



## **Bronchial Asthma in the Era of COVID-19**

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### **Authors' contributions**

*This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.*

### **Article Information**

DOI: 10.9734/JPRI/2021/v33i60B34734

### **Open Peer Review History:**

This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: <https://www.sdiarticle5.com/review-history/79948>

**Review Article**

**Received 25 November 2021**

**Accepted 20 December 2021**

**Published 23 December 2021**

### **ABSTRACT**

Coronavirus disease also (COVID 19) a worldwide pandemic contagious infection produced through the Coronavirus SAR.S-CoV2, and aberrant, overactive immunity and "chemokines" have been hypothesized as possible pathogenic reasons for rapid COVID 19 development. Because of a poor viral immunogenic reaction with a potential for aggravation evoked by groups of similar respiratory virus, asthmatic patients have increased susceptibility to and severe forms of covid infection. Existing research, however, has not found an anticipated proportion of patients with asthma between COVID patient. Features of the immune responses of type2 nature, such as type2 cytokines such as IL-4, IL-13 and eosinophil buildup, may give protection against the Corona virus. Furthermore, traditional asthma treatments like as inhalation of corticosteroid, AIT (allergens immunotherapy), and monoclonal antibodies (anti-IgE) may minimize the chance for disease by the causative agent in asthmatics by reducing inflammation and strengthening antiviral defense. The connections between COVID along asthma need to be researched upon more. Infection with a respiratory virus causes up to eighty percent of acute asthma attacks in kids and 50% of similar instances in adults, with Rhinovirus (RV) being the most common cause. (1) CoVs are also seen in asthma exacerbations, with an 8.4 % frequency. Surprisingly, no cases of asthma attacks have been reported as a result of COVID-19. As a result, during the SARS and MERS outbreaks, there seem to be minimal reports of asthma attacks. Such specific events still have to be thoroughly documented. The study's main goal was to find out how common asthma was among COVID-19 participants. COVID-19 was used to examine asthmatic and nonasthmatic patients' clinical features and comorbidities. We also looked at the possibility of being admitted to the hospital as a result of asthma and/or the usage of inhaled corticosteroids.

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*Keywords: Covid-19; bronchial asthma; immunity; allergy.*

## 1. INTRODUCTION

Infection with a respiratory virus causes up to eighty percent of acute asthma attacks in kids and 50% of similar instances in adults, with RV being the most common cause [1]. CoVs are also seen in asthma exacerbations, with an 8.4 percent frequency. Surprisingly, no cases of asthma attacks have been reported as a result of COVID19. As a result, during the SARS and MERS outbreaks, there seem to be minimal reports of asthma attacks. Such specific events still have to be thoroughly documented [2]. Asthmatic people have a weakened immune system reaction to viral infections, and respiratory viral diseases can trigger or aggravate asthmatic attacks, treating asthma patients becomes more difficult at the time of the COVID19 outbreak. In general, pre-existing asthma appears to have an effect on SARSCoV2 vulnerability & disease progression. Previous research, even though, has not found a significant presence of asthma in COVID19 patients. Few studies in published COVID19 research included it as a condition, that is inadequate to establish a strong conclusion [3].

Research from Lombardy, Italy, likewise revealed a lesser presence of it. Only data from New York City, united states of America, reveal an asthma prevalence of 9%, however, no thorough determination of the actual clinical phenotypes and therapies of included patients is available. According to State of NY mortality data, asthma is not included in the first ten comorbidities. In conclusion, their findings show demonstrate allergic illnesses are not a risk factor or exacerbating factor for COVID19 [4].

Symptoms most associated with COVID19 are dry cough, shortness of breath which may be associated with an acute asthma worsening. The most common symptom of COVID19 is fever, although it can occur with any disease triggered asthma exacerbation. Given the variety of clinical manifestations of COVID19, screening techniques for COVID19 should be used to anybody experiencing increasing symptoms of respiration, including those having asthma. People who are commencing screening must wear appropriate personal protective equipment [5].

