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RESEARCH PAPER

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Outcomes of COVID-19-associated mucormycosis epidemic in India: A prospective 2-year follow-up study

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Abstract

Objectives: The objective of this study was to study the various outcomes among coronavirus disease 2019 (COVID-19)-associated mucormycosis (CAM) in terms of morbidity and mortality.

Methods: A prospective study was done on 107 patients (60 male, 47 female) in the Department of Otolaryngology and Head and Neck Surgery, Government Medical College, Patiala, India, diagnosed with CAM from April 2021 to August 2021. The patients were managed both medically and surgically. The follow-up was done up to 2 years to assess the various outcomes.

Results: Out of 107 patients, short-term (3 months) survival was 68.22%, and long-term (2 years) survival was 52.34%. Overall mortality was 47.66%, with short-term mortality of 31.77% and long-term mortality of 15.89%. Eye loss was seen in 17 patients, residual ophthalmoplegia in 12, palatal loss in 15, depression in 56, cerebrospinal fluid rhinorrhea in two, and recurrence in two patients.

Conclusions: In conclusion, despite early management and successful initial outcome, the patients are still haunted by the after-effects of CAM like residual morbidity in terms of eye and palate loss, ophthalmoplegia, and depression. Delayed mortality has also been noticed over 2 years of follow-up.

KEYWORDS

acute invasive fungal sinusitis, COVID-19, COVID-19-associated mucormycosis, mucormycosis, rhino-orbito-cerebral mucormycosis

Key points

- Although the short-term outcomes of coronavirus disease 2019-associated mucormycosis (CAM) have been reported in recent literature, to the best of our knowledge, this is the first study in which a large cohort of CAM was regularly followed up to 2 years to evaluate the outcomes in terms of morbidity and mortality.
- Even after the patients with CAM had been fully cured, they continued to suffer the long-term after-effects of the disease.
- This study adds to the inadequate data on the effects of such a rare event in the long term.

INTRODUCTION

Rhino-orbito-cerebral mucormycosis (ROCM), once thought to be a rare opportunistic fungal infection, emerged as an epidemic during the second wave of the coronavirus disease 2019 (COVID-19) pandemic adding further to the morbidity and mortality in the affected subjects.[1,2] Various etiological factors have been identified such as steroid overuse, diabetes mellitus, oxygen delivery, and prolonged ventilatory support in intensive care units (ICUs).[3–5] As mucormycosis affects primarily the immunocompromised patients, patients with COVID-19 formed a major pool of potential victims.[6–8]

The pathological characteristics of mucormycosis are angioinvasion and thrombosis, leading to tissue necrosis and black eschar formation in the nasal cavity and palate, which is the clinical hallmark of this disease.[9–11] Other associated features could be facial swelling and numbness; nasal obstruction with discolored discharge; palatal ulcer; loosening of teeth; orbital symptoms like periorbital edema, proptosis, restricted gaze, and reduced vision; and cerebral features including headache and altered sensorium.[12]

A high index of suspicion is required, especially in immunocompromised patients, for early diagnosis and management.[13,14] Both medical and surgical management play a vital role in decreasing the morbidity and mortality in this potentially fatal disease.

Although the short-term outcome of COVID-19-associated mucormycosis (CAM) has been reported in recent literature, to the best of our knowledge, this is the first study in which a large cohort of CAM was regularly followed up to 2 years to evaluate the outcomes.

MATERIALS AND METHODS

A prospective study was conducted in the Department of Otolaryngology and Head and Neck Surgery, Government Medical College, Patiala, India, in which all the potassium hydroxide (KOH) wet-mount-proven CAM patients were included. The ethical clearance for this study was received from the Institutional Review Board (vide no. EC/NEW/INST/2020/997/14512). A total of 107 patients with CAM (60 male, 47 female) from April 2021 to August 2021 were enrolled and followed up to March 2023. The complete data was tabulated and analyzed to evaluate the outcomes (morbidity and mortality) in CAM subjects.

