

## **PERI-OPERATIVE ANAESTHETIC CONCERNS IN COVID-19 ASSOCIATED MUCORMYCOSIS**

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### **ABSTRACT**

**Introduction:** Mucormycosis is a fulminant life-threatening fungal infection requiring emergency surgical debridement. It is associated with immune-compromised status, multi-systemic involvement, and difficult airway posing challenges to anesthetic management. We conducted this study to find the peri-operative anesthesia concerns in patients of COVID-19-associated mucormycosis. **Methods:** This retrospective observational study included COVID-19-infected patients operated for invasive mucormycosis under general anesthesia. Cases operated under local anesthesia were excluded from the study. **Results:** A total of 30 patients were included in the study where the majority of the patients were ASA physical status III. ASA classification uses a grading system of I(one) through V( five), with I identifying a person in good health and V as a person with a severe, life-threatening condition. The most common co-morbidity was diabetes mellitus plus hypertension 66% (n=20), followed by only diabetes 30% (n=9). Out of all patients, 33.3% (n=10) were intubated at the first attempt using direct laryngoscope, rest 66.6% required other interventions like the use of video laryngoscope, bougie, or external laryngeal pressure. Perioperative blood transfusion was required in 40% (n=12) of the patients. Of patients who required intensive care unit (ICU) admission 40% (n=12) out of them, 10% patients (n=3) did not survive. The average hospital stay was 55.9 +/-15.8 days with a maximum of 95 days and a minimum of 15 days. **Conclusion:** Mucormycosis is mostly associated with uncontrolled diabetes mellitus in post-COVID patients. These require utmost care peri-operatively as they are associated with a difficult airway, intraoperative complications, prolonged morbidity, and mortality.

**Keywords:** mucormycosis, diabetes, intubation, intraoperative, complications

## **Introduction:**

Mucormycosis is a rare, fulminant, rapidly progressive, potentially life-threatening opportunistic fungal infection that occurs mostly in immunocompromised patients (Gupta, K. 2021). Mucormycosis results in extensive angio-invasion leading to vessel thrombosis and subsequent necrosis, most commonly involving the paranasal sinuses and orbit. It may also present with cerebral, pulmonary, gastrointestinal, renal, cardiac, and vascular involvement(Mathew, G.2019, Monte Junior, 2020). There has been a rapid rise in the number of mucormycosis cases during the COVID-19 second wave in India (Mishra N,2021). Causative factors are the immune-compromised state of COVID-19 pneumonia, diabetes, and concurrent use of steroids.

Normally, hosts kill mucorales by the generation of defensins and oxidative metabolites released by mononuclear and polymorphonuclear phagocytes, hence patients who are neutropenic or those with dysfunctional phagocytes show more susceptibility to developing mucormycosis (Mishra N,2021). In COVID-19 there is profound lymphopenia and viral replication accentuates the inflammatory response and neutrophil and monocyte influx in the blood stream (Mulakaluri,2022). This leads to an imbalance between lymphocyte and neutrophil action making the patients more susceptible to systemic fungal infections. Mucormycosis is an angioinvasive disease caused by fungi of the order Mucorales like rhizopus, mucor, and rhizomucor. It is hypothesized that severe acute respiratory syndrome COVID-19 infection may affect CD4+ and CD8+ T-cells, which are highly involved in the pathological process of COVID-19 infection. It has been shown that in severe COVID-19 cases, there is a reduction in the absolute number of lymphocytes and T-cells, which is associated with the worst outcomes. Mucorales-specific T-cells (CD4+ andCD8+) produce cytokines such as interleukin IL 4, IL-10, IL-17, and interferon-gamma that damage the fungal hyphae (Misra, S.2022)

Management of mucormycosis aims at early diagnosis, reversal, and treatment of predisposing factors, early administration of systemic anti-fungal therapy, and surgical debridement(Mulakaluri,2022). A commonly used anti-fungal agent, Amphotericin B acts by binding to ergosterol of the fungal cell membrane forming transmembrane channels, which leads to alterations in cell permeability. Mucormycosis causes vascular thrombosis which prevents Amphotericin B from reaching the infected tissue. The primary aim of surgical intervention is to debride all the necrotic tissues and to drain paranasal sinuses and orbital exenteration, which can be lifesaving in the presence of active fungal infection (Gupta, K. 2021).