### 1.1 Can have Asthma Increases the Chances of having COVID-19?

Individuals with long-term conditions and above 65 years in age were in the Covid-19 groups at risk, as per the C.D.C (Center for Disease Control and Prevention) [6]. Asthmatic patients with a medium to heavy disease were also included in this danger category. Nevertheless, asthma illness was uncommon among individuals of COVID-19, particularly the Chinese observational case series. There were no incidences of asthma or allergic rhinitis recorded in a research of 140 Wuhan patients' clinical features and allergies; nevertheless, only two cases of urticaria were identified [7]. The risk factors were examined in different research involving 549 hospitalized patients in China's Wuhan. Asthma was found to be present in 0.9 percent (n= 5) of the comorbidities [8]. The researchers hypothesized that IFN-, IL-12, IL-8, IL-6, IL-1, and TNF-cytokines were produced in response to a Th-1 cellular reaction, whereas a Th-2 immunogenic reaction might be protective opposing the illness. There were 11 different phenotypic and clinical characteristics discovered in 11 separate patients, but no instance of asthma was described. In a separate study of 1590 patients with comorbidities, no occurrence of asthma was found [9]. 180 concomitant conditions (12.1 percent) were identified between 1482 hospitalized cases in a monthly update analyzing hospitalisation and case features in the US. These were confirmed cases from the laboratory, and the occurrence of the condition was reported to be 17 percent and 27.3 percent in each age categories and in the 18-49 age range, among the 180 cases with comorbidities. However, these are the rates for comorbid conditions only; when all hospitalised cases are taken into account, the incidence drops dramatically. In the areas of New York, asthma cases were reported to be present in 9% of COVID-19 participants. While some meta-analyses found no evidence of a relation between asthmatic patients having an higher danger of Covid 19 mortality in hospitals [10], others found a link between asthma and an increased danger of COVID-19 mortality in hospitals [11]. The patient had not been utilizing inhaler steroids, which is significant.

The presence of lesser reports associated with Covid 19 and asthma, according to some experts, could be attributed to three factors [12].

## **1.2 Does Asthma and Allergy or Their Therapy Affecting ACE-2 Receptor Genes Expression in the Airway??**

By attaching to ACE2 receptors, the SARS-CoV-2 penetrates the cell. The appearance of ACE2 gene in asthma sufferers was studied [13,14]. Type 2 markers were also measured, including FeNO (fraction exhaled nitric oxides), total Ig E, and blood eosinophil. Allergy sensitivity has also been found to be inversely associated to ACE-2 appearance in the nasal epithelium. Furthermore, a strong negative connection was discovered between Type 2 biomarker (specific IgE, Total Ig E, FeNO) and nasal epithelial IL-13 and ACE-2 expressions [13]. Reduced levels of sensors in the body with which the SARS-CoV-2 attaches might protect allergic asthma patients from illness. The second research contributing to our knowledge of how asthmatic, ICS, and ACE2 expression are linked [14].

## **1.3 Does the Sars-CoV-2 Virus Cause Asthma?**

The respiratory tract virus in the past has been linked to attacks of asthma. In previous investigations, respiratory tract viruses like RV (rhinoviruses), RSV (respiratory syncytial viruses), herpes simplex viruses, EnV (enteroviruses), and IfV (influenza) were found to be the majority of the causes of the attacks [15]. Non-pandemic coronaviruses were also shown to induce asthma attacks, though less frequently. SARS-CoV and MERS-CoV, two previous pandemic coronaviruses, were not connected to the attacks. [15].

## **1.4 COVID-19 and Previously Existing Asthma**

### **1.4.1 Asthmatic patients with inadequate antiviral response**

This is widely assumed that antiviral and allergy reactions are two different arms of resistance that are mutually controlled and involve a complex network of interactions. Interferons (IFNs), a kind of antiviral cytokine, plays a critical function in this. It's been suggested that people with asthma are more sensitive to allergic reactions that can override antiviral medication, leaving them more vulnerable to viral infections and having a poor immune response [16]. In asthmatic bronchial epithelial cells, IFN production is decreased, which results in altered apoptosis and enhanced rhinovirus (RV)

replication. After RV infection, asthma patients have been found to have decreased IFN / expression by bronchial epithelial cells, which has been linked to higher viral load and worse clinical consequences. [17].

### **1.4.2 Eosinophilic inflammation and Covid disease**

Eosinophils are well-known for their function in allergic disorders, such as asthma. The prospective impacts due to eosinophil on Covid are worth noting. Although this behavior is not observed in all conditions, previously conducted research has suggested that eosinophilic reaction must have a part in viral clearance and host antiviral defense. Furthermore, eosinophils with ssRNA can be activated by activating the TLR7MyD88 signaling pathway, which could lead to the clearance of RSV and reduced dysfunction of the lung. The ability in eosinophil in its fight against viral infections may thus account for the decreased presence of asthmatics among COVID19 patients [18].

