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Original Article

The Impact of Asthma as an Underlying Disease for COVID-19 in ICU Admitted Patients

Mehdi Ahmadi[1], Masoumeh Mesgarian[2], Seyed Karen Hashemitari[3], Sepideh Darougar[4*]

[1] *Faculty of Medicine, Tehran Medical Sciences Branch, Islamic Azad University, Tehran, Iran*

[2] *Department of Infection Disease, Faculty of Medicine, Amir-al-Momenin Hospital, Tehran Medical Sciences Branch, Islamic Azad University, Tehran, Iran*

[3] *School of Medicine, Tehran University of Medical Sciences, Tehran, Iran*

[4] *Department of Pediatrics, Faculty of Medicine, Tehran Medical Sciences Branch, Islamic Azad University, Tehran. Iran*

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Abstract

Background: Asthma is one of the most common chronic diseases triggered by viral respiratory infections leading to severe exacerbations. This study was performed to compare asthma with other underlying systemic disorders in coronavirus patients of 2019 (COVID-19) to evaluate any significant difference between these two groups in terms of ICU admission.

Method: The study was a retrospective study using hospital records of patients' from Intensive Care Units of Azad University hospitals in Tehran. Adult patients admitted to intensive care unit (ICU) due to COVID19 infection for a period of one year from March 2020 to February 2021, were enrolled in this cross-sectional study and their anonymized information was collected from an electronic system.

Results: This study evaluated a total of 160 COVID-19 patients, aged 29 to 92 years old (mean age: 63.03±15.67 years). 90 (56.3%) patients were males and 70 (43.7%) were females. Comparing the mortality rate of COVID-19 patients with underlying systemic disorders to those with asthma showed that there was no significant difference between them. However, the rate of ICU admission in COVID-19 patients with diabetes and hypertension were significant compared with asthma (P =0.03).

Conclusion: Asthma does not increase the risk of ICU admission in case of COVID-19 infection. Among the ICU admitted patients due to COVID-19 infection, the presence of asthma is not necessarily associated with a significant increase in poor outcomes.

Keywords: Asthma; COVID-19; Intensive Care; SARS-CoV-2

***Corresponding Author:** Sepideh Darougar, MD
Shirmohammadi Street, Nazi-Abad Avenue, Tehran, Iran
E-mail: sepidehdarougar@yahoo.com

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Introduction

Coronaviruses (COV) are the second most frequent cause of common cold (1). Coronaviruses have the potential to cause different levels of severity according to the pathogenicity of the particular strain. SARS-COV-2 as the novel COV has posed a serious threat to global health. They are the largest positive-sense RNA-viruses among humans and animals known so far, with a wide range of hosts being affected (2). SARS-CoV-2 is a pneumotropic virus spreading by respiratory secretions or droplets expelled by coughing, sneezing or even talking from the infected individuals (3). Inadequate ventilation, lack of hand hygiene and social distancing are the factors that contribute to the spread of the virus (3). A median incubation period of approximately 5 days is estimated for COVID-19 (4).

Early COVID-19 studies from China, as the first country that reported the emergence of COVID-19, indicated mild SARS-CoV2 infection in 80% of the cases; however, the remaining 20% were severe enough to be hospitalized, while 25% of them required ICU admission (5-7). After the spread of the virus around the world, it was recognized that older age and comorbidities such as heart disease, hypertension, chronic obstructive pulmonary disease, diabetes, obesity, or taking immunosuppressive drugs (8, 9) may play roles as important risk factors that affect the individuals with COVID-19 more severely, leading to a higher mortality rate in this group of patients.

Affecting nearly 300 million people around the world, asthma is one of the most common chronic diseases with dyspnea and cough as its most common presentations (10, 11). and 250000 deaths per year reported by the world health organization, mostly in low- and middle-income countries (12). Respiratory viral infections including respiratory syncytial virus (RSV), rhinoviruses (RVs), influenza virus, CoV, enterovirus, parainfluenza, adenovirus, bocavirus and metapneumovirus (13) account for approximately 50% of asthma exacerbations in adults (14) and are among the most common triggers of asthma that can induce severe exacerbations (14, 15). Therefore, at the beginning of the pandemic, there was a great fear about the fulminant course of the infection in asthmatic patients. The pathophysiology of asthma, consisting of airway inflammation, mucus hypersecretion, epithelial damage, and airway obstruction, and the steroids as the cornerstone of the asthma treatment, were issues that caused concern for a fulminant course with high mortality rate in asthmatic patients (16). However, unlike other seasonal viruses such as influenza, the impact of COVID-19 on deteriorating the patients' condition and necessitating ICU admission has been far less prominent in asthmatic patients (17, 18). Meanwhile, chronic medical conditions including diabetes mellitus, chronic hypertension and cardiovascular disorders are suggested to have a more devastating effect on the outcome of the disease (19). Therefore, this question arises that how much asthma and systemic disorders and their complications may impact the natural course of COVID-19 and turn it into a disease with grave outcomes requiring ICU admission for better control of the disease. Considering the results of another study that evaluated the predictors of ICU admission, epidemiological characteristics, signs and symptoms at the time of admission, laboratory tests and imaging findings (20) were the most important factors determining the need for ICU admissions irrespective of any chronic systemic disorder.

