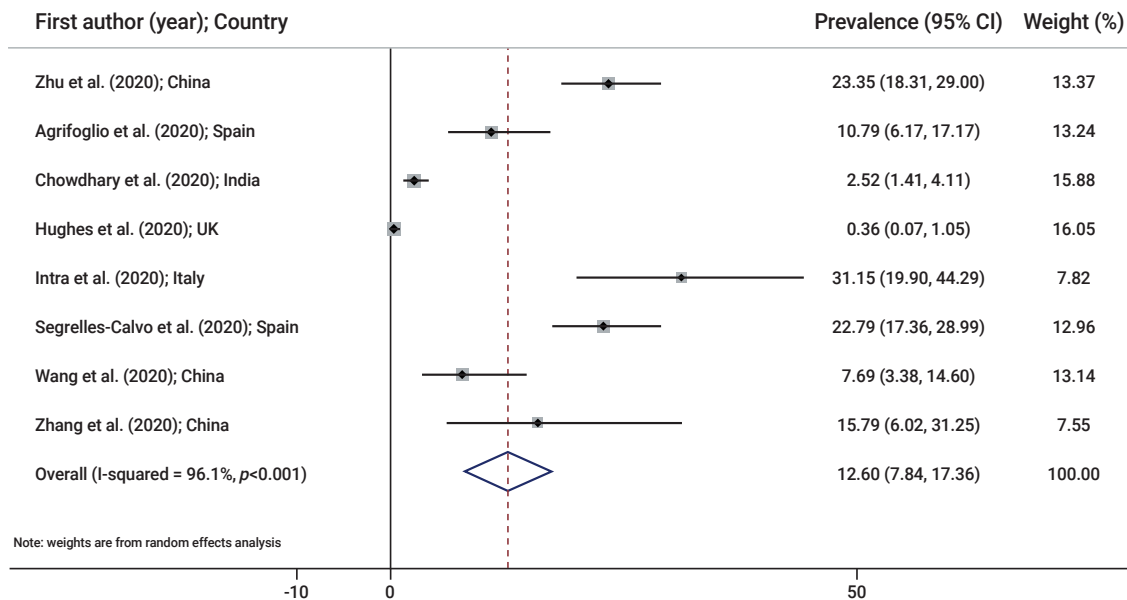
CI, confidence interval; -, not reported.

## Discussion

The fungal microorganisms in hospitals are neglected

factors contributing to the overall health risks of hospitalized patients [29].