History and examination

History taking included active or past COVID-19 infection, steroid intake, oxygen therapy, need for ICU care or ventilatory support, recent dental infection or tooth extraction, or any pre-existing comorbidities like diabetes mellitus, hypertension, chronic kidney, or liver disease. A complete ear, nose, and throat and opthalmological examination were conducted to look for any black crusting or eschar in the nasal cavity or palate, palatal or alveolar erosions, facial swelling, and orbital involvement along with a complete eye examination. A neurological examination was also done to assess intracranial involvement along with the examination of the cranial nerves.

Diagnosis

All routine hematological and biochemical investigations were sent. The 10% KOH wet-mount samples were taken from the appropriate suspicious areas of the nasal and/or oral cavity. The presence of broad aseptate hyphae with a wide-angle branching on 10% KOH mount was suggestive of mucormycetes. All KOH-positive patients then underwent radiological investigations, which included contrast-enhanced computed tomography and/or magnetic resonance imaging (MRI) of the head with nose, paranasal sinuses, and orbit to look for bony and soft tissue involvement, especially intraorbital and intracranial extension.

Management

Patients were then started on injection amphotericin B (AMB) with incremental dose up to 5 mg/kg/day. Though liposomal AMB (0.5–1.0 mg/kg in 5% dextrose over 5–6 h after prehydration with 500 mL normal saline) was the preferred choice, some patients also received conventional AMB due to an acute shortage of the drug during the pandemic. All patients were regularly monitored for kidney function, blood sugar levels, and electrolytes during the course. After preanesthesia check-up, patients were taken up for emergency surgical debridement via an endoscopic/open approach. Orbital exenteration was performed in patients with a negative perception of light (PL). Patients with orbital involvement with positive PL were given intraorbital injection of AMB along with intravenous AMB. The posterior bony wall of maxilla was removed in all the patients to evaluate the infratemporal fossa, and clearance of necrotic tissue was done in affected subjects. The debrided tissue was sent for histopathological examination. Regular endoscopic evaluation and cleaning of postoperative cavity were done in the postoperative period to look for residual disease. After the administration of the complete dose of AMB (average cumulative dose: 3.5 g), patients were discharged on oral posaconazole (300 mg twice daily for 1 day, followed by 300 mg once daily for 3 months). All the patients were followed up weekly for 4 weeks and then every fourth week to look for adequate healing and recurrent disease.

RESULTS

The study included 107 COVID-19-positive patients of suspected ROCM patients. The overall mean age in the study was 50.56 ± 11.82 years with a range of 20–85 years. There were a total of 60 males and 47 females in the study. Diabetes mellitus was the

most common comorbidity seen in 95.33% of subjects (102/107). Hypertension was the second most common comorbidity seen in 34.58% (37/107) of patients. The other comorbidities have been described in Table 1. A total of 55 patients (51.40%) received steroid therapy for treatment of complicated COVID-19 pneumonia. History of oxygen support received before the onset of mucormycosis was seen in 74 patients (69.16%). The mean duration for the occurrence of mucormycosis from the time of a COVID-19-positive report was 8.28 days (range: 0–67 days). Among the signs and symptoms, facial swelling was the most common symptom seen in 86 (80.37%) patients, followed by facial numbness in 62 (57.94%), periorbital swelling in 55 (51.40%), nasal obstruction in 46 (42.99%), and headache in 45 (42.06%) patients (Figure 1). On diagnostic nasal endoscopy, discolored nasal discharge and crusting were seen in 57 (53.27%) patients. The clinical images of the patients have been shown in Figures 2–5.

TABLE 1 Demographic profile and comorbidity data of CAM subjects.

