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Imaging related to underlying immunological and pathological processes in COVID-19

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Abstract

The introduction of coronavirus disease-2019 (COVID-19) as a global pandemic has contributed to overall morbidity and mortality. With a focus on understanding the immunology and pathophysiology of the disease, these features can be linked with the respective findings of imaging studies. Thus, the constellation between clinical presentation, histological, laboratory, immunological, and imaging results is crucial for the proper management of patients. The purpose of this article is to examine the role of imaging during the particular stages of ²⁸severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection - asymptomatic stage, typical and atypical COVID-19 pneumonia, acute respiratory distress syndrome, multiorgan failure, and thrombosis. The use of imaging methods to assess the severity and duration of changes is crucial in patients with COVID-19. Radiography and computed tomography are among the methods that allow accurate characterization of changes.

INTRODUCTION

SARS-CoV-2, the etiologic agent of COVID-19, caused a global pandemic dominated by acute respiratory failure mortality. COVID-19 manifestations are heterogeneous and overlapping. Therefore many challenges in the diagnostics and management of COVID-19 are still present^[1]. In addition, typical symptoms without positive proof of infection

(PCR/antigen tests) make the diagnosis inconclusive. However, a variety of imaging methods and techniques can be used for this purpose. Furthermore, imaging is also essential for classifying and managing patients during the infection.

Typically, imaging studies are carried out to determine the disease stage and estimate the organ involvement and severity. However, the features, such as ground-glass opacities (GGO), consolidations, interstitial fluid shifts, *etc.*, seen on imaging are not unique to COVID-19. Therefore, a combination of the clinical picture and laboratory assessment is necessary to fully evaluate the patient's state^[2].

In the era of COVID-19, radiology plays a crucial role in the disease work-up and follow-up. Initially considered a purely pulmonary process, COVID-19 turned out to be a multisystemic disease that requires a comprehensive imaging approach, involving all techniques and studying all anatomical areas. As the primary manifestation of COVID-19 is a pneumonia-like respiratory process, the radiology modalities most involved in its diagnosis and follow-up are chest imaging, mainly chest X-ray (CXR) and chest computed tomography (CT). Diagnostic imaging capabilities show that CT is more sensitive than the gold standard RT-PCR for diagnosing COVID-19^[2,3]. At the same time, it is cheaper and can be performed faster. The CT examination can give a quick, accurate diagnosis of patients, as the PCR test requires hours, even days, to complete as the number of COVID-19 infection cases grow. However, this comes with a large radiation dose, where the capacity is still lacking in many countries^[4]. CXR is ubiquitous worldwide, with a 30–70-fold lower amount of radiation. Despite its low sensitivity and specificity, it is commonly performed as an initial investigation in COVID-19^[4,5]. It is the modality of choice in the intensive care unit to detect disease progression and assess the position of the individual resuscitation means.

The imaging findings both on CXR and CT can be invaluable, especially for an atypical or organizing pneumonia with bilateral, multifocal randomly scattered GGO, in subpleural, mainly peripheral distribution with thickened pulmonary interstitium giving a reticular pattern, broncho-vascular prominence, and consolidation with increasing severity in the more seriously ill patients^[6]. High-resolution CT (HRCT) with

its modern available software techniques is the method of choice for an initial examination, staging, and follow-up of patients with suspected COVID infection. CT has higher sensitivity and specificity than radiography. On CT, the main changes are GGO, which tend to be more in the periphery, crazy paving changes are seen in later stages of the disease, thickening of the interstitium is also seen as well as dilation of the terminal lung vessels^[7]. For staging of the changes seen on CT, we use the COVID-19 Reporting and Data System (CO-RADS) classification. It is a standardized classification proposed by the Dutch Radiological Society. It has 6 levels of suspicion from CO-RADS 1 to CO-RADS 6. In CO-RADS 1 patients, the exam is normal or has non-infectious changes. CO-RADS 2 patients have low levels of suspicion, and the visualized changes are consistent with infections other than COVID. CO-RADS 3 patients are those in which the changes are unclear, and there is an indeterminate level of suspicion. CO-RADS 4 and 5 staged patients have high and very high levels of suspicion for COVID-19 infection, respectively. CO-RADS 6 patients are those who have typical changes and are PCR positive^[8].

