**Original Article** | Thoracic Imaging

eISSN 2005-8330
https://doi.org/10.3348/kjr.2020.0215
Korean J Radiol 2020;21(6):746-755



Korean Journal of Radiology
KJR

# Prediction of the Development of Pulmonary Fibrosis Using Serial Thin-Section CT and Clinical Features in Patients Discharged after Treatment for COVID-19 Pneumonia

Minhua Yu, MD[1], Ying Liu, MD[1], Dan Xu, MD[1], Rongguo Zhang, MD, PhD[2], Lan Lan, MD[1], Haibo Xu, MD, PhD[1]

[1]Department of Radiology, Zhongnan Hospital of Wuhan University, Wuchang District, Wuhan, Hubei, China; [2]Institute of Advanced Research, Infervision, Beijing, China

**Objective:** To identify predictors of pulmonary fibrosis development by combining follow-up thin-section CT findings and clinical features in patients discharged after treatment for COVID-19.

**Materials and Methods:** This retrospective study involved 32 confirmed COVID-19 patients who were divided into two groups according to the evidence of fibrosis on their latest follow-up CT imaging. Clinical data and CT imaging features of all the patients in different stages were collected and analyzed for comparison.

**Results:** The latest follow-up CT imaging showed fibrosis in 14 patients (male, 12; female, 2) and no fibrosis in 18 patients (male, 10; female, 8). Compared with the non-fibrosis group, the fibrosis group was older (median age: 54.0 years vs. 37.0 years, $p = 0.008$), and the median levels of C-reactive protein (53.4 mg/L vs. 10.0 mg/L, $p = 0.002$) and interleukin-6 (79.7 pg/L vs. 11.2 pg/L, $p = 0.04$) were also higher. The fibrosis group had a longer-term of hospitalization (19.5 days vs. 10.0 days, $p = 0.001$), pulsed steroid therapy (11.0 days vs. 5.0 days, $p < 0.001$), and antiviral therapy (12.0 days vs. 6.5 days, $p = 0.012$). More patients on the worst-state CT scan had an irregular interface (59.4% vs. 34.4%, $p = 0.045$) and a parenchymal band (71.9% vs. 28.1%, $p < 0.001$). On initial CT imaging, the irregular interface (57.1%) and parenchymal band (50.0%) were more common in the fibrosis group. On the worst-state CT imaging, interstitial thickening (78.6%), air bronchogram (57.1%), irregular interface (85.7%), coarse reticular pattern (28.6%), parenchymal band (92.9%), and pleural effusion (42.9%) were more common in the fibrosis group.

**Conclusion:** Fibrosis was more likely to develop in patients with severe clinical conditions, especially in patients with high inflammatory indicators. Interstitial thickening, irregular interface, coarse reticular pattern, and parenchymal band manifested in the process of the disease may be predictors of pulmonary fibrosis. Irregular interface and parenchymal band could predict the formation of pulmonary fibrosis early.

**Keywords:** *COVID-19; Computed tomography; Prediction; Clinical characteristic; Fibrosis; Follow-up*

## INTRODUCTION

The 2019 novel coronavirus pneumonia (COVID-19) initially broke out in Wuhan, China in early December 2019 and spread across the whole nation in two months (1, 2). In China, the COVID-19 outbreak is currently ebbing, but outside China, it is gaining exponential momentum. European countries (Italy, Spain, Germany, France), the U.S., Iran, and South Korea are facing tremendous challenges to cope with COVID-19, which was officially declared a pandemic by World

**Received:** March 3, 2020 **Revised:** March 26, 2020 **Accepted:** March 28, 2020
This study was supported by the National Natural Science Foundation of China (Grants No. 81771819).
**Corresponding author:** Haibo Xu, MD, PhD, Department of Radiology, Zhongnan Hospital of Wuhan University, Wuchang District, Wuhan 430071, Hubei Province, China.
• Tel: (86) 13545009416 • Fax: (8627) 67812533 • E-mail: xuhaibo1120@hotmail.com

Korean Journal of Radiology
KJR

Health Organization on March 11, 2020. By March 24, a total of 81767 patients have been reported as having COVID-19 pneumonia in China, of which 3283 died. Numbers outside China are surging dramatically. To date, more than 375000 COVID-19 in over 195 countries have been confirmed. Among them, 16362 patients have died.

Coronavirus mainly cause respiratory system infections in humans, which can range from a minor common cold to severe diseases such as severe acute respiratory syndrome (SARS) and middle east respiratory syndrome (MERS). Unlike SARS, which often leads to severe clinical symptoms and high mortality rates (3, 4), clinical epidemiological studies on COVID-19 have demonstrated that the majority of infected patients display mild symptoms, and many of them have recovered after appropriate medical treatments (5). Of the confirmed COVID-19 pneumonia patients 5.0% were admitted to the ICU, 2.3% of them underwent invasive mechanical ventilation, and 1.4% of patients died (5).

Thin-section chest CT scans have been contributing greatly to the disease assessment and patient condition surveillance in relation to COVID-19. Researchers in radiology have reported that typical imaging features of COVID-19 patients include ground-glass opacity (GGO) (6, 7), crazy-paving pattern, and consolidation (8). Once discharged, a sizable amount of patients had almost no CT abnormalities (9); yet many still demonstrated apparent residual parenchymal abnormalities on follow-up chest CT scans (10). However it has rarely been reported whether discharged patients develop fibrosis, and/or which group of patients is more likely to develop pulmonary fibrosis. In this study, we aimed to identify predictors for development of pulmonary fibrosis by combining follow-up thin-section CT and clinical features in patients discharged after treatment for COVID-19.

