

COVID-19 Associated Mucormycosis (CAM): A Single Hospital-Based Study

Manjunath M. Vijapur¹, Vasanth Kattimani², Varsha VK³, Girish HC³, Mamata Kamat⁴, Bhargav Ram⁵

¹Department of Oral and Maxillofacial Surgery, Karnataka Institute of Medical Sciences, Hubli, Karnataka, ²Department of Oral and Maxillofacial Surgery, District Health and Family Welfare Services, Dharwad, Karnataka, ³Department of Oral and Maxillofacial Pathology, Rajarajeswari Dental College and Hospital Bengaluru, Karnataka, ⁴Department of Oral and Maxillofacial Pathology, BV (DU) Dental College and Hospital, Sangli, Maharashtra, ⁵Department of Oral and Maxillofacial Surgery, KVG Dental College and Hospital, Sullia, Karnataka, India

Abstract

Background: Opportunistic fungal infections like Mucormycosis in Coronavirus Disease 2019 (COVID-19) patients have posed a great challenge to health care professionals, especially in developing countries like India. Hence, there is a need to understand the biological behaviour of COVID-19 associated Mucormycosis (CAM) to establish standard treatment Protocols and to reduce mortality.

Aims: This study aims is to assess the type of Mucormycosis among COVID-19 patients in study population and compare the findings with clinical, radiological and haematological parameters along with treatment and surgical management.

Methods and Material: This retrospective, observational study included 60 cases of CAM reported to the Department of Oral and Maxillofacial Surgery at the tertiary care centre, Karnataka Institute of Medical Sciences, Hubli. Data about various parameters were tabulated and analysed statistically.

Statistical Analysis Used: Bivariate analysis was done using the Chi-Square test to assess the relationship between the type of Mucormycosis and other variables. Spearman's Correlation test was used to assess the correlation between types of Mucormycosis with the other variables. Linear regression analysis was performed to assess the response variable related to the type of Mucormycosis.

Results: About 50% of subjects presented with "Rhino orbital" type of Mucormycosis. Palatal discoloration and palatal erosion was the most common oral manifestation among "only Sinus" and "Rhino orbital" types of Mucormycosis ($P = 0.00$). Significant association ($P = 0.29$) was found between the type of Diabetes mellitus and Mucormycosis.

Conclusions: The study indicates that DM is the most commonly associated comorbidity in CAM patients. Hence, a thorough understanding of the underlying comorbidity and its close monitoring during and after COVID-19 infection is mandatory for successful treatment outcomes.

Keywords: COVID-19, diabetes, mucormycosis

Address for correspondence: Dr. Varsha VK, Department of Oral and Maxillofacial Pathology, Rajarajeswari Dental College and Hospital #14, Ramohalli Cross, Kumbalgodu, Mysore Road, Bengaluru - 560 074, Karnataka, India.

E-mail: varsha.mahavir@gmail.com

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has gripped the world for more than a year creating havoc and global health crisis. While still dealing with the management of COVID-19, various secondary bacterial and opportunistic fungal infections have emerged. Among these, the rare fungal infections linked to COVID-19 are COVID-19-associated pulmonary aspergillosis and COVID-19-associated Mucormycosis (CAM).^[1] The ballooning of CAM during the second surge of the COVID-19 is a matter of apprehension. In India, with in a matter of 3 months, 47,000 CAM cases were reported.^[2]

Mucormycosis is an angioinvasive opportunistic infection caused by order Mucorales with a worldwide distribution.^[3] The genera responsible for human infection are *Rhizopus*, *Mucor* and *Rhizomucor*; *Cunninghamella*, *Lichtheimia* and *Apophysomyces*.^[4] These ubiquitous filaments normally occur in soil, manure, fruits, and decaying matter.^[3] These fungal spores can cause aggressive and life-threatening disease in immunocompromised hosts but is harmless in healthy individuals. These invasive Mucorales can provoke infections in immunosuppressed individuals, especially in those with uncontrolled Diabetes mellitus (DM) haematological malignancy, chronic malnutrition, chronic liver diseases and hematopoietic stem cell transplantation patients.^[5] Clinically, CAM can be categorised into Rhino-Orbital, Paranasal Sinus, Rhino-Cerebral, Rhino-Orbital-Cerebral, Oral, Pulmonary, Gastrointestinal, Cutaneous, and disseminated.^[6] The most common being the Rhino-cerebral and the most common oral manifestation being palatal ulceration or necrosis and later palatal perforation due to the spread of infection from the nasal cavity or paranasal sinuses via palatal vessels^[7] Hence, the dental surgeon's need has aroused to be able to identify the oral manifestation at an early stage to plan the treatment protocol to prevent its rapid spread leading to fatality. However, a link between COVID-19 and Mucormycosis need to be unearthed.

