Original Article

Clinical profile, prognostic factors, and outcomes of rhino-orbital-cerebral mucormycosis in the setting of COVID-19: A retrospective study

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Abstract:

PURPOSE: The purpose was to study the demographics, clinical and radiological presenting patterns, prognostic variables, and outcome of management of rhino-orbital-cerebral-mucormycosis (ROCM) in coronavirus disease (COVID-19) patients.

METHODS: We retrospectively analyzed COVID-19 patients with proven ROCM from April 2021 to November 2021. All included patients were given systemic antifungal therapy depending on clinical response and underwent functional endoscopic sinus surgery (FESS) with orbital wall decompression. Administration of transcutaneous retrobulbar amphotericin B (TRAMB) injection, exenteration, and maxillectomy was done when indicated as per a novel algorithm.

RESULTS: A total of 64 patients with ROCM were included in the study. The mean age of 54.5 (standard deviation [SD] - 10.6) years with a male predominance (male: female = 55:9) was observed. Pre-existing diabetes mellitus (DM) was the most common comorbid state, 47 (73.4%). The most common ophthalmic presentation was proptosis (*n* = 40) (62.5%). Bulky extraocular muscles (*n* = 64) (100%) and intraorbital fat stranding (*n* = 41) (64%) were the most common radiological findings. Twenty-eight patients received TRAMB, while 11 patients underwent exenteration with FESS. Our study had a mortality rate of 18.7% (*n* = 12). The mean glycated hemoglobin of 13.5% (SD - 1.1) and a higher serum ferritin value of 976.25 (SD - 592) were observed in the deceased group. Vision was preserved in 38 (73.7%) patients in the survived group.

CONCLUSION: ROCM has a wide array of presentations, with proptosis as the most common clinical finding. Bulky EOM and intraorbital fat stranding were the most common radiological findings. Thorough surgical debridement with systemic and local antifungal therapy results in reasonable outcomes for ROCM in COVID-19 patients. Older age, intensive care unit admissions, uncontrolled DM, central nervous system involvement, and shorter duration of antifungal treatment are poor prognostic factors associated with mortality.

Keywords:

COVID-19, rhino-orbital-cerebral mucormycosis, retrobulbar amphotericin B

Introduction

Rhino-orbital-cerebral mucormycosis (ROCM) is an acute, often fatal, fungal infection caused by members of the class Zygomycetes and the order Mucorales.[1] They are usually present in an opportunistic setting based on host susceptibility factors. The most common risk factors reported in the literature include uncontrolled diabetes mellitus (DM), prolonged neutropenia, use of corticosteroids, solid organ or hematopoietic stem cell transplantation, acquired immunodeficiency syndrome (AIDS), iron chelation with deferoxamine, burn wounds, malnutrition, extremes of age, and intravenous drug abuse.[1] During the second wave of the coronavirus disease (COVID-19) pandemic, developing countries like India were gripped by a devastating combination of COVID-19 and mucormycosis. This posed the already strained

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medical fraternity in managing such patients into a further desperate situation. ROCM refers to the entire spectrum of the disease; when untreated, it usually spreads from the sinus to the orbit or intracranial cavity eventually.[2] There has been an insurgence of the literature evidence to aid in identifying risk groups and management of these cases. The largest clusters of patients presented in various parts of the country were managed according to the institutional protocols. This study aimed to discuss the patient demographics, and to assess clinical and radiological presenting patterns, outcomes of treatment, and poor prognostic variables associated with mortality in a large case series of ROCM from southern India.

Methods

The study setting was a tertiary health-care facility in urban Tamil Nādu, South India. This study was approved by the Institutional Review Board (IRB21/252). Retrospective data of patients with COVID-19, reverse transcriptase–polymerase chain reaction positivity (recent past/concurrent) with proven fungal elements in tissue specimens of sinuses from April 2021 to November 2021 were included in the study. Patients' records were carefully studied to extract information about the patients' demographic profile, clinical presentation, associated comorbidities, ophthalmological findings, imaging features, medical and surgical intervention as well as the outcome. Informed consent was obtained from patients for publication.