## MATERIALS AND METHODS

### Patients and CT Imaging

This retrospective study was approved by the Institutional Review Board of Zhongnan Hospital of Wuhan University (IRB No. 2020004) and the requirement for written informed consent was waived. In this study, 32 patients who had been hospitalized for COVID-19 at Zhongnan Hospital of Wuhan University between January 5, 2020 and February 16, 2020 were tracked after discharge. The inclusion criteria included: 1) COVID-19 positive cases confirmed by pharyngeal swab nucleic acid testing; 2) patients have been hospitalized and then discharged after treatment; 3) patients underwent thin-section chest CT scans at least twice during the hospitalization and had at least one follow-up CT after discharge. Discharge criteria were in line with the Chinese guideline for COVID-19 pneumonia. Patients were divided into two groups according to the evidence of fibrosis on the latest follow-up CT imaging: fibrosis group (with evidence of fibrosis) and non-fibrosis group (without evidence of fibrosis). Clinical data for comparative analysis performed between the two groups included age, sex, comorbidities, signs and symptoms, laboratory test results, pulsed steroid therapy, antiviral therapy, length of hospital stay, days from illness onset to initial and worst-state CT scans, and days after discharge to latest follow-up CT scans. Laboratory test results were obtained when patients were in their most critical condition.

CT imaging features were also collected from these 32 patients. Several non-contrast thin-section chest CT scans were performed for each patient. We reviewed three CT scans for each patient: the initial CT examination after illness onset (named "initial CT"), the CT examination at the patient's worst condition (named "worst-state CT"), and the latest follow-up CT after discharge (named "latest follow-up CT").

The thin-section CT scanning was performed at the end of full inspirations in two multi-slice spiral CT (Discovery 64, GE Medical Systems, Milwaukee, Wis and SOMATOM Definition, Siemens Healthcare, Erlangen, Germany). The parameters were as follows: slice thickness, 1 mm; interval, 1 mm; tube voltage, 120 kV; tube current, automatic; window level, -700 HU; window width, 1500 HU.

### Review of CT Images

All axial and reconstructed (coronal/sagittal) CT images of initial and follow-up scans were reviewed by three experienced radiologists independently and any disagreement was resolved by discussion and consensus.

Initial and follow-up CT imaging features were reviewed and compared for the following aspects: presence or absence of specific lesions, extent, location, distribution of lesions and number of involved segments. Reviewers evaluated the presence of GGO, consolidation, crazy paving, parenchymal bands, irregular interfaces, coarse reticular pattern, and traction bronchiectasis. In addition, interstitial thickening, mosaic attenuation, air-bronchogram, lymphadenopathy (more than 1 cm in short-axis diameter) and pleural effusion were recorded as well, when detected.

 https://doi.org/10.3348/kjr.2020.0215 

The extent of the lesions were classified as small (longest diameter < 1 cm), moderate (diameter 1 cm to ≤ 3 cm), large (diameter is greater than 3 cm and less than 50% of the lung segment), and segmental (lesions involves more than 50% of the lung segment) (11). According to locations, lesions were classified as upper lobe, middle lobe or lingular segment, lower lobe, and bilateral lobes. Lesion distribution was described as peripheral (outer 1/3 of the lung), central (inner 2/3) or both central and peripheral. The number of segments containing a specific category of lesions for each patient was counted.

Pulmonary fibrosis on follow-up chest CT imaging was defined as a combination of findings including parenchymal bands, irregular interfaces, coarse reticular pattern, and traction bronchiectasis (12-14).

### Statistical Analysis

Clinical and CT features of fibrosis and non-fibrosis groups were compared. Continuous variables (i.e., age, laboratory examinations, number of segments of particular lesions, et al.) were expressed as median (interquartile range [IQR]) and compared with a two independent samples *t* test (homogeneity of variance) or Mann-Whitney U test (heterogeneity of variance). Categorical variables (i.e., comorbidity, signs and symptoms, particular characteristics on CT imaging, et al.) were expressed as numbers (%) and compared by the $\chi^2$ test or Fisher's exact test between groups. $P < 0.050$ was considered statistically significant. All statistical analyses were performed by SPSS (version 23.0, IBM Corp., Armonk, NY, USA).

## RESULTS

Thirty-two patients were included in our study. Fourteen patients (male: 12, female: 2) with evidence of fibrosis on the latest follow-up CT imaging were designated as the fibrosis group and 18 patients (male: 10, female: 8) with totally absorbed lesions as the non-fibrosis group.

### Clinical Characteristic Comparison between Groups

The demographic and clinical characteristics of the two groups are comparatively presented in Table 1. Patients in the fibrosis group were older (median age, 54.0; IQR: 49.0–65.3) than those in the non-fibrosis group (median age, 37.0; IQR: 30.5–52.5) ($p = 0.008$). There were no obvious differences in the proportion of patients with diabetes (fibrosis group vs. non-fibrosis group: 7.1% vs. 5.6%, $p > 0.050$), cardiac disease (7.1% vs. 5.6%, $p > 0.050$) and chronic obstructive pulmonary disease (7.1% vs. 0%, $p = 0.437$) between the two groups. However, the proportion of patients with hypertension in the fibrosis group was clearly higher than that in the non-fibrosis group (fibrosis group vs. non-fibrosis group: 28.6% vs. 0%, $p = 0.028$). In terms of symptoms of COVID-19 pneumonia, most patients manifested fever (27 of 32, 84.4%), cough (15 of 32, 46.9%) and fatigue (14 of 32, 43.8%), but the difference was not statistically significant between the two groups ($p > 0.050$). More patients in fibrosis group had dyspnea (6 of 14, 42.9%) and higher respiratory rate (median: 20.0; IQR: 18.8–27.8) than those in the non-fibrosis group (1 of 18, 5.6% and median: 18.5; IQR: 18.0–20.0) ($p < 0.050$). Muscle ache (8 of 32, 25.0%) and diarrhea (2 of 32, 6.25%) were uncommon in all COVID-19 pneumonia patients.

