



Changing Trend of Risk Factors of Mucormycosis Including Diabetes, Acidosis, and Serum Iron in the Second Wave of COVID-19

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Abstract To analyze the clinic-pathological profile of patients presenting with mucormycosis infection to a tertiary care center during the second wave of the COVID-19 pandemic in India. This descriptive cross-sectional study was conducted in a hospital setting from April 2021 to July 2021 and analysis was carried out to find associations between the stratified data and the extent of the disease involvement based on radiological findings. Statistical tests like percentage, average, chi-square test, etc. were used wherever relevant using software called Minitab13. All the 51 patients had involvement of at least one paranasal sinus. The incidence of previously established risk factors was diabetes (66.67%), history of severe COVID-19 disease (5.88%), raised serum iron levels (1.96%), Acidosis (3.92%), steroid administration (62.75%), oxygen administration (25.49%). Elevated serum urea levels (76.47%), alkalosis in 50.98% and hyperglycemia on multiple occasions (41.17%) were observed. The mean days between start of treatment for COVID-19 and appearance of first symptom suggesting mucormycosis were found to be 27.59 days. Only in 5.88% participants mucormycosis preceded COVID-19 infection detection. The current work finds presence of traditional risk factors and associations in significantly lower frequencies than the reviewed literature. However, blood urea was elevated in three fourths of the

participants. Larger scale studies in mucormycosis patients are warranted for finding the role of other risk factors including possible role of elevated blood urea and hyperglycemia in the present era.

Keywords Mucormycosis · COVID-19 · Pandemic · Diabetes mellitus

Introduction

The prevalence of mucormycosis was high in India even before COVID-19 rummage, approximately 0.14 cases per 1000 population, which is more than 80 times as compared to developed countries. The rising trend of mucormycosis was yet again established by Chakrabarti et al. who published three consecutive studies from a single center; the incidence of mucormycosis was 12.9 cases/year over the first decade (1990–1999), 35.6 cases/year over next 5 years (2000–2004) and, during eighteen months (July 2006–December 2007), 50 cases/year [1].

In a study that reviewed 41 cases in 16 months all over the world of COVID-19 associated mucormycosis, patients have a history of diabetes mellitus (DM) (94%), especially poorly controlled DM in two third of cases and severe or critical COVID-19 in 95% [2]. In a retrospective multi-centric analysis conducted in an Indian Metropolitan city that reviewed 18 cases of COVID associated mucormycosis in seven months, a strong association of fungal infections with diabetes, COVID-19, and administration of corticosteroids was observed. The study also concluded that COVID-19 can trigger diabetic ketoacidosis, which can trigger fungal infection even in absence of corticosteroids [3]. However, the limited body of data from recent works has shown variable percentage of patients having diabetes (76.6%, 83.9%) [4,

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5]. In contrast, another study concluded that glucocorticoids can cause mucormycosis infection even in absence of traditional risk factors like diabetes [6]. An elevated level of serum iron is another established risk factor [1]. Extensive researches in the pre COVID era have shown that elevated levels of available serum iron promote growth of mucorales. There is role of presence of diabetic acidosis and external iron in increasing this availability [1]. The few available post COVID studies have found the serum iron or serum transferrin values to be variable [4, 5, 7]. Thus, there is a need of the risk factors to be studied to suggest or refute the role of newer or neglected ones.

Due to the rare nature of the disease, there is a lack of adequate medical literature, and especially little is known about post-COVID mucormycosis infections in India. The objective of the study was to analyze the clinicopathological profile of patients presenting with mucormycosis infection in our tertiary care center with emphasis on the study of established risk factors in them during the second wave of the COVID-19 pandemic in India from April 2021 to July 2021.

Material and Methods

This prospective observational study was conducted at a tertiary care center in western India. This study involved participants presenting with mucormycosis to the hospital in the duration of second wave of COVID-19 who were microbiologically and/or histopathological confirmed cases. Ethical approval was taken from the institutional ethics committee, informed consent was taken from all participants and their privacy and confidentiality was ensured.

Inclusion criteria Mucormycosis patients admitted to our hospital from 1st April 2021 to 1st July 2021 who had been microbiologically and/ or histopathologically diagnosed.

Exclusion criteria (1) Mucormycosis patients refusing admission. (2) Mucormycosis patients admitted but unwilling to give consent for being included in the study.

