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Asthma and COVID-19 pandemic: focus on the eosinophil count and ACE2 expression

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Summary
Currently, the world is engaged with a coronavirus disease 2019 (COVID-19) caused by acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The Center for Disease Control and Prevention (CDC) has proposed moderate to severe asthma as a risk factor for COVID-19 susceptibility and severity. However, current evidences have not identified asthma in the top 10 comorbidities associated with COVID-19 fatalities. It raises the question that why patients with different type of asthma are not more vulnerable to SARS-CoV-2 infection like other respiratory infection. Increased number of eosinophils and elevated angiotensin-converting enzyme 2 (ACE2) expressions in asthma are supposed as two mechanisms which associated with decreased COVID-19 susceptibility in asthmatics. Some studies have been performed to evaluate two mentioned factors in asthmatic patients compared with healthy individuals. Herein, we address these mechanisms and investigate whether ACE2 and eosinophil could protect asthmatic patients against SARS-CoV-2 infection.

Impact statement
Increased ACE-2 expression and number of eosinophil might be an important predictor for reduced COVID-19 morbidity and mortality in asthmatic.

Introduction

SARS-CoV-2 is a causative agent of a new respiratory infection in human known as COVID-19 which is associated with pneumonia, cold, sneezing, and coughing. COVID-19 was first diagnosed and isolated from pneumonia patient who belongs to Wuhan, China, and then spread to other parts of China and other countries worldwide. On account of rapid spread, WHO reported it as a Public Health Emergency of International Concern (PHEIC) on 30 January 2020 (1). At the time of writing, the daily incidence of COVID-19 was 7,690,708 confirmed cases, with 427,630 deaths worldwide. Therefore, the identification of risks and protective factors for disease severity from COVID-19 is critical to the direct development of new treatments and infection prevention strategies. Evidence has identified that patients with diabetes, hypertension, obesity, chronic kidney disease, liver disease, immunocompromised disease, hemoglobin disorder, and cardiovascular diseases are more susceptible to COVID-19 infection and worse survival than other populations (2). In addition to such conditions, patients with asthma and allergic respiratory diseases have been proposed as higher risk populations for COVID-19 infection by CDC (3). It is based on the fact that other respiratory viral infections created by influenza and rhinovirus could affect allergic patients and those with chronic respiratory diseases such as asthma more than healthy individuals (4). Studies have shown that patients with asthma have impaired innate immune responses and interferon gamma (IFN-γ) production against respiratory virus-

es compared with non-asthmatics (5). Therefore, these days there are some concerns and issues about allergic patients due to COVID-19 pandemic. However, existing studies have not indicated a high prevalence of asthma among patients with COVID-19 infection (6, 7). It is hypothesized that asthmatic individuals are relatively resistant to COVID-19 infection due to the features of the disease or conventional asthma treatment. The purpose of this work is to discuss how COVID-19 pandemic affect asthmatic and what could be the explanation for the paucity of asthmatic in patients with COVID-19.

Evidence acquisition

A literature search in PubMed databases was separately conducted by two researchers using the following "COVID-19" OR "SARS-CoV-2" OR "Coronavirus" AND "Asthma" OR "Allergy" AND "Case series" OR "Comorbidities" OR "Epidemiology" OR "Hospitalization" OR "Risk factors." to assess how asthma is affected by COVID-19 pandemic and "Eosinophil" and "ACE2" in the English language up to November 2020 and then updated in May 2021. Relevant studies with these keywords were included in this study.

Results

Prevalence of asthma among patients with COVID-19 infection

Some clinical-epidemiological studies have performed to evaluate the risk of serious adverse outcomes in patients with COVID-19 by stratification according to the number and type of comorbidities and identified some sub-populations with poorer prognosis (8-10). A meta-analysis study on 43 studies involving 3600 patients in China has been shown that 12.0% to 67.0% laboratory-confirmed COVID-19 cases have coexisting medical comorbidity (2). In this study the most prevalent comorbidities have noted as hypertension ranged from 0.0% to 48.0% (median 16.0%; 27 studies), diabetes ranged from 0.0% to 50.0% (median 10.1%; 26 studies), cancer ranged from 0.0% to 17.0% (median 1.0%; 15 studies), chronic respiratory/lung diseases ranged from 0.0% to 17.0% (median 2.0%; 16 studies) (2). It was reasonable to anticipate that patients with chronic respiratory diseases would be more susceptible to a more severe viral infection and development of acute respiratory distress syndrome (ARDS) that can complicate SARS-CoV-2 pneumonia. On the contrary, among all the series of COVID-19 (mild or severe presentation alike), except one study conducted in the United States, the prevalence of patients with chronic asthma or with common related diseases such as allergic rhinitis or atopy was low and failed to exceed general population (11). In a US-based study, the prevalence of chronic lung disease (primarily asthma) was 34.6% among 178 hospitalized adult patients with COVID-19 (6). This unexpectedly high reported numbers of chronic lung disease prevalence among patients with COVID-19 may be owing to the small proportion of the hospitalized patients with COVID-19 (approximately 12%) included in this study While, in another study performed in the US, asthma was documented in 12.5% of 393 hospitalized patients with SARS-CoV-2 infection and chronic obstructive pulmonary disease (COPD) in 5.1% (7).

