

Worrisome COVID-19 pulmonary sequelae

Las secuelas pulmonares inquietantes de la COVID-19

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Since the first publications of patients affected by COVID-19 in December, 2019, neither the World Health Organization (WHO) nor the government health organizations could have foreseen the magnitude of the global morbidity and mortality caused by this virus, which is still present. The disease had mild, moderate, and severe clinical forms; the latter requiring hospitalization and causing sequelae worthy of being spread to alert the medical community^{1, 2}.

The first studies already reported complications: Wang et al published 138 cases treated in January, 2020 and reported that 29% of health professionals had been infected by hospitalized patients and that, besides the already known signs and symptoms (fever, dyspnea and nonproductive cough), which were widely propagated later, new symptoms were added: prolonged prothrombin time (58%), acute respiratory distress syndrome (61%), arrhythmia (44.4%) and shock (30.6%).

36 patients (26%) were treated at the ICU (Intensive Care Unit), with more probabilities of having comorbidities (72.2%), whereas chest tomographies (CT) showed “ground glass” opacities in all the cases³. Complications have been described, such as pulmonary thromboembolism, cor pulmonale, cerebrovascular disease of large vessels and, in relation to the specialty, post-Covid pulmonary fibrosis. The article from Pérez Conde, which motivated this editorial, is an example of such complications⁴⁻⁶.

Even though most patients with mild and moderate forms of COVID-19 will not show long-term pulmonary sequelae, it is assumed that 10% will tend to suffer post-COVID-19 severe pneumonia, and 5% will develop acute respiratory distress syndrome (ARDS). Some will get better throughout the course of the disease; others will experience progression towards pulmonary fibrosis⁷.

The natural recovery evolution of COVID-19 is unknown. There is poor knowledge regarding clinical evolution and health recovery in mild and outpatient forms of the disease. Tenforde et al conducted a telephone survey in adults with positive results for COVID-19 infection and, two or three weeks after result confirmation, 35% of the individuals hadn't returned yet to their previous health condition. One in five young individuals with no pre-existing diseases were in that situation, thus, COVID-19 may originate a prolonged disease, even among adults without underlying chronic conditions⁸.

One previously described characteristic, pulmonary fibrosis with detrimental physiological effects, was present in acute respiratory distress syndrome (ARDS) and Middle East respiratory syndrome (MERS).

As described in the Pérez Conde article, when he cites Thomas et al, there are four stages of COVID-19 in the chest CT:

- 1) **Early course**: characterized by normal lung or “ground glass” opacities.
- 2) **Progressive course**: increase in opacities and appearance of crazy paving.
- 3) **Peak course**: characterized by progressive consolidation.
- 4) **Late course**: characterized by a gradual decrease in consolidation and “ground glass” opacities; signs of pulmonary fibrosis can start manifesting^{9, 10}.

With regard to COVID-19 patients who attended the ICU with moderate or severe forms of the disease, the Bhatraj group reported the following as the most common causes of admission: respiratory failure requiring mechanical respiratory assistance (MRA), severe hypotension requiring vasopressor treatment and mechanical ventilation, hypotension that motivated vasopressor treatment, or

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both. The mortality rate in these critically ill patients was high: 50% of the patients died from this disease¹¹.

Every viral disease is treated with antivirals, broad spectrum antibiotics (to cover a possible bacterial superinfection), corticoids as anti-inflammatories and, for lung fibrosis sequelae, antifibrotic drugs, mostly when its natural course is unknown.

COVID-19 was also included in these general guidelines, so such treatment guidelines were extrapolated. Steroids have been used with good results, as in the cohort of Myall et al, in which 30 patients survived with pulmonary inflammatory lesions evident in imaging studies and persistent functional deficit. As observed, long-term follow-up of COVID-19 had the objective of preventing progression to pulmonary fibrosis with permanent functional deficit. Early treatment with steroids is well-tolerated and associated with rapid improvement¹².

Umemura et al wanted to investigate the certainty and activity of nintedanib in COVID-19. To that end, 30 patients with COVID-19 received nintedanib versus a similar control group who didn't receive the medication. There weren't any differences between the groups in terms of mortality after 30 days, but there was less mechanical ventilation and a lower lesion regression rate in the CT in the treated cohort, so the authors believe the administration of nintedanib may be beneficial to reduce pulmonary lesions in COVID-19.

According to Shen, there aren't any studies about the relationship between pirfenidone, a drug that is widely used for pulmonary fibrosis, and the treatment of COVID-19. Before it is indicated, it is important to consider the annual cost of treatment. In 2020, the cost was USD 40,000 (pirfenidone) and USD 20,000 (nintedanib), respectively¹³⁻¹⁵.

Tocilizumab is a monoclonal antibody that has shown a good anti-inflammatory response in rheumatoid arthritis. So, the group of Veiga et al thought it could be used for severe forms of COVID-19. In a cohort of 129 patients, results were discouraging. The Follow-up Committee recommended that the study had to be interrupted, given the high mortality rate registered 15 days after administration (17% as opposed to 3% in the control group)¹⁶.

