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Fungal Infection in Post Covid Patients, A Tertiary Care Center Experience in Dhaka City

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Abstract
Introduction: *Despite receiving complete treatment and care for Covid-19, many still face complications after successfully recovering from this disease. A significant number of patients need systemic corticosteroid supplements for their oxygen deprivationfrom inflammatory lung injury which may increase the risk of opportunistic fungal infections*
Aim of the study: *The aim of the study was to observe the different types of fungal infection in post-Covid-19 patients*
Methods: *This cross-sectional study was conducted at the Department of Pathology – Anatomic Pathology, Square Hospitals Ltd, Dhaka, Bangladesh. The study duration was 15 months from 1.7.2020 to 30.9.2021. The study sample size was determined as 24, and the participants were selected through a purposive sampling method.*
Result: *The male prevalence was high in the present study, with a male: female ratio of 2.4:1. 33.33% of the participants were from the age group of 61-70 years, and 25% were between the age group of 31-40 years. Pain, nasal obstruction, cough, and fever were the most common symptoms. Respiratory distress and internal bleeding were also observed. Among comorbidities, diabetes was present in 25% and hypertension in 16.67%. Candida was the most common type of fungal infection, followed by Mucormycosis and Aspergillosis.*
Conclusion: *Post-covid patients have a high likelihood of suffering from fungal infections, but patients who receive steroid treatment have a higher likelihood of developing black fungal infection compared to the other types of fungal infection.*

Keywords: *Fungal, Comorbidities, Steroid, COVID, Infection*

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I. Introduction

The COVID-19 disease has had a major impact all over the world since its discovery in 2019. It is a respiratory disease caused by an infection from the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus strain that had its first appearance in Wuhan, China, back in the December of 2019.[1],[2]Several symptoms and complications have evolved and are being reported during the current COVID-19 epidemic.[3] Many researchers have observed an increased risk of acute cardiac injury, arrhythmias, thromboembolic complications, secondary infections, and many more among the patients with Covid-19.[3]According to the information thus far, the cardiopulmonary systems appear to be the source of the majority of postCOVID19 problems. Myocarditis, arrhythmia, and ischemia are the most prevalent cardiac postCOVID19 symptoms, whereas bacterial pneumonia, pneumothorax, and pleural effusion are the most common pulmonary problems recorded. Fatigue, headache, body aches, dyspnea, and anxiety/depression are common systemic post-COVID-19effects.[4],[5]In addition to the Acute Respiratory Distress Syndromes (ARDS) induced by COVID-19, patients were shown to have immunological suppression due to a reduction in CD4+T and CD8+T cells. This causes a wide variety of bacterial and fungal infections, which may co-exist with pre-existing morbidity (diabetes mellitus, lung illness) or arise as a hospital-acquired infection.[6] An infection test performed in China with 99 Covid infected patients found only 5 cases of Aspergillus, one case of candida, and 3 cases of other fungal infections.[7] Aspergillus had the highest prevalence in their study, although the aim of the study was to observe Mucormycosis or black fungal infection among post-covid patients. Mucormycosis is a much rare and more harmful fungal infection compared to Aspergillus, and is caused by a group of molds called mucoromycetes.[8] It is otherwise known as the black fungus, while candida is commonly referred to as the white fungus. Although Aspergillus is generally not seen as a dangerous infection, it can cause great harm in immunocompromised

hosts.[9]In some studies, the incidence of black fungal infection in post-covid patients was reported to be much higher.[10],[11]It has been observed that some forms of medication, especiallysteroids, greatly affect the growth of fungal& bacterialinfections. Steroid therapy has been linked to a reduced response to antifungal drugs, and steroid therapy is a known risk factor for fungal infection.[12]The present study was conducted with 24 cases of post-covid patients from a tertiary hospital, with the goal of observing various fungal infections in our demographic.

II. Objective

General Objective

- To observe cases of fungal infection among post-Covidpatients

III. Methods

This cross-sectional 24 case study was conducted at the Department of Anatomic Pathology, Square Hospitals Ltd, Dhaka, Bangladesh. The study duration was 15 months, from1.7.2020 to 30.9.2021. The study sample size was determined as 24, and the participants were selected through a purposive sampling method.The Tissue biopsy & cytology sampleswereexamined and special stains for fungus, Grocott's methenamine silver (GMS) stain, Periodic acid-Schiff (PAS) stain, and Hematoxylin and eosin (H&E) were done. All the cases were selected based on the inclusion and exclusion criteria, and all necessary data were recorded in a previously prepared datasheet. Informed consent was obtained from the study participants, and ethical approval of the study was also obtained from the ethical review committee of the study hospital.

