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# Mortality and Morbidity among COVID-19-Associated Mucormycosis Patients in Iran: A Prospective Cohort Study

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## Abstract

**Background:** The key contribution of this paper is from investigating the mortality and morbidity rates and related factors associated with COVID-19-associated-mucormycosis among Iranian patients. The existing literature is scarce on this topic, particularly in the context of Iran. The present study investigates mortality and morbidity among 62 confirmed COVID-19-associated-mucormycosis Iranian patients in relation to their demographic characteristics, laboratory test results, predisposing factors, and COVID-related factors. **Material and Methods:** In this prospective cohort study, the patients were identified in the fifth wave of the disease, between 1st August and 15th October 2021, with data collected at baseline with a three-week follow-up. This was a multicenter investigation with patients admitted to two clinics in Iran. 62 participants were admitted, with the key criteria of them being COVID-19-associated-mucormycosis patients. 53 out of 60 patients underwent corticosteroid therapy and debridement surgery. Intravenous remdesivir (200 mg/kg/day at day 1, 100 mg/kg/day in following days for up to 5 days) and corticosteroids were administered for 53 out 54 patients. Oxygen therapy was only needed for 30% (n = 19) of the patients. **Results:** A 40% mortality rate was observed within the three-week follow-up, with deaths concentrated among those with controlled diabetes mellitus (61%) and long-term diabetes mellitus patients (an average of eight versus four years). Higher mortality was also observed in patients with higher leucocytes and those with rhino-orbital-

cerebral (59%), followed by nasal (55.6%) mucormycosis. Among survivors, 32% were reinfected, and 56% suffered from loss of vision. **Conclusion:** The study concludes that mucormycosis is associated with a higher mortality rate among COVID-19 patients with diabetes mellitus, particularly corticosteroid recipients. Thus, urgent attention to this coinfection is warranted in Iran.

## Keywords

Mucorales, COVID-19, Mucormycosis, Coinfection, Dexamethasone, Diabetes Mellitus

## 1. Introduction

The World Health Organization (WHO) declared COVID-19 a global health emergency on 30th January 2020 and published guidelines for using corticosteroids for treating its patients on 2nd September 2020 [1]. Despite the benefits of corticosteroids, such as dexamethasone, it has been associated with increased vulnerability to secondary fungal infections such as mucormycosis, particularly among patients with poorly controlled diabetes mellitus [2]. The symptoms of this coinfection are further exacerbated and may lead to higher mortality if COVID-19 patients have decompensated pulmonary functions or require invasive mechanical ventilation during the advanced stages of COVID-19 infection [3].

Mucormycosis is an acute, disfiguring, and angioinvasive fungal infection with a mortality rate of up to 80% [4]. This high mortality rate is further anticipated in cases where the infection is not treated early [5]. While incidences of mucormycosis are rare among the general population, it is highly prevalent in patients with diabetes mellitus [6] and leads to significant comorbidity complications in COVID-19 management [7]. In addition, prolonged corticosteroid use is also identified as a key predisposing factor related to mucormycosis [8].

The leading causes of mucormycosis are Rhizopus, Mucor, and Lichtheimia (formerly Absidia), which are responsible for 70% to 80% of all reported cases [8] [9]. These ubiquitous fungi are pioneer invaders of virgin substrates such as foodstuffs, which they degrade by the production of a wide array of enzymes [10]. From their sporangium, an abundance of spores is released and dispersed into the air, which finds its way to patients either via inhalation and entry through the paranasal sinuses or contaminated food ingestion [10] [11]. Depending on the organ infected, these infections can be classified as sino-orbital, rhino-cerebral, pulmonary, cutaneous, gastrointestinal, and disseminated [5]. Mucormycosis-affected individuals usually present symptoms such as headaches, acute sinusitis, fever, nasal congestion, purulent nasal discharge, shortness of breath, coughing, and altered mental state [12].

A heightened awareness of fungal coinfections in COVID-19 patients came after the observation of candidemia and invasive aspergillosis [12] [13]. In Iran, a nationwide study reported 208 cases of mucormycosis prior to the COVID-19

pandemic (from 2008 to 2014) [14]. However, during the fifth wave of the COVID-19 pandemic, a significant rise in COVID-19-Associated Mucormycosis (CAM) was observed across Iran. For instance, as investigated in the current study, from 1st August to 15th October 2021 (within 76 days), more than 60 CAM patients needing urgent care were admitted to Imam Reza and Qaem hospitals in Mashhad, northeast Iran. This was a substantial increase from 23 cases reported for 2019 and 2020 combined by these hospitals.