A panel of multidisciplinary doctors attended to these patients included infectious medicine, intensive care unit (ICU) intensivist, radiologist, otolaryngologist, ophthalmologist, maxillofacial surgeon, and pathologist. Ophthalmologist opinion was sought when patients either presented with eye symptoms or ENT examination revealed suspected fungal activity in the nasal sinuses. Imaging studies included computed tomography or magnetic resonance imaging with contrast of paranasal sinus (PNS), orbits, and brain screening to ascertain the stage of involvement of the disease at presentation. Imaging was repeated as per need to aid in the decision for intervention and further management. All patients included in the study were given intravenous liposomal amphotericin B (5–10 mg/kg body weight/day) for a minimum of 4 weeks under physician's guidance (duration depended on disease response and tolerability of the patient), followed by a step-down therapy with oral posaconazole 300 mg delayed-release tablets twice a day for 1 day followed by 300 mg daily for 2–4 months.[3] Patients with concurrent COVID-19 infection were managed as per the NIH guidelines.[4] All radiological or biopsy-proven sinusitis cases underwent functional endoscopic sinus surgery (FESS) with medial or inferior orbital wall decompression with amphotericin B lavage and packing of sinuses. Regular sinus lavage with amphotericin B was done for all postoperative patients until disease-free clinically. Orbital exenteration was performed in selected cases with extensive orbital involvement. A few cases needed the above procedure combined with maxillectomy when the maxilla is involved. Exenterated globe along with tissue biopsy from sinus debridement, was sent for histopathological correlation. Although most studies in the literature employed a categorization algorithm as described in the study by Honavar,[5] we devised a novel method to classify these patients to accommodate the wide variation in their clinical and radiological presentation and also to formulate the treatment. Decisions were discussed with the treating panel for further management. The protocol followed in our study is depicted in Table 1 and Figure 1.

Ophthalmological intervention:
1. Transcutaneous retrobulbar amphotericin B (TRAMB) injection: Selected patients underwent the standard procedure as recommended.[5] The procedure was uneventful in all cases. A maximum of three injections were repeated at our setup. A further decision was based on repeat imaging and the patient's general status
2. Exenteration: Lid-sparing exenteration with FESS was performed in indicated cases. Patients with maxilla involvement needed the above procedure to be combined with maxillectomy. Exenterated globe with tissue biopsy from sinus debridement, was sent for histopathological correlation.

Indications for TRAMB injection:
1. Clinical ROCM threatening vision but systemically unstable patient with intracranial extension (globe-sparing step)
2. Vision-threatening disease before definitive surgical intervention to reduce the local disease load.

Indications for exenteration:
1. Orbital apex involvement
2. Disease progression despite more than three doses of retrobulbar injection
3. No perception of light with evidence of disease spread through orbit
4. The evidence of nonenhancement of EOM (extraocular muscles) was when there was no enhancement of extraocular muscles postcontrast injection suggestive of necrosis.

Statistical analysis was done using Statistical package for social sciences version 24.0(SPSS, INC./ Chicago, Illinois). Descriptive statistics were presented as mean ± standard deviation. Discrete variables were presented as number (*n*) and percentage (%). Statistical significance was set at $P < 0.05$.

Table 1: Definitions for clinical and radiological rhino-orbital-cerebral mucormycosis

Types	Features
Radiological ROCM	Imaging evidence of inflammation in orbital content (fat/EOM)
Clinical ROCM	Radiological ROCM + clinical evidence of orbital cellulitis (proptosis/ptosis/ocular pain/restricted ocular movements)

