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A REAL-WORLD STUDY OF COVID-19 ASSOCIATED RHINO-ORBITAL-CEREBRAL MUCORMYCOSIS (ROCM)

Dr. Sudebi Roy[1], Dr. Varsha Singh[2], Dr. Radhika Paranjpe[3], Dr. (Col) O.k. Radhakrishnan[4], *Dr. Varsha Manade[5]

1. Junior Resident, Department of Ophthalmology, Dr. D.Y. Patil Medical College, Hospital and Research Centre, Dr. D.Y. Patil Vidyapeeth, Pune, Maharashtra, India
2. Junior Resident, Department of Ophthalmology, Dr. D.Y. Patil Medical College, Hospital and Research Centre, Dr. D.Y. Patil Vidyapeeth, Pune, Maharashtra, India
3. Associate Professor, Department of Ophthalmology, Dr. D.Y. Patil Medical College, Hospital and Research Centre, Dr. D.Y. Patil Vidyapeeth, Pune, Maharashtra, India
4. Professor, Department of Ophthalmology, Dr. D.Y. Patil Medical College, Hospital and Research Centre, Dr. D.Y. Patil Vidyapeeth, Pune, Maharashtra, India
5. Assistant Professor, Department of Ophthalmology, Dr. D.Y. Patil Medical College, Hospital and Research Centre, Dr. D.Y. Patil Vidyapeeth, Pune, Maharashtra, India

Corresponding author:

Dr. Varsha Singh, Department of Ophthalmology, Dr. D. Y. Patil Medical College, Hospital and Research Centre, Dr. D. Y. Patil Vidyapeeth, Pune, Maharashtra, India
Email: roysudebi@gmail.com

ABSTRACT

Background: Mucormycosis is an invasive fungal illness associated strongly with COVID-19 and found lethal in many cases. Rhino-orbital-cerebral mucormycosis (ROCM) is the most common mucormycosis infection. The worldwide disease concern for ROCM has grown recently following the spike in incidence during the COVID-19 pandemic. This study shows the clinical characteristics and therapeutic outcomes of patients with ROCM.

Material and Methods: A retrospective observational study on 77 patients with ROCM was performed between March 2021 and June 2021 at a tertiary care hospital. This study only included patients who were microbiologically tested and conformed for ROCM. Numerous clinal diagnosis tests were performed to examine vision, paralysis of the eye muscles, eyeball protrusion, orbital swelling, extra-ocular movements, fundus examination, and extent of orbital involvement on MRI.

Results: This study of 77 patients, showed a higher ratio of male patients (74.04%) for ROCM cases. The average age of all patients was 49.14 years, and 62 (80.52%) were detected for COVID in the past. These patients were hospitalised for a minimum of 1 day to a maximum of 127 days, with an average of 40.48 days. Type 2 diabetes was found in 40 (52%) cases, while hypertension was the second most common comorbid condition observed in 21 (27.27%) cases. Amphotericin B injection was the preferred therapeutic drug shown in this study for 44 patients out of 56 who used any medication. Exenteration was also shown as a possible therapy that was performed on 53.25% of patients.

Conclusion: ROCM is more prevalent in diabetic male patients of 50 years of age infected by SARS-CoV2 who have had a later bacterial or fungal illness exacerbated by SARS-CoV2. Amphotericin B injection and exenteration could be the best possible therapeutic solution for treating ROCM.

Keywords: ROCM, SARS-CoV2, Mucormycosis

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INTRODUCTION

Mucormycosis, also known as zygomycosis, is a lethal fungal condition. However, it affects a smaller sample of the population. It is caused by a group of moulds called mucormycetes. These fungi are widespread and can be found in soil and other decomposing organic matter including leaves, compost piles, and rotting wood. They feed on the dead organic matter[1]. Mucormycosis is contracted when people come into physical contact with the spores of the fungus that are found in the environment. After breathing spores, a person may develop infections within the lungs or sinuses. These forms of mucormycosis are more infectious to those with pre-existing health conditions or who have been prescribed drugs that lessen the body's ability to defend itself against infectious agents[2,3].

