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Review Article

Mapping COVID-19 functional sequelae: the perspective of nuclear medicine

Simone Cristina Soares Brandão[1], Júlia de Oliveira Xavier Ramos[2*], Gustavo Freitas Alves de Arruda[2*], Emmanuelle Tenório Albuquerque Madruga Godoi[3], Lara Cristiane Terra Ferreira Carreira[4,5], Rafael Willain Lopes[6], Gabriel Blacher Grossman[7,8], Ronaldo de Souza Leão Lima[9]

[1]Department of Internal Medicine, Divisions of Cardiology and Nuclear Imaging, Hospital das Clínicas, Federal University of Pernambuco (UFPE), Recife, PE, Brazil; [2]Recife Medical School, Federal University of Pernambuco (UFPE), Recife, PE, Brazil; [3]Department of Internal Medicine, Division of Angiology, Hospital das Clínicas, Federal University of Pernambuco (UFPE), Recife, PE, Brazil; [4]CNC Nuclear Cardiology, Curitiba, PR, Brazil; [5]Hospital Nossa Senhora do Pilar, Curitiba, PR, Brazil; [6]Nuclear Medicine Service, Hospital do Coração (HCor), São Paulo, SP, Brazil; [7]Department of Nuclear Medicine, Hospital Moinhos de Vento, Porto Alegre, RS, Brazil; [8]Cardionuclear Clinic, Porto Alegre, RS, Brazil; [9]Department of Cardiology and Division of Nuclear Imaging, Federal University of Rio de Janeiro (UFRJ), Rio de Janeiro, RJ, Brazil. [*]Equal contributors.

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Abstract: Severe acute respiratory syndrome coronavirus 2 infection is capable of affecting several organs. Direct viral toxicity, pro-inflammatory and pro-thrombotic induction, endothelial damage, immune imbalance, and dysregulation of the renin-angiotensin-aldosterone system are the mechanisms underlying the viral potential of multiple organ damage. The impairment of four organs stands out among severe patients: lung, heart, kidney, and endothelium. The nuclear medicine field holds accurate and safe exam techniques, such as positron emission tomography-computed tomography and scintigraphy, that allow the anatomophysiological study of the majority of human organ systems. By choosing the most appropriate method and radiopharmaceutical, analyzing the presence of inflammation, fibrosis, changes in perfusion, and function of desired organs is possible. Therefore, its use in the monitoring of patients with coronavirus disease 2019 becomes relevant, especially for monitoring sequelae. In this review, we discuss the use of Nuclear Medicine in the detection, monitoring, and therapeutic evaluation of pulmonary and extrapulmonary sequelae by coronavirus disease 2019.

Keywords: Nuclear medicine, scintigraphy, PET/CT, sequelae, COVID-19

Introduction

The disease caused by the second severe acute respiratory syndrome coronavirus (SARS-CoV-2), called COVID-19 (COronaVIrus Disease 2019), has affected more than 180 countries, with more than 29 million confirmed cases and approximately 940,000 deaths worldwide [1] on September 16th, 2020. The current focus of researchers and health professionals is mainly on understanding the disease and creating and testing medications and vaccines to effectively combat the pandemic. However, the disease can cause several sequelae to survivors of severe COVID-19, and follow-up should also be a health priority.

In this context, nuclear medicine, as a functional technique, can be an important ally in the evaluation of COVID-19 survivors, providing great contributions to the understanding of thrombo-inflammatory pathophysiology and its short- and long-term consequences [2]. This review mainly aims to present the possible functional repercussions of SARS-CoV-2 infection and the nuclear medicine exams that could be useful in this analysis, as it is understood that the application of these tests can transform the care of patients with COVID-19 sequelae.

Covid-19 and its biological complications

The putative mechanism of SARS-CoV-2 for infection in the human body is through its binding to angiotensin-converting enzyme 2 (ACE2) receptors [3]. To this end, Hoffmann *et al.* suggested that the virus would require the aid of

