

Systematic Review

Mucormycosis and Candida Infections in Patients of COVID-19 Pneumonia: A Systematic Review

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Abstract: Introduction: The city of Wuhan in China reported the first case of coronavirus, termed as SARS-CoV-2, in December 2019. To date, 187,827,660 cases have been reported to the WHO (3). With current research focusing on potential therapeutic agents for the coronavirus disease and vaccines, there remain major gaps in our understanding of the pathophysiology and clinical course of this viral pneumonia. Secondary infections are one of them. In this systematic review, we analyze the outcomes of two fungal infections in patients of COVID-19, viz. Mucormycosis and candida. **Methodology:** A systematic review has been done on secondary infections with mucor and candida fungi in patients of COVID-19. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were used. Twenty-three studies were included in the final analysis. Our review included studies from various countries across the globe. The risk of bias was analyzed using the NIH Quality Assessment Tool for Case Series Studies. This study did not require ethical approval as data was obtained from already available databases, and patients were not directly involved. **Results:** A total of 23 articles were included in the final review and the total number of patients included was 79 Male: female ratio was calculated to be 1.6 and the average age of patients was 52 years (ranging from 24-86 years). Various types of comorbidities were seen in the included patients, the most common being diabetes mellitus. Among the 18 patients in the cohort of mucormycosis, 7 patients died and four studies did not report patient outcomes. Among the 61 patients, 13 patients died and one patient was still ventilated at the time of publication. **Conclusion:** Secondary infections after COVID-19 are a cause of major concerns. Further studies and case reports are needed to better understand the various other types of secondary infections and also to formulate strategies to prevent these.

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Keywords: Mucormycosis, Candida, COVID-19, Pneumonia, Systematic Review

1. Introduction

The city of Wuhan in China reported the first case of coronavirus, termed as SARS-CoV-2, in December 2019 [1]. The World Health Organization (WHO) confirmed the coronavirus outbreak as a worldwide public health emergency on January 30th, 2020, and a pandemic on March 11th, 2020 [2]. Till date 187,827,660 cases have been reported to the WHO [3]. This corresponds to a crude case mortality rate of 4.57%. [4,5]

In recent times, cases of co-infections of COVID-19 and various fungal infections have been reported. Various fungi such as mucormycosis, candida, and aspergillosis have been seen to cause infections in patients affected by coronavirus disease. Even though secondary infections are common complications of viral pneumonia, [6] they increase mortality and increase the burden on the healthcare sector.

These fungal infections can be attributed to the use of corticosteroids in the treatment of COVID-19, patients requiring mechanical/invasive ventilation, high use of empirical

antibiotics, and patients having other co-morbidities such as diabetes mellitus. [7,8] Currently, the WHO recommends against prescribing antimicrobials in mild to moderate COVID-19 infections without a clear indication of a super-infection. [9]

These co-infections could be due to different pathophysiological reasons. The severe destruction caused to the lung tissues by the coronavirus is a major factor [7]. Other reasons may be the elevated inflammatory markers in the disease and the decreased T-lymphocyte, CD-4, and CD-8 cell count. [7]

With current research focusing on potential therapeutic agents for the coronavirus disease and vaccines, there remain major gaps in our understanding of the pathophysiology and clinical course of this viral pneumonia. Secondary infections are one of them. In this systematic review, we analyze the outcomes of two fungal infections in patients of COVID-19, viz. Mucormycosis and candida.

2. Methodology

A systematic review has been done on secondary infections with mucor and candida fungi in patients of COVID-19.

2.1. Search Method and Strategy

A systematic search was conducted from COVID-19 inception through June 6th, 2021, for full-length articles focusing on concomitant infections of COVID-19 and two fungal infections (candida and mucormycosis). The search strategy consisted of keywords "Mucormycosis," "SARS-CoV-2," "Candida" and "COVID-19" across the COVID 19 database provided by WHO Global Research Database, CDC COVID-19 Research Articles Downloadable Database, and PubMed database. After a thorough search was performed, full-length articles meeting the inclusion criteria were evaluated. Subsequently, a manual search of the references of the included articles was accomplished. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were used. [10]

The inclusion criteria for the systematic review are as follows:

1. Studies reporting concomitant infection of COVID-19 and fungal infections.
2. Full text, peer-reviewed articles (Meta-analysis, case studies and case series, randomized controlled trials)

The exclusion criteria were as follows:

1. Full texts not available
2. No patient data, laboratory studies, studies done on animal subjects/models
3. Studies pertaining to SARS CoV-1 and MERS

Each study was reviewed by two reviewers independently, and disagreements were resolved via a consensus.

