ARTÍCULO DE REVISIÓN

Gac Méd Caracas 2020;128(4):505-511
DOI: 10.47307/GMC.2020.128.4.6

Chronic obstructive pulmonary disease, a risk factor for SARS-CoV-2 morbidity and mortality?

Dr. Salvatore Pluchino[1]

SUMMARY

Chronic obstructive pulmonary disease (COPD) is a major health problem difficult to treat due to underlying neutrophilic inflammation resistant to inhaled corticosteroids in most patients. Increased blood and sputum eosinophils are associated with more frequent exacerbation. Novel coronavirus SRAS-CoV-2 has infected humans in all age groups of all ethnicities. COVID-19-patients with comorbidities are more likely to develop a more severe course and progression of the disease. As an inflammatory disease of the lung, COPD was expected to be frequent comorbidity of COVID-19. Analysis of available data revealed a low prevalence of chronic pulmonary diseases in patients with COVID-19. However, the presence of preexisting COPD is associated with a nearly fourfold higher risk of developing severe COVID-19. The demographic characteristic of the population has a great impact on case-fatality reporting. Clear definition of COVID-19 related deaths and transparency in testing policies are essential for reporting comparable case-fatality rates among countries.

Key words: *COPD, COVID-19, comorbidity, mortality, SARS-CoV-2.*

DOI: https://doi.org/10.47307/GMC.2020.128.4.6

[1]Department of Pharmacology, School of Medicine, Universidad Central de Venezuela, Caracas
Movil: 1-786.303.0665
E-mail: totopluchino@gmail.com

Recibido: 25 de agosto de 2020
Aceptado: 30 de agosto de 2020

RESUMEN

La enfermedad pulmonar obstructiva crónica (EPOC) es un problema de salud difícil de tratar debido a la inflamación neutrofílica subyacente que resiste a la terapia con corticosteroides inhalados. El aumento de eosinófilos en sangre y en el esputo cursa con frecuentes exacerbaciones. El nuevo coronavirus (SRAS-CoV-2) infecta a los humanos de todos los grupos etarios y étnicos. Los pacientes con COVID-19 con comorbilidades estan más expuestos a la evolución más severa de la enfermedad. Como enfermedad inflamatoria del pulmón, se esperaría que la EPOC fuera una comorbilidad frecuente del COVID-19. El análisis de los datos disponibles muestra una baja prevalencia de enfermedades respiratorias crónicas en pacientes con COVID-19. La presencia de EPOC preexistente está asociada con riesgo cuatro veces mayor de desarrollar COVID-19 severo. Las características demográficas de la población tienen impacto en el reporte de la tasa de mortalidad. La definición de muerte por COVID-19 y políticas transparentes de aplicación de las pruebas son esenciales para reportar una tasa de mortalidad comparable entre países.

Palabras clave: *COPD, COVID-19, comorbilidad, mortalidad, SARS-CoV-2.*

INTRODUCTION

A disease caused by the recently identified coronavirus family member SARS-CoV-2, named coronavirus disease 2019 (COVID-19), was recognized as a pandemic and chronic

obstructive pulmonary disease (COPD) might represent comorbidity which may increase the risk of more severe illness from COVID-19. Patients with severe COPD may have a higher risk for COVID-19 complications as both diseases affect the respiratory system since existing lung damage means that it is more difficult for the lungs to fight off an infection. Roughly half of all adults have at least one of five high-risk chronic health problems, which include hypertension, heart disease, chronic kidney disease, diabetes, obesity, and chronic pulmonary diseases. The risk for severe COVID-19 associated illness increases with older age and the presence of underlying chronic medical conditions. Severe clinic symptoms of COVID-19 may require hospitalization, intensive care unit (ICU) admission, mechanical ventilation, or may result in death. About 80 % of people recover fully from COVID-19 without medical treatment. However, the coexisting COPD puts patients at risk of getting seriously sick due to the infection by SARS-CoV-2.

