



Atopic endotypes as a modulating factor for SARS-CoV-2 infection: mechanisms and implications

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Purpose of review

Asthma patients are typically at increased risk for severe outcomes from viral respiratory infections. However, asthma and atopy do not appear to be overrepresented comorbidities in COVID-19 patients, and hypotheses attempt to explain this observation. As COVID-19 continues to spread globally, it is imperative to understand how disease outcomes may be influenced in this population to guide patient care.

Recent findings

Angiotensin converting enzyme 2 (ACE2) is the principal host cell receptor for SARS-CoV-2 entry and Transmembrane Protease Serine 2 (TMPRSS2) is the main priming protease. Models have linked atopic endotypes to reductions in ACE2 and increases in TMPRSS2 on respiratory epithelia. Epidemiologic and experimental findings imply alterations in ACE2 expression correlate with clinical COVID-19 disease, but limitations restrict the ability to draw direct conclusions.

Summary

There is reasonable evidence to assert atopic endotypes modulate COVID-19 susceptibility, but it remains premature to classify this association as protective or deleterious. Asthma is a heterogeneous disease and epidemiologic studies should focus on investigating COVID-19 outcomes by underlying endotype. Direct experimental and clinical evidence is needed to draw definitive conclusions on how the complex interplay of ACE2 and TMPRSS2 affect viral entry.

Video abstract:

<https://www.dropbox.com/sh/9sfwqhz2h78sio3/AAB0JYd4MFzM5JjDFcYwz4CXa?dl=0>

Keywords

angiotensin converting enzyme 2, asthma, COVID-19, infectious disease

INTRODUCTION

Asthma and atopy are well-established risk factors for viral respiratory infections and are associated with inferior outcomes compared to healthy populations [1,2]. Atopic asthmatics are more susceptible to clinically severe symptoms from rhinoviruses and respiratory syncytial virus whereas other common pathogens including adenoviruses, enteroviruses, seasonal coronaviruses, and influenzas are associated with clinically significant exacerbations [2–5]. For influenza, fluctuations in seasonal prevalence are associated with hospitalizations for asthma exacerbations [6]. Similarly, asthma was one of the most prevalent risk factors for hospitalization and death during the 2009 H1N1 Influenza Pandemic [7,8]. Although the available evidence indicates asthma and atopy are detrimental for respiratory viral disease outcomes, a newly discovered pathogen veers from this tendency.

Throughout 2020, the world has been confronted with a novel respiratory coronavirus termed SARS-CoV-2, which causes the disease COVID-19. Although many cases have remained mild with symptoms such as fever and shortness of breath predominating, COVID-19 may cause death by pneumonia, acute lung injury, and respiratory

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KEY POINTS

- Asthma patients are typically associated with poorer outcomes from viral respiratory infections compared to the general population; yet, this tendency has not been convincingly demonstrated in the context of SARS-CoV-2.
- Atopic endotypes of asthma reduce ACE2 and increase TMPRSS2 expression on host cells via Th2-mediated inflammatory pathways. Current hypotheses propose the ACE2 reduction in atopic endotypes may decrease SARS-CoV-2 viral entry, thus decreasing the susceptibility to COVID-19 in certain asthmatic populations.
- *In vitro* models suggest downregulation of ACE2 on host cells correlates to a reduction in SARS-CoV-2 entry, and upregulated ACE2 has been associated with the most common comorbid conditions in COVID-19 patients.
- There is limited direct *in vivo* data investigating the clinical correlation of an ACE2 reduction on COVID-19 outcomes, and the potential confounding effect on increased TMPRSS2 expression has not yet been fully examined.
- There is reasonable evidence to assert atopic endotypes are capable of modulating SARS-CoV-2 susceptibility, but a lack of direct analyses precludes us from characterizing this association as protective; further study is needed to describe clinical correlations of ACE2 reductions in the context of COVID-19.

failure in susceptible individuals [9[¶]]. Given the inflated risk asthmatic and atopic patients face with viral infections, it is vital to understand how COVID-19 outcomes are influenced in this population. Intuition would lead us to hypothesize asthma and atopy are significant risk factors for severe COVID-19 outcomes. Yet, this hypothesis proves unclear as conflicting data has led to imprecise risk characterization. In this review, we synthesize the available data behind this discrepancy and provide hypotheses on how atopic endotypes potentially modulate COVID-19 susceptibility.

