JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

*Coronavirus Pandemic*

# The hospitalization rate and clinical characteristics of mucormycosis prior and during COVID-19 pandemic: A single-center study

Mehrdad Estakhr[1,2], Zahra Ghotbi[1,2], Mahtab Rostamihosseinkhani[1,2], Etrat Hooshmandi[1], Masoud Janipour[3], Vahid Reza Ostovan[1], Nima Fadakar[1], Hanieh Bazrafshan[1], Zahra Bahrami[1], Abbas Rahimi-Jaberi[1], Maryam Poursadeghfard[1], Masoumeh Nazeri[1], Pariya Kouhi[4], Peyman Petramfar[1], Sadegh Izadi[1], Zohreh Barzegar[5], Ehsan Nikzadeh[5], Sarvin Sasannia[2], Shahram Arsang-Jang[6], Reza Tabrizi[7,8], Behzad Khademi[9], Mahsa Kohandel-Shirazi[10], Mohammad Saied Salehi[1], Nahid Ashjazadeh[1], Bijan Khademi[3], Mohammad Javad Ashraf[10], Owrang Eilami[11], Amir Roudgari[11], Mohsen Moghaddami[7], Kamiar Zomorodian[12], Hamid Badali[13], Afshin Borhani-Haghighi[1,14,15]

[1] *Clinical Neurology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran*
[2] *Student Research Committee, Shiraz University of Medical Sciences, Shiraz, Iran*
[3] *Department of Otorhinolaryngology-Head and Neck Surgery, Shiraz University of Medical Sciences, Shiraz, Iran*
[4] *Department of Internal Medicine, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran*
[5] *Shiraz University of Medical Sciences, Shiraz, Iran*
[6] *Department of Biostatistics and Epidemiology, School of Medicine, Zanjan University of Medical Sciences, Zanjan, Iran*
[7] *Noncommunicable Diseases Research Center, Fasa University of Medical Sciences, Fasa, Iran*
[8] *Clinical Research Development Unit, Vali Asr Hospital, University of Medical Sciences, Fasa, Iran*
[9] *Poostchi Ophthalmology Research Center, Department of Ophthalmology, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran*
[10] *Department of Pathology, Shiraz University of Medical Sciences, Shiraz, Iran*
[11] *Department of Family Medicine and Infectious Diseases, HIV and AIDS Research Center, Shiraz University of Medical Sciences, Shiraz, Iran*
[12] *Department of Medical Mycology and Parasitology, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran*
[13] *Department of Molecular Microbiology and Immunology, South Texas Center for Emerging Infectious Diseases, The University of Texas at San Antonio, San Antonio, TX, United States*
[14] *Department of Neurology, John Hunter Hospital, University of Newcastle, Newcastle, Australia*
[15] *Hunter Medical Research Institute and University of Newcastle, Newcastle, Australia*

## Abstract

Introduction: There have been some reports of the association between SARS-CoV-2 infection and mucormycosis. This study aims to compare the hospitalization rates and clinical characteristics of mucormycosis before and during the COVID-19 pandemic.

Methodology: In this retrospective study, we compared the hospitalization rate of mucormycosis patients in Namazi hospital in Southern Iran for two periods of 40 months. We defined July 1st, 2018 to February 17th, 2020, as the pre-COVID-19 period and February 18th, 2020, to September 30th, 2021, as the COVID-19 period. In addition, a quadrupled group of hospitalized patients with age and sex-matched SARS-COV-2 infection without any sign of mucormycosis was selected as the control group for COVID-associated mucormycosis.

Result: In the total of 72 mucormycosis patients in the COVID period, 54 patients had a clinical history and a positive RT-PCR, which confirms the diagnosis of SARS-COV2 infection. The hospitalization rate of mucormycosis showed an increase of + 306% (95% CI: + 259%, + 353%) from a monthly average value of 0.26 (95% confidence interval (CI): 0.14, 0.38) in the pre-COVID period to 1.06 in the COVID period. The use of corticosteroids prior to the initiation of hospitalization ($p \leq 0.01$), diabetes (DM) ($p = 0.04$), brain involvement ($p = 0.03$), orbit involvement ($p = 0.04$), and sphenoid sinus invasion ($p \leq 0.01$) were more common in patients with mucormycosis during the COVID period.

Conclusions: In high-risk patients, especially diabetics, special care to avoid the development of mucormycosis must be taken into account in patients with SARS-COV-2 infection considered for treatment with corticosteroids.

**Key words:** mucormycosis; SARS-CoV-2; COVID-19; invasive fungal infection; pandemic; glucocorticoids.

*J Infect Dev Ctries* 2023; 17(6):791-799. doi:10.3855/jidc.17371

(Received 10 September 2022 – Accepted 05 January 2023)



## Introduction

Mucormycosis (formerly known as zygomycosis) is still regarded as one of the emergency cases of infectious diseases despite the vast and significant breakthroughs in medical science [1,2]. If left undiagnosed and untreated, this acute but rare infection, caused by a group of fungi called mucoromycetes [3,4], can be fatal. Uncontrolled diabetes continues to be the greatest risk factor for developing mucormycosis, particularly diabetic ketoacidosis. Organ

transplantation, neutropenia, trauma, burns, hemochromatosis (iron excess), and the overuse of immunosuppressive medications like corticosteroids are additional risk factors for this infection [5–8]. Almost a year after the coronavirus pandemic began, a surge of mucormycosis cases was recorded in India among severely ill and hospitalized COVID-19 patients or those recovering from this infection. Then, so-called COVID-associated mucormycosis (CAM) was reported from many regions of the world, primarily from low- to middle-income countries like India [9], Turkey [10], and Iran [11]. Hypoxia, excessive glucose (diabetes or steroid-induced hyperglycemia), elevated ferritin, and poor phagocytic activity of white blood cells (WBCs) are all the risk factors induced by COVID-19 that led to the provision of suitable conditions for the development of mucormycosis [12–15]. Moreover, the increased cytokine levels, altered T-helper cell responses, and cytokine release syndrome may cause respiratory problems in those affected by COVID-19 and, as a result, boost pulmonary microbial growth and proliferation [16,17]

Mucormycosis requires immediate medical treatment due to its rapid progression and destructive nature. Delays in initial treatment have been linked to higher mortality rates [18]. Some studies considered corticosteroid administration to treat moderate to severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) infection a major risk factor [19], but others argue against this hypothesis [20].

