COVID -19 AND ASTHMA

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Disclosure

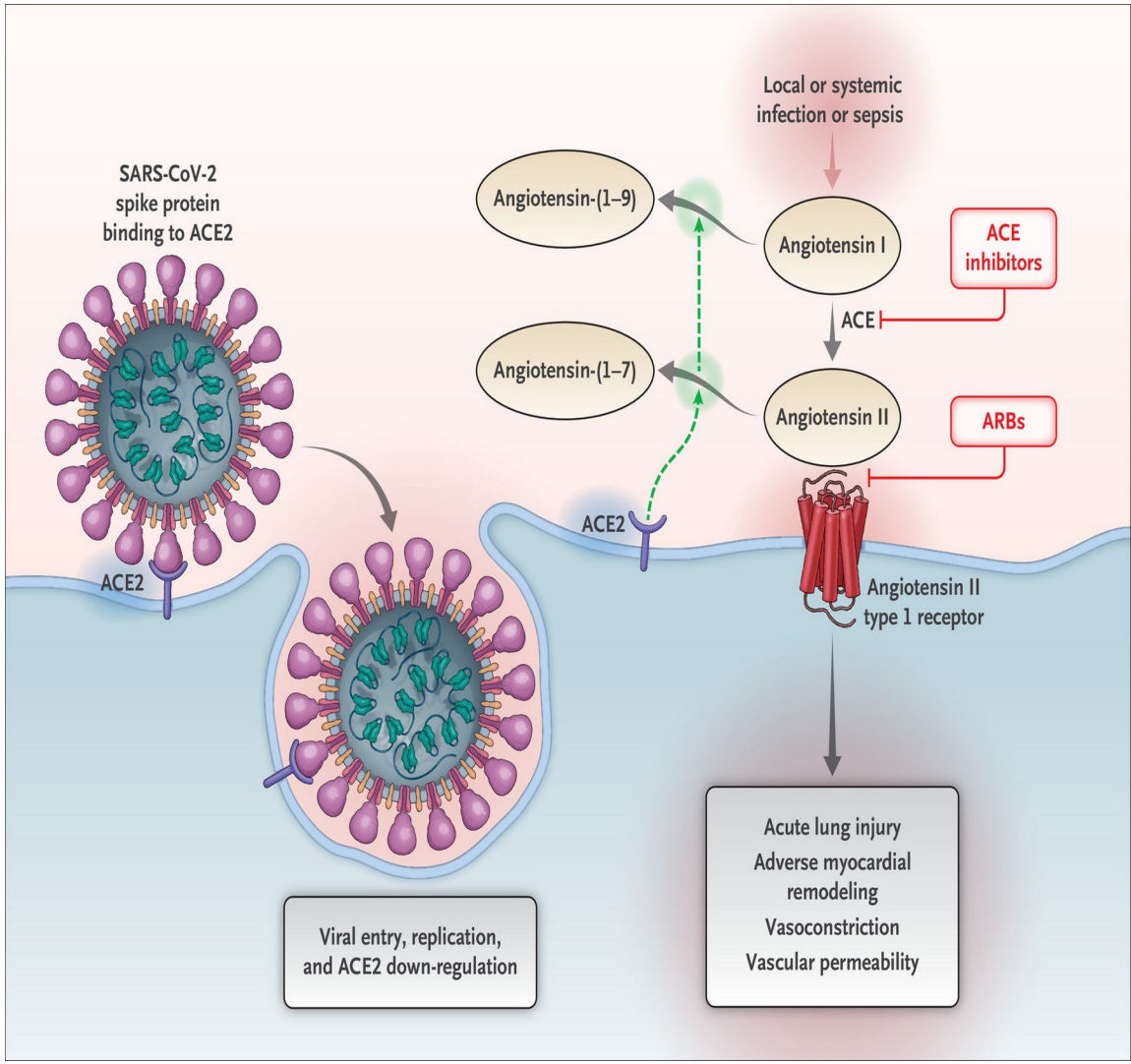
- I have nothing to declare relating to this presentation

Introduction

- Respiratory viruses are major drivers of acute exacerbations of asthma

- As the world faces the COVID-19 pandemic concerns have been raised regarding a possible increased risk of asthma exacerbations and COVID-19 severity and mortality in people with asthma.

- ACE2 is a membrane protein that is required for SARS-CoV-2 to bind and enter human cells.
- The spike protein of SARS-CoV-2 is primed by transmembrane protease serine 2 (TMPRSS2), which allows fusion of viral and cellular membranes into host cells.
- A high ACE2 expression corresponds to increased susceptibility to SARS-CoV-2 in vitro.
- ACE2 upregulation is associated with smoking, diabetes, and hypertension, which were all associated with increased COVID-19 illness severity



Jia HP et al J Virol 2005; 79(23):14614–14621.
Brake SJ. J Clin Med 2020;9(3):841

ACE2 EXPRESSION IN THE RESPIRTATORY TRACT

- ACE2 expression is highly enriched in nasal epithelial cells and type II alveolar epithelial cells, and the expression of ACE2 in airways is regulated by airway inflammation and environmental stimuli, such as allergens and viruses.

- An increased ACE2 expression exposes the lung to increased SARS-CoV-2 infectivity and COVID-19 severity

Hoffmann M et al. Cell 2020; 181: 271–280.
Li G et al. J Autoimmun 2020; 112: 102463.
Sungnak W et al. Nat Med 2020; 26: 681–687.

Does asthma increase the risk for SARS-CoV-2 infection?

- Epidemiological studies on the influenza A (H1N1) pandemics demonstrated that H1N1 infection was closely associated with asthma ,patients with asthma were more susceptible to asthma exacerbation and among patients hospitalized with H1N1 infection asthma was the most common underlying medical condition.
- Most of the asthmatic patients had an uncomplicated course of illness; however, severe disease, including intensive care unit admission and death, occurred in asthma patients who presented with pneumonia .

