


# COVID-19 infection in patients with chronic obstructive pulmonary disease: From pathophysiology to therapy. Mini-review

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## ABSTRACT

*Introduction:* Patients with chronic obstructive pulmonary disease (COPD) are a vulnerable group in terms of the outcome of coronavirus infection in relation to their disease or its treatment, with a higher risk of developing serious complications compared to the healthy population. *Aim:* The aim of our summary study is to review the background and health outcomes of chronic obstructive pulmonary disease and COVID-19 infection in the presence of both diseases. *Methods:* Review of national and international medical databases (PubMed, MEDLINE, and MOB) with keywords COPD, COVID-19, disease risk, cause, prevention, complications, and prognosis. *Results:* Meta-analyses show that COPD is one of the most common underlying conditions in patients hospitalized for COVID-19. Such patients are five times more likely to develop a serious complication due to oxygen supply problems therefore they are more likely to be admitted to intensive care units, where they may require mechanical ventilation. In the case of underlying COPD, the usual care plan for COVID-19 infection should be followed, as well as all public health recommendations to minimize the risk of developing and transmitting COVID-19. *Conclusion:* Coronavirus

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infection is especially dangerous for COPD patients, who are much more likely to become seriously ill, so increased surveillance, prevention, early detection, adequate treatment and rehabilitation of the disease group are of paramount importance.

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## KEYWORDS

chronic obstructive pulmonary disease, SARS coronavirus, COVID-19, complications, prevention

## INTRODUCTION

COVID-19 (coronavirus disease 2019) is an acute respiratory infection caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), which is currently causing a pandemic [1]. The clinical manifestations of COVID-19 are diverse. The majority of people infected with COVID-19 have mild or no symptoms, but in 20 percent of cases the condition can become severe or critical and a fraction of infected patients progress to respiratory failure, multi-organ disease and even death [1–4]. As of February 5, 2022, over 390 million individuals have been contracted SARS-CoV-2 worldwide, of whom over 5.7 million patients have succumbed to the disease.

Chronic obstructive pulmonary disease (COPD) is a progressive lung disease that is characterized by persistent respiratory symptoms, low-grade lung inflammation and airflow obstruction. The two most common conditions of COPD are emphysema and chronic bronchitis, often caused by tobacco smoking. Epidemiological studies show that COPD is a risk factor for poor clinical outcomes in established COVID-19 [5].

In this review, the interactions between COPD and SARS-CoV-2 infection are considered [6–9]. The pathophysiological mechanisms contributing to poor outcomes in COPD patients with COVID-19 are discussed. Specific recommendations for the care of COPD patients during the pandemic are described.

## COPD EXACERBATES SEVERITY OF COVID-19

Based on currently available data, COPD patients have a much higher rate of severe COVID-19 infection [6–9]. A recent meta-analysis reported a high odds ratio (OR = 5.69) for the development of severe COVID-19 (defined as acute respiratory failure and/or admission to intensive care) in COPD patients [5], while another meta-analysis reported an OR = 4.38 [10]. One review, which focused specifically on comorbidities, described that COPD had the highest odds ratio for severe COVID-19 (OR = 5.97), while hypertension (OR = 2.29), diabetes (OR = 2.47), cardiovascular disease (OR = 2.93) and cerebrovascular disease (OR = 3.89) had lower ORs [11]. In these studies, severe COVID-19 infection was defined as acute respiratory failure and/or admission to intensive care.

The mechanisms by which COPD exacerbates severity of COVID-19 are likely multifaceted. COPD is an inflammatory disease of the bronchi, which is associated with narrowing of the airways, increased secretion and reduced airway reserve [12]. Due to the constant inflammation, the lung tissue is remodeled, damaged and gradually destroyed, causing a gradual deterioration



