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Pulmonary fibrosis and follow-up of COVID-19 survivors: an urgent need for clarification

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Several patients with COVID-19 present with residual interstitial lung abnormalities in the long term, and the prevalence of such sequelae will certainly increase as the pandemic is still ongoing. However, the definition of when irreversible post-COVID-19 pulmonary fibrosis is established remains poorly understood because COVID-19 survivors may present functional and tomographic improvement in the follow-up (Figure 1).[1-3] Additionally, there are a few suggestions for the best approach in the long term regarding respiratory monitoring with ancillary tests and the frequency of evaluation to assess patients with pulmonary involvement in the acute phase of COVID-19, although definitive evidence is still lacking.[1,4]

Post-COVID-19 pulmonary fibrosis may be defined as the presence of persistent fibrotic tomographic sequelae observed during follow-up, which can be associated with functional impairment.[1] However, the prevalence, pathophysiology, potential risk factors, and therapeutic approach of such a disorder are poorly known.[1]

There are various uncertainties regarding post-COVID-19 pulmonary fibrosis that need to be widely investigated as soon as possible. First, it is still unclear when tomographic features suggestive of pulmonary fibrosis are considered definitive, especially ground-glass opacities. In this scenario, recent studies have demonstrated that improvement of post-COVID-19 pulmonary abnormalities might be demonstrated in serial tomographic assessments, although very few studies assessed patients beyond six months from diagnosis.[2,3] A study in China that evaluated patients that were hospitalized with COVID-19, not requiring mechanical ventilation, demonstrated that most of the patients showed improvement in tomography, pulmonary function, and exercise-related variables, but 24% of those remained with abnormalities on CT scans one year after discharge.[2] The impact of autoimmune inflammatory activity triggered by the viral infection and the presence of genetic features and previous interstitial lung abnormalities may determine a higher risk to develop post-COVID-19 pulmonary fibrosis; however, such hypotheses need to be better clarified.[1,5] A recent study has demonstrated that shorter blood leukocyte telomere length was identified as a risk factor for the occurrence of fibrotic-like tomographic abnormalities in patients four months after COVID-19, which reinforces the hypothesis of genetic susceptibilities for the occurrence of post-COVID-19 pulmonary fibrosis.[5] Additionally, further studies evaluating histological features obtained from patients with post-COVID-19 pulmonary fibrosis are warranted for broader knowledge of this entity. Serum biomarkers such as Krebs von den Lungen-6 are promising to predict a higher risk of post-COVID-19 pulmonary fibrosis but need to be further explored in future studies.[6]

It remains uncertain when to start and which patients will benefit from the use of therapeutic modalities, including drugs and pulmonary rehabilitation, to attenuate the impairment associated with post-COVID-19 pulmonary fibrosis. The role of pirfenidone and nintedanib, which are antifibrotic drugs that can be used in several scenarios in patients with idiopathic pulmonary fibrosis, needs to be better defined in the case of those with chronic interstitial pulmonary abnormalities after COVID-19.[7,8] These antifibrotic drugs will probably be considered for those with progressive functional decline during follow-up, although randomized controlled trials are needed to respond to this hypothesis. Additionally, the role of prolonged treatment with corticosteroids in preventing post-COVID-19 pulmonary fibrosis is still uncertain, although it seems to be useful in subgroups of patients, such as those with tomographic abnormalities suggestive of organizing pneumonia.[9]

There is no robust data available to guide which tests should be performed for respiratory assessment and how often they should be routinely carried out in the follow-up of patients who had pulmonary involvement in the acute phase of COVID-19. The British Thoracic Society[4] recommended a clinical review 4-6 weeks after discharge, as well as chest X-rays and pulmonary function tests 12 weeks after discharge for patients with severe COVID-19 or multiple comorbidities. CT should be performed if there is evidence of abnormalities in chest X-rays. For patients with mild or moderate pulmonary COVID-19, they suggested a chest X-ray 12 weeks after discharge. The tests should be performed according to clinical evolution and results of the initial evaluations.[4] Although CT is the most accurate imaging method for severity assessment and follow-up of patients with pulmonary involvement secondary to COVID-19, chest X-rays may be considered for evaluation, especially in situations in which CT is not easily available.[4,10,11] Lung ultrasonography is useful for the assessment of pulmonary involvement in the acute phase of COVID-19 and is potentially valuable in the long-term follow-up of COVID-19 survivors; however, further studies are still required to confirm this applicability.[12] We consider that the best approach in the follow-up should be individualized according to the resources available, patient features, and severity of the acute phase of the