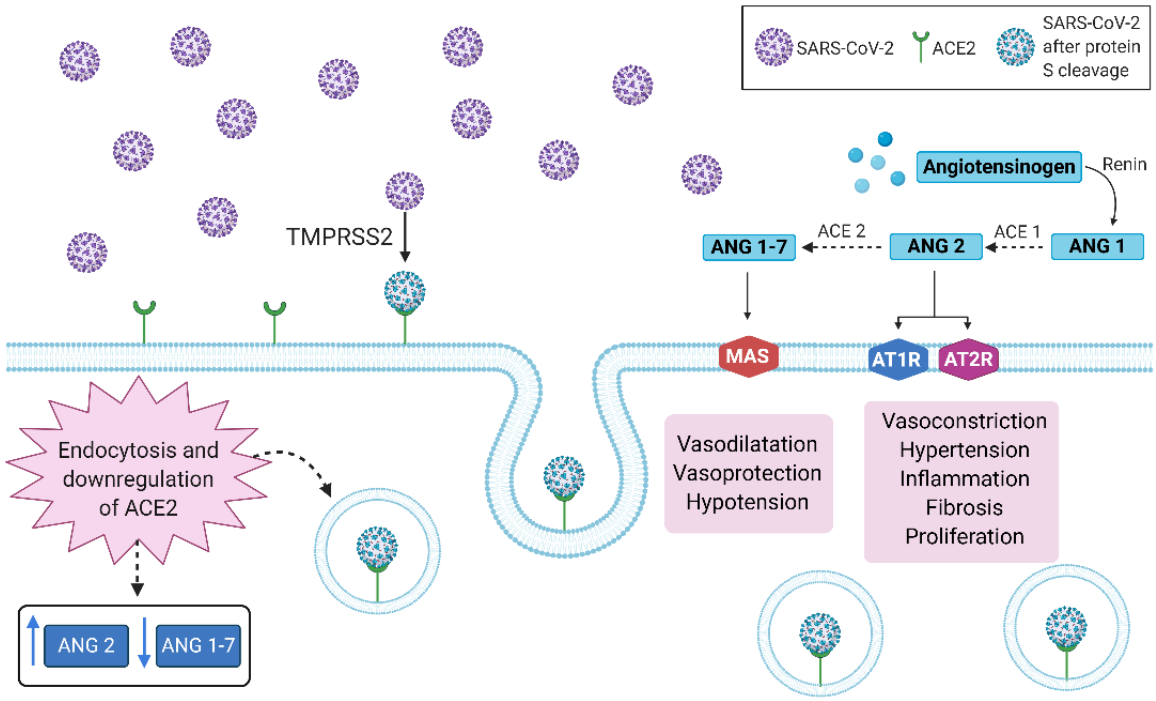

Figure 1. Actions of angiotensin 1-7 (ANG 1-7), by-product of angiotensin 1 (ANG 1) and consequences of its blockage. Angiotensin-converting enzymes (ACE) 1 and 2 act on ANG 1 and on angiotensin 2 (ANG 2). Spike (S) protein from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) binds to the human cell's ACE2 receptor, which consequently reduces ACE2 activity. TMPRSS2 is the enzyme responsible for the cleavage of the S protein from SARS-CoV-2, allowing its binding with ACE2. Created with Biorender.com.

transmembrane serine protease 2, which acts by cleaving the *Spike* (S) protein of the virus, thus allowing it to bind to ACE2 [4]. These hypotheses are supported by *in vitro* studies and by previous evidence of these associations with the first severe acute respiratory syndrome virus (SARS-CoV) [4-6].

ACE2 acts as a counterpoint to the action of angiotensin 2 by increasing angiotensin 1-7. After the virus enters the cells, the availability of ACE2 receptors reduces, which favors the action of angiotensin 2, maintaining a proinflammatory and pro-oxidative cellular environment with intense recruitment of macrophages and excess circulating aldosterone and cytokines [7, 8] (**Figure 1**). The wide distribution of these receptors in pneumocytes, endothelial cells, smooth-muscle fibers, and epithelial cells of the renal proximal tubules can be seen as one of the mechanisms for systemic damage and multiple organ dysfunction in patients with severe COVID-19 [9, 10].

About 22% of infected patients progress to the severe form of COVID-19 [11]. Another possibly involved pathophysiological mechanism is T-cell hypersensitivity, which implies a hyperinflammatory state at the systemic level, with excess cytokines and chemotactic factors. This event is called a "cytokine storm", and it is characterized by a more aggressive immune response, which contributes to the generation of severe tissue damage [12]. The potential of this runaway autoimmune response for devastation is maybe even more important than that of the infection itself, especially in vulnerable patients, such as children with the pediatric inflammatory multisystem syndrome and adults with acute respiratory distress syndrome (ARDS) [13].

Still, regarding these impacts, through a recent meta-analysis supported by data from 86 studies with a total of 52,808 patients, Li *et al.* observed a mortality rate of 5.9%. Non-survivors were generally 20 years older than survivors and were more likely to have previous conditions such as hypertension, diabetes, cancer, or cardiac, pulmonary, and renal comorbidities [11]. However, among those who survive, evidence of long-term sequelae is still

scarce, due to the rapid propagation of the pandemic.

Thus, based on the currently available literature, the next sections will seek to individually analyze the main organic complications reported in COVID-19 with the aim of understanding the possible adverse organic outcomes and then to present how nuclear medicine can help in the mapping and functional follow-up of these sequelae.

Pulmonary fibrosis

COVID-19 leads to a broad spectrum of respiratory manifestations, ranging from mild symptoms to significant hypoxia from ARDS [14]. This syndrome is an acute and severe form of microvascular lesions in the lungs associated with the deposition of fibrin exudate in the alveoli, which leads to the development of fibrosis and alteration of normal pulmonary architecture [15].

In survivors of the acute phase of ARDS, a significant number may succumb to the disease in the medium to long term, due to the progressive worsening of pulmonary fibrosis. Meduri *et al.* found that pulmonary injury in the acute phase amplifies reparative processes (fibroproliferation), resulting in a persistent release of inflammatory mediators, consequently causing more tissue damage and fibrosis [16].

Pulmonary fibrosis progresses due to the persistence of a chronic tissue repair state. This scenario is established due to changes in the alveolar microenvironment, characterized by aberrant angiogenesis, insufficient fibrinolysis, reduction of extracellular matrix turnover, increased oxidative stress, and unbalanced tissue homeostasis [17]. Postmortem studies in COVID-19 showed findings of neoangiogenesis, excessive inflammatory response, and microthrombi [18, 19]. In addition, around 5-15% of patients with ARDS from COVID-19 require ventilator support [20]. Mechanical ventilation, especially when prolonged, also favors pulmonary fibrosis [21].