Inclusion Criteria

- Patients previously diagnosed with Covid-19 by RT- PCR
- Patients free of the coronavirus at the time of study
- Only patients with some form of fungal infection
- Tissue biopsy & cytology samples of the patients sent to anatomicpathology laboratory are examined for fungus.

Exclusion Criteria

- Post Covid patients who had no fungal infection
- Patients who were still undergoing treatment for Covid-19 at the time of the study

IV. Results

The male prevalence was high in the present study, with a male: female ratio of 2.4:1. 33.33% of the participants were from the age group of 61-70 years, and 25% were between the age group of 31-40 years. Pain, nasal obstruction, cough, and fever were the most common symptoms. Respiratory distress and internal bleeding were also observed. Among comorbidities, diabetes was present in 25% and hypertension in 16.67%. Candida was the most common type of fungal infection, followed by Mucormycosis.

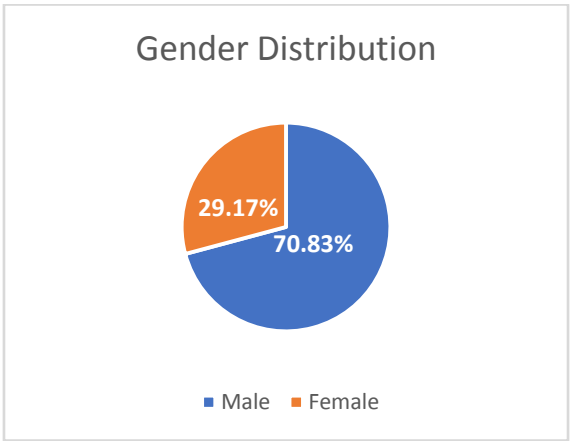


Figure 1: Gender distribution of the participants (n=24)

In the present study, 70.83% were male and only 29.17% were female. The male: female ratio was 2.4:1.

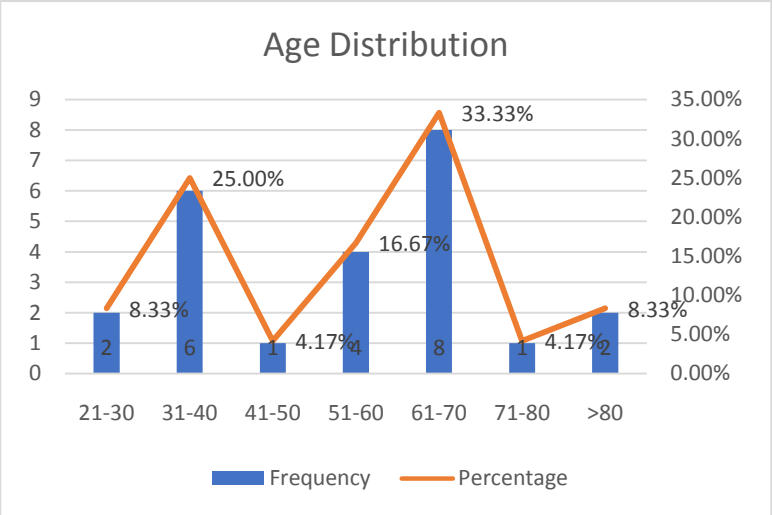


Figure 2: Age distribution of the participants (n=24)

The largest portion of the participants (33.33%) were from the age group of 61-70 years. Majority of the present study participants were over the age of 50, with only 37.5% of participants aged 50 or younger.

Table 1: Presenting symptoms among the participants (n=24)

Symptoms	Frequency	Percentage
Sinusitis	1	4.17%
Pneumonia	1	4.17%
Fever	2	8.33%
Cough	4	16.67%
Headache	2	8.33%
Pain	5	20.83%
Nasal Obstructions	5	20.83%
Respiratory Distress	2	8.33%
Internal Bleeding	2	8.33%
Others	7	29.17%

Nasal Obstructions and pain were the most commonly occurring symptoms among the participants, present in 20.83% of the participants each. 16.67% of the participants had a cough, and 8.33% had a fever. Respiratory distress and internal bleeding were also observed in 8.33% of cases each. Multiple symptoms were present in many of the participants.

