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Clinical Presentations, Management and Outcomes of Rhino-Orbital-Cerebral Mucormycosis (ROCM) Following COVID-19: A Multi-Centric Study

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Purpose: To report clinical presentations and factors affecting outcomes in rhino-orbital-cerebral mucormycosis following COVID-19.

Methods: Retrospective multi-centric interventional case series of 58 eyes with rhino-orbital-cerebral mucormycosis. Demography, clinical parameters and management outcomes were noted. Factors affecting outcome and mortality were analyzed. Outcome was defined as favorable when complete resolution or stabilization without further progression of the infection was noted at last visit.

Results: Mean age was 55 ± 11 years (median 56). The mean HbA1c value was 10.44 ± 2.84 mg% (median 10.5). The duration between the diagnosis of COVID-19 and rhino-orbital-cerebral mucormycosis was 16 ± 21 days (median: 8 days). Thirty-six eyes (62%) had no vision at presentation. Imaging revealed paranasal sinus involvement (100%), orbital apex involvement (41%), cavernous sinus involvement (30%), and central nervous system (CNS) involvement (33%). All the patients were treated with systemic Liposomal amphotericin-B and sinus debridement. Twenty-two eyes (38%) underwent exenteration. One eye underwent transcutaneous retrobulbar amphotericin-B. The mean follow-up duration was 5.62 ± 0.78 months (median 6). Favorable outcome was seen in 35 (60%) cases. Presence of uncontrolled diabetes ($p = 0.001$), orbital apex involvement ($p = 0.04$), CNS involvement ($p = 0.04$), and history of steroid use ($p < 0.0001$) resulted in unfavorable outcome. CNS involvement was the only factor predicting mortality ($p = 0.03$). Mortality was seen in 20 (34%) patients.

Conclusion: Over a third of patients with rhino-orbital-cerebral mucormycosis following COVID-19 have an unfavorable clinical outcome. Uncontrolled diabetes mellitus at presentation, involvement of the orbital apex, CNS, and the usage of steroids were associated with poorer outcomes. CNS involvement was a factor determining mortality.

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Rhino-orbital-cerebral mucormycosis (ROCM) is a life-threatening infection associated with high morbidity and mortality.[1,2] Opportunistic fungi, belonging to the order Mucorales, are responsible for this rapidly progressing fatal infection.[3,4] Mucormycosis is known to affect immunocompromised patients especially those with uncontrolled diabetes.[5] Following the inhalation of fungal spores present in the environment, the fungi colonize and infect the nasal/sinus mucosa first, before spreading to surrounding anatomical areas including the orbit, cavernous sinus, and brain. The infection consists of angioinvasion by the fungal hyphae, vascular thrombosis, and tissue necrosis[6] (Fig. 1). The clinical hallmark is tissue necrosis manifested as a necrotic lesion, eschar, or black discharge in the nasal or oral cavity.

Globally, as of May 19, 2021, 163,869,893 confirmed cases of COVID-19, including 3,398,302 deaths have been reported to WHO.[7] There is growing evidence to show that COVID-19 infection increases the risk of a patient acquiring secondary fungal infections.[8–10] This puts such patients at a high risk to develop ROCM. There is very scant literature on the occurrence of ROCM in patients with COVID-19 infection.[11–13] In the current communication, we present the largest multi-centric series of ROCM in patients with COVID-19 and discuss the management, outcomes and assess factors predicting the clinical outcomes.

METHODS

This was a multi-centric retrospective interventional study. The study included patients with ROCM following COVID-19 infection. The patients included were from a single country (India) across 9 hospitals treating patients with ROCM. Institutional Review Board approval was obtained for the study from all centers and the study adhered to the tenets of the Declaration of Helsinki. All patients signed a consent form allowing identifiable photographs to be archived and published.

