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Medical imaging technologies applied to the COVID-19 context

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ABSTRACT

Since the outbreak of COVID-19 disease, imaging methods such as X-Ray and Computed Tomography have stood out as feasible tools for diagnosing and evaluating the disease, especially regarding its lung occurrence in symptomatic patients. However, in the course of the pandemic, COVID-19 showed its effects in other tissues such as heart, brain and veins, triggering inflammatory processes. Thus, other imaging methods such as Positron Emission Tomography-Computer Tomography (PET-CT) and Magnetic Resonance have shown to be good sources of information about the location and intensity of the inflammation. This article reviews some of these imaging methods, its findings, feasibilities, advantages and limitations for COVID-19 diagnostic and evaluating.

Keywords: **COVID-19, diagnostic imaging, radiology.**

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1. INTRODUCTION

On December 31, 2019, the first case report of an acute respiratory syndrome of unknown etiology was identified in the city of Wuhan, Hubei province. From then on, authorities identified a new coronavirus (SARS-CoV-2) that causes the clinical disease COVID-19. Since then, the virus has spread globally, being characterized as a pandemic by the World Health Organization (WHO) in March 2020 [1]. This is a single-stranded RNA virus, and due to its membrane protein, has affinity to cells like pneumocytes, small intestine enterocytes, kidney proximal tubules cells, the endothelial cells of arteries and veins, and the arterial smooth muscle, among other tissues [2]. Therefore, this infection may affect pulmonary, hematologic, cardiovascular, renal, gastrointestinal and hepatobiliary, endocrinologic, neurologic, ophthalmologic, and dermatologic systems [3]. It exhibits a wide spectrum of clinical manifestations, ranging from asymptomatic infections, to mild (fever and cough), moderate, and finally severe infections, requiring hospitalization and oxygen support [4]. The gold standard for the diagnosis of COVID-19 is based on the reverse transcription polymerase chain reaction (RT-PCR). This molecular test aims to detect the RNA of the virus in respiratory samples such as nasopharyngeal swabs or bronchial aspirate [5].

According to the Brazilian College of Radiology and Diagnostic Imaging (CBR) the definition of the diagnosis of COVID-19 will be confirmed by clinical-epidemiological information added to RT-PCR and/or serology tests. Additionally, imaging diagnostic methods will be properly used as a diagnostic complement [6]. The main modalities used for different clinical indications related to COVID-19 are Medical General X-Ray (XR); Computed Tomography (CT); Ultrasound (US); Magnetic Resonance Imaging (MRI); and Nuclear Medicine (NM). Table 1 presents a summary of these technological imaging modalities.

The aim of this work was to present the diagnostic imaging technologies available to be used in COVID-19 scenario, their applications and contributions. A research was carried out on the PubMed® platform, using the terms “x-ray”, “ct”, “ultrasound”, “mri”, “petct”, each one along with “covid19”. PubMed® platform was chosen because it is a free search engine covering database of references and abstracts on life sciences and biomedical topics. The research resulted in almost twenty thousand articles. The intention of this work was to not exhaust the topic by presenting a systematic review. In this sense, a brief, unpretentious review is presented here. The selection of the papers considered their availability in our database and their relevance order.

Table I: Imaging Systems features used in Radiology for the COVID-19 diagnostic.

Modality		Technology	Radiation Type
i	Medical General X-Ray	X-Ray Tube Stationary	Atomic Ionizing Radiation
ii	Computed Tomography	X-Ray Tube Giratory	Atomic Ionizing Radiation
iii	Ultrasound	Transducer	Mechanical Wave
iv	Magnetic Resonance	Magnet and Radiofrequency Coils	Radiofrequency and Magnetic Field
v	Nuclear Medicine	Camera-Gamma	Nuclear Ionizing Radiation

2. RADIOGRAPHY

Radiography generates 2D anatomical images from X-Ray and has some advantages over other imaging methods, such as lower cost, accessibility, less radiation exposure, greater mobility (enabling bedside studies), in addition to being convenient to disinfect its surfaces after the exam [7].

This technique is, in most cases, the first imaging exam to be performed in patients with symptoms of COVID-19. Among the main findings for the disease on chest radiography are: reticular pattern, ground-glass opacities (GGO) and consolidations, with a rounded morphology and a confluent or irregular multifocal distribution, which is usually affected bilateral and peripheral, predominantly in the inferior fields. Based on these standards, the technique demonstrated lower sensitivity than the initial RT-PCR testing (69% vs 70%–91%, respectively). There are some reasons for a normal chest radiograph in COVID-19–positive patients, including early acquisition in the disease course, lack of lung involvement at the time of presentation, and subtlety of findings on a chest radiograph [8].

