Section A-Research paper

A Brief Overview about CT role in COVID-19 Post-Acute Sequelae

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Abstract

Background: The recovery from SARS-CoV-2 infection is variable. Although most will make a total recovery, others will experience sequalae long after they recover from the acute infection with severity of symptoms ranging from mild to debilitating. In a study of health care workers with mild COVID-19. The most common symptoms reported were lost of taste or smell, fatigue, and shortness of breath. Identified risk factors for symptoms after infection include increasing age and body mass index, female sex, and a higher number of symptoms during the acute illness. Studies from other viral infections with pulmonary involvement suggest that functional and radiologic impairments persist beyond hospital discharge. In the original SARS-CoV outbreak in 2003, which had 8000 confirmed cases and a mortality rate of 9%.COVID-19 starts as interstitial pneumonitis and then affects lung parenchyma. A wide variety of CT findings in COVID-19 have been reported in the different studies, and the CT findings differ according to the stage of the disease and disease severity and associated co-morbidities. opacification of the lung in the X-ray or computed tomography with no obliteration of bronchial or vascular markings. The presumed pathology includes partial filling of the lung alveoli by fluid, interstitial thickening, or partial collapse of lung alveoli. The reported sensitivity of CT in the diagnosis of COVID-19 is 60–98%, and the reported specificity is 25–56%.

Keywords: COVID-19 Post-Acute Sequelae

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Introduction

The recovery from SARS-CoV-2 infection is variable. Although most will make a total recovery, others will experience sequalae long after they recover from the acute infection with severity of symptoms ranging from mild to debilitating. In a study of health care workers with mild COVID-19 **(1),** 26% had moderate to severe symptoms for 2 months and 15% had moderate to severe symptoms for 8 months. The most common symptoms reported were lost of taste or smell, fatigue, and shortness of breath. Identified risk factors for symptoms after infection include increasing age and body mass index, female sex, and a higher number of symptoms during the acute illness**.** This constellation of symptoms, initially referred to as "long COVID," is now called post-acute sequelae of COVID-19 (PASC); the National Institutes of Health convened a workshop in December 2020 to summarize existing knowledge and to identify knowledge gaps and research priorities **(2)**. Lingering questions that were addressed include the cause and risk factors for PASC, as well as its management.

Lung Disease after COVID-19

Studies from other viral infections with pulmonary involvement suggest that functional and radiologic impairments persist beyond hospital discharge. In the original SARS-CoV outbreak in 2003, which had 8000 confirmed cases and a mortality rate of 9%, reticular abnormalities were first noticed at 2 weeks when CT abnormalities were most severe**.** While the GGOs and consolidations slowly improved, fibrosis was seen in 50%– 60% of patients on follow-up scans after discharge **(3).**

Fibrosis was more common in the older population, those with a longer length of stay, those with a higher lactate dehydrogenase in the acute phase **(3),** and those with notable exercise intolerance after recovery**.** In 2012, Middle East respiratory syndrome, or MERS, caused by the coronavirus MERS-CoV, was first identified in Saudi Arabia. As of January 2020, there were 2519 confirmed cases with a mortality rate just over 34%**.**A study of 36 patients who underwent follow-up chest radiography (median, 43 days) after recovering from MERS showed that 33% had residual reticular opacities suggestive of fibrosis **(4).**

Post-acute fibrosis has also been reported in other viral infections with lower morbidity and mortality. In H1N1 influenza infection, which was benign in most cases with an overall mortality rate of 0.5%, there are reports of fibrosis after infection**,** although the exact incidence is unknown. A recent meta-analysis of 60 studies looking at follow-up imaging after inpatient admissions for SARS-CoV-2, MERS, or influenza pneumonia found inflammatory changes (GGO or consolidation) in 56% of scans and "fibrosis" (reticulation, lung architectural distortion, interlobular septal thickening, traction bronchiectasis, or honeycombing) in 40%. Given the known association between other viral pneumonias and fibrosis as well as the incidence of pulmonary involvement in COVID-19 during the acute illness and persistent respiratory symptoms after recovery, there has been a focus on the post-acute lung disease in COVID-19 **(5).**