Most studies on CAM have been conducted as case reports, case series or reviews, which only describe the patients. To address some of the controversies surrounding mucormycosis, we conducted a retrospective cross-sectional study examining the hospitalization rate, clinical presentations and outcomes of patients with mucormycosis during and before the COVID-19 pandemic.

## Methodology

*Study population and diagnosis*

Namazi Hospital is a major referral center with more than 600 beds, which is expanded into 9 outpatient and 29 inpatient wards, including 12 intensive care units [21]. Khalili Hospital, with facilities for functional endoscopic sinus surgery (FESS), is affiliated with Namazi Hospital. Based on Iran's Ministry of health regulations, almost all patients with mucormycosis from catchment areas in the Fars province should be transferred to the Namazi Hospital.

On February 18th, 2020, Iran's first officially confirmed fatal case of COVID-19 was reported [22]. Accordingly, we conducted the study in two periods, including during the pre-COVID-19 period from July 1st, 2018, to February 17th, 2020, and the COVID-19 period from February 18th, 2020, to September 30th, 2021. Those patients with a diagnosis of mucormycosis (> 20 years of age) admitted to Namazi hospital during the study period of 40 months are included in the calculation of the hospitalization rate [23]. According to the National Population and Housing Census, the population > 20 years old was estimated for Fars Province in the years 2018, 2019, 2020, and 2021 were 3487,000, 3517,000, 3547,000 and 3578,000, respectively [23]. Accordingly, these groups of patients had recruited:

A- 18 patients with mucormycosis in the pre-COVID period

B- 90 Patients with mucormycosis in the COVID period

The second group was composed of the following individuals:

B1- 54 Patients with mucormycosis in COVID period with a definite diagnosis of SARS-Cov-2 infection (clinical manifestation AND positive SARS-COV-2 RT PCR)

B2- 18 Patients with mucormycosis in COVID period without definite SARS-CoV-2 infection.

Patients with clinical and radiologic features suggested SARS-CoV-2 infection, but negative SARS-CoV-2 RT PCR was included in group B2.

A third group was also defined as:

C- 216 Hospitalized patients with definite SARS-CoV-2 infection without any sign of mucormycosis who were age and sex-matched with group B1 (control group).

*SARS-CoV-2 infection*

COVID-19-attributed investigations were done for patients if any clinical relevance was found. COVID-19 is considered in patients with positive oro-or nasopharyngeal reverse transcriptase-polymerase chain reaction (RT-PCR).

*Mucormycosis definition and categorization*

The mucormycosis diagnosis was based on relevant clinical symptoms (such as facial swelling, runny nose, headache, nasal congestion, etc.), radiological imaging (Computed Tomography -CT-, Magnetic Resonance Imaging -MRI-), and histopathological findings. Patients with incomplete medical records and those with an indefinite diagnosis were excluded from the study.

We used the 10th version of the International Classification of Diseases (ICD-10) for full patient entry. The search was conducted on all medical records using the ICD-10 diagnostic codes B46.5 for "mucormycosis, unspecified," B46.3 for "Cutaneous mucormycosis," B46.4 for "Disseminated mucormycosis," B46.0 for "Pulmonary mucormycosis, "B46.1 for "Rhinocerebral mucormycosis" and B46.2 for "Gastrointestinal mucormycosis." After confirming the diagnosis by qualified infectious persons, all patients aged more than 20 with a final diagnosis of mucormycosis were included. Individuals with unclear diagnoses were excluded from the study. The demographic data, such as age, gender, risk factors, therapeutic measures (FESS), and in-hospital mortality, were retrieved from hospital health information systems (HIS) and considered for the analysis.

*Study Protocol and approval*

The primary outcome was the rate of mucormycosis hospitalizations before and during the COVID-19 pandemic (A and B groups). As secondary outcomes, we compared the clinical presentation and mortality of patients with mucormycosis associated with COVID-19 to patients with mucormycosis without COVID-19 (B1 versus A) and to COVID-19 patients without mucormycosis (B1 versus C).

This study was approved by the institutional review board (IRB) as well as the ethics committee at Shiraz University of Medical Sciences (SUMS) (IR.SUMS.REC.1400.270). The review board waived the need for patient consent. This research was conducted in accordance with the ethical standards of the institutional and national research committee, as well as with the Helsinki Declaration or comparable standards [24]. It is permissible to share data with other centers upon approval by the Ethics Committee.

*Statistical analysis*

Statistical analysis was conducted using IBM SPSS Statistics for Windows, Version 16.0. Armonk, NY: IBM Corp. A P-value of less than 0.05 is considered significant for all analyses. Based on a study of hospitalization rates per million people over two years (from July 1st, 2018, to February 17th, 2020, and from February 18th, 2020, to September 30th, 2021), the dependent variable was the hospitalization rate per million people. In accordance with the distribution pattern, quantitative variables were presented as mean, standard deviation (SD), or median with interquartile range (IQR). Qualitative factors were expressed as percentages (%). The Chi-square and t-tests were used to test the relevant assumptions for independent variables (e.g., the predisposing risk factors and major demographic characteristics). The Mann-Whitney test was used to analyze the non-normal distribution of our data. The crude mucormycosis hospitalization rate variation was derived from averaging monthly Mucor mycosis hospitalizations.

Throughout the study period, change in the hospitalization rates was analyzed using a Bayesian interrupted time series. While it provides for the consideration of longitudinal variation in the dependent variable. In the R 4.1 environment, time series analysis was conducted using the Causal Impact package. After adjusting for age and gender ratio variables, the final time series model was fitted. We summarized the Bayesian time series model's results using 95 percent Credible Intervals (CrI).