Chest ultrasound (US) plays a role in emergency settings as a COVID-19 screening technique. However, it is often of limited use as a highly operator-dependent method for lung disease. In addition, point of care echocardiography might have utility in hemodynamically unstable patients.

As stated above, various ⁴extrapulmonary manifestations have been reported, including in the gastrointestinal tract, brain, heart, kidneys, or muscles. The identification of most of these pathologies needs imaging, including abdominal CT, US, and magnetic resonance imaging (MRI). Imaging helps detect, diagnose, and assess the virus-induced injury and associated complications of the organs and systems affected by COVID-19. In suspected pulmonary thromboembolism (PTE) cases, CT pulmonary angiography (CTPA) may help correct the diagnosis. ¹PTE is frequently observed in patients with more severe COVID-19 pneumonia involving mainly the segmental (90.2%) and subsegmental arteries (61.0%) of pulmonary segments affected by a consolidation pattern (67.6%)^[9].

Furthermore, CXR, chest CT, and echocardiography can readily evaluate the signs of cardiac failure. However, myocardial injury can be best assessed using cardiac MRI. Potential neurovascular complications such as stroke, hemorrhage, or venous sinus thrombosis can be identified by non-enhanced head CT, and in the setting of a suspected infarct, a non-enhanced MRI of the brain can be performed for definitive assessment^[10].

The disease may present as a multisystem hyperinflammatory syndrome in pediatric patients, currently termed pediatric multisystem inflammatory syndrome (PMIS). In children with PMIS, a broad spectrum of abdominal abnormalities can be detected by both abdominal US and CT, with periportal and pericholecystic edema, gallbladder wall, and bowel wall thickening and dilatation, splenic infarcts, hepatosplenomegaly, right lower quadrant mesenteric lymphadenopathy, and free fluid in the pelvis being among the most commonly encountered abnormalities^[10,11].

The COVID-19 pandemic has facilitated research on the implementation of artificial intelligence (AI), machine learning, and its subfield deep learning into imaging, which can be used as an essential adjunct or alternative to the diagnosis and follow-up assessment of progression and therapeutic development of the disease^[12]. Deep learning is the most successful machine learning technique, which provides helpful analysis to study a large number of chest images that can critically impact the screening of COVID-19. AI algorithms have been developed to help with the early detection of COVID-19 both on CXR and CT. A deep learning model was also trained to discriminate between COVID and non-COVID pneumonia^[13]. In line with this, CT pneumonia analysis (developed by Siemens Healthineers and partners) is another algorithm designed to automatically identify and quantify abnormal patterns in the lungs, enabling simple-to-use analysis of non-contrast chest CT scans for research purposes. The results could be used to analyze the severity and progression of abnormalities in patients exhibiting COVID-19 symptoms.

ASYMPTOMATIC DISEASE

A person infected with SARS-CoV-2 who has not developed any signs or symptoms of COVID-19 is defined as an asymptomatic case. Immunological features, including any of the innate immunity pathways (*i.e.*, natural killer (NK) cells, interferon, and other cytokine production), play a role at the onset of infection^[14]. Stage I, or the asymptomatic incubation with or without detectable virus, is the period when treatment for improving immunity is given, such as the use of antiserums (ready-made antibodies from survivors), and is undoubtedly crucial^[14]. However, due to the initial pathological changes in the target organs, sometimes imaging studies are the only way of detecting problems.

In asymptomatic individuals, this stage begins with inhalation of the SARS-CoV-2 virus replicating in the epithelial cells of the nasal cavity. It is well-known that the virus primarily uses the receptors for ACE2^[15]; thus the first affected cells are ciliated cells. Therefore, PCR for SARS-CoV-2 RNA in nasal swabs can diagnose the virus at this point. The virus is then distributed in the lungs, digestive tract, reproductive system, *etc.*, while innate immune tolerance is minimal^[15].

It has been shown that asymptomatic persons can be infectious and secrete SARS-CoV-2, promoting the dissemination of COVID-19 – a significant concern from an epidemiological point of view. Moreover, while asymptomatic, some patients present with substantial lung changes, for example, when they seek medical attention. This observation requires a stringent search and examination of the interactions of proven infected persons with COVID-19 to diagnose asymptomatic infections^[14].

