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Commentary

COVID-19 in COPD: A growing concern

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As of August 24, 2020, over 23 million people around the world have been infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for the coronavirus disease 2019 (COVID-19) pandemic [1]. The case-fatality rate is between 0.5% and 1% with most dying from respiratory failure related to diffuse alveolar damage, vascular thrombosis or pulmonary edema [2]. To date, 813,000 individuals worldwide have succumbed to the disease [1].

There is considerable debate on whether (or not) chronic obstructive pulmonary disease (COPD), a common airway disease that affects ~10% of individuals over 45 years of age [3], is a risk factor for COVID-19. A recent review of the epidemiological literature revealed wide-ranging prevalence (1.1−38%) of COPD among patients with COVID-19[4]. However, these previous studies may have suffered from several important methodological limitations including small sample sizes and ascertainment bias. The study by Attaway et al. addresses some of these limitations and provides important data that fill in critical gaps in knowledge [5]. Using a large and robust Cleveland Clinic COVID-19 registry, the investigators abstracted data on patient characteristics including co-morbidities on all laboratory confirmed cases of COVID-19 at their center. Of the 15,586 symptomatic patients, who were tested for COVID-19, 1319 (9.2%) had COPD. Interestingly, after adjustment for covariates, the investigators found no significant differences in the rate of SARS-CoV-2 positivity between COPD and non-COPD patients. However, significantly higher rates of hospitalization (adjusted odds ratio of 1.36), ICU admissions (adjusted odds ratio of 1.20) and invasive mechanical ventilation (adjusted odds ratio of 1.49) were observed in COPD patients infected with the virus (versus non-COPD patients). These data are remarkably consistent with those by Guan et al., who in 1590 laboratory confirmed hospitalised patients from 575 hospitals in China showed that COPD patients were 2.6 times more likely to experience ICU admissions, invasive mechanical ventilation or death [6]. Together, these data suggest that COPD is a risk factor for severe COVID-19 that leads to hospitalization and ICU admission.

How does COPD increase the risk of severe COVID-19? Although the exact mechanisms have not been fully worked out, there are several intriguing possibilities. The first point of host engagement for SARS-CoV-2 is usually the nasal mucosa, which contains an abundance of a protein called angiotensin converting enzyme-2 (ACE-2) [4]. The virus uses this protein as its receptor to gain entry into epithelial cells. Once in, the virus usurps the cellular machinery of the host to produce a myriad of daughter virions, which are ultimately released into the extracellular milieu, causing infection of adjacent cells and propagation of the virus into more distal parts of the respiratory tract. Without ACE-2, infection is aborted and ACE-2 expression levels in lungs are associated with increased severity of COVID-19[2]. It is now well established that patients with COPD have increased expression of ACE-2 in the lower respiratory tract, which is further amplified by active smoking [7,8]. This may increase the risk for severe COVID-19. Another possibility is that patients with COPD often demonstrate perturbations in the renin-angiotensin-aldosterone system with up-regulation of ACE and angiotensin II [9] that may be exacerbated during acute SARS-CoV-2 infection, leading to acute pulmonary hypertension and pulmonary edema.

Another consideration is pharmacotherapy. COPD patients are often prescribed inhaled medications such as inhaled corticosteroids (ICS). Provocatively, in the paper by Attaway et al., they showed that those patients who tested positively for SARS-CoV-2 were 2.4 times less likely to have used corticosteroids at the time of testing than those who tested negatively (18.3% vs 44.8%, $p < 0.001$) [5]. Although these data cannot be considered definitive owing to important methodological limitations such as confounding by indication and severity, they raise the possibility that corticosteroids may offer some protection against COVID-19. Thus, during this pandemic, patients with COPD should be encouraged to use their prescribed inhalers as they did prior to the pandemic. Long-acting bronchodilators are first line therapies for COPD, followed by the addition of ICS for those who are frequent exacerbators and during significant exacerbations, they should be managed with antibiotics and oral corticosteroids [3]. For exacerbations directly related to SARS-CoV-2 infection, they should be treated with systemic dexamethasone, especially if they require supplemental oxygenation or invasive mechanical ventilation. Under these settings, the use of dexamethasone has been shown to reduce

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mortality by 18% to 36% [10]. As illustrated by Attaway et al. [5], COVID-19 is a growing concern in patients with COPD. However, with proper mitigation efforts and appropriate inhaler therapy, COPD patients may be "protected" from the severe consequences of SARS-CoV-2 during this pandemic.

Declaration of competing Interest

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