2.2. Data Collection and Analysis

Data was collected in the following categories when available:

1. Study design
2. Study country
3. Patient demographics
4. Site of infection
5. Presenting and alarming symptoms
6. Dissemination
7. Treatment
8. Patient outcomes

Our review included studies from various countries across the globe. The studies used have been listed in [Table 1](#).

We tabulated the data using Microsoft Excel. Referencing was done according to guidelines using Endnote. The included data was checked for accuracy by all authors.

This study did not require ethical approval as data was obtained from already available databases, and patients were not directly involved.

2.3. Risk of Bias

Two authors independently assessed the risk of bias of each study included. All disagreements were discussed with all the authors, and the decision was made via a consensus. Non-randomized studies were evaluated using the NIH Quality Assessment Tool for Case Series Studies. [11] Quality assessments were conducted independently, and discrepancies were resolved by consensus.

3. Results

3.1. Search results

The initial library search identified potentially relevant citations from the WHO Global Research Database, CDC COVID-19 Research Articles Downloadable Database, and PubMed database. It comprised 271 articles. Subsequently, 151 duplicates were removed. A total of 76 articles were excluded after the title and abstract reviews due to not having patient data. The remaining 44 manuscripts were scrutinized further and 21 were further excluded because of unclear evidence and non-relevance to the objective of the review. Thus, twenty-three studies were included in their entirety as shown in Table 1. The PRISMA flow chart is shown in Figure 1.