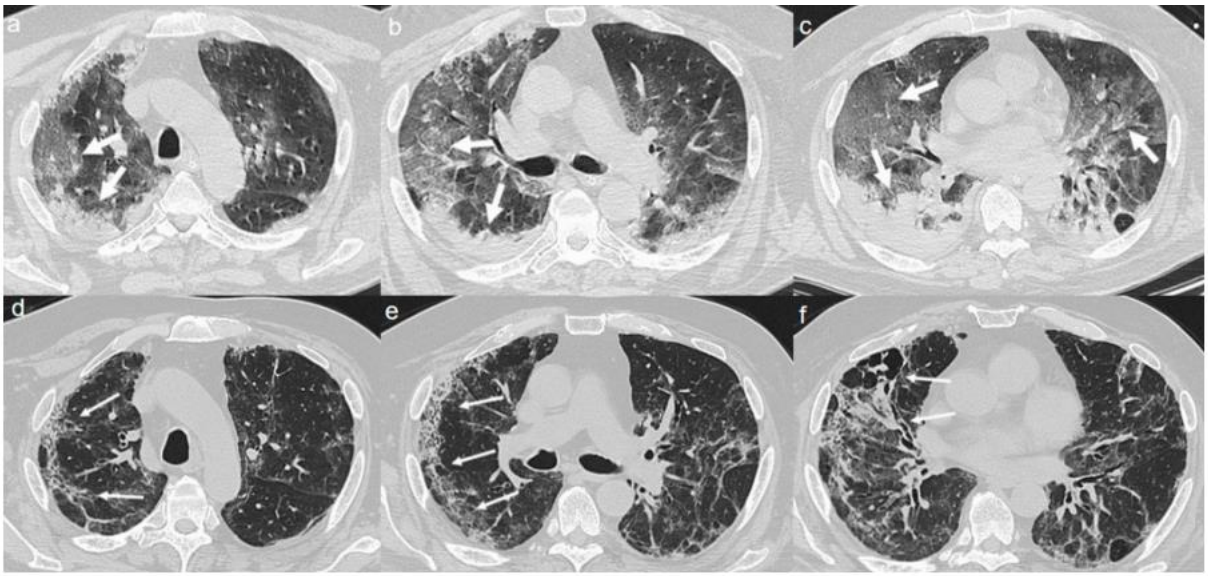


Figure 7. (**a–c**) CT shows bilateral extensive areas of GGO and consolidations, with prevalent peripheral distribution, in upper and lower lobes (arrows). (**d–f**) Follow up CT 4 months after admission shows persistence of diffuse thickening of the interlobular septa, with fibrotic appearance (thin arrows in **d**,**e**); air bubble sign with bronchiectasis (thin arrows in **f**) is recognizable.

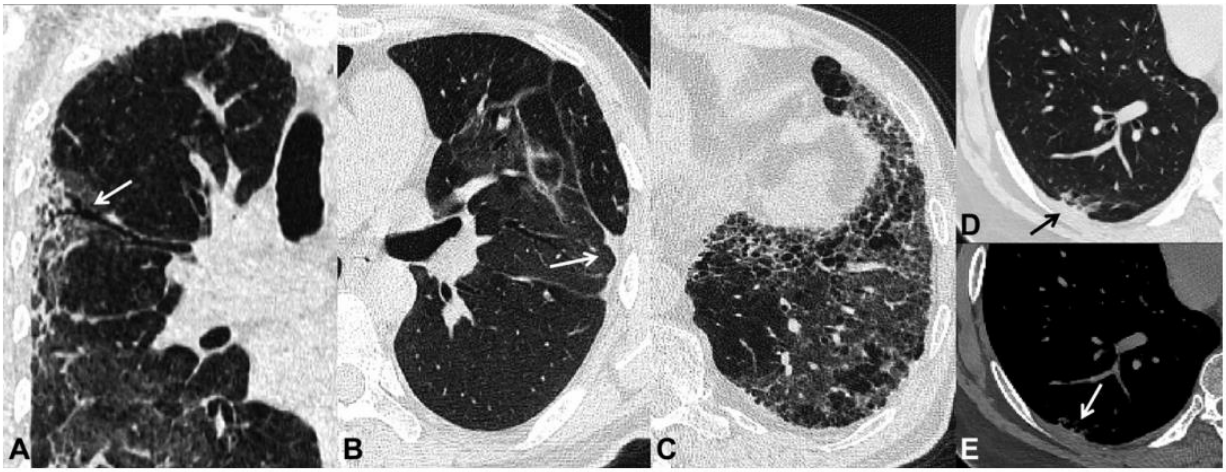
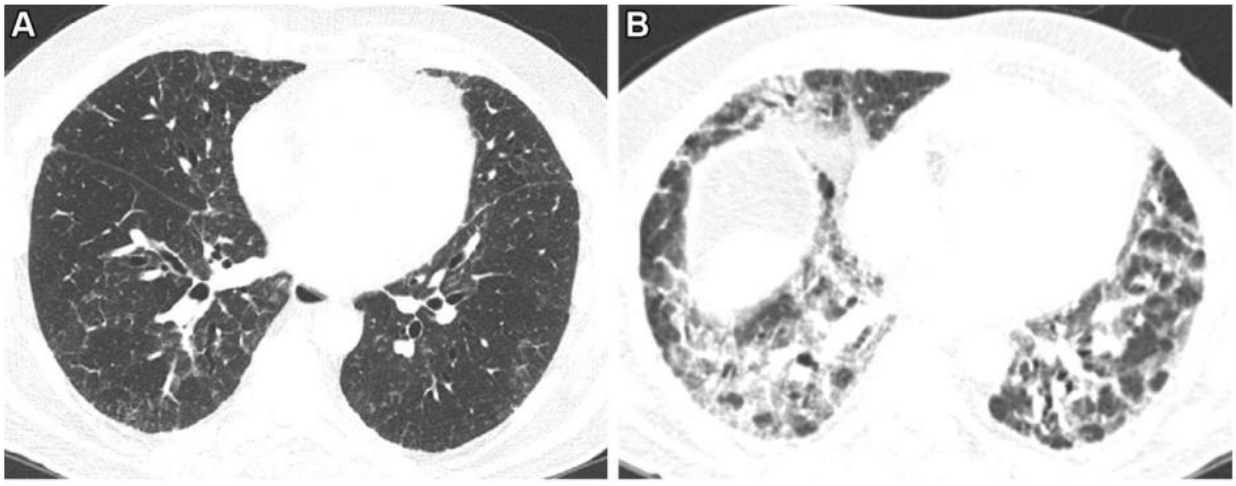


Figure 2: Follow-up chest CT findings of coronavirus disease 2019 pneumonia. Scans show, *A*, traction bronchiectasis (arrow), *B*, parenchymal bands (arrow), *C*, honeycombing, and, *D*, *E*, thickening of the adjacent pleura (arrow).

