Original Article

Investigating Factors Affecting Mortality from Mucormycosis after COVID-19 Infection: A Systematic Review

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ABSTRACT

Introduction: Examining laboratory parameters to determine acute or less severe cases of mucormycosis after contracting Covid-19, identifying patients who are at higher risk of mortality, and increasing awareness for proper practice will be useful in improving the clinical situation. Therefore, we decided to investigate factors affecting mortality from mucormycosis After Covid-19 infection.

Methods: This study was a systematic review (Conducted by PRISMA guideline). This study was conducted in Tabriz University of Medical Sciences in 2022.

Results: From examining the results of these studies (15 studies), it was found that mortality was higher in patients hospitalized in ICU and general wards, and a significant difference was observed between the average age of recovered and deceased patients. Having high blood pressure as well as diabetes mellitus also significantly led to an increase in mortality.

Conclusion: Hospitalization in the intensive care unit, advanced age, high severity of Covid-19, high blood sugar, and underlying diseases significantly increase the risk of death due to mucormycosis following Covid-19.

Keywords: Mucormycosis, Mortality, Risk factor, Systematic review.

1. Introduction

Symptoms of sore throat, headache, and runny nose have also been reported. Gastrointestinal symptoms such as nausea, diarrhea, and abdominal pain with these symptoms may occur before respiratory symptoms in about 10% of patients [1-3]. Asymptomatic patients may test positive for Covid-19 (in 30% of cases) [4-6]. However, most patients present with mild to moderate symptoms (55%). About 30% of patients show symptoms of dyspnea after 5 days from the onset of the disease. The aggravation of symptoms in the second week of the disease is a typical phenomenon in patients with more severe involvement (Figure 1) [7-9].

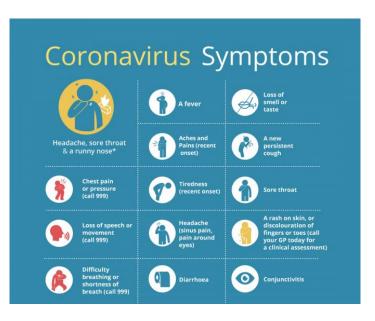


Figure 1. COVID-19 symptoms.

These patients usually require hospitalization for 7-8 days and have low blood oxygen levels and may have bilateral pneumonia (75%) (Figure 2) of the [10-13]. One common complications of this disease is acute respiratory distress syndrome (ARDS), which occurs especially in people with multiple organ failure [14-17]. In these

cases, respiratory support is unavoidable and may range from non-invasive highflow oxygen to invasive mechanical ventilation [18-20]. A group of patients may have acute inflammatory conditions with fever and an increase in inflammatory markers such as cytokines. Several laboratory findings have been observed in Covid-19 disease [21-23].

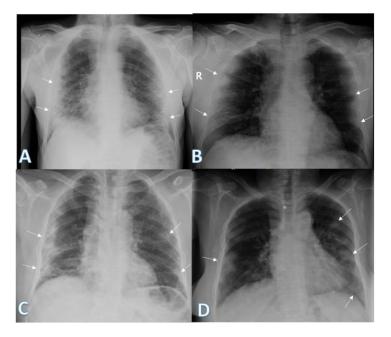


Figure 2. bilateral pneumonia in COVID-19.

Although the complete blood cell count (CBC) test in these patients may be completely normal, the most common positive findings in this test include lymphopenia (63%), leukopenia (25-9%), leukocytosis (24-30%), and thrombocytopenia (is 36%). Liver enzymes are increased in 37% of cases of this disease. Other inflammatory factors including ESR, CRP, D-dimer, ferritin, and IL-6 are also commonly elevated. Procalcitonin is usually normal. However, there is a possibility that it may be positive, especially in the case of bacterial infections [24-26].

In a study conducted on patients with MERS-CoV, Hin Chu *et al.* reported that MERS-CoV virus, but not SARS-CoV virus, effectively engages patients' T cells and induces apoptosis in these cells. These findings show that viremia in SARS patients may have different clinical significance than the viremia in MERS patients, in such a way that patients with MERS usually have a worse outcome due to the destructive nature of T cells in this disease [27-29].

Alfonso et al. conducted a systematic review with meta-analysis of 19 articles in the field of the disease of Covid-19 to obtain information about the clinical, laboratory, and imaging characteristics of the disease. In this study, the most common laboratory changes included decreased albumin level (75.8%), increased CRP (58.3%), increased lactate dehvdrogenase level (57.0%), lymphopenia (43.1%), and high ESR (41.8%). According to these findings, it can be concluded that nearly half of the people with Covid-19 have lymphopenia [30-32].