COVID-19 PREVALENCE AND ASTHMA

- The prevalence of COVID-19 in asthmatics was diverse in different parts of the world
- Initial epidemiological studies from China reported that the incidence of COVID-19 was relatively low and that there was no apparent increased risk of SARS-CoV-2 infection in those patients.
- The US and UK data suggested a higher prevalence of COVID-19 in people with asthma when compared to the national asthma prevalence.

Adir Y et al. Eur Respir Rev. 2021 Dec 15;30(162):210152.

TABLE 1 Estimated asthma prevalence (%) among patients with coronavirus disease 2019 (COVID-19) in comparison with the general population asthma prevalence in various countries [13–27, 38, 46]

Country	National asthma prevalence (%)	Asthma prevalence among SARS-CoV-2 positive patients (%)
China	~1.5–6.5	~1–1.5
USA	~8	~10–18
UK	~12–18	~14–18
Australia	~20	~10–14
Spain	~6–7	~5
Italy	~6	~1
Ireland	~9	~11
Switzerland	~5	~6.5
Germany	~7–8	~10–11
Israel	~7.5–8.5	~5
Mexico	~2.5	~2–3
Brazil	~12.5–13.0	~5–6

Adir Y et al. Eur Respir Rev. 2021 Dec 15;30(162):210152.

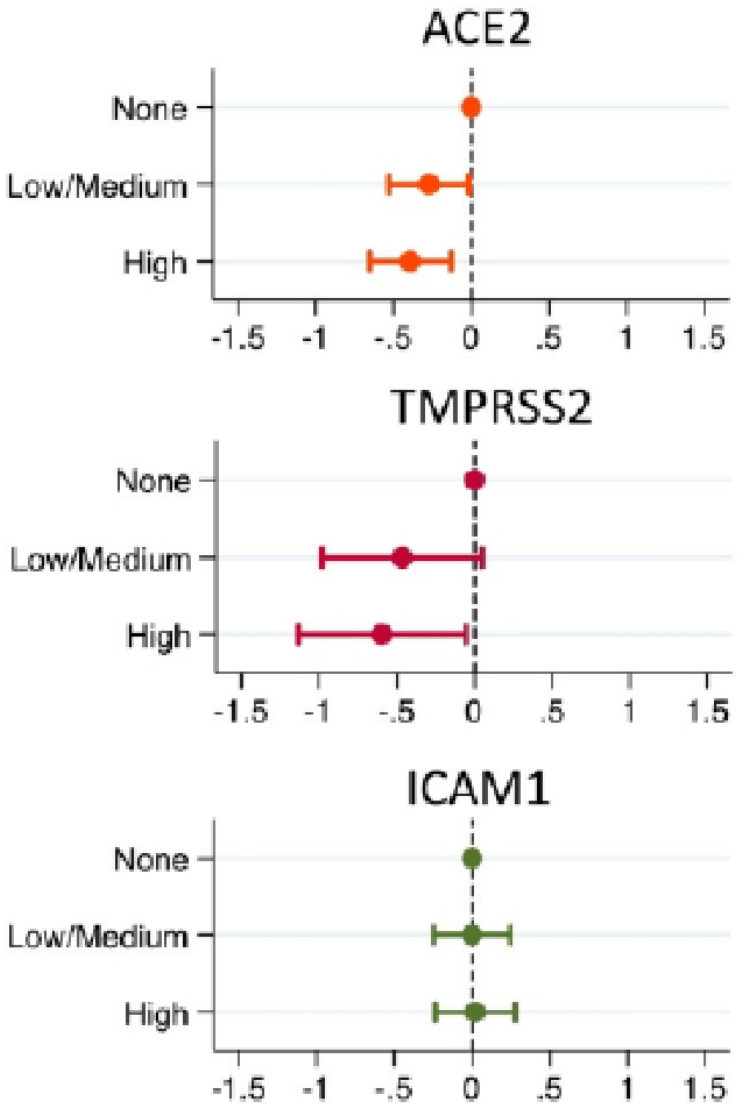
Several reasons may explain these differences in epidemiology

- The method of asthma diagnosis is different between the studies, which may result in over or under diagnosis.
- Not all studies included only PCR-confirmed COVID-19 cases.
- The prevalence of asthma in different ethnic groups is known to be different. In the US, for instance, the prevalence of asthma in African American is 10.6% while in whites American is 7.6%.
- Peters et al found a higher expression of ACE2 in African Americans which may be related to increase rate of COVID-19 infection in asthmatic African American

Peters MC, et al Am J Respir Crit Care Med 2020; 202: 83–90.

Dose ICS use in asthmatic reduced the risk for COVID-19 infection?

- In vitro studies demonstrated that ICS reduce pulmonary expression of ACE2 and TMPRSS2 (transmembrane protease serine 2) in patients with asthma.
- The use of ICS may have a protective effect.



Peters MC et al. Am J Respir Crit Care Med 2020; 202: 83–90
Halpin DMG et al. Eur Respir J 2020; 55: 2001009.
Matsuyama et al. J Virol 2020; 95: e01648-20.

Does asthma increase the risk for SARS-CoV-2 infection?

Overall, the current evidence supports the notion that asthma does not increase the risk of SARS-CoV-2 infection.

Does asthma increase the risk of severe COVID-19?

- Whether asthma should be considered as an independent risk factor is less clear.
- Beurnair et al. reported that, among hospitalized patients with severe pneumonia due to SARS-CoV-2 infection, asthma patients were not over-represented and patients with major comorbidities had worst outcomes.
- Avdevv et al. described a low prevalence of asthma (1.8%) among 1,307 intensive care unit patients with SARS-CoV-2 pneumonia who required mechanical ventilation

Beurnier A et al. Eur Respir J 2020; 56: 2001875
Avdeev S et al.COVID-19. Allergy 2020; 75: 2703–2704.