This study examined the rate of COVID-19 patients with asthma as well as those with other severe underlying systemic disorders to see if there was any significant difference between these two groups in terms of ICU admission.

Methods

Patient selection

This was a non-interventional and retrospective study using patients' data from Intensive Care Units of Azad University hospitals in Tehran. Adult patients between 29 to 92 years old admitted to ICU due to COVID19 infection for a period of one year from March 2020 to February 2021, were enrolled in this cross-sectional study.

The inclusion criteria were retrospectively ICU admitted patients with PCR-confirmed COVID-19 infection. Exclusion criteria consisted of the COVID-19 patients who did not need ICU admission and were discharged and sent home directly. The sampling method for the determination of the subjects to be investigated was based on complete census enumeration to

Table 1. The age range of the patients admitted and the control group

Variables	Total ICU Admitted Patients (%)	Number of Asthmatic Patients
Age Groups		
Younger than 40 years of age	12 (7.5%)	3
40-70 years of age	88 (55)	8
Older than 70 years of age	60 (37.5)	1
Total	160 (100)	12
Mean age±SD	63.03±15.67	

prevent selection bias.

After being enrolled in the study based on a regional surge of COVID-19, a comprehensive evaluation including history taking, physical examination and other essential information of the patients including demographic data such as age and sex, history of previous systemic disorders (diabetes, hypertension, cardiovascular disorders, kidney disease, neurological disorders, and respiratory diseases) and antecedent asthma were obtained by a single researcher who carefully reviewed medical reports, lab findings, clinical notes and treatment orders from the patients' records.

Ethical Code

This study was carried out following the recommendations of the "Ethics Committee of Islamic Azad University of Medical Sciences". The study protocol was approved by the "Ethics Committee of Islamic Azad University of Medical Sciences" with the reference number of **IR.IAU.TMU.REC.1399.499**

Statistical Analysis

Data are expressed as a mean for quantitative variables and counts (%) are applied as a mean for categorical variables. Analysis was performed using the SPSS version 24 (SPSS Inc., Chicago, IL, USA). Fisher's exact test and chi-squared test were the two statistical tests used to compare the groups of patients with different systemic disorders in the Intensive Care Unit (ICU) admitted patients with COVID-19 in this study. *P*-values less than 0.05 were considered significant.

Results

This study evaluated a total of 160 COVID-19 patients, aged 29 to 92 years old, who admitted to the ICUs of Azad University Hospitals from March 2020 to February 2021. Anonymized information was collected from an electronic system from three different hospitals. The database retrospectively contained the demographics, clinical diagnosis, associated comorbidities and systemic disorders.

Of all the patients evaluated, 90 (56.3%) were males and 70 (43.7%) were females.

The mean age of the patients was 63.03±15.67 years. **Table 1** is a summary of the patients participating in this study considering them in three age groups. The mean age of the asthmatic patients in this study was 51.16 years.

We evaluated the associations between various chronic disorders in those patients with COVID-19 who required ICU admission. Symptoms among participants varied noticeably but were consistent with those of their pre-pandemic chronic illnesses. **Figure 1** demonstrates the frequency of different disorders in comparison with asthma, indicating that impaired kidney and heart function were uncommon. Underlying chronic lung diseases were not recognized among the patients in this study and the existing chest CT abnormalities were suggestive of ongoing parenchymal inflammation because of the COVD-19 infection and not due to the previous pulmonary disorder.

Table 2 demonstrates various chronic disorders compared to asthma in patients with COVID-19. The analysis was performed by Fisher's exact test to detect if there were any non-random associations between COVID-19 and asthma, compared with other chronic disorders. A *P*- value less than 0.05 was considered significant.

As shown in table 1, diabetes and hypertension were two underlying conditions observed in the ICU admitted patients in this study with a significant difference compared to asthma and other underlying systemic disorders (*P*-value= 0.03).