in breathing, difficulty breathing and then respiratory failure. At this stage, oxygen treatment is often necessary [13]. Severe pneumonia at this stage can lead to respiratory collapse in a matter of hours. Chronic obstructive airway disease and treatment with oral corticosteroids render COPD patients more susceptible to infections, including COVID-19. The reduced respiratory reserve, which is further compromised by a possible pneumonia, makes patients particularly vulnerable and prone to severe complications [1]. In addition, COPD is associated with increased expression of angiotensin-converting enzyme 2 (ACE-2), the entry receptor of SARS-CoV-2, in the lower airway epithelial cells, which further increases the risk and severe outcome of COVID-19 infection [14]. COPD develops most often in people who are 40 or older. It has also been shown that COVID-19 can affect individuals in all age groups, yet it mostly causes severe disease in older adults. The mechanisms by which aging exacerbate the severity of COVID-19 include age-related immunosenescence, aging-induced impairment of organismal and cellular stress resilience and a greater prevalence of comorbidities in older adults [2, 12–24]. COPD patients who are former smokers tend to exhibit the highest mortality associated with COVID-19 infection [15–17]. The pathophysiological mechanisms by which smoking increases the risk of developing complications from COVID-19 include impaired innate and adaptive immune responses and impairment of the lungs' self-cleansing defense mechanisms [25, 26] (Table 1). Inhaled steroids in COPD do not increase susceptibility to viral infection and that in any case; the prescribed basal therapy should not be abandoned during a coronavirus pandemic.

## COPD, CIGARETTE SMOKING AND ACE-2 EXPRESSION

On the basis of the available evidence it can be hypothesized that changes in the expression of ACE-2 play an important role in increased susceptibility to severe COVID-19 infection. ACE-2 is implicated in the entry of the virus into the host's airway epithelium to establish an active infection [18, 19]. A recent clinical trial was conducted to explore the association between ACE-2 expression and COVID-19 mortality in COPD patients [20]. COPD was defined as cases where the ratio of forced expiratory volume in 1 s ( $FEV_{1}$ ) to forced vital capacity (FVC) ( $FEV_{1}/FVC$ ) was less than 70% or where a computed tomography (CT) scan showed clear signs of emphysema. All patients also had a sub-segmental airway sampled by brush cytology and ribonucleic acid (RNA) sequencing was performed. In addition, ACE-2 protein expression was determined from resected lung tissue samples. The results of the aforementioned study showed significantly elevated ACE-2 expression in airway epithelial cells in COPD patients compared to controls (COPD:  $2.52 \pm 0.66$  AU vs. control:  $1.70 \pm 0.51$  AU) [20]. Smoking status was also significantly associated with airway ACE-2 expression, with significantly higher gene expression in active smokers than in controls who never smoked (active smokers:  $2.77 \pm 0.91$  AU vs. never smokers:  $1.78 \pm 0.39$  AU) [20]. Another important observation was that ACE-2 gene expression was inversely correlated with  $FEV_{1}$  values, a correlation that was confirmed in three different cohorts [20].

The virus enters the cell by binding to the ACE-2 receptor expressed on the type II epithelial cells. Additionally, ACE-2 is also expressed on the surface of epithelial and endothelial cells in the heart, kidney, esophagus, stomach, intestine and blood vessels and in certain white blood cells [21]. It is important to highlight the pathogenic role of endothelitis associated with diffuse infection and inflammation of the endothelium, which can lead to activation of the coagulation



Table 1. Changes in the lungs due to cigarette smoke and SARS-CoV-2 mediated injury in COPD

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Smoker lung

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- > Mucous metaplasia
  - > Loss of club cells
  - > ↑B cells, antibodies increase
  - > ↑Alveolar macrophages
  - > **↑Cytotoxic CD8+ cells, ↑cytokines, ↑chemokines**
  - > ↑Neutrophil granulocytes
  - > ↑Proteases
  - > Exhausted T cells and ↓Regulatory T cells
  - > Loss of alveolar type 2 progenitor cells (AT2)
  - > Endothelial injury
  - > ↑Secretion production
  - > ↓Ability of the lungs to self-clean
  - > Impaired immune response
- 