- Terry et al, based on data from 150 studies conducted worldwide, found that there is no clear evidence of increased risk of hospitalization, severity or mortality in asthmatic patients.

In contrary

- Bloom et al. found that patients with asthma were more likely to receive critical care than patients without an underlying respiratory condition.
- Severe asthma was associated with increased mortality compared to non-severe asthma.

Terry PD et al. Am J Respir Crit Care Med 2021; 203: 893–905.
Bloom CI et al. Lancet Respir Med 2021; 9: 699–711

- A study in Korea included 7590 COVID-19 patients ,reported that the mortality rate for COVID-19 patients with underlying asthma (7.8%) was significantly higher than that of other patients (2.8%).
- However, after adjustment to other comorbidities, asthma was not found to be an independent risk factor for the clinical outcomes of COVID-19 .
- A study from Spain also found an increased risk of hospitalization due to COVID-19 in patients with asthma but it was largely associated with age and related comorbidities and mortality mainly affected elderly patients .

Choi YJ et al. Eur Respir J 2021; 57: 2002226.
Izquierdo JL et al. Eur Respir J 2021; 57: 2003142

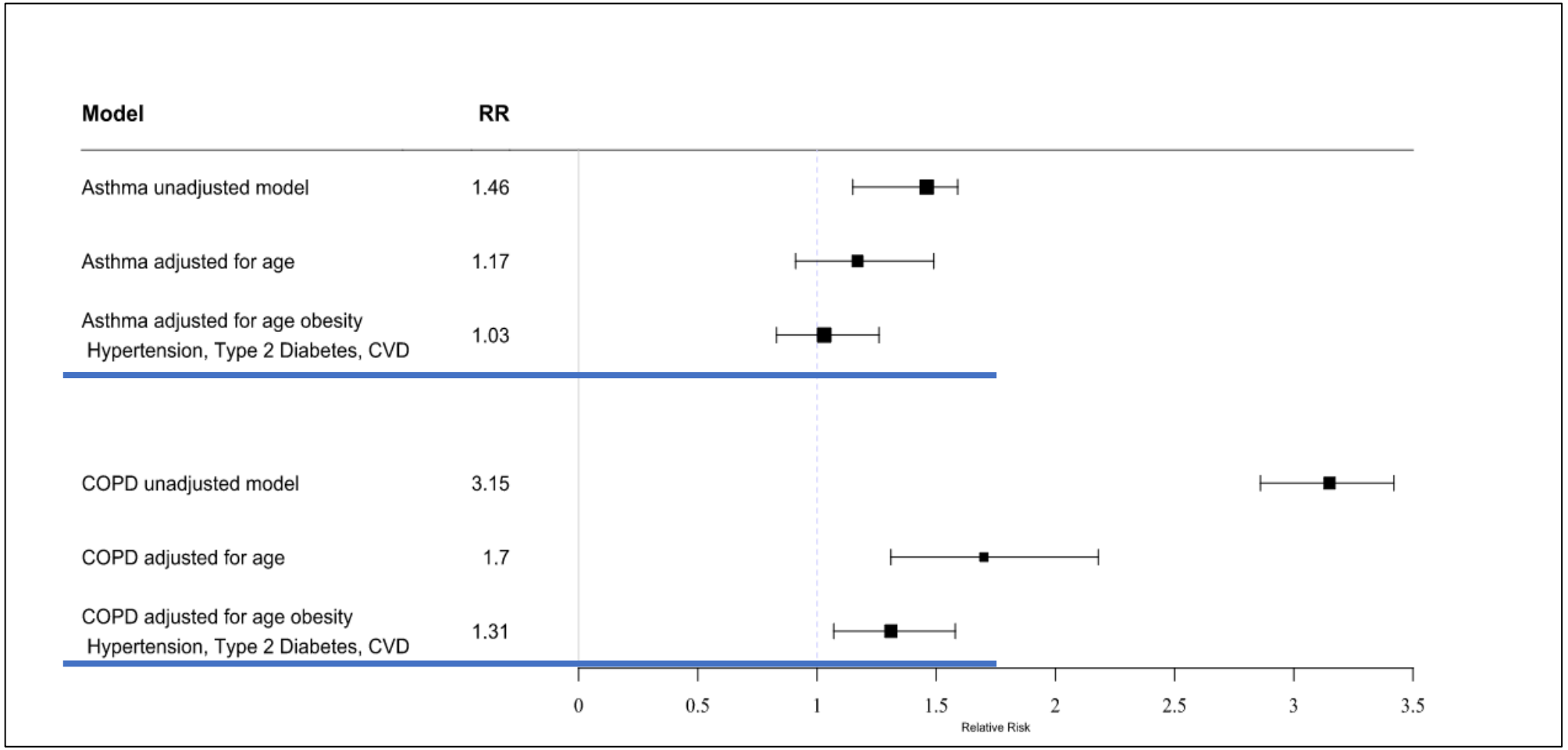
Our experience

- We conducted a retrospective cohort study. 18,000 patients included in the study, 1,378 were diagnosed with asthma and 466 were with COPD.

- The prevalence of asthma and COPD among test-positive COVID-19 patients was not statistically different from the prevalence of asthma and COPD in Israel

Adir Y et al. ERJ Open Res. 2022 Mar 7;8(1):00014-2022.

