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Molecular Imaging as a tool for evaluation of COVID-19 sequelae – A review of literature

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Abstract

Coronavirus disease 2019 (COVID-19) is caused by the novel viral pathogen, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 primarily involves the lungs. Nucleic acid testing based on reverse-transcription polymerase chain reaction of respiratory samples is the current gold standard for the diagnosis of SARS-CoV-2 infection. Imaging modalities have an established role in triaging, diagnosis, evaluation of disease severity, monitoring disease progression, extra-pulmonary involvement and complications. As our understanding of the disease improves, there has been substantial evidence to highlight its potential for multi-systemic involvement and development of long-term sequelae. Molecular imaging techniques are highly sensitive, allowing non-invasive visualization of physiological or pathological processes at a cellular or molecular level with potential for detection of functional changes earlier than conventional radiological imaging. The purpose of this review article is to highlight the evolving role of molecular imaging in evaluation of COVID-19 sequelae. Though not ideal for diagnosis, the various modalities of molecular imaging play an important role in assessing pulmonary and extra-pulmonary sequelae of COVID-19. Perfusion imaging using single photon emission computed tomography fused with computed tomography (SPECT/CT) can be utilized as a first-line imaging modality for COVID-19 related pulmonary embolism. ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT is a sensitive tool to detect multi-systemic inflammation including

myocardial and vascular inflammation. PET in conjunction with magnetic resonance imaging (MRI) helps in better characterization of neurological sequelae of COVID-19. Despite the fact that majority of the published literature is retrospective in nature with limited sample sizes, it is clear that molecular imaging provides additional valuable information (complimentary to anatomical imaging) with semi-quantitative or quantitative parameters to define inflammatory burden and can be used to guide therapeutic strategies and assess response. However, widespread clinical applicability remains a challenge owing to longer image acquisition times and the need for adoption of infection control protocols.

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Core Tip: Despite extensive global efforts, COVID-19 still remains the largest public health problem of modern times. As our understanding of the disease and its manifestations improve, we must recognize and explore the potential utility of molecular imaging modalities in evaluating the long-term sequelae of COVID-19. Molecular imaging tools can be incorporated into routine clinical practice by identifying appropriate and specific indications and addressing limitations to their practical application.

INTRODUCTION
Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the novel pathogen, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. Having its early origins in the city of Wuhan, China, the disease was transmitted across the globe at disconcertingly rapid rates, prompting the World Health Organization (WHO) to

characterize the outbreak as a pandemic way back in March 2020 [2,3]. The resurgence of the disease in several parts of the world with identification of new mutant variants has hindered a targeted global response, owing to which, COVID-19 still remains the largest public health problem of modern times [4].

Though primarily believed to involve the lungs and the respiratory tract, the clinical spectrum of COVID-19 is diverse with potential for gastrointestinal, cardiac, renal, neurological and haematological manifestations of varying severity [5].

SARS-CoV-2 is a single stranded RNA virus. Nucleic acid testing based on reverse-transcription polymerase chain reaction (RT-PCR) is the current gold standard for the diagnosis of SARS-CoV-2 infection. It is most commonly done with respiratory samples such as nasopharyngeal and throat swabs [6]. Serological tests which identify antibodies to different virus proteins have also been developed. Laboratory tests such as complete hemogram, C-reactive protein (CRP), D-dimer, prothrombin time (PT-INR), lactic dehydrogenase (LDH), ferritin and procalcitonin help in evaluation of disease severity and prognostication [7]. In spite of relatively low specificity and radiation exposure, imaging modalities have an established role in triaging, diagnosis, evaluation of disease severity, monitoring disease progression, extra-pulmonary involvement and complications [8,9].

Molecular imaging modalities in current clinical practice such as magnetic resonance imaging (MRI), single photon emission computed tomography (SPECT) and positron emission tomography (PET) have great potential in early and sensitive disease detection, accurate delineation of disease extent and assessing therapeutic response with the ultimate aim of personalized medicine. Novel molecular targets and tracers (metabolic agents, peptides, small molecules, receptor ligands) are being rapidly identified and developed. At present, multimodality molecular imaging is most commonly used for oncological applications. However, their role in systemic inflammatory and infectious conditions is being increasingly recognized [10, 11]. The utility of molecular or functional imaging in particular, for COVID-19 has been poorly defined owing to limited availability, longer imaging times, absence of clearly defined

appropriate usage criteria, lack of standardized protocols and need for infection control. In this article, we aim to review the role of molecular imaging in evaluating the sequelae of COVID-19.