False-positive findings may be related to lack of inspiration, breast prominence and poor positioning of the patient, which can condition that the scapulae and soft tissues protrude over the lung fields, increasing the density of the periphery of the lung and simulating GGO [9]. Although not indicated for COVID-19 diagnosis (due to its non-specific findings) [10], appearance on chest X-Ray, together with clinical findings such as symptoms and oxygen saturation, may help in the assessment of disease severity and guiding management [11]. Nava-Munoz et al. investigated the relationship between initial chest X-rays and laboratory findings and concluded that the Common X-Ray is a valid technique for the initial evaluation of patients with COVID-19, Its findings should be taken into account along with the laboratory and clinical data when In evaluating the clinical course of these patients, higher severity scores for X-ray images were associated with a higher incidence of hospitalization and more abnormal laboratory values [12].

3. COMPUTED TOMOGRAPHY

Computed tomography (CT) scans generate anatomical and morphological 3D images using X-Ray. The images are acquired in the axial plane and can be reconstructed in the other planes or 3D volume using computational tools. CT scanner uses a motorized X-Ray source that rotates around the circular opening structure called a gantry. The CT 3D images allow studying soft tissues, muscle damage and the internal body organs. addition to identifying bone fractures, pneumonias, and other structural changes of different densities as well as in the 2D images from the Medical X-Ray. Radiation exposure levels are an important consideration for deciding between CT scan and an X-Ray.

CT is considered the most sensitive imaging method for the detection of COVID-19, with a sensitivity that reached 98% in a clinical study [13]. However, its sensitivity may be limited when performed early after symptom onset, as the frequency of CT findings is related to infection time course. Thereby, CT is not a reliable standalone tool to rule out COVID-19 infection [14]. Among the typical findings for COVID-19 on CT images, we can mention peripheral, bilateral, GGO with or without consolidation or visible intralobular lines ("crazy-paving"); Multifocal GGO of rounded morphology with or without consolidation or visible intralobular lines; Reverse halo sign or other findings of organizing pneumonia (seen later in the disease). It is noteworthy that such features are not uniquely related to COVID-19 pneumonia and may be similar to other processes such as influenza pneumonia and organizing pneumonia. Moreover, with the evolution of the disease, patients with COVID-19 may have coexisting infections, such as secondary bacterial pneumonia, which may mimic atypical findings of COVID-19, such as lobar consolidation [15, 16].

CT images can also help patient management, such as deciding on the need for intubation, since ventilatory support is more likely to be required in those patients with extensive signs of organizing pneumonia (parenchymal bands, bronchiectasis, and peribronchovascular consolidations) [17].

COVID-19 can also predispose patients to thrombotic diseases, both arterial and venous, due to excessive inflammation, platelet activation, endothelial dysfunction, and stasis [18]. In a systematic review study, Suh et al. demonstrated an incidence rate of 16.5% of pulmonary embolism and 14.8% of deep vein thrombosis in patients with COVID-19. In a later stage of the disease, CT pulmonary angiography can easily detect pulmonary arterial thrombus and pulmonary embolism (PE). However, it is not advisable to request this test only when there is clinical suspicion (which can underestimate the pulmonary embolism incidence), but based on the screening of D-dimer levels: a laboratory test based on the search for fibrin degradation product, witch elevated levels indicates increased risk of abnormal blood clotting. For patients with COVID-19, the cutoffs of D-dimer levels are the same as the conventional ones for PE (1000 μg/L) [19, 20 , 21].

4. ULTRASOUND

Ultrasound (US) imaging uses high-frequency mechanic waves transmitted by transducers to view inside the body. US images can also show movement of the body's internal organs as well as blood flowing through the blood vessels. There is no ionizing radiation exposure associated with this imaging technology.

Before the emergence of the COVID-19 pandemic, lung ultrasound had already been used for onsite exploration of acute respiratory failure, especially in critical patients [22], and in context of pulmonary trauma [23]. In addition to being an alternative to radiation-dependent methods for diagnosing pulmonary diseases in neonates, such as atelectasis, pneumonia, bronchopulmonary dysplasia, pleural effusion, pneumothorax, respiratory distress syndrome and meconium aspiration syndrome [24].

