Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Editorial

Does asthma affect morbidity or severity of COVID-19?

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Coronavirus disease 2019 (COVID-19) has afflicted at least 4.9 million patients worldwide, causing more than 328,000 deaths to date. This pandemic impacts not only social and economic activities but also health care workers globally. Patients with COVID-19 exhibit a wide range of symptoms: from almost no symptoms to critical conditions similar to the so-called cytokine storm or fatal acute respiratory distress syndrome. However, we still do not have effective vaccines or specific remedies for this disease.

Asthma is characterized by chronic airflow limitation, with inflammation in the lung. The most frequent trigger of asthma exacerbation is airway infection, especially with weakly virulent viruses such as rhinovirus and respiratory syncytial virus, which usually cause upper respiratory tract infections in healthy subjects.[1] Because airway epithelial cells and leukocytes from patients with asthma can show impaired production of antiviral IFNs (IFN-α/β/λ), either primarily or secondary to allergic inflammation, a patient's innate immune system is unable to prevent the spread of these viruses to the lower respiratory tract.[2] This results in respiratory epithelial cell activation/damage, thereby aggravating type 2 inflammation. Such impairment of antiviral responses suggests that patients with asthma might be at high risk of COVID-19 morbidity and mortality.

However, our unbiased literature search of epidemiological studies on COVID-19 yielded interesting results. Eight studies including a total of more than 17,000 patients in multiple geographic regions found that the comorbidity rates of COVID-19 with asthma were significantly lower than the reported prevalence of asthma in the respective regions (Table I). In addition, 2 independent studies (Li et al[3] and Singer et al[4]) similarly demonstrated that patients with COVID-19 comorbid with chronic obstructive pulmonary disease or diabetes tended to be more severe, whereas those comorbid with asthma did not (Table II).

Recent basic research revealed that 2 host molecules play critical roles in the initiation of COVID-19, which is caused by severe acute respiratory syndrome (SARS) coronavirus 2 (SARS-CoV-2). SARS-CoV-2 uses the SARS-CoV receptor angiotensin-converting enzyme 2 (ACE2) for cell entry, and uses a serine protease transmembrane serine protease 2 (TMPRSS2) for S protein priming of the virus.[5] Interestingly, *in vitro* treatment of airway epithelial cells with IFNs enhanced their ACE2 expression.[6]

In sharp contrast, in this issue of the *Journal*, Kimura et al[7] reported that IL-13 exposure reduced ACE2 and increased transmembrane serine protease 2 expression in airway epithelial cells from patients with asthma and atopy. In addition, tissues from type 2 cytokine-high patients with allergy showed significantly lower expression of ACE2, and the ACE2 expression levels correlated inversely with the T2 cytokine levels and T2 signature molecule expression.[7] Therefore, expression of ACE2 is likely to be regulated reciprocally by IFNs and T2 cytokines; IFNs upregulate, whereas T2 cytokines downregulate. Indeed, ACE2 expression in asthmatic bronchial epithelium was reported to be significantly lower than in healthy subjects.[8] Moreover, patients with COVID-19 with serious disease showed significantly higher IFN-related molecular expression (IFN-γ–induced protein 10).[9] These findings suggest a hypothesis that patients with asthma are protected from COVID-19 because of the low expression of ACE2 in their epithelial cells. Children with asthma showed a low prevalence of SARS due to SARS-CoV, which uses ACE2 as an entry receptor.[10] Conversely, conventional coronaviruses exacerbate asthma upon infection.[1] Reported entry receptors for most conventional coronaviruses do not include ACE2. The reported receptors are HLA class I molecule or sialic acids, and caveolin-1 for HCoV-OC43; aminopeptidase N (CD13) for HCoV-229E; dipeptidyl peptidase 4 (also known as CD26) for HCoV-EMC; unknown for HCoV-HKU1; and only HCoV-NL63 uses ACE2. These earlier observations thus support the above hypothesis.

However, there are several limitations to acknowledge in this hypothesis. All the epidemiological data were obtained retrospectively or cross-sectionally, and no tests were performed for IFN production or ACE2 expression in patients with COVID-19, especially those comorbid with asthma. In addition, no detailed information was reported regarding the phenotype/endotype (theoretically only T2-high, but not T2-low, patients with asthma have low ACE2 expression), lung function, control status, or treatment regimen of the patients with asthma. We also do not know whether or not a diminished ACE2 expression level in patients with asthma actually reduces SARS-CoV-2 infections. Of note, a couple of recent studies using clinical specimens reported that ACE2 mRNA expression did not differ significantly between patients with asthma and control subjects. These findings differ from those of the aforementioned studies.

