

DECODING THE POTENTIAL LINK BETWEEN COVID-19 AND MUCORMYCOSIS: LITERATURE REVIEW

Descifrando el vínculo potencial entre la COVID-19 y la Mucormicosis: Revisión de la literatura

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ABSTRACT

Background: Mucorales, the causative agent of mucormycosis, is a life-threatening fungal infection that primarily affects immunocompromised hosts. This condition is becoming more severe during the current COVID-19 pandemic. The objective is to decipher the link between mucormycosis, steroids, and the associated co-morbidities of COVID-associated mucormycosis (CAM). This study is focussed on assessing the various aspects of COVID related mucormycosis. **Aim:** To systematically review the reported cases of CAM, clinical presentation with steroid therapy and associated co-morbidities.

Materials and Methods: MeSH terms like mucormycosis, diabetes, SARS-CoV-2 infection, sinus, orbit, and palate were searched in the PUBMED and Google Scholar databases, and 20 case reports and case series were identified.

Results: We found that India had the highest number of cases (60%), 55% of the infected patients were male, 65% had a history of diabetes and the associated risk factor was uncontrolled diabetes (90%). The common clinical presentation among the cases was noted to be necrosis and swelling, with 55% of the cases reported to be rhino orbital mucormycosis. In most of the cases cytological and histological examination had been performed with haematoxylin & eosin, KOH, lactophenol cotton blue, and special stains such as PAS and GMS had been used in few cases along with culture in Sabouraud dextrose agar. Regarding treatment, 85% of the cases were treated with amphotericin B and in 15% of cases a combination of amphotericin B and posaconazole was employed. The rate of mortality reported was estimated to be 25%.

Conclusion: COVID-19 infection poses a significant threat to diabetic patients, increasing their susceptibility to mucormycosis. Therefore, the careful use of steroids and routine monitoring are essential in preventing this invasive infection.

Keywords: Mucormycosis; COVID-19; Steroids; Diabetes mellitus; Risk factors; Mortality

RESUMEN

Antecedentes: Los Mucorales, agentes causantes de la mucormicosis, son una infección fúngica potencialmente mortal que afecta principalmente a pacientes inmunocomprometidos. Esta condición se está volviendo más grave durante la actual pandemia de COVID-19. El objetivo de este estudio es descifrar el vínculo entre la mucormicosis, los esteroides y las comorbilidades asociadas con la Mucormicosis asociada a COVID (MAC). Este estudio se enfoca en evaluar diversos aspectos de la mucormicosis relacionada con la COVID-19. **Objetivo:** Revisar sistemáticamente los casos reportados de MAC, la presentación clínica con terapia con esteroides y las comorbilidades asociadas.

Materiales y métodos: Se buscaron términos MeSH como Mucormicosis, diabetes, infección por SARS-CoV-2, sinus, órbita y paladar en las bases de datos PUBMED y Google Scholar, obteniendo 20 informes de casos y series de casos reportados.

Resultado: Encontramos que India tuvo el mayor número de casos (60%), el 55% de los pacientes infectados eran hombres, el 65% tenía antecedentes de diabetes y el factor de riesgo asociado era la diabetes no controlada (90%). La presentación clínica más común entre los casos observados fue necrosis e hinchazón, y el 55% de los casos fueron diagnosticados como mucormicosis rino-orbital. En la mayoría de los casos, se realizó un examen citológico e histológico utilizando hematoxilina-eosina, KOH, lactofenol algodón azul, y tinciones especiales como PAS y GMS, en algunos casos junto con cultivos en agar Sabouraud dextrosa. En cuanto al tratamiento, el 85% de los casos fueron tratados con anfotericina B y en el 15% de los casos se empleó una combinación de anfotericina B y posaconazol. La tasa de mortalidad reportada fue estimada en un 25%.

Conclusión: La infección por COVID-19 representa una amenaza significativa para los pacientes diabéticos, aumentando su susceptibilidad a la mucormicosis. Por lo tanto, el uso cuidadoso de esteroides y la monitorización rutinaria son esenciales para prevenir esta infección invasiva.

Palabras Clave: Mucormicosis; COVID-19; Esteroides; Diabetes mellitus; Factores de riesgo; Mortalidad

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CITE AS: Mounika S, V Vasanthi, Divya B, Narayan M, Kumar AR, Rajkumar K. Decoding the potential link between Covid-19 and Mucormycosis: Literature review. *J Oral Res.* 2024; 13(1):431-442. doi:10.17126/joralres.2024.038

Received: February 14, 2024.

Accepted: May 03, 2024.