Peri-operative anesthetic management of these patients was found to be associated with adversities like post-COVID systemic sequelae, immuno-compromised status, difficult airway, difficult intravenous access, micro-coagulation, side effects of amphotericin B, and repeat surgeries (Gangneux, J.2020). These patients required blood transfusions and prolonged hospital and ICU stays amounting to an increase in morbidity as well as mortality. We conducted this study to find the peri-operative concerns for patients posted for surgical debridement under general anesthesia of COVID-19-associated mucormycosis.

## Methods

This retrospective observational study was conducted in the Department of Anaesthesia at a tertiary care center after ethical committee approval. Informed consent was exempted as the identity of the patients was not revealed.

Patients who operated for invasive mucormycosis under general anesthesia from May 2021 to September 2021 were included in the study. Cases operated under local anesthesia and patients who denied a history of COVID-19 were excluded from the study. Data was collected from the medical record department of the institute after the ethical committee approval pre-printed forms and were filled manually. Data was analyzed for the defined variables in order to guide us for future management of these cases to improve the quality of care, and outcome of the patients. Data collection and analysis were done by two different investigators so as to prevent reviewer bias.

Preoperative data collection included demographic variables like age, sex, weight, ASA grade, and co-morbidities. A detailed history of COVID infection, need for O<sub>2</sub> requirement, and steroid treatment was taken; the incidence of deep venous thrombosis diagnosed on Doppler ultrasound was noted.

Symptoms of mucormycosis were noted, and the extent of involvement and diagnosis were recorded on the basis of available imaging reports. Preoperative airway assessment in terms of mouth opening and Modified Mallampatti grading, laboratory investigations like hemoglobin (Hb), renal function test, serum electrolytes, HbA1c, and arterial blood gases (ABG) for the presence of acidosis were recorded. Imaging investigations like CT scan, MRI, and 2D Echo were recorded. Ongoing medications like levetiracetam for intracerebral involvement, amphotericin B for treatment of fungal infection, and steroids for reason of causation were noted.

Intraoperative findings like the ease of intravenous cannulation and the need for the central line were recorded as prolonged hospital stays and intravenous drug infusions posed difficulty in cannulation. A number of attempts, need for advanced airway devices, mallampatti score, and Cormack Lehane grading were recorded as many patients had anticipated difficult intubation. The Mallampatti score is used to assess the ease of intubation and Cormack Lehane grading is commonly used to describe laryngeal view during direct laryngoscopy. Intra-operatively administered vasopressors and inotropes, electrolytes, or insulin were noted. Blood loss & need for blood transfusion perioperatively was also recorded.

Any complications if witnessed like delayed emergence from anesthesia, need for post-operative ventilation, or re-intubation were noted. Post-operative Aldrete score was noted and patients were followed up for 48 hours, need of ICU admission, oxygen therapy or blood transfusion, and re-operations if any were noted. The Aldrete scoring system is a widely used scale for determining when post-surgical patients can be safely discharged from the post-anesthesia care unit.

## Results:

### Demographic data

The study included 30 patients with a mean age of 49.78 years (range 28-85 years), (Table 1) 50% of them were males, with a mean body weight of 60 kg. The majority of the patients were ASA physical status III. The most common co-morbidity was diabetes mellitus with hypertension (DM and HTN) 53% (n=16), followed by only diabetes 23% (n=7). (Table 2)

**Table 1: Demographic characteristics**

Demographic Details	N	Mean	Interquartile range
Age	30	49.78 years	28-85 years
Weight	30	60 kg	45-90 kg

Others had DM and HTN along with coronary artery disease (CAD) 10% (n=3), hypothyroidism 3% (n=1), immune-compromised status 10% (malignancy-1, tuberculosis-1, chronic treatment of steroids for psoriasis-1), one patient had no comorbidity 3% (n=1).

