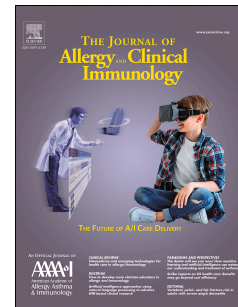


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Asthma-associated risk for COVID-19 development

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Key Words: SARS-CoV-2, COVID 19, asthma, endotypes, type 2 asthma, non-type 2 asthma

42

43 **Abbreviations**

ACE-2	Angiotensin Converting Enzyme-2
ICS	Inhaled corticosteroids
TMPRSS2	transmembrane proteases serine 2
Th2	T helper 2
TLR-7/MyD88	Toll-like receptor-7
RSV	respiratory syncytial virus
pDCs	plasmacytoid dendritic cells
1RF- α ,	Ras-binding domain of c-raf-1
MIP1- α	Macrophage inflammatory protein-1a
NFAT pathways	Nuclear factor of activated T cells
EDN	eosinophil-derived neurotoxin
HI	Heterologous immunity

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Abstract

The newly described severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) is responsible for a pandemic (Corona virus-induced disease -19, COVID-19). It is now well established that certain comorbidities define high risk patients. They include hypertension, diabetes, and coronary artery disease. In contrast, the context with bronchial asthma is controversial and shows marked regional differences. Since asthma is the most prevalent chronic inflammatory lung disease worldwide and SARS-CoV-2 primarily affects the upper and lower airways leading to marked inflammation, the question arises about the possible clinical and pathophysiological association between asthma and SARS-CoV-2/COVID-19. Here we analyze the global epidemiology of asthma among COVID-19 patients and propose the concept that patients suffering from different asthma endotypes (type 2 asthma versus non-type 2 asthma) present with a different risk profile in terms of SARS-CoV-2 infection, development of COVID-19 and progression to severe COVID-19 outcomes. This concept may have important implications for future COVID-19 diagnostics and immune-based therapy developments.

Global Epidemiology

The susceptibility of asthma patients to COVID-19

First epidemiologic studies of the COVID-19 pandemic in China included 72,314 case records, 44,672 were classified as confirmed cases of COVID-19 (diagnosis based on positive viral nucleic acid test result on throat swab samples) and did not identify asthma as a risk factor of severe COVID-19¹. 548 Patients with COVID-19 admitted to Tongji Hospital were retrospectively analyzed and 5 patients of 548 had asthma (0.9%)². Zhongnan Hospital of Wuhan University retrospectively analyzed 140 hospitalized COVID-19 patients and also concluded that allergic disease or asthma are not risk factors for SARS-CoV-2 infection³. After 3 months they had analyzed 290 hospitalized COVID-19 patients and identified only 1 patient with asthma⁴. A retrospective study of 191 patients with COVID-19 (135 from Jinyintan Hospital and 56 from Wuhan Pulmonary Hospital) didn't report on asthma among comorbidities⁵. The prevalence of asthma in the adult population of Wuhan is 6.4%. The prevalence of asthma among COVID-19 patients was subsequently reported in several other countries and regions. Studies from Russia, Saudi Arabia, and Brazil confirmed the lower rates of asthma among COVID-19 patients (1.8%, 2.7% and 1.5% respectively)⁶⁻⁸. The prevalence of asthma among COVID-19 patients in Mexico (3.6%)⁹, which like Brazil is also in Latin America, was relatively high

88 compared to Brazil. Asthma was not mentioned among the comorbidity list of
89 COVID-19 in a retrospective Indian epidemiological study ¹⁰. In Europe, the
90 prevalence of asthma varied from country to country with Swedish and Italian
91 cohort studies reporting relatively low rates of asthma, 1.8% and 2.6%, (Sweden)
92 and 1.96% and 1.92% (Italy) ^{11,12} (Tab. S1). Another retrospective case series
93 of 1591 patients hospitalized with laboratory-confirmed COVID-19 in the
94 Lombardy region of Italy did not mention patients with asthma ¹³. However, the
95 prevalence of asthma among COVID-19 patients was higher in Spain, Catalonia
96 and Ireland (5.2%, 6.8% and 8.8%, respectively) ¹⁴⁻¹⁶. The prevalence of asthma
97 in the general population in Italy, Spain and Ireland is 6.0%, 5.0%, and 7.0%,
98 respectively ^{12,17,18} (Fig. 1A and 1B).