Published online: December 31, 2024

ISSN Print 0719-2460

ISSN Online 0719-2479

INTRODUCTION

Coronaviruses are enveloped, spherical or pleomorphic, single-stranded RNA viruses. They are classified into four subtypes: alpha, beta, gamma, and delta, with each subtype containing several serotypes. The first case of a coronavirus infection was reported as a cold (flu-like symptoms) in 1960. Coronaviruses were considered non-fatal until the year 2002.

Later the emergence and spread of a type of coronavirus to the United States America, Hong Kong, Singapore, Thailand, Vietnam and Taiwan, identified and reported to cause Severe Acute Respiratory Distress Syndrome, with mortality of 1000 patients occurred in the year 2003, with 8096 patients confirmed to be infected.

The World Health Organisation (WHO) declared it a 'state emergency'. In 2012, Saudi Arabia reported many cases of this coronavirus infection¹ and is followed by the current pandemic, that is Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), an enveloped RNA beta coronavirus that originated in Wuhan, China, in December 2019² and has since led to the COVID-19 pandemic. The clinical presentation of COVID-19 varies, with symptoms ranging from mild, self-limiting respiratory issues. COVID 19 presentation ranges from mild, self-limiting respiratory tract diseases, pneumonia, multiorgan failure to death.³

Recently the rising complication seen in COVID patients is the commonly called Black fungus or the mucormycosis.⁴ Mucormycosis is a fungal infection previously known as

zygomycosis and is caused by mucormycetes. This angioinvasive disease is characterized by infarction and necrosis⁵ and it affects the sinus, lungs, or skin through inhalation of spores from the air or via penetration of skin through a cut or burn. The classification based on the anatomic localisation includes, rhino-orbital-cerebral, pulmonary, gastrointestinal, cutaneous, renal, and disseminated mucormycosis.^{6,7}

Mucormycosis presents as a secondary infection in COVID patients. The predisposing factors involved are immunocompromised patients, particularly in those with diabetes mellitus, haematological malignancy, hematopoietic stem cell transplantation, and solid organ transplantation.⁷ Though there are many proposed factors for the occurrence of mucormycosis in COVID patients, the major underlying factor among the Indian population is reported to be uncontrolled diabetes.⁸⁻¹⁰

On the other hand, hematopoietic stem cell transplantation and solid organ transplantation are the underlying factors in other countries.⁷⁻¹²

The Leading International Fungal Education (LIFE) portal estimated the load of serious fungal infections worldwide and reported an annual prevalence of around 10,000 cases of Mucormycosis globally, excluding India but, after the inclusion of data collected from India, the estimate of Mucormycosis drastically rose to 910,00.¹³

However the Epidemiology of Mucormycosis in India reported in 2021, the calculated prevalence of Mucormycosis was at an alarming rate of nearly 70 times higher

than the global data.¹⁴ This systematic review aims to decode the link between mucormycosis, their clinical presentation, steroid therapy and the associated comorbidities of COVID-associated Mucormycosis (CAM) in the prevailing COVID 19 pandemic.

Search strategy

Case reports and case series were only considered in this review. Case reports and case series of orbital, rhino-orbital, sino-orbital, sino-nasal and palatal were included. Pre-proof articles, review articles, duplicates and articles published in languages other than English were excluded.

MATERIALS AND METHODS

Data sources

Databases such as *PubMed*, *Google Scholar* were searched using the *MeSH* terms - mucormycosis, diabetes, SAARS CoV 2 infection, orbital, sinus, palate using the Boolean operators AND/OR in various combinations following the Preferred Reporting items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.

RESULTS

From the initial search, we obtained 12 articles from Pub Med and 38 articles from Google Scholar. The manuscripts were screened based on the inclusion and exclusion criteria, resulting in a total of 20 articles, which included two case series and 18 case reports that were evaluated

Figure 1.

Data extraction flowchart as per PRISMA guidelines.

