International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

Epidemiology, Risk Factors, and Clinical Profile of COVID-19 Associated Mucormycosis: Lessons Learned and Future Strategies

Dr. Tejas Gopalkrishnan[1], Dr. Poojan Thakkar[2], Dr. Shoyeb Shaikh[3], Dr. Rahul Gupta[4], Dr. RG Aiyer[5], Dr. Saransh Narang[6], Dr. Chetna Hirani[7], Dr. Kajal Patel[8], Dr. Preksha Jain[9]

Abstract: ***This comprehensive study delves into the epidemiological patterns, risk factors, and clinical manifestations of COVID-19 Associated Mucormycosis CAMCR during the pandemic, shedding light on critical insights and lessons for future healthcare strategies. Analyzing data from a single institution, predominantly from Gujarat, India, this research underscores the prominent role of steroids in CAMCR development, emphasizing the need for prudent steroid usage and diligent glycemic control. Additionally, it explores potential contributing factors such as oxygen therapy, tocilizumab, remdesivir, and broad-spectrum antibiotics. The study highlights the necessity of strengthened primary healthcare, awareness campaigns, and rigorous monitoring to prevent this devastating condition. Through a multidisciplinary approach, this research aims to inform healthcare practitioners and policymakers about CAMCRs complexities and provide a roadmap for prevention and management in future healthcare crises.***

Keywords: Epidemiology, COVID-19 Associated Mucormycosis, Risk Factors, Clinical Profile, Steroid Usage, Glycemic Control, Oxygen Therapy, Primary Healthcare, Awareness Campaigns, Multidisciplinary Approach

1. Introduction

Coronavirus Disease 2019 (COVID-19) caused by the novel SARS-CoV-2 took its origin in December 2019 in Wuhan, China. The next couple of months observed its global spread with it taking the form of a pandemic. The attempts at recovering from the effects brought by this dreadful infection were only complicated further by the sudden upsurge of secondary infections. The state of Gujarat along with isolated parts of western and northern India witnessed an explosion in the cases of Mucormycosis, to the extent that it was declared an epidemic **[1]**. In this article we aim to study the epidemiology, risk factors, and clinical profile of this debilitating disease.

2. Methods

The design of the study was non interventional, observational, analytical and cross sectional. Patients meeting the inclusion criteria and admitted in the months of May and June 2021 were identified and included in the study. The ethics committee approval was obtained. Patients diagnosed with ROCM on histopathology and/or KOH mount and/or culture report and/or MRI (in absence of a laboratory confirmation)AND having a past history of COVID-19 diagnosed using RT-PCR and/or RAT and/or HRCT(in only symptomatic cases) within three months of onset of symptoms of mucormycosis were considered. Amongst these patients, those over 18 years of age and consenting to participate were included. Data was collected by a combination of patient interviews and a review of their COVID-19 - ROCM treatment records. Subjects were interviewed on a structured questionnaire using google forms. The data was analysed for rates, ratios and proportions using google sheets. The cases were staged for the severity of the disease on the basis of MRI reports using the staging system proposed by Honavar. **[2]**

The observed trends were compared with previously published studies to draw useful inferences.

3. Results

Demographics

In the months of May and June 2021, our institution provided care to 152 patients of Rhino-Orbito-Cerebral Mucormycosis (ROCM). The data of these patients was collected and analysed. The majority of the patients were from Gujarat (94%, n=143), rest were from Rajasthan (n=8), Madhya Pradesh (n=1). The median age of the patients was 50.5 years (range, 27-75 years). A male preponderance was observed, with males at least twice as commonly affected as females (ratio, 2.2:1).

COVID-19 Correlation

Positivity

Patients tested positive for COVID-19 on RTPCR, RAT or HRCT were considered. Of these, 83.6% (n=127) had a positive history of COVID-19 or were tested positive at the time of admission for mucormycosis. Rest were negative but had a HRCT report suggestive of COVID-19 pneumonia.

Over three-fourths of our patients (87%, n=111) were diagnosed as COVID-19 positive either on the basis of RTPCR, RAT, or a combination of multiple diagnostic modalities.The rest of the patients were diagnosed as COVID-19 positive and received treatment for, solely on the basis of HRCT.

Treatment center

14.5% had obtained home based treatment, 73.7% received treatment at a hospital for COVID-19. Of those hospitalized, 77.7% had received care from private hospitals and 22.3% from government funded hospitals.

HRCT Chest score

The HRCT Chest score was available for 104 patients. The median hrct score according to the chest ct scoring (out of 25) was 12 ± 5.4 and according to CT-SS scoring (out of 40) was 16 ± 9.3.

Steroid

More than one-half (56%, n=85) of the patients had received steroids in either oral or parenteral form, as a part of treatment for COVID-19. 90.59% received them at a hospital while 9.41% received them at home. Of the total patients who had received steroids, 86% presented with hyperglycemia on admission for mucormycosis, of which 45 % patients did not have an established diagnosis of diabetes. 58.82% of who received steroids also received oxygen and 41.18% of who received steroids did not receive oxygen. Majority of our patients were treated for COVID-19 at private hospitals, of which 75% had received steroids. However, considering oxygen requirement as a marker of severity, only two-thirds of these patients received it along with steroids.

