Downloaded from http://journals.lww.com/pajo by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8K2+Ya6H515kE= on 03/01/2024

Original Article

Correlation of the severity of mucormycosis with levels of inflammatory markers in COVID-19 patients

S. Kruthika, N. Inchara, Poojitha Madala

Department of Ophthalmology, Sri Devaraj Urs Medical College, SDUAHER, Kolar, Karnataka, India

Abstract

Purpose: The purpose of the study is to explore the clinical spectrum of rhino-orbital cerebral mucormycosis (ROCM) and to correlate its severity with the levels of inflammatory markers of COVID-19 patients.

Materials and Methods: It is an observational analytical study. Clinical and laboratory data of the patients with mucormycosis admitted in COVID-19 wards in a notified nodal tertiary care center were collected and stratified clinically according to the severity of ROCM. Serum ferritin, serum lactate dehydrogenase (LDH), D-dimer, total count, neutrophils, and lymphocyte count were considered primary outcome variables. The severity of the ROCM (Stage II, Stage III, and Stage IV mucormycosis) was considered the primary explanatory variable.

Results: Forty-five participants were included, of which 38 (84%) were male and 7 (16%) were female. The mean age was 48.71 ± 10.71 years, which ranged from 29 to 75 years. In people with the severity of the ROCM, 26 (58%) were in Stage II, 15 (33%) were in Stage III, and 4 (9%) were in Stage IV. The mean serum ferritin, mean serum LDH, and D-dimer across the severity of ROCM were statistically significant. The median total count, mean neutrophils, and mean lymphocytes across the severity of ROCM were not statistically significant.

Conclusion: The study shows that raised serum ferritin, LDH, and D-dimer levels at admission significantly predict disease severity in COVID-19 patients with mucormycosis. Mucormycosis and its severity are associated with higher inflammatory markers levels than the mild disease in COVID-19 patients. Tracking these markers may allow early identification or even prediction of disease progression.

Keywords: COVID-19, D-dimer, inflammatory markers, lactate dehydrogenase, mucormycosis, rhino-orbital-cerebral mucormycosis, serum ferritin

Address for correspondence: Dr. N. Inchara, House No. 01, G Block, Staff Quarters, SDUMC Campus, Tamaka, Kolar - 563 103, Karnataka, India.
E-mail: dr.inchara@gmail.com

Received: 18 April 2023, **Revised:** 04 May 2023, **Accepted:** 08 May 2023, **Published Online:** 27 Jun 2023

INTRODUCTION

COVID-19 is caused due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Besides, COVID-19 has been associated with a wide range of opportunistic bacterial and fungal infections ranging from mild upper respiratory tract infections to fatal pneumonia.[1,2] This dreaded disease, along with the involvement of the respiratory system, induces an

Access this article online	
Quick Response Code:	Website: www.thepajo.org
	DOI: 10.4103/pajo.pajo_24_23

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Kruthika S, Inchara N, Madala P. Correlation of the severity of mucormycosis with levels of inflammatory markers in COVID-19 patients. Pan Am J Ophthalmol 2023;5:25.

Downloaded from http://journals.lww.com/pajo by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8K2+Ya6H515kE= on 03/01/2024

inflammatory response triggered by the rapid viral replication of SARS-CoV-2. Cellular destruction can recruit macrophages and monocytes and induce the release of cytokines and chemokines.[3,4]

Lately, worldwide, particularly in India, several cases of mucormycosis have been increasingly reported in patients with COVID-19 infection.[5,6] During this period, a Tertiary Care Teaching Hospital in South India, a notified nodal center for diagnosis and management of "Black Fungus," has witnessed a sudden rise in cases of invasive fungal sinusitis, with mucormycosis features needing emergency interventions.