Types of Mucormycosis

1) Rhinocerebral (sinus and brain) mucormycosis (RCM): Mucormycosis of the sinuses is a fungal infection that can extend or spread all the way to the brain. This is especially common among patients with uncontrolled diabetes or those who have received a kidney transplant[4,5].
2) Pulmonary (lung) mucormycosis: It is the form of mucormycosis that is found most frequently among individuals who have been diagnosed with cancer or undergone a transplant of an organ or stem cells.
3) Gastrointestinal mucormycosis: It affects children more than adults. Infants less than one month old who have received antibiotics, surgery, or drugs that reduce the body's capacity to fight viruses and illness are at danger[6,7].
4) Cutaneous (skin) mucormycosis: It develops when fungus enters the body through a skin break. This infection can develop after a burn, scrape, cut, surgery, or any other type of skin trauma that breaks the skin's protective barrier. Individuals with strong immune systems are likely to suffer from this form.
5) Disseminated mucormycosis: When an infection spreads through the bloodstream to another portion of the body, it is called disseminated mucormycosis. This infection most frequently affects the brain, but it can also cause damage to other organs and tissues, including the spleen, the heart, and the skin.

In this study, we examined the clinical aspects of Rhino-orbital-cerebral-mucormycosis (ROCM), also known as orbital zygomycosis, a subtype of Rhinocerebral mucormycosis. ROCM is described as the manifestation of pathologic symptoms in the orbit produced by fungi as Mucorales, most often by the species Rhizopus oryzae. ROCM often causes visual loss, ptosis, diplopia, and external ophthalmoplegia in immunocompromised hosts. It was also found that if no therapy is provided to the patients, ROCM can cause abrupt visual loss as well as death[8,9]. Exenteration, an invasive surgical procedure, has long been considered the gold standard treatment for rhino-orbital mucormycosis that infiltrates the orbit. This is because exenteration removes all the infected tissue from the affected area. Exenteration of the orbital cavity involves the removal of all the contents of the orbital cavity, including the globe, periorbita, and retrobulbar structures. However, it is not necessary to perform an orbital exenteration on every orbital disease patient. The decision to exenterate must be based on the condition of the underlying immunocompromised state, the timing of the initiation of competent medical care, the severity of predisposing factors, the amount and aggressiveness of ocular illness at presentation, and the response to the initial treatment.

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Earlier, orbital exenteration was considered the last medical solution for the treatment of rhino orbital mucormycosis. Moreover, it produces oculofacial deformity and psychological suffering, and thus it is now reserved for patients with significant orbital involvement[10,11]. The orbital mucormycosis treatment by transcutaneous retrobulbar amphotericin B (TRAMB) injection has been characterised as a successful solution with minimum invasion and effective in sparing the eye[12]. Patients with early orbital involvement were administered retrobulbar injections of 1 ml of amphotericin B deoxycholate at a concentration of 3.5 mg/ml. These injections are preceded by an antecedent retrobulbar injection of anaesthesia (2% lidocaine and 0.5% Marcaine in a 1:1 ratio[13]. Exenteration is considered the most challenging option to proceed with the patients suffering from ocular mucormycosis. This medical procedure is a life-saving strategy, but unfortunately, it requires mutilating surgery. In addition, younger patients have a higher chance of survival without undergoing exenteration. This raised a concern about using this medical treatment on younger patients who further depend on the likelihood of irreversible deformity. Moreover, patients with ocular mucormycosis are treated with antifungals (Amphotericin B) and less likely with hyperbaric oxygen[14].

The purpose of this study was to determine the patient prevalence, demographic features, risk factors, associated symptoms and signs, impact of comorbidities, and drugs used to treat rhino ocular cerebral mucormycosis linked with COVID-19. With the help of the information concluded from this study, doctors may be able to spot the early signs of ROCM and maintain a high level of suspicion when they see typical symptoms and signs. This research will aid in assessing the scope of this difficult medical issue on a nationwide scale, optimising COVID-19-care recommendations to limit risk exposure, developing regional multispecialty centres and teams for ROCM-care, and expanding antifungal medication availability. Furthermore, the study will contribute to the development of post-COVID-19 follow-up methods.

MATERIALS AND METHODS

This retrospective observational study included 77 patients diagnosed with rhino orbital cerebral mucormycosis between March 2021 and June 2021 at Dr. D.Y. Patil Medical College and Research Center in Pimpri, Pune, western Maharashtra, India. The objectives of this study were to measure the epidemiology, prevalence, and risk factors and therapeutic solutions associated with microbiologically proven cases of rhino-orbital cerebral mucormycosis during the COVID-19 pandemic.

Patients involved in this study have provided their consent before the trial was conducted, and an ethical commission approved the experiments.