EPIDEMIOLOGIC EVIDENCE

Multiple epidemiologic studies have examined asthma prevalence among COVID-19 patients with mixed results. Subsequently, asthma has yet to be convincingly shown to increase risk for severe COVID-19 outcomes, whereas other respiratory conditions such as COPD are significantly associated with unfavorable disease outcomes [10[¶],11].

Conflicting studies

Among evidence outlining a possible connection between asthma and COVID-19 susceptibility, one

retrospective study of 177 COVID-19 positive children and young adults found asthma to be the most frequent underlying condition with 20% overall prevalence, although asthma was not more common in those hospitalized or critically ill [12]. Similarly, in a review of 46 patients aged 1 month to 21 years who were hospitalized due to COVID-19, asthma had a 24.4% prevalence but was not associated with worsened outcomes or PICU admission [13]. These results were similar to the adult population as surveillance data from COVID-19 hospitalized adults across 14 states ($n = 178$) found asthma to be a frequent underlying condition with a prevalence of 17%, more than double the 7.7% US adult asthma prevalence [14,15]. Although these data insinuate asthma may be a risk factor for COVID-19 infection and hospitalization, limited cohort sizes restrict the ability to draw generalizable conclusions.

In contrast, broader epidemiologic studies of hospitalized COVID-19 patients found asthma prevalence rates similar to those of the general population [16–18,19^{¶¶},20[¶]]. A literature review conducted by Broadhurst *et al.* [19^{¶¶}] aggregated asthma prevalence rates in hospitalized COVID-19 patients across fifteen independent studies and compared these rates to the asthma prevalence in a corresponding nonhospitalized, COVID-negative population. Only 3 of the 15 investigations recorded an asthma prevalence that was greater in the hospitalized cohort than in the matched population. Of the remaining thirteen studies, the asthma prevalence in COVID-19 hospitalized patients was lower than, or not significantly different than, a corresponding control population. Additionally, Broadhurst *et al.* demonstrated asthmatic COVID-19 patients were no more likely to be intubated than nonasthmatics, but may be intubated for a longer duration [20[¶]]. Once hospitalized, asthmatic patients are not at a significantly increased risk of ICU admission, acute respiratory distress syndrome (ARDS), or death compared to nonasthmatics [20[¶],21^{¶¶}].

To summarize, we can stipulate asthma *may* be associated with increased COVID-19 susceptibility and hospitalizations, but the weight of evidence appears to favor the contrary; there is no definitive argument demonstrating poorer COVID-19 outcomes in asthmatic vs. nonasthmatic patients. Although not definitive, this observation remains significant when viewed in the context of other viral respiratory illnesses.

Epidemiologic gaps

Asthma is a heterogeneous disease, yet none of the highly cited sources above made the distinction

between subtypes, such as atopic or nonatopic asthma, which may potentially confound results as different asthma types may confer varying COVID-19 risk. Zhu *et al.* made this distinction by demonstrating 'asthma' as a general category was associated with poorer COVID-19 outcomes in their patient cohort, but when stratified by atopic or nonatopic, there was no significant risk in atopic patients whereas the nonatopic cohort remained associated with poorer outcomes [22]. Similarly, in asthmatic COVID-19 patients, a history of allergic rhinitis trended toward a protective association for hospitalizations (OR 0.77; 95% CI 0.59–1.01) [23[¶]]. These findings imply investigations should stratify by endotypes within asthma to elucidate possible mechanisms for modification of COVID-19 risk.

