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Invited Perspective

Mapping COVID-19 with nuclear imaging: from infection to functional sequelae

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Abstract: The pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, or coronavirus disease 2019, COVID-19) has been raging all over the globe for more than one year. COVID-19 virus can attack multiple organs through binding to angiotensin-converting enzyme 2 (ACE2) receptors and further induce systemic inflammation and immune dysregulation. In the last issue of 2020 AJNMMI (http://www.ajnmmi.us), Lima *et al*. summarized current biological complications of COVID-19, their underlying mechanisms, and our options of mapping these functional sequelae using nuclear imaging techniques. Four major organs, including the lung, heart, kidney, and endothelium, were identified as most vulnerable to COVID-19 viruses in severe patients. Nuclear medicine proved accurate and sensitive in assessing the onset, progression, and treatment of COVID-19 patients. By choosing the most appropriate radiotracers and imaging methods, clinicians and researchers are able to analyze and monitor the presence of inflammation, fibrosis, and changes of metabolic rates in organs of interest. With these desirable nuclear imaging methods, systematic evaluation of COVID-19, from its onset to functional sequela, can be achieved with rational patient stratification and timely treatment monitoring, which we believe will eventually lead to full victory against the pandemic.

Keywords: Nuclear imaging, radiopharmaceuticals, COVID-19, molecular imaging, nuclear medicine

Introduction

The outbreak of Corona virus disease 2019 (COVID-19) has affected 221 countries and territories worldwide, with more than 97 million confirmed cases and two million total deaths on January 21st, 2021 [1]. Its accelerating spread has assembled researchers' focus to understand its transmission and infection, develop new detection methods, search for effective drugs, and formulate vaccines to control the pandemic eventually.

COVID-19 viruses, also called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), can get internalized into host cells via interactions with human angiotensin-converting enzyme 2 (ACE2) receptors and require transmembrane serine protease 2 to cleave the spikes for receptor binding [2, 3]. Cellular attack of COVID-19 virus decreases activities of ACE2 and increases levels of angiotensin 1-7, leading to a pro-inflammatory and oxidative microenvironment and subsequently triggering macrophage recruitment [4]. ACE2 receptors are widely distributed on pneumocytes, endothelial cells, smooth-muscle fibers, and renal proximal tubules [2]. This is generally believed to be one of the reasons for COVID-19's systemic damage and mechanisms of multiple organ dysfunction/failure at its severe stage [5, 6]. While viral RNA tests are the current gold standard of diagnosis, repeated sampling is required for as long as 21 days and false-negative results remain common. In this regard, quantitative functional imaging methods, such as nuclear imaging techniques, serve as a valuable tool to obtain real-time information on COVID-19's infection, onset, progression, and sequela [7].

In the 6th issue of American Journal of Nuclear Medicine and Molecular Imaging in 2020, Lima et al. reviewed the use of nuclear medicine in

