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Clinical, laboratory and radiological assessment of patients with COVID-19 associated mucormycosis (CAM) along with their management profile: an observational study

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ABSTRACT:

Objective: The Corona Virus Disease 19 (COVID-19) has become the most significant health problem worldwide. The surge of secondary infection (particularly fungal infections) in COVID-19 cases has been encountered in the form of Mucormycosis. Diabetes, indiscriminate use of corticosteroids, severity of COVID-19 infection are the few notable risk factors. The aim of this study was to determine the risk factors associated with Mucormycosis in COVID-19 patients, to assess the laboratory and radiological changes in COVID-19 associated Mucormycosis (CAM) patients and to evaluate the management profile in CAM patients.

Materials and Methods: This is a prospective observational study carried out on 105 COVID-19 patients admitted to COVID-19/Mucormycosis isolation ward for a duration of 6 months. Patient demographic data, clinical history, laboratory investigations, radiological findings and management profile were assessed. Various risk factors were assessed against the onset of mucormycosis (early/late).

Results: This study was conducted on 105 patients with history of COVID-19 infections now presented with features of mucormycosis. Mean age was 54.29 ±10.21 years (36-78 years). Male to female ratio-10.67:1. Only 12 active COVID-19 cases. Mean time interval between the onset of mucormycosis and COVID-19 symptoms was 27.6±5.9 days, with early onset disease (n=57,54.3%) and late onset disease (n=48,45.7%). Mean lag time between onset of symptoms and diagnosis was 9.24±2.23 days. Mean duration of steroid administration was 15.46±4.67 days with short duration (n=60,57.1%) and long duration (n=45,42.9%). Most common symptom and sign in our study group was facial pain (n=102,97.1%), sinus tenderness and conjunctival congestion with 81 cases (77.1%) each, respectively. The most common comorbidity was Diabetes Mellitus (n=84,80%). Rhino-orbital was the most common system involved (n=57,54.3%) and nasal involvement in all cases. Of the various parameters, the severity of COVID-19 infection (based on CTSS score) was associated with early onset mucormycosis (*p*-value-0.0001). The mortality rate was 42.86% (n=45).

Conclusions: In a patient with COVID-19 Associated Mucormycosis, risk factors such as diabetes mellitus and indiscriminate use of corticosteroids play a prominent role. Severity of the COVID-19 infection (assessed by CTSS) was found to be associated with early onset disease.

Keywords: *COVID-19, Mucormycosis, CAM, Fungus, Steroid.*

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INTRODUCTION

Even today the pandemic corona virus-19 disease (COVID-19/SARS-CoV-2) continues to be a significant health problem worldwide. It has varied epidemiological and clinical presentation, with a cluster of risk factors affecting the progression, severity and outcome of the disease. Diabetes mellitus has been identified as an independent variable that is associated with severity of COVID-19 infection. SARS-CoV-2 virus has been implicated in causing immune response impairment with reduction in CD4/CD8 T cell counts. These factors make the COVID-19 patients a high-risk group for fungal infections like mucormycosis and aspergillosis[1].

Mucormycosis is an infection caused by fungi that belongs to the order Mucorales. *Rhizopus oryzae* is the most common (70%) organism isolated from the patients with CAM. The few major risk factors for mucormycosis in COVID-19 patients include uncontrolled diabetes, indiscriminate use of corticosteroids, organ or bone marrow transplantation, neutropenia, burns, malignant hematological disorders etc[2-4]. The ability of inhaled sporangiospores to germinate and form hyphae in the host is essential for establishing active infection[3]. Patients with corticosteroid induced immunosuppression and/or with diabetes mellitus show inability of pulmonary alveolar macrophages to inhibit germination of sporangiospores[4,5].

Systemic glucocorticoids have given most promising results among all others. Glucocorticoids are inexpensive, easily available and also have shown to effectively reduce mortality in hypoxic COVID-19 infected patients[5,6]. Unfortunately, the widespread use of steroids has led to the surge of secondary bacterial and fungal infections. Mucormycosis infection in CAM patients with diabetes mellitus has also been recorded to be increasing[7,8].

