



Chronic obstructive pulmonary disease and COVID-19: interrelationships

Dave Singh^{a,b}, Alexander G. Mathioudakis^a and Andrew Higham^a

Purpose of review

Chronic obstructive pulmonary disease (COPD) and COVID-19 have many potentially negative interrelationships, which may influence the course of infection and clinical outcomes. The aim of this review is to provide clinicians with an up-to-date perspective of the complex interactions between COPD and COVID-19.

Recent findings

We consider mechanisms that could increase SARS-CoV-2 infection susceptibility in COPD, including increased ACE2 expression, reduced antiviral defence and dysfunctional immunity. We review evidence that COPD is associated with worse clinical outcomes from COVID-19 in analyses that have adjusted for confounding factors, and describe the mechanisms responsible. We discuss the use of inhaled corticosteroids in the context of susceptibility to COVID-19, and consider the impact of COVID-19 on the usual care of COPD patients.

Summary

The current review highlights the evidence that COPD patients have worse outcomes from COVID-19, and the multiple mechanisms responsible.

Keywords

bacteria, coagulopathy, small airway disease, thrombosis, virus

INTRODUCTION

Coronavirus disease 2019 (COVID-19) pandemic has been caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. This highly transmissible virus [2] can cause mild viral illness, while more severe cases display systemic inflammation, pneumonia and acute severe respiratory failure [3]. COVID-19 respiratory failure is often associated with good lung compliance, implicating vascular injury and vasoconstriction as central mechanisms of respiratory insufficiency [4]. COVID-19 pneumonia appears to be caused by pulmonary exudate due to microvascular injury [5,6]. Systemic manifestations are common in severe COVID-19, with endothelial injury causing cardiac, renal and neurological complications [7]. These pulmonary and systemic disease components cause a high mortality in COVID-19 patients admitted to hospital, which is increased in older individuals and those with comorbidities including obesity and cardiovascular disease [3,8,9].

Chronic obstructive pulmonary disease (COPD) occurs in older individuals due to persistent inhalation of noxious particles, commonly from cigarette

smoking [10]. The pulmonary disease includes airway inflammation and remodelling, with variable alveolar destruction (emphysema) [11]. COPD patients suffer with dyspnoea, cough and sputum production, and may experience sudden worsenings (exacerbations) that are often caused by respiratory tract infections [10]. In addition, COPD is associated with a high prevalence of comorbidities such as cardiovascular disease and diabetes, which is not

^aDivision of Infection, Immunity and Respiratory Medicine, School of Biological Sciences, Faculty of Biology, Medicine and Health, Manchester Academic Health Science Centre, The University of Manchester and Manchester University NHS Foundation Trust and ^bMedicines Evaluation Unit, The Langley Building, Manchester, UK

Correspondence to Dave Singh, The University of Manchester Faculty of Biology Medicine and Health, Manchester, M23 9QZ, UK.

Tel: +44 161 946 4050; e-mail: dsingh@meu.org.uk

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KEY POINTS

- Analyses adjusted for confounding variables show increased hospitalization and mortality in COPD patients with COVID-19.
- COPD patients may be at an increased risk for microthrombosis, the detrimental effect of increased intrapulmonary shunting and secondary bacterial infection.
- Systemic and inhaled corticosteroids improve COVID-19 related outcomes.

surprising in an older population with a significant smoking history. COPD and COVID-19 therefore have many potentially negative interrelationships, which may lead to worse outcomes from COVID-19, including impaired pulmonary function, older age and the presence of comorbidities in COPD patients. Furthermore, COPD patients may also be more susceptible to acquiring viral infections including SARS-CoV-2 [12].

This review addresses interrelationships between COPD and COVID-19. The mechanisms that could cause increased SARS-CoV-2 infection susceptibility in COPD patients are considered. The evidence that COPD is associated with worse clinical outcomes from COVID-19 is reviewed, and whether the use of inhaled corticosteroids (ICS) alters outcomes. We also consider the impact of COVID-19 on the usual clinical care of COPD patients.