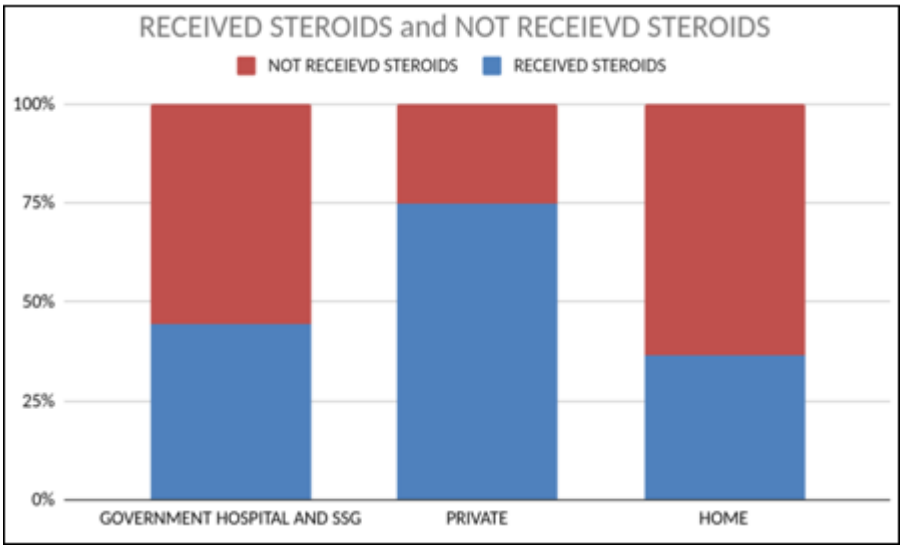

Figure 1

Oxygen

46.7% (n=71) patients had received oxygen via various methods during their hospitalisation for the treatment of COVID-19.

Remdesivir

42.1% patients (n=64) had received Remdesivir. The median dose was 600mg.

Tocilizumab

Only two patients had received Tocilizumab.

Clinical Presentation and Features

The symptoms were categorised into five categories namely, ocular, oral, nasal, facial, and cerebral. Table I shows the frequency of symptoms for individual categories.

	Ocular	Facial	Oral	Cerebral	Nasal
(n)	65	42	37	27	12

The most frequently observed complaints were periorbital swelling, facial pain, headache, toothache and pain in the eyes.

The median duration of symptoms at presentation was 7 days.

Table II

Category	Symptom	n
Ocular	Periorbital swelling	37
	Eye pain	17
	Diminution of vision	10
	watering	6
	ptosis	5
	Double vision	4
	Blurring of vision	3
	Lid weakness	1
Nasal	Nasal blockage	5
	Bleeding from the nose	3
	Nasal discharge	3
	Swelling over nose	2
	Nasal pain	1
	Bad smell	1
Oral	toothache	19
	Tooth mobility	7
	Oral ulcer	5
	Palatine pain	3
	Jaw edema	3
	Blackish lesion	2
Facial	Facial pain	28
	Facial swelling	14
	Facial numbness	11
Headache		26
Dizziness		1

Time interval between diagnoses

The median interval of time between the diagnosis of COVID-19 and onset of symptoms of mucormycosis was 14 ± 12 days (range, 0 - 57 days) (n= 84). Approximately 18% of patients were diagnosed with ROCM within 7 days of diagnosis of COVID-19 and 80% within 14 days.

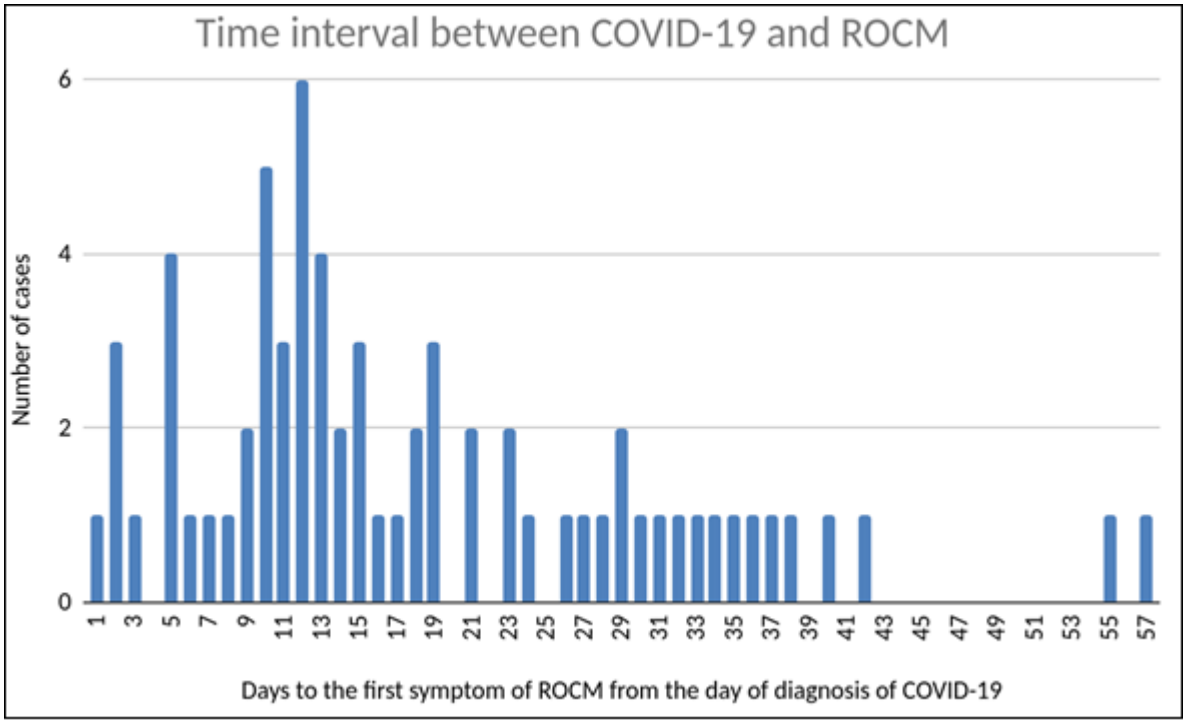

Figure 2

Diagnosis of COVID-19 associated ROCM

Patients who were positive for or had a HRCT chest report suggestive of COVID-19 pneumonia were further diagnosed for Mucormycosis on the basis of histo-pathology report, potassium hydroxide mount studies, culture reports or MRI findings. 90% of patients were diagnosed on the basis of histo-pathology report. KOH mount was done for 41% patients. Culture was done for less than 10% of patients. In cases where tissue sampling was negative for invasive fungal disease, robust clinico-radiological evidence guided the management according to ROCM protocol.