ROCM: Rhino-orbital-cerebral mucormycosis, EOM: Extraocular muscle

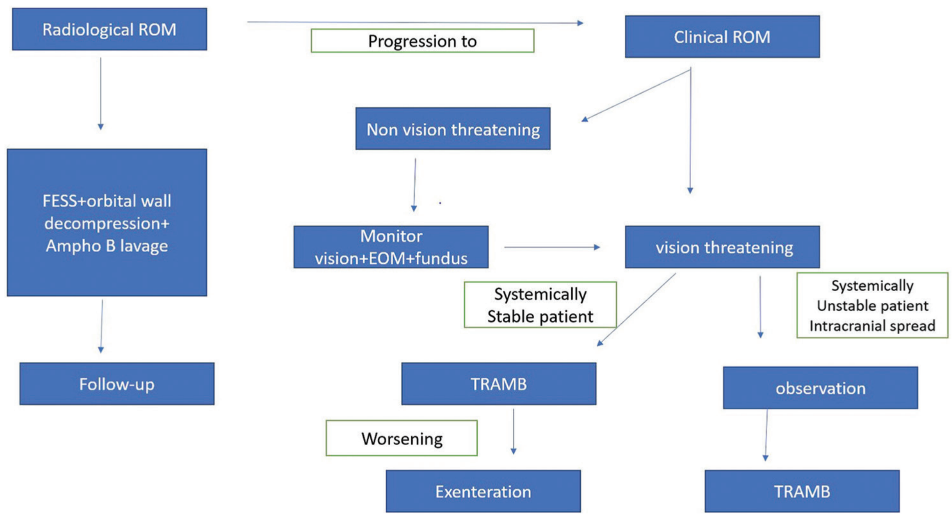

Figure 1: Management protocol of ROCM in our study. ROCM = Rhino-orbital-cerebral mucormycosis, TRAMB = Transcutaneous retrobulbar amphotericin B injection, EOM = Extraocular movements, FESS = Functional endoscopic sinus surgery

Any association between variables was studied using the Chi-square test for categorical variables and the independent *t*-test for continuous variables.

Results

A total of 64 patients with proven fungal ROCM were included in the study. Male predominance of 55 (85.9%) was observed in our study. The average duration of presentation of ROCM ranged from 0 to 40 days (mean – 10.69 days). Fifty-one (79.69%) patients were treated for COVID-19 infection in the recent past, and 13 (20.31%) patients had concurrent COVID-19 infection. Pre-existing DM was the most common comorbid state (73.4%), followed by hypertension (39.1%), acute kidney injury (17.25%), chronic renal disease (6.3%), coronary artery disease (12.5%), and cerebrovascular accident (6.3%). Other cases had hypothyroidism, bronchial asthma, and COVID-19-associated pneumonia (6.3%). Seventeen patients (26.6%) were found to have developed new-onset DM during the treatment for COVID-19 infection. The demographic distribution of the patient data is briefed in Table 2.

Table 2: Demographic distribution of the patient data (*n*=64)

Variables	Frequency, *n* (%)
Mean age (years)	54.59±10.68
Gender	
Male	55 (85.9)
Female	9 (14.1)
Comorbidities	
Hypertension	25 (39.1)
AKI	11 (17.2)
CKD	4 (6.3)
CAD	8 (12.5)
CVA	4 (6.3)
Hypothyroidism	2 (3.1)
ACS	1 (1.6)
BA	1 (1.6)
COVID pneumonia	4 (6.3)
Pre-existing DM	47 (73.4)
New-onset DM	17 (26.6)
COVID status	
Past infection	51 (79.69)
Concurrent infection	13 (20.31)
Eye involvement	
Right eye	34 (53.1)
Left eye	25 (39.1)
Both eyes	5 (7.8)

AKI=Acute kidney injury; CKD=Chronic kidney injury; CAD=Coronary artery disease; CVA=Cerebrovascular accident; ACS=Acute coronary syndrome; BA=Bronchial asthma; DM=Diabetes mellitus

ROCM patients at our institute presented with an array of clinical symptoms and signs, which are elaborated on in Figures 2 and 3. Clinical symptomatology differed among cases depending on the predominant sinus involved at the time of presentation. Maxillary and ethmoid sinus involvement was the most common to have ophthalmological manifestation early in the disease course. PNS involvement was observed to have included various combinations of unilateral or bilateral continuous sinuses. Imaging findings aided in the management of ROCM are elaborated in Table 3 and Figure 4.

Medical management

All patients under the study were given systemic antifungals as mentioned for at least 4 weeks, followed by oral posaconazole as a step-down therapy. Twenty-eight patients received TRAMB ranging from 1 to 3 doses (mean – 1.2). None of the patients reported any adverse effect following injections.

Surgical management

All patients were subjected to FESS with medial or inferior wall decompression. Seventeen patients underwent FESS with orbital decompression and maxillectomy. Eleven patients had

FESS with orbital decompression along with exenteration. Intraoperative findings during exenteration/maxillectomy are depicted in Figure 5.