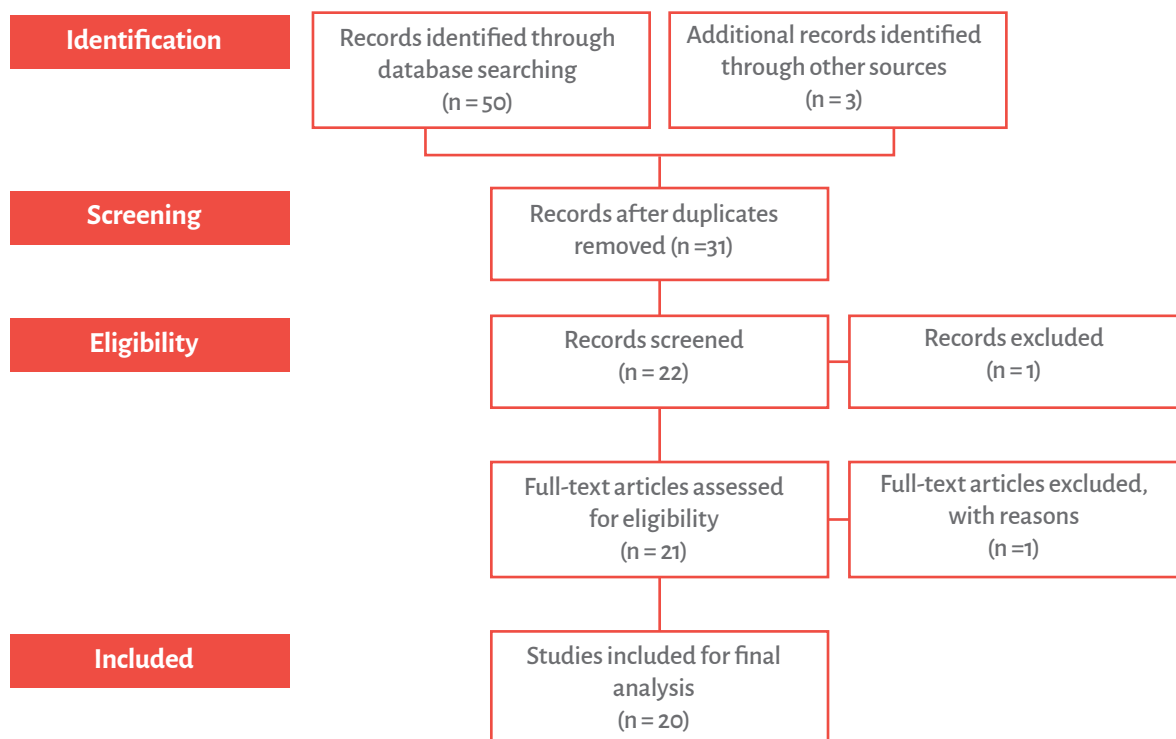


Table 1. Overview of the reported mucormycosis cases.

Author & Year	Country	Age/Sex	Risk Factor/ Comorbid Condition	Clinical Presentation	Day Of Mucor	Site	Clinical workup	Staining	Special Stain	Culture	Treatment	Prognosis
Waizel-Haiat et al., ¹⁵ (2021)	Mexico, USA	24/M	Diabetic ketoacidosis	Pain of left mid face, progressive left eye lid swelling, maxillary hypoesthesia and vasoconstriction of left nasal mucosa	6	ROM	Smear	-----	-----	SDA	AMB	Died
Mehta et al., ¹⁶ (2020)	India	60/M	Uncontrolled diabetes	Proptosis of eye, edema, swelling and necrosis	10	OM	Biopsy	-----	-----	SDA	AMB	Died
Pauli et al., ¹⁷ (2021)	Brazil	50/F	Uncontrolled diabetes	Ulcer on the hard palate with progression in size affecting the entire palate and middle third of the face	8	Palatal	CT, Incisional biopsy	H&E	----	GMS, PAS	AMB, anti histamines	Lesion resolved after 60 days and asymptomatic
Bachchan et al., ¹⁸ (2021)	India	70/M	Uncontrolled diabetes, anemia, farmer as occupation	Swelling with tenderness on the left malar region, blocked ethmoid sinus	25	Maxillary and ethmoidal air sinus	Anterior, rhinoscopy	PAP, KOH	GMS	----	AMB	Patient was not willing to receive treatment
Roopa et al., ¹⁹ (2021)	India	59/M	Uncontrolled diabetes	Bleeding and painful gums during treatment for covid, intermittent pain radiating to left side of the head to left maxilla	20	Hard palate and left maxilla	CT, MDCT, BIOPSY	-----	-----	----	AMB	Good prognosis
Pathak et al., ²⁰ (2021)	India	65/M	Uncontrolled diabetes	Asymptomatic, necrotic ulcerative lesion on the hard palate with blackish grey slough	20-25	Hard palate	Biopsy & CT	H&E	-----	----	Not mentioned	Good prognosis
Baskar et al., ²¹ (2021)	India	28/M	Corticosteroid treatment	Sudden loss of vision, swelling of right eye, ecchymosis	5	ROM	Biopsy	H&E	-----	----	AMB, PZS	Good prognosis
Seth et al., ²² (2021)	India	55/M	Uncontrolled diabetes, steroids	Peri orbital pain, nasal stuffiness, white crusting of the hard palate	16	ROM	Smear	KOH	-----	----	AMB	In follow up
Maini et al., ²³ (2021)	India	38/F	Corticosteroid treatment	Proptosis, ecchymosis, pain and swelling of the left	18	Maxillary and ethmoidal air sinus	Biopsy	H&E	-----	----	AMB	Good prognosis
Revannavar et al., ²⁴ (2021)	India	Middle aged woman	Uncontrolled diabetes	Complete ptosis of left eye, facial pain	5	Maxillary, frontal ethmoidal air sinus	Biopsy	-----	PAS	----	AMB	Good prognosis
Awal et al., ²⁵ (2021)	India	65/F	Uncontrolled diabetes	Left orbital pain, ptosis, nasal congestion	short duration	ROM	Smear	KOH, LPCP	-----	SDA	AMB	Good prognosis