Mucormycosis infection in COVID-19 patients case reports so far is shown to involve rhino-cerebral, rhino-orbito-cerebral region, disseminated gastro-intestinal mucormycosis[9,10]. Many cranio-facial skeletal osteomyelitis cases secondary to fungal infections are also being reported[11,12].

In this study we aspire to assess the biochemical/laboratory changes, radiological findings in COVID-19 associated mucormycosis patients along with assessing various risk factors and patient demographic profile.

PATIENTS AND METHODS

This is a prospective observational study carried out on 105 patients admitted to COVID-19/Mucormycosis isolation ward in our institute. Patient selection was performed by consecutive sampling. The study period of 6 months was between 01.04.2021 and 30.09.2021. Informed consent was taken from the patients and/or from their relatives before including them in the study.

Inclusion Criteria

All patients who were admitted with previous history of COVID-19 positive status through the flu OPD (Out Patient Department) or emergency ward having concurrent mucormycosis infection identified by radiological findings and clinical features which are suggestive of mucormycosis.

Exclusion Criteria

All patients below 18 years of age were excluded from this study. Isolated cases of mucormycosis with no association to COVID-19 infections were also excluded.

The demographic data of the patients and underlying systematic conditions were recorded in a predesigned proforma. Brief history regarding the complaints was extracted. Detailed history and comprehensive clinical examinations including general examination, ophthalmologic and otorhinolaryngological evaluation, and neurological examinations were done. Detailed history included time and duration of onset of first symptom/s, time interval between onset of COVID-19 symptom/s and mucormycosis infection, duration of mucormycosis infection, site of infection (ocular/cranial/para-sinuses), if ocular, and involvement of optic nerve or external oblique muscle. Co-morbidities, days of steroid usage, oxygen requirement and clinical outcome were also assessed. Laboratory investigations such as Hemoglobin (Hb), Total Leucocyte Count (TLC), Neutrophil & Lymphocyte count, C-Reactive Proteins (CRP), HbA1C, D-Dimer, Serum Creatinine and Serum Ferritin levels were assessed. Radiological investigations included High Resolution CT scan chest and CT Head and Face. Diagnosis of mucormycosis was based on radiological and microbiological demonstration of broad aseptate hyphae with right-angled branching on 20% potassium hydroxide (KOH) as well as PAS (Periodic Acid-Schiff) staining of specimen preparations from the nasal cavity and/or paranasal sinuses. Diabetic patients were started on insulin therapy. Corticosteroid treatment was tapered down and eventually ceased. Patients with predominant ophthalmic involvement received systemic and retrobulbar (intraconal) liposomal amphotericin-B injection. The systemic dose was 1.0 mg/kg/day, increasing to a total dose of 2.5-3 g, and the retrobulbar injection dose was 1 ml of 3.5 mg/ml concentration. Patients with extensive sinus involvement underwent extensive debridement of involved sinus along with amphotericin-B lavage. Repeat procedures were performed whenever necessary based on the clinical response. Follow-up was done for ninety days.

Statistical Analysis

SPSS version 24.0 software (SPSS, IBM Inc., Armonk, NY, USA) was used for data analysis. All continuous variables with normal distribution were presented as

Table 1. Demographic profile of the study group.

Demography	Categories	No. of cases	Percentage (%)
Gender	Male	96	91.4
	Female	9	8.6
Anemia	Anemic	69	76.5
	Non-Anemic	24	23.5
Diabetes	Diabetic	84	80
	Non-Diabetic	21	20
BMI	Underweight <18.5	6	5.7
	Normal 18.5-22.9	6	5.7
	Overweight 23-24.9	9	8.6
	Pre-obese 25-29.9	75	71.4
	Obese ≥30	9	8.6

mean ± standard deviation (SD). Time interval between onset of COVID-19 symptoms and onset of mucormycosis symptoms (Onset of mucormycosis-early/late) were compared with various parameters and other risk factors along with their statistical tests for significance (Chi-square test).

