Received: 4 February 2022 | Accepted: 8 March 2022 | Revised: 8 March 2022

DOI: 10.1111/myc.13437

ORIGINAL ARTICLE

mycoses Diagnosis, Therapy and Prophylaxis of Fungal Diseases WILEY

As the virus sowed, the fungus reaped! A comparative analysis of the clinico-epidemiological characteristics of rhino-orbital mucormycosis before and during COVID-19 pandemic

Manjul Muraleedharan[1] | Naresh Kumar Panda[1] | Prerna Angrish[1] | Kanika Arora[1] | Sourabha Kumar Patro[1] | Sandeep Bansal[1] | Arunaloke Chakrabarti[2] | Shivaprakash Mandya Rudramurthy[2] | Jaimanti Bakshi[1] | Satyawati Mohindra[1] | Rijuneeta Gupta[1] | Ramandeep Singh Virk[1] | Roshan Kumar Verma[1] | Anurag Snehi Ramavat[1] | Gyanaranjan Nayak[1]

[1]Department of Otolaryngology Head and Neck Surgery, Postgraduate Institute of Medical Education and Research, Chandigarh, India

[2]Department of Medical Microbiology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Correspondence
Naresh Kumar Panda, Department of Otorhinolaryngology Head and Neck Surgery, PGIMER, Chandigarh 160012, India.
Email: npanda59@yahoo.co.in

Abstract

Background: The sudden surge of mucormycosis cases which happened during the second wave of COVID-19 pandemic was a significant public health problem in India.

Objectives: The aim of this study was to analyse the clinico-epidemicological characteristics of the mucormycosis cases to determine the changes that had occurred due to COVID-19 pandemic.

Methodology: A retrospective cross-sectional study was conducted at the Department of Otolaryngology Head and Neck Surgery, PGIMER, Chandigarh, India. Patients diagnosed with rhino-orbital mucormycosis were categorised into the following groups: *Pre-pandemic*(May 2019 to April 2020), *Pandemic Pre-epidemic* (May 2020 to April 2021) and *Epidemic* (1 May 2021 to 12 July 2021). The epidemiological, clinical and surgical data of all the patients were retrieved from the hospital records and analysed.

Results: The *epidemic* period had 370 cases, compared with 65 during *pandemic* period and 42 in the *pre-pandemic period*. Diabetes mellitus was seen in 87% of cases during *epidemic* period, 92.9% in the *pre-pandemic* period and 90.8% in the *pre-pandemic pre-epidemic* period. The proportion of patients suffering from vision loss, restricted extra-ocular movements, palatal ulcer and nasal obstruction was higher in the pre-epidemic groups, and the difference was significant (p, <.01). There was no history of oxygen use in 85.9% of patients and no steroid use in 76.5%. The death rates were the lowest during epidemic (10%).

Conclusion: COVID-19 has caused a statistically significant increase in the number of mucormycosis infections. The mortality and morbidity which showed an increase during the first wave of COVID-19 decreased significantly during the epidemic period.

KEYWORDS
COVID-19, epidemic, invasive fungal infection, long COVID, mucorales, mucormycosis, pandemic, steroid

1 | INTRODUCTION

The COVID-19 pandemic has brought about sweeping changes in our lives as we have known it. Epidemiology and its concepts took a centre stage, and the general population became aware of the concepts of disease progression and prevention like never before. 'Social distancing' became an integral part of social discipline and public hygiene.

It also catapulted mucormycosis, a hitherto rare but deadly fungal infection mainly affecting the uncontrolled diabetics in India, to the status of a public health emergency and thus acted as coming-of-age moment for the mycosis. Discussions were held, committees formed, and legislations drafted to tackle the golden march of the 'black fungus'.

A multi-centric study on mucormycosis conducted in four major referral centres around India concluded that PGIMER, Chandigarh, India, treated majority (68.8%) of the mucormycosis cases being diagnosed and treated in these centres.[1] Majority of those cases were managed by the ENT surgeons by virtue of major portion of them presenting with involvement of nose, sinuses and orbit. In the present study, we did the chart review to analyse the clinico-epidemicological characteristics of the mucormycosis cases to determine the changes that had occurred during the pre-pandemic, pandemic and the epidemic period.

2 | METHODOLOGY

2.1 | Patient selection and data collection

A retrospective cross-sectional study was conducted at the Department of Otolaryngology Head and Neck Surgery, PGIMER, Chandigarh. The epidemiological, clinical and surgical data of all the patients diagnosed with rhino-orbital mucormycosis and had been operated/worked up for surgery were retrieved from the hospital medical records. The collection of data was done using pre-defined protocol.

2.2 | Data management

The data set was cleaned in MS Excel and exported in SPSS V23 to conduct the univariate and bivariate analyses. The records of mucormycosis were collected before and after the emergence of COVID-19 disease, and patients were categorised into the following groups.

1. *Pre-pandemic*(May 2019 to April 2020).
2. *Pandemic Pre-epidemic* (May 2020 to April 2021) and
3. *Epidemic* (1 May 2021 to 12 July 2021).

[The term 'epidemic' has been used with respect to 'Mucormycosis'. The number of cases of mucormycosis during the initial waves of COVID-19 has not been in epidemic proportions and was termed 'Pandemic pre-epidemic' and the three months of sudden surge in cases of mucormycosis (May, 2021 to July, 2021) has been termed 'Epidemic' ('Pandemic epidemic' period in real, but shortened to 'epidemic')].