Aim: Our aim was (1) Assessment of type of Mucormycosis among COVID-19 patients in north Karnataka population reported at Department of oral and Maxillofacial Surgery, Tertiary care centre, Karnataka Institute of Medical Sciences, Hubli. (2) To compare the type of Mucormycosis across the demographic variables, oral manifestations, vaccination status, Diabetes type, diabetes status, comorbidities, radiological features, haematological factors, treatment, and surgical management.

Methodology: This was a retrospective, observational

study carried out in COVID-19 cases confirmed either by Real-Time reverse transcriptase Polymerase chain reaction or Rapid antigen test in North Karnataka Population at the tertiary care centre, Karnataka Institute of Medical sciences, Hubli, reported between June 1, 2021, to September 31, 2021. A total of 60 cases of CAM were included in this study and reported to the Department of Oral and Maxillofacial Surgery after magnetic resonance imaging, functional endoscopic sinus surgery and confirmed histopathological report of Mucormycosis [Figure 1]. Data about demographics, oral manifestations, comorbidities, radiological features, haematological investigations, treatment, surgical management and prognosis was collected after obtaining informed consent from all patients. The study was accepted by the institutional ethics committee.

Statistics: The data obtained were compiled systematically in a Microsoft Excel sheet and subjected to statistical analyses using Statistical package for social sciences software version 20. The significant level was fixed at $P < 0.05$. Descriptive statistics were generated in terms of frequencies or percentages. Bivariate analysis was done using the Chi-Square test to assess the relationship between the type of Mucormycosis and other variables. Spearman's a correlation test was used to assess the correlation between types of Mucormycosis with the other variables. Linear regression analysis was performed to assess the response variable related to the type of Mucormycosis.

RESULTS

Table 1: Among the 60 COVID-19 positive patients, 21 (35%) patients had "only Sinuses" type of Mucormycosis, 30 (50%) patients suffered from "Rhino orbital" type of Mucormycosis followed by only 9 (15%) were with "Rhino orbito cerebral" type of Mucormycosis.

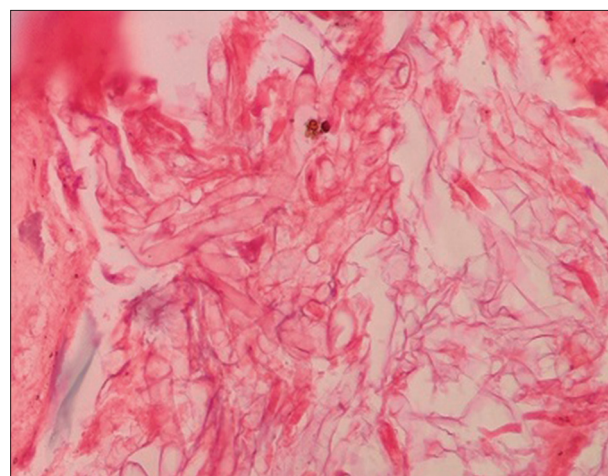


Figure 1: Photomicrograph of Mucormycosis showing non-Septate Hyphae (H & E stain, 40X)

Table 2: There was a significant association found between the type of Mucormycosis and the appearance of oral manifestation ($P = 0.00$). Among which palatal discoloration and palatal erosion [Figure 2] was common and higher in “only Sinus” and “Rhino orbital” type of Mucormycosis followed by occurrence of draining sinus in “Rhino orbital” type of Mucormycosis. Similarly, when compared with the type of DM and Mucormycosis, a significant association was also found ($P = 0.29$). But the frequency of occurrence of different types of Mucormycosis was found to be high in an uncontrolled type of DM patients and the frequency

of “Rhino orbital” type of Mucormycosis was high among controlled diabetes mellitus patients.