Mechanisms of inflammation of COPD

Underlying inflammation, corticosteroid-resistant in most patients, makes of COPD a major health problem frequently difficult to treat. This disease, reflecting smoking patterns, represents a global epidemic and affects about 10 % of people over 45 years of age with a similar prevalence in males and females. More than 250 million people around the world live with COPD and millions more remain undiagnosed. COPD is ranked as the 3thcause of death in the world and the 5th cause of morbidity and a leading cause of emergency hospital admission with acute exacerbation (1). The COVID-19 pandemic has put patients with COPD and other comorbidities at high risk for poor outcomes. Airflow obstruction, measured by spirometry with FEV_1/FVC ratio <70 % is characteristic of COPD; several clinical phenotypes determine that patients may show different clinical features like the rates of progression, the frequency of exacerbations and some associated comorbidities. COPD is characterized by small airways disease with peribronchiolar fibrosis and emphysema with alveolar wall destruction. An important clinical phenotype is based on the frequency of exacerbation which is mainly determined by upper respiratory tract infections. Patients with COPD have a chronic pulmonary inflammation determined by activated macrophages and neutrophils which can be found in the sputum, recruited from the circulation in response to chemotactic mediators released from airway epithelial cells and macrophages in the lung. Lymphoid cells are increased: these lymphocytes are responsible for the neutrophilic inflammation and may account for its persistence, induced by cigarette smoke, bacteria, viruses, and oxidative stress. Chronic neutrophilic inflammation does not respond to inhaled corticosteroids (ICS). The symptomatology of some COPD patients may improve to the ICS therapy: these patients are characterized by an increase in the sputum of eosinophils and FeNO, which are a feature of asthma. Approximately 15 % of patients with COPD appear to have a clinical feature of asthma. This may be the concurrence of two diseases, especially as asthma onset may occur in elderly people (2). Acute exacerbation may be a severe complication for patients with COPD, mostly precipitated by upper respiratory tract viral infections which may be related to bacterial colonization of the lower airways. Bacterial infections may be associated with increased sputum eosinophils as well as neutrophils (3).

It has been shown that increased oxidative stress in the lung is an important mechanism of the disease. Oxidative stress is the consequence of the impairment of the endogenous antioxidant defenses which might be reduced or overwhelmed by the excessive presence of reactive oxygen species. Increased oxidative stress in COPD patients may determine an acceleration of the normal lung aging process and, as a consequence, the accumulation of senescent cells (4). Oxidative stress is an important driving mechanism for the pathophysiology of COPD, its reduction represents an important therapeutic strategy.

In the inflammatory process observed in the lungs of patients with COPD also participate airway and alveolar epithelial cells activated by cigarette smoke and other inhaled irritants; fibroblasts are also involved. Moreover, the inflammation includes innate immunity (neutrophils, macrophages, eosinophils, mast cells, natural killer cells, innate lymphoid cells, and dendritic cells) and adaptive immunity (T

and B lymphocytes).

The relation between COPD, smoking, and vaping needs to be further investigated to better understand the impact of nicotine exposure and the influence of COPD on COVID-19 outcomes. Nicotine has previously been associated with the upregulation of the angiotensin-converting enzyme 2 (ACE2), the well-known receptor for SARS-CoV-2, widely expressed including in the lungs: results of related research suggest the importance of emphasizing smoking and vaping cessation.

COPD prevalence as a comorbidity of COVID-19

SARS-CoV-2 primarily invades the pulmonary epithelial cells and it has infected humans in all age groups of all ethnicities, both males and females. The clinical manifestations range from a common cold to more severe diseases such as bronchitis, pneumonia, severe acute respiratory distress syndrome, multiorgan failure, and even death. It is believed that COVID-19, in those patients with comorbidities, has an increasingly rapid and severe progression, often leading to death. Patients with COVID-19 disease who have comorbidities are more likely to develop a more severe course and progression of the disease. Patients 65 years old and above, who have comorbidities and are infected, have the worst prognosis, and an increased admission rate into ICU and mortality from the COVID-19 disease. Some individuals infected do not develop any symptoms, and about 80 % of positive cases recover from the disease without any treatment. Symptoms may appear anytime from 2 to 14 days after exposure; therefore, 14 days of quarantine is recommended. People with underlying conditions such as diabetes, hypertension; lung, liver, and kidney diseases; cancer patients on chemotherapy; smoker; transplant recipients; and patients taking steroids chronically are at increasing risk of COVID-19 infections. Among other comorbidities, COPD has also been associated with poor disease progression. Patients with acute respiratory distress syndrome and respiratory failure associated with the novel coronavirus may be linked to a prothrombotic coagulopathy. The autopsy of COVID-19 related deaths revealed dispersed microthrombi in the pulmonary vasculature, which corresponds to occlusive lung disease.

