Respiratory Fungal Co-Infections in Covid-19 Patients.

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19), caused by a novel coronavirus (SARS-CoV-2), has been known to cause mild respiratory illness to severe pneumonia. During its pandemic, an increase in viral, bacterial, and fungal coinfections was observed. With Candida, Aspergillus, and Mucor species being the primary fungal pathogens causing secondary pulmonary infections. Risk factors such as prolonged immunosuppressive drug use and comorbidities such as diabetes mellitus and solid organ transplantation increase susceptibility to these coinfections.

Objective: The study aimed to determine the incidence of pulmonary candidiasis, invasive aspergillosis, and pulmonary mucormycosis in COVID-19 patients and evaluate various risk factors.

Methods: Lower respiratory samples from COVID-19 patients with suspected fungal coinfections were analyzed microbiologically. Macroscopic features such as the morphology of colonies and microscopic characters such as the presence or absence of septations in hyphae, the arrangement of hyphae, the arrangement of conidiophores and conidia, and the presence or absence of rhizoids on lactophenol cotton blue (LPCB) mounts were used for the identification of molds. Morphology of colony, Gram stain, and germ tube test were used for identification of Candida spp.

Results: Of 1789 suspected cases, 216 (12.1%) showed positive fungal culture, predominantly in males (67.9%). Candida spp. accounted for 62.9% of cases, followed by Aspergillus spp. (22.2%) and Mucor spp. (7.4%), with 7% showing mixed Aspergillus and Candida infections. Non-albicans Candida spp. were the most common Candida spp., followed by Aspergillus flavus, fumigatus, and nidulans, and Rhizopus among Mucorales. All of the COVID-19 patients were under steroid therapy, and 89.8% of patients had immunocompromising conditions, primarily diabetes mellitus (76.2%), followed by hypertension (14%), both diabetes and hypertension (9.3%), and organ transplantation (0.5%).

Conclusion: COVID-19 is associated with a high number of respiratory fungal coinfections, driven by prolonged hospitalization, steroid use, and comorbidities. Careful measures should be adopted by healthcare professionals to minimize the risk of respiratory fungal coinfections and associated fatality.

Keywords: COVID-19, Coinfections, Candidiasis, Aspergillosis, Mucormycosis

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INTRODUCTION

Coronavirus disease 2019 (COVID-19), first identified in Wuhan, China, in December 2019, is a contagious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Since then, it has been an emergency global public health event, a pandemic[1,2]. Illness caused by coronavirus was termed "COVID-19" by the WHO, which is derived from "coronavirus disease 2019". The name was selected to avoid stigmatizing the virus's origins in terms of populations, geography, or animal associations[3]. Over 111 million coronavirus cases have been reported, and over 2.4 million people have died of Covid-19 worldwide[4].

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A wide range of symptoms is often presented by the patients. These may range from asymptomatic cases to mild symptoms such as fever, cough, sore throat, malaise, etc., to pneumonia, acute respiratory distress syndrome (ARDS), sepsis, and multiorgan failure. Patients with comorbidities are known to have higher case fatality rates[5].

SARS-CoV-2, a type of beta-CoV, is accountable for 5%–10% of acute respiratory tract infections. Around 2% of the population are believed to be healthy carriers of the novel coronavirus[6, 7]. Immunosuppression is a common manifestation that occurs following reduction in CD4+ T and CD8+ T cells. This can make COVID patients prone to secondary infections or co-infections[6]. Many bacteria, such as *Streptococcus pneumoniae, Mycoplasma pneumoniae, Legionella pneumophilia, Staphylococcus aureus, Haemophilus influenzae, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa*; viruses, such as influenza virus, rhinovirus/enterovirus, non-SARS-CoV-2 coronavirus, respiratory syncytial virus, parainfluenza, and metapneumovirus and fungal pathogens, such as *Candida*, *Aspergillus*, *Cryptococcus*, and *Mucorales*, have been reported as possible co-pathogens among COVID-19 patients[7].

