Trends in Clinical and Medical Sciences

PSR Press

Original Research Article

Clinical profile of rhino-orbito-cerebral mucormycosis cases during second wave of COVID-19 pandemic presenting to tertiary care Hospital-A retrospective study

Dorkar Shashikant Narayan[1,*], Nilakhe Sachin Sharad[1] and Panchal Shivani Bhagwatkumar[1]

[1] Department of Otorhinolaryngology, Bharati Hospital Medical College & Hospital, Bharati Vidyapeeth (Deemed To Be University), Sangli, Maharashtra, India.

* Correspondence: shashikantdorkar@yahoo.in

Received: 7 March 2023; Accepted: 20 May 2023; Published: 28 May 2023.

Abstract: Background: A retrospective study of records of 113 patients presenting to a tertiary care hospital during the 2nd wave of the COVID-19 pandemic was carried out with an aim to study the clinical profile of rhinoorbitocerebral mucormycosis (ROCM) patients.

Results: Out of 113 patients, 80 were males and 33 were females with a male-to-female ratio of 2.42:1. The most common age group affected was 51-60 years for both males (n=24) and females (n=37). The most common clinical presentation was headache (n=80) followed by ptosis, proptosis, and ophthalmoplegia (n=77). Based on radiology, all patients had nose and paranasal sinuses involvement, 71.68% had orbital involvement, and 13.27% had intracranial involvement. The most common extrasinus involvement was maxillofacial soft tissue. 89% were either COVID positive or COVID like on HRCT or post-COVID. Only 11% had no history of COVID or COVID like on HRCT (High Resolution Computed Tomography). 83 were diabetic, 55 had kidney disease, and 38 were hypertensive. 45.13% of patients had a history of steroid use, 21.23% had used oxygen, and 4.42% had a history of ventilator support.

Conclusion: Mucormycosis is a multi-system fungal infection with a significant surge in incidence in the second wave COVID era, which suggests a possible correlation of COVID infection with mucor. Uncontrolled diabetes is the commonest risk factor for mucor infection. The disease primarily involves the nose and paranasal sinuses, extending to the surrounding areas. MRI with contrast is the gold standard diagnostic modality to define the disease extent. Retromaxillary fissure involvement is an important cause for ophthalmoplegia in the majority of patients. Limited endoscopic orbital debridement with preservation of the globe avoids gross disfigurement and mental trauma to the patients. Early diagnosis with aggressive anti-fungal treatment combined with surgical debridement results in improving overall prognosis and survival in post-COVID mucormycosis patients.

Keywords: COVID-19 pandemic; Rhinoorbitocerebral mucormycosis.

1. Introduction

Mucormycosis,recently also known as black fungus [1] is a life threatening,rapidly progressive angio-invasive fungal disease starting with sporangiospores inhalation, direct extension into paranasal sinuses and hyphae angioinvasion in immunocompromised hosts leading to necrotizing vascultis,fungal thrombi and tissue infarction [2–4].

COVID -19 infection caused bySARS-CoV-2 had predisposed to multiple secondary bacterial and fungal infections of which mucormycosis is one [5].

The primary reason thought to be facilitating Mucorales spores to germinate in COVID patients is an ideal environment of high glucose (diabetes, new-onset hyperglycaemia, steroid-induced hyperglycaemia), low oxygen, increased levels of ferritin, acidic medium (metabolic acidosis, diabetic ketoacidosis),and decreased phagocytic activity of white blood cells due to immunosuppression combined with considerable other shared risk factors including prolonged hospitalization with or without mechanical ventilators [6].

Patients with compromised immune status [7,8] due to DM, haematological malignancy and chemotherapy, haematopoietic stem cells and solid-organ transplant recipients on immunosuppressive therapy, with iron overload, on dialysis, extensive cutaneous injury, HIV infection, and voriconazole therapy are at high risk of infection are at higher risk [7–9].

Mucormycosis involvement in the head and neck region is divided into -Isolated nasal,sino-nasal, rhino-orbital and rhino-orbito-cerebral mucormycosis [4].

Compared to developed countries, India has a higher prevalence of mucor cases. However since onset of second wave of COVID-19 pandemic there was an unprecedented rise in mucor cases [10].

