

Frequency and survival of Covid associated mucormycosis patients at tertiary care hospitals in Pakistan: A retrospective observational study

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Abstract

Background: Mucormycosis is a serious fungal infection associated with uncontrolled diabetes and immunocompromised patients. This angioinvasive infection emerged as a post-covid complication worldwide especially in developing countries. Due to the common socio-demographic status of South Asian countries, we expected a surge in mucormycosis cases in Pakistan. This study aims to observe the frequency and survival of Covid associated mucormycosis patients at tertiary care hospitals in Pakistan during the third wave of Covid-19 in 2021.

Materials and Methods: In this retrospective study, we collected the data of clinically and histopathologically confirmed cases of rhino-occipito-cerebral mucormycosis from three tertiary care hospitals of Lahore. These cases were analysed for history of Covid-19 and other associated comorbidities using SPSS28. History of steroid medication was also taken. Data were retrieved from May to July 2021 after the approval from the ethical review board.

Results: Out of the total 43 reported patients of mucormycosis in the set time frame only 22 cases had a history of Covid-19. The mean age was 50 ± 13.27 years with slight male predilection (60%). Diabetes mellitus was the most common comorbidity (88.4%) and all the patients with covid associated mucormycosis (CAM) had taken corticosteroid regimen for covid management ($p < 0.0001$). The survival of the patient was not significantly different between CAM and non-CAM patients of Mucormycosis ($p = 0.747$).

Conclusion: Covid-19 and mucormycosis make a lethal duo against the weakened health system of Pakistan. This problem can be prevented by avoiding nonjudicial use of corticosteroids and proper diabetes control program following Covid-19 infection. Furthermore, large-scale epidemiological studies should be carried out to evaluate the true burden of Mucormycosis in the population.

KEYWORDS

covid-19, diabetes mellitus, hyperferritinemia, hypertension, mucormycosis, SARS-CoV-2

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1 | INTRODUCTION

Fungal infections (FI) are common in Pakistan due to a significant number of high-risk populations but are mostly under-diagnosed and unreported due to limited surveillance by National Health care system.¹ The recent pandemic of Covid-19 has further precipitated the incidence of opportunistic and deep FIs especially mucormycosis which has emerged as an emergency in the region.² Mucormycosis is an opportunistic fulminant infection caused by saprobic mold growing in a damp environment and can invade the respiratory tract.^{3,4} Although, this is not a contagious disease, immunosuppressed individuals, especially diabetics, organ transplant recipients, and patients with other comorbidities are at risk for such opportunistic infections. Post-covid patients treated with steroids also emerged as a high-risk group of mucormycosis as an aftermath of uncontrolled diabetes mellitus (DM) precipitated by Covid-19. In India, during the second wave of Covid-19 where the health system got saturated with highly infectious delta variant of SARS-CoV-2, spike in mucormycosis was seen.⁵ Contaminated oxygen cylinders and ventilator tubing, in a humid hospital environment further facilitated the spread of infection.⁵ To assess the situation of mucormycosis under this scenario, we conducted a descriptive study on patients presented with rhino-orbital-cerebral mucormycosis (ROCM), one of the most common and lethal type, from June 2021 to August 2021 in three local tertiary care hospitals, after the second wave of Covid-19 in 2021. The objective was to observe the clinical, pathological and demographic presentation of mucormycosis and to find out the history of Covid-19 infections in these patients.

2 | MATERIALS AND METHODS

This was a retrospective observational study. The outcome of interest was covid-associated mucormycosis (CAM). The study population included the clinically and histopathologically confirmed cases of ROCM from the ENT and maxillofacial departments of three tertiary care hospitals of Lahore namely Fatima Memorial Trust Hospital, Sheikh Zayed Hospital and Lahore General Hospital from May 2021 to July 2021. The data of these patients were retrieved after the IRB approval (FMH-09-2021-IRB-947-M). Being a retrospective study it was exempted for Patient's consent and patient's names and hospital ID. numbers were not revealed to protect their privacy. A separate study ID was assigned for each case. Data was verified and entered by two physicians. Mucormycosis patients with pulmonary, gastrointestinal or any other clinical type other than ROCM were excluded from the study. Also, the patients having a co-infection of mucormycosis with any other FI either superficial or deep were excluded as that could have impacted the final outcome of the patient. For patients with Covid-19 positive history, the time interval between Covid-19 infection and Mucormycosis was also noted based on their laboratory reports. Only PCR-confirmed cases of Covid-19 were considered positive. All genders and age groups were included. The total no. of cases of ROCM reported in these hospitals in a given

time frame was 43 only. Patient survival status was taken from hospital discharge reports.