99
100 On the other hand, recent studies from the USA and UK indicated high rates of
101 asthma in COVID-19 patients. The prevalence of asthma among patients with
102 COVID-19 was 14.4% versus the national asthma prevalence of 8-9% in the
103 USA. Asthma and inhaled corticosteroids were not associated with risk of
104 hospitalization due to COVID-19 ¹⁹. A huge retrospective study included 11 acute
105 care hospitals of a public hospital system and described demographic and
106 clinical characteristics and outcomes of patients tested for COVID-19. Of the
107 22,254 patients who were tested, 13,442 patients tested positive, 6,248 required
108 hospitalization, and 1,724 died. Asthma prevalence rate was 7% among positive
109 patients and 11 % among negative patients ²⁰. A case series of 5,700 patients

with confirmed COVID-19 in the New York City area provides characteristics of hospitalized patients, asthma prevalence was determined as 9%²¹. The ISARIC study based on 16,749 patients with COVID-19 in the UK reported about 14% of asthma prevalence²². A population-based prospective cohort study analyzed data from the UK Biobank and reported about 17.9% prevalence of asthma in COVID-19 patients²³. Another study which analyzed UK Biobank data reported an asthma rate of about 13% and added that adults with asthma had a higher risk of severe COVID-19²⁴. An Australian pediatric study retrospectively included all pediatric patients (aged 0–18 years) who presented to the Emergency Department or the newly established Respiratory Infection Clinic who tested for SARS-CoV-2 from the day of the first positive confirmed case. One in 4 COVID-19 positive patients had a comorbidity, which was asthma (1/4, 25%)²⁵. In the group of SARS-negative subjects, asthma was the most common comorbidity with a prevalence of 11%²⁵. The “usual” prevalence of asthma among young Australians aged 0–17 is 10.3% in 2017–2018²⁶.

Overall, in most countries around the world, asthma patients were not reported with higher rates of COVID-19 infection compared with the general population in the corresponding area. There is a big difference of the incidence of COVID-19 in asthma patients among different areas and countries with some of them reporting low rates of COVID-19 with asthma, probably due to the multiple factors including the rigorous self-protection awareness and low proportion of

non-type 2 phenotypes.

Severity of COVID-19 in patients with asthma

Except for the susceptibility of asthma patients to COVID-19, another important issue is whether there is a shift in severity and mortality among COVID-19 patients with asthma compared to those without. Among the 548 COVID-19 patients admitted to Tongji Hospital, there were 5 asthmatics, including 2 of 279 with non-severe asthma (0.7%) and 3 of 269 with severe asthma (1.1%). There was no significant difference in asthma prevalence between severe and non-severe COVID-19 patients². Saudi Arabia reported that the prevalence of asthma was 3 (2.9%), 0 (0%), and 1 (7.7%) in mild, moderate, and severe COVID-19 patients, respectively⁷. In the Brazilian retrospective study including 51770 COVID-19 cases, the prevalence of “moderate to severe asthma” is 1.5%⁸. Asthma was identified in 5.2% of COVID-19 patients in a Spanish study, with a lower prevalence rate of 3.7% in fatal cases and 5.5% in live discharge case¹⁴. An Italian study of 355 lethal patients’ cases with COVID-19 reported that comorbidities were associated with an increased mortality risk, but asthma was not mentioned on the list of comorbidities²⁷. A study conducted in Switzerland included 200 COVID-19 patients hospitalized in the Lausanne University Hospital and reported 4.0% asthma prevalence, 1/37 (2.7%) asthma prevalence among those patients who required mechanical ventilation and 7/163 (4.3%)

asthma prevalence among those patients who did not require mechanical ventilation²⁸. Wil Lieberman-Cribbin et al. describe results from the Mount Sinai Health System and found that there was no statistically significant association between asthma status and mortality among patients with COVID-19²⁹. Therefore, we provisionally conclude that asthma is not associated with a higher risk of mortality among COVID-19 patients who have a history of asthma. So far, there is no clear evidence that patients with asthma are more likely to be infected with SARS-CoV-2 or to become severely ill.