### **1.4.3 Asthma patients' susceptibility to COVID-19 infection**

During initial stages of pandemic, research from China and Italy highlighted asthma as one of the key clinical risk factors for SARSCoV2 infection.

According to research conducted India, Brazil, U.A.E and Russia, decrease asthma incidence has been reported in COVID19 patients. However, research from the US and UK found that asthma comorbidities percentages in COVID19 patients were comparable to or greater than in the general population [19].

In summary, the presence of asthma in COVID19 patients varies greatly with different countries; Most countries did not report higher rates of COVID19 infection in asthma patients, but instead comparable or lesser rates of COVID19 disease in comparison to the general public in the relevant area, likely owing to several factors, consisting of a lesser percentage of non-type 2 phenotypes. In fact, a cohort from the nation of Korea appeared that nonallergic asthmatic people had increase chances for a positive SARSCoV2 test than patients with allergic asthma [20].

### **1.4.4 Asthma (severe form) along with COVID-19**

Despite extensive therapy, a small percentage of asthma cases (5-10%) have uncontrolled or

inadequately managed asthma. As one might anticipate these patients to be more susceptible to SARS-CoV2 infection, but little data is obtainable to support such a theory. Regardless of the lack of solid data, the U.S.A CDC (center for Control and Prevention) issued a warning for patients having moderate forms to severe forms of asthma are more likely of contracting COVID19 and suffering catastrophic consequences as a result of the disease [21]. Although patients with level 5 asthma spent more time in the hospital compared with level 1 asthmatic patients.

A huge COVID19 hospital community in Italy revealed that patients with an adverse COVID19 outcome (death / requirement for ventilation versus release from home without intrusive treatments) had more severe asthma. [22] At last it is considered everywhere that old age, obese body, having cardiovascular diseases, and diabetic patient are all at risk of having a poor COVID19 score. Chronic respiratory disorders, such as asthma, may or may not be considered risk factors. Many studies on this topic have devised contradicting plans, suggesting that to types of factors that may affects Covid 19 vulnerability along with the intensity in asthmatic patient (Memon et al., 2021). This would include severity of asthma, asthmatic genotypes/phenotype, asthmatic prescriptions, and comorbidities.

The documented occurrences of significant COVID19 incidences in patients with asthma are influenced by the factors other than the patient. Furthermore, local circumstances (screening recommendations or screening suggestions, including the elderly or those with comorbidities such as asthma) and the diagnostic tools used to diagnose asthma and COVID19 can have a crucial influence [23].

#### **1.4.5 In the context of COVID-19, do anti-asthmatic medications play a protective or beneficial role??**

##### **1.4.5.1 COVID-19 and inhaled antiasthmatic treatments**

Maintaining inhaled corticosteroids (ICS) is expected to give protection as well, however, there is no indication for CSI advantages or downsides in COVID19. Numerous key questions emerge. Currently, there is no indication of a higher danger for COVID19 disease among patients with asthma who use ICS regularly [24].

Asthma patients should continue to use their inhaler corticosteroids and incorporate therapies during the outbreak, according to guidelines and experts [25-28]. It is suggested that nebulizers not be used in hospitals because of the danger of illness transmission to healthcare workers and others, and that spirometry need not be performed unless absolutely required. In asthma attacks, a measured dose inhalation through a mouthpiece or a closely fitting ventilation mask should be utilized instead of a nebulizer [25]. It has been proven that attaching a nebulizer with a filter is useful in catching inhaled aerosolized particles [29-31]. The filters help to limit the number of aerosols that are released into the environment. Mesh nebulizers are a good alternative to jet nebulizers [29]. These recommendations should be taken into account when treating COVID19 and asthma patients. There is a recommendation to postpone routine check-up appointments for patients with mild asthma and also those who have controlled asthma and instead tell them by phone calls, e-mail, or text message [25-28]. The potential of COVID-19 transmission makes hospital visits for these individuals unfavorable. Patients who are well and have not had an urgent appointment within past 6-12 months, as well as those who have had one oral steroid in the previous 6 months, may have their face-to-face examinations postponed. Telehealth services may be used to manage these patients remotely [28]. Patients who have had an attack in the last 3-6 months and have a history of an emergency visit or hospitalisation should be given priority. COVID19 screening should be administered to patients admitted with worsening asthma or an acute attack, and the risk of SARS-CoV-2 infection and the need for testing should be questioned. [28].

