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Radiological and Biochemical Findings of COVID-19

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ABSTRACT

Coronavirus disease-2019 (COVID-19) is a new COVID-19 that causes various health and safety concerns and socioeconomic difficulties worldwide. Early and accurate diagnosis, isolation, and management are critical public health concerns. Real-time reverse transcription polymerase chain reaction (RT-PCR) of viral nucleic acids was the reference in diagnosing COVID-19. In addition to RT-PCR, serological tests based on antibodies tested against severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) have been used for diagnosis and epidemiological research. In cases where the reference tests are negative, radiological imaging guides the diagnosis. Chest radiography and thoracic computed tomography (CT) are the most commonly used radiological methods in imaging for COVID-19. Chest radiography and CT play a critical role in diagnosing, following, and staging pneumonia. However, it can also evaluate the progression of the disease, prognosis prediction, and treatment follow-up. The clinical forms of COVID-19 can range from asymptomatic infection to severe pneumonia. Biochemical findings vary in patients with different clinical forms. Therefore, biochemical parameters help diagnose the disease, determine disease severity, and predict clinical outcomes. SARS-CoV-2 is present in many tissues, including the endothelium, liver, and kidney. It can also progress with multiorgan involvement. Among the biochemical parameters, those showing organ damage play a significant role.

Keywords: COVID-19, biochemical parameters, CT, radiologically features

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Introduction

Radiological Findings of COVID-19

In December 2019, the disease caused by the virus called severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), which emerged in Wuhan, Hubei Province of the People's Republic of China, was officially named coronavirus disease-2019 (COVID-19) by the World Health Organization. Later, it was declared on March 11, 2020, that this disease was developed into a pandemic (1).

Clinical forms of COVID-19 have spread across a wide spectrum, ranging from asymptomatic infection, mild upper respiratory tract disease, severe viral pneumonia-causing respiratory failure, sepsis, multiple organ failure, and death (2). The most common symptoms are fever, cough, sore throat, headache, fatigue, muscle pain, and dyspnea. Real-time reverse transcription polymerase chain reaction (RT-PCR) of viral nucleic acids is the reference standard in diagnosing COVID-19. While the sensitivity of RT-PCR is 60-70% in the early period, it reaches 95% in the later period

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(3). In the early period of the pandemic, false-negative results appeared due to technical problems during inappropriate viral sample material or nucleic acid extraction. Computed tomography (CT) was the diagnostic test because of the RT-PCR study and access difficulties, long duration of the outcome, or exceedance of test usability with the accumulation of suspicious cases, and early RT-PCR false negativity, particularly at the beginning of the epidemic. The COVID-19 pandemic has caused a unique situation in this respect.

Chest radiography and thoracic CT are the most commonly used radiological methods for COVID-19. Thoracic ultrasonography was used in some centers for diagnosis and follow-up. Chest radiography and CT play a significant role in diagnosing, following up, and staging pneumonia. However, it can also predict disease severity and prognosis. CT is also extensively used to evaluate the progression of the disease and response to treatment. Therefore, recognizing CT findings, frequently present in COVID-19 patients, is critical in their complementary role in the early diagnosis and follow-up of disease progression.

Lung radiography and CT are frequently used radiological methods in COVID-19 and are described in the following section.

Chest Radiography

Chest radiography is the first preferred radiological method. Its sensitivity in showing lung involvement varies between 30 and 60%. The fact that the radiograph is normal because to its low sensitivity does not exclude COVID-19 pneumonia. The multifocal opacity with bilateral middle and lower zone involvement may be diagnostic. However, the foci of low-density pneumonia can also be present in other viral pneumonia. It is insufficient to show the appearance of ground glass opacities in the early period compared to CT (Figure 1).

