Invited perspective

Imaging in post-COVID lung disease (PCLD): does [18F]-FDG-PET/CT have the key?

Olivier Gheysens[1] MD, PhD, Leïla Belkhir[2] MD, PhD, François Jamar[1] MD, PhD.

1. Department of Nuclear Medicine, Cliniques universitaires St-Luc and Institute for Clinical and Experimental Research (IREC), Université catholique de Louvain, Brusssels, Belgium.

2. Department of Internal Medicine and Infectiology, Cliniques universitaires St-Luc and Institute for Clinical and Experimental Research (IREC), Université catholique de Louvain, Brusssels, Belgium.

Correspondence to: Prof. François Jamar, MD, PhD, Nuclear Medicine Department, Cliniques universitaires St-Luc, Avenue Hippocrate, 10, B-1200 Brussels, Belgium. Tel: +32-2-764 25 71 Fax: +32-2-764 54 08 E-mail: francois.jamar@uclouvain.be

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In this issue of the Journal, Thornton et al. present [18F]-FDG-PET/CT data obtained in COVID-19 patients at several disease stages (1). The study includes predominantly oncology patients in whom the diagnosis of 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 days after 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 of the patients had ongoing corticosteroid treatment. Although retrospective in nature, this study triggers an interesting discussion on the potential role of [18F]-FDG-PET/CT in patients with late COVID-19 infection.

After the initial outbreak of the SARS-CoV-2 in December 2019, three to four waves of the pandemic have been observed worldwide. As of September 26th, 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 three phases of the disease: acute COVID-19 infection with signs and symptoms up to 4 weeks, ongoing symptomatic COVID-19 between 4 and 12 weeks and post-COVID-19 syndrome beyond 12 weeks, when persisting symptoms cannot be attributed to alternative diagnoses (3). The term long COVID commonly refers to both ongoing symptomatic and post-COVID-19 as defined above. Several studies describe persistent symptoms in patients following acute COVID-19 with one-third or more experiencing more than one symptom including fatigue, abnormal breathing, chest/throat pain, headache, cognitive symptoms up to 3 to 6 months post-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 % 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 serendipitous findings in asymptomatic oncology patients. Several studies

indicated a two- to fourfold 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 (CO-RADS)

and metabolic changes (5). 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 limited if no role 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 to 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 are 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 two peaks of COVID-19. Using [^{18}F]-FDG-PET/CT,

they not only studied the functional/morphological pattern at different disease stages but demonstrated

the time-relationship between these changes. In asymptomatic patients, without any history or clue of

COVID-19 diagnosis, they identified two distinct patterns. One group of acute patients in the early-stage

(n=8) with typical ground-glass changes on CT-scan 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-scan and significantly higher SUV_{max} (median: 4.0) and TBR_{lung} (median: 13.7), P=0.001. Similar SUV_{max} were observed in a small series of convalescing patients by Bai et al., but these were patients recovering from severe infection (7). Temporal data in Thornton et al.'s study was retrieved from the electronic health record system, with 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's r_s=0.595, P=0.003). These findings are in keeping with the current pathophysiological hypotheses of COVID-19 infection. Firstly, presenting as a viral infection, with no or moderate symptoms, and seemingly low [18F]-FDG uptake, followed by an acute immune response, endothelial activation and inflammation, 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 [18F]-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 of [18F]-FDG-PET/CT patterns, it does not provide information on the severity of the disease owing to the lack of clinical outcome data, as stated by the authors in their conclusions.

Nevertheless, in the PCLD group of 18 patients, a condition that has hardly been studied with [18F]-FDG-PET/CT, higher SUV_{max} (median: 5.8) were observed in patients who had not been treated with high dose steroids for at least ten days. Conversely, patients treated with steroids after discharge had lower SUV_{max} (median: 2.4) and TBR_{lungs} (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 dexamethasone in oxygen-dependent or ventilated patients with a lower 28-day mortality (9). To our

knowledge, little is known about the benefit on pulmonary function and survival on the long term. In addition, an observational study by Myall et al. including 35 patients with lung functional deficit beyond 6 weeks after the acute phase (due to interstitial disease and organizing pneumonia), demonstrated a morbidity benefit, defined by improvement in lung functional tests, in the thirty patients treated with steroids (4). Furthermore, a recent report on long COVID not only demonstrated increased residual lung [18F]-FDG uptake (with similar SUV_{max} data) but also evidence of multisystemic inflammation (10).

From the published data and long COVID-19 perspectives, it may be wise to envision that metabolic imaging with [18F]-FDG-PET/CT may help identifying patients with persistent symptoms after 6-12 weeks, for whom additional therapy with e.g., corticosteroids could be proposed. This is in keeping with previous observations that increased [18F]-FDG uptake in chronic interstitial lung disease of other etiologies was reported as a marker of evolution towards lung fibrosis and poor prognosis. At this stage, there is no evidence that this may be justified, nor information on the optimal timing and dosing of steroids is available. Therefore it is worth challenging this issue for instance with a two-arm randomized study in which all patients with persistent pulmonary symptoms beyond 6 weeks of PCR negativation would undergo [18F]-FDG-PET/CT upfront but blinded prior to randomization. Patients could then receive either corticosteroids or placebo and as outcome, the results of the clinical benefit would be correlated to the [18F]-FDG-PET/CT results.

In conclusion, although it is agreed upon that [18F]-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 [18F]-FDG-PET/CT can help identifying patients who will develop a severe or even dramatic course of lung fibrosis remains to be determined: prospective and where possible, randomized therapeutic trials blinded to [18F]-FDG-PET/CT results would be extremely helpful.

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