Fungal co-infections are likely to develop in critically ill patients[8]. Several risk factors, such as ICU admission, corticosteroid therapy, endotracheal intubation, prolonged hospital stays, underlying respiratory diseases, and cytokine storms, along with the damage to the lung tissue, are responsible for an increase in fungal co-infections. Development of fungal infections can be an alarming state during the middle and latter stages of COVID-19[9]. The risk factors for invasive aspergillosis include graft vs.-host disease (GVHD) and its treatment (corticosteroid therapy), lymphopenia, and viral infection. Also, neutropenia, host (underlying malignancy), or transplant (stem cell source) variables often contribute to IA[10].

Several studies have reported fungal co-infections in COVID-19 pneumonia. Around 5% of the patients were found to be infected with *Aspergillus* spp. and *Candida* spp. in a study done by Chen *et al*.[11]. A total of 5 cases of invasive pulmonary aspergillosis (IPA) were described in Germany[12].

In a study done in Spain, fungal co-infection was identified in 0.7% of patients with COVID-19[13]. In another study, 5.8% of critically ill patients were co-infected with *Aspergillus flavus, Aspergillus fumigatus,* and *Candida albicans*[8].

Other than *Candida and Aspergillus*, another fungal pathogen of importance in COVID-19 disease is angio-invasive fungi of the order *Mucorales. Mucorales* cause mucormycosis, which is characterized by rapid development of tissue necrosis. The types include rhino-orbital-cerebral, pulmonary, cutaneous, gastrointestinal, and/or disseminated disease[13].

The overuse of high-dose glucocorticoids and the administration of highly immunosuppressive drugs to treat patients with the coronavirus disease 2019 (COVID-19) are responsible in part for the increasing number of COVID-associated mucormycosis. Prolonged administration of corticosteroids leads to impaired migration, ingestion, and phagolysosome fusion in macrophages. The global incidence rate of mucormycosis in COVID-19 globally varies from 0.005 to 1.7 per million population. Mucormycosis is almost exclusively seen in patients with immunocompromised status. It has been noted that people who are diabetic and have recovered from COVID-19 infection are more predisposed to mucormycosis. Around 85% of people with uncontrolled diabetes develop mucormycosis[13,14].

Fungal infection among SARS patients was 14.8-33%, depending on the severity, and up to 73.7% of patients died[15-17]. Also, fungal infections were shown to complicate ARDS caused by influenza. Studies have shown that SARS-CoV and SARS-CoV-2 belong to the same species and have similar prevalence and biological and clinical characteristics[16].

Based on the experience of SARS in 2003 and the cases of invasive aspergillosis, candidiasis, and mucormycosis combined with severe influenza, it is critically important to pay attention to the probability of COVID-19 accompanied by fungal infections. This study was aimed to highlight the importance of microbiological analysis of the respiratory secretions and possibly guide the treating physician in the management of COVID-19 patients.

METHODS:

We conducted an observational study among all COVID-19 patients above age 18 years admitted to wards or ICUs between April 2020 and February 2022. Non-COVID patients and those who refused to give consent were not included in the study. The study was carried out in the Department of Pulmonary, Critical Care and Sleep Medicine and the Department of Microbiology, Nepal Mediciti Hospital, Saibu, Lalitpur.

Sampling method

Lower respiratory tract samples (sputum, bronchoalveolar lavage, and endotracheal aspirates) were collected from patients, and the samples were sent to the microbiology laboratory for fungal culture and evaluation. Samples suspected of mucormycosis with extrapulmonary involvement were not included.

Procedure

Each sample was inoculated on two tubes of Sabouraud Dextrose Agar (SDA) and incubated aerobically at 260°C and 370°C for 21 days. Study of morphology of colonies on SDA, Gram stain, and germ tube test were applied to identify Candida spp. Similarly, identification of molds was done on the basis of morphology grown on SDA. The remarkable macroscopic features, such as colony diameter, color of conidia, and colony texture, were used for species

identification. Direct microscopy was used for final identification by tease mount using lactophenol cotton blue (LPCB). Microscopic characteristics such as the presence and absence of septations in hyphae, the type of conidial heads, stipes, color and length of vesicles, shape and seriation, metula covering and, size, shape, and color of conidia and mycelia were undertaken. LPCB mounts showing molds with septate hyphae and distinct conidiophores with vesicular heads and phialides were identified as Aspergillus spp., while molds showing broad, non-septate or sparsely septate hyphae with sporangiophores, sporangia, and spores were characterized as Mucor spp.