The study protocol was in accordance with the principles of the Declaration of Helsinki following GCP guidelines and was approved by the Institution Review Board of Fatima Memorial Hospital.

2.1 | Statistical analysis

Data were analyzed for the demographic and clinical findings including the history of DM, corticosteroid therapy, other comorbidities and the outcome of the patient using SPSS28. Means and SD were used to summarize continuous variables in line with the properties of the distribution. Categorical variables were expressed as the counts and percentages in each category. The Pearson Chi square test was used to statistically compare two groups for a categorical variable. When the *p* value was less than 0.05, the results were deemed statistically significant (by two tail testing).

3 | RESULTS

Total 43 histopathologically confirmed cases of mucormycosis were reported in these centers in the given time frame as per the available hospital data. The mean age of patients was 50 ± 13.27 years ranging from 15 to 68 years. Male to Female ratio was 3:2 with 26 male and 17 female patients. Out of 43 reported ROCM patients 38 (88.4%) had underlying DM at the time of hospital admission and only 27 (62.8%) patients had received intravenous corticosteroids before Mucormycosis for the treatment of Covid-19 or other comorbidities. Only 22 (51%) patients had positive history of Covid-19. Among these 22 CAM patients, the median time interval between the confirmation of SARS-CoV-2 infection and Mucormycosis was 12 days (2–40) as noted by their PCR and histopathological reports. The median age of CAM (37 years) was lower as compared to non-CAM patients (52 years). The comparison of study variables with Covid-19 is given in Table 1.

Other comorbidities included hypertension 7 (16%), systemic lupus erythematosus 1 (2%), rheumatoid arthritis 1 (2%), chronic obstructive pulmonary disease 2 (5%), and renal transplant 1 (2%) tabulated in Table 2.

The survival of the patient is not significantly different in both groups ($p = 0.747$), hence Covid-19 infection history does not seem to play any role in the prognosis of Mucormycosis.

The clinical, radiographic and histopathological pictures of one of the patients is shown in Figure 1.

4 | DISCUSSION

Mucormycosis is an angioinvasive infection that causes tissue infarction and necrosis.⁶ According to Baldin and Ibrahim,⁷ it is the third most common invasive FI effecting patients with organ

TABLE 1 The relationship of CAM and non-CAM patients with gender, diabetic status, history of steroid intake and outcome of patients.

	History of covid-19		p-value
	Negative (%) non-CAM	Positive (%) CAM	
Gender			
Male	12 (27.9)	14 (32.6)	0.76
Female	9 (20.9)	8 (18.6)	
Diabetic			
No	3 (7.0)	2 (4.7)	0.664
Yes	18 (41.9)	20 (46.5)	
History of steroid intake			
No	16 (37.2)	0 (0.0)	0.0001
Yes	5 (11.6)	22 (51.2)	
Survival status			
Expire	7 (16.3)	6 (14.0)	0.747
Alive	14 (32.6)	16 (37.2)	

Note: Bold value indicates statistically significant at *p* value.

Abbreviation: CAM, covid associated mucormycosis.

TABLE 2 Relationship of CAM and non-CAM patients with other comorbidities.

Other comorbidities	CAM	non-CAM
Hypertension	3	4
SLE	0	1
Rheumatoid arthritis	0	1
COPD	0	2
COPD + hypertension	0	2
Renal transplant recipient + hypertension	1	0
None	0	2

Abbreviations: CAM, covid associated mucormycosis; COPD, chronic obstructive pulmonary disease; SLE, systemic lupus erythematosus.

transplantation and haematological malignancies in the last two decades and now it has emerged as a life-threatening complication of Covid-19. ROCM is the most prevalent and often lethal type that tends to involve nasal cavity, oral cavity, orbital tissues and can also extend to the brain. Other common clinical types of mucor are pulmonary, gastrointestinal, cutaneous and disseminated infections. In 2020, its rise was first noted in India as an aftermath of Covid-19 and was declared an epidemic in two states of India by May 2021. Most of the infected cases were either active or recovered COVID-19 patients.⁵ Now CAM has become a separate entity with reportedly 82% cases from India and 19% from rest of the world with a slight male predilection.⁸ Pakistan and other South Asian countries also have a worrisome surge in CAM due to similar socioeconomic conditions.

