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Invasive Mucormycosis (Zygomycosis) in the pre-COVID-19 and COVID-19 Eras: A Comparative Retrospective Study at a Tertiary Care Center in Chennai

İnvazif Mukormikoz (Zigomikoz) COVID-19 Öncesi Dönem ve COVID-19 Dönemi: Chennai'deki Üçüncü Basamak Sağlık Merkezinde Karşılaştırmalı Retrospektif Bir Çalışma

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Abstract

Introduction: In India, the incidence of mucormycosis is high among patients with uncontrolled diabetes mellitus, with a prevalence of approximately 0.02–9.5 cases per 100,000 persons. There was a localized epidemic of mucormycosis during the second wave of Coronavirus disease–2019 (COVID-19), which could be attributed to the indiscriminate use of steroids and lapses in infection control practices, both in the hospital and at home. Treatment of mucormycosis is challenging because it is highly invasive and intrinsically resistant to some of the antifungal agents. In this study, we aimed to compare the prevalence, clinical presentations, and antifungal susceptibility pattern of mucormycosis between the pre-COVID-19 era and COVID-19 eras.

Materials and Methods: This single-center retrospective study included patients admitted during the pre-COVID-19 era and COVID-19 era at a tertiary care center in Chennai. The samples were subjected to culture techniques, and the positive isolates were tested for antifungal susceptibility to amphotericin B, itraconazole, posaconazole, voriconazole, and isavuconazole via the microbroth dilution method, according to the CLSI M38–A2 guidelines.

Results: Among the 365 samples received at the laboratory during the pre-COVID-19 era, 52 were positive for mucormycosis. During the COVID-19 era, out of the 886 samples received, 174 were positive for mucormycosis. The incidence of mucormycosis was high during the COVID-19 era. Although most of the risk factors and clinical presentations were similar during the pre-COVID-19 and COVID-19 eras, clinical complications were more common during the pre-COVID-19 era. The mean minimum inhibitory concentration (MIC) of amphotericin B was higher during the pre-COVID-19 era than during the COVID-19 era. Furthermore, the mean MIC of posaconazole was higher during the COVID-19 era than during the pre-COVID-19 era. This may be attributable to the increased usage of posaconazole during the COVID-19 era. Due to its low MIC value, newer azoles such as isavuconazole can be considered a good therapeutic option for future resistant infections.

Conclusion: Early diagnosis and timely management of mucormycosis with appropriate antifungals, on the basis of antifungal susceptibility tests, may help improve the patient outcomes and prevent the development of resistance.

Keywords: Mucormycosis, pre-COVID-19 era, COVID-19 era, antifungal susceptibility testing

Öz

Giriş: Hindistan'da kontrolsüz diyabetli hastalar arasında yüksek oranda mukormikoz görülmektedir. Mukormikozun tahmini prevalansının 100.000 kişi başına 0,02 ila 9,5 olgu olduğu tahmin edilmektedir. İkinci dalga sırasında, steroidlerin gelişigüzel kullanılmasından ve hem hastanede hem de

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Öz

evde enfeksiyon kontrol uygulamalarındaki aksaklıklardan kaynaklanabilecek lokalize bir mukormikoz salgını vardı. Bu enfeksiyonun tedavisi, oldukça invazif olması ve bazı antifungal ajanlara karşı doğası gereği dirençli olması nedeniyle zordur. Bu çalışma, Koronavirüs hastalığı-2019 (COVID-19) öncesi ve COVID-19 döneminde mukormikoz prevalansını ve klinik görünümünü karşılaştırmak ve ayrıca her iki dönemde de mukormikozun antifungal duyarlılık testi (AFST) paternini karşılaştırmak için yapıldı.

Gereç ve Yöntem: Bu, Chennai'deki üçüncü basamak bir sağlık merkezine COVID-19 öncesi ve COVID-19 döneminde kabul edilen hastaları içeren tek merkezli, retrospektif bir çalışmadır. Örneklerin kültürü yapıldı ve kültür pozitif izolatlar için CLSI M38-A2'ye göre mikro sıvı besiyeri seyreltme yöntemiyle amfoterisin B, itraconazol, posakonazol, vorikonazol ve izavukonazol ile AFST yapıldı.