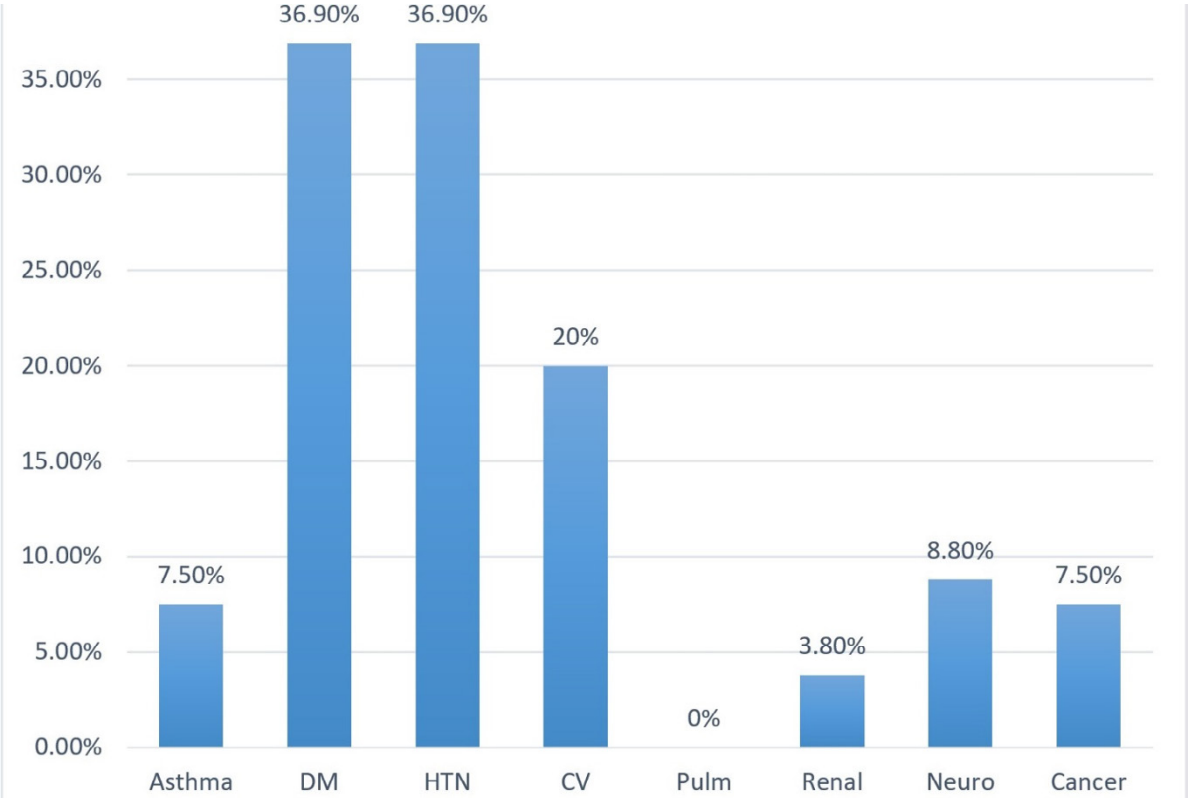

Figure 1. A comparison of different underlying causes of ICU admission in COVID-19 patients (DM, diabetes mellitus; HTN:, hypertension; CV, cardiovascular; Pulm, pulmonary; Neuro, neurologic).

Table 2. A comparison of ICU admission in COVID-19 patients with asthma and other chronic disorders

Chronic disorders	*P*-value
Diabetes	0.03
Hypertension	0.03
Cardiovascular disorders	0.12
Chronic renal disorders	1
Neurologic disorders	0.6
Malignancies	0.6

Discussion

This study was conducted to evaluate the effect of asthma as a risk factor for worsening the outcome of COVID-19 infection compared to other systemic disorders including diabetes mellitus, hypertension, cardiovascular, neurologic, and renal diseases. Based on our results, asthma did not increase the rate of ICU admission in patients with COVID-19 infection and most of the patients with asthma who had been infected with COVID-19 overcame the infection without further need for ICU admission.

According to reports on the associated comorbidities with COVID-19 infection, certain underlying conditions such as diabetes and hypertension may increase ICU admission and death rates (31-33). Although it was anticipated that chronic respiratory diseases predispose patients to SARS-CoV-2 infection or its complications (6, 22, 24, 25), the reported incidences of respiratory diseases were significantly lower than expected (25-29). However, similar to previous studies (5, 30), the results of our study did not identify asthma as a risk factor of severe COVID-19.

