



Editorial article

Clinical challenges in chronic obstructive pulmonary disease in patients who suffered SARS-CoV-2 infection[☆]

Retos clínicos en pacientes con enfermedad pulmonar obstructiva crónica que han sufrido una infección por SARS-CoV-2

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The World Health Organization (WHO) has declared SARS-CoV-2 (COVID-19) a pandemic. Although the evidence to date suggests that most cases manifest mildly, up to 16% of cases may require hospital admission.¹ To date, the relationship between chronic obstructive pulmonary disease (COPD) and COVID-19 is not clear. Although various studies show that the main comorbidities related to the development of a serious form of the disease are high blood pressure, diabetes mellitus or cardiovascular disease,² we know that COPD is associated with an increased risk of admission to an intensive care unit, as well as death.³

Many of the most common chronic diseases occur more frequently in patients with COPD compared to the general population. Up to 60–90% of COPD patients develop some comorbidity, an aspect that will contribute to the severity of symptoms and jeopardize patient survival. Reported complications of SARS-CoV-2 infection, such as extensive pneumonia/acute lung damage or adult acute respiratory distress syndrome, the occurrence of myocarditis/cardiac arrhythmias or the development of thromboembolic episodes are events that may worsen the baseline condition of the COPD patient surviving the process, having to take into account their existence when planning their outpatient follow-up.

Unfortunately, we do not have information about how the SARS-CoV-2 infection will impact our patients in the medium-long term and, for the time being, we must make assumptions based on the knowledge gained from other coronaviruses such as SARS-CoV-1 or MERS-CoV.

Viral infections cause an intense systemic inflammatory response resulting in an imbalance between the homeostatic pro-coagulant and anticoagulant mechanisms,⁴ therefore, thromboembolic disease is an aspect to analyse. Based on the limited evidence we currently have, there is a possibility that SARS-CoV-

2 infection increases the risk of a venous thromboembolic event.⁵ Multiple pathogenic mechanisms appear to be involved including endothelial dysfunction, elevation of von Willebrand factor, Toll-like receptor or tissue factor pathway activation.⁴ However, apart from infection, we must be aware that other factors such as strict and prolonged quarantine and, subsequently, immobilization could lead to it.

Despite what has been described, there is a lack of evidence about the incidence of pulmonary embolism in patients with SARS-CoV-2.^{6,7} A study published by Cui et al.⁷ determined that the incidence of pulmonary thromboembolism in 81 patients admitted to an intensive care unit for a severe SARS-CoV-2 infection was 25%. In the case of SARS-CoV-1, *post-mortem* studies in infected patients detected thrombi in the pulmonary vascular bed.⁸ A study carried out in Singapore that included autopsies of 8 confirmed cases of SARS-CoV-1 described pulmonary thrombi in 4 patients, deep vein thrombosis in 3 and generalized multiorgan infarctions due to thrombi in two of the patients.⁸ Although the main scientific societies have formulated positions and consensus related to the diagnosis of COVID-19 and the role of tests such as CT in this procedure, no specific proposals have been made on the indication of CT angiography to diagnose a thromboembolic pulmonary event. Despite the lack of sufficient evidence at the moment, the results reported to date and the pathogenic mechanisms plausibly involved, make it advisable to consider this aspect in those patients with COPD who, after hospital discharge, develop in the medium to long term an increase in dyspnoea not justified by spirometric parameters.

On the other hand, we have to consider the risk of cardiovascular disease development. Abnormal biomarkers consistent with heart damage are a prominent feature of SARS-CoV-2 infection and are associated with a poorer prognosis.⁹ The underlying mechanisms are not well established, but it is likely that it involves the presence of myocardial stress in relation to hypoxemia, or it might be related to a direct effect of the viral infection, with a systemic inflammatory response, or with a combination of the 3 factors. A *post-mortem* real-time PCR of heart tissue during the SARS-CoV-1 epidemic detected the presence of the viral genome

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in 35% of those deceased.¹⁰ It is noteworthy that these hearts had a decrease in the expression of angiotensin 2 receptors (an aspect that could highlight the relationship of this receptor in the mediation of the infection) and a greater hypertrophy.¹⁰ Myocardial pericytes, which play an important role in maintaining endothelial function, express angiotensin-2 receptors abundantly.¹¹ Pericyte and endothelial cell dysfunction, either due to direct infection or global inflammation, can lead to coronary microcirculation disruption with subsequent ischemic consequences, but its possible relationship with SARS-CoV-2 infection is pure conjecture for now. We do not know if patients suffering from a SARS-CoV-2-related myocarditis will develop any type of medium to long-term heart failure.