Reports of 1 590 patients in China, hospitalized with COVID-19, laboratory-confirmed (RT-CPR), highlighted a low incidence of patients reported COPD (1.5 %). None of the cases had physician-diagnosed asthma. Patients rarely reported as having comorbid respiratory diseases, particularly COPD. However, it is interesting to note that the prevalence of COPD in China in people ≥40 years old was 13.7 % as reported in 2018. The reasons underlying this observation could have arisen from the lack of awareness and the lack of spirometry testing that collectively contributed to the under-diagnosis of respiratory diseases. However, COPD had a significant impact on risk for poor outcome reflected by a hazard ratio (HR) of 2.681 (95 % CI 1.424-5.048); COPD comorbidity as a risk factor was second only to malignancy (HR 3.50, 95 % CI 1.60-7.64). The hazard ratio is a predictor of the risk factors associated with the composite end-points (admission to ICU, invasive ventilation, or death). The most prevalent patients reported comorbidity was hypertension (16.9 %), followed by diabetes (8.2 %). Patients with any comorbidity yielded poorer clinical outcomes than those without. A higher number of comorbidities also were followed by poorer clinical outcomes. Two or more comorbidities were more commonly observed in severe cases than in non-severe cases (40.0 % vs 29.4 %). Patients with two or more comorbidities, compared with those who had single comorbidity, were older (mean: 66.2 vs 58.2 years) and had more probability to have shortness of breath (55.4 % vs 34.1 %). These findings show that patients with comorbidities have greater disease severity compared with those without. Underreporting of comorbidities might contribute to the underestimation of the true strength of the disease-combination and the relative impact on the clinical prognosis. A trough assessment of comorbidities may help establish risk stratification of patients with COVID-19 upon hospital admission (5). A large (1 099 patients) case series reporting the clinical characteristics of COVID-19 in China shows a high prevalence of COPD in patients with severe presentation (3.5 %) and worse outcome (10.4 %) (6). A meta-analysis of ten studies in China was directed to explore the risk

of severe COVID-19 in patients with pre-existing COPD. The pooled odds ratio of COPD and the development of severe COVID-19 was 4.38 (fixed-effects model; 95 % CI: 2.34-8.20), which shows that the presence of COPD is associated with a nearly fourfold higher risk of developing severe COVID-19 (7).

Characteristics, comorbidities, and outcomes are reported among patients hospitalized with COVID-19 in the New York area. This case series includes 5 700 patients hospitalized with COVID-19 (median age, 63 years). The most common comorbidities were hypertension (56.6.%), obesity (41.7 %), and diabetes (33.8.%). As for chronic respiratory diseases, asthma and COPD reached 9 % and 5.4 %, respectively. The mortality rate was 0 % for male and female patients younger than 20 years. Mortality rates were higher for males compared with female patients every 10-year interval, older than 20 years. Mortality rates for patients in the 18 to 65 and >65 age groups who received mechanical ventilation were 76.4 % and 97.2 %, respectively; for those without mechanical ventilation, mortality rates were 1.98 % and 26.6 %, respectively. The median score on the Charlson Comorbidity Index was 4 points, which corresponds to a 53 % estimated 10-years survival; a score of 7 points and above corresponds to a 0 % estimated 10-years survival. Of the patients who died, those with diabetes as comorbidity were more likely to have received mechanical ventilation compared with those who did not have diabetes. Older persons, men, and those with preexisting diabetes or hypertension had a similar pattern to those reported from China: mortality rates were significantly lower in this case series. Home medication information was available for 92 % of the included laboratory-confirmed patients who were discharged or who died. Of the hypertensive patients, 7.8 % were taking an angiotensin-converting enzyme inhibitor (ACEI) and 11,1 % were taking an angiotensin II receptor blocker (ARB) (8). ACEI and ARB medication can increase mRNA expression of cardiac ACE2: possible adverse events, protective, or biphasic effect of these medications have been proposed (9).