Inclusion criteria

- Male and female patients.
- Patients diagnosed with Rhino orbital cerebral Mucormycosis (ROCM).
- Patients having smear and/or histopathological evidence of ROCM were only included.
- Patients having a history of COVID-19.

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Exclusion criteria

- Patients with other causes of proptosis.
- Patients with mucormycosis that is not ROCM.
- Patients who do not have smear or histological evidence of ROCM.
- Presence of any other clinically significant disease or laboratory findings that in the investigator's opinion may affect the study outcomes or continued participation of patient in the study.
- Participation in another study at the same time or within 4 weeks of the screening visit.

Methodology

The study followed clinical diagnosis based on the orbital involvement that is examined under various headers mentioned below:

1. Visual acuity – sharpness of vision was diagnosed.
2. Ophthalmoplegia (Yes/No) – tests were conducted to detect paralysis of the eye muscles.
3. Ptosis (Yes/No) - the condition in which the top eyelid droops.
4. Proptosis (Yes/No) - eyeball protrusion from orbit.
5. Orbital Swelling (Yes/No) – swelling in orbit of the eyeball.
6. Extra-ocular movements - examines the ocular muscles' function.
7. Anterior segment and Fundus Examination - a diagnostic method that uses mydriatic eye drops to dilate or widen the pupil to acquire a better view of the fundus of the eye.
8. Extent of orbital involvement on MRI - removal of the complete globe and its surrounding tissues, including muscles, fat, nerves, and eyelids, by a surgical surgery, is known as exenteration.
9. Treatment - medical care for an illness or injury given to a patient.
10. Complications of Exenteration - a secondary disease or ailment that exacerbates an already existing one.
11. Contraindications of Exenteration – a medicine, operation, or surgery should not be utilized 3 during exenteration since it may be harmful to the individual.
12. Condition at the time of discharge - the patient's health status at the time of discharge.

A case of mucormycosis was defined as one who had clinical and radiological features consistent with mucormycosis along with demonstration of the fungus in tissue via KOH mount/culture/histopathological examination (HPE). Data pertaining to epidemiology, risk factors, and clinico-radiological features were analysed using the percentage of total cases. Direct examination of biopsy or aspirated material was performed using 10% potassium hydroxide (KOH) or calcofluor white (CFW) staining solution. This study also focused on the optic nerve and the optic chiasm in patients who have lost vision owing to a visual pathway problem due to ROCM. In this condition, magnetic resonance imaging (MRI) was used for examination as it allows superior soft-tissue differentiation of intracranial anatomy.

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RESULTS

The data of 77 patients with COVID-19-associated ROCM from Dr. D.Y. Patil Medical College, Hospital and Research Centre, Pimpri, Pune was collected and examined. The demographics of the patients were used to comprehend the variance among the patients. The mean age of the total population considered was 49.41 years. The majority of mucormycosis cases in underdeveloped nations are found among those with poorly managed diabetes or in immune-compromised individuals, and it often causes significant morbidity and mortality. ROCM is the most prevalent clinical manifestation among patients with diabetes, although lung involvement is rare in this disease. In this investigation, the rhino-orbital area was the most critical location of mucormycosis. Early presentation, rapid diagnosis, and urgent start of therapy with liposomal Amphotericin B and surgical debridement can result in a favourable outcome. However, in all conditions, patients require continuous follow-up and monitoring.

Table 1 displays all the demographic information for all the patients, showing the 49.41 years average age, with a minimum of 10 years and a maximum of 79 years. Males' population has outnumbered the females, with 57 males and 20 females, which implies males accounted for approximately 77.04 % of total patients. Furthermore, it displays the average hospitalization duration for all patients ≈ 40 days, with 1 being the shortest and 127 days being the longest hospitalization period. This study addressed surgery or exenteration of patients. The data was not strongly conclusive where 41 (53.24%) patients required surgery while the remaining 36 (46.75%) did not undergo the surgery. Accounting for the prior COVID condition of patients, 62 were positive, accounting for 80% of the total population, while the remaining 15 (20%) were COVID negative. In this study, it was found that 67 (87.01%) of patients survived well after complete treatment at the time of discharge, however, the remaining 10 (13%) patients died.

Table 1. Summary Statistics of patient's demographics.