Data analysis

MS Excel and SPSS 20.0 were used. Data has been presented by number, percentage, mean, and standard deviation (SD).

RESULTS

Over a period of two years, a total of 1789 patients with COVID-19 disease were suspected of having fungal co-infections. Lower respiratory samples (bronchoalveolar lavage, sputum, and endotracheal aspirates) were sent to the lab for fungal culture and evaluation. A total of 216 (12.1%) patients showed positive fungal culture growth (Figure 1, Table 1).

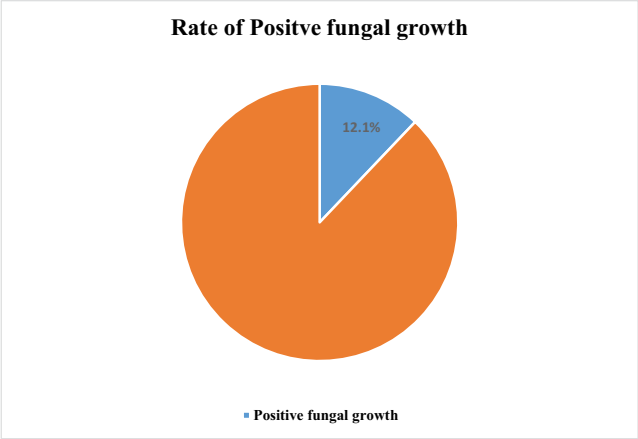

Figure 1. Rate of culture-positive respiratory fungal co-infection among clinically suspected cases of pulmonary mucormycosis in COVID-19 patients.

Table 1. Distribution of COVID cases with fungal co-infection.

Clinically suspected cases of respiratory fungal co-infection	Total number of culture positive cases	Total number of isolated fungal pathogens
1789	216	245

The median age for the patients was 68 years. Men were more likely to have a fungal infection than women and made up 67.9% (n=147) of patients with dual COVID-19 and fungal infections (Figure 2).

Figure 2. Number of males and females with fungal co-infections showing positive fungal growth.

A total of 245 fungal pathogens were isolated from the samples. The two most common pathogens were Aspergillus spp., solely involved in 22.2% of cases, and Candida, solely involved in 62.9% of cases. A total of 16 patients (7%) were found to be infected with both Aspergillus spp. and Candida spp., as shown in Table 2. And a total of 17 (7.4%) patients showed growth of Mucor spp., among which all were isolated from bronchoalveolar lavage.

Table 2. Distribution of culture positive cases co-infected with fungal pathogens.

Number of patients with positive fungal growth	Total number	Percent (%)
No. of patients co-infected with Candida spp. alone	131	62.9
No. of patients co-infected with Aspergillus spp. alone	52	22.7
No. of patients co-infected with Candida and Aspergillus spp.	16	7
No. of patients co-infected with Mucor spp.	17	7.4
Total	216	100.0

A total of 245 fungal pathogens were isolated from 216 samples. Candida spp. were the predominant species (65.3%), followed by Aspergillus spp. (27.8%) and Mucor (6.9%) (Table 3). Non-albicans Candida spp. were the most common Candida spp. Among Aspergillus, A. flavus predominated, followed by A. fumigatus and A. nidulans. While among Mucorales, Rhizopus was the most common isolate, followed by Rhizomucor and Mucor in equal numbers (Table 4).

Table 3. Different fungal pathogens isolated from total cases of respiratory fungal co-infection among COVID-19 patients.

Isolated fungal pathogens	Total number	Percent (%)
Candida spp.	160	65.3
Aspergillus spp.	68	27.8
Mucor spp.	17	6.9

Table 4. Distribution of isolated fungal pathogens.