METHODS

The literature search was based on three electronic databases (Pubmed, Scopus, and Embase) using selected keywords which included, "COVID-19," "sequelae," "molecular imaging," "functional imaging," and "nuclear medicine" linked through the "AND" and "OR" boolean operators to build specific strings for each electronic search engine. Original studies, case reports, case series and review articles were included. No restriction was placed in terms of country or language of publication. Only full length articles were considered. Information from websites of different professional associations and national/international organizations was searched to retrieve relevant information.

ANATOMICAL IMAGING

Chest radiography (CXR) and computed tomography (CT) have been extensively used for imaging evaluation of COVID-19. CXR findings in COVID-19 include consolidatory changes and bilateral ground glass & peripheral air opacities. However, these findings are non-specific and are highly dependent on duration & severity of infection at the time of acquisition [12]. The advantages of CXR over CT include its near universal availability, lower ionizing radiation exposure, ability to perform multiple repeat examinations and portability of equipment which reduces risk of cross-infection. CXR is limited by its lower sensitivity compared to RT-PCR and CT, particularly in early stages of the disease [13, 14].

Similar to CXR, the typical findings of COVID-19 on CT are multiple ground-glass opacities (GGOs) in a posterior, subpleural & peripheral distribution, commonly showing bilateral lung involvement. Consolidatory changes, reticular opacities, intra- & inter-lobular septal thickening, crazy paving pattern have also been described. CT

abnormalities progress rapidly after symptom onset and are reported to peak between days 6 and 13 of the illness. Late stage disease shows gradual decrease in GGOs and consolidation with appearance of signs of fibrosis [15,16]. CT findings of COVID-19 are highly non-specific and may be seen with other viral pneumonias [17-18]. A recent meta-analysis of the accuracy of diagnostic tests for COVID-19 found CT to have high sensitivity (91.9%, 95% CI 89.8%-93.7%) and low specificity (25.1%, 95% CI 21.0%-29.5%). Hence CT findings must be interpreted in light of clinical presentation, history of exposure and pre-test probability [6].

At present, most consensus guidelines, recommend against the routine use of CT for screening and diagnosis of COVID-19 pneumonia. However, the role of chest CT as a rapid-triage tool in resource-limited facilities (Eg: limited access to/Longer processing time of RT-PCR) has also been acknowledged [19]. The use of CT has been deemed most appropriate in patients with moderate to severe respiratory symptoms or mild respiratory symptoms with risk factors for disease progression (such as presence of co-morbidities and advanced age) [20,21]. The major advantage of CT is the ability to stratify patients based on their risk for clinical decompensation and progression. To that end, different standard reporting and scoring systems have been proposed such as COVID-19 Reporting and Data System (CO-RADS), Radiological Society of North America (RSNA) imaging classification for COVID-19, chest CT severity score (CT-SS) and total severity score (TSS) [22, 23]. CT-SS is positively correlated with age, inflammatory biomarkers, clinical severity and disease phases [24]. Lieveld *et al* showed that the chest CT-SS was significantly positively associated with hospital & ICU admission, and in-hospital and 30-day mortality for all age groups in patients with COVID-19 and CT patterns ≥ CO-RADS 3 [25].

MRI owing to its lack of exposure to ionizing radiation has been found to be useful in select patient-groups such as pregnant women and children. Several case-reports have been published highlighting the utility of MRI in evaluation of extra-pulmonary involvement, particularly cardiac and neurological manifestations of COVID-19 [26-28].

Chest ultrasonography (US) is now being advocated as a useful point-of-care (POC) imaging tool for evaluation particularly in the emergency and ICU settings. Vascular US of the limbs is useful in the diagnostic workup of patients with suspected deep vein thrombosis, a common complication of COVID-19 [29,30].

WHERE DOES MOLECULAR IMAGING FIT IN?

