REVIEW

How did COPD pose a lower risk than expected for COVID-19?

Pınar MUTLU[1], Arzu MİRİCİ[1]

[1]*Çanakkale Onsekiz Mart University, Faculty of Medicine, Department of Chest Disease, Çanakkale.*

Date of arrival: 09.08.2021; Date of acceptance: 21.10.2021
Corresponding author: Pınar MUTLU, *Address*: Çanakkale Onsekiz Mart Üniversitesi Göğüs Hastalıklari Anabilim Dalı Barbaros Mahallesi Prof. Dr. Sevim Buluç Sokak Terzioğlu Yerleşkesi A Blok No:2 B Blok No:4 Çanakkale, Turkey, *E-mail*: pinarmutlu78@yahoo.com, *Phone*:+905052629529.

ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a respiratory disease characterized by progressive airflow restriction affecting more than 5% of the world's population. The disease progresses with exacerbation attacks, leading to worsening of the patient's respiratory symptoms and drug change. 70% of these exacerbations are caused by viral and bacterial infections. At the beginning of the pandemic, the expectation of all chest disease specialists worldwide was that COPD patients would be hospitalized for more frequent exacerbations and pneumonia, and mortality would be higher in these patients due to developing complications. However, in the following days, COPD patients were not as high as expected in patient groups admitted to the hospital. In this article, we wanted to share possible reasons for this.

Keywords: COVID-19, COPD, exacerbation, pandemics

KOAH, COVID-19 için nasıl beklenenden daha düşük bir risk oluşturdu?

ÖZET

Kronik obstrüktif akciğer hastalığı (KOAH), dünya nüfusunun %5'inden fazlasını etkileyen ilerleyici hava akımı kısıtlaması ile karakterize bir solunum hastalığıdır. Hastalık, hastanın solunum semptomlarının kötüleşmesine ve ilaç değişikliğine neden olan alevlenme atakları ile ilerler. Bu alevlenmelerin %70'i viral ve bakteriyel enfeksiyonlardan kaynaklanır.

COVID-19 pandemisi ilk başladığında dünya genelindeki tüm göğüs hastalıkları uzmanlarının beklentisi, KOAH hastalarının daha sık alevlenmeler ve pnömoni nedeniyle hastaneye yatırılması ve bu hastalarda gelişen komplikasyonlar nedeniyle mortalitenin daha yüksek olmasıydı. Ancak ilerleyen günlerde hastaneye başvuran hasta gruplarında KOAH hastaları beklendiği kadar yüksek çıkmadı. Bu yazımızda bunun olası nedenlerini paylaşmak istedik.

Anahtar kelimeler: COVID-19, KOAH, alevlenme, pandemi

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a condition that is characterized by pulmonary inflammation in the presence of irritants, and smoke in particular. Both structural and inflammatory cells secrete proinflammatory mediators, thereby causing the inflammation to continue in response to etiological agents. Chronic inflammation, on the other hand, contributes to the development of recurrent respiratory tract infections by affecting innate and adaptive immune responses. During these periods, defined as exacerbation in COPD patients, the patient can experience increased respiratory symptoms, impaired respiratory function, a reduction in quality of life and decreased physical performance.

Lower respiratory tract infections can affect the course of a disease in two ways. The first occurs with viral and bacterial respiratory tract infections, in which more infections occur as the airway obstruction increases and the disease progresses; and the second relates to especially to bacterial colonization in the airway due to infection, which increases the frequency of infective attacks. For all these reasons, COPD patients would be expected to be a significant risk group during a viral pandemic and this expectation is supported by the increased expression of angiotensin converting enzyme 2 (ACE2), which plays a role in the pathogenesis of not only COPD, but also several other pulmonary diseases [1-4].

COPD, somewhat surprisingly, has not emerged as a high-risk factor during the pandemic, despite the usual susceptibility to lower respiratory tract infections. In this review, we tried to discuss why COPD patients were admitted to the hospital less often than expected during the coronavirus disease 2019 (COVID-19) pandemic. Below, we have tried to explain the possible reasons for this in the form of subheadings such as ACE gene expression, inhaled therapies, immune disorders and altered colonization balance in COPD.