We considered 1 May as the cut-off date as we witnessed a sudden surge (more than 10 cases a day) of cases from this month and lasted till 12 July 2021, the day we registered *zero* fresh cases for the first time.

2.3 | Data analysis

The univariate analysis consisted of the frequency distribution of socio-demographic and comorbidity profile, the clinical features, surgical procedure performed and intraoperative findings. The distribution was presented as number and per cent.

The bivariate analysis consisted of comparisons between the above-mentioned factors (ie independent variables) of patients during pre-epidemic and epidemic period (ie the dependent variables). Chi-squared test of association was used to test the difference in distribution of various patient characteristics during the pre-epidemic and epidemic period. The classification of continuous data on age was done by dividing data into four equal proportions. The p-value of $<.05$ was considered as significant association.

2.4 | Ethics statement

The authors confirm that the ethics policies of the journal, as noted in author guidelines page, have been adhered to. No ethics approval was required as the study was done by reviewing the charts available in the department.

3 | RESULTS

3.1 | Socio-demographic profile

The percentage of males presenting with mucormycosis was consistently higher (65.6%) than females over the last three years, and there was no significant difference in this proportion in the three groups. (Table 1).

The mean age of all the patients considered for the study was 51.36 ± 12.6 years. The distribution of age among participants according to the groups is given in Figure 1.

The difference in the age distribution of study participants was statistically significant (p, .048).

3.2 | The association with COVID-19

In the first wave of epidemic, the end point of which has been kept as April 2021, the department has had a total of 65 cases of rhino-orbital mucormycosis. Of them, 55.4% (n = 36) were negative for

TABLE 1 Comparison of socio-demographic profile of study participants amongst three groups

		Group								
		Pre-pandemic, pre-epidemic ($n = 42$)		Pandemic, pre-epidemic ($n = 65$)		Epidemic ($n = 370$)		Total ($N = 477$)		
Characteristic	**Category**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***p*-value**
Gender	Female	14	33.3	23	35.4	127	34.3	164	34.4	.975
	Male	28	66.7	42	64.6	243	65.7	313	65.6	
Age (years)	Up to 43	17	40.5	20	30.8	89	24.1	126	26.4	.048
	44–54	7	16.7	23	35.4	104	28.1	134	28.1	
	55–62	11	26.2	15	23.1	88	23.8	114	23.9	
	More than 62	7	16.7	7	10.8	89	24.1	103	21.6	
COVID-19 status	Negative	42	100	36	55.4	34	9.2	112	23.5	<.01
	Presently positive	0	0	26	40.0	313	84.6	339	71.1	
	Presently negative	0	0	3	4.6	23	6.2	26	5.5	