RESULTS

This study was conducted on 105 patients with history of COVID-19 infection now presented with features of mucormycosis. Mean age of this study group was 54.29 ±10.21 standard deviation (SD) years. Minimum and maximum patient age are 36 years and 78 years respectively. There were 9 females (8.6%) and 96 males (91.4%) with male to female ratio of 10.67:1. Majority of the patients were residing in rural areas (n=69,65.7%). Regarding their COVID-19 status at the time of hospitalization, only 12 patients (11.4%) were active cases and rest (n=93,88.6%) were declared as recovered from COVID-19 infection. In our study we have assessed the mean time interval between the onset of symptoms of mucormycosis after the patient was symptomatic for COVID-19 and it was found to be 27.6±5.9 days, median is of 25 days, patients with days onset of disease less than 25 days were classified as early onset disease(n=57,54.3%) and those above 25 days are classified as late onset disease(n=48,45.7%).

The average Body Mass Index (BMI) in our study group was 26.26±3.65 belonging to the pre-obese group (Table 1) according to Asian criteria. Majority of the cases belonged to pre-obese category (n=74,71.4%).

All the patients in our study had some kind co-morbid conditions. Most common comorbidity found to be Type-2 Diabetes Mellitus (n=84,80%) of which 12 patients (11.4%) had associated hypertension too (Table 1). Three patients (2.9%) were known cases of Chronic renal disease with history of ongoing dialysis and associated diabetes and hypertension. Six patients were found to be HIV positive (5.7%).

The mean duration of illness at the time of presentation was found to be 9.24±2.23 days which corresponds to the mean lag time between onset of symptoms and diagnosis. In our study all the 105 patients had history of steroid administration as a part of treatment for COVID-19 infection. Mean duration of steroid administration was 15.46±4.67 days with minimum duration being 9 days (6 cases) and maximum duration of 32 days (2 case). The median is of 15 days. Cases with duration of steroid administration less than or equal to 15 days are of short duration (n=60,57.1%) and those with more than 15 days is taken as long duration (n=45,42.9%).

In terms of symptoms, the most common symptom in our study group was facial pain (n=102,97.1%), followed by headache (n=99,94.3%) and fever (n=96, 91.4%). Most common clinical signs in our study were sinus tenderness and conjunctival congestion with 81 cases (77.1%) each, followed by proptosis (n=66, 62.9%) (Table 2).

Absolute neutrophil count, CRP, D-Dimer, Serum Ferritin and HbA1C levels were found to be elevated in our study (Table 3).

Table 2. Clinical features (signs and symptoms).

Symptoms	No of cases	Percentage	Signs	No of cases	Percentage
Eye pain	84	80	Sinus tenderness	81	77.1
Eye swelling	81	77.1	Conjunctival congestion	81	77.1
Loss of vision	81	77.1	Proptosis	66	62.9
Facial pain	103	97.1	Ptosis	42	60
Headache	99	94.3	Diplopia	6	5.7
Fever	96	91.4	Altered sensorium	6	5.7
Facial swelling	66	62.9			
Epistaxis	27	25.7			

Table 3. Hemogram and Laboratory profile of the study group.

