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Evaluation of Hematological Parameters in Coronavirus Disease 2019 Patients with *Aspergillus* Rhinosinusitis, Northeastern Iran

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ABSTRACT

Introduction:
Aspergillus rhinosinusitis is a potentially lethal complication in patients with underlying immunodeficiencies. Critical laboratory findings, such as lymphopenia and leukocytosis, were highly reported in coronavirus disease 2019 (COVID-19) patients. Based on the correlation between COVID-19 and fungal infections, this study was designed to evaluate the hematologic parameters in COVID-19 patients associated with *Aspergillus* rhinosinusitis in northeaster Iran.

Materials and Methods:
During eight months and among 80 COVID-19 patients suspected of fungal rhinosinusitis, in two tertiary referral hospitals of Mashhad, hematological parameters, such as white blood cell (WBC) count, of 14 patients affected to COVID-19 with *Aspergillus* rhinosinusitis were precisely evaluated to check leukopenia and leukocytosis.

Results:
The patients showed a range of 42 to 67 years old and a median age of 59. Of the 14 patients, 8 (57.4%) had diabetes mellitus, 9 (64.2%) died, and two patients has normal leukocyte count. The three, two, and one patients showed leukocytosis, lymphopenia, and leukopenia, respectively. The combination of leukocytosis and lymphopenia was significant in four patients. However, leukopenia and lymphopenia were observed in just one subject. Moreover, leukopenia, lymphopenia, and neutropenia were detected together in one case.

Conclusion:
Aspergillus rhinosinusitis had high mortality among COVID-19 patients. Moreover, the high rate of diabetes mellitus was a severe predisposing factor for COVID-19-associated *Aspergillus* rhinosinusitis. Leukocytosis (neutrophilia) and lymphopenia were the most common hematological abnormalities among COVID-19 patients with *Aspergillus* rhinosinusitis.

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Introduction

The pioneer coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus (SARS-CoV-2), has affected all the world and led to an emerging pandemic (1,2). Along with damaging the respiratory system, this virus involves other organs of the body, such as the heart and liver. Also, the host immune system responses and hematological parameters may change (3). Many microbial agents, including other viruses, fungi, bacteria, can correlate together and interrelate in the complex pathogenesis of SARS-CoV-2 (2). Some more identified co-pathogens of SARS-CoV-2 are opportunistic fungi such as *Mucor*, *Candida,* and *Aspergillus* (2). The interplay/interaction between co-pathogens, SARS-CoV-2, and the host is a principal factor that may eventually lead to *misdiagnosis*, delayed *diagnosis*, inadequate *treatment*, and prognosis of COVID-19. Furthermore, microorganisms have new mechanisms for escaping the host immune system (immune responses of innate and adaptive) that exacerbate the pathogenesis of SARS-CoV-2. The importance of co-infections is evident in improving the patient's condition, treating and controlling the SARS-CoV-2 (2). COVID-19 patients were found to show immune suppression caused by a decreased number of CD4+T and CD8+T cells or changes in the balance between these cells. It will predispose the patient to other infections, especially opportunistic fungal infections, and can be associated with underlying diseases, including diabetes mellitus too (3). There are some factors that combination and co-occurrence of them increase the pathogenesis of opportunistic infections in SARS-CoV-2 patients. These include decreased oxygen levels, increased blood glucose levels, an acidic environment (metabolic acidosis), diabetic ketoacidosis (DKA), high iron concentration, and reduced phagocytic activity (4). Acute invasive fungal rhinosinusitis (AIFR) can cause lethal complications, particularly in patients with underlying immunodeficiencies. *Aspergillus* rhinosinusitis can be an opportunistic fungal infection caused by various *Aspergillus* species (5). The most susceptible individuals to this infection are those with diabetes mellitus, malignancies, AIDS, individuals taking immunosuppressive drugs, and, latterly, COVID-19 (3,6). Hence, some biomarkers can be associated and reflect the progression of the disease in these patients as a diagnostic potential role. Paraclinical parameters would be helpful for screening, management, and prevention of fire complications and problems (7).