Underrepresentation of chronic respiratory diseases as a comorbidity of COVID-19

COVID-19 is an acute respiratory disease that can lead to respiratory failure and death. The previous epidemic of novel coronavirus diseases, such as SARS and MERS was associated with similar clinical features and outcomes. One might have anticipated that patients with chronic respiratory diseases, particularly COPD and asthma, would be at increased risk of SARS-CoV-2 infection and more severe presentation of COVID-19. However, it is striking that both diseases appear to be under-represented in the comorbidities reported for patients with COVID-19, compared with the global burden of diseases estimates of the prevalence of these conditions in the general population; moreover, respiratory tract virus infection is a common trigger for acute exacerbations of COPD.

The lower reported prevalence of asthma and COPD in patients diagnosed with COVID-19 might be due to several factors. First, it is possible that, in contrast to the diagnosis of diabetes and hypertension, there was substantial underdiagnosis or poor recognition of COPD in patients with COVID-19, particularly in China. However, in favor of China, we have to say that in a recent report from Italy, among 355 patients dying with COVID-19, diabetes was reported in 20.3 % of patients but COPD was not listed as a comorbidity for any patients. Moreover, data from the United States (March 31, 2020) show that chronic respiratory disease and diabetes were comorbidities in 8.5 % and 10.2 % of patients with COVID-19, respectively, compared with figures of the population as a whole of 11.3 % for chronic respiratory disease and 10.2 % for diabetes (10). A second possibility is that chronic respiratory disease protects against COVID-19, perhaps through a different immune response elicited by the chronic disease itself. However, this theory is not supported by the finding that among those with COVID-19 who have COPD as comorbidity, mortality is increased. A third possibility is that therapies used by patients with chronic respiratory diseases can reduce the risk of infection or of developing symptoms leading to diagnosis. *In vitro*, inhaled corticosteroids alone or in combination with bronchodilators have been shown to suppress coronavirus replication and cytokine production. Yet, the possibility that

inhaled corticosteroid might partly prevent the development of symptomatic infection or severe presentation of COVID-19 cannot be ignored.

Comparison of case-fatality rates reporting between different countries

In Italy as in most countries, COVID-19 cases were identified by RT-PCR as the test for severe acute respiratory syndrome SARS-CoV-2. In the Italian population, the overall fatality rate of patients with confirmed COVID-19 was 7.2 % (1 625 deaths/22 512 cases, up to March 17) (12). This rate is higher than that observed in China (2.3 %); this difference may be due to demographic characteristics where people aged 65 years or older represented 23 % of the Italian population (2019). The case-fatality rate in Italy and China are similar for age groups up to 69 years, but rates become higher in Italy for patients aged ≥70 years, and among those ≥80 years. The distribution of cases is different in the two countries: patients aged 70 years or older represent 11.9 % of cases in China and 37.6 % in Italy. Moreover, an important number of cases in Italy are in people aged 90 years or older (fatality-rate of them, 22.7 %), while in China cases of ≥ 90 years were not reported. Data from China on 2,114 COVID-19 related deaths, among 55,924 laboratory-confirmed cases, reported fatality-rate among patients aged 80 years or older similar to the rate in the Italian sample (21.9 % in China vs 20.2 % in Italy) (13). Death related to COVID-19 is not clearly defined in the international reports. The presence of comorbidity might have increased the risk of mortality independent of COVID-19 infection. The lack of definition of COVID-19-related death might be the reason for variation in case-fatality rates among different countries. On February 25, 2020, the Italian Ministry of Health recommended prioritizing testing for patients with more severe clinical symptoms requiring hospitalization. This testing strategy determined a high proportion of positive results and an increase in the case-fatality rate because patients who presented with the less severe clinical disease were no longer tested. Other countries adopted different testing strategies. North Korea applied a strategy of widely testing forSARS-CoV-2. This may cause the identification of a large number of individuals with mild or limited symptoms but a much lower case-fatality rate compared with Italy (1.0 % vs 7.2 %) because many patients with mild disease who would not be tested in Italy were included in the denominator in Korea.

