Original Article

The changing trend of fungal infection in invasive rhinosinusitis in the COVID era

Parul Garg[1], Vikash Ranjan[1], Avnisha[1], Sneha Hembrom[1], Sachin Goel[2], Shalini Malhotra[1]

[1]Department of Microbiology, ABVIMS and RML Hospital, New Delhi, India, [2]Department of ENT, ABVIMS and RML Hospital, New Delhi, India

Abstract

Background: SARS-COV virus operates as a significant risk factor for invasive fungal aspergillosis and mucormycosis. Successful management of this fulminant infection requires early recognition of the disease and aggressive medical or surgical interventions to prevent the high morbidity and mortality associated with the disease process. **Aims and Objective of the Study:** 1. To isolate and identify different species of fungi among acute rhinosinusitis patients. 2. To assess the association of risk factors causing fungal rhinosinusitis. 3. To assess the changing trend in fungal rhinosinusitis during the COVID era. **Material and Methods:** This is a retrospective observational study conducted from May 2020 to October 2022, attending the ENT department and relevant data were collected from the medical records department of ABVIMS and Dr RML Hospital, New Delhi, a Tertiary Care Referral Centre in India. The major risk factors studied were age, gender, COVID-19 infection and underlying diseases (such as diabetes mellitus, ischaemic heart disease, hypertension, malignancies, chronic kidney DISEASES, etc.); details of corticosteroid use of all patients were recorded in the datasheet. The pandemic data was divided into three distinct time periods/waves/eras, i.e., first, second, and third waves, each of which included ten months, to examine the changing trend in fungal rhinosinusitis in the pandemic era of COVID-19. **Results:** A total of 412 patients out of which 236 patients were clinically diagnosed with fungal sinusitis based on revised EORTC criteria. The most common site involved was the orbit with paranasal sinus and eye 86/236 (36.4%), followed by involvement of nasal and paranasal sinus alone 68/236 (28.8%). The most prevalent age range affected was 40 to 50 years. The most commonly associated comorbidity was diabetes mellitus (DM) in 176 (74.5%), followed by head and neck malignancies in 22 (9.32%) patients. Thirty-eight (50.6%) *Rhizopus* species and 18 (24%) *Aspergillus flavus* were the most common isolated fungal species on culture, followed by *Mucor* spp. 14 (18.6%) and *Aspergillus fumigatus* 5 (6.6%) in the period. In the second wave of COVID, there was a surge in *Zygomycetes* cases 36 (45%) and after the second wave, the *Aspergillus* cases increased by 14 (19%) during Jan-Oct 2022. **Conclusion:** With the continuing coronavirus pandemic, there is an unprecedented and discernible rise in the prevalence of acute invasive fungal sinusitis certainly a spike in cases of Aspergillus infection was observed, probably due to unprecedented usage of Amphotericin B for the treatment of mucormycosis during the third wave This underlines the importance of the need to tailor our treatment protocol as per the etiological agents hence the right antifungal drugs combined with urgent surgical procedures on a case-to-case basis may certainly increase the chances of survival.

Keywords: Changing trend, fungal rhinosinusitis, Covid era

Address for correspondence: Dr. Shalini Malhotra, Department of Microbiology, ABVIMS and RML Hospital, New Delhi, India.
E-mail: malhotra439@gmail.com

Received: 26-05-2023 **Revised:** 10-12-2023
Accepted: 15-12-2023 **Published:** 22-04-2024

Access this article online

Quick Response Code:

Website: http://journals.lww.com/JFMPC

DOI: 10.4103/jfmpc.jfmpc_871_23

Introduction

Fungi are ubiquitous organisms which are widely distributed in air, water, soil and decaying matter. Transmission occurs by inhalation of airborne conidia. The infection may develop less often when spores enter the body through a cut or an

How to cite this article: Garg P, Ranjan V, Avnisha, Hembrom S, Goel S, Malhotra S. The changing trend of fungal infection in invasive rhinosinusitis in the COVID era. J Family Med Prim Care 2024;13:1428-33.

open wound. Acute invasive fungal rhinosinusitis (AIFRS) is a fulminant infection characterised by invasion of the nasal cavity and paranasal sinuses with fungus and has a high propensity to infiltrate the palate, orbit, skin and intracranial structures.