SARS-COV-2 INFECTION SUSCEPTIBILITY

Cellular tropism of SARS-CoV-2 infection is determined by the expression of receptors for the virus, including angiotensin-converting enzyme 2 (ACE2) [13]. Bronchial and alveolar epithelial cells, and pulmonary endothelial cells express ACE2, and are infected with virus in COVID-19 cases [6,14]. Protein and gene expression studies have reported increased expression of ACE2 in COPD epithelial cells compared to controls [15–17], with increased expression in COPD patients with a higher BMI and more frequent exacerbations also observed [18,19]. There are inconsistent findings regarding changes in accessory protein expression, including transmembrane serine protease 2 (TMPRSS2) and furin [20]. Expression of intracellular adhesion molecule-1 (ICAM-1), the receptor for rhinovirus, is also increased in the lungs of COPD patients. [21,22] Overall, these observations suggest increased opportunities for viral entry in COPD lungs. However, this by itself is unlikely to determine the clinical outcome to infection; reduced host antiviral defence

and immune system dysfunction in COPD patients may also combine to promote host permissiveness.

There is evidence that host antiviral responses, notably interferons, are dampened in COPD patients. During experimental rhinovirus infection, the production of interferon (IFN)- α , β and λ from bronchoalveolar lavage cells was lower in COPD patients than in controls, albeit only significant for IFN- β [23]. COPD patients experienced more respiratory symptoms and also had a higher viral load and increased markers of inflammation. An immunohistochemistry study showed significantly lower bronchial epithelial and alveolar macrophage expression of IFN- β in COPD patients compared to controls [24]. Furthermore, sputum levels of IFN- β and IFN- λ are lower from COPD patients with more exacerbations, suggesting that reduced host defence against viral infection associates with worse clinical outcomes [25]. Reduced IFN production may be caused by reduced signalling by pattern recognition receptors; bronchial epithelial expression of melanoma differentiation-associated gene-5 (MDA-5) and retinoic acid-inducible gene-1 (RIG-1) are reduced in COPD patients compared with controls [24], suggesting that COPD bronchial epithelial cells are less adept at mounting antiviral responses. Indeed, Veerati *et al.* [26] reported that IFN- β production and antiviral gene expression by COPD epithelial cells were delayed following rhinovirus infection. Although antiviral responses using COPD lung cells exposed to SARS-CoV-2 have not been studied, evidence using other viral exposure models indicates a downregulation of interferon defence mechanisms.

Lymphopenia and T cell dysfunction are associated with worse outcomes in COVID-19 [27]. T cells in the lungs of COPD patients display increased expression of programmed cell death protein 1 (a marker of T-cell exhaustion), while T-cell receptor (TCR) expression is decreased compared with controls [28,29]. These observations indicate that COPD T cells are dysfunctional; this is supported by reports of reduced degranulation by COPD lung T-cells in response to influenza infection, and reduced cytokine production from COPD blood T-cells following TCR activation [28,30]. T-cell dysfunction in COPD patients may cause suboptimal host defence responses to SARS-CoV-2 infection.

CLINICAL OUTCOMES IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS WITH COVID-19

Despite extensive published research, our knowledge concerning risk factors for developing COVID-19 and for adverse outcomes of COVID-19

has been hampered by poor methodological design of some studies coupled with inadequate consideration of confounding factors [20,31].

It was proposed that COPD or smoking (either a current or previous history) confers a protective effect against contracting COVID-19, based on the lower-than-expected prevalence of COPD and current or previous smoking history among patients diagnosed with COVID-19 [32–35]. However, patients with COPD or other conditions associated with smoking have been shielding during the pandemic, thus limiting their likelihood of contracting SARS-CoV-2 infection [20]. Furthermore, the proposed protective effects were mostly based on studies retrospectively evaluating routinely collected hospital clinical data. The quality and completeness of such clinical records could be questioned [36] during the pandemic that pressurized health systems [37] increasing the likelihood of under-reporting of smoking history or COPD.

The potential for negative effects of COPD on COVID-19 outcomes can be overestimated if confounding factors, including age, sex and comorbidities, are not fully addressed [38,39]. We previously reviewed cohort studies performed in 2020 [20], which mostly reported that COPD was a risk factor for worse clinical outcomes in hospitalized COVID-19 patients, although most did not adequately address for confounding [17]. In order to overcome potential selection bias in these studies, which can arise due to only considering the cohort of individuals admitted to hospital with COVID-19, Aveyard *et al.* [40^{***}] performed an analysis using a UK community-based population of more than 8 million individuals with 14 479 hospitalised with COVID-19. COPD was a significant risk factor for hospitalization and death [hazard ratio 1.54, confidence interval (CI) 1.45–1.63, and hazard ratio 1.54, CI 1.42–1.67, respectively] after adjustment for age, sex and comorbidities. The unadjusted hazard ratios were considerably higher (>5), highlighting the influence of confounding factors. Interestingly, using the adjusted model data, the risk was higher in younger COPD patients, probably reflecting the dominant poor prognostic influence of age (relative to COPD) in older individuals.