In present study, we aimed to look at clinical profile of mucor patients during second wave of COVID-19 pandemic.

2. Materials and Methods

This is a retrospective study of records of 113 patients during the 2nd wave of the COVID-19 pandemic fulfilling the inclusion and exclusion criteria, presenting to a tertiary care Hospital from March 2021 to November 2021. Permission to access the data from records was obtained from the Medical Superintendent. The study was carried out after approval from the Research Review Committee (RRC). Ethical approval from the institutional ethical committee was obtained on 08/03/2023 (BV(DU)MC & H/Sangli/IEC/513/23). All the patients diagnosed with mucormycosis who underwent CT/MRI (with or without contrast) of the paranasal sinuses, orbit, and brain to determine the disease extent were included in the study. Risk factors associated with the study were determined. The data was entered in an MS Excel sheet, and statistical calculations were performed with the help of a statistician using SPSS 24.0.

2.1. Inclusion criteria

Cases of mucormycosis were included, defined as patients in whom clinical and radiological findings were indicative of mucormycosis and fungus was revealed in the tissue by KOH or deep biopsy examination.

2.2. Exclusion criteria

Recurrent or relapse cases of mucormycosis were excluded.

3. Results

Out of 113 patients, 80 were males and 33 were females, with a male-to-female ratio of 2.42:1. The most common age group affected was 51-60 years for both males (n=24) and females (n=37).

Age and gender-wise distribution of mucormycosis patients during the 2nd wave of COVID-19 pandemic, shown in Figure 1. The most common clinical presentation was headache (n=80), followed by ptosis, proptosis, and ophthalmoplegia (n=77).

Clinical presentation in patients with mucormycosis, presented in Table 1. A patient with hard palatal involvement is shown in Figure 2.

Based on radiology, all patients had nose and paranasal sinuses involvement, 71.68% had orbital involvement, and 13.27% had intracranial involvement. The most common extrasinus involvement was maxillofacial soft tissue.

Table 2 shows the radiological extent on MRI with contrast/CT scan findings. CT scan findings suggested changes of sinusitis with periorbital tissue destruction, as shown in Figure 3. MRI PNS with contrast displayed the black turbinate sign, as shown in Figure 4. MRI orbit with contrast revealed eye involvement (salt pepper appearance), shown in Figure 5. Axial STIR cuts of MRI PNS with contrast demonstrated pre-maxilla involvement, as seen in Figure 6. Coronal STIR cuts of MRI PNS with contrast showed pre-maxilla involvement, as shown in Figure 7. Axial STIR cuts of MRI PNS with contrast displayed retro-maxillary involvement, as seen in Figure 8. Coronal STIR cuts of MRI PNS with contrast showed retro-maxillary involvement, as shown in Figure 9.

Out of the patients, 89% were either COVID positive or had COVID-like findings on HRCT or post-COVID. Only 11% had no history of COVID or COVID-like findings on HRCT (High-Resolution Computed Tomography).

The association between COVID and mucormycosis is illustrated in Figure 10.

Among the patients, 83 were diabetic, 55 had kidney disease, and 38 were hypertensive. Additionally, 45.13% of patients had a history of steroid use, 21.23% had used oxygen, and 4.42% had a history of ventilator support. The association of mucor with risk factors and comorbidities is presented in Table 2.

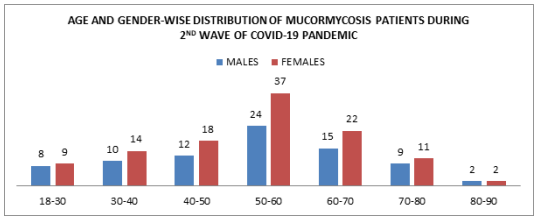

Figure 1. Age and gender-wise distribution of mucormycosis patients during 2nd wave of covid-19 pandemic