The data collected included demographic, including name, age, sex, and residence, history of comorbidities and addictions, biochemical tests including random blood sugar level, total WBC count, serum urea, serum creatinine, HbA1c, serum iron, and arterial blood gas analysis at the time of admission, COVID-19 related information as—history present or absent, severity, the time between the start of treatment and appearance of the first symptom suggestive of mucormycosis infection, steroid and oxygen administration during treatment of COVID-19. Findings including histopathological, microbiological, and extent of spread based on latest radiological findings were also recorded.

The relevant data was then stratified based on normal or standardized ranges including: (1) Age: Below 40, 41–50, 51–60, 61–70, 71 years and above. (2) Sex: Male, female,

other. (3) Random blood sugar level: above or below 200 mg/dl as per American Diabetic Association and WHO [8]. (4) Total WBC count: 4000–11,000/mm³ (5) Serum Creatinine: 0.7–1.3 mg/dl for males and 0.6–1.1 mg/dl for females. (6) Serum urea: 7–18 mg/dl for males and 8–21 mg/dl for females. (7) Serum iron: 49–181 mcg/dl for males and 37–170 mcg/dl for females. (8) HbA1c—classified as per American Diabetic association: (a) < 5.7 mg/dl as non-diabetic, (b) 5.7–6.4 as pre diabetic, (c) 6.5–8 as controlled diabetes, (d) > 8 mg/dl as poorly controlled diabetes [6–8]. (9) Arterial blood gas analysis as per Castro & Keenaghan 2020: (a) pH—7.35 to 7.45. (b) HCO₃—22–26 mmol/L and (c) PaCO₂—35–45 mmol/L [9]. (10) COVID-19 severity—Mild, moderate, and severe based on previous computed tomography (CT) findings. (11) Time between the start of treatment of COVID-19 up to the first symptom of mucormycosis was divided based on long COVID syndrome (beyond 3 weeks) and Chronic COVID syndromes (beyond 12 weeks) [10] into: (a) Mucormycosis in Non-COVID-19, (b) From the admission for COVID-19 treatment to 21 days, (c) 21–84 days (long COVID syndrome). (d) More than 84 days (chronic COVID syndrome). The sampling strategy was universal sampling. Fifty-one patients participated in the study.

Analysis to find associations between the stratified data and the extent of the disease involvement based on radiological findings was carried out. The extent of the disease was considered as an invasion of mucormycosis into the nose, paranasal sinuses, orbits, and brain.

Statistical tests like percentage, average, chi-square test, and others were used wherever relevant using software called Minitab13.

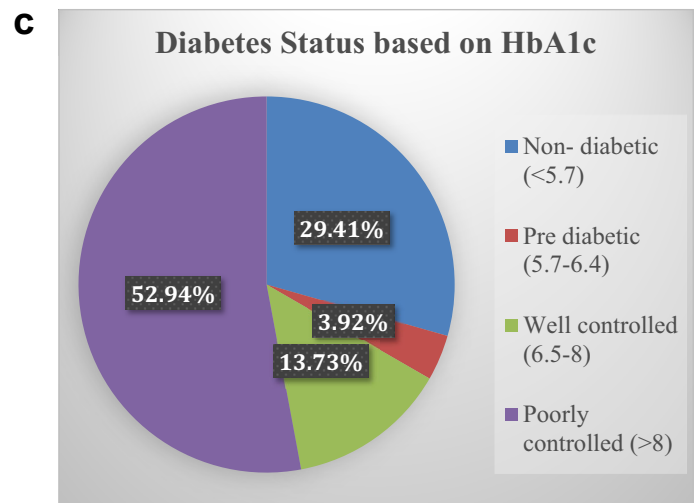
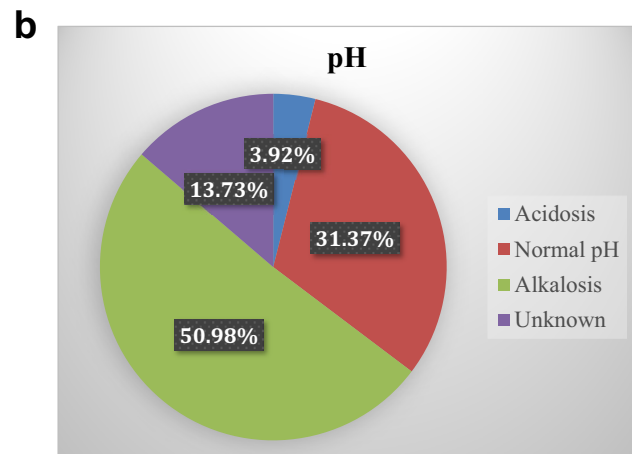
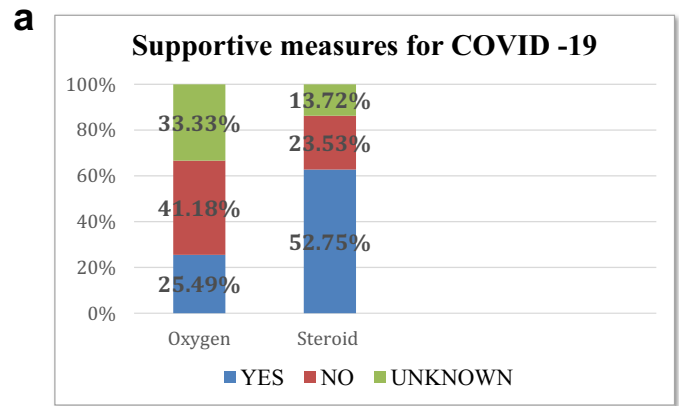
Results

