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Survival and prognostic factors in rhino-orbito-cerebral mucormycosis: A 3-year cohort study

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Mucormycosis, a severe fungal infection, has exhibited a concerning increase in recent years, particularly during the COVID-19 outbreak. This three-year cohort study aims to investigate an overview of the epidemiology, clinical and radiographic signs, treatment, and prognosis of Rhino-Orbito-Cerebral Mucormycosis (ROCM). This prospective cohort study was conducted from 2019 to 2022 at Khalili Hospital in Shiraz, Iran. It focused on proven cases of ROCM. Patients underwent a stepwise treatment protocol, with meticulous documentation of findings from ophthalmological examinations and imaging studies. Additionally, a three-year follow-up period was implemented to monitor patient progress and assess the effectiveness of treatment strategies. Statistical analyses were performed using IBM SPSS statistics. In this study, 77 patients with ROCM participated. Most patients presented with facial pain (75.3%), swelling (62.3%), and vision loss (51.9%). Treatment included combined antifungal therapy and surgical debridement, with 7.8% undergoing ocular exenteration. Notably, despite the extensive disease, all cases that underwent orbital exenteration survived during the 3-year follow-up. Impaired V2 nerve function was associated with higher mortality rates, and patients presenting with an initial visual acuity of No Light Perception (NLP) had higher mortality compared to those with other degrees of visual impairment. The convergence of mucormycosis, specifically in the form of ROCM, with COVID-19 has led to an outbreak characterized by high mortality and morbidity rates. This cohort study meticulously documented the long-term follow-up of these patients, aiming to provide novel insights into the epidemiology, clinical and radiographic signs, treatment, and prognosis of this fungal infection.

Keywords Mucormycosis, Morbidity, COVID-19, Prognosis, Mycoses, Follow-Up studies, Antifungal agents

Mucormycosis is an acute and life-threatening infection in humans caused by saprophytic fungi (Phycomycota, Zygomycota). The main risk factors for mucormycosis infection are immunosuppressive factors such as uncontrolled diabetes (diabetic ketoacidosis), blood malignancies (such as leukemia and lymphoma), and the COVID-19 outbreak-associated systemic immunodeficiency and corticosteroid use was a new emerging risk factor for mucormycosis. The Histopathology is characterized by the presence of fungal filaments that are branched without septum and tend to invade intravascularly[1–5].

Mucormycosis can infect any tissue, rhino-orbito-cerebral mucormycosis (ROCM), disseminated mucormycosis, cutaneous mucormycosis, pulmonary mucormycosis, and gastrointestinal mucormycosis are the most common forms of this disease that have been reported among which the most common disease-causing form by this fungus is rhino-orbito-cerebral involvement[3,6]. Successful treatment of mucormycosis is based on a multi-pronged approach[5–7]. The emergence of the COVID-19 pandemic has led to a global surge in the incidence of ROCM. This cohort study aims to fill a critical gap by investigating the long-term, three-year clinical profile, treatment approaches, prognostic and survival factors in ROCM patients. Given the scarcity of such comprehensive long-term follow-up studies in Iran, our research provides essential insights into survival rates and prognostic indicators, which are crucial for improving treatment protocols and patient outcomes.

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Methods

This study was a single centered prospective cohort study that conducted from 2019 to 2022 in a tertiary care hospital. All patients with ROCM who diagnosed with ROCM based on the clinical presentation, image findings, and pathological and microbiological evidence in the ophthalmology department of Khalili Hospital in Shiraz for 6 months' period were enter the study after signed the written consent and then followed up for 3 years. The Ethics Committee of SUMS approved the study under the code IR.SUMS.MED.REC.1400.169. The manuscript adhered to the ethical principles outlined in the Declaration of Helsinki. All participants in this study completed an informed consent form for participation, publication of information, and use of images in the article.

Patients' data were recorded containing, demographic data: Age, sex, city of residence, underlying disease: specially history of Diabetic mellitus (DM), any types of cancer or organ transplantation, intensive care unit (ICU) admission, and drug history such as immunosuppressant, Remdesivir or corticosteroid usage. COVID-19 infection as the most important immunosuppressive causes concurrent infection or past infection (less than 3 months) was confirmed by use of real-time reverse transcriptase-polymerase chain reaction (RTPCR) test, and a set of clinical symptoms and signs in the physical examination by ophthalmologist were defined for the diagnosis of patients.