According to the research, the fungi that grow in the nose and paranasal sinuses most frequently are *Mucor* and *Aspergillus* species.[1] Disease presentation by fungi mostly depends on the host's immune status rather than the fungus itself.[2] It is notably found in immunocompromised patients, mainly in uncontrolled diabetes, malignancy, AIDS, and chemotherapeutic/immunosuppressive drugs.[3]

AIFRS prevalence has significantly increased since the most recent COVID-19 infection. During the continuing COVID-19 pandemic, an increase in invasive fungal rhinosinusitis has been noted. This may be related to secondary infections brought on by lung damage, prolonged hypoxemia, hyperglycaemia, overuse of corticosteroids, as well as immunosuppression brought on by decreased CD4 and CD8 + T-cells due to SARS-Cov-2 virus.[4] Previous research from 2003 to 2007 found that fungal infections were among SARS patients' major causes of death.[5,6] Along with other fungal diseases, the SARS-Cov virus type may also operate as a significant risk factor for invasive fungal aspergillosis and mucormycosis. Thus, to facilitate early detection and intervention, a high index of suspicion of fungal infection should be raised in patients who appear with minimal symptoms.

Systemic corticosteroids are often prescribed by primary care physicians for patients with acute bronchitis, acute sinusitis, carpel tunnel and allergic sinusitis. The use of corticosteroids for the treatment of COVID-19 was seen to increase after WHO recommendations (September 2020) on the use of corticosteroids only for severely and critically ill patients, corresponding to the period when mucormycosis cases increased. Opportunistic fungal infections are expected to rise in the upcoming years due to the predicted increase in the incidence of diabetes and other risk factors. Most patients in our study presented to the OPD, a tertiary care facility, with orbital involvement already apparent. Since primary care providers are often the patient's initial point of contact, there should be a strong suspicion of invasive fungal infection in immunocompromised patients with rhinosinusitis. The diagnosis of these patients is delayed because of non-specific symptoms at an earlier stage. The straightforward process of doing direct microscopy on nasal specimens and subsequent identification of causative organisms will prevent this delay.

Successful management of this fulminant infection requires early recognition of the disease and aggressive medical or surgical interventions to prevent the high morbidity and mortality associated with the disease process.

Aims and Objective of the Study

1. To isolate and identify different species of fungi among acute rhinosinusitis patients.
2. To assess the association of risk factors causing fungal rhinosinusitis.
3. To assess the changing trend in fungal rhinosinusitis during the COVID era.

Material and Methods

This retrospective observational study was conducted from MAY 2020 to October 2022. A total of 412 patients attended the ENT OPD and were admitted to the IPD, out of which 236 patients clinically suspected of fungal rhinosinusitis as per the revised EORTC criteria were included in the present study and the relevant data were collected from the medical records department of ABVIMS and Dr RML Hospital, New Delhi, a Tertiary Care Referral Centre in India. The major risk factors of all patients recorded in the datasheet were age, gender, COVID-19 infection, underlying diseases (such as DM, ischaemic heart disease, hypertension, malignancies, chronic kidney diseases, etc.) and details of corticosteroid use.

The pandemic data was collected from May 2020 to October 2022, which was divided into three distinct time periods/waves, that is, first, second, and third waves, each of which included ten months, to examine the changing trend in fungal rhinosinusitis in the pandemic era of COVID 2020–2022. To compare with the various COVID waves, the pre-COVID era spanned 10 months before the onset of COVID-19. April to May 2020 saw the implementation of a strict lockdown; as a result, this time frame was left out of the study. The initial first wave lasted from June 2020 to March 2021, time period between April 2021 to December 2021 was considered the second wave during which the delta variant of COVID was prominent. Thereafter, there was a surge in the omicron variant from January 2020 to October 2022, which covered the third wave [Figure 1].

Inclusion criteria

Patients suspected of fungal rhinosinusitis of all age groups and both sexes were included.

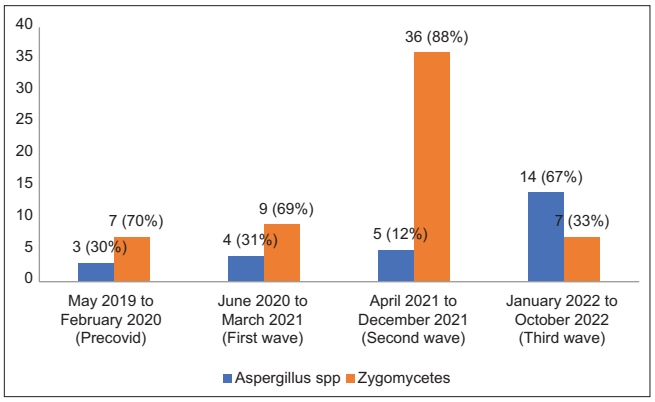

Figure 1: Distribution of fungal species throughout the COVID pandemic

Exclusion criteria

Patients who were not on antifungal medication 14 days prior to sample collection.