Table 1. Clinical presentation in patients with mucormycosis

Sr. no.	Clinical presentation	Number of patients	Percentage %
1.	Headache	92	81.4
2.	Ptosis, Proptosis, Ophthalmoplegia	81	71.7
3.	Facial swelling	77	68.1
4.	Facial numbness	56	49.6
5.	Dental pain/loosening of teeth	41	36.28
6.	Loss of vision	36	31.9
7.	Blackish nasal discharge	28	24.8
8.	Nasal blockage	26	23
9.	Facial asymmetry	24	21.2
10.	Palate involvement	21	18.58

Figure 2. Patient with hard palatal involvement

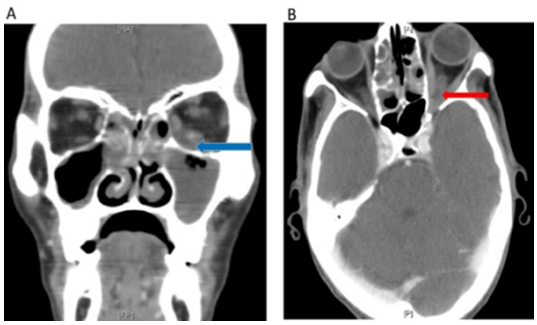

Figure 3. CT scan findings suggestive of changes of sinusitis with periorbital tissue destruction

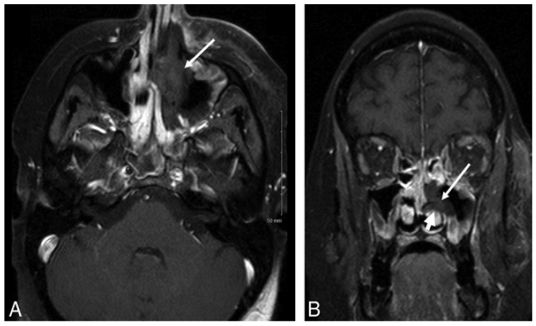

Figure 4. MRI PNS with contrast showing black turbinate sign

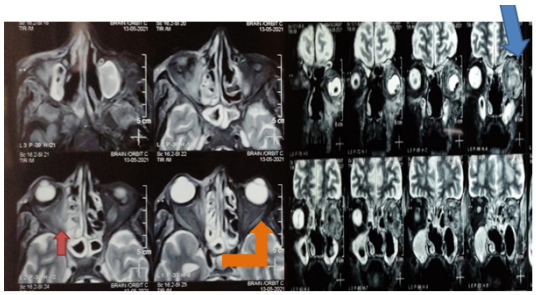

Figure 5. MRI orbit with contrast showing eye involvement (salt pepper appearance)

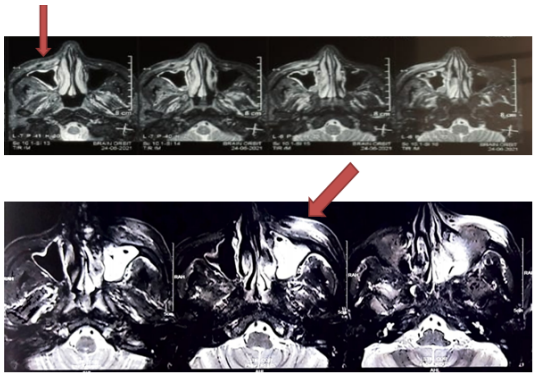

Figure 6. Pre-maxilla involvement in axial stir cuts of mri pns with contrast

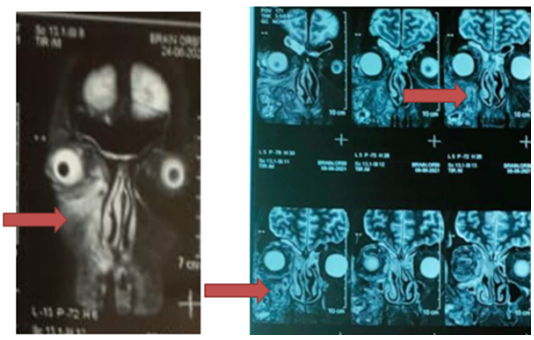

Figure 7. Pre-maxilla involvement in coronal stir cuts of mri pns with contrast

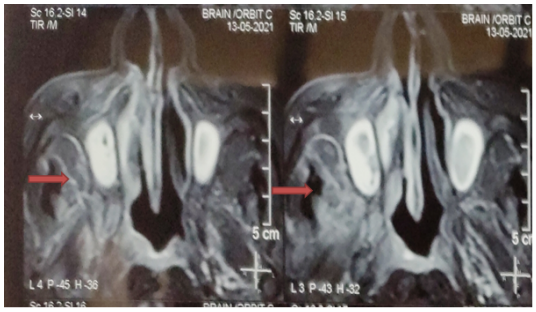

Figure 8. Retro-maxillary involvement on axial stir cuts of mri pns with contrast