#### **1.5 Asthma Attacks and Systemic Corticosteroids**

The usage for systemic steroids in the treatment of COVID-19 associated lung damage is a source of debate. Prednisolone has been linked to the prolongation of viral replication. Short-term administration of systemic steroids at modest doses (0.5-1 mg/kg, 7 days) is effective for COVID-19 associated lung damage, according to the Chinese Thorax Society [30]. According to Russel et al., the use of systemic steroids in the SARS-CoV and MERS-CoV infections slowed viral RNA clearance, induced different side effects, and there was no clinical evidence to justify steroid treatment in the COVID-19 illness

[31]. During the pandemic, the Global Initiative for Asthma (GINA) recommends using oral steroids for moderate attacks since it reduces hospitalizations [25]. The Canadian Society recommends the use of systemic steroids in asthma attacks, whether or not they are caused by COVID-19 [27]. It's vital to keep patients safe from asthma episodes during this period... Patients' inhaler steroid doses could be increased to prevent them from having an attack [25,28]. During this time, giving patients a written action plan and following up via remote telemedicine are appropriate ways [25,28]. During the COVID-19 pandemic, Levin et al. published an acute asthma care protocol for doctors [32]. They believe that high-dose MDI and quick systemic corticosteroid treatment can help prevent asthma attacks from worsening.

## 1.6 COVID-19 and Biological Therapies

Biologics are used to treat severe asthma in people who have been unable to control their symptoms with existing therapies. These three anti-IL5 / IL5r drugs work primarily to combat eosinophils by lowering or depleting eosinophils in tissues and peripheral circulation. Another 2 therapies (antiIgE and antiIL4 / IL13) mostly decrease type 2 immunity. As a result, another central issue is whether eosinophils and/or immunomodulation via the type 2 pathway play a part in changing vulnerability, intensity, resistance, or tolerance to SARS-CoV-2 infection. Even though the significance of eosinophils during COVID-19 sickness is unknown, this has been demonstrated that such a viral disease is linked with significant eosinopenia and that prolonged eosinopenia is related with clinical deterioration and an increased risk of mortality. Various reasons for COVID-19-related eosinopenia have been proposed [33].

According to new recommendations, biological agents should be used throughout the epidemic. Biological drugs do not appear to reduce the immune response to a viral infection, according to the findings. These medicines, when administered in severe cases of asthma, are known to lessen asthma episodes [25-28]. In a randomized controlled study of children with allergic asthma aged 9 to 17, it was discovered that omalizumab reduced viral shedding and duration of rhinovirus, the most commonly found virus in asthma attacks [34]. During the COVID-19 pandemic, the FDA has approved omalizumab for short-term home administration [35]. Biological treatments as home-based

administration are encouraged by national recommendations in several nations during pandemics [26,36-38]. Clinical trials with omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab shown that such medications reduced asthma exacerbations while without increasing the risk of viral infection [39-42]. During the pandemic, these drugs should be continued in people with severe asthma., based on existing information. The question is whether these medications should be continued as part of COVID-19 treatment. These medicines may be compatible with biologics in severe asthma, although no data is currently available. The decision to keep a biologic agent or postpone it till a patient recovers should be made on a case-by-case basis with the help of a multidisciplinary council [43].

## 2. METHODOLOGY

To analyze the connection of asthma and Covid 19 utilizing papers of the English language till the June 15, 2020, a systematic research was conducted in the following four digital libraries: PUBMED, MEDLINE, MedRxiv, and Google scholar. "COVID-19" OR "SARS-CoV-2" OR "Coronavirus" AND "Asthma" OR "Allergy" OR "Case series" OR "Comorbidities" OR "Epidemiology" OR "Hospitalization" OR "Risk factors" In addition, the references of the first included research were manually examined to discover other potentially acceptable studies.

Following the application of the aforementioned criteria, 45 papers were subjected to a full-text review. Finally, they included 15 papers in their analysis. Within each trial, they utilized the Cloper Pearsons approach in generating 90 percent C.I (confidence intervals) for prevailing cases of asthma. They also used local available information of cases from their hospitals to run a multivariate logistical regression model having numerous inputs to see if having asthma affected intubating chances after managing for gender, age, and Body Mass Index (BMI).

## 3. RESULTS

As a result, the proportion of patients with asthma among COVID-19 hospitalised patients is similar to the incidence of asthma in the general community at each research site.