Bulgular: COVID-19 öncesi dönemde laboratuvara alınan 365 numunenin 52'si kanıtlanmış mukormikoz olgularına ait idi. COVID-19 döneminde alınan toplam 886 numuneden 174'ü kanıtlanmış mukormikoz olgularına ait idi. Mukormikozis insidansı COVID-19 döneminde yüksekti. Risk faktörlerinin ve klinik tabloların çoğu, COVID-19 öncesi dönemde ve COVID-19 döneminde benzerdi. Yine de, ikinci dönemde klinik komplikasyonlar daha yaygındı. Amfoterisin B'nin ortalama MİK değerlerinin COVID-19 öncesi dönemde COVID-19 dönemine göre yüksek olması ve posakonazolün COVID-19 döneminde COVID-19 öncesine göre ortalama MİK değerinin daha yüksek olması bu mantar önleyici ilaçların kullanımının artmasına bağlı olabilir. İzavukonazol gibi daha yeni bir azol, MİK değerlerinin düşük bulunması nedeniyle dirençli enfeksiyonların gelecekteki tedavisi için iyi bir tedavi seçeneği olarak düşünülebilir.

Sonuç: Mukormikoz tanısı alan hastaların zamanında yönetimi ve AFST yapılarak doğru antifungal ajan seçimi, sonuçların iyileşmesine ve direnç gelişimiyle mücadeleye yardımcı olacaktır.

Anahtar Kelimeler: Mukormikoz, COVID-19 öncesi dönem, COVID-19 dönemi, antifungal duyarlılık testi

Introduction

Zygomycosis is a broad category of mycotic infections caused by members of the highly invasive zygomycetes class. The prevalence of zygomycosis in India is approximately 80 times the prevalence in developed countries i.e., approximately 0.14 cases per 1,000 population^[1,2]. The common forms of zygomycosis are rhino-orbito-cerebral, pulmonary, cutaneous, and gastrointestinal^[3]. Pulmonary zygomycosis is predominantly seen in immunocompromised individuals, and the primary route of entry is via inhalation of the spores.

The risk factors attributing to the development of zygomycosis are diabetic ketoacidosis, deferoxamine treatment, cancer, solid organ or bone marrow transplantations, prolonged steroid use, extreme malnutrition, and neutropenia^[4]. In India, mucormycosis is commonly seen in patients who have been involved in road traffic accidents and those with uncontrolled diabetes mellitus (DM), especially those with ketoacidosis. In India, pulmonary zygomycosis has been commonly reported among patients who are solid organ transplant (SOT) recipients and those with hematological malignancy and DM^[5]. A rise in ferritin levels may be associated with an increase in mucormycosis cases, and a change in iron metabolism has been observed in severe Coronavirus disease-2019 (COVID-19) cases^[6,7]. Patients undergoing renal dialysis are also at a higher risk of developing mucormycosis due to deferoxamine therapy^[8]. During the second wave of the COVID-19 pandemic, several patients were administered supplemental oxygen via a concentrator in their homes due to the unavailability of hospital beds. Thus,

these unsanitary conditions could have increased the risk of developing mucormycosis during COVID-19^[9].

The common clinical presentations of mucormycosis are sinusitis, nasal discharge, and nasal congestion. In severe cases of mucormycosis, one-sided facial swelling and facial pain may be observed. If the infection spreads to the eye, it can cause proptosis, ptosis, diplopia, orbital cellulitis, and even epistaxis.

The management of mucormycosis can be very challenging. The two-prong strategy warrants both surgical and medical treatment with antifungal agents. There is no standard antifungal therapy for zygomycosis as there is insufficient clinical data regarding their efficiency. Currently, amphotericin B is considered an effective drug, and posaconazole is used as a salvage therapy due to its broad spectrum activity^[10]. Studies that have discussed the clinical and laboratory spectrum of mucormycosis during the pre-COVID-19 and COVID-19 eras are limited. Thus, herein, we compared the clinical and mycological profile as well as the antifungal susceptibility pattern of patients admitted during the pre-COVID-19 and COVID-19 eras in the same clinical setting. The study results will aid in providing a better understanding of the various challenges faced during the COVID-19 era, which will help better manage the patients because the infection severity differs between both the periods. In this study, the changing trends in mucormycosis and its treatment during both the eras were analyzed. Furthermore, we have highlighted the need for increased awareness of the potential for secondary fungal infections and the need for early and accurate identification during a pandemic.

Materials and Methods

Study Design

A single-centered, retrospective, hospital-based, descriptive study was conducted. Similar time intervals were considered when screening the patient data to accurately evaluate the prevalence of mucormycosis before and during the COVID-19 pandemic. This study included individuals admitted during the pre-COVID-19 and COVID-19 eras. The pre-COVID-19 era was defined as the period before the COVID-19 pandemic (January 2017–December 2019), and the COVID-19 era was defined as the period during the COVID-19 pandemic (January 2020–December 2022).

