'A Pictorial Essay with Long-term Follow-up of Chest CT Manifestations of COVID-19 Pneumonia'

Running title: Long-term Radiologic Follow-up of COVID-19 Pneumonia

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Abstract

Having almost one year elapsed since the COVID-19 pandemic onset, the long-term radiologic consequences of COVID-19 can be evaluated. Although about 30% to 40% residual disease has been reported in mid-term follow-up, no survey on long-term radiologic changes has been conducted. To our knowledge through literature and our experience in follow-up of COVID-19 patients in the frontline, we classified the long-term radiological sequels into the following three groups: complete resolution, fibrotic-parenchymal sequels (mild, moderate, or extensive), and ischemic-parenchymal sequels(cavitation). For each group, some cases with interesting serial imaging were discussed in detail.

Keywords: COVID-19; Pneumonia; Tomography, X-ray computed; Long-term; Sequels.
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Key points

- Long-term radiologic sequels of COVID-19 is highly important.
- Fibrotic-parenchymal and ischemic-parenchymal sequels are the most common types.
- Long-term serial imaging of patients are presented.

Abbreviations

Severe acute respiratory syndrome (SARS); coronavirus infectious disease 2019 (COVID-19); white blood cell (WBC); diffuse alveolar damage (DAD);ground-glass opacity (GGO)

Introduction

After each viral outbreak, the virus's long-term sequels on clinical and radiological aspects are highly significant. Consistently, studies have shown that signs and symptoms of coronavirus infectious disease 2019(COVID-19) have changed over time(1, 2). One-year follow-up in 97 recovered patients from severe acute respiratory syndrome (SARS) showed 27.8% abnormal chest x-ray findings(3) and 23.7% impaired pulmonary function tests. Besides, persistent lung abnormalities in chest computed tomography (CT) examinations were detected in H7N9 survivors 64 months after discharge(4). Therefore, some survivors may complain of respiratory symptoms or impaired daily functioning that necessitates long-term follow-up.

The detrimental consequences and mortality attributed to coronavirus infectious disease 2019 (COVID-19) are confirmed to have an association with the extent of pulmonary involvement(5, 6).Hence, the chest CT scan has been increasingly recommended for diagnosis, prognosis prediction, and follow-up(7). According to the Radiological Society of North America (RSNA) consensus, the most common typical CT patterns are peripheral bilateral GGO with or without consolidation or crazy-paving, multifocal ground-glass opacity (GGO) of rounded morphology, and reverse halo sign(8). Residual radiologic abnormalities have been reported in 40% to 70% of patients three months after discharge(9, 10). The most prevalent CT findings in residual diseases were GGO, subpleural parenchymal bands,interstitial thickening, and crazy-paving(9, 10).

Having almost one year elapsed since the first report of COVID-19 in Wuhan, China, greater attention to the long-term consequences of this new infectious disease in different clinical and radiological aspects is needed. Although the literature is overfilled with the prognostic value of chest CT in COVID-19 patients and some limited previous studies have investigated the changes in short- and mid-term follow-ups(9-11), no previous study has reported such long-term changes. In this pictorial review, we aimed to report the various types of long-term (six months) changes in radiologic findings of COVID-19 patients.

Complete Radiological Resolution

To the experience from previous viral pneumonia, most patients are expected to show complete radiologic resolve on long-term follow-up, particularly non-severe cases(12). To confirm this notion, complete resolution in approximately 57% to 70% of patients was observed in mid-term (3 months) follow-up studies(9, 10). Patients with lower initial pulmonary involvement score, lower hospitalization, lower white blood cell (WBC) count, or less underlying medical diseases are more likely to show complete radiological resolution(9). During the evolution to complete resolution, GGO area might be extended and faded slowly presenting as 'Tinted sign' (Figure 1) (13). This evolution pattern might be due to the gradual resolution of disease and inflammation and consequently re-expansion of alveoli(13). Figures 1-2 present the long-term sequential changes of radiological findings in two patients with complete resolution.

Fibrotic-Parenchymal Sequel

The main histopathological findings in postmortem core biopsies of COVID-19 non-survivors were all components of diffuse alveolar damage (DAD) —damage to alveolar epithelial cells, inflammation and edema, type II pneumocytes hyperplasia, and hyaline membrane formation— in different stages(14, 15). The late phase of DAD corresponds to

fibroblastic tissue and fibrosis. Pieces of evidence of pulmonary fibrosis, including architectural distortions (i.e., traction bronchiectasis, irregular interfaces), reticular pattern (i.e., parenchymal band, interstitial thickening), or honeycombinghave been cited as the most common long-term sequels of various types of viral pneumonia(4, 16). These findings have also been detected in the mid-term follow-up of COVID-19 patients, possibly due to the relatively same underlying histopathological features of different types of viral pneumonia(10). Figures 3-5illustrate long-term temporal changes of chest CT manifestation in three COVID-19 patients who developed pulmonary fibrosis to a different extent. Figures 3, 4, and 5 demonstrate extensive, moderate, and mild fibrosis, respectively.