Several meta-analyses have evaluated whether COPD and smoking history are risk factors for COVID-19 outcomes. Only three of them adjusted for potential confounding factors [41,42]. Izcovich *et al.* [41] included preferably adjusted data, without excluding nonadjusted data, and identified both COPD and current smoking status as strong predictors of worse outcomes including mortality. A sensitivity analysis, including adjusted data only, showed consistent results, but were not presented in detail. However, this meta-analysis adjusted for age, at least one

comorbidity and one estimate of COVID-19 severity, such as respiratory rate. The latter violates the temporality between the prognostic factor and outcome, creating difficulties in interpretation. Xiao *et al.* [42] only included adjusted data in their meta-analysis, and reported an association between COPD and COVID-19 mortality [odds ratio (OR) 1.53, CI 1.29–1.8]. This meta-analysis had two important limitations: ORs were pooled with hazard ratios, which is questionable, and any adjustment strategy was acceptable regardless of the adjusting factors used. Interestingly, eight of the 11 included studies presenting adjusted ORs did not yield significant results.

However, these meta-analyses were followed by the publication of adjusted data from larger cohorts (Fig. 1). The US National COVID Cohort Collaboration (N3C), with more than 3.4 million patients, including more than 387 000 patients with COVID-19 including more than 7500 COPD patients demonstrated an association between COPD and COVID-19 mortality (OR: 2.1, 95% CI: 1.96–2.26), after adjusting for age, sex and comorbidities [43^{***}]. Similarly, data from the Kaiser-Permanente Southern California electronic patient records based on 61 338 adults with COVID-19, including 820 patients with COPD, found a significant association of COPD with COVID-19 related 60-day mortality (hazard ratio: 1.67, 95% CI: 1.37–2.03), hospitalization (OR: 1.27, 95% CI: 1.05–1.53) and intensive respiratory support (OR: 1.49, 95% CI: 1.16–1.92), after adjusting for relevant covariates, including age, sex, ethnicity, main demographics and the Charlson's comorbidity score [44].

Risk factors associated with severe COVID-19 among patients with COPD ($n = 68\,902$) were evaluated in the Swedish National Airway Register [45]. Multivariate analyses revealed that severe COVID-19 was associated with older age, male sex, lower educational level, underweight or obesity, FEV₁ less than 50% predicted and a COPD Assessment test score at least 18.

Overall, although confounding factors exist in the multiple studies on this topic, the large cohort studies of Aveyard *et al.* [40^{***}], the N3C and Kaiser-Permanente databases demonstrate that COPD is associated with worse outcomes from COVID-19 after adjusting for confounding factors.

WORSE COVID-19 CLINICAL OUTCOMES IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS; MECHANISTIC EXPLANATIONS

COVID-19 hypoxaemia arises due to widespread pulmonary intravascular clots and alveolar oedema, which reduces perfusion and ventilation, respectively, in the capillary bed [46]. This ventilation/perfusion (V/Q)

