Review Article

Pulmonary Manifestations of SARS-CoV-2 Infection in Mild/Severe Patients

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Abstract

The coronavirus disease 2019 (COVID-19) caused viral pneumonia in Wuhan City in China in December of 2019. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) primarily targets the lungs with severe hypoxia, which usually results in death. COVID-19 is highly heterogeneous regarding severity, clinical phenotype, and more importantly, global dispersal. The respiratory system in all aspects such as respiratory airways, endothelium of pulmonary vessels, conducting airways, the alveoli, neuromuscular breathing structure, and pulmonary circulation are affected by this virus. A comprehensive concept of the source and dynamic action of the SARS-CoV-2 and the possible causes of heterogeneity in COVID-19 is required for predicting and managing the illness in acute and chronic stages of the pulmonary sign.

Keywords: COVID-19, SARS-CoV-2, Pulmonary manifestations, Lung involvement

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Introduction

The initiation of unusual pneumonia which was caused by a novel type of coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and following its human-to-human transference was proved to lead to the quickly develop of coronavirus disease 2019 (COVID-19) worldwide as a pandemic[1, 2]. SARS-CoV-2 is a virus with respiratory damage manifestations that enters the host cells through angiotensin-converting enzyme 2 (ACE 2) receptors within the airway epithelium[3, 4]. Even though coronavirus disease is a systemic infection that may affect different parts of the body, lung damage is the common and main reason for death in many severe cases[5]. Patients presented with symptoms ranging from asymptomatic to morphological stages. These stages are named (1) the early stage (which takes 0–1 day) and include edema, capillaritis/endothelialitis, and incipient epithelial damage, and (2) the stage that was shown by diffuse alveolar damage (DAD) (including 3 to 5 days), (3) the late stage (takes 1 to 2 weeks), and the final one (4) the fibrotic stage of DAD (fibrotic stage) (takes weeks-months)[6]. If prophylactic

anticoagulation is not performed, usually venous thromboembolism occurs. However, microcapillary thrombosis is nearly ubiquitous, proposing it correlates to hypoxemia[7, 8]. In the absence of acute data on the pathobiology of these viruses, pulmonary vascular effects in the acute and chronic stages were described in COVID-19 patients as vascular enlargement mixed ground-glass opacity (GGO), consolidation, and traction bronchiectasis[9]. Other pulmonary symptoms of COVID-19, such as septal and pleural thickening, bronchiectasis, and subpleural involvement, were reported as less than GGO patchy opacities confined to a single segment or multiple segments in both lungs' zones in the middle and peripheral regions/subpleural areas may manifest in the progression stage. Multiple consolidations and GGO are seen in both lungs in severe patients, some of which are fused into larger consolidations, with pleural effusion or thickening of the pleura. A "white lung" is a consolidation of the lungs due to multiple diffusive processes caused by a critical illness that arises from lesions. During the absorption stage, previous lesions were less dense, or they developed into fiber-like or cord-like opacities. As a result, digital radiography is proper for only the first step of hospitals without computerized tomography (CT) or critically severe patients[10]. For months, some survivors may reduce whole lung capacity, dispersion potential, and maximal oxygen usage. Lung transplant offers chronic patients new hope. This article attempts to provide the pathobiology of COVID-19, emphasizing the role of pulmonary vasculature in the severe stage and its potential for initiating chronic pulmonary manifestations.

