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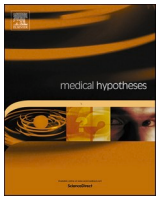

Diseased lungs may hinder COVID-19 development: A possible reason for the low prevalence of COPD in COVID-19 patients

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ABSTRACT

Presently, it remains unclear why the prevalence of lung diseases, namely chronic obstructive pulmonary disease (COPD), is much lower than other medical comorbidities and the general population among patients with coronavirus disease 2019 (COVID-19). If COVID-19 is a respiratory disease, why is COPD not the leading risk factor for contracting COVID-19? The same odd phenomenon was also observed with other pathogenic human coronaviruses causing severe acute respiratory distress syndrome (SARS) and Middle East respiratory syndrome (MERS), but not other respiratory viral infections such as influenza and respiratory syncytial viruses. One commonly proposed reason for the low COPD rates among COVID-19 patients is the usage of inhaled corticosteroids or bronchodilators that may protect against COVID-19. However, another possible reason not discussed elsewhere is that lungs in a diseased state may not be conducive for the severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2) to establish COVID-19. For one, COPD causes mucous plugging in large and small airways, which may hinder SARS-CoV-2 from reaching deeper parts of the lungs (i.e., alveoli). Thus, SARS-CoV-2 may only localize to the upper respiratory tract of persons with COPD, causing mild or asymptomatic infections requiring no hospital attention. Even if SARS-CoV-2 reaches the alveoli, cells therein are probably under a heavy burden of endoplasmic reticulum (ER) stress and extensively damaged where it may not support efficient viral replication. As a result, limited SARS-CoV-2 virions would be produced in diseased lungs, preventing the development of COVID-19.

Introduction

In 2019, the severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2), a novel respiratory RNA virus that causes coronavirus disease 2019 (COVID-19) was discovered [1]. Entering June 2021, COVID-19 has reached over 168 million cases and 3.5 million deaths worldwide (https://covid19.who.int/). However, few have raised an odd pandemic phenomenon: If SARS-CoV-2 is a respiratory viral infection, then why respiratory diseases, such as chronic obstructive pulmonary disease (COPD), are not the leading risk factor for contracting COVID-19? COPD, a disease of expiratory airflow limitation, is caused by prolonged exposure to gaseous toxins, usually cigarette smoke [2]. The same phenomenon can be observed in other pathogenic human coronaviruses that cause severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), where COPD was rarely found (i.e., 0.4–2%) as medical comorbidity among patients [3–8]. In contrast, the prevalence of COPD is often higher than other comorbidities at 20–40% among patients with other common respiratory viral infections, such as influenza and respiratory syncytial viruses [9–14].

Background

In a meta-analysis of 11 studies, the pooled prevalence of COPD among COVID-19 patients was only 1.76%, which equated to a 54% reduced risk of hospitalization compared to the general population [15]. Other meta-analyses synthesizing more studies have also found a low prevalence of COPD among COVID-19 patients at around 2–10% (Table 1). Notably, in a meta-analysis of 77 studies covering 38,906 COVID-19 patients, only 9% had COPD. Intriguingly, this meta-analysis also calculated that, among the Chinese, the prevalence of smoking history and COPD was only 11% and 4% among COVID-19 patients, respectively, which are lower than the general population at 25% and 14% [16]. Using more appropriate data collection methods and analyses, a nationwide study has found that 10–20% of adults in China have COPD [17]. Globally, the prevalence of COPD stands at 13.1% [18]. In contrast, the global prevalence of hypertension, diabetes, and cardiovascular diseases is 30%, 9%, and 6%, respectively [19–21], which is similar to or lower than that observed among COVID-19 patients (Table 1). However, all meta-analyses found COPD as the leading risk

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Table 1
Meta-analyses investigating the prevalence of medical comorbidities among COVID-19 patients.

