

REVIEW

COVID-19 Susceptibility in chronic obstructive pulmonary disease

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Abstract

In barely nine months, the pandemic known as COVID-19 has spread over 200 countries, affecting more than 22 million people and causing over than 786 000 deaths. Elderly people and patients with previous comorbidities such as hypertension and diabetes are at an increased risk to suffer a poor prognosis after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

Although the same could be expected from patients with chronic obstructive pulmonary disease (COPD), current epidemiological data are conflicting. This could lead to a reduction of precautionary measures in these patients, in the context of a particularly complex global health crisis.

Most COPD patients have a long history of smoking or exposure to other harmful particles or gases, capable of impairing pulmonary defences even years after the absence of exposure. Moreover, COPD is characterized by an ongoing immune dysfunction, which affects both pulmonary and systemic cellular and molecular inflammatory mediators. Consequently, increased susceptibility to viral respiratory infections have been reported in COPD, often worsened by bacterial co-infections and leading to serious clinical outcomes.

The present paper is an up-to-date review that discusses the available research regarding the implications of coronavirus infection in COPD. Although validation in large studies is still needed, COPD likely increases SARS-CoV-2 susceptibility and increases COVID-19 severity. Hence, specific mechanisms to monitor and assess COPD patients should be addressed in the current pandemic.

KEYWORDS

biomass smoke, COPD, coronavirus, pneumonia, SARS-CoV-2, smoking

1 | INTRODUCTION

In the middle of December 2019, Chinese health authorities detected a series of pneumonia cases caused by an unknown agent in Wuhan, the capital of Hubei province. The causative agent was soon identified as a new strain of human-infecting coronavirus,¹ firstly named 2019 novel coronavirus (2019-nCoV) and later renamed as severe acute respiratory

syndrome coronavirus 2 (SARS-CoV-2). The infection disease caused by SARS-CoV-2, known as coronavirus disease 2019 (COVID-19), varied from asymptomatic or common cold-like symptoms such as dry cough, fever and tiredness to severe dyspnoea and respiratory failure.² This initial outbreak alarmingly spread through China and other countries, and barely three months later, the World Health Organization (WHO) formally declared COVID-19 a global pandemic.³

As of August 19, there have been more than 22,418,000 cases and 786,664 deaths by COVID-19 worldwide.⁴

Like in other infectious diseases, certain population groups have been reported to suffer a higher risk of severe clinical course of COVID-19. Among them, patients with hypertension and diabetes seem the most significant, comprising the 23.7% and 16.2% of patients in critical conditions, respectively.^{5,6} To a lesser extent, patients with coronary heart disease and cerebrovascular disease have also been repeatedly reported in severe cases, while older adults are the age group with highest mortality rates by COVID-19.^{7,8} Moreover, it is reasonable to expect that patients with chronic respiratory diseases are also in the population risk group. Indeed, WHO acknowledges that conditions that increase oxygen needs or reduce the ability of the body to use it properly will put patients at higher risk of serious lung conditions such as pneumonia.⁹

Chronic obstructive pulmonary disease (COPD) is a leading cause of death and disability globally, characterized by persistent respiratory symptoms and airflow limitation due to airway inflammation and/or alveolar abnormalities.¹⁰ The Global Initiative for Chronic Obstructive Lung Disease (GOLD) recognizes COPD patients among the worst affected by COVID-19.¹¹ In the present review, the available evidence pointing to COPD patients as more prone to suffer a severe