Mucormycosis belongs to the order *Mucorales*, and the most common presentation is rhino-orbital-cerebral mucormycosis (ROCM) conventionally and in COVID-19 patients. The upsurge of mucormycosis amidst the ongoing pandemic was hypothesized to be driven by the interplay between host factors such as weakened immunity following COVID-19, poorly controlled diabetes mellitus, rampant use of steroids/immunomodulators, and other factors such as a prolonged hospital stay, continuous oxygen support, poor hospital infection control, and nursing care practices.[7] Mortality is high with invasive mucormycosis by its complication such as intracranial involvement, cavernous sinus thrombosis, and osteomyelitis. In extremely rare situations, such infections can be seen in immunocompetent patients.[8] They cause tissue necrosis which leads to severe morbidity and mortality by angioinvasion and thromboembolism.[9,10] Clinically, ROCM presents with atypical signs and symptoms similar to complicated sinusitis, including nasal blockade, crusting, proptosis, facial pain, edema, ptosis, chemosis, and even ophthalmoplegia, with headache and fever. Rapid disease progression may occur, with reported mortality rates of 50%–80% from intra-orbital and intracranial complications without early diagnosis and treatment.[11]

We carried out this study to explore and correlate the inflammatory markers and severity of mucormycosis in COVID-19 patients, which can help to decide on early intervention to prevent morbidity and mortality among these patients.

MATERIALS AND METHODS

Study setting and design

An observational analytical study was conducted at the notified nodal Tertiary Care Center for Black Fungus cases in Kolar District, Karnataka, India, for 3 months, from April 2021 to June 2021.

Inclusion criteria

Patients with a history of COVID-19 infection with proven fungal elements in fungal culture or histopathological examination belonging to the *Mucorales* family were included in the study.

Exclusion criteria

Those with no history of COVID-19 infection and a history of surgical debridement elsewhere were excluded from the study.

Study population and sample size

Nodal center had 98 cases of invasive ROCM during the second wave of the COVID-19 pandemic. Forty-five patients admitted to the hospital with COVID-19-positive infection with proven fungal culture belonging to *Mucorales* during the period were included in the study using nonprobability sampling.

Data collection

Clinical history and inflammatory laboratory parameters (including serum ferritin, serum lactate dehydrogenase (LDH), D-dimer, and total and differential white blood cell [WBC] count) were recorded. A detailed ophthalmological examination was performed, and the findings were noted.

Statistical analysis

We considered inflammatory markers as primary outcome variables. Whereas the severity of the ROCM (Stage II, Stage III, and Stage IV) from the Directorate of Medical Education guidelines, the proposed staging of post-COVID-19 ROCM suggested by the Government of Tamil Nadu, India, was considered as a primary explanatory variable.[12,13] The proposed staging is Stage I – Involvement of the nasal mucosa, Stage II – Involvement of the paranasal sinus, Stage III – Involvement of the orbit, and Stage IV – Involvement of the central nervous system.[14-16] We conducted a descriptive analysis using mean and standard deviation for quantitative variables and proportion for categorical variables. Data were checked for normal distribution, and the data with normally distributed quantitative parameters and the mean values were compared between study groups using the ANOVA test. For nonnormally distributed quantitative parameters, descriptive analysis was measured using medians and interquartile range (IQR). The comparison between study groups was tested using the Kruskal–Wallis test with a statistically significant $P < 0.05$. Data were analyzed using SPSS software, version 22.0 (Chicago, IL, USA).

Downloaded from http://journals.lww.com/pajo by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8K2+Ya6H515kE= on 03/01/2024

Ethics approval and confidentiality

The Institutional Ethics Review Committee approved this study. The patient's identity and privacy were concealed, and confidentiality of data was ensured during the study.