Table 2: Presenting comorbidities among the participants (n=24)

Comorbidity	Frequency	Percentage
Chronic Kidney Disease	4	16.67%
Diabetes Mellitus	6	25.00%
Hypertension	4	16.67%
Ischemic Heart Disease	2	8.33%
Heart Failure	1	4.17%
Benign Prostatic Hyperplasia	1	4.17%

Diabetes was the most prevalent comorbidity, present in 25% of the participants. Chronic kidney disease and hypertension were observed in 16.67% of cases each. Ischemic heart disease, heart failure, and benign prostatic hyperplasia were also observed among the patients.

Table 3: Steroid Treatment given to the participants (n=24)

Steroid Treatment	Frequency	Percentage
Glucocorticoid	2	8.33%
Betamethasone	2	8.33%
Methyl Prednisolone	2	8.33%
Dexamethasone	3	12.50%
Notknown	15	62.50%

Among the participants of the present study, majority (62.50%) had no known steroid treatment. Among the remaining,Dexamethasone was used by 12.50%, and glucocorticoid, betamethasone, and methylprednisolone were given to 8.3% of the participants each.

Table 4: Distribution of fungal infections (n=24)

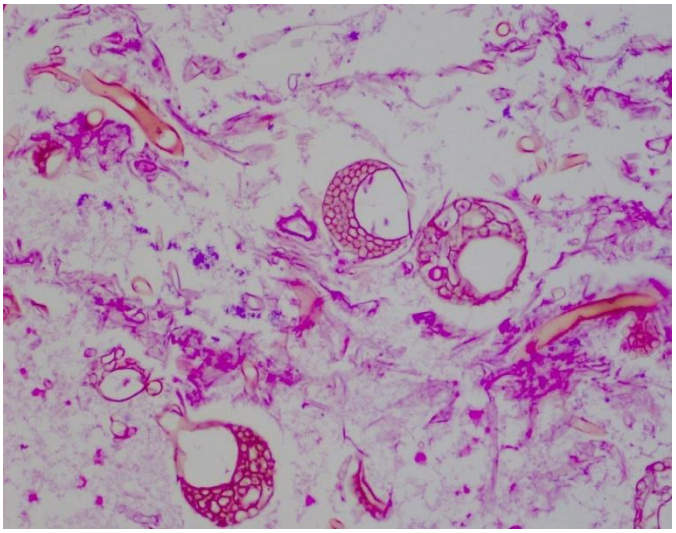
Organisms	Frequency	Percentage
Mucormycosis	6	25.00%
Aspergillus	4	16.67%
Candida	11	45.83%
Actinomycosis	1	4.17%
Aspergillus & Candida	1	4.17%
Aspergillus & Mucormycosis	1	4.17%

In the present study, 4 different forms of fungal infection were present. White fungus (candida) was the most common, present in 45.83% of cases individually, and in 1 patient along with aspergillus. Mucormycosis or black fungus had the second-highest prevalence among the fungal infections, present in 7 cases in total. 25% of the patients had only black fungus, and 4.17% had black fungus along with aspergillus. Aspergillus was also present in 16.67% of cases individually, and in 1 case with black fungus and one with white fungus. The remaining 1 patient had an actinomycosis infection.