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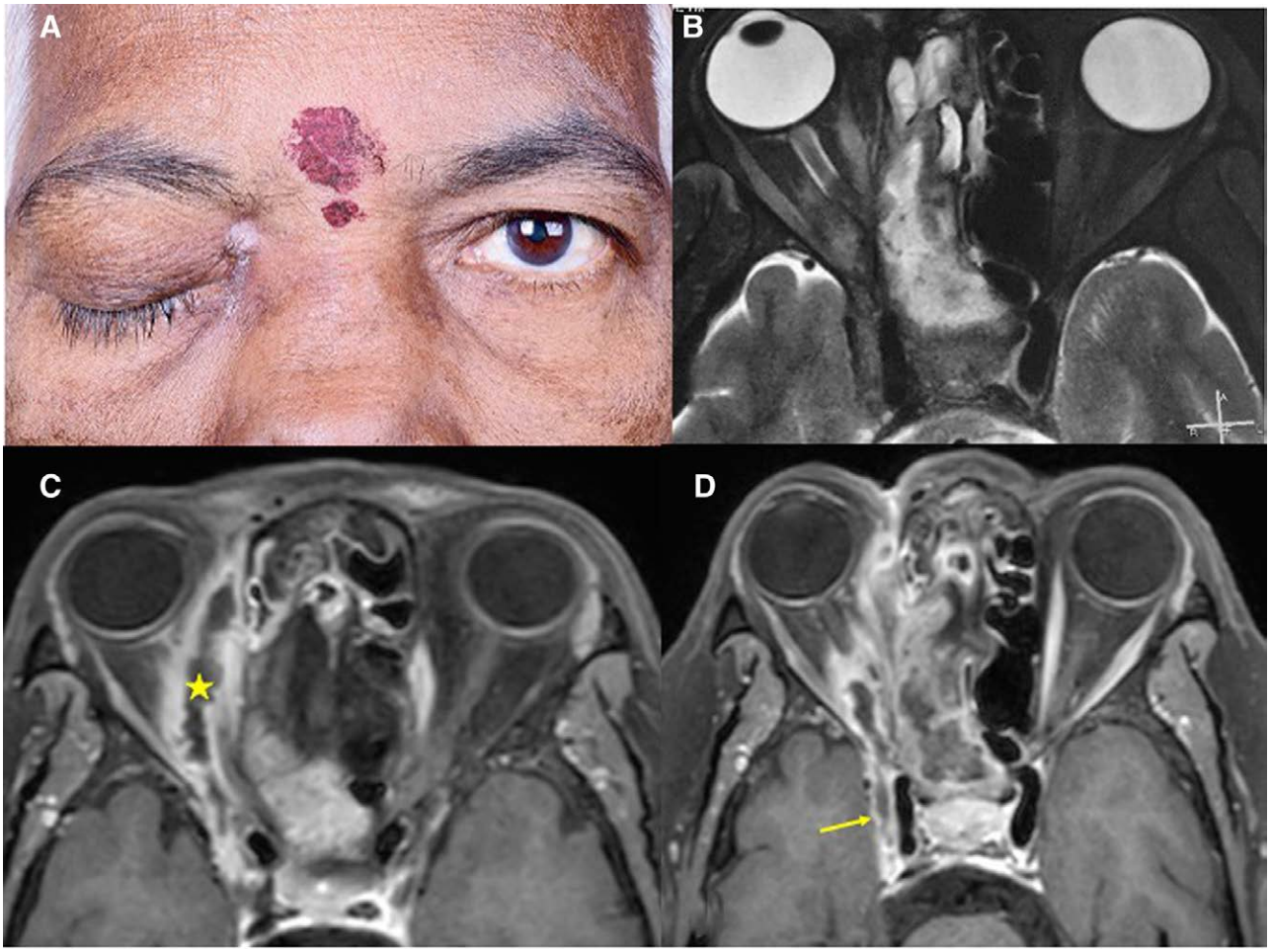

FIG. 1. Clinical picture and orbital MRI with contrast of a patient with right rhino-orbital-cerebral mucormycosis. **A,** Standard photograph with right complete ptosis and a superior discharging sinus. **B,** T2 weighted MRI in axial cut demonstrating the involvement of the ethmoid sinuses, orbital apex, and the cavernous sinus. **C,** Contrast-enhanced MRI demonstrating superior ophthalmic vein thrombosis (yellow star). **D,** Contrast-enhanced MRI demonstrating cavernous sinus thrombosis (yellow arrow).

According to the criteria put forth by a recent editorial on ROCM post-COVID-19 infection,[14] we looked at A) host factors relevant to the subset of COVID-19 and ROCM, B) diagnostic criteria, and C) mycological criteria for diagnosing possible, probable, and proven mucormycosis (Table 1). In the presence of clinical features suggestive of ROCM such as s*igns of* eyelid, periocular or facial edema or discoloration, ptosis, proptosis, chemosis, ophthalmoplegia, central retinal artery occlusion, panophthalmitis and palatal eschar, the following host factors, diagnostic criteria and mycologic criteria were looked for:

1. The host factors (one of the following).

i. Concurrently or recently (<6 weeks) treated for COVID-19;
ii. Uncontrolled diabetes mellitus (DM) (HbA1c of >7% was considered as the cutoff value for diagnosing uncontrolled diabetes);
iii. Treated for COVID-19 with steroids;
iv. Treated for COVID-19 with immunomodulators (tocilizumab).

2. The diagnostic criteria.

i. Diagnostic nasal endoscopy: Signs of nasal eschar, discoloration, and ulceration over the nasal mucosa were examined in the region of the middle turbinate, middle meatus, and the septum.
ii. MRI orbit, paranasal sinus and brain with gadolinium contrast was performed and fat saturation postcontrast sequences were examined.

Features evaluated were:

a. Early osseous erosion or marrow edema;
b. Haziness of the paranasal sinuses;
c. Soft tissue inflammation around the paranasal sinuses;
d. Retroantral extension;
e. Intraorbital extension;
f. Intracranial extension.