Clinical symptoms included, any history of nasal block, nasal discharge, facial or dental pain/numbness/swelling, blurred vision, binocular diplopia, trigeminal hypoesthesia/hyperalgesia. All the patients had complete ophthalmology and ear, nose, throat, and trigeminal nerve examination. All the patients underwent orbital CT and Gadolinium enhanced MRI and fat saturation post contrast sequence and based on clinical pictures and image findings treatment started based on step-by-step approach in Algorithm[8].

All patients included in our study were proven cases of mucormycosis. The fungal etiology was determined pathologically based on the morphologic diagnosis made by the histopathologist. Histopathological confirmation of mucormycosis was performed using PAS staining. Subsequently, they were diagnosed with ROCM following the Code Mucor guidelines[8–10]. Upon final diagnosis and considering availability, all patients were initiated on intravenous Liposomal Amphotericin B (5–10 mg/kg/day) with renal monitoring. Additionally, they received tablet Posaconazole 300 mg twice daily on the first day, followed by 300 mg once daily for a period of 1 to 3 months, based on the recommendations from an infectious disease specialist. Following consultation with an Ear, Nose, and Throat (ENT) specialist, all the patients underwent Functional Endoscopic Sinus Surgery (FESS). Based on clinical deterioration of symptoms and radiographic findings (illustrated in Fig. 1), the decision was made to administer retrobulbar injection of amphotericin B, orbital debulking, and proceed with orbital exenteration. Following surgery, the patients received intravenous antifungal therapy for 1–3 months. Subsequently, they underwent follow-up assessments by ENT specialists, infectious disease experts, neurologists, and ophthalmologists over a period of approximately 3 years.

Statistical analyses performed with IBM SPSS statistics (software version 26; SPSS Inc., Chicago, Illinois, USA) and MedCalc Version 19.7.2 (MedCalc Software, Mariakerke, Belgium). The normality of the data was assessed using the Kolmogorov-Smirnov test.

A P-value less than 0.05 was considered statistically significant. For examining the background qualitative variables, and normality distribution was assessed using the Shapiro-Wilk test. Determining the variables from statistical indices such as mean, standard deviation, minimum, maximum, frequency and percentage of frequency, and for comparing them at different levels of response variables, Chi-square and exact Fisher tests were used. Survival analysis was represented with expiry serving as the censoring variable and Kaplan-Meier curves were plotted to showed the cumulative likelihood of survival[11].

Result

Demographic data

Out of 77 patients, 43 (55.8%) were male and 34 (44.2%) were female. The average age of the cases in the study was 57.44 ± 12.74 years. The minimum age was 22 and the maximum was 88 years.

The analysis revealed that 83.1% (64) of the patients had a history of diabetes mellitus (DM), and 74% (57) tested positive for COVID-19 PCR either at the study initiation or within the preceding 3 months. The frequency distribution and percentage of underlying diseases or any systemic disease in the patients are presented in Table 1.

Clinical and radiographic data

The majority of patients experienced facial pain (75.3%), facial swelling (62.3%), and various degree of vision loss (51.9%) as the first presenting signs. Forty four patients (57.1%) had limitation in ocular motility in all directions (Frozen eye), and 16 patients (20.8%) had various degree of limitation eye movements, while 17 patient (22.1%) had normal eye movements. The frequency distribution and percentage of the presenting clinical signs and symptoms of the patients are listed in Table 2.

Generalized and central nervous system (CNS) symptoms were prevalent. Chest pain occurred in 5.3% of cases, bloody sputum in 14.5%, and altered consciousness (indicative of brain involvement) in 17.1%. Among the patients, 44 cases (57.1%) had right eye involvement, 32 (41.6%) had left eye involvement, and one patient (1.3%) had both eyes affected. The overall rate of ocular involvement was 92.3%. Detailed ophthalmological examination findings are presented in Table 3.

Forehead sensation (V1 branches of trigeminal cranial nerve) was impaired in 53 cases (68.4%) and the cheek sensation (V2) was impaired in 61 cases (80.3%).

