



Original Article

To Study the Factors Influencing Outcomes of Rhino-Orbito-Cerebral Mucormycosis

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ABSTRACT

Background: Rhino-orbito-cerebral mucormycosis (ROCM) is a rapidly progressive fungal infection causing vascular invasion and tissue necrosis, and has a very high mortality. Common in immunocompromised individuals, especially those with uncontrolled diabetes, it spreads from the sinuses to the orbit and the brain. Early diagnosis using imaging and microbiology, combined with multidisciplinary approach, including systemic antifungal therapy and surgical debridement, is essential for improving outcomes.

Objectives: To evaluate the effect of various demographic and risk factors on the outcome of rhino-orbito-cerebral mucormycosis and to analyse the seasonal pattern of presentation of rhino-orbito-cerebral mucormycosis.

Methods: A 15-month hospital-based ambispective observational study was conducted at a tertiary-care center in Mumbai, including retrospective (Jan 2023–Jan 2025) and prospective (Feb 2025 onwards) patients, with follow-up up to 3 months or until death, whichever came earlier. A total of 76 patients with histopathologically confirmed rhino-orbito-cerebral mucormycosis (ROCM) involving the sinonasal region were included using consecutive sampling after ethical approval and consent. Detailed clinical, laboratory, radiological (CECT/MRI), endoscopic, microbiological, and histopathological evaluation was done. Using appropriate statistical methods, all the data collected in the study were analysed at the end of the study period for the association of the multiple variables with the clinical outcome.

Results: The study found that middle-aged males working as farmers and labourers constituted the majority of ROCM cases, although age, sex, and occupation were not significantly associated with mortality. Headache, facial pain, visual disturbances, and nasal symptoms were common presentations, with facial pain/numbness and vision loss strongly linked to death. Diabetes mellitus was the predominant risk factor, and poor glycaemic control (HbA1c >8%) emerged as an independent predictor of mortality. Anaemia and elevated ESR were also associated with poorer outcomes. Disease stage at presentation was the strongest predictor of mortality, increasing markedly with orbital and intracranial extension. Frontal sinus involvement, palatal involvement, facial palsy, and intracranial spread were significant adverse prognostic factors.

Conclusions: The findings have important implications for clinical practice and public health, particularly in India and other low- and middle-income countries. Greater awareness of early ROCM symptoms among healthcare providers is essential, especially in diabetic patients presenting with facial pain, vision disturbances, or sinusitis. Timely referral, imaging, biopsy, and prompt initiation of combined medical and surgical treatment are crucial. Adherence to early diagnosis, strict glycaemic control, multidisciplinary management, and radiological staging can significantly improve patient outcomes.

INTRODUCTION

Rhino-orbito-cerebral mucormycosis (ROCM) is a rapidly progressive, angioinvasive fungal infection caused by organisms of the order Mucorales. It is one of the most aggressive forms of invasive fungal disease, characterized by vascular invasion, thrombosis, tissue necrosis, and high mortality if not diagnosed and treated early. Mucormycosis can present in several forms, including rhino-orbital/cerebral, pulmonary, cutaneous, gastrointestinal, and disseminated types, with ROCM being the most common. [1,2]

The global incidence of mucormycosis has been increasing, with a disproportionately high burden reported in India and other developing countries. This is largely attributed to the high prevalence of uncontrolled diabetes mellitus, which remains the most significant risk factor. Other susceptible groups include patients with haematological malignancies, organ transplant recipients, chronic kidney disease, and those receiving prolonged corticosteroid therapy. A notable surge in ROCM cases was observed during the COVID-19 pandemic, linked to immune dysregulation, excessive steroid use, prolonged hospitalization, and hyperglycaemia. Despite advances in management, mortality rates remain high, ranging from 40% to 80%, depending on disease severity and timing of intervention. [3,4,5]

The pathogenesis of ROCM involves inhalation of fungal spores into the nasal passages and sinuses, followed by angioinvasion. Fungi such as *Rhizopus*, *Mucor*, and *Lichtheimia* invade blood vessels, causing thrombosis, ischemia, and extensive tissue necrosis. This vascular invasion also limits antifungal drug penetration, complicating treatment. The infection spreads from the sinuses to the orbit through the lamina papyracea and can extend intracranially via vascular or direct routes, leading to life-threatening complications. [6]