Opportunistic infections can often be seen in patients



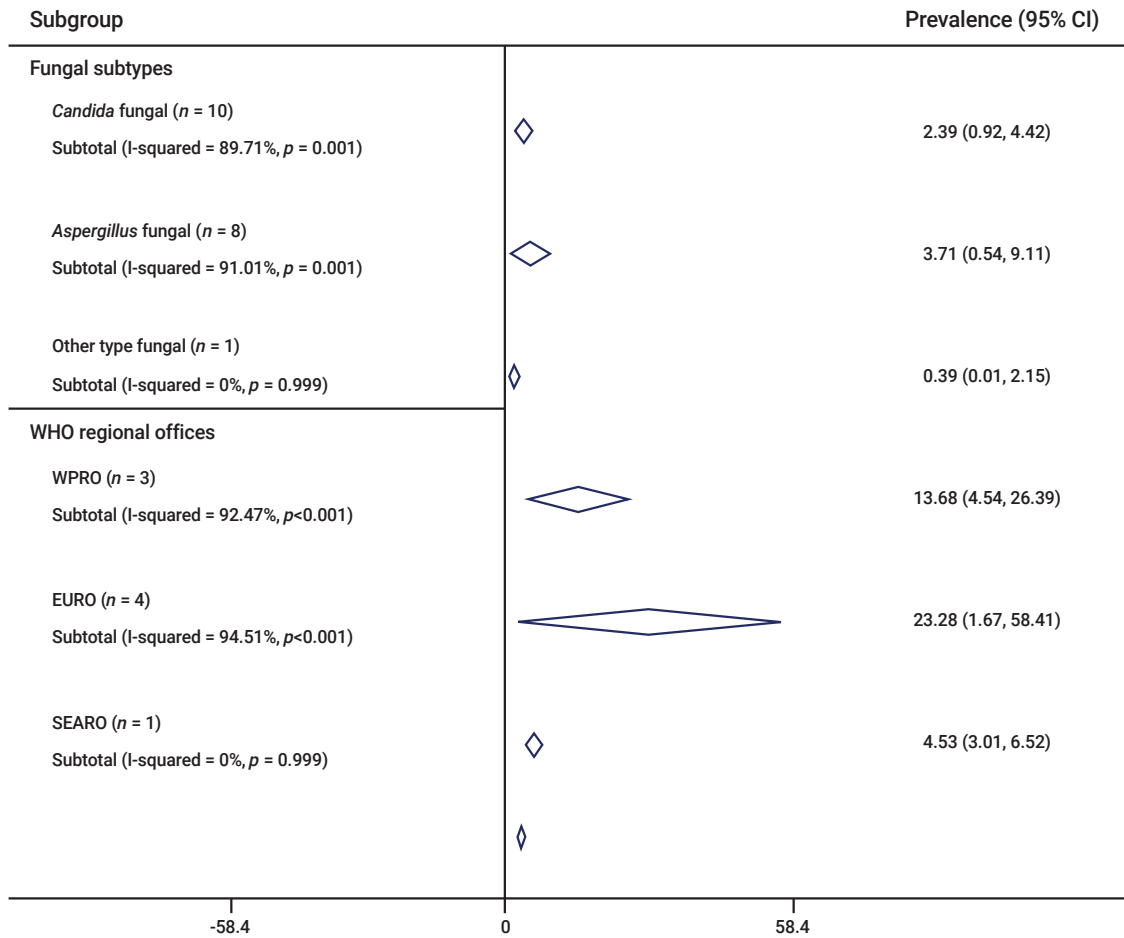
**Figure 2.** Forest plot of fungal coinfections among coronavirus disease 2019 cases. Each study is denoted in terms of author, year, and region. Each line sector's midpoint shows the estimated prevalence, the length of the line segment shows the 95% confidence interval (CI), and the diamond shows the pooled estimate.

infected with respiratory viruses [30]. Microbial agents including *Acinetobacter*, *Klebsiella*, *Enterobacter*, *Aspergillus*, and *Candida* are common causative agents of secondary infections in COVID-19 patients [5]. Invasive fungi play an important role among the different types of microbial pathogens causing coinfections in COVID-19 patients and are associated with increased mortality rates [31]. Invasive fungal infections, including *Candida* and *Aspergillus* infections, are common among immunocompromised patients in critical condition [32]. Respiratory viruses and fungal pathogens have similar clinical features, which may create difficulties for clinicians in their differential diagnosis, especially at the early onset of the disease [33]. For example, diagnosing a blood infection with *Candida* is challenging, even today, because of the low number of pathogens in the infected tissue. An estimated 50% of candidiasis cases cannot be detected by blood culture [34]. This problem is critical because it can interfere with determination of the correct drug to prescribe for patients in the initial stages of the infection [35]. The early detection of COVID-19-associated pulmonary aspergillosis (CAPA) has become problematic. A study in France reported negative serology and culture tests for *Aspergillus* coinfection in COVID-19 patients during the initial stage of the viral infection, and the CAPA was only confirmed after the patients' deaths [36]. This report shows the importance of early detection of fungal coinfections and the impact of a late diagnosis on increasing the mortality rate. Fungemia has

been reported as a complication of SARS-CoV-2 infection [37]. Another risk factor for fungal coinfection could be probiotic consumption, especially in patients admitted to the intensive care unit (ICU). Two patients admitted to the ICU presented with blood infections from *Saccharomyces cerevisiae* after receiving a probiotic supplement. Data suggested that damage to the intestinal mucosal barrier due to the COVID-19 infection created an opportunity for the fungi to relocate from the probiotics to the bloodstream and cause a blood infection. The study suggests avoiding consumption of prophylactic probiotics by COVID-19 patients in the ICU [38]. Central venous catheterization, frequent use of antibiotics, and steroid therapy are risk factors for fungal coinfection [39]. Different types of antifungal treatment have been used to treat COVID-19 patients infected with fungal pathogens. Antifungal drugs including amphotericin B, micafungin, and fluconazole are some of the main drugs prescribed to treat fungal coinfections [5].

