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Research Article

Invasive Fungal Infections in A Teritiary ICU in Hyderabad

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Abstract

The COVID-19 pandemic has caused more than 500 million cases and 6 million fatalities globally, with India particularly heavily struck by the second wave. This has significantly increased the prevalence of invasive fungal diseases, such as COVID-19-associated pulmonary mucormycosis (CAPM) and COVID-associated pulmonary aspergillosis.

A retrospective study was conducted to examine the incidence of IFI in a tertiary care ICU in South India during the pandemic. Data was collected from medical records of patients with documented positive fungal cultures. Results showed that the incidence of COVID-19-associated pulmonary mucormycosis (CAPM) and COVID-associated pulmonary aspergillosis had increased significantly.

The study examined 41 medical and surgical patients admitted to ICU in a tertiary care hospital in Hyderabad from January 2020 – December 2022 with documented culture-positive invasive fungal infections. The most common source of fungal infection was from lung, followed by the maxillary sinus tissue, nasal cavity, peritoneal fluid, Frontal sinus tissue, and urine. Fungal cultures were positive in 36 cases (87.8%) and negative in 1, and not done in 4 patients. Rhizopus was the first most frequently identified fungus, followed by Aspergillus flavus (26.8%), Aspergillus fumigatus (7.3%), Aspergillus niger (7.3%), Candida tropicalis and albicans (2.4%), Candida parapsilosis (7.3%), Mucormycosis (2.4%), and seedosporium (2.4%).

Keywords: Invasive Fungal Infections; COVID 19; Mucor; Aspergillus; Critical Care; Candida

Introduction

In the adult population receiving critical care, fungal infections are becoming more common. It significantly affects morbidity, mortality, and medical research. Due to underlying disorders that are associated with certain fungal infections, critical care patients are particularly susceptible to them.

More than 500 million cases and more than 6 million fatalities have been reported globally since the start of coronavirus disease 2019 (COVID-19), which SARS-CoV-21 brought on. The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has caused various symptoms and consequences over the past 1.5 years [1,2]. While the first COVID-19 wave was contained and the globe was able to recover, the second wave, brought on by the SARS-CoV-2 virus, has left the world at a complete loss. India has been particularly heavily struck by the second wave, which has significantly increased the prevalence of invasive fungal diseases.

Covid 19 Superinfection is expected, frequently brought on by bacteria, fungi, or other viruses, and is a significant COVID-19 side effect in critically sick patients [2-7]. The viral infection itself, along with underlying chronic structural lung disease, immunosuppressive therapies like corticosteroids and immunomodulators, leukopenia, malignancy, longer duration (> 14 days) on mechanical ventilation, prior antibiotic use, cardiovascular disease, liver disease, and uncontrolled diabetes have all been identified as predisposing risk factors for COVID-19-associated Invasive Fungal Infections [8-11].

In post-COVID patients, the uncommon acute invasive fungal rhinosinusitis cases have increased [12-14]. Because population-based research is needed to define the baseline incidence/prevalence rate of mucormycosis in India [15], it is impossible to state that the general incidence rate of COVID-19-associated pulmonary mucormycosis (CAPM) has increased. Another new occurrence noted during the initial COVID pandemic is COVID-associated pulmonary aspergillosis [16]. However, mixed invasive fungal infections linked to COVID-19 have only occasionally been documented.

Generally speaking, regional and temporal variability best describes the epidemiology of invasive fungal diseases. Understanding regional epidemiologic trends and the antifungal susceptibility of the etiological agents is crucial since IFIs have poor prognosies in critically ill patients. We were interested in learning how the covid pandemic has changed the epidemiology of IFI in a tertiary care ICU in South India. So far, to our knowledge, no studies have depicted the incidence of IFI from south India during the covid pandemic.

Methodology

This is a retrospective study. The study is done after approval from Institutional Ethics Committee. The medical records of patients with invasive fungal infections proven by positive fungal cultures and fungal smears were studied, and data was collected. All medical and surgical patients admitted to ICU in tertiary care hospital in Hyderabad from January 2020-December 2022 with invasive fungal infections were taken into the study. Patients with reported invasive fungal infections were identified, and demographic characteristics of patients like age, sex, and underlying comorbid conditions were collected**.** Clinical data like primary diagnosis, organ dysfunction, length of stay, presence of invasive lines, steroid therapy, total parenteral nutrition, duration of mechanical ventilation, concomitant bacterial infections, antibiotic therapy, antifungal prophylaxis, and treatment were collected. Data of positive fungal culture, etiological agents was collected**.** The data of fungal markers and fungal smears was also collected and tabulated. The patient's outcome- improved or not improved, discharged or expired was collected. After data collection, statistical analysis was done, and the results were analyzed.