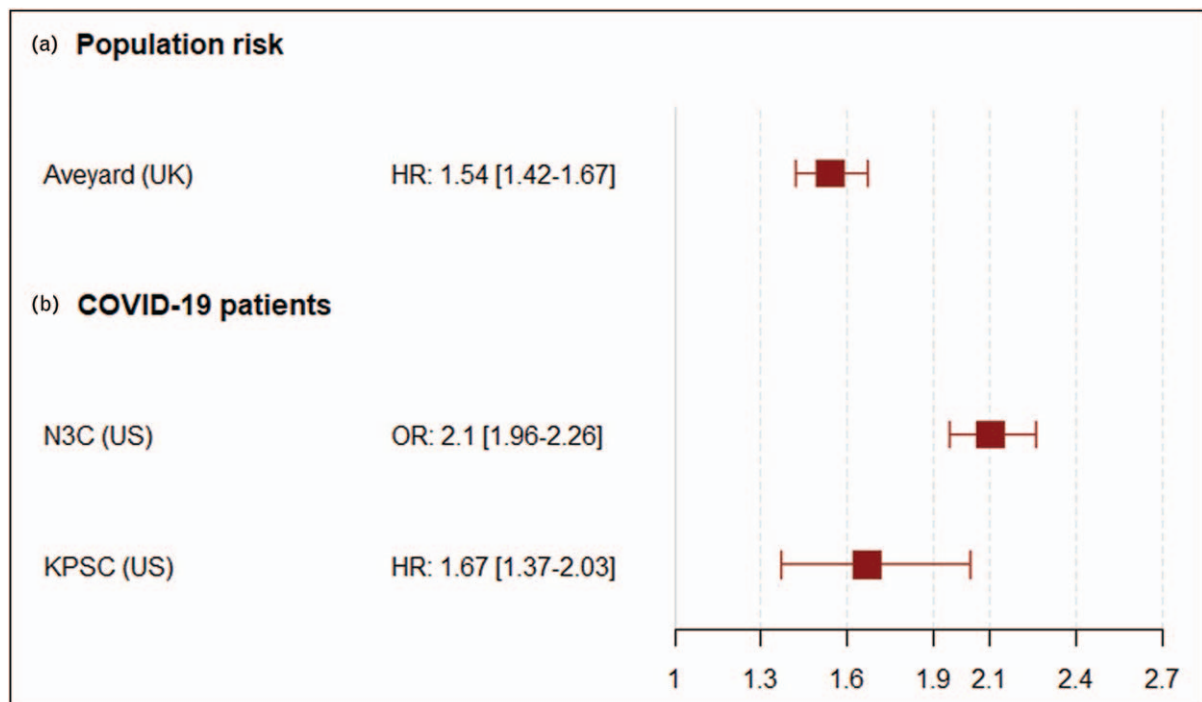


FIGURE 1. Preexisting chronic obstructive pulmonary disease and adjusted COVID-19 mortality risk. Risk was evaluated (a) in a population-based cohort, (b) in extensive cohorts of patients with confirmed COVID-19.

mismatching causes hypoxic pulmonary vasoconstriction, thereby restricting blood flow to areas of impaired gas exchange [47] and causing intrapulmonary shunting of blood to other areas. Kotwica *et al.* [48] showed that increased intrapulmonary shunting was associated with worse COVID-19 outcomes, including mortality. COPD patients have compromised ventilation due to small airway disease and emphysema [11], and therefore have poor respiratory functional reserve to cope with intrapulmonary shunting, as this may divert blood to areas with impaired gas exchange due to COPD pathophysiology.

Hypoxic pulmonary vasoconstriction increases fluid shear stress in pulmonary vessels, leading to platelet aggregation and increased risk for thrombus formation [49,50]. Hypoxic pulmonary vasoconstriction occurs in COPD patients (without COVID-19) due to reduced ventilation [51], which predisposes to in-situ thrombus formation; this pathophysiology can be worsened by COVID-19. Hypoxic pulmonary vasoconstriction is associated with increased pulmonary hypertension in COPD due to vascular remodelling [52]; again, this may be further worsened by COVID-19.

Pulmonary thromboembolism is typical of severe COVID-19 [53], due to the development of thrombosis within smaller pulmonary vessels [6] due to increased coagulation and endothelial cell dysfunction [54]. COPD patients (without COVID-19) also display higher circulating pro-coagulation

markers, which are further increased during exacerbations [55–58], and increased numbers of apoptotic endothelial cells and markers of endothelial cell dysfunction [59]. These data suggest increased susceptibility of COPD patients to thromboembolic events due to coagulopathy and endothelial cell dysfunction may be further worsened by COVID-19.

Secondary bacterial infection is common amongst COVID-19 patients, causing worse outcomes [60]. Many COPD patients have colonizing pathogenic bacteria in the airways during the stable state, which cause secondary bacterial infections following respiratory viral infections [61,62]. This may be due to dampened antimicrobial responses; viral infection reduces bacterial phagocytosis by COPD alveolar macrophages and reduces antimicrobial peptide release in COPD patients [61,63].

Overall, there are multiple mechanisms to explain worse COVID-19 outcomes in COPD patients. The most important mechanisms are increased risk for micro-thrombosis, the effects of intrapulmonary shunting and the potential for secondary bacterial infection (Fig. 2).