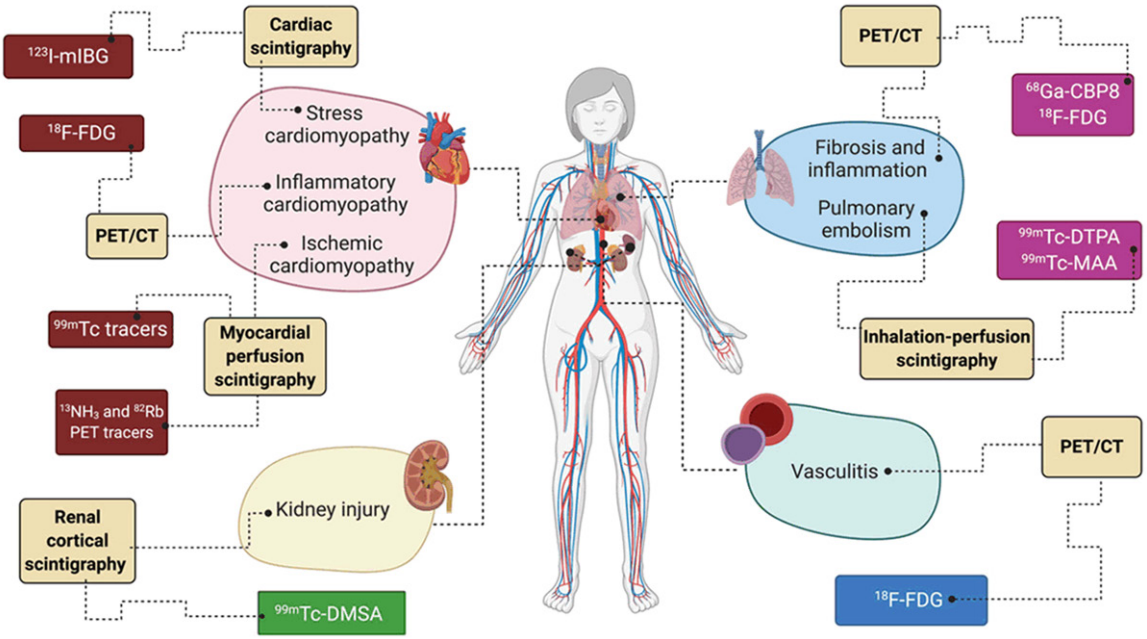

Figure 1. Mapping COVID-19 invasion and sequela using different nuclear imaging tracers. Adopted with permission from Ref. [8].

detection and evaluation of COVID-19, starting from its early infection to potential sequela [8]. By choosing the most appropriate radiopharmaceuticals, positron emission tomography (PET) or single-photon emission computed tomography (SPECT) imaging can be used to identify the occurrence of inflammation, fibrosis, rate changes of heart perfusion, kidney excretion, and brain metabolism (**Figure 1**). The high detection sensitivity of PET and SPECT can facilitate the finding of new biological information during COVID-19 disease initiation, progression, and treatment evaluation.

Nuclear imaging proves valuable for early detection of COVID-19. On February 10th, 2020, Lan, Yen and colleagues first reported four patients with high suspicion of virus infection after performing ^{18}F-FDG PET/CT imaging [9]. Computed tomography (CT) imaging of these cases revealed typical ground-glass opacities (GGOs) and bilateral pulmonary consolidations. ^{18}F-FDG PET imaging further identified peripheral GGOs and lymph nodes with elevated glucose metabolism and indicated that COVID-19 may cause lymphadenitis, similar with previous findings from MERS-CoV. Later, Alavi and co-workers re-emphasized the role of functional imaging for accurate assessment of COVID-19 [10]. Traditional chest CT or X-ray shows structural alterations of the lung and can determine the extent of pulmonary involvement at a given disease stage. However, increased interstitial septal thickening and increased paving patterns are uncommon manifestations of COVID-19 on chest CT or X-ray, exposing their lack of specificity to inform and assess the disease [10, 11]. As such, ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET imaging may offer quantitative information on the infection and inflammation of pulmonary disorders, leading to improved systematic evaluation of COVID-19 in patients.

Besides imaging the progression of COVID-19, nuclear medicine can also be used for mapping its functional sequela. For example, Wang and co-workers reported pulmonary inflammation response in convalescing patients via ^{18}F-FDG PET/CT imaging [12]. Seven patients recovered from severe COVID-19 infection were tested negative twice but quantitative PET imaging revealed different levels of inflammation remained in their lungs, lymph nodes, liver, and spleen. Although these patients received two consecutive negative viral test results, PET imaging unveiled pulmonary lesions with elevated metabolic activities, indicative of persistent inflammation not only in the lungs, but also in liver, spleen, and mediastinal lymph nodes. ^{18}F-FDG PET revealed enhanced tracer uptake

in lung regions with normal CT characteristics. These findings highlighted the sensitivity of functional nuclear imaging and revealed the persistent impact of COVID-19 in patients even after their recovery.