Despite Iran being among the first countries to be severely hit by the COVID-19 pandemic, there are very few studies investigating CAM in this context; those too involve small samples, *i.e.*, one patient [15], two patients [16], 15 patients [17], and 12 patients [18]. Therefore, given the lack of robust investigations and the severity of the coinfection, the present study investigates 62 proven CAM cases, the largest identified CAM sample in Iran to date, to highlight related risk factors and make recommendations for better management of this coinfection.

As such, the present study's main contribution to the existing literature comes from investigating the mortality of CAM patients with respect to COVID-19-related factors and treatments, including COVID-19 severity, location of mucormycosis, use of corticosteroids, hospitalisation status, and vaccination status. A secondary contribution comes in considering the roles of patients' demographic characteristics and predisposing factors, such as diabetes mellitus and hypertension, in their mortality. Moreover, initial symptoms and ex-post survival complications experienced are reported to inform the anticipatory observations for this coinfection. Finally, the present study also reports and discusses key endoscopic, ocular, imaging, and laboratory test reports where relevant, which allows for a more accurate overview of conditions surrounding this coinfection.

## 2. Data and Methods

### 2.1. Sample and Variables of Interest

During the fifth COVID-19 wave, from 1st August to 15th October 2021, patients affected with COVID-19 were diagnosed through reverse transcription-polymerase chain reaction (RT-PCR) from nasopharyngeal or oropharyngeal swabs. Suspected rhino-orbito-cerebral mucormycosis cases were referred to the Ear, Nose, and Throat (ENT) department of two COVID-19 centres, namely Imam Reza and Qaem hospitals, in Mashhad, a major city in the northeast of Iran. There the patients' diagnoses were further confirmed through nasal endoscopy and computed tomography scans of the paranasal sinuses. The presence of Mucoralean fungi was ascertained through a complete oral and maxillofacial clinical examination followed by microbiological and histological evaluations using biopsy specimens. Nasal turbinate/palatal mucosal biopsies submitted for histopathology were examined using haematoxylin and eosin, periodic acid Schiff, or Gomori methenamine silver stain. Direct microscopy was performed using potassium hydroxide mount. The samples were inoculated on sabouraud dextrose

agar and incubated at 25˚C and 37˚C. Positive cultures were identified by macroscopic and microscopic characteristics and approved by the presence of aseptate hyphae. As a result, mucormycosis was confirmed among the 62 COVID-19 patients included in this study. On average, this confirmation took 17.2 days after a positive COVID-19 diagnosis. It is noteworthy that these patients reported no previous history of mucormycosis.

Baseline data included patients' demographic characteristics (age and gender), COVID-19-related factors and treatments (COVID-19 severity, location of mucormycosis, corticosteroid, hospitalisation status, and vaccination status), and various symptoms consisting of headache, moderate-to-severe pneumonia, peri-orbital or retro-orbital pain, palsies of cranial nerves, visual loss, facial numbness, rhinorrhoea, fever, altered mental status, diplopia, epistaxis, facial skin problems, erythema, ulceration, neurologic loss of consciousness, endoscopy findings (necrosis, discharge, crusting, oedema, paleness, and polyps), imaging findings (mucosal thickening, opacification of sinus, bony destruction of sinus, orbit, orbital involvement, central nervous system lesions), and ocular symptoms (vision loss, ptosis, proptosis, ophthalmoplegia, chemosis, pre-orbital swelling, pre-orbital inflammation).

Data relating to predisposing factors covered hypertension, cardiovascular disease, obesity, hypercholesterolemia, renal disease, and diabetes mellitus (type, status, duration, and related drug use). Laboratory test results included leucocyte, lymphocyte, haemoglobin, platelets, haemoglobin a1c, glucose, and c-reactive protein. The severity of COVID-19 was classified as mild, moderate, and severe according to the World Health Organization guideline [1]. Within a three-week follow-up, data relating to COVID-19 medical treatment, debridement surgeries, and survival were also collected for all patients. The data on debridement surgeries included 15 types of surgeries. Finally, information on ex-post complications was collected for surviving patients and included loss of vision, cerebral vascular accident, cranial nerve palsy, and reinfection rate.

### 2.2. Statistical Analysis

All data were analysed using Statistical Package for the Social Sciences (SPSS) version 27.0 (SPSS Inc. Chicago, IL, USA, 2020). Descriptive statistics were reported as frequency (percentages) and mean ± standard deviation (sd). Inferential statistics included the chi-squared test ($\chi 2$) for the former and the non-parametric Mann-Whitney (U) test for the latter. Note that the Fisher's Exact test was used to infer statistical significance for groups with zero members in one or more categories. A 95% confidence interval (CI) assumption was applied in all inferential tests.

