

# [The possible dual role of the ace2 receptor in asthma and coronavirus (sars-cov2)...](https://assignbuster.com/the-possible-dual-role-of-the-ace2-receptor-in-asthma-and-coronavirus-sars-cov2-infection/)

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A new virus belonging to the *coronaviridae* family has been identified and named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) ( [Zhu et al., 2020](#B84) ). This virus can generate a severe respiratory disease named coronavirus disease-2019 (COVID-19). In November 2019, SARS-CoV-2 began to infect humans and cause high rates of respiratory disorders worldwide; accordingly, COVID-19 was declared a pandemic in March 2020 ( [Li J. Y. et al., 2020](#B41) ). COVID-19 has already affected millions of people and killed over 600, 000 individuals worldwide ( [WHO, 2020](#B71) ).

Similar to severe acute respiratory syndrome coronavirus-1 (SARS-CoV-1), which was responsible for the 2002 pandemic, SARS-CoV-2 infection is initiated when its S-protein binds to the angiotensin-converting enzyme 2 (ACE2) receptor through which it gains entry into the host's cells ( [Kuba et al., 2005](#B38) ; [Walls et al., 2020](#B68) ). The affinity of SARS-CoV-2 for the ACE2 receptor is 10 times higher than that of SARS-CoV-1 ( [Wrapp et al., 2020](#B74) ). This receptor is mainly expressed in the lungs and to a lesser degree in other organs, such as the heart, kidneys, and intestines ( [Bavishi et al., 2020](#B9) ), which could explain the increased prevalence of lung infection.

Many risk factors are associated with the course and severity of COVID-19, including older age, systemic arterial hypertension (SAH), pregnancy, and obesity ( [Alberca et al., 2020a](#B2) , [b](#B1) ). Although asthma is a debilitating pulmonary syndrome, initial reports have not identified asthmatic patients as having a higher risk for COVID-19 ( [Guan et al., 2020](#B31) ; [Zhang et al., 2020](#B82) ). In this manuscript, we review the possible association between the SARS-CoV-2 entry receptor ACE2 and asthma.

## Asthma

Asthma is a complex respiratory syndrome that affects ~350 million people worldwide ( [Global Initiative for Asthma, 2018](#B29) ). This disease is generally defined by restricted airflow, airway inflammation, and airway hyperresponsiveness, resulting in symptoms such as shortness of breath, wheezing, and cough; moreover, if untreated, asthma can be lethal ( [Global Initiative for Asthma, 2018](#B29) ). Asthma mortality seems to be declining worldwide ( [Ebmeier et al., 2017](#B22) ), and it is estimated that in 2015, over 400, 000 deaths occurred due to asthma complications ( [Soriano et al., 2017](#B63) ). Asthma is also associated with other comorbidities, including SAH ( [Ferguson et al., 2014](#B25) ) and pulmonary hypertension ( [Rosival, 1990](#B55) ), which are two established risk factors for COVID-19 ( [Zhang et al., 2020](#B82) ). Other characteristics associated with the worst asthma symptoms, such as obesity and old age, are also associated with poor COVID-19 prognoses ( [Schatz et al., 2014](#B57) ; [Skloot et al., 2016](#B61) ; [Płusa, 2017](#B52) ; [Zhang et al., 2020](#B82) ).

Asthmatic patients can suffer from a progressive worsening of symptoms called asthma exacerbation, which necessitates treatment with systemic corticosteroids and eventually mechanical ventilation and intensive care ( [Dougherty and Fahy, 2009](#B21) ). A common concept in asthma is that viral infections can be associated with asthma exacerbation ( [Costa et al., 2014](#B17) ), and in respiratory viral infections, asthma patients can upregulate a wide range of molecules expressed in the lungs; one of these molecules is ACE2 ( [Bai et al., 2015](#B7) ).

## SARS-COV and ACE2

The ACE2 receptor is crucial for COVID-19, as SARS-CoV-2 can only enter ACE2-expressing cells ( [Zhou et al., 2020](#B83) ). Nevertheless, ACE-2 expression is also important for the control of lung inflammation and damage upon viral infection ( [Imai et al., 2005](#B36) ; [Yang et al., 2014](#B78) ; [Zou et al., 2014](#B86) ).