Thus, due to the pandemic nature of SARS-CoV-2 infection, the worldwide prevalence of pulmonary fibrosis disease most probably will significantly increase, and its consequences will include not only a decrease in pulmonary performance but also the development of pulmonary hypertension [22]. Therefore, monitoring these patients to ensure better care is necessary.

Thrombotic events

The endothelium plays a key role in the pathophysiology of many viral infections [23, 24]. Thus, endothelial dysfunction is usually associated with a worse prognosis, since the loss of endothelial integrity implies an increase and spread of the immune and inflammatory response as well as organ failures through increased cytokine secretion, vascular permeability, and induction of a procoagulant state [23-25]. During follow-up of 184 patients with COVID-19 admitted to intensive care units and in use of prophylactic anticoagulants, Klok *et al.* found a 49% incidence of thrombotic events, of which 87% were pulmonary embolisms and 6.6% were strokes [26]. Moreover, they observed a higher probability of death among those who had thrombotic complications [26, 27]. In addition, in postmortem studies of COVID-19 cases, Varga *et al.* showed the viral involvement of endothelial cells, with immune cell infiltration and diffuse endothelial inflammation in the heart, lungs, kidneys, liver, and intestines, which could explain the high frequency of thrombotic events in patients with COVID-19 [18].

Regarding the reports of stroke in COVID-19 [28, 29], Divani *et al.* proposed that vasodilatation, neuroinflammation, oxidative stress, and increased thrombogenesis may contribute to its occurrence during SARS-CoV-2 infection [30]. Also, according to the European Stroke Organization, one third of stroke patients will have permanent sequelae and remain dependent on third-party care [31], suggesting that the viral infection may leave disabling neurological sequelae.

Evidence also suggests that severe COVID-19 may be associated with coagulation disorders, especially disseminated intravascular coagulation [32, 33], with prothrombotic characteristics and a higher risk of venous thromboembolism [34]. The modulation of the immune response of endothelial cells, performed by sphingosine-1-phosphate receptor 1, could also be compromised in severe COVID-19, similar to influenza. In consequence, this initiates an

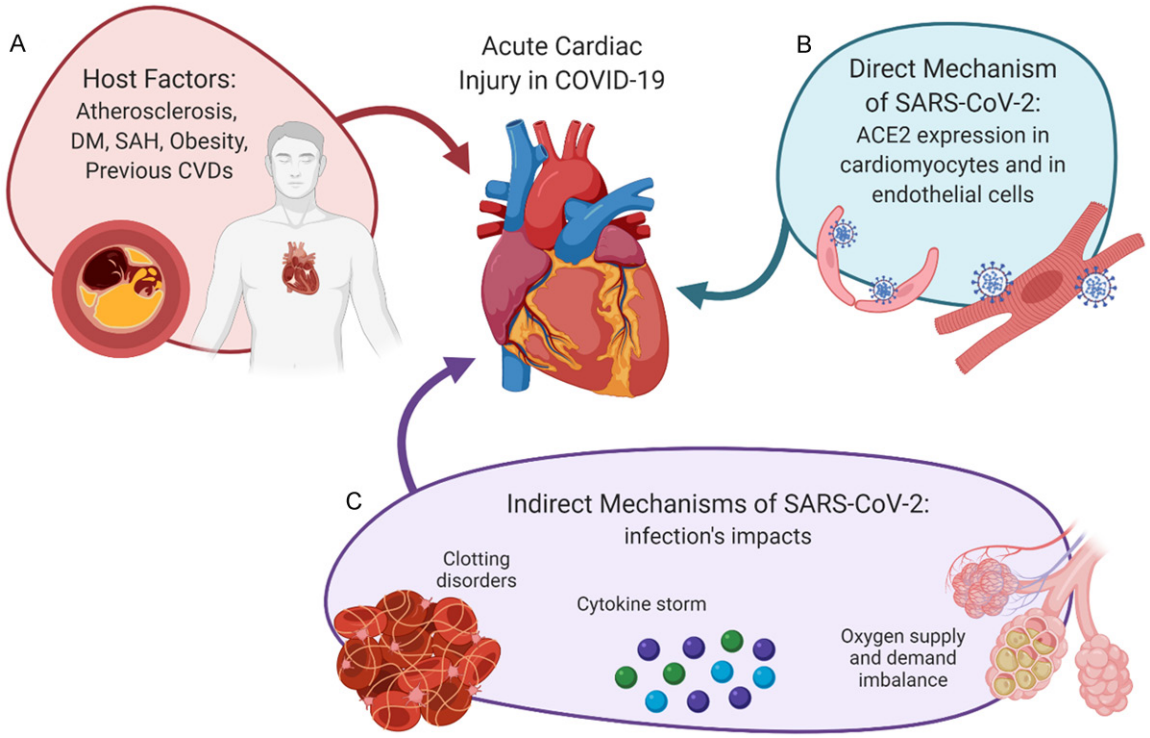

Figure 2. Possible Mechanisms of Acute Cardiac Injury in COVID-19. A. Patients with preexisting conditions are more reactive to inflammatory states and might have higher risk of cardiac injury during infections, such as SARS-CoV-2. B. It is suggested that SARS-CoV-2 itself can infect myocardial and endothelial cells, via ACE2 receptors present on their cell membrane surface. Although plausible, no evidence of direct myocardial infection has been found. C. The injury can also occur due to indirect mechanisms resulting from hypoxia, prothrombotic state, and systemic inflammatory response syndrome. ACE2: angiotensin-converting enzyme 2; DM: diabetes *mellitus*; SAH: systemic arterial hypertension; CVDs: cardiovascular diseases; COVID-19: Coronavirus Disease 2019; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2. Created with Biorender.com.

amplification circuit of cytokine production and leukocyte recruitment, showing a higher risk of congestion and thrombosis of vessels [25].