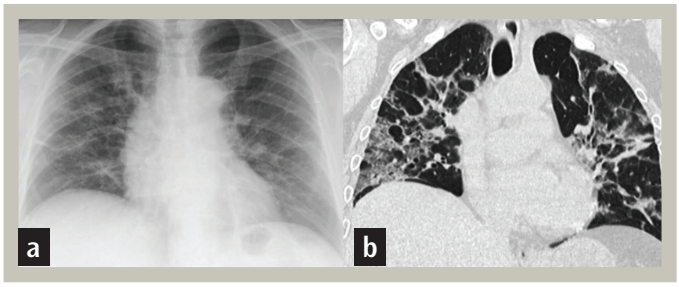

Figure 1. (a) CXR image. (b) CCT imaging, coronal reconstruction. COVID-19-positive patient. GGO are more easily identified on CCT imaging compared to CXR

CXR: Chest X-ray, CCT: Cardiac computed tomography, COVID-19: Coronavirus disease-2019, GGO: Ground-glass opacity

Lung radiography is preferred because it is practical, easily accessible and contains a low-dose radiation. It is crucial for monitoring the course of lesions in patients with severe progression (4,5).

Computed Tomography

SARS-CoV-2 uses the angiotensin-converting enzyme-2 (ACE-2) receptor in humans and first causes pulmonary interstitial damage and then parenchymal changes (6). Although bilateral ground glass opacities and consolidation have been reported as dominant imaging features in COVID-19, chest CT findings may vary in different patients and stages (7). In addition to the diagnosis of COVID-19, CT is also critical in monitoring the progression of the disease and evaluating its therapeutic effectiveness.

The studies reported various values for the sensitivity of CT. This may be related to the day of the symptoms of CT scanning and the variability of the disease according to the stage of the disease. In a meta-analysis, the sensitivity and specificity of the first chest CT scan were 87% and 43%, and the positive predictive and negative predictive values were 67% and 84%, respectively. This means that 67% of individuals with CT findings have positive RT-PCR, and 84% of individuals with negative CT scans have negative RT-PCR. Therefore, CT scanning is a complementary diagnostic tool compared to RT-PCR. CT is involved in staging the disease rather than being a screening test (8).

Ground Glass Opacities

The most critical and most common CT feature of COVID-19 is the bilateral distribution of consolidated or unconsolidated ground-glass opacities, mainly in the periphery and posterior of the lungs. Increases in lung parenchyma density due to alveolar partial filling of ground-glass opacity (GGO), partial collapse, and increased capillary blood flow, which tend to retain multiple segments. In a meta-analysis, the incidence of ground-glass opacities was 14-91% (9). In another study, ground-glass opacities were present with consolidation in 41% of 1099 cases (10). Studies have revealed that ground-glass opacities are the most common imaging feature and the earliest CT finding. Reticular and/or interseptal thickening, consolidation, and subsegmental vasodilation frequently accompany ground-glass opacities. This appearance may be due to hyaline membranes and pulmonary edema (11).

Various CT imaging features, such as “crazy paving”, air bronchograms, inverted halo signs, bronchiectasis, bronchial and pleural thickening, vascular enlargements, nodules, and pleural effusion, which are associated with the possible lung injury mechanism, have also been present. Typical and

atypical CT features are in Table 1 (5). Typical imaging features are not specific to COVID-19 and can also be present in other viral pneumonia. They are influenza pneumonia, acute lung injury, drug toxicity, lung involvement of connective tissue diseases, and organized pneumonia. In the presence of ground-glass opacities with no specific distribution, acute hypersensitivity pneumonia, pneumocystis infection and alveolar bleeding should be considered in the differential diagnosis. The differential diagnosis of atypical findings includes lobar and aspiration pneumonia and necrotizing pneumonia. Therefore, if atypical findings are present, it would be appropriate to confirm with PCR. If it cannot be confirmed, it would be appropriate to reach the diagnosis with the epidemiological factors of the case (7).

Consolidation

The lung parenchyma condensation occurs by erasing the veins and airways with pus, pathological fluid, blood, or cell filling into the alveoli (12). COVID-19 is accused of filling fibromyxoid exudate into the alveoli. In COVID-19, segmental, peripheral, and irregular limited consolidations appear. It is the most common finding after GGO, and the most accompanying finding of GGO (13). While ground glass is an early finding, consolidation is an advanced finding. It can also be present as a unilateral lesion in the early period. The newly emerging consolidations in the follow-ups predict that the disease may be progressive (14).