Pulmonary developments of COVID-19

The first and foremost site for the involvement of the new coronavirus is the respiratory tract of the patients. However, this virus infection is known as a systematic disease and affects diverse parts of the body. Studies have confirmed that lung damage related to a fatal COVID-19 infection causes death in most cases of severe COVID-19. Pneumonia initiates by the replacement of infection in the upper respiratory tract that is easily transmitted between humans that leads to lung damage as a fatal factor[11, 12]. Numerous valuable methods like chest X-ray and high-resolution computed tomography (HRCT), nuclear medicine scans, and catheter angiography were used to diagnose these manifestations[11]. Due to the quick diffusion of COVID-19 across the world, in the first year of its presence, it infected 94 million persons with 2031875 deaths[13]. Till February 2021, up to 110 million patients and other than 2.4 million losses people in the world were reported, even though actual numbers are likely to be much higher[12]. According to the WHO coronavirus dashboard, this rate reached 438,968,263 infected cases of COVID-19, plus 5,969,439 deaths by the beginning of March 2022[14]. Many efforts have been put on until now to discover this virus's origin, transmission, and pathogenesis, but initial investigation proposes that patients' lungs are the key sites of SARS-CoV-2 infection[15]. Among seven known coronaviruses (CoVs), 229E, NL63, OC43, and HKU1 are involved in upper respiratory tract infections[16], although Middle East respiratory syndrome coronavirus (MERS-CoV), severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1), and SARS-CoV-2 cause respiratory system life-threatening conditions, and lead to multi-organ dysfunctions[17]. The recognition of ACE 2 by COVID-19 stimulates its pathogenicity, as demonstrated in numerous studies. Spike (S) glycoprotein equips SARS-CoV-2 to recognize and bind to the human angiotensin-covering enzyme 2 (hACE 2) receptors widespread on type II alveolar epithelial cells and capillary endothelial cells for its entry. Aggressive properties of SARS-CoV-2 can be attributed to the stronger binding desire with ACE 2 with cellular transmembrane serine protease 2 (TMPRSS 2) of it, which leads to easy replication and initiates the cytokine-release syndrome or macrophage activation syndrome in alveolar epithelial cells. The pulmonary alveolar cell type II, colon and small intestine, gallbladder, brain stem, testes, heart, and basal layer of blood vessels are the locations of ACE 2 receptors[18]. In the following, interleukins (IL-1, IL-6, IL-8) are produced and promote dyspnea and acute respiratory distress syndrome (ARDS) that end up in death[19,20]. Reducing blood pressure in renal juxtaglomerular, renin is released into the bloodstream and acts as an antagonist. ACE 2 affects this production in some processes and leads to blood pressure reduction, heart rate, and alveolar surface

tension, which is essential for ARDS treatment[21].

The pulmonary pathology and the manifestation of fatal COVID-19

As a result of the limited access to biopsy and autopsy research in infected persons, its histopathology has been revealed in a limited area. One case report revealed mottled pneumocytes and hyaline membrane establishment that is consistent with ARDS in the right lung of the infected person along with edema and hyaline membrane formation in the left lung. Also, pneumocytes located within the alveolar spaces showed viral cytopathic-type modification with no other histopathology evidence[22]. In another histopathology study of three case reports, viral bodies that existed in endothelial cells in one patient who received a transplanted kidney were seen in electron microscopy. A combination of immunohistochemistry and light microscopy revealed inflammation and apoptosis of endothelial cells in numerous organs, including the small bowel, kidney, heart, and liver. The laboratory reports showed low lymphocyte counts in patients' peripheral blood, which could contribute to the chemokine's service-specific immune cells like lymphocytes in the infection region[23]. On the other hand, COVID-19 is specified by symptoms such as a flu-like result of viral infection. Acute lung damage that initiates pneumonia, was developed in numerous patients conduct to coagulopathy[24]. The risk factor for the majority of COVID-19 severe infected are age (mainly, elderly males with a mean age of 64 and a range from 31 to 96 years), ATTR amyloidosis, atherosclerosis, ischemic cardiomyopathy, and/or coronary heart disease, chronic obstructive respiratory disease, hypertension, diabetes, and obesity[25]. As mild cases of this virus, upper respiratory tract infections, coughs, and sore throats were categorized along with pneumonia and fever. The severe exhibition of COVID-19 is ARDS[26]. Only a small number of patients with a mild to moderate stage of the disease develop a severe form of extrapulmonary systemic inflammatory response syndrome with high serum inflammation markers. These markers include C-reactive protein (CRP) or fibrinogen. Cytokines, interleukins (IL-2, IL-6, IL-7), ferritin, and/or D-dimer, granulocyte colony-stimulating factor (G-CSF), and tumor necrosis factor-alpha (TNF-α) are considerably higher in patients with more severe forms of infection[27]. A severe form of the disease may be revealed by respiratory failure, myocarditis, and shock that is enhanced by severe systemic inflammation[28]. Silent hypoxia was observed in some cases of patients with fever[29]. An upper respiratory tract infection and cough may lead to ARDS or an unexpected mass of disease in silent form and hypoxia in COVID-19. Computed tomography (CT) scans can sometimes prove helpful for cases of COVID-19 without symptoms, and in some cases, we also need the assistance of other tests.