Knowing these facts, we tried to find out the incidence of CAM in three major tertiary care hospitals in Lahore. Though initially the data is analyzed for 3 months post-third wave of Covid-19 only, results were alarmingly high. Out of 43 patients reported with ROCM, 22 had a positive history of Covid-19 in the last 2 months, whereas only one patient was coinfecting with Covid-19 and mucormycosis at the time of presentation. The median age of patients with CAM was 37 years, whereas another descriptive study on CAM from Iran reported the median age of 52 years.⁹ Multiple studies reported male predilection among CAM patients which is in concordance with our result with 63% male patients.^{9,10} The mean duration between Covid-19 and mucormycosis in our study was 12 days which is shorter than another international study from India (23.5 days).¹¹ In accordance with other international studies, DM was found to be the most common comorbidity in both groups of Mucormycosis demanding the importance of developing national diabetes control programs.^{11,12} According to the National Diabetes Survey of Pakistan, the prevalence of diabetes is as high as 26.3% i.e., almost 27.4 million adult population is suffering from diabetes in Pakistan alone providing a soft bed for the fungus to grow.¹³

Another important contributing factor was corticosteroid medication. All the CAM patients in our study had received corticosteroid therapy whether or not justified. Due to limitations of data availability, we could not find out the exact duration and dosage of corticosteroids given to all the participants. However, 13 patients were confirmed to have received steroid therapy for more than 5 weeks. This prolonged and nonjudicial use of corticosteroids is also reported in other studies.¹⁴

4.1 | Mucormycosis and Covid-19 coinfection

The possible role of Covid-19 in the pathogenesis of mucormycosis is explained by different theories. According to Janjua et al. SARS-CoV-2 opens the ground for opportunistic infections by impairing the cell-mediated immunity with significant reduction in the of T-lymphocytes (CD4+ and CD8+)¹² Pandiar et al.¹⁵ explained the multisystem tropism of the virus due to its high affinity for the angiotensin converting enzyme 2 (ACE-2) receptors. These ubiquitous receptors are predominantly expressed on alveolar cells, endothelial cells, epithelial cells of GIT, ocular and cardiovascular cells facilitating multiple organ damage in Covid-19. This ACE-mediated endothelial and alveolar cell damage facilitates the spread of Mucorales by providing the port of entry. Virus induced alveolar cell damage leads to hypoperfusion and lactic acidosis creating an acidic environment favorable for the fungus to grow.¹² Also, this SARS-induced ACE mediated pancreatic Beta-cell damage causes acute diabetes-like state even in nondiabetic patients.¹²

Some of the studies also explore the possible role of hyperferritinemia in the pathogenesis of CAM. Depending on the severity of Covid-19, there is concurrent increase in the serum ferritin levels, an iron binding protein. It has been theorized that SARS-CoV-2 detaches the iron from haemoglobin molecule increasing free iron overload