Other aspects of cardiac involvement to consider in SARS-CoV-2 infection are cardiac arrhythmias. Such events may arise from severe hypoxemia, from ion disorders, from systemic inflammation, from the use of drugs to combat coronavirus, or from direct damage to the myocardium caused by SARS-CoV-2.¹²

Furthermore, patients with SARS-CoV-2 can develop acute coronary syndromes and acute myocardial infarction, but the incidence of such events is unclear. *A priori*, the risk of coronary event in these patients may increase due to an increased thrombotic predisposition, as evidenced by the significantly high levels of D-dimer in these patients.¹³ Underlying this risk are predisposing factors related to inflammation that will have a relevant role in this process, such as endothelial and smooth muscle cell activation, macrophage activation and tissue factor expression, in addition to platelet activation.

Cardiovascular complications are possible even after recovery from infection. In Italy, the development of fulminant myocarditis has been described in a convalescent patient one week after respiratory symptoms had resolved.¹⁴ This suggests that the underlying inflammation may persist and progress “silently” with its complications manifesting in a delayed manner. In the SARS-CoV-1 epidemic, some of the survivors developed avascular necrosis, pulmonary fibrosis, and dyslipidaemia after viral infection,^{15,16} which may have a relevant impact on those patients who already had some underlying respiratory or cardiovascular condition.

Taking into account the aforementioned, we must carefully evaluate, case by case, the worsening or the *de novo* onset of cardiovascular comorbidity when planning outpatient follow-up in patients with COPD who have suffered a SARS-CoV-2 infection, since patients with COPD and concomitant heart disease suffer a greater degree of dyspnoea and exercise intolerance and an increased risk of hospitalization.

Finally, we must evaluate acute lung damage (severe pneumonia/adult acute respiratory distress) and lung function deterioration. Similar to that described in the MERS-CoV and SARS-CoV-1, the most common radiological findings are ground glass opacities with or without consolidation and predominantly in the lung bases with posterior and peripheral location. Although considerable information is available on the acute radiological manifestations of the disease, we do not yet have information on its long-term progression, nor on its possible impact on lung function. Therefore, at the moment, one can only speculate about whether future changes will be similar to those described in other viral infections. Chen et al.¹⁷ conducted a follow-up of 56 patients for H7N9 influenza with the intention of assessing the functional and radiological progression on CT during 2 years after infection. Despite the persistence of interstitial changes and fibrosis on imaging tests, the functional parameters of ventilation and diffusion showed a tendency to improve after 6 months. However, after 2 years, a mild-moderate impairment in the diffusing capacity of lung for CO (DLCO) persisted in 77% of cases. Ong et al.¹⁸ evaluated lung function in 94 patients one year after suffering from a SARS-CoV-

1 respiratory infection. This study demonstrated that 18% of the cases had a slight-moderate reduction in DLCO values, while 63% of patients showed no anomalies in the spirometric parameters. Zhang et al.¹⁹ monitored the functional respiratory and radiological progression of SARS-CoV-1 infection patients for 15 years. They described how in the first year of follow-up there was a radiological improvement that stabilized in subsequent years. From a functional point of view, patients without interstitial changes on CT showed a more significant improvement in spirometric parameters compared to those with interstitial involvement. If SARS-CoV-2 infection behaves similarly to that described by these authors, a radiological and functional improvement is expected in the months following infection, but we do not know whether a certain degree of irreversible deterioration will persist, especially in patients with COPD, or if there will be changes in functional decline. Nor do we know if the hypothetical functional impact depends on the prevalence of a phenotype of airway or lung parenchyma involvement (emphysema).

Finally, there is evidence that severe SARS-CoV-2 infection cases may develop traction bronchiectasis.²⁰ The potential impact of this fact in a patient with COPD is very great, since the presence of bronchiectasis in these subjects increases the risk of chronic bronchitis and neutrophilic inflammation of the airway and is associated with a greater functional decline, quality of life deterioration and increased risk of exacerbation and death.