Radiologic findings showed the ethmoid sinus was the most commonly affected paranasal sinus, with a prevalence of 75.2%, followed closely by the maxillary sinus at 70.8%.

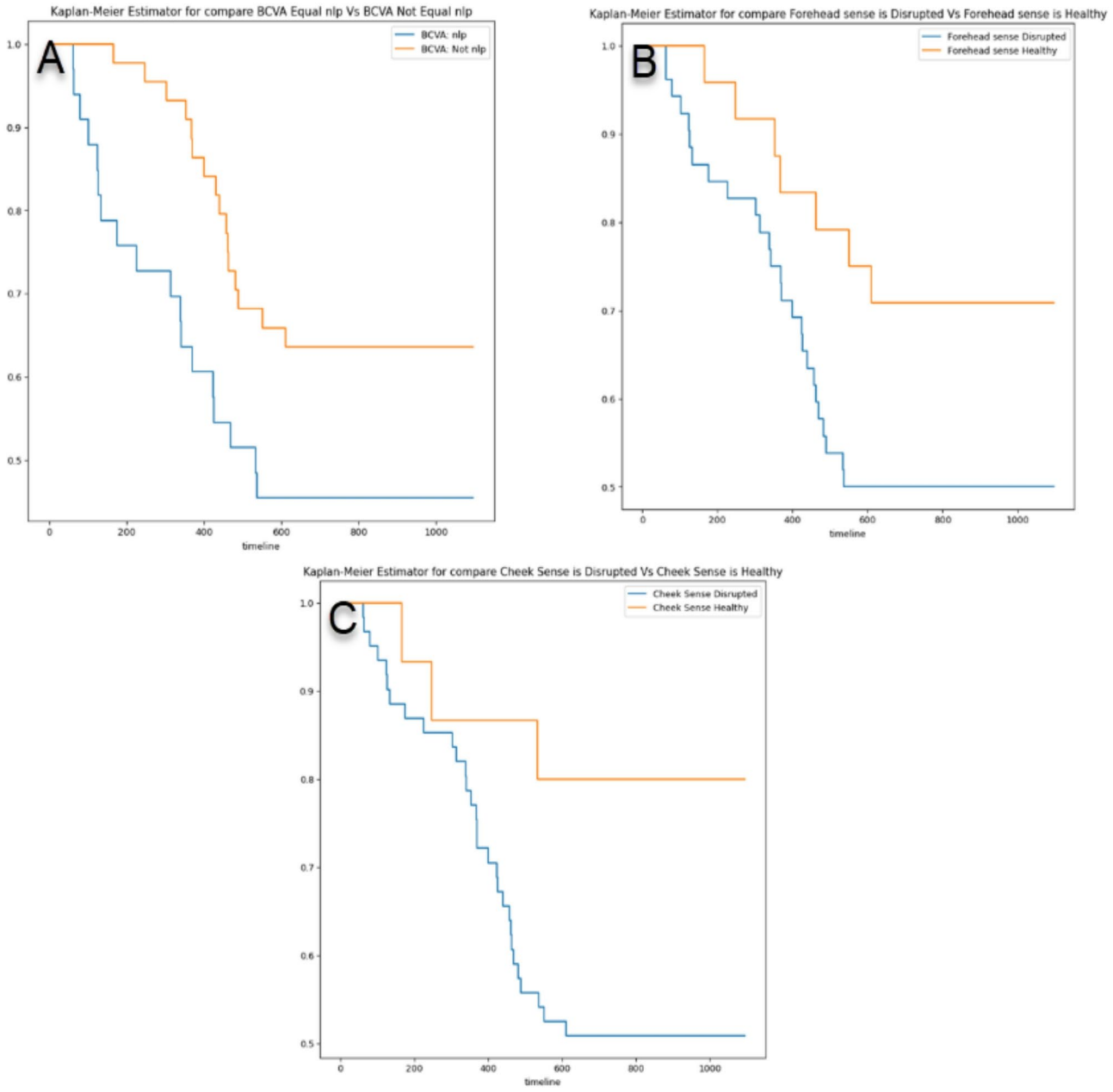

Fig. 1. **A**) Kaplan-Meier estimator according to visual acuity **B**) Kaplan-Meier estimator according to forehead sensation **C**) Kaplan-Meier estimator According to cheek sensation.