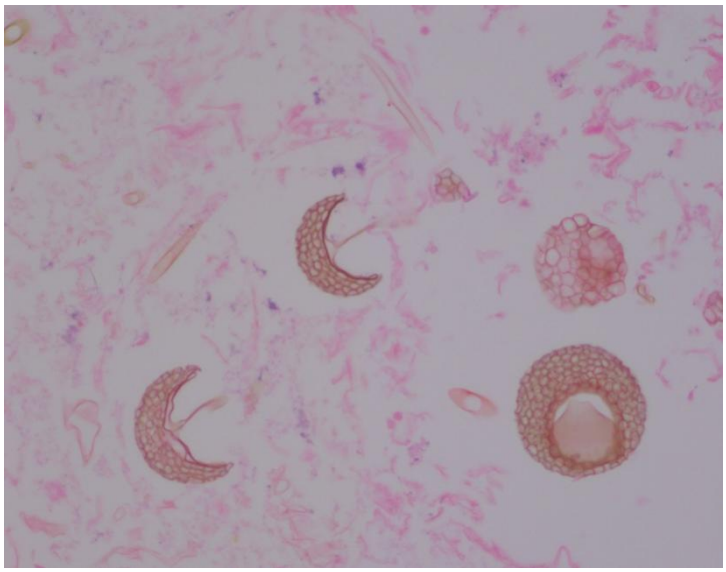
V. Discussion

COVID-19, a contagious respiratory infection caused by severe acute respiratory syndrome–coronavirus 2 (SARS-CoV2), has now expanded worldwide. COVID 19 disease manifests itself in a variety of ways, from asymptomatic to fatal. Fever is most likely one of the disease's most common symptoms.[13] COVID-19 symptoms can last for weeks or months in older persons and people with a variety of serious medical issues, but even young, otherwise healthy people can feel ill for weeks or months following infection. Although COVID-19 is thought to be a disease that mostly affects the lungs, it can also harm other organs such as the heart, kidneys, and brain. Organ damage may result in long-term health problems after COVID-19 infection, like long-term breathing problems, heart complications, chronic kidney damage, stroke, and Guillain-Barre syndrome.[14]This virus is capable of dysregulating the host's immune mechanisms. The impaired cell-mediated immune responsesand overexpression of inflammatory cytokines cause extensive collateral damage,increasing the morbidity and mortality associated with the COVID-19 pandemic. Also, the COVID-19 patients with immunocompromised states like neutropenia, chronic diseases like Diabetes, CKD, inherited immunodeficiencies, tumors, or long-term corticosteroid administration have an increased likelihood of fungal coinfections.[15]Intensively ill COVID- 19 Patients in intensive care units (ICUs) or on mechanical ventilation are more likely to get bacterial or fungal infections.[7],[16] Infected patients have been found to have a higher rate of invasive maxillofacial fungal infections like mucormycosis, candidiasis, and aspergillosis. Understanding secondary infections and their causation are critical for effective patient care. *Candida* species is a frequent inhabitant ofthe oral mucosa, but its growth is inhibited by other organismsin the body that prevents any pathological alteration ofthe mucosa by this fungus.[17]Mucormycosis is a rare and fatal deep fungal infectionoccurring in rare and aggressive forms caused by the familyMucoraceae which is difficult to diagnose.[18]This fungusis a usual commensal of the nasal mucosa. The fungal sporesgerminate into hyphae on entering the tissues of hosts initiatingclinical symptoms and causing infection in immunocompromised individuals with defective phagocytic functions.[19] Fungal spores can germinate in the nasal cavity, paranasal sinuses, palate, orbit, and even

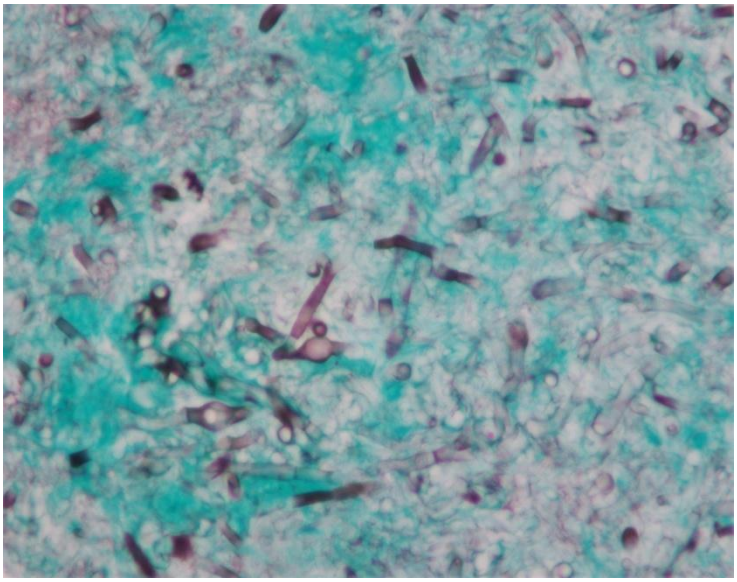
the brain in patients with diabetes, tumor, or those on corticosteroids, leading to death in certain cases.[20]. There are six clinical forms of mucormycosis, the most common being the rhino-Cerebro-orbital form(44–48%) followed by the cutaneous variety (10–19%),then pulmonary (10–11%), disseminated (6–10%) and last being the gastrointestinal form (2–11%).[21],[22]One of the common fungal infections that can cause secondarypulmonary infection in severely immune-compromised patients is Aspergillosis, which is caused by Aspergillus fumigatus.[23]