Items	Number
Age (years)	50.56 ± 11.82 (mean ± SD)
	20–85 (range)
Gender [*n* (%)]	
Male	60 (56.07)
Female	47 (43.93)
Comorbidities [*n* (%)]	
Diabetes mellitus	102 (95.33)
Hypertension	37 (34.58)
HCV positivity	3 (28.04)
HIV positivity	1 (0.93)
Dyslipidemia	1 (0.93)
Hyperuricemia	1 (0.93)
Hepatitis B+	1 (0.93)
Seizure disorder	1 (0.93)
CAD	5 (4.67)
CKD	2 (1.87)
Hypothyroidism	3 (2.80)

Abbreviations: CAD, coronary artery disease; CAM, COVID-19-associated mucormycosis; CKD, chronic kidney disease; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

Out of 107 subjects, sinonasal involvement was seen in 26 patients (24.30%), rhino-orbital involvement was seen in 61 patients (57.00%), 19 patients (17.76%) had rhino-orbito-cerebral involvement, and, interestingly, one patient (0.93%) had isolated mandibular mucormycosis who also had a history of both COVID-19 and chronic kidney disease (Table 2). Out of 107 patients, 80 underwent surgical debridement to remove all the dead necrotic tissue and fungal debris. The rest of the 27 patients were hemodynamically unstable and were on ventilatory support due to COVID-19 pneumonia. They expired before they could be operated upon. Out of the 80 patients who were operated, the posterior wall of maxilla was removed in all of them to inspect the infratemporal fossa. We observed a unique feature that even in cases with healthy-looking posterior maxillary wall, disease involvement was seen in the pterygopalatine and infratemporal fossa. Infratemporal clearance was done in 68 patients, and palate (partially or as a part of maxillectomy) was removed in 15 patients among the operated patients. Periorbita was opened in 56 patients to remove the necrosed tissue preserving the extraocular muscles, whereas orbital exenteration was done in 15 patients with negative PL. However, among the patients in which orbital sparing was done, two patients developed negative PL later on despite receiving intraorbital AMB and underwent orbital exenteration as well. Thus, orbital exenteration was done in a total of 17 patients.

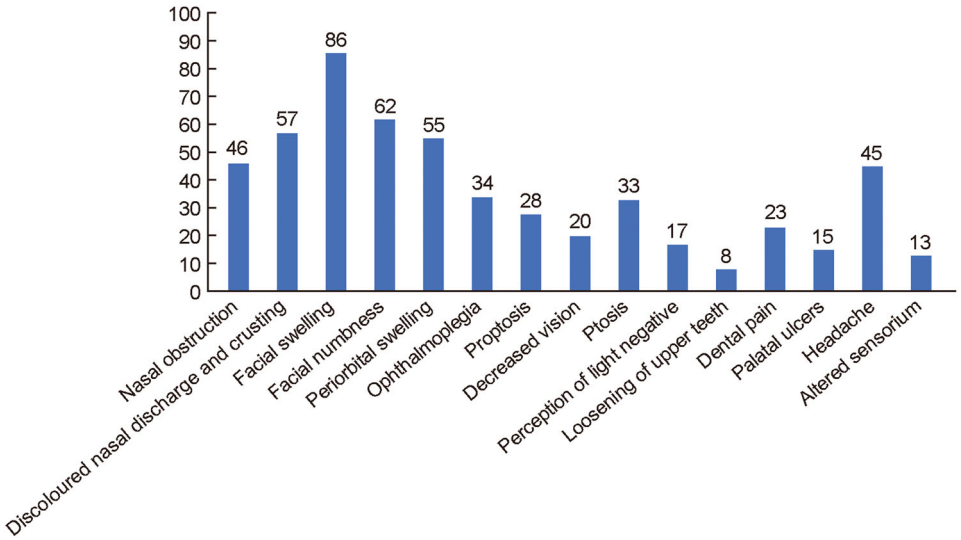

FIGURE 1 Spectrum of clinical presentation in subjects of coronavirus disease-associated mucormycosis.