Antifungal and surgical management

All of cases have received combine medical and surgical treatments: intravenous liposomal Amphotericin-B (100.0%), debridement of mucous membranes and sinuses with functional endoscopic sinus surgery (FESS) (100.0%), retro-bulbar injection of Amphotericin-B (76.6%), oral adjuvant antifungal therapy (98.7%), and orbital exenteration in 6 cases (7.8%). Repeated sinus surgeries were performed based on consultations with an ENT specialist. In first 6 months of follow up, 2 more patients underwent orbital exenteration due to the disease progression and overall mortality rate due to ROCM complication at the end of 3-year follow up period was 44.2% (34) patients. At start of study, the majority of cases (45.5%) exhibited NLP vision. In follow up, there was no significant change in the percentage of NLP vision. However, treatment in 20 cases (26.0%) causing improvement in the V/A, and in 54 cases (70.1%) V/A before and after treatment remained unchanged, and in 3 cases (3.9%) causing a worsening of it. According to the Wilcoxon test, the treatment had a significant effect on improving the VA level ($P < 0.001$) in the patients with pretreatment V/A more than NLP.

Seven cases (20.0%) with a pre-treatment vision status of NLP and 1 case (2.4%) with a pre-treatment vision status of count figure (CF) underwent orbital exenteration surgery. The odds ratio was 0.098, indicating that

Background Variable	*N*	Percentage
Cardiovascular Disease, Hypertension	28	36.4%
Neurological Problems, (MS, Stroke)	4	5.2%
Kidney Diseases	8	10.3%
History of Sinusitis	3	3.4%
Pulmonary Diseases	1	1.3%
Gastrointestinal Disease	1	1.3%
History of Diabetes Mellitus	64	83.1%
History of Organ Transplantation	5	6.5%
History of Steroid Use	54	70.1%
PCR of COVID-19 (Positive)	57	74%
History of Remdesivir Use	35	45.4%
History of ICU care	12	15.5%
History of Cancer	3	3.4%

Table 1. The frequency of underlying systemic disease. MS: Multiple Sclerosis, ICU: Intensive Care Unit.

Presenting signs and symptoms	*N*	Percentage
Facial pain	58	75.3%
Facial swelling	48	62.3%
Vision reduction	40	51.9%
Toothache	52	67.5%
Facial numbness	19	24.7%
Ptosis	27	35.1%
Headache	59	76.6%
Fever	14	18.2%
Body pain	29	37.7%
Nasal block	54	70.1%
Nasal discharge	26	33.8%
Mucosal necrosis	58	75.8%
Periocular pain	44	57.1%
Periocular swelling	57	74%
Proptosis	24	31.2%
Diplopia	4	5.2%
Ophthalmolpegia	26	33.8%
Chemosis	28	36.6%
Skin Necrosis	5	6.5%
Mucosal ulceration	15	19.5%
Palate numbness	7	9.1%

Table 2. Frequency distribution and percentage of the presenting clinical symptoms and signs.

the chance of exenteration in patients at the LP – 10/10 level is 90% less than those at the NLP level over 3-year follow up, and this odds ratio is statistically significant correlation with orbital exenteration rate ($P = -0.034$).

In 8 cases (18.2%) with the Frozen eye, orbital exenteration was done. According to the fact that all the orbital exenteration cases had frozen eye, the exenteration rate was statistically correlated with complete extraocular muscles movement restriction ($P = 0.033$).

The prevalence of orbital exenteration in cases with different underlying diseases did not have a significant difference ($P > 0.05$), except for the variable of DM, where patients with a history of DM had undergone orbital exenteration more frequently, which is also statistically significant ($P = 0.024$). Although most of the cases had DM and COVID-19 infection as the underlying disease, and had history of corticosteroid usage, but in our analysis these variables were not statistically correlated with mortality rate. ($P > 0.05$)

All the patients who had orbital exenteration for controlling the disease progression, survived after 3-year follow up. The incidence of mortality in individuals with and without exenteration differs significantly ($p = 0.008$).