Nugroho et al did a meta-analysis of the use of tocilizumab in post-COVID-19 pneumonia, since there isn't any certified treatment for that

complication.

They evaluated 26 studies investigated in PubMed, EMBASE, Medline and Cochrane, published between March and October, 2019, with 2112 patients enrolled in the COVID-19 cohort versus 6160 in the control group.

Tocilizumab has an effective result against mortality for all the causes. For optimum results, it should be cautiously administered and adapted to patients according to selection criteria¹⁷.

To conclude, it is necessary to highlight the importance of strict checkups of large groups of COVID-19 survivors by means of periodic functional and tomographic studies. This will allow us to eventually determine the course of the viral infection, the natural history of the disease and also the therapeutic response of these patients.

REFERENCES

1. Zhu N, Zhang D, Wang W y col. A Novel Coronavirus from Patients with Pneumonia in China, 2019 *N Engl J Med* 2020; 382: 727-33. <https://doi.org/10.1056/NEJMoa2001017>
2. Hui D, Azhar E, Madani T y col. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health: the latest 2019 novel coronavirus outbreak in Wuhan, China *Int J Infect Dis.* 2020; 91: 264-6. <https://doi.org/10.1016/j.ijid.2020.01.009>
3. Wang D, Hu B, Hu C y col. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China *JAMA.* 2020; 323: 1061-9. <https://doi.org/10.1001/jama.2020.1585>
4. Xie Y, Wang X, Yang P. COVID-19 Complicated by Acute Pulmonary Embolism Radiology: Cardiothoracic Imaging 2020; 2: e2000 <https://doi.org/10.1148/ryct.2020200067>
5. Creel-Bulos C, Hockstein M, Amin N, Melhem S, Truong A, Sharifpour M. Acute Cor Pulmonale in Critically Ill Patients with Covid-19. *New Engl J Med* 2020; 382: e70. <https://doi.org/10.1056/NEJMc2010459>
6. Oxley T, Mocco J, Majidi S y col. Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young. *N Engl J Med.* 2020 May 14; 382(20): e60. <https://doi.org/10.1056/NEJMc2009787>
7. Udwardia Z, Koul P, Richeldi L. PostCOVID lung fibrosis: The tsunami that will follow the earthquake Lung India. 2021;38(Supplement):S41-S47. 2021; 38: S41-7.
8. Tenforde M, Kim S, Lindsell Ch y col. Symptom Duration and Risk Factors for Delayed Return to Usual Health Among Outpatients with COVID-19 in a Multistate Health Care Systems Network - United States, March-June 2020. *MMWR Morb Mortal Wkly Rep* 2020; 69: 993-8.
9. Pérez Conde L. Fibrosis pulmonar pos neumonía causada por COVID-19. (Reporte de 3 Casos) *Rev Am Med Resp* 2022; 21: 160-3.
10. Kwee TC, Kwee RM. Chest CT in COVID-19: What the Radiologist Needs to Know. *Radiographics.* 2020; 40(7): 1848-65. <https://doi.org/10.1148/rg.2020200159>.

11. Bhatraju P, Ghassemieh B, Nichols M y col. Covid-19 in Critically Ill Patients in the Seattle Region - Case Series *N Engl J Med* 2020;382:2012-22. <https://doi.org/10.1056/NEJMoa2004500>
12. Myall K, Mukherjee B, Castanheira A y col. Persistent Post-COVID-19 Interstitial Lung Disease An Observational Study of Corticosteroid Treatment *Ann Am Thorac Soc* 2021; 18: 799-806. <https://doi.org/10.1513/AnnalsATS.202008-1002OC>
13. Umemura Y, Mitsuyama Y, Monami K y col. *J infect Dis* 2021; 108:454-60.
14. Shen H, Zhang N, Liu Y y col. The interaction between pulmonary fibrosis and Covid 19 and the application of related antifibrotic drugs. *Front Pharmacol* 2022; 12: 805535. <https://doi.org/10.3389/fphar.2021.805535>
15. Corral, M, De Young K, Kong AM. Treatment Patterns, Healthcare Resource Utilization, and Costs Among Patients with Idiopathic Pulmonary Fibrosis Treated with Antifibrotic Medications in US-Based Commercial and Medicare Supplemental Claims Databases: a Retrospective Cohort Study. *BMC Pulm Med* 2020; 20: 188. <https://doi.org/10.1186/s12890-020-01224-5>
16. Veiga V, Prat J, Farias D y col. Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial *BMJ* 2021; 372: n84 | <https://doi.org/10.1136/bmj.n84>
17. Nugroho C; Suryantoro S, Yuliasih Y y col. Yuliasih Optimal use of tocilizumab for severe and critical COVID-19: a systematic review and meta-analysis [version 1; peer review: 1 approved, 2 approved with reservations *F1000Research* 2021, 10:73 <https://doi.org/10.12688/f1000research.45046.1approved,2approvedwithreservations>