

## Ophthalmology

**KEYWORDS:** Covid-19, Diabetes mellitus, Corticosteroids, Covid-19-associated ROCM, Retrobulbar liposomal amphotericin-B, Orbital exenteration,.

## CLINICAL CHARACTERISTICS, MANAGEMENT AND OUTCOME OF COVID-19 ASSOCIATED RHINO-ORBITAL-CEREBRAL-MUCORMYCOSIS PATIENTS DURING SECOND WAVE OF COVID-19



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**Abstract**

**Purpose:** Covid-19-associated Rhino-orbital-cerebral Mucormycosis (ROCM) has reached epidemic proportion during India's second wave of Covid-19 pandemic, with several risk factors being implicated in its pathogenesis. The present study aimed to document cases of rhino-orbital Mucormycosis and to evaluate risk factors including comorbidities, clinical characteristics, diagnosis, management and outcome at Tertiary care centre during Covid-19 (2021) pandemic. **Methods:** It is retrospective study, carried out at tertiary care centre from April 2021 to September 2021. 42 patients of biopsy proven Mucormycosis were included in the study. These patients' records were reviewed from hospital data. All patients were subjected to complete ophthalmological, ENT examination and imaging studies. Orbital staging was done. Each case was treated by multidisciplinary approach with Functional Endoscopic Sinus Surgery (FESS) and intravenous amphotericin B (AMB). Retrobulbar liposomal amphotericin-B and Exenteration was done whenever indicated. A minimum 60 day follow up period was attributed from the day of discharge to all study patients. Statistical analysis was done using Chi square test. A P value  $\leq 0.05$  was taken as significant. **Results:** Total 42 patients of ROCM were documented. Most of the cases showed onset of symptoms of ROCM between day 20 and day 30 from the diagnosis of Covid-19. The mean age was 50.48 years with a male preponderance (82.9%). A total of 95.1% of patients had diabetes (30) and Covid-19 positivity (40). Concurrent steroid use was seen in 83.3% where 73.1% of patients had received oxygen support during Covid-19 infection. The most common ophthalmologic presentation was orbital/facial oedema (33) and pain, diminution of vision (24) and ophthalmoplegia (26). Direct nasal endoscopy and biopsy was done to establish diagnosis. The most common imaging findings were orbital cellulitis (30), extra ocular muscle involvement (26) and pansinusitis (33). Orbit was involved in 58.5% of patients, with stage ranging from 2a-4d. All patients were treated with FESS and intravenous AMB. Retrobulbar AMB was given in 11 patients. Exenteration was done in (n = 4)

10.5% of cases. 41 patients recovered and mortality was seen in 1 patient. **Conclusion:** Corticosteroids and DM are the most important predisposing factors in the development of Covid-19-associated ROCM. Covid-19 patients must be followed up beyond recovery. Awareness regarding red flag symptoms and high index of clinical suspicion in Covid-19 recovered patients with prompt diagnosis and early initiation of treatment are essential for successful outcome with less mortality.

**INTRODUCTION:**

Rhino-Orbital-Mucormycosis is an acute and often lethal opportunistic fungal infection typically affecting diabetic (50% of the cases) or immunocompromised patients caused by fungi of the class zygomycetes<sup>1,3</sup>. Mucorales are rare but opportunistic pathogens and primarily affect immunocompromised people. Their invasion in blood vessels and vasculo-tropism leads to tissue infarction<sup>2</sup>.

The coronavirus disease 2019 (Covid-19) infection caused by the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) may be associated with a wide range of disease patterns along with altered immune system and neutropenia<sup>5</sup>. The increased incidence of rhino-orbital-cerebral mucormycosis (ROCM) in the setting of Covid-19 in India and elsewhere had become a matter of concern. The term Rhino-orbital-cerebral mucormycosis refers to entire spectrum of the disease. With rare exceptions it usually starts in the sino-nasal tissues (limited Sino-nasal disease), progresses to the orbits (limited rhino-orbital disease) and finally affects the central nervous system (rhino-orbital-cerebral disease). Patients manifest with signs and symptoms relating to the involved tissues.<sup>19</sup>

A hallmark of mucormycosis infection is the presence of extensive angioinvasion with resultant vessel thrombosis and tissue necrosis.<sup>6</sup> Thus demonstration of tissue invasion on histopathology is mandatory for diagnosis.<sup>19</sup>

Aggressive surgical debridement of all involved tissues including exenteration of involved orbits with prolonged administration of Amphotericin B is the most common treatment regime.<sup>7,8,9,10</sup> This

retrospective study was carried out to evaluate risk factors including comorbidities, clinical characteristics, diagnosis, management and outcome.