Thus, a high incidence of venous thromboembolism, with a primary pattern of microthrombi in the lungs, has been observed in severe COVID-19, and therefore, it is suggested that prophylactic anticoagulants be indicated [26, 27]. Intermediate doses of heparin are also being studied, and full anticoagulation is indicated in confirmed cases or in those with strong clinical suspicion of venous thromboembolism. The use of anticoagulants is believed to reduce the risk of fibrosis and consequently of pulmonary hypertension [26, 27].

Heart injury

Acute myocardial injury has been reported as one of the main complications of COVID-19 and can be defined as the elevation of cardiac biomarkers, especially troponin, above the 99th percentile [35-37]. This manifestation has an estimated incidence of 7%-17% in hospitalized patients, and Chinese studies suggest that it increases according to the severity of the disease, reaching up to 59% in non-survivors [36].

In patients with severe COVID-19, mortality in those affected by acute myocardial injury is 11 times higher; thus, its presence can function as an independent predictor of death [38]. Among survivors, after observing abnormalities (mainly myocardial inflammation) in magnetic resonance imaging (MRI) scans of 78 of 100 patients recruited, even after 71 days (on average) since the first positive result for SARS-CoV-2, Puntmann *et al.* suggested that this cardiac condition may become chronic [39, 40].

Despite this, pathophysiological mechanisms for cardiac injury in COVID-19 have not yet been well clarified and are probably multifactorial (**Figure 2**). These factors are not neces-

sarily independent and can overlap [37, 41]. Patients in the risk groups (mentioned in Section 2) are also those who are more likely to have atherosclerotic lesions prior to infection, which predisposes them to a higher risk of cardiovascular complications [42, 43].

The mechanisms of acute myocardial injury can be direct (possible direct SARS-CoV-2 infection of endothelial and myocardial cells) or indirect, due to a systemic inflammatory response or an imbalance between oxygen supply and demand [38, 41, 42, 44]. Therefore, these heart lesions can appear in a broad spectrum of presentations, including arrhythmias, acute coronary syndrome, myocardial ischemia and infarction, heart failure, or even fulminant myocarditis and cardiogenic shock [36].

Kidney injury

In patients progressing to the severe form of COVID-19, impaired renal function is a frequent finding. Acute kidney injury was reported in 11% of patients hospitalized with COVID-19 and in up to 23% of severe patients [45]. The imbalanced inflammatory immune response due to cytokine storm contributes to renal tubule injury from hypoperfusion [46]. In addition, studies indicate that renal tubular epithelial cells are directly infected by the virus, which results in tubular damage and can lead to acute kidney injury [47, 48]. Kidney injury may also be a consequence of distributive shock caused by the cytokine cascade, *cor pulmonale*, endothelial dysfunction, hypercoagulation (microthrombi), hypervolemia, ARDS, mechanical ventilation, and extracorporeal membrane oxygenation as well as of the use of nephrotoxic medications [49].

Acute kidney injury can alter kidney architecture and function, leaving sequelae which will lead to the development of chronic kidney disease [50]. Renal failure, characterized by proteinuria, hematuria, and worsening of creatinine clearance, is a significant cumulative worsening factor in those who progress to multiple organ failure. Moreover, it is one of the complications responsible for increased morbidity and mortality [49].

Transplanted patients may present a higher risk of developing severe COVID-19 with a faster clinical progression due to chronic immunosuppression and the presence of comorbidities [51].

Mapping the sequelae of COVID-19 through nuclear medicine

Planar scintigraphy, SPECT or SPECT/CT, and PET/CT are the imaging techniques of nuclear medicine [52]. One of these three techniques is chosen to map the patient, depending on the objective, the radiopharmaceutical, and the scintigraphic examination protocol (**Figure 3**).

Lung

^{18}F-2-fluoro-2-deoxyglucose (^{18}F-FDG) is a radioactive analog of glucose, captured by cell membrane carriers (glucose transporter) and subsequently phosphorylated by hexokinase, remaining momentarily retained in the intracellular space [53]. It is used in PET/CT scans to identify areas of abnormal metabolic activity. The main indications of ^{18}F-FDG PET/CT are in oncology and the mapping of inflammatory or infectious diseases [53, 54].

In inflammatory and infectious processes of the lungs, ^{18}F-FDG uptake primarily occurs by activated neutrophils, whose metabolism is highly dependent on anaerobic glycolysis, requiring a high glucose uptake [55, 56]. ^{18}F-FDG PET/CT allows the quantification of inflammatory activity in the lungs, in both interstitium and airways, making it possible to study the behavior of inflammatory cells [56].

Inflammation and pulmonary fibrosis

Nuclear medicine has been assisting in evaluating patients with pulmonary fibrosis. The activation of fibroblasts is crucial in the fibrotic process, thus increasing glucose consumption [57]. In idiopathic pulmonary fibrosis, an increase in glycolytic metabolism is observed, as a consequence of either inflammatory processes or disordered fibrinogenesis, leading to an increase in the uptake of ^{18}F-FDG [58, 59]. Meissner *et al.* reported that changes in the activity of fibrotic disease lead to changes in the uptake of ^{18}F-FDG, making a better follow-up of the patient possible [58]. Thus, the use of ^{18}F-FDG PET/CT appears to help establish the prognosis and evaluate the therapeutic response in the follow-up of patients recovered from severe COVID-19 (**Figure 4**).