3. Mycologic criteria included the presence of one of the following.

i. Mycological evidence of mucormycosis in tissue biopsy taken during sinus debridement or from the orbital biopsy. Direct examination of biopsy or aspirated material was performed using 10% potassium hydroxide or calcofluor white staining solution. The specimens were inoculated on Sabouraud dextrose agar and blood agar and incubated at 37°C and 25°C for up to 1 and 2 weeks, respectively. Rapid growth of gray fluffy colonies was identified on conventional morphologic assessment. The growth was sub-cultured and reported as significant if

the direct examination of the sample showed the presence of fungal filaments.[15]

ii. Histopathologic evidence of mucormycosis in tissue biopsy was performed by examining for aseptate hyphae branching at wide-angle and ribbon-like hyphae associated with tissue damage on slides stained by Hematoxylin and Eosin, Periodic acid Schiff, and Gomori's methenamine silver stains.

Along with indicative clinical signs and symptoms, mucormycosis was classified as possible if any of the host factors were present, probable if host factors and any of the diagnostic factors were present, and proven if host factors and diagnostic factors were present with mycological criteria being met.

The diagnosis of COVID-19 was based on real-time polymerase chain reaction test on nasopharyngeal/oropharyngeal swabs. All demographic and clinical characteristics including ophthalmic signs, systemic manifestations, underlying conditions, and medical and surgical interventions were noted. The data recorded included age, gender, duration of the symptoms, history of DM, status of control of DM at presentation, any other immune deficiencies, clinical/radiologic involvement of the orbital apex, cavernous sinus, or the central nervous system (CNS), history of steroid use and that of immunomodulators (tocilizumab), the CT severity scores (1–25) and the CORAD scores. The presence of thrombo-embolic phenomenon related to COVID-19 was evaluated by the treating internist. A favorable outcome was defined as a complete resolution of the infection or stabilization without further progression on radiology at the end of follow-up.

Statistical Analysis. The data was arranged on an Excel spreadsheet. Relevant statistical analysis was done using MedCalc version 12.2.1.0 (Ostend, Belgium). Continuous parametric data were reported using the mean (±SD) and nonparametric data were reported as median. Multivariate logistic regression analysis and chi-square test were performed to assess the effect of multiple factors that might have influenced the outcome and mortality. A p-value of <0.05 was assigned as statistically significant. Outcomes of both the bivariate and multivariate analysis were reported for comparison.

RESULTS

The study included 58 eyes of 58 patients. All patients developed ROCM following COVID-19 infection. There were 44 males (76%). The mean age was 55 ± 11 (median 56) years. Forty-three patients (74%) had a history of DM. On presentation with COVID-19 symptoms, 46 (79%) patients had uncontrolled diabetes based on the glycosylated hemoglobin values (HbA1c). An HbA1c of 7% or higher was considered as the cutoff value for diagnosing uncontrolled DM. The mean HbA1c value among those with controlled DM was 5.84 ± 0.54 mg% (median: 6), while that in uncontrolled cases was 11.57 ± 1.86 mg% (median 11.25) ($p < 0.0001$). The mean chest CT severity score was 15.95 ± 4.74 (median: 17). No thrombo-embolic phenomenon attributable to COVID-19 was noted in any of the patients in this subset. The duration between the diagnosis of COVID-19 and ROCM was 16 ± 21 days (median: 8 days). Thirty-six eyes (62%) had no perception of light at presentation. A further 9 patients (16%) patients had perception of light only, 7 patients (12%) had to count fingers close to face at presentation and the rest had ambulatory vision or more. Three patients had a presenting visual acuity of 20/20.

Orbital pain and headache were noted in 78% and 59% of cases, respectively. Seventy-two percent of patients had proptosis while ptosis was noted in 69%. Extraocular muscle limitation was noted in 93% of cases. Of interest, mouth lesions were seen in 14% and the classic black eschar was noted in 33% of cases. On imaging, features of orbital cellulitis and orbital abscess were seen in 74%. Other imaging features included paranasal sinus involvement (100%), orbital apex involvement (41%), CNS involvement (33%), and cavernous sinus involvement (30%). The mean C-reactive protein was elevated to 47.19 ± 53.43 mg/L (median 26.9) (Table 2).