Ischemic-Parenchymal Sequel (Cavitation)

Pulmonary cavitation has been reported as a rare finding in the late stages of COVID-19 through limited case-reports(17). Although cavitation's pathophysiology in such patients has yet to be understood, some hypothesize that ischemic, infectious, immunological, or mechanical ventilationetiologies might have a role(18). In detail, ischemic parenchymal damage and micro-thromboembolism due to SARS-CoV2 infection could result in cavity formation(19). Viral damage to endothelial cells could also lead to DAD and necrotizing pneumonia and, subsequently, cavity formation and air-fluid level(18). Besides, the host immune system dysregulation due to SARS-CoV2 could result in post-consolidation alveolar wall injuries and cavitation, which increases the susceptibility to further infectious complications. Other pathologies including secondary infections (bacterial or fungal) and thrombo-embolic disease should be ruled out to guide the treatment.Figure 6 illustrate the temporal changes of cavity formation in a laboratory-confirmed COVID-19 patient.

Summary

About one year after the pandemic onset, we can evaluate the long-term radiologic sequels of COVID-19. To our knowledge through literature and our experience in follow-up of COVID-19 patients in the frontline, we classified the long-term imaging consequences into the following threegroups: complete resolution, fibrotic-parenchymal sequels (mild, moderate, or extensive), and ischemic-parenchymal sequels(cavitation). For each group, some cases with interesting serial imaging were discussed in detail.

Putting all pieces of evidence together, it appears that most patients with initial lung involvement will be radiologically unremarkable on long-term investigations. In contrast, patients with more severe initial lung involvement, a history of certain medical conditions, and some laboratory findings are more susceptible to develop long-term pulmonary sequels(9). Due to either direct virus damage or secondary immune system dysfunction, alveolar wall injuries result in DAD, which present with evidence of pulmonary fibrosis or cavitation in imaging investigations(14, 15).

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Figures

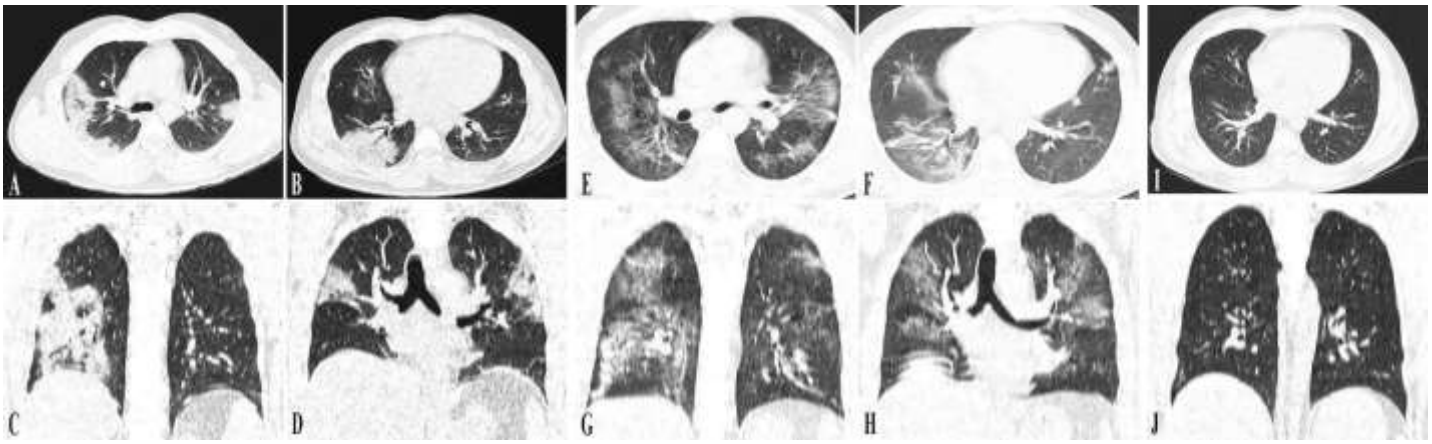


Figure 1: On-admission chest CT scan of a 45 y/o male COVID-19 patient. (A-B): bilateral peripheral air space consolidation typical for Covid-19 pneumonia are visible. (C-D): coronal images depict basilar accentuation on the right side.Axial (E,F) and coronal (G,H) CT images obtained on day 8 of admission in the same patient represent decrease attenuation of consolidation turning from air space consolidation to GGO along with a mild increase in the extent of the involved area (Tinted sign). The long-term CT scan (I,J) of the same patients obtained six months later reveals almost complete improvement with barely visible residual GGO in the right lower lobe.