Histopathological reporting revealed isolated mucor in 49 (76.6%) cases, followed by combined aspergillus and mucor infection in nine cases (14.1%). Mucor mixed with candida and aspergillus in three cases (4.7%), mucor with candida in two cases (3.1%), and actinomycosis with mucor in one case (1.6%) formed the rest of the cases.

Twelve (18.75%) patients succumbed to death, while the rest 52 (81.25%), survived and were under regular follow-up. For clinical comparison, patients were divided into two groups, survived patients (52 patients) and deceased patients (12 patients). Survived patients were followed up for a minimum period of 3 months. Patients were analyzed for various parameters which influenced the course of the patient's recovery in terms of clinical betterment and potential visual preservation (best-corrected visual acuity of >3/60 in the involved eye) [Table 4].

Discussion

Epidemiology of mycosis varies in developing countries than that in developed countries, as observed by Chakrabarti and Singh.[6] Patients are susceptible to coinfection due to immune dysregulation caused by COVID-19 infection.[7] Additional risk factors such as uncontrolled DM, diabetic ketoacidosis,[8,9] worsening of COVID-19-induced respiratory disease, and ICU admissions played an undeniable role. In a systematic study, Prakash *et al*. found a higher occurrence of mucormycosis infection in uncontrolled DM before the pandemic evolved in India.[10]

In our study, the average age of presentation (54.5 years) with male preponderance (89.9%) was consistent with published reports.[11,12] Duration of ROCM presentation showed an average of 10.7 days, as observed elsewhere in the country.[11] The most common ophthalmic symptom was proptosis (62.5%), followed by ptosis (35.9%) and ophthalmoplegia (10.93%).[13] Maxillary followed by ethmoid sinus were commonly involved among our patients, likewise in a study by Gupta *et al*.[14] Thinner walls of the sinuses and direct tissue plane spread of mucormycosis explained the ocular signs observed in a majority of these patients.[15] DM, both pre-existing and new onset, was the most common comorbid state found in all patients, followed by hypertension.[12,13] Survived group had younger age patients (mean – 53.38 years) compared to older age in the deceased group (mean – 59.83 years), which was not statistically significant in our study. The mean glycated hemoglobin (HbA1c) of 13.5% ± 1.1% in the deceased group

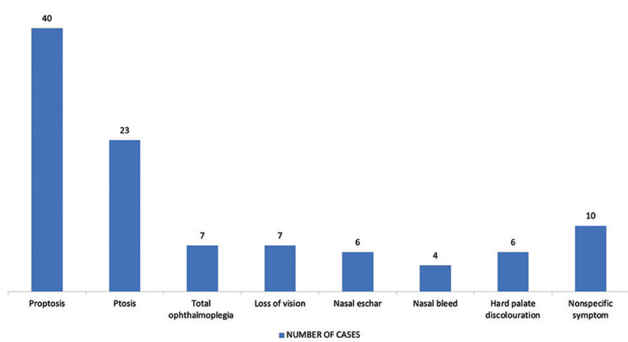

Figure 2: Graph depicting clinical spectrum of ROCM. X-axis denotes various clinical symptoms, while the y-axis denotes number of patients. ROCM = Rhino-orbital-cerebral mucormycosis

Table 3: Radiological signs of rhino-orbital-cerebral mucormycosis (*n*=64)

Imaging findings	Frequency, *n* (%)
Bulky extraocular muscles (atleast two)	64 (100)
Diffusion restriction to optic nerve	14 (21.8)
Fat stranding of intra orbital contents	41 (64.1)
Orbital cellulitis	24 (37.5)
Superior ophthalmic vein prominence	5 (7.8)
Orbital bony wall erosion	6 (9.4)
Bilateral pan sinusitis	2 (3.1)
Bilateral predominantly maxillary + ethmoid sinusitis	6 (9.4)
Unilateral maxillary + ethmoid sinusitis	43 (67.2)
Cerebral infarct	11 (17.1)
Cavernous sinus thrombosis	8 (12.5)
Cerebritis	7 (10.9)
Brain abscess	5 (7.8)