Anatomical and Radiological Involvement

The magnetic resonance imaging reports of the patients were analysed to study the involvement of various structures. Bilateral involvement of the sinuses was more frequent than unilateral involvement, with bilateral maxillary sinuses being involved most frequently. In cases of unilateral involvement, the most common sinus affected was left frontal. In cases with orbital involvement the most common sinus involved was bilateral maxillary. In the orbit, unilaterality(left > right) was more common than bilaterality. Pansinusitis was seen in 17% (n=21). 15% of patients with orbital involvement and 3.7% of patients with CNS involvement had pansinusitis.

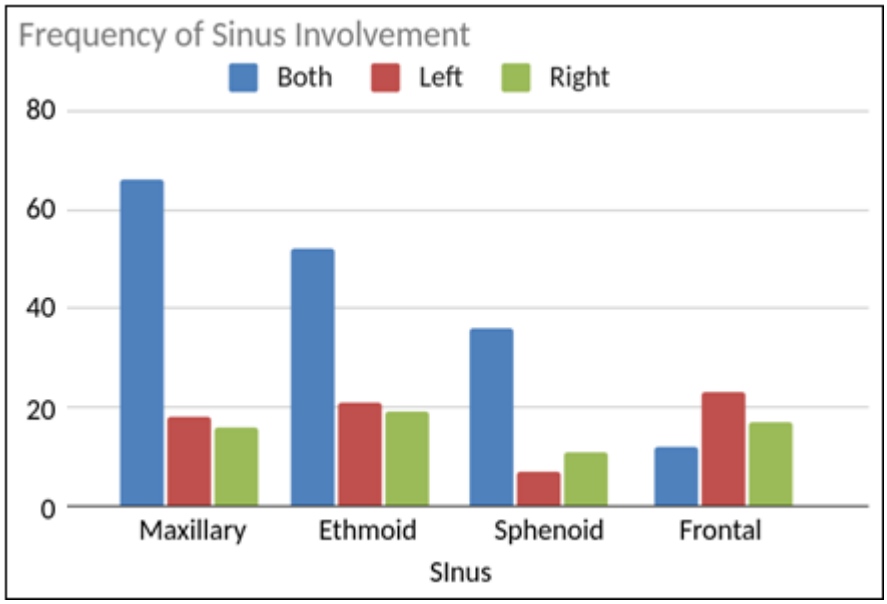

Figure 3

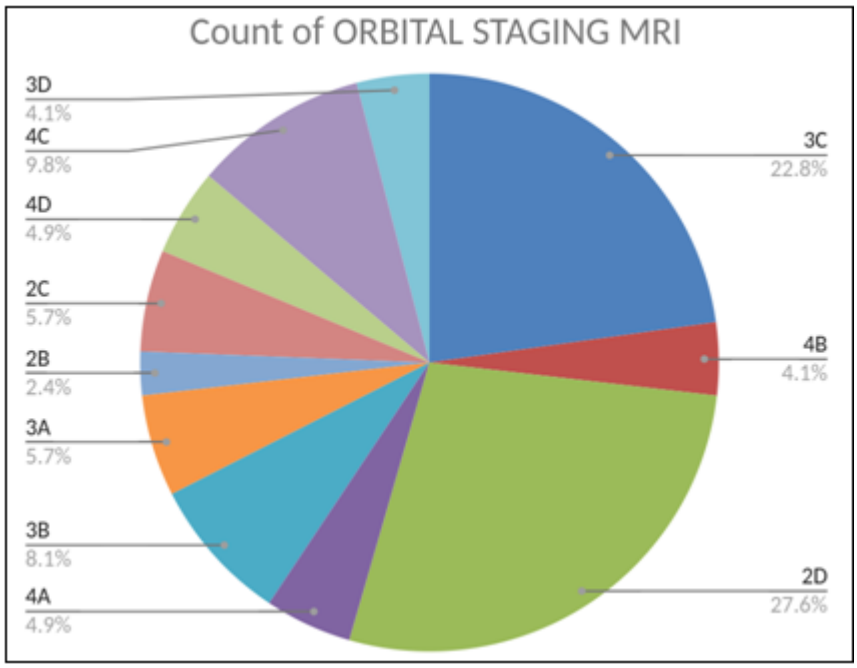

Figure 4

A MRI staging system based on the anatomical progression of the disease from point of entry to at nose till the brain, proposed by Honavar, was used to study the severity of ROCM in our series. According to it, the most common stage in our series was 2D followed by 3C. **[2]**

Comorbidity

Of the 137 patients presenting with hyperglycemia on admission for ROCM, 52% (n=71) were a known case of diabetes with a median duration of 6 years. Majority (n=61) of these patients were on oral hypoglycemic agents. The rest were on insulin (n=4) or a combination of both insulin and OHA (n=4. 3 patients were not on any medication for diabetes. Half of the 48% patients who were hyperglycemic on admission without established diagnosis of diabetes had a documented history of receiving steroid therapy. Overall, of the patients who had hyperglycemia on admission, the ratio of those who had received steroids to those who had not was 3:1. In stage 2D, 91% were diabetic and 60% had received steroids. In stage 3C, 93% having diabetes and 88% having taken steroids.