Consolidations may also be accompanied by airway changes, such as air bronchograms, bronchial wall thickening, and bronchiectasis. Air bronchograms can manifest frequently. While air-filled low attenuated alveoli between liquid-filled alveoli are as bronchograms in CT, fibrosis resulting from bronchial wall damage is as bronchial wall thickening (12). Studies associate bronchial thickening with poor prognosis.

The sidewalk stone pattern is interlobular septa accompanying the ground glass, which results from edema and inflammation by lung damage (15). Although it is not as common as ground glass, it can be defined as poor progression of the disease when present.

Pulmonary vascular enlargement is the enlargement of the subsegmental vessels with a diameter greater than 3 mm. Studies reported a rate of 50%, although not as often as ground glass or consolidation. Vascular enlargement accompanying the lesions is of diagnostic significance for COVID-19 (Figures 2, 3) (9).

Table 1. COVID-19 CT imagine features

Typical features	Atypical features
Ground glass opacities	Pleural effusion
Consolidation	Lymphadenopathy
Crazy paving	Pericardial effusion
Air bronchograms	Cavitation
Airway cysts	
Reticular pattern	
Nodules (with halo/revers halo sign)	

CT: Computed tomography, COVID-19: Coronavirus disease-2019

Other Findings

Nodules are common in viral pneumonia, but are rare in COVID-19. Halo and reverse halo marking may also accompany. Invasive fungal infections can be confused with lung metastases.

Air bubble signs, subpleural lines, pleural effusion, and thickening are rare atypical findings. While subpleural streaking occurs during the recovery period, pleural effusion and thickening manifest in the advanced stages of the disease (Figure 4).

Lymphadenopathy and pericardial effusion are rare atypical findings (16).

According to the abovementioned findings, the COVID-19 Reporting and Data System (CO-RADS) created a categorical

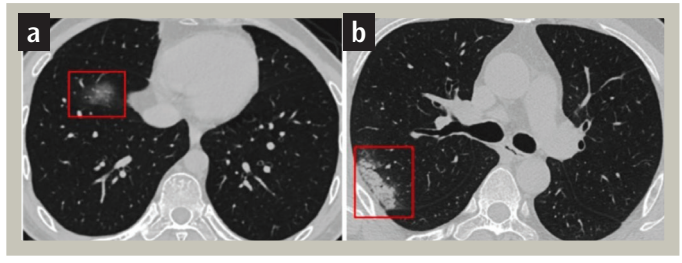

Figure 2. a) CT scan shows pure ground glass opacity in the right lower lobe (red frame). b) CT scan shows consolidation in the right lobe subpleural area (red frame) (9)

CT: Computed tomography

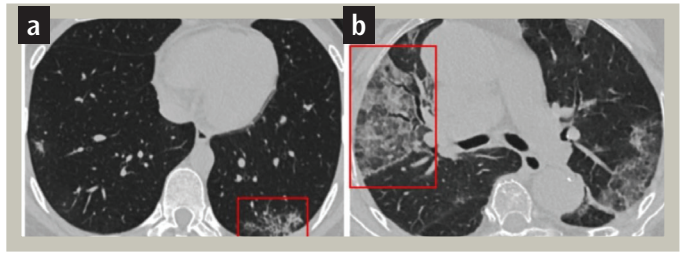

Figure 3. a) Reticular pattern in the left lower lobe and subpleural area (red frame). b) Reticular pattern superimposed on the background of GGO, resembling the sign of crazy paving stones (red frame) (9)

GGO: Ground-glass opacity

evaluation scheme for pulmonary involvement of COVID-19 in non-contrast chest CT, which performed well in predicting COVID-19 CO-RADS definitions are in Table 2 (17). Although it created a common language in the reporting system of radiologists, it has been the scale that clinicians frequently use in practical life.

Although CT findings occur over an average of four days, they may also occur before symptoms begin. According to the change in thoracic CT images, the disease can progress in four stages (18).

Early period: It covers the first four days from the first symptoms of the disease. Ground-glass opacities are in the lower lobes. Uni/bilateral subpleural areas are the main radiological findings.