RESULTS

A total of 45 participants were included in the final analysis. Majority were male, 38 (84%), and 7 (16%) were female. The mean age was 48.71 ± 10.71 years, ranging from 29 to 75. In people with the severity of the ROCM, 26 (58%) were in Stage II, 15 (33%) were in Stage III, and 4 (9%) were in Stage IV. The mean serum ferritin was 491.48 ± 320.46 ng/mL, ranging from 46.80 to 1000; the mean serum LDH (IU/L) was 416.91 ± 221.24, ranging from 100 to 897; the mean D-dimer (ng/mL) was 1248.67 ± 2117.29, ranging from 53.10 to 10,000; the mean total count (/μL) was 15.77 ± 11.81, ranging from 5.61 to 87; the mean neutrophils (%) was 78.55 ± 8.51 ranging from 56 to 94; the mean lymphocytes (%) was 12.30 ± 6.71 ranging from 2.10 to 31.40. Among the study participants, 25 (56%) had high levels of serum ferritin (ng/mL), 20 (44%) had a normal level, 30 (67%) had a high level of serum LDH (IU/L), and 15 (33%) had a normal level, 34 (76%) had high-level D-dimer (ng/mL), and 11 (24%) had a normal level, 39 (87%) had high total WBC count (/μL), and 6 (13%) had normal count, 44 (98%) had high neutrophils (%) count, and 1 (2%) had normal count, 41 (91%) had low lymphocytes count, and 4 (9%) had normal count. A summary of the demographic and baseline characteristics is given in Table 1.

The mean serum ferritin (ng/mL) with the severity of the ROCM in Stage II was 397.94 ± 268.73, it was 592.07 ± 311.76 in Stage III, and it was 682 ± 251.33 in Stage IV, the mean difference of serum ferritin across the severity of ROCM was statistically significant [$P = 0.048$, Figure 1].

The mean serum LDH (IU/L) with the severity of the ROCM in Stage II was 327.27 ± 180.15, it was 563.13 ± 211.23 in Stage III, and it was 451.25 ± 247.18 in Stage IV, a mean difference of serum LDH across the severity of ROCM was statistically significant [$P = 0.003$, Figure 2].

The mean D-dimer (ng/mL) with the severity of the ROCM in Stage II was 614.6 ± 272.36, was 776.79 ± 241.05 in Stage III, and it was 901.42 ± 158.45 in Stage IV, the mean difference of D-dimer across the severity of ROCM was statistically significant [$P = 0.044$, Figure 3].

Table 1: Demographic and baseline characteristics of the subjects (*n*=45)

Parameter	Summary, *n* (%)
Total cases	45
Diabetes mellitus	35 (78)
Hypertension	10 (22)
Steroid use	29 (64)
Sinusitis	45 (100)
Low vision	22 (49)
Ptosis	32 (71)
Proptosis	26 (58)
EOM affected	14-reduced (31) 17-no movements (38)
Complete ophthalmoplegia	14 (31)
CRAO	10 (22)
Lid edema	35 (78)
Chemosis	29 (64)
Congestion	20 (44)
Lab parameter (mean±SD)	
Serum ferritin (ng/mL)	491.48±320.46 (ranged 46.80–1000)
Serum LDH (IU/L)	416.91±221.24 (ranged 100–897)
D-dimer (ng/mL)	1248.67±2117.29 (ranged 53.10–10000)
Total count (/μL)	15.77±11.81 (ranged 5.61–87)
Neutrophils (%)	78.55±8.51 (ranged 56–94)
Lymphocytes (%)	12.3±6.71 (ranged 2.10–31.40)
Serum ferritin (ng/mL)	
High	25 (56)
Normal	20 (44)
Serum LDH (IU/L)	
High	30 (67)
Normal	15 (33)
D-dimer (ng/mL)	
High	33 (73)
Normal	12 (27)

EOM: Extraocular movement, CRAO: Central retinal artery occlusion, SD: Standard deviation, LDH: Lactate dehydrogenase

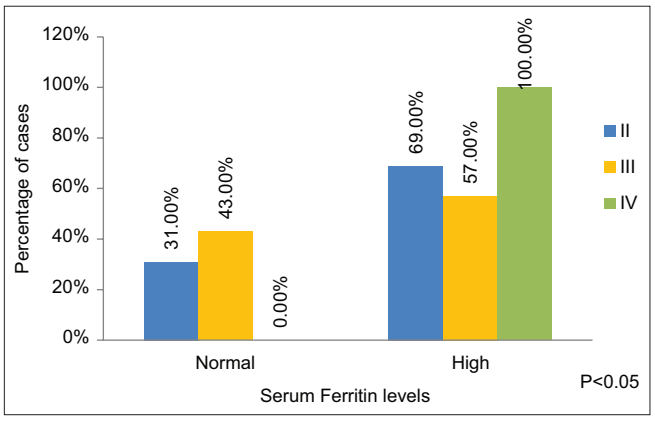

Figure 1: Serum ferritin level versus ROCM stage. ROCM: Rhino-orbital-cerebral mucormycosis

The median total count (/μL) was 13.61 (IQR 12.18, 16.04) in Stage II, 12.20 (IQR 10.50, 14.90) in Stage III and 18.56 (IQR 11.47, 29.97). The difference in the median total count across the severity of the ROCM was not statistically significant [$P = 0.323$, Table 2].