CLASSIFICATION OF ATOPIC ENDOTYPES

By recognizing asthma as a heterogeneous disease, we can investigate underlying mechanisms to further clarify our epidemiologic observations. The term 'asthma' refers to a recurrent, often reversible, inflammatory process of the airways that causes variable pulmonary obstruction, and is clinically characterized by bronchial hyperresponsiveness, wheezing, and chest tightness [24,25]. Within this definition, asthma may be classified by its observable presentations, known as phenotypes, and by its underlying molecular mechanisms, known as endotypes [24,26,27]. Common phenotypes include atopic and nonatopic and eosinophilic vs. noneosinophilic asthma, which are subsequently classified into T2-high and non-T2 (T2 low or T1) endotypes, respectively (Fig. 1) [24,26,27,28[¶]]. Subsets of CD4⁺ T-cell mediators define asthma endotypes, and the T2-high and non-T2 endotypes describe the underlying pathophysiology as it relates to the extent of Th2-mediated inflammation [24,26,27].

Atopic asthma is categorized as a T2-high endotype [25,27,29]. Detailed molecular pathways have been described by Kuruvilla *et al.* and Woodruff *et al.* (Fig. 2) [24,27]. Briefly, dysregulated airway epithelial cells respond to allergic or nonallergic (smoke, virus, irritant) stimuli by releasing alarmins that activate mast cells, eosinophils, innate lymphoid cells (ILC2s), and induce differentiation of Th2 cells. ILC2s and Th2 cells produce IL-4, IL-5, and IL-13 which propagate inflammation and IgE production. IL-13 is a key cytokine and its downstream effector genes, such as *POSTN*, *CLCA1*, and *SERPINE2*, correlate with Th2 inflammation and define the T2-high endotype [27,30]. In contrast, the non-T2 endotype pathophysiologic mechanisms remain unclear, although inflammation appears to be associated with Th1 and Th17 CD4⁺⁺ cells and

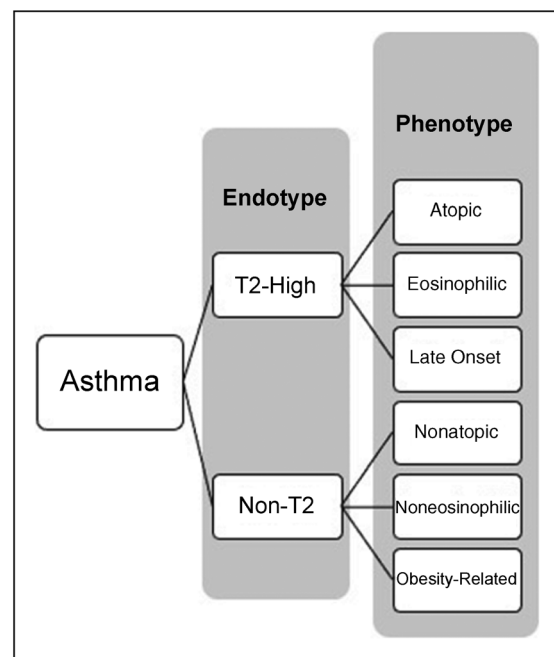


FIGURE 1. Classification of Select Asthma Phenotypes into Endotypes. Each endotype represents a distinct underlying molecular mechanism whereas phenotypes represent observable clinical characteristics. T2-high endotypes are mediated mainly by Th2-driven inflammation whereas non-T2 endotypes are thought to be driven by Th1 and Th17 CD4⁺ mediators.

neutrophilia [31]. The non-T2 endotype is classified by a lack of T2-high biomarkers such as IL-13, eosinophilia, and IgE [24,31].

Approximately 50% of asthmatics and 37% of severe asthmatics have the T2-high endotype [27,32]. Despite this heterogeneity, the discussed COVID-19 epidemiologic studies did not establish this distinction, making it unclear if certain asthmatic endotypes were disproportionally represented, possibly distorting findings such as prevalence and morbidity [29]. In conjunction with the findings from Zhu *et al.*, who implied COVID-19 outcomes vary by asthma presentation, focus should be placed on specific pathophysiologic mechanisms to gain insight toward possible infection modifying effects.