Despite the previous study that showed a decrease in the number of leukocytes and lymphocytes in patients

with Covid-19, Nanshan et al. in a study conducted on 99 patients with Covid-19 reported that the rate of leukopenia in these patients was only about 9%. Other findings in the CBC test of these patients included leukocytosis (24%), increased number of neutrophils (38%), leukopenia and anemia in 33% and 50% of patients, respectively. According to the results of this study, it can be mentioned that leukopenia and lymphopenia do not necessarily exist together in Covid-19 patients and the lymphopenia incidence in these patients is higher than leukopenia [33-35]. Ali Mohammadi et al. also state in their research results that the rate of spread of infection caused by Covid-19 in Iran can be reduced by interfering with effective factors such as health education, preventing the formation of human gatherings, active disease detection, contact tracing, and isolation of sick people [36-38]. During the period of disease transmission from the rest of the community and guarantine, it reduced to a great extent [39-41].

However, the researchers' information about the different aspects of this disease as well as the diseases resulting from this disease such as mucormycosis are being updated (Figure 1), and accurate information is limited due to the global geographical features. Therefore, for a more detailed analysis of such data, attention should be paid to the available data related to patients with mucormycosis after contracting Covid-19. Hence, systematic review studies can be mentioned among the methods that can be effective in this field. Therefore, the current study was conducted as a review with the aim of investigating the mortality due to mucocormycosis after rate contracting Covid-19 (Figure 3) [42-44].

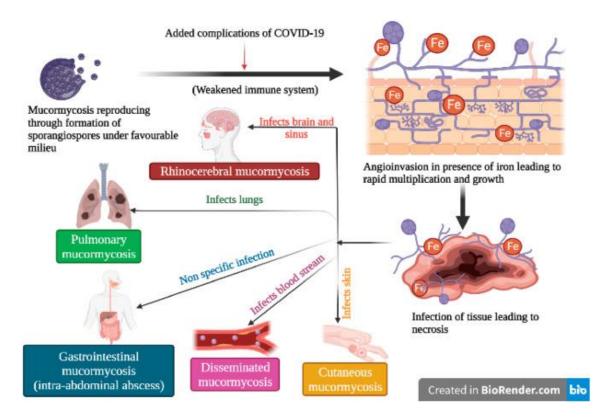


Figure 3. Mucormycosis associated COVID-19.

Method

This study was a systematic review (Conducted by PRISMA guideline). This study was conducted in Tabriz University of medical sciences in 2022. Inclusion criteria included definitive diagnosis of Covid-19 through lung CT scan or polymerase chain reaction (PCR) test or doctor's diagnosis. Furthermore, the exclusion criteria included patients for whom more than half of the examined variables were unclear before or after contracting the corona virus. To find articles, use the keywords "2019-nCoV", "COVID-19", "SARS-CoV-2", "Coronaviruses", "mortality", "risk factor", and "Mucormycosis", all possible combinations.

To obtain the texts of the articles published in the field of Covid-19 and mucormycosis, the research team of the present study tried their best to find all the articles. At first, a meeting consisting of both researchers was held in an academic place, and in this meeting, the keywords were determined based on the mesh system. This system can provide us with keywords that are related to medicine. After the keywords were confirmed, a database search was initiated by both authors. This search was done without time limit and separately by the researchers of this study. Among the articles that were found in the search, those that had a good quality entered the final stage. In the final stage, the most important parts of each article were extracted to be used for the purposes of this study.

Results

From examining the results of these studies (15 studies), it was found that mortality was higher in patients hospitalized in ICU and general wards, and a significant difference was observed between the average age of recovered and deceased patients. Having high blood pressure and diabetes mellitus also significantly led to an increase in

mortality [45-47]. A mean age of 54.2 years, 73.7 of whom were male and infected with Covid-19 were reviewed (14 articles included). The most reported symptoms in these patients were respectively fever (82.3%), cough (58%), shortness of breath (33.2%), and fatigue (30.7%) (6). Acute kidney injury was observed in 34.1% of patients. Mucormycosis patients with Covid-19 were treated with prednisone (77%). 20% of patients required Overall, intensive care unit (ICU) admission and 24.6% of patients required mechanical ventilation. Totally, 18.8% of patients with mucormycosis had died, which was much higher than the overall mortality due to COVID-19, which was reported at 3.4%. Clinical manifestations of Covid-19 in patients with mucormycosis may differ from the general population in terms of disease severity, complications including renal failure, and mortality [48-50].