**Table 2: Preoperative assessment and surgical procedure**

Variable	N	%
Sex		
Male	15	50
Female	15	50
Predisposing factors		
COVID-19-associated mucormycosis	30	100
History of requirement oxygen (ICU/ward) during COVID-19 infection	7	23.3
History of requirement steroids (ICU/ward) during COVID-19 infection	22	73
Diabetes mellitus	7	23.3
Diabetes Mellitus with Hypertension	16	53.3
Diabetes mellitus with Hypertension and Coronary artery disease	3	10
Diabetes mellitus with Hypertension and Hypothyroidism	1	3
Diabetes mellitus with Malignancy	1	3
Diabetes mellitus with Tuberculosis	1	3
Diabetes mellitus with Psoriasis	1	3
No comorbidity	1	3
ASA		
II	10	33
III	20	66
Pre-operative		
O <sub>2</sub> inhalation	2	6.6
Room air	28	93.3
Diagnosis		
Sino-orbital	4	13.3
Sino-nasal	14	46.6
Sino-nasal-orbital	4	13.3
Sino-nasal-orbital-cerebral	8	26.6

Surgery		
B/L endoscopic debridement ± palletectomy ± septoplasty	12	40
B/L endoscopic debridement ± Orbital decompression	8	26.6
B/L endoscopic debridement ± orbital exenteration	2	6.6
B/L endoscopic debridement ± medial maxillectomy	8	26.6

### Pre-operative parameters

Corticosteroid treatment was received in 26% of patients (n=7) for COVID-19 during their hospital stay. Most of the patients complained of eye and facial pain, nasal block, and diminution of vision. All the patients had imaging evidence in the form of CT paranasal sinuses and MRI brain which revealed mucosal thickening of sinuses, adjacent bony erosions, and orbital involvement, if any. Patients commonly presented with rhino-facial, orbital, and palatal mucormycosis 74% (n=22) while 26% (n=8) had cerebral involvements as well. (Figure 1)

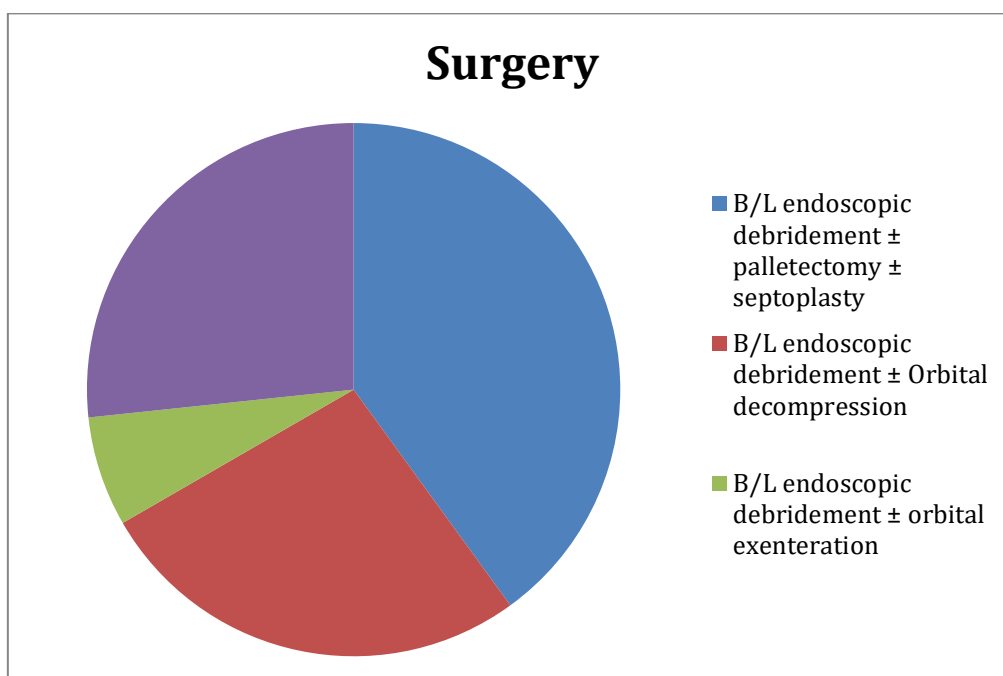


Figure 1: Type of surgery denoting extent of mucormycosis

### Intra-operative concerns

Deep venous thrombosis was found to be present in 30% (n=9) patients, which was diagnosed on Doppler ultrasound done pre-operatively. Central venous access cannulation was done pre-operatively in 20% (n=6) of the patients due to difficult peripheral access.