Biological markers tools for differential diagnosis and determination of disease severity grade

Differential diagnosis of COVID-19 is challenging due to the ongoing symptomatology of COPD, and often leads to delayed diagnosis as patients have fiber, fatigue, and other systemic symptoms, while respiratory symptoms are relatively light. After 6 to 7 days, rapid deterioration of lung function may occur. Once infected with SARS-CoV-2 pneumonia, lung function in COPD patients can deteriorate rapidly leading to respiratory failure. The finding of delayed diagnosis of COPD patients infected with COVID-19 due to misdiagnosis because of COPD exacerbation has been described. Considering the high incidence of COVID-19 at present time, it seems imperative to test COPD patients with symptoms of exacerbation to prevent further dissemination.

C-reactive protein (CRP) levels are a strong indicator to reflect the presence and severity of COVID-19 infection. In Wuhan, China, patients in the severe cohort had a significantly higher level of CRP compared to the non-severe cohort (57.9 mg/L vs 33.2 mg/L). Levels of interleukin-6 (IL-6), the most common type of cytokine released by macrophages, rise sharply in the severe manifestation of COVID-19. Another study concludes that high neutrophils and low lymphocytes counts are frequently found in severely affected patients; the increased neutrophil/lymphocyte ratio could be a potential biomarker for early detection of severe COVID-19. Significantly higher levels of lactic acid dehydrogenase (LDH) were found in ICU patients than non-ICU patients (248 U/L vs 151 U/L, P=0.002). LDH may be a predictive biomarker of severe disease. Elevated levels of D-dimer in non-survivors compared to survivors have been found. Covid-19 infection is responsible for severe hematological alterations leading to thrombocytopenia. Cardiovascular disease is an important comorbidity of COVID-19, and cardiac troponin-I is a marker of disease progression and

mortality. Chronic kidney disease is associated with severe forms of COVID-19, it has been found significantly higher levels of renal biomarkers such as serum urea, creatinine, and altered marker of glomerular filtration rate in severe cases. Computed tomography is more sensitive than radiography, bilateral pneumonia is frequently reported (14).

On the other hand, forced expiratory volume in the first second (FEV_1) has conventionally been used to guide therapy in stable COPD; however, it is a poor indicator of a patient's exacerbation status. Instead, biomarkers may better reflect disease activity and fluctuate in accordance with disease state, they could provide more objective determination of a patient's health status before, during, and after an exacerbation event. For instance, certain biomarkers could point to a bacterial or viral origin, thus guiding appropriate therapy. It is important to define stable COPD as being free of exacerbation in the preceding 4 weeks. CRP, IL-6, and TNFα concentrations were higher in acute exacerbation compared with stable COPD or healthy control; however, only CRP concentrations appeared to be consistently elevated in acute exacerbation of COPD state compared to convalescence (15). Ideally, a clinically useful biomarker should consistently and accurately reflect disease activity.