Isolated fungal pathogens	Candida spp.		Aspergillus spp.			Mucor spp.		
	Candida albicans	Non-albicans Candida (NCA) spp.	A. flavus	A. fumigatus	A. nidulans	Rhizopus spp.	Rhizomucor spp.	Mucor spp.
Subtotal	68	92	44	22	2	11	3	3
	160		68			17		
Total	245							

All of the COVID-19 patients with clinically suspected respiratory fungal co-infections were under steroid therapy. A total of 194 (89.8%) patients co-infected with fungal pathogens had underlying conditions leading to immunocompromising status, while 22 (10.2%) of them had no comorbidity. Diabetes mellitus was the leading comorbidity (76.2%), which was predominantly followed by hypertension (14%), both diabetes and hypertension (9.3%), and organ transplantation (0.5%), as shown in Table 5.

Table 5. Distribution of co-morbidities among patients with culture positive respiratory fungal co-infections.

Culture positive patients (N=216)					
Comorbidities	N	Percentage (%)	No Comorbidities	Number (n)	Percentage (%)
Diabetes Mellitus	148	76.2		22	10.2
Diabetes mellitus and hypertension	18	9.3			
Hypertension only	27	14			
Organ transplantation	1	0.5			
Total	194	89.8		22	10.2

All patients with clinically suspected fungal co-infection were under steroid therapy for more than 4 weeks. A total of 194 patients had some underling medical condition, while 22 of them did not have a history of any comorbidities. The following table shows existing comorbidities among patients with culture positive respiratory fungal co-infections.

DISCUSSION

The current study was conducted in the Department of Microbiology at Nepal Mediciti Hospital for a period of 2 years. A total of 1789 lower respiratory samples were received from patients with COVID-19 suspected of respiratory fungal co-infection, from which 216 samples showed positive fungal growth.

Fungal co-infections in ventilated COVID-19 patients were first reported in China. Cases of COVID-19 associated mucormycosis (CAM) were reported by both America and Europe. CAM cases were also reported by Iran, Bangladesh, Iraq, Pakistan, and other countries[18].

The incidence of fungal co-infections was 6.7% in a study done by Lamichhane et al.[19] in Bhaktapur, Nepal. The burden of diabetes mellitus and its complications related to hyperglycemia may explain the reasons for the significantly higher prevalence of fungal co-infections in low and middle-income countries[18].

Among a total of 216 patients showing positive fungal growth, the majority were male with a median age of 68 years. In a study conducted by Muhammd et al.[20] in Iraq, male had a greater proportion (55.9%) than females, and co-infections with fungi were more common in the 60-69 age group.

A total of 216 samples from the lower respiratory tract showed positive fungal growth from a total of 1789 samples, with a rate of 12.1%. A total of 62.9% (131) of patients were infected with Candida spp. alone, 22.7% (52) of them were solely co-infected with Aspergillus spp., followed by 7% (16) co-infected with both Candida and Aspergillus and 7.4% (17) with Mucor spp.

Among the total 245 isolates, the majority of organisms isolated were Candida spp. (65.3%), followed by Aspergillus spp. (27.8%) and Mucor spp. (6.9%). The number of non-albicans Candida spp. (n=92) was higher than Candida albicans (n=68). This was predominantly followed by Aspergillus flavus (n=44), A. fumigatus (n=22), and A. nidulans (n=2). Among Mucorales, Rhizopus spp. predominated (n=11), followed by Rhizomucor (n=3) and Mucor (n=3). The findings are similar to the studies done by Lamichhane et al[19] in Nepal and Dillirani et al[21] in India. Another literature review suggests similar findings.[18]

Viral respiratory diseases, such as COVID-19, may predispose patients to fungal, bacterial, and other viral coinfections and superinfections[22, 23]. There are several factors that might favor fungal infection and germination in COVID-19 patients.

Some of these include hyperglycemia secondary to diabetes, acidic environment due to diabetic ketoacidosis, steroid treatment, low oxygen perfusion secondary to patient's hypoxemia, steroid-induced hyperglycemia, and/or decrease in anti-microbial action of phagocytic cells secondary to viral immunosuppression. Similarly, prolonged hospital stay and host iron depletion may also contribute. It is believed that fungi can infect and germinate in COVID patients[18, 25].