Among *Candida* species, *Candida albicans* is the organism most frequently found in critically ill COVID-19 patients. *Candida auris* is the second most common species causing invasive candidiasis [39,40]. Resistance to antifungal therapy is another problem reported in the studies of fungal infection. Multiple studies reported differing percentages of antifungal resistance in *C. auris*. One study indicated that 67% of the patients who died from an invasive *C. auris* coinfection had received micafungin, yet manifested persistent candidemia [23]. *Aspergillus* is another frequent





**Figure 3.** Pooled prevalence with 95% confidence intervals (CIs) and heterogeneity indices of coronavirus disease 2019 fungal coinfection cases based on fungal taxa and geographic area. The diamond shows the pooled prevalence and the diamond length indicates the 95% CI. WHO, World Health Organization; WPRO, Regional Office for the Western Pacific; EURO, Regional Office for the European Region; SEARO, Regional Office for Southeast Asia.

**Table 2.** Meta-regression results for the identification of heterogeneity determinants in the studies

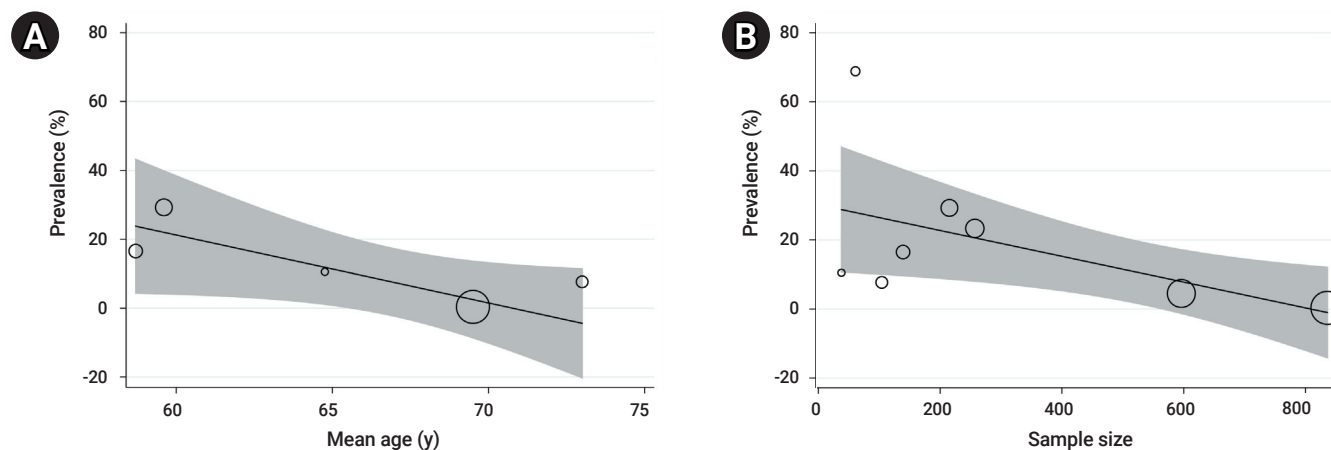
Variable	Coefficient	95% CI	p-value
Age (y)	-0.0171	-0.0414 to 0.007	0.110
WHO region (score)	-0.0118	-0.304 to 0.280	0.924
Sample size (n)	-0.001	-0.001 to 0.001	0.132
Quality score	0.001	-0.002 to 0.002	0.297

CI, confidence interval; WHO, World Health Organization. Coding of WHO regions: Regional Office for the Western Pacific (WPRO), Regional Office for Europe (EURO), Regional Office for Southeast Asia (SEARO).

opportunistic fungal genus. A study conducted in England showed invasive *Aspergillus* infection to be an underestimated danger in COVID-19 patients. Our study showed that COVID-19 patients had a 12.6% coinfection rate with *Aspergillus* [41].

A recent study showed that patients infected with the influenza virus who presented with severe acute respiratory distress syndrome (ARDS), rapidly developed invasive pulmonary aspergillosis (IPA). This finding is concerning because almost 40% of COVID-19 cases develop ARDS and are therefore susceptible to IPA [42]. A study conducted in China reported a 23.3% rate of *Aspergillus* coinfection among COVID-19 patients [21].