SARS-CoV-2 ENTRY AND THE HOMEOSTATIC ROLE OF ANGIOTENSIN CONVERTING ENZYME 2

To understand the potential role of atopic endotypes on COVID-19 susceptibility, it is necessary to appreciate the relationship between SARS-CoV-2 and its host cell receptor, angiotensin converting enzyme 2 (ACE2). SARS-CoV-2 initially infects the

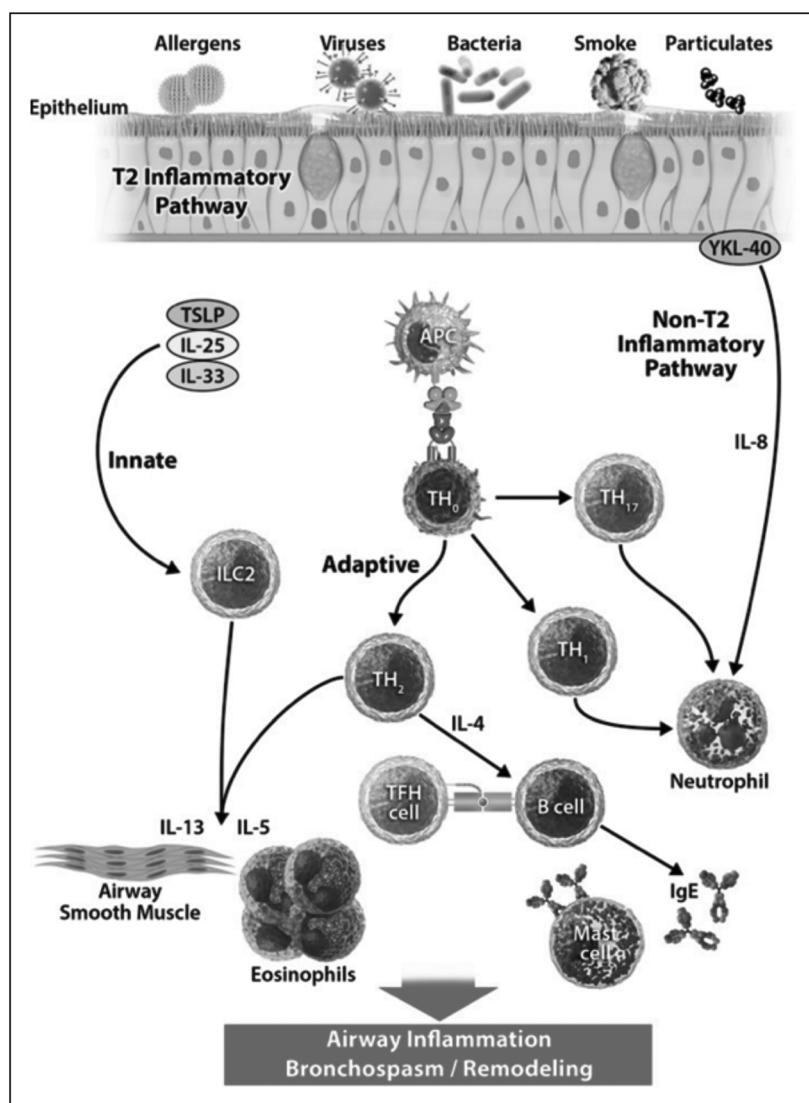


FIGURE 2. Overview of T2 and Non-T2 Endotype Pathways in Asthma. T2 endotypes result in release of Th2 cytokines IL-4, IL-5, and IL-13 to drive inflammatory changes. Non-T2 endotypes are mediated by Th1 and Th17 cells and culminate in neutrophil-predominated inflammatory changes. Reprinted from *The Journal of Allergy and Clinical Immunology*, Vol 144, Issue 1, Ravdeep Kaur and Geoffrey Chupp, Phenotypes and endotypes of adult asthma: Moving toward precision medicine, Pages 1–12, 2019, with permission from Elsevier.

epithelial mucus membranes of the upper or lower respiratory tract, particularly type II pneumocytes [33,34]. Entry occurs when the SARS-CoV-2 spike (S) protein is primed by host cell protease TMRSS2 and subsequently binds to ACE2, the principal receptor for infection [35^{*}]. Ensuing symptoms typically involve fever and shortness of breath, but may progress to pneumonia and viremia, leading to potential infection of other ACE2-expressing organs such as the GI tract and heart [34,36^{*}].