Table 3: Depicts the spearman’s correlation between the type of Mucormycosis and demographic variables, oral manifestations, vaccination status, comorbidity, type and status of DM. A significant correlation ($P = 0.000$) was seen between oral manifestation and type of Mucormycosis and also significant correlation ($P = 0.038$) was seen between the type of associated illness and Type of Mucormycosis.

Table 4: Depicts the relationship between the type of Mucormycosis with Altered signal density. A significant the relationship was noticed between the type of Mucormycosis and altered signal density of Sinus with a P value of 0.021.

Table 1: Frequency distribution of type of mucormycosis

Type_Mucormycosis	Frequency	Percentage
“only sinuses”	21	35.0
“Rhino orbital”	30	50.0
“Rhino orbito cerebral”	9	15.0
Total	60	100.0

Table 2: Comparison of type of mucormycosis across different demographic variables, site, oral manifestations, vaccination status, comorbidity, type and status of diabetes

	Type of Mucormycosis			Chi-Square value	P
	“Only sinuses”	“Rhino orbital”	“Rhinoorbito cerebral”		
Age				12.316	0.264
<30	2	1	0		
31-40 yrs	4	5	1		
41-50 yrs	6	11	2		
51-60 yrs	5	11	2		
61-70 yrs	4	1	4		
>70 yrs	0	1	0		
Gender				0.465	0.793
Male	14	22	7		
Female	7	8	2		
Site				1.397	0.966
Left maxilla	5	8	3		
Right Maxilla	5	5	1		
Bilateral Maxilla	10	16	5		
Oral manifestation				120.000	0.000
Palatal discoloration	9	11	2		
Palatal erosion	6	11	3		
Teeth mobility	3	2	0		
Draining sinus	1	5	1		
Swelling of cheek	1	2	3		
Vaccination Status				5.740	0.219
No vaccination	14	27	7		
First dose	4	3	1		
Second dose	3	0	1		
DM type				7.114	0.029
Controlled	6	14	0		
Uncontrolled	15	16	9		
DM Status				4.411	0.110
DM with Ketoacidosis	13	15	8		
DM without Ketoacidosis	8	15	1		
Type of illness				18.414	0.189
No illness	16	18	4		
Hypertension	5	6	2		
Ischemic heart diseases	0	1	2		
HIV	0	1	0		
Cavernous Sinus Thrombosis	0	1	0		
Hepatitis	0	0	1		
Pulmonary Mucormycosis	0	1	0		
OSMF	0	1	0		

Table 5: Illustrates the spearman’s correlation between Type of Mucormycosis with Altered signal density of Nasal cavity, Maxilla, Mandible, and Maxillary Sinus, wherein no a significant correlation was seen.

Table 6: Demonstrates comparison of the difference in haematological parameters such as Neutrophil: lymphocyte ratio (NLR), D dimer levels, Ferritin levels, and C reactive proteins (CRP) levels across the types of Mucormycosis. P value for NLR between only sinuses and rhino orbital type, only sinuses, and “rhino orbito cerebral type” and rhino orbital and “rhino orbito cerebral type” was 0.069, 0.156 and 0.880, respectively. P value for D dimer between only sinuses and rhino orbital type, only sinuses and “rhino orbito cerebral type” and rhino orbital and “rhino orbito cerebral type” were 0.370, 0.143 and 0.287, respectively. P value for Ferritin levels between only sinuses and rhino orbital type, only sinuses and “rhino orbito cerebral type” and rhino orbital and “rhino orbito cerebral type” were 0.108, 0.844 and 0.149, respectively. P value for CRP levels between only sinuses and rhino orbital type, only sinuses and “rhino orbito cerebral type” and rhino orbital and “rhino orbito cerebral type” were 0.782, 0.672 and 0.789, respectively. No statistically significant relationship was noticed between these haematological parameters and the type of Mucormycosis.