Molecular imaging is a highly sensitive modality that allows non-invasive visualization of physiological or pathological processes at the cellular or molecular level. Pathophysiological changes in affected tissues are believed to occur earlier than anatomical changes in a variety of infectious and inflammatory conditions and hence molecular imaging may detect these functional changes before conventional radiologic imaging modalities [31]. Different molecular imaging modalities can help in evaluating the sequelae of COVID-19 (Figure 1).

PULMONARY VASCULAR SEQUELAE - ROLE OF VENTILATION-PERFUSION IMAGING

It is now well established that COVID-19 is associated with thrombotic complications such as venous thromboembolism (VTE), myocardial infarction (MI) and ischemic stroke [32]. A recent meta-analysis found the overall prevalence of COVID-19 related VTE to be 14.7% (95%CI 12.1% to 17.6%), which was significantly higher in patients with severe systemic inflammation and respiratory failure [33–35]. However, these thromboembolic phenomena have also been documented in patients with milder forms of the disease [36].

From a histological stand-point, direct viral infection of endothelial cells with perivascular T-cell infiltration, thrombotic microangiopathy and angiogenesis have been used to differentiate COVID-19 from other respiratory viruses [37]. Hence, both thromboembolic phenomena and in-situ thrombotic microangiopathy can be responsible for pulmonary vascular manifestations of COVID-19. Ventilation-Perfusion (VQ) imaging is the current gold-standard screening modality for evaluation of chronic

thromboembolism [38]. Distal subsegmental small vessel thrombi can be missed on conventional CT pulmonary angiogram (CTPA), which is designed to visualize a luminal clot rather than assess how a clot affects lung perfusion; thereby underestimating the extent of micro-vascular injury [39]. Hence, VQ scintigraphy, a functional imaging modality which directly evaluates lung perfusion, can potentially help better identify vascular pathology and guide therapeutic decisions.

The possible patterns of perfusion defects seen in COVID-19 are closely related to their pathophysiology. Typically described segmental or subsegmental ventilation–perfusion mismatch defects are usually the result of large- and medium-vessel thromboembolic phenomena. Patchy, mottled peripheral pattern of ventilation-perfusion mismatch not adhering to typical segmental distribution may suggest micro-angiopathy [40,41].

Dhawan *et al* recently proposed an algorithm to incorporate perfusion imaging instead of angiographic imaging as a first-line modality in the post-COVID recovery patients for follow-up of pulmonary vascular sequelae. It would serve as a triage tool to exclude or evaluate residual clot burden and small vessel injury [42].

A few recent publications have discouraged the use of ventilation imaging by nuclear medicine departments to reduce the risk of cross-contamination *via* aerosols [43,44]. Reporting perfusion studies without concordant ventilation imaging might hinder interpretation by increasing the likelihood of false positives. However, such limitation can be significantly overcome by the use of hybrid imaging. SPECT with CT fusion (SPECT/CT) for perfusion studies can be used as a substitute for ventilation imaging, by providing corroborating anatomical information about the lung parenchyma [45-47]. Perfusion-only SPECT/CT has been shown to have practical utility in the diagnosis of pulmonary embolism in COVID-19 patients with a moderate-to-high pre-test probability. A 60-year old male underwent perfusion-only SPECT/CT (Figure 2) in our department, two months following COVID-19 infection, to rule out pulmonary thromboembolism. The study revealed subsegmental mismatched defects suggestive of pulmonary thromboembolism.

The use of VQ imaging in the setting of contraindications to iodinated contrast material also makes it preferable over CTPA as a first-line imaging modality for COVID-19 related pulmonary embolism [48].