Study	Study design	Comorbidity	% Prevalence	Clinical outcome
Rogliani et al. [15]	11 studies (10 from China and 1 from the U.S.); N = 8,476 hospitalized patients	Hypertension	23.24% among patients	RR = 1.10 for hospitalization
		Diabetes	13.89% among patients	RR = 2.02 for hospitalization
		CVD/CeVD	11.84% among patients	RR = 1.13 for hospitalization
		CKD	2.34% among patients	N/A
		COPD	1.76% among patients	RR = 0.46 for hospitalization
		CLD	1.44% among patients	N/A
		Asthma	1.2% among patients	RR = 0.86 for hospitalization
Alqahtani et al. [37]	15 studies (14 from China and 1 from the U.S.); N = 2,473 hospitalized patients	COPD	2% among patients	RR = 1.88 for severe cases; RR = 1.10 for death.
Zhang et al. [38]	16 studies (all from China); N = 3,975 patients	Hypertension	34.5% in severe; 16.1% in non-severe cases	OR = 2.50 for severe cases
		Diabetes	17.5% in severe; 7.7% in non-severe cases	OR = 2.06 for severe cases
		CVD	10.8% in severe; 3.4% in non-severe cases	OR = 3.53 for severe cases
		COPD	5% in severe; 1.1% in non-severe cases	OR = 4.67 for severe cases
		CLD	2.5% in severe; 3.2% in non-severe cases	OR = 0.99 for severe cases
		CKD	2.2% in severe; 1.2% in non-severe cases	OR = 1.26 for severe cases
		Malignancy	4% in severe; 1.9% in non-severe cases	OR = 1.66 for severe cases
		CeVD	4.2% in severe; 1.5% in non-severe cases	OR = 2.88 for severe cases
Wang et al. [39]	25 studies (all from China); N = 4,881 cases	Hypertension	33.4% in severe; 21.6% in non-severe cases	RR = 1.4 for severe cases
		Diabetes	14.4% in severe; 8.5% in non-severe cases	RR = 1.53 for severe cases
		CVD	10.4% in severe; 3.3% in non-severe cases	RR = 1.79 for severe cases
		COPD	6.8% in severe; 1.8% in non-severe cases	RR = 2.10 for severe cases
		CLD	3.5% in severe; 3.8% in non-severe cases	No significant differences
		Malignancy	3.5% in severe; 3.7% in non-severe cases	No significant differences
Yin et al. [40]	41 studies (all from China); N = 12,526 hospitalized patients	Hypertension	19% among patients	OR = 2.13 for severe cases
		Diabetes	9% among patients	OR = 2.49 for severe cases
		CVD	6% among patients	OR = 2.76 for severe cases
		COPD	3% among patients	OR = 3.14 for severe cases
		CeVD	3% among patients	OR = 3.7 for severe cases
		CLD	3% among patients	No significant differences
		CKD	2% among patients	OR = 3.6 for severe cases
		Malignancy	1% among patients	OR = 2.63 for severe cases
Gulsen et al. [41]	53 studies (32 from China, 9 from the U.S., and 12 from other countries); N = 658,073 patients	COPD	0.9% among patients	OR = 2.58 for severe cases; OR = 2.42 for death
		CRD	2.9% among patients	OR = 2.14 for severe cases; OR = N/A for death
		Asthma	2% among patients	No significant differences
Dorjee et al. [16]	77 studies (35 from China, 18 from the U.S., 10 from Europe, and 6 from other countries); N = 38,906 hospitalized patients	Hypertension	50% among patients	RR = 1.76 for severe cases; RR = 1.46 for death; CFR = 28%
		Diabetes	28% among patients	RR = 1.48 for severe cases; RR = 1.5 for death; CFR = 24%
		CVD	17% among patients	RR = 1.54 for severe cases; RR = 2.08 for death; CFR = 52%
		COPD	9% among patients	RR = 1.71 for severe cases; RR = 1.7 for death; CFR = 51%
		CLD	2% among patients	RR = 1.63 for severe cases; RR = 2.65 for death; CFR = 39%
		CKD	13% among patients	RR = 1.56 for severe cases; RR = 2.52 for death; CFR = 48%
Badawi and Vasileva [42]	124 studies (105 from China and 19 from North	Obesity	2.1% among patients in China; 22.9% among	N/A