Laboratory examinations varied widely between the two groups (Table 1). The median lymphocyte count in the fibrosis group (median: 0.6 x $10^9$/L; IQR: 0.4–0.9) was obviously lower than the non-fibrosis group (median: 1.1 x $10^9$/L; IQR: 0.8–1.3) ($p = 0.003$). Levels of C-reactive protein (CRP) (fibrosis group: 53.4 mg/L; IQR: 29.6–111.2 vs. non-fibrosis group: 10.0 mg/L; IQR: 5.2–23.6) and interleukin-6 (IL-6) (fibrosis group: 79.7 pg/L; IQR: 10.5–98.3 vs. non-fibrosis group: 11.2 pg/L; IQR: 4.4–19.2) were increased in all patients but higher in the fibrosis group than in the non-fibrosis group ($p < 0.050$). Levels of lactic dehydrogenase were increased in the fibrosis group (median, 289.0 U/L; IQR: 179.0–428.5), but in the normal range in the non-fibrosis group (median, 180.0 U/L; IQR: 148.5–191.0) (normal range 110–245 U/L).

Patients in the fibrosis group had a longer period of hospital stay than those in the non-fibrosis group (fibrosis group vs. non-fibrosis group: 19.5 days vs. 10.0 days, $p = 0.001$), as well as a higher proportion of patients at the intensive care unit admission (35.7% vs. 0%; $p = 0.010$). During their hospital stay, most patients received pulsed steroid therapy (11 of 14, 78.6% in fibrosis group and 10 of 18, 55.6% in non-fibrosis group, $p = 0.266$). Moreover, patients in the fibrosis group also received a longer time of pulsed steroid therapy than those in the non-fibrosis group (median, 11.0 days vs. 5.0 days, $p < 0.001$). All (32 of 32, 100%) patients received antiviral therapy (oseltamivir and arbidol hydrochloride) during hospitalization, and patients in the fibrosis group received a longer treatment with antiviral therapy than the non-fibrosis group (median, 12.0 days vs. 6.5 days, $p = 0.012$). The median number of


https://doi.org/10.3348/kjr.2020.0215

Korean Journal of Radiology
KJR

**Table 1. Clinical and Laboratory Characteristics of Included Patients**

| | Fibrosis Group (n = 14) | Non-Fibrosis Group (n = 18) | *P* |
|---|---|---|---|
| Clinical characteristic | | | |
| Age (year) | 54.0 (49.0–65.3) | 37.0 (30.5–52.5) | 0.008 |
| Male: female ratio | 12:2 | 10:8 | 0.124 |
| Comorbidity | | | |
| Diabetes | 1 (7.1) | 1 (5.6) | > 0.050 |
| Hypertension | 4 (28.6) | 0 (0) | 0.028 |
| Cardiac disease | 1 (7.1) | 1 (5.6) | > 0.050 |
| Chronic obstructive pulmonary disease | 1 (7.1) | 0 (0) | 0.437 |
| Signs and symptoms | | | |
| Fever | 14 (100) | 13 (72.2) | 0.052 |
| Dyspnea | 6 (42.9) | 1 (5.6) | 0.027 |
| Cough | 6 (42.9) | 9 (50.0) | 0.735 |
| Fatigue | 7 (50.0) | 7 (38.9) | 0.721 |
| Muscle ache | 5 (35.7) | 3 (16.7) | 0.252 |
| Diarrhea | 0 (0) | 2 (11.1) | 0.492 |
| Respiratory rate (breaths per min) | 20.0 (18.8–27.8) | 18.5 (18.0–20.0) | 0.026 |
| Laboratory examinations | | | |
| White blood cell count ($x10^9$/L) | 3.8 (2.8–5.4) | 4.0 (2.9–4.4) | 0.687 |
| Lymphocyte count ($x10^9$/L) | 0.6 (0.4–0.9) | 1.1 (0.8–1.3) | 0.003 |
| Lactic dehydrogenase (U/L) | 289.0 (179.0–428.5) | 180.0 (148.5–191.0) | 0.014 |
| Creatine kinase (U/L) | 112.0 (68.0–203.5) | 62.0 (51.5–114.5) | 0.031 |
| C-reactive protein (mg/L) | 53.4 (29.6–111.2) | 10.0 (5.2–23.6) | 0.002 |
| Alanine transaminase (U/L) | 52.0 (31.0–142.0) | 23.5 (12.0–39.0) | 0.021 |
| Creatinine (μmol/L) | 81.2 (73.1–94.8) | 69.1 (61.5–80.3) | 0.029 |
| Interleukin-6 (pg/mL) | 79.7 (10.5–98.3) | 11.2 (4.4–19.2) | 0.040 |
| Treatment | | | |
| Pulsed steroid therapy | 11 (78.6) | 10 (55.6) | 0.266 |
| Days of pulsed steroid therapy | 11.0 (8.0–13.0) | 5.0 (3.0–6.3) | < 0.001 |
| Antiviral therapy | 14 (100) | 18 (100) | - |
| Days of antiviral therapy | 12.0 (9.5–14.8) | 6.5 (5.0–12.0) | 0.012 |
| Others | | | |
| Length of hospital stay (day) | 19.5 (11.5–21.8) | 10.0 (6.0–15.3) | 0.001 |
| Intensive care unit admission | 5 (35.7) | 0 (0) | 0.010 |
| Days from illness onset to initial CT scan | 5.5 (3.0–7.3) | 2.5 (1.0–5.3) | 0.039 |
| Days from illness onset to worst CT scan | 11.0 (7.0–15.0) | 9.5 (6.5–11.0) | 0.042 |
| Days after discharge to latest follow-up CT scan | 9.0 (7.0–11.0) | 9.0 (7.8–11.3) | - |

Data are median (interquartile range) or n (%).

days from illness onset to initial CT scan were 5.5 (IQR: 3.0–7.3) in the fibrosis group and 2.5 (IQR: 1.0–5.3) in the non-fibrosis group ($p$ = 0.039), while the number of days from illness onset to worst-state CT scan were 11.0 (IQR: 7.0–15.0) in the fibrosis group and 9.5 (IQR: 6.5–11.0) in the non-fibrosis group ($p$ = 0.042). Regarding the time after discharge to the latest follow-up CT scan, the median was 9.0 days both in the fibrosis group (IQR: 7.0–11.0) and the non-fibrosis group (IQR: 7.8–11.3).

