Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Archivos de Bronconeumología 58(S1) (2022) 6–7

Sociedad Española de Neumología y Cirugía Torácica SEPAR

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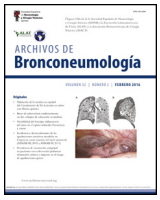

Editorial

Pulmonary Fibrosis in the Time of COVID-19

Fibrosis pulmonar en tiempos de COVID-19

Although a common long-term outcome observed in COVID-19 pneumonia survivors is the persistence of respiratory symptoms and/or radiological interstitial lung abnormalities, the long-term development of pulmonary fibrosis hides several mysteries and caveats, and most articles published so far are frequently speculative. Therefore, many uncertainties remain unanswered and new compelling questions will undoubtedly arise. Here we pose several questions to be solved in the future.

Will patients who had severe COVID-19 develop pulmonary fibrosis?

This is likely the most discussed question on the topic, and intuitively, we believe that this is going to occur. The bases to sustain the hypothesis that some post-COVID-19 patients will develop pulmonary are: first, acute COVID-19 frequently produces an acute respiratory distress syndrome, and it is well known that some patients with this syndrome, if survive, may develop pulmonary fibrosis.[1] On the other hand, SARS-COV-2 is similar to the coronaviruses responsible for SARS-COV in 2002 and MERS-COV in 2012, from which it was suggested that approximately 30% of patients developed diffuse interstitial lung disease and fibrotic abnormalities. But these were studies performed with few patients and follow-ups of less than 1 year.[2,3] What happened next? We don't know. In one study, patients with interstitial lung disease associated with SARS-COV improved in the first 2 years and remained stable at 15 years of follow-up.[4] However, SARS-COV was described in around 8000 patients worldwide, and MERS-COV affected less than 2000 people. In sharp contrast, COVID-19 pneumonia has affected millions of people worldwide, and even a very small proportion of patients with pulmonary fibrosis may represent a considerable clinical and health system problem.[5] Finally, viral infections have been associated (indirectly) with pulmonary fibrosis.[6]

But what do we know so far about COVID-19? First, it is important to note that it's been only 2 years since the first case was reported in China, and long-time experience is scanty. In our practice in Mexico with 118 patients followed by 1 year, most healed (either by spontaneous resolution or with corticosteroids), while around 20% of them remain with predominantly inflammatory parenchymal lesions not very functionally relevant and fibrotic changes such as parenchymal bands, traction bronchiectasis, and reticular opacities.

But these observations do not clarify the uncertainties, because pulmonary infectious diseases can leave sequelae in computed tomography or small decreases in DLCO, for example, but remain stable without greater clinical relevance.

The important question here is what percentage of these patients will develop life-threatening progressive pulmonary fibrosis and force the use of anti-fibrosing therapy. This scenario is currently unclear, and it will take a while to be known with some precision.

Special attention will be required in individuals with some putative risk factors such as male gender, aging, active smoking,[5] accelerated biological age, and abnormal telomere shortening.[7]

Are patients with pulmonary fibrosis more susceptible to the infection by SARS-COV-2?

A national cohort of COVID-19 patients (n = 8070) and a non-COVID control group matched by age, gender, and residential area (n = 121,050) were evaluated in Korea. They found that the proportion of patients with previous ILD was significantly higher in the COVID-19 cohort than in the control cohort (0.8% versus 0.4%; $P < .001$), indicating that they were more susceptible to becoming infected (oddas ratio [OR] = 2.02; 95% confidence interval [95%CI], 1.54-2.61).[8] However, we do not currently know how this risk will change after vaccination in this group of patients.

Do patients with pulmonary fibrosis have more severe lung disease?

In the same study by Lee et al.[8], it was found that among patients who had COVID-19, those with a previous ILD presented more severe disease (47.8% versus 12.6%) and higher mortality (13.4% versus 2.8%) (all $P < .001$).

Likewise, in a meta-analysis that included 15 studies (135,263 COVID-19 patients), the rate of ICU admission and mortality was significantly higher in patients with ILD than those without, indicating that ILD may be a risk factor for poor clinical outcomes of patients with COVID-19.[9]

In a smaller case-control study, patients with ILD who contracted COVID-19 had a greater than fourfold increased adjusted odds of death, were more likely to be hospitalized and require ICU level of care, and were less likely to be discharged, compared with a matched cohort of patients with COVID-19 without ILD.[10]

https://doi.org/10.1016/j.arbres.2022.03.007

Will the intersection of COVID-19 and autoimmunity enhance the development of ILD?

It has been suggested that viruses may be putative environmental triggers of autoimmunity in genetically predisposed individuals.[11] Some clinical features of COVID-19 are similar to those observed in autoimmune diseases such as antiphospholipid syndrome, inflammatory arthritis, and lupus. Moreover, the abnormal coagulation, micro- and macrovascular thrombosis that has been observed in severe COVID-19 resemble antiphospholipid syndrome.[12] In addition, there are numerous reports of patients developing varying autoantibodies or autoimmune diseases such as rheumatoid arthritis or psoriatic arthritis concomitantly or after infection with SARS-CoV-2 infection.