In the context of the COVID-19 pandemic, the use of ultrasound (US) proved to be useful for the diagnosis and assessment of complications resulting from the disease, such as pneumonia and thromboembolism. Its use was encouraged to evaluate patients with COVID-19 due to its intrinsic characteristics such as low cost, radiation free, practical method, with easy to sanitize equipment, and its possibility of being used in a bedside evaluation [25].

In a study comparing US and CT for the assessment of the severity of pneumonia caused by SARS-CoV-2, Zieleskiewicz *et al.* demonstrated a high association between the findings of the two modalities, indicating the feasibility of chest US replacing chest CT in the initial assessments of pulmonary involvement for most symptomatic patients with the diagnosis confirmed for SARS-CoV-2 [26]. In a similar study, Tung-Chen *et al*. showed great statistical agreement when comparing US and CT on detecting COVID-19 abnormal lung findings: all abnormal CT findings were detected in lung US, demonstrating that, for this purpose, this technique presents a low proportion of false-negative rates, which in this pandemic key to avoiding additional infections [27].

For the evaluation of thromboembolic complications of COVID-19, US is advantageous over CT angiography as it does not require the administration of intravenous contrast, an important factor, considering that some COVID-19 patients have acute kidney injury, predisposing to the occurrence of nephropathies associated with the use of contrast [28]. Another point where US stands out over radiation-dependent imaging methods is its application to pregnant women and children, being a useful technique for diagnosing and monitoring COVID-19 pneumonia while avoiding unnecessary radiation exposure for these groups sensitive to it [29, 30].

US can also be useful to assess the evolution of the disease and in decision-making in the management of the patient: The technique demonstrated an excellent prediction for oxygen therapy, being useful to motivate its increase or prevent its inappropriate early reduction [31]. The pulmonary involvement scores evaluated by US also proved to be useful to estimate the prognosis of patients with COVID-19, since patients with high US scores tend to have greater complications, such as cardiac injury, coagulopathy and inflammation, respiratory failure, acute respiratory distress syndrome, sepsis, in addition to a greater need for mechanical ventilation and higher mortality [32]. Assuming the presence of professionals proficient in US in emergency services, the use of US, associated with the clinical assessment of the patient, can be useful and readily available for making decisions to screen suspected cases, which can result in a lower risk of spread of SARS-Cov-2 in crowded emergencies [33]. However, like other imaging methods, US has limitations in detecting changes in the early stages of the disease (before pulmonary involvement), therefore, for the diagnosis of COVID-19, it should be a complementary method to RT-PCR and laboratory tests [27]. Its use is also limited due to its operator-dependent nature, in addition to patient-related factors (such as cases of obesity and immobility) [33].

5. MAGNETIC RESONANCE IMAGING

Magnetic Resonance Imaging (MRI) scanners use strong magnetic field, gradients, and radiofrequency waves to generate images of the anatomy and the physiological processes of the organs in the body. This modality is particularly well suited to image the soft tissues of the body. MRI does not use ionizing radiation but employs a strong magnetic field that requires specific care when entering metal materials into the examination room.

Despite being a little-used technique in the diagnosis of COVID-19 due to its high cost and long scanning time, magnetic resonance (MRI) can demonstrate involvement in soft tissues, such as lungs, heart and brain. In the lungs, the findings on MRI are similar to those shown by CT, such as GGOs, consolidation, interlobular septal thickening and fibrosis, with a substantial agreement between the two techniques having been demonstrated, except for the findings of GGOs [34].

Due to the inflammatory nature of COVID-19 infection, residual myocarditis can often occur in disease survivors, predisposing cardiovascular complications, particularly heart failure. Thus, cardiac MRI mapping allows for distinguishing healthy and sick myocardium, monitoring the healing process, as well as guiding the treatment, and it can be considered a first-line test to assess post-COVID myocardial injuries [35].

It is known that SARS-Cov-2 can enter the nervous system through the olfactory nerve and through the blood circulation, resulting in neurological disorders [36]. In the brain, the main MRI finding in patients with COVID-19 is acute and subacute infarcts. Other common findings included a constellation of leukoencephalopathy and microhemorrhages, leptomeningeal contrast enhancement, and cortical abnormality in the FLAIR signal (Fluid-Attenuated Inversion Recovery sequence) [37]. The identification of hypersignal in the olfactory bulb in MRI images may help to suggest or support the etiologic diagnosis of COVID-19 during and after this new pandemic [38].