Method

Nasal tissues and secretions were collected from the study population. These specimens were processed with 10% KOH, and fungal culture was performed immediately after receiving them at the lab. A microscopic examination was performed and observed for fungal hyphae. Clinical samples were inoculated on two sets of Sabouraud's dextrose agar and incubated at 25°C and 37°C, respectively. Fungal cultures were routinely examined until growth occurred or till 4-6 weeks. Positive fungal growth culture was identified by macroscopic and microscopic characteristics as per standard protocol.[7] The data was collected and analysed. The clinical staging was done based on the clinical features and the anatomical site involved.[8]

Statistical analysis

All descriptive variables were presented in numbers or percentages. For comparison of quantitative variables between the groups, Chi-square was used using SPSS Software version 20.0. After analysing all the data, the value of $P < 0.001$ was considered statistically significant for the Chi-square trend analysis used to compare different COVID waves.

Results

Out of a total of 412 individuals, 236 patients had fungal sinusitis based on clinical signs and symptoms that met the new EORTC criteria. There were 150 males and 86 females (male/female ratio: 2:1 approx.). The most common site involved was the orbit with paranasal sinus and eye 86/236 (36.4%), followed by involvement of nasal and paranasal sinus alone 68/236 (28.8%). The patients were 26–80 years old, while the most prevalent age range affected was 40 to 50 years. The most commonly associated comorbidity was diabetes mellitus (DM) in 176 (74.5%), followed by head and neck malignancies in 22 (9.32%) patients. Fifty-two (29.5%) patients out of a total of 176 diabetic patients had a recent onset DM diagnosed either during or after COVID-19 infection. Out of 176 total diabetic patients, 110 (62.5%) patients were found to be having uncontrolled blood sugar levels. Other reported medical diseases included chronic kidney diseases 15 (6.35%), chronic liver diseases 7 (2.96%), hypertension 7 (2.96%), COPD 6 (2.54%), and renal transplant 3 (1.2%) on immunosuppressive drugs [Table 1].

Thirty-two patients were COVID-19 positive at the time of presentation, and 150 had been documented with infection earlier and had recovered. A mean of 12 days (range: 3–45) of corticosteroids were administered to 90 (72.6%) patients during their treatment for COVID-19.

Among the 236 patients, 125 were treated with combined antifungal therapy and surgery, while 70 patients were on antifungal therapy alone without surgical debridement.

The fungal organism was identified by direct microscopy and culture. On culture, *Rhizopus* spp. And *Mucor* spp. Were in 38 (50.6%) and 14 (18.6%) cases, followed by *Aspergillus flavus* and *Aspergillus fumigatus* in 18 (24%) and 05 (6.6%) cases, respectively. In 4 (5.3%) cases, fungal hyphae were seen, but fungal cultures were sterile. There were also 3 (4%) cases of coinfection – *Mucor* spp. and *Aspergillus flavus*, *Rhizopus* spp., *Aspergillus flavus*, *Mucor* spp. and *Aspergillus fumigatus* [Table 2].

In the detailed analysis of the pre-COVID era, rhino fungal sinusitis caused by *Aspergillus* spp. 3 (30%) and *zygomycetes* 7 (70%) in cultured confirmed cases were substantially fewer. During the subsequent period, i.e., when the COVID pandemic had set in, in the first wave, there were 4 (31%) cases of *Aspergillus* spp. and 9 (69%) cases of *Zygomycetes* causing rhino fungal sinusitis. In the second wave of COVID, there was a surge in *Zygomycetes* cases, 36 (88%) of the total culture-confirmed cases and after the second wave, the *Aspergillus* cases increased by 14 (67%) from January to October 2022, which is the era of the third wave [Figure 1].