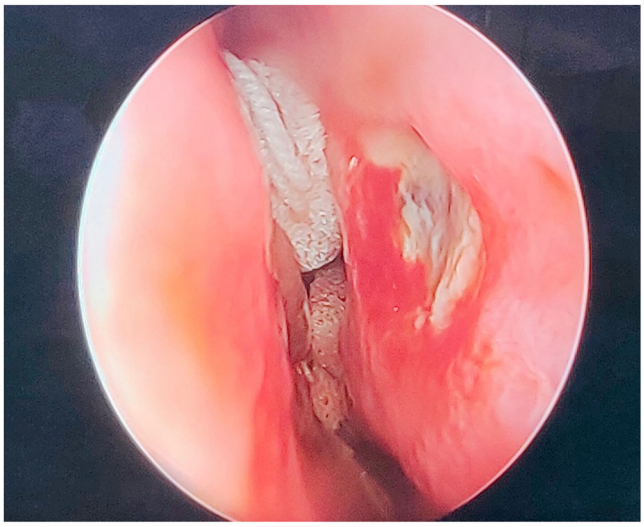

FIGURE 2 Intraoperative endoscopic picture of left nasal cavity showing necrotic area on the lateral wall.

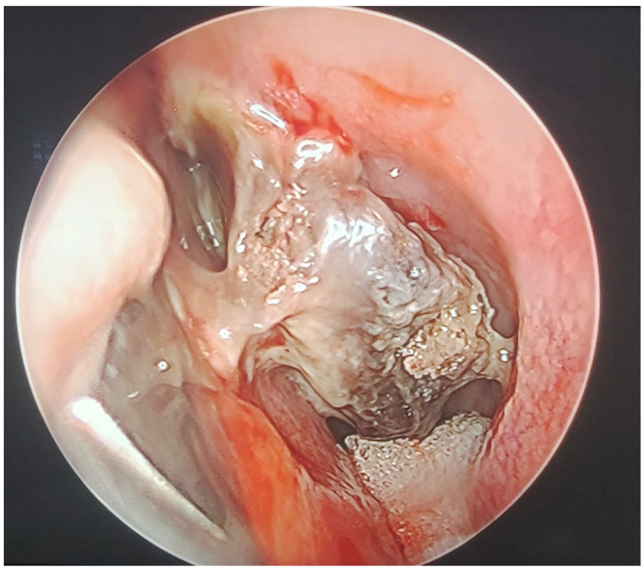

FIGURE 3 Endoscopic picture of left nasal cavity showing necrotic middle turbinate.

Neurosurgery opinion was taken for the 19 patients who had rhino-orbito-cerebral involvement. They did not undergo any neurosurgical intervention and were managed conservatively for intracranial component on AMB after surgical debridement of the rhino-orbital component. In our study, the mean follow-up period was 10.8 months, ranging from 20 days to 2 years.

Mortality

Initially, 73 patients were completely cured and 34 patients expired, out of which 27 were not operated and seven were operated. No statistically significant association was seen between mortality and

FIGURE 4 Patient with right orbital involvement with necrosis of infraorbital skin.

FIGURE 5 Intraoperative picture of a patient with maxillary involvement undergoing partial maxillectomy.

diabetes, steroid use, and oxygen therapy with a p value of 0.652, 0.063, and 0.827, respectively (Table 3).

On studying the long-term outcomes in these patients, we found that out of the 73 patients who were cured initially, 17 patients expired later on owing to causes unrelated to CAM. Of these, 10 patients died within the first 6 months, 6 within 6–12 months, and the remaining one expired after 1 year of follow-up. The overall mortality in our study was 47.66% (51/107), short-term mortality (from Day 0 to 3 months after surgery) was 31.77% (34/107), and the long-term mortality (from 3 to 24 months) was 15.89% (17/107).

TABLE 2 Subclassification of CAM and respective outcome [*n* (%)].

Type of disease	All patients (*n* = 107)	Short-term mortality (*n* = 34)	Long-term mortality (*n* = 17)
Sinonasal	26 (24.30)	4 (11.77)	3 (17.65)
Rhino-orbital	61 (57.00)	17 (50.00)	12 (70.59)
Rhino-orbito-cerebral	19 (17.76)	13 (38.23)	2 (11.76)
Mandibular	1 (0.90)	0 (0)	0 (0)

Abbreviation: CAM, coronavirus disease-associated mucormycosis.