## Results

*Demographic data and clinical variables*

Ninety mucormycosis patients were hospitalized (mean age 56.00 ± 14.53 years, male-to-female ratio 1.30). Among the 72 patients in the COVID period (Group B), only 54 had a documented positive RT-PCR test prior to admission (Group B1). The mean and standard deviation days between COVID-19 infection and admission for mucormycosis infection was 18.51 ± 5.25. Table 1 illustrates the comparison between groups A, B1, and C.

COVID-period mucormycosis patients' mean age was 54.09 ± 14.60 years, which was not different from pre-COVID mucormycosis patients (mean ± SD = 56.44 ± 16.04, $p$ = 0.82) and COVID-19 matched controls (mean ± SD = 54.82 ± 14.27, $p$ = 0.94). Both COVID (B1 group) (57.4%) and pre-COVID periods (61.1%) consistently showed higher rates of male mucormycosis patients than female patients. No significant relationship between genders was observed among the studied groups.

Regarding risk factors, around 67.3 % of CAM patients had taken corticosteroids prior to getting admitted. This usage was significantly higher compared to patients with mucormycosis in the pre-COVID period (22.2 %, $p < 0.01$) and COVID-19 controls (3.3 %, $p < 0.01$).

CAM patients had a significantly higher diabetes mellitus (DM) rate compared to pre-COVID period mucormycosis (70.4% vs 44.4%, $p$ = 0.04) and also controls (70.4% vs 24.5%, $p < 0.01$). While there was no statistically significant difference ($p$ = 0.94) between CAM patients (239.82 ± 116.73) and pre-COVID mucormycosis (228.16 ± 138.53) patients in the initial

admission mean blood sugar (BS). In contrast, we found that CAM patients had a significantly higher mean BS level than COVID-19 controls (B1 vs. C, 239.82 ± 116.73 vs. 158.78 ± 113.43, $p = 0.01$).

Compared to patients with pre-COVID mucormycosis, CAM patients had a considerably decreased risk of malignancies (44.4% vs. 9.3%, $p = 0.01$). When compared to patients with pre-COVID mucormycosis, the use of immunosuppressive medications, such as chemotherapeutic drugs and polyclonal or monoclonal antibodies, was considerably lower in CAM patients (14.8 % vs. 50 %, $p = 0.01$). Malignancies (9.3 % vs. 3.7 %, $p = 0.08$) and immunosuppressive medication use (14.8 % vs. 4.6 %, $p = 0.01$) rates, however, were greater in comparison to COVID-19 controls.

A CT scan was used to determine mucormycosis patients' organ and sinus involvement. Sinus involvement in patients did not differ substantially across the two time periods, except that 83.3% of CAM patients had sphenoid involvement, which was considerably higher than that in pre-COVID mucormycosis patients (83.3% vs. 55.6%, $p = 0.01$). The percentage of patients with orbital involvement rose considerably from 16.7% in pre-COVID mucormycosis to 42.6% in CAM ($p = 0.04$). Brain invasion is another vital organ significantly involved in CT scanning during the pandemic among mucormycotic patients. CT scans revealed brain involvement in 37% of CAM patients, which is considerably greater than the 11.1% of pre-COVID mucormycosis patients ($p = 0.03$). Rare complications

**Table 1.** Baseline demographic and major epidemiological information.

| Variables | Study Period: July 1st, 2018, to September 30th, 2021 | | | | |
|---|---|---|---|---|---|
| | **CAM (N = 54)** | **pre-covid period Mucormycosis (N = 18)** | **SARS COV 2 infection (N = 216)** | $p_a$ | $p_b$ |
| **Age** | 54.09 ± 14.60 | 56.44 ± 16.04 | 54.82 ± 14.27 | 0.82 | 0.94 |
| **Sex** | | | | | |
| Male | 31 (57.4) | 11 (61.1) | 125 (57.9) | 0.78 | 0.95 |
| Female | 23 (42.6) | 7 (38.9) | 91 (42.1) | | |
| **Predisposing factor** | | | | | |
| DM | 38 (70.4) | 8 (44.4) | 53 (24.5) | **0.04** | < 0.01 |
| Malignancies | 5 (9.3) | 8 (44.4) | 8 (3.7) | **< 0.01** | 0.08 |
| Immunosuppressive drug | 8 (14.8) | 9 (50) | 10 (4.6) | **< 0.01** | < 0.01 |
| Renal disease | 7 (13) | 1 (5.6) | 14 (6.5) | 0.38 | 0.11 |
| Organ transplant | 3 (5.6) | 2 (11.1) | 4 (1.9) | 0.59 | 0.12 |
| Corticosteroid usage before the admission | 35 (67.3) | 4 (22.2) | 7 (3.3) | **< 0.01** | < 0.01 |
| First admission BS | 239.82 ± 116.73 | 228.16 ± 138.53 | 158.78 ± 113.43 | 0.94 | < 0.01 |
| Radiologic involvements | | | | | |
| Lung | 1 (1.9) | 1 (5.6) | — | 0.44 | — |
| Maxillary sinus | 48 (88.9) | 17 (94.4) | — | 0.49 | — |
| Frontal sinus | 37 (68.5) | 9 (50) | — | 0.15 | — |
| Sphenoid sinus | 45 (83.3) | 10 (55.6) | — | **0.01** | — |
| Ethmoid sinus | 49 (90.7) | 16 (88.9) | — | 0.81 | — |
| Orbit involvement | 23 (42.6) | 3 (16.7) | — | **0.04** | — |
| Brain | 20 (37) | 2 (11.1) | — | **0.03** | — |
| Bone destruction | 29 (53.7) | 6 (33.3) | — | 0.13 | — |
| **Therapeutic measurements** | | | | | |
| FESS | 46 (85.2) | 9 (50) | — | **< 0.01** | — |
| LAMB | 43 (79.6) | 10 (55.6) | — | **0.04** | — |
| CAMB | 33 (61.1) | 10 (55.6) | — | 0.67 | — |
| Amphotericin retrobulbar | 26 (48.1) | 2 (11.1) | — | **< 0.01** | — |
| Posaconazole | 28 (51.9) | 1 (5.6) | — | **< 0.01** | — |
| Voriconazole | 3 (5.6) | 1 (5.6) | — | 1.00 | — |
| Fluconazole | 6 (11.1) | 2 (11.1) | — | 1.00 | — |
| Itraconazole | 5 (9.3) | 3 (16.7) | — | 0.38 | — |
| Caspofungin | 12 (22.6) | 4 (22.2) | — | 0.97 | — |
| Maxillectomy | 4 (7.4) | 1 (5.6) | — | 1.00 | — |
| **Mortality and disability** | | | | | |
| In-hospital mortality | 14 (25.9) | 6 (33.3) | 37 (17.1) | 0.54 | 0.14 |