Some studies have tried to compare the clinical outcomes of COVID-19 infection in patients with or without asthma (12, 13). Wang *et al*. performed a meta-analysis based on 4 studies from 744 patients with asthma and 8,151 patients without asthma and reported that asthma had no significant effect on mortality (14). Due to limited data in previous study, Wang *et al*. performed a meta-analysis study based on 14 publications with 17,694 precipitants and found that severe COVID-19 was not associated with an increased risk of asthma compared with non-severe COVID-19 while asthma was not associated with increased risk of mortality in patients with COVID-19 (15). In this context, a recent systematic and meta-analysis review performed by Liu *et al*. has compared the COVID-19 outcomes between patients with and without asthma based on 131 studies. They showed that asthma is not associated with higher COVID-19 severity or worse prognosis, and patients with asthma are found to have a lower risk of death compared with patients without asthma (16). It raises the question of why SARS-CoV-2 is associated with potential for reduced severity of COVID-19 infection in patients with asthma unlike other respiratory viruses such as influenza and rhinovirus that affect both adult (7.6%-46%) and children (8.3%-42%) with asthma (17-19). Recently, some asthma features including reduced angiotensin-converting enzyme 2 (ACE2) gene expressions in airway cells, and eosinophilia have been proposed as protective mechanisms against COVID-19 susceptibility and severity. For future literature review, we aimed to assay protective effects of these mechanisms in the context of COVID-19.

Asthma, COVID-19, and ACE2 expression

ACE2 is an enzyme attached to the cell membranes of cells in the lungs, arteries, heart, kidney, and intestines which processes angiotensin (Ang) I and II into Ang (1-10) and (1-8), respectively. Ang (1-8) peptide has been shown to mediate vasodilatative (hypotension), antiproliferative and apoptotic effects through Mas receptor (20). ACE2 serves as a cellular receptor for some coronaviruses, including HCoV-NL63, SARS-CoV and SARS-CoV-2 (21). More specifically, the binding of the spike S1 protein of viruses to the enzymatic domain of ACE2 on the surface of cells results in endocytosis and translocation of both the virus and the enzyme into endosomes located within cells. This entry process also requires priming of the S protein by the host serine protease TMPRSS2, the inhibition of which is under current investigation as a potential therapeutic (22).

Some studies have tried to investigate the relationship between ACE2 expression as the main host cell receptor and COVID-19 susceptibility in different populations. It has been shown that higher ACE2 expression in some situations such as smoking, diabetes, and hypertension increases *in vitro* susceptibility to SARS-CoV-2 infection, while its down-regulation in children is associated with decreased susceptibility (23, 24). Given the lower risk of COVID-19 among asthmatics, it is hypothesized that it may be due to differential expression of ACE2 in asthma. Therefore, some studies have performed to analyze ACE2 levels in asthmatics compared with non-asthmatics. First study has performed by Jackson *et al.*, it has been shown that respiratory allergy and controlled allergen exposures are associated with significant reductions in ACE2 expression (25). Another study by Song *et al.* has also reported decreased ACE2 gene and protein expression in asthmatics compared to healthy control (26). Evidence has shown that Type-2 inflammation modulates ACE2 expression in airway epithelial cells in asthma. A study reported that IL-13 exposure reduced ACE2 and increased transmembrane serine protease 2 expressions in airway epithelial cells from patients with asthma and atopy (27). In sharp contrast, *in vitro* treatment of airway epithelial cells with IFNs enhanced their ACE2 expression (28). Contrary to previous studies, there are some evidences that show no significant difference for ACE2 mRNA expression between asthmatic patients and healthy controls (29, 30). However, these conflicting results may be due the known heterogeneity in asthma. In a recent study, Camiolo *et al.* has reported that expression of ACE2 among asthmatic patients varies by asthma inflammatory endotypes. They showed that ACE2 gene expression in a subset of type-2 low asthmatics (low blood eosinophil and increased type-1 immunity) is higher than type-2 High asthma (high blood eosinophil and increased type 2 immunity) (31). In addition to type-2 low asthma endotype, increased expression of ACE-2 has been reported in type2-low phenotypes including obesity, smoking, and age associated asthma (32). Using asthma treatments should be also considered as main factor related to ACE-2 level. Low dose, inhaled corticosteroids (ICS) might exert protective effects on asthma patients by reducing airway inflammation, ACE2 and TMPRSS2 expression in SARS-CoV infection (33). However, some studies reported increased airway ACE2 expression in asthmatics on long-term treatment with ICS (27, 34). Other confounding factors such as male sex, African-American ethnicity, and a history of diabetes mellitus or other comorbidities may affect ACE2 expression among asthmatics (33).