Data Collection

The clinical and laboratory data of all the patients were manually obtained from the hospital records. Additionally, data such as demographic data, age, sex, risk factors, clinical manifestations, and treatment administered were extracted from the hospital records. According to the EORTC/MSGERC guidelines, a fungus must be identified via blood culture, histology, or culture of a tissue sample obtained from a clinical site that is typically sterile to "prove" the presence of an invasive fungal disease. Cases that were either positive for direct microscopy, histopathological examination or culture were considered as confirmed cases of mucormycosis^[11,12].

Statistical Analysis

Statistical Package for the Social Sciences (version 17) was used to analyze all the data. A p value of <0.05 was considered statistically significant. The antifungal susceptibility test results are presented as means and standard deviations. Categorical data were compared using chi-square test. Continuous variables were compared using either Student's t-test or Mann-Whitney U test based on the normality.

Direct Microscopy

Direct microscopic examination of a potassium hydroxide wet mount revealed broad, aseptate, ribbon-like, hyphal structures. Furthermore, histopathological examinations of H&E-, PAS-, and GMS-stained sections revealed broad aseptate hyphae with angioinvasion. These findings confirmed the presence of mucormycosis.

Culture

Samples were inoculated onto Sabouraud's dextrose agar and incubated at 25 °C. All the isolates demonstrated broad aseptate hyphae and sporangiophores, sporangia, rhizoids, columella, apophysis, and stolons. Based on the morphology of the LPCB mount, the isolates belonged to the order Mucorales or Entomophthorales and genus zygomycetes. Further

characterization and speciation of the isolates were performed via temperature variation studies if required^[13].

Antifungal Susceptibility Test

Antifungal susceptibility was analyzed using the broth microdilution method, CLSI M38-A2 guidelines, and colonies grown (positive culture). *Paecilomyces variotii* (Centraalbureau voor Schimmelcultures 132734) was used as the control strain.

The antifungal drugs and range of concentrations evaluated were as follows: Amphotericin B (A9528-50MG; Sigma-Aldrich, USA), 0.25–32 µg/ml; itraconazole (16657-100MG; Sigma-Aldrich, USA), 0.125–16 µg/ml, voriconazole (PZ0005-5MG; Sigma-Aldrich, USA), 0.125–16 µg/ml; posaconazole (32103-25MG; Sigma-Aldrich, USA), 0.125–16 µg/ml; and isavuconazole (2357-5MG; Sigma-Aldrich, USA), 0.125–16 µg/ml.

The results were analyzed and interpreted according to the CLSI M38-A2 guidelines. After each test, the complete absence of turbidity in the media control well was examined for quality control.

Results

In this study, 365 and 886 patients had been admitted during the pre-COVID-19 and COVID-19 eras, respectively. Of the included patients, 52 and 174 patients in the pre-COVID-19 and COVID-19 eras, respectively, were proven to have mucormycosis. Only a few severe clinical symptoms such as facial swelling, nasal block, nasal discharge, orbital cellulitis, and loss of vision were seen during the COVID-19 era. Furthermore, the percentage of risk factors was more in the COVID-19 era than in the pre-COVID-19 era (Table 1). A comparison of the treatments administered during the pre-COVID-19 and COVID-19 eras is included in Table 2. Usage of amphotericin B reduced from 20% in the pre-COVID-19 era to 9.7% in the COVID-19 era. Posaconazole, a salvage therapy for mucormycosis, was administered more during the COVID-19 era (29.9%) than during the pre-COVID-19 era. More patients underwent surgical procedures such as wound debridement, orbital exenteration, orbital decompression, and functional endoscopic sinus surgery (FESS) during the COVID-19 era than during the pre-COVID-19 era (Table 3). The minimum inhibitory concentration (MIC) values of the zygomycetes isolated from patients with invasive mucormycosis during the pre-COVID-19 and COVID-19 eras are shown in Table 4. The antifungal susceptibility pattern differed between the two eras. Amphotericin B was the most effective drug as demonstrated by a low mean MIC during both eras. Posaconazole demonstrated varying MIC values, with a higher mean MIC during the COVID-19 era than during the pre-COVID-19 era. Newer triazoles such as isavuconazole were administered only during the COVID-19 era, and they demonstrated low mean MIC values. Thus, isavuconazole is a

