

# MUCORMYCOSIS IN COVID-19 AND NON COVID-19 PATIENTS: A COMPARATIVE CROSS SECTIONAL STUDY

Muhammad Izaz<sup>1</sup>, Amara Bibi<sup>1</sup>, Basheer Rehman<sup>1</sup>

<sup>1</sup>Department of Oral and Maxillofacial Surgery, Khyber College of Dentistry, Peshawar

## ABSTRACT

**Objectives:** To compared mucormycosis in COVID-19 patients versus non-COVID-19 patients.

**Materials and Methods:** This cross-sectional study was conducted in the Department of Oral and Maxillofacial Surgery, Khyber College of Dentistry Peshawar Pakistan from July 2021 to December 2021. A total of 50 cases of Mucormycosis were included by dividing into two groups. One of the groups had a positive history of COVID-19 infection while the second group had negative COVID-19 history. Diagnosis of Mucormycosis was confirmed on histopathology or fungal culture. For group 1, a history of COVID-19 infection was confirmed from patient records having positive COVID PCR within 2 months of the onset of Mucormycosis. For group 2, no COVID-19 infection was confirmed from the absence of signs and symptoms such as cough, fever, body aches and no contact with COVID-19-positive patient within 6 months of the onset of Mucormycosis. A logistic regression model was applied to determine the predictors of Mucormycosis while multi-logistic regression was run to see potential confounders.

**Results:** Out of the total 50 patients, the mean age of the patients was 50+9.45S.D. Steroids usage was high in COVID-19 positive patients [15 (60%), P value; 0.001] while pus discharge was low 5 (20%) in CoVID-19 patients in contrast to Non-COVID-19 Patients which was high [17 (68%): P value; 0.001]. Multivariate Logistic regression analysis showed that the adjusted odds ratio (OR) for female patients was 2.74 (95 % CI 0.66-4.25) as compared to male patients. Similarly, patients with steroid use have about 3.58 times higher odds of catching the disease as compared to non-steroid use (95 % CI 1.066-19.3). The OR for pus discharge was 0.40 (95 % CI 0.08-2.00), Left side 0.45 (95 % CI 0.06-2.9,) and Bilateral 0.93 (95 % CI 0.14-6.17).

**Conclusion:** Covid-19 seems to have a causal, coincidental or contributory role in the development of mucormycosis in the background of comorbidities such as diabetes. The role of Covid-19 needs to be specified and its association with Mucormycosis needs to be established.

**Key words:** Mucormycosis, COVID-19, Comorbidities, Oral & Maxillofacial infections

## INTRODUCTION

In December 2019, an outbreak of mysterious pneumonia was seen in Wuhan, China which was the beginning of the most prevailing pandemic of the history.<sup>1</sup> Two months later, the name coronavirus disease (COVID-19), an acute severe respiratory syndrome causing pneumonia was given to it by the

World Health Organization (WHO).<sup>2</sup> They declared COVID-19 as a pandemic demonstrating global spread.<sup>3</sup>

The COVID-19 infection has been linked to numerous opportunistic infections.<sup>4</sup> Recently, there have been a growing number of incidences of fungal infections, such as mucormycosis, in people with COVID-19 all over the world.<sup>5</sup> Moreover, the presence of other comorbid conditions such as diabetes and the judicious use of corticosteroids for regulating immune-mediated lung injury and decreasing the mortality rate in the COVID-19 patients may render the patients more prone to secondary infections.<sup>6</sup>

### Correspondence:

**Basheer Rehman**

Associate Professor

Department of Oral & Maxillofacial Surgery,

Khyber College of Dentistry Peshawar

Cell: +923339199288

Email: trygeminal76@gmail.com

Mucormycosis is potentially angioinvasive and acute fungal infection caused Class- Zygomycetes, Order- Mucorales, genus- Mucor, Rhizopus, Absidia and Rhizomucor.<sup>6-8</sup> The most common symptoms in mucormycosis include facial pain, headache, peri-orbital swelling, ophthalmoplegia, proptosis, eyelid drooping, vision loss and necrosis of the maxilla and palate.<sup>9</sup> Severe complication of mucormycosis is cavernous sinus thrombosis which results palsy of the cranial nerves III, IV, V1, V2, and VI.<sup>6</sup>