Categorical variables are shown as number (%); Continuous variables were shown as mean § SD or median [IQR]; LAMB: liposomal amphotericin B; CAMB: conventional amphotericin B; $p_a$: Comparison between covid-19 associated mucormycotic patients and pre-COVID period mucormycotic patients; $p_b$: Comparison between COVID mucormycotic patients and covid-19 controls.

such as lung invasion and bone destruction did not change due to the pandemic.

The monthly crude hospitalization rate for mucormycosis for the two time periods is depicted in Figure 1. The hospitalization rate of mucormycosis showed an increase of + 306% (95% CI: + 259%, + 353%) from a monthly average value of 0.26 (95% confidence interval (CI): 0.14, 0.38) in the pre-COVID period to 1.06 in the COVID period. A significant increase in the hospitalization rate of mucormycosis was observed by 20.17 ($p$ = 0.001). However, without COVID-19, we anticipated a value of around 4.96 (95% CI: 2.66 to 7.31). Including confounder variables in the Bayesian interrupted time series model showed an increasing trend in hospitalization rates (Posterior Beta of time*period interaction = 0.20; 95% CI: 0.12, 0.31). Using a time series model, Figure 2 shows the estimated expected and observed trends in mucormycosis hospitalization rates.

*Mucormycosis treatment and outcome*

FESS plays an essential role in the diagnosis and treatment of mucormycosis. During admission for fungal infection, FESS was performed on 80.6% of CAM patients, which was considerably greater than non-COVID-19 mucormycosis ($p$ = 0.008). Overall, CAM patients used antifungals more frequently than non-COVID-19 mucormycosis patients. However, only liposomal amphotericin B (LAMB) significantly increased ($p$ = 0.027).

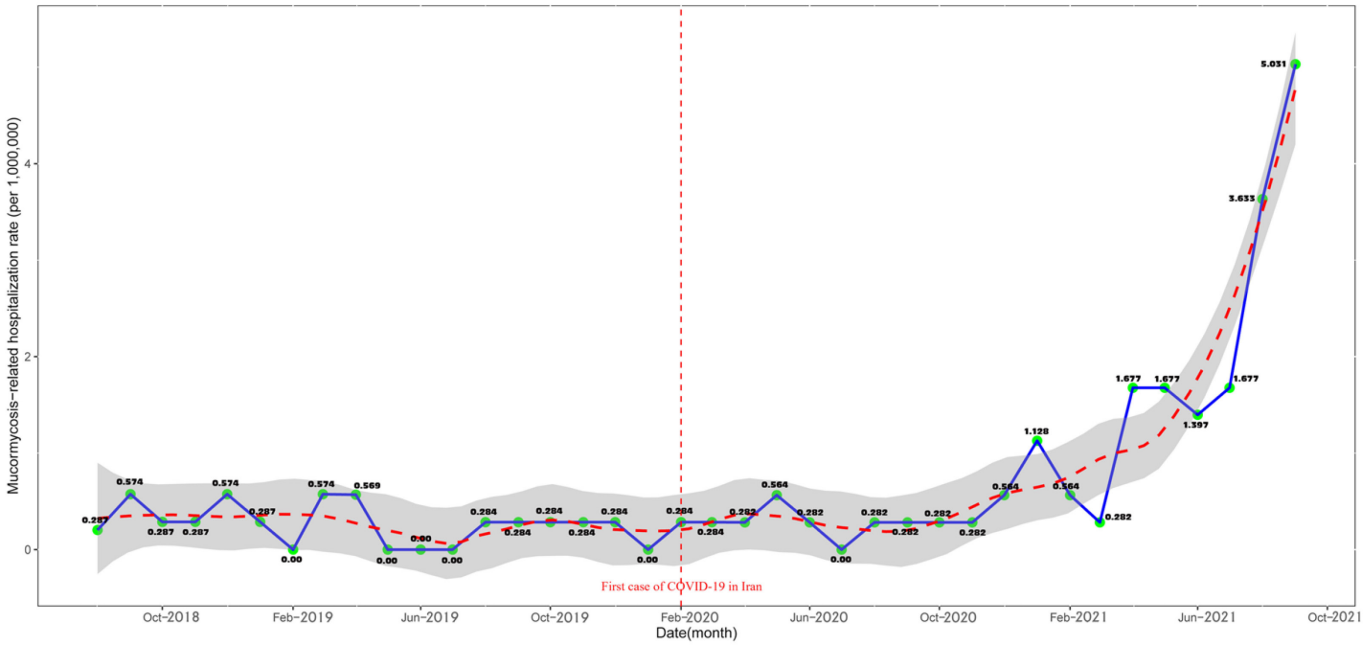
According to Table 1, the overall death rate of CAM patients was 25.9%, which was lower than the 33.3 % mortality rate experienced by non-COVID mucormycosis patients, although this difference was not statistically significant ($p$ = 0.54). Compared to COVID-19 controls, CAM patients had a statistically significantly higher death rate (25.9% vs. 17.1%, $p$ = 0.14).

## Discussion

Mucormycosis is an additional COVID-19 milestone that has become a fatal consequence of this infection.