## 3. Result

Of the 62 patients admitted and followed by the study, 37 survived the disease, and 25 were announced dead upon the three-week follow-up, indicating a 40.3%

mortality rate among COVID-19 patients with mucormycosis. The sample was almost equally distributed between males (53%) and females (47%) with a median age of about 58 years old; there were no significant gender and age differences between the two outcomes (survivors and those who died at the follow-up) (see Table 1: section A).

The key symptoms experienced by the patients included headaches (76%), moderate-to-severe pneumonia (76%), peri- or retro-orbital pain (61%), palsies of cranial nerves (53%), visual loss and facial numbness (45% and 42%). Other prevalent symptoms came from endoscopic findings, which included necrosis (70%), discharge (61%), and crusting (54%); imaging findings including mucosal thickening (69%), opacification of the sinus (69%), and bony destruction of the sinus (35%); and ocular symptoms (82%, 17, 30, and 3 in right, left and both eyes, respectively). A majority (56%) experienced vision loss, followed by 50% ptosis and 44% proptosis as the second and third most prevalent ocular symptoms. Moreover, rhinorrhoea and fever were present among 29% and 25% of the patients, and about one-fifth of all admitted showed symptoms of altered mental state, diplopia, epistaxis, and facial skin problems. See Appendix A: Table A1 for other lesser observed symptoms.

The predisposing factors prevalent across the sample included diabetes mellitus (95%), hypertension (43%), cardiovascular disease (17%), obesity (12%), hypercholesterolemia (17%), and renal disease (8%). However, only diabetes mellitus status and duration were significantly associated with patient mortality. As reported in Table 1: section B, higher deaths were observed among those with controlled diabetes (61% mortality rate), followed by recently diagnosed and uncontrolled with 26% and 20% death rates, respectively. All of those without diabetes survived, albeit there were only three patients in this group. Moreover, while the use of medicines for diabetes did not significantly relate to survival prospects, those who had diabetes for four years on average had significantly higher survival rates than those having diabetes for twice as long (eight years on average). See Appendix A: Table A2 for the comparative statistics on all the predisposing factors listed above, classified by survivors and non-survivors. It is important to note that only two cases were reported for each chronic sinusitis/otitis media, thyroid, malignancy, smoking, immunosuppressive therapy, and cerebrovascular, and single cases for each transplantation, liver failure, cerebrovascular, autoimmune disease, and chronic obstructive pulmonary disease or asthma. None were infected by HIV, hepatitis, arthritis, pancreatitis, myeloma, or chronic lung disease. Thus, these factors escape our comparative investigation.

According to laboratory test results, only higher leucocytes were significantly associated with higher deaths (see Table 1: section C). In contrast, other tests yielded no substantial difference between the two outcomes, died and survived (see Appendix A: Table A3). The mean values for various tests were 12.44 × $10^3$/μL for leucocytes, 1.42 and 2.5 × $10^3$/μL for lymphocytes and platelets, 12.25% and 8.42% for haemoglobin and haemoglobin A1c, and 252.28 and 95.25

mg/dL for glucose and c-reactive protein. Despite insignificant relations with mortality, except for leucocytes, it is noteworthy that abnormal levels of C-reactive protein (n = 44 out 45 cases with available data, >15 mg/L) (normal <6 mg/L), glucose (n = 36, >200 mg/dL) (normal <200 mg/dL), absolute leukocyte count (n = 35, $<1100 \times 10^3/\mu L$) (normal 4.4 - 11.3 $\times 10^3/\mu L$), lymphocyte (< normal for n = 23 and > normal for n = 1) (normal 1000 - 4800 $\times 10^3/\mu L$), alanine transaminase (n = 23, >45 IU/L) (normal 5 - 40 IU/L), haemoglobin (n = 17, male <13 mg/dL, female <12 mg/dL) (normal >13.5 mg/dL), platelets (< normal for n = 6 and > normal for n = 4) (normal 150 - 450 $\times 10^3/\mu L$), and creatinine (< normal for n = 7 and > normal for n = 8; according to the body weight) (0.7 - 1.4 mg/dL) were observed for all patients. Similar abnormal patterns were observed in fasting blood sugar (n = 29, >200 mg/dL) (normal <100 mg/dL), total bilirubin (n = 11, >1.2 gm/dL) (normal <1.1 gm/dL), haemoglobin A1c (n = 2, >6.4%) (normal <5.7%).