4. Discussion

Invasive Rhino-Orbital-Cerebral Mucormycosis was a rare fungal disease before the recent epidemic. It belongs to the family mucoromycotina and has three genera which are usually implicated in the disease namely Rhizopus, Absidia and Mucor. Two studies, one of Iran and another of Japan have reported mucormycosis more commonly in months of autumn to September whereas in India the cases are more commonly reported post rainy season and in the autumn months **[3]**.

Various risk factors have been studied in relation to this fungus. Out of these, diabetes mellitus and malignancies have been most widely studied. Apart from this, the organ transplants, which leave patients immunocompromised, are also implicated. In a study conducted in France, out of 101 patients of mucormycosis, 50% had a hematological malignancy, 23% had diabetes mellitus and 3% had undergone solid organ transplant **[4]**. A study similar to this conducted in India suggested that out of 173 cases of mucormycosis, 73.6% cases occurred in diabetics **[5].** The most important predisposing factor in the causation of mucormycosis has been the use of steroids. Steroids lead to double trouble. At one end they cause blunting of the host defense mechanisms by decreasing the host cell phagocytosis and at the other end they lead to hyperglycemia which leads to mucormycosis. There has been a case of pulmonary mucormycosis reported in a patient of well controlled diabetes mellitus who developed hyperglycemia due to steroid use **[6, 7, 8].** The use of ventilation systems and its contamination**[9],** contaminated hospital linen **[10]**, iron overload in patients **[11],** use of iron chelators and high serum iron levels**[12]** have also been implicated to be a risk factor in causation of the disease**.** In a review of the available literature on COVID associated mucormycosis, the study concluded that 43% of patients who were admitted for COVID associated mucor, had uncontrolled diabetes at presentation **[9].** Another study showed that out of 23 COVID associated mucor cases, 21 had diabetes and out of which 12 had uncontrolled diabetes and 9 had controlled diabetes **[10].** In another study on orbital mucormycosis, the 10 patients who were studied, all diabetic, 9 out of them had presented with DKA **[13].** Increase in glucose levels upregulates the action of GRP 78 **[14]**, which is the fungus binding receptor in humans**.** Another factor which upregulates the action of the GRP 78 receptor is the acidosis in the body **[14]**. This acidosis can result from DKA or in the present scenario, COVID-19 associated CO2 retention. However COVID associated mucormycosis has also been seen in patients with well controlled diabetes **[15] [16].** This underlines the need for further research in the subject of risk factors of COVID-19 associated mucormycosis. COVID-19 has seen a rise in the use of corticosteroids. Steroid use had already been a risk factor for COVID-19 and now various case studies show

that steroid use is a major predisposition for COVID-19 associated mucormycosis **[6, 15, 16, 17, 18, 19, 20].**

Clinically COVID-19 associated mucormycosis presents as rhino orbital cerebral mucormycosis (ROCM) **[15, 16, 17, 19, 21, 22]**, pulmonary mucormycosis **[23, 24]**, cutaneous mucormycosis, disseminated mucormycosis and rarely Gastrointestinal mucormycosis **[25]** and invasive hepatic mucormycosis **[26].** Isolated renal mucormycosis **[27]** has also been reported, although not in association with COVID-19 pneumonia.

ROCM and pulmonary mucormycosis are found to be the most common presentations in patients of diabetes mellitus and isolated pulmonary and disseminated mucormycosis were most frequent types in patients of hematological malignancies **[4].**

Epidemiology

In a large multi-institutional study conducted in India on 2826 patients **[28]**, the mean age of COVID-19 associated Mucormycosis was 51.9 years with a male preponderance (71%). In our single institution study the median age of the patients was 50.5 years with male preponderance (68%).

Potential risk factors

Oxygen:

In the COSMIC study**[28]**, the history of oxygen therapy was seen in 56.7% patients. In our study it was seen in 46.7% of patients. However, all of these patients had either received steroids or were a known case of diabetes or presented with hyperglycemia on admission. This suggests that oxygen may not be an independent risk factor for COVID-19 associated Mucormycosis. On the contrary, fomites such as reused oxygen masks, contaminated bed linen and ventilation systems might be more probable suspects than oxygen. An interesting point to consider is the reuse of disposable face masks or contaminated cloth masks as a potential spreader of mucormycosis.

Remdesivir:

64 out of 152 CAMCR patients had received Remdesivir therapy. The doses of 42 of these patients were known. The median dose of Remdesivir was 600mg (range, 100-900mg), over 5 days, which is in keeping guidelines **[29]**. 9 patients had received only the loading dose (200mg) on day 1. This may reflect an acute shortage of the drug in India during the pandemic. There was not a single patient who had received Remdesivir without concurrently receiving steroid or oxygen therapy or being hyperglycemic at admission, which makes commenting on its role in Mucormycosis difficult.

Tocilizumab:

In our study 2 patients had received Tocilizumab for COVID-19. However, they had a history of steroid therapy as well as presented with hyperglycemia on admission. In presence of such strong risk factors for CAMCR, it is difficult to comment upon the association between Tocilizumab as a risk factor for Mucormycosis. Both these patients had also received Remdesivir along with oxygen and steroids. Further research is needed regarding the isolated use of remdesivir and tocilizumab on the patients of COVID-19 and their risk of getting mucormycosis.