ACE2 plays a significant physiologic role as a negative regulator of the renin-angiotensin-aldosterone system (RAAS), whereas TMRSS2 is not required for homeostasis [37]. In the RAAS, renin is released

from juxtaglomerular cells and cleaves circulating angiotensinogen into angiotensin I (Ang I). Ang I is then cleaved by ACE to form angiotensin II (Ang II). Ang II is pro-inflammatory and pro-fibrotic, inducing vasoconstriction and sodium reabsorption [38]. ACE2 regulates RAAS by hydrolyzing Ang II into Ang (1–7) which counteracts Ang II by serving as a vasodilatory, anti-inflammatory mediator [39]. ACE2 is widely distributed throughout the body including in the alveoli, bronchi, endothelial cells, nasal mucosa, GI tract, and kidneys [40,41]. As a result, further investigations on the role ACE2 may lend insight into SARS-CoV-2 susceptibility and risk modulation.

ATOPIC ENDOTYPES MODULATE ACE2 EXPRESSION

The hypothesis that asthma and atopy may modulate SARS-CoV-2 entry via changes in ACE2 was first explored by Jackson *et al.* [42²²]. Investigators sequenced respiratory epithelial RNA from participants with varying presentations of asthma and allergic disease for evidence of ACE2 gene expression. Their findings demonstrated IgE sensitization and other T2 biomarkers, such as IL-13, were negative predictors of ACE2 expression in nasal epithelial samples, independent of asthma phenotype or status. These findings indicate allergy and underlying T2 molecular endotypes, rather than asthma in general, are the impetus for observed reductions in ACE2. This interpretation was further supported when participants with allergic rhinitis or allergic asthma were exposed to allergen provocation; postexposure samples produced significant reductions in ACE2 expression in respiratory epithelia, suggesting acute increases in T2 inflammatory mediators facilitate the observed decrease. Here, Jackson *et al.* has demonstrated that atopy, likely via a Th2 mechanism, may be a key driver in host cell ACE2 reductions. However, before drawing further assumptions, it is necessary to elucidate mechanisms of these findings and determine if other effector enzymes, such as TMPRSS2, are concurrently affected.

Kimura *et al.* built upon these findings by more precisely characterizing T2 endotypes as the modulating mechanism and by demonstrating concomitant changes in TMPRSS2 expression [43²²]. Investigators accomplished this by demonstrating IL-13 directly reduces ACE2 and increases TMPRSS2 expression in airway epithelial cells from atopic patients *ex vivo*, independent of asthma status. This result corroborates Jackson *et al.* who found atopy and T2 biomarkers were predictors of ACE2 reduction, rather than asthma, although also identifying IL-13 as a precise mediator [42²²]. Additionally, the authors categorized participants with asthma and/or allergic rhinitis into T2-low and T2-high endotypes by utilizing specific gene markers *CLCA1*, *POSTN*, and *SERPINE1* [27]. The T2-high endotype had significantly reduced ACE2 and increased TMPRSS2 expression compared to both a healthy control and the T2-low endotype, which had ACE2 and TMPRSS2 levels that did not differ from each other. These findings provide the most direct evidence that T2-high endotypes are uniquely capable of modulating the SARS-CoV-2 entry receptors, albeit in opposing directions. The clinical correlation of this potential link between atopy, inflammation, and COVID-19 has yet to be precisely determined, but these investigations provide a strong incentive for further studying the impact

of atopy on them mechanisms of COVID-19 infection.

The role of other Th2-mediated cytokines in downregulating ACE2 expression is less clear. Kimura *et al.* were unable to definitively correlate IL-4 and IL-5 with ACE2 reductions in their data set, although previous studies indicated IL-4 can decrease ACE2 in certain cell lines [43²²,44]. Accordingly, there has been clinical interest into whether asthmatic patients should continue certain biologic therapies, namely dupilumab that targets IL-4 and IL-13. Currently, there is no clinical evidence demonstrating poorer outcomes in asthmatic patients who take these medications, and the American Academy of Allergy, Asthma, and Immunology does not recommend individuals stop taking biologic medications during the COVID-19 pandemic, including anti-IL-4 alpha (dupilumab), anti-IL5/IL-5R (mepolizumab, reslizumab, benralizumab), and anti-IgE (omalizumab) treatments [45²,46].