During SARS-CoV-1 infection, the overexpression of ACE2 increases viral infection and replication rate ( [Li et al., 2003](#B42) ), and in animal models, infection with SARS-CoV-1 is ACE2-dependent ( [Kuba et al., 2005](#B38) ). However, in SARS-COV-2 infection, Chen et al. proposed a negative association linking ACE2 expression and COVID-19 fatality, as ACE2 expression is reduced in elderly and type II diabetic patients ( [Yoon et al., 2016](#B80) ; [Chen et al., 2020](#B16) ).

Interestingly, children also express low levels of ACE2 in the lungs ( [Bunyavanich et al., 2020](#B13) ), and the death rate in this group has been described as low ( [Bialek et al., 2020](#B10) ). In addition to the lower ACE2 expression in the lungs of elderly patients ( [Wu and McGoogan, 2020](#B76) ), other characteristics, such as the presence of other comorbidities, immune senescence, or low-grade inflammation associated with aging (inflammaging), could influence COVID-19 outcomes ( [Franceschi and Campisi, 2014](#B27) ; [Fuentes et al., 2017](#B28) ).

Another important finding is that men infected with SARS-CoV-2 have more severe disease and higher mortality than women ( [Sharma et al., 2020](#B59) ). The primary female sex hormone (estrogen), in addition to being able to directly influence immune responses, is able to upregulate the expression of ACE2 ( [Bukowska et al., 2017](#B12) ).

Recently, it has also been described that some structural variations in the ACE2 receptor can lead to differences in protein binding with SARS-CoV-2, helping to understand different infection profiles in humans and even cases of viral resistance ( [Hussain et al., 2020](#B35) ). ACE2 may also play a larger role in SARS-CoV-2 infection, participating in postinfection regulation of the immune response, cytokine secretion, and viral genome replication ( [He et al., 2020](#B32) ).

## Asthma and Covid-19

A report from Wuhan, China, identified a low number of asthmatic patients among COVID-19 patients (0. 9%); however, asthma was not associated with greater COVID-19 severity or mortality ( [Li X. et al., 2020](#B43) ). Another study with 5, 700 COVID-19 patients from New York City, USA, identified 479 patients with asthma (9%) ( [Richardson et al., 2020](#B54) ). In addition to this discrepancy in the incidence of asthma among COVID-19 patients, a recent study with 1, 827 patients identified that mortality was similar in asthmatic and non-asthmatic COVID-19 patients ( [Wang et al., 2020](#B69) ).

Song et al. evaluated the prevalence of asthma and chronic obstructive pulmonary disease (COPD) in patients from a cohort of COVID-19 patients in China and found that 2. 3% of the patients had asthma and 2. 2% had COPD; none of the patients had asthma and COPD ( [Song et al., 2020](#B62) ). They verified that COPD patients had a higher risk of severe COVID-19 than asthmatic patients. In addition, the number of ACE2-positive cells in alveolar epithelial cells was lower in asthmatic patients and higher in COPD patients than that in patients without asthma or COPD ( [Song et al., 2020](#B62) ).

## Asthma, Coronaviruses, and ACE2

Asthma is the most common chronic disease in children ( [Ferrante and La Grutta, 2018](#B26) ), and in the previous pandemic caused by SARS-CoV-1, asthmatic children infected with SARS-CoV-1 did not sustain an increase in asthma exacerbation ( [Van Bever et al., 2004](#B65) ). Moreover, a 2019 report indicated that the most common chronic condition in Middle East respiratory syndrome coronavirus (MERS-CoV) patients was asthma ( [van Kerkhove et al., 2019](#B66) ). In another report, two patients who died from MERS-CoV complications had chronic respiratory syndromes: one had COPD and one had asthma ( [Min et al., 2016](#B47) ). Therefore, similar viral infections do not present a clear picture of how SARS-CoV-2 infection progresses in asthmatic patients.

In a murine asthma model, ACE2 activation has been implicated in a reduction in airway inflammatory response ( [Dhawale et al., 2016](#B20) ). It is important to highlight that asthma can be divided into four different endotypes: T helper cell (Th)2 high/eosinophilic, Th17/neutrophilic, Th2/Th17/mixed inflammation, and paucigranulocytic (without an increase in polymorphous nuclear cells in the lungs) ( [Wenzel, 2013](#B70) ).