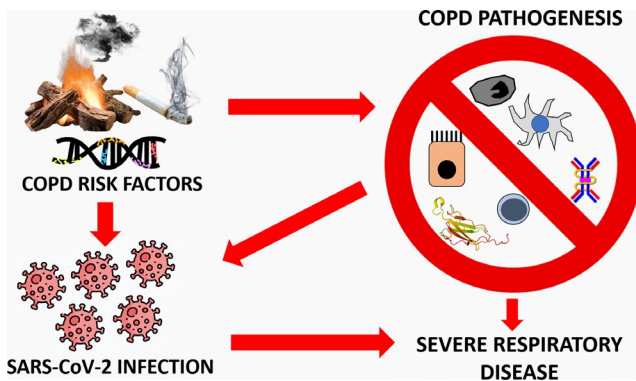


FIGURE 1 Pathophysiological mechanisms involved in COPD and SARS-CoV-2 infection. Chronic obstructive pulmonary disease risk factors include genetic predisposition and exposure to certain noxious particles or gases, among others. These factors could also favour COVID-19 development. Hence, the increased genetic expression of ACE-2 or the chronic exposure to cigarette or biomass smoke found in patients with COPD could favour SARS-CoV-2 infection in pulmonary cells. Moreover, COPD patients have been shown to have an immune dysfunction, affecting the mucociliary clearance and the activity of alveolar macrophages, dendritic cells, cytotoxic and regulatory T cells, as well as the production of antiviral molecules such as IFN- β and sIgA. These make those individuals more susceptible to suffer respiratory infections and exacerbations that impair lung function. Consequently, COPD patients are at higher risk to be infected by SARS-CoV-2 and to suffer a severe prognosis of COVID-19

Key messages

- Although COPD is under-represented in the comorbidities reported for patients with COVID-19, substantial evidence points to COPD patients as ‘at high-risk’ population in this pandemic.
- Most COPD patients have a long history of exposure to harmful particles or gases, capable of impairing pulmonary defences even years after the absence of exposure.
- COPD mechanisms include an immune dysfunction state that renders patients a higher vulnerability to viral and bacterial infections.

COVID-19 clinical course is discussed, and the pathophysiological mechanisms linking both diseases are explained (Figure 1).

2 | THE INFLUENCE OF COPD RISK FACTORS ON COVID-19

COPD emerges from a complex interaction between genetic predisposition and environmental factors. While over 97 independent genetic associations with lung parameters defining COPD and with COPD risk have been described,¹² cigarette smoking is by far the main environmental risk factor for COPD. Hence, between 15% and 50% of smokers develop COPD, whereas 80 to 90% of COPD patients are smokers or ex-smokers.^{13,14} To date, no definitive evidence on whether ever-smokers is at an increased risk of COVID-19. However, WHO argues that tobacco users may be at higher risk of SARS-CoV-2 infection, since smoking implies repetitive hand-to-face contact and often sharing of mouthpieces and hoses, all of which could facilitate the virus entry.⁹ In turn, a recent study on 1,099 COVID-19 patients reported that 12.7% of current smokers died or suffered a severe clinical condition compared to only 4.7% among never-smokers.¹⁵ Moreover, 16.9% of severe cases were ever-smokers compared to 11.8% of milder cases.¹⁵ In this sense, a recent systematic review by Vardavas and Nikitara concluded that smoking is most likely associated with negative progression and adverse outcomes of COVID-19.¹⁶ On the other hand, a meta-analysis conducted by Lippi and Henry based on data from Chinese patients suggests that active smoking is not significantly associated with COVID-19 severity.¹⁷

In spite of this contradictory data, the deleterious effects of cigarette smoking on lung defences are well-known.^{18,19} Smoking impairs the mucociliary clearance, alters humoral

response to antigens and affects alveolar macrophages responsiveness, thus increasing the susceptibility to respiratory infections.²⁰⁻²² Moreover, it has also been reported that cigarette smoking decreases the number and cytotoxic activity of natural killer (NK) cells, one of the main lines of defence against viral infections.^{23,24} It is not strange, thus, to find increased death rates from influenza and pneumonia among smokers.^{25,26} Cigarette smoking is also associated with a systemic inflammatory pattern.²⁷

Importantly, it has been shown that the immune changes found in COPD patients are an amplification of those present in smokers who do not develop COPD.^{28,29} In addition, these pulmonary and systemic alterations persist after smoking cessation.^{30,31} Hence, an impaired response against SARS-CoV-2 or other pathogens could be expected despite current smoking status in COPD patients. Although the molecular basis for the amplification and 'chronification' of these alterations remains obscure, it is accepted that both genetic and epigenetic factors are involved.²⁸ In this sense, a recent study from Mostafaei and colleagues used machine-based learning algorithms to find novel genes associated with COPD.³² They identified 44 candidate genes whose expression was significantly regulated by smoking and/or COPD. Among the most significant, the authors stressed the novel *PRKAR2B* gene, which encodes an important protein kinase in cAMP signalling, a protective factor in the lung and COPD. Interestingly, *PRKAR2B* expression was significantly downregulated in COPD patients who smoked more than 50 packs per year.³²