Statistics

All the data was entered in MS. Excel and analyzed by using SPSS23.0v. p value less than 0.05 was considered significant. All the qualitative factors like diagnosis, comorbidities, type of fungal infection, fungal culture report, etc. represented with the frequencies and percentages. All the quantitative parameters, like the average duration of mechanical ventilation and the average length of ICU stay, will be defined as mean.

Results

Between January 2020 and December 2022, a total of 41 patients with invasive fungal infections who were hospitalized to the ICU were examined.

Age, gender, and underlying comorbid illnesses were identified as demographic factors. The demographic characteristics of the study population are shown in table 1.

Age (Years)	Frequency	Percentage
30-45	6	14.6
46-60	18	43.9
61 and Above	17	41.5
Sex	Frequency	Percentage
Male	29	70.7
Female	12	29.3
Total	41	100.0

Table 1: Demographic characteristics of the study population.

22 patients (53.7%) of the study group had COVID-19 infection and encountered fungal infection during the course of hospital stay. While 19 (46.3%) did not have primary COVID infection, but presented with sepsis with organ dysfunction and their stay in hospital was complicated with invasive fungal infection. Figure 1 represents the COVID 19 positive population in the study.

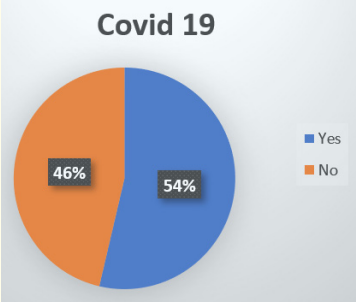

Figure 1: Representing the COVID 19 positive population in the study.

33 patients had comorbid illnesses that were all different from one another. Among them the most common were hypertension, diabetes, COPD. 22 of them (or 53.7%) had hypertension, 28 patients (68.3%) had Type II diabetes, 3 patients (7.3%) had COPD. The additional comorbid illnesses include hypothyroidism, CAD, etc. were seen in 18 (43.9%) of study population. Figure 2 representing the study population having comorbidities.

8 out of 41 had no comorbid conditions. Among those who didn't have any comorbid conditions, the invasive fungal infections is because of their longer hospital stay and use of steroids. The diagnosis of 8 of the patients without any comorbids include. Table 2 represents list of the patients without comorbidities but having invasive fungal infections.

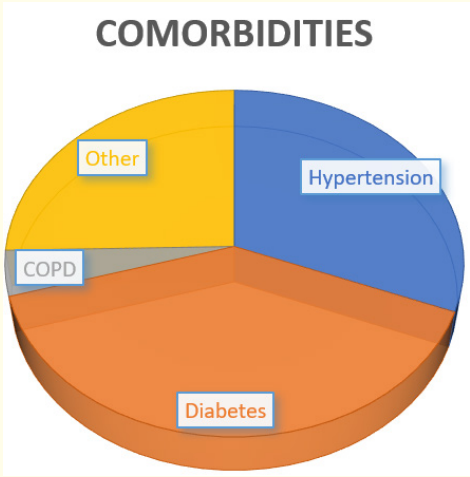

Figure 2: Representing the study population having comorbidities.

S.no	Age/ gender	Diagnosis	Steroid usage	Organ dysfunction
1	56 M	Post COVID, b/l pneumothorax	Yes	Yes, Aki
2	31 F	Septic shock, ards-ileostomy-for closure, post-op anastamotic LEAK	Yes	Yes, respiratory failure
3	32 F	Post partum sepsis, Dic, Aki	No	Yes, Aki
4	56 M	Post covid 19, MDR klebsiella VAP, septic shock	Yes	Yes, respiratory failure
5	55 M	Post Covid 19 pneumonia, type1 respiratory failure, septic shock, MODS	Yes	Yes, mods
6	66 M	Severe Covid-19 pneumonia	Yes	Yes, Aki
7	65 F	Pulmonary nocardiosis, sjogrens syndrome	Yes	Yes, Aki
8	60 F	Polytrauma, vap, b/l pleural effusion wound site fungal infection	No	No

Table 2: Represents list of the patients without comorbidities but having invasive fungal infections.