**Materials and methods:**

This is a retrospective study of patients with ROCM with concurrent or past history of Covid-19 infection reported between April 2021 and September 2021. Total of 42 patients who were biopsy proven Mucormycosis were enrolled in the study and their hospital records were reviewed.

At the time of presentation each patient was subjected to complete history taking, otorhinolaryngologic, ophthalmic and neurologic examinations. Detailed history and examination including visual acuity assessment, slit lamp evaluation, extraocular movements, and fundus examination was done to note the presenting ophthalmic complaints and clinical characteristics. A complete history regarding Covid-19 infection with report and systemic illness was elicited. Covid-19 reports along with CT scores were collected in patients who had concurrent Covid-19 with ROCM.

Diagnosis was made on histopathological examination and KOH preparation of biopsy specimens obtained from the nasal cavity and/or paranasal sinuses. Contrast-enhanced magnetic resonance imaging (MRI) and computerised tomographic (CT) scans of the paranasal sinuses, orbits and brain were obtained to assess the extent of disease. Proven ROCM was defined as clinic-radiological features along with microbiological confirmation on direct microscopy and/or culture. Initial investigations included complete blood counts, blood urea, serum creatinine, serum glucose. Following this all the patients were classified into proposed staging system7 and managed accordingly.

Treatment with intravenous liposomal amphotericin B was given in all the diagnosed patients under the physician's guidance in a dose of 3 to 5 mg/kg body weight/day and these patients were also treated to correct metabolic derangements on an average of 2 weeks. Functional endoscopic sinus surgery (FESS) with debridement was done by otorhinolaryngologist. Retrobulbar liposomal amphotericin-B injection was given by Ophthalmologists in cases with ocular movements restriction ie stage2-3b. A minimum of 5 doses and maximum of 7 doses through transcutaneous retrobulbar route was given. The dose given was 3.5mg/ml in retrobulbar space on alternate days. Reconstitution done as: dilute a 50mg/ml vial with 10ml of sterile water, in that 0.7ml is taken which contains 3.5mg, which is further diluted to 1ml by adding 0.3ml of sterile water. Exenteration was considered in patients with stage 3a-c in the absence of light perception, total ophthalmoplegia, obvious necrosis of orbital tissue and worsening despite the above concurrent systemic management.

These patients were subjected to repeat ophthalmological, ENT examination and imaging studies to know the disease resolution or worsening. Repeat sinus and/or local tissue debridement was done on worsening. The resolution was confirmed by a negative sinus biopsy and normal metabolic parameters. Thereafter, the patient was discharged with continued medical management of comorbidities. Oral Posaconazole (5 mg/kg body weight/day) was continued even after discharge for a minimum of 8 weeks as per protocol.11,15

The patients were then followed up for 2 months to know the outcome.

Statistical analysis: Statistical analysis was done using Chi-square test. A P value ≤ 0.05 was taken as significant. Informed consent was obtained from all the patients. The study was approved by the institutional Ethical Committee.

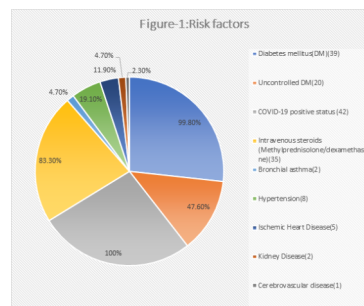
**Results:**

Total of 42 patients of Covid-19 patients associated ROCM was

analysed. Mean age noted was 50.48 (range, 28–78) years with a male preponderance (82.9%) and is tabulated below.