Steroids:

The COVID-19 pandemic saw a multitude of treatment options. However none were considered as effective as the use of steroids. The Indian Council of Medical Research guidelines classified patients of COVID-19 into three severity categories based mainly on oxygen saturation levels **[29]**. The patients in the mild severity category were advised home based symptomatic treatment without the use of oral or injectable steroids or oxygen therapy. In our study, 85 patients had a history of exposure to steroids during treatment of COVID-19. Of those who were admitted at a government setup, 44% received steroids as compared to 75% of patients admitted to a private setup. Assuming that hospitals in India closely followed the guidelines provided by ICMR, there appears to be a significant difference in the occurrence of Mucormycosis in COVID-19 patients admitted in government setups vs private hospitals. This is reflective of the easy hand with which steroids are dealt with in the private setups. Approximately one third of 21 patients who did not require hospitalisation and were treated at home, received steroids. All of these, except one, had presented with hyperglycemia at admission (n=7) and only 3 were on anti diabetic medication. The use of steroids without hospitalisation and proper monitoring of blood sugar levels could be one of the reasons for the mucor epidemic in India. Approximately 41% (n=35) patients were administered steroids without them being a candidate for oxygen therapy. In the private hospitals, one-third of the patients received steroids but had no oxygen requirement. This suggests the overcautious use of steroids as a possible contributing factor in the causation of mucormycosis. For every patient who had mild COVID-19, the steroid therapy was started within the first five days of the symptoms. This might have been the possible mechanism of weakening of the immune system creating a fertile bed for mucormycosis. Mucormycosis is known to thrive in hyperglycemia. 86% of the patients who were administered steroid therapy had hyperglycemia on admission. Injudicious use of steroids might be implicated as another reason for the increase in the cases of mucormycosis.

However, the ICMR guidelines on COVID-19 treatment do not mention the caution to be taken while prescribing steroids in terms of its maximum permissible dose and duration. Hence this highlights the importance of thorough guidelines to prevent such occurrences. **[30]**

Hyperglycemia and diabetes:

Diabetes and hyperglycemia have been implicated time and again as the risk factor for mucormycosis. In a case series from India, 74% of patients had an underlying diagnosis of uncontrolled diabetes, of which 43% were undiagnosed **[31]**. In studies previously conducted in India **[32-40]**, the mean percentage of diabetics was 63.3% (range, 53.6 - 76.3%). A study conducted in the state of Gujarat with 27 patients found 55.6% of patients to be diabetic. In our case series, 51.8% were diabetic. A majority of the patients in our series (90%) had presented with hyperglycemia. Approximately one-half of patients (48.2%) had hyperglycemia but were not established diabetics. Out of these patients, 50% had a

history of steroid therapy. Such a significant number of patients might point towards steroid induced hyperglycemia. The other influencing factors may be the diabetogenic potential of SARS-CoV-2**[41]** and the underdiagnosis of diabetes in Indian communities reflective of the typical iceberg phenomenon. Additionally, of those patients who received neither oxygen nor steroids, 95.24% were diabetic. This proves beyond doubt that diabetes must be an independent risk factor for mucormycosis and underlines the need to improve the primary healthcare and awareness among the patients regarding diabetes and urge them to be screened for it. 4 % patients who had a known case of diabetes were not on any medication for it, which is representative of the non compliant patients. Hence an emphasis should be laid on ensuring adherence to the blood glucose management. The present guidelines of COVID-19 management must ensure incorporation of adequate blood glucose monitoring of the patients.

Unexplored risk factors

There are other possible unexplored risk factors for mucormycosis which need to be explored further. First is the commentary on changing the nasal microflora as a reason for growth of mucor. This could be due to the use of broad spectrum antibiotics, oxygen therapy, oxygen humidification and corticosteroid use. **[42]**

Second, the unhygienic practice of handling and reusing face masks to the point of their contamination could serve as a possible source of infection. Third is the reuse of oxygen masks and bipap circuits in hospitals. A lot of anecdotal evidence suggests that there had been rampant reuse of oxygen delivery equipment without ensuring proper disinfection.

Timing of Occurrence

In a nationwide study conducted in India on 2826 ROCM patients (COSMIC) **[28]** the mean interval between diagnosis of COVID-19 and first symptom of ROCM was 14.5 ± 10 days and median duration of 13 days, with 56% patients developing symptoms within 14 days. In our study the median interval was 14 days(± 12 days) with 80% patients developing symptoms within the first 14 days. A spike was noted on day 12 in a range from days 0-57. Since cases were recorded until 2 months after the diagnosis of COVID-19, follow-up of patients treated for COVID-19 should be conducted. Patients must be educated about the signs and symptoms of Mucormycosis and encouraged to seek immediate care. Information should be disseminated in the form of pamphlets at the time of discharge.

Signs and symptoms

Periorbital swelling, facial pain, headache, tooth pain and eye pain were the most frequently encountered symptoms in the patients of our study. General practitioners must keep a high degree of suspicion of mucormycosis in patients presenting with these symptoms, especially with a history of COVID-19.

80.48% patients had bilateral involvement of paranasal sinuses. Approximately three-fifths of these patients progressed to involve the orbits. About one-fifths of these had brain involvement.

Amongst patients with CNS involvement, the most frequently affected site was cavernous sinus (15 out of 26) and the most commonly associated paranasal sinus was maxillary. Only 3 patients had CNS involvement along with bilateral paranasal sinuses without any orbital affection. Hence a high index of suspicion for brain involvement should be maintained in cases with bilateral paranasal sinus involvement irrespective of the orbital affection. In 4 out of the total cases of CNS involvement, non hemorrhagic infarcts were noted. This may be explained by the angioinvasive nature of the fungus leading to occlusion and infarction.