According to the literature and personal experience of our team, the incidence of asymptomatic occurring COVID-19 infection is much higher, about four times more common than symptomatic moderate to severe ongoing cases^[16]. The described histological changes in the respiratory system in an asymptomatic case of COVID-19 infection based on autopsy and biopsy are exceptional^[17]. The only way to examine histological changes, mainly of the lung, in asymptomatic infection in the early stages of the disease is to take a biopsy for other pathological processes. “accidental” sampling of COVID-19, most often in the case of neoplastic diseases in which surgeries were

performed for lung tumors at a time when superimposed infections were not recognized^[16-20].

The main morphological changes found in routine histopathological examinations in the lungs are edema, proteinaceous exudate, focal reactive hyperplasia of pneumocytes, some with viral inclusions, and polymorphonuclear inflammatory infiltration composed mainly of lymphocytes and multinucleated giant cells. Hyaline membranes are scattered or not apparent in the early (asymptomatic) stage of COVID-19 infection, unlike in acute respiratory distress syndrome (ARDS). In addition, histologically, protein and fibrin exudates can be found in the lung parenchyma, as well as diffuse thickening of the alveolar walls, consisting of proliferating interstitial fibroblasts and type II pneumocystic hyperplasia, with random cell atypia and multinucleated giant cells, indicating varying degrees of the proliferative phase of diffuse alveolar damage. In some areas, an abundance of alveolar macrophages can be found together with type II pneumocystic hyperplasia^[17,18,21].

Most patients with COVID-19 infection are diagnosed with pneumonia. The patients who have no symptoms could be transmitters. However, some asymptomatic patients progress quickly, even to ARDS. In asymptomatic patients, radiography has lower sensitivity and specificity than CT. In patients with slight changes, X-ray imaging can appear normal. This is why CT is the preferred method for diagnosis. Based on the published data, to date, almost all patients with COVID-19 have characteristic changes on CT^[8,22].

The X-ray of a 60-year-old female patient is presented in Figure 1. The patient had no symptoms, but a positive PCR test was performed because her husband had COVID pneumonia. Her X-ray showed no abnormalities. This is a typical case of an asymptomatic patient with negative radiography.

We also present the CT scan of a 45-year-old male, shown in Figure 2. He had no symptoms but a positive PCR test because he had been in contact with a verified

COVID-19 patient. Both lungs showed no abnormalities, no infiltrates, no GGO, and no pleural effusions.

³¹ Atypical clinical findings in pregnant women with COVID-19 may increase the difficulty in establishing the diagnosis. Recently, data have demonstrated that pregnant women are more vulnerable to severe COVID-19, the development of complications, and death. CT is the favored approach for detecting pulmonary involvement early, especially in asymptomatic cases^[22]. In asymptomatic children or those with atypical presentation of COVID-19, CT may be beneficial, especially in sparing time while waiting for PCR results or false-negative results.

In the case of pregnant women or children, it is always preferred to perform CT instead of waiting because any delay in confirming the diagnosis and management of the disease can be fatal and can contribute to the spread of the virus. Furthermore, the CT results in asymptomatic COVID-19 are usually distinct from the normal appearance, where the most common findings are GGO and consolidations in the lungs^[22].

MILD TO MODERATE CASES – TYPICAL COVID-19 PNEUMONIA

¹⁸ The onset of pneumonia in COVID-19 includes extreme antigen presentation, followed by enhanced production of C-reactive protein (CRP), D-dimer, and liver aminotransferases, accompanied by infiltrates in the lungs, representing involvement of antigen-presenting cells, T-helper cells, B cells, and NK cells^[14].

The virus spreads across the airways in the respiratory tract and further to the gastrointestinal tract. It activates robust innate immune reactions. Nasal secretion, sputum or swabs contain SARS-CoV-2 but also early immune response molecules. Cytokine production during this stage may predict the clinical presentation and the subsequent disease course^[23]. Significant amounts of interferon type I can confine the infection within the lungs, which is valid for approximately 80% of affected patients. Most of those with typical COVID-19 pneumonia on conservative symptomatic

treatment can stay at home. However, about 20% of infected patients will progress to the next severe stage of the disease. Around 2% will develop life-threatening illnesses^[23].