In our study, all patients clinically suspected of secondary fungal respiratory infections were under steroid therapy. A total of 194 (89.8%) patients co-infected with fungal pathogens had underlying conditions leading to immunocompromising status, while 22 (10.2%) of them had no comorbidity. Diabetes mellitus was the leading comorbidity (76.2%), which was predominantly followed by hypertension (14%), both diabetes and hypertension (9.3%), and organ transplantation (0.5%).

Corticosteroids have both immunosuppressive effects and the risk of causing hyperglycemia among hospitalized COVID-19 patients who are under steroid treatment. Hyperglycemia is often linked to double the risk of coinfection and superinfection in COVID-19 patients. While diabetes increases the risk for various infections, mucormycosis and candidiasis show a particularly strong association with the disease. Therefore, use of corticosteroids, presence of diabetes, and COVID-19 can be a horrifying but favorable triad for fungal co-infections[12]. Also, there was more than a 3-times increased likelihood of the development of invasive fungal infections in patients under steroid therapy compared to patients who were not receiving any. Furthermore, studies show an association of prolonged use of steroids, in particular, with fungal coinfections[25, 26].

Prolonged use of immunosuppressant's can risk patients with solid organ transplants (SOT) having an increased chance of developing symptomatic COVID-19 disease. A COVID-19 incidence of 5% was reported in kidney recipients in a French study by Shafiekhani et al[27]; sixty-six liver and kidney recipients with positive RT-PCR for SARS-CoV-2 were included in this study.

A total of 21% COVID-19 patients with SOT had at least one episode of fungal and/or bacterial co-infections, and a total of 21.2% of patients had 22 episodes of co-infections.

CONCLUSION

The overall rate of culture-positive cases of fungal co-infection among COVID-19 patients was 12.1% in this study. The surge was high during the second wave, which could be due to a sudden increase in the number of COVID-19 cases. Research shows an association of COVID-19 with a high number of secondary fungal infections. The increased use of corticosteroids to minimize inflammation combined with underlying medical conditions such as diabetes mellitus appears to increase the risk of the development of opportunistic fungal infections. This study aims to make physicians and healthcare professionals aware to consider the risk factors and the possibility of coinfections while treating COVID-19 patients. Careful measures should be opted to minimize the dose and duration of corticosteroids, broad-spectrum antibiotics, and other immunosuppressive drugs.

LIMITATIONS

Ideally, histological preparation of lung biopsy tissue observed through microscopy, tissue culture, or PCR is required to confirm invasive fungal diseases. In this study, cultures of respiratory secretions and microscopic analysis of colonies could be done, which can only rule out possible invasive fungal infection (CAPA-Covid-19-associated pulmonary aspergillosis). Also, negative cultures do not rule out invasive candidiasis and/or aspergillosis.

ABBREVIATIONS

ARDS	Acute Respiratory Distress Syndrome
CAPA	Covid-19 associated pulmonary aspergillosis
CD4/CD8	Cluster of differentiation 4/8
GVHD	Graft versus host disease
COVID-19	Coronavirus disease 2019
ICU	Intensive Care Unit
IPA	Invasive pulmonary aspergillosis
LPCB	Lacto-phenol cotton blue
SARS	Severe acute respiratory syndrome
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SDA	Sabouraud Dextrose Agar
SD	Standard deviation
PCR	Polymerase Chain Reaction

AUTHOR'S CONTRIBUTION

AG: study design, data collection, data analysis, supervision, and guidance. **YB**, **SR**, **SB**, and **SKS**: manuscript writing and editing. All authors reviewed the paper and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors read and approved the final manuscript.

ETHICS STATEMENT

The study involving access to human participant samples, analysis, and interpretation was approved by the ethics committee of Nepal Mediciti Hospital. Ethical clearance was taken from NHRC.

CONFLICT OF INTERESTS

We declare that we do not have any conflict of interest.

FUNDING STATEMENT

None

CONSENT FOR PUBLICATION

Written informed consent was obtained from all the patients for publication of their personal and clinical details to be published in the study. The patients provided written consent regarding publishing their disease information in the article.

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