Lessons for 3rd wave of COVID-19

As of today, the pendulum of cases of COVID-19 is swinging between overall increase and decrease and there is an expectation of it gaining endemicity between waves. The analysis of the Mucormycosis epidemic would therefore be futile if the lessons are not learnt. First, the overzealous use of steroids as a risk factor cannot be emphasized upon more. The need for a guideline highlighting the maximum permissible dose and duration of steroids in the treatment of COVID-19 may help in reducing the cases of Mucormycosis. Second, strict glycemic control in patients of steroid therapy is crucial. Apart from providing a scrupulous guideline to manage COVID-19, the government along with ICMR should also construct a glycemia control protocol. The authors recommend instituting a Diabetes Control Task Force (DCTF) to monitor and course correct the glycemic control protocol of various hospitals managing such patients. Mechanisms should be set in place to counsel diabetics and take their telephonic follow-ups regarding control of their sugar levels. Third, strengthening of primary healthcare by training the primary care physicians, ASHA workers, multi-purpose health workers to create awareness, diagnose and guide the patients with symptoms of COVID-19, mucormycosis, and diabetes. This initiative can be extended to the household level with health workers screening for blood sugar with point-of-care devices. The authors observations of the use of face masks beyond their lifespan and the careless handling of such masks leading to contamination could be a preventable risk factor in the occurrence of mucormycosis.

5. Limitations

Our data was collected from a single institution in a time bound fashion. A collaborative study including institutions from all over India carrying out the research over a longer time frame would be much more representative of the incidence and recurrence of CAMCR. A more detailed disease study would have helped to understand the disease progression better. Also the data suffers the systemic problem of poor record keeping by healthcare professionals. Surprisingly, private setups had a relatively incomplete documentation and hastily prepared discharge summaries. Species specific data was not available. The role of the living conditions of the patient in causation of Mucormycosis could not be commented upon because of lack of data regarding their socio-economic status. Data regarding education or the lack thereof in patients would have enabled us to describe its role in compliance, hygiene, follow-up, and awareness of the disease. A more rigorous

documentation of steroid dose and duration could have helped us better analyse its dose response relationship with Mucormycosis.

6. Conclusion

COVID-19 associated mucormycosis predominantly affected middle aged males. Steroid has been widely used as a life saving drug in COVID-19 pneumonia, but it has proven to be a double edged sword because it may also have led to the highly morbid condition of mucormycosis. Effective counselling of the patients regarding dose and duration of the steroid drug is paramount along with meticulous monitoring of its use and follow up for its adverse effects. The mucormycosis epidemic has highlighted the importance of glycemic control during the use of steroids. Also, strengthening the screening programme for diabetes mellitus at primary healthcare level is the need of the hour. However, along with the above mentioned risk factors, oxygen therapy, tocilizumab, remdesivir, zinc, broad spectrum antibiotics and ivermectin are other potential causatives which need to be examined further.

Periorbital swelling, facial pain, toothache, eye pain and facial swelling were the most commonly occurring symptoms of mucormycosis which need to be looked into with high degree of suspicion. The diagnosis for mucormycosis is based on an MRI scan which needs to be appropriately followed by nasal endoscopy to obtain specimens for histopathology, KOH mount and culture study to establish the diagnosis and ascertain the species. The ROCM management needs teamwork of general physicians, otorhinolaryngologists, ophthalmologists, pathologists and radiologists. Ideally a task force needs to be in place to guide the team.

In the end, our entire analysis should be able to drive home the point that rational use of steroids, dutiful glycemic monitoring, and robust primary healthcare will enable us to prevent the occurrence of such a health catastrophe.

Abbreviations

- SSG - Sir Sayajirao General Hospital
- COVID-19 - Coronavirus Disease 2019
- CAMCR - COVID-19 Associated Mucormycosis
- SARS-CoV-2 - Severe Acute Respiratory Syndrome Coronavirus 2
- ROCM - Rhino-Orbito-Cerebral Mucormycosis
- RTPCR - Reverse Transcriptase Polymerase Chain Reaction
- RAT - Rapid Antigen Test
- HRCT - High Resolution Computed Tomography
- MRI - Magnetic Resonance Imaging
- OHA = Oral Hypoglycemic Agents
- GRP 78 - Glucose Regulated Protein 78
- DKA - Diabetic Ketoacidosis
- ICMR - Indian Council of Medical Research
- DCTF - Diabetes Control Task Force

Acknowledgement
We acknowledge the scientific and technical support extended by Dr. Ranjan Aiyer, Professor and Head of Otorhinolaryngology and Medical Superintendent of Sir Sayajirao General Hospital.

Conflict of Interest
None.