Figure 2: Chest CT images of a 34 y/o male patient managed in outpatient. Axial (A) and coronal (B) images reveal a reverse halo sign in the left lower lobe. One month later (C-D), the findings were markedly changed with bilateral peripheral GGO. The long-term (six months) follow-up (E-F) showed

complete resolution.

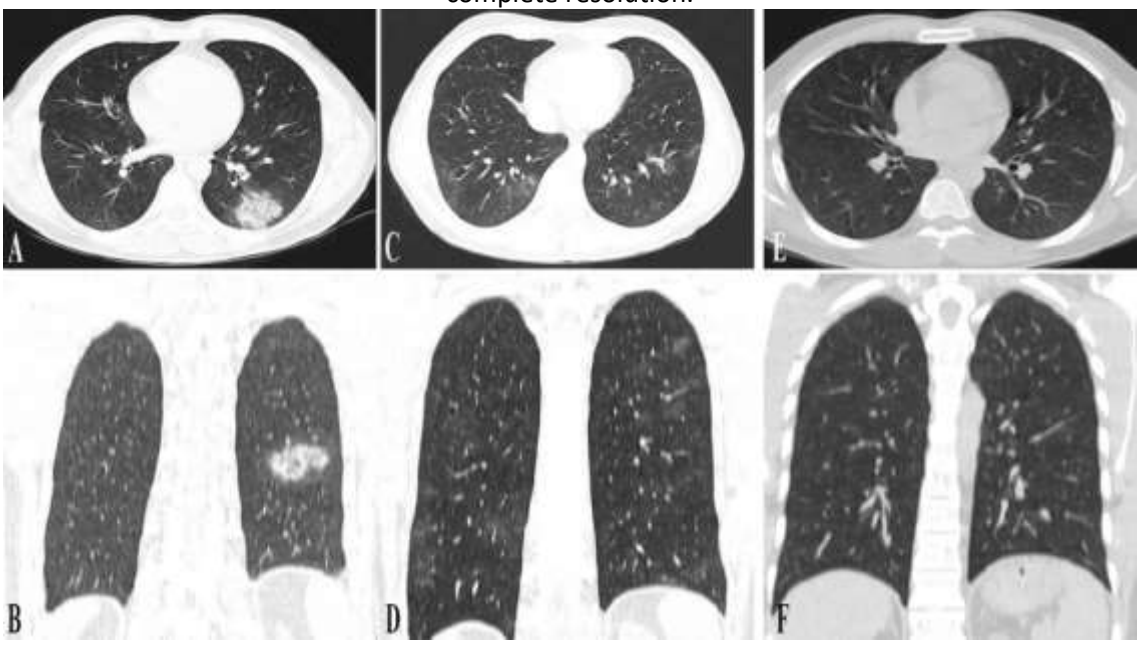


Figure 3: On-admission chest CT scan of a 57 y/o male patient confirmed as a COVID-19 case. Axial images (A-B) depict multiple bilateral GGO and reverse halo sign. Coronal images (C-D) show lower lobe predominance of findings. Follow-up chest CT scan of the same patient obtained one and six months after the initial CT scan (E,F,G,H). Axial (E) and coronal (F) images on the fourth week of ICU admission reveal marked worsening of findings with diffuse GGO along with posterior septal lines and occasional tractional bronchiectasis. The axial (G) and coronal (H) CT images six months after presentation show diffuse GGO, tissue distortion, especially at peripheral parts, honeycombing (Asterix), and tractional bronchiectasis (arrowhead).