Clinically, ROCM often begins with nonspecific symptoms such as nasal congestion, facial pain, headache, and fever, which may delay diagnosis. As the disease progresses, orbital involvement leads to periorbital oedema, proptosis, ptosis, ophthalmoplegia, and vision loss. Intracranial extension may result in cranial nerve palsies, cavernous sinus thrombosis, altered consciousness, and death. The hallmark of the disease is its rapid progression, often within days, necessitating a high index of suspicion. [2,7]

Diagnosis requires a combination of clinical evaluation, imaging, and microbiological confirmation. CT and MRI are essential for assessing the extent of sinus, orbital, and intracranial involvement. Definitive diagnosis is established through KOH mount, fungal culture, and histopathological identification of broad, aseptate hyphae with right-angle branching. Nasal endoscopy aids in early detection and targeted biopsy. [1,7]

Management is aggressive and multidisciplinary. Early initiation of systemic antifungal therapy, particularly liposomal Amphotericin B, is critical. Surgical debridement of necrotic tissue is equally important to reduce fungal load and improve drug delivery. In severe cases with orbital involvement, exenteration may be required. Optimal management also includes strict glycaemic control and correction of underlying immunosuppression. [8,9]

Prognosis depends on several factors such as disease extent, comorbidities, and promptness of treatment. Delayed diagnosis and intracranial spread are associated with poor outcomes. [10]

Given the variability in clinical outcomes, identifying factors influencing disease severity and mortality is essential. This study aims to evaluate these determinants to improve risk stratification, guide timely interventions, and enhance survival in patients with ROCM.

MATERIALS AND METHODS

Study Design and Setting

This was a 15-month hospital-based ambispective observational study conducted at a tertiary-care center in Mumbai, including retrospective (Jan 2023–Jan 2025) and prospective (Feb 2025 onwards) patients, with follow-up up to 3 months or until death, whichever came earlier. A total of 76 patients with histopathologically confirmed rhino-orbito-cerebral mucormycosis (ROCM) involving the sinonasal region were included using consecutive sampling after ethical approval and consent.

Inclusion criteria

- Age \geq 18 years, either gender, and willing to participate in the study
- Histopathologically confirmed mucormycosis with nasal mucosal or sinus involvement
- Retrospective cases with complete data as per study criteria

Exclusion criteria

- No sinonasal involvement
- Not histopathologically proven mucormycosis
- Incomplete data as per study criteria or loss to follow-up

All patients underwent detailed clinical, laboratory, radiological (CECT/MRI), endoscopic, microbiological, and histopathological evaluation. Disease was staged based on extent (sinus, orbital, intracranial). Management included Amphotericin B therapy, surgical debridement, and glycaemic control. The primary outcome was survival or death at 3 months, with additional assessment of seasonal trends.

ETHICS APPROVAL AND CONSENT

The study was approved by the Institutional Ethics Committee of Grant Government Medical College and Sir J. J. Group of Hospitals, Mumbai, prior to commencement of the study (Approval dated 14th February 2025). Written informed consent was obtained from all participants before enrolment. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical Analysis

Sample size was calculated at 76 using a 95% confidence interval ($Z = 1.96$), expected proportion of 80%, and 9% precision.

Data was summarized as percentages for categorical variables and mean \pm SD or median (IQR) for quantitative variables. Associations with outcomes were tested using Chi-square or Fisher's exact test for categorical data, and unpaired t-test or Mann-Whitney U test for quantitative data. Significant variables on univariate analysis were included in multivariate logistic regression to identify independent predictors, with model fit assessed by the Hosmer-Lemeshow test. Analysis was performed using SPSS, with $p < 0.05$ considered statistically significant.

RESULTS

Seventy-six patients aged 18 years and above with a histopathologically confirmed diagnosis of rhino-orbito-cerebral mucormycosis involving the nasal mucosa or paranasal sinuses, fulfilling the inclusion and exclusion criteria, were enrolled in the study. The patients were evaluated with detailed clinical examination, laboratory investigations, radiological imaging (CECT and / or MRI of the nose, paranasal sinuses, orbit and brain), and histopathological confirmation, and were managed with the standard institutional protocol of intravenous Amphotericin B with surgical debridement wherever feasible. Patients were followed up for three months or until death, whichever came first, and the results are as follows.

Table 1:- Summary of univariate analysis of predictors of mortality.