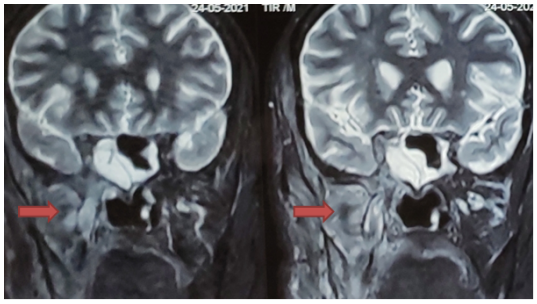

Figure 9. Retro-maxillary involvement on coronal stir cuts of mri pns with contrast

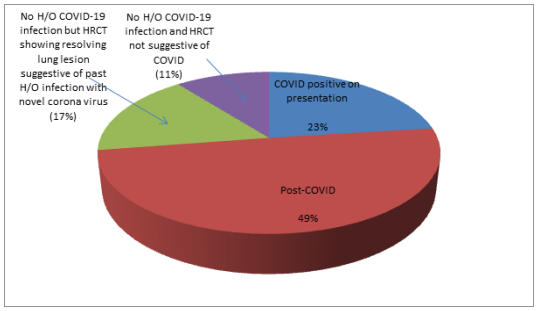

Figure 10. COVID and mucormycosis

Table 2. Mucor and associated risk factors and comorbidities

Risk factors and comorbidities	Number of patients(%)
Diabetes Mellitus	83(73.45%)
Hypertension	38 (33.6%)
Acute Kidney Injury	18(15.9%)
Chronic Kidney Disease	37(32.7%)
Chronic Obstructive Pulmonary Disease(COPD)	8(7.1 %)
History of steroid use	51(45.13 %)
Use of oxygen therapy	24(21.23%)
Ventilation (NIV/IMV)	5(4.42 %)

4. Discussion

The 2nd wave of COVID-19 brought sharp rise in the mycosis infections rate globally. Researchers have identified at least 20 or more fungal species in hospital setting in COVID-19 patients e.g. Aspergillus fumigatus, Candida albicans, and mucormycosis [11]. In India, the increase in the incidence of mucormycosis also has steep curve. Fungal co-infections were expected in SARS-CoV-2 wave, as same was observed during earlier outbreaks of other corona viruses such as the severe acute respiratory syndrome (SARS) and the middle

east respiratory syndrome (MERS) [10].Mucormycosis is the 3rd leading reason of invasive fungal infection subsequent to Aspergillus and Candida spp in homo sapiens [12]. It is an opportunistic infection and infarction and necrosis of the tissues of the host is seen due to fungal angio-invasion. It has been more and more observed in the patients of COVID-19 infection [13,14].

4.1. Age and gender wise distribution

In our study, male preponderance was seen with male : female ratio of 2.42 : 1. Most common age group affected was 51-60 years for both males and females.

Male predominance was observed in a study conducted by Lokhande *et al.*,. Of the total patients, fifty-six (61.34%) were males and thirty-five (38.46%) were females. The mean age of patients was 52.47±12.84 years in their study [15]. A research by Patel *et al*., observed that the median age was 48 years and 69.5% of patients were men among their study participants having mucormycosis [16]. Sen *et al.,* conducted a multicentric study and found out that the mean age was 51.9 years and 71% of them were male having mucormycosis [17]. A study conducted by Guptaobserved that the mean age of the study participants was fifty years and shows slight male preponderance with the ratio of male-female 2.5:1 [18]. Singla *et al.,* [13] also observed that, more prevalence of mucormycosis was seen in males as compared to females. Restrepo *et al.,* proposed the oestrogen had protective role in females [19]. Singla *et al.,* observed that gender had no role [13] (p-value = 0.-979, non-significant) similar to a study by Kashkouli *et al.,* where no gender preponderance was observed in the results [20].