The phenotype of asthma patients with COVID-19

Although there is yet little information about asthma phenotypes in COVID-19 patients, we may speculate asthma patients with different phenotype hold various susceptibility and severity of COVID-19. The study by the UK Biobank reported that adults with asthma had a higher risk of severe COVID-19, which was driven by the increased risk in patients with non-allergic asthma²⁴. By contrast, the risk of severe COVID-19 was not significantly elevated in patients with allergic asthma.

Potential lower risk of type 2 asthmatics to develop COVID-19

Type 2 asthma is characterized by Th2-driven airway inflammation with increased levels of IL-4, IL-5, and IL-13 production, blood and airway eosinophilia and (in the case of allergic asthma) increased levels of total and allergen-specific IgE antibodies associated with mast cell activation. Lymphopenia, particularly due to the reduction of T-cells, is a well established marker for COVID-19 severity, and as asthmatic COVID-19 patients have increased numbers and activation level T-cells and show a less severe course of the disease, it is suggested that both CD4⁺ and CD8⁺ T-cells reduce the destructive power of SARS-CoV-2³⁰. ACE-2 serves as a major receptor for SARS-CoV-2 to enter host cells via its structural spike glycoprotein (Fig. 2). ACE-2 is predominantly expressed on nasal epithelium, lung, heart, kidney, and intestine, but is rarely expressed on immune cells^{31,32}. Markedly reduced levels of ACE-2 transcripts have been detected in nasal and bronchial epithelial cells of allergy sufferers, and this is associated with allergen exposure, allergen sensitization, and high IgE levels³³, with lowest levels among patients with both high levels of allergic sensitization and asthma. Conversely, non-atopic asthma was not associated with reduced ACE-2 expression³³. This is observed in both asthmatic children and adults. However, data on the protein level are still lacking³³. Furthermore, ACE-2 gene expression levels correlate inversely with type 2 biomarkers^{34,35} and a functional contribution of these cytokines is indicated

since IL-13 reduces ACE-2 gene expression in both the nasal and bronchial epithelium³³. In addition, inhaled corticosteroids (ICS), the first line anti-inflammatory drug in type 2 asthma, also lowers ACE-2 gene expression in sputum³⁶.

On the other hand, there is an increasing amount of data providing evidence that inhaled corticosteroids (ICS) is associated with reduction on ACE2 and TMPRSS2 gene expression³⁶. This presumably occurs by a mechanism independent of any ICS-mediated suppression of Th2 inflammation. Additionally there is evidence to support that taking ICS may be beneficial in dealing Corona virus infections, based on in-vitro studies with Corona virus application and cytokine production as an outcome³⁷.

Host transmembrane proteases serine 2 (TMPRSS2) cleaves a viral spike protein and facilitates virus fusion to the cellular membrane^{38,39}. In contrast to ACE-2, TMPRSS2 gene expression is upregulated under Th2 conditions⁴⁰. However, there are very few cells co-expressing ACE-2 and TMPRSS2 simultaneously. Therefore, it is questionable whether this increased TMPRSS2 expression favors SARS-CoV-2 infection in asthmatic allergic patients⁴⁰.

Blood eosinophilia is an established biomarker for type 2 inflammation^{41,42} and eosinophils have important antiviral properties. This includes single-stranded

RNA activating eosinophils via TLR-7/MyD88 dependent mechanisms ⁴³, and eosinophil-derived neurotoxin (EDN) which serves as a ribonuclease ⁴⁴. Conversely, eosinopenia has been observed in severe COVID-19 patients, and blood counts normalize following lopinavir treatment suggesting that they may serve as a marker for improvement ^{3,45,46}. In a Russian retrospective study, absolute blood eosinophil counts were below $0.02 \times 10^9/L$ in 85.7% of asthmatic patients, and no patient showed blood eosinophilia ⁶.