		Involved eye
RAPD	Negative Positive	22(31.0%) 49(69.0%)
BCVA	NLP LP-1/10 2/10-4/10 5/10-10/10	35(45.5%) 21(27.3%) 10(13%1) 11(14.3%)
Conjunctiva	Chemosis Redness Normal	33(42.9%) 5(6.5%) 27(35.1%)
Cornea	Clear Haze Edema Opacity leukoma, scar Normal	71(92.2%) 1(1.3%) 1(1.3%) 1(1.3%) 1(1.3%) 2(2.6%)
Lens	Normal Not visible Cataract Psudophakic Not visible	74(96.1%) 2(2.6%) 11(14.3%) 22(28.6%) 2(2.6%)
Anterior Vitrous	No cell Vitritis Not visible	71(92.2%) 2(2.6%) 4(5.2%)
Fundus examination	Normal Disc palor Not visible PDR NPDR No diabetic retinopathy Narrowing of vessel CRAO Pale retina AMD	34(44.2%) 39(50.6%) 4(5.2%) 4(5.2%) 21(27.3%) 5(6.5%) 1(1.3%) 17(22.1%) 9(11.7%) 3(3.9%)

Table 3. Ophthalmology examination of the patients. RAPD: Relatively Afferent Pupillary Defect, BCVA: Best Corrected Visual Acuity, NLP: No Light Perception, LP: Light Perception, PDR: Proliferative Diabetic Retinopathy, NPDR: Non- Proliferative Diabetic Retinopathy, CRAO: Central Retinal Atery Oclussion, AMD: Age Related Macular Degeneration.

Survival rate

In cases with a Frozen eye at starting the study, 20 people (52.3%) have survived after 3-year followed up, and in cases with a normal or slightly impaired motility before treatment, 23 people (60.6%) have survived. The odds ratio was 1.405, indicating that the survival chances in patients without frozen eye were 40% higher than those with Frozen eye.

In patients with a pre-treatment vision status of NLP, out of 35 patients, 16 (45.7%) have survived after three months. Out of 42 patients with a pre-treatment vision status of above NLP, 27 cases (64.3%) have survived after three years. The odds ratio was 2.137, indicating that the survival chances in individuals at the LP – 10/10 vision level are twice as high as those at the NLP vision.

Of the 24 patients with intact forehead sensation(V1), 17 individuals (70.8%) have survived after 3-year, and of the 52 individuals with impaired forehead sensation, 26 individuals (50.0%) have survived. The odds ratio was 2.429, indicating that the survival chances in cases with intact forehead sensation are twice as high as those with impaired forehead sensation. The survival chances in patients with intact V2 sensation are 4 times as high as those with impaired sensation, and this odds ratio was borderline statistically significant related to mortality rate ($P = 0.051$). The Kaplan-Meier survival analysis plots are displayed in Fig. 1.

Discussion

In our comprehensive study of ROCM, a striking pattern emerged regarding the underlying health conditions of the patients. Out of the 77 individuals diagnosed with ROCM, a predominant majority of 64 patients were suffering from DM, reinforcing the established link between uncontrolled DM and increased vulnerability to this fungal infection. Although patients with ROCM infection had higher random blood sugar (RBS) levels at presentation, Sharma.et al. did not find the correlation between higher RBS and poorer outcome in terms of mortality. But they found a statistically significant association between higher RBS levels at the time of presentation and higher staging of ROCM[12]. COVID-19 has been shown to significantly disrupt immune cell functions and even increase glycemic level and cause uncontrolled DM[13]. In another study of mucormycosis in the Iranian population, the average time between COVID-19 infection and the diagnosis of CAM was found to be less than one month[14]. Specifically, COVID-19 can lead to an expansion of immature and dysfunctional neutrophil populations, characterized by altered surface marker expression and activation features. This phenomenon may contribute to the hyper inflammatory response observed in severe cases[15,16].

Orbital involvement may lead to destruction of the ophthalmic artery and optic nerves resulting in ptosis of the eyelid, proptosis, vision disturbances and blindness. In a large retrospective study from India (19%) patients

presented with vision loss[17]. In our recent study on common symptoms and signs of ROCM, we found that 64.9% of cases exhibited complete ptosis, while 57% showed impaired extraocular muscle movement and a condition informally referred to as 'frozen eye'. The degree of ocular motility impairment correlated with extensive orbital involvement and the likelihood of orbital exenteration. Interestingly, although the mortality rate was higher in cases with 'frozen eye,' this correlation did not reach statistical significance, possibly due to the limited number of cases.