THYROID DISORDERS

SARS-CoV-2 infection has been linked to multiple thyroid disorders including destructive thyroiditis, autoimmune thyroid disease, central hypothyroidism and euthyroid sick syndrome [49]. The binding of the viral spike protein to the angiotensin-converting-enzyme-2 (ACE2) receptors on the surface of the thyroid follicular cells has been implicated in the etiopathogenesis of the COVID-19-related destructive thyroiditis [50]. Further, an aberrant systemic inflammatory syndrome in the wake of COVID-19 can also account for the abovementioned thyroid disorders. Thyrotoxicosis, due to destructive thyroiditis or activated/relapsed Graves' disease, can exacerbate the cardiovascular complications and contribute to poor outcomes, especially in severe COVID-19 disease. Thyroid scintigraphy, with either ^{99m}Tc-pertechnetate or ^{123}I-sodium iodide, can rapidly and reliably differentiate between these etiologies of thyrotoxicosis and guide the further course of treatment [49]. A 36-year-old male had complaints of painful neck swelling and fever for 1 wk with past history of COVID-19, two months ago. He was found to have suppressed levels (0.013 microIU/mL) of thyroid stimulating hormone (TSH). Ultrasound neck revealed a diffusely heterogeneous thyroid parenchyma with mildly increased vascularity suggestive of thyroiditis. He was referred to our department for thyroid scintigraphy to further evaluate the cause of thyrotoxicosis. Thyroid scintigraphy revealed (Figure 3) very faint heterogeneous tracer uptake in the region of the thyroid with increased background tracer activity. With the given clinical and biochemical context, scan findings were suggestive of thyroiditis, likely related to COVID-19.

^{18}F-FLUORODEOXYGLUCOSE (FDG) PET/CT

^{18}F-FDG PET/CT is a functional imaging modality with established clinical utility in diagnosis, staging, re-staging and therapeutic response evaluation for a variety of oncological conditions [51,52]. However, in the recent past, the role of ^{18}F-FDG PET/CT as a hybrid imaging tool for detecting and characterizing various inflammatory disorders has also been validated. ^{18}F-FDG PET/CT provides complimentary anatomical and functional information with the ability to non-invasively quantify inflammation [53,54]. SARS-CoV-2 viral infection results in a complex inflammatory cascade leading to release of pro-inflammatory cytokines and activation of cells such as neutrophils, monocytes and effector T-cells. Activated inflammatory cells are highly glycolytic and hence non-physiological FDG uptake can be reliably used as a surrogate marker for active inflammation [55].

Multiple studies have demonstrated incidental findings in otherwise asymptomatic or mildly symptomatic patients who underwent PET/CT for oncology/non-COVID related indications. Hence, nuclear medicine physicians must be aware of the radiological manifestations of COVID-19 and must nurture a high index of suspicion so that infection may be promptly identified at early stages and appropriate treatment may be initiated in such patient population, majority of whom may have a compromised immune status [56-60].

The currently accepted gold standard for diagnosing COVID-19 infection is RT-PCR to detect viral RNA [6]. Despite being fairly sensitive, multiple sources of false negative test results have been reported such as insufficient viral genome, incorrect sampling technique, sampling outside the appropriate time-window for viral replication and viral mutation. The role of ^{18}F-FDG PET/CT has been sought to be explored at early stages when clinical symptoms are not specific and differential diagnosis is challenging [61]. An early case series by Qin *et al* described four patients in Wuhan, with strong clinical suspicion of COVID-19, who underwent ^{18}F-FDG PET/CT during the acute phase of illness. FDG uptake was observed in regions corresponding to GGOs and/or consolidatory changes, with maximum standardized uptake (SUVmax) values ranging from 4.6 to 12.2. FDG uptake was also reported in the mediastinal and hilar lymph

nodes with no obvious anatomical lymphadenopathy [62]. However, given the fact that increased FDG uptake is noted in various acute inflammatory and infectious conditions and is hence non-specific, 18F-FDG PET/CT is not routinely recommended for the initial evaluation of patients with known or suspicious COVID-19 infection [63].

Nevertheless, data by Qin *et al* also raised the possibility that higher SUVmax of pulmonary lesions on 18F-FDG PET may be correlated with longer duration of healing [62]. 18F-FDG-PET/CT could, therefore, potentially be used to monitor treatment response and predict recovery. However, these trends need to be evaluated in larger populations before meaningful conclusions can be drawn.

CARDIOVASCULAR SEQUELAE

The cardiovascular manifestations of COVID-19 include arrhythmias, acute or fulminant myocarditis, acute coronary syndromes and heart failure [64].