Progressive period: This period covers the 5th-8th days from the onset of symptoms. The progression of the disease is rapid during this period. Radiological findings in this period are as follows: Bilateral, common, multilobar ground glass opacities, paving stone appearance, and consolidations.

Peak period: It covers the 9th-13th days from the onset of symptoms. During this period, infiltration areas in the lungs reach the highest level. Intensive consolidation areas are more prominent, and parenchymal bands can appear.

Regression period: It covers the 14th day and after the onset of symptoms. The infection is now under control, and consolidations are gradually regress. Sidewalk stone views are lost. Sequelae fibrotic bands may occur.

There is no need to provide a contrast agent in imaging for diagnosing COVID-19. However, if pulmonary embolism is considered a complication, contrast-enhanced CT angiography is recommended.

Table 2. CO-RADS definitions

		CT findings
CO-RADS 1	No	Normal or non-infectious abnormalities
CO-RADS 2	Low	Abnormalities consistent with infections other than COVID-19
CO-RADS 3	Indetermine	Unclear whether COVID-19 is present
CO-RADS 4	High	Abnormalities suspicious for COVID-19
CO-RADS 5	Very high	Typical COVID-19
CO-RADS 6	PCR+	

CO-RADS: COVID-19 Reporting and Data System, CT: Computed tomography, PCR: Polymerase chain reaction, COVID-19: Coronavirus disease-2019

Biochemical Findings of COVID-19

The clinical forms of COVID-19 can range from asymptomatic infection to severe pneumonia (1,2). Biochemical findings vary in patients different clinical forms (19). Therefore, biochemical parameters help diagnose the disease, determine the severity of the disease and predict clinical outcomes (20). SARS-CoV-2 can be present in many tissues, including the endothelium, liver, and kidney (21). It can also progress with multiorgan involvement. Among the biochemical parameters, those showing organ damage play a critical role (20). Biomarkers, according to the systems and situations in which they are used, are reviewed in the following section.

Inflammatory biomarkers: SARS-CoV-2 replicates at the site of infection after host cell invasion. Thus, the response