References

[1] https://timesofindia.indiatimes.com/city/ahmedabad/13-out-of-every-1k-COVID-patients-in-guj-got-black-fungus-infection/articleshow/84659619.cms
[2] Honavar SG. Code Mucor: Guidelines for the Diagnosis, Staging and Management of Rhino-Orbito-Cerebral Mucormycosis in the Setting of COVID-19. Indian J Ophthalmol. 2021 Jun;69(6):1361-1365. doi: 10.4103/ijo.IJO_1165_21. PMID: 34011699; PMCID: PMC8302268.
[3] Chakrabarti A, Dhaliwal M. Epidemiology of Mucormycosis in India. Current Fungal Infection Reports. 2013;7(4):287-292.
[4] Lanternier F, Dannaoui E, Morizot G, Elie C, Garcia-Hermoso D, Huerre M et al. A Global Analysis of Mucormycosis in France: The RetroZygo Study (2005-2007). Clinical Infectious Diseases. 2012;54(suppl 1):S35-S43.
[5] Chakrabarti A, Singh R. Mucormycosis in India: unique features. Mycoses. 2014;57:85-90.
[6] Ferguson A. Rhinocerebral Mucormycosis Acquired After a Short Course of Prednisone Therapy. Journal of Osteopathic Medicine. 2007;107(11): 491-493
[7] Hoang K, Abdo T, Reinersman J, Lu R, Higuita N. A case of invasive pulmonary mucormycosis resulting from short courses of corticosteroids in a well-controlled diabetic patient. Medical Mycology Case Reports. 2020;29:22-24.
[8] Koushiappi E, Porfyridis I, Karagiannis C, Adamide T, Georgiou A. Pulmonary Mucormycosis (Zygomycosis) Presenting as an Infective Exacerbation of Chronic Obstructive Pulmonary Disease. European Journal of Case Reports in Internal Medicine. 2018;5(12):1.
[9] Sundermann A, Clancy C, Pasculle A, Liu G, Cumbie R, Driscoll E et al. How Clean Is the Linen at My Hospital? The Mucorales on Unclean Linen Discovery Study of Large United States Transplant and Cancer Centers. Clinical Infectious Diseases. 2018;68(5):850-853.
[10] Sharma S, Grover M, Bhargava S, Samdani S, Kataria T. Post coronavirus disease mucormycosis: a deadly addition to the pandemic spectrum. The Journal of Laryngology & Otology. 2021;:1-6.
[11] Perricone C, Bartoloni E, Bursi R, Cafaro G, Guidelli G, Shoenfeld Y et al. COVID-19 as part of the hyperferritinemic syndromes: the role of iron depletion therapy. Immunologic Research. 2020;68(4):213-224.
[12] Ibrahim A, Spellberg B, Walsh T, Kontoyiannis D. Pathogenesis of Mucormycosis. Clinical Infectious Diseases. 2012;54(suppl_1):S16-S22.
[13] Deb A, Sarkar S, Gokhale T, Choudhury S. COVID-19 and orbital mucormycosis. Indian Journal of Ophthalmology. 2021;69(4):1002.
[14] Gebremariam T, Liu M, Luo G, Bruno V, Phan Q, Waring A et al. CotH3 mediates fungal invasion of

host cells during mucormycosis. Journal of Clinical Investigation. 2013;124(1):237-250.
[15] Mehta S, Pandey A. Rhino-Orbital Mucormycosis Associated With COVID-19. Cureus. 2020;.
[16] Maini A, Tomar G, Khanna D, Kini Y, Mehta H, Bhagyasree V. Sino-orbital mucormycosis in a COVID-19 patient: A case report. International Journal of Surgery Case Reports. 2021;82:105957.
[17] Mekonnen Z, Ashraf D, Jankowski T, Grob S, Vagefi M, Kersten R et al. Acute Invasive Rhino-Orbital Mucormycosis in a Patient With COVID-19-Associated Acute Respiratory Distress Syndrome. Ophthalmic Plastic & Reconstructive Surgery. 2020;37(2):e40-e80.
[18] Khatri A, Chang K, Berlinrut I, Wallach F. Mucormycosis after Coronavirus disease 2019 infection in a heart transplant recipient – Case report and review of literature. Journal of Medical Mycology. 2021;31(2):101125.
[19] Veisi A, Bagheri A, Eshaghi M, Rikhtehgar M, Rezaei Kanavi M, Farjad R. Rhino-orbital mucormycosis during steroid therapy in COVID-19 patients: A case report. European Journal of Ophthalmology. 2021;:112067212110094.
[20] Monte Junior E, Santos M, Ribeiro I, Luz G, Baba E, Hirsch B et al. Rare and Fatal Gastrointestinal Mucormycosis (Zygomycosis) in a COVID-19 Patient: A Case Report. Clinical Endoscopy. 2020;53(6):746-749.
[21] Skiada A, Pavleas I, Drogari-Apiranthitou M. Epidemiology and Diagnosis of Mucormycosis: An Update. J Fungi (Basel). 2020 Nov 2;6(4):265. doi: 10.3390/jof6040265. PMID: 33147877; PMCID: PMC7711598.
[22] Patil S, Sarate D, Chopade S, Khade M, Dhage S, Kangate S. Emerging Challenge of Mucormycosis in post-COVID Patients. IAR Journal of Medical Case Reports [Internet]. 2021 [cited 2021 Nov 3];2(3):7-10. Available from: https://www.iarconsortium.org/articles/788_Emerging_Challenge_of_Mucormycosis_in_postCOVID_Patients
[23] Khan N, Gutierrez C, Martinez D, Proud K. A case report of COVID-19 associated pulmonary mucormycosis. Archive of Clinical Cases. 2020;07(03):46-51.
[24] Kanwar A, Jordan A, Olewiler S, Wehberg K, Cortes M, Jackson B. A Fatal Case of Rhizopus azygosporus Pneumonia Following COVID-19. Journal of Fungi. 2021;7(3):174.
[25] Verma D, Bali R. COVID-19 and Mucormycosis of the Craniofacial skeleton: Causal, Contributory or Coincidental?. Journal of Maxillofacial and Oral Surgery. 2021;20(2):165-166.
[26] Karigane D, Kikuchi T, Sakurai M, Kato J, Yamane Y, Hashida R et al. Invasive hepatic mucormycosis: A case report and review of the literature. Journal of Infection and Chemotherapy. 2019;25(1):50-53.
[27] Devana SK, Gupta VG, Mavuduru RS, Bora GS, Sharma AP, Parmar KM, Kumar S, Mete UK, Singh SK, Mandal AK, Kakkar N, Banerjee N, Ghosh A. Isolated Renal Mucormycosis in Immunocompetent Hosts: Clinical Spectrum and Management Approach. Am J Trop Med Hyg. 2019 Apr;100(4):791-797. doi: 10.4269/ajtmh.18-0103. PMID: 30652661; PMCID: PMC6447097.
[28] Sen M, Honavar SG, Bansal R, Sengupta S, Rao R, Kim U, et al. Epidemiology, clinical profile, management, and outcome of COVID-19-associated rhino-orbital-cerebral mucormycosis in 2826 patients in India - Collaborative OPAI-IJO Study on Mucormycosis in COVID-19 (COSMIC), Report 1. Indian J Ophthalmol. 2021 Jul;69(7):1670-1692. doi: 10.4103/ijo.IJO_1565_21. PMID: 34156034; PMCID: PMC8374756.
[29] https://www.icmr.gov.in/pdf/COVID/techdoc/COVID_Management_Algorithm_17052021.pdf (17th may 2021)
[30] Mulakavalupil B, Vaity C, Joshi S, Misra A, Pandit RA. Absence of Case of Mucormycosis (March 2020-May 2021) under strict protocol driven management care in a COVID-19 specific tertiary care intensive care unit. Diabetes Metab Syndr. 2021 Jul-Aug;15(4):102169. doi: 10.1016/j.dsx.2021.06.006. Epub 2021 Jun 9. PMID: 34198110; PMCID: PMC8188750.
[31] Chakrabarti A, Singh R. The emerging epidemiology of mould infections in developing countries. Curr Opin Infect Dis. 2011 Dec;24(6):521-6. doi: 10.1097/QCO.0b013e32834ab21e. PMID: 21799406.
[32] Chakrabarti A, Das A, Sharma A, Panda N, Das S, Gupta KL, Sakhuja V. Ten years' experience in zygomycosis at a tertiary care centre in India. J Infect. 2001 May;42(4):261-6. doi: 10.1053/jinf.2001.0831. PMID: 11545569.
[33] Chakrabarti A, Das A, Mandal J, Shivaprakash MR, George VK, Tarai B, Rao P, Panda N, Verma SC, Sakhuja V. The rising trend of invasive zygomycosis in patients with uncontrolled diabetes mellitus. Med Mycol. 2006 Jun;44(4):335-42. doi: 10.1080/13693780500464930. PMID: 16772227.
[34] Chakrabarti A, Chatterjee SS, Das A, Panda N, Shivaprakash MR, Kaur A, Varma SC, Singhi S, Bhansali A, Sakhuja V. Invasive zygomycosis in India: experience in a tertiary care hospital. Postgrad Med J. 2009 Nov;85(1009):573-81. doi: 10.1136/pgmj.2008.076463. PMID: 19892892.
[35] Manesh A, Rupali P, Sullivan MO, Mohanraj P, Rupa V, George B, Michael JS. Mucormycosis-A clinicoepidemiological review of cases over 10 years. Mycoses. 2019 Apr;62(4):391-398. doi: 10.1111/myc.12897. Epub 2019 Feb 19. PMID: 30685896.
[36] Chander J, Kaur M, Singla N, Punia RPS, Singhal SK, Attri AK, Alastruey-Izquierdo A, Stchigel AM, Cano-Lira JF, Guarro J. Mucormycosis: Battle with the Deadly Enemy over a Five-Year Period in India. J Fungi (Basel). 2018 Apr 6;4(2):46. doi: 10.3390/jof4020046. PMID: 29642408; PMCID: PMC6023269.
[37] Patel AK, Patel KK, Patel K, Gohel S, Chakrabarti A. Mucormycosis at a tertiary care centre in Gujarat, India. Mycoses. 2017 Jun;60(6):407-411. doi: 10.1111/myc.12610. Epub 2017 Mar 9. PMID: 28276102.