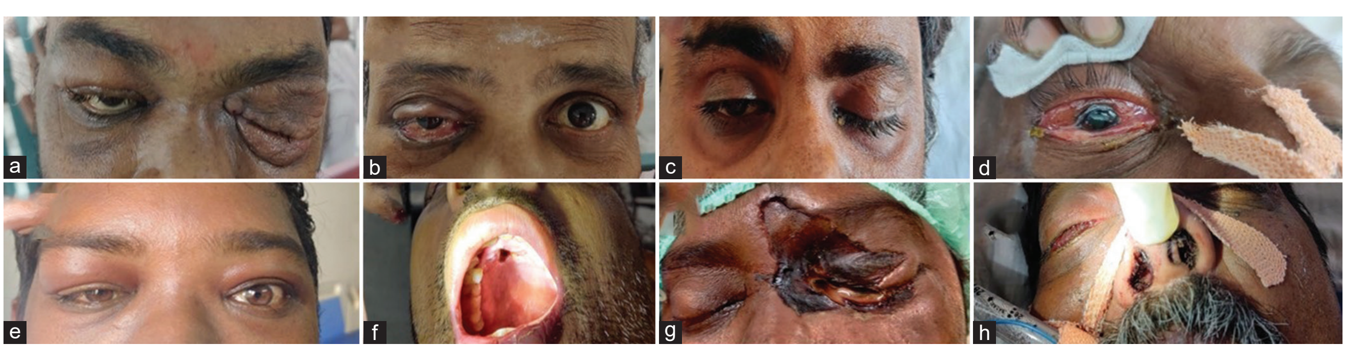

Figure 3: Clinical photograph demonstrating various presentations of ROCM patients. (a) orbital cellulitis, (b) lid edema/chemosis, (c) complete ptosis, (d) proptosis with chemosis, (e) bilateral periorbital edema, (f) hard palate erosion, (g) periocular necrosis, (h) nasal eschar. ROCM: Rhino-orbital-cerebral mucormycosis

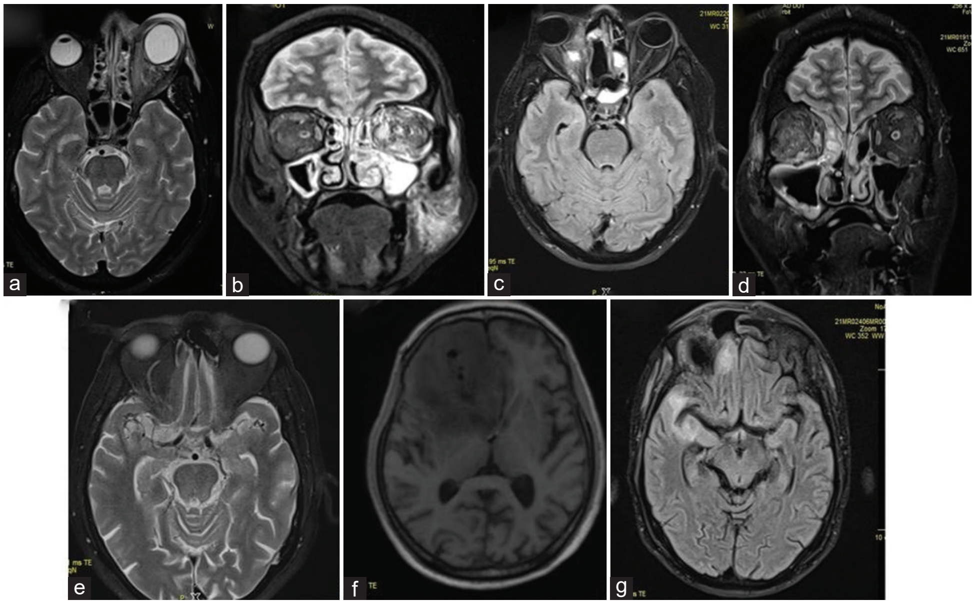

Figure 4: Radiological signs of ROCM. (a) Bulky extraocular muscles, proptosis (b) mucosal thickening in the left maxillary and ethmoid sinuses (c) intraconal collection (d) hypoenhancement of the optic nerve (e) prominent right superior ophthalmic vein (f) diffusion restriction in the right basifrontal lobe (g) hypointense area in the right frontal lobe with midline shift. ROCM = Rhino-orbital-cerebral mucormycosis