As per the above table, there is overall a significant difference (P value 0.002) in the trend as observed from pre-COVID up to the third wave regarding *Aspergillus* spp. and *Mucor* species identified in the received specimens, using Chi-square for trend. However, considering the wave comparison, a significant trend was observed only from wave 2 to wave 3, as there is increased isolation of *Aspergillus* sp. and a reduction in the *Mucor* sp. identified in the third wave [Table 3].

Discussion

As evident, COVID-19 is an infectious disease which mainly affects the respiratory system. There is an increased risk of

Table 1: Comorbidities associated with fungal infections

Comorbidities	Number (Percentage) COVID era (236 pts)
DM (Total)	176 (74.5)
DM (uncontrolled)	110/176 (62.5)
CKD/AKD	15 (6.35)
Malignancy	22 (9.32)
CLD	7 (2.96)
COPD	6 (2.54)
HTN	7 (2.96)
Renal transplant	3 (1.2)

Table 2: Distribution of Fungal agents on different diagnostic methods (236)

Fungal agent	Positive on KOH COVID era	Positive on Culture COVID era
Rhizopus spp.	42 (46.1%)	38 (50.6%)
Mucor spp.	18 (19.07%)	14 (18.6%)
Aspergillus flavus	21 (23.0%)	18 (24%)
Aspergillus fumigatus	6 (6.5%)	05 (6.6%)
Others	04 (4.3%)	0
Total	91	75

Table 3: Observation of linear trend significance

Time	*Aspergillus* spp	Zygomycetes	Significance between the waves		
Pre-COVID	3	7	*P*-value 1.0		
First wave	4	9		*P*-value 0.194	
Second wave	5	36			*P*-value <0.001(s)
Third wave	14	7	Pre-COVID to first wave		
Over all linear trend association; p-value <0.005(s)				First to second wave	Second to third wave

secondary infection with fungi due to altered innate immunity and decreased number of lymphocytes, which is further complicated by the use of corticosteroids as the treatment. AIFRS is a highly virulent form of fungal infection with a high morbidity and mortality rate that exponentially increased during the COVID-19 pandemic.

In our study, orbit with paranasal sinus involvement alone was present in 86/236 (36.4%) cases with symptoms of headache and facial/periorbital swelling. This was followed by nasal and paranasal sinus involvement in 68/236 (28.8%) cases, with nasal discharge and epistaxis as presenting features. After a few days of COVID-19 infection recovery, headache, nasal obstruction, localised pain and a loss of eyesight were the main symptoms. These clinical characteristics may be used as the first signs of a subsequent fungus infection in COVID-19-recovered individuals. El-Kholy *et al.*[9] also showed similar results, with headache and facial pain as the most common symptoms in 75% of patients among post-COVID AIRFS patients. Abu El-Naaj *et al.*[10] mentioned that symptoms such as pain mimicking sinusitis, facial swelling and dental pain were common in most patients.

DM was the most common concomitant disorder in various studies of AIRFS performed both before COVID-19 and during the COVID-19 pandemic.[11] This is in accordance with our study, as the most commonly associated disease was DM 176 (74.5%). In a study by Bakhshaee *et al.*,[12] leukaemia (44.44%) and DM (50%) were the most prevalent underlying diseases. Even before COVID-19, the prevalence of diabetes mellitus was a major risk factor, with regional differences ranging from 67% in North India to 22% among patients from the South of India.[13]

Additionally, out of a total of 176 diabetic patients in our study, 92 (52.2%) were recently diagnosed with DM during/after the treatment of COVID-19 infection, reflecting a direct effect of COVID-19 on hyperglycaemia or a metabolic dysfunction caused by steroid overuse. Glucocorticosteroids have anti-inflammatory and immunosuppressive effects. Steroids also affect glycaemic status, causing hyperglycaemia in turn preparing conditions for invasive fungal infections.[14]

Several case reports and series about aspergillosis and post-COVID mucormycosis have been published.[15-20] In our study, *Zygomycetes* spp. were the most common fungi isolated from these patients, 52 (69%), followed by *Aspergillus* species 23 (31%), while coinfection with both of these species was seen in three patients (2%) similar to another study.[21] Hence, it has been hypothesised that the triad of COVID-19 infection, uncontrolled diabetic status and prolonged use of corticosteroids may act as cofactors for each other, causing a vicious cycle for suppression of immunity and allowing secondary fungal infection.