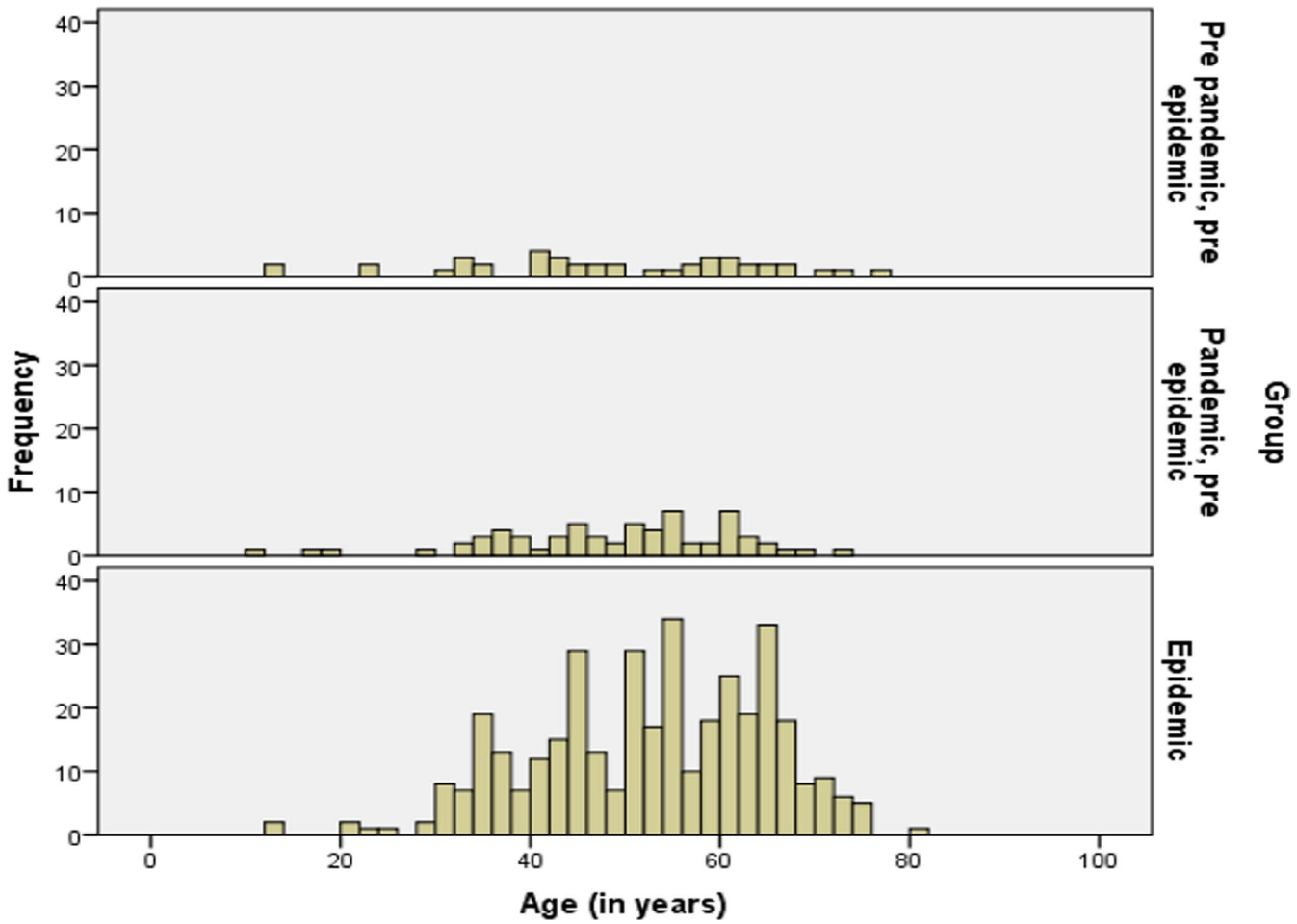

FIGURE 1 Age distribution of patients

SARS-CoV-2 by RT PCR and never had previous history of COVID-19 infection. A total of 26/65 was diagnosed with COVID-19 for the first time at admission or within a week before the date of admission (suggestive of a recent infection). Very few (3, 4.6%), who had been treated for COVID-19 (before 2 weeks of presentation), developed mucormycosis.

During the epidemic period, a total of 370 fresh cases of mucormycosis were diagnosed and were taken for immediate surgical debridement. The majority 313 (84.6%) were positive for SARS-CoV-2 infection (became positive on testing at admission or detected positive within a week after admission to our hospital), whereas 34 (9.2%) were negative for SARS-CoV-2. The post-COVID cases stood at 23 (6.2%).

The association of the COVID-19 infection with mucormycosis was statistically significant with a *p*-value of <.01. (Table 1).

3.3 | Medical history

Diabetes mellitus was undoubtedly the single most comorbidity predisposing to the infection. In total, 92.9% of patients with mucormycosis had diabetes in the *pre-pandemic* period, while almost a similar percentage (90.8%) had diabetes during the *pandemic pre-epidemic* period but slightly lower (87%) during epidemic period The other significant comorbidity was hypertension (32.1%). There was no significant difference in the proportion of cases having associated hypertension over the years. No statistically significant changes in the comorbidity profile could be seen over the study period.

The other comorbidities present in the study group were haematological malignancies, chronic kidney disease, tuberculosis, HIV, chronic liver disease and interstitial lung disease. There was a statistically significant difference in the association with haematological malignancies, CKD and tuberculosis across the three periods, as they were very rare and not found uniformly across all the study periods (Table 2).

3.4 | Clinical presentation

The major presenting complaints of the patients with rhino-orbital mucormycosis included diminished or loss of vision, restricted extra-ocular movements, peri-orbital/facial swelling, palatal ulcer, nasal obstruction and facial skin changes (Table 3).

3.4.1 | Changes in vision

The most common presenting symptom over the years has been vision-related complaints. 69.1% complained of either loss of vision or diminished vision in the *pre-pandemic* era. It was as high as 76.9% during the *pandemic pre-epidemic* period. The percentage dropped to just above 50% during the *epidemic* period at 52.7%. However the absolute number of patients with vision issues ($n = 274$) was due to increased number of patients during the epidemic period.

3.4.2 | Other ocular symptoms

A similar trend was noticed in rest of the eye symptoms too. There was an increase in percentage of patients presenting with restricted extra-ocular movements and peri-orbital swelling during the *pandemic pre-epidemic period* compared with the *pre-pandemic period* (restricted extra-ocular movements, 67.7% vs. 54.8% and peri-orbital swelling 72.3% vs. 61.9%). There was a decrease in this per cent in the *epidemic* period (40.5% and 54.9%) suggestive of lesser eye involvement.

3.4.3 | Rhino-facial symptoms

The other complaints were palatal ulcer, nasal obstruction, facial swelling and skin ulceration. Both the groups in pre-epidemic era had greater proportion of patients suffering from these symptoms individually.

On the contrary, it is also interesting to note the co-existence of these symptoms at the time of presentation. 40.5% and 41.5% of patients presented with four or more of these symptoms in the two pre-epidemic groups, while during the epidemic, the proportion of patients presenting with four or more of these symptoms was 9.2%.

Thus, the proportion of patients suffering from vision loss, restricted extra-ocular movements, palatal ulcer and nasal obstruction was higher among the pre-epidemic groups and this difference was statistically significant (Table 3). Similarly, the higher number of patients having more than four symptoms was also statistically significant (<0.01).

3.5 | Hospitalisation, steroids and oxygen use

An overwhelming 318 patients had no history of oxygen use (85.9%), and 283 (76.5%) had no history of steroid usage. It is also noteworthy that 80.8% ($n = 299$) had no history of hospitalisation prior to being infected with Mucorales (Table 4).

Of the 87 patients who had history of steroid usage, 71 patients have taken it either orally or as intravenous preparations under monitoring in a hospital setting, whereas16 of them had it at home without any blood sugar monitoring.