- In model adjusted for age and comorbidities, COPD was an independent risk factor for severe disease 30% higher compared to non-COPD **while asthma was not found to be a risk factor for severity and mortality.**



Severe asthma and COVID-19

- The data on severe asthma and COVID-19 are scarce.
- A recent study from the Belgian Severe Asthma Registry reported a relatively low incidence of COVID-19 and no association with a higher risk of infection or poor outcome.
- Heffler et al. described the data from 1504 patients included in the Severe Asthma Network in Italy (SANI) and conclude that in patients with severe asthma was not an independent factor for severe COVID 19.

Hanon S et al. Eur Respir J 2020; 56: 2002857.
Heffler E et al. Allergy 2021; 76: 887–892.

Does asthma increase the risk of severe COVID-19?

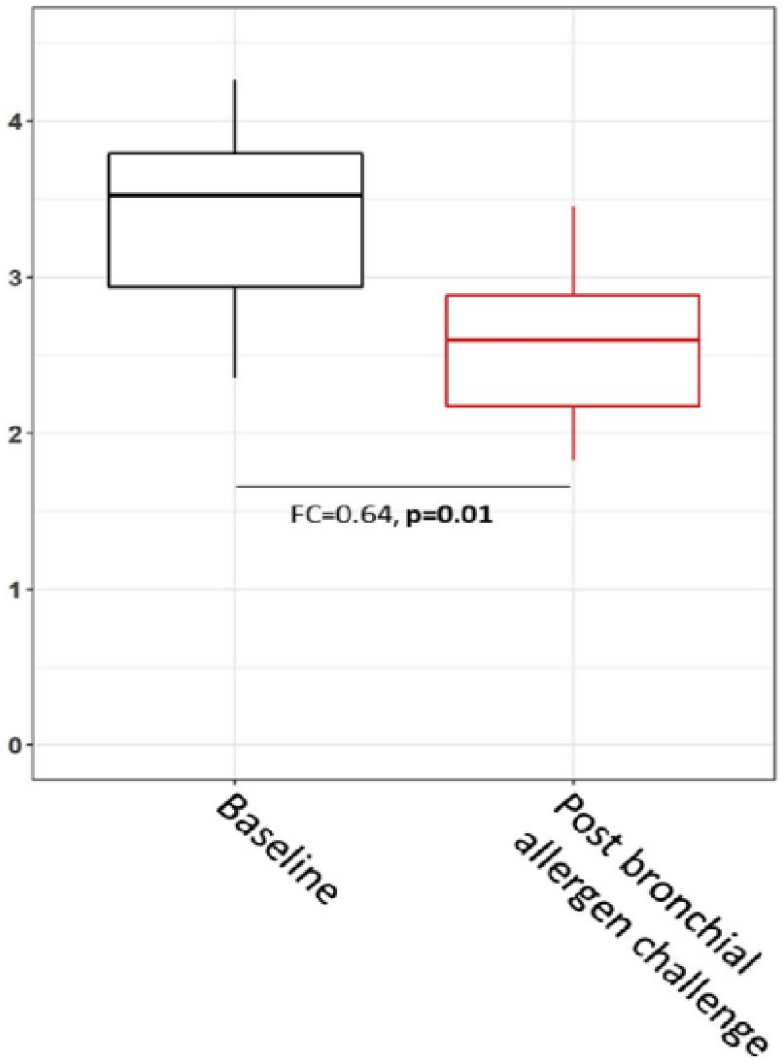
Asthma including severe asthma is not an independent risk factor for increased COVID-19 severity and mortality

Are different asthma phenotype, mainly T2-high and T2-low, might have a different susceptibility to SARS-CoV-2 infection and disease severity?

- Camiolo et al reported in a subset of patients with asthma which exhibits a T2 low epithelial gene expression signature in the bronchial epithelium, there is an increased expression of ACE2 receptor.
- The authors suggest that asthmatics with T2-low inflammation may be at increased risk for adverse outcomes from COVID-19.
- In bronchial brush airway epithelial cells from asthmatic patients, Bradding et al. identified a positive correlation between ACE2 gene expression and interleukin (IL)-17-dependent gene expression signature, with an inverse association with T2-high gene expression.

Camiolo M et al. J Allergy Clin Immunol 2020; 146: 315–324.
Bradding P et al. J Allergy Clin Immunol 2020; 146: 208–211.

- Jackson et al. reported that ACE2 expression was significantly reduced in nasal and bronchial epithelial cells of patients with allergy and asthma.
- Furthermore, it was associated with allergen exposure, allergen sensitization and high IgE levels.
- Conversely, nonatopic asthma was not associated with reduced ACE2 expression.



Jackson DJ et al J Allergy Clin Immunol 2020;146(1): 203–206

- In a Korean nationwide cohort, patients with non-allergic asthma had a greater risk of SARS-CoV-2 test positivity and severe clinical outcomes of COVID-19 than those with allergic asthma

Patients who tested positive for SARS-CoV-2			
None	Severe clinical outcomes of COVID-19	24/537 (4.5)	Reference
Allergic asthma		30/493 (6.1)	1.40 (0.83 to 2.41)
Nonallergic asthma		7/44 (15.9)	**4.09 (1.69 to 10.52)**

Yang JM et al. J Allergy Clin Immunol 2020; 146: 790–798.