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Table 1 (*continued*)

Study	Study design	Comorbidity	% Prevalence	Clinical outcome
	America); N = 72,025 cases		patients in North America	
		Hypertension	25.6% among patients in China; 47.6% among patients in North America	N/A
		Diabetes	11.8% among patients in China; 34.1% among patients in North America	N/A
		CVD	7.9% among patients in China; 20.8% among patients in North America	N/A
		COPD	3.3% among patients in China; 11.6% among patients in North America	N/A
		Cancer	9.7% among patients in China; 6.6% among patients in North America	N/A
		Liver disease	3.3% among patients in China; 3.1% among patients in North America	N/A
		CKD	2.1% among patients in China; 11.8% among patients in North America	N/A

Abbreviations: CeVD, cerebrovascular diseases; CFR, case fatality rate; CKD, chronic kidney disease; CLD, chronic liver disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease-2019; CRD, chronic respiratory disease; CVD, cardiovascular disease; N/A, not available; OR, odds ratio; RR, risk ratio or relative risk.

factor for poor clinical outcomes of COVID-19 with odds ratio, relative ratio, or case fatality rate similar to or greater than other comorbidities (Table 1).

Notably, these meta-analyses mainly investigated studies performed in China, with a few in the United States (Table 1). Despite that, low COPD prevalence is still evident among COVID-19 patients from other countries. In a South Korea population-based retrospective cohort study of 122,040 COVID-19 cases, only 3.6% had COPD, whereas the prevailing comorbidities were asthma, hypertension, and malignancy at 27%, 26%, and 18%, respectively [22]. This result is consistent with another South Korea cohort study of 4,610 COVID-19 patients, which reported a 3.1% prevalence of COPD [23]. In another retrospective study in Mexico involving 38,342 COVID-19 patients, 29% had hypertension, 28% had obesity, 25% had diabetes, but only 3.1% had COPD [24]. In a Spain registry study of 10,420 COVID-19 patients, comorbidity prevalence was 50% for hypertension, 33% for obesity, 19% for diabetes, and 7% for COPD [25]. An Iran retrospective study of 12,870 COVID-19 patients found that only 2% had a chronic respiratory disease, presumably including COPD [26]. In a prospective cohort study of 3995 COVID-19 patients in Kuwait, 19% had hypertension, 18% had diabetes, and only 0.4% had COPD [27]. These cohort studies, however, did find that COPD patients had a worse prognosis for severe and fatal COVID-19 [22–27]. For reference, the COPD prevalence in the adult general population is 13–15% in South Korea [28,29], 8% in Mexico [30], 10% in Spain [31], 5% in Iran [32], and 7% in Kuwait [33].

More recent studies have, interestingly, compared the prevalence of COPD among patients with COVID-19 and influenza. For example, a nationwide registry study in France has found that only 5.4% of 89,530 COVID-19 patients had COPD, whereas 10% of 45,819 patients with 2018–2019 seasonal influenzas had COPD, with the difference being statistically significant. Other chronic respiratory diseases, namely asthma, cystic fibrosis, and pulmonary hypertension, were also significantly lower in prevalence in the COVID-19 cohort than the influenza cohort [34]. Similarly, in a smaller retrospective study in Italy of 74 critically ill patients, the prevalence of COPD was significantly lower in the COVID-19 group than the influenza group at 20% vs. 58%, respectively [35]. This study reported a high COPD prevalence because only patients with critical disease in the intensive care unit (ICU) were studied, and COPD is a known risk factor for severe COVID-19 (Table 1) and influenza [36].