### Characteristics of Lesions on Follow-Up CT Imaging

We reviewed the three CT scans for every patient. As shown in Figure 1 and Table 2, pure GGO (19 of 32, 59.4%), GGO with consolidation (20 of 32, 62.5%), interstitial thickening (18 of 32, 56.3%), crazy paving (12 of 32, 37.5%), irregular interface (19 of 32, 59.4%) and parenchymal band (23 of 32, 71.9%) located mainly in bilateral (28 of 32, 87.5%) and lower lobes (31 of 32, 96.9%) with peripheral distribution (14 of 32, 43.8%) were the most common CT features in all patients with

 https://doi.org/10.3348/kjr.2020.0215 

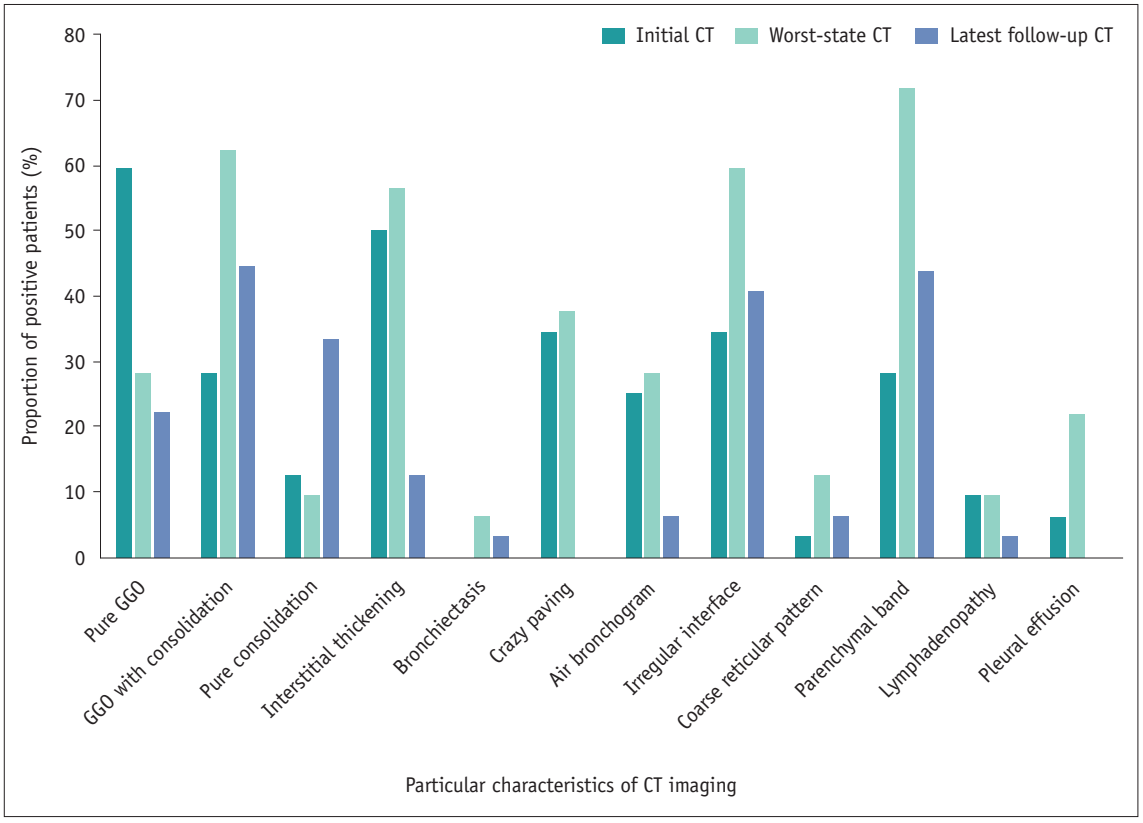


**Fig. 1. Proportion of positive patients for typical imaging features of COVID-19 pneumonia on thin-section CT at different stages.** Pure GGO, GGO with consolidation, interstitial thickening, crazy paving, irregular interface, and parenchymal band are most common CT features in COVID-19 pneumonia. GGO = ground-glass opacity

COVID-19 pneumonia. However, pure consolidation (4 of 32, 12.5%), bronchiectasis (2 of 32, 6.3%), mosaic attenuation (0 of 32, 0%), coarse reticular pattern (4 of 32, 12.5%), lymphadenopathy (3 of 32, 9.4%) or pleural effusion (7 of 32, 21.9%) were uncommon in patients with COVID-19 in this study.

We made a comparative analysis of imaging features in follow-up CT in all patients (Tables 2, 3). As shown in Tables 2, 3 and Figure 2, compared with the initial CT, more segments were involved (worst-state CT vs. initial CT: median 11.0 vs. median 7.0, $p = 0.017$) on worst-state CT. Further, in the worst-state CT there were more segments affected with moderate (worst-state CT vs. initial CT: median 3.5 vs. median 2.0, $p = 0.011$) and large lesions (worst-state CT vs. initial CT: median 3.5 vs. median 1.0, $p = 0.021$). In terms of CT features, more patients manifested pure GGO on initial CT imaging and GGO with consolidation on worst-state CT ($p = 0.019$). There was no significant difference in interstitial thickening, bronchiectasis, crazy paving, air bronchogram, coarse reticular pattern, lymphadenopathy and pleural effusion between initial CT and worst-state CT ($p > 0.050$). However, more patients displayed irregular interface (19 of 32, 59.4% vs. 11 of 32, 34.4%, $p = 0.045$) and parenchymal band (23 of 32, 71.9% vs. 9 of 32, 28.1%, $p < 0.001$) on worst-state CT than on initial CT. For the latest follow-up CT after discharge, typical features such as interstitial thickening (4 of 32, 12.5%) and crazy paving (0 of 32, 0%) were almost resolved (Figs. 2, 3), but evidence of fibrosis, such as irregular interface (13 of 32, 40.6%) and parenchymal band (14 of 32, 43.8%) were still obvious (Table 2, Fig. 2).