Etiology of Lung Disease after COVID-19

It is unclear if changes after acute COVID-19 are a sequela of lung injury or acute respiratory distress syndrome (ARDS), the effects of mechanical ventilation, or direct injury from the virus. Pulmonary fibrosis is known to develop in a subset of patients with ARDS and the duration of acute respiratory failure in ARDS has been independently implicated in the development of pulmonary fibrosis **(6).** In a subset of survivors of ARDS, persistent fibrotic changes often correlate with restrictive physiology on pulmonary function tests and a worse health- and pulmonary related quality of life up to 2 years after index hospitalization**.** Ventilator-induced lung injury—a direct injury to alveoli that leads to pulmonary interstitial edema, hyaline membrane formation, and alveolar collapse—is commonly seen in patients with ARDS and can directly contribute to the development of pulmonary fibrosis **(7)**. It may have a role in the development of lung disease after COVID-19 given the longer duration of mechanical ventilation and higher incidence of barotrauma seen in patients with COVID-19 ARDS compared with non-COVID-19 ARDS. Autopsy studies of patients dying from COVID-19 show evidence of ARDS on biopsy as well as SARSCoV-2 in pneumocytes**,** fibroblast proliferation, and microscopic honeycombing **(8).** Viruses are known to influence responses to other fibrotic stimuli and in select cases cause fibrosis on their own**.** The relative contributions of these factors to lung disease after COVID-19 are currently unknown. In a small subset of patients, the etiology of lung disease after COVID-19 appears to be an exacerbation of underlying interstitial lung disease**,** a known complication in patients with fibrotic lung disease after lung infection **(9).**



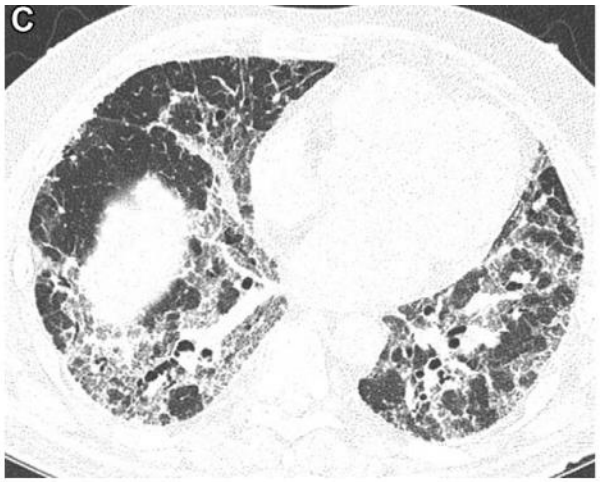


Figure 1: Images show progressive pulmonary fibrosis in a 67-yearold man with a history of relatively mild, stable, fibrotic hypersensitivity pneumonitis. **(A)** Baseline axial CT shows mild ground-glass and reticular abnormality. **(B)** Axial CT angiogram obtained 2 months after infection shows substantially increased reticular abnormality with mild traction bronchiectasis. **(C)** Axial CT obtained 2 months later shows increased traction bronchiectasis indicating progressive fibrosis.

Correlation with clinical and radiological features

severe COVID-19 is characterized by virally induced hyperactivation of the innate immune system resulting in a cytokine storm in early phases of the disease, with striking increases of C-reactive protein, IL1-β and IL-6**,** lymphopenia, and a profound vascular dysfunction resulting in hypercoagulability and thrombo-inflammation, reflected by increased D-dimer levels in almost all patients and an increased incidence of both venous and arterial thrombosis and pulmonary thromboembolism. The late stage of the disease is dominated by DAD and its complications, including progressive respiratory insufficiency and frequent superinfections **(10)**

The most frequent radiological manifestation of COVID-19 is ground-glass opacities (GGO). GGO is defined as increased attenuation on chest CT, which does not obscure the bronchovascular structures. Bilateral lung involvement is typical, and the right lower lobe is the most commonly affected area. Since the pathogen is inhaled with respiratory droplets, and pulmonary infection may be reinforced through active viral replication in the upper and lower respiratory tract**,** the disease is usually in bronchocentric distribution. As the disease progresses, GGO may disappear or may become more confluent and widespread and evolve into frank consolidation. Histology correlates with the imaging patterns. GGO with reticular interstitial thickening in CT is associated with mid-phase DAD, whereas the consolidation pattern is mainly associated with late-phase DAD. Our own observations suggest that GGO and consolidations correlate with multiple pathologic processes, notably DAD, capillary dilatation and congestion, and microthrombosis. Acute superposed bronchopneumonia is more frequently associated with bronchial wall thickening and consolidation and vascular enlargement sign; capillary dilatation and congestion are tightly linked to microthrombosis **(11)**.

SARS-CoV-2

SARS-CoV-2, the causative agent of COVID-19, belongs to the family of coronaviruses, single-stranded positive-sense RNA viruses, with a diameter of 80–120nm. Two other coronaviruses, severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), can also cause ALI resulting in adult respiratory distress syndrome (ARDS). Infections show many similarities in clinical presentation and pathological findings. In the few autopsies of patients, who died from SARS, the predominant pattern of ALI was DAD, including exudative and proliferative phases, inflammatory infiltrates, edema, pneumocyte hyperplasia, and fibrinous exudate. Similar to COVID-19, a prominent vascular endothelial injury and extensive ALI has been observed. Autopsy studies of patients, who died from MERS, are very limited. The ALI is characterized by exudative DAD, pneumocyte hyperplasia, and septal inflammatory infiltrate **(12).**

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2, or SARSCoV-2, has become a global pandemic. **(13)** Pathology studies have shown that COVID-19 causes injuries in multiple organs and tissues, with extensive pulmonary involvement similar to that found in other coronavirus infections (ie, severe acute respiratory syndrome coronavirus and Middle East respiratory syndrome coronavirus infection). **(14).**

Chest CT plays a crucial role in the diagnosis and follow-up of patients with COVID-19 pneumonia. Numerous studies have documented radiographic changes in the acute course of COVID-19, which range from mild to severe cases **(15).**

Recent publications have found that approximately 94% of hospitalized patients have persistent lung parenchymal findings on their discharge CT scans. In addition, **Liu et al (10)** reported that lung opacities in 53.0% of patients with mild COVID-19 resolved with no adverse sequelae within 3 weeks after discharge. **(13)**

Data from previous coronavirus infections (ie, severe acute respiratory syndrome and Middle East respiratory syndrome) suggest that there may be substantial fibrotic consequences in patients with COVID-19. However, little is known about the long-term lung changes after COVID-19 infection. **(16)**

CT protocol and image interpretation

All patients underwent a single inspiratory phase nonenhanced chest CT scanning in two multi-detector CT scanners. All patients were instructed on breath-holding and in the supine position, with the scanning scope covering the entire thorax. The following CT parameters were used: tube voltage 120 kVp with automatic tube current modulation, pulmonary reconstructed kernel and mediastinal reconstructed kernel with a thickness of 5 mm and increment of 5 mm. Meanwhile, a pulmonary reconstructed kernel with a thickness of 1.5 mm and increment of 1.5 mm was for evaluation of the detail of lung CT findings**. (17).** The terminology defined by Fleischner Society was used to describe the patterns of CT images, including:

ground-glass opacity (GGO), consolidation, reticular pattern, and mixed pattern.