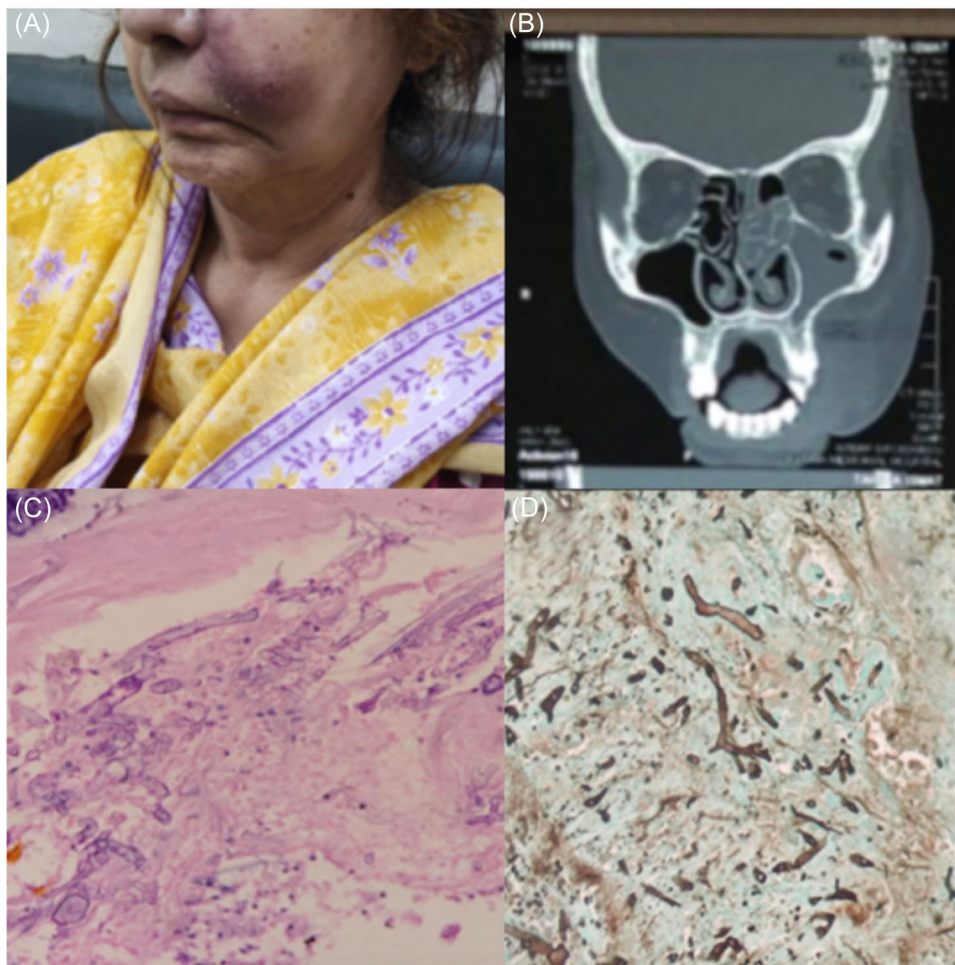


FIGURE 1 (A) Clinical photograph of a patient with swelling and discoloration on the left cheek with nasal discharge. The patient was Covid positive 1.5 months before this condition and treated with Remdesivir and I/V + oral dexamethasone for 6 weeks during and posthospitalization. (B) Coronal slices of CT scan showing opacity of maxillary sinus and nasal turbinate on left side. (C) H&E stain showing pauciseptate hyphae of mucormycosis branching at right angle ($\times 40$ HPF). (D) Grocott Methenamine Silver (GMS) stain showing ribbon-like pauciseptate hyphae of mucormycosis ($\times 40$ HPF). CT, computerized tomography; H&E, hematoxylin and eosin.

resulting in hyperferritinemia. The increased free iron radicals induces cellular damage and aids the fungal metabolic process and growth.¹⁶ The combination of hyperglycemia, acidosis, and high iron enhances the upregulation of 78-kDa glucose-regulated protein (GRP78) at the endothelial cells. This heat shock protein mediates the binding of fungal hyphae on the laminin and type IV collagen at the basement membrane of the endothelial cells causing angioinvasion and tissue necrosis.^{15,17} Thus, hyperferritinemia associated with Covid-19 plays an integral part in the pathogenesis of mucormycosis.¹⁸

Furthermore, the aggressive use of steroids for the management of cytokine storm in Covid-19 infection worsens the diabetes control and the immune system of the body making the fungus more invasive and lethal.^{11,19,20} These hormones not only suppress the immune cells but also increase insulin resistance. Together Covid-19, steroid therapy, and uncontrolled diabetes make a favorable triad for the proliferation of mucormycosis. Chakrabarti et al.²¹ have explained similar results from India and he has also reasoned that the reduced immune potential

and alteration of various proteins in the spleen causes a reduction of combatants against fungi.

Hence, it can be concluded that these preceded predisposing factors play a cardinal part in pathogenesis and increased occurrence of mucormycosis (Figure 2).