The asthma endotype is especially important, as cytokines can modify ACE expression. IL-17 can upregulate ACE2 expression ( [Song et al., 2020](#B62) ), whereas IL-4 and IL-13 can downregulate ACE2 expression ( [Kimura et al., 2020](#B37) ; [Song et al., 2020](#B62) ).

Eosinophils may also play a larger role in COVID-19, as non-asthmatic patients with COVID-19 who present an absence of eosinophils in the first day of hospitalization have a worst prognose than non-asthmatic patients with eosinophils ( [Tanni et al., 2020](#B64) ). Another study suggested that eosinophil count in peripheral blood has prognostic value, as patients with a low number of eosinophils were more likely to exhibit shortness of breath and require longer hospitalization time ( [Xie et al., 2020](#B77) ). An increase in eosinophils is associated with COVID-19 improvement and hospital release ( [Liu et al., 2020](#B44) ; [Xie et al., 2020](#B77) ). We hypothesize that different endotypes of asthma may modify ACE2 expression differently, thereby affecting COVID-19.

ACE2 expression in the lungs is also modulated in other respiratory diseases. In an experimental model of smoke-induced acute respiratory distress, a Th17/neutrophilic syndrome, ACE2 was upregulated ( [Wösten-Van Asperen et al., 2011](#B73) ). In addition, cytokine release from smoking-associated lung injury induces upregulation of ACE2 in the lungs ( [Leung et al., 2020](#B40) ). In summary, different endotypes of asthma and patients with multiple characteristics, such as smoking asthmatic patients or asthmatic patients with other morbidities, may also present a difference in lung ACE2 levels.

## Asthma Treatment and Covid-19

Approximately 50–70% of asthmatic patients have Th2 high/eosinophilic asthma ( [Peters et al., 2014](#B50) ; [Seys et al., 2017](#B58) ). Th2 high/eosinophilic asthma can be treated with allergen-specific immunotherapy or symptomatic medication. Allergen-specific immunotherapy is a process that usually increases the circulation of regulatory IL-10-producing cells ( [Asamoah et al., 2017](#B5) ; [Alberca-Custodio et al., 2020](#B3) ), which could help to curb the pro-inflammatory cytokine storm in COVID-19. Asthma medications, such as corticosteroids and long-acting beta agonists, reduce lung inflammation and provide symptomatic control ( [Asamoah et al., 2017](#B5) ). Recently, the usage of inhaled corticosteroids was also associated with lower expression of ACE2 in the sputum of asthmatic patients ( [Peters et al., 2020](#B51) ).

Dexamethasone, a long-acting glucocorticoid commonly used in the treatment of asthma exacerbation ( [Shefrin and Goldman, 2009](#B60) ; [Cross et al., 2011](#B18) ), has recently shown positive results in COVID-19 ( [Recovery Collaborative Group et al., 2020](#B53) ). Dexamethasone treatment reduced mortality among COVID-19 patients receiving respiratory support (RS) but not among patients not receiving RS ( [Recovery Collaborative Group et al., 2020](#B53) ).

Other anti-asthma drugs (AADs), mainly cromolyn, fenoterol, montelukast, and reproterol, have been postulated to be of potential use in SARS-CoV-2 infection ( [Wu et al., 2020](#B75) ). These drugs could help reduce inflammation and improve lung function ( [Mombeini et al., 2012](#B48) ; [Davino-Chiovatto et al., 2019](#B19) ). Therefore, both dexamethasone and AAD usage for the treatment of asthma could confer additional protection to asthmatic patients.

Immunobiological treatment, including the use of monoclonal antibodies targeting asthma-related molecules, such as IL-5 and IgE, has proven effective in reducing asthma symptoms ( [Samitas et al., 2015](#B56) ; [Farne et al., 2017](#B24) ). To date, there is no report on the influence of anti-IL-5 on SARS-CoV-2 infection; therefore, the usage of this immunobiological agent during COVID-19 is contraindicated, as this type-2 cytokine could potentially counteract the type-1 cytokines released during infection ( [Vultaggio et al., 2020](#B67) ).