The quantitative CT was assessed with a semi-quantitative scoring method according to previous study [10]. The scoring was performed on the 5 mm lung window (window width: 1200–1500 Hu, window level: -700 to - 800 Hu) according to area percentage of lung involvement. Each of lobes was visually scored from 0 to 5 for percentage of lung involvement:

0, no involvement;(1) < 5% involvement; (2) 6–25% involvement; (3) 26–49% involvement; (4) 50–75% involvement; (5) > 75% involvement. Overall CT score was the sum of the individual lobar scores and the maximum score was 25. The evolution tendency of pattern and score over time was evaluated. **(18)** .

CT signs of coronavirus pneumonia

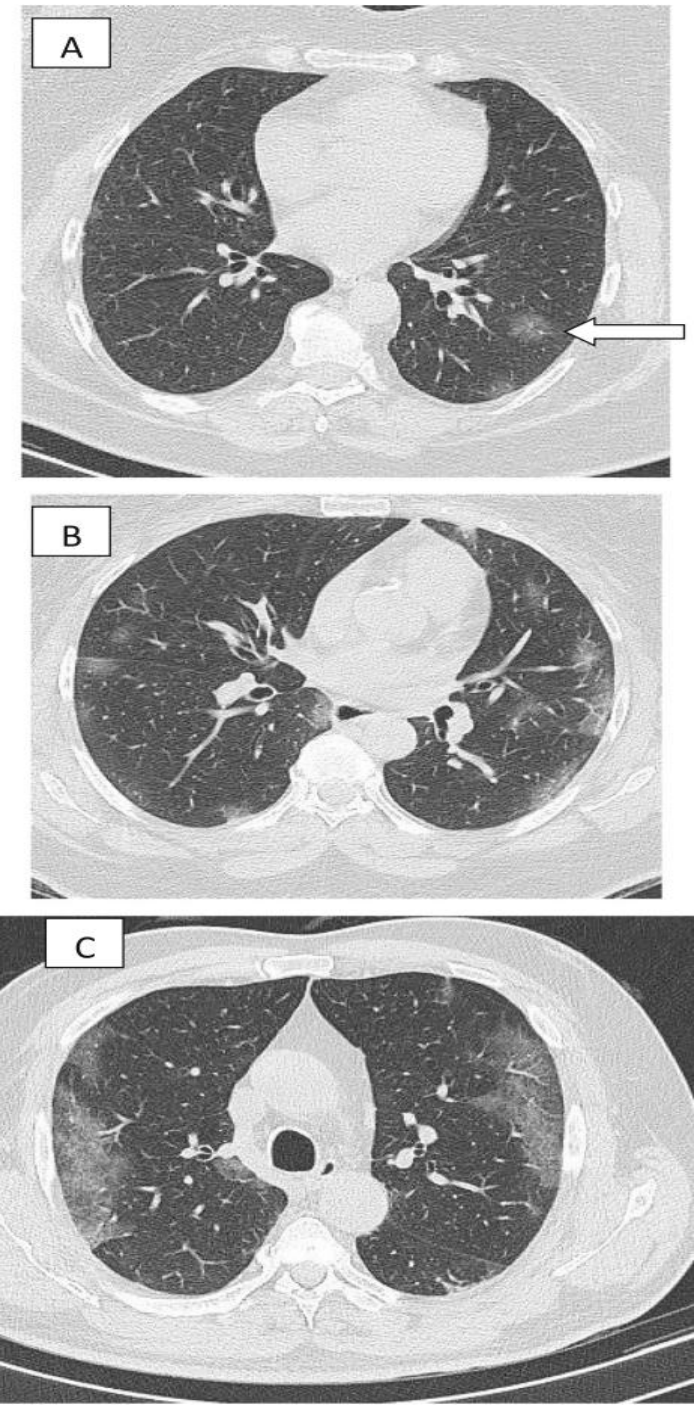
COVID-19 starts as interstitial pneumonitis and then affects lung parenchyma. A wide variety of CT findings in COVID-19 have been reported in the different studies, and the CT findings differ according to the stage of the disease and disease severity and associated co-morbidities**. (14).**

Ground glass opacity Ground glass opacity (GGO) is the non-specific hazy opacification of the lung in the X-ray or computed tomography with no obliteration of bronchial or vascular markings. The presumed pathology includes partial filling of the lung alveoli by fluid, interstitial thickening, or partial collapse of lung alveoli**.** In patients with COVID-19 pneumonia, the most common findings in chest CT is GGO, which is usually described as patchy, peripheral, bilateral, and subpleural. **(19)** in a meta-analysis of 13 studies found

that GGO was the most common manifestation, reported in 83.31% of cases. The meta-analysis involved 13 studies; GGO was the main finding in 11 of them.

The expert recommendations from the Chinese Medical Association Radiology Branch classified the CT manifestations according to the appearance of GGO into four stages **(20)**;

the early stage is characterized by dilatation of capillaries and engorgement of vessels, mild fluid exudates in the alveoli, and interstitial edema, resulting in single or multiple patchy ground glass opacities. The ground glass opacities are mostly peripheral and subpleural.