The imaging features on initial CT and worst-state CT were further compared between the fibrosis group and the non-fibrosis group (Table 4). For initial CT, the number of involved segments in patients in the fibrosis group (median, 11.0; IQR: 4.0–13.0) was larger than that in the non-fibrosis group (median, 3.5; IQR: 1.0–10.0) ($p = 0.040$). Additionally, more patients in the fibrosis group manifested irregular interface (8 of 14, 57.1% vs. 3 of 18, 16.7%; $p = 0.027$) and parenchymal band (7 of 14, 50.0% vs. 2 of 18, 11.1%; $p = 0.022$). For worst-state CT, more segments were involved in patients in the fibrosis group (median, 14.0;


https://doi.org/10.3348/kjr.2020.0215

Korean Journal of Radiology
KJR

**Table 2. Particular Characteristics on CT Imaging of All 32 Patients**

| Characteristic | Initial CT (n = 32) | $P^1$ | Worst-State CT (n = 32) | $P^2$ | Latest Follow-Up CT (n = 32) |
|---|---|---|---|---|---|
| Number of affected segments | 7.0 (1.3–11.8) | 0.017 | 11.0 (4.5–14.0) | 0.001 | 3.5 (0.0–10.5) |
| Location* | | | | | |
| Upper lobe | 19 (59.4) | | 24 (75.0) | | 14 (43.8) |
| Middle lobe or lingula | 16 (50.0) | | 19 (59.4) | | 13 (40.6) |
| Lower lobe | 29 (90.6) | | 31 (96.9) | | 17 (53.1) |
| Bilateral lobes | 23 (71.9) | | 28 (87.5) | | 17 (53.1) |
| Distribution | | 0.302 | | 0.584 | |
| Central | 0 (0) | | 0 (0) | | 0 (0) |
| Peripheral | 14 (43.8) | | 10 (31.3) | | 7 (21.9) |
| Both central and peripheral† | 18 (56.3) | | 22 (68.8) | | 11 (34.4) |
| Opacification | | 0.019 | | 0.105 | |
| Pure GGO | 19 (59.4) | | 9 (28.1) | | 4 (22.2) |
| GGO with consolidation | 9 (28.1) | | 20 (62.5) | | 8 (44.4) |
| Pure consolidation | 4 (12.5) | | 3 (9.4) | | 6 (33.4) |
| Interstitial thickening | 16 (50.0) | 0.616 | 18 (56.3) | < 0.001 | 4 (12.5) |
| Bronchiectasis | 0 (0) | 0.472 | 2 (6.3) | 0.554 | 1 (3.1) |
| Mosaic attenuation | 0 (0) | - | 0 (0) | - | 0 (0) |
| Crazy paving | 11 (34.4) | 0.794 | 12 (37.5) | 0.001 | 0 (0) |
| Air bronchogram | 8 (25.0) | 0.777 | 9 (28.1) | 0.02 | 2 (6.3) |
| Irregular interface | 11 (34.4) | 0.045 | 19 (59.4) | 0.134 | 13 (40.6) |
| Coarse reticular pattern | 1 (3.1) | 0.352 | 4 (12.5) | 0.668 | 2 (6.3) |
| Parenchymal band | 9 (28.1) | < 0.001 | 23 (71.9) | 0.023 | 14 (43.8) |
| Lymphadenopathy | 3 (9.4) | - | 3 (9.4) | 0.606 | 1(3.1) |
| Pleural effusion | 2 (6.3) | 0.150 | 7 (21.9) | 0.016 | 0 (0) |

Data are median (interquartile range) or n (%). $P^1$: positive patients in worst-state CT period compared to that in initial CT period, $P^2$: positive patients in worst-state CT period compared to that in latest follow-up CT period. *Each patient may have multiple lung lobes affected, †Lesions located both central and peripheral in patient. GGO = ground-glass opacity

**Table 3. Number of Segments with Lesions of Particular Extents in All Patients**

| Lesion Diameter | Number of Segments* | | | | |
|---|---|---|---|---|---|
| | Initial CT (n = 32) | $P^1$ | Worst-State CT (n = 32) | $P^2$ | Latest Follow-Up CT (n = 32) |
| < 1 cm | 3.0 (0.3–6.0) | 0.320 | 4.0 (2.0–6.8) | 0.016 | 1.5 (0.0–4.8) |
| 1 to < 3cm | 2.0 (1.0–4.0) | 0.011 | 3.5 (2.0–6.0) | 0.013 | 1.5 (0.0–4.8) |
| 3 cm to < 50% of segment | 1.0 (0.0–3.8) | 0.021 | 3.5 (2.0–5.0) | 0.004 | 0.0 (0.0–3.0) |
| 50% of segment or more | 0.0 (0.0–0.8) | 0.162 | 0.0 (0.0–2.8) | 0.029 | 0.0 (0.0–0.0) |

Data are median (interquartile range). *Each segment may have several lesions of different extents. $P^1$: number of positive segments on worst-state CT imaging compared to that on initial CT imaging, $P^2$: number of positive segments on worst-state CT imaging compared to that on latest follow-up CT imaging.

IQR: 11.8–18.0) than in the non-fibrosis group (median, 6.5; IQR: 3.0–11.3) ($p < 0.001$). As for CT imaging features, more patients in the fibrosis group manifested interstitial thickening (11 of 14, 78.6% vs. 7 of 18, 38.9%; $p = 0.036$), air bronchogram (8 of 14, 57.1% vs. 1 of 18, 5.6%; $p = 0.004$), irregular interface (12 of 14, 85.7% vs. 7 of 18, 38.9%; $p = 0.012$), coarse reticular pattern (4 of 14, 28.6% vs. 0 of 18, 0%; $p = 0.028$), parenchymal band (13 of 14, 92.9% vs. 10 of 18, 55.6%; $p = 0.044$) and pleural effusion (6 of 14, 42.9% vs. 1 of 18, 5.6%; $p = 0.027$).