Author & Year	Country	Age/Sex	Risk Factor/ Comorbid Condition	Clinical Presentation	Day Of Mucor	Site	Clinical workup	Staining	Special Stain	Culture	Treatment	Prognosis
Awal et al., ²⁵ (2021)	India	45/F	Not mentioned	Hemifacial pain and right orbital swelling	21	ROM	Smear	KOH, LPCP	----	SDA	AMB	Good prognosis
Awal et al., ²⁵ (2021)	India	36/M	COVID pneumonia	Left hemifacial pain with intracranial extension	Not mentioned	ROM	Smear	KOH, LPCP	----	SDA	AMB	Good prognosis
Wertlman-Ehrenreich et al., ²⁶ (2021)	USA	33/F	Diabetic ketoacidosis	Left eye ptosis, proptosis	3	ROM	Smear, MRI	----	----	----	----	----
Mekonnen et al., ²⁷ (2021)	USA	60/M	Uncontrolled diabetes	Prominence of right eye, proptosis, asymmetric retrobulbar fat and opacification	8	Acute invasive ROM	Biopsy	----	----	----	----	----
Venugopal et al., ²⁸ (2021)	India	53/F	Uncontrolled diabetes	Painful lesion in the hard palate, pain radiating to mid face, jaw, with putrid halitosis	8	Hard Palate	Biopsy	----	----	----	----	----
Tabarsi et al., ²⁹ (2021)	Iran	50/F	Uncontrolled diabetes	Facial swelling and numbness, periorbital edema, head ache, erythema	26	Rhinosinusitis	Nasal endoscopy, biopsy	----	----	----	----	----
Veisi et al., ³⁰ (2021)	Iran	40/F	Uncontrolled diabetes	Bilateral visual loss, complete ophthalmoplegia of the right eye	15	ROM	CT, MRI, endoscopy of sinus	H&E	H&E	SDA	AMB	Died
Veisi et al., ³⁰ (2021)	Iran	54/M	Uncontrolled diabetes	Loss of vision, proptosis, orbital inflammation, complete ophthalmoplegia of left side	13	ROM	CT, MRI, endoscopy of sinus	----	H&E	PAS	AMB, PSZ	Alive
Dilbag et al., ³¹ (2021)	India	60/M	Uncontrolled diabetes	Periorbital swelling, discolouration, proptosis, chemosis of the right eye	10	ROM	CT	----	Gram stain, PAS	----	AMB	Gradual improvement

OM: Orbital mucormycosis. **ROM:** Rhino orbital mucormycosis. **SDA:** Sabouraud dextrose agar. **PAS:** Periodic acid Schiff. **GMS:** Grocott methenamine silver. **H&E:** hematoxylin and eosin. **PAP:** Papanicolaou stain. **LPCP:** Lactophenol cotton blue. **AMB:** Amphoterin B. **PSZ:** Amphoterin B and posaconazole. **CT:** Computed tomography. **MRI:** Magnetic resonance imaging. **MDCT:** multi-detector computed tomography.

according to the objectives of the study (Figure 1). Overview of the case reports and case series included in the systematic review were tabulated (Table 1). A total of 20 cases were analysed in the review.

Based on the data collected, we found that India accounted for 60% of the cases, followed by the USA (20%), Iran (15%), and Brazil (5%). The review also revealed that 55% of the affected individuals were male, while 45% were female, with various variants of mucormycosis; the age of patients ranged from 28 to 70 years of age.

Among the 20 patients, 65% had a history of diabetes, 5% had the history of hypertension and asthma, 5% had obesity as a risk factor and in 20% of the cases the underlying medical history was not mentioned. In 90% of the cases, diabetic ketoacidosis was identified as the associated risk factor for mucormycosis, COVID-associated pneumonia accounted for 5%, while the risk factors for the remaining 5% were not specified.