A total of 51 subjects were included in this study, who were diagnosed and treated for mucormycosis and COVID-19 and consented to participate. The age ranged from 30 to 86 years with 53 years median age. There were almost twice men affected than females (male: female = 1.83:1).

All the patients (100%) had at least one paranasal sinus involvement, followed by nasal (82.35%), orbital (35.29%), and brain involvement (25.49%).

76.47% of patients had a past history of COVID-19 infection, 62.75% had awareness of received steroid therapy and 25.49% had history of oxygen administration (Fig. 1a). The unknown status of oxygen and steroid therapy was 33.33% and 9.22% respectively due to the unavailability of the COVID-19 admission discharge slips with the patients and lack of awareness of the treatment received. Among post COVID-19 patients, majority (37.25%) had moderate disease; followed by mild disease in 23.53%

Fig. 1 **a** Frequency distribution of the supportive measures in patients of COVID-19. **b** Frequency distribution of the pH in Mucormycosis patients. **c** Frequency distribution of the Diabetes status based on HbA1c of Mucormycosis patients



and severe disease in 5.88%. 33.34% of the participants were unaware of the severity. Absence of COVID-19 history could not be medically confirmed by anti-COVID-19 antibody titre testing or CT-Thorax. The first symptom of mucormycosis appeared as early as 2 days after the initiation of treatment of COVID-19 up to as late as 115 days after the start. 37.25% of the participants could be placed in the long COVID syndrome category and 1.96% in the chronic

COVID-syndrome category. Highest burden of cases was observed in the time period between 3 and 8 weeks (long COVID syndrome) and the period upto three weeks after the start of treatment for COVID-19 infection which was 37.25% each. Based on HbA1c levels, more than half of the participants (52.94%) had uncontrolled diabetes, whereas almost one third (29.41%) did not have diabetes. 13.73% had well-controlled diabetes and 3.92% were pre-diabetic

(Fig. 1c). Arterial blood gas analysis could be performed in only 86.27% of the participants at the time of admission (Fig. 1b). Only 4.54% of all participants were in acidosis, whereas 59.09% of participants were in a state of alkalosis at the time of admission. Serum iron levels, the specific growth factor for mucormycosis, was below the normal range in 37.25% of participants against only 1.96% of participants with increased values (Fig. 2a). The presence of elevated blood urea was seen in 76.47% of subjects, the frequency of which was higher than the presence of raised blood glucose, serum iron, and acidosis (Tables 1, 2) (Fig. 2b).

Significant associations (95% confidence interval), found between the stratified data and the radiological extent of the involvement of mucormycosis, were as follows:

1. Presence of comorbidities and addictions including hypertension, thyroid disorders, tobacco, and alcohol with nasal involvement of mucormycosis ($P=0.03$).
2. Duration between the initiation of COVID-19 treatment and the appearance of the first symptom suggestive of mucormycosis infection with nasal involvement of mucormycosis ($P=0.03$).
3. Serum creatinine levels and orbital involvement of mucormycosis ($P=0.01$).