Table 7: Divulges descriptive analysis between the span of COVID and Type of Mucormycosis. Meantime span of COVID-19 and the appearance of CAM was 37.93 ± 25.41 days. There is no significant relationship observed.

Table 8: Describes the relationship between Types of Mucormycosis and the number of days of administration

Table 3: Relationship between the type of Mucormycosis with demographic variables, oral manifestations, vaccination status, comorbid type, and status

	Spearman's Correlation value (rho)		P
Age	0.162		0.217
Gender	-0.088		0.504
Oral manifestation	1.000		0.000
Vaccination status	-0.183		0.162
Diabetes mellitus type	0.074		0.574
Diabetes mellitus status	-0.087		0.507
Type of illness	0.269		0.038

Table 4: Altered signal density of nasal cavity, maxilla, mandible, and maxillary sinus across the type of Mucormycosis

	ASD NASAL		χ^2 & P	ASD-MAX		χ^2 & P	ASD-MAN		χ^2 & P	ASD-SINUS		χ^2 & P
	Present	Absent		Present	Absent		Present	Absent		Present	Absent	
“Only sinuses”	10	11	0.29 &	15	6	2.813 &	1	20	0.443	18	3	7.762 &
“Rhino orbital”	16	14	0.864	22	8	0.245	1	29	& 0.801	28	2	0.021
“Rhino orbito cerebral”	4	5		4	5		0	9		5	4	

of Steroid therapy. Although a large number of patients, that is, 11 patients of “only Sinus type” of Mucormycosis received steroid therapy for a range of duration, it did not illustrate a statistically significant relation.

Table 9: Describes the relationship between Type of Mucormycosis and the number of days of administration of Oxygen Supplements. Eleven, Fourteen, and one patient of ‘Only sinus type’, Rhino-orbital type, and Rhino-orbital cerebral type respectively received oxygen supplements. But no significant relationship was seen between them.

DISCUSSION

India, being one of the most affected countries by COVID-19 infection has witnessed a rapid surge in opportunistic infections like Mucormycosis during the second wave. A distinctive characteristic of Mucormycosis is angioinvasion followed by thrombosis and tissue necrosis. Inherent thermotolerance, swift growth, an affinity for endothelial cells and aptitude to gain iron from the host makes these Mucorales aggressive.^[8] Various contributing factors have been suggested for CAM. Hence to analyse the profile of patients affected by CAM and understand the pathogenesis, this hospital-based study was conducted.

In this observational study at the tertiary care centre, the most the common type of Mucormycosis observed in the present set of patients was Rhino-orbital form (50%) [Table 1]. Jose et al. also have found most of the cases in the rhino-orbital

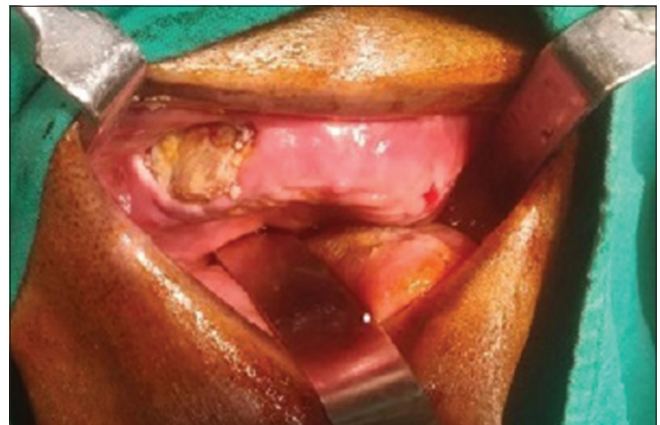


Figure 2: Clinical Image showing the denuded area in the right maxilla of an edentulous patient

region. In the literature, it has been reported that the Rhino-orbito-cerebral form is most common followed by other variants (like Cutaneous, pulmonary, disseminated and gastrointestinal types).^[9]

In our study, the majority of CAM-affected patients were between the 2nd and 7th decades of life with a maximum a number of cases above the age of 40 years [Table 2]. Similar studies have also reported analogous findings. The maximum number of patients included in the present study were males (n = 43). This is in accordance with previous reports.^[10,11] This might be due to the fact that most of the COVID-19 affected patients globally are males. Mucormycosis has not shown any gender predilection both in COVID-19 and non-COVID-19 era; however, it has been suggested that oestrogen might protect females from systemic fungal infections.^[4]