Infections with respiratory viruses including rhinovirus, respiratory syncytial virus (RSV) and influenza virus are major triggers for asthma exacerbation, particularly in children ⁴⁷⁻⁵⁰. Moreover, asthma has consistently been one of the most frequent comorbidities among patients hospitalized due to influenza. In contrast, this is not always the case for SARS-CoV-2. We hypothesize that the main reason for this is a high prevalence of type 2 airway signatures, even in non-atopic children ⁴⁰. This could be a major reason why the prevalence of COVID-19 is relatively low in this age group, particularly since allergic, eosinophilic asthma is the major asthma endotype among young asthmatics. Mast cells also contribute to combat viral infections and, in particular, SARS-CoV-2, since they are a major source of interferon ^{51,52}.

Potential role of allergen-induced cross-reactive T cell responses to SARS-CoV-2 among asthmatics

T cell responses against SARS-CoV-2 are first detectable approximately one week following symptom onset and remain in convalescence, while numbers of virus-specific T cells correlate with neutralization antibody titers⁵³. Patients who recovered from SARS-CoV infection developed long-lived virus-specific T memory cells, detectable up to 2 years following infection resolution^{54,55}.

Heterologous immunity (HI) has been originally described as a consequence of previous infections, which alter the immune response to a subsequent infection with a different pathogen⁵⁶. This mechanism may occur between closely related or completely unrelated antigens. HI may ultimately alter the outcome of infections due to cross-reactive recognition and immune protection or due to induction of immunopathology⁵⁷. Cellular-mediated HI may be elicited by means of T cell receptor (TCR) cross-reactivity, recognizing similar but distinct antigens or by cytokine-induced non-specific activation of T cells⁵⁸.

We have previously reported on influenza-induced heterologous immune responses against allergens, which mediated protection from experimental allergic asthma⁵⁹. We recently hypothesized that SARS-CoV-2 may show protein sequence homology to allergens, which may generate cross-reactive T

cell epitopes. We thus applied two independent but complementary bioinformatic approaches in order to identify potentially cross-reactive allergen- and SARS-CoV-2- T cell epitopes. Our *in silico* analysis revealed numerous candidate epitope pairs, including previously published as well as predicted peptides, and highlighted an important role of MHC Class I aero-allergens in this regard (Balz K et al submitted) (Fig. 2). In hosts, who are sensitized to one of the predicted allergens, the identified similarities with the SARS-CoV-2 proteome may be protective or harmful. Allergen-specific T cells may develop a memory-type of response against heterologous SARS-CoV-2 epitopes, which is by definition faster and more efficient. Quite recently, the role of SARS-CoV-2-specific T cells in exposed and non-exposed individuals, has been discussed, which further underlines the potential importance of HI in COVID-19 outcome^{60,61}. Specifically, it was suggested that cross-reactive CD4+ T cells in some populations may be recruited into an amplified primary SARS-CoV-2 specific response. Therefore, allergic asthmatics may carry potential SARS-CoV-2 cross-reactive T-cells in their T-cell repertoire, if they are sensitized to the respective cross-reactive allergens. This would provide a significant advantage of allergic-asthmatics over other asthmatic patients in combating SARS-CoV-2 infections. Further experimental studies are underway to provide supporting functional data and confirm this concept.

Progression of COVID-19 in type-2 asthmatic patients

We hypothesize that if the SARS-CoV-2 virus succeeds to establish clinical manifestations in allergic asthmatics, the risk for disease progression is higher as compared to non-allergic asthmatic COVID19 patients. This may occur because of several reasons: (i) Th2 inflammation counteracts Th1 immunity and limits the production of pro-inflammatory cytokines (e.g. IL-1 β , TNF- α , IL-6, IL-12) which are required to combat viral infections, (ii) an impaired production of type I and type III interferons (interferon- α , - β , - λ) by airway epithelial cells has been described in asthmatic patients in response to viral infections^{62–65}; (iii) plasmacytoid dendritic cells (pDCs) represent the primary source of IFN- α to defend against viral infections and IgE negatively regulates IFN- α production through inhibition of TLR signaling in these cells^{66–69}.