DO CHANGES IN ANGIOTENSIN CONVERTING ENZYME 2 AND TMPRSS2 CORRELATE WITH COVID-19 OUTCOMES?

The clinical correlate between changes in host receptor expression and COVID-19 pathogenesis remains obscure. In the absence of *in vivo* data, we utilize observational and experimental evidence to discuss how the complex modulation of ACE2 and TMPRSS2 by T2-high endotypes may shape COVID-19 outcomes.

Comorbid correlations

Multiple well-characterized COVID-19 comorbidities are associated with increased ACE2 expression [34]. Diabetes, hypertension, and cardiovascular disease represent the most prevalent risk factors for severe COVID-19, and each is associated with upregulated ACE2 [47–53]. Elderly individuals are also disproportionately afflicted with severe COVID-19, and advanced age is positively correlated with ACE2 expression in the nasal epithelium [54]. Other well-linked COVID-19 comorbidities including obesity and male gender have been associated with both critical illness and increased ACE2 expression [53,55–57]. Of particular interest, COPD, a chronic respiratory disease that is an established risk factor, and smoking are associated with upregulated ACE2 in the lungs [58,59²,60²]. In addition to viral entry, SARS-CoV-2 uses ACE2 on platelets to induce a prothrombotic state, which has been intimately linked with mortality; although, it is unclear if ACE2 is upregulated on platelets in the discussed comorbidities [61]. It is important to recognize this

circumstantial evidence does not prove causality between ACE2 and increased risk; rather, it demonstrates a possible mechanism by which these patients may face increased COVID-19 susceptibility. As these comorbidities commonly present concurrently, further investigations are needed to independently assess pathways leading to inferior clinical outcomes.

Experimental evidence

ACE2 has been largely established as the functional receptor for SARS-CoV-2 entry [34,62]. In accordance with our observation that T2-high endotypes decrease *ACE2* gene expression, *in vitro* models indicate a negative correlation between SARS-CoV-2 host cell entry and graded inhibition of ACE2 receptors [35[■]]. Additionally, a complete absence of ACE2 results in no detectable SARS-CoV-2 mRNA in *in vitro* models [62]. Whether these findings correlate to reduction of COVID-19 clinical symptoms has yet to be determined; but, analyses of SARS-CoV, the virus causing the 2003 SARS outbreak, may lend insight. Both SARS-CoV and SARS-CoV-2 use ACE2 as their functional receptor and infect respiratory epithelia [35[■]]. *In vivo* models found ACE2 expression correlates with clinical SARS disease, and the affinity of the SARS-CoV spike protein for ACE2 positively correlates with viral entry [63,64]. Notably, the spike protein on SARS-CoV-2 has an affinity for ACE2 that is 10–20 times greater than on SARS-CoV [35[■],65]. Taken in conjunction, it is reasonable to hypothesize decreases in ACE2, via T2-high mechanisms, may correlate with decreased viral entry and clinical disease, although it is imperative to examine these findings in context; decreases in ACE2 may affect other homeostatic functions and T2-high endotypes modulate multiple pathways, including TMPRSS2.

Although the majority of data have focused on modulation of ACE2, the role of TMPRSS2 deserves mention. TMPRSS2 is not the sole protease able to promote SARS-CoV-2 entry, as infection can occur with priming by cysteine proteases cathepsin B and L in the lungs [35[■]]. However, in a cell line with constant ACE2 expression, the presence of TMPRSS2 results in a 10-fold increase in SARS-CoV-2 viral load *in vitro*, compared to cells without the protease [66]. Given the significant increase in *TMPRSS2* gene expression caused by T2-high endotypes, it is plausible to contend this increase may negate the corresponding decrease in *ACE2* expression. Yet, the weight of evidence appears to favor ACE2 as the necessary receptor for viral entry, and further investigations are needed to determine if the decrease in ACE2 can be overcome by a concomitant increase in TMPRSS2.