In addition to clinical symptoms and pulmonary computed tomography (CT) findings, other screening assays can be helpful to show the hyper inflammation state and prognosis. One of these can be hematologic parameters such as CBC to following-up. It seems that some laboratory test findings in these patients are taking can significantly affect these results, which show the patient conditions (1). Although formerly decreased lymphocytes and normal or increased monocytes have been mentioned among the COVID-19 confirmed cases, many discrepancies have been observed among them. The most common laboratory findings in previous studies are lymphopenia, while the increase in leukocytes count was less repetitious (1). Clarifying those factors will aid in better clinical management decisions in this emerging disease. Therefore, this study was conducted to evaluate the hematologic parameters in COVID-19 patients' associated *Aspergillus* rhinosinusitis in northeastern Iran.

Materials and Methods

The eighty patients diagnosed *with* COVID-19 suspected of fungal rhinosinusitis and referred to two tertiary referral hospitals of Mashhad were evaluated in eight months (from June 2021 to January 2022). All patients diagnosed as COVID-19 by polymerase chain reaction (PCR) had abnormal computed tomography (CT) scans in paranasal sinuses and lungs (for diagnosis of invasive fungal sinusitis). All patients who participated in this study underwent endoscopic evaluation and were utilized with serial debridement to eradicate infection. The sinus biopsy specimens were examined using mycological procedures and histopathology and tested by direct 20% potassium hydroxide (KOH) wet mounts and cultured

on Sabouraud dextrose agar (Merk, Germany). The cultures were then examined and evaluated to identify. The characteristics of COVID-19- associated *Aspergillus* rhinosinusitis patients, including demographic information, clinical signs, radiological features, and laboratory findings, were collected. Hematological parameters such as the white blood cell (WBC) count, were precisely evaluated and measured for any abnormalities.

Results

Among the evaluated 80 patients, 14 patients showed both COVID-19 infection and *Aspergillus* rhinosinusitis.

The patients had 42 to 67 years old, with a median age of 59. Of the 14 patients, 8 (57.4) had diabetes mellitus, 9 (64.2%) died, and two patients had normal leukocyte counts (Figure 1).

The specimens showed acute-angle branching hyphae (hyaline septate hyphae) in direct experiments, positive culture as *Aspergillus* spp. (11 *Aspergillus* section *Flavi* and 3 *Aspergillus* section *Nigri*), and positive histopathology results. The three (21.42%), two (14.28%), and one (7.14%) patients showed leukocytosis, lymphopenia, and leukopenia, respectively. The details of hematological indexes of the patients showed in Table 1.

Although leukocytosis and lymphopenia were observed in 4 patients, one patient indicated both leukopenia and lymphopenia. Moreover, leukopenia, lymphopenia, and neutropenia were simultaneously observed in one patient (Figure 2).

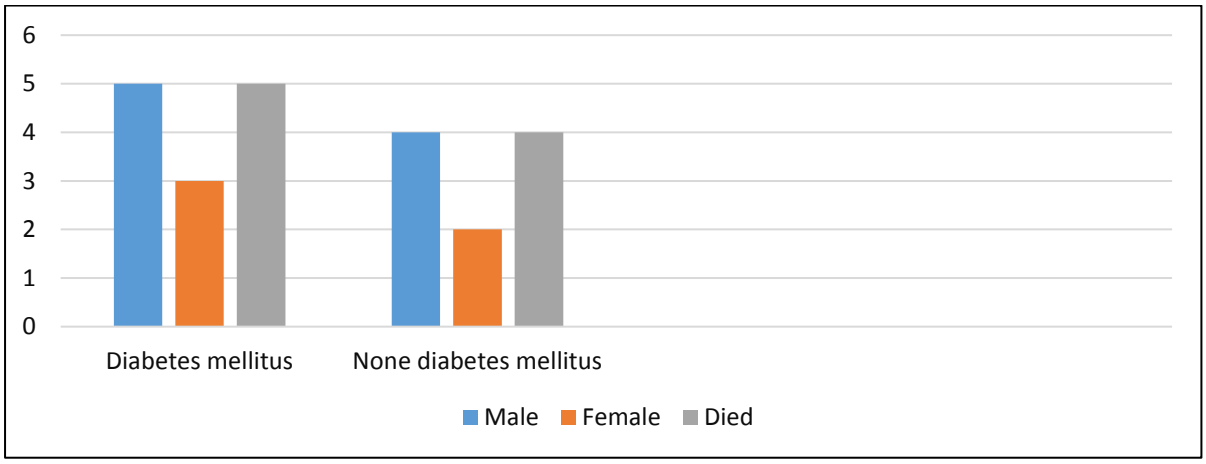

Figure 1: The patients with COVID-19-associated *Aspergillus* rhinosinusitis among diabetic and non-diabetic patients