3.6 | Intra-operative findings

The ethmoid sinuses were the most commonly affected sinus across all the periods with the percentage involvement being 97.6%, 89.2% and 88.5% during the *pre-pandemic*; *pandemic pre-epidemic;* and *epidemic* groups respectively. The palatal involvement during the epidemic with 32.1% showed palatal ulceration, while in the pre-epidemic period, it was seen in 61.7% of patients and the difference was statistically significant (p, <.01). The maxillary sinus was surprisingly involved in a similar manner during the pre-pandemic and epidemic periods with 61.9% and 58.1% respectively. During the first wave of COVID-19, significantly more number of patients (83.1% $p = .01$) had involvement of the maxillary sinus.

The intra-orbital involvement as evident intra-operatively showed a statistically significant decrease during the epidemic period compared with the pre-epidemic period (p, <.01). The orbital involvement was the highest during the pandemic period before the epidemic with 65.1% of patients affected. The epidemic period showed only 25.6% of patients having orbital involvement.

There was an increase in the percentage of patients with disseminated rhino-orbital mucormycosis, specifically with intra-cranial and lung involvement during the epidemic period. While 22.7% of the

TABLE 2 Comparison of presence of comorbidities among study participants

		Group								
		Pre-pandemic, pre-epidemic ($n = 42$)		Pandemic, pre-epidemic ($n = 65$)		Epidemic ($n = 370$)		Total ($N = 477$)		
Comorbidity	**Category**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***p*-value**
Diabetes Mellitus	No	3	7.1	6	9.2	48	13.0	57	11.9	.417
	Yes	39	92.9	59	90.8	322	87.0	420	88.1	
Hypertension	No	31	73.8	43	66.2	250	67.6	324	67.9	.676
	Yes	11	26.2	22	33.8	120	32.4	153	32.1	
Haematological Malignancy	No	42	100	63	96.9	370	100	475	99.6	.002
	Yes	0	0	2	3.1	0	0	2	0.4	
CKD/AKI	No	40	95.2	60	92.3	367	99.2	467	97.9	.001
	Yes	2	4.8	5	7.7	3	0.8	10	2.1	
TB	No	42	100	65	100	369	99.7	476	99.8	.865
	Yes	0	0	0	0	1	0.3	1	0.2	
HIV/HBsAg/HCV	No	40	95.2	65	100	364	98.4	469	98.3	.349
	HIV	2	4.8	0	0	5	1.4	7	1.5	
	HCV	0	0	0	0	1	0.3	1	0.2	
Trauma	No	40	95.2	65	100	366	100	471	99.6	<.01
	Yes	2	4.8	0	0	0	0	2	0.4	
Dental procedure	No	39	92.9	55	84.6	359	97.0	453	95.0	<.01
	Yes	3	7.1	10	15.4	11	3.0	24	5.0	
Insect bite	No	42	100	64	98.5	370	100	476	99.8	.042
	Yes	0	0	1	1.5	0	0	1	0.2	
Number of comorbidities	None	2	4.8	1	1.5	35	9.5	38	8.0	.027
	One	22	52.4	29	44.6	203	54.9	254	53.2	
	2 or more	18	42.9	35	53.8	132	35.7	185	38.8	

patients during the epidemic had intra-cranial ($n = 82$) and pulmonary ($n = 2$), the percentages during the *pandemic pre-epidemic* and *pre-pandemic* periods were 12.3% and 14.2% respectively. The difference was not statistically significant (Table 5).

3.7 | Surgical procedures

The surgical management of mucormycosis involved the debridement of the affected sinuses and the tissues. We had classified the procedures into the following types, signifying the extent of the disease. The procedures most commonly performed were total/ extended total maxillectomy, partial maxillectomy, orbital exenteration, debridement of the sinuses, debridement of facial skin and drainage of facial abscess.

Total maxillectomy, indicative of an extensive disease, was performed in 45.2% in the *pre-pandemic* group and 49.2% in the *pandemic pre-epidemic* group. Thus, rate of total maxillectomy in the epidemic period was 12.4%. The difference was statistically significant (p, <.01).

Orbital exenteration also showed a statistically significant reduction (p, <.01) in the epidemic period. 193 patients underwent exenteration in the two months after epidemic (36%). The rates were 52.4% and 66.2% during the previous years.

There has been but an increased number of patients requiring debridement of the facial skin and subcutaneous tissue during the epidemic period (p, <.01). The involvement usually occurred on the cheek along the distribution of the inferior orbital nerve. Approximately half of the patients required debridement of the skin ($n = 180$, 50.6%) while the percentages were 11.9% and 20% in the pre-epidemic periods.

The number of these different procedures an individual patient undergoes as part of debridement can be considered as being indicative of the extensiveness of the disease. An analysis of this aspect points out to the fact that the proportion of patients undergoing more than 3 of these procedures was the highest among the *pandemic pre-epidemic* group with 63.1% of the patients undergoing extensive procedures. In the *pre-pandemic* group, it was 45.2%, while in *epidemic* group, it was 48.9%. The difference was not statistically significant though (Table 6).

3.8 | Endoscopic versus combined approach

The percentage of endoscopic procedures went down drastically during the *pandemic pre-epidemic* period when it consisted just 7.7% of the procedures. The difference between the three groups was not statistically significant though (Table 7).