Sl no.	Parameter	Mean ± SD	Normal Values	Minimum Value in this study	Maximum Value in this study
Laboratory investigations					
1	Hemoglobin (Hb)	10.65±2.19	6-15 gm/dL	6 gm/dL	15 gm/dL
2	Total Leucocyte Count (TLC)	10585±5101.9	4200-11,0000/cu-mm	4200/cu-mm	30000/cu-mm
3	Lymphocytes (%)	23.46±8.42	18-45%	7%	37%
4	Neutrophils (%)	74.46±8.63	40-60%	61%	91%
5	C-Reactive Protein (CRP)	32.66±23.9	3-10 mg/L	4 mg/L	86 mg/L
6	HbA1C	9.54±0.66	4-5.6%	8%	11%
7	D-dimer	1322.54±1696	<0.5 g/L	64 g/L	7431 g/L
8	S. Creatinine	0.74±0.51	0.7-1.2 mg/dL	0.4 mg/L	2.02 mg/L
9	S. Ferritin	1283.83±344.56	10-250 ng/mL	610 ng/mL	1974 ng/mL

All these patients had undergone some form of radiological investigations like HRCT chest at the time of COVID-19 infection as well as CT head and face for mucormycosis. CT Severity Score obtained from HRCT chest was compiled and classified into different grades based on the extend of lung involvement, higher the score greater the lung involvement (Table 4). Mean CT severity score (CTSS) in our study group was found to be 15.5 implying that most of the patients had significant lung involvement during COVID-19 infection stage who were found to have early onset of fungal infection (*p*-value=0.0001, 95% CI) with minimum value of 10 and maximum value of 23.

Most patients had CTSS of 16 (n=24,22.9%) followed by 11 (n=15,14.3%). The majority of the patients had history of severe lung involvement (CTSS value 16-25) during their COVID-19 infection stage (n=57,54.3%) and moderate severity (CTSS 9-15) in 48 cases (45.7%). In our study no patients were present in Mild grade group (CTSS value: 0-8) (Table 4).

Nasal involvement was seen in all patients (100%) in the form of infiltration into nasal turbinates. In this study, most common sinus to be involved is Maxillary sinus (n=75,71.4%) and most common ocular structure involvement is extraocular muscle edema, seen in 30 patients (28.6%). Right side was found to be more commonly involved (n=78,74.3%).

Most common site-system found to be involved in our study was Rhino-Orbital mucormycosis seen in 57 patients (54.3%) followed by Rhino-Orbital-Sinus mucormycosis (n=33,31.4%). Rhino-sinusoidal involvement was seen in 15 cases (14.3%).

Table 4. Classification of patients based on severity of COVID-19 infection (as per CTSS).

Grading†	CTSS value (0-25)	No. of Cases	Percentage (%)
Moderate	9-15	48	45.7
Severe	16-25	57	54.3
Total	0-25	105	100.0

†Mild: 0-8 CTSS. No patients in this group.

Only 9 patients (8.6%) required oxygen support during the study period and majority of the patients required in-hospital admission (n=81,77.14%)

Some form of surgical intervention was required in 81 (77.1%) patients and the rest 24 patients (22.9%) were managed conservatively. Nasal scraping as well as excised/debrided specimens were stained with specialized satins (e.g., PAS) with positivity rate of 100% (Figure 1).

Retrobulbar Amphotericin-B injection was given for 57 cases (54.3%) followed by Debridement (n=15,14.3%), Evisceration (n=6,5.7%), and Modified Denker's Procedure in 9 cases (8.6%) along with retrobulbar injection (n=3,2.9%) and Debridement (n=6,5.7%).

Comparison and cross tabulations of various risk factors and patient demographics, with onset of mucormycosis (early and late onset) are shown in Table 5. Of the various parameters and patient demographics severity of COVID-19 infection (based on CTSS) was found to be statistically significant (*p*-value-0.0001). Gender, anemia status, history of Diabetes Mellitus, elevated D-Dimer, elevated CRP, and long duration of steroid usage were associated with early onset of Mucormycosis infection (Table 6) but *p*-values of each of them were >0.05 (statistically insignificant). The cumulative mortality rate of this study group during this period was 42.86% (n=45).