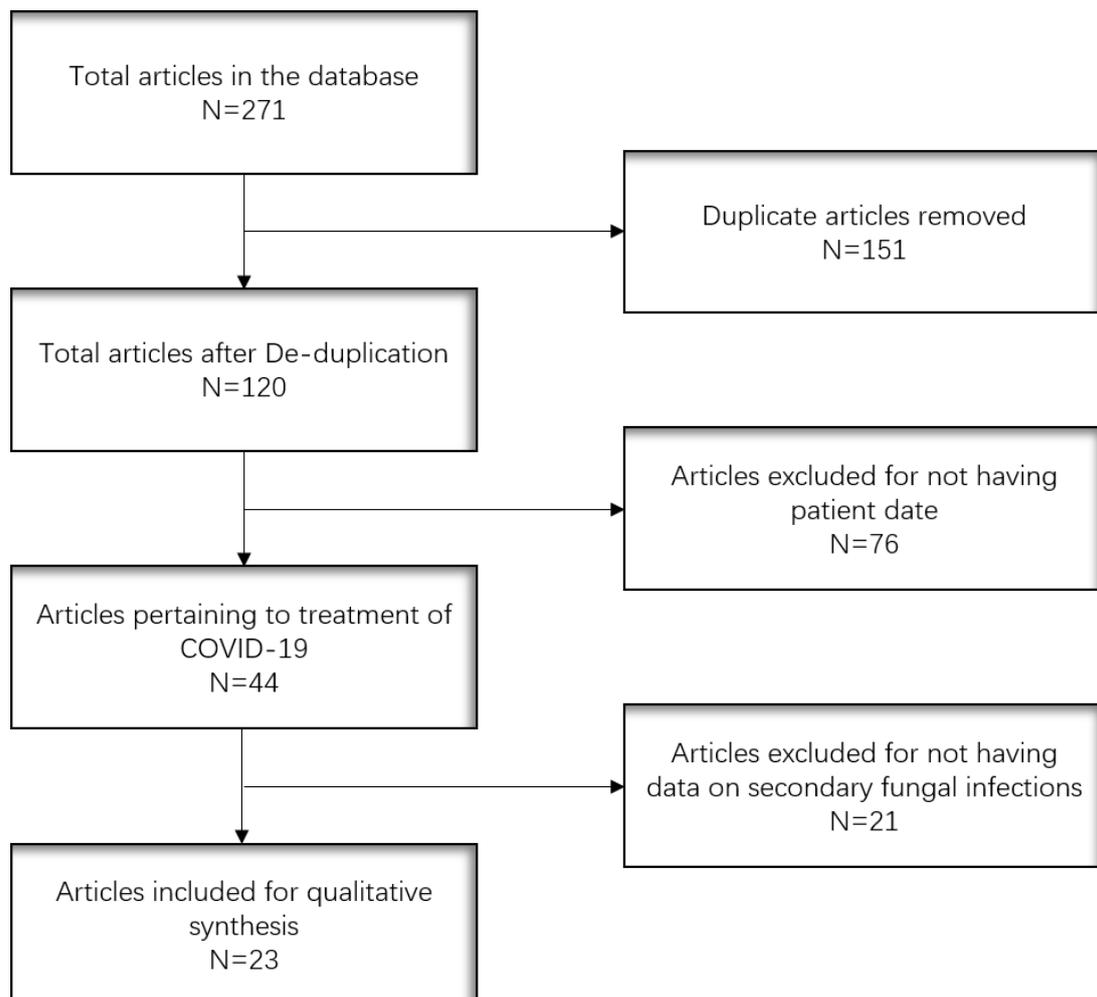


Figure 1. PRISMA flow chart

Table 1. Summary of the included studies

Name of the Study	DOI	First Author
Candida auris outbreak in a COVID-19 specialty care unit—Florida, July–August 2020	10.15585/mmwr.mm7002e3	Prestel, C.
Role of tocilizumab for concomitant systemic fungal infection in severe COVID-19 patient	10.1097/MD.00000000000025173	Anggraini Permata Sari
Increased incidence of candidemia in a tertiary care hospital with the COVID-19 pandemic	10.1111/myc.13225	Nucci, M.
Epidemiology and Mycology of Candidaemia in non-oncological medical intensive care unit patients in a tertiary center in the United States: Overall analysis and comparison between non-COVID-19 and COVID-19 cases	10.1111/myc.13258	Macauley, P.
Post COVID-19 opportunistic candida retinitis: A case report	10.4103/jjo.IJO_3047_20	Bhagali, R.,
Pulmonary Pathology of COVID-19 Following 8 Weeks to 4 Months of Severe Disease: A Report of Three Cases, Including One With Bilateral Lung Transplantation	10.1093/ajcp/aqaa264	Aesif, S.W.
Mixed mold infection with Aspergillus fumigatus and Rhizopus microsporus in a severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) patient	10.1016/j.idnow.2021.01.010	A.-P. Bellanger
Rhinocerebral Mucormycosis and COVID-19 Pneumonia	10.14740/jmc3637	Alekseyev, K.
Rare and Fatal Gastrointestinal Mucormycosis (Zygomycosis) in a COVID-19 Patient: A Case Report	10.5946/ce.2020.180	do Monte Junior ES
Coronavirus disease (Covid-19) associated mucormycosis (CAM): case report and systematic review of literature	10.1007/s11046-021-00528-2	Garg, D
Pulmonary aspergillosis and mucormycosis in a patient with COVID-19	10.1016/j.mmcr.2021.03.006	Johnson, A.K.
A fatal case of Rhizopus azygosporus pneumonia following COVID-19	10.3390/jof7030174	Kanwar, A.
Fulminant mucormycosis complicating coronavirus disease 2019 (COVID-19)	10.1002/alr.22785	Karimi-Galougahi, M.
Mucormycosis after Coronavirus disease 2019 infection in a heart transplant recipient—case report and review of literature	10.1016/j.mycmed.2021.101125	Khatri, A
Sino-orbital mucormycosis in a COVID-19 patient: A case report	10.1016/j.ijscr.2021.105957	Maini, A.
A challenging complication following SARS-CoV-2 infection: a case of pulmonary mucormycosis. Infection	10.1007/s15010-020-01561-x	Pasero, D.
Bronchopleural fistula development in the setting of novel therapies for acute respiratory distress syndrome in SARS-CoV-2 pneumonia	10.1016/j.radcr.2020.09.026	Placik, D.A.
COVID-19 triggering mucormycosis in a susceptible patient: a new phenomenon in the developing world?	10.1136/bcr-2021-241663	Revannavar, S.M.
Paranasal Mucormycosis in COVID-19 Patient	10.1007/s12070-021-02574-0	Saldanha, M.
Rhino-orbital mucormycosis during steroid therapy in COVID-19 patients: A case report.	10.1177/11206721211009450	Veisi, A.