Therefore, people with COPD seem to have a lower chance of contracting or developing COVID-19 compared to the general population and other medical conditions. However, once COVID-19 is established, people with COPD face an increased risk of mortality on par with, or even greater than, other medical conditions. This brings the question, to restate: If SARS-CoV-2 is a respiratory viral infection, then why is COPD not the leading risk factor for contracting COVID-19?

One plausible explanation is that people with COPD may be stricter in practicing physical distancing or mask-wearing [43,44]. Alternatively, the inhaled corticosteroids and bronchodilators COPD patients use may suppress coronavirus replication [45–48]. Systemic corticosteroid usage has been associated with decreased odds of COVID-19 diagnosis [49]. However, early steroid usage may also induce some level of immunosuppression supportive of coronavirus infection [50,51]. Thus, the relationship between steroid use among COPD patients and the risk of COVID-19 remains ambiguous [52,53]. Current guidelines still advise that COPD patients continue to take their prescribed medications, including corticosteroids, amidst the COVID-19 pandemic, unless under certain situations where the attending physician suggests otherwise [54–56]. Underdiagnosis and overdiagnosis of COPD are also common problems with rates of 10–95% and 5–60%, respectively, worldwide [57,58]. Moreover, persons with COPD are more likely older and have other comorbidities than non-COPD persons [59,60], which further heightens the risk of severe COVID-19. While these are the proposed explanations for the interplay between COPD and COVID-19 thus far, one unnoticed question is how does SARS-CoV-2 interacts with lungs in a diseased state?

SARS-CoV-2 exploits the surface angiotensin-converting enzyme 2 (ACE2) as a receptor to infect cells [61,62]. COPD or active smoking have been shown to upregulate ACE2 mRNA and protein expressions on secretory and epithelial cells in the upper and lower respiratory tracts, respectively, of humans [63–68]. Although the increased ACE2 expression may serve as a protective anti-inflammatory mechanism against the increased inflammation and lung injury COPD or smoking imposed

[69,70], it may also promote the cell binding and replication of SARS-CoV-2. Indeed, an *in vitro* airway epithelium study has revealed increased SARS-CoV-2 replication in primary human bronchial cells isolated from a COPD patient [71]. Furthermore, the SARS-CoV-2-ACE2 binding may decrease the circulating levels of soluble ACE2 and dysregulate the ACE/ACE2 balance to favor the predominance of the pro-inflammatory ACE that perpetuates tissue damage [55,72,73]. Hence, from a mechanistic standpoint, the increased ACE2 expression may explain why patients with COPD (and active smoking history) are more susceptible to severe COVID-19.

However, one study has found decreased ACE2 mRNA and protein levels in bronchial and alveolar epithelial cells from COPD patients compared to healthy controls in two independent cohorts [74]. Moreover, in this study, chronic cigarette smoke treatment *in vivo* and *in vitro* further attenuated ACE2 levels and SARS-CoV-2 replication, respectively [74]. A previous study has also found decreased ACE2 expression in a rat model of COPD exposed to cigarette smoke [75]. In another study, ACE2 expression in the airway epithelium was lower in asthmatic patients but not significantly different between COPD patients and healthy controls [76]. Therefore, the evidence is still conflicting regarding the impact of COPD and smoking on the cellular ACE2 expression. Additional variables are likely involved in the interactions between COPD (and smoking) with SARS-CoV-2.

Hypothesis

COPD causes airflow obstruction through various methods, such as increased airway wall thickness, ciliophagy, and hyperplasia of goblet cells, resulting in airway remodeling and mucous plugging in large and small airways [77,78]. Such mucous plugging compromises the lung immune defenses and trap pathogens and promote respiratory infections, most commonly *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Streptococcus pneumoniae*, and *Moraxella catharralis* [79,80]. Coincidentally, none of these common infections affecting COPD patients are viral in origin. Nonetheless, it may also be possible that mucous plugging hinders pathogens from reaching deeper parts of the lungs, such as the alveoli. SARS-CoV-2 is one prime example where it causes severe COVID-19 once alveolar cells got infected [81,82].