Even though they didn't have any comorbid conditions, these patients were on steroids for certain period of time and also had organ dysfunction. That could have predisposed to fungal infection.

The 8th patient in this above table is a 60 year old lady, with no comorbidities. She got admitted with polytrauma. She had got fun-

gal infection at the wound site of trauma. This could be because of prolonged hospital stay and prolonged immune suppression related to trauma and hospital stay. She was hospitalized for 4 months, with recurrent ICU admissions for about 6 times.

Twelve patients (29%) out of the total population studied did not use steroids. In addition, 29 hospitalised patients (71%) were receiving steroid treatment.

Amongst them infected with COVID-19 were 15 patients who were using steroids. On average, approximately 9,068 days are spent using steroids. Figure 3 represents study population received steroids.

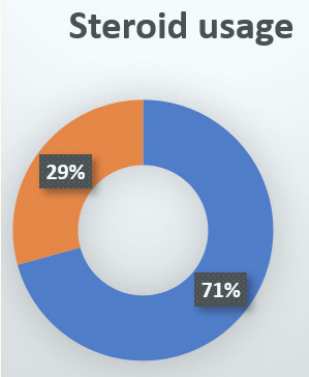

Figure 3: Represents study population received steroids.

50% of diabetic patients, had uncontrolled sugar levels, complicated probably by the steroid usage. 28 patients (68.3%) had organ dysfunction. Most common organ dysfunction encountered was AKI in 22 patients. Among them 15 patients required dialysis during their stay. Invasive lines were present in 34 (82.9%) of the 41 patients. 7 (17.1%) of the 41 patients used TPN while they were in the hospital. 28 (68.3%) of the 41 patients were mechanically ventilated throughout their stay. The patients' average percentage of time on the ventilator is 6.5%. Concurrent bacterial infections were present in 26 individuals (63.4%).

Gram-negative MDR bacterial infections with Acinetobacter, klebsiella, Pseudomonas are the concurrent bacterial infections that were common with the fungal infections. Other concurrent bacterial infections were stenotrophomonas and enterococcus. For bacterial infections, most of the population received Meropenem, along with other broad-spectrum antibiotics like colistin, Imipenem-cilastatin, tigecycline, teicoplanin as per their culture-sensitivity reports. In 22% of patients, tests for fungi markers were conducted, and out of them, 17 patients (41.5%) had positive serum galactomannan results and 5 patients (12.2%) had negative results. Figure 4 represents the fungal markers reports in the study population.

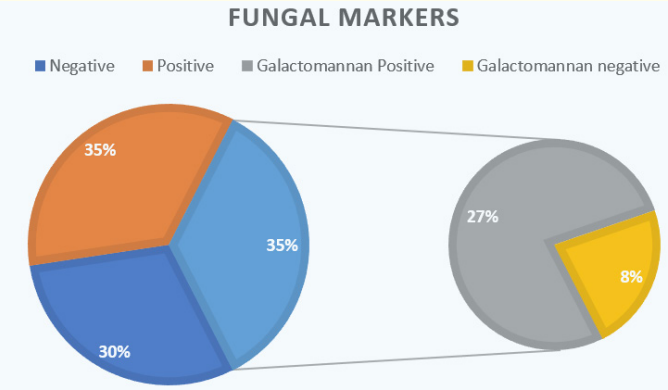

Figure 4: Represents the fungal markers reports in the study population.

Fungal cultures were positive in 36 cases (87.8%) and negative in 1, and not done in 4 patients representing a population of 41 patients. Fungal cultures were not done in 4 patients, as these patients died even before sending a culture. But these patients were treated as having invasive fungal infections as the fungal markers were positive and fungal smear was also positive in this 4 patients. These patients were treated clinically on the basis of fungal markers and smear report.

The familiar sources of fungal infection isolation during culture are shown in the following table 3. Most common source of fungal isolation from culture is from lung in 24.4%.