**Table 1: Epidemiology**

|                    | Number (%) |
|--------------------|------------|
| <b>AGE (years)</b> |            |
| Mean age           | 50.48%     |
| 25-40              | 5          |
| 41-55              | 10         |
| 56-70              | 25         |
| 71-85              | 2          |
| <b>GENDER</b>      |            |
| Male               | 31         |
| Female             | 11         |
| <b>LATERALITY</b>  |            |
| OD                 | 23         |
| OS                 | 17         |
| Bilateral          | 02         |



**Table 3: Clinical presentation**

|                                     |    |
|-------------------------------------|----|
| Nasal stuffiness/block              | 40 |
| Redness/itching in eyes             | 6  |
| Ptosis                              | 23 |
| Loss of vision/diminution of vision | 24 |
| Orbital/facial swelling             | 33 |
| Proptosis                           | 15 |
| Orbital/facial pain                 | 32 |
| Head ache                           | 20 |
| Diplopia                            | 1  |
| Loose tooth/pain                    | 4  |
| Facial deviation                    | 2  |
| Fever                               | 7  |
| <b>ON EXAMINATION</b>               |    |
| <b>Visual assessment</b>            |    |
| 6/6-6/18                            | 16 |
| 6/18-6/60                           | 11 |
| <6/60                               | 11 |
| PL negative                         | 4  |
| <b>Ocular findings</b>              |    |
| Frozen globe                        | 5  |
| EOM restriction                     | 26 |
| Lagophthalmos                       | 4  |
| Proptosis                           | 26 |
| Ptosis                              | 23 |
| Facial palsy                        | 2  |
| Chemosis                            | 19 |
| Necrosis/nasal ulcer/eschar         | 12 |
| Non-reactive Pupils                 | 5  |
| Relative Afferent Pupillary Defect  | 3  |
| CSF rhinorrhoea                     | 1  |

|  |    |
|--|----|
| Eyelid swelling/orbital edema/facial edema | 33 |
| Significant fundus findings                |    |
| Central Retinal Artery Occlusion           | 4  |
| Vitritis                                   | 1  |
| Glaucoma                                   | 2  |
| Disc Edema                                 | 2  |
| Disc Pallor                                | 1  |
| Non-Proliferative Diabetic Retinopathy     | 2  |
| Proliferative Diabetic Retinopathy with VH | 1  |

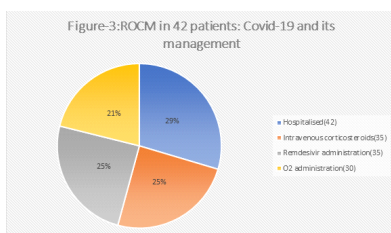
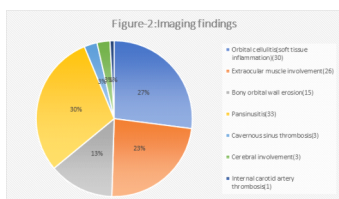


Table 6: Treatment of mucormycosis

| Treatment                             | Number (percentage) |
|---------------------------------------|---------------------|
| IV Amphotericin B (liposomal)         | 42                  |
| IV AMB + Posaconazole/isavuconazole   | 15                  |
| Sinus debridement                     | 33                  |
| Exenteration                          | 4                   |
| Retrolbulbar liposomal amphotericin-B | 11                  |
| Craniotomy                            | 3                   |

Graph-3 shows the details of the severity of Covid-19 and its management. All patients were symptomatic and hospitalized for covid treatment. Of those 71.4% (30) patients required oxygen support. Remdesivir was used in 83.3% (35) of the patients. Systemic corticosteroids (either oral or intravenous or both) were used in 83.3% (35) patients.

**RISK FACTORS:**

Of total 42 patients 39 were diabetic and steroid was used for treatment in 35. So, among all systemic comorbidities, DM status, irrespective of control, emerged as the risk factor. Of the 42 patients with other comorbidities, 38.09% (16) had hypertension and 2% (1) had acute or chronic renal failure [Graph-1]. The proportion of patients who developed ROCM but were neither diabetic nor received corticosteroids was 2%.

**CLINICAL PRESENTATION:**

Out of 42 patients, 38 patients presented mucormycosis after 20 days to 1 month after the Covid-19 infection and 4 patients presented with concurrent Covid-19 infection. Even though most common primary symptoms of ROCM was nasal block/nasal stuffiness, common orbital complaint seen was orbital pain and swelling. All orbital symptoms are tabulated in Table 3-clinical presentation. Eyelid swelling and facial edema was the most common sign orbital signs followed proptosis, EOM restriction and ptosis. Mean amount of proptosis measured was 3.1.