4.2. Clinical presentation

In our study most common clinical presentation was headache followed by ptosis , proptosis and ophthalmoplegia and this findings were very consistent with the study conducted by Dubey *et al.,* [21] Some other presentations in the same study of Dubey *et al*., were Retro-orbital pain, numbness over face, loss of vision , Tooth ache/loosening, Diplopia , and Facial deviation.In a research done by Patel *et al*., [22], most common symptom was nasal blockage followed by facial swelling on same side and bloody nasal discharge. Facial swelling was prominent in maxillary region (cheek) and over zygoma in a some patients. Other presentations were orbital swelling, palatal ulceration, and headache. Some rare conditions were diminution of vision, loss of vision and loosening of teeth.

4.3. Radiological extent on MRI and CT

Based on radiological findings in our study:All patients had nose and/or paranasal sinuses involved.The most common extrasinus involvement was maxillofacial soft tissue with orbital involvement in 71.68 % patients and intracranial involvement in 13.27 % patients .

In a study by Agrawal *et al*., [23], 70 % had orbital involvement and 20 % had intracranial extension. The perimaxillary soft tissue and orbits were the commonest sites of extension of disease in a study by Agrawal *et al*., [23]. Therakathu *et al*., [24] conducted a study and showed that orbits are the most frequent location of extra-sinus involvement seen in 76% of patients, followed by soft tissue of face (57%). Metwally *et al*., [4] too found that periantral soft tissue was involved in 74.6% of patients. Nonetheless, pterygopalatine fossa involvement and invasion was more common in their study (77.8%). Yadav *et al*., [25] in their study carried out on 50 patients with mucormycosis established involvement of soft tissue of periantral region and orbital involvement in 74% and 76% of patients, correspondingly. The close propinquity to the frequently infected maxillary paranasal sinus, bony erosion causing direct invasion and its propensity to spread along neural and vascular routes perhaps explain the recurrent involvement of peri antrum fat. The two orbits are detached from sino-nasal mucosa by a thin plate of lamina papyracea and communes to the nasal cavity via the NLD-nasolacrimal duct. Hence orbits are also anatomically more prone to invasive fungal disease.

4.4. COVID and mucor

In our study, 17 % patients had no history of COVID-19 infection but HRCT was showing resolving lung lesion which suggested past history of infection with novel corona virus, 11 % patients had no history ofCOVID-19 infection and HRCT was also not suggestive of COVID, 23% were COVID positive on presentation and 49 % were post-COVID.

In a study by Kamath et. al [10],33.3% had active COVID-19 infection, 53.3% were in the post-COVID-19 state, 13.4% had COVID-19 like illness and two 13.4% patients did not have COVID-19 in the recent past.

4.5. COVID and Risk factors and Co-Morbidities

In our study, 73.45% were diabetic, 48.67% had kidney disease and 33.62% were hypertensive. 45.13 % patients had history of steroid use, 57.52% had raised serum ferritin levels, 21.23% had use of oxygen and 4.42 % had history of ventilator support.