In terms of the causes of fungus, Rhizopus is the most prevalent, occurring in 29.3% (12 patients). This is followed in 11 patients (26.8%) by Aspergillus flavus. *Aspergillus spp* (1 patient), *Aspergillus fumigatus* (3 patients), *Aspergillus niger* (3 patients), *Candida tropicalis* (1 patient), *Candida parasilosis* (3 patients), *Candida albicans* (1 patient), and *mucor* (1 patient) are some other isolated species. The distribution of the etiological agents of fungal infection is shown in the following table 4.

Source	Frequency	Percent
Not done	4	9.75
Bal	8	19.51
Et	1	2.4
Knee joint	1	2.4
Lung	10	24.4
Maxillary sinus tissue	1	2.4
Nasal cavity	5	12.2
Nasal tissue	1	2.4
Peritoneal fluid	1	2.4
Rt. frontal sinus tissue	1	2.4
Sputum	2	4.9
Sinus tissue	5	12.2
Urine	1	2.4
Total	41	100.0

Table 3: Represents the sources of fungal infection.

	Frequency	Percent
Not done	4	9.8
Aspergillus species	1	2.4
Aspergillus flavus	11	26.8
Aspergillus flavus, rhizopus	1	2.4
Aspergillus fumigatus	3	7.3
Aspergillus niger	3	7.3
Candida parapsilosis	3	7.3
Candida tropicalis, candida albicans	1	2.4
Mucor	1	2.4
Rhizopus	12	29.3
Scedosporium apiospermum	1	2.4
Total	41	100.0

Table 4: Represents the etiological agent of fungal infection.

All patients received antifungal therapy. Dual anti-fungal therapy was administered to all 15 patients (36.58%) in order to treat invasive fungal infections. Most of them were treated with Voriconazole, Amphotericin B, Anidulafungin, Posaconazole.28 patients (68.3%) of the total patients died, 5 patients (12.2%) were discharged, and 8 patients (19.5%) went on discharge against medical advice. When a fungal swab was performed on the patients, it revealed hyphal segments in 22 patients while being negative in 7. Additionally, we saw a connection between the fungus and the fungal smear test. But it had no real impact.

Discussion

The greatest challenge in the history of intensive care medicine, was to treat COVID-19 pneumonia in critically ill patients. ICU-admitted COVID-19 patients are particularly susceptible to secondary bacterial and fungal infections, which may contribute significantly to a poor prognosis [17]. Even in the absence of other factors, severe COVID-9 infections can suppress the immune system by modifying the T-cell response in a variety of ways [18]. Numerous factors contribute to the increased susceptibility of critically ill COVID-19 patients to opportunistic fungal infection, including the extensive and irrational use of antibiotics and corticosteroids, associated comorbidities, and invasive medical devices including central venous catheters, total parenteral nutrition, and invasive and non-invasive mechanical ventilation. These medical devices penetrate the epidermis barrier, allowing direct access to the host's interior [19,20].

In this study, we investigated the epidemiological profile and incidence of fungal infections in patients admitted to a multidisciplinary ICU during the COVID era to understand how COVID has influenced or changed the distribution of invasive fungal infections in a multidisciplinary ICU setting from South-India.

In our study, the total study population of 41 patients represent those with invasive fungal infections. In our investigation, fungal cultures were positive in 87.8% of the 41 patients, and negative fungal cultures were found in 2.4% of the patients.

In our study, 22 patients (53.7%) of the study group were tested positive for COVID-19 infection while 19 (46.3%) did not have primary COVID infection. The population without COVID infection also sustained invasive fungal infection as this group of patients had sepsis with organ dysfunction and were having invasive lines and were on steroids and mechanical ventilator which all contributed to invasive fungal infection.

The identification of COVID 19 infection was done by RT-PCR in our study. Real-time RT-PCR tests face risks of false-negative

and false-positive results, as many suspected cases with COVID-19 clinical characteristics and CT images were not diagnosed. Negative results should not exclude infection, and combining real-time RT-PCR with clinical features can improve SARS-CoV-2 outbreak management [21]. In our study we have taken the clinical factors into consideration while diagnosing COVID infection.

Numerous risk factors have been identified for invasive Candida infections, including higher Acute Physiology and Chronic Health Evaluation II scores, diabetes mellitus, renal insufficiency, surgery (especially abdominal surgery), pancreatitis, the use of broad-spectrum antibiotics, parenteral nutrition, hemodialysis, mechanical ventilation, the presence of central vascular catheters, and immunosuppressive therapy [22]. 71% of our study population received steroids. 68.3% of them had organ dysfunction. 82.9% had invasive lines. 68.3% were mechanically ventilated and 17.1% of them received TPN during their stay in the hospital.