EFFECT OF GLUCOCORTICOIDS

The potential influence of glucocorticoids must be considered as they are prescribed in approximately half of asthmatics [67[■]]. Glucocorticoids have been demonstrated to reduce ACE2 expression in airway epithelia [68,69[■]]. These observations spur hypotheses on whether prophylactic treatment with glucocorticoids may lend protection to SARS-CoV-2 entry, an advantage that would be conferred to asthmatics utilizing this treatment. Currently, there are no investigations stating whether previous or continued glucocorticoids are advantageous for COVID-19 outcomes [70]. Preliminary evidence found glucocorticoids may improve outcomes by inhibiting SARS-CoV-2 RNA replication and are effective at preventing replication of coronavirus HCoV-229E [71[■],72]. Glucocorticoids have also been shown to reduce mortality in patients with severe COVID-19 and are currently recommended for treatment in this population [73[■],74]. In contrast, the immunosuppression initiated by glucocorticoids may increase susceptibility to upper respiratory viral infections and reduce innate responses [70]. Additionally, the reduction in Th2 inflammation conferred by glucocorticoids may theoretically inhibit the T2-high mechanism responsible for ACE2 decreases in this population [24]. Epidemiologic and experimental studies are needed to examine these factors and allow for more precise patient counseling.

LIMITATIONS

The complex connection between asthma, atopy, entry receptors, and COVID-19 lends itself to limitations when drawing conclusions. Secondary consequences from the loss of ACE2 merits attention. Dysregulation of the ACE/ACE2 balance may have deleterious effects such as increasing ARDS susceptibility and has been implicated in cardiometabolic disorders [34,75]. Theoretically, the loss of ACE2 may also promote chronic fibrosis as sequelae after COVID-19 recovery [76]. Further investigation is needed to examine the downstream consequences an ACE2 reduction may have on homeostasis. Additionally, some assert the hypothesized link between ACE2 and infection modulation is premature given uncertainties in ACE2 polymorphisms and differential expression of the enzyme [77]. Recent evidence implies other cellular receptors such as CD147 and CD26 may play a role in SARS-CoV-2 entry, and investigations are needed to clinically evaluate these effects [78]. Moreover, drawing conclusions from epidemiologic studies is challenging because many of these studies failed to control for certain risk factors, and countries such as China may underestimate asthma prevalence within their population

[79]. As such, it is difficult to determine if the prevalence of asthma and/or atopy has been confounded by commonly occurring comorbidities such as obesity and smoking.

CONCLUSION

Here, we summarize the current knowledge linking atopic endotypes to COVID-19 outcomes and evaluate if this population may have a protective predisposition. Asthma is an underrepresented risk factor for severe COVID-19, even though asthmatics are generally more susceptible to viral respiratory illness. This disconnect led to hypotheses asserting atopy and T2-high mechanisms reduce ACE2 and thus is a possible reason for these observations. Epidemiologic and experimental data provide further support for the association between altered ACE2 expression and varying COVID-19 outcomes, but limitations prevent definitive judgments about protection. Given the current strength of evidence, we can theorize with reasonable confidence that atopic endotypes are capable of *modulating* COVID-19 susceptibility, although it is much too early to declare this effect *protective*. At the least, we can infer atopic asthmatics, given no other comorbidities, possess no significant COVID-19 risk differences compared to the general population. The complex interplay between ACE2, TMPRSS2, and their effects on disease progression present gaps in the knowledge. A dearth of direct clinical and epidemiologic evidence further prevents drawing correlations and should be the focus of future investigations. Our goal is to encourage deeper study of COVID-19 risk and how these associations may translate to patient care.

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Conflicts of interest

Dr Bernstein is a consultant and PI for Akari Pharmaceuticals currently investigating nomacopan in COVID patients exhibiting in hospital acute respiratory decline.

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