TABLE 3 Comparison of clinical features of illness among study participants between three groups

		Group								
		Pre-pandemic, pre-epidemic (*n* = 42)		Pandemic, pre-epidemic (*n* = 65)		Epidemic (*n* = 370)		Total (*N* = 477)		
Feature	Category	*n*	%	*n*	%			*n*	%	*p*-value
Vision	Intact	13	31.0	15	23.1	175	47.3	203	42.6	<.01
	Lost	23	54.8	42	64.6	113	30.5	178	37.3	
	Diminished	6	14.3	8	12.3	82	22.2	96	20.1	
Restricted EOM	No	19	45.2	21	32.3	220	59.5	260	54.5	<.01
	Yes	23	54.8	44	67.7	150	40.5	217	45.5	
Peri-orbital swelling	No	16	38.1	18	27.7	167	45.1	201	42.1	.027
	Yes	26	61.9	47	72.3	203	54.9	276	57.9	
Palatal ulcer	No	19	45.2	28	43.1	271	73.2	318	66.7	<.01
	Yes	23	54.8	37	56.9	99	26.8	159	33.3	
	No	5	11.9	26	40.0	213	57.6	244	51.2	
	Yes	37	88.1	39	60.0	157	42.4	233	48.8	
Facial Swelling/Skin Changes	No	31	73.8	33	50.8	233	63.0	297	62.3	.047
	Yes	11	26.2	32	49.2	137	37.0	180	37.7	
Number of clinical features	Up to 2	15	35.7	15	23.1	196	53.0	226	47.4	<.01
	Three to four	10	23.8	23	35.4	140	37.8	173	36.3	
	More than 4	17	40.5	27	41.5	34	9.2	78	16.4	

TABLE 4 Pre-Mucor pharmacological management of study participants receiving treatment during epidemic era (*N* = 370)

Management parameter	Category	Frequency	Valid Per cent
Oxygen received	No	318	85.9
	Yes	52	14.1
Steroids received	No	283	76.5
	Yes	87	23.5
Hospitalised	No Hospitalisation	288	77.8
	Steroid treatment under hospital settings	71	19.2
	Steroid treatment at home	11	3.0

3.9 | Treatment outcomes

As the long-term follow-up data of the epidemic period are not available, the treatment outcomes on a short-term basis have been analysed based on whether the patients could be discharged or not. The intra-hospital death rates during the three periods were 16.7%, 30.8% and 10% during the *pre-pandemic*, *pre-epidemic; pandemic*, *pre-epidemic;* and *epidemic* periods respectively. Thus, the epidemic period showed the least death rates (Table 8).

3.10 | The pre-epidemic follow-up

Of the 42 patients treated in the *pre-pandemic* group, follow-up data of 32 are available. 4.8% had recurrences and underwent repeat procedures (*n* = 2). 23 are still alive after 2 years, thus bringing the survival rate among the ones who could be followed up to 71.9%.

Among the *pandemic pre-epidemic* group, 6/65 were lost to follow-up. Of the remaining 59, the recurrence rates were 7.7%, and death rate was 40.7%.

It has to be noted that deaths on follow-up include the in-hospital deaths during admission and also deaths which are due to reasons other than mucormycosis. It is of particular importance that the *pandemic pre-epidemic* period saw the most morbidity and mortality (statistically significant, $p < .01$; Table 9).

4 | DISCUSSION

The world in general and India in specific was entering into a phase of extended fight against the novel corona virus, when, to add to the

TABLE 5 Comparison of intraoperative findings due to illness among the three groups

		Group								
		Pre-pandemic, pre-epidemic ($n = 42$)		Pandemic, pre-epidemic ($n = 65$)		Epidemic ($n = 370$)		Total ($N = 477$)		
Structure involved	**Category**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***p*-value**
Palate	No	16	38.1	25	38.5	247	67.9	288	61.1	<.01
	Yes	26	61.9	40	61.5	117	32.1	183	38.9	
Maxillary Sinus	No	16	38.1	11	16.9	149	41.9	176	38.0	.01
	Yes	26	61.9	54	83.1	207	58.1	287	62.0	
Ethmoids	No	1	2.4	7	10.8	41	11.5	49	10.6	.190
	Yes	41	97.6	58	89.2	315	88.5	414	89.4	
Frontal	No	40	95.2	59	90.8	186	52.2	285	61.6	<.01
	Yes	2	4.8	6	9.2	170	47.8	178	38.4	
Sphenoid	No	15	35.7	40	61.5	286	80.3	341	73.7	<.01
	Yes	27	64.3	25	38.5	70	19.7	122	26.3	
Facial abscess	No	35	83.3	55	84.6	276	77.7	366	79.2	.359
	Yes	7	16.7	10	15.4	79	22.3	96	20.8	
Intra-orbital	No	20	47.6	22	34.9	264	74.4	306	66.5	<.01
	Yes	22	52.4	41	65.1	91	25.6	154	33.5	
Intra-cranial/ disseminated	No	37	88.1	56	87.5	284	77.5	377	79.8	.105
	Yes	5	11.9	8	12.5	82	22.4	95	20.1	