The role of corticosteroids in the management of Covid-19 cannot be ignored but physicians should use evidence-based protocols in individual cases as according to WHO interim guidance of May 2020, the use of dexamethasone or other corticosteroids can be more harmful than beneficial in patients who do not require supplemental oxygen.²² The initial guidelines from the NIH., United Kingdom supported the use of 6 mg dexamethasone once daily (intravenous or by mouth) for up to 10 days to reduce the 28-day mortality.²³

The overall mortality rate of mucormycosis is estimated to be 54% by the American Center for Disease Control and Prevention and it varies with the site of infection with almost 46% among people with ROCM, which is far more than Covid-19 itself.²⁴ Early diagnosis is the key to

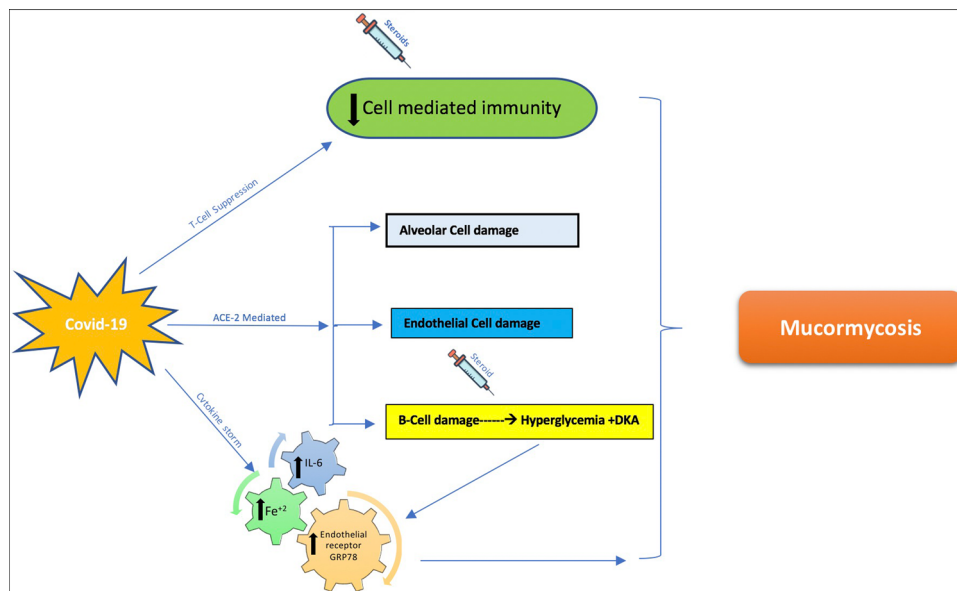


FIGURE 2 Pathogenesis of covid associated mucormycosis.

reduce the disease associated fatality it is important not to overlook the symptoms, especially in patients with uncontrolled diabetes and Covid-19. Nasal congestion or discharge (blackish or bloody), local pain over the cheekbone, unilateral facial pain, numbness, or swelling over the face are all symptoms to look out for. Blackish discoloration of the bridge of the nose or the palate, toothache, loosening of teeth, pain in the jaw, blurred or double vision, fever, chest pain, hemoptysis, and worsening respiratory symptoms all require immediate attention and should be reported to the nearest health facility as soon as possible.²⁵

5 | CONCLUSION

The aftermath of this study and many alike is that the DM and steroid medication are key factors deciding the potential vulnerability of population to mucormycosis and Covid-19 is another precipitating factor. Physicians should weigh benefits against risks of prescribing steroids as per national and international guidelines and glycemic control of Covid-19 patients should be given utmost importance. Moreover, media awareness campaigns can educate the masses against the harm of self-medication and the over-the-counter use of steroids. A multidisciplinary approach and rigorous management plan are required to manage this FI especially when more waves of SARS-CoV-2 are expected to emerge in Pakistan from around the world.

6 | LIMITATIONS

Main limitation of our study was its retrospective design itself as due to limitations of data availability and record-keeping in public hospitals did not allow us find out the exact duration and

dosage of corticosteroids given to all the participants and status of diabetes control. Moreover, in many cases during the pandemic, the Covid-19 infection went undetected and unreported due to limited resources and awareness among the masses. Thus, the absence of PCR positive reports of Covid-19 does not completely nullify the history of infection. Further population-based studies are required to truly understand the epidemiology of the disease.

AUTHOR CONTRIBUTIONS

Ayesha Irfan: conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; software; supervision; validation; visualization; writing – original draft; writing – review & editing. **Afshan Hussain Kamran:** conceptualization; data curation; investigation; methodology; project administration; resources; supervision; writing – review & editing. **Muhammad Ammar:** conceptualization; data curation; formal analysis; investigation; methodology; resources; software; visualization; writing – original draft; writing – review & editing. **Saeed ur Rahman:** formal analysis; investigation; methodology; resources; software; supervision; validation; writing – original draft. All authors have read and approved the final version of the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

TRANSPARENCY STATEMENT

The lead author Ayesha Irfan affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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