Variable	Significance 'P' value
Orbital extension	0.0003
Vision disturbance	0.0008
Facial pain / numbness	0.0037
Intracranial extension	0.0042
Vomiting	0.0059
Fever	0.0267
Kidney disease	0.193
Hypertension	0.226
Nasal obstruction	0.235
Diabetes mellitus	0.277
Smell disturbance	0.407
Headache	0.490
Sex	0.560
Nasal discharge	0.773

On univariate analysis, six variables were found to be significantly associated with mortality: orbital extension ($p = 0.0003$), vision disturbance ($p = 0.0008$), facial pain or numbness ($p = 0.0037$), intracranial extension ($p = 0.0042$), vomiting ($p = 0.0059$) and fever ($p = 0.0267$). Demographic factors (sex, occupation), basic rhinological symptoms (nasal obstruction, nasal discharge, smell disturbance, headache) and the presence of comorbidities (diabetes mellitus, hypertension, kidney disease) were not significantly associated with mortality on univariate analysis.

Table 2: Multivariate logistic regression for independent predictors of mortality.

Variable	Adjusted OR	95% CI	p value
Age	1.04	0.98–1.09	0.175
Sex	0.87	0.21–3.63	0.849
Diabetes mellitus	0.05	0.001–1.76	0.100
HbA1c	3.57	1.05–12.16	0.041*
Severity stage	7.83	2.25–27.16	0.001*

On multivariate logistic regression analysis, after adjustment for age, sex and the principal comorbidities, two variables emerged as independent predictors of mortality — HbA1c (adjusted odds ratio 3.57; 95% CI 1.05–12.16; $p = 0.041$) and disease severity stage (adjusted odds ratio 7.83; 95% CI 2.25–27.16; $p = 0.001$). Disease severity stage emerged as the single strongest independent predictor of mortality, with each step increase in severity stage approximately eight-fold increasing the odds of death. The Hosmer–Lemeshow goodness-of-fit test ($p = 0.304$) confirmed adequate model fit, and the pseudo R^2 of 0.04 indicates that the modelled variables explain a small but statistically significant proportion of the variance in mortality, consistent with the multifactorial nature of mortality in rhino-orbito-cerebral mucormycosis.

DISCUSSION:

This study, titled “To Study the Factors Influencing Outcomes of Rhino-Orbito-Cerebral Mucormycosis (ROCM),” was conducted at a tertiary-care centre in Mumbai and aimed to evaluate demographic, clinical, and seasonal factors affecting outcomes in ROCM. It included 76 histopathologically confirmed cases in a contemporary post-COVID cohort, reflecting the increased burden of mucormycosis observed during and after the pandemic. ROCM is an aggressive angioinvasive fungal infection, most commonly caused by *Rhizopus* species, predominantly affecting immunocompromised individuals and patients with uncontrolled diabetes mellitus. Despite combined medical and surgical treatment, mortality remains high, ranging from 30% to 70%. [3,4,5]

In this cohort, the majority of patients were middle-aged adults, with 46.1% below 50 years and 40.8% between 50–65 years. There was a clear male predominance (68.4%). Both the above findings are consistent with existing literature. [11,12,13] However, neither age nor sex was significantly associated with mortality, indicating that demographic factors alone were not reliable predictors of outcome.

Occupational distribution showed that farming (32.9%), housewives (25%), and laborers (18.4%) formed the majority, suggesting environmental exposure to fungal spores as a contributing factor. This is consistent with the ecology of Mucorales spores that thrive in decomposing organic matter. [7,9] However, occupation was not significantly associated with mortality.

Clinically, the most common presenting symptom was headache (94.7%), followed by facial pain or numbness (71.1%), vision disturbance (67.1%), nasal obstruction (65.8%), and nasal discharge (61.8%). The high prevalence of orbital and neurological symptoms at presentation indicates that many patients presented in advanced stages of disease. Importantly, certain symptoms were strongly associated with mortality, including facial pain or numbness, vision disturbance, fever, and vomiting. All deaths occurred in patients presenting with both facial pain/numbness and visual symptoms, highlighting these as critical early warning signs of severe disease.