First stage affection

Fig. 2 Three different cases of early COVID-19 pneumonitis. **(21).**

a. Patient in second day after appearance of symptoms with ill-defined early ground glass infiltration patches in the left lower lobe.

b. Patient in third day of symptoms with multiple patchy areas of sub pleural ground glass infiltration in both lungs.

c. Another patient 4days after symptoms with bilateral wide area of ground glass infiltration.

The second stage is the advanced stage in which the lesions increase in density and size, forming mixed pattern of GGO and consolidation with or without air bronchogram. The cause of this appearance is the exudation into the alveolar space and the lung interstitium **(22)**.

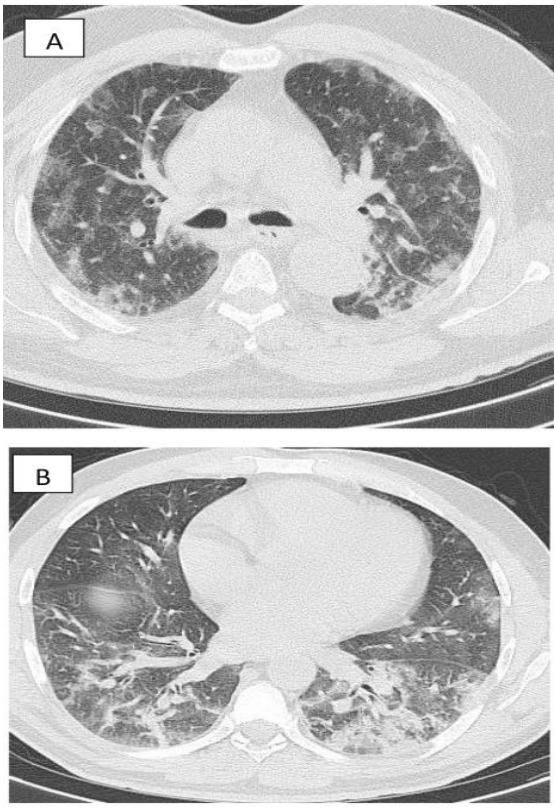


Fig. 3 Two different cases with bilateral multiple patches of ground glass infiltration and subsegmental consolidation, lesions mainly peripheral and posterior. **a.**Patient in third day of symptoms with multiple patchy areas of subpleural ground glass infiltration in both lungs. **b**.Another patient 4 days after symptoms with bilateral wide areas of ground **(21).**

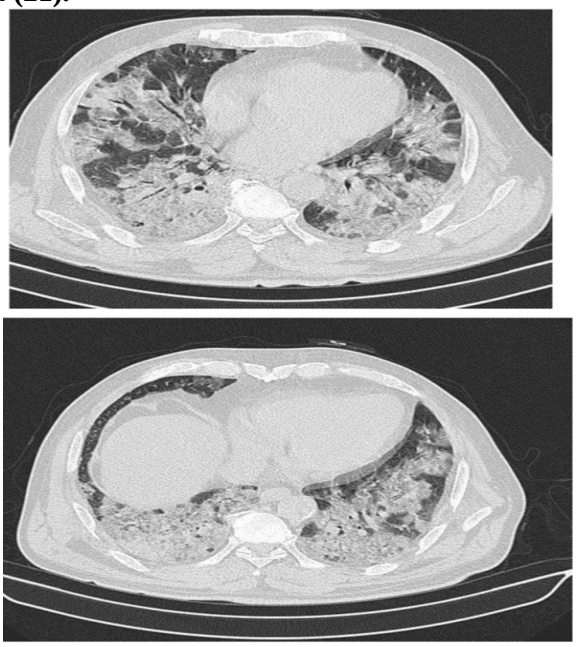
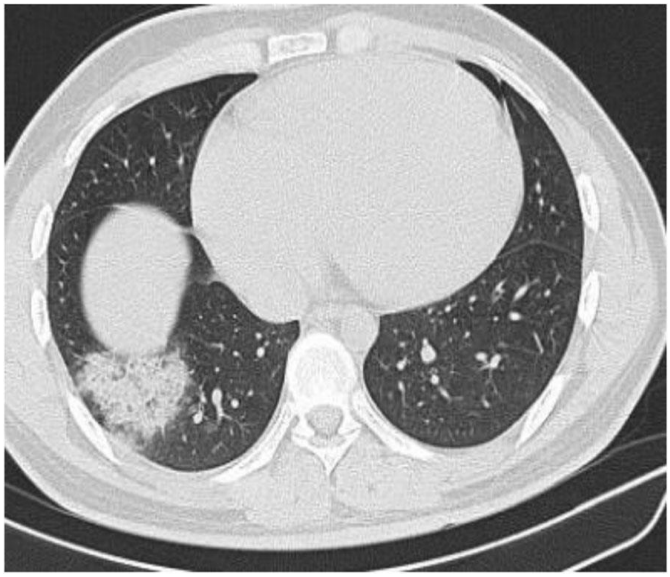


Fig. 4 Patient with COVID-19 pneumonia 10 days after onset ofsymptoms. Wide areas of ground glass appearance andconsolidation with fibrous bands **(21).**

The third severe stage in which there is fibrous exudates into the alveoli reflected in the chest CT as wide areas of consolidation with air bronchogram, with the nonconsolidated area showing patchy ground glass infiltration.

In the 4th dissipation stage, the consolidation and ground glass infiltration gradually resolve, with small areas of residual fibrosis. In some cases, the diffuse ground glass infiltration may give the lungs a white lung appearance .



Fourth stage affection Fig. 5 Patient about 24 days after onset of symptoms. A well-defined area of consolidation/fibrosis seen in the right lower lobe, no other abnormality was noted in both lungs **(21).**

In summary, GGO is the most common and the earliest sign of COVID-19 pneumonia.