In addition to cigarette smoking, other risk factors for COPD development could also be related to COVID-19 incidence and prognosis. For instance, exposure to smoke coming from biomass burning (biomass smoke, BS), which affects 3 billion people worldwide, has also been recognized as one of the main risk factors for COPD, especially among nonsmokers.³³ Importantly, like tobacco smoke (TS), BS has been shown to alter pulmonary defences, and this effect could conceivably also be enhanced and sustained in COPD patients.³⁴ In this regard, although COPD caused by BS and TS present some differential hallmarks, patients with double exposure have worse blood oxygenation.³⁵ In any case, the impact of BS on lungs is supported by several epidemiological studies reporting increased risks of acute respiratory infections (ARIs) in people exposed to this environmental pollutant.^{36,37} Also, *in vitro* studies confirm that BS exposure alters or impairs antiviral response of lung cells.^{38,39} Although no study is available yet on the risk of SARS-CoV-2 infection and BS exposure, a recent report from investigators of University of Harvard reported an increased mortality rate by COVID-19 associated to long-term exposure to PM_{2.5}, one of the main components of BS.⁴⁰

Suffering from respiratory infections during childhood also been long recognized as a risk factor for COPD

development.⁴¹ However, whether these infancy infections are involved in COPD development per se or are a consequence of previous factors determining an impaired lung function is a subject of debate. Hence, although it has been reported that respiratory syncytial virus infection (RSV) or a history of pneumonia during childhood are associated to impaired lung function and risk of developing COPD,⁴²⁻⁴⁴ it has also been demonstrated that people born with a diminished airway function are more likely to suffer COPD symptoms and subsequent viral infections.⁴⁵⁻⁴⁷ In any case, there is no doubt that subjects who develop COPD are at an increased risk of suffering respiratory infections, a matter of importance in the context of COVID-19 pandemics. This subject is discussed in the next section.

3 | SUSCEPTIBILITY TO RESPIRATORY VIRAL INFECTIONS IN COPD

Although COPD is mainly a chronic disease, a substantial number of patients suffer from exacerbations, defined as acute and sustained worsenings of the patient's condition from stable state and beyond normal day-to-day variations, requiring medication changes or hospitalization.⁴⁸ Exacerbations arise from several risk factors and triggers, being viral infections one of the most important causes.⁴⁹ Hence, viruses are responsible for a half to two-thirds of COPD exacerbations,⁵⁰ while these pathogens are also identified in over 10% of all stable COPD patients, being associated with worse clinical outcomes.⁵¹ Picornaviruses, influenza A, RSV and parainfluenza are among the most detected viruses in COPD exacerbations.⁵² Regarding the incidence of coronavirus infection in COPD patients, the available data are scarce. Notwithstanding, a study assessing the presence of SARS-CoV through RT-PCR in 141 patients with mild to moderate COPD reported no trace of infection.⁵³ By contrast, another study reported presence of coronavirus in 5.9% of stable COPD patients,⁵⁴ whereas several coronaviruses were associated with multiple respiratory and systemic symptoms, as well as with hospitalizations, in a cohort of 2,215 COPD patients.⁵⁵

The fact that COPD patients could be more susceptible to respiratory infections is sustained by mounting evidence. Thus, *in vitro* and *in vivo* studies have demonstrated that patients with COPD have increased viral titre and copy numbers after rhinovirus infection than control subjects.⁵⁶⁻⁵⁸ Moreover, an upregulation of intercellular adhesion molecule-1 (ICAM-1), which is the rhinovirus major group receptor, has been reported in airways and parenchyma of COPD patients.^{59,60} Likewise, Seys and co-workers showed an upregulated expression of dipeptidyl peptidase IV (DPP4), a type II transmembrane glycoprotein that serves