DISCUSSION

Our study was conducted with the aim of evaluating the patient profile and assessing the risk factors involved in secondary mucormycosis infection in COVID-19 patients over a period of 6 months. In this study, the majority were middle aged men (mean age-54.29±10.21, range 36-78 years) as also seen in the studies by Arora et al[13] where median age was 57 years; range 29-75 years and by Pakdel et al[14] where median age was 52 years; range 14-71 years. But as per a study by Bayram et al[15], the mean age was 73.1±7.7 years (range 61-88 years). The male to female ratio of our study group was 10.67:1. Male predominance in incidence was also seen studies by Patel et al[12] (323; 69.5%), Arora et al[13] (45; 75%), Pakdel et al[14] (66%), and Bayram et al[15] (9; 81.8%).

Table 5. Radiological profile of the study group.

Site Of Involvement	Part Involved	No. of cases	Percentage (%)
Nasal	Turbinate (middle and lower)	105	100
	Floor	57	54.3
	Osteo-meatal complex	81	77.1
Sinus	Maxillary sinus	75	71.4
	Ethmoid sinus	72	68.6
	Sphenoid sinus	69	65.7
	Frontal sinus	60	57.1
Intracranial	Cavernous Sinus	3	2.9
Ocular	EOM edema†	30	28.6
	Erosion of Lamina Papyracea	18	17.1
	Optic nerve involvement	12	11.4

†EOM – Extra Ocular Muscle

In the study by Arora et al[13], active COVID-19 cases (n=11) were less, when compared to recovered cases (n=49) as that seen in our study where active cases (n=12, 11.4%) are less than recovered cases (n=93, 88.6%). This signifies that the secondary infection can occur any time after the first course of active COVID-19 infections. The mean time interval between onset of COVID-19 symptoms and onset of mucormycosis was 27.6±5.9 days. While in the studies of Pakdel et al[14] (7 days) and Bayram et al[15] (14.4±4.3 days; Range 7-23 days), the time interval was found to be less than ours. The mean lag time between onset of symptoms and diagnosis of mucormycosis infection in our study (9.24±2.23 days) and Bayram et al[15] (5.1±1.8 days) was found to be closer.

Wenzhong and Hualan et al[16] state that the novel COVID-19 virus attack causes a reduction in the release of functioning hemoglobin leading to respiratory deprivation and distress as proven in our study, where mean Hb levels were lower than normal (10.65±2.19) and it was also observed that among those who developed an early onset of CAM, 42.85% (n=45) of them were anemic.

The most common co-morbidity observed in our study was type-2 diabetes mellitus (84 cases; 80%). In the studies by Patel et al[12] (n=342, 79.7%; Total cases=465); Arora et al[13] (n=59, 98.3%; Total cases=60) and Bayram et al[15] (n=8,73%; Total cases=11) also had diabetes as the dominant predisposing factor. The mean HbA1c was found to be higher i.e., 9.54±0.66 (minimum-8%; maximum-11%) as also seen by Arora et al[13] (mean-9.25).

In the study done by Arora et al[13] on 60 cases, 22 cases (36.67%) were treated with home quarantine while other 38 patients (63.33%) required in-patient management in hospitals as was in our study where majority of the patients required in hospital admission (n=81,77.14%).

Similar to our study, Rhino- Orbital Mucormycosis had highest incidence as found by Patel et al[12] and Nehara et al[9]. The most involved sinus in Bayram et al[15] was ethmoid sinus (90.9%) followed by maxillary (81.8%), whereas in ours it was maxillary sinus (n=75,71.4%). In their study, left sided (6 patients; 54.5%) involvement was more in contrary to ours, where we had right side

Table 6. Crosstabulations between various risk-factors and onset (early/late) of Mucormycosis.