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TABLE I. Numbers and percentages of comorbidity in patients with COVID-19

Region	No. of COVID-19 patients	Mean or median age (y)	No. of comorbid patients (%)*			Regional asthma prevalence	Reference
			Asthma	COPD	Diabetes		
Wuhan, China	140	57	0 (0)	2 (1.4)	17 (12.1)	6.4%†	Zhang et al, 2020
Wuhan, China	548	60	5 (0.9)	17 (3.1)	83 (15.1)	6.4%†	Li et al,[3] 2020
Whole China	1,590	48.9	0 (0)	24 (1.5)	130 (8.2)	6.4%†	Guan et al, 2020
Georgia, USA	305	60	32 (10.5)	16 (5.2)	121 (39.7)	7.7%‡	Gold et al, 2020
California, USA	54	53.5	3 (0.6)	0 (0)	11 (20.4)	7.7%‡	Rubin et al, 2020
New York, USA	5,700	63	513 (9)	308 (5.4)	1927 (33.8)	7.7%‡	Richardson et al, 2020
New York, USA	1,651	50	99 (6)	66 (4)	248 (15.0)	7.7%‡	Singer et al,[4] 2020
Whole Mexico	7,497	46	270 (6)	202 (2.7)	1252 (16.7)	8.7%§	Solís et al, 2020
Total	17,485		922 (5.3)‖	635 (3.6)	3789 (21.6)	8.0%	

COPD, Chronic obstructive pulmonary disease.
*The number of patients was calculated only if the total number of patients and percentages were presented.
†Regional asthma prevalence data are cited from Huang et al.
‡Regional asthma prevalence data are cited from the Centers for Disease Control and Prevention.
§Regional asthma prevalence data are cited from Solé et al.
‖$P < .0001$ by Mantel-Haenszel test.

TABLE II. Association of asthma, COPD, and diabetes comorbidity with the severity of COVID-19

Region, country/comorbidity	Comorbidity+/− (%)			*P* value*
	Total	Nonsevere	Severe	
Wuhan, China†	548	279	269	
Asthma	5/543 (0.9)	2/277 (0.7)	3/266 (1.1)	.483
COPD	17/531 (3.1)	4/275 (1.4)	13/256 (4.8)	.019
Diabetes	83/465 (15.1)	31/248 (11.1)	52/217 (19.3)	.010
New York, USA‡	1651	914	737	
Asthma	99/1552 (6.0)	47/867 (5.1)	52/685 (7.1)	.128
COPD	66/1585 (4.0)	14/900 (1.5)	52/685 (7.1)	.000
Diabetes	248/1403 (15.0)	49/865 (5.4)	199/538 (27.0)	.000
Total	2199	1193	1006	
Asthma	104/2095 (4.7)	49/1144 (4.1)	55/951 (5.5)	.111
COPD	83/2116 (3.8)	18/1175 (1.5)	65/941 (6.5)	.000
Diabetes	331/1868 (15.1)	80/1113 (6.7)	251/755 (25.0)	.000

COPD, Chronic obstructive pulmonary disease.
**P* values were calculated by Fischer exact test, χ^2 test, or Mantel-Haenszel test.
†Li et al.[3]
‡Singer et al.[4]

Finally, we would like to emphasize that this Editorial should not lead physicians to underestimate COVID-19 in their patients with asthma. There are no current data that support or recommend step-down of current treatments of patients. In particular, a recently approved biologic, dupilumab—an antibody to IL-4 receptor α chain that blocks both IL-4 and 13—should not be reduced or discontinued only for the purpose of ACE2 down-regulation. Further careful investigations are definitely needed to determine whether asthma affects the morbidity and mortality of COVID-19. Recent news released from the National Institutes of Health said that a study called Human Epidemiology and Response to SARS-CoV-2 (HEROS) has just begun enrolling participants. The purpose of this study is to determine the rate of SARS-CoV-2 infection in children and their family members in the United States, and to examine whether rates of SARS-CoV-2 infection differ between children who have asthma or other allergic conditions and children who do not. Intervention studies that prevent the onset and severity of COVID-19 by reducing ACE2 expression are also of great interest. However, currently available data may provide some peace of mind to all physicians who are simultaneously managing patients with asthma and fighting against COVID-19.

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