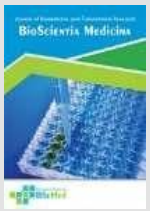
eISSN (Online): 2598-0580



Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: www.bioscmed.com

Asthma as a Protective Factor against COVID-19 Infection: A Narrative Literature Review

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ARTICLE INFO

Keywords:
Asthma
Bronchodilator
Comorbid
COVID-19
Protective factor

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All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/bsm.v7i3.785

A B S T R A C T

Asthma and COPD comorbidities are expected to exacerbate the clinical manifestations of COVID-19. However, many reported studies show that asthmatic patients infected with COVID-19 do not show severe clinical manifestations, and some are asymptomatic. This literature review aimed to describe COVID-19 in asthmatic patients along with the hypothesis that asthma is a protective factor against COVID-19 infection. Systemic corticosteroids have been shown to reduce the death/mortality rate in patients who are hospitalized due to COVID-19 infection. This is possibly due to the suppression of the immune system against a hyperinflammatory state which can result in further damage from SARS-CoV-2 infection. Mucus hypersecretion, which is one of the hallmarks of asthma, can prevent the SARS-CoV-2 virus from reaching the distal lung and can protect the lungs from pathological processes. The secreted mucus is rich in glycoproteins, such as MUC5AC, which act as the first line of defense against infection. Mucus hypersecretion in asthmatic patients may prevent SARS-CoV-2 from penetrating far enough to gain access to type-2 alveolar cells, which are the cells that predominantly express ACE2 in the lungs. In conclusion, comorbid asthma in patients infected with COVID-19 does not cause adverse clinical manifestations to appear, but on the contrary, it will have a protective effect on patients.

1. Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory coronavirus 2 (SARS-CoV-2) that first spread in Wuhan, Hubei Province, China.[1] COVID-19 is transmitted from animals to humans and from humans to humans. Common signs and symptoms of COVID-19 infection include acute respiratory distress, such as fever, cough, and shortness of breath. Clinically, the severity of COVID-19 can vary from mild to severe and can even cause death in some patients.[1-3] Comorbid diseases, such as cardiovascular disease, diabetes mellitus, and hypertension, will exacerbate the clinical manifestations of COVID-19. However, many reported studies have shown that infected asthma patients do not show severe clinical manifestations, and some are asymptomatic.

Asthma in COVID-19 can provide protection and exacerbate the clinical manifestations of COVID-19.[4] There is little data proving asthma to be protective against COVID-19. Previous studies have stated that asthma is not a risk factor for severe SARS-COV-2 disease. Research by Guan et al. stated that asthma was not identified as a risk factor for COVID-19.[5] This literature review aimed to describe COVID-19 in asthmatic patients along with the hypothesis that

asthma is a protective factor against COVID-19 infection.

COVID-19 in asthma patients

The prevalence of COVID-19 in asthma patients varies between 1.1-16.9%, but specifically for the East Asia and Pacific region, it has a prevalence of 2.2%.[6] Patients with asthma are at increased risk of infection with SARS-CoV-2 and experience a more severe impact when infected.[7] There are several pathogenesis mechanisms that describe the protective effect of asthma against COVID-19 infection (Figure 1).

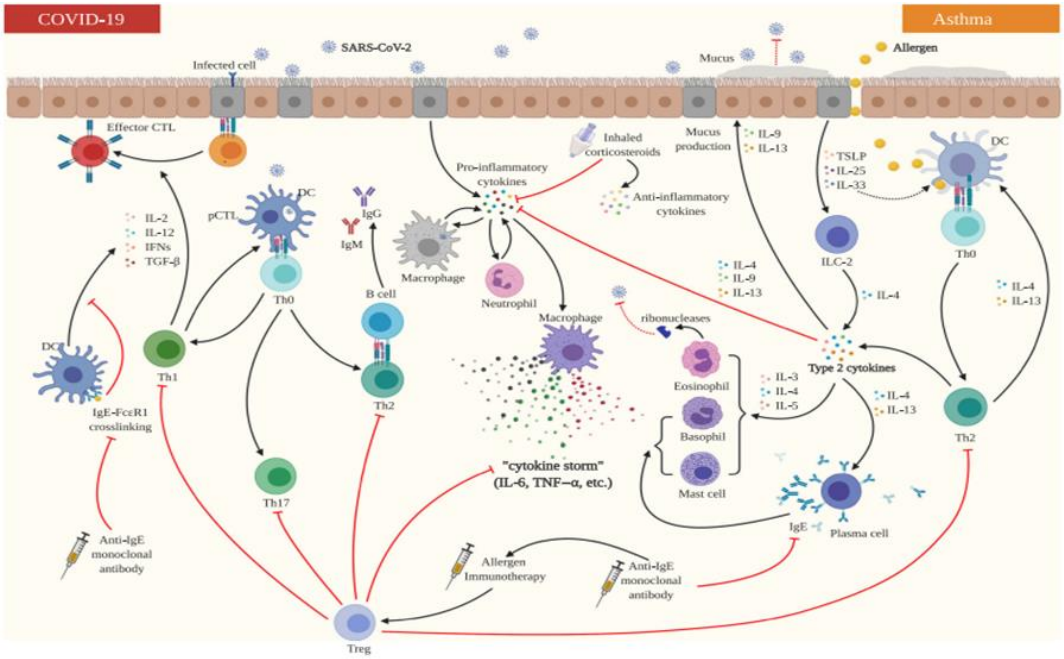

Figure 1. Schematic of the interaction between COVID-19 and asthma.[6]