PREVALENCE OF COPD IN COVID-19 CASES

Accordingly, the increased susceptibility to viral infections in COPD and the increased ACE2, the entry receptor of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), in COPD patients led to predictions of an extreme prevalence and severity of COVID-19 among COPD patients when the COVID-19 pandemic broke [5]. Contrary to expectations,

however, COPD did not emerge as a common comorbidity in COVID-19 patients, and surprisingly, there were even published studies identifying COPD less frequently in COVID-19 patients when compared to the general population of similar age and gender [6–9]. Studies in China revealed that COPD was a lower risk (1.4-2.9%) compared to other comorbidities [10,11]. A systematic meta-analysis including 10 studies examining a total of 3403 patients hospitalized with COVID-19 reported that a COPD rate of 0.95%, with hypertension (16%), cardiovascular disease (12%) and diabetes (8%) recording much higher rates [6].

We believe that there is a need for further studies of people of the same ethnicity, age and gender before conclusions can be drawn regarding the lower prevalence of COPD than other comorbidities in COVID-19 patients. There have also been studies, however, that report COVID-19 progressing more severely in COPD patients. A meta-analysis including six studies and 1592 patients established a 5.69-fold increase in the incidence rate of severe COVID-19 infection in COPD patients [12].

Another meta-analysis of 1558 diseases found the highest odds ratio (OR: 5.97, 95% CI: 2.49-14.29, P<0.001) for COPD, while it was lower for such common comorbidities as hypertension (OR: 2.29, 95% CI: 1.69-3.10, P<0.001), cardiovascular disease (OR:2.93, 95% CI: 1.73-4.96, P<0.001), cerebrovascular disease (OR:3.89, 95% CI: 1.64-9.22, P=0.002) and diabetes (OR: 2.47, 95% CI: 1.67-3.66, P<0.001), among patients with severe COVID-19 infections [13]. The abovementioned studies defined severe infection as acute respiratory failure and/or intensive care unit requirement.

Another meta-analysis found the prevalence of COPD to be 2% in COVID-19 cases in a laboratory diagnosis, although the study reported a higher rate of complications with pneumonia (63% vs. 33.4%) and mortality during disease progression when compared to non-COPD patients [14].

ACE EXPRESSION IN COPD AND COVID-19

ACE2 regulates renin-angiotensin-aldosterone system (RAAS) and so reduced ACE2 function leads to the dysfunction of RAAS, affecting blood pressure and fluid/electrolyte balance, and resulting in increased vascular permeability in the respiratory tract in the presence of COVID-19.

A meta-analysis examining the association between ACE gene expression and susceptibility to COPD identified differences in races and ethnicities [15]. The ACE gene is located on the chromosome 17, and has three different genotypes (DD, ID, and II) with insertion (I) and deletion (D) polymorphisms. The DD genotype is associated with a high concentration in the blood and tissue, and therefore with a high activity. A low ACE activity, in turn, is believed to have a potentially positive effect on COPD prognosis. Similarly, it has been demonstrated that the DD genotype is more common and increases mortality in patients with adult respiratory distress syndrome. A meta-analysis by Ma et al. [15] reported that the homozygous DD genotype was significantly associated with COPD, but that such an effect was not prominent in the case of a heterozygous deletion. Additionally, it is understood that such effect is only applicable to the Asian population (OR=2.38, p=0.086, 95% CI, 1.34-4.22), as such an association is not prominent in the Caucasian population (OR=1.24, p<0.001, 95% CI, 0.89-1.72). A study conducted in Turkey and assessed in the abovementioned meta-analysis [15] obtained similar findings [16]. The study by Ulasli et al. [16] evaluated the relationship between pulmonary hypertension, which can occur due to the pulmonary vascular involvement of COPD, and the ACE gene expression. The authors concluded that the homozygous DD genotype in COPD cases with and without pulmonary hypertension did not significantly differ from that of the control group. There is a significant negative relationship between ACE2 gene expression and percent forced expiratory volume in one second [5], although it is controversial to assess all these in the same way with ACE2, as the entry receptor of the virus. The SARS-CoV-2 infection decreases ACE2 expression in the lung cells [17-20]. Is it likely that the disease pathology does not occur because the ACE2 overexpression in COPD patients prevents SARS-CoV-2 from downregulating ACE2?