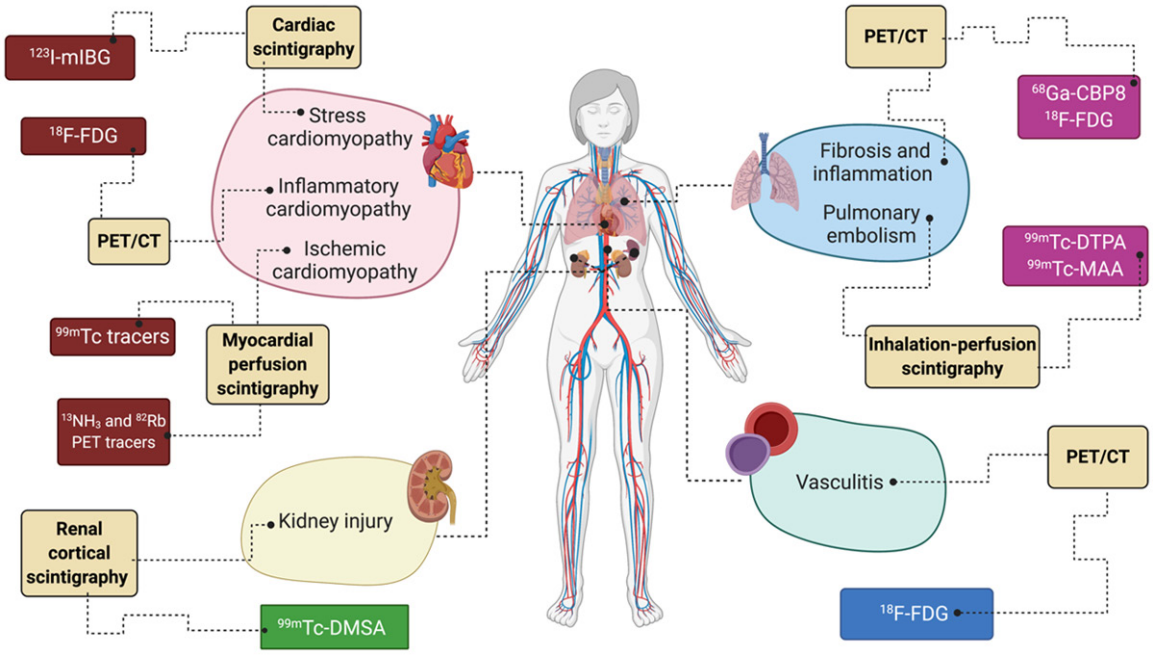

Figure 3. Mapping of COVID-19's functional sequelae with Nuclear Medicine. Created with Biorender.com.

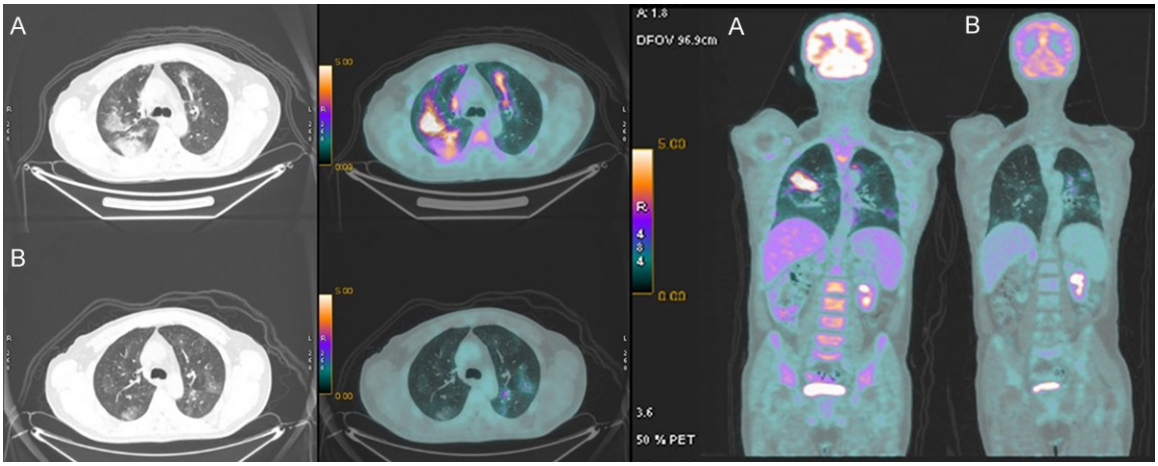

Figure 4. ^{18}F-FDG PET/CT use in diagnosis and monitoring of lung inflammation caused by SARS-CoV-2. Male, 48 y/o, had follicular lymphoma. He was given chemotherapy until April, 2020 and is currently receiving rituximab. In June, he had mild flu-like symptoms and tested positive for COVID-19. After 17 days, due to a persistent daily fever, a ^{18}F-FDG PET/CT was performed and demonstrated glycolytic hypermetabolism in areas of multiple opacities with "ground-glass" attention and sparse pulmonary consolidations with air-permeable bronchograms in both lungs (A). These findings were related to COVID-19 and not to lymphoma. One month later, the patient presented clinically well, although with persistent fever episodes. He underwent another ^{18}F-FDG PET/CT that has shown impressive improvement of pulmonary inflammatory lesions and no lymphoma evidence (B) (images from the authors' personal files).