COVID-19 in non-type 2 asthma patients

There is circumstantial evidence that patients suffering from non-type 2 asthma are at higher risk for progression to severe COVID-19. Non-type 2 is defined as asthmatics with other inflammatory profile such as Th1 or Th17 dominated inflammation including COPD-asthmatics. A recently published nationwide South-Korean study reported that among asthmatics, particularly non-allergic asthmatics confer a greater risk of susceptibility to SARS CoV-2 infection and

severe clinical outcomes of COVID-19⁷⁰. Elderly asthmatics are at higher risk for morbidity and mortality than younger asthmatics. In many of these individuals, the inflammatory response is non-type 2 mediated⁷¹, and the inflammatory endotype is dominated by type 1 and/or type 17 T-cell responses. A molecular phenotype is characterized by inflammasome-associated and metabolic/mitochondrial pathways⁷². Many of these asthmatics suffer from comorbidities including obesity type 2 diabetes and hypertension as part of the metabolic syndrome⁷³. This endotype is particularly prevalent in inner-city adults⁷⁴, and among African Americans⁷⁵.

CD147 activation suppresses several T-cell functions through the inhibition of NFAT pathways^{76,77}. CD147 expression correlates positively with BMI in COVID-19 patients, and is also upregulated by high glucose concentrations⁷⁸. IL-6 serves as a biomarker for systemic inflammation and metabolic dysfunction as well as for severity in these asthmatics⁷⁹. This subset of asthmatics may be particularly susceptible to develop severe COVID-19 disease. It is striking that increased cytokine levels with particularly high levels of IL-6 are characteristic for severe COVID-19 patients as well⁸⁰. It is well established that COVID-19 patients with these comorbidities are at higher risk for severity and mortality⁸¹. The increased expression of ACE-2 detected in subgroups³³ with type 2 diabetes, COPD, African Americans, smokers, and males³⁶ further contributes to this^{36,82}. This may be regulated through IL-17 and supported because of the

positive correlation between ACE-2 expression and Th17 gene signatures³⁴.

The latter are more frequent among females and based on known age- and gender-induced influences on immune responses, it is likely that such skewing could also take place independently of the presence of asthma.

In contrast to allergic asthmatics, asthma patients with this endotype have low number of blood eosinophils³⁴ and therefore lack the contribution of these effector cells in anti-SARS-CoV-2 defense. CD147, also termed basigin, acts as a receptor for SARS-CoV-2 in T-cells and epithelial cells, and humanized anti-CD147 antibody treatment has been shown to reduce inflammation and to improve severe COVID-19 patients⁸³⁻⁸⁵.

Conclusion

This model may provide a comprehensive explanation for regional differences in asthma prevalence among COVID-19 patients in North America, Europe, Russia, China, and other nations around the world.

However, in order to further validate this novel concept, more data and studies are required. Many of the so far published studies are retrospective and are non-discriminating regarding asthma phenotypes. There is a considerable lack of additional clinical and immunological parameters. Deep endotyping of COVID-19 asthma plus patients would be required in order to get a better

understanding about the immunological and metabolic association between these two entities. Also on the level of virus-host interactions with regard to the cellular entry mechanism used by the virus, more data on the transcriptional and translational level of receptor regulation is certainly needed. Additionally, there is a lack of longitudinal prospective studies as well.

A high proportion of type 2 (allergic, eosinophilic) asthmatics in the population may help to limit SARS-CoV-2 dissemination. However, if allergic asthmatics develop COVID-19, they may have a higher risk of disease progression. This is mainly due to diminished intrinsic interferon signaling pathways. This might be in contrast to regions with a relatively high population of non-type 2 asthmatics, which are in particular elderly patients with metabolic comorbidities such as obesity, metabolic syndrome and glucose dysregulation. This group of asthmatics has a different inflammatory profile, and due to the chronic sub-clinical inflammation associated with the metabolic dysregulation, there is circumstantial evidence that the immune system is already (pre-) programmed to develop hyper-inflammation in the context of a cytokine storm in association with COVID-19. In both situations, asthmatics with metabolic dysregulation and COVID-19 patients with associated hyper-inflammation, the IL-6 signaling pathways contribute to the disease among other pro-inflammatory cytokines.

This concept may illustrate that different asthma endotypes have a differential impact on the infection of airway epithelial cells with SARS-CoV-2, and the development and the progression of COVID-19 disease. This concept requires further clinical and experimental evidence and we propose to include immunological endotyping in SARS-CoV-2-infected patients with regard to the presence (or absence) of underlying inflammatory profiles on both the level of innate and adaptive immunity. This could have further implications for immunomodulatory therapies in COVID-19 patients with asthma comorbidity.