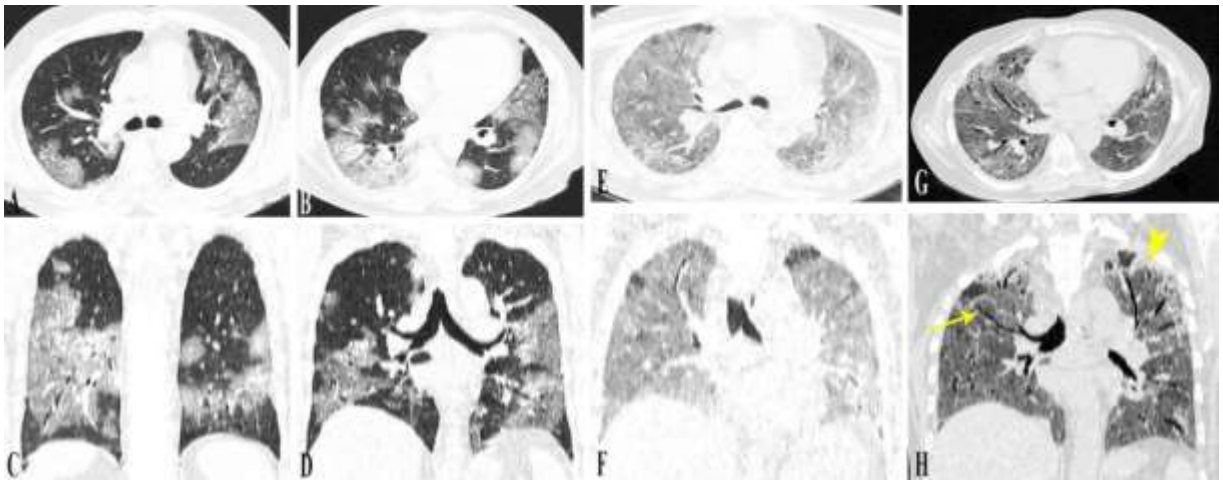
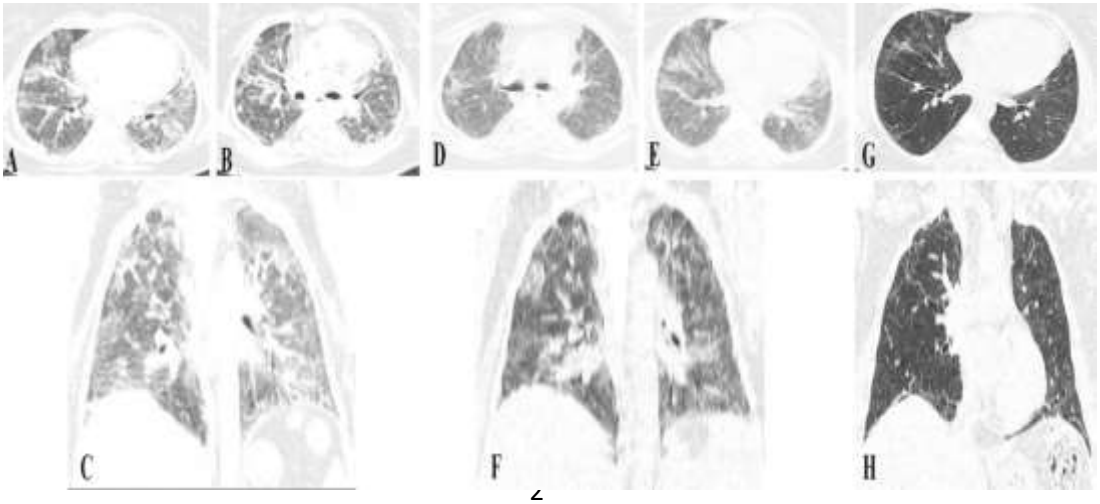


Figure 4: On-admission axial (A-B) and coronal (C) chest CT scan of a 41 y/o female patient represent non-round peripheral and peribroncho-vascular GGO as well as a few consolidations with septal thickening. The chest CT investigation in the same patient two weeks later (D,E,F) shows mild decrease attenuation of GGOs and more prominence of septal lines. On CT scan obtained five months later (G-H), minimal residual GGOs, and mild subpleural fibrosis are evident.