Patients with cerebral involvement were on anti-epileptic drugs like levetiracetam 500 mg twice a day; it was ensured that the anti-epileptic drug was administered pre-operatively. For patients with diabetes oral hypoglycemic drugs were stopped peri-operatively, and patients were put on insulin, morning arterial blood gases (ABG), blood sugar, and serum electrolytes on the day of surgery were noted. Intra-operative hyperglycemia and hypoglycemia were corrected with insulin and dextrose,

potassium, and magnesium replacements were done in view of hypokalemia and hypomagnesemia encountered in 50% of the patients (n=15).(Table 3)

**Table 3: Problem during peri-operative anesthesia management**

Variable	N	%
Mouth opening		
2-2.5 fingers	20	66.6
>2.5 fingers	10	33.3
Modified Mallampatti grading (MPG)		
MPG 2	8	26.6
MPG 3	20	66.6
MPG 4	2	6.6
Intubation with macintosh laryngoscope in first attempt	10	33.3
Intubation with macintosh laryngoscope in first attempt required additional manoeuvres like external laryngeal pressure or use of bougie or stellate	5	16.6
Intubation with help of videolaryngoscope in first attempt	11	36.6
Intubation with help of videolaryngoscope in second attempt	2	6.6
Intubation with help of videolaryngoscope in second attempt required additional manoeuvres like external laryngeal pressure or use of bougie or stellate	2	6.6
Preoperative anaemia		
Hb 8-10gm%	8	26.6
Hb >10gm%	22	73.3
Preoperative elevated serum creatinine		
0.5-1 mg/dl	15	50
> 1 mg/dl	15	50
Preoperative elevated HbA1c		
6-8	3	10
8-10	8	26.6
>10	19	63.3
Preoperative Potassium Levels(K <sup>+</sup> )		
2.5-3	12	40
3-3.5	5	16.6
3.5-4	13	43.3
Preoperative magnesium Levels(Mg <sup>2+</sup> )		
< 2 mg/dl	12	40
> 2 mg/dl	18	60
Pre-operative lactic acidosis (Ph<7.35, lactate>4)	12	40
Preoperative diagnosed deep venous thrombosis	9	30
Hemodynamic instability during surgery	6	20
Intraoperative Nitroglycerine infusion	3	10

Intraoperative Noradrenaline infusion	3	10
Intraoperative correction of hypokalemia	17	56.6
Intraoperative correction of hypomagnesemia	12	40
Intraoperative insulin therapy	15	50
Need for central line	6	20
Perioperative blood transfusion	12	40

### Recovery and postoperative period

Post-operatively, re-intubation was required in 1 patient (3.3%) given seizure followed by hypoxia, and delayed emergence from anesthesia was observed in 10% of patients (n=3). ICU admission was required in 40% of patients (n=12). Post-operative ventilator support was needed in 20 % (n=6) of patients, out of them, 10% of patients (n=3) did not survive. Patients requiring repeat operations were 14 (46.6%) where 12 (40%) patients were operated on twice and 2 (6.6%) patients were taken for surgery 3 times. (Table 4)

**Table 4: Post-operative concerns**

Variable	N	%
Postoperative re-intubation	1	3.3
Postoperative ventilator support	6	20
Delayed emergence from anaesthesia	3	10
Post operative modified Aldrete score (< 8)	12	40
Repeat operations	14	46.6

The average duration of ICU stay accounted for 11.95 days, with a maximum of 40 days for a few patients. The average hospital stay was 55.9±15.8 days with a maximum of 95 days and a minimum of 15 days.

### Discussion

Mucormycosis is a known complication of post-COVID infection. It can present as rhino, orbital, palatal, and cerebral forms of fungal disease. Better outcomes in terms of increased survival have been observed after surgical debridement in comparison to conservative management, encounters of anaesthesiologists with such types of patients may be frequent(Sharma, S., 2021).