The timing of mucormycosis occurrence after COVID infection ranged from 5th-26th day and the common clinical presentation was necrosis and swelling. Based on the anatomical site of involvement, rhino-orbital mucormycosis was observed in 55% of cases, sinus involvement in 20%, palatal mucormycosis in 20%, and orbital mucormycosis in 5%.

In most of the cases, cytological and histopathological examination was done for identification of the Mucor species. For culture studies, Sabouraud Dextrose Agar

(SDA) was used in 25% of the cases, while a combination of KOH wet mount and lactophenol cotton blue was employed in the remaining cases. Amphotericin B was the treatment of choice in 85% of the cases and in 15% it was amphotericin B along with posaconazole; 5% of the patients were not willing to receive treatment. While 70% of the patients had good prognosis, 25% of the patients were lost due to complications.

DISCUSSION

The presented systematic review documents 60% of the cases are reported from India, the majority of the affected individuals were males with a history of diabetes who received glucocorticoids for the treatment of COVID 19.

In the pre-COVID era, Roden *et al.*,³² conducted a review of 929 cases spanning from 1940 to 2003, where they found that diabetes was the most common underlying factor. The majority of these patients presented with sinus and rhino-cerebral types of infections. This is in agreement with the present review where, the rhino orbital mucormycosis was the most common form, representing 55% of the cases, while sinus involvement presented in 20% of the patients.

This systematic review primarily focuses on the relationship between COVID-19 and diabetes, and secondarily explores the connection between mucormycosis and diabetes. With approximately 77 million people living with diabetes in India,³³ and given that mucormycosis is known to primarily affect individuals with a history of diabetes, this

likely explains the higher number of cases reported in India. According to Patel *et al.*,³⁴ who conducted a multicentric study across 12 centres in India and Bala *et al.*,³⁵ who conducted a prospective study in North India, the major risk factor for mucormycosis was reported to be diabetes and rhino orbital mucormycosis was the most common form. John *et al.*,³⁶ documented that the glycemic index was contributing to the development of mucormycosis in diabetic patients in their review on CAM among 41 patients.

SARS-CoV-2 can infect and replicate in the human islet cells.³⁷ causing damage with reduction in endogenous insulin secretion. This in combination with the huge amount of cytokines released from the COVID infection results in insulin resistance.³⁸ In severe cases of COVID-19, elevated levels of IL-6 interfere with the phosphorylation of the insulin receptor and insulin receptor substrate, thereby contributing to insulin resistance.³⁹ Drugs such as glucocorticoids, lopinavir and remdesivir which are used for treating COVID infection also contribute to poor control of glucose thus making the patients more susceptible to mucormycosis.

An additional factor that predisposes individuals to mucormycosis is the virulence of the organism, which can cause the disease by utilizing iron from the host, an essential element for its growth. Normally, iron is bound to host cells in the forms of transferrin, ferritin, and lactoferrin, which help prevent the toxic effects of free iron. However, in COVID-19-infected patients, particularly those with diabetes, hemoglobin dissociates from its porphyrin structure, leading to increased iron release

into the bloodstream. This excess iron impairs hemoglobin's ability to deliver oxygen to vital organs, resulting in multiorgan failure and, in severe cases, death.⁴⁰ This occurs due to the elevated free iron causing oxidative damage, inflammation from iron overload and immune dysregulation.⁴¹

In diabetic ketoacidosis patients, elevated free iron levels contribute to the growth of the *Rhizopus oryzae* by providing an acidic environment and hence ketoacidosis patients are more severely affected with mucormycosis than the non ketoacidic patients. So chelation therapy is advised for the patients with COVID infection.

Chelators such as deferasirox, deferoxamine, deferiprone have been proven to be effective.⁴² These iron chelators not only seize the iron and help in reducing the inflammation but are also proven to prevent the virus from binding to the receptors for its entry into the host.⁴³⁻⁴⁵ Mucormycosis infection is characterized by extensive angioinvasion resulting in thrombosis and tissue necrosis.⁴⁶

Earlier it was considered that *Rhizopus oryzae* adhere to the extracellular matrix laminin and type IV collagen and thereby causing damage by penetration.⁴⁷ It was found that the Glucose Regulated Protein (GRP78) acts as a mediator to penetration of Mucorales by causing damage to the endothelial cells. GRP78 is a cellular protein induced by glucose starvation and is a member of the HSP70 protein family present in the endoplasmic reticulum which functions as a cellular chaperon protein.⁴⁸

In case of diabetic ketoacidosis where there

is increased concentration of glucose and iron results in enhanced GRP78 expression thus helping the Mucorales penetration. According to Blandin *et al.*,⁴⁹ the fungal ligand belongs to the CoTH family of proteins and binds GRP78 to enhance the penetration in diabetic ketoacidosis patients and makes them more prone to mucormycosis infection.