Sinus debridement and systemic treatment with antifungals were performed in all patients. Induction treatment was initiated with intravenous liposomal amphotericin-B in a dose of 5 mg/kg/day under monitoring by an infectious disease specialist for renal paraments for 2 weeks. Following this, maintenance therapy was with oral posaconazole in a dose of 300 mg BD for day 1 followed by 300 mg OD for a period of 4–6 weeks. Eight (14%) patients, were unable to complete the 2 weeks induction therapy with liposomal amphotericin-B in view of systemic complications and were shifted to maintenance therapy early. The antifungals were stopped after no progression on clinical examination or on radiology was noted. A small subset of 3 patients had panophthalmitis with localized orbital abscess in the anterior orbit. These patients underwent evisceration along with orbital debridement of the necrotic tissue until fresh bleeding was noted. Following debridement, the orbital cavity was irrigated with 5 ml of amphotericin-B in a dose of 1 mg/ml. One of these 3 patients progressed on treatment and required exenteration (Fig. 2). One patient who had localized orbital apex involvement with contrast uptake was treated with transcutaneous retrobulbar amphotericin-B in a dose of 3.5 mg/ml for 5 consecutive days. External ophthalmoplegia reversed in this patient and she was radiologically stable at the end of follow-up >6 months (Fig. 3). The radiologic involvement, clinical presentation, and tissue diagnosis from the sinus debridement were used as a guide to decide on exenteration versus globe salvage. Patients with proven mucormycosis, extensive orbital involvement producing globe tenting, those with diffuse loss of contrast enhancement in the orbit and those with apical involvement were considered for exenteration. Exenteration was also performed when there was documented progression of disease despite maximal medical therapy and surgical debridement. Twenty-two eyes (38%) underwent exenteration with debridement of the necrotic sinonasal tissue (Fig. 4). The mean follow-up duration was 5.62 ± 0.78 months (median 6). A favorable final outcome with respect to management of ROCM was seen in 35 (60%) cases. An unfavorable outcome was seen in 23 patients (40%). Of these mortality was seen in 20 (34%) and in the remaining 3 (6%) patients the disease remained unchanged on radiology at the end of follow-up.

Various demographic and clinical factors were assessed by bivariate and multivariate regression analysis to predict those that determined an unfavorable outcome (Table 3). Age, gender, duration of complaints, controlled DM, and usage of immunomodulator tocilizumab had no effect on the final outcome. Bivariate regression analysis showed a significant negative effect of cavernous sinus involvement on the final outcome but this effect was not statistically significant in multivariate analysis. Similarly, CT severity score ($p = 0.03$) and exenteration

TABLE 1. Diagnostic pathway followed for suspected rhino-orbital-cerebral mucormycosis

Possible	Probable	Proven
Classic signs and symptoms of ROCM	Signs and symptoms	Clinico-radiologic features
Concurrently or recently (<6 weeks) treated for COVID-19	Diagnostic nasal endoscopy	Microbiology evidence on direct microscopy*
Uncontrolled diabetes mellitus	Diagnostic MRI	Microbiology evidence on culture*
Treated for COVID-19 with corticosteroids		Microbiology evidence with molecular mechanisms*
Treated for COVID-19 with immunomodulators		Histopathology evidence of fungus with special stains*

*Tissue diagnosis was done on material obtained during sinus or orbital debridement or exenteration.
ROCM, rhino-orbital-cerebral mucormycosis.

TABLE 2. Demography and treatment outcomes in patients ROCM with COVID-19

Total eyes	58
Presenting features	N (%)
Extraocular muscle limitation	54 (93)
Orbital pain	45 (78)
Proptosis	42 (72)
Ptosis	40 (69)
Headache	34 (59)
Conjunctival chemosis	33 (57)
Disc edema	23 (40)
Black eschar in the nose	19 (33)
Facial fullness	16 (28)
Central retinal artery occlusion	15 (26)
Epistaxis	11(19)
Mouth lesions	8 (14)
Presenting visual acuity	
No light perception	36 (62)
Light perception only	9 (16)
CFCF	7 (12)
>CFCF <20/20	3 (5)
20/20	3 (5)
Imaging features	
Orbital cellulitis	43 (74)
Cavernous sinus involvement	17 (30)
Orbital apex involvement	24 (41)
CNS involvement	19 (33)
Sinus involvement	58 (100)
Systemic status	
Known diabetic before contracting COVID 19	43 (74)
De-novo diagnosis of DM while on treatment for COVID-19	13 (22)
Known case of leukemia	1 (2)
Known case of Hepatitis B	1 (2)
Uncontrolled diabetes	46 (79)
Mean HbA1c in controlled group	5.84 ± 0.54 mg% (median 6)
Mean HbA1c in uncontrolled group	11.57 ± 1.86 mg% (median 11.25)
Management of COVID-19	
Intravenous steroids for COVID given	37 (64)
Oral steroids for COVID given	35 (60)
Tocilizumab administered for COVID	27 (47)
Mean C-reactive protein levels (median)	47.19 ± 53.43 mg/L (26.9)
Chest CT severity score (on a 1–25 point system)	15.95 ± 4.74 (median 17)
Diagnosis of mucormycosis	
Proven mucormycosis	40 (69%)
Probable mucormycosis	18 (31%)
Management of mucormycosis	
Intravenous liposomal Amphotericin B followed by oral Posaconazole	58 (100)
Sinus debridement	58 (100)
Orbital exenteration	22 (38%)
Debridement of orbital necrotic tissue and orbital irrigation with amphotericin B	3 (5%)
TRAMB	1 (2%)
Outcome	
Favorable	35 (60)
Unfavorable	23 (40)
Mortality	20 (34)
Mean follow up duration (months)	5.62 ± 0.78 (median 6 months)

CFCF, counting fingers close to face; CNS, central nervous system; DM, diabetes mellitus; TRAMB, transcutaneous retrobulbar amphotericin B; ROCM, rhino-orbital-cerebral mucormycosis.