**DIAGNOSIS AND RADIOLOGICAL FINDINGS:**

Diagnostic nasal endoscopy was performed for all 42 patients. Microbiological evidence was obtained in the form of KOH preparation direct microscopy in 42, HPE in 42 and fungal culture positive in 20 cases. Graph-2 shows imaging findings. Pansinusitis followed by orbital cellulitis were the most common imaging findings noted.

**MANAGEMENT:**

Management of ROCM associated with Covid-19 was multidisciplinary approach.

Primary initiation of medical management was done in all 42 patients with IV amphotericin B. Of 42 patients, 33 received intravenous amphotericin B for a mean duration of 9.1 (range, 1–60) days, liposomal amphotericin B was provided in 40 and amphotericin B deoxycholate in 2. Combination therapy with amphotericin B and Posaconazole or isavuconazole was provided in 15. Step-down therapy (following cessation of intravenous amphotericin B) with oral Posaconazole or isavuconazole was administered in 33.

33 patients underwent FESS/PNS debridement, in whom 10 underwent multiple sessions to clear the residual/recurrent disease. Retrolbulbar Amphotericin B injection was given in 11 patients and was repeated in a range 5-7 injections based on clinical recovery. Orbital exenteration was performed in 4. Four patients who had cerebral involvement, 2 patients underwent FESS combined with exenteration. One patient was treated only with IV AMB and FESS. Another patient was intervened with FESS and cerebral abscess was drained by neurologist. Treatment given is briefed in Table 6.

**Outcome of Covid-19 associated ROCM:**

All patients were followed up with oral Posaconazole as a step-down therapy. Out of 33 patients who received IV AMB and underwent FESS, 10 had recurrent disease and underwent multiple sessions of sinus debridement. 11 patients received retrolbulbar AMB, did not have further progression of orbital disease. They had stable vision, normal fundus but EOM restriction remained same. 1 patient developed frontal osteomyelitis during follow up.

4 patients underwent exenteration simultaneously with FESS. 2 patients were successfully treated and doing well. One patient developed recurrence and underwent repeat sinus debridement. One patient succumbed due to spread infection and cerebral involvement. 2 patients had treatment success with no recurrent disease at follow-up.

**Discussion:**

Although mucormycosis is extremely rare in healthy individuals but several immunocompromised conditions predispose it. These includes uncontrolled DM with or without DKA, haematological and other malignancies, organ transplantation, prolonged neutropenia, immunosuppressive and corticosteroid therapy, iron overload or hemochromatosis, deferoxamine or deferoxamine therapy, voriconazole prophylaxis for transplant recipients, severe burns, acquired immunodeficiency syndrome (AIDS), intravenous drug abusers, malnutrition and open wound following trauma.<sup>11</sup>

Mucormycosis can involve nose, sinuses, orbit, central nervous system (CNS), lung (pulmonary), gastrointestinal tract (GIT), skin, jaw bones, joints, heart, kidney, and mediastinum (invasive type), but ROCM is the commonest variety seen in clinical practice worldwide.<sup>12,13</sup> The spores are inhaled into the nasopharynx and tissue invasion, thrombosis, and necrosis progresses from the nose, to the PNS, orbit, and CNS. The prevalence has been estimated to be 0.005–1.7 per million population worldwide before the pandemic. But the second wave of Covid-19 had seen a surge of mucormycosis. We know from the pathogenesis of mucormycosis that mononuclear and polymorphonuclear phagocytes of normal hosts kill Mucorales by generation of oxidative metabolites and defensins,

hence neutropenic patients and those with dysfunctional phagocytes are susceptible to develop invasive mucormycosis.<sup>13,14</sup>

Covid-19 produces a hypoxic environment with high glucose levels, high levels of ferritin, and attenuated phagocytic activity of leukocytes due to immunosuppression by the virus itself and the corticosteroids used in the management. This setting is highly conducive for the fungal spores to germinate and proliferate.<sup>15</sup> Recent published evidence says that Covid-19 is a pro-coagulable state and there is increased incidence of thrombotic events.<sup>16</sup>

This pro-coagulable state provides a perfect ground for the angioinvasion of mucor invasion due to vessel thrombosis and leading to disseminated infections.