The present systematic review has certain limitations. Publication bias is more likely as the reported cases may be an underrepresentation of the real burden in the present scenario. Most of the cases are in the pre-proof stage, few being not published due to lack of culture/histopathology proof and the details on the HbA1c profile is not mentioned in the cases.

CONCLUSION

COVID infection in diabetic patients appears to be a major threat by making the diabetic patients more liable to mucormycosis infection than the others. Thus judicious administration of the steroids and routine monitoring of the patients with timely intervention is needed in preventing the invasive infection.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

ETHICS APPROVAL

Does not apply.

FUNDING

Self-funded.

AUTHORS' CONTRIBUTIONS

S Mounika: Conceptualization, data curation, formal analysis, investigation, methodology, supervision, validation, writing - reviewing and editing

V. Vasanthi: Conceptualization, data curation, formal analysis, investigation, methodology, supervision, validation, writing - reviewing and editing

Bose Divya: Formal analysis, supervision, validation, writing - reviewing and editing.

Madhu Narayan: Formal analysis, supervision, validation, writing - reviewing and editing.

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ACKNOWLEDGEMENTS

None.

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PUBLISHER'S NOTE

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PEER REVIEW

This manuscript was evaluated by the editors of the journal and reviewed by at least two peers in a double-blind process.

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ISSN Print 0719-2460 - ISSN Online 0719-2479.

<https://www.joralres.com/index.php/JOralRes/issue/archive>

REFERENCES

1. Tamsheel Fatima Roohi (2020); An insight review on history, outbreak, pathogenesis, transmission of SARS-CoV-2 virus and COVID-19 *Int. J. of Adv. Res.* 846-863(ISSN 2320-5407).
2. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *The Lancet.* 2020;395(10224):565-74.
3. Izda V, Jeffries MA, Sawalha AH. COVID-19: A review of therapeutic strategies and vaccine candidates. *Clin Immunol.* 2020;108634.
4. Ahmadikia K, Hashemi SJ, Khodavaisy S, Getso MI, Alijani N, Badali H, Mirhendi H, Salehi M, Tabari A, Mohammadi Ardehali M, Kord M. The double-edged sword of systemic corticosteroid therapy in viral pneumonia: A case report and comparative review of influenza-associated mucormycosis versus COVID-19 associated mucormycosis. *Mycoses.* 2021.
5. Frater JL, Hall GS, Procop GW. Histologic features of zygomycosis: emphasis on perineural invasion and fungal morphology. *Archives of pathology & laboratory medicine.* 2001 Mar;125(3):375-8.
6. Roden MM, Zaoutis TE, Buchanan WL, Knudsen TA, Sarkisova TA, Schaufele RL, Sein M, Sein T, Chiou CC, Chu JH, Kontoyiannis DP. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. *Clinical infectious diseases.* 2005 1;41(5):634-53.
7. Jeong W, Keighley C, Wolfe R, Lee WL, Slavin MA, Kong DC, Chen SA. The epidemiology and clinical manifestations of mucormycosis: a systematic review and meta-analysis of case reports. *Clinical Microbiology and Infection.* 2019 1;25(1):26-34.
8. Prakash H, Ghosh AK, Rudramurthy SM, Singh P, Xess I, Savio J, Pamidimukkala U, Jillwin J, Varma S, Das A, Panda NK. A prospective multicenter study on mucormycosis in India: Epidemiology, diagnosis, and treatment. *Medical mycology.* 2019 1;57(4):395-402.
9. Patel A, Kaur H, Xess I, Michael JS, Savio J, Rudramurthy S, Singh R, Shastri P, Umabala P, Sardana R, Kindo A. A multicentre observational study on the epidemiology, risk factors, management and outcomes of mucormycosis in India. *Clinical Microbiology and Infection.* 2020, 1;26(7):944-e9.
10. Patel AK, Patel KK, Patel K, Gohel S, Chakrabarti A. Mucormycosis at a tertiary care centre in Gujarat, India. *Mycoses.* 2017; 60(6):407-11.
11. Skiada A, Pagano LI, Groll A, Zimmerli S, Dupont B, Lagrou K, Lass-Flörl C, Bouza E, Klimko N, Gaustad P, Richardson M. Zygomycosis in Europe: analysis of 230 cases accrued by the registry of the European Confederation of Medical Mycology (ECMM) Working Group on Zygomycosis between 2005 and 2007. *Clinical Microbiology and Infection.* 2011, 1;17(12):1859-67.
12. Kontoyiannis DP, Yang H, Song J, Kelkar SS, Yang X, Azie N, Harrington R, Fan A, Lee E, Spalding JR. Prevalence, clinical and economic burden of mucormycosis-related hospitalizations in the United States: a retrospective study. *BMC infectious diseases.* 2016;16(1):1-6.
13. Prakash H, Chakrabarti A. Global epidemiology of mucormycosis. *Journal of Fungi.* 2019;5(1):26
14. Prakash H, Chakrabarti A. Epidemiology of mucormycosis in India. *Microorganisms.* 2021;9(3):523.
15. Waizel-Haiat S, Guerrero-Paz JA, Sanchez-Hurtado L, Calleja-Alarcon S, Romero-Gutierrez L. A case of fatal rhino-orbital mucormycosis associated with new onset diabetic ketoacidosis and COVID-19. *Cureus.* 2021;13(2).
16. Mehta S, Pandey A. Rhino-orbital mucormycosis associated with COVID-19. *Cureus* 12 (9): e10726.
17. Pauli MA, de Melo Pereira L, Monteiro ML, de Camargo AR, Rabelo GD. Painful palatal lesion in a patient with COVID-19. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology.* 2021
18. Bachchan N , Yadav S, Rawal G , Rai P. Mucormycosis involving paranasal sinuses in a post-COVID-19 patient with an uncontrolled diabetes-A rare presentation in an ongoing pandemic. *IP Indian J Immunol Respir Med* 2021;6(2):137-140
19. Roopa R, Thanthoni M, Warriar AS. COVID-19 Coinfection With Mucormycosis in a Diabetic Patient. *Cureus.* 2021,22;13(6).
20. Pathak K, Karadwal A, Nayak P, Nayak S. Mucormycosis in Post Covid Patient-A Case Report. *Indian Journal of Forensic Medicine & Toxicology.* 2021, 1;15(3):241.