[38] Prakash H, Ghosh AK, Rudramurthy SM, Singh P, Xess I, Savio J, Pamidimukkala U, Jillwin J, Varma S, Das A, Panda NK, Singh S, Bal A, Chakrabarti A. A prospective multicenter study on mucormycosis in India: Epidemiology, diagnosis, and treatment. Med Mycol. 2019 Jun 1;57(4):395-402. doi: 10.1093/mmy/myy060. PMID: 30085158.

[39] Patel A, Kaur H, Xess I, Michael JS, Savio J, Rudramurthy S, Singh R, Shastri P, Umabala P, Sardana R, Kindo A, Capoor MR, Mohan S, Muthu V, Agarwal R, Chakrabarti A. A multicentre observational study on the epidemiology, risk factors, management and outcomes of mucormycosis in India. Clin Microbiol Infect. 2020 Jul;26(7):944.e9-944.e15. doi: 10.1016/j.cmi.2019.11.021. Epub 2019 Dec 4. PMID: 31811914.

[40] Priya P, Ganesan V, Rajendran T, Geni VG. Mucormycosis in a Tertiary Care Center in South India: A 4-Year Experience. Indian J Crit Care Med. 2020 Mar;24(3):168-171. doi: 10.5005/jp-journals-10071-23387. PMID: 32435094; PMCID: PMC7225759.

[41] Rubino F, Amiel SA, Zimmet P, Alberti G, Bornstein S, Eckel RH, Mingrone G, Boehm B, Cooper ME, Chai Z, Del Prato S, Ji L, Hopkins D, Herman WH, Khunti K, Mbanya JC, Renard E. New-Onset Diabetes in COVID-19. N Engl J Med. 2020 Aug 20;383(8):789-790. doi: 10.1056/NEJMc2018688. Epub 2020 Jun 12. PMID: 32530585; PMCID: PMC7304415.

[42] Singh R, Kumari A. Nasal Microbiota Imbalance as a Contributory Link in the Emergence of COVID-19 Associated Mucormycosis. ACS Infect Dis. 2021 Aug 13;7(8):2211-2213. doi: 10.1021/acsinfecdis.1c00371. Epub 2021 Jul 30. PMID: 34328718.