Diabetes mellitus emerged as the most significant underlying risk factor, present in 81.6% of patients. More importantly, poor glycaemic control, reflected by HbA1c $>8\%$, was strongly associated with mortality. Patients with HbA1c $>8\%$ had a mortality rate of 35.9%, compared to much lower rates in those with better glycaemic control. On multivariate analysis, HbA1c was identified as an independent predictor of mortality, reinforcing the importance of strict glycaemic management in ROCM. This is in line with multiple studies which consistently report the association between uncontrolled diabetes mellitus and disease severity in ROCM. [12,14]

Laboratory parameters also played a role in predicting outcomes. Anaemia was significantly associated with mortality, with nearly half of patients having haemoglobin levels between 7–10 g/dL succumbing to the disease. Additionally, elevated ESR levels were associated with worse outcomes, suggesting that systemic inflammatory burden contributes to disease severity and prognosis. Similar findings correlating systemic inflammatory markers with disease severity and outcome in ROCM were reported by Saxena et al in 2025. [15]

Disease severity at presentation was the strongest predictor of outcome. Patients were staged into Stage I (sinonasal), Stage II (orbital extension), and Stage III (intracranial extension). [7,11,16,17] There was no mortality in Stage I disease, while mortality increased to 25.7% in Stage II and 53.8% in Stage III. On multivariate analysis, disease stage emerged as the single most powerful independent predictor of mortality, with a markedly increased risk of death with each advancing stage. This underscores the critical importance of early diagnosis before disease progression, and confirms the timing of presentation as one of the most critical determinants of outcomes in ROCM. [18]

Regarding sinus involvement, maxillary, ethmoid, and sphenoid sinuses were commonly affected but not significantly associated with mortality. However, frontal sinus involvement showed a strong association with death, likely due to its proximity to the anterior cranial fossa and risk of intracranial spread.

Extension of disease beyond the sinuses significantly worsened outcomes. All deaths occurred in patients with orbital involvement, and more than half of patients with intracranial extension died. These findings reinforce that orbital and especially intracranial spread are major adverse prognostic factors requiring aggressive management. [19,20]

Local disease features such as palatal involvement and facial palsy were also significantly associated with mortality. Palatal involvement increased mortality risk fourfold, while facial palsy, although rare, had a very high mortality rate. These findings reflect extensive tissue invasion and advanced disease are associated with worse prognosis.

In terms of treatment, nearly all patients (98.7%) underwent combined medical and surgical management, including Amphotericin B therapy and surgical debridement. The overall mortality rate in this study was 21.1%, which is lower than many reported series, likely reflecting the high rate of combined treatment. [12,13] No significant difference in mortality was observed between conventional and liposomal Amphotericin B, though this may be influenced by selection bias.

Seasonal variation showed that most cases presented during winter (46.1%), followed by monsoon (36.8%) and summer (17.1%). The increased prevalence of the disease in monsoon and post monsoon periods can be attributed to the longer survival of fungal spores in humid environmental conditions [21] and the indoor crowding associated with winter season in the metropolitan setting; also there is a higher incidence of upper respiratory tract infections in winters, which can give rise to superadded fungal infections. Although mortality was highest in summer, seasonal variation was not statistically significant, and conclusions remain limited due to small sample size.

On multivariate logistic regression, two independent predictors of mortality were identified: poor glycaemic control (HbA1c) and disease severity stage, with disease stage being the strongest predictor. The statistical model demonstrated good fit.

Based on these findings, key recommendations include early recognition of warning symptoms (especially facial pain and vision disturbances), prompt referral and imaging, aggressive glycaemic control, and early initiation of combined antifungal therapy and surgical debridement. Radiological staging at presentation is essential for risk stratification, and close follow-up is necessary to monitor outcomes and detect recurrence. Increased awareness among healthcare providers is also crucial, particularly in diabetic and post-COVID populations.

Overall, the study highlights that early diagnosis and control of modifiable risk factors, particularly hyperglycaemia, are critical to improving survival in ROCM, while advanced disease at presentation remains the most important determinant of poor outcome.

CONCLUSION

This study highlights the high burden of rhino-orbito-cerebral mucormycosis, predominantly affecting middle-aged males with uncontrolled diabetes. Poor glycaemic control (HbA1c >8%) and advanced disease at presentation were key drivers of mortality. Clinical features such as facial pain, vision disturbance, fever, and vomiting were associated with worse outcomes. The strongest predictors of death were disease severity, orbital and intracranial extension, and local complications. Early diagnosis and aggressive glycaemic control emerged as the main modifiable factors. Combined antifungal therapy and surgical debridement reduced mortality.

Improving awareness, prompt referral, and early intervention are critical to enhancing survival in ROCM.

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