

# Prevalence, distribution and correlates of pain in patients with mucormycosis-A cross-sectional study

## ABSTRACT

**Context:** COVID-19 has led to a spate of rhino-orbital-cerebral mucormycosis cases in India, the epidemiology of which was least understood before. Only a few case series and case reports discuss the symptomatology of mucormycosis.

**Aims:** The primary objective of our study was to estimate the prevalence of pain in patients with mucormycosis. The secondary objectives include the type, regional distribution, characteristics and determinants of pain in patients with mucormycosis.

**Settings and Design:** A cross-sectional study was conducted on consecutive adult patients with mucormycosis in our hospital.

**Materials and Methods:** Following recruitment, a preplanned written questionnaire that was tested for validity with peers, with closed-ended queries was filled on a sole visit by an anesthesia postgraduate based on the response by the patient.

**Statistical analysis used:** Categorical variables were summarized as proportion and percentage. To compare quantitative variables, Chi-square test was used.


**Results:** A total of 69 out of the 80 patients recruited complained of pain ( $P$  value = 0.468). A total of 76.8% of patients had pain in the supraorbital region with 84% of the patients complaining of throbbing pain and 98.6% needing analgesics. Gender, pre-existing diabetes mellitus, organs affected due to mucormycosis, prior steroid usage, prior COVID illness, surgical intervention, and previous experience of pain in the same region had no influence on the presence or severity of pain.

**Conclusions:** Pain is one of the presenting symptoms in patients with mucormycosis which is usually in the supraorbital and maxillary region, nociceptive type and throbbing in nature, and moderate to severe in intensity usually managed with simple analgesics.

**Key words:** COVID19, mucormycosis, pain

## Key messages

The majority of the patients recruited in our study had supraorbital or maxillary region pain of moderate to severe intensity signifying probably the parallel involvement of these sinuses by mucormycosis. Hence, the clinician should have a high degree of suspicion of mucormycosis if patients with pain present with such manifestation

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## Introduction

The COVID-19 pandemic, though on the wane, is leaving behind a trail of long-standing effects in patients recovering, especially one's with comorbid illness. Although the lung is the most commonly affected organ, more than one-third of patients have neurological involvement and a variety of other systems.<sup>[1,2]</sup>

In India, moreover, after the second wave of the COVID-19 pandemic, a spate of mucormycosis has stretched the overburdened health care system. Around 8800 patients were affected with mucormycosis in India in mid-May. Survivors of COVID-19 have multidomain impairment like mucormycosis that needs multidisciplinary care.<sup>[2]</sup> Mucormycosis usually presents with symptoms of one-sided facial pain and orbital involvement in the form of proptosis with a decrease in visual acuity. We observed that most of these patients are now presenting to our pain clinic with moderate to severe pain either presurgically or postsurgically.

In order to develop better treatment strategies, the pain originating from mucormycosis needs to be understood in the context of distribution, characteristics, and other determinants. Studying the distribution and determinants of pain allows us to understand and manage the problem at the individual and population levels. Additionally, ascertaining and managing risk factors and elements of risk factors that are modifiable may allow the prevention of pain or the reduction of its duration and severity.<sup>[3]</sup>

Hence, we planned to conduct a cross-sectional study in confirmed patients of mucormycosis admitted to our hospital with the primary objective to estimate the prevalence (proportion) of pain in patients with mucormycosis. The secondary objectives include the type, regional distribution and characteristics of pain in patients with mucormycosis and the determinants of pain including the presence of pre existing COVID illness, diabetes mellitus (DM), any surgical intervention done, extent of disease and relieving medications.

## Subjects and Methods

### Material and Methods

Following ethical committee approval with registration number KIMS:ETHICS:COMM:300:2021-22, we started recruiting patients diagnosed clinically and radiologically as a possible/probable/confirmed case of mucormycosis admitted in the ENT ward of our hospital for the month of July 2021. The Clinical Trials Registry- India (CTRI) registration was done

with registration number as follows CTRI/2021/09/036517. A convenient sampling of patients was done by selecting patients getting admitted with either possible/probable/confirmed diagnosis of mucormycosis as per the National Center of Disease Control guidelines.<sup>[4]</sup> To avoid any form of selection bias, all consecutive patients getting admitted were taken for the study. All patients underwent a biopsy preoperatively and intraoperatively for confirmation of mucormycosis. Patients unable to give proper history, unable to communicate, or unable to understand the questions, those on central nervous system (CNS) depressants, Alzheimer's disease, or any other CNS disease (other than mucormycosis) poor general condition were excluded from the study.