Discussion

There is documented evidence of increasing cases of invasive mucormycosis in India since the past 3 decades, with the highest of 50 cases per year [1]. However, an official estimate of these cases in May 2021 was 11,700 [11]. Due to this unprecedented spike, mucormycosis could be called a public health concern as of now. In the present study a higher incidence in men (64.71%) than women (35.29%) has been found similar to the other post covid studies [7]. The youngest patient was 30 years old and the eldest was 86 years. The absence of pediatric mucor cases could have been because COVID-19 did not affect children as severely as adults [12]. Mean or average age of our study (53.96 years) was similar in that of other post covid studies (49 years, 51.7 years and 55 years) [4, 5, 7].

There was a significant association found between the presence of co-morbidities (other than diabetes mellitus) & addictions and the nasal involvement of the disease. However, other structures involvement including the brain, eye, and orbit did not show such significant association.

There were no patients with pulmonary involvement or with disseminated disease in present work unlike others [5].

Many studies have established a strong association of diabetes mellitus with mucormycosis [2, 3, 6]. A random blood glucose level over 200 was seen in 47.06% of our participants; however symptoms of hyperglycemia could not

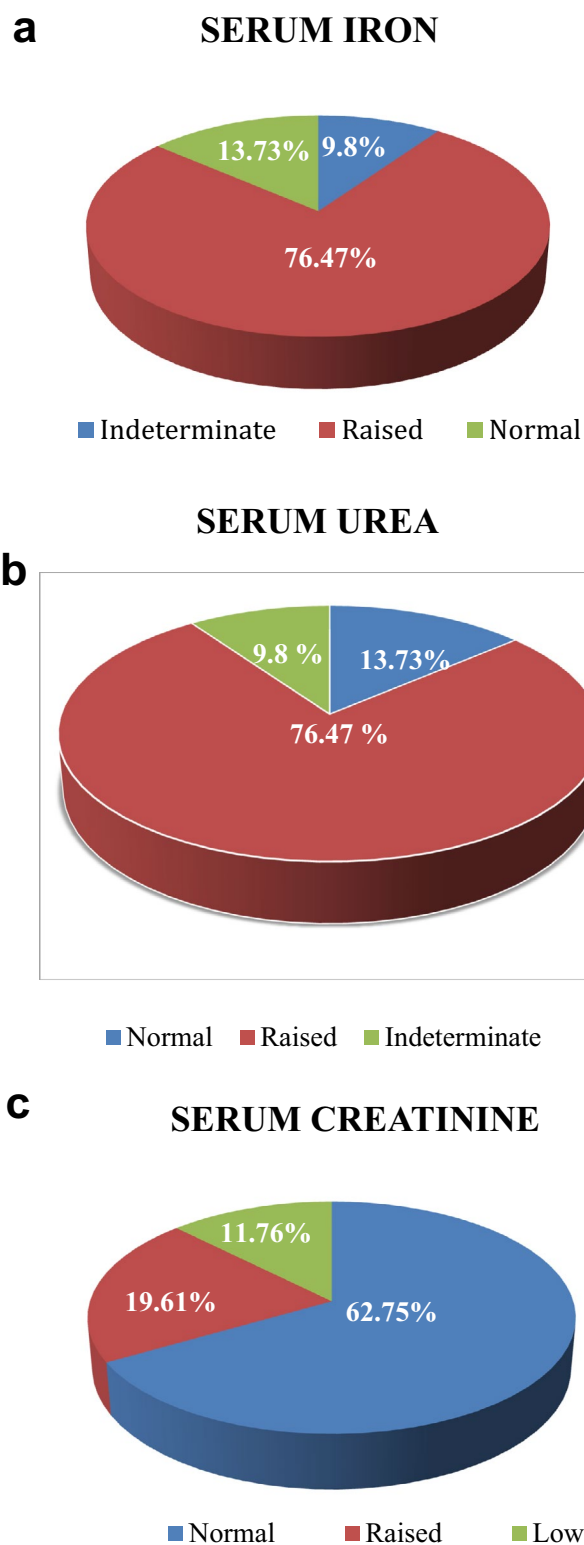


Fig. 2 a Frequency distribution of the serum iron levels in Mucormycosis patients. b Frequency distribution of serum urea levels in mucormycosis patients. c Frequency distribution of serum creatinine levels in patients of mucormycosis