(p = 0.008) were associated with higher mortality on bivariate regression analysis. However, this significance was not maintained on multivariate regression analysis (p = 0.7 and 0.6, respectively). The presence of uncontrolled diabetes, orbital apex involvement, CNS involvement, and the usage of steroids were responsible for an unfavorable outcome. These factors were also assessed for their effect on mortality (Table 4). Both bivariate and univariate analysis showed CNS involvement at presentation as the only factor predicting mortality (p = 0.002 and 0.03, respectively).

DISCUSSION

The current study is the largest multi-centric series of ROCM following COVID-19 with long-term outcomes. We noted 40% of all cases have an unfavorable outcome. Factors determining unfavorable outcome included uncontrolled DM at presentation, involvement of the orbital apex and CNS, and the usage of steroids during the active phase of COVID-19 infection. The mere presence of DM, or usage of immunomodulators did not pose a significant risk for an unfavorable outcome. Twenty-two patients (38%) required an orbital exenteration.

COVID-19 and mucormycosis share risk factors, such as presence of DM, which can independently contribute to mortality, but have conflicting management principles. While immune suppression with steroids may be required in moderate to severe COVID-19, the use of steroids and the worsening glycaemic control provide an opportunity for mucor to become invasive.[9,16–21] Mucor produces keto-reductase as a virulence factor enabling them to grow in the acidic and glucose-rich environment generated in ketoacidotic states.[9,17–19] Additionally, Müller et al[22] have postulated that the human pancreas could be a possible target for the SARS-CoV-2 virus and that the β-cell infection may result in insulin resistance. This metabolic dysregulation, in previously nondiabetic or well-controlled diabetic COVID-19 patients, might predispose them to develop mucormycosis.

Moorthy et al[21] recently reported the association of COVID-19 infection with uncontrolled DM and usage of corticosteroids. Similarly, Sen et al[13] reported a series of 6 diabetic patients with concurrent mucormycosis and COVID-19 infection. Sarkar et al[23] reported a series of 10 diabetic patients with ROCM post-COVID-19. All their patients had uncontrolled blood sugar values and were treated with steroids during active COVID-19 infection. Current literature suggests that usage of systemic steroids in patients, who otherwise may have controlled diabetes, or may not be diabetics at all, can precipitate mucormycosis.[24–28] Mekonnen et al[29] reported a case of invasive fungal rhinosinusitis with orbital involvement in a patient with COVID-19 with uncontrolled DM and HbA1c of 14%. In the current study too, we found usage of steroids as a factor predicting unfavorable outcome. Mehta and Pandey[11] reported a case of a patient with COVID-19 infection, treated with steroids and tocilizumab, who during the course of the treatment, developed rhino-orbital mucormycosis. Due to persistent hypotension, repeat imaging or debridement measures were not possible and the patient died on day 6 of admission. Waizel-Haiat et al[12] reported a case of rhino-orbital mucormycosis associated with ketoacidosis secondary to recent onset DM and COVID-19 infection. Despite aggressive management the patient developed multi-organ failure and died. Similar to this particular patient, 27 (47%) patients in our series received tocilizumab, an immunomodulator (anti-interleukin 6 receptor antibody) that improves the outcome of COVID-19 infections. It is known that tocilizumab can precipitate invasive fungal infections.[30,31] Though, in our study the usage of tocilizumab had a near significance (p = 0.07) in bivariate analysis, this was not maintained in the multivariate analysis (p = 0.89). This may suggest that usage of tocilizumab had some bearing on an unfavorable outcome but could not be proven statistically in our subset.