Similar to previous reports, most CAM cases in our study occurred in male patients [1,25]. Although this difference in gender disparity is not exactly clear, it may be due to different sex susceptibilities since diabetic ketoacidosis female mice were more resistant to infection and survived longer than diabetic ketoacidosis male mice [26]. In the present study, the mean interval between COVID-19 infection and admission for mucormycosis was 18.51 ± 5. Days (range: 1-37 days). Similarly, Hoenigl *et al*., in analyses of CAM cases from 18 countries, reported that mucormycosis was clinically diagnosed at a mean of 12.6 days (range = 0–42 days) after COVID-19 diagnosis [12]. Given the current data, physicians should be aware of the possibility of mucormycosis in high-risk COVID-19 patients during the second and third weeks of the infection.

**Figure 1.** Crude monthly Mucormycosis hospitalization rate per 1,000,000 before and during the COVID- 19 pandemic. Results from Recruiting center Namazi Hospital, Fars, Iran.



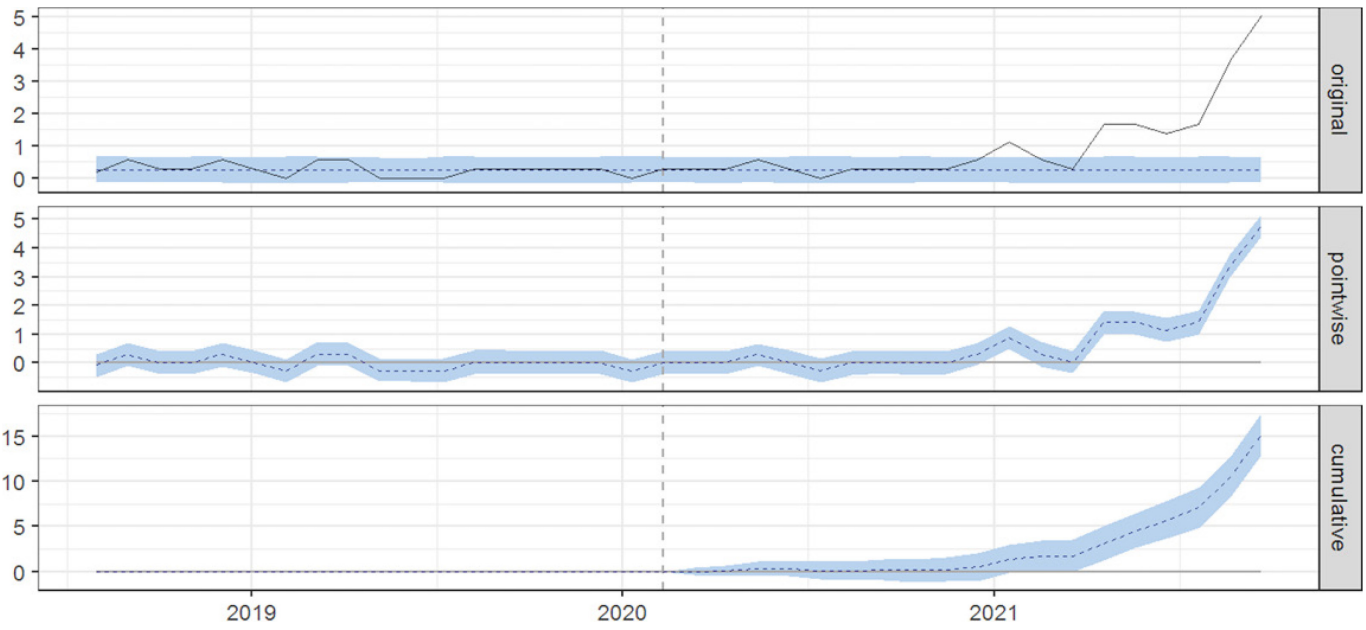
In our study and others [12,27], diabetes is considered the leading risk factor for CAM. Compared to the general population, the prevalence of DM was high among COVID-19 patients. More than two third of the patients with CAM in our study had DM, and the incidence of DM between CAM patients and those having either mucormycosis without COVID or COVID-19 without mucormycosis (controls) was statistically significant. Moreover, SARS-CoV2 can cause hyperglycemia by damage to the pancreatic islet cells, insulin resistance induced by a cytokine storm, and acute cortisol stress responses [28]. Although DM has been found as the predominant predisposing factor of CAM, prior to the COVID-19 Pandemic, malignancy was the primary risk factor for mucormycosis in this investigation, and a previous report of mucormycosis from the same center around a decade earlier [29].

In CAM and pre-COVID mucormycosis patients, respectively, 67.3% (35/54) and 22.2% (4/18) received systemic corticosteroids prior to diagnosis. Many clinicians have excessively recommended steroids to handle the escalating COVID-related cytokine storm. According to WHO clinical care guidelines updated on September 2nd, 2020, corticosteroids should be used in patients with severe and critical COVID-19 under medical supervision [30]. Although steroids diminish inflammation and subsequent cell damage in SARS-CoV-2 infection, they may also augment glucose levels, suppress the immune system, impair neutrophil function, and downregulate genes encoding pro-inflammatory cytokine [16,31]. These circumstances facilitate the invasion of Mucorales and create ideal conditions for their rapid expansion. The COVID-19 pandemic resulted in an increase in mucormycosis hospitalizations that may demand revisions to this guideline; particularly, people with diabetes should be subject to more stringent criteria before starting high-dose corticosteroids.

In recent decades, mucormycosis has been on the rise due to various factors, with an especially high incidence rate among patients with uncontrolled diabetes [32,33]. There has been a significant increase in mucormycosis incidence after the COVID-19 pandemic. In their study of 52,966 patients, Hussein *et al*. [34]reported a pooled prevalence of CAM patients that was 50 times higher than the highest background status of mucormycosis. Mucormycosis prevalence has been evaluated in a few studies prior to and after the pandemic [20]. To the best of our knowledge, this is the first study that uses a BASIAN time series model to examine mucormycosis hospitalization rates over time.