Table 1 Variable frequency table

Variable	Percentage (frequency) % (n)
Gender—Male	64.71% (33)
Comorbidities and addictions	74.51% (38)*
HBA1C (mg/dL)	
6.5–8	13.73% (7)
> 8	52.94% (27)
COVID-19 History	
Concurrent	5.88% (3)
Sequential	76.47% (39)
Absent	21.57% (11)
Unknown	1.96% (1)
Time between start of treatment of COVID-19 and appearance of first symptom of mucormycosis (weeks)	
Before treatment	5.88% (3)
< 3	37.25% (19)
3–12	37.25% (19)
> 12	1.96% (1)
COVID-19 Severity	
Mild	23.53% (12)
Moderate	37.25% (19)
Severe	5.88% (3)
Oxygen administration	25.49% (13)
Steroid administration	67.25% (32)
Mixed infection	13.73% (7)
Antifungal treatment	98.04% (50)
In hospital mortality	5.88% (3)
Radiological involvement	
Brain	25.49% (13)
Orbit	35.29% (18)
Nasal	82.35% (42)
Sinuses	100% (51)

*Significant association between co-morbidities and addictions with nasal involvement ($p=0.01$)

Table 2 Variable mean and standard deviation

Variable	Mean ± SD
Time between start of treatment of COVID-19 and appearance of first symptom of mucormycosis (days)	27.59 ± 22.48 [#]
Serum urea (mg/dl)	32.59 ± 18.55
Serum creatinine (mg/dl)	1.11 ± 0.45*
Serum iron (mg/dl)	57.39 ± 37.34
Random blood glucose (mg/dl)	211.30 ± 98.55
Total white blood cell count (/mm ³)	10,504 ± 4005.2
HbA1c (gm %)	8.32 ± 2.7
Age (years)	53.96 ± 12.94

[#]Significant association found between nasal involvement and time between start of treatment of COVID-19 and appearance of first symptom of mucormycosis in days. ($p=0.01$)

*Significant association found between orbital involvement and serum creatinine levels ($p=0.03$)

be ascertained in many of them. This could be attributed to the attention paid to symptoms of mucormycosis more than hyperglycemia or the intrinsic stress of mucormycosis could also result in elevated levels of random blood sugar. However, 66.67% of participants had HbA1c levels over 6.5 mg/dL, and were considered diabetic [8], of whom 79.4% had uncontrolled diabetes which constituted 52.94% of all study participants (Fig. 1c). The percentage of diabetic patients ranged from 31.7 to 85.71% of the post COVID 19 mucormycosis ones in other works [4, 5, 7].

Of the 33.33% participants who were non diabetic and pre diabetic, 41.17% had elevated levels of random blood glucose on multiple occasions. It is hypothesized that sustained hyperglycemia possibly of even a considerable short phase, while COVID-19 stress may play a role in the causation of the mucormycosis infection. The frequency of patients having diabetes and uncontrolled diabetes was relatively lower than the known literature i.e., 94% and 67%, respectively [2]. This might indicate the increasing role of risk factors other than or coexisting diabetes and uncontrolled diabetes in etiopathogenesis of

mucormycosis in this second wave COVID-19. Also, in non-diabetic patients of mucormycosis there are known causes of immunosuppression, including corticosteroid use, hematological and other malignancies, organ transplantation and prolonged neutropenia etc. But in this work the possible risk factor—corticosteroid use—as well as the others was also not found consistently in them. This also may indicate role of lesser known or unknown risk factors.

A history of severe COVID-19 and diabetic ketoacidosis are documented to have a role in pathogenesis of mucormycosis [2, 13, 14]. However, only 5.88% of subjects were found to have a past history of severe COVID-19 in the present study. This is in contrast to the 45% of subjects in other studies, especially in pulmonary or disseminated disease (80%) [15]. Almost one fifth of the patients did not have a known history of COVID-19 but this absence of history could not be confirmed by serology testing for COVID-19 antibodies or CT scan of thorax, therefore any inference is indeterminate. Almost one fourth patients had only mild COVID-19, similarly, only two participants displayed acidosis at the time of admission out of which only one had diabetes. Among the participants whose arterial blood gas analysis was conducted, 59.09% suffered from alkalosis instead of the expected acidosis [3] (Fig. 1b). Another study also has mentioned the absence of the diabetic ketoacidosis in their subjects [4]. Exact cause of the alkalosis could not be determined as majority of the patients were referred from other hospitals and the non-receipt of amphotericin B could not be ascertained before admission. Also, no significant associations were found in other parameters of ABG that is pH, bicarbonate ions and PCO₂ with radiological involvement of mucormycosis.