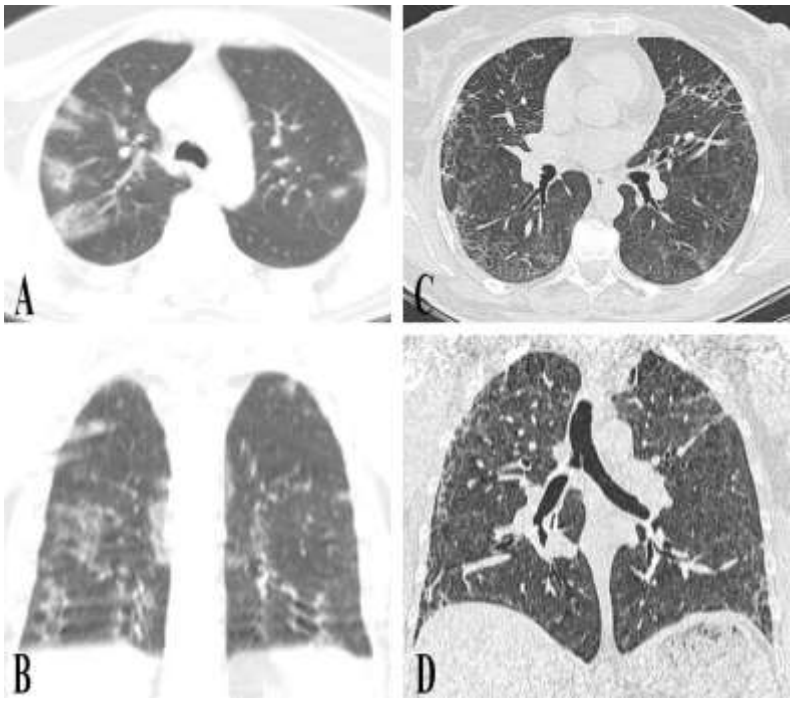


Figure 5: Initial chest CT scan in a 54 y/o female patient. Axial and coronal images (A-B) illustrate bilateral peripheral GGO and reverse halo sign on the right side with lower lobes predominance, typical for Covid-19 pneumonia. The axial and coronal CT images obtained three months later (C-D) depict the almost complete disappearance of GGOs with development of subpleural fibrotic bands (arrow).

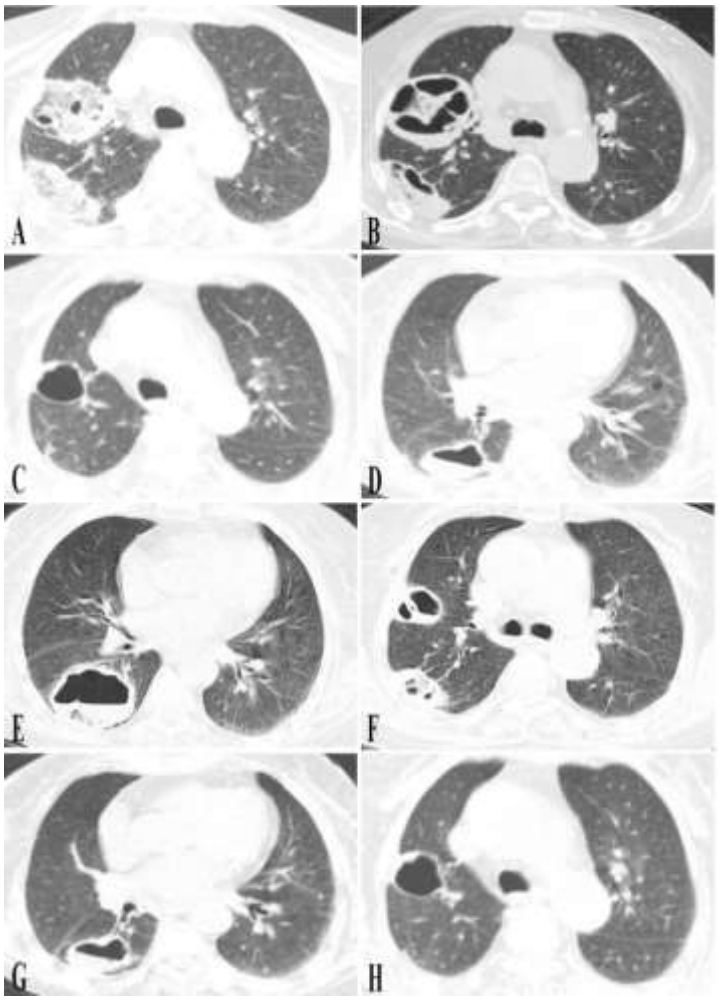


Figure 6: An 84 y/o female patients with no significant past medical history presented with tachypnea and dyspnea. Her PCR test for COVID-19 was positive and she had not undergone mechanical ventilation. In the axial chest CT images at the time of hospital referral, reverse halo sign (A) in the right upper lobe (RUL) with small central cavitary changes were detected. Cavity progression (B) was observed ten days later, and another chest CT (C-D) 10 days later again in the same patient demonstrated that the reverse halo sign was almost resolved and cavities were well-formed. Chest CT images in the same patient one (E-F) and five (G-H) months after the last CT: persistence of lung cavities and air-fluid level are seen.