Comparing cases of mucormycosis in the pre-COVID and COVID periods, cephalic, sphenoid sinus, and orbital involvement were significantly higher in CAM patients. Amphotericin-B deoxycholate and its liposomal formulation are still acceptable options, but the latter is favored due to its reduced nephrotoxicity. Posaconazole might be considered the second

**Figure 2.** Association between COVID-19 and Mucormycosis hospitalization rate, trend. Original panel: The blue line and its associated 95% confidence interval (CI) represent the expected change in hospitalization rates in the absence of COVID-19, while the solid line represents the observed change in hospitalization rates; Pointwise Panel: Indicates the estimated trend of hospitalization rate; Panel Cumulative: The cumulative hospitalization rate following the interruption point was revealed.



medication for mucormycosis when amphotericin treatment has failed or is intolerable [35]. Repeated surgical debridement may be necessary to prevent the fungus from invading nearby tissue. Although adding mucormycosis to COVID-19 infection significantly increased the death rate, the mortality of the mucormycosis patients did not differ between pre-COVID and COVID periods. This observation could be because, on the one hand, physicians are more aware of this infection's clinical symptoms and treatment. On the other hand, CAM patients had easier access to FESS and liposomal amphotericin B during the COVID era.

## Limitations

The cumulative dose of the steroid could not be determined. Different forms of steroids, such as dexamethasone and methylprednisolone, were administered to COVID patients via different routes, including intramuscular (IM), intravenous (IV), and oral administration. It would be wise for future studies to determine the effective dosage that would pose a serious risk of infection with mucormycosis. A further limitation of this study is our inability to utilize logistic regression analysis to assess the effects of corticosteroids due to the small sample size.

## Conclusions

Despite the overall decline of the COVID pandemic, recent SARS-1 and SARS-2 outbreaks indicate the possibility of a new virus-based pandemic. Patients with SIRS often respond well to corticosteroids, which can be life-saving; however, in patients with risk factors such as diabetics, we must take special care to minimize the chance of developing opportunistic infections such as mucormycosis. We still have time to develop protocols for early diagnosis and treatment of mucormycosis or guidelines for using specific types and dosages of corticosteroids in inflammatory processes caused by potential viral agents.

## Acknowledgements

We would like to thank Dr.Amir Arastehfar for his assistance in reviewing and editing the draft.

## Authors' Contributions

Conceptualization: ME, ZG, EH, KZ, ABH; Methodology: ABH, SA, RT; Data curation: ME, ZG, EH, KZ, ABH; Investigation: ME, ZG, MR, HB, ZB, EN, SS, ZB; Validation: EH, MJ, ABH; Formal analysis: SA, RT; Supervision: ABH; Project administration: EH, MJ, ABH, BK, OE; Writing - original draft: ME, ZG, EH, VRO, KZ, HB, ABH; Writing - review and editing: ME, ZG, MR, EH, MJ, VRO, NF, ARJ, PK, BK, BK, MJA, OE, KZ, HB, ABH, HB, ZB, SI, MP, MN, PP, ZB, EN, SS, SA, RT, MKS, MSS, NA, AR, MM.

## References

1. Pal R, Singh B, Bhadada SK, Banerjee M, Bhogal RS, Hage N, Kumar A (2021) COVID-19-associated mucormycosis: An updated systematic review of literature. Mycoses 64: 1452–1459. doi: 10.1111/myc.13338.
2. Prakash H, Chakrabarti A (2019) Global epidemiology of mucormycosis. J Fungi 5: 26. doi: 10.3390/jof5010026.
3. Kwon-Chung KJ (2012) Taxonomy of fungi causing mucormycosis and entomophthoramycosis (zygomycosis) and nomenclature of the disease: molecular mycologic perspectives. Clin Infect Dis 54: S8–S15. doi: 10.1093/cid/cir864.
4. Manesh A, Rupali P, Sullivan MO, Mohanraj P, Rupa V, George B, Michael JS (2019) Mucormycosis— a clinicoepidemiological review of cases over 10 years. Mycoses 62: 391–398. doi: 10.1111/myc.12897.
5. Prabhu RM, Patel R (2004) Mucormycosis and entomophthoramycosis: a review of the clinical manifestations, diagnosis and treatment. Clin Microbiol Infect 10: 31–47. doi: 10.1111/j.1470-9465.2004.00843.x.
6. Stemler J, Hamed K, Salmanton-García J, Rezaei-Matehkolaei A, Gräfe SK, Sal E, Zarrouk M, Seidel D, Abdelaziz Khedr R, Ben-Ami R, Ben-Chetrit E, Roth Y, Cornely OA (2020) Mucormycosis in the Middle East and North Africa: analysis of the FungiScope® registry and cases from the literature. Mycoses 63: 1060–1068. doi: 10.1111/myc.13123.
7. Ibrahim AS (2014) Host-iron assimilation: pathogenesis and novel therapies of mucormycosis. Mycoses 57: 13–17. doi: 10.1111/myc.12232.
8. Vaezi A, Moazeni M, Rahimi MT, De Hoog S, Badali H (2016) Mucormycosis in Iran: a systematic review. Mycoses 59: 402–415. doi: 10.1111/myc.12474.
9. Selarka L, Sharma S, Saini D, Sharma S, Batra A, Waghmare VT, Dileep P, Patel S, Shah M, Parikh T, Darji P, Patel A, Goswami G, Shah A, Shah S, Lathiya H, Shah M, Sharma P, Chopra S, Gupta A, Jain N, Khan E, Sharma VK, Sharma AK, Chan ACY, Ong JJY (2021) Mucormycosis and COVID-19: an epidemic within a pandemic in India. Mycoses 64: 1253–1260. doi: 10.1111/myc.13353.
10. Bayram N, Ozsaygılı C, Sav H, Tekin Y, Gundogan M, Pangal E, Cicek A, Özcan İ (2021) Susceptibility of severe COVID-19 patients to rhino-orbital mucormycosis fungal infection in different clinical manifestations. Jpn J Ophthalmol 65: 515–525. doi: 10.1007/s10384-021-00845-5.