Coronavirus disease 2019 (COVID-19) began in late 2019 in Wuhan, China, and spread worldwide, causing a pandemic and a global shutdown around the world. The first case of COVID-19 in India was detected in late January 2020; thereafter, the lockdown began on 25 March 2020 as the cases began to rise. The gradual removal of the lockdown began on 1 June 2020. In the first wave, patients with comorbidities like DM, heart problems, body mass index >40 kg/m^2 and age >60 years were more severely affected.

In May 2021, the second wave's peak occurred. The second COVID-19 wave was more severe, necessitating the use of plasma therapy, remdesivir injections, corticosteroids and oxygen therapy. On 19 May 2021, India's mucormycosis, a typical opportunistic invasive fungal infection, was recognised as a condition that needed to be reported under the Epidemic Diseases Act of 1897. Some studies have shown that prolonged use of corticosteroids to control cytokine storms contributed to more susceptibility to fungal infection due to their immunosuppressive behaviour in the second wave of COVID.[22]

The disease presentation varied during the first and second waves in terms of clinical pattern, severity and outcome of the disease.[4] In India, the number of COVID cases increased slowly during the latter part of 2020, subsiding in the early part of 2021 and late March 2021. Infectivity and virulence increased during the second COVID-19 wave's propagation. As of January 2022, the third wave stuck, which was unique in clinical presentation and natural history. The third wave likewise happened after the nation's extensive vaccination effort. WHO declared COVID-19 a global pandemic on 11 March 2020 and has completed almost 2 years of human circulation.

Even in the first wave, incidences of mucormycosis were reported, but they only got more pronounced in the second. Similar results are shown in this study, with 19/109 mucor cases from June 2021 to March 2021 and a surge in mucormycosis cases from April to December 2021, or 76/109. The surge in cases of COVID-19 in India during the second wave of the pandemic had been associated with increased reporting of invasive mucormycosis in post-COVID-19 patients.[16–18] The

occurrence of mucormycosis, a rare disease, in the general population was previously cited as 0.005 to 1.7 per million population.[19] However, compared to other regions of the world, India reported a mucormycosis incidence of 0.14/1000 diabetes individuals, which is 80 times higher.[22] Among numerous mucormycosis cases in this era of the COVID-19 pandemic, we experienced a surge of Aspergillus infection after the second wave. There have been reports of newly emerging fungi, like aspergillosis, in severely ill individuals receiving steroid therapy.[20] Immunocompromised patients with invasive fungal infection may be easily misdiagnosed due to non-specific symptoms, as discussed in the case series by You *et al.*[23] Due to persisting symptoms, the patients visit various clinics including primary care physicians and present to the tertiary care setup once the disease has progressed and the symptoms worsen.

The role of early and accurate diagnosis in the aggressive containment of the fungal infection at the initial stages to the primary care physician becomes crucial, thus preventing the development of a life-threatening situation.

Conclusion

During the second wave, there was an unprecedented and discernible rise in cases of Mucor mycosis, which resulted in greater scrutiny of clinical, laboratory, and radiological diagnoses of overall fungal infection. Eventually, this led to increased reporting of aspergillosis cases in the subsequent third wave. Moreover, antifungal therapy during the second wave was directed against only Mucor mycosis. All these, along with the immunocompromised state due to COVID, paved the way for an increase in spikes of Aspergillus cases.