Parameter		Onset of Mucormycosis		Total No. of cases n	Net Percentage (%)	*p*-value‡
		Early onset n (%)	Late Onset n (%)			
Gender	Male	54 (51.4)	42 (40)	96	91.4	0.446
	Female	3 (2.86)	6 (5.71)	9	8.6	
Anemia	Anemic	45 (42.85)	33 (31.43)	69	76.5	0.317
	Non-Anemic	9 (8.6)	15 (14.3)	24	23.5	
Diabetes	Diabetic	42 (40)	42 (40)	84	80	0.309
	Non-Diabetic	15 (14.3)	6 (5.71)	21	20	
D-Dimer	Normal	0(0)	6 (5.71)	6	5.7	0.112
	Elevated	57 (52.3)	42 (40)	99	94.3	
CRP	Normal	9 (8.6)	12 (11.43)	21	20	0.497
	Elevated	48 (45.7)	36(34.3)	84	80	
Severity of COVID-19 infection (CTSS based)	Moderate Severe	12 (11.43)	36 (34.3)	48	45.7	0.0001
	Severe	45 (42.85)	12 (11.43)	57	54.3	
Steroid usage	Short duration	24 (22.9)	21 (20)	45	42.9	0.922
	Long duration	39(37.1)	21 (20)	60	57.1	
Outcome	Recovering	54 (51.4)	45 (42.85)	99	94.3	0.9
	Death	24 (22.86)	21 (20)	45	42.86	

‡Chi-square test

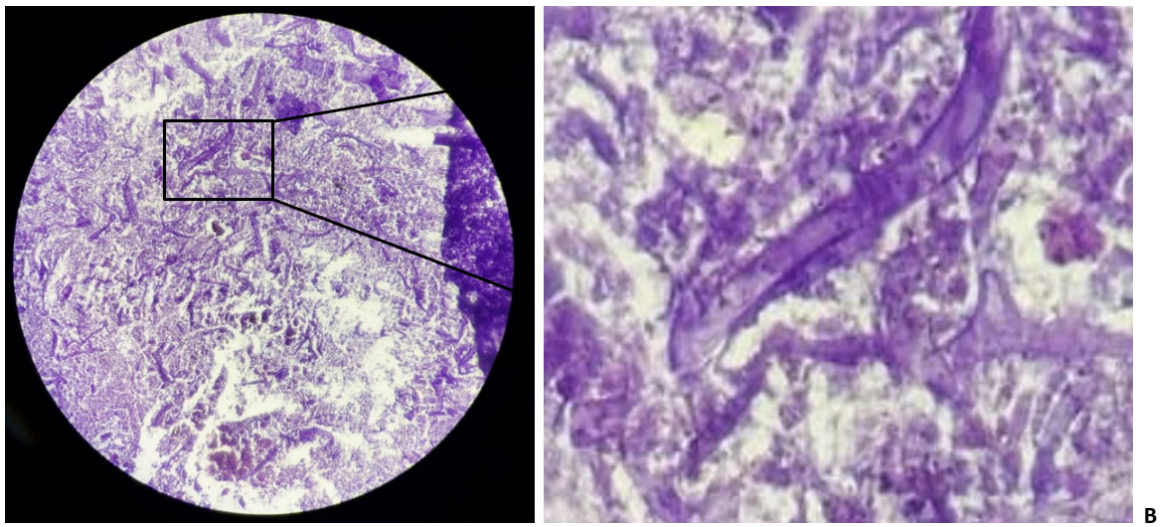

Figure 1. PAS (Periodic Acid-Schiff) staining of specimen showing fungal hyphae. **A**, Microscopic image of specimen. **B**, Magnified part (x400) showing fungal hyphae.

preponderance (n=78,74.3%) and intracranial involvement was seen in 3 patients as that of ours (n=3,2.9%) which was involvement of cavernous sinus in both the studies. Pakdel et al[14] study had cavernous sinus involvement (n=7, 46%).