As it is an ionizing radiation-free technique, MRI can play an important role in the diagnosis and follow-up of cases of pneumonia caused by COVID-19, as an alternative to CT, especially for pregnant patients and children.

6. POSITRON EMISSION TOMOGRAPHY / COMPUTED TOMOGRAPHY

Nuclear medicine (NM) imaging produces images detecting gamma radiation from different parts of the body after a radioactive tracer is administered to the patient. The images are digitally reconstructed and generated on a computer. The detectors or gamma cameras generate static and/or dynamic images applied to biochemical, metabolic, and functional study of organs and tissues of body.

The application of positron emission tomography/computed tomography (PET/CT) for COVID-19 is based on the high uptake of ^{18}F-labelled fluorodeoxyglucose (^{18}F-FDG) during the inflammatory phase of SARS-Cov-2 infection: after viral infection, a cascade of reactions recruits cells such as neutrophils, monocytes and T cells through the local release of chemokines. Once activated, these inflammatory cells overexpress glucose receptors to supply their increased metabolism [39]. Therefore, in the context of PET/CT examination, glucose uptake in the form of ^{18}F-FDG proportionally reflects the metabolic rate of these cells at their sites of activation. In this way, PET/CT allows the study of the inflammatory process, through the quantification of radioactivity emitted at ^{18}F-FDG concentration points through the lungs, in the air spaces and interstitium, allowing the study of the behavior of inflammatory cells in its micro -native environment [40]. This technology may thus be useful to detect or rule out the presence of Covid-19 infections [41], particularly in the early stages of the disease in patients with non-specific clinical symptoms or before the onset of symptoms and in the presence of a false-negative finding. [42].

It may also play a role in monitoring disease progression, estimating the involvement of other organs and evaluating the effectiveness of treatment [43, 44]. Due to this ability to indicate local changes in the inflammatory patterns of the disease, PET/CT may be able to detect COVID-19 in still asymptomatic patients: In retrospective review studies of cancer patients undergoing elective PET/CT examinations, it was possible the incidental detection of COVID-19 pneumonia patterns before the onset of disease symptoms, suggesting that this imaging modality is sensitive to demonstrate the presence of SARS-CoV-2 pneumonia in cancer patients, even those asymptomatic. [45, 46, 47]. The intense and diffuse uptake of FDG by the lower lobes of the lungs during the PET/CT examination demonstrates a tropism of the inflammatory process of the disease in these regions [48, 49, 45]. Similarly, uptakes were observed in paratracheal, right hilar, mediastinal and subclavicular lymph nodes, as well as in bone marrow [49, 48, 50]. Vascular regions also demonstrated high ^{18}F-FDG uptake in a study with patients who had persistent symptoms of the disease (greater than 30 days), in which the thoracic aorta, right iliac artery and femoral arteries were the main sites of uptake, suggesting that vascular inflammation caused by SARS-Cov-2 may be responsible for the persistence of symptoms [51].

Given its ability to identify changes in radiopharmaceutical uptake patterns, PET/CT can play an important role in identifying the location and intensity of inflammatory processes associated with COVID-19 at different stages of the disease. However, it is a complex and costly test, and further research are needed to justify its use for the diagnosis and monitoring of the disease.

7. CONCLUSION

Different imaging modalities can play an important role in complementing the diagnosis of COVID-19 or monitoring the evolution of the disease. Radiography (especially portable) and Lung Ultrasound have advantages concerning their portability and can be used bedside to monitor the disease's evolution, as well as guide its management. To aid in the diagnosis of COVID-19 itself, CT is the most sensitive method for this purpose, however, its findings should be interpreted together with laboratory findings, such as RT-PCR, and careful clinical analysis; it is also an efficient technique to follow the evolution of the disease. PET-CT and MRI, on the other hand, despite being able to demonstrate valid findings for the diagnosis of COVID-19, their uses are not viable for this purpose given their long scanning times and high cost, however, they can be useful for the study of difficult-to-diagnose extrapulmonary affections. Furthermore, it is necessary to carry out more studies, with a large-size sample, to validate the different imaging techniques in the diagnosis and follow-up of COVID-19.

8. ACKNOWLEDGMENT

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