	PARAMETER	COUNT (N= 77)
AGE (YEARS)	N	75
	Mean	49.41
	Standard Deviation	12.13
	Minimum	10
	Maximum	79
GENDER	Male	57 (74.04 %)
	Female	20 (25.97 %)
NUMBER DAYS OF HOSPITALIZATION	N	65
	Mean	40.48
	Standard Deviation	24.36
	Minimum	1.00
	Maximum	127.00
SURGERY (EXENTRATION)	Yes	41 (53.25 %)
	No	36 (46.75 %)
PREVIOUS CASE OF COVID	Yes	62 (80.52 %)
	No	15 (19.48 %)

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CURRENT COVID STATUS	Positive	6 (7.79 %)
	Negative	61 (79.22 %)
	Not Applicable (Dead)	10 (12.99 %)
STATUS DURING DISCHARGE	Alive	67 (87.01 %)
	Death	10 (12.99 %)

Table 2 shows the summary statistics of other medical problems diagnosed in the patients. It was observed that 39 (50.9%) of patients suffered from multiple diseases at the same time. Type-2 Diabetes Mellitus was found as the most diagnosed disease, with 40 (52%) patients. The second most common disease was hypertension, found in 21 (27.27%) patients, while the headache condition was followed by hypertension in 10 (13%) of patients.

Table 2. Summary statistics of other medical condition in addition to ROCM.

Row Labels	Count of Other medical problem
Breathlessness	2
Corneal sensation intact	1
Decrease in the sensation on right side	1
Dental pain	3
Drowsy	1
Facial pain and swelling	9
Fever	2
Fungal element seen	1
Headache	11
Hypertension	21
Invasive sinusitis	2
Joint pain	1
Maxillary sinus/ swelling and pain	3
Mild deviation of mouth	2
Nasal discharge	1
Pain in nose	1
Periorbital swelling and pain	2
Pneumonia	3
Pregnant	1
Psychitric Rx	1
Rhino eistal Mucormycosis	1
Seizure	1
Stroke	1
Thyroid	3
Type-2 Diabetes Mellitus	40

Statistical significance was found for the two most common other medical conditions in the ROCM patients: (1) Type 2 Diabetes and (2) Hypertension. It has already been observed that 52% of patients were diagnosed with type 2 diabetes and 27.27% with hypertension. Concluding that these two medical conditions are common with ROCM, a statistical test was

performed as shown in Table 3. Here, the null hypothesis (Ho) was treated as 50% of patients had Type 2 diabetes, hypertension, or any of the two conditions. This implies the following:

$$H_o: \mu = 0.05$$
$$H_A: \mu \neq 0.05$$

One sample t-test was conducted, and the p-value shown in Table 3 indicated the acceptance of the null hypothesis (Ho) at a 95% confidence level in the case of type 2 diabetes and any of two conditions where the p-value > 0.05. This indicates that the chances of type 2 diabetes are 50% for the ROCM patients and that is statistically significant.

Table 3. Statistical Test on other major medical conditions for ROCM patients

Statistical Parameters	Type 2 Diabetes	Hypertension	Any of two Condition
Mean	0.519480519	0.272727273	0.571429
Standard Deviation	0.502896599	0.448282208	0.498117
Count	77	77	77
Standard Error of Mean	0.057310386	0.051086499	0.056766
Degree of Freedom	76	76	76
Hypothesized Mean	0.5	0.5	0.5
T-statistic	0.339912548	4.448782605	1.258306
p value	0.367430013	1.4544E-05	0.106067

Table 3 indicates the number of patients with the number of drugs given to them for the treatment of rhino orbital cerebral mucormycosis. Here, 56 patients were given medication treatment, and it was observed that 29 (52%) of them received a single medicine treatment. There were 16 (28.57%) patients that had been medicated with 2 medicines at a time, while 9 (17.3%) were on 3 medicines. Overall, 27 (48%) of the patients were treated with more than one drug. This means that both single-drug and multidrug approaches were used on about the same number of patients.

Table 4: Number of different drugs administered

Number of Drugs	Number of Patients
1	29
2	16
3	9
4	2

Figure 1 indicates the frequency of specific drugs administrated to the rhino orbital cerebral mucormycosis patients. It clearly showed that Amphotericin B commonly used to prevent serious fungal infections throughout the body, was found as the most effective drug against rhino orbital cerebral mucormycosis. It was administered to 44 (78.57%) patients who constituted a large proportion of the population. Posaconazole, another antifungal drug, was the second most frequently used medicine, accounting for 15 (27%) patients.