Concerning the COVID-19-associated factors and treatments (see **Table 1**: section D), the only mortality-related statistically significant factor was the location of mucormycosis, with significantly higher deaths versus survivors among those with rhino-orbital-cerebral mucormycosis (59.1% versus 40.9%), followed by nasal/sinus mucormycosis (55.6% versus 44.4%). On the other hand, there were fewer deaths than survivors in the group with rhino-orbital mucormycosis (25% versus 75%). The severity of COVID-19 was determined for 56 patients, among which 25%, 55%, and 20% suffered from mild, moderate, and severe cases of COVID-19. However, the differences between these groups in relation to survival rate were insignificant. A similar insignificant result can be observed for hospitalisation status (where 69% were outpatients), vaccination status (57% unvaccinated), medical treatment (received by 79%), and debridement surgery (operated on 97%) (see Appendix A: **Table A4** for types of debridement surgeries carried). Notably, the interval between the start of steroid treatment and the emergence of mucormycosis ranged between 3 to 30 days, with 10.5 days on average. Intravenous remdesivir (200 mg/kg/day at day 1, 100 mg/kg/day in following days for up to 5 days) and corticosteroids were administered for 53 out 54 patients with available data with drugs of choice being intravenous dexamethasone (2 - 60 days, 2 - 24 mg/day) for 79%, followed by prednisolone (7 - 14 days, 25 - 100 mg/day) for 11%. The mean time-lapse from diagnosis to corticosteroid therapy ranged from 1 to 25 days, with a mean of 6.5 days. On the other hand, oxygen therapy was only needed for 30% (n = 19) of the patients. Since almost all the patients (on which the data was available) received corticosteroid therapy debridement surgeries, the comparative statistics cannot be meaningfully interpreted. Instead, the current sample can be considered representative of patients who has undergone these two treatments.

**Table 2** reports post-recovery complications among the 37 survivors, among whom about 57% and 21.6% suffered from loss of vision and cranial nerve palsy, respectively. Furthermore, 32.4% experienced reinfection with the COVID-19 disease. A cerebral vascular accident was observed in only one of the survivors.

**Table 1.** Comparing COVID-19-related, demographic, and clinical and predisposing factors between CAM survivors and non-survivors.

| Characteristics | Total ($N = 62$) | Outcomes | | |
|---|---|---|---|---|
| | | Died ($n_d = 25$) | Survived ($n_s = 37$) | *P*-value |
| **A.** Demography | | | | |
| Age in years | 58.29 ± 10.17 | 60.24 ± 10.27 | 56.97 ± 10.03 | 0.21 |
| Gender | | | | |
| Male | 33 (100.00) | 16 (48.50) | 17 (51.50) | 0.11 |
| Female | 28 (100.00) | 8 (28.60) | 20 (71.40) | |
| **B.** Predisposing Factors | | | | |
| Diabetes mellitus status | | | | |
| Without | 3 (100.00) | 0 (0.00) | 3 (100.00) | 0.03* |
| Recently diagnosed | 19 (100.00) | 5 (26.30) | 14 (73.70) | |
| Uncontrolled | 10 (100.00) | 2 (20.00) | 8 (80.00) | |
| Controlled | 23 (100.00) | 14 (60.90) | 9 (39.10) | |
| Diabetes mellitus drug-use | | | | |
| None | 23 (100.00) | 5 (21.70) | 18 (78.30) | 0.11 |
| Antidiabetic agent | 22 (100.00) | 11 (50.00) | 11 (50.00) | |
| On insulin | 4 (100.00) | 2 (50.00) | 2 (50.00) | |
| Both | 6 (100.00) | 4 (66.70) | 2 (33.30) | |
| Diabetes mellitus duration in years | 5.85 ± 6.42 | 8.59 ± 7.02 | 4.03 ± 5.35 | 0.007** |
| **C.** Laboratory Test Results | | | | |
| Leucocyte | 12.44 ± 5.52 | 14.79 ± 5.06 | 10.85 ± 5.31 | 0.003** |
| Lymphocyte | 1427.97 ± 1338.71 | 1154.00 ± 923.68 | 1613.08 ± 1542.90 | 0.07 |
| **D.** COVID-19-related Factors and Treatments | | | | |
| COVID-19 Severity | | | | |
| Mild | 14 (100.00) | 8 (57.10) | 6 (42.90) | 0.07 |
| Moderate | 31 (100.00) | 8 (25.80) | 23 (74.20) | |
| Sever | 11 (100.00) | 6 (54.50) | 5 (45.50) | |
| Location of Mucormycosis | | | | |
| Nasal/sinus | 9 (100.00) | 5 (55.60) | 4 (44.40) | 0.04* |
| Rhino-orbital | 28 (100.00) | 7 (25.00) | 21 (75.00) | |
| Rhino-orbital-cerebral | 22 (100.00) | 13 (59.10) | 9 (40.90) | |