ROCM initially manifests with facial pain, nasal congestion, local tenderness, fever, and discolored discharge (bloody/brown/black). Subsequently, patients may develop an eschar over the nasal mucosa or skin, chemosis (conjunctival swelling), proptosis, and palate perforation. The infection can spread transneuronally, affecting individual cranial nerves (such as the 2nd, 5th, and 7th cranial nerves). This progression can lead to orbital apex syndrome, thrombosis in cavernous sinus, and involvement of multiple cranial nerves. Additionally, central retinal artery occlusion or posterior ischemic optic neuropathy may contribute to optic nerve damage in ROCM[18]. In our follow up, we observed periorbital swelling in 74%, periorbital pain in 57%, conjunctival chemosis in 36%, and a notably high incidence of necrosis in the mouth and nasal mucosa at 76%. This high prevalence of necrosis differs from previous studies where it was less common and associated with late-stage disease and increased mortality[19]. Commonly, necrotic mucormycosis begins in the nasal lining, turbinate, or palate, and then extends to the paranasal sinuses. It can potentially reach the retro-orbital area by infiltrating through the ethmoid sinus. Initially originating in the nasal passages, the infection advances toward the paranasal sinuses and orbital region. If it invades the orbit, there is a risk of further progression into the CNS. It has been suggested that the fungi may initially invade the anterior ethmoidal sinus without causing noticeable symptoms until reaching the orbital region. Additionally, the disease can penetrate intracranially by breaching the thin cribriform plate or orbital roof. In our follow up, especially in the first 6 months, we observed a high incidence of neurologic signs such as headaches (78.6%) and loss of consciousness requiring ICU admission and intubation (17.1%). However, it's important to note that these signs cannot be exclusively attributed to ROCM, as the majority of our cases were also infected with COVID-19. COVID-19 can cause systemic illness affecting various body parts, including pulmonary involvement that may necessitate ICU care.

Regarding the extension of intraorbital and intracranial disease in our patients, CT and MRI imaging contribute to diagnosis and determine disease extension. Radiological assessments have revealed several characteristic findings. These include signs of sinusitis, such as thickened mucosa and opacification of the paranasal sinuses, as well as the presence of air-fluid levels. Additionally, imaging has identified orbital invasion, cavernous sinus thrombosis, infiltration of the internal carotid artery, cerebritis, cerebral infarction, thrombosis of surface veins and dural venous sinuses, mycotic aneurysms, subarachnoid hemorrhage, and abscess formation[18]. Other radiologic features of ROCM was showed that the maxillary sinus was the most commonly affected PNS (96.2%).[20]In our center, consistent paranasal inflammation was observed in all patients. The ethmoid sinuses were most frequently affected (97.9%). Among the extra sinus sites, retro antral soft tissue (89.6%) and the orbital cavity (87.5%) showed frequent involvement. Notably, dacryocystitis occurred in 50% of cases, while optic nerve inflammation was present in 43.2%. Globe involvement was noted in 18.9%, and trigeminal nerve participation occurred in 16% of patients. Remarkably, inflammation extended into the cavernous sinuses and alongside the internal carotid arteries in 24% of cases[21]. Other studies have also observed the intracranial extension of ROCM. While various routes exist for fungal invasion into the intracranial space, the pterygopalatine space frequently serves as the primary entry point. Subsequently, the infection can propagate to the orbital and facial soft tissues, eventually reaching the retro-globular area of the orbit via the inferior orbital fissure. This progression often manifests in ocular symptoms[22–26]. This pattern of pterygopalatine involvement and also high prevalence of mucosal necrosis at the time of disease diagnosis may be linked to the high prevalence of COVID-19 infections among our cases.

Early signs of cavernous sinus involvement, such as double vision and ophthalmoplegia, may occur before visible changes on diagnostic imaging. The fungus enters posteriorly through the optic foramen, causing swelling, inflammation, and damage to the optic nerves and ophthalmic artery. As a result, orbital apex syndrome can manifest with chemosis, eyelid drooping, eye bulging, vision loss, and potential blindness[22,27,28].