India made an appearance as centre for COVID associated Mucormycosis during the 2nd wave of COVID -19 pandemic, with over 4 thousand documented cases. Bhanuprasad *et al.*, studied that while conventional risk factors like uncontrolled DM (diabetes mellitus) contributed, the extensive use of steroids, yet for mild COVID-19, was a foremost driver of COVID associated Mucor. Furthermore, there were indicators towards a multifactorial complex reaction and union of diverse factors, counting possibly the SARS-CoV-2 infection as well itself. Higher blood sugar levels , rampant corticosteroid use and iron overload -each and every one lead to dysfunction of phagocytes , more likely the more instantaneous reason of mucormycosis. The enormous bulk of patients in a study by Bhanuprasad *et al*., [26] that is 97% had underlying diabetes , a pace superior than that noticed in multicentric COVID associated Mucor study from Indian nation carried out during the 1st wave COVID-19 pandemic,which-in 2/3 rd of patients had this diabetes mellitus (Patel *et al*., 2021) [27].Raised blood glucose levels lasting up to three months related with COVID-19 has been noted. An atypical cytokine background and resistance to insulin, in place of beta-cell infection, appears to be the rationale. (Montefusco *et al*., 2021) [28]. Steroid use causes increase in blood sugar, and hence was significantly associated with mucormycosis in the research of Bhanuprasad *et al*., [26]. In spite of widespread use in rheumatology, the incidence of mucormycosis remains low in such cases. Hence, it points to the fact that steroid use in combination with some other factors has determined the COVID-Mucor epidemic in India. The commonest etiological factors associated with the risk of mucormycosis in a study by Patel *et al*., and Gupta *et al*., [16,23] were uncontrolled DM , irrational use of steroids, and prolong ICU hospitalization with oxygenation therapy. This were similar to a study by Singh *et al*., [6] and Singla *et al*., [13] .Marker of dysregulation of immunity system and a fundamental element of iron metabolism, mean serum ferritin levels were increased exponentially in the patients as researched by Bhanuprasad *et al*., [26]. Additional to hyperglycaemia and use of steroid , infection with SARS-CoV-2 with probable modification in iron metabolism may perhaps would have predisposed to mucor(Lammaert *et al*., 2012 [29]; Kentaro *et al*., 2021 [30]). At length, the topical increase in COVID-19 cases was linked with an unparalleled scarcity of oxygen accessibility in India, resulting in the utilization of industrial-grade oxygen in several parts of the country. Whilst impure oxygen exposure was contemplated as one of potential risk factors, merely a portion of patients in study by Bhanuprasad *et al*., [26] needed oxygen support or ventilatory support, signifying it as an unlikely a considerable factor. In a study by Patel et. al [22], 28.5 % patients were hypertensive and 5.17 % patients had kidney disease.

Hence, management includes a multidisciplinary squad approach. The stronghold of treatment is antifungal drugs and debridement surgically of the affected areas . The survival rate of patients with mucormycosis has raised from 6% to approximately 60% with the accessibility of amphotericin B intravenously [31–33]. Surgical debridement and exploration helps to bound the infection spread and permits better dissemination of intravenous medications into the tissues which are infected.

Figure 11. Diabetic (covid positive on presentation) mucormycosis patient with left facial blackish eschar formation

Figure 12. Post covid patient with left sided maxillofacial soft tssue involvement , facial asymmetry and left orbital involvement

Figure 13. Male diabetic post -covid patient with right eye involvement (ptosis, proptosis and ophthalmoplegia and sudden diminution of vision) along with nose and paranasal sinus involvement

5. Key message

Rhino-Orbito-Cerebral Mucormycosis is a multi-system fungal infection with sudden momentous surge in incidence in the second wave COVID era.Early diagnosis with aggressive anti-fungal treatment combined with less radical surgical debridement results in improving overall prognosis and survival in post-COVID mucormycosis patients.

Author Contributions: All authors contributed equally to the writing of this paper. All authors read and approved the final manuscript.

Conflicts of Interest: "The authors declare no conflict of interests."

References

[1] Choudhary, N. K., Jain, A. K., Soni, R., & Gahlot, N. (2021). Mucormycosis: A deadly black fungus infection among COVID-19 patients in India. *Clinical epidemiology and global health*, *12*, 100900.

[2] Liu, M., Spellberg, B., Phan, Q. T., Fu, Y., Fu, Y., Lee, A. S., ... & Ibrahim, A. S. (2010). The endothelial cell receptor GRP78 is required for mucormycosis pathogenesis in diabetic mice. *The Journal of clinical investigation*, *120*(6), 1914-1924.

[3] Serris, A., Danion, F., & Lanternier, F. (2019). Disease entities in mucormycosis. *Journal of Fungi, 5*(1), 23.

[4] Metwally, M. I., Mobashir, M., Sweed, A. H., Mahmoud, S. M., Hassan, A. G., ElKashishy, K., ... & Idris, S. K. (2022). Post COVID-19 head and neck mucormycosis: MR imaging spectrum and staging. *Academic Radiology, 29*(5), 674-684.