**Continued**

| | | | | |
|---|---|---|---|---|
| Corticosteroid Therapy | | | | |
| No | 1 (100.00) | 1 (100.00) | 0 (0.00) | 0.41 |
| Yes | 53 (100.00) | 21 (39.60) | 32 (60.40) | |
| Hospitalisation Status | | | | |
| Inpatient | 19 (100.00) | 10 (52.60) | 9 (47.40) | 0.19 |
| Outpatient | 43 (100.00) | 15 (34.90) | 28 (65.10) | |
| Vaccination Status | | | | |
| No dose | 32 (100.00) | 14 (43.80) | 18 (56.20) | |
| First dose | 20 (100.00) | 7 (35.00) | 13 (65.00) | 0.77 |
| Completed | 4 (100.00) | 2 (50.00) | 2 (50.00) | |
| Debridement Surgery | | | | |
| No | 2 (100.00) | 1 (50.00) | 1 (50.00) | 0.78 |
| Yes | 60 (100.00) | 24 (40.00) | 36 (60.00) | |
| Medical Treatment | | | | |
| No | 13 (100.00) | 6 (46.20) | 7 (53.80) | 0.63 |
| Yes | 49 (100.00) | 19 (38.80) | 30 (61.20) | |

*Note*: * and ** denote significance at 5% and 1%, respectively. $N$ denotes the total number of patients considered at baseline, $n_d$ and $n_s$ denote the numbers of patients declared dead (died) and alive (survived), respectively, within the three-week follow-up.

**Table 2.** Ex-post complications among the survivors.

| Characteristics | Survived ($n_s = 37$) |
|---|---|
| Loss of Vision | |
| No | 15 (40.50) |
| Yes | 21 (56.80) |
| Unspecified | 1 (2.70) |
| Cerebral Vascular Accident | |
| No | 35 (94.60) |
| Yes | 1 (2.70) |
| Unspecified | 1 (2.70) |
| Cranial Nerve Palsy | |
| No | 28 (75.70) |
| Yes | 8 (21.60) |
| Unspecified | 1 (2.70) |
| Reinfection Rate | |
| No | 25 (67.6) |
| Yes | 12 (32.4) |

Note: Parameters reported are in frequency (percent). $n_s$ denotes the number of patients marked as alive (survived) upon the three-week follow-up.

## 4. Discussion

While numerous previous studies have investigated other fungal infections, such as candidiasis and aspergillosis, among COVID-19 patients [19] [20], mucormycosis is relatively scarcely investigated in this context [21]. Nevertheless, due to the severity of CAM cases, it is important to discuss our findings retrospectively.

Relating to demographic factors, the median age in our study was 58 years which is consistent with previous studies in the Iranian context with median age ranging between 47 to 62 years [15] [16] [17] [18]. However, these figures are higher than some studies in other contexts, e.g., 44.5 - 55 years median age in the case of India [22] [23] [24]. Concerning the literature, it is important to pay attention to this age discrepancy as it may be correlated with the prevalence of predisposing factors among the patients, as discussed below.

Symptoms including headache, peri-orbital or retro-orbital pain, visual loss, facial numbness, rhinorrhoea, altered mental status, diplopia, and epistaxis are reported across the literature [25]. Most CAM cases also present fever [26], sinusitis, and facial oedema [27], and cranial nerve palsy [28]. These symptoms were also observed in the patients of the present study. Consistent with previous studies, ophthalmologic symptoms were mostly present as vision loss [21], followed by ptosis [27]. Furthermore, in line with the literature, unilateral presentation was more common compared to bilateral ones [25]. Endoscopic findings, including necrosis, discharge, crusting, oedema, and paleness, and findings such as mucosal thickening, opacification of sinus, and bony destruction of sinus and orbit, were seen in our study as well as others [24]. Similar to the present study, the orbits in the maxillofacial are documented to be the most affected regions, followed by the paranasal sinuses, the nasal cavity, and the palate [27].