Clinical Findings

Numerous studies showed the epidemiologic and clinical character of infected individuals. In heterogeneous populations, contradictory results might result from sample size differences, selection bias, and racial characteristics[30]. A high range of patients underwent mild indications such as fever, cough, headache, malaise, myalgia, and dyspnea that recovered without specific treatments[31]. Lymphopenia, high inflammatory factors including D-dimer, procalcitonin, ferritin, CRP, lactate dehydrogenase (LDH), and IL-6, along with hypercoagulability of blood and disseminated intravascular coagulation (DIC) are frequent in acute forms of the disease, with 2.3%-12.2% of patients requiring mechanical ventilation[32]. The most magnification of intensive care unit (ICU) admission of COVID-19 patients was ARDS which was also the primary etiology of death[30]. With the announcement of the United States Center for Disease Control and Prevention (CDC), pulmonary diseases that show symptoms such as > 50% lung involvement on CT or dyspnea and hypoxia are assumed as severe in 14% of cases, and manifestations including shock, multi-organ failure or respiratory failure are known as critical in 5% of cases[22]. The cross-examination of the lungs showed an increase in lung weight with irregularly distributed consolidation regions plus edema and diffuse congestion. In some cases, hemorrhage or infarction was seen in infected people, and visible thrombosis was seen in Feeder Vessels[33]. Probably thrombotic occlusion of multiple vessels rather than a single embolus leads to the infarcts frequently lacking the normal wedge shape[34]. In the exudative stage of diffuse alveolar damage, viral

inclusions, and variably prominent hyaline membranes are not present, although fibrin-rich edematous fluid is present in the alveolar spaces, which triggers the growth of giant cells of epithelial origin with multinucleated nuclei. In the region of dilated alveoli and disturbed alveoli, thrombotic vessel occlusions and/or superinfections were present[12]. It was shown that platelet-fibrin thrombi in small arterial vessels, with megakaryocytes in some areas of vascular, were seen with significant vascular inflammation[35]. Furthermore, in autopsy cases, microthrombi were detected in 57% of COVID-19, 24% of influenza H1N1, and 58% of SARS patients. Thrombosis of vessels in intermediate and large-size, mainly arteries, was seen by diffuse endothelial cells as a specific feature but not a specific characteristic of this virus. Deep venous thrombosis leads to pulmonary embolism and is a direct cause of death[36]. Bacterial and fungal superinfections that are not prevalent result in bronchopneumonia in 32-57% of COVID-19 patients, but the reason for death in subsequent superinfections have remained unclear[37]. MicroRNAs (miRNAs) have been implicated as crucial controllers in the pathogenesis of inflammatory lung disorders, but they also play a critical role in the immune response to pulmonary viral infections. Next-generation sequencing (NGS) analysis showed an elevated dysregulation of miRNA expression in a severe form of this infection. Patients with severe respiratory dysfunction showed 41.7% dysregulated miRNAs at the acute phase of COVID-19. Increased dysregulation of miRNA expression was observed with the development of disease severity associated with extreme downregulation of miR-320a, miR-320b, and miR-320c[38].

Specific population in clinical findings

The pediatric population has been studied less than other groups of patients with COVID-19 infection. In a study, among five positive cases in the age range of 10 months to 6 years old, three had modest GGO, and two others had standard CT without any cases of chest x-ray (CXR)[39]. In some other studies, CT scans showed nonspecific to mild forms of the disease in child patients, which proposes the idea of having a milder disease in the pediatric population. Study in these populations demonstrated that compared to adults, pediatrics presented with fewer severe features like GGO, high-aggregation shadows, and patchy and parenchymal links that were common in CT findings; although, no abnormal CT features exist in some of these child patients[40]. Findings of pregnant women encountering COVID-19 were limited. In a study, 15 positive COVID-19 pregnant women in gestational weeks 12-38[41] were found. The neonates in these groups did not show any infections and CT findings were similar to controls with GGO, primarily in the time course of consolidation and fluctuating paving patterns with disease development. Some other studies showed conflict that may be related to pregnancy's physiological and anatomic changes[40].

Radiologic Findings

Some studies have documented CT image manifestations in infected individuals[42]. CT values in the diagnosis of COVID-19 rely on its short investigation period and high resolution in detecting and classifying lung deficiency. Furthermore, it is easy to check CT scans and estimate disease progression accurately, detect lung lesions in COVID-19 patients, assess disease severity, and follow up with the patients at the stage of treatment of lung lesions[43]. The known feature of COVID-19 on primary CT is bilateral multilobar GGO with a posterior distribution, predominantly localized in the lower lobes and less frequent in the right middle lobe[30]. A less common finding than GGO is septal and pleural thickening, bronchiectasis, and subpleural involvement[44]. According to a survey from China, 64.4% mixed GGO and consolidation, 71.3 %vascular enlargement within lesions, and 52.5% traction bronchiectasis were reported in patients[9]. In some studies, bacterial pneumonia was found in 45.2% of the vacuolar signs, 56.5% of the microvascular dilation sign, 33.9% of the fibrous streaks, and 53.2% of the subpleural line, 72.6% of the air bronchogram, 48.4% of the thickening, and 56.5% of the pleural retraction sign[45]. On the primary CT images, some COVID-19 patients had pulmonary nodules, which showed an increase in the number and size next to CT[42]. Pathological changes in the lungs were observed in chest CT scans in COVID-19 patients. The process of pathological lung injury in COVID-19 pneumonia has not been studied enough, although new studies claim that SARS-CoV-2 reveals a likeness in pneumonia pathogenesis with SARS and MERS coronaviruses.