21. Baskar HC, Chandran A, Reddy CS, Singh S. Rhino-orbital mucormycosis in a COVID-19 patient. *BMJ Case Reports CP.* 2021;1;14(6):e244232.
22. Sethi HS, Sen KK, Mohanty SS, Panda S, Krishna KR, Mali C. COVID-19-associated rhino-orbital mucormycosis (CAROM)—a case report. *Egyptian Journal of Radiology and Nuclear Medicine.* 2021;52(1):1-6.
23. 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 ,1;82:105957.
24. Revannavar SM, Supriya PS, Samaga L, Vineeth VK. COVID-19 triggering mucormycosis in a susceptible patient: a new phenomenon in the developing world?. *BMJ Case Reports CP.* 2021,1;14(4):e241663.
25. Awal SS, Biswas SS, Awal SK. Rhino-orbital mucormycosis in COVID-19 patients—a new threat?. *Egyptian Journal of Radiology and Nuclear Medicine.* 2021;52(1):1-6.
26. Werthman-Ehrenreich A. Mucormycosis with orbital compartment syndrome in a patient with COVID-19. *The American journal of emergency medicine.* 2021 1;42:264-e5.
27. Mekonnen ZK, Ashraf DC, Jankowski T, Grob SR, Vagefi MR, Kersten RC, Simko JP, Winn BJ. Acute invasive rhino-orbital mucormycosis in a patient with COVID-19-associated acute respiratory distress syndrome. *Ophthalmic plastic and reconstructive surgery.* 2021;37(2):e40.
28. Venugopal A, Marya A. Palatal mucormycosis in a patient with SARS-CoV-2 infection. *CMAJ.* 2021 16;193(32):E1254.
29. Tabarsi P, Khalili N, Pourabdollah M, Sharifynia S, Safavi Naeini A, Ghorbani J, Mohamadnia A, Abtahian Z, Askari E. Case Report: COVID-19-associated Rhinosinusitis Mucormycosis Caused by *Rhizopus arrhizus*: A Rare but Potentially Fatal Infection Occurring After Treatment with Corticosteroids. *Am J Trop Med Hyg.* 2021 Jul 8;105(2):449-453. doi: 10.4269/ajtmh.21-0359. PMID: 34237015; PMCID: PMC8437195.
30. Veisi A, Bagheri A, Eshaghi M, Rikhtehgar MH, Rezaei Kanavi M, Farjad R. Rhino-orbital mucormycosis during steroid therapy in COVID-19 patients: a case report. *European Journal of Ophthalmology.* 2021. DOI: 10.11206721211009450.
31. Dilbag S, Harveen K and NC K. Covid-19 and Rhino-Orbital Mucormycosis – A Case Report. *Int J Pul & Res Sci.* 2021; 5(1): 555654. doi: 10.19080/IJOPRS.2021.05.555654
32. Roden MM, Zaoutis TE, Buchanan WL, Knudsen TA, Sarkisova TA, Schaufele RL, Sein M, Sein T, Chiou CC, Chu JH, Kontoyiannis DP. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. *Clinical infectious diseases.* 2005 ;41(5):634-53.
33. IDF DIABETES ATLAS Ninth Edition 2019. Accessed May 12, 2020.
34. Patel A, Kaur H, Xess I, Michael JS, Savio J, Rudramurthy S, Singh R, Shastri P, Umabala P, Sardana R, Kindo A. A multicentre observational study on the epidemiology, risk factors, management and outcomes of mucormycosis in India. *Clinical Microbiology and Infection.* 2020, 1;26(7):944-e9.
35. Bala K, Chander J, Handa U, Punia RS, Attri AK. A prospective study of mucormycosis in north India: experience from a tertiary care hospital. *Medical mycology.* 2015 , 1;53(3):248-57.
36. John TM, Jacob CN, Kontoyiannis DP. When uncontrolled diabetes mellitus and severe COVID-19 converge: the perfect storm for mucormycosis. *Journal of Fungi.* 2021;7(4):298.
37. Müller JA, Groß R, Conzelmann C, Krüger J, Merle U, Steinhart J, Weil T, Koepke L, Bozzo CP, Read C, Fois G. SARS-CoV-2 infects and replicates in cells of the human endocrine and exocrine pancreas. *Nature Metabolism.* 2021;3(2):149-65.
38. Pal R, Bhadada SK. COVID- 19 and diabetes mellitus: an unholy interaction of two pandemics. *Diabetes Metab Syndr Clin Res Rev.* 2020:513- 517
39. Rehman K, Akash MSH, Liaqat A, Kamal S, Qadir MI, Rasul A. Role of interleukin- 6 in development of insulin resistance and type 2 diabetes mellitus. *Crit Rev Eukaryot Gene Expr.* 2017:229- 236.
40. W. Liu, H. Li, Read R. Flawed methods in “COVID-19: attacks the 1-beta chain of hemoglobin and captures the porphyrin to inhibit human heme metabolism”.
41. Moreira AC, Mesquita G, Gomes MS. Ferritin: an inflammatory player keeping iron at the core of pathogen-host interactions. *Microorganisms.* 2020;8(4):589.