Regarding the predisposing factors, except for three out of 62 cases, all patients had at least one risk factor, which is close to the study done by Ramaswami et al., who observed at least one risk factor in 93% of their patients [23]. The study also observed diabetes among 70% of its patients, which, although significantly lower than our findings of 95% prevalence, is consistent with our observation of diabetes being the most prevalent predisposing factor in CAM cases. Patients with diabetes and hyperglycemia often have an inflammatory state which, along with activation of antiviral immunity to severe acute respiratory syndrome coronavirus 2 infection, could favour secondary infections [29]. Due to the severity of this coinfection, the relationship between diabetes mellitus status and mortality rate in CAM patients, established in the present study, is also previously documented [30]. Moreover, the literature from Iran [18] and other countries [21] also affirms our observation of hypertension as the second most prevalent predisposing factor (affecting 43% of patients) among CAM patients.

Elevated levels of c-reactive protein, glucose, and total bilirubin; and abnormal levels of absolute leukocyte, lymphocyte, haemoglobin, platelets, creatinine, blood sugar, and haemoglobin were observed in survivors and non-survivors,

among which leukocytes levels were significantly associated with mortality. Inflammatory organ injury may occur in severe cases of COVID-19 in patients having elevated levels of inflammatory markers such as c-reactive protein higher than 10 mg/L [26]. The literature also documents abnormal levels of platelets in such cases [26] while associating leukocyte levels, neutrophil count, and lymphopenia with the severity of COVID-19 [31]. On the other hand, patients presented with uncontrolled diabetes are characterised by diabetic ketoacidosis, hyperglycemia, elevated haemoglobin A1c, and/or end-stage renal disease [21], which aligns with our study, where most patients had diabetes.

COVID-19 severity did not significantly contribute to patient mortality, also well-founded in previous studies [32]. Relating to mucormycosis, according to a review by Hoenigl *et al.*, mucormycosis usually develops within 10 - 12 days after COVID-19 diagnosis [21], which is extended to about 15.6 ± 9.6 days in a report by Rocha *et al.* [12]. This time-lapse was 17.2 days in our study, confirming the findings above in the Iranian context and reinforcing that clinicians should pay heed to potential mucormycosis coinfection within the first two to three weeks of COVID-19, particularly in high-risk patients [22]. Among mucormycosis patients, the lungs, nose, and sinuses are the most frequent infection sites, from where the infection can spread to the eyes, causing vision loss, or to the brain - causing headaches and seizures [33]. Consistent with this pattern, rhino-orbital and rhino-orbital-cerebral mucormycosis were the most dominant in the present study (85%). Previous studies also document rhino-orbital-cerebral mucormycosis as the most common [13], followed by pulmonary mucormycosis [22].

The use of corticosteroids as a common therapy for COVID-19 patients is also found in other studies from Iran [18] and India [16]. Regardless of the severity of their COVID-19 condition, almost all patients had received corticosteroids. This is because corticoids are inexpensive and widely available, thus becoming the drug of choice in reducing mortality in hypoxemic patients with COVID-19 [27].

Relating to treatment, the recommended first-line therapeutic strategy for mucormycosis includes the use of amphotericin B in addition to surgery and among different injectable formulations, liposomal amphotericin B has been recommended at a dose of 5 mg/kg per day in 200 ml of 5% dextrose over 2 - 3 h for 3 - 6 weeks by the European Confederation of Medical Mycology (ECMM) and the International Society for Human and Animal Mycology (ISHAM) [34]. This was the main treatment strategy applied to the patients in the present study.

According to a global review, all-cause mortality for CAM cases was 48.8%, and mortality was higher for rhino-orbital-cerebral mucormycosis compared to pulmonary, gastrointestinal, and disseminated ones [21]. This is consistent with the present study, where 46% of patients were announced dead within a three-week follow-up. However, the survival length has varied across the literature, ranging from 7 days [22] to five months [24]. On the other hand, significant life-changing morbidities are anticipated for survivors. Our finding of about 57% loss of vision

aligns with 46% and 67% observed in the studies by Hoenigl *et al.* [21] and Moorthy *et al.* [35].

## 5. Conclusions

The present study investigates mortality and morbidity among 62 confirmed CAM patients in relation to their demographic characteristics, laboratory test results, predisposing factors, and COVID-related factors with data collected at baseline with a three-week follow-up. Among these factors, higher deaths were observed among those with controlled diabetes, followed by recently diagnosed and uncontrolled, while all without diabetes survived. Additionally, those with a shorter history of diabetes (four years on average) had significantly higher survival rates than those having diabetes for twice as long. Moreover, concerning the mucormycosis location, rhino-orbital-cerebral, followed by sinus mucormycosis, were the main factors linked with significantly higher mortality.