Asthma phenotype and COVID-19

It seems that patients with asthma with T2-low inflammation may be at increased risk for adverse outcomes from COVID-19 while T2 high inflammation has a protective effect

Asthma medications and the risk for SARS-CoV-2 infection and disease severity

Inhaled corticosteroids (ICS)

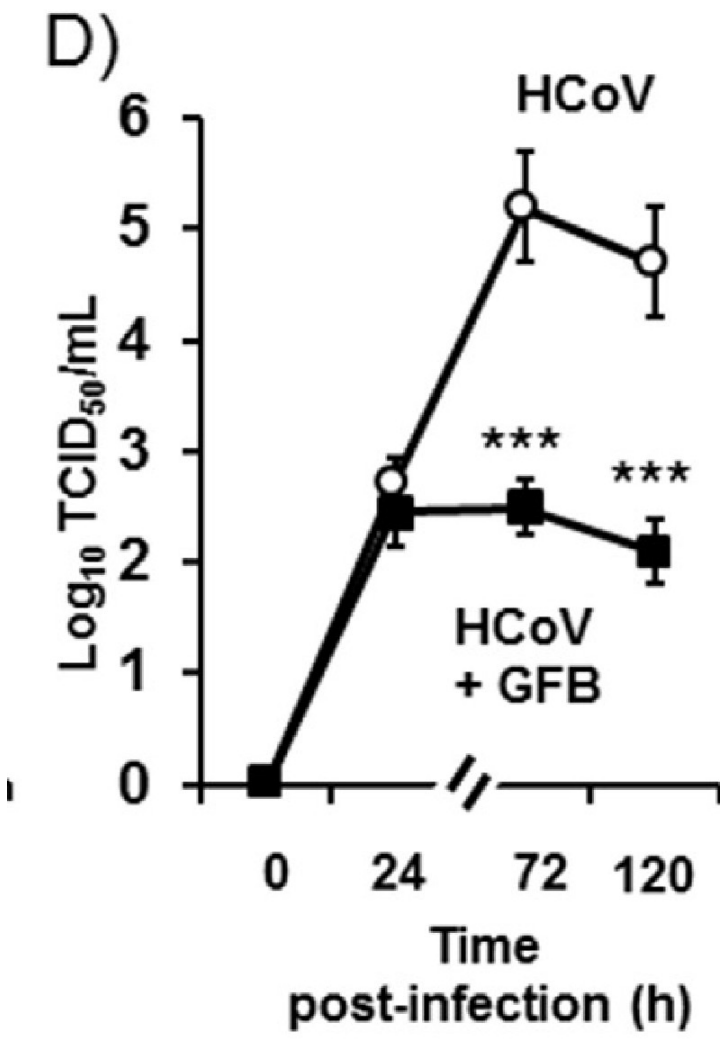
- The potential immunosuppressive effects of ICS, which may promote viral replication, delayed viral clearance and increased risks of secondary infections, raised concern regarding their use in asthma patients with COVID-19.

- Furthermore, in vitro studies reported that ICS led to decreased rhinovirus elimination and decreased immune response to rhinoviral infection.

Myles P et al. Eur Respir J 2013; 41: 824–831

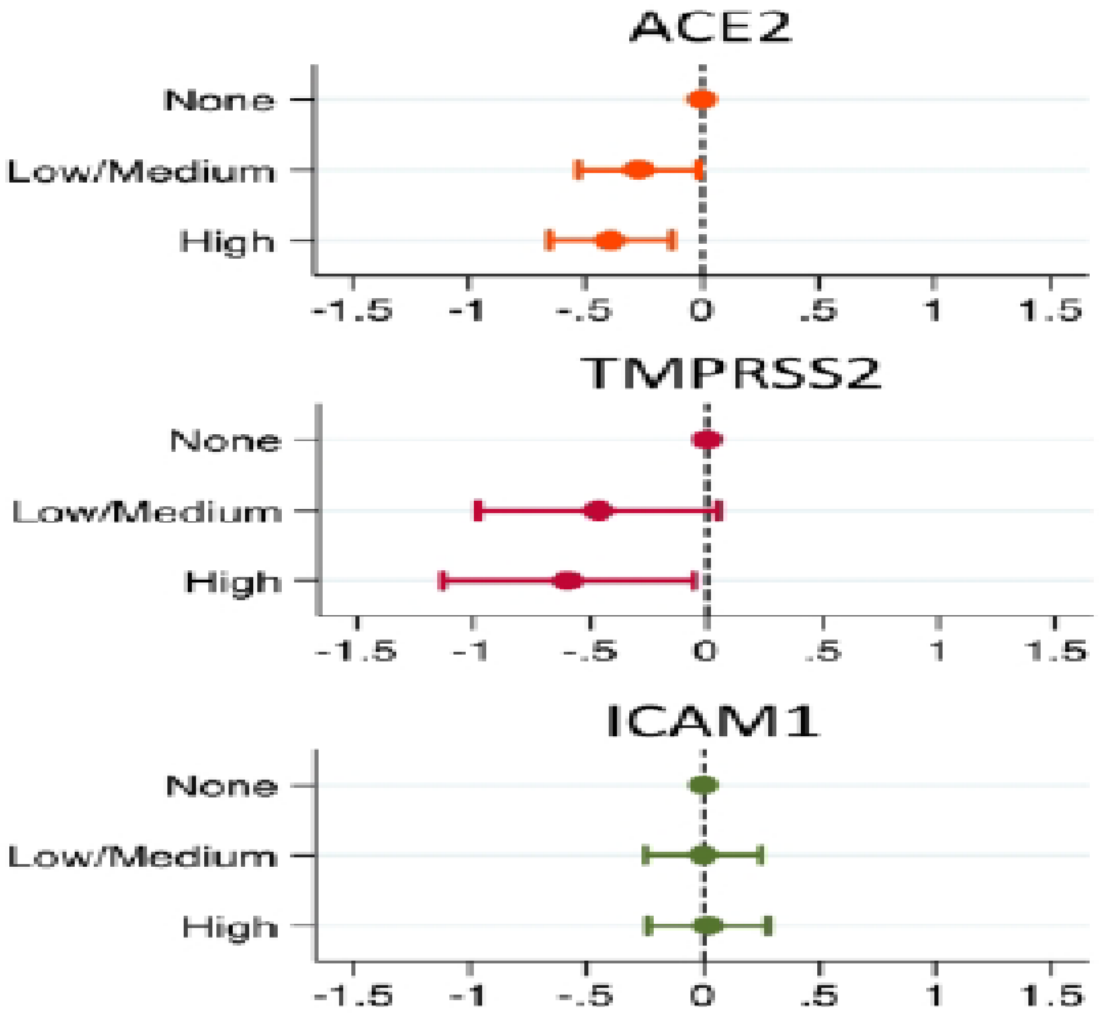
COVID-19 and ICS

- Pre-treatment of human respiratory epithelial cells in vitro with budesonide, in combination with glycopyrronium and formoterol, has inhibitory actions on coronavirus HCoV-229E replication and cytokine production.
- Ciclesonide found to suppressed SARS-CoV-2 replication in cultured cells and inhibits SARS-CoV-2 cytopathic activity.