Consolidation and air bronchogram

Consolidation is defined as an area of increased attenuation which obscures the bronchial and vascular markings and caused by filling the alveolar spaces by fluid, exudates, transudate, blood, or neoplastic cells **(17).**

Consolidation in COVID-19 pneumonia tends to be **patchy or segmental, irregular or nodular, and mainly subpleural and peripheral**. Consolidations usually appear after 10–12 days of the onset of symptoms, after the appearance of GGO. **(23)** reported high mortality in patients with consolidation**.** in a series including 83 patients also reported consolidation in patients with severe or advanced disease. In a study by **(24)**, the incidence of consolidation was significantly higher in older patients (> 50 years) than younger patients and in patients with symptoms more than 4 days.

Air bronchogram,

which is defined as air-filled bronchi in area with high density, has variable incidence in different reports ranging from 28 to 80% of patients **(25).** Air bronchogram is usually a sign of advanced disease, usually seen after the second week from the onset of symptoms. Air bronchogram can be seen in both GGO and consolidation.

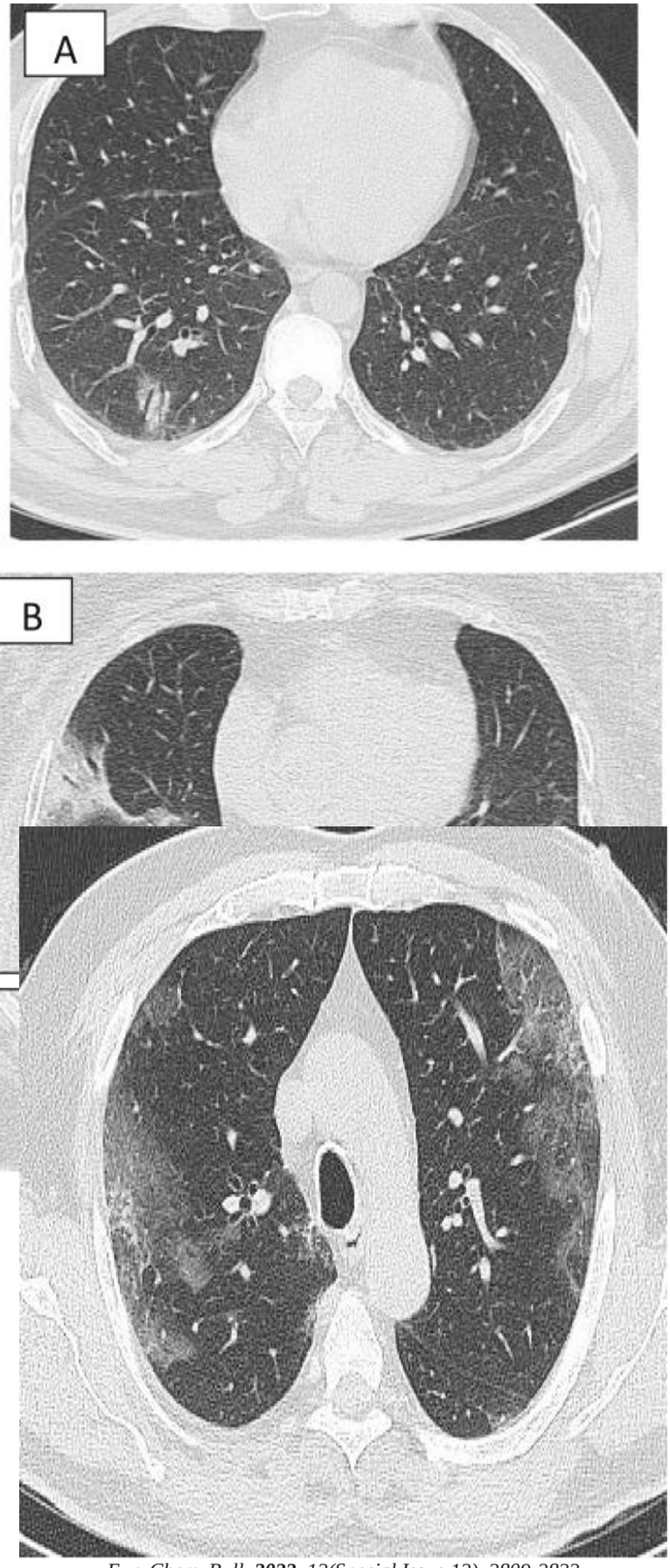


Fig. 6

a Ground glass infiltration with air bronchogram.

b small area of consolidation with air bronchogram. Note the presence of subpleural line (white arrow) **(21).**

Reticulations

Reticulations which appear as lineal interlobular or intralobular density are a relatively late finding in patients with COVID-19, and its reported incidence is 48.5–59% **(26).** The appearance of reticulations is usually associated with clinical progression of the disease. The cause of reticulations is probably caused by lymphocyte infiltration of the interstitial tissues with interlobular and septal thickening. In some studies, the reticular pattern was a common pattern, considered the third common sign after GGO and consolidation **(15).**

Fig. 7 Patient with COVID-19 pneumonia, 8 days after appearance of symptoms with ground glass infiltration and reticulations **(21).**

Crazy paving sign

The crazy paving signs represent thickened interlobular septa superimposed on GGO. This sign represents alveolar edema and interstitial inflammatory reaction **(18).** though the crazy paving sign is a sign of progressive disease and its appearance may indicate that the disease is entering the peak stage **(18),** yet it is the first CT sign to resolve in the absorptive stage while the consolidation, and GGO may persist for up to 26 days **(27)**.