## DISCUSSION

To date, many patients with COVID-19 have been discharged. However, little attention has been paid to the follow-up of the recovered patients. In our study, we compared clinical data between patients with or without fibrosis on CT images after discharge, and also reviewed CT images from 32 patients in three different stages before and after discharge to investigate changes in imaging features with disease progression.


https://doi.org/10.3348/kjr.2020.0215

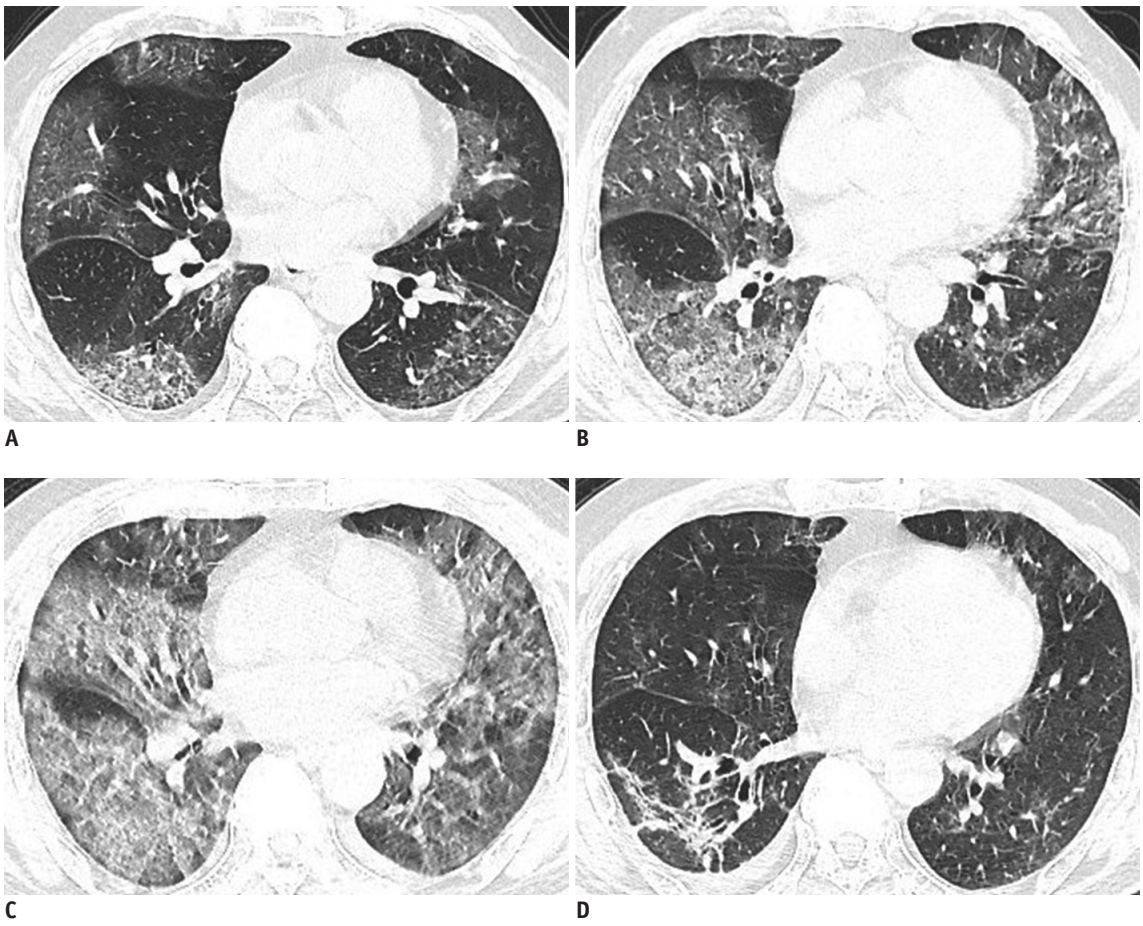


**Fig. 2. Follow-up thin-section CT imaging of 72-year-old man with confirmed COVID-19 pneumonia with fever and muscle aches.**
**A.** First thin-section chest CT scan in our hospital on January 12, 2020 (10 days after symptoms onset). CT imaging shows GGO and little interstitial thickening in bilateral lobes and mainly peripheral sections. **B.** Three days later, crazy paving is obvious, with also some consolidation. Extent of lesions is increased. **C.** On January 18, patient was admitted to ICU due to aggravation of disease. CT imaging shows consolidation in bilateral lobes with increased lesion extent. **D.** On February 8, 5 days after discharge, most lesions are absorbed and parenchymal bands with residual GGO are observed. ICU = intensive care unit

Clinically, patients with fibrosis after discharge were older than those without fibrosis ($p$ = 0.008), which implied that fibrosis was likely to be more common in elderly or immunocompromised patients, similar to SARS (13). More patients in the fibrosis group had dyspnea and higher respiratory rate than those in the non-fibrosis group, indicating that patients with evidence of fibrosis after discharge had worse lung function at the time of illness onset.

The normal median for white blood cell count, levels of CK, ALT and creatinine perhaps had no diagnostic value for COVID-19, which is consistent with an associated study (15). Reduced lymphocyte count may be significant for the diagnosis of COVID-19 pneumonia. The increase in the inflammatory indicators CRP and cytokine factor leukomyin-6 indicated inflammatory damage caused by COVID-19 virus, and generated a series of immune responses, similar to the immunopathogenesis observed in SARS (16). Furthermore, considering the higher level of CRP and IL-6 in patients with fibrosis ($p$ < 0.050), an increased inflammatory reaction might lead to the formation of pulmonary fibrosis during recovery. Therefore, these clinical parameters might contribute to predicting which patients with COVID-19 pneumonia are at a higher risk of developing pulmonary fibrosis after discharge. Patients with fibrosis had a longer period of hospital stay than those without fibrosis, and also a higher rate of admission to the intensive care unit. During their hospital stay, patients in the fibrosis group also received pulsed steroid therapy and antiviral therapy for a longer period of time compared to the non-fibrosis group, which revealed that patients with fibrosis after discharge might have a more serious experience of the disease during hospitalization.

