

Imaging in Post-COVID Lung Disease: Does ^{18}F -FDG PET/CT Have the Key?

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In this issue of *The Journal of Nuclear Medicine*, Thornton et al. present ^{18}F -FDG PET/CT data obtained on coronavirus disease 2019 (COVID-19) patients at several disease stages (1). The study includes predominantly oncology patients in whom the diagnosis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was not known before the PET/CT procedure ($n = 32$), as well as 18 patients with known infection and persistent shortness of breath 28 d after the onset of disease and who were previously admitted to the hospital for oxygen therapy. The latter group was categorized as potential post-COVID-19 lung disease (PCLD) (2). In this PCLD group, half the patients had ongoing corticosteroid treatment. Although retrospective, this study triggers an interesting discussion on the potential role of ^{18}F -FDG PET/CT in patients with late COVID-19 infection.

After the initial outbreak of SARS-CoV-2 in December 2019, 3–4 waves of the pandemic have been observed worldwide. As of September 26, 2021, and according to the data of the Johns Hopkins University (<https://coronavirus.jhu.edu>), more than 230 million people were diagnosed worldwide, with a death toll close to 5 million, making it the largest and deadliest pandemic since the 1918 flu. Importantly, the disease presentation at the early phases ranged from asymptomatic contamination to mild symptoms over overt symptoms requiring hospitalization with oxygen therapy and, at the extreme, assisted ventilation or extracorporeal membrane oxygenation. Shah et al. defined 3 phases of the disease: acute COVID-19 infection with signs and symptoms up to 4 wk, ongoing symptomatic COVID-19 between 4 and 12 wk, and PCLD syndrome beyond 12 wk, when persisting symptoms cannot be attributed to alternative diagnoses (3). The term *long COVID* commonly refers to both ongoing symptomatic COVID-19 and PCLD as defined above. Several studies describe persistent symptoms in patients after acute COVID-19, with one third or more experiencing more than one symptom, including fatigue, abnormal breathing, chest or throat

pain, headache, and cognitive symptoms up to 3–6 mo after diagnosis. Such persistent symptoms are more frequently reported after COVID-19 than after influenza infection.

However, this perspective will focus on subacute and chronic lung disease, referred to as PCLD. Five percent of COVID-19 survivors evolve to chronic respiratory failure, manifested by breathlessness, cough, or even oxygen needs (4).

From the very beginning of the outbreak, multiple casuistic reports on ^{18}F -FDG PET/CT were published, without emphasis on the time course, since the initial observations focused either on the most acute phase in severely ill patients or on serendipitous findings in asymptomatic oncology patients. Several studies indicated a 2- to 4-fold increased incidence of interstitial pneumonia detected on ^{18}F -FDG PET/CT in the latter group during the early phase of the pandemic (5). Other authors identified a relationship between the structural changes as assessed using the COVID-19 Reporting and Data System and metabolic changes (6). Albeit informative, such reports did not take into account the temporal kinetics of the disease. It has become clear that ^{18}F -FDG PET/CT has a limited role, if any, in establishing the diagnosis of active COVID-19 infection. From a logistic viewpoint, organizing a PET/CT scan in a nuclear medicine department had more drawbacks than advantages, as compared with dedicated CT-scan suites, with a rapid turnover even with the implementation of all necessary hygiene measures. Several reports indicate that ^{18}F -FDG PET/CT results in the early phase of the disease were similar to those observed in the literature on pneumonia due to other aggressive viruses.

In this retrospective observational study, Thornton et al. were able to distinguish several temporal patterns in a limited number of subjects during the first 2 peaks of COVID-19. Using ^{18}F -FDG PET/CT, they not only studied the functional and morphologic pattern at different disease stages but also demonstrated the time relationship between these changes. In asymptomatic patients, without any history or suggestion of a COVID-19 diagnosis, the authors identified 2 distinct groups: one group of acute patients in the early stage ($n = 8$) with typical ground-glass changes on CT and relatively low ^{18}F -FDG uptake (median SUV_{max} , 1.6, and median target-to-background ratio [TBR_{lung}], 6.4, where the background refers to the lowest lung uptake) and a second group of acute patients in the late stage, with a more extensive consolidation pattern on CT and a significantly higher SUV_{max} (median, 4.0) and TBR_{lung} (median, 13.7) ($P = 0.001$). SUV_{max} was similar in a small series of convalescing patients reported by Bai et al., but these were patients recovering from severe infection (7). Temporal data in the study of