A case of fatal rhino-orbital mucormycosis associated with new onset diabetic ketoacidosis and COVID-19	10.7759/cureus.13163	Waizel-Haiat, S
Mucormycosis with orbital compartment syndrome in a patient with COVID-19	10.1016/j.ajem.2020.09.032	Werthman-Ehrenreich, A.
The double-edged sword of systemic corticosteroid therapy in viral pneumonia: A case report and comparative review of influenza-associated mucormycosis versus COVID-19 associated mucormycosis	10.1111/myc.13256	Kazem Ahmadikia

3.2. Study characteristics

A total of 23 articles [12–34] were included in the final review with six studies [12,16,23,25,28,31] describing candida and the rest describing mucormycosis. The total number of patients included was 79 (61 from the candida infection pool and 18 from mucormycosis). Male: female ratio was calculated to be 1.6 and the average age of patients was 52 years (ranging from 24–86 years). All of the patients included were tested positive for COVID-19 by RT-PCR.

Various types of comorbidities were seen in the included patients, the most common being diabetes mellitus. In the cohort of patients with diabetes, the most commonly found type was Type 2 DM, although a few cases of Type 1 DM were also noted. [14,32] Two cases of diabetic ketoacidosis were also seen and reported. [14,33] These two cases were seen in patients diagnosed with mucormycosis. Hypertension, chronic kidney disease, immunosuppression, and cardiac abnormalities were noted in patients of both mucormycosis and candidemia. One patient was a previously diagnosed case of follicular lymphoma [15] and one was a case of CLL [12].

A summary of the demographic features of the patients is included in [Table 2](#).

Table 2. Demographic features of patients.

Total number of patients	79
Male: female ratio	1.6
Average age	52 years
Age range	24–86 years
All of the patients included were tested positive for COVID-19 by RT-PCR	

3.3. Outcomes

3.3.1. From the cohort of patients diagnosed with mucormycosis:

The most common site of presentation of mucormycosis was pulmonary as seen in six out of the 18 total patients.

[15,18–20,26,27] This was followed by rhino-orbital, [21,32,33], sino-orbital, [24,29,34] and rhino-cerebral [14,30,32] presentation with three patients in each group. Fever, malaise, shortness of breath, and cough were the predominant symptoms found in almost all patients. One patient presented with altered mental status [34] and one patient presented

with left-sided facial pain. [29] A bronchopulmonary fistula was found in one of the patients presenting with pulmonary mucormycosis. [27] Ophthalmoplegia was noted in three of the patients. [29,30,34] The patient with infection in the GI tract had a history of both melena and upper GI bleeding and hence presented with severe anemia. [17] Six patients from the cohort were found to have disseminated infections, [20–22,26,29,32] while others had a localized infection. Eschar formation was also present in five patients. [14,17,17,21] One patient who presented with pulmonary mucormycosis [20] and the patient with cutaneous presentation [22] received convalescent plasma. Nine patients underwent surgical treatment, while one patient underwent an upper GI biopsy for diagnosis. [17] Orbital exenteration had been offered to one of the patients but she refused. [32] Two patients had also received IL-6 inhibitor drugs, [20,27] while another patient had received an interferon-alpha inhibitor. [21] Patients with cutaneous presentation received mycophenolate and tacrolimus. [22] All of the patients received antifungal therapy with two patients receiving it before the diagnosis of mucormycosis [22,24] and the rest after. Among the 18 patients, 7 patients died and four studies did not report patient outcomes.