Other than damaging the lung, acute myocardial injury is another major complication caused by COVID-19. Enhanced expression of troponin could be found in 7-17% of hospitalized patients, and was suspected to be as high as 59% in deceased patients [13]. Direct ACE2 receptor binding and indirect systemic inflammatory response may both affect the heart functions and lead to arrhythmias, myocardial ischemia/infarction, heart failure, and even cardiogenic shock. Many nuclear imaging probes can be used to image functional alterations of the heart, such as ^{18}F-FDG for imaging of glucose metabolic activity, ^{123}I-MIBI for cardiac scintigraphy, and ^{13}N-ammonia for myocardial perfusion. While myocardial perfusion scintigraphy using ^{123}I-MIBI or ^{13}N-ammonia may help with comprehensive evaluation of myocardial function and injury, ^{18}F-FDG PET directly observes myocardial viability and abnormal glucose metabolism. Multiple choices of tracers enable combinational systemic diagnosis and evaluation of heart injury, the most common complications of COVID-19 [14].

Acute kidney injury is found in 11% of hospitalized COVID-19 patients and the percentage doubles in patients with severe symptoms [15]. Abundant expression of ACE2 receptors in renal tubular epithelial cells surrendered these cells to COVID-19 virus. Moreover, inflammatory immune response caused by cytokine storm may further lead to hypoperfusion and renal tubular injury. Unattended structural kidney injury may lead to chronic renal diseases and even end-stage kidney failure, where COVID-19 patients with transplanted kidneys are more susceptible to these kidney injuries due to their suppressed immune functions and faster disease progression. Nuclear imaging again provided alternatives to actively monitor renal functions of patients non-invasively [16, 17]. Static ^{99m}Tc-DMSA renal scintigraphy can be used to image renal proximal tubules and the first part of Helen-loop, revealing the onset of kidney fibrosis or pyelonephritis. Dynamic renal PET imaging with ^{99m}Tc-DTPA or ^{99m}Tc-MAG3 can help quantify the glomerular filtration rates and be used to obtain split renal function. Nuclear imaging methods supply additional information to traditional ultrasound imaging by providing better tissue penetration and accurate quantification of excretory kidney functions with versatile tracer choices [18-20].

COVID-19 virus also has cerebral invasion in forms of autoimmune encephalitis, acute cerebrovascular disease, and meningitis [21]. Grimaldi et al. reported a COVID-19 patient with autoimmune encephalitis. ^{18}F-FDG PET imaging showed diffuse cortical hypometabolism, suggesting cerebellitis. Immunological tests revealed increased levels of IgG autoantibodies in the serum and CSF directed against neurons. Treatment using steroids allowed fast resolve of symptoms. Cerebral ACE2 expression (especially in the brainstem) and systemic immune activation were believed to initiate COVID-19's neurological attack. PET imaging is able to identify elevated inflammatory response in the whole body and may contribute to a timely assessment of potential brain damage caused during and after COVID-19 infection [22].

Accumulating evidences revealed that COVID-19 invaded through ACE2 receptor binding, induced strong immune response, and caused multiorgan injury including the lung, heart, kidney, and brain [23]. Nuclear imaging using various radiotracers against biomarkers during different disease stages can not only imaging the onset of inflammation and pulmonary damage, but also help evaluate functional sequela caused by the virus. Metabolic PET imaging with ^{18}F-FDG is widely used to inform and assess inflammatory response in the whole body. Other tracers, such as ^{123}I-MIBI, ^{13}N-ammonia, ^{99m}Tc-DMSA, ^{99m}Tc-DTPA and ^{99m}Tc-MAG3, are also clinically accepted for examination of heart and kidney function, offering robust quantified methods for COVID-19 imaging and treatment monitoring. In addition, more efforts can be devoted to develop PET or SPECT contrast agents targeting ACE2 or cyclooxygenase 2 [24], (e.g. in forms of small molecules or monoclonal antibodies [25, 26]), since these agents are anticipated to give an objective evaluation for the extent of COVID-19 infection and damage. We believe that nuclear imaging can provide more useful insights in every stage of COVID-19 infection, and this diagnostic information is beneficial to the recovery and life quality of COVID-19 patients.

Disclosure of conflict of interest

None.

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