Other studies indicated lower rates of *Aspergillus* coinfection among SARS-CoV-2 cases, ranging from 3.2% to 5%. It is crucial to note that none of these articles mentioned the specific diagnostic procedures necessary to confirm the presence of fungal pathogens in patients. This may have been because of low sensitivity or the limited availability of gold standard tests during the studies [42,43]. CAPA has been widely reported in the European region, up to 35% [44]. The



**Figure 4.** The relationship between age (A) and sample size (B) with the prevalence of fungal coinfections using meta-regression. The circle's size indicates the study's precision. There is no significant association of the prevalence of fungal coinfections with age or sample size.

overall mortality rate among reported case series with confirmed CAPA ranged from 44.5% to 66.7% [42]. A meta-analysis performed on fungal coinfection studies reported the overall proportion of fungal coinfections in COVID-19 patients was 0.12%, the overall proportion of *Aspergillus* was 0.06%, and the overall pooled mortality rate was 0.17%. This study also showed a significant difference when comparing ICU cases with mixed hospitalized populations (0.36 vs. 0.06) [45]. Another study reported a 4% fungal coinfection rate among COVID-19 cases and an 8% rate of fungal superinfections [46]. Our results showed more consistency, with a uniformly high prevalence of fungal coinfections among COVID-19 patients. We found that *Aspergillus* was the most frequent fungal taxon in COVID-19 cases and candidiasis the second most frequent fungal coinfection. We also found that the Regional Office for Europe reported the highest coinfection rate (23.28%) and that the Regional Office for Southeast Asia reported the lowest coinfection rate (4.53%). As previously mentioned, the low rate of reported coinfections in Southeast Asia (especially China) could be because there was a lack of detection equipment or the specific or gold standard tests were not performed to detect fungal coinfections. Our results also support the practical use of antifungal treatment, especially in the early stages of COVID-19 infection, to reduce the mortality rate for critically ill patients. It should be noted that the results of some studies were based on small sample populations and therefore do not provide robust evidence from which to draw conclusions.

### Strengths and Limitations

We faced some limitations while performing our analysis. First, we could not conduct a sex-specific estimation

because of limited data in the primary research. Secondly, we estimated the pooled prevalence based on geographical data provided by the WHO. Therefore, our estimations in the spatial analysis of the different geographical areas [47–51] were not robust because of inconsistent study numbers. It should be noted that many of the studies suffered from significant sources of bias, but we assessed the quality of the included studies and considered the effect of the quality score as a source of heterogeneity. The meta-regression analysis showed that the quality score did not affect the pooled frequency estimates. Finally, in many instances, the analysis was based on very few studies. Therefore, the evidence supporting the results is low, and the findings must be interpreted with caution. Nonetheless, strength of this study is that it performed a comprehensive search and meta-analysis to determine the pooled prevalence of different fungal subtypes. Another limitation in our study is the significant heterogeneity and difficulty in interpreting results due to different sets of data, including various regimens, drug doses, durations, center settings, and population samples. The fact that many of the reviewed studies suffered from significant sources of bias should also be taken into consideration.

### Conclusion

Our results showed that 12.60% of COVID-19 patients were infected with fungal pathogens. We also found that *Aspergillus* and *Candida* were the most frequent fungal genera among the patients. Due to the difficulties in detecting fungal coinfections, particularly in the initial stages of COVID-19 infection, we support the routine use of antifungal treatments in COVID-19 patients.

## Supplementary Material

**Table S1.** Details of fungal coinfections in included studies; **Suppl. 1.** PRISMA 2020 checklist; **Suppl. 2.** Search strategy for Medline (MeSH, Medical Subject Headings). Supplementary data are available at <https://doi.org/10.24171/j.phrp.2021.0293>.

## Notes

### Ethics Approval

Not applicable.

### Conflicts of Interest

The authors have no conflicts of interest to declare.

### Funding

None.

### Availability of Data

All data extracted and analyzed during this study are included in this published article. For other data, these may be available through the corresponding author upon reasonable request.

### Authors' Contributions

Study Design and Idea: SS; Conceptualization: JM, NJ, MZ, RS; Data curation: SAR, MZ, SF; Formal analysis: RP, PM, RS; Funding acquisition: all authors; Investigation: IP, SAR, SF; Methodology: RP, PM; Project administration: RS, SS, RP; Resources: JM, NJ, SF; Software: RP, PM; Supervision: IP, MV, SS, RP; Validation: JM, NJ, MV; Visualization: MV; Writing—original draft: all authors; Writing—review & editing: all authors.

### Additional Contributions

I would like to express our very great appreciation to Ilam University of Medical Sciences, Ilam and Tehran University of Medical Sciences, Iran.

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