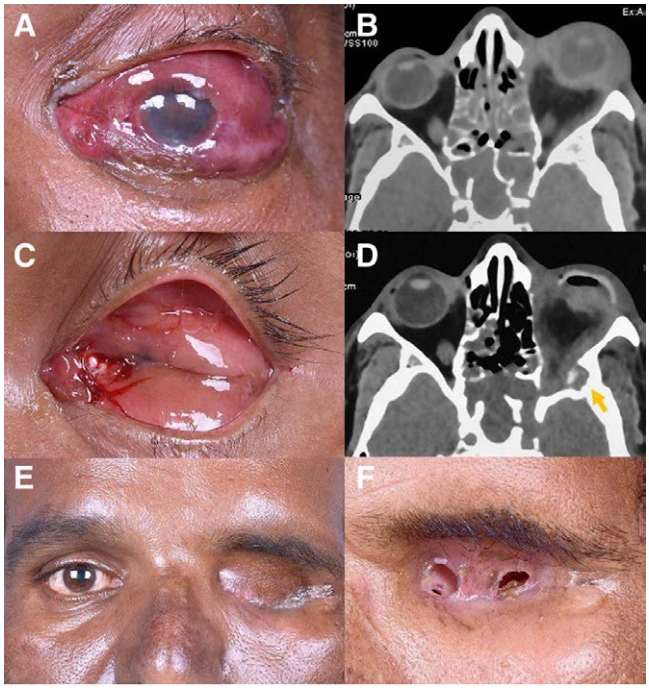

FIG. 2. Clinical pictures and CT Orbit of a patient with left rhino-orbital mucormycosis. **A,** A 45-year-old diabetic gentleman presenting with OS pain, proptosis, decreased vision, and restricted extraocular motility 3 weeks following COVID-19 infection. **B,** CT orbit revealed a deformed left globe and left proptosis with pansinusitis. **C,** OS high magnification picture post evisceration with orbital and sinus debridement and iv amphotericin-B, he developed a medial scleral frill necrosis and had persistent inflammation. **D,** Repeat imaging suggested erosions over the greater wing of sphenoid (yellow arrow). **E,** He underwent eyelid sparing exenteration. **F,** High magnification photograph 3 months post eyelid sparing exenteration with a cutaneous fistula.

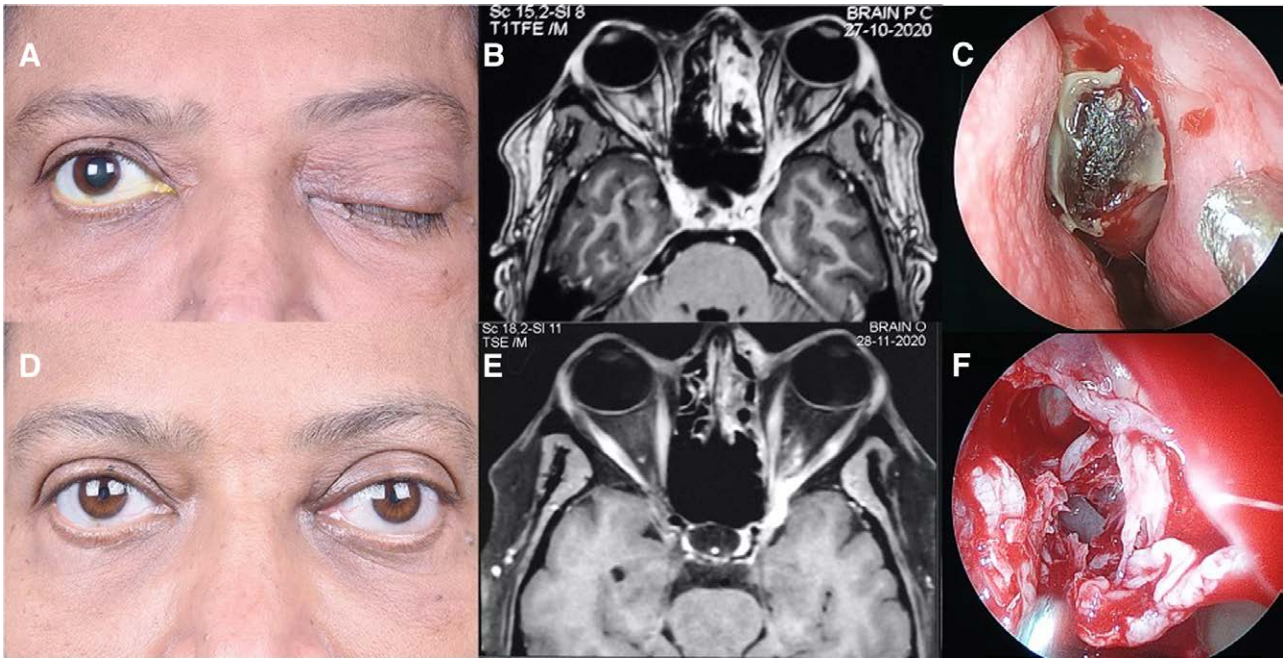

FIG. 3. Pre and post-operative clinical, MR and endoscopic images of a patient with left rhino-orbital-cerebral mucormycosis. **A,** A 53-year-old diabetic lady presented with complaints of severe peri-orbital pain, ptosis, and vision loss. **B,** MRI orbit was suggestive of left orbital cellulitis with cavernous sinus thrombosis and left ethmoidal sinusitis. **C,** diagnostic endoscopy revealed a black eschar in the left nasal cavity. **D,** She was treated with sinus debridement and iv amphotericin-B following which there was partial resolution of ptosis. **E,** Post debridement MRI demonstrating a decrease in the sinus load. **F,** Post endoscopic sinus debridement.