CHRONIC OBSTRUCTIVE PULMONARY DISEASE, COVID-19 AND INHALED CORTICOSTEROIDS

Experimental studies using cultured cells have shown that corticosteroids can attenuate SARS-

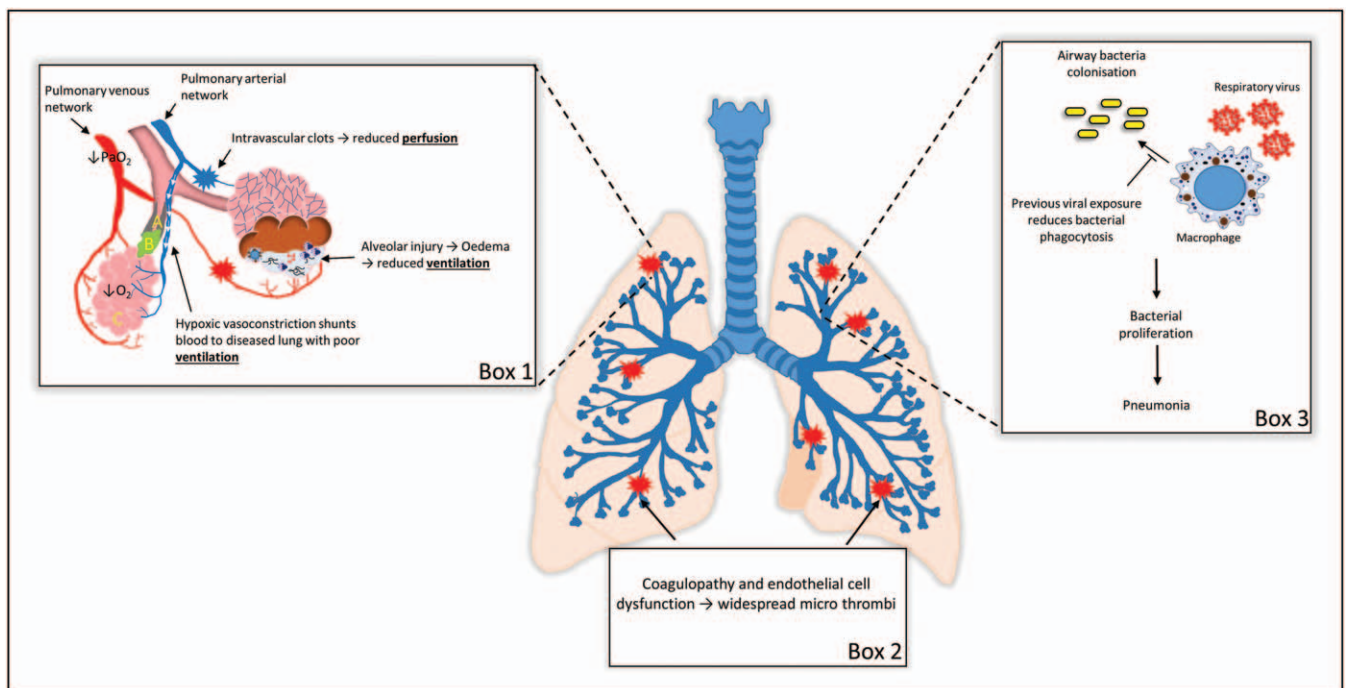


FIGURE 2. Worse clinical outcomes from COVID-19 in chronic obstructive pulmonary disease patients. Box 1: Reduced perfusion and ventilation leads to hypoxic vasoconstriction and intrapulmonary shunting of blood to other areas of the lung. In COPD patients, this may divert blood to areas with poor ventilation as a result of COPD pathophysiology: (a) reduced lumen diameter and increased airway wall thickening; (b) mucous plugs; (c) alveolar wall destruction. Box 2: coagulopathies and endothelial cell dysfunction increase the risk of micro-thrombosis. Box 3: secondary bacterial infection as a result of reduced host defence may lead to pneumonia.

CoV-2 replication [64,65]. The RECOVERY clinical trial ($n = 6435$) demonstrated that the corticosteroid dexamethasone (administered orally or intravenously) decreased mortality in hospitalized COVID-19 patients requiring oxygen or mechanical ventilation [66²²]. In addition, a phase 2 clinical trial ($n = 146$) showed that inhaled budesonide administered in the community in the early stages of COVID-19 reduced the need for urgent medical care and improved the recovery time [67]. Overall, these laboratory and clinical studies support a protective role for corticosteroids against COVID-19.