The predisposing risk factors for Mucormycosis include uncontrolled diabetes including Diabetic ketoacidosis, immunosuppressive and corticosteroid therapy, neutropenia, iron overload, deferoxamine therapy, intravenous drug abusers, renal failure, organ transplantation, acquired immunodeficiency syndrome (AIDS), extensive burns, malignancy and malnutrition.<sup>6,7</sup> In normal healthy individuals the inhaled spores are cleared by phagocytes. While in immunocompromised individuals, these spores gets transformed into hyphae.<sup>5</sup> Leukocytes have less phagocytic activity against the hyphae form of fungi and the pathogens get proliferated more fastly.<sup>7</sup> The fungal hypae proliferates extensively and invades the vascular walls of the infected region causing thrombosis that results in ischemia and eventually necrosis. The infection may spread directly or through the blood to the paranasal sinuses, orbit, and intracranial regions.<sup>6</sup>

There has been an increase in cases of mucormycosis in patients with COVID-19. These findings have not been reported before in such temporal relationship and have an impact on the public health, primarily because of the high fatality rate with mucormycosis, as the cerebral involvement may increase the mortality rate upto 90%. The spread of mucormycosis is very fast and delay in treatment could be fatal. This prompted us to conduct a study of mucormycosis in patients with COVID-19, to know its associations with comorbidities such as diabetes mellitus and drugs such as corticosteroids being used in COVID-19 infection. We will also give an explanation that why mucormycosis extensively occurs in individuals with COVID-19.<sup>7</sup>

This study aims to compare the prevalence of mucormycosis between COVID-19-positive and non-COVID-19-positive patients.

## MATERIALS AND METHODS

This comparative cross sectional study was conducted in the Department of Oral and Maxillofacial Surgery, Khyber College of Dentistry Peshawar Pakistan from July 2021 to December 2021. Total of 50 cases of Mucormycosis were included in this study. These cases were divided into two equal groups. Group 1 had a positive history of COVID-19 infection and group 2 had negative COVID-19 history. An inclusion criterion was set in such a way that patients age 16 and above irrespective of gender were the part of study. Diagnosis of Mucormycosis was made on histopathology or fungal culture. For Group 1, history of COVID-19 infection was confirmed from patient records having positive COVID-19 PCR within 2 months of the onset of Mucormycosis. For Group 2, no COVID-19 infection was confirmed from absence of sign and symptoms such as cough, fever, body aches and no contact with COVID-19 positive patient within 6 months of the onset of Mucormycosis.

Ethical approval was obtained from the Research Review Board Khyber College of Dentistry Peshawar, Pakistan (Vide No.44/ADR/KCD dated 7.10.2022. Diabetic status was assessed on fasting blood sugar, random blood sugar or HBA1c. Previous steroids use and oxygen or ventilator support was confirmed from patient's history and past medical record. Pus discharge was confirmed from clinical examination. Apart from these investigations other necessary blood investigations were performed. Orthopantomogram (OPG) and Cone Beam Computed Tomography (CBCT) or CT scan were done in every case to know the extent of bony involvement. Patients were assessed on clinical signs and symptoms and radiographical findings and referral was considered if ophthalmological or intracranial involvement was suspected.

Data were analyzed using SPSS version 22. Continuous variables such as age was expressed as mean and SD. Frequency and percentages were determined for categorical variables such as gender, diabetic status, steroid use, pus discharge, extent of bony involvement and laterality. The independent sample T test was used to compare the mean ages of the two groups. Categorical variables were subjected to the Chi square test or Fisher's exact test. The variables with  $p < 0.05$  were included in a logistic regression

model to determine the predictors of Mucormycosis. In order to get adjusted odds ratios (OR) for potential confounders, multi-logistic regression was used.  $P < 0.05$  was considered to indicate significance.

## RESULT

Out of the total 50 patients of Mucormycosis, 25 were COVID-19 positive (Group 1) and 25 were non COVID patients (Group 2). The mean age of patients was  $50 \pm 9.45$  S.D. The most common age group was 41-60 years. Males outnumbered females with a ratio of 1.17:1. 60% of the patient had a history of diabetes, 32% had a history of steroids use in the last 2 months, 34% of the patients required oxygen or ventilator support during COVID-19 infection. Pus discharge was present in 44% of cases. On CBCT alveolus was involved in 4% cases, alveolus upto maxillary sinus in 52% cases, Alveolus paranasal sinuses in 30% cases, Alveolus PNS orbit in 8% cases, Alveolus PNS orbit CNS in 2% cases and bony involvement along with soft tissue involvement in 4% cases. Bilateral involvement was seen in 46% cases, right side involvement in 16% cases and left side in 38% cases. Details are given in Table 1. The independent sample T test was used to compare the mean ages of the two groups which showed an insignificant p value. Details are given in Table 2.