MEDICATIONS OF COPD PATIENTS AND COVID-19

Another factor that could explain the low number of COPD patients being affected by COVID-19 pneumonia than expected around the world is the medications used for treatment. The treatment involves inhaled corticosteroids combined with short-/long-acting anticholinergic and short-/long-acting beta-adrenergic drugs as bronchodilators. The effects of inhaled corticosteroids on viruses are varied and controversial. Several *in vitro* studies have shown that inhaled steroids impair antiviral innate immune response [21] and delay the viral clearance [4]. Most of these studies were conducted on rhinoviruses, while studies of other viruses have produced different results [22]. An *in vitro* study showed that human respiratory epithelial cells pretreated with budesonide, formoterol and glycopyrronium (long-acting beta2-agonist/long-acting muscarinic antagonist/inhaled corticosteroid [ICS]) prevented the replication of SARS-CoV-2 and the associated cytokine production [23]. In another *in vitro* study, it was established that bronchial epithelial cells incubated with budesonide and formoterol could affect the replication of the virus encountered 24 hours later, as well as interferon production [24]. A more recent *in vitro* study found that ciclesonide and mometasone inhibited SARS-CoV-2 replication by targeting the non-structural protein 15 of the virus [25].

Despite these *in vitro* studies, there is a lack of clinical study data reporting the effects of inhaled steroids since the pandemic outbreak. Although inhaled steroids are likely to have an effect on viruses, and coronavirus in particular, the dose and duration for the occurrence of such an effect are unknown. Research should thus be conducted involving large-scale patient series. Previous clinical studies conducted in our country, however, indicate that inhaled steroids are prescribed more frequently than recommended by the guidelines, and so the frequent use of ICSs, whether indicated or not, may lead to difficulties in creating an ICS-native group for comparison.

IMMUNE DYSFUNCTION IN COPD PATIENTS AND COVID-19

The predominant pathological changes in COPD occur in the respiratory tract, although changes also occur in the parenchyma and pulmonary vascular structure. An individual with COPD may experience pathological changes depending on individual susceptibility, disease severity and the underlying disease (e.g., chronic bronchitis, emphysema, and alpha-1 antitrypsin deficiency) [26]. The airway abnormalities in COPD include chronic inflammation, increased numbers of goblet cells, hyperplasia of the mucous glands, fibrosis, and small airway narrowing [27,28]. Chronic hypoxemia results in intimal hyperplasia and smooth muscle hypertrophy/hyperplasia in small pulmonary arteries [29]. A series of papers have been published reporting increased numbers of macrophages, neutrophils, CD4+ and CD8+ T cells in the small airway in COPD [30,31]. Additionally, eosinophils, which were mostly a subject for the pathogenesis and treatment goal of asthma, have recently been identified as being involved in the pathogenesis of COPD phenotypes with frequent exacerbations and asthma-COPD overlap syndrome. The presence of eosinophils above 3% in the peripheral blood has been shown to be associated with exacerbation frequency in COPD. Thus, a high level of eosinophils is used as a measure for the use of inhaled corticosteroids. As there have been studies reporting that eosinophils, as a component of allergic inflammation, can prevent viral infections [32], their effect also in COPD should be studied.

SARS-CoV-2 affects primarily the pulmonary airway epithelial cells, alveolar epithelial cells, vascular epithelial cells, and macrophages. When the virus begins to replicate in the infected host cell, it can cause virus-associated proptosis [33], and programmed cell death [34].

The release of cytokines and chemokines into systemic circulation results in an intense migration of monocytes and T lymphocytes to the pulmonary site, while neutrophils remain in systemic circulation [35,36]. This results in lymphopenia and an increased neutrophil-to-lymphocyte ratio in approximately 80% of patients [37]. In COVID-19, it is the increased inflammatory cell infiltration that is responsible for the diffuse alveolar damage, including the hypersecretion of proteases and reactive oxygen radicals, alveolar cell desquamation, hyaline membrane formation and pulmonary edema [35].