Pulmonary fibrosis is an important prognostic


https://doi.org/10.3348/kjr.2020.0215

Korean Journal of Radiology
KJR

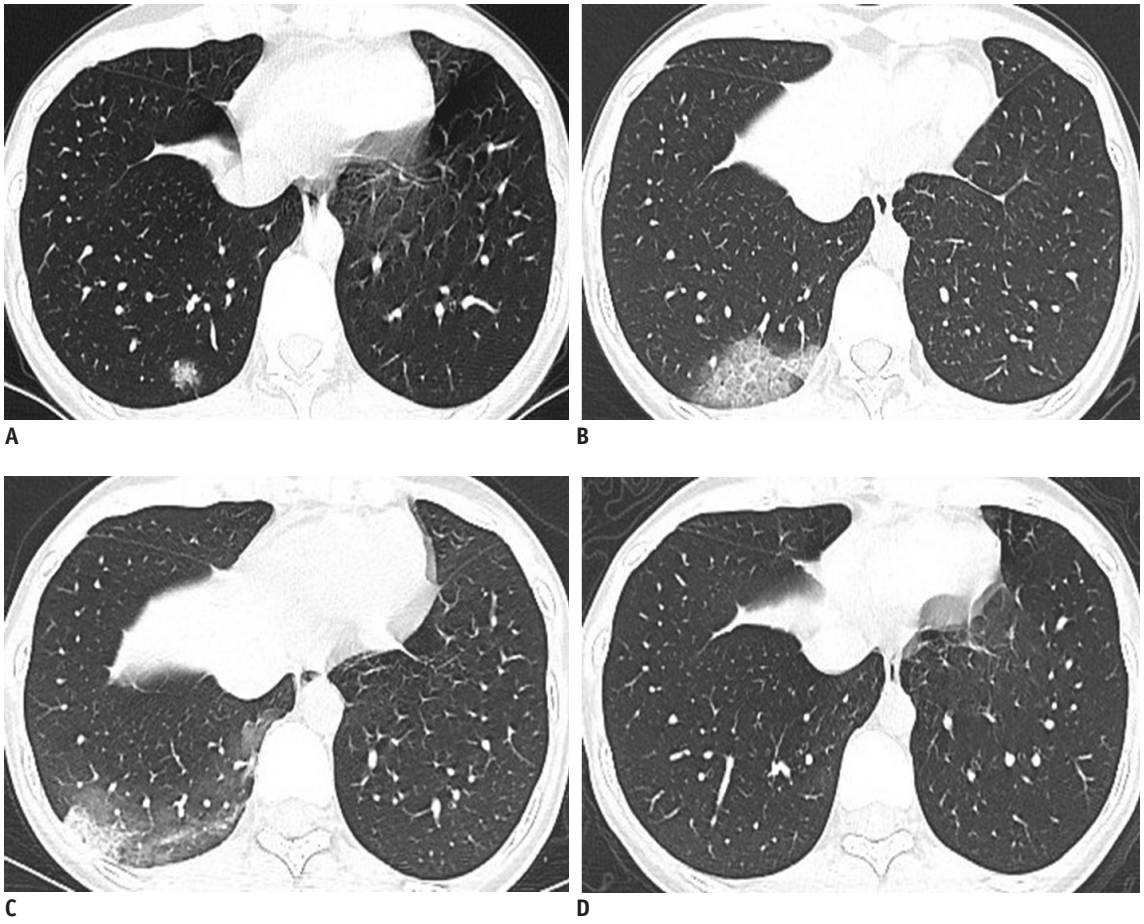


**Fig. 3. Typical CT imaging findings of 22-year-old woman with fever.**
**A.** On January 21 (1 day after illness onset), CT imaging shows small region of GGO located in right lower lobe. **B.** Five days later, extent of lesion is increased, typical features of interstitial thickening and crazy paving are observed. **C.** Ten days after initial CT imaging, CT imaging shows consolidation with GGO in edge and little parenchymal bands. **D.** Nine days after discharge during follow-up, all lesions are totally absorbed and there is normal pulmonary parenchyma appearance.

manifestation of a series of lung diseases (17, 18). In our study, follow-up thin-section CT scans from all discharged patients showed that evidence of fibrosis, such as irregular interface and parenchymal band, was found in almost half of patients. We further reviewed and compared the initial and worst-state CT imaging to investigate the process of COVID-19 pneumonia and imaging features that might indicate the formation of fibrosis after discharge. The results revealed that the most common CT features in COVID-19 pneumonia were pure GGO, GGO with consolidation, interstitial thickening, crazy paving, irregular interface, and parenchymal band located mainly in bilateral lower lobes with peripheral distribution. As the disease progressed, there were more segments involved and a larger lesion diameter manifested on worst-state CT imaging. More patients on worst-state CT exhibited irregular interface and parenchymal band than on initial CT. For the latest follow-up CT after discharge, typical features such as interstitial thickening and crazy paving were almost absorbed, but evidence of fibrosis, such as irregular interface and parenchymal band were still obvious. These results indicate that irregular interface and parenchymal band may manifest during the whole course of COVID-19 pneumonia, although part of them was resolved eventually. However, most of the other lesions were gradually absorbed, with the exception of residual GGO, which is partly consistent with a previous study (19).

When comparing the imaging features of patients between the two groups on initial CT and worst-state CT, more patients in the fibrosis group manifested interstitial thickening, air bronchogram, irregular interface, coarse reticular pattern, parenchymal band and pleural effusion on worst-state CT. However, on the initial CT, only irregular interface and parenchymal band showed significant