New data emerging rapidly and deepening our understanding about COVID-19 disease in asthmatic/allergic individuals. From the present perspective, current recommendations for treatment of asthma in the context of COVID-19 should not be changed. Patients should receive guideline-based pharmacological treatment including inhaled corticosteroids and biological therapies if needed.

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703

Figure legends

Figure 1 A/B

Asthma prevalence. A) Countries with high prevalence of asthma among COVID-19 comorbidities in comparison with asthma prevalence in the general population (High Asthma-COVID-19 zone) are marked in red color. Countries with low/equal prevalence of asthma among COVID-19 comorbidities in comparison with asthma prevalence in the general population (Low Asthma-COVID-19 zone) are marked in green. B) Asthma prevalence among patients with COVID-19 in comparison with the general population in various countries, %^{12,17,86–93}. ICS: Inhaled corticosteroids.

Figure 2

The impact of asthma endotypes on infection of airway epithelium with SARS-CoV-2, development and progression of COVID-19. The two major asthma endotypes, type 2 asthma and non-type 2 asthma, are defined by unique inflammatory patterns on the level of adaptive immunity and effector cell responses. Type 2 asthma is characterized by the presence of Th2 cells secreting IL-4, IL-5 and IL-13. These cytokines have a strong impact on the regulation of helper cell subsets, airway epithelial function and regulation of effector cell responses, including eosinophils and mast cells. In contrast, non-type 2 asthma is defined by the presence of Th1 cells and/or Th17 cells amongst other effector T cell responses. The subset of these patients show vascular and metabolic-comorbidities which are underlined by the presence of subclinical chronic

726 inflammatory responses (e.g. activation of IL-1 signaling pathways).