11. Ahmadikia K, Hashemi SJ, Khodavaisy S, Getso MI, Alijani N, Badali H, Mirhendi H, Salehi M, Tabari A, Mohammadi Ardehali M, Kord M, Roilides E, Rezaie S (2021) The double-edged sword of systemic corticosteroid therapy in viral pneumonia: a case report and comparative review of influenza-associated mucormycosis versus COVID-19 associated mucormycosis. Mycoses 64: 798–808. doi: 10.1111/myc.13256.
12. Hoenigl M, Seidel D, Carvalho A, Rudramurthy SM, Arastehfar A, Gangneux J-P, Nasir N, Bonifaz A, Araiza J, Klimko N, Serris A, Lagrou K, Meis JF, Cornely OA, Perfect JR, White PL, Chakrabarti A (2022) The emergence of COVID-19 associated mucormycosis: a review of cases from 18 countries. Lancet Microbe 3: e543–e552. doi: 10.1016/S2666-5247(21)00237-8.
13. Kumar H M, Sharma P, Rudramurthy SM, Sehgal IS, Prasad KT, Pannu AK, Das R, Panda NK, Sharma N, Chakrabarti A, Agarwal R, Muthu V (2022) Serum iron indices in COVID-19-associated mucormycosis: a case–control study. Mycoses 65: 120–127. doi: 10.1111/myc.13391.
14. SeyedAlinaghi S, Karimi A, Barzegary A, Pashaei Z, Afsahi AM, Alilou S, Janfaza N, Shojaei A, Afroughi F, Mohammadi P, Soleimani Y, Nazarian N, Amiri A, Tantuoyir MM, Oliaei S, Mehraeen E, Dadras O (2022) Mucormycosis infection in patients with COVID -19: a systematic review. Health Sci Rep 5: e529. doi: 10.1002/hsr2.529
15. Ostovan VR, Tabrizi R, Bazrafshan H, Bahrami Z, Khazraei H, Khazraei S, Borhani-Haghighi A, Moghadami M, Grant M (2022) Mortality-related risk factors for coronavirus disease (COVID-19)-associated mucormycosis: a systematic review and meta-analysis. Curr Fungal Infect Rep 16: 143–153. doi: 10.1007/s12281-022-00440-2.
16. Choudhary S, Sharma K, Silakari O (2021) The interplay between inflammatory pathways and COVID-19: a critical review on pathogenesis and therapeutic options. Microb Pathog 150: 104673. doi: 10.1016/j.micpath.2020.104673.
17. Ostovan VR, Rezapanah S, Behzadi Z, Hosseini L, Jahangiri R, Anbardar MH, Rostami M (2021) Coronavirus disease (COVID-19) complicated by rhino-orbital-cerebral mucormycosis presenting with neurovascular thrombosis: a case report and review of literature. J Neurovirol 27: 644–649. doi: 10.1007/s13365-021-00996-8.
18. Cornely OA, Alastruey-Izquierdo A, Arenz D, Chen SCA, Dannaoui E, Hochhegger B, Hoenigl M, Jensen HE, Lagrou K, Lewis RE, Mellinghoff SC, Mer M, Pana ZD, Seidel D, Sheppard DC, Wahba R, Akova M, Alanio A, Al-Hatmi AMS, Arikan-Akdagli S, Badali H, Ben-Ami R, Bonifaz A, Bretagne S, Castagnola E, Chayakulkeeree M, Colombo AL, Corzo-León DE, Drgona L, Groll AH, Guinea J, Heussel C-P, Ibrahim AS, Kanj SS, Klimko N, Lackner M, Lamoth F, Lanternier F, Lass-Floerl C, Lee D-G, Lehrnbecher T, Lmimouni BE, Mares M, Maschmeyer G, Meis JF, Meletiadis J, Morrissey CO, Nucci M, Oladele R, Pagano L, Pasqualotto A, Patel A, Racil Z, Richardson M, Roilides E, Ruhnke M, Seyedmousavi S, Sidharthan N, Singh N, Sinko J, Skiada A, Slavin M, Soman R, Spellberg B, Steinbach W, Tan BH, Ullmann AJ, Vehreschild JJ, Vehreschild MJGT, Walsh TJ, White PL, Wiederhold NP, Zaoutis T, Chakrabarti A (2019) Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium. Lancet Infect Dis 19: e405–e421. doi: 10.1016/S1473-3099(19)30312-3.
19. Guzmán-Castro S, Chora-Hernandez LD, Trujillo-Alonso G, Calvo-Villalobos I, Sanchez-Rangel A, Ferrer-Alpuin E, Ruiz-Jimenez M, Corzo-Leon DE (2022) COVID-19–associated mucormycosis, diabetes and steroid therapy: experience in a single centre in Western Mexico. Mycoses 65: 65–70. doi: 10.1111/myc.13383.
20. Muraleedharan M, Panda NK, Angrish P, Arora K, Patro SK, Bansal S, Chakrabarti A, Rudramurthy SM, Bakshi J, Mohindra S, Gupta R, Virk RS, Verma RK, Ramavat AS, Nayak G (2022) As the virus sowed, the fungus reaped! A comparative analysis of the clinico-epidemiological characteristics of rhino-orbital mucormycosis before and during COVID-19 pandemic. Mycoses 65: 567–576. doi: 10.1111/myc.13437.
21. Namazi hospital (2022) Specialty and subspecialty wards. Available: https://gsia.sums.ac.ir/en/page/18720/Nemazee-Hospital. Accessed: 14 Apr 2022.
22. Nojomi M, Moradi-Lakeh M, Pourmalek F (2021) COVID-19 in Iran: what was done and what should be done? Med J Islam Repub Iran 35: 97. doi: 10.47176/mjiri.35.97.
23. Statistical center of Iran (2022) Population (under enumeration). Available: https://www.amar.org.ir/english/Metadata/Definitions-Concepts/Population. Accessed 7 Mar 2022.
24. World Medical Association (2022) Declaration of helsinki – ethical principles for medical research involving human subjects. In: world medical association. Available: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/. Accessed: 29 May 2022.
25. Sen M, Honavar S, Sengupta S, Rao R, Kim U, Sharma M, Sachdev M, Grover A, Surve A, Budharapu A, Ramadhin A, Tripathi A, Gupta A, Bhargava A, Sahu A, Khairnar A, Kochar A, Madhavani A, Shrivastava A, Desai A, Paul A, Ayyar A, Bhatnagar A, Singhal A, Nikose A, Bhargava A, Tenagi A, Kamble A, Nariani A, Patel B, Kashyap B, Dhawan B, Vohra B, Mandke C, Thrishulamurthy C, Sambare C, Sarkar D, Mankad D, Maheshwari D, Lalwani D, Kanani D, Patel D, Manjandavida F, Godhani F, Agarwal G, Ravulaparthi G, Shilpa G, Deshpande G, Thakkar H, Shah H, Ojha H, Jani H, Gontia J, Mishrikotkar J, Likhari K, Prajapati K, Porwal K, Koka K, Dharawat K, Ramamurthy L, Bhattacharyya M, Saini M, Christy M, Das M, Hada M, Panchal M, Pandharpurkar M, Ali M, Porwal M, Gangashetappa N, Mehrotra N, Bijlani N, Gajendragadkar N, Nagarkar N, Modi P, Rewri P, Sao P, Patil P, Giri P, Kapadia P, Yadav P, Bhagat P, Parekh R, Dyaberi R, Chauhan R, Kaur R, Duvesh R, Murthy R, Dandu R, Kathiara R, Beri R, Pandit R, Rani R, Gupta R, Pherwani R, Sapkal R, Mehta R, Tadepalli S, Fatima S, Karmarkar S, Patil S, Shah S, Shah S, Shah S, Dubey S, Gandhi S, Kanakpur S, Mohan S, Bhomaj S, Kerkar S, Jariwala S, Sahu S, Tara S, Maru S, Sharma S, Gupta S, Kumari S, Das S, Menon S, Burkule S, Nisar S, Kaliaperumal S, Rao S, Pakrasi S, Rathod S, Biradar S, Kumar S, Dutt S, Bansal S, Ravani S, Lohiya S, Ali Rizvi S, Gokhale T, Lahane T, Vukkadala T, Grover T, Bhesaniya T, Chawla U, Singh U, Une V, Nandedkar V, Subramaniam V, Eswaran V, Chaudhry V, Rangarajan V, Dehane V, Sahasrabudhe V, Sowjanya Y, Tupkary Y, Phadke Y (2021) 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 69: 1670-1692. doi: 10.4103/ijo.IJO_1565_21.