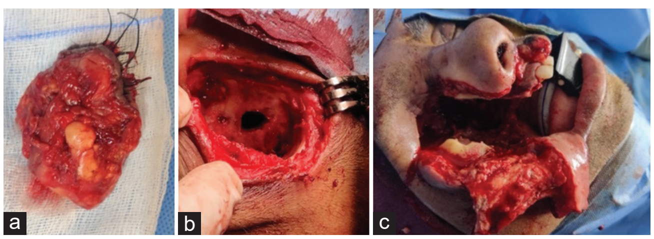

Figure 5: Intraoperative images. (a) Exenterated globe (b) empty socket with eroded orbital floor and (c) exenteration and open maxillectomy

was significantly higher than 10.74% ± 2% in the survival group. Previous studies have provided absolute evidence that uncontrolled DM leads to complications which are directly related to the mean glycemic values measured as HbA1c and increased susceptibility of COVID-19-infected patients for mucor.[12,16,17]

This further adds to the evidence of the dysregulated glycemic condition in these patients. A higher serum ferritin value of 976.25 ± 592.08 among the deceased group, as opposed to 742.70 ± 586.17 in the survived group, was noted.[18] Bhadania *et al*. observed a hyperferritinemic milieu fueling fungal flora to thrive more aggressively in these patients.[19] ICU admissions were more frequent ($n = 12$, $P = 0.000$ significant) in succumbed group.[20,21]

Four out of five patients with bilateral disease survived and did not show a statistically significant impact on the survival of our study group, but was a poor prognostic factor in the study by Yohai *et al*.[22] Antifungal therapy followed in our study is shown to have a favorable outcome as in the existing literature.[17,21] The deceased group received a lesser duration of systemic therapy due to severe comorbidities, faster deterioration, leading to death before completion of the course of antifungals, nonaffordability of treatment, and extensive involvement at presentation.

Table 4: Comparison of parameters between survived patients and deceased patients

Variables	Survived patients (*n*=52)	Deceased patient (*n*=12)	*P*
Age (years)	53.38±10	59.83±9.04	0.058
ICU admission (number of patients)	11	12	0.000
HbA1c (%)	10.74±2	13.5±1.1	0.000
Serum ferritin (mg/dl)	742.70±586.17	976.25±592.08	0.219
Bilaterality of disease	4	1	0.663
CNS involvement	13	8	0.005
Duration of antifungals (>4 weeks)	38	1	0.000
Vision preserved	38	2	0.000

ICU=Intensive care unit; HbA1c=Glycated hemoglobin; CNS=Central nervous system

TRAMB is recommended[23] for ocular containment of fungal spread along tissue planes. Increased concentration of amphotericin B given in local tissues has been speculated to limit the disease spread and obvious elimination of systemic side effects.[23] At our institute, the maximum of three doses was practiced, although it varied from 1 to 9 in the literature.[12]

Vision alteration caused by ROCM could be due to direct invasion of central retinal artery by mucor resulting in occlusion, optic nerve compression by bulky EOM or intraconal fluid accumulation. Currently, there exists three treatment options for infected orbital tissue, i.e., exenteration, conservative debridement, and TRAMB. Conservative debridement and TRAMB are increasingly considered reasonable first-line options.[23] Less aggressive initial intervention is justified, as increasingly invasive options are available if the deterioration is noted. Consistent with the above literature, 23 (44.2%) patients received TRAMB in the survived group, whereas only five patients (41.6%) received TRAMB in the deceased group, which did not affect the outcome in our study. The mean TRAMB (5.58 ± 2.36) was observed in the study by Mohan *et al*.,[24] and an average of 1.2 injections were observed in our study. Exenteration was not considered for those improving well with treatment. Eleven patients underwent exenteration after carefully contemplating the decision. Two patients succumbed to death in our study, despite surgical debridement and exenteration due to poor response to management.