Following recruitment, informed written consent was taken from the patient. A preplanned written questionnaire that was tested for validity with peers, with closed-ended queries was filled on a sole visit by an anesthesia postgraduate based on the response by the patient. The questionnaire included the following:-

1. Demographic details like name, address, age, gender, and weight.
2. Presence or absence of complaints of pain. Those with pain were assessed further for the presence of determinants and for those without pain, the assessment stopped here.
3. Correlates were enquired such as the presence of pre existing DM before admission, history of COVID illness in the past, pre existing pain in the head region, any surgical intervention done for mucormycosis, any recent or past known history of steroid usage.
4. Extent of disease which was quantified/coded based on radiology reports<sup>[5]</sup> as follows:-
 

Involving the nose only	R
Involving the nose and orbit	O
Involving the nose and palate (with or without orbit)	P
Involving the nose, orbit, and cerebrum	C
Involving other systemic organs	S

In case of any discrepancy/lack of clarity, concerned surgeons and radiologists were enquired regarding the appropriate group.
5. Patients were enquired regarding the pain relieving medications they were receiving at the time of admission. They were divided into four groups as follows:-
  - a. Simple analgesics like paracetamol and tramadol S
  - b. Above medications with adjuvants A
  - c. Above medications with strong opioids or patches O
  - d. None N

6. Type of pain was classified into neuropathic/non-neuropathic pain based on Douleur Neuropathique 4 questionnaire.<sup>[6]</sup>
7. Patients were enquired regarding laterality (unilateral/bilateral) if unilateral which side, quality of pain (throbbing/stabbing/dull-aching/hypoesthesia/other), and severity based on visual analog score (VAS) at presentation and when worse. Based on patient's VAS, the patients were graded to have mild (1–3), moderate (4–7), and severe (8–10) pain.
8. Distribution of pain was studied by questioning/inspection/palpation of these five regions for presence or absence of pain. The patient's response in affirmation to the presence of pain in either one or any of the above methods was considered – Supraorbital/occipital/maxillary/post-auricular/temporal.

From our clinical experience, we considered a proportion of 70% of mucormycosis cases to be having pain. Hence, a sample of 81 patients was needed for our study with 10% absolute precision and 95% confidence. To avoid a loss to attrition, a sample of 100 patients was considered for our study. Statistical analysis was done using the R Core Team.<sup>[7]</sup> Continuous variables were summarized as mean ± standard deviation (SD). Categorical variables were summarized as proportion and percentage. To compare quantitative variables, Chi-square test was used. This paper was written according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.<sup>[8]</sup>

## Results

A total of 90 patients were recruited for the study during the month of July 2021. Ten of these patients were excluded from the study as they were unable to complete the questionnaire due to causes such as disorientation or unable to understand the questionnaire after recruitment. A total of 80 patients were analyzed [Figure 1 - Flow chart].

The pain was present in 69 patients (86.25%) and absent in 11 (13.75%). The other determinants evaluated included gender, pre-existing DM, organs affected due to mucormycosis, prior steroid usage, prior COVID illness, surgical intervention, and previous experience of pain in the same region. None of these had a significant effect on the occurrence of pain in mucormycosis patients [Table 1].

The regional distribution due to mucormycosis was varied with the supraorbital region being affected in 76.8% (53) of patients, the maxillary region in 62.3% (43) of patients, the

temporal region in 29% (20) patients, the occipital region in 24.6% (17) patients, and the postauricular region in 20.3% (14) patients. Most of the patients had involvement of multiple regions at presentation as shown in Figure 2. A total of 46.4% (32) of patients had left side pain, 36.2% (25) had right side pain, and 17.4% (12) had bilateral pain.