Different etiological mechanisms have been proposed to explain cardiac involvement in COVID-19 which include –

Direct myocardial cellular injury by the virus. The spike protein of the SARS-CoV2 virus binds to ACE2 receptors, which serves as an entry point to the cell. ACE2 is a membrane protein with documented expression on ciliated columnar respiratory epithelium, type II pneumocytes and cardiomyocytes.

Severe systemic inflammatory response. High levels of proinflammatory cytokines and procoagulants result in endothelial dysfunction, microthombi formation within the coronary circulation and increased plaque vulnerability.

Mismatch of the myocardial oxygen supply and demand. Increased cardio-metabolic demand is the result of systemic inflammation and ongoing hypoxia due to severe pneumonia or acute respiratory distress syndrome [65].

A recent case report highlighted the role of multi-modality imaging for assessment of myocardial injury in COVID-19. 18F-FDG PET/CT (with 18-hour prolonged fasting protocol to suppress glucose uptake) was performed in a 69-year-old woman with COVID-19 who had complaints of dyspnea and chest pain. PET showed FDG uptake in

the apex, anterior wall and septum and 99mTc-MIBI SPECT done subsequently revealed resting perfusion defects in the same segments of the left ventricular myocardium suggestive of an acute inflammatory response to MI precipitated by COVID-19. Severe left anterior descending artery (LAD) artery disease was found on angiography performed later confirming anterior wall MI. Segmental FDG uptake (due to inflammation) with matching perfusion defect (due to inflammatory microvascular dysfunction) though suggestive of myocarditis, can also be seen in an acute inflammatory response to MI precipitated by COVID-19, as seen in the case described above [66].

Another case report highlighted the role of ^{18}F-FDG PET/CT in assessing myocardial inflammation in COVID-19 related multisystem inflammatory syndrome in children (MIS-C). ^{18}F-FDG PET-CT, performed after 18 h of fasting and high-fat, low-carbohydrate diet preparation in a 14-year-old child with a clinical diagnosis of COVID-19-related MIS-C demonstrated hypermetabolism in the inferolateral wall of the LV myocardium suggestive of active inflammation (Figure 4, attached with permission). A repeat ^{18}F-FDG PET/CT, performed six weeks later with the same protocol, showed resolution of hypermetabolism, consistent with clinical and biochemical improvement, thus highlighting the role of ^{18}F-FDG PET/CT in the timely diagnosis and follow-up of this potentially life-threatening hyperinflammatory syndrome [67].

VASCULITIS

Recently there has been increasing recognition of the utility of ^{18}F-FDG PET/CT in inflammatory disorders and, in particular, vasculitis. The European League Against Rheumatism (EULAR) recommends ^{18}F-FDG PET/CT as an alternative imaging modality in cases of suspected large vessel vasculitis [68,69]. The advantages of ^{18}F-FDG PET/CT are its high sensitivity and the ability to non-invasively quantify inflammatory activity. Semi-quantitative methods of grading FDG uptake have been proposed. Total vascular score (TVS) and PET vascular activity score (PETVAS), have recently been suggested as PET based global inflammatory burden parameters, with potential for

differentiation of active *vs* non-active inflammation, predicting relapse & treatment response monitoring in large vessel vasculitis [70,71].

Sollini M *et al* recently evaluated the role of ^{18}F-FDG PET/CT in assessing systemic inflammation in 10 patients who had recovered from COVID-19. Significantly higher target-to-blood pool ratio (a quantitative parameter of FDG uptake) was noted in COVID-19 patients, in comparison to controls in three arterial territories - thoracic aorta, right iliac artery, and femoral arteries. This study suggested that COVID-19 induces vascular inflammation, and FDG PET has a potential role for evaluation of whole body vascular inflammatory process [72].

Central nervous system (CNS) vasculitis can occur as a part of systemic vasculitides or as primary angiitis of CNS (PACNS). Viral infections such as Varicella zoster, Hepatitis C virus, West Nile virus and Human immunodeficiency virus (HIV) are known to trigger CNS vasculitis [73]. SARS-CoV-2 infection related vasculitis has also been proposed as a possible mechanism to explain COVID-19 related neurologic dysfunction and encephalopathy with clinical improvement post steroid administration [74]. MR angiography may reveal concentric vessel wall enhancement as a direct sign of regional mural inflammation [75]. However, majority of the published literature on COVID-19 vasculitis is limited to case reports and case series. Further prospective studies are required to unequivocally establish a causal relationship between SARS-CoV-2 and vasculitis.