as receptor for Middle East respiratory syndrome coronavirus (MERS-CoV), in COPD patients.⁶¹ Interestingly, both DPP4 mRNA and protein levels were inversely correlated with lung function and diffusing capacity. The authors concluded that increased DPP4 expression could partially explain why COPD patients are more susceptible to MERS-CoV.⁶¹ Regarding COVID-19, a recent paper by Leung and co-workers investigated the expression of angiotensin-converting enzyme II (ACE-2) in the lower tract of COPD patients,⁶² since this transmembrane metalloproteinase has been shown to act as the doorway that allows SARS-CoV-2 into the lungs.⁶³ The authors reported that COPD patients show an increased airway gene expression of ACE-2 compared to control subjects and ACE-2 were inversely related to FEV₁, suggesting a dose-dependent response.⁶² Hence, these findings reinforce the idea of a higher risk for SARS-CoV-2 in subjects with COPD. Finally, it has been shown that viral infection may increase the number of bacteria in the lower airways and even facilitate a subsequent bacterial infection in COPD.⁶⁴ Indeed, 20 to 30% of COPD patients hospitalized for exacerbations present viruses and bacteria coinfection, and these coinfections increase the severity of the exacerbations.⁶⁵⁻⁶⁷ Hence, one may anticipate that COPD patients with COVID-19 are at higher risk to develop a more severe pneumonia.

4 | IMMUNE DYSFUNCTION IN COPD

The increased susceptibility to respiratory infections leading to disease severity may reflect a defective immunity in COPD.⁶⁸ Indeed, both the innate response to pathogens and the role of adaptive immune system to such challenges are impaired in COPD, which can result in recurrent infections.^{29,69,70}

Hence, despite increased numbers of alveolar macrophages have been reported in COPD patients, their phagocytic ability is reduced as compared to smokers without COPD.⁷¹⁻⁷³ Moreover, alveolar macrophages of patients with COPD also exhibit an altered capacity to secrete proinflammatory mediators and proteases, express surface and intracellular markers, induce oxidative stress and engulf apoptotic cells.⁷⁴ In turn, some studies have found reduced numbers and impaired maturation of dendritic cells in COPD patients.⁷⁵⁻⁷⁷ In addition, interferon (IFN) signaling which plays a key role in the innate antiviral response is also impaired in COPD. Thus, Mallia and co-workers reported a reduced production of IFN- β in bronchoalveolar lavage (BAL) cells from subjects with COPD after rhinovirus infection.⁵⁷ Recent results from our research group also showed a significant reduction expression of IFN- β and its main transcription factor, IRF-7, in lung epithelium

and alveolar macrophages of COPD patients.⁷⁸ This reduction was also observed in pulmonary mRNA levels of these immune mediators. Since IFN- β has proven to inhibit coronavirus replication,^{79,80} COPD patients could be especially susceptible in front of COVID-19.

Regarding adaptive immunity, a downregulation of the epithelial polymeric immunoglobulin receptor (pIgR) has been observed in COPD patients.⁸¹ pIgR is essential for generation of mucosal sIgA, an effective virus-neutralizing molecule,⁸² and its reduction was positively correlated with COPD's severity.⁸¹ On another front, CD8 + T cells are critical for respiratory viral clearance and provide protection against secondary infections.⁸³ In this sense, McKendry and co-workers have demonstrated a defective response of CD8 + T cells against H3N2 influenza virus in subjects with COPD.⁸⁴ Interestingly, they found a downregulation of the T-cell receptor signalling molecule CD247 (ζ -chain) in lung CD8 + of these patients compared with smokers and healthy controls. They also observed a reduced T-cell cytotoxicity and an upregulation of programmed cell death protein-1 (PD-1), which renders immunosuppressive actions on CD8 + cells.⁸⁴ In another study, the same research group demonstrated that the impaired cytotoxic activity of CD8 + T cells was paralleled by a reduced proportion of CD4 + T cytotoxic cells in lung tissue from COPD patients.⁸⁵ In addition to cytotoxic T cells, other T subtypes seem to be altered in COPD. Regulatory T cells (Tregs) are a subtype of lymphocytes that express the transcription factor FoxP3, which, among other functions, have been shown to limit the extent of tissue damage that occurs during a virus infection.^{86,87} Importantly, COPD patients exhibit decreased numbers of pulmonary Treg cells, as well as reduced levels of FoxP3 mRNA and lung interleukin 10 secretion than controls.⁸⁸ Collectively, these findings indicate a characteristic immune dysfunction in COPD that could impact on the pulmonary antiviral defence.