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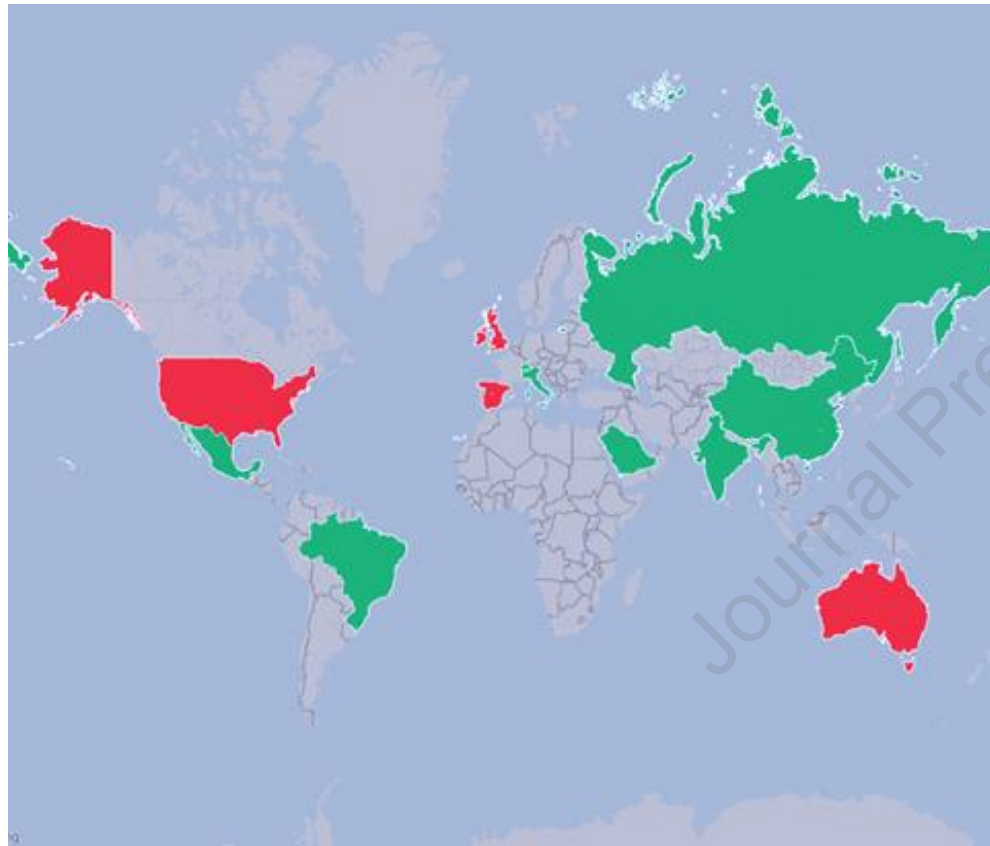
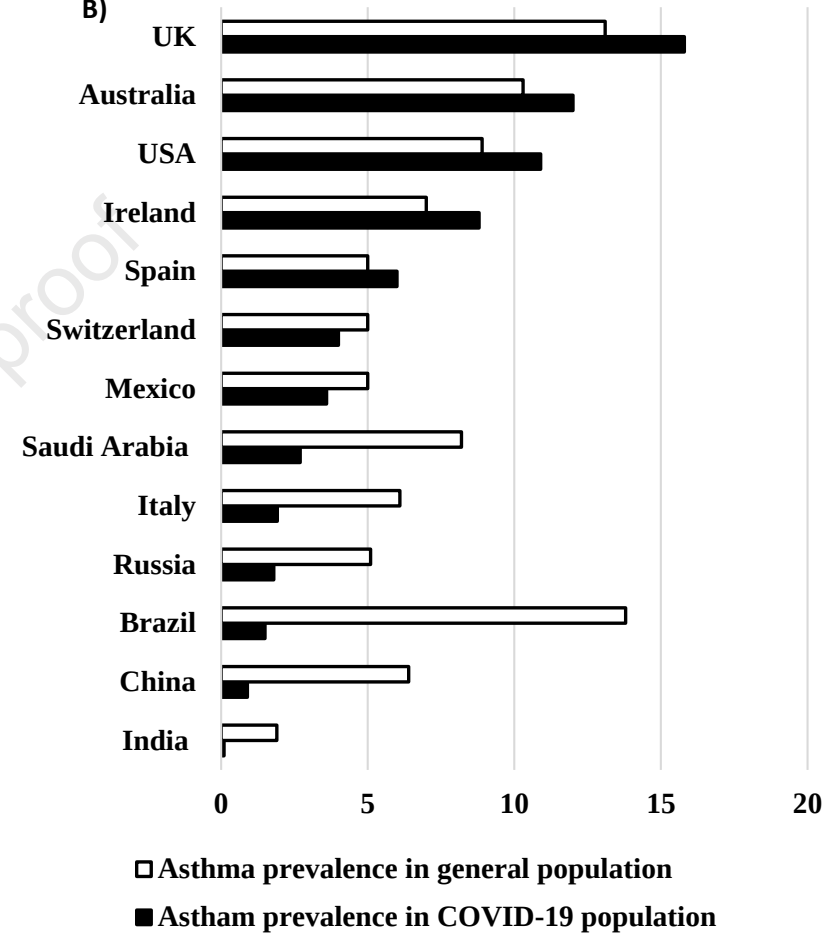
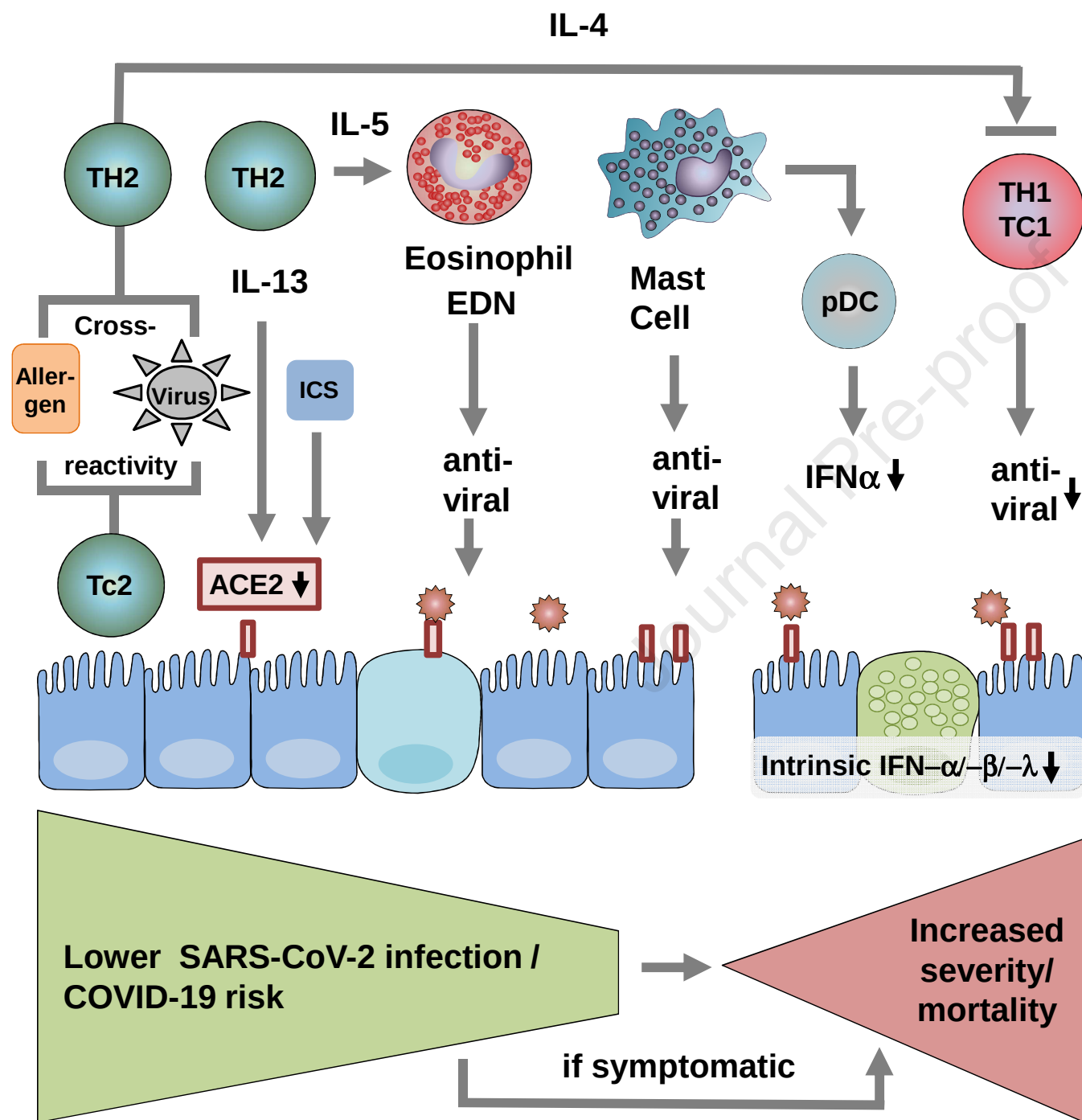
Fig. 1A and B**A)****B)**