Excessive collagen deposition is a hallmark of fibrotic disease, and in addition to ^{18}F-FDG, other markers have been used to evaluate pulmonary fibrosis. An example is ^{68}Ga-CBP8, which binds with high affinity and specificity to collagen type 1, making it possible to differentiate old scar tissue from newly formed tissue, by binding to the newly synthesized collagen [60, 61]. According to a study in humans conducted by Montesi *et al.*, an increase in the uptake of this tracer was detected in already established areas of fibrosis by CT and

in areas wherein CT had not identified fibrosis [61]. This result suggests that sites with increased ^{68}Ga-CBP8 uptake are sites of active or recent collagen synthesis and that this radiopharmaceutical can detect active collagen deposition not yet visible to anatomical studies [61]. Thus, since ^{68}Ga-CBP8 PET/CT can detect recent fibrotic activity, it could be used to measure pulmonary sequelae of COVID-19 and to evaluate the therapeutic response in the chronic phase of the disease.

Abnormalities in perfusion

Pulmonary ventilation and perfusion (V/Q) scintigraphy is an important tool for detecting abnormalities of regional pulmonary perfusion and ventilation, allowing accurate diagnosis of pulmonary embolism with low radiation exposure and minimal risk of complications [62, 63].

For the ventilation or inhalation phase, the most commonly used radiotracers are ^{99m}Tc-diethylenetriaminepentaacetic acid and xenon-carrying gas. The latter presents a more uniform distribution in the lungs with less retention in the airways and bronchi; however, it is less easily available. For the perfusion study, the most commonly used radiopharmaceutical is ^{99m}Tc-macroaggregated albumin [63-65].

The main indication of V/Q scintigraphy is the detection of acute pulmonary thromboembolism (PTE) [63, 66]. Analyzing the clinical conditions of patients in conjunction with the result of the examination is pertinent. PTE culminates in decreased perfusion of the area irrigated by the obstructed artery. Normally, bronchial circulation maintains the viability of the embolized volume, and ventilation remains mostly intact. These two parameters can be evaluated through this examination [67].

A normal V/Q scan is sufficient to rule out a diagnosis of PTE [63, 66, 67], whereas a result suggesting a high probability of PTE in a patient with an already high clinical probability is sufficient to confirm the diagnosis. If the scan indicates a low probability of PTE in a patient with high clinical probability, further investigation is mandatory. False-positive results may occur in patients with asthma or previous PTE [63, 67].

In addition to the evaluation of PTE, V/Q scintigraphy is used to perform a differential quantification of pulmonary function [63, 68]. Thus, the quantification of pulmonary functional loss due to COVID-19 complications is possible, notably ARDS, pulmonary embolism, or primary thromboses, which assists in the establishment of prognosis and follow-up strategies in patients who recovered from the disease.

Zuckier *et al.* suggested that in patients with COVID-19 and suspected PTE, the patients should first be investigated with an X-ray or a chest CT [69]. If pulmonary opacifications are confirmed, PTE should be performed using multiple-detector CT pulmonary angiogram.

However, in the absence of pulmonary opacifications, pulmonary perfusion scintigraphy becomes clinically relevant. If negative, it excludes PTE with high sensitivity, and if positive, the study should be supplemented with ventilation scintigraphy rather than CT pulmonary angiogram [69]. This investigation algorithm was suggested because CT pulmonary angiogram has lower sensitivity in the detection of minor and peripheral embolisms. The nephrotoxicity of the iodized contrast used in CT pulmonary angiogram is also a disadvantage. In patients hospitalized with COVID-19, especially in those with previous renal failure, worsening renal function may occur in 11%-23% of the cases [45, 70, 71].

Heart

Myocardial perfusion abnormalities and cell viability

As observed in the lungs recovered from ARDS, in the long term, the immune system hyperactivation and tissue injury caused by COVID-19 can lead to fibrosis and cardiac microvascular disease, characterizing residual cardiomyopathy with loss of function and increased cardiovascular risk [72]. Inflammatory stress can also destabilize pre-existing cardiovascular diseases and worsen chronic ischemia, especially in patients who have discontinued treatment for whatever reason [73]. Thus, to evaluate microcirculation dysfunctions and the extent and evolution of ischemic damage, myocardial perfusion scintigraphy (MPS) with thallium-201 (^{201}Tl) tracers bound to technetium-99m, or PET/CT techniques using positron-emitting radiopharmaceuticals, such as rubidium-82 (^{82}Rb) or ^{13}N-ammonia ($^{13}NH_3$), are suggested [74].

MPS allows a very thorough observation of myocardial damage, including diagnostic information, risk stratification, and evaluation of ventricular function [75]. Especially when performed using the PET/CT technique or CZT gamma cameras, MPS can evaluate microcirculation and coronary flow reserve, which are important for planning therapy and cardiovascular risk [76]. Normal MPS scans are associated with a low rate of occurrence of cardiovascular events in one year (<1%), whereas a finding of significant myocardial ischemia or other high-risk findings is predictive factor of adverse cardiovascular outcomes, guiding more aggressive treatment strategies in these patients [77, 78]. Besides, all these data are still important to verify the effectiveness of the treatment adopted and to strengthen evidence-based strategies [78, 79], especially in the current context wherein these strategies are still scarce.