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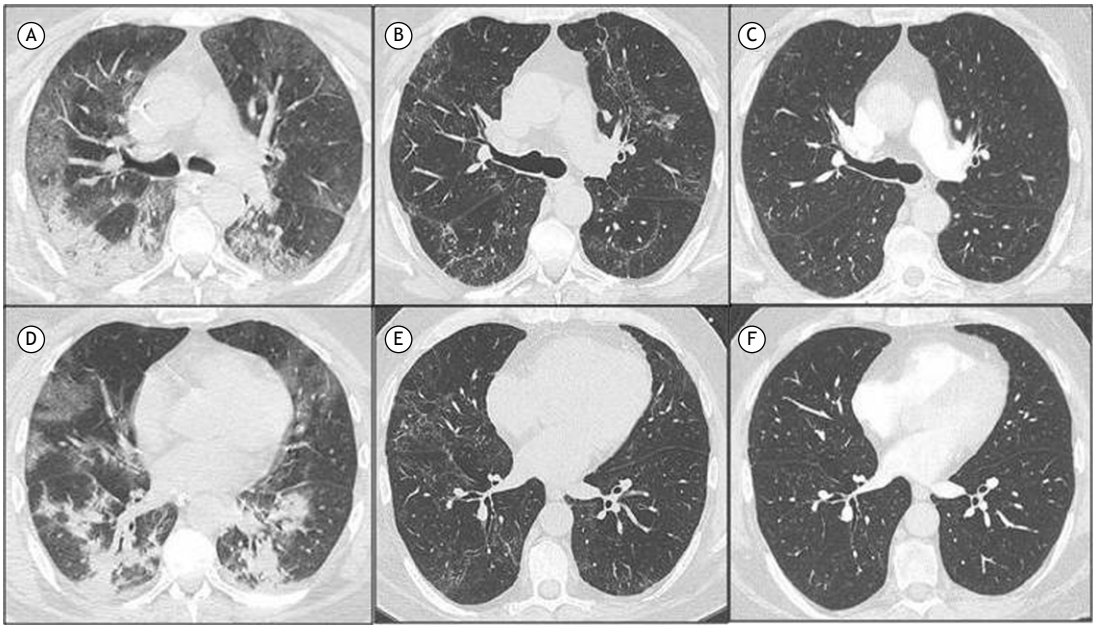

Figure 1. Chest CT scans of a 63-year-old male patient who had COVID-19 with severe pulmonary involvement and progressive improvement during the follow-up period. In A and D, CT scans in the acute phase of COVID-19, demonstrating diffuse ground-glass opacities and consolidations, predominantly in lower lung lobes. In B and E, chest CT scans obtained three months after discharge, showing a smaller extension of multifocal bilateral ground-glass and reticular opacities when compared with that in the acute phase (A and D). In C and F, chest CT scans obtained nine months after discharge, demonstrating discrete and sparse ground-glass opacities.

infection. We suggest a clinical visit and performance of an imaging test, preferably CT, at 1, 3, 6, and 12 months after discharge for those with moderate or severe pulmonary involvement in the acute phase of COVID-19 in order to assess resolution or progression of persistent interstitial lung abnormalities. Pulmonary function tests, including a six-minute walk test, should be preferably performed at 3, 6, and 12 months after discharge.

In conclusion, the various uncertainties related to pulmonary fibrosis and the optimization of respiratory follow-up after COVID-19 are expected to be clarified in the near future. Studies with longer follow-up periods are required to determine how post-COVID-19 interstitial lung disease (ILD) progresses and what the best approach for such patients in the long term is. It is essential that health care centers be organized for clinical follow-up and use of ancillary tests to care for the growing number of patients with post-COVID-19 ILD that will need to be monitored in the long term, preferably adopting a multidisciplinary approach. Additionally, various examples reinforce the potential role and expansion of telehealth in supporting the management of COVID-19 survivors, which may be helpful in such a scenario. Due to the heterogeneity of health care centers, we suggest that the implementation and standardization of care of patients with post-COVID-19 ILD should be individualized according to the resources available and the priorities established at each outpatient clinic.

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