In contrast with SARS-CoV-2, conventional coronaviruses and some respiratory viruses especially rhinovirus, which exacerbate asthma upon infection use different entry receptors from ACE2. The reported receptors for conventional coronaviruses are HLA class I molecule, and caveolin-1 for HCoV-OC43; aminopeptidase N (CD13) for HCoV-229E; dipeptidyl peptidase 4 (CD26) for HCoV-EMC; and intercellular adhesion molecule 1 (ICAM-1) for rhinovirus, which expression is high in allergic airways as a marker of allergic inflammation (35). Thus, varied effects on respiratory allergic diseases between SARS-CoV-2 and other respiratory viruses may be due to using different molecular receptors expressed by respiratory epithelial cells.

Asthma, COVID-19, and eosinophils

Eosinophils are special polymorphonuclear leukocytes. They develop in the bone marrow and migrate into blood, making up about 1-6% of white blood cells. The presence of large specific granules including major basic protein, eosinophil peroxidase, and 2 RNAses (eosinophil cationic protein and eosinophil neurotoxin) are characteristic features of these cells. In addition to their pro-inflammatory effects, pieces of evidence have revealed that eosinophils play pleiotropic roles as regulatory cells involved in protective immunity, including antiviral responses and shaping diverse physiological responses, such as organ development and metabolism (36). It has been documented by preclinical studies (mainly in mice) that eosinophils have the main role against respiratory viruses via endosomal Toll-like receptors (TLRs) - including TLR3, TLR7, and TLR9 - eosinophil-derived neurotoxin (EDN/RNAse2) and eosinophil cationic protein (ECP/RNAse3), nitric oxide (NO) production via inducible NO synthase, MHC-I and CD86 up-regulation, and cytokines production, which enable them to recognize, respond and orchestrate effective responses (37). Studies showed that the adoptive transfer of eosinophils from *Aspergillus fumigatus* antigen-sensitized mice into the airways of influenza virus-infected mice decreases viral titers and increases virus-specific $CD8^+$ T cells in comparison to that of animals who did not receive eosinophils (38). Also, human subjects with asthma were treated with the anti-eosinophil drug mepolizumab (an anti–IL-5 humanized mAb) or placebo, and subsequently challenged with rhinovirus; mepolizumab-treated patients demonstrated significant increases in their rhinovirus viral titers in the upper airway, supporting an antiviral role for eosinophils (39).

There is little indication that eosinophils have a protective or exacerbating role during SARS-CoV-2 infection. However, based on some evidences, it seems that eosinophils may play a protective role, and decreased eosinophils levels (eosinopenia) are associated with a poor prognosis in patients with COVID-19 (40). Liu *et al.* reported that more than half the patients admitted with COVID-19 (53%) had eosinopenia (defined as absolute eosinophil counts $< 0.02 \times 10^9$ cells/L) on the day of hospital admission (40). Similarly, medical records of 85 fatal cases of COVID-19 showed that 81% of the patients had absolute eosinophil counts below the normal range (absolute eosinophil counts $< 0.02 \times 10^9$ cells/L) at the time of admission (41). Notably, eosinophils levels improved in all patients