This underlines the importance of conducting a thorough evaluation of COVID-19 patients exhibiting sinusitis-related signs and symptoms. Accurate clinical suspicion and an early diagnosis of fungal rhinosinusitis are predicted to result in a better morbidity outcome. At the same time, we also need to tailor our treatment protocol as per the etiological agents; hence, the right antifungal drugs combined with urgent surgical procedures on a case-to-case basis may certainly increase the chances of survival.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Monroe MM, McLean M, Sautter N, Wax MK, Andersen PE, Smith TL, *et al.* Invasive fungal rhinosinusitis. Laryngoscope 2013;123:1583–7.
2. Ziaee A, Zia M, Goli M. Identification of saprophytic and allergenic fungi in indoor and outdoor environments. Environ Monit Assess 2018;190:574.
3. Lop-Gros J, Gras-Cabrerizo JR, Bothe-González C, Montserrat-Gili JR, Sumarroca-Trouboul A, Massegur-Solench H. Bola fúngica sinusal: Análisis de nuestra casuística. Acta Otorrinolaringológica Esp 2016;67:220–5.
4. Wang W, Su B, Pang L, Qiao L, Feng Y, Ouyang Y, *et al.* High-dimensional immune profiling by mass cytometry revealed immunosuppression and dysfunction of immunity in COVID-19 patients. Cell Mol Immunol 2020;17:650–2.
5. Zhang Y, Li WX, Huang KW, Cao ZX, Hao JY. Hospital acquired pneumonia occurring after acute stage of the serious SARS and its treating strategies. Chin J Nosocomiol 2003;11:1081–7.
6. Li C, Pan S. Analysis and causation discussion of 185 severe acute respiratory syndrome dead cases. Zhongguo Wei Zhong Bing Ji Jiu Yi Xue 2003;15:582–4.
7. ICMR. Antimicrobial Resistance Surveillance and Research Network, Standard Operating Procedures for Fungal Identification and Detection of Antifungal Resistance. 2nd ed, Vol. 131. Published by the Division of Publication and Information on behalf of the Secretary, DHR and Director General, ICMR, New Delhi, 2019.
8. Shanthimalar R, Muthuchitra S, Mary S, Thamizharasan P, Udhayachandrika 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.
9. El-Kholy NA, El-Fattah AMA, Khafagy YW. Invasive fungal sinusitis in post COVID-19 patients: A new clinical entity. Laryngoscope 2021;131:2652-8.
10. Abu El-Naaj I, Leiser Y, Wolff A, Peled M. The surgical management of rhinocerebral mucormycosis. J Craniomaxillofac Surg 2013;41:291–5.
11. Ismaiel WF, Abdelazim MH, Eldsoky I, Ibrahim AA, Alsobky ME, Zafan E, *et al.* The impact of the COVID-19 outbreak on the incidence of acute invasive fungal rhinosinusitis. Am J Otolaryngol 2021;42:103080.
12. Bakhshaee M, Bojdi A, Allahyari A, Majidi MR, Tavakol S, Najafzadeh MJ, *et al.* Acute invasive fungal rhinosinusitis: our experience with 18 cases. Eur Arch Otorhinolaryngol 2016;273:4281–7.
13. Prakash H, Chakrabarti A. Epidemiology of mucormycosis in India. Microorganisms 2021;9:523.
14. Michalakis K, Ilias I. COVID-19 and hyperglycemia/diabetes. World J Diabetes 2021;12:642–50.
15. Kermani W, Bouttay R, Belcadhi M, Zaghouani H, Ben Ali M, Abdelkéfi M. ENT mucormycosis. Report of 4 cases. Eur Ann Otorhinolaryngol Head Neck Dis 2016;133:83–6.
16. Kursun E, Turunc T, Demiroglu YZ, Alışkan HE, Arslan AH. Evaluation of 28 cases of mucormycosis. Mycoses 2015;58:82–7.
17. Ketenci I, Unlü Y, Kaya H, Somdaş MA, Kontaş O, Oztürk M, *et al.* Rhinocerebral mucormycosis: Experience in 14 patients. J Laryngol Otol 2011;125:e3.
18. Ingley AP, Parikh SL, DelGaudio JM. Orbital and cranial nerve presentations and sequelae are hallmarks of invasive fungal sinusitis caused by mucor in contrast to aspergillus. Am J Rhinol 2008;22:155–8.
19. Jeong W, Keighley C, Wolfe R, Lee WL, Slavin MA, Kong DCM, *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.

20. Shetty S, Shilpa C, Kavya S, Sundararaman A, Hegde K, Madhan S. Invasive aspergillosis of nose and paranasal sinus in COVID-19 convalescents: Mold goes viral? Indian J Otolaryngol Head Neck Surg 2022;74(Suppl 2):3239–44.
21. Vadher PR, Mistry SN, Vasani A. Post Covid-19 acute invasive fungal rhinosinusitis (AIFR): A study of histopathological findings after FESS in radiologically diagnosed AIFR. Indian J Otolaryngol Head Neck Surg 2023;75(Suppl 1):689-95.
22. Singh AK, Singh R, Joshi SR, Misra A. Mucormycosis in COVID-19: A systematic review of cases reported worldwide and in India. Diabetes Metab Syndr 2021;1:102146.
23. You YS, Koh JH, Kim BJ, Lee EJ, Kwon SH, Kim JS. Life-threatening sinonasal invasive aspergillosis easily misdiagnosed. Korean J Otorhinolaryngol Head Neck Surg 2023;66:234-40.