A total of 98.6%(68) of mucormycosis patients with pain needed analgesics with 81.16%(56) having a severe form of pain and 18.84%(13) having moderate pain. The mean duration

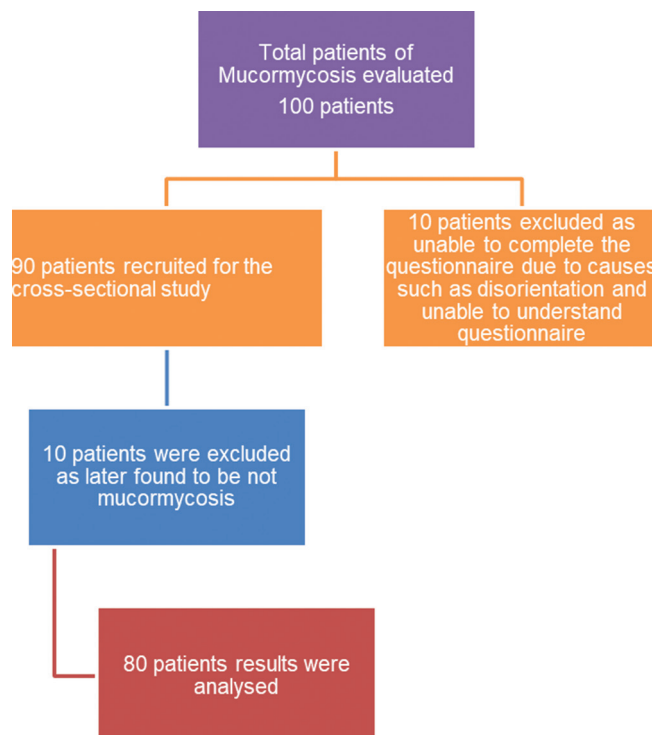


Figure 1: Flow diagram

Table 1: Determinants evaluated for the presence of pain

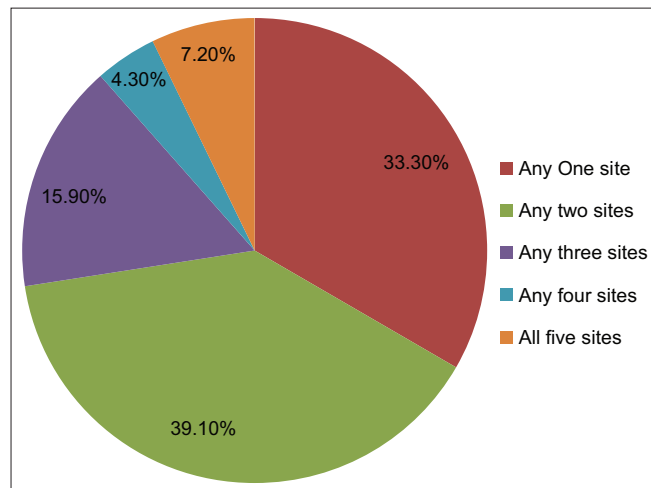
Variables	Presence of pain (%)	Chi-square test (P)*
Gender		
Male n=53	44 (83)	0.24
Female n=27	25 (92.6)	
Organs		
Cerebral n=4	4 (100)	0.29
Orbit n=22	20 (90.9)	
Nasal n=32	29 (90.6)	
Palatal n=15	11 (73.3)	
Systemic n=7	5 (71.4)	
Diabetes Mellitus n=69	61 (88.4)	0.161
Steroid used n=35	33 (94.3)	0.066
Post COVID illness n=64	56 (87.5)	0.685
Surgical intervention done n=64	56 (87.5)	0.685
Previous experience of pain n=8	6 (75)	0.33

\*P< 0.05 is considered significant

**Table 2: Duration and pain score summary measures**

	Count	Mean (SD*)	Median (IQR <sup>†</sup> )	Minimum	Maximum
Duration	69	28.64 (18.07)	30 (15-30)	4	90
VAS <sup>‡</sup> when worst	69	7.62 (1.69)	8 (6.5-9)	4	10
VAS <sup>‡</sup> at Presentation	69	4.85 (2.22)	5 (3-6.5)	1	9