Due to variations in treatment protocols with institutions and controlling bodies, indiscriminate use of corticosteroids has occurred. For this reason, patients were more prone to secondary infections. In our study as well as in the study by Bayram et al[15] steroid therapy was given to all the patients. However, in the study by Arora et al[13] and Pakdel et al[14] only 63.3% and 46% respectively were administered with the same. IV Amphotericin-B was the primary anti-fungal drug used and was administered to all patients and retrobulbar injections in few. Similarly, in the studies by Patel et al[12], Arora et al[13], Pakdel et al[14], and Jeong et al[17] (760/785; 96.8%), IV amphotericin-B was found to be the most commonly prescribed first line anti-fungal drug. In the study by Arora et al[13] (6 /60 patients) and Bayram et al[15] (the mean number of injections were 2.2± 0.6) retrobulbar injections were considered only in few early cases of orbital disease.

In the study done by Arora et al[13] and Pakdel et al[14], 30 patients (N = 60) and 9 patients (N=39) were given oxygen support respectively, while rest had no oxygen requirement. Only 9 (8.6%) of our patients required oxygen support. Furthermore, in our study, advanced cases were managed by debridement, evisceration, Modified Denker's procedure and Modified Denkers procedure with extensive debridement was done in 15 cases (14.3%), 6 cases (5.7%), 3 cases (2.9%) and 6 cases (5.7%) respectively. In the study by Arora et al[13], out of 60 cases, 10 patients underwent Functional Endoscopic Sinus Surgery (FESS), in 2 patients FESS was combined with maxillectomy and orbital exenteration and the rest of 48 patients underwent radical sinus debridement. While in another study by Pakdel et al[14], 14 out of total 15 patients underwent sinus debridement; 5 (33%) patients underwent orbital exenteration and 2 (13%) patients had extensive palatal debridement. Bayram et al[15] performed a second surgical procedure for extensive debridement of involved tissues on 8 patients (72.7%).

The severity of COVID-19 infection (as per CT Severity Score) was found to be statistically significant (p-value= 0.0001; CI = 95%) based on chi-square test in our study. The other factors such as gender, diabetes mellitus, anemia, D-Dimer and steroid usage were found to be statistically in-significant (p-value > 0.05). Similar results were also seen by Arora et al[13] and Pakdel et al[14], where age, gender, CTSS severe score and corticosteroids therapy were found to be statistically in-significant (p-value > 0.05). While in the study by Prakash et al[18] uncontrolled diabetes, (n=172; 56.8%; p-value = 0.0001), was found to be statistically significant.

While comparing other laboratory investigations, the mean D-Dimer value and mean CRP values were higher than normal i.e., 1322.54±1696 and 32.66±23.9, respectively. Similar results were also obtained by Bayram et al[15] (mean D-Dimer-1362.4±468.9 g/L), but in a study by Pakdel et al[14] the mean CRP was found to be more elevated (81.73±61.2). Elevated levels of D-Dimer are associated with poor prognosis, as well as higher risk of mortality[19].

In the studies of Pakdel et al[14], Bayram et al[15] and Jeong et al[17], 90-day follow-up mortality was 63.6%, 47% and 41.0% (349/851) respectively similar to that in our study (n=45; 42.86%).

CONCLUSIONS

In a patient with COVID-19 Associated Mucormycosis, risk factors such as diabetes mellitus and indiscriminate use of corticosteroids play a prominent role due to immunosuppression. Severity of the COVID-19 infection (assessed by CTSS) was found to be associated with early onset disease. Elderly patients are found to be most commonly affected.

The main limitation of this study was the small sample size. Due to lack of a centralized data regarding treatment given, especially dosage of corticosteroid ad-

ministered during the COVID-19 infections hampered in calculating a cumulative as well as amount given per body weight and their association with onset of CAM.

Further prospective cohort studies are required to assess the long-term effects of COVID-19 as well as CAM in various demographic groups which will further enhance our ability to deal with such situations in future and help in formulating effective treatment protocols.

Ethics Approval:
Not required as it was an observational study.

Informed Consent:
Obtained from the patients and/or from legal guardians.

Availability of Data and Materials:
All data are available upon reasonable request by contacting the Corresponding Author of the manuscript.

Conflict of Interests:
The authors declare that they have no conflict of interests.

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All authors were involved in every aspect of the study.

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