Therefore, it can be hypothesized that patients with COPD may be protected from alveolar infection of SARS-CoV-2. If this hypothesis is correct, SARS-CoV-2 may just localize in the upper respiratory tract, causing asymptomatic or mild infections requiring no hospital care. About 81% of SARS-CoV-2 infections are mild and asymptomatic that are restricted to the upper airways [1,83]. In macaque research model, SARS-CoV-2 replication in the upper respiratory tract only enables viral transmission between hosts, whereas the disease development happens during lower respiratory tract infection [82]. Hence, lungs in a diseased state may make it harder for SARS-CoV-2 to establish COVID-19 at the alveolar level that is sufficiently severe to receive hospital attention.

Another possible hypothesis is that diseased cells may not possess efficient cellular machinery that viruses can exploit. In a diseased state, the cell would be under a heavy burden of oxidative stress and inflammation that damages cell organelles [84,85]. Indeed, oxidative stress-induced endoplasmic reticulum (ER) stress is implicated in the unfolded protein response (UPR) pathophysiology in COPD, where protein translation and synthesis are downregulated to alleviate ER stress [86,87]. Analyzing lung fibroblasts of COPD patients has revealed deficient and disorganized ER and Golgi apparatus, which cannot heal despite being cultured for several weeks in the absence of cigarette smoke [88].

The ER and Golgi apparatus are also essential components for the virion assembly of viruses, including SARS-CoV-2 [89,90]. Indeed, ER capacity is integral for viral replication that demands large amounts of membrane proteins and lipids made in the ER [91,92]. Viruses have, thus, evolved complex mechanisms to modulate and subdue ER stress in the host cell [93,94]. For example, certain RNA viruses can activate the regulated IRE1-dependent degradation (RIDD) to enhance viral protein synthesis via reducing ER stress [92,95]. Coronaviruses, including SARS-CoV-2, could deplete miRNA levels in the host cell to augment viral replication by preventing ER stress and UPR activation [96]. Hence, a heavy cellular ER stress burden would be unfavorable for efficient SARS-CoV-2 replication.

In addition to large and small airways dysfunction, COPD also involves alveolar damage and apoptosis due to mechanisms such as oxidative stress, inflammation, and vascular activation [77,97]. Thus, even when SARS-CoV-2 reaches the alveoli, there may already be a low abundance of healthy cells capable of supporting efficient viral replication. Indeed, viruses including SARS-CoV-2 commonly encode both pro- and anti-apoptotic proteins, of which the latter prevent early cellular apoptosis before viral replication is completed [98–100]. Correspondingly, this also means that apoptotic and damaged cells would not be conducive for SARS-CoV-2 replication. As a result, fewer SARS-CoV-2 virions would be manufactured in the diseased lungs of COPD patients, hindering the successful establishment of COVID-19 (Fig. 1).

These arguments rely on the unfavorable conditions in diseased lungs that prevent SARS-CoV-2 from establishing COVID-19 at the alveolar level. If this argument is accurate, the same should apply to similar viruses and the opposite to dissimilar viruses. During the past SARS and MERS outbreak, only 0.4–2% of infected patients had COPD compared to other comorbidities, such as 10–50% for diabetes, 10–30% for cardiac diseases, and 30–50% for hypertension [3–8]. The latter three comorbidities are also the three most common ones among COVID-19 patients (Table 1). Importantly, their causative agents, SARS-CoV-1 and MERS-CoV, also mainly target the alveolar epithelial cells in the lower respiratory tract to cause diseases [82,101,102]. In contrast, COPD is more prevalent among patients infected with influenza and respiratory syncytial viruses at 20–40% of cases [9–14], higher than the general population at 10–15% [17,18]. Notably, influenza and respiratory syncytial viruses primarily cause upper respiratory tract diseases [103–106]. Thus, it is reasonable to postulate that COPD may promote upper respiratory tract infections but hinder the development of lower respiratory tract infections, such as COVID-19.