Our follow up data demonstrated that, due to fungal extension to the orbital apex, there was a significant occurrence of NLP vision loss, positive RAPD, optic disc pallor and retinal vessel occlusion. Additionally, over half of our patients experienced restricted eye movement or 'frozen eye' due to orbital apex and cavernous sinus involvement. Trigeminal nerve involvement also indicated intracranial spread. Notably, our findings revealed that patients with an intact V1 nerve during the study period had a twofold higher chance of survival compared to those with impaired V1 nerve function. Additionally, patients with intact V2 nerve sensation had a fourfold higher survival chance therefore, the involvement of the V2 nerve had a statistically borderline association with mortality rates, with higher mortality observed in cases with impaired V2 function. Our study's analysis of the impact of cranial nerve involvement on survival is unprecedented, as no previous studies have examined this aspect. This phenomenon could potentially be associated with the transneural spread of the disease, indicating more widespread involvement.

In previous report, 96.7% of patients exhibited gingival and palatal abscesses, while 63.3% had palatal ulceration[29]. In our study, we observed a high incidence of nasal discharge and obstruction, present in nearly all cases, along with toothache reported by almost 70% of patients. Notably, the predominant presenting symptom in our cohort was prolonged, persistent toothache, often without any accompanying symptoms or signs.

Effective management of ROCM centers around several key strategies. The management of COVID-19-associated mucormycosis (CAM) presents significant challenges, compounded by the rapid mutations of the COVID-19 virus and the limited knowledge available for treating mucormycosis, traditionally considered a rare infection[2,28,30–32]. Meticulous management of DM and its associated complications is paramount in mitigating the risk and impact of ROCM infections. In previous cases of ROCM, 80% of patients received medical treatment

with Amphotricine B and other Azole drugs besides the surgical debridement and sinus surgery[18,20,33,34]. The current recommendations consider that liposomal amphotericin B plus surgical debridement are the first options for the treatment of mucormycosism while isavuconazole and posaconazole are considered the second option therapy[2,27,30,35,36].

High mortality is often associated with initial CNS involvement, and delayed diagnosis and treatment in ROCM can result in facial necrosis, bilateral sinus affliction, and hemiparesis[22,25]. Delaying the initiation of treatment by more than 6 days can lead to a twofold increase in mortality rates at 12 weeks. However, early, aggressive surgical management combined with high-dose systemic antifungal therapy has been associated with a 1.5-fold increase in survival rates[18]. Endoscopic sinus surgery is beneficial for patients with localized disease, offering low morbidity[36]. COSMIC study showed Surgical debridement of the paranasal sinus and orbit led to a reduction in mortality rates from 52 to 39% in patients with advanced ROCM[18].

We employed intravenous amphotericin B as the primary medical treatment for all cases and performed FESS as the surgical intervention in all patients. Notably, due to the extensive disease observed in our cases, particularly those who tested positive for COVID-19 by PCR, the utilization of additional oral antifungal therapy was remarkably high, reaching 90% of cases.

There are several previous studies which uses the transcutaneous retrobulbar amphotericin B for treatment of intraorbital extension of ROCM[23,24,37]. These injections should be considered as an adjuvant therapy for ROCM to reduce disease progression as well as to preserve globe or sight. It has a promising role in preventing potential orbital and central nervous system exenterations[37].

We administered retrobulbar liposomal amphotericin B (1 mililiter from concentration of 3.5 mg/mL) as an adjunct therapy in 76.7% of cases over a 3-day period. Notably, there was a 26% improvement in V/A post-treatment and long term follow up. While this improvement aligns with our findings, it's essential to consider the multifaceted treatment approach. Simultaneously combining medical amphotericin and azole therapy with FESS alongside retrobulbar injections makes it challenging to isolate the specific impact of retrobulbar injections on visual outcomes. However, early use of these injections, in conjunction with other therapeutic approaches, appears to enhance visual results. Unfortunately, patients with NLP vision at the study's outset did not experience any improvement in vision.

In the line of previous study, our study, analysis revealed that glycemic levels and DM were not statistically associated with increased mortality rates. However, consistent with prior research, these factors were correlated with a greater extent of orbital disease and a higher incidence of orbital exenteration.