SARS CoV-2 patients have involvement in ACE 2, which leads to the progression of acute lung collapse. This virus induces lung injury by this enzyme affecting pulmonary epithelial cells, diffusing alveolar damage and edema that reveals the pathological basis of consolidation and GGO in rapid alteration in a chest CT image of COVID-19-infected individuals[46]. Individuals over 50 years old and involved with risk factors including dyspnea, comorbidities, chest discomfort, cough, expectoration, enhanced serum inflammatory factors, and low lymphocyte count experienced a critical phase of illness more than others[47]. Peripheral and lower lung distributions are the most common in radiographic findings; although CXR is not proposed for routine diagnosis of COVID-19, it may be helpful for the next process[48]. The chest CT of the disease varies at diverse levels of the disease, which aids the researchers in differentiating the diagnosis of other known pneumonia viruses or bacteria and COVID-19[42].

Diverse stages of COVID-19 virus patients on chest CT

Studies have been conducted to demonstrate and categorize COVID-19 findings in several stages of onset symptoms to date. Four morphological stages were defined in pulmonary COVID-19. These four main successive stages were proposed for this classification: early, intermediate, late, and a fourth /Absorption stage[49].

Early-stage: It starts during the first two days of infection, and almost 50 % of the infected individuals have a negative chest CT (56%). This stage is long with edema, epithelial damage, and capillaritis/endothelialitis[33]. GGO manifests in 44% and consolidation in 17% of patients at the early stage[50]. Another study revealed that 16.1 % of cases had solitary lesions, mostly in the right lower lobe[51].

Intermediate stage: It occurs during days 3 to 5 after infection onset, and 9% of infected persons have negative chest CTs. This stage is known as the exudative stage of DAD. About 80% and 55% of infected people show GGO and consolidation, respectively. Additionally, 76 % of patients had bilateral distribution with peripheral lung involvement in 64 % of cases[50].

Late stage: It manifests on days 6–12 of infection, starting with most positive chest CT cases. GGO and consolidation were detected in 88% and 60% of patients; however, imaging findings showed that the rate of bilateral is 88 % and peripheral-predominant at 72%, respectively[50].

The fourth stage: Manifested within 14 days with CGO at 65 %, consolidation of 75 %, and imaging findings at 88% bilateral and 72 % peripheral. This stage is known as the fibrotic stage of DAD (Figure 1)[50-52].

Atypical Radiologic Findings

Asymptomatic and atypical cases occur in approximately 1% of contaminated people[53]. Case reports of bilateral pleural effusions in asymptomatic COVID-19 pneumonia were detected in 2020 for the first time[54]. In the following, 2 other cases of mild to severe development of lung infiltrate were reported. In these cases, the pulmonary vessels are tubular and enlarged, but their size has decreased more than in pleural effusions. It was shown in the center of the insurgent lung lesion. Moreover, deteriorated cases were characterized by mediastinal lymphadenopathy with short-axis oval nodes[55]. There is some utility to detecting metabolic imaging in patients with no symptoms, and innumerable preclinical studies suggested using F-fluorodeoxyglucose (FDG-PET) imaging as a valuable assessment of the response of the immune system to viral infection. In this way, lymph node involvement could be detected by showing high activity in the mediastinum and axilla cells (drainage of damaged lung tissue) even though pathologic results on CT or clinical findings after contact with the virus did not show anything. It was observed in circulating monocytes in lymph nodes that cellular activity was elevated five days after infection, which shows the monocytes act in the body's response to viral infection[56]. Researchers suggested that FDG-PET imaging could be a handy diagnostic approach to diagnose primary alters in the responses of the immune system to the infection of asymptomatic patients, leading to pivotal differential diagnosis in the early phase.

SARS-CoV-2 respiratory co-infections

COVID-19 can concurrently exist with other respiratory infections including influenza and tuberculosis therefore, it can be hard to differentiate the signs of these conditions from each other.