TABLE 3 Correlation of diabetes status and steroid and oxygen therapy with final outcome.

	Short-term outcome (*n* = 107)			Long-term outcome (*n* = 73)		
Items	Cured (*n*)	Expired (*n*)	*p* Value	Cured (*n*)	Expired (*n*)	*p* Value
Diabetes						
Present	70	32	0.652	54	16	0.554
Absent	3	2		2	1	
Total	73	34		56	17	
Steroid therapy						
Present	42	13	0.063	31	11	0.495
Absent	31	21		25	6	
Total	73	34		56	17	
Oxygen therapy						
Present	50	24	0.827	42	8	0.030
Absent	23	10		14	9	
Total	73	34		56	17	

Morbidity

Residual ophthalmoplegia was seen in 12 patients postoperatively out of the 34 patients with preoperative ophthalmoplegia. *Complete eye loss* was seen in 17 patients with orbital exenteration, out of which eight patients opted for artificial eye prosthesis after 6 months. A total of 15 patients had partial *palatal loss* who were fitted with an obturator. All the patients who survived (56/107, 52.34%) underwent psychological evaluation and were diagnosed with mild to moderate depression. They were managed with the help of a psychiatrist.

Other complications seen in our study were cerebrospinal fluid rhinorrhea and recurrence. *Cerebrospinal fluid rhinorrhea* occurred in two patients, which was observed during surgery and repaired during primary surgery only. The site of leak was the cribriform plate in one patient and the frontal part of orbit in the other. The first patient continued to have cerebrospinal fluid rhinorrhea even after repair, which resolved spontaneously within 2 weeks of conservative management without the need for further surgical intervention. *Residual/recurrent disease* was seen in infratemporal fossa in two patients within 3 weeks of primary surgery and underwent revision debridement. Mortality and morbidity data have been summarized in Table 4.

TABLE 4 Mortality and morbidity data among CAM subjects (*n* = 107).

Items	*n* (%)
Mortality	
Short-term mortality (at the end of 3 months)	34 (31.77)
Long-term mortality (at the end of 20 months)	17 (15.89)
Overall mortality	51 (47.66)
Morbidity	
Eye loss (orbital exenteration)	17 (15.89)
Residual ophthalmoplegia	12 (11.21)
Palatal loss	15 (14.02)
Depression	56 (52.34)
CSF rhinorrhea	2 (1.87)
Recurrence	2 (1.87)

Abbreviations: CAM, COVID-19-associated mucormycosis; CSF, cerebrospinal fluid.

DISCUSSION

Patients with COVID-19 were at an increased risk of mucormycosis, with etiologies being poorly controlled diabetes and need for high-dose steroid therapy to treat complicated COVID-19 pneumonia. Ponnoaiah et al.[15] showed that hyperglycemia and steroid use increase the risk of ROCM regardless of COVID-19 hospitalization. Furthermore, invasive procedures like mechanical ventilation and extracorporeal membrane oxygenation, extended hospital stays, inadequate asepsis, and use of tap water for hydrating oxygen acted as risk factors, which led to the introduction of pathogens on top of this diminished immunity. Consequentially, they became susceptible to secondary bacterial and fungal infections, flaring up the risk of secondary opportunistic infections.[13,16]

Diabetes mellitus is already an immunocompromised state etiopathogenesis being chronic hyperglycemia in diabetics leads to defective phagocytosis and suppression of cytokines.[17–20] In COVID-19, the virus causes a cytokine storm which damages the pancreatic islet cells causing further hyperglycemia.[21,22] To counteract the cytokine storm, patients with COVID-19 were given corticosteroids, which is another culprit causing hyperglycemia. Thus, when patients with diabetes got infected, their blood sugar level increased significantly reinforcing their immunocompromised status.[23] In our