However, we have to keep in mind that COVID-19 pneumonia is a heterogeneous disease. It may include tracheobronchitis, vascular injury, and capillary microthrombi, along with inflammation^[23]. Active injury leads to chronic and permanent lung trauma. The late effects of SARS-CoV-2 on the lungs have not been elucidated, but fibrosis development is suggestive.

Histologically, a hallmark of typical viral pneumonia is the interstitial nature of the inflammatory reaction. In addition, the most common morphologic changes in the lungs correlate with ARDS, which is described in the next section (Severe cases of COVID-19). On the other hand, no apparent morphological changes were observed in cardiac tissue due to the direct action of the coronavirus^[17]. However, other findings established on necropsy material taken at autopsy are hypertrophy of cardiomyocytes with microscopic evidence of acute ischemia due to hypertensive heart disease and coronary artery atherosclerosis, but no other substantial damage^[5].

Interestingly, we documented a case of sinus cavernosus thrombosis in a 49-year-old man hospitalized with COVID 19 pneumonia. One week after hospitalization, he lost vision in his right eye, and presented with exophthalmos and swelling of the soft tissues around the eye. CT with contrast enhancement was performed immediately after the onset of symptoms. Thrombosis of the right sinus cavernosus is presented in Figure 3A and B.

COVID-19 pneumonia is classified as atypical pneumonia because it overlaps with the radiographic findings seen in interstitial pneumonia, including other coronavirus infections (SARS, MERS)^[24,25]. Therefore, imaging methods are the first choice for diagnosing COVID-19 pneumonia including CXR and chest CT, with CT being a more sensitive and specific method than CXR, especially in the early stages of the disease^[5].

Imaging findings on conventional radiography range from normal findings to diffuse changes in the lung parenchyma. Patients with multiple comorbidities are more likely to have bilateral and diffuse lesions. Findings considered as highly specific for COVID-19 pneumonia on CRX are GGO (Figure 4) and areas of non-segmental consolidation of parenchyma (Figure 5) with peripheral and caudal distribution^[26]. These findings are most pronounced 10–12 days after the onset of symptoms^[27]. Additional findings are confluent ill-defined patchy opacities (Figure 6), an interstitial lung pattern, decreased lung attenuation, inhomogeneous and linear parenchymal opacities (Figure 7), and often different features are combined.

On the one hand, for intensive care unit patients, CRX plays a crucial role in detecting disease progression and assessing the position of the individual resuscitation means - endotracheal tubes, drains, and venous sources as it is performed at the patient's bedside with a mobile X-ray machine^[26].

On the other hand, CT is a vital component in the diagnosis of suspected COVID-19 infection. CT features vary with the patient's age, immunity status, disease stage, underlying diseases, and drug interventions at the time of scanning^[28]. CT findings considered "typical" for COVID-19 pneumonia include GGO, parenchymal consolidations, and crazy-paving pattern (Figure 8)^[29]. The changes are usually multifocal, bilateral with a peripheral subpleural distribution predominantly in the posterior segments of the inferior lobes^[30,31].

A GGO is the most frequent and earliest finding defined as increased attenuation on CT, which does not obscure the bronchovascular structures. It can be observed in three typical patterns: rounded, linear and crazy paving^[30] (Figure 9). In the area of GGO, widening of vessels and traction bronchiectasis are commonly seen^[32,33]. GGO with reticular interstitial thickening, known as crazy-paving, is defined as thickening of the pulmonary interstitium with thickened interlobular septae and visualization of

intralobular pulmonary septae^[34]. Crazy paving may be seen with areas of GGO or consolidation in the subacute to chronic phase of the disease^[35] (Figure 10).

By definition, consolidation is a homogenous increase in the lung parenchyma's attenuation with obscuration of the underlying vessels (Figure 11) and bronchi^[34]. Therefore, it is considered a sign of disease progression, especially in the intermediate and late stages of the disease^[30,34].

The distribution of lung abnormalities was recorded as predominantly subpleural (involving mainly the peripheral one-third of the lung), random (without predilection for subpleural or central regions), or diffuse (continuous involvement without respect to lung segments)^[33] (Figure 8). Additional CT features of COVID-19 pneumonia include vascular dilation, bronchial wall thickening, and traction bronchiectasis within the areas of GGO, architectural distortion with reticular thickening and subpleural bands formation, halo sign, or reversed halo sign (Figure 12). Changes considered atypical for COVID-19 pneumonia include lobar or segmental consolidations, small nodules (centrilobular lung nodules and tree-in-bud opacities), pulmonary cavitation, lymphadenopathy, and the presence of pleural or pericardial effusions^[34].