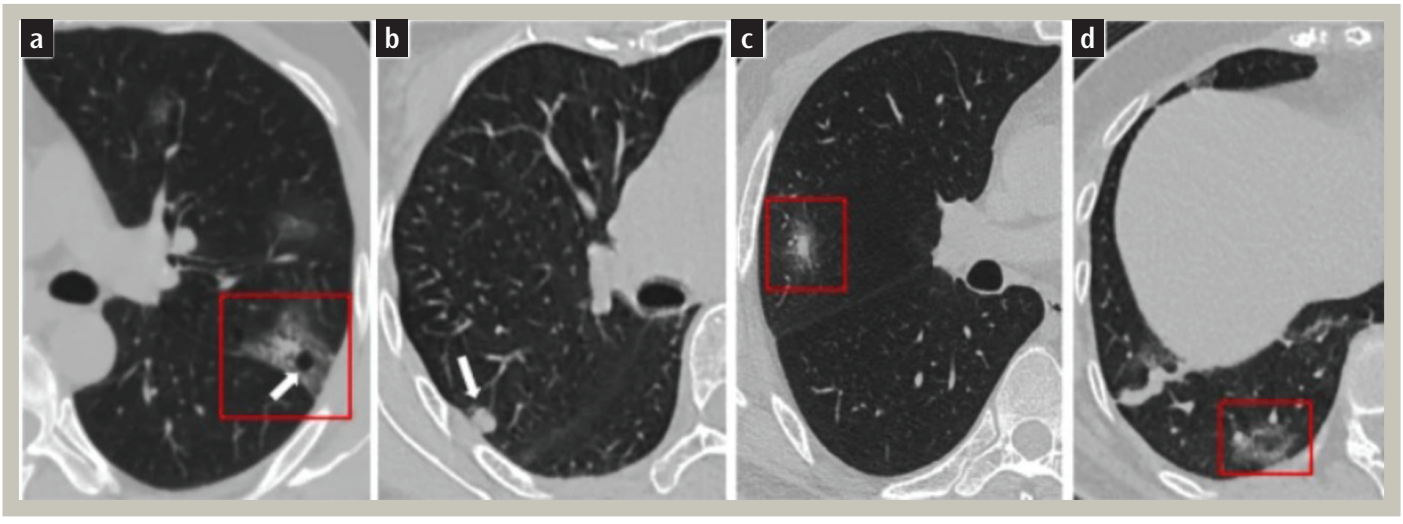

Figure 4. a) CT scan showing a patchy GGO (red frame) with an air bubble sign (white arrow) in the apicoposterior segment of the upper left lobe. b) An irregular nodule (white arrow). c) A solid nodule surrounded by a ground glass halo (red frame). d) A reversed halo sign (red frame) (9)

CT: Computed tomography, GGO: Ground-glass opacity

to innate and adaptive immunity is triggered (22). The inflammatory response to systemic immunity is activated. If this response cannot be controlled, it evolves into an inflammatory response called a cytokine storm (23). This response causes damage to different tissues, worsens the patient (20). In severe cases, it may result in multiple organ failure. Proinflammatory cytokines, particularly interleukin (IL)-6 and tumor necrosis factor (TNF)-α, have been associated with death in severe COVID-19 patients. Other examples are as follows: IL-1b, IL-2, IL-8, interferon-g-induced protein 10, granulocyte colony-stimulating factor, monocyte chemoattractant protein 1, and macrophage inflammatory protein-1. Additionally, cluster differentiation (CD) 3+, CD4+, CD8+, CD25+, CD127- T-cells, and natural killer cells were depressed in severe COVID-19 (24). Cytokine testing is not routine in laboratories. CRP and ESR, routine biomarkers, can evaluate the severity of the disease (25). Procalcitonin levels are an indicator that they are accompanied by bacterial infection. Among the hematological parameters, a high platelet-to-lymphocyte ratio, high neutrophil-to-lymphocyte ratio (NLR), and lymphopenia are strongly associated with the severity of the disease (26,27,28).

Pulmonary involvement: Although not specific to lung disease, various biomarkers have been identified in different stages of lung involvement in COVID-19 and have been associated with pulmonary, systemic hyperinflammation, and fibrotic damage (23,29). In the early period of the disease, neuron-specific enolase (NSE) can distinguish patients who will develop dyspnea. At baseline, the following conditions are associated with a lower risk of death: Higher lymphocyte and platelet counts, lower ferritin, D-dimer, lactate dehydrogenase (LDH), and aspartate transaminase (AST) (22,28). Surfactant protein-D, angiopoietin 2, triggers receptor expressed on myeloid cell (TREM)-1, and TREM-2 levels were higher in mild/moderate and severe COVID-19 pneumonia than in asymptomatic patients. Thiol, ferritin, and LDH are prognostic biomarkers for Acute respiratory distress syndrome (ARDS) in severe COVID-19 cases. After extubation, survivors of COVID-19 have higher platelet counts and NLRs but low levels of C-reactive protein (CRP), D-dimer, ferritin, LDH, and AST (27,30).

Cardiac biomarkers: It causes coagulopathy because SARS-CoV-2 triggers endothelial dysfunction. Endothelial damage and the generalized inflammatory response conduct the process of thrombosis, which constitutes cardiovascular findings (21). Clinical evidence has shown that severe COVID-19 patients have a significant cardiovascular impairment (31). The increase in the D-dimer coagulation margin indicates an increased likelihood of various thrombosis; it has the following conditions: worsening disease and pulmonary microthrombosis, pulmonary embolism, deep vein thrombosis, and diffuse intravenous coagulation (26). Similarly, plasma fibrinogen is associated with hyperinflammation and disease severity. The following are coagulopathy-associated indicators: Elevated levels of soluble vascular cell adhesion molecule (sVCAM)-1, von Willebrand factor (vWF), thrombomodulin, soluble TNF receptor I (sTNFRI), heparan sulfate, C5b9 complement, plasminogen activator inhibitor-1, and alpha-2 antiplasmin. Some of these markers are also associated with the severity of the disease: sVCAM-1, vWF, sTNFRI, heparan sulfate, and ADAMTS13 activity (21,23).