The study findings suggest that mucormycosis has a higher mortality rate among COVID-19 patients with diabetes mellitus, particularly those receiving corticosteroids. As such, risks related to this coinfection and the treatment method should be assessed towards developing strategies to improve patients' outcomes. To that end, rapid control of diabetics, reduction or discontinuation of steroids, antifungal prophylaxis, radio imaging, and clinical monitoring of fungal progression may be considered.

## List of Abbreviations

| | |
|---|---|
| World Health Organization: | WHO |
| COVID-19-Associated Mucormycosis: | CAM |
| Ear, Nose, and Throat: | ENT |
| Transcription-polymerase chain reaction: | RT-PCR |
| Statistical Package for the Social Sciences: | SPSS |
| Confidence interval: | CI |
| Human immunodeficiency virus: | HIV |
| European Confederation of Medical Mycology: | ECMM |
| International Society for Human and Animal Mycology: | ISHAM |

## Declarations

*Ethical Permission*: This research was approved by the Ethics Committee of Mashhad University of Medical Sciences (no. IR.MUMS.MEDICAL.REC.1400.733).

*Consent for publication*: Consent for publication has been obtained.

*Availability of data and materials*: Approval for use of data was obtained for this paper from the respected organizations; thus these materials are not publicly available.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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# Appendixes

## Appendix A. Complete Results

**Table A1.** Main symptoms.

| Symptoms | Total ($n_s$ = 62) |
|---|---|
| Headache | 47 (76%) |
| Moderate-to-severe pneumonia | 42 (67%) |
| Peri-orbital or retro-orbital pain | 38 (61%) |
| Visual loss | 28 (45%) |
| Facial numbness | 26 (42%) |
| Rhinorrhea | 18 (29%) |
| Fever | 15 (24%) |
| Altered mental status | 13 (21%) |
| Diplopia | 12 (19%) |
| Epistaxis | 11 (18%) |
| Facial skin problems | 12 (19%) |
| Erythema | 9 (15%) |
| Ulceration | 1 (2%) |
| Neurologic loss of consciousness | 12 (19%) |
| Palsies of cranial nerves | 33 (53%) |
| Endoscopy findings | |
| Necrosis | 44 (70%) |
| Discharge | 38 (61%) |
| Crusting | 34 (54%) |
| Edema | 11 (17%) |
| Paleness | 11 (17%) |
| Polyps | 7 (11%) |
| Imaging findings | |
| Mucosal thickening | 43 (69%) |
| Opacification of sinus | 43 (69%) |
| Bony destruction of sinus | 22 (35%) |
| Orbit | 16 (25%) |
| Orbital involvement | 13 (20%) |
| Central nervous system lesions | 1 (1.7%) |
| Ocular symptoms (right eye = 17, left = 30, both = 3) | 51 (82%) |
| Vision loss | 35 (56%) |
| Ptosis | 31 (50%) |
| Proptosis | 27 (44%) |
| Ophthalmoplegia | 25 (40%) |
| Chemosis | 20 (32%) |
| Pre-orbital swelling | 19 (31%) |
| Pre-orbital inflammation | 18 (29%) |

*Note*: Parameters reported are in frequency (percent). $n_s$ denotes the number of patients marked as alive (survived) upon the three-week follow-up.