[5] Sahu, M., Shah, M., Mallela, V. R., Kola, V. R., Boorugu, H. K., Punjani, A. A., ... & Sahoo, P. R. (2023). COVID-19 associated multisystemic mucormycosis from India: a multicentric retrospective study on clinical profile, predisposing factors, cumulative mortality and factors affecting outcome. *Infection, 51*(2), 407-416.

[6] Singh, A. K., Singh, R., Joshi, S. R., & Misra, A. (2021). Mucormycosis in COVID-19: a systematic review of cases reported worldwide and in India. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews, 15*(4), 102146.

[7] Roden, M. M., Zaoutis, T. E., Buchanan, W. L., Knudsen, T. A., Sarkisova, T. A., Schaufele, R. L., ... & Walsh, T. J. (2005). Epidemiology and outcome of zygomycosis: a review of 929 reported cases. *Clinical infectious diseases, 41*(5), 634-653.

[8] Jeong, W., Keighley, C., Wolfe, R., Lee, W. L., Slavin, M. A., Kong, D. C. M., & Chen, S. A. (2019). The epidemiology and clinical manifestations of mucormycosis: a systematic review and meta-analysis of case reports. *Clinical microbiology and infection, 25*(1), 26-34.

[9] Reid G., Lynch J.P., Fishbein M.C., Clark N.M. Mucormycosis. Semin. Respir. Crit. Care Med. 2020;41:099-114. doi: 10.1055/s-0039-3401992.

[10] Kamath, S., Kumar, M., Sarkar, N., Ahmed, T., Sunder, A., KAMATH, S. D., & SUNDER, A. (2022). Study of profile of mucormycosis during the second wave of COVID-19 in a tertiary care hospital. *Cureus, 14*(1), e21054.

[11] Ezeokoli, O. T., Gcilitshana, O., & Pohl, C. H. (2021). Risk factors for fungal co-infections in critically ill COVID-19 patients, with a focus on immunosuppressants. *Journal of Fungi, 7*(7), 545.

[12] Chander, J., Kaur, M., Singla, N., Punia, R. P. S., Singhal, S. K., Attri, A. K., ... & Guarro, J. (2018). Mucormycosis: battle with the deadly enemy over a five-year period in India. *Journal of fungi, 4*(2), 46.

[13] Singla, N., Sharma, N., Sharma, N., Behera, A., & Bhatia, M. (2022). Clinical Profile of Patients Admitted With Mucormycosis During the COVID-19 Pandemic in Medicine Emergency of a Tertiary Care Hospital in North India. *Cureus, 14*(9), e29219.

[14] Gangneux, J. P., Bougnoux, M. E., Dannaoui, E., Cornet, M., & Zahar, J. R. (2020). Invasive fungal diseases during COVID-19: we should be prepared. *Journal de mycologie medicale, 30*(2), 100971.

[15] Lokhande, G. S., Bavaskar, Y. G., Malkar, V. R., Ramanand, J., Surwade, J. B., Saji, D. A., & Suryawanshi, S. (2022). Mucormycosis in patients with COVID-19: A descriptive study at a tertiary care hospital in North Maharashtra. *MGM Journal of Medical Sciences, 9*(1), 72-76.

[16] Patel A, Kaur H, Xess I, Michael JS, Savio J, Rudramurthy S, *et al*. Multicenter epidemiologic study of coronavirus disease-associated mucormycosis, India. Clin Microbiol Infect 2020;26:944.e9-944.e15.

[17] Sen, M., Honavar, S. G., Bansal, R., Sengupta, S., Rao, R., Kim, U., ... & Sowjanya, Y. (2021). 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 journal of ophthalmology, 69*(7), 1670-1692

[18] Gupta, E. M. S. (2017). Clinical Profile of Mucormycosis: A Descriptive analyses. *INTERNATIONAL JOURNAL OF SCIENTIFIC STUDY, 5*(6), 160-163.

[19] Restrepo, A., Salazar, M. E., Cano, L. E., Stover, E. P., Feldman, D., & Stevens, D. (1984). Estrogens inhibit mycelium-to-yeast transformation in the fungus Paracoccidioides brasiliensis: implications for resistance of females to paracoccidioidomycosis. *Infection and immunity, 46*(2), 346-353.