Moorthy et al[21] reported 18 patients with ROCM with COVID-19 infection. Loss of vision was noted in 67% of patients and 39% underwent orbital exenteration. Mortality was seen in 33%. In our series, 20 (34%) patients died. Ravani et al[32]

FIG. 4. All the photos in this panel belong to a 58-year-old diabetic gentleman who presented with central retinal artery occlusion and progressed to orbital cellulitis with sinusitis, orbital apex, and cavernous sinus involvement. Top panel has the preoperative pictures and bottom panel the post-operative pictures. **A,** Standard photograph demonstrating left ptosis (at presentation). **B,** Follow-up photograph after 2 weeks demonstrating left orbital cellulitis and panophthalmitis. **C,** Mouth eschar seen on follow-up. **D,** Scan suggestive of orbital abscess with paranasal sinus, orbital apex, and cavernous sinus involvement. **E,** Standard picture post left exenteration. **F,** High magnification picture post exenteration. **G,** Postoperative picture following hemimaxillectomy. **H,** Scan following sinus debridement and exenteration.

TABLE 3. Factors predicting unfavorable clinical outcome in cases of ROCM with COVID 19

	Bivariate regression		Multivariate regression		
				Correlation coefficient	
Factor	**Coefficient of regression**	***p***	**Coefficient of regression**	**r**	***p***
Age	0.58	0.55	−0.005	−0.21	0.18
Gender	−0.22	0.72	0.13	0.2	0.22
Tocilizumab	−0.96	0.07	0.08	0.14	0.89
Uncontrolled diabetes	−2.92	**0.007**	0.5	0.56	**0.0002**
Cavernous sinus involvement	−1.48	**0.01**	−0.08	−0.12	0.43
Orbital apex involvement	−2.42	**0.0001**	−0.23	−0.32	**0.04**
CNS involvement	−2.23	**0.0002**	−0.17	−0.28	**0.04**
Exenteration done	0.19	0.13	0.03	0.06	0.7
Steroid administration	−22.02	**<0.0001**	−0.56	−0.66	**<0.0001**
Chest CT severity score	0.18	0.13	−0.01	−0.21	0.52

Boldface values indicate statistically significant *p*.
CNS, central nervous system; ROCM, rhino-orbital-cerebral mucormycosis.

TABLE 4. Regression analysis of factors predicting mortality in ROCM following COVID-19

	Bivariate regression			Multivariate regression			
Factor	**Coefficient of regression**	**AUROC fraction**	***p***	**Coefficient of regression**	**Correlation coefficient (*r*)**	***p***	**Variance inflation factor**
Age	−0.01	0.54	0.51	−0.005	−0.13	0.36	1.27
Gender	0.47	0.54	0.45	0.15	0.14	0.3	1.25
Uncontrolled diabetes	0.78	0.56	0.29	0.24	0.18	0.6	4.13
Cavernous sinus involvement	−1.12	0.62	0.06	−0.08	−0.07	0.59	1.63
Orbital apex involvement	−0.85	0.6	0.13	−0.11	−0.12	0.39	1.43
CNS involvement	−1.89	0.7	0.002	−0.3	−0.3	**0.03**	1.28
Exenteration done	0.33	0.56	0.008	0.08	0.07	0.6	2.88
Chest CT severity score	0.58	0.87	0.03	0.01	−0.16	0.7	5.1
Steroid administration	−1.62	0.66	0.02	−0.18	−0.19	0.18	1.3
Tocilizumab	−0.8	0.6	0.14	−0.08	−0.09	0.52	1.19

Boldface value indicates statistical significance.
CNS, central nervous system; ROCM, rhino-orbital-cerebral mucormycosis.

published a series of 31 patients with ROCM following COVID-19 and suggested that the presence of cerebral involvement and a HbA1c value of ≥8 were found to be significant in the prediction of mortality in this subset. Our findings are in accordance to this observation. A comparison of our study with published literature on COVID-associated mucormycosis is summarized in Table 5.

The largest series on ROCM from a geographically similar area with patients who did not have COVID-19 was published

TABLE 5. Comparison of present study with that of other recent literature on ROCM post-COVID-19