Among the 35 patients with NLP vision, seven underwent orbital exenteration within 2 months of study initiation due to the severity and progression of orbital involvement. Remarkably, there was a significant correlation between NLP vision and the rate of orbital exenteration. NLP vision often resulted from central retinal vessel and optic nerve involvement, which are indicative of orbital apex disease. Mortality was higher in patients presenting with initial V/A of NLP. Patients presenting with visual acuity greater than NLP at the time of diagnosis have a twofold increase in survival chances. However, NLP vision did not statistically correlate with mortality rates. Other factors, such as comorbidities like COVID-19, may have independently influenced mortality outcomes.

We observed that orbital exenteration as part of treatment protocols in some patients, played a crucial role in preventing mortality. All patients who underwent orbital exenteration survived during the 3-year follow-up period, even in cases of extensive orbital involvement. Research on ROCM patients in Peru demonstrated that survival analysis indicated a reduced likelihood of survival for those who did not undergo surgical intervention[38].

In our 3-year follow up, overall mortality rate was 44%, aligning with previous research about ROCM was done in Iran[25]; Similar survival rates were reported a 40% survival rate in other studies on COVID-19 and ROCM[22,25]. Mortality rates vary in the literature. The fatality rate of cases with ROCM are less than the other forms of mucormycosis systemic involvement[39]. This is likely the result of the different forms of the disease, the challenging diagnosis, especially for pulmonary mucormycosis, and the association with either mild, moderate or severe COVID-19, which also affects mortality. In Europe, mortality ranges from 53.8 to 88%. But overall, the conclusive data on mucormycosis-related mortality are lacking in the literature and follow up periods are somehow short.[75] Delay in diagnosis may be an important prognostic factor related to the mortality.[75] Also, a shorter duration of antifungal therapy was linked to decreased patient survival. All patients who underwent orbital exenteration due to extensive orbital disease in our study survived during the 3-year follow-up period. Despite the aggressive nature of exenteration, these findings underscore the importance of timely and aggressive surgical intervention in patients with extensive orbital and intracranial involvement to enhance survival rates, particularly in developing countries. Our findings on the impact of orbital exenteration on survival diverged from a prior study conducted in India. The earlier study, using Kaplan-Meier survival analysis, indicated no survival advantage of exenteration at 3 and 6 months for CAM. This discrepancy might be attributed to a smaller sample size, a shorter follow-up period, or variations in postoperative care[40]. The 10-year cohort study demonstrated that tailored surgical management of ROCM based on the impacted structures is crucial. This approach not only enhances patient survival but also takes into account aesthetic and functional outcomes[41].

However, it is difficult to determine the exact mortality rate of the COVID-19-related ROCM because the death might be due to other complications of COVID-19 in certain patients.[77].

Our study stands out due to its comprehensive 3-year follow-up of patients during the outbreak of ROCM in the context of the COVID-19 pandemic. Obtaining data from patients' medical records posed challenges due to the majority being in the red zone of COVID-19-related hospitals, receiving oxygen therapy, or intubated. Consequently, gathering a comprehensive history and conducting physical examinations proved difficult, leading to incomplete information in the patient case sheets and missed cases of ROCM.

Conclusion

Mucormycosis had come an emergency worldwide. Delay in diagnosis may be an important prognostic factor related to the mortality. Our study's results show the impact of cranial nerve involvement on survival is surprising. Notably, our findings revealed that patients with an intact V1 and V2 nerve during the study period had higher chance of survival compared to those with impaired nerve function. We observed that orbital exenteration as part of treatment protocols in some patients, played a vital role in preventing mortality.

Data availability

The datasets supporting the conclusions of this article are included within the article.

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Conception and design: BKData acquisition: ZZ, MJSData analysis and interpretation: BK, ZZ, MJS, MJManuscript drafting and revisions: HB, ZZ, BKFinal approval of manuscript: HB, BK.

Declarations

Ethics approval and consent to participate

The study was approved by the Shiraz university of Medical Sciences Institutional Review Board (IRB) with the ethical approval number IR.SUMS.MED.REC. IR.1400.169. The study adhered to the tenets of the Declaration of Helsinki. All participants in this study completed an informed consent form for participation, publication of information, and use of images in the article.

Competing interests

The authors declare no competing interests.

Additional information

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