42. Perricone C, Bartoloni E, Bursi R, Cafaro G, Guidelli GM, Shoenfeld Y, Gerli R. COVID-19 as part of the hyperferritinemic syndromes: the role of iron depletion therapy. *Immunologic research*. 2020 :1-2.
43. Chang R, Ng TB, Sun WZ. Lactoferrin as potential preventative and adjunct treatment for COVID-19. *International Journal of Antimicrobial Agents*. 2020;56(3):106118.
44. Wang B, Timilsena YP, Blanch E, Adhikari B. Lactoferrin: Structure, function, denaturation and digestion. *Critical reviews in food science and nutrition*. 2019;59(4):580-96.
45. Rainey NE, Moustapha A, Saric A, Nicolas G, Sureau F, Petit PX. Iron chelation by curcumin suppresses both curcumin-induced autophagy and cell death together with iron overload neoplastic transformation. *Cell death discovery*. 2019;5(1):1-5.
46. Ibrahim AS, Edwards JE, Filler SG. *Zygomycosis*. 241–251. *Clinical mycology*. Oxford University Press, New York, NY. 2003.
47. Bouchara JP, Oumeziane NA, Lissitzky JC, Larcher G, Tronchin G, Chabasse D. Attachment of spores of the human pathogenic fungus *Rhizopus oryzae* to extracellular matrix components. *European journal of cell biology*. 1996;70(1):76-83.
48. Wang M, Wey S, Zhang Y, Ye R, Lee AS. Role of the unfolded protein response regulator GRP78/BiP in development, cancer, and neurological disorders. *Antioxidants & redox signaling*. 2009;11(9):2307-16.
49. Baldin C, Ibrahim AS. Molecular mechanisms of mucormycosis—the bitter and the sweet. *PLoS pathogens*. 2017;13(8):e1006408.