Yamaya et al Respir Investig 2020; 58: 155–168

Peters et al found a significantly lower expression of ACE2 and TMPRSS2 in patients treated with **ICS**



Peters MC, et al Am J Respir Crit Care Med 2020; 202: 83–90.

- Using big-data analytics and artificial intelligence through the SAVANA Manager clinical platform, Izquierdo et al. analyzed clinical data from 71182 patients with asthma.
- They concluded that ICS showed a safe profile.
- Compared to asthma patients who required hospitalization due to COVID-19, a significantly higher percentage of non-hospitalized patients used ICS.

Izquierdo JL et al. Eur Respir J 2021; 57:2003142

ICS treatment for prevention of severe covid-19 in the genereal population

- In the Steroids in COVID-19 (**STOIC**) trial, an open-label, parallel-group, phase 2, RCT. Inhaled budesonide, when given to adults with early COVID-19, reduced the likelihood of hospitalization, with faster symptom resolution.
- This led to the **PRINCIPLE** trial- inhaled budesonide in high risk patients infected with COVID-19.
- Inhaled budesonide reduced symptom burden and time to recovery, with a high probability of also reducing the need for hospital admission, albeit just below the prespecified superiority threshold in the primary analysis population.

Ramakrishnan S et al. Lancet Respir Med 2021; 9: 763–772.
Yu LM et al. Lancet 2021; 398: 843–855.

Systemic corticosteroids (SCS)

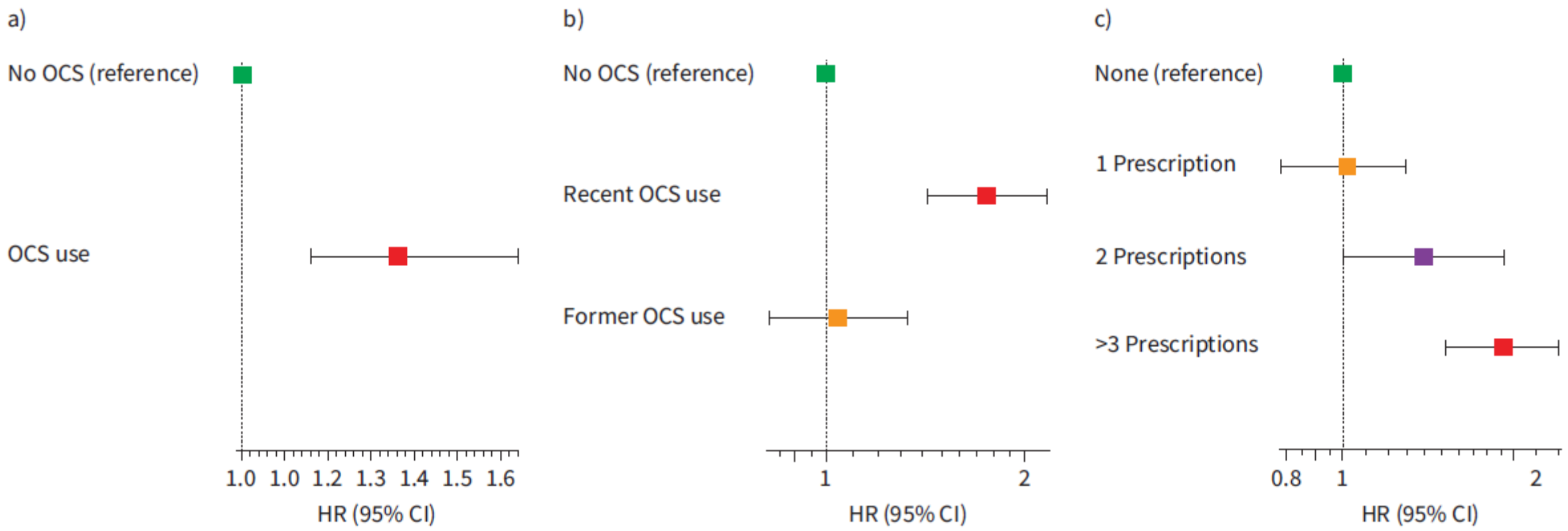
- The data on COVID-19 in patients receiving SCS therapy for asthma remain scarce.
- Using the OpenSAFELY platform, severe asthma defined by recent SCS use was associated with increased mortality
- Recent large nationwide study of 80602 adult asthma patients in Israel, reported that:

- Chronic SCS
- Recent use
- More than two prescriptions of SCS for asthma exacerbation

were all an independent risk factor for worst COVID-19 severity and all-cause mortality

Adir Y et al. J Allergy Clin Immunol 2021; 148:361-367
Matsuyama S et al Virol 2020; 95: e01648-20

The use of SCS, whether for chronic, recent or for recurrent exacerbations, is a clear risk factor for increased COVID-19 severity and mortality



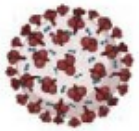
Adir Y et al. J Allergy Clin Immunol 2021; 148:361-367