Interestingly, treatment with anti-IgE decreases endothelin-1 ( [Zietkowski et al., 2010](#B85) ), and the decrease in endothelin-1 upregulates the expression of ACE2 in bronchial epithelial cells ( [Zhang et al., 2013](#B81) ). On the other hand, a case of COVID-19 in a patient with severe asthma treated with the anti-IgE antibody did not provide evidence of asthma exacerbation or pneumonia ( [Lommatzsch et al., 2020](#B45) ). Hence, further studies with a larger cohort are necessary to better understand the role of this immunobiological treatment during COVID-19 and the corresponding influence on the ACE-2 receptor.

## Covid-19 Cytokines, ACE2, and Asthma

SARS-CoV-2 infection can generate a process called a cytokine storm, which is characterized by an increase in the levels of mainly type-1 cytokines, including IL-1, IL-8, IFN-γ, IP10, MCP1, and TNF, in the blood ( [Huang C. et al., 2020](#B33) ). The concentration of these cytokines can be a predictive factor in a patient's disease course ( [Huang C. et al., 2020](#B33) ). Investigations on the influence of the interaction between comorbidities, COVID-19 and cytokines on ACE2 expression are crucial for the development of new treatments for COVID-19 ( [Pagliaro and Penna, 2020](#B49) ). The upregulation of ACE2 is associated with an increase in the levels of IL-1, IL-10, IL-6, and IL-8 ( [He et al., 2020](#B32) ), which are important cytokines in the pathophysiology of COVID-19 ( [Guan et al., 2020](#B31) ; [Zhang et al., 2020](#B82) ). IL-1 and IL-6 are likely involved in the development of fever, which is the most common COVID-19 symptom ( [Cartmell et al., 2000](#B14) ; [Fabricio et al., 2006](#B23) ). IL-8, or CXCL8, is an important chemokine for the migration of neutrophils to the lungs in acute respiratory distress and the formation of neutrophil extracellular traps in COVID-19 ( [Wong et al., 2004](#B72) ; [Gong et al., 2020](#B30) ; [Middleton et al., 2020](#B46) ).

Although ACE2 plays a crucial role in SARS-CoV-2 viral infection, the use of ACE2 inhibitors may not be possible due to ACE2 being a protective factor in acute lung injury ( [Ye and Liu, 2020](#B79) ). Currently, no specific treatment or vaccine is available for SARS-CoV-2/COVID-19 ( [Huang L. et al., 2020](#B34) ). A preliminary study by Leng et al. showed that transplantation of seven patients from Beijing YouAn Hospital, China, with ACE2-negative mesenchymal stem cells (MSCs) was effective in improving the clinical outcomes of pneumonia, mainly due to immune modulation, with decreased TNF and increased IL-10 ( [Leng et al., 2020](#B39) ). Other reports have highlighted the usage of anti-TNF ( [Brito et al., 2020](#B11) ) and anti-IL-1β to regulate inflammation in COVID-19 patients ( [Cauchois et al., 2020](#B15) ).

IL-4 and IL-13, which are cytokines highly produced in Th2/eosinophilic asthma, can downregulate ACE2 expression in airway epithelial cells ( [Kimura et al., 2020](#B37) ; [Song et al., 2020](#B62) ), whereas, TNF, IL-12, and IL-17A, which are cytokines highly produced in Th17/neutrophilic asthma and COPD ( [Alcorn et al., 2009](#B4) ), can upregulate ACE2 expression in *in vitro* BEAS-2B cells ( [Song et al., 2020](#B62) ). In addition, circulating soluble angiotensin-converting enzyme 2 (sACE2) is upregulated in the blood of asthmatic patients ( [Ayada et al., 2015](#B6) ); hence, sACE2 could act as a competitive interceptor, limiting SARS-CoV-2 attachment to airway cell membranes ( [Batlle et al., 2020](#B8) ).

Further investigations are needed to better understand the role of ACE2 in asthmatic patients during SARS-CoV-2 infection, which would enable the development of better and more effective treatments for the COVID-19 pandemic while mitigating deaths in asthmatic individuals and the overall population.

## Author Contributions

AB and MS: write and review. RA: conception, write, and review. All authors contributed to the article and approved the submitted version.

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## Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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