Post-COVID-19 pneumonia, patients may have residual interstitial lung disease(Huang, Y., 2020). A detailed respiratory assessment, risk stratification, and postoperative pulmonary complications should be considered. Mucormycosis has been shown to have a high association with diabetes mellitus, accounting for 96.6% (n= 29) of the patients who where a known case of diabetes or had a recent onset. This may be attributed to the ketone reductase system of rhizopus, which helps in the survival of the fungus in a high glucose, acidotic environment. Also, decreased chemotactic and phagocytic activity of neutrophils is found in these conditions which promote fungal growth(John NM, 2019, Desai D 2020). In our study, 50% of the patients had uncontrolled sugars requiring intraoperative insulin supplementation. Pre-operatively 40% of patients (n=12) had lactate acidosis which co-relates with another study where 53.3% of patients had lactic acidosis (Solanki, N,2022).COVID-19 infection was

observed to cause myocardial injury and stress cardiomyopathy, for which pre-operative echocardiography may be advised(Lala, A.,2020). In our study 3 (10%) patients were observed to have regional wall motion abnormality preoperatively.

In this study, 30% of the patients were found to have deep venous thrombosis preoperatively. This may be attributed to an increased risk of thromboembolism due to a hypercoagulable state seen in COVID-19 infection(Bilaloglu, S.,2020).

In our study, 6 patients had intra-operative hemodynamic instability, 3 patients had hypertension who received intra-operative nitroglycerine infusions and 3 patients had intra-operative hypotension who received nor-adrenaline infusions. peri-operative hypertension may be because of primary hypertension as a co-morbidity, or due to renal hypertension as a side effect of amphotericin B. Peri-operative hypotension was frequently found in these patients which may be due to poor intake attributing to the facial swelling and pain associated with mucormycosis, associated cardiac causes of hypotension, diabetes insipid, intravascular hypovolaemia (bleeding) , sepsis, acute kidney injury may be associated with amphotericin side effects (Karaaslan E., 2019). and prolonged use of steroids. We had one case of psoriasis which was on chronic steroid treatment.

Video laryngoscopy, bougie, external pressure, and multiple attempts were required in 66.6% of patients in our study. Solanki et al(Solanki, N,2022)., reported 74% of patients (42 out of 57) have difficult mask ventilation and 77% (44 out of a total of 57 patients) of the patients have difficulty intubation. These patients may present with difficult mask ventilation and endotracheal intubation due to facial and supraglottic edema associated with fungal debris. Difficult airway equipment must be ready and tracheostomy consent may be considered(Kulkarni PK,2015).

Perioperative blood and blood product transfusion was done in 40% of the patients due to extensive surgeries and surgeries, and perioperative central venous cannulation was required in 20% of the patients. Due to Amphotericin-B induced side effects like nephrotoxicity, hypotension, hypokalaemia, hypomagnesemia, arrhythmias, seizures, allergic reactions, anemia, and fever, multiple patients required electrolyte replacements mostly potassium, magnesium, and calcium intraoperatively (Spellberg, B.,2005).

Delayed emergence from anesthesia was also witnessed in 26.6% of the patients which may be associated with dyselectrolemia, and decreased requirement of muscle relaxants due to multi-organ involvement (Bilaloglu, S.,2020, Spellberg, B.,2005).

In our study, we found prolonged ICU as well as hospital stay. It is supported by the literature which shows increased morbidity and mortality due to septicemia, multiple organ failure, absolute neutropenia, and immunosuppression(Spellberg, B.,2005). Spellberg et al, published a mortality rate of 70% in patients that received antifungal treatment alone as opposed to 14% that underwent antifungal and surgical treatment(Spellberg, B.,2005). Patients at our center were on both medical and surgical treatment with a mortality of 10%.

There are limitations pertinent to this study as this study was conducted in a single centre with a small sample size. A multicentric trial with a large sample size will be more relevant, also our study was a retrospective study, prospective study will be more appropriate.



## Conclusion

Patients with diabetes mellitus are more prone to developing rhino-orbital-cerebral mucormycosis. More vigilance is an utmost requirement on the part of anesthesia team. Considering the fulminant nature of mucormycosis, early surgical debridement needs to be planned. Peri-operative glucose control, difficult airway cart preparation, need for a central line in view of difficult intravenous access, maintenance of metabolic and electrolyte balance, correction of drug-induced side effects, and postoperative ICU management are mandatory for better outcomes in COVID-recovered patients posted for ROC mucormycosis. Any lack of preparation can be detrimental to the already compromised patients.

## Conflicts of Interest

The authors declare no conflicts of interest.

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