Parameter studied	Current study	Ravani et al[32]	Moorthy et al[21]	Sarkar et al[23]	Sen et al[13]	Mekonnen et al[29]	Mehta and Pandey[11]	Rao et al[27]
n	58	31	18	10	6	1	1	1
Duration between COVID-19 and ROCM (days) (median)	16 ± 21 (8)	60	All patients were COVID + at presentation with ROCM	NA	18 ± 16 (16)	1	10	9
Mean age in years	56 ± 11	56	55 ± 11	46 ± 15	61 ± 12	60	60	66
Male gender (%)	44 (76%)	20 (65%)	15 (83%)	8 (80%)	6 (100%)	Yes	Yes	Yes
Presence of uncontrolled blood sugar at presentation	31 (53%)	30 (97%)	16 (89%)	9 (90%)	5 (83%)	Yes	Yes	Yes
Known case of diabetes mellitus	51 (88%)	30 (97%)	16 (89%)	10 (100%)	6 (100%)	Yes	Yes	Yes
Usage of steroids	48 (83%)	19 (61%)	16 (89%)	10 (100%)	5 (83%)	Yes	Yes	Yes
Usage of tocilizumab	27 (47%)	NA	NA	NA	NA	No	Yes	NA
Decrease in vision at presentation	55 (95%)	29 (94%)	12 (67%)	8 (80%)	6 (100%)	Yes	Yes	Yes
Intracranial extension	19 (33%)	10 (32%)	9 (50%)	1 (10%)	5 (83%)	No	Yes	No
Liposomal Amphotericin B usage	56 (97%)	31 (100%)	18 (100%)	10 (100%)	6 (100%)	Yes	Yes	Yes
Sinus debridement	58 (100%)	31 (100%)	18 (100%)	3 (30%)	6 (100%)	Yes	Yes	Yes
Exenteration	22 (38%)	4 (13%)	7 (39%)	1 (10%)	2 (33%)	No	No	Yes
Orbital debridement	2 (3%)	NA	No	No	1 (2%)	No	No	No
TRAMB	1	NA	No	No	No	Yes	No	No
Mean follow up duration (months)	5 months	2.5 months (min. follow up)	NA	NA	1.4 months	1month	1 week	NA
Mortality	20 (34%)	3 (10%)	6 (33%)	4 (40%)	0	Yes	Yes	No

NA, not available; TRAMB, transcutaneous retrobulbar amphotericin B.

by Nithyanandam et al.[33] They reported a retrospective series of 34 cases of ROCM treated more than 8 years (1992–2000). The cases were treated with intravenous amphotericin-B and appropriate debridement and exenteration as per the clinical condition. Uncontrolled diabetes constituted 82% of their cases, as against 76% in the current series ($p = 0.5$). Intracranial disease in that series was seen in 7 of 34 cases (21%) while in the current series it was 33% ($p = 0.2$). The overall mortality in the series was seen in 11 patients (32%). This was comparable to the mortality rate in our study which was 34% ($p = 0.87$). The treatment success rates of their study and the current study were 53% and 60%, respectively ($p = 0.49$). The commonest parameters between the 2 studies were not statistically different. This indicates that the concurrent COVID-19 infection does not alter either the final outcome or the mortality in cases with mucormycosis.

One of the most important decisions that needs to be made in the course of the management of ROCM is that regarding orbital exenteration. It has been previously reported that the indications for orbital exenteration are ophthalmoplegia, proptosis, cranial involvement, and ocular involvement.[32–39] Some have even reported that exenteration could increase the patients' survival in the presence of intracranial spread and rapid progression.[34] Kashkouli et al[17] in their series found that survival was not significantly different in patients with and without exenteration. However, a significantly longer duration of symptom to death was observed in patients with exenteration indicating that performing orbital exenteration may delay the time of death. There have been attempts to create a scoring system to assist in the management of ROCM. Shah et al[40] proposed the "Sion Hospital Scoring System" which relies on clinical signs, ophthalmoscopic features, and imaging characteristics. However, it is also possible that exenteration, by itself, may not be associated with improved survival due to end-stage disease at the time of exenteration.[35] In our study, bivariate regression analysis showed exenteration to be associated with higher mortality ($p = 0.008$) although the significance was not maintained on multivariate analysis. This statistical observation could be confounded by the possibility that patients with the most severe infections and the highest risk of dying were exenterated. Another possibility might be that exenteration did not confer a survival benefit. We believe, in cases of ROCM involving the sinuses, the orbit along with intracranial extension, orbital exenteration at best may help in reducing the disease load; which by itself cannot be curative.

The current study has its strengths and limitations. This is the largest study to date on ROCM in COVID-19 patients and also the first one to objectively demonstrate the factors predicting poor clinical outcomes along with those predicting mortality in such a subset. The current study proposes various independent factors that determine clinical outcomes in ROCM following COVID-19 infection. As seen in the regression tables, the variance inflation factors of all the significant independent variables are on the lower side. This rules out multi-collinearity and we can thus propose each of these to be an independent significant factor not affected by the other. This is a major strength of this study. This study also has limitations of being a retrospective study across different practices separated by geography. Thus a slight difference in management protocols cannot be adjusted for.

In conclusion, ROCM is a known occurrence in COVID-19 affected patients. Over a third of patients can have unfavorable final outcome. Uncontrolled DM at presentation, involvement of the orbital apex and CNS by the infection, and the usage of steroids determined an unfavorable outcome. Involvement of the CNS was seen to be the only factor determining mortality. In a similar geographic setup, as compared to previous non-COVID-related cases, the coexistence of COVID-19 in this series, did not seem to worsen the final outcome in terms of mortality. It is prudent that physicians and ophthalmologists, alike, involved in the care of patients with COVID-19 be aware of the outcomes of ROCM in COVID-19 patients.

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