Biologics for asthma

- The current biologics block pathways of T2 high inflammation, which might have a protective effect against COVID-19.
- Eosinophils have a role in fighting viral infections, especially against RNA viruses. Eosinopenia was found in patients presenting with moderate-to-severe COVID-19 and might be related to disease severity
- Therefore, concerns have been raised whether the use of biologics - reducing the number of eosinophils and their products may be associated of increased risk of SARS-CoV-2 infection or increased COVID-19 severity

COVID-19 risk and outcomes in adult asthmatic patients treated with biologics or systemic corticosteroids : nationwide real-world evidence in Israel

80,602 asthmatics (514 on biologics) were tested with PCR for SARS-CoV-2

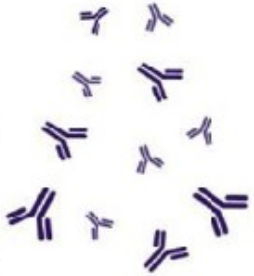


8,242 were positive

Patients Previously Treated with Systemic Corticosteroids (n=1358)

Increased Risk	COVID-19 Severity	No Increased Risk
Increased Risk	90-days Mortality	No Increased Risk

Patients on Biologics (n=50)



COVID-19: Coronavirus Diseaese 2019
PCR: Polymerase chain reaction
SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

Adir Y et al. J Allergy Clin Immunol 2021; 148:361-367

- A significantly lower eosinophil count (42±39·µL–1) in patients treated by biologics in our study was not found to be associated with increased COVID-19 severity and mortality.
- A study from Greece including 591 severe asthmatics on biologics confirms that the use of biologics safe. COVID-19 is not more common in asthmatics treated with biologics compared with the general population

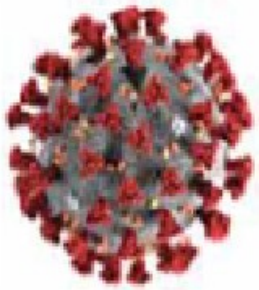
The current data support the notion that the use of biologics is safe

Adir Y et al. J Allergy Clin Immunol 2021; 148:361-367
Papaioannou AI et al. J Allergy Clin Immunol Pract. 2022 Oct;10(10):2588-2595.

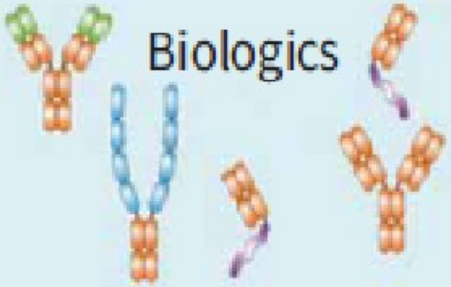
In summary

- Despite the concerns that asthma patients could be at increased risk for SARS-CoV-2 infection and disease severity, it appears that asthma is not an independent risk factor for both.
- A large difference in the incidence of COVID-19 in asthma patients was found in different geographical areas.
- Findings suggest that T2-high inflammation may reduce the risk of SARS-Cov-2 infection and disease severity

Asthma medication



Asthmatic patients with positive PCR for SARS-CoV-2

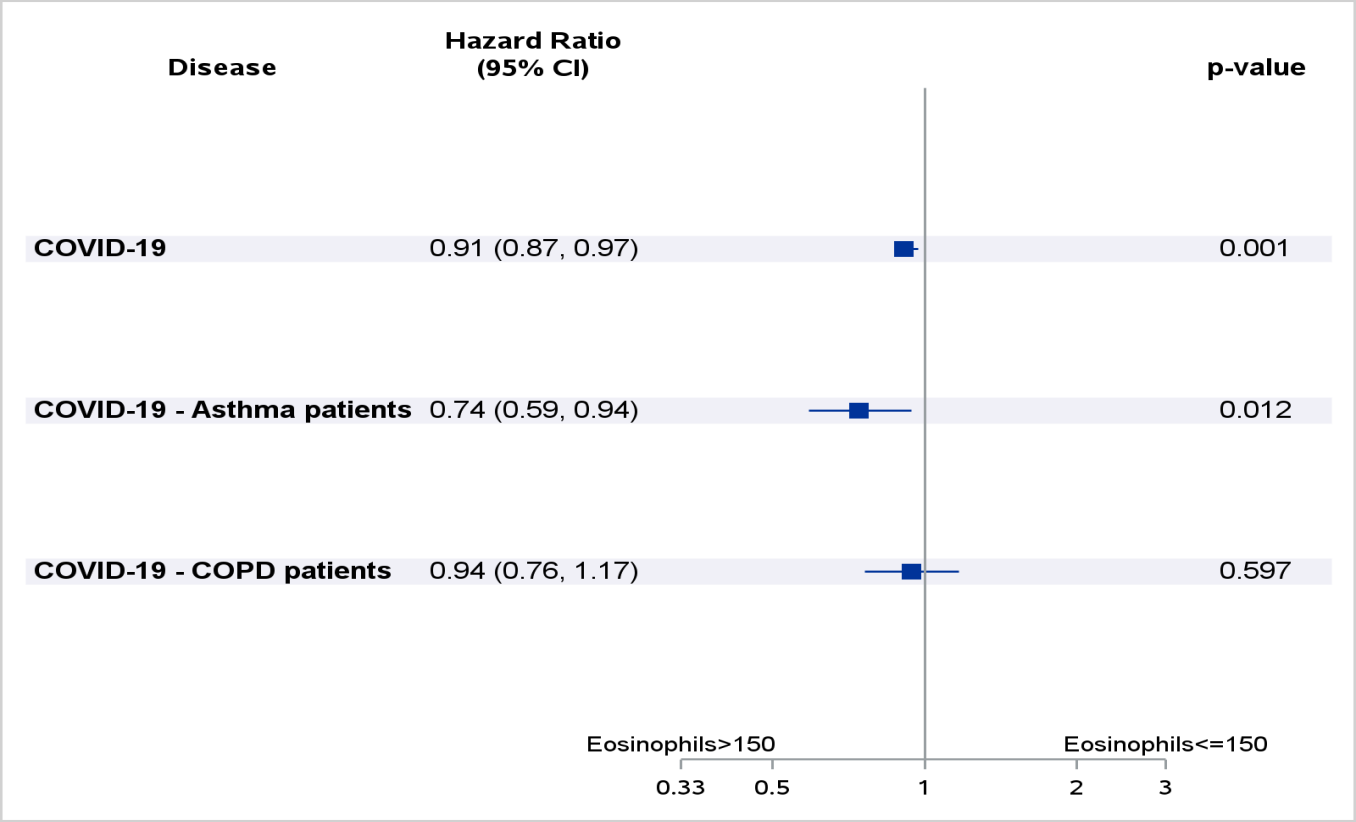
	Previous treatment with SCS 	ICS 	Biologics 
Infection with SARS-CoV-2	No increased risk	No increased risk	No increased risk
COVID-19 severity	Increased risk	No increased risk	No increased risk
COVID-19 mortality	Increased risk	No increased risk	No increased risk