TABLE 6 Comparison of surgical treatments performed on study participants

		Group								
		Pre-pandemic, pre-epidemic ($n = 42$)		Pandemic, pre-epidemic ($n = 65$)		Epidemic ($n = 356$)		Total ($N = 463$)		
Treatment done	**Category**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***p*-value**
Abscess drainage	No	36	85.7	58	89.2	247	69.4	341	73.7	.001
	Yes	6	14.3	7	10.8	109	30.6	122	26.3	
Total maxillectomy	No	23	54.8	33	50.8	310	87.6	366	79.4	<.01
	Yes	19	45.2	32	49.2	44	12.4	95	20.6	
Partial maxillectomy	No	31	73.8	41	63.1	227	63.9	299	64.7	.430
	Yes	11	26.2	24	36.9	128	36.1	163	35.3	
Orbital exenteration	No	20	47.6	22	33.8	228	64.0	270	58.3	<.01
	Yes	22	52.4	43	66.2	128	36.0	193	41.7	
Debridement—nasal cavity	No	6	14.3	3	4.6	126	35.4	135	29.2	<.01
	Yes	36	85.7	62	95.4	230	64.6	328	70.8	
Skin debridement	No	37	88.1	52	80.0	176	49.4	265	57.2	<.01
	Yes	5	11.9	13	20.0	180	50.6	198	42.8	
Number of procedures performed on fresh case	Up to 2	23	54.8	24	36.9	182	51.1	229	49.5	.084
	Three or more	19	45.2	41	63.1	174	48.9	234	50.5	

chaos, the country was overtaken by a rare but fatal epidemic. While the virus sowed, the fungi reaped the benefits. Mucormycosis, the hitherto little known fungal disease, talked about and managed only at specialised centres, caught the collective imagination of the lay population under the moniker 'black fungus'.

COVID-associated mucormycosis thus became a reality and the discussions as to why, how, what to do and what not to do gained traction across the medical circles.

One of the initial epidemiological studies on the new entity by Sen et al, under the aegis of COSMIC study, provided the earliest glimpses

TABLE 7 Table comparing endoscopic versus combined procedures

	Group								
	Pre-pandemic, pre-epidemic ($n = 42$)		Pandemic, pre-epidemic ($n = 65$)		Epidemic ($n = 356$)		Total ($N = 463$)		
Type of procedure	*N*	%	*n*	%	*n*	%	*n*	%	*p*-value
Combined	32	76.2	60	92.3	308	86.5	400	86.4	.110
Endoscopic alone	10	23.8	5	7.7	48	13.5	63	13.6	

TABLE 8 Treatment outcomes in the three groups

		Group							
		Pre-pandemic, pre-epidemic ($n = 42$)		Pandemic, pre-epidemic ($n = 65$)		Epidemic ($n = 370$)		Total ($N = 463$)	
Summary variable	Category	*n*	%	*n*	%	*n*	%	*n*	%
Follow-up <0.01	Death	7	16.7	20	30.8	37	10.0	64	13.4
	Discharge	35	83.3	45	69.2	319	86.3	399	84.5
	LAMA	0	0	0	0	14	3.7	14	2.1

TABLE 9 Follow-up findings among the study participants with mucormycosis reporting to hospital during pre-epidemic era

		Group					
		Pre-pandemic, pre-epidemic ($n = 42$)		Pandemic, pre-epidemic ($n = 65$)		Total ($N = 107$)	
Follow-up finding	Category	*n*	%	*N*	%	*n*	%
Recurrence	No	30	71.4	54	83.1	84	78.5
	Yes	2	4.8	5	7.7	7	6.5
	NA (loss to follow-up)	10	23.8	6	9.2	16	15.0
Current Status ($n = 91$)	Dead	9	28.1	24	40.7	33	36.3
	Alive	23	71.9	35	59.3	58	63.7

into the epidemiology, risk factors, clinical profile, management and outcomes of CAM.[2] Corticosteroids and diabetes mellitus were identified to be the most important predisposing factors. This and the general understanding that over the counter steroids were being used even in mild cases of COVID led to an increased audit of the usage of the same. The study showed 87% of cases having an association with steroid use, both monitored and unmonitored. 57% of the patients had history of oxygen support. The use of industrial grade oxygen so as to overcome the sudden crunch in oxygen availability also came under scanner and was held by many as being responsible for the fungal crisis. The mean age was found to be 51.9 years.

Another study by Bhanuprasad et al.[3] into the risk factors associated with the mucormycosis epidemic studying 164 patients (132 COVID and 32 non-COVID-Mucor cases) concluded that there was a high association with steroid use (71%). Oxygen use was found to be present only in minority of the cases. Diabetes mellitus again was the most significant predisposing factor in both COVID and non-COVID cases. The mean age was 51 years with a male predisposition.

Our findings also show a similar demographic profile. Males were significantly more affected during the epidemic as well as pre-epidemic and pre-pandemic phases with 65.6% of the patients treated over the three years being males. Mean age of all patients considered in the study also showed similar values with an average age of 51.36 years.