[20] Kashkouli, M. B., Abdolalizadeh, P., Oghazian, M., Hadi, Y., Karimi, N., & Ghazizadeh, M. (2019). Outcomes and factors affecting them in patients with rhino-orbito-cerebral mucormycosis. *British Journal of Ophthalmology, 103*(10), 1460-1465.

[21] Dubey, S., Mukherjee, D., Sarkar, P., Mukhopadhyay, P., Barman, D., Bandopadhyay, M., ... & Ray, B. K. (2021). COVID-19 associated rhino-orbital-cerebral mucormycosis: An observational study from Eastern India, with special emphasis on neurological spectrum. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews, 15*(5), 102267.

[22] Seema Patel, B.D Bokare, A. Keche, D. Birhade, A. Kuthe and R. Darokar (2022); Mucormycosis in covid 19- 2nd wave : clinical profile in central india Int. J. of Adv. Res. 10 (Jan). 785-789] (ISSN 2320-5407).

[23] Agrawal, A., Dixit, Y., Yonati, V., Nigam, P., & Kheti, P. (2022). Imaging of COVID-19-associated rhino-orbital-cerebral mucormycosis: imaging analysis of 120 patients. *The Egyptian Journal of Otolaryngology, 38*(1), 1-8.

[24] Therakathu J, Prabhu S, Irodi A, Sudhakar SV, Yadav VK, Rupa V. Imaging features of rhinocerebralmucormycosis: a study of 43 patients. Egypt J RadiolNucl Med. 2018;49:447-452.

[25] Yadav, T., Tiwari, S., Gupta, A., Garg, P. K., Khera, P. S., Rajagopal, R., ... & Misra, S. (2022). Magnetic resonance imaging in coronavirus disease-2019 associated rhino-orbital-cerebral mucormycosis (CA-ROCM)-imaging analysis of 50 consecutive patients. *Current Problems in Diagnostic Radiology, 51*(1), 112-120.

[26] Bhanuprasad, K., Manesh, A., Devasagayam, E., Varghese, L., Cherian, L. M., Kurien, R., ... & Varghese, G. M. (2021). Risk factors associated with the mucormycosis epidemic during the COVID-19 pandemic. *International Journal of Infectious Diseases, 111*, 267-270.

[27] Patel, A., Agarwal, R., Rudramurthy, S. M., Shevkani, M., Xess, I., Sharma, R., ... & Network, M. (2021). Multicenter epidemiologic study of coronavirus disease–associated mucormycosis, India. *Emerging infectious diseases, 27*(9), 2349.

[28] Montefusco, L., Ben Nasr, M., D'Addio, F., Loretelli, C., Rossi, A., Pastore, I., ... & Fiorina, P. (2021). Acute and long-term disruption of glycometabolic control after SARS-CoV-2 infection. *Nature Metabolism, 3*(6), 774-785.

[29] Rammaert, B., Lanternier, F., Poirée, S., Kania, R., & Lortholary, O. (2012). Diabetes and mucormycosis: a complex interplay. *Diabetes & metabolism, 38*(3), 193-204.

[30] Tojo, K., Sugawara, Y., Oi, Y., Ogawa, F., Higurashi, T., Yoshimura, Y., ... & Goto, T. (2021). The U-shaped association of serum iron level with COVID-19 severity: Is iron a potential therapeutic target?. *medRxiv*, 2021-02.

[31] Pillsbury, H. C., & Fischer, N. D. (1977). Rhinocerebral mucormycosis. *Archives of Otolaryngology, 103*(10), 600-604.

[32] Petrikkos, G. L. (2009). Lipid formulations of amphotericin B as first-line treatment of zygomycosis. *Clinical Microbiology and Infection, 15*, 87-92.

[33] Revankar, S. G., Shahbaz Hasan, M., & Smith, J. W. (2007). Cure of disseminated zygomycosis with cerebral involvement using high dose liposomal amphotericin B and surgery. *Medical Mycology, 45*(2), 183-185.