Perineural invasion is a common finding in invasive zygomycosis, as are angioinvasion and infarcts.[25] Histopathological examination of tissue biopsy report revealed positive for angioinvasion by fungal elements; 49 cases of isolated mucor (76.5%), mixed infection with aspergillus, candida, and actinomycetes (23.07%) were observed. Vision was preserved in 38 (73.07%) patients in survived group which were significant ($P = 0.00$). Retrograde extension of fungi into the brain through the optic nerve can be postulated for the central nervous system (CNS) involvement in these patients.[23] The contiguous spread was predominant in the study by Roden *et al*.[26] Eight patients out of 12 in the deceased group had CNS involvement in the form of brain infarcts, cavernous sinus thrombosis, cerebritis, pachymeningitis, and abscess. This finding in our study is also corroborated by evidence from the existing literature.[12,27,28]

Our study had a mortality rate of 18.75% compared to 34% as observed by Pal *et al*.,[29] Nagalli and Kikkeri had 48.7%,[15] and Bhattacharyya *et al*. had 37.3%.[30]

Nine survived exenterated patients were on regular follow-up. Eight exenterated sockets healed well with epithelialization [Figure 6]. One patient developed gaping in the lids and suppuration with frontal bone erosion in the roof of the orbit. This patient was treated with repeated sinus lavage with broad-spectrum antibiotics. The patient was lost to follow-up subsequently. In another patient ptosis improved with regained partial motility of the eye. One Patient with preserved globe had neurotrophic keratopathy.

Limitations of our study include, retrospective study design, details of the treatment of COVID-19 treated elsewhere was not accessible for analysis, and severity of COVID-19 disease was not taken into account to categorize ROCM. Further prospective studies are needed for risk factor analysis of involved parameters, early versus late surgical intervention, duration of antifungal treatment, the role of TRAMB, and exenteration and their impact on patient morbidity and survival.

Conclusion

ROCM has a wide array of presentations, with proptosis as the most common clinical finding. Bulky EOM and intraorbital fat stranding were the most common radiological findings. Thorough surgical debridement with systemic and local antifungal therapy results in reasonable outcomes for ROCM in COVID-19 patients. Older age, ICU admissions, uncontrolled DM, CNS involvement, and shorter duration of antifungal treatment are poor prognostic factors associated with mortality.

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Conflicts of interest

There are no conflicts of interest.

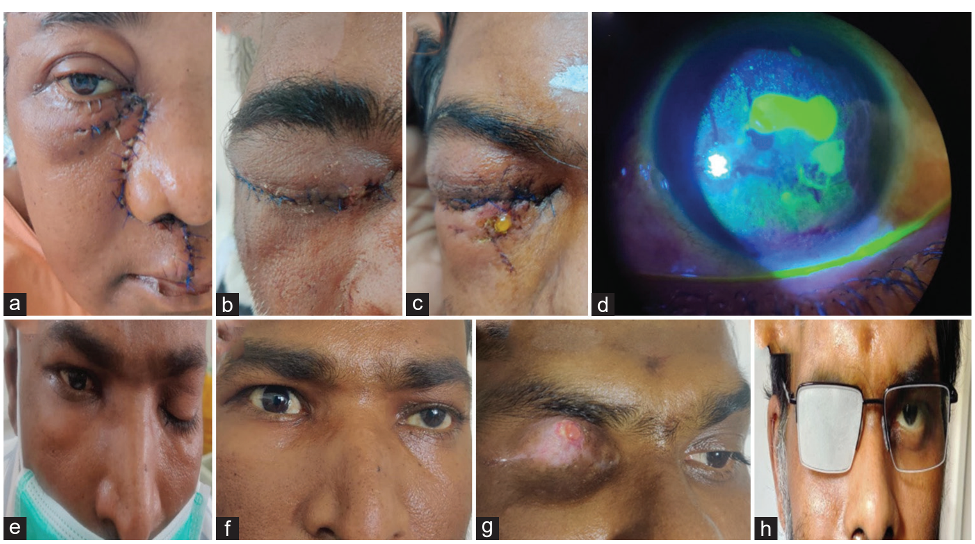

Figure 6: Postoperative images on follow-up. (a) Healing open maxillectomy wound, (b) well-opposed postexenteration wound, (c) infected exenteration wound, (d) neurotrophic keratopathy, (e and f) improvement of ptosis, (g and h) well-epithelialized socket with rehabilitation glasses

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