The risk factors but show very interesting findings. Our study shows no significant association with steroid usage or the use of oxygen with the development of mucormycosis. 85.9% had no history of oxygen use, while 76.5% had no history of steroid usage. The fact that 80.8% had no history of hospitalisation prior to being infected with mucormycosis also rules the hygiene of oxygen supply/ instruments/ interventions at the hospitals triggering the epidemic. The *steroid story*, on the contrary, needs a closer look. In our first analysis of data which included 63 patients presenting from 1 May to 20 May 48% had history of steroid usage (considering only the post-COVID cases, 81%). In a subsequent analysis of data including 202 patients up to 10 July 2021, the percentage of patients with steroid usage

came down to 30.7% and the final analysis kept the percentage at 23.5%. Due to lack of a standardised documentation of treatment and the rampant over the counter treatment of mild upper respiratory tract infections during the pandemic, the numbers may not be absolutely correct, but the decreasing trend is noticeable. This can be attributed to the increased awareness among the physicians and the general public about the side effects of unmonitored steroid usage. The facts that mucormycosis cases continued to come unabated in spite of this reduction in steroid usage and that steroid has been a mainstay of management in organ transplant recipients, autoimmune disorders, nerve palsies and airway stenoses for a long time with no evidence of any increased incidences of mucormycosis over the years, suggest that maybe we need to look beyond steroids as the main cause of concern.

4.1 | The COVID Association

There is overwhelming evidence that COVID-19 infection, especially in the second wave, is strongly associated with the spike in the mucormycosis cases. There were isolated reports during the first wave of the pandemic about the development of mucormycosis in people recovering from COVID-19.[4] Of the 65 patients who presented during the period (April 2020 to April 2021), 55.4% (n = 36) were COVID negative, while 40% (n = 26) were diagnosed with COVID-19 while being worked up for mucormycosis. Post-COVID mucormycosis cases were just 3. Thus, COVID-Mucor co-infection seemed like a clinically significant entity, rather than post-COVID mucormycosis.

During the epidemic period too, the majority of cases were not *post-COVID*. 59.7% (n = 221) were never diagnosed to have/ treated for COVID-19. The COVID infection was picked up during the routine pre-operative GeneXpert examination. Only, 31.08% (n = 115) were post-COVID. This would suggest that the disease process itself might be triggering the fungal infections, and the initial hypotheses which put the primary responsibility for causing the outbreak on the management of COVID-19 might have been misplaced.

The cases of post-influenza mucormycosis have been reported earlier too, albeit rarely. The institute had a case of an isolated subglottic mucormycosis in a diabetic after a bout of H1N1 infection.[5]

Muthu et al.[1] analysed the difference in the epidemiology and pathophysiology of the COVID-associated mucormycosis in India versus the rest of the world. The mortality rates were lesser in India with 36.5% deaths, while the average reported deaths in the world stood at 61.9%. This can be attributed to the predominance of rhino-orbital mucormycosis (89% of reported cases) mainly due to the gross underreporting of pulmonary mucormycosis.

4.2 | How the virus changed the fungus—evolution of clinico-pathological characteristics

In two papers from the Institute published 18 years apart, it is evident that the risk factors have not changed much.[1,6] Uncontrolled diabetes was the most common cause, and rhino-orbital mucormycosis remained the most common type. The mortality rates were 48% in 2001, while in 2018, it remained similar at 46.7%. In another study involving 27 patients with rhino-orbito-cerebral mucormycosis, the survival rate in people undergoing surgery for at least the rhino-orbital part followed by medical management with amphotericin (conventional) was 78.3%.[7] In unoperated ones, the condition was fatal with 100% death rates.

Our data for the three years showed comparable survivals. The management principles based on radical debridement, regular wound examination and revision debridement, and medical management with liposomal amphotericin were quite effective with just 16.7% mortality in the *pre-pandemic* period. This could be the seen as a result of the protocols developed as a result of managing the condition for over 40 years. There was a sudden rise in mortality during the *pandemic* period with 30.8% people losing their fight against the fungus. The difficulties associated with the management of co-existing COVID-19, the extensive nature of the disease due to the difficulty in accessing hospital services in view of lockdowns/ fear of the COVID virus, lack of control of the comorbidities etc might have played a role in this outcome.

The *epidemic* period, in spite of overwhelming the hospital services with the sheer volume of the patients and lack of medications, had the least mortality at 10%. The operation theatres used to run on an emergency basis for 16 h, operating up to 10 patients a day, for over 2 months to make this possible. There was shortage of the drug of choice, liposomal amphotericin, which made the initial days difficult. This was overcome with the use of posaconazole in the intermediate period. The increased awareness and the very early presentation with limited disease may have also played a role in the outcomes being better than normal times.

The early presentation of patients was evident from the statistically significant fall in the intra-orbital involvement of the disease. More than 50% of the patients usually presented with extension of the disease to the orbits (52.4% in the *pre-pandemic* and 65.1% in the *pandemic pre-epidemic* period). The percentage was the lowest during the *epidemic* period with just a quarter of the patients presenting with the orbital involvement (25.6%). The initial studies showed up to 72% orbital involvement, but this may be attributed to the fact that it was a study based on ophthalmology practice.[2]

4.3 | The how and why of COVID-associated mucormycosis

Prakash et al in a review put forward the following as the causes as to why COVID-19 might have caused a surge in mucormycosis, especially in India—the heavy spore burden of Mucorales in tropical countries; virus-induced endothelial dysfunction, hyperglycaemia (damage of beta cells by COVID-19 virus); along with hyperferritinaemia caused by the virus acting as a source for Mucorales growth.[8] The previous reports of mucormycosis occurring in otherwise

immunocompetent patients point to the fact that more is to be learnt regarding the pathophysiology of the infection.[9,10] Further studies in this direction are the need of the hour as the medical world is bracing itself to face further waves of COVID and also to manage what is left as a result of the previous waves.