In our study, CAM was more commonly seen in the bilateral

maxilla (n = 31) compared to the right, left, or anterior Maxilla, as SARS-COV-2 is transmitted through aerosols and droplets to the nasal and oral cavity.^[12] Thus, this rapidly spreading aggressive fungal infection involves the bilateral maxilla swiftly. Frequently seen oral manifestation here were Palatal discoloration (n = 22) and Palatal erosion (n = 20) [Table 2]. Similar findings were noted by Janjua et al.^[13] There was also a significant correlation between oral manifestation and Type of Mucormycosis with a P value of 0.000 [Table 3] suggesting the palate is an untimely involved structure in the oral cavity.

With respect to vaccination status, most of the CAM patients did not receive the COVID-19 vaccine (n = 48) [Table 2]. The study by Petrikkos et al.^[14] also found that most of their patients were not vaccinated for COVID-19. Although it has been observed that vaccination reduces the severity of the disease, only 3% of the population was vaccinated^[11] during the second wave, and its role in the occurrence of CAM cannot be commented upon.

Among the comorbidities, DM (n = 60) was the most commonly associated illness in CAM patients and most of them had uncontrolled DM (n = 40) which was statistically significant with a P value of 0.029 [Table 2]. This is in accordance with studies both in Pre-COVID-19 and COVID-19 era.^[10,11,14] Literature reports indicate DM to be

Table 5: Relationship between the type of Mucormycosis with an altered signal density of nasal cavity, maxilla, mandible, and maxillary sinus

	Spearman's Correlation value (rho)	P
ASD NASAL	0.006	0.962
ASD MAX	-0.133	0.311
ASD MAN	-0.079	0.546
ASD SINUS	-0.164	0.210

Table 6: Comparison of the difference in haematological parameters across the type of Mucormycosis

Lab Parameters	Type of Mucormycosis	Between only sinuses and rhino orbital type of mucormycosis									
		n	Mean	SD	SEM	t	df	P	Mean difference	95% CI	
										Lower	Upper
N_L	"only sinuses"	21	2.5848	1.01116	0.22065	-1.86	48.354	0.069	-0.60237	-1.2528	0.04813
	"Rhino orbital"	30	3.1871	1.29642	0.23669						
D_dimer	"only sinuses"	21	507.2857	157.72639	34.41872	0.904	49	0.370	37.21905	-45.4899	119.92807
	"Rhino orbital"	30	470.0667	134.90455	24.63009						
Ferritin levels	"only sinuses"	21	452.0476	251.67409	54.91979	1.661	27.751	0.108	99.64762	-23.2762	222.57151
	"Rhino orbital"	30	352.4000	132.14167	24.12566						
CRP	"only sinuses"	21	54.1905	25.10502	5.47836	0.278	49	0.782	1.89048	-11.7782	15.55919
	"Rhino orbital"	30	52.3000	23.04291	4.20704						
Between only sinuses and "rhino orbito cerebral type of mucormycosis											
N_L	"only sinuses"	21	2.5848	1.0116	0.22065	-1.459	28	0.156	-0.68024	-1.63545	0.27497
	"Rhino orbito cerebral"	9	3.2650	1.49624	0.49875						
D_dimer	"only sinuses"	21	507.2857	157.72639	34.41872	1.507	28	0.143	94.9523	-34.1150	224.01979
	"Rhino orbito cerebral"	9	412.333	159.20584	53.06861						
Ferritin levels	"only sinuses"	21	452.0476	251.67409	54.91979	0.198	28	0.844	18.49206	-172.73050	209.71462
	"Rhino orbito cerebral"	9	433.5556	183.86552	61.28851						
CRP	"only sinuses"	21	54.1905	25.10502	5.47836	0.429	28	0.672	4.30159	-16.26021	24.86339
	"Rhino orbito cerebral"	9	49.8889	25.41872	8.47291						
Between rhino orbital and "rhino orbito cerebral type of mucormycosis											
N_L	"Rhino orbital"	30	3.1871	1.29642	0.23669	-0.153	37	0.880	-0.07787	-1.1114	0.95568
	"Rhino orbito cerebral"	9	3.2650	1.49624	0.49875						
D_dimer	"Rhino orbital"	30	470.0667	134.90455	24.63009	1.081	37	0.287	57.73333	-50.4736	165.9429
	"Rhino orbito cerebral"	9	412.3333	159.20584	53.06861						
Ferritin levels	"Rhino orbital"	30	352.4000	132.14167	24.12556	-1.474	37	0.149	-81.15556	-192.737	30.42646
	"Rhino orbito cerebral"	9	433.5556	183.86552	61.28851						
CRP	"Rhino orbital"	30	52.3000	23.04291	4.20704	0.269	37	0.789	2.41111	-15.74479	20.5670
	"Rhino orbito cerebral"	9	49.889	25.41872	8.47291						