3.3.2. Outcomes from the cohort of patients diagnosed with candida:

Candida infection was found mostly in the bloodstream - seen in 57 out of the 61 patients. [23,25,28,31] Three patients had the infection in their respiratory tract, [12] and one patient presented with features in bilateral eyes. [16] The infection was noted mostly as worsening of clinical and laboratory parameters of COVID. A few patients did not have signs and symptoms of candida, but it was confirmed microbiologically. One patient presented with progressive decreasing vision in bilateral eyes. [16] Three patients from the cohort were found to have disseminated candida infection, [12] while others had a localized infection. The same three patients also received convalescent plasma therapy and underwent surgeries. One of these patients underwent a lung transplant. [12] Anticoagulation was achieved mainly by enoxaparin and dexamethasone was the steroid of choice in most of the patients. 26 out of the 61 patients received antibiotics [12,16,23,31] and two of the patients received anti-fungal treatment. [16,31] Four patients had also received IL-6 inhibitor drugs. [12,16,31] Among the 61 patients, 13 patients died and one patient was still ventilated at the time of publication.

3.3.3. Risk of bias assessment

Two authors independently assessed the risk of bias for each study included. All disagreements were discussed with all the authors and a decision was made via a consensus. Non-randomized studies were evaluated using the NIH Quality Assessment Tool for Case Series Studies. [11] This is summarized in Table 3. Overall, the risk of bias assessment showed that the included studies had a low to medium risk of bias with every study being of either 'Good' or 'Average' rating.

Table 3. Risk of bias assessment.

Studies	Was the study question or objective clearly stated?	Was the study population clearly and fully described, including a case definition?	Were the cases consecutive?	Were the subjects comparable?	Was the intervention clearly described?	Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?	Was the length of follow-up adequate?	Were the statistical methods well-described?	Were the results well-described?
10.1097/MD.00000000000025173	Yes	Yes	N/A	N/A	Yes	Yes	Yes	N/A	Yes
10.4103/ijo.IJO_3047_20	Yes	Yes	N/A	N/A	Yes	Yes	Yes	N/A	Yes

10.1111/myc.13258	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
10.1111/myc.13225	Yes								
10.15585/mmwr.mm70 02e3	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes
10.1093/ajcp/aqaa264	Yes	Yes	N/A	N/A	Yes	Yes	Yes	N/A	Yes
10.1007/s12070-021- 02574-0	Yes	Yes	N/A	N/A	Yes	Yes	Yes	N/A	Yes
10.1007/s15010-020- 01561-x	Yes	Yes	N/A	N/A	Yes	Yes	Yes	N/A	Yes
10.3390/jof7030174	Yes	Yes	N/A	N/A	Yes	Yes	N/A	N/A	Yes
10.1136/bcr-2021- 241663	Yes	Yes	N/A	N/A	Yes	Yes	No	N/A	Yes
10.1111/myc.13256	Yes	Yes	N/A	N/A	Yes	Yes	No	N/A	Yes
10.5946/ce.2020.180	Yes	Yes	N/A	N/A	Yes	Yes	N/A	N/A	Yes
10.1016/j.ajem.2020.09. 032	Yes	Yes	N/A	N/A	Yes	Yes	N/A	N/A	Yes
10.1002/alr.22785	Yes	Yes	N/A	N/A	Yes	Yes	No	N/A	Yes
10.1177/1120672121100 9450	Yes	Yes	No	N/A	Yes	Yes	Yes	N/A	Yes
10.7759/cureus.13163	Yes	Yes	N/A	N/A	Yes	Yes	No	N/A	Yes
10.1007/s11046-021- 00528-2(0123456789	Yes	Yes	N/A	N/A	Yes	Yes	Yes	N/A	Yes
10.1016/j.id- now.2021.01.010	Yes	Yes	N/A	N/A	Yes	Yes	No	N/A	Yes
10.1016/j.mmcr.2021.03 .006	Yes	Yes	N/A	N/A	Yes	Yes	No	N/A	Yes
10.1016/j.ijscr.2021.105 957	Yes	Yes	N/A	N/A	Yes	Yes	No	N/A	Yes
10.1016/j.radcr.2020.09. 026	Yes	Yes	N/A	N/A	Yes	Yes	N/A	N/A	Yes
10.1016/j.my- cmed.2021.101125	Yes	Yes	N/A	N/A	Yes	Yes	N/A	N/A	Yes
10.14740/jmc3637	Yes	Yes	N/A	N/A	Yes	Yes	Yes	N/A	Yes