Thank you

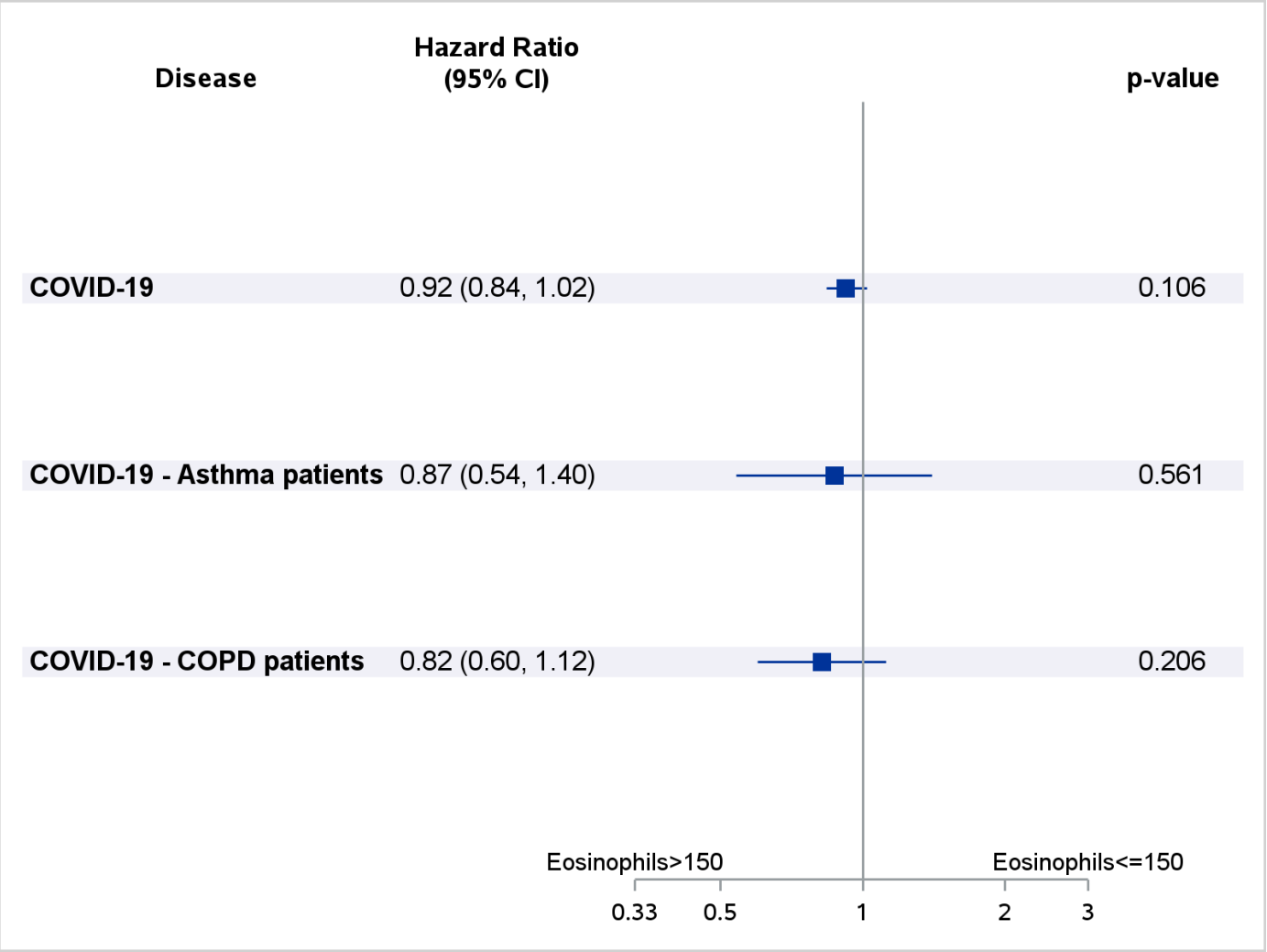

THE DAILY TOON
BY MARK LYNCH
I READ THAT DRINKING BEER CAN CURE COVID AND BRING WORLD PEACE
PROBABLY FAKE NEWS, BUT WHY TAKE A CHANCE?
LYNCH

Is peripheral blood eosinophils count as one of the biomarkers of type 2 inflammation in asthma associated with COVID-19 severity and mortality

COVID-19 – Moderate/severe disease



30 days mortality – COVID -19 patients



days mortality 30