Discussion

About 20% of the patients in the study had died. The mortality rate is different in different studies. In different studies, percentages between 9 and 21 percent have been reported [51-53].

The results of multiple Cox regression showed that increasing one year of age increases the chance of death by 5%. Based on the single Cox regression test, it further showed that increasing one year of age raises the chance of death by 6%. The results of a study in America showed that 80% of the deaths of Covid-19 patients were in people over 65 years old. These findings are similar to Chinese data, which show that 80% of deaths occurred among people over 60 years old (Figure 4).

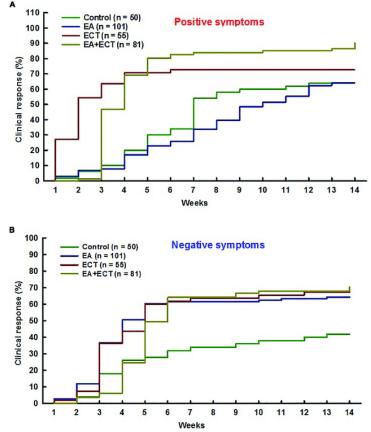


Figure 4. Cox regression results.

In studies conducted in America and European countries, the average length of stay of the examined patients was between 16 and 25 days [54-56]. The difference in the results of the studies can be related to the difference in the strategies used by different countries in the prevention and treatment of the disease, the time of occurrence, and peak of the disease in the countries and the treatment facilities in the hospitals [57-59].

The results of hospitalization in the special care department also show that 30% of patients have used special care services. The results of meta-analysis study by Taylor et al. showed that the mortality rate of patients under mechanical ventilation was 72%. In similar studies, mortality and length of stay of patients under mechanical ventilation were higher than other patients. Patients who need mechanical ventilation are admitted to special care units, which are usually associated with acute respiratory problems, and therefore need more care than other patients. In these people, the length of stay and the percentage of death are higher [60-62].

In another study by Goffin et al., the mortality rate and outcome of COVID-19 disease in dialysis patients as well as with mucormycosis patients were investigated. Among the patients studied in this study, which was equal to 1670 patients, 16.9% of kidney transplant patients and 23.9% of hemodialvsis patients died within 28 days of the onset of the disease. The risk of mortality in mucormycosis patients was significantly higher in the first year after the disease. Mortality risk in mucormycosis patients was 78% higher than hemodialysis patients after adjustment for multiple factors. The numbers obtained for mortality were also true for other characteristics examined, such as the need for hospitalization or ICU admission [63-65].

In a case report study by Qiu *et al.*, the clinical status of a 30-year-old male mucormycosis patient with after developing severe COVID-19 disease in Wuhan, China, was investigated. This patient suffered from an acute lung and kidney injury, and therefore required including systemic treatment. readjustment of the immunosuppressive drug regimen. In this study, the patient was followed up for 1 year after discharge from the hospital [66-68]. There was no evidence for pulmonary fibrosis or lung dysfunction in this individual. Unlike the damage caused by the Covid -19 disease to the person's kidney, transplant rejection did not occur. The immunological profile of this patient showed the activity of cellular and humoral immunity against this virus. This issue shows that transplant patients who are treated with immunosuppressive drugs, benefit from the injection of this disease vaccine [69-71].

In Elhadedy's study, which was conducted on the outcome of Covid-19 in 8 kidney transplant patients, 4 of whom were women and the other 4 were men, it was reported that high blood pressure is the most important factor predicting the severity of the disease in these people [72]. Likewise, the most common clinical symptoms in these patients were fever and cough. The most common radiological method used in these patients was portable chest radiology. Other common findings in these patients include lymphopenia, high CRP, and very high ferritin levels. In general, among these 8 patients, 1 patient was treated on an outpatient basis, but the other patients required hospitalization, one of them was admitted to the ICU [73]. All 7 patients studied in this study were discharged from the hospital and recovered [74-76].

Conclusion

One of the patients required mechanical ventilation. In addition to

these findings, this study showed that a short stay in the hospital and home quarantine after leave reduces the burden on health services and the transmission of disease to the surrounding people. Hospitalizations in the intensive care unit, advanced age, high severity of Covid-19, high blood sugar and underlying diseases significantly increase the risk of death due to mucormycosis following Covid-19.

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