The mean neutrophils (%) with the severity of the ROCM in Stage II was 78.72 ± 8.98, it was 77.26 ± 7.9 in Stage III, and it was 82.28 ± 8.44 in Stage IV, the mean difference

Table 2: Comparison of mean laboratory parameters across the severity of the rhino-orbital-cerebral mucormycosis (*n*=45)*

Parameter	The severity of the ROCM			*P*
	Stage II (*n*=26)	Stage III (*n*=15)	Stage IV (*n*=4)	
Serum ferritin (ng/mL)	434.06±307.45	560.2±345.5	607±302.32	0.368
Serum LDH (IU/L)	327.27±180.15	563.13±211.23	451.25±247.18	0.003*
D-dimer (ng/mL)	780 (439.68–924.57)	788 (493.24–899)	789.43 (533.25–904.34)	0.960
Total count (/μL)	13.61 (12.18–16.04)	12.20 (10.50–14.90)	18.56 (11.47–29.97)	0.323
Neutrophils (%)	78.72±8.98	77.26±7.9	82.28±8.44	0.581
Lymphocytes (%)	11.62±7.33	14.4±5.5	8.88±5.53	0.254

*$P<0.05$ statistically significant. ROCM: Rhino-orbital-cerebral mucormycosis, LDH: Lactate dehydrogenase

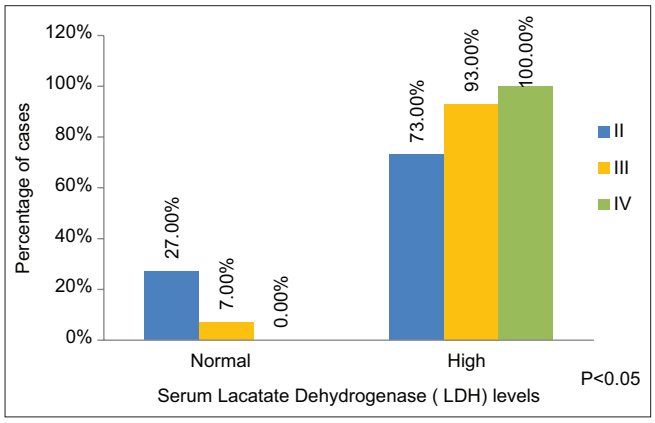

Figure 2: Serum LDH level versus ROCM stage. LDH: Lactate dehydrogenase, ROCM: Rhino-orbital-cerebral mucormycosis

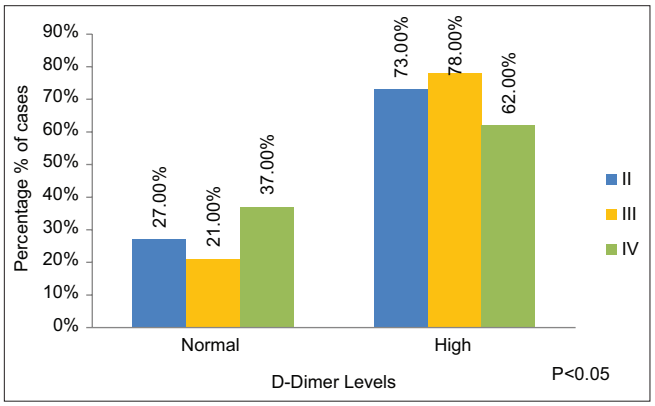

Figure 3: D-dimer level versus ROCM stage. ROCM: Rhino-orbital-cerebral mucormycosis

of neutrophils across the severity of ROCM was not statistically significant [$P = 0.581$, Table 2].