NEUROLOGICAL SEQUELAE

Neurological manifestations of COVID-19 can range from mild symptoms like headache, dizziness and anosmia to more serious complications such as encephalopathy, posterior reversible encephalopathy syndrome (PRES), acute demyelinating encephalomyelitis (ADEM), cerebrovascular events including acute ischemic stroke, intracranial haemorrhage (ICH), cortical vein and/or sinus thrombosis (CVST), and neuro-inflammatory syndromes [76].

Important neuropathological findings in COVID-19 patients include edema, gliosis with diffuse activation of microglia and astrocytes, inflammatory infiltrates, cortical and sub-cortical infarcts, haemorrhagic lesions and arteriosclerosis. It is hypothesized that they represent a combination of direct cytopathic effects of the virus and indirect effects *via* the host immune-inflammatory response owing to ACE2 & heme dysregulation along with release of pro-inflammatory cytokines. However, further studies are required to better understand the pathologic mechanisms which drive the neurological manifestations of COVID-19 [77-79].

In COVID-19 patients with neurological manifestations, MRI neuroimaging may be performed to detect the underlying casual pathology, particularly, if CT reveals no abnormality. The recommended basic MRI protocol includes pre and post-contrast T1 weighted-images, T2-weighted, fluid-attenuated inversion recovery (FLAIR), diffusion-weighted images and haemorrhage-sensitive sequences such as susceptibility weighted imaging (SWI) [80]. The most common neuroimaging manifestations are acute and subacute infarcts with large clot burden, ICH, microhaemorrhages, asymmetrical diffuse or tumefactive T2 and FLAIR white matter hyperintensities consistent with ADEM, mesial temporal lobe, corpus callosum & olfactory bulb involvement and cranial nerve enhancement [81-83].

Lu *et al* explored the role of diffusion tensor imaging (DTI) and 3D high-resolution T1 weighted sequences in assessing possible disruption of micro-structural and functional brain integrity in the recovery stages of COVID-19. They reported significantly higher bilateral gray matter volumes (GMV) in olfactory cortices, hippocampi & insulas and changes in MRI-based measures of water diffusion in white matter of COVID-19 patients three months after acute illness, compared to age and sex-matched non-COVID controls, suggesting neuro-invasion potential of SARS-CoV-2 [84].

High costs, long acquisition times, limited access in developing nations and lack of specificity of nearly all reported neuroradiological findings in COVID-19 are the major limitations of MRI [85].

Delorme *et al* reported a case series with 4 COVID-19 patients suspected to have autoimmune encephalitis. ^{18}F-FDG PET/CT of the brain demonstrated prefrontal or orbito-frontal cortical hypometabolism and hypermetabolism in the cerebellar vermis. These findings were consistent in all 4 patients, with no specific MRI features nor significant cerebrospinal fluid (CSF) abnormalities, possibly suggesting a parainfectious cytokine storm or immune-mediated mechanism at play rather than direct neural invasion [86].

Similarly, Grimaldi *et al* also reported diffuse cortical hypometabolism with hypermetabolism in the putamen and cerebellum in autoimmune encephalitis concomitant with SARS-CoV-2 infection. These findings, along with normal morphological data on MRI, might suggest reduced neuronal activity and functional alterations in neuro-COVID-19 patients [87]. Increased FDG uptake in the bilateral basal ganglia with T2/FLAIR hyperintensities in the bilateral hippocampi was also reported in a case of SARS-CoV-2 infection related autoimmune limbic encephalitis [88].

Further, ^{18}F-FDG PET has also been used in the evaluation of patients with persistent functional neurological symptoms after apparent recovery from COVID-19. In a retrospective series comprising 35 such patients, ^{18}F-FDG brain PET demonstrated hypometabolism in the bilateral rectal/orbital gyrus, including the olfactory gyrus, connected limbic/paralimbic regions; brainstem and the bilateral cerebellar hemispheres. This metabolic picture was seen to be associated with the patients' symptoms and could be used to reliably identify these patients from normal controls. Brain inflammation related to the neurotropism of the SARS-CoV-2 from the olfactory bulb has been suggested as a possible mechanism underlying these findings [89].