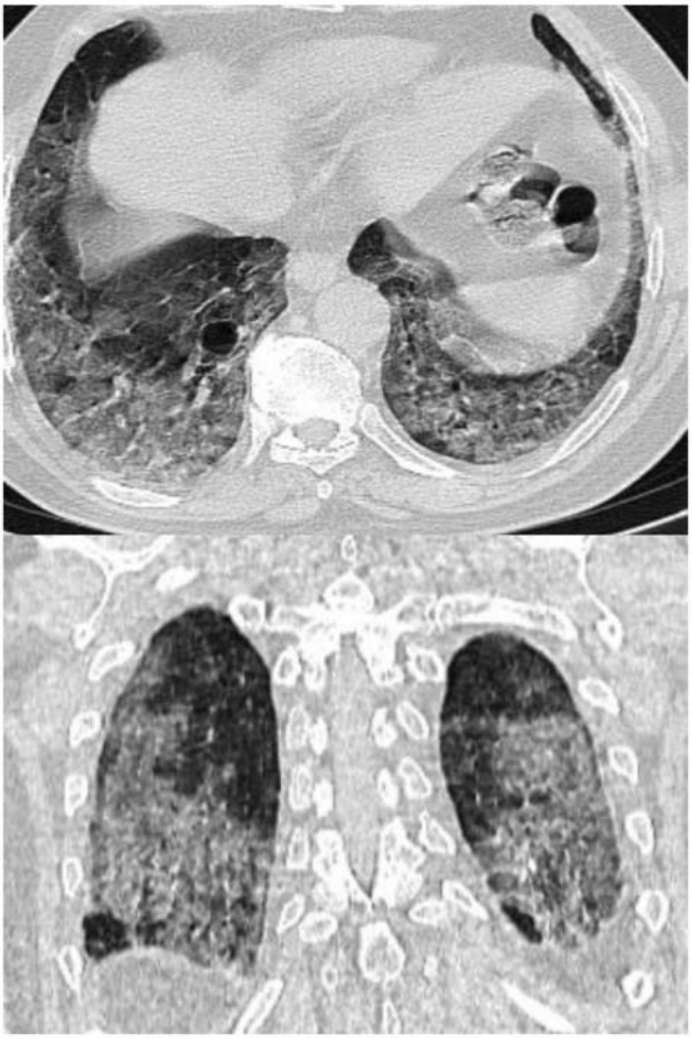


Fig. 8 Axial and coronal CT images of patient with COVID-19, 10 days after the onset of symptoms, showing extensive ground glass infiltration with crazy paving infiltration. The appearance of crazy paving appearance indicates a progressive disease.

Nodules

A nodule is an opacity less than 3 cm in diameter with regular or irregular outline. In general, viral pneumonitis is characterized by the presence of nodules (Franquet 2011). The reported incidence of pulmonary nodules in patients with COVID-19 pneumonia is 3–13% **(18)** and may be associated with surrounding halo **(28).**

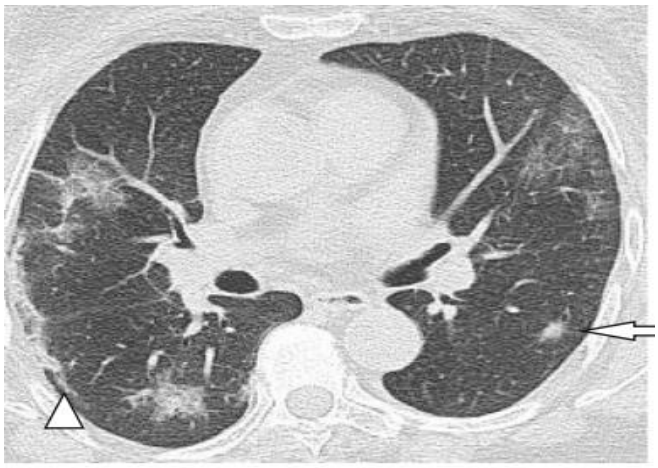
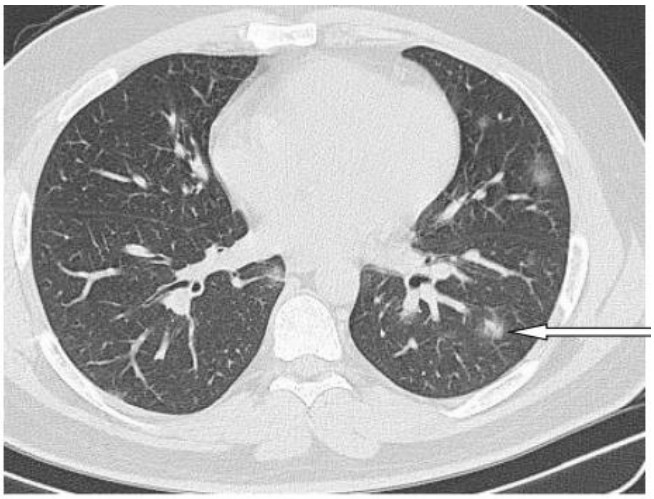


Fig. 9 Patient with COVID-19 pneumonia, with left lower nodule (arrow), note also the presence of ground glass patches and subpleural line (arrow head) **(21).**

Subpleural transparent line

Subpleural transparent line is defined as thin and transparent line between the areas GGO or consoled

ation and the visceral pleura, and they suggested that the presence of this sign indicates advanced stage**.**



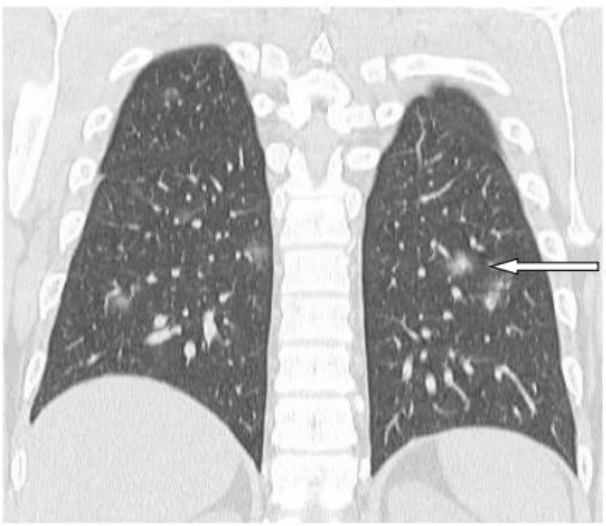


Fig. 10 Subpleural transparent line in three different patients with COVID-19 pneumonia **(21)**