**Table A2.** Comparing predisposing factors between CAM survivors and non-survivors.

| Characteristics | Total ($N = 62$) | Outcomes | | |
|---|---|---|---|---|
| | | Died ($n_d = 25$) | Survived ($n_s = 37$) | $P$-value |
| Hypertension | | | | |
| No | 34 (100.00) | 13 (38.20) | 21 (61.80) | 0.75 |
| Yes | 26 (100.00) | 11 (42.30) | 15 (57.70) | |
| Cardiovascular disease | | | | |
| No | 49 (100.00) | 18 (36.70) | 31 (63.30) | 0.17 |
| Yes | 10 (100.00) | 6 (60.00) | 4 (40.00) | |
| Obesity | | | | |
| No | 52 (100.00) | 21 (40.40) | 31 (59.60) | 0.25 |
| Yes | 7 (100.00) | 3 (42.90) | 4 (57.10) | |
| Hypercholesterolemia | | | | |
| No | 50 (100.00) | 20 (40.00) | 30 (60.00) | 0.56 |
| Yes | 10 (100.00) | 5 (50.00) | 5 (50.00) | |
| Renal disease | | | | |
| No | 55 (100.00) | 22 (40.00) | 33 (60.00) | 1.00 |
| Yes | 5 (100.00) | 2 (40.00) | 3 (60.00) | |
| Diabetes mellitus | | | | |
| No | 3 (100.00) | 0 (0.00) | 3 (100.00) | 0.27 |
| Yes | 59 (100.00) | 25 (42.40) | 34 (57.60) | |
| Diabetes mellitus type | | | | |
| Without DM | 3 (100.00) | 0 (0.00) | 3 (100.00) | 0.26 |
| Type 2 | 56 (100.00) | 24 (42.90) | 32 (57.10) | |
| Diabetes mellitus status | | | | |
| Without | 3 (100.00) | 0 (0.00) | 3 (100.00) | 0.03* |
| Recently diagnosed | 19 (100.00) | 5 (26.30) | 14 (73.70) | |
| Uncontrolled | 10 (100.00) | 2 (20.00) | 8 (80.00) | |
| Controlled | 23 (100.00) | 14 (60.90) | 9 (39.10) | |
| Diabetes mellitus drug-use | | | | |
| None | 23 (100.00) | 5 (21.70) | 18 (78.30) | 0.11 |
| Antidiabetic agent | 22 (100.00) | 11 (50.00) | 11 (50.00) | |
| On insulin | 4 (100.00) | 2 (50.00) | 2 (50.00) | |
| Both | 6 (100.00) | 4 (66.70) | 2 (33.30) | |
| Diabetes mellitus duration in years | 5.85 ± 6.42 | 8.59 ± 7.02 | 4.03 ± 5.35 | 0.007** |

*Note*: * and ** denote significance at 5% and 1%, respectively. $N$ denotes the total number of patients considered at baseline. $n_d$ and $n_s$ denote the numbers of patients who were declared dead (died) and alive (survived), respectively, within the three-week follow-up.

**Table A3.** Comparing laboratory test results between CAM survivors and non-survivors.

| Characteristics | Total ($N = 62$) | Outcomes | | |
|---|---|---|---|---|
| | | Died ($n_d = 25$) | Survived ($n_s = 37$) | $P$-value |
| Leucocyte ($\times 10^9$/L) | 12.44 ± 5.52 | 14.79 ± 5.06 | 10.85 ± 5.31 | 0.003** |
| Lymphocyte (/mL) | 1427.97 ± 1338.71 | 1154.00 ± 923.68 | 1613.08 ± 1542.90 | 0.07 |
| Platelets (/mL) | 250.15 ± 112.28 | 252.36 ± 129.55 | 248.65 ± 100.84 | 0.80 |
| Haemoglobin (%) | 12.25 ± 2.56 | 12.02 ± 2.59 | 12.41 ± 2.56 | 0.84 |
| Hemoglobin A1c (%) | 8.42 ± 2.27 | 7.86 ± 1.97 | 8.74 ± 2.40 | 0.28 |
| Glucose (mg/dL) | 252.28 ± 124.97 | 246.75 ± 113.68 | 255.87 ± 113.19 | 0.87 |
| C-reactive protein (mg/dL) | 95.25 ± 71.13 | 105.80 ± 73.15 | 88.85 ± 70.44 | 0.27 |

*Note*: * and ** denote significance at 5% and 1%, respectively. $N$ denotes the total number of patients considered at baseline. $n_d$ and $n_s$ denote the numbers of patients who were declared dead (died) and alive (survived), respectively, within the three-week follow-up. L = liter; mL = milliliter; mg/dL = milligrams/deciliter.

**Table A4.** Types of debridement surgeries and their distributions: right, left, and both eyes.

| Type of debridement surgery | Total cases | Right | Left | Both |
|---|---|---|---|---|
| Inferior turbinate | 31 | 11 | 16 | 4 |
| Middle turbinate | 50 | 12 | 25 | 13 |
| Superior turbinate | 8 | 6 | 2 | 0 |
| Anterior of septum | 18 | 6 | 9 | 3 |
| Middle of septum | 23 | 8 | 12 | 3 |
| Posterior of septum | 20 | 5 | 9 | 6 |
| Maxillary sinus | 54 | 16 | 23 | 15 |
| Frontal sinus | 30 | 9 | 19 | 2 |
| Ethmoid sinus | 56 | 15 | 32 | 8 |
| Sphenoid sinus | 49 | 13 | 31 | 5 |
| Pterygopalatine | 19 | 7 | 11 | 1 |
| Hard palate | 10 | 4 | 4 | 2 |
| Soft palate | 5 | 3 | 1 | 1 |
| Nasal floor | 13 | 7 | 4 | 2 |
| Nasal roof | 8 | 5 | 3 | 0 |

*Note*: 60 out of 62 patients admitted underwent debridement surgeries listedinthis table.