The mean lymphocytes (%) with the severity of the ROCM in Stage II was 11.62 ± 7.33, it was 14.4 ± 5.5 in Stage III, and it was 8.88 ± 5.53 in Stage IV, the mean difference of lymphocytes across the severity of ROCM was not statistically significant [$P = 0.254$, Table 2].

DISCUSSION

COVID-19, during the second wave in early 2021, has caused an alarming increase in cases encountering health infrastructure inadequacy and demand for hospital beds, drugs, vaccines, and oxygen adding more burden to such a challenging situation, mucormycosis created chaos.[17] Patients with SARS-CoV-2 infection appear in large numbers with various clinical symptoms, from asymptomatic manifestations to life-threatening illnesses like acute respiratory distress syndrome.[5]

India had been significantly impacted by COVID-19, which also posed a fatal risk of mucormycosis. Historically, the prevalence ranged from 0.005 to 1.7/million people worldwide. However, following COVID-19, the frequency has increased to 1.4/1000 in India alone.[5,6] In India, there have been 25,000 instances reported over 3 months during the pandemic.[18] Our institute experienced a dramatic increase in mucormycosis cases during the final 3 months of the second wave of the pandemic.

Initial ocular issues in ROCM are brought on by tissue inflammation and necrosis of the surrounding orbital tissue and decreased blood supply. Occlusion of the retina's central artery and infarction of the orbit, which also affects the optic nerve, are two potentially serious ophthalmic issues related to ROCM that could ultimately result in total blindness. ROCM can move from the orbit to the brain through the cribriform plate and orbital apex, resulting in potential problems such as internal carotid artery occlusion, cranial nerve palsy, chiasmal infarction, intracranial aneurysm, fungal meningitis, and even death.

Several previous studies have reported hyperglycemia and the use of systemic corticosteroids as the main risk factors for the development of COVID-19-associated ROCM.

Irrespective of hospitalization for COVID-19, hyperglycemia is an independent risk factor. Published reports indicate that COVID-19 is associated with hyperglycemia in general. Hyperglycemia or new-onset diabetes mellitus has been observed with COVID-19 and is hypothesized to predispose to ROCM through phagocyte dysfunction, defective chemotaxis, and impaired intracellular killing of *Mucorales*.[19,20] Hyperglycemia during COVID-19 could be due to SARS-CoV-2 infection per se and steroid usage

Downloaded from http://journals.lww.com/pajo by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8K2+Ya6H515kE= on 03/01/2024

Downloaded from http://journals.lww.com/pajo by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8K2+Ya6H515kE= on 03/01/2024

during treatment of COVID-19.[17] COVID-19 infection is a pro-inflammatory disease characterized by an excessive release of inflammatory molecules. A catecholamines, cytokines, and cortisol surge promotes glucagon production and gluconeogenesis, resulting in hyperglycemia.[21] This emphasizes tight monitoring of plasma glucose, even among nondiabetic COVID-19 patients. Our finding is consistent with published studies reporting a higher risk of mucormycosis among people with diabetes and more so after COVID-19.

In this study, we documented substantial steroid usage among all COVID-19 patients and more so among the never-hospitalized group indicating irrational and unmonitored use. Poor adherence to the guidelines on steroid use for COVID-19 has been reported widely in India.[22] Hyperglycemia is a known side effect of steroid intake.[23] Before COVID-19, steroid usage was not considered an independent risk factor for mucormycosis. However, studies on COVID-19-associated mucormycosis have reported steroids as an important predisposing factor.[24,25] Mucormycosis among steroid users has been mediated through macrophages/neutrophil dysfunction or hyperglycemia.[26] The viral-induced lymphopenia and endothelitis add to the favorable environment produced by steroids, diabetes mellitus, and hyperglycemia, causing COVID-19-associated ROCM. Therefore, COVID-19 patients on steroid treatment must be monitored for their glycemic status and educated to recognize and report symptoms and signs of ROCM. Further, prescribing steroids for COVID-19 patients in home isolation or nonhospital care centers needs to be done rationally, along with stringent monitoring and control of plasma glucose levels.