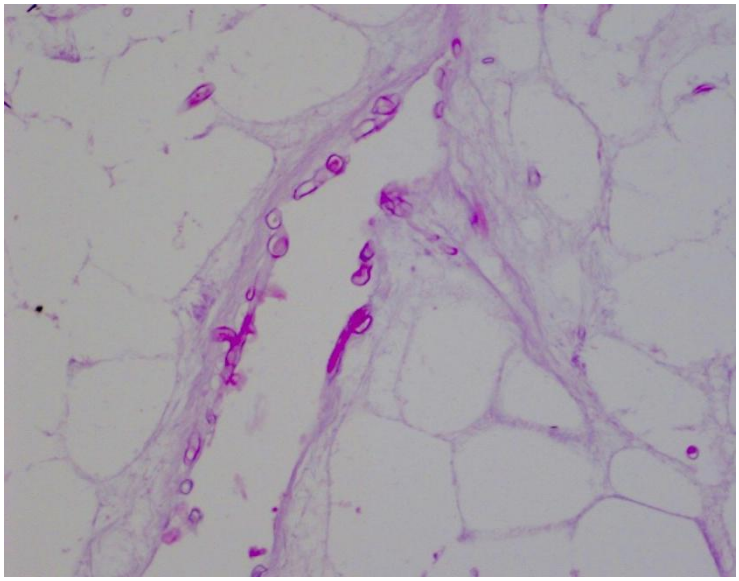
Photomicrograph 1: Mucor sp & spore PAS stain, 40x



Photomicrograph 2: Mucor sp & spore H&E stain, 40x



Photomicrograph 3: AAspergillussp.GMS stain, 40x



Photomicrograph 4: Aspergillus sp, blood vessel invasion,PAS,40x

The present study was conducted with 24 selected cases who had recovered from Covid and were facing various fungal infections. Over 70% of the present study participants were male, with fewer female participants, this might be due to the high prevalence of covid among the male population.[24]Age-wise, the majority of the participants were older than 50 years of age, which was similar to many other covid studies, reaffirming the statement that the elderly are more at risk of Covid.[25],[26] Among the presenting symptoms, pain and nasal obstructions were the highly prevalent ones in our study, but most Covid-related articles found fever and cough to behighly prevalent symptoms. In our study, fever was present in 8.33%, and cough in 16.67%. Diabetes was the most common comorbidity in the present study, observed in 25% of cases, followed by chronic kidney disease and hypertension in 16.67% of cases each. These findings were somewhat similar to a meta-analysis, where hypertension had the highest prevalence.[27]For the majority of the present study participants (62.50%) steroid treatment was not known.For the remaining participants, dexamethasone was used by 12.50%, and glucocorticoid, betamethasone, and methylprednisolone were given to 8.3% of the participants each.Corticosteroid treatments are given to covid patients who require supplementary oxygen in hopes of better clinical outcomes and a reduced mortality rate.[28] But using steroids comes with its own risks. Corticosteroids can produce several tropical, systematic, and clinical complications in the patients.[29] The use of such steroids is a known risk factor for fungal infection. In the present study, 4 different types of fungal infections were observed. Among them, Candia, or the white fungus was the most common one, present in 11 cases individually, and along with aspergillus in one patient. Mucormycosis, or black fungus, had the second-highest

prevalence, present in 6 of the patients individually, and with aspergillus in one patient.While comparing the steroid treatments, 4 out of the total 7 mucormycosis patients (57.1%) received steroid treatment, while 5 out of the total 12 candida patients (41.6%) received steroid treatment. While the remaining patients did not receive any form of steroid treatment but still presented with fungal infection.

Limitations of The Study

The study was conducted in a single hospital with a small sample size. So, the results may not represent the whole community.

VI. Conclusion

Post-covid patients have a high likelihood of suffering from fungal infections, but patients with comorbidities&who receivesteroid treatment have a higher likelihood of developing black fungal infection compared to the other types of fungal infection.

VII. Recommendation

We recommend a multi-center study with a large sample size to get more reliable results for this infection.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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