Evaluation of the hypothesis

This paper addresses the peculiar phenomenon of low COPD rates among patients with COVID-19. For one, the airway obstruction in COPD may hamper SARS-CoV-2 from reaching deeper parts of the lungs, the alveoli. This can be tested by exposing animal models of COPD to an equivalent SARS-CoV-2 dose as non-COPD animal controls, and determine how often COVID-19 develops. Notably, the doses used should be reasonable and may be low in such cases. The point is to avoid high doses that induce COVID-19 every time, which defeats the purpose of determining rates of COVID-19 development.

In the second part of the hypothesis, even if SARS-COV-2 manages to gain access to the alveoli, cells in a diseased state therein may not be conducive to SARS-CoV-2 replication. One caveat to this hypothesis, however, is that infectious diseases may not solely depend on viral replication, but the host immune responses to the infection or antigen as well [107]. Therefore, future studies might be interested in understanding and comparing how SARS-CoV-2 interacts with healthy and diseased respiratory cells, as well as the immune responses involved. If the hypothesis is correct, respiratory cells in a diseased state would produce fever virions but mount more pathological immune responses than healthy cells.

Last but not least, the currently proposed hypothesis is not without limitations. For one, this hypothesis is founded on the observation that COPD prevalence is higher in the general population than in COVID-19 patients, which is circumstantial evidence that suggests a possible association or causation. However, the observation that prevalence of other comorbidities (e.g., hypertension, diabetes, and cardiovascular