Since autoimmune diseases frequently provoke ILD, the questions here are: will these autoimmune alterations/diseases contribute to the development of ILD and subsequent pulmonary fibrosis? Or in the follow-up, these autoimmune alterations will be not relevant and be auto-limited?

Deaths from ILD without COVID-19 due to lack of medical care

The pandemic resulted in hospital reengineering and most of the institutions that take care of ILD patients were transformed into COVID-19 hospitals. As a result, hospital capacity for other conditions (including ILD) and face-to-face contact consultation showed a marked decrease. The magnitude of this problem is only recently emerging and it will be evident in the next few years.

A significant number of patients cancel their visits, abandon treatment, or were lost, and the real mortality in this group of patients for different causes is unknown yet.

Are there alternatives to follow-up of ILD patients in a crisis situation?

Telemedicine was proposed as a useful tool in the care of patients with ILD, and there are reports in the last 5 years about the feasibility and reliability of home monitoring and home spirometry in this group of patients.[13,14] In a survey performed to 207 clinicians from 23 countries of Europe, Asia, and America, 39% reported using telehealth and most of them rated it to be quite or more effective than face-to-face visits;[15] however, not all countries were able to use it for different reasons: policy makers, implementation, access, among others. Nevertheless, this pandemic can be an incentive to further evaluate its usefulness by alternating face-to-face visits and telemedicine in all countries.

Has the COVID-19 pandemic helped to uncover incipient cases of pulmonary fibrosis?

A few older-age patients consulting for acute COVD-19 show from the beginning, in addition to the extensive inflammatory changes associated with the disease, subtle subpleural basal reticular/fibrotic abnormalities that persist after hospital discharge. Were they having a previously unaware incipient subclinical idiopathic pulmonary fibrosis?

Certainly, in the coming months/years we will reveal the answer of these questions, but we will also have new mysteries to unravel.

References

1. Matthay MA, Zemans RL, Zimmerman GA, Arabi YM, Beitler JR, Mercat A, et al. Acute respiratory distress syndrome. Nat Rev Dis Primers. 2019;5:18.
2. Das KM, Lee EY, Singh R, Enani MA, Al Dossari K, Van Gorkom K, et al. Follow-up chest radiographic findings in patients with MERS-CoV after recovery. Indian J Radiol Imaging. 2017;27:342–9.
3. Hui DS, Joynt GM, Wong KT, Gomersall CD, Li TS, Antonio G, et al. Impact of severe acute respiratory syndrome (SARS) on pulmonary function, functional capacity and quality of life in a cohort of survivors. Thorax. 2005;60:401–9.
4. Zhang P, Li J, Liu H, Han N, Ju J, Kou Y, et al. Long-term bone and lung consequences associated with hospital-acquired severe acute respiratory syndrome: a 15-year follow-up from a prospective cohort study. Bone Res. 2020;8:8.
5. Vianello A, Guarnieri G, Braccioni F, Lococo S, Molena B, Cecchetto A, et al. The pathogenesis, epidemiology and biomarkers of susceptibility of pulmonary fibrosis in COVID-19 survivors. Clin Chem Lab Med. 2021;60:307–16.
6. Britto CJ, Brady V, Lee S, Dela Cruz CS. Respiratory viral infections in chronic lung diseases. Clin Chest Med. 2017;38:87–96.
7. Mongelli A, Barbi B, Gottardi M, Atlante S, Forleo L, Nesta M, et al. Evidence for biological age acceleration and telomere shortening in COVID-19 survivors. Int J Mol Sci. 2021;22:6151.
8. Lee H, Choi H, Yang B, Lee SK, Park TS, Park DW, et al. Interstitial lung disease increases susceptibility to and severity of COVID-19. Eur Respir J. 2021;58:2004125.
9. Ouyang L, Gong J, Yu M. Pre-existing interstitial lung disease in patients with coronavirus disease 2019: A meta-analysis. Int Immunopharmacol. 2021;100:108145.
10. Esposito AJ, Menon AA, Ghosh AJ, Putman RK, Fredenburgh LE, El-Chemaly SY, et al. Increased odds of death for patients with interstitial lung disease and COVID-19: A case-control study. Am J Respir Crit Care Med. 2020;202:1710–3.
11. Smatti MK, Cyprian FS, Nasrallah GK, Al Thani AA, Almishal RO, Yassine HM. Viruses and autoimmunity: a review on the potential interaction and molecular mechanisms. Viruses. 2019;11:762.
12. Knight JS, Caricchio R, Casanova JL, Combes AJ, Diamond B, Fox SE, et al. The intersection of COVID-19 and autoimmunity. J Clin Invest. 2021;131:e154886.
13. Moor CC, Mostard RLM, Grutters JC, Bresser P, Aerts JGJV, Chavannes NH, et al. Home monitoring in patients with idiopathic pulmonary fibrosis. A randomized controlled trial. Am J Respir Crit Care Med. 2020;202:393–401.
14. Nakshbandi G, Moor CC, Wijsenbeek M. Home monitoring for patients with ILD and the COVID-19 pandemic. Lancet Respir Med. 2020;8:1172–4.
15. Althobiani M, Algahtani JS, Hurst JR, Russell A, Porter J. Telehealth for patients with interstitial lung diseases (ILD): results of an international survey of clinicians. BMJ Open Respir Res. 2021;8:e0011088.

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