Evidence for factors critical in COVID-19 severity

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- > Smoke-induced changes in numbers of the main ACE-2-producing cells
  - > SARS-CoV-2 S protein cleavage by proteinases
  - > Smoke-induced altered antiviral responses
  - > Smoke-induced inflammation
  - > Smoke-induced altered lung structure and endothelial damage
  - > Other smoke-induced unknown factors
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SARS-CoV-2 mediated injury

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- > Vasoconstriction
  - > Vascular permeability↑
  - > Oedema
  - > Lung injury
  - > Pulmonary inflammation
  - > Respiratory failure
  - > ACE-2 activity reduced
  - > Angiotensin II levels increased
- 

ACE-2 = angiotensin-converting enzyme 2; CD = cluster of differentiation; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.



system and the complement cascade, resulting in vascular injury and thromboembolism, ischemia, thus increasing further organ damage in patients [22, 23]. A recently recognized important feature of COVID-19 is the abnormal activation of the coagulation system, which clinically predisposes to arterial and venous thromboembolism [24–28]. The degree of coagulopathy is proportional to the severity of the disease and thromboinflammatory biomarkers predict worse outcomes [29]. The pathophysiological mechanisms promoting thrombogenesis in COVID-19 patients include hyperactive coagulation and complement systems induced associated with excessive inflammation, platelet activation and endothelial dysfunction and injury [30]. Because of the exacerbated pro-thrombotic state, anti-coagulation therapies may be most effective in patients with chronic illness [31].

## TREATMENT OF COPD PATIENTS INFECTED WITH COVID-19

Specific data and research evaluating the specific treatment of COPD patients with COVID-19 are not available. However, it is essential that chronic lung patients adhere to medication and medication monitoring instructions, with regular preventive inhaled bronchodilator medication being of particular importance [32]. It is important to avoid smoking completely and to maintain regular physical activity [33, 34]. Most patients are given long-acting bronchodilators or a combination of different types of bronchodilators in their inhalers (so-called “sprays” or “dry powder inhalers”), and abandoning these preparations is particularly dangerous [35]. In the case of acute deterioration, aerosol or dry powder inhaler formulations are recommended instead of mechanical nebulizers. If necessary, oxygen therapy should be used to maintain SpO<sub>2</sub> levels above 88–90% [36]. All patients with COPD showing signs of respiratory failure should have arterial blood gas monitoring. If the pH < 7.35 (hypercapnic acidosis), ventilatory support, i.e. non-invasive ventilation (NIV) invasive ventilation or high-flow oxygen therapy, should be considered. The effect of systemic corticosteroids on COVID-19 is still controversial [37], but due to COPD-induced deterioration, oral or intravenous corticosteroid administration may be used in the setting of COVID-19 infection. As with other COVID-19 patients, low molecular weight heparin should be used prophylactically to prevent thromboembolic complications unless there are other contraindications.

In COPD, on the one hand, the body’s defense system does not work properly, and on the other hand, the breathing surface is reduced, decreasing the respiratory reserve, which in the case of pneumonia quickly leads to respiratory failure [38]. Some patients already require oxygen therapy on a daily basis and may be particularly at risk from coronavirus infection [39]. Of particular interest for COPD research will be the ongoing COPD follow-up studies after the COVID-19 pandemic to assess the potential interactions between COVID-19 and COPD, with particular focus on its symptoms, exacerbations, respiratory function, consequences of reduced physical activity, mental, social and societal effects [40].

## PULMONARY REHABILITATION PROGRAMS FOR PATIENTS WITH COPD

During the coronavirus outbreak, several pulmonary rehabilitation programs were suspended to reduce the risk of SARS-CoV-2 spreading [41]. Therefore, patients should be encouraged and