Clinical symptoms of COVID-19 and asthma

COVID-19 infection can cause mild, moderate, severe, and critical symptoms. The main clinical symptoms that appear are fever (body temperature over 38°C), cough, difficulty breathing, fatigue, myalgia, and gastrointestinal symptoms.[8] In severe cases, deterioration occurs rapidly and progressively, such as acute respiratory distress syndrome (ARDS), metabolic acidosis, bleeding, and dysfunction of the coagulation system. The symptoms shown in patients suffering from asthma include wheezing, shortness of breath, coughing, and/or feeling of heaviness in the chest. The symptoms experienced can be of more than one type, are usually worse at night and in the morning, vary in terms of time and intensity, and can be triggered by infection and exposure to certain allergens (Table 1). [9]

Diagnosis of COVID-19 in asthmatic patients

In fact, although respiratory viruses are the most common cause that can cause exacerbations in asthma patients, this does not apply to asthma patients who are infected with the SARS-CoV-2 virus.[10] The symptoms that occur in asthma patients who are infected with COVID-19 are not much different from other asthma patients. The method of diagnosis is still the same as the diagnosis of asthma and COVID-19 in general. Although the tendency for COVID-19 infection to occur in asthma patients is relatively higher than in the normal population (1.41% compared to 0.86%), the clinical manifestations that appear do not become more severe, nor do they increase the number of hospitalizations.[11] Another study found that 34% of asthma patients studied did not have any symptoms when infected with COVID-19.

44% had mild symptoms, while the remaining 22% were hospitalized. Of these inpatients, only 11.7% (2 people) were treated in the ICU and required a ventilator.[12]

Table 1. Degree of severity of asthma.[9]

	Intermittent	**Mild persistent**	**Moderate persistent**	**Severe persistent**
Symptoms	Monthly	Every week	Daily	Continuously
	< 1 x a week	> 1 x a week	Every day	Continuously
	Symptoms (-) outside the attack	<1 x/day	Need a bronchodilator	Frequent relapses
	Short attack	Attacks disrupt activity and sleep	Attacks disrupt activity and sleep	Limited physical activity
Night symptoms	≤ 2 x/ month	≥ 2 x months	> 1 x a week	Often
VEP1	≥ 80% prediction	≥ 80% prediction	60-80% prediction	≤ 60% prediction
APE	≥ 80% best	≥ 80% best	60-80% best	≤ 60% best
Variability	< 20%	20-30%	> 30%	> 30%

Complications

Comorbidities have a major role in the occurrence of complications in COVID-19 infection. Comorbidities such as high blood pressure, dyslipidemia, diabetes, and obesity are major risk factors for hospitalization which can lead to conditions with a poor prognosis. The lower risk associated with rhinitis and eczema is consistent, where it is known that allergic sensitization in asthma is associated with lower ACE2 receptor expression in the upper and lower respiratory tract, indicating the potential for a protective effect.[23] General population, complications in the form of death (mortality) The consequences of COVID-19 in asthma patients are mainly related to old age.[11]

Prognosis

There was no increased risk of death/mortality, hospitalization, ICU admission rate, or length of stay among asthmatic patients with COVID-19 infection compared to patients without asthma. Interestingly, there is a trend toward a lower risk of death in patients with asthma than those without asthma, although this finding is not statistically significant.[13]

Management of COVID-19 and asthma

Systemic and inhaled corticosteroids

Systemic corticosteroids have been shown to reduce the death/mortality rate in patients who are hospitalized due to COVID-19 infection.[14,15] This is possibly due to the suppression of the immune system against a hyperinflammatory state which can result in further damage from SARS-CoV-2 infection.[16] Inhaled corticosteroids are more common, widely available, inexpensive, and generally safe, and are thought to have a role in the treatment of COVID-19.[17,18] Research conducted on epithelial cells in vitro, and inhaled corticosteroids were indeed found to reduce the replication of SARS-CoV-2.[31] Low-dose inhaled corticosteroids provide a protective effect in asthma patients by reducing airway inflammation in the early stages of SARS-CoV infection.[19] Inhaled corticosteroids actually have 2 roles, first, reduce the

inflammatory response that occurs, and second, directly inhibit the replication of the SARS-CoV-2 virus.[18] Further research has found that inhalation of budesonide can increase recovery time, with the possibility of reducing hospitalization or death rates, even in people with COVID-19 who are in communities that are at higher risk for complications.[20]

Asthma protection hypothesis against COVID-19

Asthma, which was initially thought to be a risk factor for poor manifestations of COVID-19 infection along with other respiratory diseases, turned out to have the opposite effect, asthma being a protective factor against COVID-19 infection in patients. Not much research has been conducted to reveal how the mechanism of asthma can provide a protective effect on COVID-19 infection, but here are several hypotheses that are thought to play a role in the occurrence of this effect (Figure 2).