an independent risk factor for Mucormycosis.^[11] The effects of DM like; Neutrophil dysfunction, that is, impaired chemotaxis and phagocytosis have been suggested for this association. It is also postulated that SARS-CoV-2 results in the dysfunction of β cells of the pancreas leading to insulin resistance by binding to ACE-2 receptors of pancreatic β cells. This is exaggerated by a cytokine storm caused by SARS-COV-2.^[14-18] DKA was seen in 36 patients, Patel

et al.^[19] found DKA to be less frequent in CAM patients compared to non-CAM patients. Acidosis-associated with DKA has the following effects: (a) stimulates the expression of GRP78 and coat protein homologue CotH. These proteins of Mucorales attach to the GRP78 endothelial receptors of the host, (b) increases levels of free-iron by a detachment of iron-protein complexes, thus favoring the growth of Mucorales.^[11,14,15,20,21] Most of the CAM patients did not have any illness at the time of CAM (n = 38), and very few of them were hypertensive [Table 2]. This finding in our study is in contrast to the observations made by Patel *A et al.*,^[19,22] wherein they reported that 58.6% of patients had more than one comorbidity.

All 60 cases of CAM in this study were reported to the Department of Oral and Maxillofacial Surgery after Magnetic resonance imaging, functional endoscopic sinus surgery, and confirmed histopathological report of Mucormycosis. Altered signal density in nasal cavity (n=30), maxilla (n=21), mandible (n=2) and Maxillary sinus (n=40) was noted. Altered signal density in the maxillary sinus showed a significant *P* value of 0.021 [Table 4]. This finding is in accordance with Mehta *S et al.*^[23] suggestive of maxilla being the most commonly involved structure. Rhino-orbital-cerebral mucormycosis usually affects the maxillary sinus with the involvement of maxillary teeth, orbits, and ethmoidal sinuses. According to Sanghvi *et al.*,^[24] contrast-enhanced magnetic resonance imaging (MRI) is the best mode of choice for the demonstration of CAM. Black turbinate is the classical imaging sign but there was no positive correlation seen between the type of Mucormycosis with an altered the signal density of nasal cavity, maxilla, mandible and maxillary sinus [Table 5].

The NLR is an easily accessible biological marker to assess the severity of the disease and can serve as an early warning signal. The mean NLR among various types of Mucormycosis was 2.9880 in our study [Table 6]. It has been hypothesized that COVID-19 may act on T lymphocytes,

Table 7: Comparison of time span between COVID19 and onset of type of mucormycosis

Days of covid	"only sinuses"	"Rhino orbital"	"Rhino orbito cerebral"	Total case of mucormycosis
.00	4	6	0	10
10.00	0	0	1	1
12.00	0	0	1	1
14.00	0	0	1	1
15.00	1	0	0	1
16.00	1	0	0	1
18.00	0	1	0	1
21.00	0	1	0	1
22.00	0	1	1	2
26.00	1	0	0	1
30.00	1	1	1	3
31.00	1	1	0	2
32.00	0	2	1	3
35.00	0	1	0	1
38.00	1	0	0	1
41.00	0	1	0	1
42.00	1	1	0	2
45.00	0	1	0	1
46.00	2	0	1	3
48.00	1	1	0	2
50.00	0	1	0	1
53.00	0	1	0	1
55.00	0	2	0	2
56.00	1	0	0	1
57.00	0	1	1	2
59.00	0	1	0	1
60.00	1	2	0	3
65.00	0	2	0	2
70.00	0	1	0	1
73.00	0	1	0	1
75.00	2	0	0	2
76.00	1	0	0	1
78.00	1	0	0	1
86.00	1	0	0	1
90.00	0	0	1	1