\*SD - Standard deviation, <sup>†</sup>IQR - interquartile range <sup>‡</sup>VAS - visual analog score



**Figure 2: Regional distribution of pain with respect to number of sites**

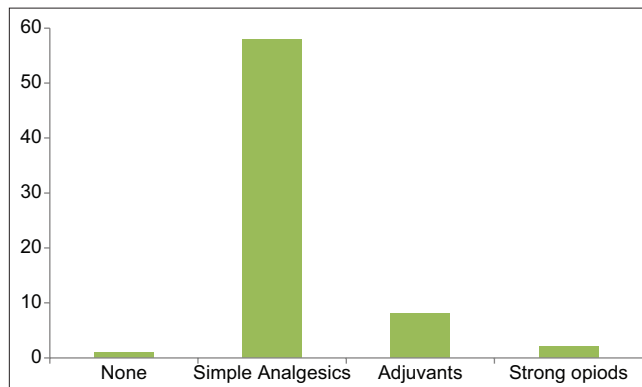
of pain in these patients was  $28.64 \pm 18.07$  days [Table 2] Ongoing pain treatment of mucormycosis is as depicted in Figure 3.

Neuropathic pain was present in only 3 patients. (4%). A total of 84% (58) described a throbbing type of pain, 8% (6) stabbing type, and 7% (5) dull aching type. Comparison of pain characteristics with gender, comparison of pain scores with determinants did not show any significance. Male patients had more right-sided and bilateral pain than female sex which was statistically significant [Tables 3 and 4].

### Discussion

Mucormycosis is a fatal fungal infection affecting patients who are immunocompromised like organ transplantation, DM, cancer patients. The incidence rate of mucormycosis globally varies from 0.005 to 1.7 per million people. In India, the prevalence of mucormycosis was estimated as 140 per million people, which is about 80 times higher than the prevalence in developed countries before the COVID pandemic started.<sup>[9]</sup>

Following the second wave of the COVID-19 pandemic, we have seen a surge of mucormycosis, especially in the post-COVID diabetic population. COVID-19-associated mucormycosis (CAM) is now recognized as an epidemic in itself and is declared a notifiable disease. Already >30,000 cases of CAM have been notified in India.<sup>[10]</sup> With the increase of



**Figure 3: Ongoing pain treatment of patients with mucormycosis**

these cases, there is a dearth of knowledge with regards to the disease manifestations and epidemiology. Better insights are needed into the disease burden, population characteristics, risk factors, clinical spectrum, and outcomes of these patients.<sup>[9]</sup> Recognizing that mucormycosis has fulminant and rapid prognosis, early identification is of utmost importance. Our study was one such attempt to study the pain manifestations of patients of mucormycosis.

Majority of patients with mucormycosis present with pain as per analysis in our study. Mucormycosis can also present with facial swelling/numbness, nasal congestion/discharge, toothache, jaw involvement, blurred or double vision, and fever.<sup>[4]</sup> However, pain is the most important symptom that makes the patient of mucormycosis seek medical advice. According to a study done in 2826 post COVID patients in India, orbital/facial pain was the primary and most prolific symptom accounting for 23% patients of rhino orbital mucormycosis patients.<sup>[11]</sup>

Though DM is known to be an important determinant of developing mucormycosis, our study did not show any correlation of DM with the presence of pain or its severity. Probably this could be due to altered pain processing in the diabetic population as found in earlier studies.<sup>[12,13]</sup>

Similarly, the other determinants like gender, organs affected due to mucormycosis, prior steroid usage, prior COVID illness, surgical intervention, and previous experience of pain in the same region had no role in the development of pain. A large multicentric study would have probably found some correlation with these factors if present.