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Thornton et al. were retrieved from the electronic health record system, with the inherent limitations of such a retrospective approach. Notwithstanding, the authors demonstrated a significant positive correlation between TBR_{lung} and the estimated time since onset (Spearman $r_s = 0.595$, $P = 0.003$). These findings are in keeping with the current pathophysiologic hypotheses of COVID-19 infection—that it first presents as a viral infection, with no or moderate symptoms and seemingly low ^{18}F -FDG uptake, and then is followed by an acute immune response, endothelial activation and inflammation, and variable levels of immune cell infiltration (including neutrophils, lymphocytes, and monocyte–macrophages), as well as angiogenesis. This second phase, characterized by the presence of many glucose-avid cells, is responsible for the increased ^{18}F -FDG uptake. However, the responsible mechanisms of PCLD are not well understood and are probably numerous and intertwined as reflected by the wide diversity of the symptoms. The main hypotheses include a persisting chronic inflammatory process or a dysregulated immune phenomenon (8).

Although the study by Thornton et al. illustrates the temporal changes in ^{18}F -FDG PET/CT patterns, it does not provide information on the severity of the disease because of the lack of clinical outcome data, as stated by the authors in their conclusions.

Nevertheless, in the group of 18 patients with PCLD, a condition that has hardly been studied with ^{18}F -FDG PET/CT, a higher SUV_{max} (median, 5.8) was observed in patients who had not been treated with high-dose steroids for at least 10 d. Conversely, patients treated with steroids after discharge had a lower SUV_{max} (median, 2.4) and TBR_{lung} (median, 6.6 under steroids, vs. 18.1 without steroids), like those observed in the early stage of the acute phase. The RECOVERY study clearly demonstrated the benefit of 6 mg of dexamethasone in oxygen-dependent or ventilated patients with a lower 28-d mortality (9). To our knowledge, little is known about the benefit to pulmonary function and survival over the long term. In addition, an observational study by Myall et al. including 35 patients with lung functional deficit beyond 6 wk after the acute phase (due to interstitial disease and organizing pneumonia) demonstrated a morbidity benefit, defined by improvement in lung functional tests, in the 30 patients treated with steroids (4). Furthermore, a recent report on long COVID demonstrated not only increased residual lung ^{18}F -FDG uptake (with similar SUV_{max} data) but also evidence of multi-systemic inflammation (10).

From the published data and long-COVID-19 perspectives, it may be wise to envision that metabolic imaging with ^{18}F -FDG PET/CT may help identify patients with persistent symptoms after 6–12 wk, for whom additional therapy with, for example, corticosteroids could be proposed. This possibility is in keeping with previous observations that increased ^{18}F -FDG uptake in chronic interstitial lung disease of other etiologies was reported as a marker of evolution toward lung fibrosis and poor prognosis. At this stage,

there is no evidence that such imaging may be justified, nor is information available on the optimal timing and dosing of steroids. Therefore, it is worth challenging this issue with, for instance, a 2-arm randomized study in which all patients with persistent pulmonary symptoms beyond 6 wk of a negative PCR test would undergo ^{18}F -FDG PET/CT upfront but in which the interpreters would be masked to patient data before randomization. Patients could then receive either corticosteroids or placebo, and as the outcome, the clinical benefit results would be correlated with the ^{18}F -FDG PET/CT results.

In conclusion, although it is agreed that ^{18}F -FDG PET/CT has little role in diagnosing COVID-19 as such, its potential role in the later phases of the disease must be considered. Whether ^{18}F -FDG PET/CT can help identify patients who will develop a severe or even dramatic course of lung fibrosis remains to be determined: prospective and, when possible, randomized therapeutic trials with masking of the ^{18}F -FDG PET/CT results would be extremely helpful.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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