Table 8: Frequency of different types of mucormycosis on number of days of administration of steroid therapy

Type of mucormycosis	OXTGEN therapy/cycles															Chi-square value	P	
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14			15
"Only sinuses"	10	0	0	1	2	1	1	0	1	1	3	0	1	0	0	0	12.174	0.0.838
"Rhino orbital"	15	2	3	0	0	1	0	3	1	0	3	1	0	0	0	1		
"Rhino orbito cerebral"	8	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0		

Table 9: Frequency of different types of Mucormycosis on number of days of administration of oxygen supplements

Type of Mucormycosis	Number of days of Oxygen Supplements															Chi square value	P	
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14			15
"only sinuses"	9	1	0	1	2	1	1	0	1	1	3	0	0	0	0	1	22.529	0.659
"Rhino orbital"	16	1	2	0	0	2	0	3	1	0	3	1	1	0	0	0		
"Rhino orbito cerebral"	8	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0		

and damage to these cells is a significant factor that causes deterioration of the patient's condition. A high leukocyte count is common in critically ill patients due to damaged cells that induce innate inflammation in the lungs, which is largely mediated by proinflammatory macrophages and granulocytes.^[25] Thus, NLR can be considered a promising predictive factor in CAM patients.

Serum Ferritin level and D dimer are the two commonly used diagnostic tools to determine the extent of inflammation. The mean of Ferritin levels among various types of Mucormycosis in our study was 399 micrograms per litre [Table 6]. Although Ferritin levels were higher in CAM patients, it was not statistically significant. Cantinieaux *et al.*^[26] suggested an increase in iron concentration promotes fungal growth by decreasing phagocytosis and IFN production. Free iron is a must for Mucorales species for their biological processes, thus iron availability might represent an essential mechanism involved in the pathogenesis of CAM.^[27]

D dimer is a fibrin degradation product, a small protein fragment present in the blood after a blood clot is degraded by fibrinolysis.^[28] High levels of these indicate active clot formation. Our study showed a mean D dimer range of 474 ng/ml. Although the D dimer range was higher in CAM patients, it was not statistically significant [Table 6].

CRP is a non-specific, annular pentameric protein found in plasma, whose circulating concentration increases in response to inflammation. COVID-19 patients demonstrate elevated levels of CRP, hence can be used as an aid in triage, diagnosis, and prognosis.^[29] Mean range of CRP levels in CAM patients in our study were 52.6 mg/L. Although there was an increase in CRP levels, it was not statistically significant [Table 6].

The mean time interval between the COVID-19 and Occurrence of mucormycosis was 37.93 days and there was no significant correlation was found [Table 7]. It is suggested that during the recovery period, the clinicians should observe the patients for the occurrence of Mucormycosis and tapering of steroid levels along with close follow-up for control of DM is recommended.^[10]

In our study, 31 patients received steroids, and 29 patients presented with CAM without steroid treatment [Table 8]. Most of the studies have reported CAM cases in patients who received steroids.^[10,11,14] Steroid therapy causes disruption of glycaemic control and poor response of pulmonary macrophages in the prevention of growth of spores of Mucorales. The National Institute of Health,

conferring on the Randomized Evaluation of COVID-19 In therapy ("RECOVERY") collaborative group, recommended that the use of steroids must be reserved only for patients on supplemental oxygen or ventilator and not in milder cases. In addition, the risk of secondary infection is also specified.^[11,30] About 33 patients in our study received oxygen supplements during the treatment for COVID-19 [Table 9], and most of them presented with a Rhino-orbital form of Mucormycosis. However, there was no significant correlation.