The mean age of presentation was 50.3 with male preponderance during the presentation of ROCM found to be similar to the study done by Sen et al<sup>15</sup> and they attributed this to greater outdoor exposure and, therefore, to fungal spores may be the possible reason for this majority.

#### RISK FACTORS:

92.8% of patients were Diabetic out of which 47.6% were uncontrolled DM and it turned out to be the major independent risk factor in our study. Similarly in a series of 41 cases done by John et al<sup>20</sup>, 93% were diabetics and further literature review of the existing global data by Singh et al<sup>21</sup> and Hoeningl et al<sup>18</sup> showed that diabetics account for 80% of the cases and concomitant DKA was found in 15–41% of the patients. Of these, 90–97% of the cases were type 2 and 80.3% were uncontrolled<sup>21,18</sup>.

A cumulative dose greater than 600 mg for prednisolone and 2–7 g of methylprednisolone has been found to predispose immunocompromised patients to mucormycosis<sup>19</sup>. In our study 83.3% of the patients were given steroids but the dosage and time of administration during Covid-19 management was unknown. Other literatures showed 76% of the patients with Covid-19-associated ROCM gave history of systemic corticosteroids<sup>21</sup> and study done by Sen et al<sup>15</sup> data revealed that systemic corticosteroids was used in 87% of the patients, proposed that Irrational or injudicious use of corticosteroids can be a possible cause for ROCM.

Even though 71.4% of patients received oxygen treatment during Covid-19 management, we don't know the type of oxygen requirement in these patients so this data is not comparable to other studies.

#### CLINICAL PRESENTATION:

In a collaborative study done by Sen et al<sup>15</sup> the median time for diagnosis of mucormycosis was ten days from the day of Covid-19 diagnosis and for those who developed signs of mucormycosis after the diagnosis of Covid-19, the duration was 14.5 days.<sup>18</sup> Whereas in our study it was 20 days. This delayed presentation may be because of late identification of symptoms and less access to the health care facility in rural areas.

The most common non ocular presenting symptom in our data was nasal stuffiness (95.2%). Orbital/facial swelling and pain was the most common ocular symptom seen in 78.5 % followed by Ptosis (54.7%), Loss of vision/diminution of vision (57.1%),

Headache (47.6%), proptosis (35.7%). In meta-analysis done by Battacharya et al<sup>32</sup> the most common presenting features were proptosis (60.6%), lid edema (60.7%), ophthalmoplegia (57.3%), loss of vision (53.7%), facial edema (34.7%), and ptosis (4 studies, 72.7%). Similar signs and symptoms are also seen in study by Sen et al<sup>15</sup>.

CNS involvement has been documented in 37% of the cases of Covid-19-associated ROCM<sup>18</sup> and 21% (573 of 2669) patients had CNS involvement seen in collaborative study. In our study 7.1%(3 of 42) of patients had cerebral involvement and 1 patient had internal

carotid artery thrombosis.

#### Diagnosis and imaging:

Diagnostic nasal endoscopy (DNE) allows a quick inspection and sampling from the nasal cavity<sup>15</sup>. Rapid diagnosis of mucormycosis can be achieved with direct microscopy using KOH wet mounts and with calcofluor white<sup>15</sup>, and this was done in 88.8% by Sen et al. In our study following DNE, direct microscopy was done in all patients. The patients with negative swab but with clinical and radiological evidence of ROCM, turned positive with direct sinus sample obtained during debridement.

Even though contrast-enhanced MRI is the imaging modality of choice in other studies<sup>15</sup>, contrast enhanced CT scan was also preferred in some studies<sup>22</sup> and done in most of the patients in our study as well. Because it is relatively faster, can be used for even unstable patients and also cost effective. MRI was preferred in cases where extensive orbital and CNS involvement was suspected. In a retrospective analysis<sup>22</sup> of 34 patients, 18 patient's orbital changes on CT, 3 patients had intracranial disease and 2 had cavernous sinus thrombosis. Similarly in our study also 30 had orbital cellulitis and 26 had EOM involvement, 3 had cerebral involvement like brain abscess, 3 had cavernous sinus thrombosis and 1 had internal carotid artery thrombosis.

#### MANAGEMENT:

An early diagnosis with a prompt, well-coordinated, multidisciplinary approach has been vital to save both the life and sight of the patient. Microbiological diagnosis, control of the underlying systemic condition, and antimicrobial therapy with debridement of necrotic tissue have remained the mainstay of management of rhino-orbital mucormycosis over the years. Exenteration may not be absolutely necessary if well managed<sup>23</sup>.