In severe SARS-CoV-2 infection, a complex immunopathology including viral replication

and overactive immune and inflammatory responses exists (9). These responses consist of cytokine storm syndrome (CSS) (increased IL-1 and IL-6) along with elevated inflammation markers (including C-reactive protein, lactic dehydrogenase and ferritin), as well as an acquired immunodeficiency state (lymphopenia with a reduced number of T cells). In addition, CSS can lead to coagulopathy, with elevated D-dimers and fibrin split products, which may result in a generalized severe endovascular process.

The above reasons appeared rational enough to expect high incidence rates of severe exacerbation in asthmatic patients in the course of COVID-19 infections. However, controlled asthma is not considered as an independent risk factor for COVID-19, while those asthmatics receiving GINA 4/5 therapy, but still not adequately treated, are at higher risk of worse COVID-19 outcomes (31), without the risk of mortality being increased (15).

In asthmatic patients, antiviral and allergic responses are two distinct arms in immunity. In addition, IFNs are important antiviral cytokines produced by bronchial epithelial cells and plasmacytoid dendritic cells (pDCs) (2) that play a key role in defense against viral infections (42) and appear to be impaired in asthmatic patients (2) particularly after respiratory viral infections. The deficient and delayed innate anti-viral immune responses were major concerns in the case of respiratory viral infections in asthmatic patients who have been affected by COVID-19 at the beginning of the pandemic. Furthermore, a suboptimal interferon response including low concentrations of IFN-α, IFN-β, and IFN-λ could theoretically explain the increased severity of asthma exacerbations (33, 34). On the other hand, IgE cross-linking may be also expected to diminish antiviral immune responses through diverse mechanisms including abrogation of the IFN-alpha response, attenuation of the TLR-7 upregulation and the lack of pDC maturation, which are seen after rhinovirus and influenza infections in allergic patients (35). In addition, coronaviruses have the capability of actively counteracting host innate immune responses and therefore, estimating the accurate degree of reduction in these responses is often difficult in asthmatic patients.

Eosinophils are also known to have potential roles in defense against viral infections with their eosinophil-derived neurotoxin as a major ribonuclease which targets the single-stranded RNA (ssRNA) genome of respiratory viruses. Interestingly, it is reported that in some patients with severe COVID-19 infections, eosinopenia was detected while it raised significantly after the improvement of the patients (36, 37).

Despite all these facts, asthma and allergy are not represented as comorbid conditions accompanying COVID-19 (38). Among cytokines associated with asthma, IL-13 decreases the expression of ACE2 and increases the expression of TMPRSS2 in the airway epithelial cells of asthmatic patients (38). The action of the renin-angiotensin system in regulating multiple tissue and organ functions was previously shown in the kidney, liver, lung and cardiovascular system. ACE2 is a potent negative regulator of the above-mentioned system with an anti-inflammatory nature as well as the ability to inactivate Angiotensin II and activate Ang 1-7. These are two counteractive systems related to asthma. Previous studies showed the potential of Ang1-7 to modulate the increase in eosinophils, lymphocytes and neutrophils with a subsequent decrease in perivascular and peribronchial inflammation, fibrosis and goblet cell hyperplasia in asthmatic airways (39).

The mean age of the asthmatic patients in our study was 51.16 years. This finding reinforces this probability that the trend for fewer comorbidities associated with asthma could be a function of patients' age, as was suggested in another study before (9).

In addition, when encountering asthmatic patients, the pathophysiological mechanisms and even pharmacological responses may somehow influence the outcome of the infection.

Since the beginning of the pandemic, the news has paid considerable attention to vulnerable and high-risk populations. Because of the predominant respiratory nature of both asthma and COVID-19, there were concerns about the increased rates and fulminant outcomes of this infection in asthmatic patients. Therefore, these patients might have paid extremely careful attention to their personal hygiene and social distancing.

Furthermore, inhaled corticosteroids (ICSs) as the mainstay of asthma management have the potential to modulate SARS-CoV-2 infectivity. As an example, ciclesonide has been suggested to decrease viral replication. In addition, ICSs have been associated with reducing expression of ACE2, the co-receptor for SARS-CoV-2, and therefore, diminishing viral susceptibility (40).

These data cast light on why asthma did not modify the outcomes of COVID-19 in the studied patients.

However, there were some limitations to this study. Asthma cases were self-reported and this may carry the risk of reporting bias. In addition, some records did not provide us with any information concerning asthma and/or COVID-19 infection severity and the timely use of corticosteroids at the onset of the first symptoms of asthma.

Conclusion

Asthma does not appear to increase the risk of ICU admission and mortality in case of COVID-19 infection. Among the ICU admitted patients due to COVID-19 infection, the presence of asthma is not necessarily associated with a significant increase in poor outcomes.

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Conflict of Interest

All authors declare that they have no conflict of interest.

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