CT findings also vary depending on the onset of clinical symptoms. Approximately four stages of COVID-19 on chest CT have been described: (a) Early stage (0–5 days after onset of symptoms) marked by either normal or predominantly GGO (Figure 13); (b) Progressive stage (5–8 days after onset of symptoms) marked by enhanced GGO and a crazy-paving look (Figure 14); (c) Peak stage (9–13 days after onset of symptoms) characterized by progressive consolidation (Figure 15); and (d) Late stage (≥ 14 days after the onset of symptoms) denoted by a gradual decrease in consolidation and GGO, although signs of fibrosis (including parenchymal bands, architectural distortion, and traction bronchiectasis) may occur^[31,36–39] (Figure 16). It should also be remembered that

the temporal development and degree of lung defects are heterogeneous among different individuals, depending on the disease severity^[31,36]. Similar findings can be observed in other viral types of pneumonia, pneumonia caused by Mycoplasma or Chlamydia, vasculitis, and connective tissue disease. Therefore, the clinical-laboratory correlation with the radiological finding is essential for the diagnosis of COVID-19 pneumonia.

CT scanning²¹ can be a useful tool in evaluating the individual disease burden^[40]. The quantitative severity can be assessed using a visual method²⁶ or software that determines the percentage of affected lung volumes using deep learning algorithms^[41,42]. Furthermore, the severity of lung involvement on CT correlates with the severity of the disease. It can be measured by scoring the percentages of each of the five lobes that are involved and can range from 0 (no involvement) to 25 (maximum involvement) when all five lobes show more than 75% involvement^[41] (Figure 17).

Lung ultrasound (LUS) is increasingly used as a complementary method in diagnosing COVID-19 pneumonia. It allows assessment of both the lung parenchyma and the pleural space²⁷ with the ability of bedside and real-time assessment of pulmonary function and changes. In addition, US can easily distinguish normally aerated from pathologically altered lung parenchyma. The most common findings observed in interstitial pneumonia are irregularly thickened pleura, B-lines, and subpleural consolidations of the parenchyma^[43,44].

B-lines are vertical hyperechoic artifacts arising from the pleura that resemble a comet tail (Figure 18) and move with the lung sliding. The increase in subpleural lung density (in the absence of consolidated tissue) may lead to the coalescence of many vertical artifacts in more extended echogenic patterns and a single homogeneous subpleural echogenic area can be seen. This phenomenon is known as “white lung”^[44] (Figure 19). In addition to B-lines, small, oval subpleural consolidations are visible in the parenchyma (Figure 20). With disease progression to ARDS, the number of B-lines and

parenchymal consolidations increases with the formation of sizeable gravitational consolidation^[44], and the characteristic lung sliding is no longer visible. In the recovery phase of the disease, the consolidations and B-lines gradually disappear. Instead, A-line artifacts found in normally aerated parenchyma reappear and lung sliding is improved.

SEVERE CASES OF COVID-19

ARDS/cytokine storm

In some cases, COVID-19 pneumonia proceeds to the typical complications such as ARDS and cytokine storm. ARDS remains the most frequent immunopathological complication in SARS-CoV-2, SARS-CoV, and MERS-CoV viruses. The cytokine storm is one of the critical pathways for ARDS^[45]. Both ARDS and cytokine storm represent an unregulated autoimmune inflammatory response arising from the release of significant quantities of pro-inflammatory cytokines (such as IFN γ , IFN α , IL-1 β , IL-6, IL-12, IL-18, IL-33, TNF- α , TGF β , etc.) and chemokines (C-C Motif Chemokine Ligand 2 (CCL2), CCL3, CCL5, C-X-C motif ligand 8 (CXCL8), CXCL9, CXCL10, etc.) from immune or viral-infected cells^[46]. Therefore, it is essential that these factors be detected and evaluated early. Thus, the appropriate therapy can be administered.