5 | CONCLUSION

COVID-19 has caused a statistically significant increase in the number of mucormycosis infections. The major predisposing factors, especially uncontrolled diabetes mellitus, have remained the same. The mortality and morbidity due to mucormycosis, which showed an increase during the first wave of COVID-19, decreased significantly during the epidemic period. There was neither significant association with the use of oxygen nor steroids with the development of the disease. The management principles have remained the same over the period, with radical debridement and aggressive medical management with liposomal amphotericin-B remaining the cornerstone.

ACKNOWLEDGEMENTS

The authors would love to acknowledge the untiring efforts of all the consultants, residents of the departments of Otolaryngology, Anaesthesia and Microbiology and of the other entire supporting medical staff which made the management of the unprecedented fungal epidemic possible.

CONFLICT OF INTEREST

The authors do not have any conflict of interest to declare.

AUTHOR CONTRIBUTIONS

Manjul Muraleedharan: Conceptualization (equal); Data curation (equal); Investigation (equal); Methodology (equal); Resources (equal); Writing – original draft (lead). **Naresh Panda:** Conceptualization (lead); Formal analysis (lead); Methodology (lead); Resources (lead); Supervision (lead); Writing – review & editing (lead). **Prerna Angrish:** Data curation (equal); Investigation (equal). **Kanika Arora:** Data curation (equal); Investigation (equal). **Sourabha Kumar Patro:** Formal analysis (equal); Methodology (equal); Writing – review & editing (equal). **Sandeep Bansal:** Supervision (equal); Writing – review & editing (equal). **Arunaloke Chakrabarti:** Supervision (equal); Writing – review & editing (equal). **Shivaprakash Mandya Rudramurthy:** Supervision (equal); Writing & editing (equal). **Jaimanti Bakshi:** Supervision (equal); Writing – review & editing (equal). **Satyawati Mohindra:** Supervision (equal); Writing & editing (equal). **Rijuneeta Gupta:** Supervision (equal); Writing & editing (equal). **Ramandeep Singh Virk:** Supervision (equal); Writing – review & editing (equal). **Roshan Kumar Verma:** Supervision (equal); Writing & editing (equal). **Anurag Snehi Ramavat:** Supervision (equal); Writing – review & editing (equal). **Gyanaranjan Nayak:** Supervision (equal); Writing – review & editing (equal).

ORCID

Naresh Kumar Panda https://orcid.org/0000-0002-1767-7013
Sourabha Kumar Patro https://orcid.org/0000-0002-4819-7928
Shivaprakash Mandya Rudramurthy https://orcid.org/0000-0002-9097-9253

REFERENCES

1. Prakash H, Ghosh AK, Rudramurthy SM, et al. A prospective multicenter study on mucormycosis in India: epidemiology, diagnosis, and treatment. *Med Mycol*. 2018;57(4):395-402.
2. Sen M, Honavar SG, Bansal R, et al. Epidemiology, clinical profile, management, and outcome of COVID-19-associated rhino-orbital-cerebral mucormycosis in 2826 patients in India-Collaborative OPAI-IJO Study on Mucormycosis in COVID-19 (COSMIC), Report 1. *Indian J Ophthalmol*. 2021;69(7):1670-1692.
3. Bhanuprasad K, Manesh A, Devasagayam E, et al. Risk factors associated with the mucormycosis epidemic during the COVID-19 pandemic. *Int J Infect Dis*. 2021;111:267-270.
4. Sharma S, Grover M, Bhargava S, Samdani S, Kataria T. Post coronavirus disease mucormycosis: a deadly addition to the pandemic spectrum. *J Laryngol Otol*. 2021;135(5):442-447.
5. Mohindra S, Gupta B, Gupta K, Bal A. Tracheal mucormycosis pneumonia: a rare clinical presentation. *Respir Care*. 2014;59(11):e178-e181.
6. Chakrabarti A, Das A, Sharma A, et al. Ten Years' experience in zygomycosis at a tertiary care centre in India. *J Infect*. 2001;42(4):261-266.
7. Mohindra S, Mohindra S, Gupta R, Bakshi J, Gupta SK. Rhinocerebral mucormycosis: the disease spectrum in 27 patients. *Mycoses*. 2007;50(4):290-296.
8. Prakash H, Skiada A, Paul RA, Chakrabarti A, Rudramurthy SM. Connecting the dots: Interplay of pathogenic mechanisms between COVID-19 disease and mucormycosis. *J Fungi*. 2021;7(8):616.
9. SuryanarayanRao S, Panda NK, Pragache G, Chakrabarti A, Saravanan K. Sinoorbital mucormycosis due to Apophysomyceselegans in immunocompetent individuals–an increasing trend. *Am J Otolaryngol*. 2006;27(5):366-369.
10. Sridhara SR, Paragache G, Panda NK, Chakrabarti A. Mucormycosis in immunocompetent individuals: an increasing trend. *J Otolaryngol*. 2005;34(6):402-406. doi:10.2310/7070.2005.34607

How to cite this article: Muraleedharan M, Panda NK, Angrish P, et al. As the virus sowed, the fungus reaped! A comparative analysis of the clinico-epidemiological characteristics of rhino-orbital mucormycosis before and during COVID-19 pandemic. *Mycoses*. 2022;65:567–576. doi:10.1111/myc.13437