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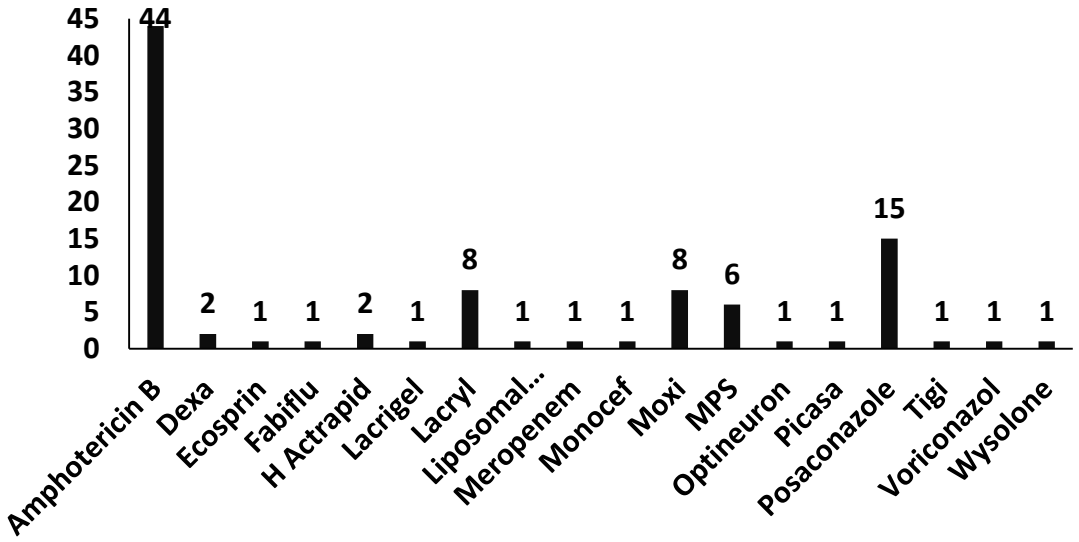

Figure 1. Type of drugs administered with the number of patients.

DISCUSSION

Mucormycosis is an angioinvasive, opportunistic fungal infection that can be exacerbated by uncontrolled diabetes, hypertension, corticosteroids, immunosuppressive therapy, primary or secondary immunodeficiency, haematological malignancies, haematological stem cell transplantation, solid organ malignancies, solid organ transplantation, and iron overload[15]. Other less common risk factors include intravenous drug use, infection with the human immunodeficiency virus, renal failure, liver problems, chronic alcoholism, and undernutrition in children and infants. Low birth weight and malnutrition in children and adolescents are also risk factors. According to studies conducted on the Indian population, post-pulmonary tuberculosis and chronic renal sickness were found as two risk factors that are on the rise[16,17]. It has the potential to affect the nasal cavity, the sinuses, the orbit, the central nervous system, the lungs, the gastrointestinal tract, the skin, the jawbones, the heart, the kidneys, and the mediastinum. ROCM is the most common symptom of mucormycosis, accounting for roughly two-thirds (2/3rd) of all cases[9,18]. It starts with the inhalation of the spores, tissue invasion, thrombosis, and necrosis spread from the nose to the peripheral nervous system (PNS), the central nervous system (CNS), and the orbit. Prior to the pandemic, the prevalence of the disease worldwide was between 0.005-1.7 cases per million people. India has historically had a significantly higher prevalence, almost 80 times that of the rest of the world, which is 0.14 cases per 1000 people[19–21]. It was shown that there is an 8% possibility that the COVID-19 infection might exacerbate a later bacterial or fungal illness, with aspergillosis and candida being the fungi that are most frequently observed[22,23]. An increase in cases of mucormycosis has been fairly connected with the COVID-19 wave. Other risk factors linked with the increased prevalence of COVID-19-associated ROCM include the use of immunosuppressants, concurrent comorbidities, unsanitary procedures, and prolonged hospital stays with the possibility of nosocomial infection[19]. The main objective of this study was to get a deeper understanding of ROCM in COVID-19 patients so that both therapy and diagnosis may be improved.

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In this study, male patients showed higher susceptibility to rhino orbital cerebral mucormycosis than female patients; out of 77 patients, 57 (74.04%) were male, 20 (25.97%) were female. This observation was consistent with findings from previous investigations. Mrittika et al. found similar results in a survey of 2826 people, infected with the ROCM, where it was observed a male preponderance with 71% of cases, while 29% of cases were females[24]. Another retrospective study based on Coronavirus Disease - 2019 associated Rhino-Orbital-Cerebral Mucormycosis (CAM) showed similar results with 62% males out of total 50 patients that accounts 31 male patients[25]. Pakdel F. et al. conducted a three-month cross-sectional study in Iran between April and September 2020 on patients with biopsy-proven mucormycosis and an RT-PCR-confirmed COVID-19 test. They studied 15 cases and found that 66% of them were male[26].