26. Gebremariam T, Alkhazraji S, Alqarihi A, Wiederhold NP, Najvar LK, Patterson TF, Filler SG, Ibrahim AS (2021) Evaluation of sex differences in murine diabetic ketoacidosis and neutropenic models of invasive mucormycosis. J Fungi 7: 313. doi: 10.3390/jof7040313.
27. Kumar A, Verma M, Hakim A, Sharma S, Meena R, Bhansali S (2022) Epidemiology of mucormycosis cases during the second wave of covid-19 in a tertiary care institute in western Rajasthan, India. Cureus 14: e22973. doi: 10.7759/cureus.22973.
28. Kothandaraman N, Rengaraj A, Xue B, Yew WS, Velan SS, Karnani N, Leow MKS (2021) COVID-19 endocrinopathy with hindsight from SARS. Am J Physiol-Endocrinol Metab 320: E139–E150. doi: 10.1152/ajpendo.00480.2020.
29. S Sarvestani A, Pishdad G, Bolandparvaz S (2013) Predisposing factors for mucormycosis in patients with diabetes mellitus; an experience of 21 years in Southern Iran. Bull Emerg Trauma 1: 164–170.
30. World Health Organization (2022) Updates clinical care guidance with corticosteroid recommendations. Available: https://www.who.int/news-room/feature-stories/detail/who-updates-clinical-care-guidance-with-corticosteroid-recommendations. Accessed: 29 May 2022.
31. Soni S, Pudake R, Jain U, Chauhan N (2022) A systematic review on SARS-CoV-2-associated fungal coinfections. J Med Virol 94: 99–109. doi: 10.1002/jmv.27358.
32. Roden MM, Zaoutis TE, Buchanan WL, Knudsen TA, Sarkisova TA, Schaufele RL, Sein M, Sein T, Chiou CC, Chu JH, Kontoyiannis DP, Walsh TJ (2005) Epidemiology and outcome of zygomycosis: a review of 929 reported cases. Clin Infect Dis 41: 634–653. doi: 10.1086/432579.
33. Parra Fariñas R, Alonso-Sardón M, Velasco-Tirado V, Pérez IG, Carbonell C, Álvarez Artero E, Romero-Alegría Á, Pardo-Lledías J, Belhassen-García M (2022) Increasing incidence of mucormycosis in Spanish inpatients from 1997 to 2018. Mycoses 65: 344–353. doi: 10.1111/myc.13418.
34. Hussain S, Riad A, Singh A, Klugarová J, Antony B, Banna H, Klugar M (2021) Global prevalence of COVID-19-associated mucormycosis (cam): living systematic review and meta-analysis. J Fungi 7: 985. doi: 10.3390/jof7110985.
35. Song G, Liang G, Liu W (2020) Fungal co-infections associated with global COVID-19 pandemic: a clinical and diagnostic perspective from China. Mycopathologia 185: 599–606. doi: 10.1007/s11046-020-00462-9.

## Corresponding author

Afshin Borhani-Haghighi, MD
Clinical Neurology Research Center,
Shiraz University of Medical Sciences,
P.O.Box: 7193635899, Shiraz, Iran.
Tel/Fax: +98-713-6281572
E-mail addresses: neuro.ab@gmail.com

**Conflict of interests:** No conflict of interests is declared.