As another factor worthy of discussion among the possible reasons for the lower-than-expected rate of COPD during the pandemic, can the immune dysfunction in COPD patients lead to conflict between COVID-19's viral replication and T-lymphocyte response?

With the advances in diagnostic technologies, specific microorganisms are today commonly identified in the airways in stable COPD and are considered as "colonizers" in the absence of acute infective symptoms [38]. These microorganisms induce airway and systemic inflammation that cause disease progression. The presence of permanent stimulus, irrespective of cigarette smoke, since the airway inflammation continues despite cessation of smoking, is consistent with bacterial colonization in the COPD pathogenesis [39,40]. Pathogenic microorganisms have been isolated in 74% of stable COPD patients [41]. The most detected bacteria are *Haemophilus influenzae*, *Moraxella catarrhalis*, *Streptococcus pneumoniae*, *Pseudomonas aeruginosa*, and *Chlamydophila pneumoniae* [42]. Bacterial colonization is a dynamic process that results in changes in pathogen type, load, and strain in time. On the other hand, the total viral load (influenza, cytomegalovirus, and Epstein-Barr virus) is increased in COPD patients [43,44]. Colonized COPD patients present with a systemic inflammatory response that can be characterized by higher blood concentrations of C-reactive protein. A chronic microbial colonization contributes to chronic inflammation and the progressive loss of pulmonary function [37,45].

The lung microbiota includes multiple bacterial taxa and bacterial families, and the relationships between these bacteria are highly likely to influence which species are dominant in the lower respiratory tract of COPD patients [46–48]. It is possible that viruses may affect bacterial colonization and contribute to the emerging immune response [49]. Can the dominant bacterial and viral species colonizing in the respiratory tract of COPD patients produce an immune response that prevents the development of COVID-19?

Other speculative explanations we encountered in studies with a low COPD prevalence during the COVID-19 pandemic included a stricter adherence of such patients to general precautions, such as early self-isolation at the start of the outbreak, the avoidance of close contact and hand washing [9].

DISCUSSION

Chronic obstructive pulmonary disease, somewhat surprisingly, has not emerged as a high-risk factor during the pandemic, despite the usual susceptibility to lower respiratory tract infections. It would be insightful to investigate the reasons for this situation. The potential factors that determine the SARS-CoV-

2 infection in COPD can be listed as chronic inflammation of the airway, the medications used for treatment, and the potential for the colonized microorganisms to have an influence on the virus. The role of ACE2 in the COPD pathogenesis should also be investigated with extensive studies in various geographical areas. The findings obtained through such studies could contribute both to the reduction of COPD exacerbations and a better understanding of SARS-CoV-2.

During the COVID-19 pandemic, we tried to discuss why COPD patients were admitted to the hospital less often than expected. But we think that more studies should be done on COPD and COVID-19.