4. Discussion

With the increasing use of steroids, and an increase in the hospital stay of COVID-19 patients, secondary infections are being noted much more commonly now. Among these are some fungal infections like mucormycosis, candida infections, aspergillosis, etc. We performed a systematic review about two secondary fungal infections in patients of COVID-19 pneumonia, viz. mucormycosis and candida. Our results showed that both of these infections were seen in many COVID-19 patients and increased ICU admissions and mortality. Almost all of the included patients had one or more comorbidities, the most common being diabetes mellitus and immunosuppression.

It has been known for a long time that viral respiratory tract infections predispose patients to secondary bacterial infections. A commentary by Vaillancourt et. al. published in August 2020 found that 30% of patients were diagnosed with secondary bacterial infections during the first Sars-CoV outbreak in 2003. [35] COVID-19 is no exception. Many cases from around the world have been identified wherein patients have a worse outcome with superimposed infections. [36] Bengoechea and colleagues [37] and Manna et.al. [38] mentioned various important mechanisms of the molecular pathogenesis of secondary infections in COVID-19. Damage caused by the virus to the respiratory epithelium, the antagonizing of the interferon response by the virus, and effects of the virus on both the adaptive as well as innate immunity could be some important mechanisms. Zang et al in their large cross-sectional study found that nearly 58% of the included COVID-19 patients developed secondary infections. [39] Another study by Ripa et. al. found secondary infections in 9.3% of their patients. [40]

Hence, secondary infections should always be considered in patients with worsening clinical and laboratory features. Presenting with alarming symptoms and worsening of COVID, these infections can lead to ICU admissions, mechanical ventilation, and also mortality. Further studies and case reports are needed to better understand the various other types of secondary infections and also to formulate strategies to prevent these.

By comparing the two most commonly found fungal infections in COVID-19 patients, we present a narrative synthesis that brings to light a relatively new but rather important concern. Our review includes studies from across the globe and includes a diverse group of population. Also, the analysis relies on shared subjectivity rather than objectivity so that the results can be generalized to a larger population. However, our study does have limitations. We summarized large amounts of varying information in terms of single numbers and this could ignore essential differences between studies. Also, we saw a significant amount of heterogeneity in our studies which could be due to different geographical locations of the studies, each location having a different set of management guidelines. We were also unable to pool data or run a meta-analysis of our findings due to the vast heterogeneity. The number of patients included in our review is few. Our analysis relied on data from case reports and case series which could have publication biases.

5. Conclusion

Secondary infections after COVID-19 are a cause of major concerns. With an increased time of hospitalization of COVID patients and increasing use of steroids, secondary infections should always be considered in patients with worsening clinical and laboratory features. Presenting with alarming symptoms and worsening of COVID, these infections can lead to ICU admissions, mechanical ventilation, and also mortality. Further studies and case reports are needed to better understand the various other types of secondary infections and also to formulate strategies to prevent these.

Conflicts of Interests - The authors declare no conflicts of interests

Ethics approval - An ethical board approval was not required as data was obtained from already available sources and direct patient contact was not present

Consent to participate - Not applicable

Consent for publication - The authors consent to publish this work by the journal and transfer all copyrights to the journal and publication house.

Availability of data and material - All data has been included in the manuscript file

Code availability - Not applicable

Author's contribution - Screening: Ishita, Ekta; Data extraction: Ekta, Ishita; Risk of bias assessment: Ishita, Ekta; Data analysis: Ishita; Drafting of the manuscript: Ishita, Ekta

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