before discharge, suggesting that resolution of eosinopenia may be an indicator of improving clinical status in patients with COVID-19 (40). The exact immune mechanism performed by eosinophils against coronaviruses has remained unknown and most studies are focused on other respiratory viruses such as influenza, rhinovirus, and human orthopneumovirus (RSV) (37). However, some literatures have pointed to TLR7, EDN, ECP, increased MHC-I, and CD86 expression as the potential immune mechanisms used by eosinophils against single strand RNA (ssRNA) viruses like SARS-CoV-2 (42). TLR-7 recognizes ssRNA and its expression is higher in eosinophils compared with neutrophils, suggesting the possible antiviral activity of this cell against ssRNA viruses. TLR-7 stimulation is associated with eosinophil cytokine production, degranulation, superoxide, and NO generation (37). In addition, ECP along with EDN reduce the infectivity of SARS-CoV-2 by a ribonuclease-dependent mechanism (43). Moreover, increased MHC-I and CD86 expression by eosinophils enable them to directly interact with $CD8^+$ T cells and promote the recruitment of virus-specific $CD8^+$ T cells into the lungs to enhance antiviral immunity (38). As approximately 50-70% of asthmatic patients have Th2 high/eosinophilic asthma, eosinophilia may be a reason for reducing COVID-19 susceptibility among these patients. There are limited studies investigated role of eosinophilia in COVID-19 susceptibility and outcomes for asthmatic population. Ferastraoaru *et al.* showed that in asthmatics, pre-existing eosinophilia (AEC ≥ 150 cells/mL) was protective from severe COVID-19 infection, and also development of eosinophilia (AEC ≥ 150 cells/mL) during hospitalization was associated with decreased mortality (44). However, some studies reported that eosinophilia, both in those with and without asthma, may be associated with reduced mortality risk (45, 46).

Discussion

Regarding the pathophysiology of asthma, it seems reasonable to consider asthma as a risk factor for higher susceptibility and severity of COVID-19 infection. Patients with asthma have deficient viral immune responses due to impaired interferon production that predispose them to increase susceptibility to viral infection (47). These patients have also a tendency for severe form of viral respiratory tract infections associated with adverse outcomes (48). Despite the concern that patients with asthma might suffer from severe form of COVID-19 infection, the results of most clinical-epidemiological studies did not indicate asthma as a risk factor for COVID-19 (16, 17). It hypothesized that asthma features including reduced ACE-2 expression, type 2 immune response, eosinophilia, and conventional therapeutics might provide potential protective effects against infection with SARS-CoV-2. In the current study, we reviewed studies that investigated ACE-2 expression and eosinophil in asthma related to COVID-19 infection.

Most studies have reported decreased ACE-2 expression in patients with allergic asthma. However, it should be considered that ACE-2 expression in asthmatic is varied and might be influenced by asthma endotypes (type2-high or type2-low), phenotypes (non-atopic and atopic), treatment, ethnicity and other comorbidities. These mentioned factors may be a reason for reporting different proportion of asthma patients in US and China (7). Therefore, these factors should be considered in studies that investigated ACE2 level and COVID-19 susceptibility among asthmatics.

Eosinophils in the respiratory tract might represent a "double-edged sword" response against some respiratory viruses. Eosinophil promotes antiviral responses against some respiratory viruses through the release of RNAses and reactive nitrogen species, while it dysregulated responses during allergic disease given their increased numbers and/or activation status, ultimately resulting in an exaggerated host response that can lead to host tissue damage (36). In the context of COVID-19, it seems that eosinophil may play a protective role, and eosinopenia has been noted to be a marker of early severe COVID-19 disease, which may result from eosinophils exhaustion, viral inhibition of eosinophils production, or induction of eosinophils apoptosis (44). Like to ACE-2 expression, different asthma endotypes might modify eosinophil counts differently, thereby affecting COVID-19 outcomes. Eosinophilia has reported in type-2 high asthma, while type-2 low asthma has generally characterized with neutrophilic inflammation (49). There is no study that investigated COVID-19 outcomes in varied asthma endotypes regarding eosinophil counts or their metabolites. Future studies are needed to help better distinguishing the impact of different asthma phenotypes and comorbidities on COVID-19 outcomes. In the current work, we have tried to include all important relevant papers (but not necessarily every paper written on the topic). Therefore, some relevant article might be left out due to space limitations.

Conclusions

In summary, it seems that having a Th2-asthma phenotype associated with increases ACE-2 expression and eosinophilia might be an important predictor for reduced COVID-19 morbidity and mortality in asthmatic that need to be more investigated in prospective and mechanistic studies.

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Conflict of interests

The authors declare that they have no conflict of interests.

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