Table 1. Comparison of the baseline clinical characteristics of patients with mucormycosis in the pre-COVID-19 and COVID-19 eras

Variable	Pre-COVID-19 era (n=365)	COVID-19 era (n=886)	p value
Proven cases	52 (14.2%)	174 (19.6%)	0.024
Age, years (mean)	45	48	<0.001*
Sex, n (%)			
Male	215 (58.9%)	650 (73.3%)	<0.001*
Female	150 (41%)	236 (26.6%)	
Clinical features, n (%)			
Headache	126 (34.6%)	284 (32%)	0.39
Fever	133 (36.5%)	300 (33.9%)	0.38
One-sided facial pain	63 (17.3%)	305 (34.4%)	<0.001*
Facial numbness	50 (11.5%)	305 (34.4%)	<0.001*
Facial swelling	63 (17.3%)	305 (34.4%)	<0.001*
Nasal congestion	50 (11.5%)	275 (31.03%)	<0.001*
Nasal discharge	50 (11.5%)	254 (28.7%)	<0.001*
Ptosis	14 (3.8%)	51 (5.7%)	0.16
Orbital cellulitis	35 (9.6%)	290 (32.7%)	<0.001*
Epistaxis	-	5 (0.57%)	
Diplopia	-	10 (1.14%)	
Loss of vision	14 (3.8%)	81 (9.19%)	0.0012*
Loss of smell	-	71 (8.04%)	
Risk factors, n (%)			
Type 2 diabetes mellitus	226 (62%)	585 (66%)	0.166
Coronary artery disease	28 (7.6%)	150 (16.9%)	<0.001*
Cerebrovascular accident	28 (7.6%)	110 (12.4%)	0.014*
Transplant recipient	21 (5.7%)	11 (1.2%)	<0.001*
Steroid therapy	21 (5.7%)	19 (2.2%)	<0.001*
Acute kidney injury	26 (7.1%)	35 (4%)	0.017*
COVID-19 infected individuals	-	254 (28.7%)	

*p<0.05, statistically significant.

COVID-19: Coronavirus disease-2019

Table 2. Comparison of the treatment administered during the pre-COVID-19 and COVID-19 eras

Treatment received	Pre-COVID-19 era, n (%)	COVID-19 era, n (%)
Amphotericin B	73 (20%)	86 (9.7%)
Posaconazole	-	265 (29.9%)
Itraconazole	3 (0.8%)	2 (0.2%)
Voriconazole	30 (8.2%)	5 (0.5%)
Combination therapy	29 (7.9%)	9 (1%)
Antibiotics	230 (63%)	519 (58.5%)

COVID-19: Coronavirus disease-2019

Table 3. Surgical procedures performed during the pre-COVID-19 and COVID-19 eras

Surgical procedures	Pre-COVID-19 era	COVID-19 era
Wound debridement	7 (1.9%)	45 (5.07%)
Orbital exenteration	3 (0.82%)	20 (2.25%)
Orbital decompression	2 (0.5%)	15 (1.69%)
Radical mastoidectomy with labyrinthine fistula	2 (0.5%)	9 (1.01%)
FESS with polypectomy	5 (1.3%)	35 (3.9%)
FESS with septoplasty	6 (1.64%)	25 (2.8%)
Maxillectomy	7 (1.91%)	15 (1.6%)
Partial alveolectomy of mucormycosis	2 (0.54%)	4 (0.45%)
Tympanoplasty	2 (0.54%)	2 (0.22%)
Amputation	3 (0.82%)	20 (2.25%)

FESS: Functional endoscopic sinus surgery, COVID-19: Coronavirus disease-2019

promising alternative therapy for mucormycosis in patients with nephrotoxicity.

Discussion

Before the outbreak of the COVID-19 pandemic, the global prevalence of mucormycosis ranged from 0.005 to 1.7 per million population^[14]. A sudden rise in mucormycosis incidence was observed during the second wave of the COVID-19 pandemic. In our study, the total number of suspected cases of mucormycosis increased from 365 in the pre-COVID-19 era to 886 during the COVID-19 era. This drastic increase in the suspicion of fungal infections during the COVID-19 era may be attributed to several reasons, including increased awareness among physicians, increased testing for fungal infections, and unavailability of proper care for co-morbidities such as DM. COVID-19 rendered the patients vulnerable to other infections, which increased the incidence of invasive fungal infections during the period. Furthermore, steroid therapy during the COVID-19 era drastically increased the number of mucormycosis cases^[15]. The disease presentation can range from a local sinusitis to a severe and aggressive form. In our study, the patients were aged 45-50 years, irrespective of the era, were predominantly male in the COVID-19 era (pre-COVID-19 vs. COVID-19 era, 58.9% vs. 73.3%). Similarly, Chavda and Apostolopoulos^[16] and Bhandari et al.^[17] reported a considerable increase in the rate of infection in patients aged >45 years of age, with 41-50 year olds being the most frequently impacted by mucormycosis. The male predominance may be partially attributed to the fact that women exhibit more potent humoral and cell-mediated proinflammatory responses than males. This is due to the sexual variations in the immunological response, which improves the phagocytic activity against Mucorales^[18].