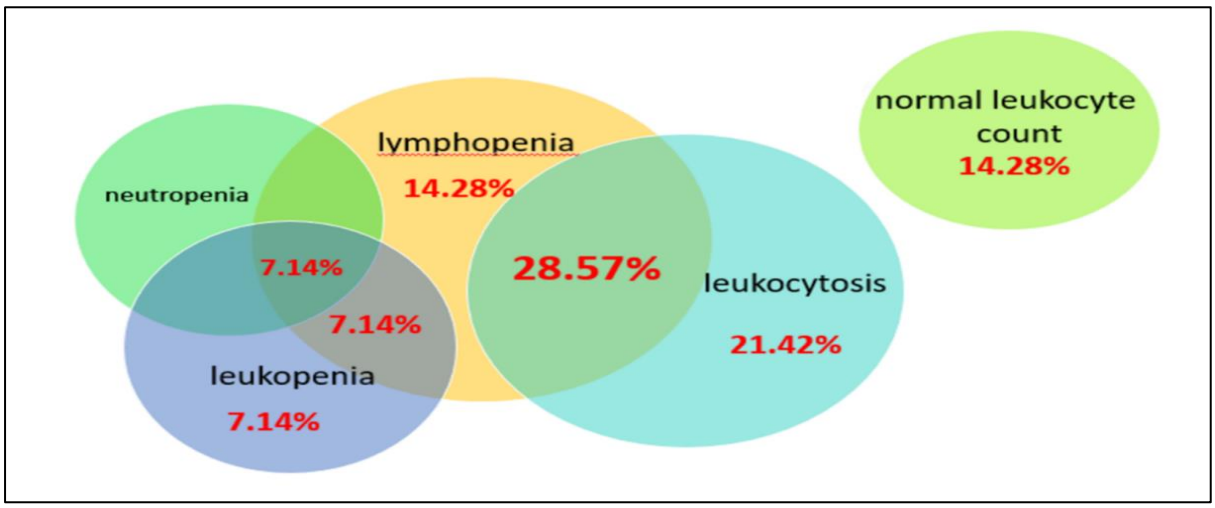

Figure 2: The frequency of hematological disorders among patients with COVID-19-associated *Aspergillus* rhinosinusitis.

Table 1: The details of hematological indexes of patients with COVID-19-associated *Aspergillus* rhinosinusitis

	Patient number	WBC count unit: $\times 10^3/\mu L$ with reference value of 4.4 – 11.3	Neut unit:% with reference value of 45 – 73.1	Lymph unit: % with reference value of 20 – 45	Mixed (Eos, Baso, Mono)unit: % with reference value of 6 – 15
Normal count	**1**	**N**	**N**	**N**	**N**
	2	**N**	**N**	**N**	**N**
Leukocytosis	**1**	**H**	**H**	**N**	**N**
	2	**H**	**H**	**N**	**N**
	3	**H**	**H**	**N**	**L**
Lymphopenia	**1**	**N**	**N**	**L**	**L**
	2	**N**	**N**	**L**	**L**
leukopenia	**1**	**L**	**N**	**N**	**N**
leukocytosis/ lymphopenia	**1**	**H**	**H**	**L**	**L**
	2	**H**	**H**	**L**	**N**
	3	**H**	**H**	**L**	**L**
	4	**H**	**H**	**L**	**L**
leukopenia/ lymphopenia	**1**	**L**	**N**	**L**	**L**
Leukopenia/ lymphopenia/ neutropenia	**1**	**L**	**L**	**L**	**L**

N: normal; H: high; L: low; WBC: *White blood cells;* Neut: neutrophil; Lymph: lymphocyte; Eos: eosinophil; Baso: basophils; Mono: monocytes

Discussion

Previous studies have shown that SARS-CoV and SARS-CoV-2 viruses belong to the same species and have similar characteristics (1). Previous studies were reported fungal infections among SARS patients (2). Hence, it can be critical to pay attention to the probability of mycoses accompanying COVID-19 and evaluate the hematologic parameters in these patients**.**