Stratification of different variables was done with COVID-19 status which showed non-significant p value for Diabetic status cases [15(60%),  $p=1.0$ ] and the most common reported extension on CBCT was Alveolus upto Maxillary sinus [10(40%),  $p=0.13$ ]. In contrast, males were most commonly affected in COVID-19 positive patients having Mucormycosis [10(40%),  $p=0.04$ ]. P value was significant for gender [10(40%),  $p=0.04$ ], steroid use [15(60%),  $p=0.00$ ], oxygen/ventilator support [17(68%),  $p=0.00$ ], pus discharge [5(20%),  $p=0.001$ ] and laterality [15(60%),  $p=0.003$ ]. Detail are given in Table 3.

Logistic regression analysis showed that the odds ratio (OR) for female patients was 2.74 (95 % CI 0.66-4.25) as compared to male patients. Similarly, patients with steroid use have about 3.58 times higher odds of catching the disease as compared to non-steroid use (95 % CI 1.066-19.3). OR for pus discharge was 0.40 (95 % CI 0.08-2.00), Left side 0.45 (95 % CI 0.06-2.9) and Bilateral 0.93 (95 % CI

0.14-6.17). In other words, patients who were having a positive history of Covid-19 were associated with greater odds of Pus discharge as compared to non covid-19 patients. Details are given in Table 4.

Figure 1. A 45 year old female known hypertensive and diabetic, with positive history of COVID-19 infection and steroid use, presented with chief complaint of swelling and pain left side of face. Intraorally patient had exposed necrotic bone in the posterior maxillary alveolus region with loosening of associated teeth. Associated mucosa was erythematous with necrotic margins. Excisional biopsy showed extensive colonies of non septate branching hyphae, suggestive of mucormycosis. On CBCT le-

**Table 1: Descriptive statistics of different variables**

Variables		n	%
Gender	Male	27	54
	Female	23	46
Age (Years)	0-20	1	2
	21-40	7	14
	41-60	38	76
	60 and above	4	8
Diabetic Status	Yes	30	60
	No	20	40
Steroids Use	Yes	16	32
	No	34	68
Ventilator/Oxygen Support	Yes	17	34
	No	33	66
Pus Discharge	Yes	22	44
	No	28	56
Extension on CBCT	Alveolus only	2	4
	Alveolus upto Maxillary sinus	26	52
	Alveolus plus all Paranasal Sinuses	15	30
	Alveolus, PNS, Orbit	4	8
	Alveolus, PNS, Orbit and CNS	1	2
	Bony involvement along with soft tissue involvement	2	4
Laterality	Right Side	8	16
	Left Side	19	38
	Bilateral	23	46
<b>Total</b>		<b>50</b>	<b>100</b>

sion has caused extensive lysis of maxilla, extending to ethmoid and sphenoid sinuses and medially toward lateral nasal wall.

Figure 2. 45 years old diabetic female presents with exposed bone in the left half of the maxilla for the last 2 months. Previously she had history of COVID 19 3 months back. There is no history of

**Table 2: Mean age difference between COVID positive and COVID negative patients**

	Past COVID Status	Number of patients (n)	Mean age + S.D	Mean Difference	95% Confidence Interval	P value
Age	Positive	25	50.6+11.67	1.36	-4.05 to 6.77	0.616*
	Negative	25	49.3+6.71			

**Table 3: Stratification of different variables with COVID-19 status**

Variables		Group 1 (COVID-19 Positive)	Group 2 (COVID-19 Negative)	P-value
Gender	Male	10(40%)	17 (68%)	0.047*
	Female	5(20%)	8(32%)	
Diabetic Status	Yes	15(60%)	15(60%)	1.0*
	No	10(40%)	10(40%)	
Steroids Use	Yes	15(60%)	1(4%)	0.00*
	No	10(40%)	24(96%)	
Ventilator/Oxygen Support	Yes	17(68.0%)	0(0.0%)	0.000*
	No	8(32.0%)	25(100%)	
Pus Discharge	Yes	5(20%)	17(68%)	0.001*
	No	20 (80%)	8 (32%)	
Extension on CBCT	Alveolus only	1 (4%)	1 (4%)	0.133**
	Alveolus upto Maxillary sinus	10 (40%)	16 (64%)	
	Alveolus plus all Paranasal Sinuses	7 (28%)	8 (32%)	
	Alveolus, PNS, Orbit	4 (16%)	0 (0%)	
	Alveolus, PNS, Orbit and CNS	1 (4%)	0 (0%)	
	Bony involvement along with soft tissue involvement	2 (8%)	0 (0%)	
Laterality	Right Side	4 (16%)	4 (16%)	0.003*
	Left Side	15 (60%)	4 (16%)	
	Bilateral	6 (24%)	17 (68%)	