Conflict of interest: None
Funding: None

REFERENCES

1. Toru U, Ayada C, Genç O, et al. Serum levels of RAAS components in COPD [abstract]. Eur Respir J 2015;46 (suppl 59):PA3970.
2. Bhat TA, Panzica L, Kalathil SG, et al. Immune dysfunction in patients with chronic obstructive pulmonary disease. Ann Am Thorac Soc 2015;12 Suppl 2(Suppl 2):169-75.
3. Brusselle GG, Joos GF, Bracke KR. New insights into the immunology of chronic obstructive pulmonary disease. Lancet 2011;378(9795):1015-26.
4. Singanayagam A, Glanville N, Girkin JL, et al. Corticosteroid suppression of antiviral immunity increases bacterial loads and mucus production in COPD exacerbations. Nat Commun 2018;9:2229.
5. Leung JM, Yang CX, Tam A, et al. ACE-2 expression in the small airway epithelia of smokers and COPD patients: Implications for COVID-19. Eur Respir J 2020;55: 2000688.
6. Emami A, Javanmardi F, Pirbonyeh N, et al. Prevalence of underlying diseases in hospitalized patients with COVID-19: a systematic review and meta-analysis. Arch Acad Emerg Med 2020;8:e35.
7. Grasselli G, Zangrillo A, Zanella A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. JAMA 2020;323:1574-81.
8. Goyal P, Choi JJ, Pinheiro LC, et al. Clinical characteristics of Covid-19 in New York City. N Engl J Med 2020;382:2372-4.
9. Halpin DMG, Faner R, Sibila O, et al. Do chronic respiratory diseases or their treatment affect the risk of SARS-CoV-2 infection? Lancet Respir Med 2020;8:436-8.
10. Zhang JJ, Dong X, Cao YY, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy 2020;75:1730-41.
11. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. JAMA 2020;323:1061-9.
12. Lippi G, Henry BM. Chronic obstructive pulmonary disease is associated with severe coronavirus disease 2019 (COVID-19). Respir Med 2020;167:105941.
13. Wang B, Li R, Lu Z, et al. Does comorbidity increase the risk of patients with COVID-19: Evidence from meta-analysis. Aging (Albany NY) 2020;12:6049-57.
14. Alqahtani JS, Oyelade T, Aldhahir AM, et al. Prevalence, severity and mortality associated with COPD and smoking in patients with COVID-19: A rapid systematic review and meta-analysis. PLoS ONE 2020;15:e0233147.
15. Ma Y, Tong X, Liu Y, et al. ACE gene polymorphism is associated with COPD and COPD with pulmonary hypertension: a meta-analysis. Int J Chron Obstruct Pulmon Dis 2018;13:2435-46.
16. Ulasli SS, Eyuboglu FO, Verdi H, et al. Associations between endothelial nitric oxide synthase A/B, angiotensin converting enzyme I/D and serotonin transporter L/S gene polymorphisms with pulmonary hypertension in COPD patients. Mol Biol Rep 2013;40:5625-33.
17. Imai Y, Kuba K, Rao S, et al. Angiotensin-converting enzyme 2 protects from severe acute lung failure. Nature 2005;436:112-6.
18. Imai Y, Kuba K, Penninger JM. The discovery of angiotensin-converting enzyme 2 and its role in acute lung injury in mice. Exp Physiol 2008;93(5):543-8.
19. Kuba K, Imai Y, Rao S, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nat Med 2005;11:875-9.
20. Kuba K, Imai Y, Penninger JM. Angiotensin-converting enzyme 2 in lung diseases. Curr Opin Pharmacol 2006;6(3): 271-6.
21. Halpin DMG, Singh D, Hadfield RM. Inhaled corticosteroids and COVID-19: A systematic review and clinical perspective [editorial]. Eur Respir J 2020;55(5):2001009.
22. Bochkov YA, Busse WW, Brockman-Schneider RA, et al. Budesonide and formoterol effects on rhinovirus replication and epithelial cell cytokine responses. Respir Res 2013;14:98.
23. Southworth T, Pattwell C, Khan N, et al. Increased type 2 inflammation post rhinovirus infection in patients with moderate asthma. Cytokine 2020;125:154857.
24. Yamaya M, Nishimura H, Deng X, et al. Inhibitory effects of glycopyrronium, formoterol, and budesonide on coronavirus HCoV-229E replication and cytokine production by primary cultures of human nasal and tracheal epithelial cells. Respir Investig 2020;58:155-68.
25. Matsuyama S, Kawase M, Nao N, et al. The inhaled corticosteroid ciclesonide blocks coronavirus RNA replication by targeting viral NSP15 [preliminary report]. 2020.03.11.987016. Located at: https://www.biorxiv.org/cotent/10.1101/2020.03.11.987016v1
26. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease 2019 Report. Global Initiative for Chronic Obstructive Lung Disease Inc.; 2019.
27. McDonough JE, Yuan R, Suzuki M, et al. Small-airway obstruction and emphysema in chronic obstructive pulmonary disease. N Engl J Med 2011;365:1567-75.
28. Cosio MG, Saetta M, Agusti A. Immunologic aspects of chronic obstructive pulmonary disease. N Engl J Med 2009;360(23):2445-54.
29. Harkness LM, Kanabar V, Sharma HS, et al. Pulmonary vascular changes in asthma and COPD. Pulm Pharmacol Ther 2014;29:144-55.