Histological examination of lung specimens in patients with severe infection is characterized by severe and extensive diffuse alveolar damage, fibromyxoid exudates, interstitial and intra-alveolar edema. However, in one of the cases described in the literature, the respiratory bronchial mucosa was intact, without evidence of squamous metaplasia. This is a significant difference compared with the pathology observed in the first epidemic of SARS^[48]. In such patients, it is often found denuded with necrosis of type I pneumocytes and the formation of hyaline membrane and the proliferation of type II pneumocytes, which indicate ARDS in the acute stage without evidence of interstitial organization^[17,21]. In addition, there is diffuse thickening of alveolar walls due to congestion, and patchy to mild mononuclear inflammatory infiltrate comprised of lymphocytes, macrophages, and some plasma cells. Perivascular lymphocyte aggregates have also been identified^[47]. No eosinophils or neutrophils were identified,

but if these are found, they usually suggest secondary bacterial infection^[21,47]. Occasionally, in proliferated alveolar epithelial cells, viral inclusions in intranuclear and/or intracytoplasmic and multinucleated syncytial cells with atypical enlarged pneumocytes can be seen characterized by large eosinophilic nuclei with prominent nucleoli and granular cytoplasm (probably representing a viral effect similar to that reported in the first SARS epidemic)^[17,47,489]. Common in ARDS, pulmonary thrombi and microangiopathy may be noted within a few small pulmonary artery branches and pleural adhesions^[21,47]. This thrombotic process may involve activation of megakaryocytes, probably those that are naturally found in the lung, with platelet aggregation and platelet formation, in addition to fibrin deposition. The formation of small vascular thrombi in the lungs is often accompanied by focal alveolar hemorrhage^[47,49].

With regard to imaging, COVID-19 related ARDS is diagnosed when a patient with confirmed COVID-19 infection meets the Berlin 2012 ARDS diagnostic criteria: acute hypoxemic respiratory failure; presentation within one week of worsening respiratory symptoms; bilateral airspace disease on CRX, CT, or US that is not fully explained by effusions, lung collapse, or nodules; and cardiac failure is not the primary cause of acute hypoxemic respiratory failure^[50,51]. The risk factors for patients with COVID-19 to develop ARDS in the course of the disease are older age, concomitant conditions – most often hypertension and diabetes, and specific clinical symptoms on initial presentation such as marked dyspnea and fever $\geq 39^{\circ}\text{C}$ ^[52]. However, clinical manifestations may be relatively mild regarding the severity of imaging findings in COVID-19^[53].

Imaging studies have an essential role in the initial evaluation of the pattern and extent of lung involvement and in the follow-up of hospitalized patients. Chest radiographic findings of ARDS are non-specific and resemble those of typical pulmonary edema or pulmonary hemorrhage with diffuse, patchy or homogeneous, bilateral, and coalescent opacities^[54] (Figure 21 and 22). Radiography in the first 24 h of deterioration may be unchanged^[55]. CT imaging features depend on the phase of the disease^[56]. In the early exudative stage (first week), CT scans usually display a non-homogeneous distribution

and ventrodorsal gradient of density. More dense consolidations are observed in dependent regions, extensive GGO, and comparatively regular or hyper-inflated parenchyma (in the case of mechanical ventilation) in non-dependent areas^[54] (Figure 23).

In the late fibrotic phase (over two weeks), CT appearance can be variable. Complete resolution may occur in some cases, but the coarse reticular pattern and ground-glass opacification in the anterior (non-dependent) part of the lungs are considered more typical CT features. Pulmonary cysts of varying sizes and bullae have also been reported, which probably developed due to prolonged ventilation^[56]. Subsequent imaging studies can show the development of pneumomediastinum, pneumothorax (often hypertensive in mechanically ventilated patients), and subcutaneous emphysema^[54] (Figure 24).

Multiorgan failure

The cytokine storm causes ARDS and multiorgan failure, leading to death in severe cases of coronavirus infections^[45]. Although COVID-19 is known to cause pulmonary disease, including pneumonia and ARDS, various extrapulmonary manifestations of COVID-19 have been reported, affecting the gastrointestinal tract, brain, heart, kidneys, or muscles. Therefore, imaging helps to estimate the presence of complications and the extend of COVID-19.