supported to remain active at home, participating in self-monitored pulmonary rehabilitation. It may be worth using a home respiratory trainer to improve inhalation muscle strength, thereby reducing breathing difficulties and increasing endurance [42]. New technologies and increased individual internet connectivity also provide opportunities to develop a suitable tele-rehabilitation strategy for patients [43]. Telerehabilitation is also used to treat chronic diseases, including heart disease [44], stroke [45], and multiple sclerosis [46]. Self-monitored home exercise has been shown to improve patient outcomes in many diseases, including respiratory function and quality of life in COPD [47], and home tele-rehabilitation has been shown to be as effective as hospital rehabilitation in reducing the risk of acute exacerbations and hospitalizations, as well as emergency department admissions [48, 49]. Using digital tools can also improve medication adherence in chronic respiratory patients and, thanks to real-time data analysis, it is possible to detect symptoms at an early stage of exacerbation and, if necessary, change medication with a doctor [50, 51]. Global Initiative for Chronic Obstructive Lung Disease (GOLD) has developed a device to support the remote monitoring of COPD patients by enabling home measurement of peak expiratory flow (PEF) [52, 53]. The professional spirometry system for monitoring lung disease is a smart device consisting of a portable spirometer, a built-in heart rate monitor and an online management interface that can be downloaded to a smartphone. The spirometer monitors the exhalation and inhalation curves and displays the most important parameters in real time on the smartphone screen, measures FEV<sub>1</sub>, FVC, PEF, heart rate, provides high accuracy flow measurement, respiratory function analysis and, if the user wishes, a training plan. Once the measurement is complete, that can be easily shared with the physician via the internet. From this data, the GP or pulmonologist can determine whether the medication needs to be changed. Given the accuracy, predictability and personalization of digital remote monitoring devices, there is a strong case for current and future technologies to be incorporated into the management of chronic respiratory patients.

## DISEASE-SPECIFIC RECOMMENDATIONS FOR COPD PATIENTS ON THE COVID-19 PANDEMIC [53]

- If the possibility of coronavirus infection arises, the prescribed epidemiological procedure is justified (use of masks, keeping distance, observance of hygiene rules). Only one patient may use an inhalation device.
- If a coronavirus infection is suspected or confirmed, the patient can be treated at home if symptoms are mild, it is important to control fever and drink plenty of fluids.
- If, during home treatment of a mild illness, underlying condition cause exacerbation of choking symptoms, immediate help should be obtained from the appropriate hospital ward, as hospital admission is necessary for severe symptoms. These include choking, dyspnea or pneumonia in addition to fever (above 38 °C).
- The patient should make sure that they have enough medication and/or prescriptions for several weeks of inhaled medicines for the preventive treatment of COPD.
- As discontinuation or dose reduction of justified maintenance treatment for COPD may cause adverse health effects, there is no reason to stop or adjust the dose of therapy used.
- If home oxygen therapy is needed, discuss in advance with the supplier how to ensure continuous oxygen supply.



- If the patient is using a long-acting bronchodilator inhaler, it is important and necessary to maintain the same dose. Discontinuation of these preparations is particularly dangerous in COPD.
- In addition to bronchodilators, some patients are also given a medicine called inhaled corticosteroid. These drugs have been shown to be safe even in the presence of confirmed COVID infection, but their omission may increase the likelihood of acute exacerbations as COPD worsens.

## CONCLUSION

The coronavirus pandemic has dramatically shifted the landscape of the healthcare sector, which did not adapt rapidly enough to limit the initial number of doctor-patient encounters, resulting in numerous avoidable deaths of individuals with comorbidities such as COPD. Patients with COPD are more likely to develop severe complications from COVID-19 disease due to oxygen supply problems, thus are more likely to be admitted to intensive care units, where they may require mechanical ventilation. Active smokers and patients with COPD have increased ACE-2 expression in the lower airways, which may partly explain why COVID-19 is an increased risk in this population. The available evidence highlights the importance of smoking cessation and the particular importance of increased surveillance, prevention, early detection, treatment and rehabilitation of this patient group.

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## LIST OF ABBREVIATIONS

ACE-2	angiotensin-converting enzyme 2
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CT	computed tomography
FEV <sub>1</sub>	forced expiratory volume in 1 second
FVC	forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
OR	odds ratio
PEF	peak expiratory flow
RNA	ribonucleic acid
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
MOB	Hungarian Medical Bibliography (Magyar Orvosi Bibliográfia)
WHO	World Health Organization



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