According to their data, asthma prevalence among COVID-19 hospitalised patients appeared as were comparable to asthmatic patients and

the prevalence was much decreased among influenza hospitalized group. Even after correcting for Body mass index along with age, which is the principal risk factor for severity, asthma is not an independent factor for cause for intubating hospitalized patients having Covid-19.

Primary cause of hospitalization in asthmatic patients with worsening is due to upper respiratory tract infections, coronavirus has no contribution towards this [4]. Patient suffering from asthma are not appeared to be largely impacted in instances of SARS-Cov (not the virus that causes Covid 19), despite the lack of data to make this comparison [5, 6].

During the 2019–20 influenza period, 25.2 percent of cases hospitalised having asthma along with flu like symptoms, that was significantly more compared to the four season aggregate of 21% from 2016 till 2020 although, it is significantly larger than the combined presence estimated from the 16 Covid 19 study. [44]. In spite of early concerns about asthma patients having unreasonable higher morbidity and death [45], data provided here and elsewhere indicate little indication of a clinically significant link [46,47].

#### **4. DISCUSSION**

Although after correcting for Body Mass Index and lifespan, that are widely in knowledge risk factors for severe forms and are widely linked with intubation in their design, information through the hospitals may not demonstrate any notable links in asthmatics with increasing intubating odds within COVID-19 cases. The location of the angiotensin Converting enzyme receptor (ACE2) in the respiratory airway epithelium could be one reason why COVID-19 isn't linked to higher hospitalisation rates in people with asthma. Diabetes and hypertension have been linked to increased ACE2 expression, whereas inhaled corticosteroid use has been linked to decreased ACE2 expression, resulting in more difficulty with viral entry [48, 13]. Furthermore, patients with asthma, especially those with a primarily allergic phenotype, may have significantly decreased ACE2 expression [13,49-57]. Although the relationship between ACE2 receptor expression and total COVID-19 susceptibility and illness severity is yet unknown, further research is warranted. Unfortunately, we do not have any inhaled-corticosteroid data on patients in our study or at our hospital to further investigate the potential benefits of these drugs,

as has been suggested [12]. COPD, unlike asthma, increases chances of severe forms of Covid 19 disease in hospitalised cases [9]. Higher chances of comorbidity are connected to higher ACE-2 response tissues of the lungs and small airways is linked to this comorbidity [49]. Given the varying prevalence of asthma among COVID-19 hospitalised groups, it's probable that comorbidity reporting was uneven across studies, especially since the authors didn't explain how asthma or chronic respiratory illness diagnoses were acquired in any of these investigations. In contrast to the higher-than-expected rates of hypertension and diabetes mellitus among hospitalised patients, which are comorbidities known to be related to severe COVID-19, studies of COPD have revealed prevalence rates that are lower than the population norm [58-61]. Finally, we realize that our findings could be due to a small sample size, and that more data from asthma and intubation risk investigations would be desirable. Although asthma prevalence varies among COVID-19 publish studies, it appears to be comparable to community prevalence and is certainly lower than what would be expected during seasonal influenza. According to the findings, asthma does not appear to be a substantial risk factor for severe COVID-19 that necessitates hospitalisation or intubation.

#### **5. CONCLUSIONS**

According to our analysis of the current data on asthma and COVID19, asthma doesn't really enhance vulnerability to SARS-CoV2 disease or result in a poorer treatment outcome in people with the disease. Asthma doesn't really seem to become a contributing factor for COVID19 in general; nevertheless, its precise role in danger might rely mostly on existence of some of the other behavioral & environmental variables (e.g., smoking, illnesses), as well as the depending upon the severity of asthma (e.g., adherence).

International Asthma Guidelines recommend adhering to basic measures to protect against COVID19 and following asthmatic medications, ICS and biological agents are examples of ICS in asthma patients during the COVID19 pandemic. Some suggested asthmatic patients should manage their existing condition with regulator medicines, especially biologics, because continuous ICS usage doesn't really carry the chance of admission in asthmatic patients with concurrent COVID19 disease. Finally, the choice to prolong or discontinue biological treatment for

individuals who have already been infected with SARSCoV2 must be made on an individual basis.

Extensive experimental and clinical research is needed in corroborating such early uncovering of a "dangerous connection" between COVID19 and asthma.

## DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

Ethical clearance has been approved by IEC-DMIMS.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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