In this study, the patients with rhino orbital cerebral mucormycosis had a mean age of 49.41 years (range 10 to 79 years). Mritikka et al. found that most patients with ROCM come from the states of Gujarat (22%) and Maharashtra (21%), and that their average age was 51.9 years[24]. Another study examined clinical and imaging data from CA-ROCM patients between December 2020 and June 2021, diagnosed that all patients had microbiologically or histologically proven sino-nasal mucormycosis, and their mean age was 49.5 years (range 28 – 70 years)[25]. On a similar note, a study enrolled 50 patients for the purpose of analysing clinical characteristics, contributing factors, and outcome of patients with coronavirus disease 2019 (COVID19) associated mucormycosis (CAM). Here again, the mean age was 52 years, with a range of 14 to 71 years[26]. This showed that mean age of patients with mucormycosis was found ≈ 50 yrs in various surveys including our study.

Our study also determined the correlation between mucormycosis with diabetes and hypertension and found that more than half of the patients (40) had diabetes ($p > 0.05$) while 27.27% had hypertension ($p < 0.05$) out of a total of 77 patients. Mritikka et al. found that diabetic mellitus (DM) was diagnosed in 78% of the cases out of 2826 participants in their investigation[24]. In another study where 50 individuals were enrolled with verified SARS-CoV-2 positive RT-PCR test and/or typical lung imaging characteristics of COVID-19 infection, diabetes was observed as the most prevalent comorbid condition. Here, seven individuals were diagnosed with stage I disease, 18 with stage II disease, and 25 with stage III disease. Using Pearson's correlation, the stage of illness demonstrated a positive statistical association with HbA1c values[25]. An earlier study found that 13 of the 15 patients (86.66%) had diabetes mellitus, and 7 (%) had gone through intravenous corticosteroid therapy[26].

In our study, the average hospitalisation days for those with ROCM was 40 days. Padkel et al. studied the demographic data of 15 patients and determined that the average hospitalisation days for patients with COVID-19 associated mucormycosis was 30 days, with a minimum of 3 days and a maximum of 90 days[26]. Another clinical study indicated that the average duration of admission for diabetic and nondiabetic patients with Rhino orbital cerebral mucormycosis was 37.81 and 29.20 days, respectively[27]. This showed that the average hospitalisation for ROCM patients was 30–40 days, including the finding shown in this study.

Amphotericin B is the most commonly used drug for the treatment of ROCM in patients, and in this study, it was prescribed to 44 patients, occasionally in combination with other antifungal drugs. Amphotericin alone contributed 70% of the 63 patients who were on any

medication, while orbital exenteration was performed on 41 patients, 53.25% of a total of 77 patients. The mortality rate was 13% at the early COVID stage, but it was reduced to 0% at the time of discharge. Earlier studies also indicated a reduction in the death rate following therapy, which complemented our findings. In one study, intravenous Amphotericin B was utilised in 73% of cases for 2826 patients, whereas orbital exenteration was performed in 17% of the total patients. This study found a 14% fatality rate at the final follow-up[24]. Yadav et al. found that despite antifungal therapy and surgical treatments, the death rate was as high as 47% of 15 patients. Therefore, considering the severity and virulence of the illness, rapid identification and antifungal medication were strongly advised to reduce death. They observed that patients who got combination antifungal therapy (8 patients) survived[25].

CONCLUSION

This study showed the clinical analysis of rhino cerebral orbital mucormycosis (ROCM) for 77 patients with COVID and non-COVID conditions. Male populations were found more prone to ROCM compared to females, but the overall mean age was ≈ 50 Yrs. This study also showed that 80% of the patients had been detected with COVID in the past. This concludes the high likelihood of ROCM among the male population ≈ 50 yrs of age if they infected with COVID. ROCM was found to have a strong comorbid condition for type 2 diabetes patients, followed by hypertension. This clearly indicates that these two diseases enhance the chances of ROCM. On the therapy side, this study concludes that Amphotericin B was the most administered drug to ROCM patients. Moreover, exenteration surgery was also performed on 50% of the total patient population. Overall, this study demonstrated and discussed the clinical observations for ROCM patients that could be further used to design effective medical treatment to reduce the mortality rate.

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