Hemochromatosis or iron overload is also a traditional risk factor for mucormycosis as iron acts as a growth factor for the fungus [1]. Discordant to this only 1.96% of participants were found to have elevated serum iron levels (Fig. 2a). Another work has found elevated serum iron in people with COVID-19 and ketoacidosis [15]. Serum ferritin values have been found elevated in two studies [5, 7], and yet another mentions variable result [4]. However, 37.25% of the participants had serum iron values below normal range (Fig. 2a). Also, no significant association of serum iron levels and extent of radiological involvement by the fungus were found. It is known that even in the patients expected to have elevated available serum iron, such as those with diabetic ketoacidosis, most iron remains bound to carrier molecules, and free serum iron would still be present in submicromolar concentrations that induce the high-affinity rather than the low-affinity uptake system, for example iron regulated high-affinity ferric reductase activity [14]. This might explain the occurrence of mucormycosis in these patients in spite of having low serum iron.

A significant association was found between serum creatinine levels and orbital involvement of the disease. Noteworthy was the presence of elevated blood urea in 76.47% of subjects (Fig. 2b), the frequency of which was higher than the presence of raised blood glucose, serum iron, and acidosis. Such high frequency of uremia could be attributed to preexisting diabetes mellitus, previous administration of amphotericin, and dehydration [16, 17]. Some patients displayed clinical features of dehydration at the time of admission, though it was not assessed critically. About 12% of the patients had both raised serum urea and serum creatinine, however only one patient had creatinine levels high enough to contra-indicate administration of amphotericin, therefore 50 out of the 51 participants received amphotericin at the time of admission. Another work found raised blood urea and blood creatinine levels [7].

The use of glucocorticoids and ventilator-based oxygen supply has also been associated with mucormycosis [3, 6]. 62.75% of the participants stated to have received steroid therapy, and 25.49% of participants stated to have received oxygen supply during their treatment of COVID-19 (Fig. 1a), however since the patients did not provide medical records as proof, recall bias cannot be ruled out which is a limitation to our study.

When long and chronic COVID syndrome relation with mucormycosis was studied, a significant association was found in the duration between the initiation of treatment of COVID-19 and the appearance of the first symptom suggestive of mucor infection and nasal involvement of mucormycosis. Highest burden of cases was observed in the time period between 3 and 8 weeks (long COVID syndrome) and the period between first day to three weeks after the start of treatment for COVID-19 infection which was 37.25% each.

Three deaths occurred during the period of the study. No significantly common clinical and/or laboratory findings were found in these subjects. The first patient succumbed to respiratory failure with renal failure few days after surgery. This patient was getting injectable lipophilic amphotericin intermittently when his creatinine was low. Other two patients had extensive rhino-nasal-orbital-cerebral mucormycosis; extensive intracerebral involvement was the cause of death in these cases.

There were seven cases of mixed infections of mucormycosis with aspergillosis (five cases), candidiasis (one case), and actinomycetes (one case), respectively.

Present study is one of the first few works providing clinical and investigational findings of mucormycosis cases in the second wave of COVID-19 with their associations in a considerable number of subjects from a single tertiary care center; which is the strength of this study.

Conclusion

The current work finds presence of traditional risk factors and associations with mucormycosis in much lower frequencies than the reviewed literature including serum iron, diabetic ketoacidosis and severe COVID 19. Low serum iron availability inducing the high-affinity rather than the low-affinity uptake system for example iron regulated high-affinity ferric reductase activity may play a major role in the causation of mucor in these patients. Sustained hyperglycemia may also play an important role rather than just diabetes in COVID-19 stress in the causation. Significant associations were found between the presence of comorbidities (other than diabetes mellitus) & addictions with nasal involvement of mucormycosis; serum creatinine levels with orbital involvement of mucormycosis; the duration between the start of treatment of COVID-19 and the appearance of the first symptom suggestive of mucor infection with nasal involvement of mucormycosis. At least one paranasal sinus was affected in all the patients. Blood urea was elevated in three-fourth of the participants and alkalosis was found in more than half of the participants. Larger scale studies in mucormycosis patients are warranted for finding the role of other risk factors and possible role of elevated blood urea in the present era.

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Data Availability (data transparency) Yes.

Code Availability (software application or custom code) Not applicable.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval The study was approved by the Institutional Ethical Committee (IEC). No. IEC/DUPMCH/05/2021.

Consent to Participate Informed consent was obtained from all individual participants included in the study.

Consent for Publication The authors affirm that human research participants provided informed consent for publication of the images in Figs. 1 and 2.

Human and Animals Rights This study was performed in line with the principles of the Declaration of Helsinki.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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