study, 95.32% (102/107) of the patients were diabetic. Although the presence of diabetes was not statistically associated to outcome of the disease, the presence of diabetes itself was definitely a significant risk factor for the occurrence of CAM. In our study, 51.40% (55/107) of the patients had also received corticosteroid therapy. In the study by Meher et al.,[4] 101 out of 131 patients were known diabetics and 23 were newly diagnosed. Contrary to our study, Meher et al.[4] reported a statistically significant correlation between diabetes and final outcome with 6 deaths among patients with diabetes. However, among the 67/131 patients who received steroid therapy, no statistically significant correlation with the final outcome was seen in their study similar to our study. Another associated comorbidity seen in our study was hypertension (34.58%, 37/107). A significant correlation has been seen between hypertension and COVID-19 in literature. Zhou et al.[24] reported hypertension (30%), diabetes (19%), and coronary heart disease (8%) in his research. Wu et al.[25] reported that the most frequent comorbidities in patients with COVID-19 who developed acute respiratory distress syndrome were hypertension (27%), diabetes (19%), and cardiovascular disease (6%). Uncontrolled hypertension increases the susceptibility to contracting COVID-19 as it lowers immunity, increases the risk of lung injury, and increases the chances of hospital exposure due to its associated complications, which was a breeding ground of COVID-19 infection in those days.[26] Castro and Frishman[27] observed that in patients with COVID-19, there was an increased level of angiotensin II, causing an atherosclerotic effect on vessel walls, which further increased the risk of thrombosis and necrosis in these already hypertensive patients with mucormycosis. Other comorbidities seen in our study (Table 1) were not statistically significant. No association with other morbidities has been found in the reported literature.

In our study, 69.16% of patients with COVID-19 had a history of oxygen support received before the onset of mucormycosis. No significant correlation was found in our study between patients receiving oxygen therapy and outcome. In the COSMIC (Collaborative OPAI-IJO Study on Mucormycosis in COVID-19) study, which is one of the biggest studies comprising 2826 patients, 57% of patients were receiving oxygen therapy, and steroids had been given to 87% of patients, out of which 21% received them for more than 10 days.[14] However, they did not study the correlation of steroid and oxygen therapy with the outcome of the disease.

Sinonasal involvement was seen in 26 patients (24.30%), rhino-orbital involvement was seen in 61 patients (57%), and 19 patients (17.76%) had rhino-orbito-cerebral involvement. Among its varied presentations, mucormycosis presented in our patients most commonly as rhino-orbital mucormycosis (57%), followed by isolated sinonasal mucormycosis (24.30%) and rhino-cerebral mucormycosis (17.76%). A very rare form of mucormycosis which is mandibular mucormycosis was also seen in one (0.93%) of our patients who had a known case of chronic kidney disease and had a history of dental infection after COVID-19 infection. However, no statistically significant correlation was seen between the presentation of disease and its outcome. The systematic review and meta-analysis by Jeong et al.[7] in 2018, before the pre-COVID-19 era showed ROCM as the most common presentation (288/851, 34%), followed by cutaneous mucormycosis (187/851, 22%), pulmonary mucormycosis (172/851, 20%), and gastrointestinal mucormycosis (72/851, 8.4%). Meher et al.[4] classified the patients with CAM into three types, 77 patients with rhino-orbital involvement, 39 with sinonasal disease, and six with ROCM. In the systematic review by Pal et al.,[28] rhino-orbital mucormycosis was again the most common (42%), followed by ROCM (24%) and pulmonary mucormycosis in 10 patients (10%).