Finally, it is noteworthy that the impaired immune response is not only restricted to pulmonary cells of COPD patients. Interestingly, a recent paper by Agarwal and co-workers have demonstrated that human peripheral blood mononuclear cells (PBMC) from COPD patients have a reduced ability to metabolize carbohydrate or fatty acids, suggesting a metabolic impairment in systemic immune cells in COPD.⁸⁹ Moreover, the neutrophil-to-lymphocyte ratio (NLR) is increased both in stable and exacerbated COPD patients.^{35,90} This is particularly relevant, since a recent paper by Liu and co-workers has shown that NLR is an independent risk factor for the in-hospital mortality for COVID-19.⁹¹ The study, which was performed on 245 COVID-19 patients, reported that subject in the highest tertile had a 15.04-fold higher risk of mortality (OR = 16.04; 95% CI, 1.14 to 224.95; $P = .0395$) after adjustment for potential confounders, when compared with patients in the lowest tertile.⁹¹

5 | COPD AND COVID-19: AVAILABLE EPIDEMIOLOGICAL DATA

So far, information on COVID-19 incidence and clinical course on COPD patients is scarce. A recent meta-analysis by Lippi and Henry has reported that COPD is associated with a significant, over fivefold risk of severe COVID-19 infection.⁹² However, the reported prevalence of COPD in patients diagnosed with COVID-19 is surprisingly low. Hence, the prevalence of chronic respiratory disease and COPD in two cohorts of Chinese COVID-19 patients has been only 2.4% (44,672 patients studied)⁹³ and 1.4% (140 patients studied),⁹⁴ respectively. Moreover, in the USA population, chronic respiratory diseases were comorbidities in 8.5% of COVID-19 patients.⁹⁵ In this regard, a group of investigators led by Dr Àlvar Agustí recently published a paper suggesting that the use inhaled corticosteroids could reduce the risk of infection or of developing COVID-19 symptoms, since previous *in vitro* studies has shown that these drugs are capable of suppressing coronavirus replication.⁹⁶ The same authors, however, warned about the fact that systemic corticosteroids were counterproductive to treat SARS.^{96,97} In this respect, it has also been shown that fluticasone propionate, an inhaled corticosteroid, impairs innate and acquired antiviral immune responses leading to delayed virus clearance and increases pulmonary bacterial load during virus-induced exacerbations in a murine model of COPD exacerbation.⁹⁸

6 | CONCLUSIONS

In nine months, the COVID-19 pandemic has spread to more than 200 countries and now the main focus of infection is centred in North and South America. Consequently, governments and institutions work relentlessly to stop the spread of the SARS-CoV-2 worldwide, while trying to manage the sanitary, economic and social crisis we are facing. Since a vaccine against this coronavirus is not available yet, the most important thing is to take steps to stop its spread and to protect those people at highest risk of infection or developing a more serious clinical course.

While hypertension and diabetes are the two comorbidities most clearly related to COVID-19 susceptibility, available data regarding COPD are contradictory. It is probable that COPD patients are under-represented in intensive care settings due to their pre-existing poor prognosis and decisions to limit the treatment to palliative care in situations of poor prognosis. Peoples in risk groups are advised to self-isolate, and most severe COPD patients most probably do not move out of their homes due to the limits of the disease for their performance in general. Therefore, the incidence of COVID-19 may be lower in COPD patients.

Nevertheless, substantial evidence points to COPD patients as a particularly susceptible group to SARS-CoV-2 infection and to a worst prognostic. Indeed, most COPD patients are or, at least, have been exposed to noxious gases or pollutants capable of altering pulmonary defences during many years. Also, the immune dysfunction observed in COPD may cause increased susceptibility to respiratory viral infections and an impaired inflammatory response against these challenges. Finally, it is noteworthy that SARS survivors showed a significative impairment of pulmonary function months after recovery.⁹⁹ If the same is confirmed for COVID-19 patients, a serious impact in the clinical course and quality of life in those with COPD as comorbidity could be expected, since they already have a diminished lung function. In any case, more research in larger patient groups will bring more data on COPD and COVID-19 severity and associations of immune dysfunction in COPD with COVID-19 risk. It would be important to know whether the patients are more prone for severe infection due to impaired immune responses and whether the clinical picture of the disease and the cytokine storm differ in these patients. Also, genotyping and complete phenotyping (including serological, radiological and histopathological assessment) will help to understand the mechanistic insights of the susceptibility to COVID-19.¹⁰⁰

In light of all these facts, COPD patients should be considered as a high-risk group in COVID-19. Hence, sanitary authorities must apply specific mechanisms to monitor and assess patients with COPD in the context of the current pandemic.

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CONFLICTS OF INTEREST

None to declare.

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