A retrospective analysis of electronic health records has been performed to investigate clinical outcomes in COPD patients in the UK treated with or without ICS. The OpenSAFELY UK primary care cohort analysed mortality outcomes in COPD patients ($n = 148\,557$); COVID-19 associated mortality was increased in ICS users versus nonusers [68²³]. Importantly, adjusting for confounding factors decreased the hazard ratio, and the fully adjusted model in patients of white ethnicity showed no detrimental effects of ICS use. Non-COVID-19 deaths were also higher in patients using ICS, highlighting the confounding effect of disease severity on mortality outcomes. Aveyard *et al.* [40²⁴] studied outcomes

in 193 520 COPD patients using primary care records; we discussed earlier that hospitalization and mortality rates were increased in COPD patients. The authors also reported increased hospitalization and mortality rates in ICS users versus nonusers in an unadjusted analysis, but that no detrimental effect of ICS use was observed after adjustment for demographic factors and medication use.

The overall weight of scientific information does not support any detrimental effect of ICS use with regard to COVID-19 outcomes in COPD patients. Indeed, the beneficial effects of systemic and ICS administered acutely to treat COVID-19 indicates a protective effect of this drug class in this scenario. The GOLD 2020 science committee report on COVID-19 accordingly recommends that for COPD patients the use of ICS as a maintenance treatment should not be changed during this pandemic [69²⁵].

CLINICAL CARE OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE DURING COVID-19 PANDEMIC

The COVID-19 pandemic has caused virtual COPD outpatient care to become commonplace, minimizing exposure risks and offering time savings through

Table 1. COPD and COVID-19 interrelationships; key points

SARS-CoV-2 infection; mechanisms of increased susceptibility in COPD	Clinical outcomes in COPD patients with COVID-19	Worse COVID-19 clinical outcomes in COPD patients; mechanistic explanations	COPD, COVID-19 and ICS
Increased ACE2 expression in lung epithelium [15–17] Reduced antiviral defence [25] Dysfunctional immunity [27,29]	Confounding factors need to be controlled for in epidemiological data. Analyses adjusted for confounding variables show increased hospitalization and mortality [40 [■] ,43 [■] ,44]	Increased risk for micro-thrombosis due to endothelial cell dysfunction and coagulopathy [55–59] Detrimental effects of increased intra-pulmonary shunting [48 [■]] Secondary bacterial infection [61,62]	Corticosteroids reduce SARS-CoV-2 replication [64,65] Systemic and inhaled corticosteroids improve COVID-19 related outcomes [66 [■] ,67], although not studied specifically in COPD

less travel. However, reduced personal contact can cause problems in scenarios, such as inhaler technique training and complex discussions.

Shielding strategies reduce the risks of viral transmission, and there have been reports of decreased COPD hospitalizations for exacerbations during the COVID-19 pandemic [70]. However, avoidance of hospitals for fear of contracting COVID-19 might also contribute to these observations. Shielding has placed restrictions on the mobility and social interactions of COPD patients. In the author's personal experience, this can cause problems with physical deconditioning in some patients due to weight gain and/or loss of muscle strength, while social isolation can cause negative psychological issues.

Access to spirometry has been reduced to reduce risks associated with aerosolization of viral particles. Nevertheless, spirometry remains an essential part of COPD diagnosis and follow-up monitoring, and efforts should be made to conduct this in well tolerated environments.

CONCLUSION

This review highlights evidence from epidemiological analyses that COPD patients have worse outcomes from COVID-19. There are biological mechanisms that cause COPD patients to be more susceptible to acquiring viral infections, and to the pathophysiological consequences of COVID-19, including micro-thrombosis, the effects of intrapulmonary shunting and secondary bacterial infection. Interestingly, evidence suggests that ICS may protect against COVID-19, although this has not been directly confirmed in COPD patients. These interrelationships between COPD and COVID-19 are summarized in Table 1. A consequence of COVID-19 has been increased anxiety and isolation in COPD patients, with potentially harmful long-term consequences.

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Conflicts of interest

D.S. received personal fees from Aerogen, AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici S.p.A., Cipla, Genentech, GlaxoSmithKline, Glenmark, Gossamerbio, Novartis, Pfizer Inc., Pulmatrix, Teva, Theravance Biopharma, Menarini and Verona Pharma. A.H. and A.G. have no conflicts of interest.

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