Fig. 2

T2 Asthma

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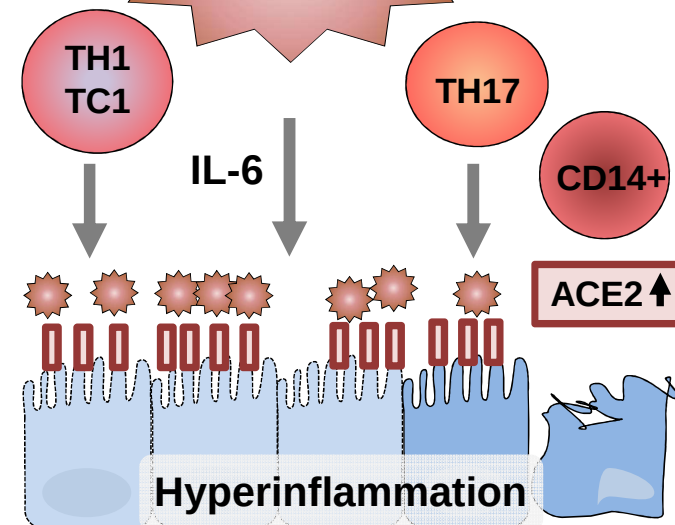
Non-T2 Asthma



Older age
Metabolic comorbidities

- Obesity
- T2D
- Metabolic syndrome

chronic (subclinical) inflammation



High risk COVID-19 (severity, lung destruction)