If persistent ventricular dysfunction is observed after COVID-19, a myocardial viability assessment may also be necessary, due to its importance for therapeutic decisions in patients who have experienced acute or chronic ischemic episodes [74, 80]. The preferred examination is ^{18}F-FDG PET/CT for evaluating myocardial glycolytic metabolism in regions with ischemic defects that appear fixed on MPS. The tissue is known to be viable when myocardial segment perfusion is reduced at rest but ^{18}F-FDG uptake is preserved [74].

For the diagnosis and follow-up of myocarditis, one of the most common cardiac complications of COVID-19, nuclear techniques are little specific; hence, cardiac MRI is more adequate, ensuring better spatial resolution and greater specificity in these cases [81].

Cardiac sympathetic activity

Remembering that the impact of COVID-19 includes social, economic, and psychological aspects, which may have repercussions in the organic sphere, is important. In recent literature, an increasing number of studies have reported on the possible association between *Takotsubo* syndrome (stress-induced cardiomyopathy) and the pandemic, either through a direct causal relationship with SARS-CoV-2 infection or through the generation of extreme anxiety due to various uncertainties and fears [82-84].

Jabri *et al.* observed a five-fold higher incidence of this syndrome between March and April 2020, compared to the time before the pandemic [84]. This results in a need for attention to the occurrence of stress-induced cardiomyopathy when acute coronary syndrome is suspected without associated thrombotic events, regardless of the results of SARS-CoV-2 tests. To this end, the performance of cardiac scintigraphy with metaiodobenzylguanidine labeled with iodine-123 (^{123}I-MIBG) is suggested [74, 85, 86].

The ^{123}I-MIBG molecule is similar to norepinephrine, and it is stored in cardiac sympathetic presynaptic nerve endings [74, 85, 86]. Moreover, it is used in the evaluation of the sympathetic function of the heart, and it is important in the investigation of *Takotsubo* syndrome since one of its most widely accepted pathophysiological mechanisms involves sympathetic hyperstimulation and excess catecholamines [74, 85]. The analysis of cardiac scintigraphy with ^{123}I-MIBG allows the observation of defects in its uptake by the myocardium, with a higher rate of radiopharmaceutical clearance from the heart and with a possible mismatch between myocardial perfusion and innervation, which would signal the presence of transient denervated areas with increased risk for ventricular arrhythmias [74, 86]. These changes are often not visible in MPS, which justifies the preference for ^{123}I-MIBG in these cases [74].

Endothelium: inflammation in the vascular wall

Despite evidence of direct infection of the endothelium by SARS-CoV-2, studies that estimate the occurrence of thrombotic events are still scarce and inaccurate, and this directly impacts the guidance of the conduct and subsequent follow-up [87].

This suggests the importance of screening thrombotic events and vascular disease in patients with COVID-19, which could be performed with the aid of imaging tests [37, 88]. Initial studies with CT have reported a higher incidence of vascular thickening in patients with COVID-19, compared to those with pneumonia due to other etiologies. Other findings

have also been reported, such as hypertrophic pulmonary vessels and vascular congestion, even if their mechanisms are not yet well elucidated [88, 89].

In this context, the evaluation using ^{18}F-FDG PET/CT can be promising, due to its ability to detect metabolic changes early and with high sensitivity in medium- and large-caliber vessels or in cases of suspected fever of unknown origin [90]. This examination makes the molecular detection of vascular inflammation possible long before any morphological changes appear. It also allows a reconnaissance of the extent of the inflammation, ensuring accuracy in the diagnosis and the monitoring of the effectiveness of vasculitis treatment [91].

All these advantages in the investigation of vasculitis could also be beneficial in the evaluation of pediatric inflammatory multisystem syndrome, which is potentially associated with COVID-19. The first cases of this new syndrome were first observed in the United Kingdom in April 2020 in school-age children and adolescents [92, 93]. It can manifest with fever, severe abdominal pain, and transient dilatation of the coronary arteries or even with cardiac dysfunction and shock, in addition to having similarities with the diagnostic criteria of Kawasaki disease, which suggests a possible but still unproven overlap between their pathophysiological mechanisms [92, 93]. Therefore, due to the high risk of aneurysm persistence and development of long-term coronary stenosis in Kawasaki disease [94], it is suggested that pediatric inflammatory multisystem syndrome patients be monitored through the use of ^{18}F-FDG PET/CT as a prevention measure. Furthermore, MPS could be effective in this context, ensuring the observation of the extent of myocardial damage produced by ischemic injury from aneurysms or coronary stenoses [74].

Finally, in the case of suspected fever of unknown origin, the whole-body ^{18}F-FDG PET/CT approach can adequately locate hidden etiologies, which are within a range of multiple diagnostic possibilities when no signs that could help to locate the disease are present [95]. This advantage is added to the others previously explained, suggesting the beneficial use of ^{18}F-FDG PET/CT to improve research on vascular involvement from COVID-19, expanding the current knowledge about the pathophysiology of the disease and its repercussions in the short, medium, and long term and assisting in the formulation of therapeutic strategies and in the follow-up of these patients, whether adult or pediatric.