30. Martínez-García MA, de la Rosa Carrillo D, Soler-Cataluña JJ, et al. Prognostic value of bronchiectasis in patients with moderate-to-severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2013;187:823-31.
31. Huang CT, Tsai YJ, Wu HD, et al. Impact of non-tuberculous mycobacteria on pulmonary function decline in chronic obstructive pulmonary disease. Int J Tuberc Lung Dis 2012;16:539-45.
32. Oliver BG, Robinson P, Peters M, et al. Viral infections and asthma: An inflammatory interface? Eur Respir J 2014;44:1666-81.
33. Zhang H, Zhou P, Wei Y, et al. Histopathologic changes and SARS-CoV-2 immunostaining in the lung of a patient with COVID-19. Ann Intern Med 2020;172:629-32.
34. Fink SL, Cookson BT. Apoptosis, pyroptosis, and necrosis: Mechanistic description of dead and dying eukaryotic cells. Infection and Immunity 2005;73:1907-16.
35. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med 2020;8:420-2.
36. Tian S, Hu W, Niu L, et al. Pulmonary pathology of early-phase 2019 novel coronavirus (COVID-19) pneumonia in two patients with lung cancer. J Thorac Oncol 2020;15:700-4.
37. Qin C, Zhou L, Hu Z, et al. Dysregulation of immune response in patients with coronavirus 2019 (COVID-19) in Wuhan, China. Clin Infect Dis 2020;71:762-8.
38 .Sethi S, Murphy TF. Infection in the pathogenesis and course of chronic obstructive pulmonary disease. N Engl J Med 2008;359:2355-65.
39. Lapperre TS, Postma DS, Gosman MM, et al. Relation between duration of smoking cessation and bronchial inflammation in COPD. Thorax 2006;61:115-21.
40. Gamble E, Grootendorst DC, Hattotuwa K, et al. Airway mucosal inflammation in COPD is similar in smokers and ex-smokers: A pooled analysis. Eur Respir J 2007;30:467-71.
41. Matkovic Z, Miravitlles M. Chronic bronchial infection in COPD. Is there an infective phenotype? Respir Med 2013;107:10-22.
42. Simpson JL, Baines KJ, Horvat JC, et al. COPD is characterized by increased detection of Haemophilus influenzae, Streptococcus pneumoniae and a deficiency of Bacillus species. Respirology 2016;21:697-704.
43. McManus TE, Marley AM, Baxter N, et al. High levels of Epstein-Barr virus in COPD. Eur Respir J 2008;31:1221-6.
44. Tan DB, Amran FS, Teo TH, et al. Levels of CMV-reactive antibodies correlate with the induction of CD28(null) T cells and systemic inflammation in chronic obstructive pulmonary disease (COPD). Cell Mol Immunol 2016;13:551-3.
45. Sethi S, Maloney J, Grove L, et al. Airway inflammation and bronchial bacterial colonization in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2006; 173:991-8.
46. Cabrera-Rubio R, Garcia-Núñez M, Setó L, et al. Microbiome diversity in the bronchial tracts of patients with chronic obstructive pulmonary disease. J Clin Microbiol 2012;50:3562-8.
47. Pragman AA, Kim HB, Reilly CS, et al. The lung microbiome in moderate and severe chronic obstructive pulmonary disease. PLoS One 2012;7:e47305.
48. Huang YJ, Kim E, Cox MJ, et al. A persistent and diverse airway microbiota present during chronic obstructive pulmonary disease exacerbations. OMICS 2010;14:9-59.
49. Bosch AATM, Biesbroek G, Trzcinski K, et al. Viral and bacterial interactions in the upper respiratory tract. PLoS Pathog 2013;9:e1003057.