**Table 4: Logistic regression analysis by using COVID-19 and Non COVID-19 groups as dependent Variable and its association with other factor**

		Unadjusted Odds Ratio	P value	95% Confidence interval	Adjusted Odds Ratio	P value	95% Confidence interval
Gender	Male	Reference					
	Female	1.31	0.64	0.41-4.13	2.74	0.16	0.66-11.25
Steroid use	No	Reference					
	Yes	4.3	0.04	1.04-18.0	3.58	0.13	0.66-19.3
Pus Discharge	No	Reference					
	Yes	1.3	0.64	0.41-4.13	0.40	0.26	0.08-2.00
Laterality	Right	Reference					
	Left	0.35	0.24	0.06-1.9	0.455	0.41	0.06-2.9
	Bilateral	0.91	0.91	0.18-4.58	0.934	0.94	0.14-6.17

use of steroids. On examination there is mild diffuse swelling in the left cheek region, hypernasal voice. Ocular examination is unremarkable. On intraoral examination there was exposed bone on buccal aspect of left half of maxilla with apical retraction of overlying soft tissues. Multiple perforation in palatal soft tissues with suppuration, mobility in left hemimaxilla with individually mobile teeth on left side. CBCT findings shows extensive perforation on the anterior wall of maxillary sinus extending upto zygomatic region superiorly and medially involving left nasal wall

**DISCUSSION**

There is still much to learn about the threat that has emerged from the COVID-19 pandemic, but moving forward, it will be especially important to carefully monitor any underlying medical conditions with patients before beginning treatment in COVID-19-affected individuals. Mucormycosis has been increasingly reported in patients with COVID-19 and a strong association exists between the two.<sup>10</sup> However, diabetes and steroid use are two significant confounders that must be taken into account.<sup>8</sup> Multiple factors that could lead to Mucor-



**Fig 1:**



**Fig 2:**

mycosis in COVID-19 individuals can be intuitively explained as follows.

Diabetes has a very prominent role in mucormycosis development.<sup>11</sup> Population that is at greatest risk for the development of Mucormycosis are immunocompromised patients with diabetes. In diabetic ketoacidosis (DKA), due to low pH and hyperglycemia, the phagocytes become malfunctioning and have poor chemotaxis and defective oxidative and nonoxidative intracellular killing.<sup>12</sup> Ketoacidosis also affects the binding of iron to transferrin, causing a rise in serum iron level. The growth of these fungi is promoted by iron.<sup>13</sup>

The role of Corticosteroids remains yet to be clearly understood.<sup>14</sup> Most frequently, corticosteroids are used to treat the severe form of COVID-19 disease and help to regulate immune-mediated lung injury during COVID-19 infection.<sup>15</sup> At the same time, corticosteroids are also responsible for immunosuppression and blood sugar rise. Apart from this, the phagocytes become dysfunctional, with impaired of migration, and ingestion of macrophages.<sup>6,16</sup> These effects are potentially responsible for contributing to Mucormycosis development. A dose of prednisone higher than 600 mg or a cumulative dose of methyl prednisone 2–7g per month, has a higher risk of Mucormycosis development in immunocompromised people. Few mucormycosis cases have been reported in immunocompromised individuals even with a few days course (5–14 days) of steroid therapy, in patients with diabetes mellitus particularly. In a study conducted by the European Confederation of Medical Mycology<sup>7</sup>, 46% of the patients had received corticosteroids within the past month prior to the diagnosis of mucormycosis.