Rhizopus was the first most frequently identified fungus in 12 individuals (32.3%). This is followed by *Aspergillus flavus* (26.8%), *Aspergillus fumigatus* (7.3%), *Aspergillus Niger* (7.3%), *Candida tropicalis* and *albicans* (2.4%), *Candida parapsilosis* (7.3%), *Mucormycosis* (2.4%), and *scedosporium* (2.4%) were the other most often isolated fungi.

It is crucial to make a prompt and accurate diagnosis of invasive fungal infection so that appropriate antifungal agents can be administered without delay. However, early detection is not always straightforward. Blood cultures are only positive in 50-70% of cases [23]. In addition, it can take several days for Candida to be identified to the species level and for antifungal susceptibility data to become accessible. Moreover, blood cultures rarely yield a positive result in patients with invasive candidiasis [23]. In such patients, it is possible to conduct cultures of infected tissues, despite their limitations, which include the need for invasive surgical procedures and low sensitivity [23].

Fungal cultures were positive in 36 cases (87.8%) and negative in 1, and not done in 4 patients representing a population of 41 patients. Fungal cultures were not done in 4 patients, as these patients died even before sending a culture. But these patients were treated as having invasive fungal infections taking into consideration the clinical criteria also.

Nonculture-based diagnostic techniques for the detection in blood of fungal cell wall components (such as galactomannan and beta-D-glucan) by immunoassays, DNA by polymerase chain reaction (PCR), and antibodies by serology have recently been established [24]. There is considerable variation in how the galactomannan ELISA is currently employed in clinical settings. The galactomannan ELISA is used in clinics as a screening tool to monitor invasive aspergillosis risk. It is tested once or twice a week, sometimes in serum when no BAL fluid is present. In most cases, the ELISA is used as a triage test, referring patients for further diagnostic testing or antifungal therapy if positive [24]. Further diagnostic testing may involve laboratory tests, CT scanning, radiography, or a combination of tests.

The EORTC/MSGERC classification of invasive aspergillosis (IPA) in critically ill patients has been improved by incorporating fungal biomarkers like the GM antigen and Aspergillus qPCR. The AspICU algorithm, focuses on separating Aspergillus colonized patients from probable IPA, was validated by a prospective multicenter study. However, it does not use GM antigen detection, which has been shown to be less reliable in non-neutropenic patients [25]. However, in our study we didn't use any algorithm for defining fungal infection as this criteria is less reliable in non-neutropneic patients and the entire population in our study is non-neutropenic.

In 22% of patients, tests for fungi markers were conducted, and out of them, 17 patients (41.5%) had positive serum galactomannan results and 5 patients (12.2%) had negative results. When a fungal swab was performed on the patients, it revealed hyphal segments in 22 patients while being negative in 7. Additionally, we saw a connection between the fungus and the fungal smear test. But it had no real impact.

In terms of the causes of fungus, Rhizopus is the most prevalent, occurring in 29.3% (12 patients). This is followed in 11 patients (26.8%) by *Aspergillus flavus*. *Aspergillus spp* (1 patient), *Aspergillus fumigatus* (3 patients), *Aspergillus niger* (3 patients), *Candida tropicalis* (1 patient), *Candida parasilosis* (3 patients), *Candida albicans* (1 patient), and *Mucor* (1 patient) are some other isolated species.

In contrast to our investigation, Candida was the most prevalent fungal isolate, accounting for 61/153 (24.1%) of all cases accord-

ing to Negm., *et al.* [26] followed by Aspergillosis (11/253 (4.3%) and mucormycosis (5/253 (1.97%) of the study population. However, the study by Negm., *et al.* [26] evaluated the patients, only during the third wave of the covid pandemic. In contrast, during the pandemic from 2020 to 2022, we retrospectively collected data for all covid patients. According to Oguz., *et al.* [27], 39 (33.1%) individuals had fungal infection or colonisation. 34 (288%) patients had fungi isolated from them. 51 samples yielded ten distinct fungus species, with Candida Albicans being the most prevalent which is in contrast to our study. Ten different fungus species were found in our investigation, with Rhizopus being the most prevalent because of the effect of the pandemic.