Aspergillosis is one of the most common opportunistic fungal diseases among patients with hematological malignancies and hematopoietic stem cell transplantation (HSCT). Invasive *Aspergillus* rhinosinusitis is a severe opportunistic infection rarely reported in COVID-19 patients. Therefore, a precise diagnosis can be achieved using mycological techniques, histopathological evidence, and CT scans (3). Currently, some viral pulmonary infections have been shown to be associated with an increased risk of fungal opportunistic infections. However, it is not yet known whether COVID-19 patients are at risk for *Aspergillus* infections development or not. From early reports from Wuhan, we know that patients with COVID-19 may develop complicated mycoses (4). However, reports of fungal infections such as aspergillosis, mucormycosis, and candidiasis in COVID-19 patients are rising. Fungal infections can be a major factor of co-infection to viral infections such as influenza infection in which *Aspergillus*, *Candida* was observed as common secondary infections (5, 6). In the current study, we observed a high mortality rate of 64% which was much unexpected.

Because another report by Rimesh et al. showed a mortality rate of 34% for mucormycosis, as an emergency fungal infection, among COVID-19 patients (7). Although this finding is interesting and uncommon, other factors such as the patient immune system may play an important role. In this study, diabetes mellitus was shown in 57% of the COVID-19 patients. In general, among fungal infections, diabetes mellitus is a significant risk marker for mucormycosis and is seldom reported as a predisposing item to affect aspergillosis. Other factors such as some treatments with corticosteroids in COVID-19 patients during hospitalization can be as decreasing of the immune system to get aspergillosis. However, Rimesh et al. reported an 85% rate among COVID-19 patients affected by mucormycosis that is higher than the current study (7). Some studies have estimated the severity of COVID-19 based on several blood parameters, mainly WBC count, lymphocyte to monocyte ratio, granulocytes, and platelet. The patients who lack phagocytes or have impaired phagocytic function are at higher risk to affect mucormycosis (8). Among WBCs, neutrophils are critical for inhibiting the proliferation of fungal agents, especially spores. Moreover, both mononuclear and polymorphonuclear phagocytes can omit them by using generating reactive oxygen species and defensins (9,10). Hence, the patients with uncontrolled diabetes mellitus will show abundant disorders such as phagocyte dysfunction, impaired chemotaxis, and oxidative and non-oxidative mechanisms to kill fungal agents (11). Although the current study showed low neutropenia, it seems phagocytic dysfunction in the cells is affected due to high uncontrolled diabetes mellitus. Hematological parameters such as leukocytes and neutrophil-to-lymphocyte ratio can be indicators of the systematic inflammatory response, especially during COVID-19 disease. However, it can be advantageous in predicting the severity of the infection, particularly in developing countries with limited resources. Because of the decisive role of lymphocytes in maintaining immune homeostasis, COVID-19 patients are more likely to have co-infections (12). In another study, Fan et al. reported a case of a 36-year-old male who had co-infection with COVID-19 and mycoplasma. The patient had severe lymphopenia and moderate thrombocytopenia needed ICU admission and ventilator support (13).

A study displayed by Zheng et al. has revealed that CTLs and NK cells were significantly diminished in patients with COVID-19 (14). Unfortunately, in this study was not possible to assess and evaluate these cells thoroughly. Animesh et al. reported a relative neutrophilia ≥ 70% and relative lymphopenia ≤ 20% among COVID-19 patients (15). While these results are relatively similar to our study, neutrophilia percent is different and less than them. On the other hand, in a meta-analysis of 15 studies, higher neutrophil but lower lymphocyte counts were shown in critical cases of COVID-19 (16). Thus, it seems the dysregulation of neutrophils and lymphocytes can affect the inflammatory and immune response, and also the chemotactic effects or cytokines imbalances. These disorders significantly confirm clinical evidence on the predictive and prognostic value of hematological parameters in COVID-19 patients. Unfortunately, most of these obtained data are related to patients affected by COVID-19 generally, and hematological parameters have not been measured among those affected by fungal infections simultaneously. One of the significant points in the present study is that these factors were evaluated in this group of patients.

The present study included some limitations. The sample size was small and there was a selection bias due to the hospital-based design (two tertiary Hospitals). Moreover, the study lacked follow-up of the COVID-19 patients along with the serial assessment of the hematological parameters.

Conclusion

The present study showed that *Aspergillus* rhinosinusitis has high mortality among COVID-19 patients. Moreover, the high rate of diabetes mellitus can be an important predisposing factor for COVID-19 - associated *A*spergillus rhinosinusitis. The

hematological parameters of leukocytosis and lymphopenia were significant in evaluated patients.

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