CONCLUSION

COPD might represent comorbidity which may increase the risk of more severe illness from COVID-19 as both conditions affect the respiratory system. In most patients, the inflammation of COPD is corticosteroid resistant. The COVID-19 pandemic has put patients with COPD and other comorbidities at high risk for poor outcomes. Patients with COPD may have frequent exacerbations mainly determined by upper respiratory tract infections. The prevalence of COPD in China in adult people is 13.7 % (2018 report), while a study of 1 590 patients hospitalized with COVID-19, laboratory-confirmed, showed a low incidence of patients reported COPD (1.5 %). In patients with severe presentation and worse outcomes, the prevalence of COPD was higher, 3.5 %, and 10.4 %, respectively. Moreover, it was found that the coexisting COPD is associated with about fourfold higher risk of developing severe COVID-19. In the New York area, asthma and COPD reached 9 % and 5.4 %, respectively, as comorbidities of COVID-19 in 5 700 hospitalized patients (hypertension 56.6 %, obesity 41.7 %, and diabetes 33.8 %). Mortality rate varied according to age, comorbidities, severities of disease, and worse outcome. It is interesting to note that chronic respiratory diseases, asthma, and COPD, appear under-represented in the comorbidities reported for patients with COVID-19. The lower reported prevalence of asthma and COPD in patients diagnosed with COVID-19 might be due to several factors; likely, therapies used for these patients reduce the risk of infection or of developing symptoms leading to diagnosis. Fatality-rate reporting differs between countries; demographic characteristics, testing strategy, and lack of definition of COVID-19-related death might be the reason for this variation. Differential diagnosis in patients infected with SARS-CoV-2 during COPD exacerbation is of capital importance; and appropriate use of biomarkers might be of paramount importance.

REFERENCES

1. Burney P, Jarvis D, Perez Padilla R. The global burden of chronic obstructive pulmonary disease in adults. Int J Tuber Lung Disease. 2015;19:10-20.
2. Barnes PJ. Cellular and molecular mechanisms of asthma and COPD. Clin Sci. 2017;131:1541-1558.
3. Han MK, Quibrera PM, Carretta EE, Barr G, Bleecker ER, Bowler R, et al. Frequency of exacerbations in patients with chronic obstructive pulmonary disease: An analysis of the SPIROMICS cohort. Lancet Respir Med. 2017;5:619-626.
4. Barnes PJ, Baker J, Donnelly LE. Cellular senescence as a mechanism and target in chronic lung diseases. Am J Respir Crit Care Med. 2019;200:556-564.
5. Guan W, Liang WH, Zhao Y, Liang H, Chen Z, Li Y, et al. Comorbidity and its impact on 1 590 patients with COVID-19 in China: A nationwide analysis. Eur Respir J. doi.org/10.1183/13993003.00547-2020.
6. Guan WJ, Ni ZY, Hu Y, Liang W, Ou C, He J, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382:1708-1720.
7. Zhao Q, Meng M, Kumar R, Wu Y, Huang J, Lian N, et al. The impact of COPD and smoking history on the severity of COVID-19: A systemic review and meta-analysis. J Med Virol. 2020; doi:10.1002/

jmv.25889.

8. Richardson S, Hisch J, Narasimhan DO, Crawford JM, McGinn T, Davidson K, et al. Presenting characteristics, comorbidities and outcomes among 5 700 patients hospitalized with COVID-19 in the New York area. JAMA. 2020;323:2052-2059.
9. Sommerstein R, Kochen MM, Messerli FH, Grani C. Coronavirus disease 2019: Do angiotensin-converting enzyme inhibitors/angiotensin receptor blockers have a bio-phasic effect? J Am Heart Assoc. 2020;9(7):e0165509.
10. CDC COVID-19 Response Team. https://www.cdc.gov/mmvr/volumes/69/wr/ pdfs/mm6913e2-H.pdf
11. China CDC Weekly. 2020;2:113-122.
12. Livingston E, Bucher K. Coronavirus disease (COVID-19) in Italy. JAMA. 2020;323(14):1335.
13. Report of the WHO-China. Available from:https://www.who-china-joint-mission-on-covid-19-final-report.pdf
14. Kermali M, Khalsa RH, Pillai K, Ismail Z, Harky A. The role of biomarkers in the diagnosis of COVID-19—A systematic review. Life Sci. 2020;254:117788.
15. Chen Y-W, Leung JM, Sin DD. A systemic review of diagnostic biomarkers of COPD exacerbation. PLoS One. doi:10.1371/journal.pone0158843 2016;July 19:1-16.