Kidneys: inflammation, fibrosis, and renal function

Renal cortical scintigraphy with dimercaptosuccinic acid labeled with technetium-99m (^{99m}Tc-DMSA) can be very useful in the analysis of renal injury resulting from SARS-CoV-2 infection. This radiotracer is well established as the choice for the detection and evaluation of pyelonephritis and renal fibrosis in children. The typical finding of acute pyelonephritis is reduced uptake of ^{99m}Tc-DMSA while preserving the renal contour. When this reduced uptake is added to cortical tapering and volume reduction, cortical fibrosis is established [96, 97].

Scintigraphy with ^{99m}Tc-DMSA has high sensitivity and specificity for the diagnosis of pyelonephritis, providing important information about kidney function and the extent of parenchymal inflammation [96].

In addition to its usefulness in the diagnosis of pyelonephritis, Hitzel *et al.* demonstrated that scintigraphy with ^{99m}Tc-DMSA during acute pyelonephritis may be important in predicting the risk of renal fibrosis formation [98].

As previously seen, acute kidney injury by SARS-CoV-2 may occur in COVID-19 through both direct and indirect mechanisms. Thus, renal scintigraphy with ^{99m}Tc-DMSA can measure the extent of renal involvement and help in the prediction of fibrosis after acute injury.

Future prospects for research and clinical use

As shown above, several radiopharmaceuticals are already available in the nuclear medicine routine, with diagnostic, prognostic, and management-defining value. Nevertheless, new radiopharmaceuticals, with higher physiological specificity, can expand the horizon of clinical investigation. In this section, we discuss some examples of potential radiopharmaceutical markers of specific inflammatory receptors and angiotensin 2.

Cyclooxygenase 2 inhibitors

Cyclooxygenase (COX) is an important contributor to the inflammatory response. Among its three subtypes, COX-2 is either absent or poorly expressed in most epithelial cells. However, high levels of this enzyme are found in tissues with inflammatory activity [99-101].

Scintigraphy with COX-2-specific radiotracers can identify tissues with higher densities of this enzyme [101, 102]. Uddin *et al.* showed that isomeric analogs of celecoxib, efficiently bound with iodine-123, can map COX-2 through SPECT images [102]. Radiopharmaceuticals for PET images of fluoro-iodinated COX-2 inhibitors have also been developed to locate tissues with high COX-2 levels [101].

Thus, the use of these radiopharmaceuticals seems promising for detecting sites with higher inflammatory activity, providing data for more accurate therapy in COVID-19 survivors.

Angiotensin 2 ligands

Linares *et al.* showed the use of a specific radiopharmaceutical to map angiotensin 2 receptors in animals [103]. As mentioned above, increased levels of angiotensin 2 are expected in patients with COVID-19 due to an imbalance of the renin-angiotensin-aldosterone system caused by SARS-CoV-2. Also, tissues with higher ACE2 expressions have a greater susceptibility to viral infection [47].

Thus, scintigraphy with radiolabeled ligands of angiotensin 2 can trace the distribution of these receptors in humans in a non-invasive, objective, and real-time way, increasing knowledge about which individuals and tissues are most susceptible to COVID-19 and contributing to the creation and consolidation of therapeutic strategies.

Inflammatory biomarkers

In addition to ^{18}F-FDG, other radiopharmaceuticals exist that map inflammatory processes. An example is ^{18}F-JNJ-64413739, which targets P2X purinoceptor 7 purinergic receptors. These receptors are ion channels expressed predominantly in macrophages and monocytes in the periphery and in microglia and astrocytes in the central nervous system [104]. These channels are extensively involved in inflammatory diseases, participating in the control of cytokine secretion and being key elements in the regulation of inflammation [105]. Their inhibition can decrease the secretion of cytokines, such as interleukin-1β and tumor necrosis factor-alpha, reduce pulmonary edema and exudates, and significantly improve pulmonary oxygenation during episodes of ischemia/reperfusion. Thus, their inhibitors can be studied as candidates for anti-inflammatory therapies in the fight against COVID-19 [106].

Conclusions

COVID-19 has proved to be a multisystemic disease triggered by renin-angiotensin-aldosterone system imbalance and by the human body's inflammatory and thrombogenic response to SARS-CoV-2. In survivors of the severe form of the disease, several sequelae are expected, the most significant of which is pulmonary fibrosis. Both V/Q scintigraphy and ^{18}F-FDG PET/CT can help in the mapping of these sequelae and in the follow-up of the therapeutic response by evidencing the volume of lung tissue affected and the active foci of inflammation, respectively.

Cardiovascular and renal sequelae are also expected. Cardiac scintigraphy, depending on the radiopharmaceutical and technique used, can map disorders of coronary macrocirculation and microcirculation, cardiac sympathetic activity, cell viability, tissue inflammation, and ventricular dysfunction, thus helping in diagnosis, prognosis, and therapeutic definition. In the kidneys, renal scintigraphy can map and quantify renal sequelae, defining the renal prognosis and helping to enhance kidney-protective treatment.

In this study, we focused on the scintigraphic study of the most likely functional repercussions of COVID-19, with radiopharmaceuticals that are already well established and available in nuclear medicine services worldwide. Furthermore, new radiopharmaceuticals have emerged with the potential to further expand the understanding of the sequelae left by COVID-19.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Simone Cristina Soares Brandão, Department of Internal Medicine, Divisions of Cardiology and Nuclear Imaging, Hospital das Clínicas, Federal University of Pernambuco (UFPE), Avenida Professor Moraes Rego, 1235 Recife, PE 50670-901, Brazil. E-mail: sbrandaonuclearufpe@gmail.com; simone.brandao@ufpe.br

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