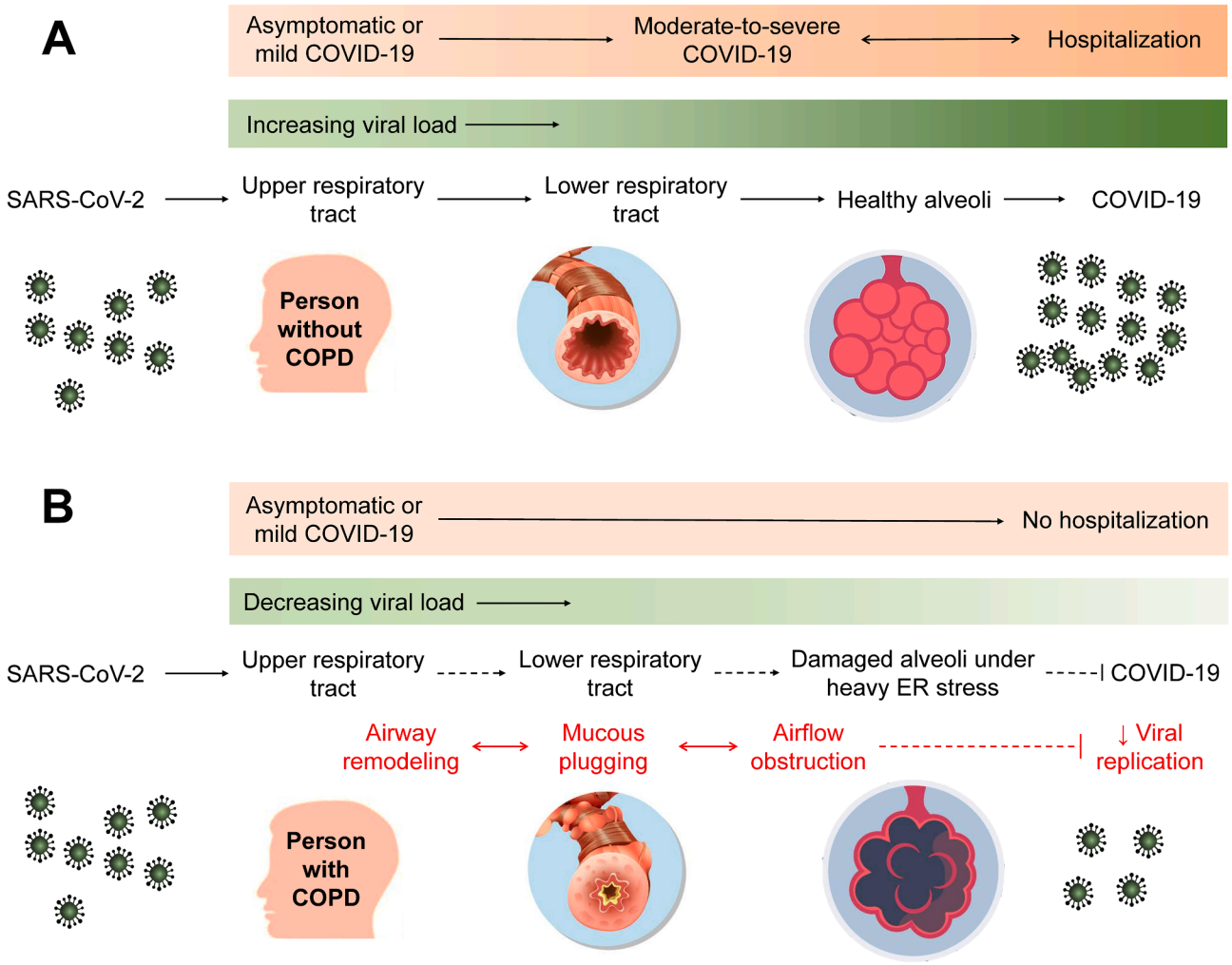

Fig. 1. An overview of hypothetical scenarios in which SARS-CoV-2 may replicate in persons with and without COPD. (A) In people without COPD, initially contracted viral load may increase over time as SARS-CoV-2 reaches the lower respiratory tract and replicates itself. (B) In people with COPD, initially contracted viral load may decrease over time as the airway remodeling and mucous plugging pathology may hinder SARS-CoV-2 from reaching the lower respiratory tract. Moreover, the alveolar cells of COPD persons may be overly damaged and under a heavy ER stress burden to support efficient viral replication. As a result, fewer SARS-CoV-2 virions would be manufactured, lowering the chances of COVID-19 establishment. Abbreviations: COPD, chronic obstructive pulmonary disease COVID-19, coronavirus disease 2019 ER, endoplasmic reticulum SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. Note: Icons were derived from Vecteezy.com.

diseases) was similar or higher in COVID-19 patients than the general population further lends credence to the discrepant COPD prevalence argument. Nevertheless, no studies with proper control groups have confirmed that COPD patients are less likely to develop symptomatic COVID-19 requiring hospital attention than the general population, which future studies might want to investigate. Second, the proposed hypothesis argues that diseased lungs are unfavorable for efficient SARS-CoV-2 replication; however, this concept remains speculative that contrasts the conventional view that infections develop easier in compromised than in healthy hosts.

Consequences of the hypothesis

If the hypothesis proposed herein is accurate, it will advance the understanding of virus-host interactions one step further, particularly in the area of coronavirus and pulmonology. Thus far, at least to the author's knowledge, limited or no mechanisms have been characterized in how viruses interact with respiratory cells in diseased versus healthy states. Interestingly, the odd phenomenon of low COPD rates among patients seems unique to COVID-19 (Table 1), as well as SARS and MERS [3–8]. In contrast, the prevalence of COPD and other pulmonary diseases were often higher than other medical comorbidities among patients with influenza or respiratory syncytial virus infections at about 20–40% [9–14]. Deciphering why host susceptible factors vary in response to different respiratory viral infections would also be an area of research interest. Discovering why COPD is remarkably rare in patients with COVID-19 may also cast light on new aspects of the disease not previously understood.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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