Brunet and Rammaert[8] have recommended liposomal amphotericin B as the first-line therapy for the treatment of mucormycosis along with surgery whenever possible<sup>24</sup>. In our study intravenous AMB was given in all the patients, where 40 received liposomal form and 2 patients received deoxycholate form. 35.8% was given combined therapy with Posaconazole because of non-availability of AMB initially. In other literature, it has been used in 88% of the patients<sup>18</sup> in one study and 73% of the patients<sup>15</sup> in another because of the logistic reasons.

A study from India has shown Posaconazole to be highly effective as salvage therapy for ROCM with life salvage and complete resolution in 67% of the patients<sup>26</sup>. However, there is no data supporting the use of combination therapy and has not been recommended in any of the major treatment guidelines<sup>25,26,27</sup>.

Intraorbital injection of amphotericin B deoxycholate in a concentration of 3.5 mg/mL has shown to be effective for life and eye salvage in certain case reports<sup>29,30,31</sup>. In our study 11 patients in a stage 2 were given retrobulbar liposomal AMB along with systemic AMB and sinus debridement. These patients had orbital cellulitis with EOM involvement on imaging. This was considered mainly as salvage procedure in patients with good vision and recovering patients following sinus debridement. Direct infiltration of the drug into the orbit helps in higher levels of drug reaching the affected areas.<sup>12,15,16,17</sup>. On follow up all these patients were doing well with residual EOM restriction on examination with preserved vision. We observed minimal redness and chemosis in all patients but eventually resolved in few days.

PNS debridement serves both diagnostic and therapeutic purpose<sup>15</sup>. In our study sinus debridement was performed in 78.6% of patients. Whereas in study by Sen et al<sup>15</sup> PNS debridement was performed in 67% overall and 27 of 34 patients underwent same in a study by Nithyanandam et al<sup>22</sup>.

Orbital exenteration was done in 4 patients in our study and was

performed simultaneously with FESS in all. In all these 4 cases, involved eye had no visual potential, with diffuse orbital involvement and along with that one had disease limited to the orbit with minimal extension to the cavernous sinus. Similar criteria are also followed in other studies where 9 of 34<sup>22</sup> patients and 37%<sup>15</sup> required orbital exenteration with extensive sinus debridement. The decision lies with the treating physician because there is no firm consensus regarding the indications and timing of orbital exenteration. No significant difference has been found in survival with or without orbital exenteration<sup>33,34</sup>.

### Conclusion

Covid-19 associated ROCM predominantly affects middle aged and older males with majority of the patient's developing onset of ROCM symptoms between day 20 and day 30 from the diagnosis of Covid-19. Delayed presentation can occur up to 2 months. Post Covid-19 follow up for a period of 2 months is recommended, possibly in the setting of a formal post Covid-19 follow up clinic. DM and corticosteroids are consistent, important, and independent risk factors for Covid-19 associated ROCM. Glycemic control is of paramount importance in a patient with Covid-19.

Periorbital and facial pain and edema, stuffiness, proptosis, ptosis, and diminution of vision are the common symptoms and signs. The common clinical symptoms and signs should be recognized promptly, followed by an expedited diagnosis by diagnostic nasal endoscopy, an endoscopy guided nasal swab for microbiological evaluation and nasal microbiopsy for rapid histopathology. Contrast enhanced MRI is the imaging modality of choice, in the absence of which a CT scan is suggested. ROCM should be staged, triaged, and managed by a team of doctors with various specialities. Covid-19 associated ROCM needs to be tackled as aggressively as the disease itself with a concerted effort from multidisciplinary medical teams and the government. Accepting the facts that Indians inherently have a higher prevalence of DM, the tropical climate predisposes to mucormycosis, and moderate to severe cases of Covid-19 will need corticosteroids for life salvage, we can expect to continue to see ROCM in the days to come. Logistical preparedness to ensure adequate supply of amphotericin B and creation of well equipped, dedicated regional hubs of multidisciplinary ROCM management centres, each connected to spokes of COVID-19-treatment facilities, may help salvage the life and eyes of these patients.

### Acknowledgments

#### Declaration of patient consent

patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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