In our study, 88.89% of the subjects underwent early surgical debridement, and the rest were either unfit for surgery, eventually expired before they could be taken up for surgery. Among the operated patients, 60% underwent endoscopic debridement, 18.75% underwent debridement with an open approach (mid-facial degloving), and 21.25% patients had to undergo additional orbital exenteration along with surgical debridement of sinonasal disease. Although 61 patients had orbital involvement, exenteration was done in only 17 (19.77%) of these as the eye was clinically dead in these patients with a negative PL. Orbital features like orbital swelling, ophthalmoplegia, proptosis, chemosis, and reduced vision improved postsurgery and with AMB. Residual ophthalmoplegia was seen in 12 patients postdebridement, but vision was normal on follow-up. The COSMIC study reported orbital involvement in 72% patients.[14] Desai et al.[29] reported normal vision in only 25% of patients, while 22% had complete loss of vision and 52% of patients had ophthalmoplegia in their study with 100 patients. Patients undergoing eye and palatal removal were rehabilitated with prosthesis and obturators once the wound had healed. Regular follow-up was absolutely necessary in all these patients to ensure adequate wound healing as it was already hampered by their immunosuppressed state. Also, recurrence or residual disease had to be looked for. An MRI was done in all the patients 3 months postsurgery and earlier in those with suspicion of residual or recurrent disease. Two patients had recurrent disease within 3 weeks of primary surgery for which a revision debridement was done with complete clearance of the disease. One of the most underevaluated outcomes of CAM was depression, which was observed in almost all the CAM survivors in our study. These patients had to suffer a great deal of mental and physical trauma during the course of their treatment, and thus, psychological evaluation is a must in all subjects to ensure recovery in both physical and psychological aspects.

The overall mortality seen in the study was 47.66% (51/107), among which 31.77% (34/107) of the patients expired during the course of treatment and the rest of the 15.89% (17/107) deaths occurred later on. In such a devastating disease with a high early mortality rate of more than 50% as per majority of literature, we could achieve a lower early mortality rate (31.77%, 34/107) as prompt diagnosis was made, and empirical amphotericin was started even on clinical suspicion of mucormycosis without waiting for positive histopathological and microbiological reports.[30] The COSMIC study also showed that early surgical management reduced the mortality rate from 52% to 39%.[14] In our study, out of the 17 late deaths, 58.82% (10/17) late deaths occurred within 6 months of discharge and the rest (7/17) within the next 6–24 months. This

TABLE 5 Review of literature of CAM.

Reference	Year	Number of patients	Short term	Long term
[4]	2021	131	Upto 1 month	-
[31]	2021	20	Upto discharge	-
[14]	2021	2218	(14.4 ± 21.3) days	-
[32]	2021	31	51.6 days	-
[33]	2021	47	Upto discharge	-
[34]	2022	178	3 months	-
[35]	2022	1733	3 months	-
[36]	2023	211	(126.6 ± 16.4) days	-
Present study	2023	107	Upto 3 months	4–20 months

Abbreviations: CAM, COVID-19-associated mucormycosis; -, no data.

shows that even though these patients were cured initially and successfully discharged, the secondary impact of the disease followed them home. To the best of our knowledge, our research is the first one in literature to evaluate the outcomes of CAM up to 2 years as shown in Table 5. These patients possibly continued to suffer from sequelae of COVID-19, diabetes, and other unknown factors. Since this was a rare event, without sufficient evidence, we cannot possibly comment on the definitive processes that are still occurring in the body long after the patients were declared cured of CAM.

CONCLUSION

Although mucormycosis was majorly hit by the COVID-19 wave, its cases still continue to present in our clinics. So, its early diagnosis and management remain crucial even after the COVID-19 wave has subsided. Knowledge of the long-term outcome is necessary to know what to expect from the disease and how it haunts the patients even after cure. Thus, a long-term follow-up with regular check-ups in terms of diabetes control and cardiac, pulmonary, renal, and hepatic functions is essential to decrease long-term mortality.

Early rehabilitation of the orbit and palate is essential to boost the morale of patients. All patients should undergo a mandatory psychological evaluation to ensure sound mental health.

LIMITATIONS

Sixteen patients were lost to follow-up, although they were contacted telephonically to ensure their well-being. Also, the exact cause of death in patients who expired after discharge could not be ascertained.

AUTHOR CONTRIBUTIONS

All the authors have contributed in the preparation of the manuscript.

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The authors have nothing to report.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Research data are not shared.

ETHICS STATEMENT

The study protocol was approved by the Institutional Review Board for Ethical Clearance of Government Medical College and Rajindra Hospital, and it was performed in accordance with the Code of Ethics of the World Medical Association according to the Declaration of Helsinki of 1975, as revised in 2000.

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