Histologically, there is no noticeable viral cytopathic effect on the heart in the case of moderate infection on light microscopy^[21,47]. However, liver biopsy specimens in patients with COVID-19 showed moderate fatty degeneration of hepatocytes and mild lobular and portal activity with slight interstitial mononuclear inflammatory infiltrates, indicating that the injury that could have been caused by either COVID-19 infection or drug-induced liver injury.

The pathogenesis of kidney injury due to COVID-19 is not well-described. However, it seems to be multifactorial, involving mechanisms related to systemic hypoxia,

coagulation disorders, inflammatory changes, or even cell destruction due to viruses. According to the literature, renal impairment was related to multiple organ failure^[57]. Furthermore, post-mortem examination of the kidney from a patient who died of COVID-19 infection demonstrated that viral antigens accumulated in the renal tubules, inducing acute kidney injury^[57].

Histological examination confirmed that a diffuse proximal tubular lesion, loss of brush border, non-isometric vacuolar degeneration, and a small area of necrosis were observed. In addition, interstitial inflammation and hemorrhage were found in some of the published cases, probably due to secondary bacterial infection^[58]. However, most of these findings are caused by comorbidities. The renal changes described above may be directly due to COVID-19 infection. These pathological observations may only provide a basis for further study and investigation of COVID-19^[58].

The main focus of COVID-19 is respiratory system complications, which are also a leading factor determining the severity of the disease course. More and more is known about the pathophysiology of the disease and the mechanism of lung damage. However, the extrapulmonary manifestations of the disease remain unclear, which in some cases is decisive for the disease course^[59]. Cardiovascular complications are receiving increasing attention, and according to various studies range from 30 to 78 %^[60-62]. Cardiovascular disease (CVD) is known to be one of the main risk factors for severe disease. A study of 44,672 patients with COVID-19 infection in China showed that a history of concomitant CVD was associated with nearly five-fold higher mortality (10.5% *vs* 2.3%) than patients without a history of CVD^[63]. In addition, increasing evidence suggests that the virus may directly affect the cardiovascular system and lead to complications such as myocarditis, acute coronary syndrome, arrhythmias, and venous thromboembolism^[64].

Cardiomagnetic resonance imaging (CMR) represents the gold standard in assessing the structure and function of the heart and provides information on the tissue characteristics of the myocardium. That, together with its non-invasive nature and lack

of ionizing radiation, makes it essential for both early diagnosis and monitoring of cardiac complications due to COVID-19.

The ⁶ pathogenesis of cardiac damage is currently unclear. However, presumed mechanisms include direct viral invasion, cytokine-mediated injury, a mismatch between needs and oxygen supply, and ischemic impairment resulting from microvascular thrombosis^[65,66].

The CMR findings in the acute phase of the disease reported so far are based on small groups of patients. The presence of myocardial edema is a characteristic feature observed in almost all reported cases^[67-70]. In a review of 31 publications with 51 patients, only one patient did not have edema at baseline, and two patients developed reversible edema within two weeks^[68].

The extent of edema varies - from diffuse to limited to separate segments of the myocardium - most often in the LV inferior wall regions, the mid inferoseptal regions, and the apical region^[68]. Another characteristic CMR sign is late gadolinium enhancement (LGE) of the myocardium due to necrosis/fibrosis following nonischemic myocardial injury localized at the sub-epicardial and/or intramural regions in the non-coronary territory. The presence and extent of zones of LGE correlate with the prognosis^[68]. An additional feature in the acute phase of the disease is diffuse hypokinesis of the left and/or right ventricle and, much less frequently, segmental hypokinesis^[68].

Similar CMR findings - edema, necrosis/fibrosis, and impaired systolic function are also found in patients following COVID-19 infection^[62,67,69-71]. Signs of persistent inflammation with prolonged T2 relaxation time due to edema, prolonged T1 relaxation time and LGE with a different distribution, and pericardial enhancement are seen. In some cases, reduced ejection fraction^[62] is found.

Coagulopathy and thrombotic accidents

The cytokine storm is one of the leading causes of disseminated intravascular coagulation (DIC) affecting the entire organism. Pro-inflammatory cytokines, such as TNFa and IL-1, are able to inhibit endogenous anticoagulation. Inflammation injures the

endothelium and results in activation of tissue plasminogen activator, which may explain the rise in D-dimer and fibrin degradation products^[72,73]. In summary, COVID-19 is associated with a hypercoagulable disease and an elevated risk of thromboembolic complications.