In our study, there was a male preponderance of 38 (84.44%) which was consistent with other studies in the literature.[27-29]

The mean age group of patients with COVID-19 ROCM was 48.71 ± 10.71 years. Because COVID-19 afflicted comparatively more young persons during the second wave, there was a substantial percentage of younger patients and adults between the ages of 29 and 75.

The higher mean serum D-dimer, ferritin, and LDH levels were discovered to be significantly associated with concurrent COVID-19 with ROCM patients in our investigation and were also suggested by Godatti *et al*.[30] COVID-19-mediated tissue damage and inflammation might increase free iron levels in the serum and cause a concomitant increase in serum ferritin levels.[30] Since iron metabolism is vital for mucorale growth, the release of iron in patients following tissue damage from SARS-CoV-2 infection might be one of the major factors determining the establishment of mucorale infection suggested by Sharma *et al*.[31,32] Patients with elevated levels of free iron (not bound to transferrin) are uniquely susceptible to *Rhizopus oryzae* and other Zygomycetes infections but not other pathogenic fungi, such as candida or aspergillosis.[33] However, the research on the interaction between the COVID-19 ROCM and inflammatory markers could not be located.

D-dimer, a protein fragment, is a fibrin degradation product in the blood after a blood clot is degraded by fibrinolysis. In the present study, the mean difference of D-dimer across the severity of ROCM has seen a statistically significant increasing trend. The rise in the D-dimer level has been attributed to endothelialitis, endothelial damage, and dysfunction of the hemostatic system leading to a hypercoagulable state induced by the virus.[28] In a study by Pal *et al*. of 10 patients and He *et al*., D-dimer was raised in all cases.[34-36]

In the current study, LDH has seen an increasing trend with the severity of ROCM. LDH is usually released from the cytosolic compartment of injured or dead cells, revealing a significantly elevated component in *Mucorales* infection.[37,38]

The study by Bhadania *et al*. suggested that hyperferritinemia presents a systemic inflammatory process in COVID-19 but also indicates increased free iron, which thereby aids the growth and extent of involvement by the *R. oryzae*.[39]

Strengths and limitations

The strength of this study is that the data are representative of the entire district as it was conducted in a notified nodal center during the COVID-19 pandemic. The study is limited due to the cross-sectional nature of the data and sample size. A comparative study with non-COVID-19 ROCM and longitudinal data could have given a more realistic and causal direction to disease progression and the natural history of the disease.

CONCLUSION

This study shows that increased levels of various inflammatory indicators, including serum ferritin, LDH, D-dimer, total neutrophils, and lymphocytes, have been strongly related to the increased risks of developing rhino-ocular-cerebral mucormycosis and its progression. Considering the high morbidity and mortality, especially in a pandemic, tracking these markers may allow early