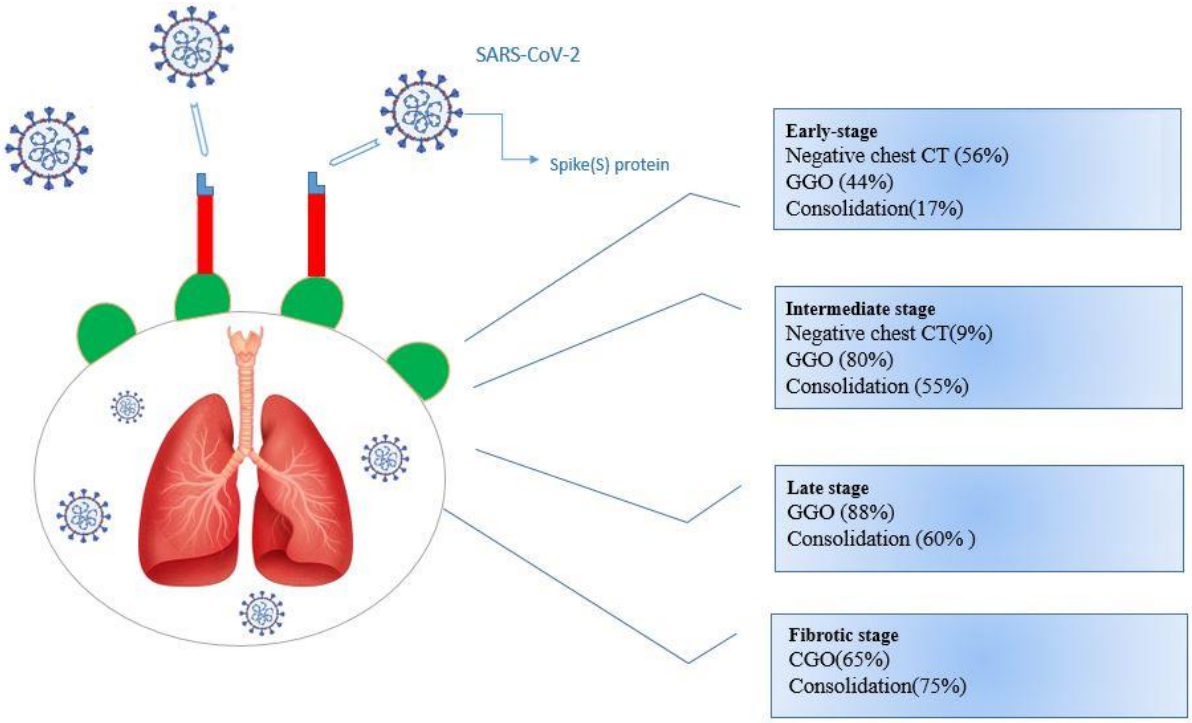

Figure 1. Stages of COVID-19 infection on chest CT characteristics.

However, there are modifications including influenza individuals can be asymptomatic due to herd immunity. Also, severe disease and ARDS can occur in COVID-19 (with 3–4% mortality) but most of the influenza infections are mild to moderate (with Less than 1% mortality)[57]. Based on a systematic reviews and meta-analyses study conducted by Dadashi et al., the worldwide prevalence of SARS-CoV-2 and influenza coinfection was 0.8% that the highest frequency belonging to Asia (4.5%), and the lowest was reported in America (0.4%)[58]. On the other hand, the global prevalence of SARS-CoV-2 and tuberculosis coinfection was 1.1%, and the highest and lowest statistics were in Africa(3.6%) and Asia (1.5%), respectively[59]. Notably, the most imaging manifestations in TB were unilateral pulmonary infiltrate, unilateral pulmonary cavitary lesion, and bilateral pulmonary infiltrate (no cavities) respectively[60].

Conclusion

In this study, we explained the pathobiology of pulmonary vessels in COVID-19. By looking at specific patterns in CT scans, it may be possible to diagnose the condition and begin appropriate treatment. Briefly, the chest CT signs of COVID-19 show patchy or mixed GGO and consolidation, including the peripheral zones of bilateral lungs, which can rapidly change over a short period. There are cases in the primary stage that show laboratory and radiologic results similar to severe pneumonitis. These cases are more prone to entering a severe phase. Additionally, our review highlighted that, even though radiological results might be contrasting, it is suggested to image suspected patients who might have COVID-19 clinically. Decisions for these people must be made according to a clinical need basis and consider the infection control implications.

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Conflict of interest

The authors further declare that they have no conflict of interest.

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