Few case reports have also highlighted the role of molecular imaging in the evaluation of parkinsonian features post COVID-19. Cohen *et al* reported a case of parkinsonism after SARS-CoV-2 infection in a 45-year-old man. Brain CT, MRI and EEG were normal. However, ^{18}F-fluorodopa (^{18}F-FDOPA) PET scan revealed decreased radiotracer uptake in both putamina (left>right) and mild decreased uptake in the left caudate nucleus.

The authors reported clinical improvement of rigidity and bradykinesia after initiation of pramipexole [90].

Morassi *et al* described consistent findings of diffuse cortical hypometabolism (with relative sparing of sensorimotor areas) associated with hypermetabolism in the brainstem, mesial temporal lobes, and basal ganglia on ^{18}F-FDG PET/CT in two patients with COVID-19 related encephalopathy who developed a rapidly progressive form of atypical parkinsonism. ^{123}I-ioflupane DaT-SPECT performed in one of the two patients showed asymmetrical presynaptic dopaminergic dysfunction in the bilateral putamina, more severe on the left side consistent with a parkinsonian disorder [91].

OTHER RADIO-TRACERS

Scarlattei *et al* have reported incidental findings of ^{68}Ga-labelled prostate-specific membrane antigen (^{68}Ga-PSMA) and ^{18}F-labelled choline (^{18}F-choline) radiotracer uptake in regions corresponding to subpleural GGOs in two patients who underwent PET/CT for evaluation of prostate cancer [59]. Understanding the exact mechanisms that lead to uptake of these radiotracers in acute infective/inflammatory pulmonary lesions offers an important research prospect.

There is ongoing research directed at identifying targets for molecular imaging of inflammation with several novel radiotracers being described in pre-clinical and early clinical studies such as ^{18}F-AzaFol, ^{89}Zr-labebed Feraheme and ^{18}F-GE180 [92–94].

Further potential targets for new radiotracers include chemokine receptor CXCR4, interleukin IL-6, and fibroblast activation protein inhibitors, inhibitors of the type 1 angiotensin-II receptor ATR1 and ACE2. A radiolabeled ACE2-receptor antagonist has already been developed for autoradiography analysis, setting in motion the potential for a PET radiotracer to be developed [95,96]. Since SARS-CoV-2 spike proteins bind to the ACE2 receptors, novel targeted radiotracers can have potential utility in the drug development process.

LIMITATIONS TO MOLECULAR IMAGING

Widespread utilization of molecular imaging in suspected or confirmed cases of COVID-19 is primarily limited by relatively longer imaging times (in comparison to anatomical imaging with CXR, CT or USG) and the need for adopting infection control protocols. Further, there is a need for simultaneously ensuring optimal utilization of resources, such as finite amounts of radiotracer, which has economic ramifications. Nuclear medicine departments across the globe have to bear in mind these feasibility issues and ensure undisrupted services to patients with non-COVID-19 related indications, in particular oncological cases in which PET is mandated for crucial treatment decisions [97-99].

To summarize, the present review comprehensively highlights the tremendous potential utility of molecular imaging in evaluation of COVID-19 sequelae such as pulmonary thromboembolism, vasculitis, multi-systemic inflammation, cardiovascular and neurological sequelae. Despite the fact that majority of the published literature is retrospective in nature with limited sample sizes, it is clear that molecular imaging provides additional valuable information (complimentary to anatomical imaging) with semi-quantitative or quantitative parameters to define inflammatory burden and can be used to guide therapeutic strategies and assess response. The authors believe that clinical translation and appropriate utilization of molecular imaging and associated imaging biomarkers can greatly benefit both the diagnosis and management of COVID-19 sequelae.

CONCLUSION

The potential of molecular imaging and nuclear medicine, as a whole, in contributing to this pandemic largely remains underutilized. Identifying appropriate indications, establishing standardized protocols and developing structured clinical trials employing novel radiotracers will help in realizing that potential [100].

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