identification, prediction of disease progression, and intervention.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Adhikari SP, Meng S, Wu YJ, Mao YP, Ye RX, Wang QZ, *et al*. Epidemiology, causes, clinical manifestation and diagnosis, prevention and control of coronavirus disease (COVID-19) during the early outbreak period: A scoping review. Infect Dis Poverty 2020;9:29.
2. Gupta S, Goyal R, Kaore NM. Rhino-orbital-cerebral mucormycosis: Battle with the deadly enemy. Indian J Otolaryngol Head Neck Surg 2020;72:104-11.
3. Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LF. The trinity of COVID-19: Immunity, inflammation and intervention. Nat Rev Immunol 2020;20:363-74.
4. Dorward DA, Russell CD, Um IH, Elshani M, Armstrong SD, Penrice-Randal R, *et al*. Tissue-specific immunopathology in fatal COVID-19. Am J Respir Crit Care Med 2021;203:192-201.
5. Kubin CJ, McConville TH, Dietz D, Zucker J, May M, Nelson B, *et al*. Characterization of bacterial and fungal infections in hospitalized patients with coronavirus disease 2019 and factors associated with health care-associated infections. Open Forum Infect Dis 2021;8:ofab201.
6. Rudramurthy SM, Hoenigl M, Meis JF, Cornely OA, Muthu V, Gangneux JP, *et al*. ECMM/ISHAM recommendations for clinical management of COVID-19 associated mucormycosis in low- and middle-income countries. Mycoses 2021;64:1028-37.
7. Pal R, Singh B, Bhadada SK, Banerjee M, Bhogal RS, Hage N, *et al*. COVID-19-associated mucormycosis: An updated systematic review of literature. Mycoses 2021;64:1452-9.
8. Xia ZK, Wang WL, Yang RY. Slowly progressive cutaneous, rhinofacial, and pulmonary mucormycosis caused by mucor irregularis in an immunocompetent woman. Clin Infect Dis 2013;56:993-5.
9. Ben-Ami R, Lewis RE, Leventakos K, Kontoyiannis DP. *Aspergillus* fumigatus inhibits angiogenesis through the production of gliotoxin and other secondary metabolites. Blood 2009;114:5393-9.
10. Soliman SS, Baldin C, Gu Y, Singh S, Gebremariam T, Swidergall M, *et al*. Mucoricin is a ricin-like toxin that is critical for the pathogenesis of mucormycosis. Nat Microbiol 2021;6:313-26.
11. Sharma S, Grover M, Bhargava S, Samdani S, Kataria T. Post coronavirus disease mucormycosis: A deadly addition to the pandemic spectrum. J Laryngol Otol 2021;135:442-7.
12. Shanthimalar R, Muthuchitra S, Mary Nirmala S, Thamizharasan P, Udayachandrika G, Balaji C, *et al*. Comprehensive study on manifestation, management and outcome of post COVID rhino orbito cerebral mucormycosis in our institution. Int J Otorhinolaryngol Head Neck Surg 2021;7:1799-806.
13. 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;69:1361-5.
14. Sreshta K, Dave TV, Varma DR, Nair AG, Bothra N, Naik MN, *et al*. Magnetic resonance imaging in rhino-orbital-cerebral mucormycosis. Indian J Ophthalmol 2021;69:1915-27.
15. Naik MN, Rath S. The ROC staging system for COVID-related rhino-orbital-cerebral mucormycosis. Semin Ophthalmol 2022;37:279-83.
16. 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;69:1670-92.
17. Aranjani JM, Manuel A, Abdul Razack HI, Mathew ST. COVID-19-associated mucormycosis: Evidence-based critical review of an emerging infection burden during the pandemic's second wave in India. PLoS Negl Trop Dis 2021;15:e0009921.
18. Kumar S. Effect of meteorological parameters on spread of COVID-19 in India and air quality during lockdown. Sci Total Environ 2020;745:141021.
19. Khunti K, Del Prato S, Mathieu C, Kahn SE, Gabbay RA, Buse JB. COVID-19, Hyperglycemia, and new-onset diabetes. Diabetes Care 2021;44:2645-55.
20. Michalakis K, Ilias I. COVID-19 and hyperglycemia/diabetes. World J Diabetes 2021;12:642-50.
21. Mishra Y, Prashar M, Sharma D, Akash Kumar VP, Tilak TV. Diabetes, COVID 19 and mucormycosis: Clinical spectrum and outcome in a tertiary care medical center in Western India. Diabetes Metab Syndr 2021;15:102196.
22. Ponnaiah M, Ganesan S, Bhatnagar T, Thulasingam M, Majella MG, Karuppiah M, *et al*. Hyperglycemia and steroid use increase the risk of rhino-orbito-cerebral mucormycosis regardless of COVID-19 hospitalization: Case-control study, India. PLoS One 2022;17:e0272042.
23. Ministry of Health and Family Welfare. Indian council of medical research; all india insitute of medical sciences. Advisory for rational use of steroids and tocilizumab in the treatment of COVID-19 patients 2020.
24. Moorthy A, Gaikwad R, Krishna S, Hegde R, Tripathi KK, Kale PG, *et al*. SARS-CoV-2, Uncontrolled diabetes and corticosteroids-an unholy trinity in invasive fungal infections of the maxillofacial region? A retrospective, multi-centric analysis. J Maxillofac Oral Surg 2021;20:418-25.
25. 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:e13163.
26. Jeong W, Keighley C, Wolfe R, Lee WL, Slavin MA, Kong DC, *et al*. The epidemiology and clinical manifestations of mucormycosis: A systematic review and meta-analysis of case reports. Clin Microbiol Infect 2019;25:26-34.
27. Soni K, Das A, Sharma V, Goyal A, Choudhury B, Chugh A, *et al*. Surgical & medical management of ROCM (Rhino-orbito-cerebral mucormycosis) epidemic in COVID-19 era and its outcomes – A tertiary care center experience. J Mycol Med 2022;32:101238.
28. Cavezzi A, Troiani E, Corrao S. COVID-19: Hemoglobin, iron, and hypoxia beyond inflammation. A narrative review. Clin Pract 2020;10:1271.
29. Qiu PL, Liu SY, Bradshaw M, Rooney-Latham S, Takamatsu S, Bulgakov TS, *et al*. Multi-locus phylogeny and taxonomy of an unresolved, heterogeneous species complex within the genus *Golovinomyces* (*Ascomycota*, *Erysiphales*), including *G. ambrosiae*, *G. circumfusus* and *G. spadiceus*. BMC Microbiol 2020;20:51.
30. Goddanti N, Reddy YM, Kumar MK, Rajesh M, Reddy LS. Role of COVID 19 inflammatory markers in rhino-orbito-cerebral mucormycosis: A case study in predisposed patients at a designated nodal centre. Indian J Otolaryngol Head Neck Surg 2022;74:3498-504.
31. Sharma R, Kumar P, Rauf A, Chaudhary A, Prajapati PK, Emran TB, *et al*. Mucormycosis in the COVID-19 environment: A multifaceted complication. Front Cell Infect Microbiol 2022;12:937481.
32. Artis WM, Fountain JA, Delcher HK, Jones HE. A mechanism of susceptibility to mucormycosis in diabetic ketoacidosis: Transferrin and iron availability. Diabetes 1982;31:1109-14.
33. Ibrahim AS, Spellberg B, Edwards J Jr. Iron acquisition: A novel perspective on mucormycosis pathogenesis and treatment. Curr Opin Infect Dis 2008;21:620-5.