Air bubble sign (vacuolar sign) Air bubble sign (vacuolar sign) refers to a small air containing space < 5 mm

in length within the lung lesion. Some authors called it small cystic changes **(15)**

Vascular enlargement

Vascular dilatation within or around the lesions in CT chest is a common finding in patients with COVID-19. it has been correlated to hyperemia induced by acute inflammatory response and the disruption of the capillary wall inflammatory mediators**.** Interestingly, the vascular enlargement was reported in asymptomatic patients with COVID-19, as an association with GGO **(29)**

Bronchial changes

Bronchial wall thickening in patients with COVID-19 pneumonia has been attributed to inflammatory changes in the bronchial wall, bronchial obstruction, and fibrosis **(28).** (Found in patients with severe or progressive disease **(28).** Bronchial wall thickening is more common in pediatric patients than adult patients.

Bronchiectasis

considered this sign, together with architectural distortion and pleural effusion, a reflection of the severity of the disease and expression of viral load and virulence of the disease**.**

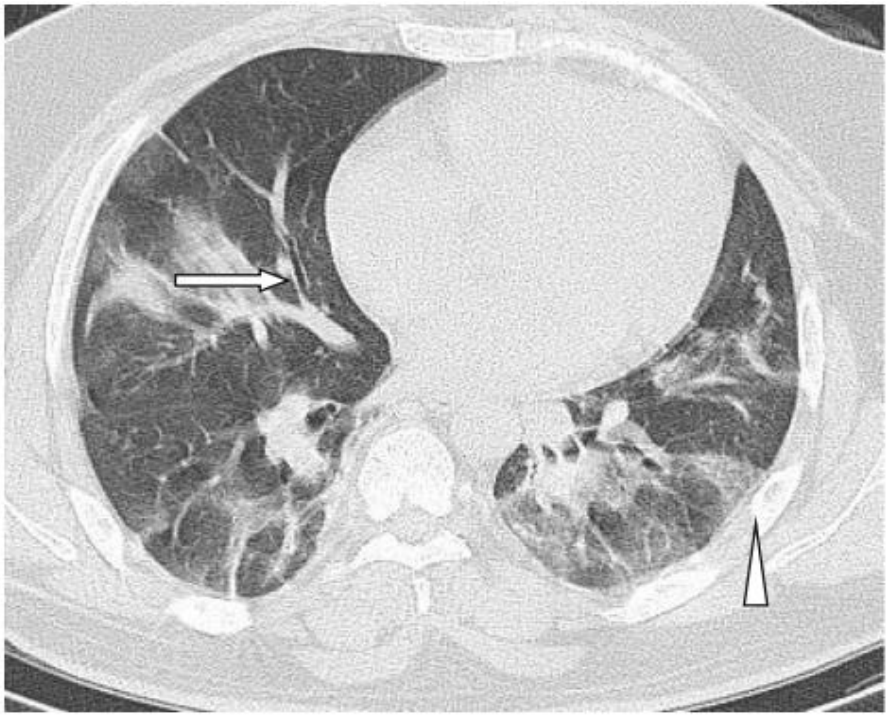


Fig. 11 Mild bronchial dilatation, bronchial wall thickening (arrow). Note the presence of spider web sign in the left lower lobe (arrow head) **(21)**

Spider web sign Originally described by **Wu et al., (26),** spider web sign represents subpleural triangular area of GGO, with weblike thickening of the interlobular septa and retraction of the adjacent pleura.

Pericardial effusion

Pericardial effusion is relatively uncommon in patients with COVID-19.

Mediastinal lymphadenopathy.

Mediastinal lymph nodes are said to be enlarged when the short axis diameter is 1 cm or more **(17).** In patients with COVID-19, mediastinal lymphadenopathy is not a typical feature. **(30)**

In general, the presence of enlarged lymph nodes is considered a sign of severe or critical disease **(28).** Also, the presence of enlarged lymph nodes may indicate superimposed bacterial infection **(31).**

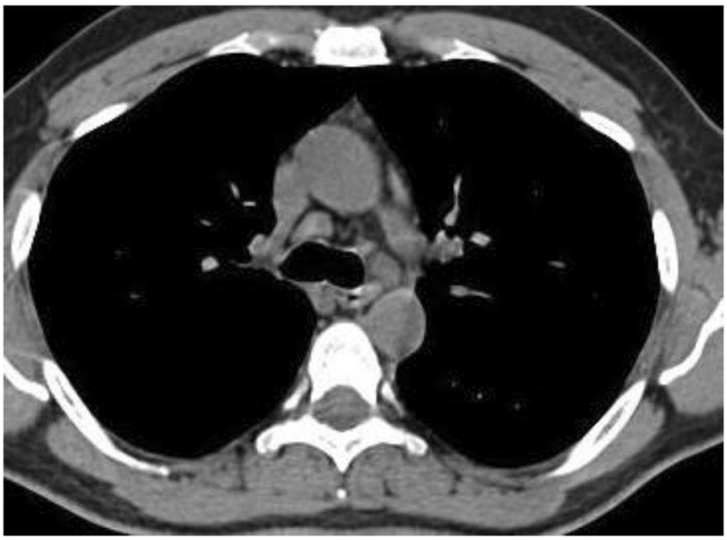


Fig. 12 Enlarged mediastinal lymph nodes in patient with COVID-19 (30)

Fibrosis

Lung fibrosis and fibrous strips have been reported in patients with COVID-19, with reported incidence about Some authors consider it a sign of regression of disease severity and carries good prognosis **(18)**, but other authors consider it a sign of severe disease **(30)** or a warning sign of development of interstitial fibrosis **(5).**

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