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COVID-19 Pandemic: The Road to Recovery

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As of June 2022, there have been over 530 million confirmed cases of COVID-19, including 6.3 million deaths, reported to the World Health Organization. Post-acute sequelae of SARS-CoV-2 infection (PASC), defined by the presence of prolonged symptoms (long COVID) or development of new or recurring symptoms after the acute phase of infection, occur in more than 70% of COVID-19 survivors, with the most common symptoms being fatigue, shortness of breath, cough, anosmia, and insomnia (1). Persistent respiratory symptoms are believed, in part, to be due to structural lung damage that may result directly from SARS-CoV-2 infection or may represent collateral injury from development of acute respiratory distress syndrome and use of mechanical ventilation.

In this issue of *Radiology*, Luger and colleagues (2) assessed the chest CT patterns and rate of improvement of pulmonary parenchymal disease at 2, 3, 6, and 12 months after initial onset of symptoms in 142 participants infected by SARS-CoV-2. COVID-19 severity in 91 participants who underwent 12-month follow-up CT was categorized as mild (outpatient care) in 21% (n = 19), moderate (hospitalization without respiratory support) in 25% (n = 23), severe (hospitalization with supplemental oxygen) in 25% (n = 23), and critical (intensive care unit admission with noninvasive or mechanical ventilation) in 29% (n = 26).

On the first follow-up CT examination at 2 months, parenchymal abnormalities were identified in 76% (58 of 76) of participants. Ground-glass opacities, reticulation, and subpleural curvilinear lines were the most common findings and were present in 74%, 58%, and 36% of participants, respectively. Investigators used a qualitative CT severity scale (CTSS) of disease ranging from 0 (normal) to 25 (all lobes involved) and found that most participants showed gradual improvement in terms of their parenchymal abnormalities. The rate of improvement was significantly faster in the early postinfectious period between 2 and 3 months than in the later period between 6 and 12 months ($P < .001$). CT scans at 12 months showed persistent parenchymal abnormalities in 54% (49 of 91) of participants, with 34% (31 of 91) having minimal ground-glass opacities, reticular opacities, or both (CTSS score ≤5), and the remaining 20% (18 of 91) having similar but more extensive findings in association with architectural distortion, bronchial dilatation, microcystic change, or a combination thereof (CTSS score >5). Side-by-side comparison of 6- and 12-month CT scans showed no further change in parenchymal findings in 63% (31 of 49) of participants. Persistent CT parenchymal abnormalities at 12 months were associated with critical COVID-19 severity (odds ratio, 29; 95% CI: 4.8, 280; $P < .001$), age older than 60 years (odds ratio, 5.8; 95% CI: 1.7, 24; $P = .009$), and male sex (odds ratio, 8.9; 95% CI: 2.6, 36; $P < .001$).

The findings of Luger et al (2) are largely concordant with those of prior prospective longitudinal studies (3–7) that reported the temporal evolution of pulmonary abnormalities at CT in patients with COVID-19 extending to 12 months after acute infection. In these studies, the reported prevalence of CT parenchymal abnormalities at 3 and 12 months ranged from 39% to 78% and from 24% to 73%, respectively. This variability in the prevalence of persistent CT abnormalities likely reflects heterogeneity in the studies' enrolled patient populations, with differences in underlying comorbidities, severity of COVID-19 disease, development of acute respiratory distress syndrome, and use of ventilation. In a study of 83 patients hospitalized for COVID-19 that excluded individuals with comorbidities, smoking history, or need for mechanical ventilation, persistent CT parenchymal abnormalities consisting primarily of ground-glass and reticular opacities were found in 24% of patients 12 months after discharge (5). By comparison, in the study by Luger et al (2), 100% (13 of 13) of patients who developed acute respiratory distress syndrome had persistent CT findings at 12 months. Significant associations between older age (>60 years) and severity of COVID-19 with persistence of CT findings at 12 months have been corroborated in other studies (3,6).

Despite concerns earlier in the pandemic that infection with SARS-CoV-2 may incite an autoinflammatory response that initiates or potentiates (in the setting of occult interstitial lung abnormality) an interstitial (fibrotic) lung disease (ILD), to date, longitudinal observational studies have not documented cases of progressive fibrosis in patients without previously known ILD. SARS-CoV-2–triggered acute exacerbations in patients with known ILD have been reported and are likely contribute to the increased mortality observed in the ILD population who become infected with COVID-19. With no data on the histopathologic correlates of persistent CT pulmonary abnormalities after the acute stage of infection in COVID

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Conflicts of interest are listed at the end of this article.

Se also the article by Luger and Sonnweber et al in this issue.

survivors, the nature of these findings is unknown but likely represents a continuum in patterns of lung injury, including organizing pneumonia and diffuse alveolar damage. Physicians should exercise caution in presuming that CT findings, such as subpleural cysts, bronchial dilatation, and linear bands, represent fibrosis, particularly during the first 3–6 months after acute infection, as these findings have been observed to resolve in some COVID-19 survivors (6,7). Whether further regression of persistent CT findings, such as ground-glass and reticular opacities, will occur beyond 12 months after acute infection remains to be investigated. A 15-year follow-up study of patients infected in 2003 with SARS-CoV-1 showed slow improvement of persistent CT lung abnormalities for several years after acute infection (8).

Advances in medical treatment not available during the earlier stage of the COVID-19 pandemic likely altered the course of infection and limited the generalizability of results in the Luger et al study (2), where corticosteroid therapy was not administered. Lack of correlation of the observed persistent CT findings to clinical data, such as patient symptoms and pulmonary function tests, leaves unanswered the important question, "What is the clinical relevance of these CT findings?" Given the frequency of respiratory symptoms in COVID-19 survivors with PASC, with its attendant morbidity magnified on a global scale, large-scale national trials have begun to address this and other important questions.

The United Kingdom Interstitial Lung Disease–Long Covid Study (9) is a prospective multicenter observational study that will enroll 12 000 patients with stratified severity of COVID-19; the study's primary objective is to determine the prevalence of interstitial lung disease at 12 months after infection and whether clinical severity correlates with CT findings. In the United States, the National Institutes of Health–sponsored Researching COVID to Enhance Recovery (RECOVER) initiative on PASC (10) will enroll 17 680 adults with COVID-19 and aggregate both retrospective and prospective data using an ambi-directional longitudinal study design. Radiography, CT, and MRI are embedded as integral components of patient assessment algorithms. The purpose of RECOVER is to characterize the spectrum of PASC symptoms and define its incidence, prevalence, and underlying mechanism with the study's overarching goal to better treat and prevent the development of PASC.

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