Recent evidence has shown that cardiac biomarkers and troponin levels, including natriuretic peptides (NPs), may reflect the cardiovascular involvement and are strongly associated with poor prognosis and mortality. Troponin elevation in COVID-19 has been associated with changes in ECG, intensive care unit admission, and in-hospital death. However, routine testing is still controversial despite the confirmed prognostic effect of troponin levels (32).

These cardiac and non-cardiac biomarkers have been findings of cardiovascular diseases associated with COVID-19: Creatine kinase-MB, myoglobin, brain NP (BNP) and its N-terminal prohormone (NT-proBNP), mid-regional pro-adrenomedullin (MR-proADM) (22).

Metabolic Functions

Lipid metabolism plays a role in the regulation of inflammation and immunity. Fat-soluble vitamins such as vitamin D also suppress the cytokine storm and strengthen the immune response. Therefore, investigating lipid metabolism and biomarkers may have diagnostic and prognostic value in COVID-19 (23).

Metabolic comorbidities such as obesity, diabetes, cardiovascular diseases, and hypertension have been associated with poor prognosis in COVID-19 (22,23).

COVID-19 patients with low levels of high-density lipoprotein levels are more prone to hospitalization. However, higher low-density lipoprotein resulted in more hospitalization. Critical patients with COVID-19 showed significantly lower vitamin A levels than non-critical patients. This has been associated with high inflammation. Vitamin A levels below 0.2 mg/L were significantly associated with the development of ARDS and higher mortality. Vitamin D does not appear to affect mortality or length of hospital stay despite known immunomodulatory function.

Thyroid hormones showed a significant relationship with disease severity. It is recommended to evaluate thyroid

function early in hospitalized COVID-19 patients and to initiate thyroid therapy when necessary (22).

Neurological involvement: Although COVID-19 primarily rarely affects the brain, neurological complications are common. Because of neurological involvement, various biological markers can detect neuroinflammation and damage. In addition to the inflammatory and coagulopathy markers mentioned in other sections, these indicators can be beneficial: antiphospholipid antibodies, fibrillary acidic protein (GFAP), neurofilament light polypeptide, tau, S100B calcium-binding protein, and NSE (33).

Hepatic biomarkers: Several studies have shown abnormal liver function in severe COVID-19 patients. High aminotransferase levels were present in 14-58% of hospitalized patients. AST and ALT elevations are usually mild (<5 times the upper limit of normal). However, higher aminotransferase levels and severe acute hepatitis are also present (25).

Increased GGT, increased bilirubin, and decreased serum albumin levels were associated with severe COVID-19.

Possible mechanisms of liver dysfunction during COVID-19 include the following:

1. Immune-mediated damage due to a severe inflammatory response because of infection.

2. Direct cytotoxicity by active viral replication in biliary epithelial cells expressing ACE-2.

3. Hypoxic hepatitis by anoxia.

4. Drug-induced liver injury (20).

Renal biomarkers: COVID-19 is associated with acute kidney injury (AKI), although the mechanism is not fully known. The prevalence of AKI was between 0.5-19.1% in various studies. Blood urea nitrogen and creatinine levels are the general indicators of kidney damage. According to Cheng et al. (34), 102 patients with higher basal blood creatinine levels were more likely to be admitted to intensive care.

COVID-19 care, early diagnosis and management of kidney injury, adequate physiological balance, and restriction of toxic drugs can be critical. Therefore, monitoring creatinine and other renal markers is crucial. In addition to serum and urine albumin, total protein may be beneficial as a prognostic marker in COVID-19 (20).

Additionally, it should be considered that biochemical markers may vary with the development of SARS-CoV-2 variants (35,36).

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: D.Y.S., C.A.T., Design: D.Y.S., C.A.T., Data Collection or Processing: D.Y.S., C.A.T., Analysis or Interpretation: D.Y.S., C.A.T., Literature Search: D.Y.S., C.A.T., Writing: D.Y.S., C.A.T.

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