Table 4. Antifungal susceptibility test results

Pre-COVID-19 era					
Organisms	Amphotericin B, µg/ml	Itraconazole, µg/ml	Voriconazole, µg/ml	Posaconazole, µg/ml	Isavuconazole, µg/ml
Zygomycetes (n=17)	1.05±0.4	1.29±1.8	1.8±2.5	0.41±0.3	-
<i>Rhizopus</i> sp (n=16)	1.09±0.4	1.34±1.95	1.49±2	0.41±0.33	-
<i>Apophysomyces variabilis</i> (n=1)	0.5±0	0.5±0	8±0	0.5±0	-
COVID-19 era					
Zygomycetes (n=31)	0.75±0.3	8.52±6.6	12.8±5.3	12.52±5	1.76±2.1
<i>Rhizopus</i> sp (n=26)	0.74±0.29	8.3±6.8	12.64±4.66	13.42±4.5	1.83±2.27
<i>Rhizomucor pusillus</i> (n=2)	1.5±0.7	16±0	16±0	16±0	1.125±1.23
<i>Mucor</i> sp (n=2)	0.5±0	4.25±5.3	8.25±10.9	12±5.65	2.25±2.47
<i>Basidiobolus ranarum</i> (n=1)	0.25±0	8±0	0.25±0	0.25±0	0.25±0

Data are presented as minimum inhibitory concentration±standard deviation.

sp: species, COVID-19: Coronavirus disease-2019

DM is the most common risk factor for the development of mucormycosis. In our study, approximately 62% and 66% of the participants in the pre-COVID-19 and COVID-19 eras, respectively, had uncontrolled DM. In India, the onset of DM is much earlier (20-30 years) than that in the rest of the world^[19]. We also found that the incidence of other risk factors such as SOT decreased from 5.7% during the pre-COVID-19 to 1.2% during the COVID-19. Among SOT recipients, approximately 2.6-11% and 7-14% of mucormycosis cases have been reported in India and globally, respectively. Chronic kidney disease, steroid therapy, pulmonary tuberculosis, and chronic obstructive pulmonary disease are additional risk factors for mucormycosis in India^[20-22]. In our study, 4% of the patients in the COVID-19 era developed acute kidney disease.

According to Narayanan et al.^[23], approximately 3.7 million COVID-19 cases were active at its peak in India. Of these patients, approximately 0.5 million people with severe COVID-19 would have been at risk for CAM if we assumed that 15% of those infected would need treatment and that symptomatic COVID-19 and its treatment predisposed patients to mucormycosis. In our study, COVID-19 was a major risk factor for developing mucormycosis during the COVID-19 era.

Although the clinical characteristics during the pre-COVID-19 and COVID-19 eras were similar in our study, the clinical complications and their incidence was higher during the COVID-19 era than during the pre-COVID-19 era. This difference may be attributed to the underlying comorbid conditions as well as the highly invasive nature of the fungus. The common presentations of mucormycosis are reportedly facial and periorbital swelling, orbital pain, and headache^[24,25], which was similar to our study findings. Complications such as one-sided facial pain, facial numbness, facial swelling, nasal congestion, nasal discharge, orbital cellulitis, and loss of vision were observed during the COVID-19 era in our study and in previous

studies^[26]. Furthermore, epistaxis, diplopia and loss of smell were only seen during the COVID-19 era and not during the pre-COVID-19 era in our study. The initial signs and symptoms of mucormycosis resemble those of COVID-19 and include fever, headache, and nasal congestion. Thus, individuals may delay seeking medical attention because they misinterpret the mucormycosis symptoms for COVID-19 symptoms. This could also explain the greater clinical severity of mucormycosis during the COVID-19 era^[27].