In conclusion, the SARS-CoV-2 pandemic will involve changes in the care of COPD patients suffering from the infection. There is sufficient theoretical basis to fear that some of these patients will suffer new comorbidities or the worsening of the existing ones (with special impact on cardiovascular health) and that the infection could have an impact on lung function of uncertain extent. The effect on the symptoms, exacerbations and the vital prognosis of our patients is still an area of uncertainty, and in the coming months we will have to incorporate the information generated regarding the foreseeable modifications that will be made in the monitoring and treatment schedules of the disease.

References

- Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020. <http://dx.doi.org/10.1056/NEJMoa2002032>.
- Guan WJ, Liang WH, Zhao Y, Liang HR, Chen ZS, Li YM, et al. Comorbidity and its impact on 1590 patients with Covid-19 in China: a nationwide analysis. *Eur Respir J*. 2020. pii: 2000547.
- 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. <http://dx.doi.org/10.1002/jmv.25889>.
- Subramaniam S, Scharrer I. Procoagulant activity during viral infections. *Front Biosci Landmark Ed*. 2018;23:1060–81.
- Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost*. 2020;18:844–7.
- Danzi GB, Loffi M, Galeazzi G, Gherbesi E. Acute pulmonary embolism and COVID-19 pneumonia: a random association? *Eur Heart J*. 2020. <http://dx.doi.org/10.1093/eurheartj/ehaa254>, pii: ehaa254.
- Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. *J Thromb Haemost*. 2020. <http://dx.doi.org/10.1111/jth.14830>.
- Chong PY, Chui P, Ling AE, Franks TJ, Tai DYH, Leo YS, et al. Analysis of deaths during the severe acute respiratory syndrome (SARS) epidemic in Singapore: challenges in determining a SARS diagnosis. *Arch Pathol Lab Med*. 2004;128:195–204.
- Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiol*. 2020. <http://dx.doi.org/10.1001/jamacardio.2020.0950>.
- Oudit GY, Kassiri Z, Jiang C, Liu PP, Poutanen SM, Penninger JM, et al. SARS-coronavirus modulation of myocardial ACE2 expression and inflammation in patients with SARS. *Eur J Clin Invest*. 2009;39:618–25.
- Chen L, Li X, Chen M, Feng Y, Xiong C. The ACE2 expression in human heart indicates new potential mechanism of heart injury among patients infected with SARS-CoV-2. *Cardiovasc Res*. 2020;116:1097–100.
- Akhmerov A, Marban E. COVID-19 and the heart. *Circ Res*. 2020. <http://dx.doi.org/10.1161/CIRCRESAHA.120.317055>.

13. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395:1054–62.
14. Inciardi RM, Lupi L, Zaccone G, Italia L, Raffo M, Tomasoni D, et al. Cardiac involvement in a patient with coronavirus disease 2019 (COVID-19). *JAMA Cardiol*. 2020. <http://dx.doi.org/10.1001/jamacardio.2020.1096>.
15. Wu Q, Zhou L, Sun X, Yan Z, Hu C, Wu J, et al. Altered lipid metabolism in recovered sars patients twelve years after infection. *Sci Rep*. 2017;7(1):9110.
16. Antonio GE, Wong KT, Hui DS, Wu A, Lee N, Yuen EH, et al. Thin-section CT in patients with severe acute respiratory syndrome following hospital discharge: preliminary experience. *Radiology*. 2003;228:810–5.
17. Chen J, Wu J, Hao S, Yang M, Lu X, Chen X, et al. Long term outcomes in survivors of epidemic Influenza A (H7N9) virus infection. *Sci Rep*. 2017;7:17275.
18. Ong KC, Ng AW, Lee LS, Kaw G, Kwek SK, Leow MK, et al. 1-year pulmonary function and health status in survivors of severe acute respiratory syndrome. *Chest*. 2005;128:1393–400.
19. Zhang P, Li J, Liu H, Han N, Ju J, Kou Y, et al. Long-term bone and lung consequences associated with SARS. *Bone Res*. 2020;8:8.
20. Zhao W, Zhong Z, Xie X, Yu Q, Liu J. Relation between chest CT findings and clinical conditions of coronavirus disease (COVID-19) pneumonia: a multicenter study. *AJR Am J Roentgenol*. 2020;214:1072–7.