In COVID-19 patients, inflammation leads to an unbalanced iron homeostasis. This condition is characterized by elevated ferritin levels and a decrease in the amount of circulating iron. Oral candidiasis is usually accompanied by low iron levels. The use of TNF-antagonists has been linked to hyperferritinemia, ferroptosis, and organ damage, rendering COVID-19 patients more susceptible to fungal coinfections [26].

Of the 627 patients observed in the ICU with a COVID-19 diagnosis in the study by Coskun., *et al.* [28], 32 individuals (5.10%) had an opportunistic fungal infection. Candida tropicalis (33.33%) from tracheal aspirates, Candida albicans (48.27%) from urine cultures, and Candida parapsilosis (43.7%) from blood cultures were the opportunistic fungal agents most frequently isolated. However, in our investigation, we found that Rhizopus infection was more common in patients than candida infection. This is undoubtedly impacted by patient factors, including the presence of several concomitant conditions in addition to COVID-19 infection, as well as regional variability, temporal distribution, and patient features.

Similar to our findings, Ezeokol., *et al*. [29] came to the conclusion that aspergillosis and candidemia have higher rates of incidence for fungal coinfections in critically ill COVID-19 patients admitted to the ICU. In our study, 41 patients had an average of 68.3% organ dysfunction, 82.9% underwent invasive surgeries, 17.1% used TPN while they were hospitalised, and 68.3% required mechanical breathing.

80.48% of patients in our study have several comorbidities (more than two). In this case, our study is comparable to prior studies. 28 patients (68.3%) died in the current study, 5 patients (12.2%) were discharged, and 8 patients (19.5%) went on DAMA. This is similar to the study by Coskun., *et al*. [28]. where 78.12% died. In 3 patients who passed away and 1 patient who was taking DAMA, candida was found. The relationship between a candida infection and a clinical result was not statistically significant. However, according to some writers, invasive candidiasis and COVID infection have a death rate of 40-70% [30]. Our death rate for patients with invasive candidiasis is also lower, possibly as a result of the use of dual antifungal medication (36.58%). However, candida was isolated from BAL, knee joint, peritoneal fluid, and urine in addition to the most typical sources of isolation, which were the lung, tissue, and nasal cavity.

Uncontrolled diabetes was shown to be the most common underlying ailment in both CAM and non-CAM patients in India, according to retrospective research [32]. The second most prevalent comorbidities disease group among COVID-19 fungal infection patients was diabetes mellitus. An increased incidence of mucormycosis in COVID-19 patients has been associated to poorly controlled diabetes and diabetic ketoacidosis. 14 individuals (50%) of the 28 diabetic participants in the current study had uncontrolled blood sugar levels. In the Coskun., *et al.* [28] study 11 (34.4%) of the 19 individuals who experienced fungal infections also had diabetes mellitus.

Multiple factors, including the excessive and irrational use of antibiotics and corticosteroids, associated comorbidities, and invasive medical devices like central venous catheters, total parenteral nutrition, and invasive and non-invasive mechanical ventilation, contribute to the increased susceptibility of critically ill COVID-19 patients to opportunistic fungal infection [22].

With an average use of steroids of 9.068 days, 51% of the patients had COVID-19 infection and were taking steroids. Negm., *et al*. [26]. also described the usage of steroids in 40.7% of the population.

Conclusion

Following the COVID pandemic, critical care patients are now more at risk for developing invasive fungal infections. This is linked to uncontrolled steroid use which increased during the COVID pandemic, poor glycemic management, the use of invasive catheters

and lines, prolonged antibiotic use, and the absence of appropriate antibiotic administration recommendations. Patients with COVID-19 positivity had a higher mortality rate due to opportunistic fungal infections. Unnecessary invasive procedures should be avoided, continual blood sugar regulation should be used, and needless antibiotics should be avoided. This is true for managing patients during pandemic and providing optimal intensive care. The study demonstrates how, in comparison to other locations, the covid pandemic has altered the landscape of invasive fungal infections in a tertiary centre in South India. We need to conduct additional research after the pandemic to determine how local conditions and factors affect the frequency and distribution of fungus infections.

Conflict of Interest

There is no conflict of interest in publishing this study.

Financial Disclosure

There is no funding source for this study.

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