Surgical removal of necrotic tissue is the cornerstone of treatment for mucormycosis^[28]. A combination of prompt surgical debridement and antifungal administration produces a 2-5-fold improvement in clinical results and 1-5-fold enhancement in survival rates^[29]. Until clinical improvement is established, daily repeated debridement may be required. Furthermore, orbital exenteration and sinus excision may be required for widespread distribution of the disease^[30]. Surgical interventions such as maxillectomy, mucosal lining resection, orbital exenteration, orbital floor resection, and nose debridement can be performed to avoid the spread of the disease. In the study by Pippal et al.^[31], by the end of the four-month followup period, 72.5% of the patients had undergone FESS and surgical debridement in addition to antifungal drug administration^[32]. FESS is crucial for the identification and management of mucormycosis^[33]. The majority of the patients in our study had undergone FESS during the pre-COVID-19 and COVID-19 eras.

Amphotericin B lipid formulations have become the mainstay of treatment for mucormycosis. Soman et al.^[34] and Ghazi et al.^[35] reported that the usage of amphotericin B was reduced during the COVID-19 era due to its limited availability. Similarly, 29.9% of the individuals in our study were administered posaconazole instead of amphotericin B during the COVID-19 era. Posaconazole was not frequently administered during the pre-COVID-19 era. Studies have demonstrated that aggressive

surgical debridement in combination with amphotericin B is a reasonably effective treatment approach for mucormycosis. Similarly, in our study, a combination of surgical debridement and liposomal amphotericin B administration was used for the better management of affected individuals. Although the efficacy of itraconazole and voriconazole against Mucorales is low, they are administered in cases of mixed mucormycosis and aspergillosis. Studies have demonstrated that combination therapy is a crucial to lower the high mortality rate and the resistance caused by monotherapy administration^[36].

The standard guidelines for antifungal susceptibility by CLSI or EUCAST have not yet established any antifungal breakpoints against any Mucorales^[37,38]. During the pre-COVID-19 era, our study isolates demonstrated lower MIC values for posaconazole (0.75 µg/ml) than for amphotericin B (1.05 µg/ml). Furthermore, itraconazole and voriconazole demonstrated varying MIC values according to the species. During the COVID-19 era, our study isolates demonstrated higher MIC values for itraconazole (8.5 µg/ml), voriconazole (12.8 µg/ml), and posaconazole (12.52 µg/ml) than for amphotericin B. The higher mean MIC of posaconazole may be attributed to its over-usage during the COVID-19 era due to the limited availability of amphotericin B. Higher MIC values were found against only certain species in this study, which could be due to the species-specific susceptibility pattern of the drugs. Lower MIC values were seen with amphotericin B (0.75 µg/ml) and isavuconazole (1.76 µg/ml), a newer triazole used during the COVID-19 era. Hence, currently, amphotericin B and isavuconazole appear to be promising drugs in the management of mucormycosis. Amphotericin B is the best choice of drug for mucormycosis because it has excellent activity against Mucorales. Isavuconazole can be used as an alternative therapy in patients with nephrotoxicity because it demonstrates better activity than posaconazole against Mucorales.

Study Limitations

The study has some limitations. The outcomes of the patients were not assessed, and the study duration was short.

Conclusion

Mucormycosis is associated with a high morbidity and mortality, and its upsurge during the COVID-19 pandemic may be related to the increased invasiveness of zygomycetes. We found a significant difference in the risk factors as well as clinical severities between the pre-COVID-19 and COVID-19 eras. The mean MIC of the drugs also drastically changed, with posaconazole demonstrating a higher mean MIC and amphotericin B demonstrating a lower mean MIC in the COVID-19 era than in the pre-COVID-19 era. Newer azoles such as isavuconazole may be a good alternative for the management of resistant infections due to the low MIC value. This can be

verified via future studies. This study stresses the importance of increased vigilance toward the early and accurate diagnosis of fungal infections and the possibility of a fungal pandemic when mucormycosis occurs in conjunction with another infectious pandemic such as COVID-19. Thus, timely management of the infected individuals with appropriate antifungals is crucial.

Ethics

Ethics Committee Approval: The study was approved by the Sri Ramachandra Institute of Higher Education and Research of Institutional Ethics Committee (ref: IEC-NI/22/JAN/81/13, date: 25.03.2022).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: S.P., Concept: T.P., S.P., A.J.K., Design: T.P., S.P., A.J.K., Data Collection or Processing: M.K., T.P., Analysis or Interpretation: M.K., T.P., S.P., Literature Search: M.K., Writing: M.K., T.P., S.P., A.J.K.

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