**Table 3: Comparison of worst pain scores in different subgroups**

	Worst pain scores		
	Mild (1-3) n=0	Moderate (4-6) n=17	Severe (7-10) n=52
Diabetes	0 (0)	14 (82.4)	47 (90.4)
Steroid used	0 (0)	4 (23.5)	29 (55.8)
Post COVID illness	0 (0)	13 (76.5)	43 (82.7)
Surgical Intervention done	0 (0)	11 (64.7)	45 (86.5)
Previous experience of pain	0 (0)	2 (11.8)	4 (7.7)

**Table 4: Comparison of other Pain characteristics with Gender**

	Male (%)	Female (%)	Chi square test (P)
Supra Orbital n=53	31 (58.5)	22 (41.5)	0.097
Occipital n=17	12 (70.6)	5 (29.4)	0.500
Maxillary n=43	25 (58.1)	18 (41.9)	0.211
Post Auricle n=14	10 (71.4)	4 (28.6)	0.504
Temporal n=20	13 (65)	7 (35)	0.385
Side			
Right (n=25)	17 (68)	8 (32)	0.032 *
Left (n=32)	16 (50)	16 (50)	
Bilateral (n=12)	11 (91.7)	1 (8.3)	
Pain type			
Dull aching (n=5)	4 (80)	1 (20)	0.098
Stabbing (n=6)	6 (100)	0 (0)	
Throbbing (n=58)	34 (58.6)	24 (41.4)	
Neuropathic n=3	3 (100)	0 (0)	0.182

\*P< 0.05 was considered significant

The majority of the patients recruited in our study had supraorbital or maxillary region pain of moderate to severe intensity signifying probably the parallel involvement of these sinuses by mucormycosis. Hence, the clinician can have a high degree of suspicion of mucormycosis, if a patient with pain presents in supraorbital and maxillary areas. The majority of the previous literature before the COVID pandemic started described the pain of mucormycosis as headache, facial pain, or pain in the teeth or gums or paraesthesias and decreased sensation over half of the face.<sup>[14,15]</sup> A systemic review done in post covid rhino-orbital-cerebral mucormycosis cases noted the commonest manifestations to be nasal block, ocular pain, or swelling of the eyelids. None of the studies included in the review have noted supraorbital or maxillary pain or described the characteristics of pain.<sup>[16]</sup> Our study findings are in stark contrast to this systemic review. Whereas one Iranian cross-sectional multicenter study had results similar to ours, noted 73% of the post COVID mucormycosis coming with periorbital pain at presentation.<sup>[17]</sup>

Though the majority of patients were diabetic, only four patients had neuropathic pain. This is a contrasting finding as DM is known to cause neuropathy.<sup>[13]</sup> This could be explained as DM has varied mechanisms of causing neuropathy or loss of sensation.<sup>[15]</sup> Also, mucormycosis is described by its

angio-invasive nature causing necrosis rather than being neuro-invasive. Mucormycosis is characterized by host tissue infarction and necrosis resulting from vasculature invasion by hyphae starting with specific interaction with endothelial cells.<sup>[5]</sup> This also can explain the finding that most of our patients were on simple analgesics like NSAIDs and tramadol. The pain quality mimicked a nociceptive picture with a throbbing type of pain. However, as our study was done in the early course of illness for a period of just one month, long term follow up of these patients is needed to understand postsurgical chronic pain or development of neuropathic pain.

### Limitations

1. As our hospital is a tertiary care hospital catering to patients coming in the advanced stage, the cases may not be truly representative of all mucormycosis. Considering the dwindling number of COVID and mucormycosis cases, a larger multicentric study can be considered if there is a spate of cases again.
2. Pain is subjective in nature and multifactorial. A stratified analysis with respect to radiological illness could not be done due to this. Standardizing the patient characteristics with respect to severity may not be possible due to dwindling numbers.
3. As most of these cases were post COVID status of mucormycosis, whether this pain symptomology can be generalizable to non-COVID mucormycosis cases is a question of debate. However, our study partially answers this question by finding no correlation between post-COVID illness and pain in mucormycosis.
4. As mucormycosis is neuro-invasive in nature too, long-term is needed to understand whether it can cause chronic neuropathic pain.

In conclusion, pain is one of the presenting symptoms in patients with mucormycosis which is usually in the supraorbital and maxillary region, nociceptive type and throbbing in nature, moderate to severe in intensity usually managed with simple analgesics.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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