SARS-CoV-2 virus<sup>17</sup> causes immunological dysregulation by reducing the CD4+ and CD8+ T cells and there is a rise in the level of many inflammatory markers such as IL-2, IL-6, IL-10, and TNF- $\alpha$ .<sup>6</sup> Also COVID-19's pathophysiology is similar to the spectrum of thrombotic microangiopathies causing angioinvasion and endothelial damage much like that of mucormycosis, aggravating the disease.<sup>7,15</sup> Additionally, a COVID-19 infection can directly raise blood sugar levels, which creates an ideal setting for the growth of mucormycosis.<sup>18</sup> Diabetogenic state in COVID-19 infection can be caused by multiple factors such as systemic inflammatory response syn-

drome or severe sepsis. The initial response to these conditions is a rise in the levels of some cytokines, which is compounded by high blood glucose levels. The pro-inflammatory phase is characterized by metabolic stress, which causes glycogen breakdown, the production of glucagon and adrenocorticotrophic hormones, and insulin resistance, all of which raise blood sugar levels.<sup>19</sup> Another plausible explanation for the hyperglycemic state in Covid-19 infection could be high expression of ACE2 receptors in pancreatic islets along with increased insulin resistance brought on by cytokine storm.<sup>20</sup> All these factors play together to make COVID-19 individuals a high-risk population for mucormycosis.<sup>15</sup>

The miscellaneous elements that could lead to the emergence of mucormycosis in COVID-19 patients include tropical climate, high spore burden, reuse of tubing of ventilators, absence of filters in ICU and wards, and inadvertent use of antibiotics.<sup>21</sup>

In summary, the main factors that can be incriminated for the fungus spores to grow and multiply in COVID-19 patients are affected by the environment of hypoxia, high blood glucose (new-onset hyperglycemia, diabetes mellitus, steroid-induced hyperglycemia), an acidic medium (diabetic ketoacidosis, metabolic acidosis), reduced phagocytic activity of WBCs due to immunosuppression (COVID-19 mediated, underlying comorbidities or steroid-mediated) and high iron levels (increased ferritins), together with many other predisposing risk factors including prolonged hospital stay.<sup>7</sup>

It is proposed that the SARS-CoV-2 virus causes thrombosis in the microvasculature of maxilla that result in osteomyelitis and necrosis of the maxilla. The fungal infection acts as a superimposed secondary infection in osteomyelitis of the maxilla in patients with COVID-19. Diabetes and corticosteroid act as additive risk factors.

Smith and Krichner<sup>7</sup> proposed a criteria for that is considered as standard for clinical diagnosis of mucormycosis.

Blackish necrosis of turbinates.

Discharge from nose along with facial pain.

Discoloration, induration and swelling of peri-orbital or peri-nasal soft tissues.

Eyelid ptosis with eyeball proptosis and oph-

thalmoplegia.

Many cranial nerve involvement.

Early diagnosis of mucormycosis requires direct microscopy with KOH mounted slides and confirmatory diagnosis is made on histopathology. Histopathological specimen shows broad, thick walled non-septate hyphae with branching at 90 degrees, necrotizing granulomatous inflammation, and vasculitis together with mucor hyphae within the vessel wall and associated lumen.<sup>18</sup> Fungal cultures take weeks, and the aggressive nature of this disease often leaves little time for fungal culture.<sup>15</sup>

In mucormycosis, Survival depends upon early diagnosis, attenuation of underlying predisposing risk factors, aggressive debridement of the involved necrotic tissues, and appropriate systemic antifungal drugs. Debridement of necrotic tissues should be carried out until the necrotic tissues is completely removed and there is fresh bleeding bone and soft tissue. Diabetes should be controlled strictly and steroid therapy should be stopped. All other predisposing factors should be monitored and dealt accordingly. Systemic amphotericin B and liposomal amphotericin are the drug of choice for the management of mucormycosis and it has a positive impact on the survival rate. When mucormycosis is initially controlled by amphotericin B, an oral antifungal agent such as Posaconazole is started as step-down therapy. Debridement of necrotic tissues from paranasal sinuses is done on daily basis to stop the progression of mucormycosis. Also, it is recommended that the sinuses and all the involved regions should be irrigated with diluted amphotericin B. In cases of orbital involvement, orbital exenteration has been suggested in most studies.<sup>6,15</sup> Rhinoorbitocerebral mucormycosis is a fatal disease and mortality rises to 50%–85% in cases of brain involvement.<sup>6</sup>

## CONCLUSION

It can be concluded from the results of this study that COVID-19 seems to have causal, coincidental or contributory role in development of Mucormycosis in the background of comorbidities such as diabetes and use of corticosteroids. The role of COVID-19 needs to be specified or its association established. Further large scale studies are required where role of diabetes and COVID-19 would be understood clearly. The limitation of our study included as Sam-

ple sizes for the study groups were small. Because of this, the results for these two subgroups should be interpreted with particular caution. It is well recognized that statistical findings from small sample sizes tend to be less broadly generalizable to other groups. Moreover the use of steroid and Diabetes might have affected the statistical results.

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