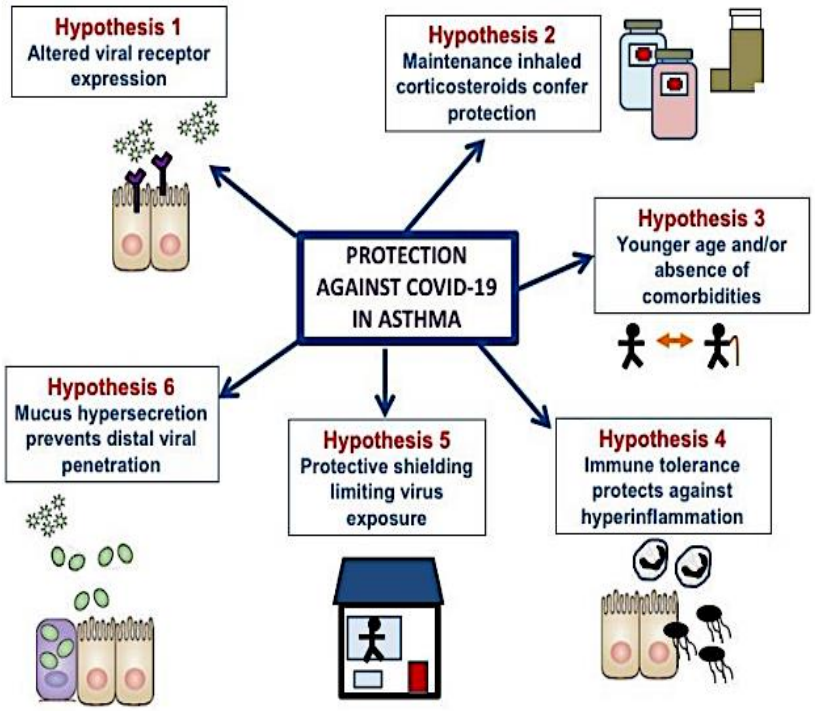

Figure 2. The hypothesis of asthma protection against COVID-19 infection.[21]

The first hypothesis states that there is a lower expression of angiotensin-converting enzyme-2 (ACE-2) in asthma, which is the entry receptor of the SARS-CoV-2 virus.[22] The second hypothesis is that the use of inhaled corticosteroids is associated with decreased sputum ACE-2 expression in asthmatic patients. The relatively young age of the patient and the absence of other comorbidities may also provide a protective effect from increased mucus or other biologic mechanisms.[23] The chronic inflammatory process in the lungs of asthmatics, arising from repeated damage to the epithelium by aeroallergens, pollutants, and viruses, may shape the immune system, which may eventually act to limit the progression of the exaggerated inflammatory response in COVID-19.[23] Restricting interactions to specific at-risk groups, including those with asthma, has been widely encouraged in international guidelines during the pandemic. This restrictive attitude has an impact on reducing exposure to SARS-CoV-2 among asthma patients, which in turn may contribute to the lower prevalence of asthma in cohorts who are hospitalized with COVID-19.[23]

Mucus hypersecretion, which is one of the hallmarks of asthma, can prevent the SARS-CoV-2 virus from reaching the distal lung and can protect the lung from pathological processes. The secreted mucus is rich in glycoproteins, such as MUC5AC, which act as the first line of defense against infection. Asthma is associated with increased expression of MUC5AC, which, when overexpressed in transgenic mice, can provide protection against influenza virus infection by reducing viral load and limiting the inflammatory process that occurs in the airways. Mucus hypersecretion in asthmatic patients may prevent SARS-CoV-2 from penetrating far enough to gain access to type-2 alveolar cells, which are the cells that predominantly express ACE2 in the lungs.[23]

2. Conclusion

Initially, the researchers assumed that COVID-19 infection that occurred in asthma patients would have a negative impact on their clinical condition. This assumption is based on the finding that other respiratory viruses, such as influenza, if they infect patients with comorbid asthma, will trigger a worsening of symptoms in patients. on the severity of COVID-19 infection in these patients. In further research, interesting facts were found that comorbidities associated with atopic phenotypes, such as asthma, turned out to have a protective effect against COVID-19 infection, both originating from the direct pathogenesis of the disease, as well as the effects of the medical therapy used. Therefore, further research is needed on the relationship between COVID-19 and asthma.

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