The histological findings in organs other than lungs do not indicate significant changes directly related to COVID-19. However, the most commonly observed histological changes were due to thrombotic microangiopathy involving the lungs, spleen, and kidney. The most common complications which have been described in the literature include acute limb ischemia, aortic and mesenteric thrombosis, myocardial and brain infarction, and DIC^[74].

A retrospective study on CT pulmonary angiography (CTPA) reported that pulmonary embolism in COVID-19 patients appears to be primarily distributed in the segmental arteries of the right lung^[76]. Furthermore, only the determination of D-dimer and IL-6 at admission to CT scan appears to differentiate patients with pulmonary embolism from patients with a negative CT pulmonary angiogram. However, inter-individual heterogeneity calls for the establishment of cut-off values in COVID-19 patients in future research^[75].

The pre-pandemic understanding of the predictive value of perfusion scintigraphy in assessing chronic thromboembolic disease and chronic thromboembolic pulmonary hypertension is well-established. Dhawan *et al* proposed perfusion imaging as a triage tool for post-COVID-19 recovery^[76]. They suggested the potential of perfusion imaging to examine the *in situ* thrombotic small vessel signature of COVID-19. It is widely accepted that *in situ* thrombotic microbial pulmonary hypertension is present. Thus, lung perfusion imaging provides a primary triage instrument within the broader panel of investigations to enhance understanding of the natural history of thromboembolic phenomena in COVID-19 and distinguish hemodynamic sequelae from deconditioning dysfunctional breathing-related functional limitations. The authors also suggest that such imaging should be incorporated in routine post-COVID-19 follow-up pathways^[76].

CONCLUSION

Early observed changes in critical organs such as lungs, kidneys, blood vessels, *etc.*, might benefit the timely and appropriate treatment of COVID-19 to alleviate the complications and avoid fatal outcomes. Along with typical clinical and imaging results, atypical results are also beneficial. Early detection of pathological changes at different stages of life-threatening COVID-19 can improve patient management, treatment, and outcome.

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18 Tsvetelina Veselinova Velikova, Stanislav Vasilev Kotsev, Daniel Stefanov Georgiev, Hristiana Momchilova Batselova. "Immunological aspects of COVID-19: What do we know?", *World Journal of Biological Chemistry*, 2020

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21 www.medrxiv.org

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22 Sufang Tian, Weidong Hu, Li Niu, Huan Liu, Haibo Xu, Shu-Yuan Xiao. "Pulmonary Pathology of Early-Phase 2019 Novel Coronavirus (COVID-19) Pneumonia in Two Patients With Lung Cancer", *Journal of Thoracic Oncology*, 2020

Crossref

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23 Bin Zhou, Shinsuke Kojima, Atsuhiko Kawamoto, Masanori Fukushima. "COVID - 19 pathogenesis, prognostic factors and treatment strategy: urgent recommendations", *Journal of Medical Virology*, 2020

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24 Xiaolong Qi, Chuan Liu, Zicheng Jiang, Ye Gu et al. "Multicenter analysis of clinical characteristics

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25 Aditya Borakati, Adrian Perera, James Johnson, Tara Sood. "Diagnostic accuracy of X-ray versus CT in COVID-19: a propensity-matched database study", BMJ Open, 2020

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26 Ghufran Aref Saeed, Waqar Gaba, Asad Shah, Abeer Ahmed Al Helali et al. "Correlation between Chest CT Severity Scores and the Clinical Parameters of Adult Patients with COVID-19 Pneumonia", Radiology Research and Practice, 2021

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27 Hasse Møller-Sørensen, Jakob Gjedsted, Vibeke Lind Jørgensen, Kristoffer Lindskov Hansen. "COVID-19 Assessment with Bedside Lung Ultrasound in a Population of Intensive Care Patients Treated with Mechanical Ventilation and ECMO", Diagnostics, 2020

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29 Sudhen B. Desai, Anuj Pareek, Matthew P. Lungren. "Deep learning and its role in COVID-19 medical imaging", Intelligence-Based Medicine, 2020

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