Management

The management of mucormycosis is a multidisciplinary approach involving neurosurgery, ophthalmology, ENT surgeon, oral and maxillofacial surgeon, oncosurgery, plastic surgery, critical care, and pathology. Due to blood vessel thrombosis and tissue necrosis, the antifungal agents have poor penetration in the affected site in Mucormycosis. So, debridement of involved tissue is necessary to maximise the outcomes of disease. Biopsy from the nasal mucosa and/or sinuses can help achieve the diagnoses. The use of an intraoperative frozen section can be a great aid in deciding the surgical extent.^[31]

Orbital exenteration along with debridement of the pterygopalatine fossa and inferior orbital fissure should be performed in patients with progressive ocular involvement to reduce the fungal load and to prevent further extension of disease to the cranium. Functional endoscopic surgery has been routinely performed as a successful treatment option in treating mild and early rhinocerebral Mucormycosis in selected patients.^[32] Orbital exenteration is although life saving, not necessary in all patients and is a case-by-case base.^[33] The decision of Orbital exenteration is based on the progression of disease, involvement, and response to anti-fungal treatment. Surgical treatment must be always associated with systemic antifungal agents (polyenes, azoles, etc.) for better outcomes. In the case of vital structures where vital tissue cannot be completely resected, the anti-fungal agents can be used to control the infection.^[34]

The only signs and symptoms of isolated pterygopalatine fossa involvement is limited to the nasal cavity and sinuses. In such cases, endoscopically guided debridement along with anti-fungal therapy can control mucormycosis. Occasionally sphenopalatine foramen is also involved and in such instances, the foramen must be debrided or resected. The spread of mucormycosis can involve a greater palatine canal after involving pterygopalatine fossa with the invasion of nasopalatine and descending palatine vessels causing black necrosis of the palate or erosion of the hard palate. The involvement of internal maxillary artery and

its tributaries can cause complete necrosis of the maxilla and palate.^[35]

The surgical intervention may range from simple alveoloplasty to radical maxillectomy along with palatal debridement. The vitality of the palatal flap plays an important role in primary closure. The surgical options for a maxillofacial surgeon are maxillary sinus debridement via the Caldwell-Luc approach, marginal maxillectomy, Hemi maxillectomy, partial maxillectomy, complete and radical maxillectomy along with hard palate debridement. The surgical access can be gained by crestal incision, vestibular gloving incision, lateral rhinotomy with subciliar or supra orbital, and Weber Ferguson approaches.^[36]

The maxillary sinus, hard palate, and infratemporal fossa should be inspected and debrided if necessary. After the resection of involved tissue, the tissue defects can be closed by means of primary closure, obturators, and local pedicled flaps, such as Galealfrontalis-peri cranial nasolabial flap temporalis muscle flap, sub-mental flap, or facial artery island flap. Large defects can be reconstructed with free flaps such as anterolateral thigh flap, fibula osteocutaneous flap latissimus dorsi free flap, radial forearm free flap, scapula osteocutaneous free flap, transverse rectus abdominis musculocutaneous flap, vascularized iliac osteocutaneous flap, and chimeric flaps. Immediate reconstruction is not recommended in hemodynamically unstable patients, cellulitis, aggregated infections, incomplete resection, and when the recipient's vessels are involved and unhealthy.^[37]

Cavernous sinus and central nervous system (CNS) involvement can develop after the invasion of the orbital apex. Extension from the sphenoid sinus, frontal sinus, and cribriform plate to the CNS is rare. Signs and symptoms of involvement of CNS and cavernous sinus are unilateral headache, loss of consciousness and unilateral neurological signs on the opposite side, and seizures. Craniotomy and partial or complete lobectomy is advised in advanced diseases, although it is associated with some form of neurological deficit.^[38]

To conclude, the above findings indicate that there are multiple factors that can be linked to the occurrence of Mucormycosis in COVID-19 patients. The effect on the immune system of various suggested contributing factors results in CAM. The present study indicated that the factors may act independently (mainly DM) or jointly to cause CAM. Hence, the CAM cases must be addressed by a multidisciplinary team focussing on the control of co-morbidities, judicious use of steroids; zinc supplements,

and so on, along with appropriately planned individualized treatment modalities.

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Conflicts of interest

There are no conflicts of interest.

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