Downloaded from http://journals.lww.com/pajo by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8K2+Ya6H515kE= on 03/01/2024

34. Pal P, Chatterjee N, Ghosh S, Ray BK, Mukhopadhyay P, Bhunia K, *et al*. COVID associated mucormycosis: A study on the spectrum of clinical, biochemical and radiological findings in a series of ten patients. J Assoc Physicians India 2021;69:11-2.
35. He J, Sheng G, Yue H, Zhang F, Zhang HL. Isolated pulmonary mucormycosis in an immunocompetent patient: A case report and systematic review of the literature. BMC Pulm Med 2021;21:138.
36. Yesupatham ST, Mohiyuddin SA, Arokiyaswamy S, Brindha HS, Anirudh PB. Estimation of ferritin and D-Dimer levels in COVID-19 patients with mucormycosis: A cross-sectional study. J Clin Diagn Res 2022;16-1.
37. Belic S, Page L, Lazariotou M, Waaga-Gasser AM, Dragan M, Springer J, *et al*. Comparative analysis of inflammatory cytokine release and alveolar epithelial barrier invasion in a Transwell(®) bilayer model of mucormycosis. Front Microbiol 2018;9:3204.
38. Avatef Fazeli M, Rezaei L, Javadirad E, Iranfar K, Khosravi A, Amini Saman J, *et al*. Increased incidence of rhino-orbital mucormycosis in an educational therapeutic hospital during the COVID-19 pandemic in Western Iran: An observational study. Mycoses 2021;64:1366-77.
39. Bhadania S, Bhalodiya N, Sethi Y, Kaka N, Mishra S, Patel N, *et al*. Hyperferritinemia and the extent of mucormycosis in COVID-19 patients. Cureus 2021;13:e20569.

Downloaded from http://journals.lww.com/pajo by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8K2+Ya6H515kE= on 03/01/2024