 https://doi.org/10.3348/kjr.2020.0215 

**Table 4. Comparison of Particular Characteristics between Groups on Worst-State CT Imaging**

| Characteristic | Initial CT | | | Worst-State CT | | |
|---|---|---|---|---|---|---|
| | Fibrosis Group (n = 14) | Non-Fibrosis Group (n = 18) | *P* | Fibrosis Group (n = 14) | Non-Fibrosis Group (n = 18) | *P* |
| Number of affected segments | 11.0 (4.0–13.0) | 3.5 (1.0–10.0) | 0.040 | 14.0 (11.8–18.0) | 6.5 (3.0–11.3) | < 0.001 |
| Location* | | | | | | |
| Upper lobe | 11 (78.6) | 8 (44.4) | | 14 (100) | 10 (55.6) | |
| Middle lobe or lingula | 11 (78.6) | 5 (27.8) | | 14 (100) | 5 (27.8) | |
| Lower lobe | 13 (92.9) | 16 (88.9) | | 14 (100) | 17 (94.4) | |
| Bilateral lobes | 11 (78.6) | 12 (66.7) | | 14 (100) | 14 (77.8) | |
| Distribution | | | 0.165 | | | 0.124 |
| Central | 0 (0) | 0 (0) | | 0 (0) | 0 (0) | |
| Peripheral | 4 (28.6) | 10 (71.4) | | 2 (14.3) | 8 (44.4) | |
| Both central and peripheral† | 10 (55.6) | 8 (44.4) | | 12 (85.7) | 10 (55.6) | |
| Opacification | | | 0.714 | | | 0.929 |
| Pure GGO | 9 (64.3) | 10 (55.6) | | 4 (28.6) | 5 (27.8) | |
| GGO with consolidation | 4 (28.6) | 5 (27.8) | | 9 (64.3) | 11 (61.1) | |
| Pure consolidation | 1 (7.1) | 3 (16.7) | | 1 (7.1) | 2 (11.1) | |
| Interstitial thickening | 8 (57.1) | 8 (44.4) | 0.722 | 11 (78.6) | 7 (38.9) | 0.036 |
| Bronchiectasis | 0 (0) | 0 (0) | - | 2 (14.3) | 0 (0) | 0.183 |
| Mosaic attenuation | 0 (0) | 0 (0) | - | 0 (0) | 0 (0) | - |
| Crazy paving | 6 (42.9) | 5 (27.8) | 0.465 | 6 (42.9) | 6 (33.3) | 0.718 |
| Air bronchogram | 6 (42.9) | 2 (11.1) | 0.096 | 8 (57.1) | 1 (5.6) | 0.004 |
| Irregular interface | 8 (57.1) | 3 (16.7) | 0.027 | 12 (85.7) | 7 (38.9) | 0.012 |
| Coarse reticular pattern | 1 (7.1) | 0 (0) | 0.437 | 4 (28.6) | 0 (0) | 0.028 |
| Parenchymal band | 7 (50.0) | 2 (11.1) | 0.022 | 13 (92.9) | 10 (55.6) | 0.044 |
| Lymphadenopathy | 3 (21.4) | 0 (0) | 0.073 | 3 (21.4) | 0 (0) | 0.073 |
| Pleural effusion | 2 (14.3) | 0 (0) | 0.183 | 6 (42.9) | 1 (5.6) | 0.027 |

Data are median (interquartile range) or n (%). *Each patient may have multiple lung lobes affected, †Lesions located both central and peripheral in patient.

differences between groups. More segments were involved in patients in the fibrosis group than in the non-fibrosis group both on initial and worst-state CT. Since they have a common mechanism of pathogenesis, we could speculate that interstitial thickening, irregular interface, coarse reticular pattern and parenchymal band, manifested in the process of disease, might be predictors of pulmonary fibrosis in patients recovered from COVID-19 pneumonia (20). Irregular interface and parenchymal band could be two early predictors of pulmonary fibrosis.

This study has some limitations. Firstly, the sample size of 32 patients was relatively small. However, as more COVID-19 patients are being discharged, further studies will consider increasing the sample size of discharged patients. Secondly, only patients who were discharged from hospitals after being cured were included in this study. Thus, this may introduce a selection bias for the distribution and extent of pulmonary lesions. Finally, the follow-up time for these patients is relatively short, and it is unknown whether irregular interface and parenchymal band features will permanently remain. In addition, in this study, irregular interface and parenchymal band on initial CT were more common in the fibrosis group, but this may be because the interval between illness onset and initial CT exam in the fibrosis group was longer.

In conclusion, we found that pure GGO, GGO with consolidation, interstitial thickening, crazy paving, irregular interface and parenchymal band located mainly in bilateral lower lobes with peripheral distribution were the most common CT features in COVID-19. Fibrosis was more likely to develop in patients with severe clinical conditions, especially patients with high inflammatory indicators. Interstitial thickening, irregular interface, coarse reticular pattern, and parenchymal band, manifested in the process of the disease, may be predictors of pulmonary fibrosis. Irregular interface and parenchymal band could predict the formation of pulmonary fibrosis early.


https://doi.org/10.3348/kjr.2020.0215

Korean Journal of Radiology
KJR

### Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

### ORCID iDs

Haibo Xu
https://orcid.org/0000-0002-8451-8979
Minhua Yu
https://orcid.org/0000-0001-9360-4177
Ying Liu
https://orcid.org/0000-0003-1343-5399
Dan Xu
https://orcid.org/0000-0001-9128-5328
Rongguo Zhang
https://orcid.org/0000-0001-6566-8843
Lan Lan
https://orcid.org/0000-0002-4599-1042

## REFERENCES

1. Wang FS, Zhang C. What to do next to control the 2019-nCoV epidemic? *Lancet* 2020;395:391-393
2. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med* 2020;382:727-733
3. Lee N, Hui D, Wu A, Chan P, Cameron P, Joynt GM, et al. A major outbreak of severe acute respiratory syndrome in Hong Kong. *N Engl J Med* 2003;348:1986-1994
4. Lew TW, Kwek TK, Tai D, Earnest A, Loo S, Singh K, et al. Acute respiratory distress syndrome in critically ill patients with severe acute respiratory syndrome. *JAMA* 2003;290:374-380
5. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020 Feb 28 [Epub]. https://doi.org/10.1056/NEJMoa2002032
6. Song F, Shi N, Shan F, Zhang Z, Shen J, Lu H, et al. Emerging 2019 novel coronavirus (2019-nCoV) pneumonia. *Radiology* 2020;295:210-217
7. Wei J, Xu H, Xiong J, Shen Q, Fan B, Ye C, et al. 2019 novel coronavirus (COVID-19) pneumonia: serial computed tomography findings. *Korean J Radiol* 2020;21:501-504
8. Chung M, Bernheim A, Mei X, Zhang N, Huang M, Zeng X, et al. CT imaging features of 2019 novel coronavirus (2019-nCoV). *Radiology* 2020;295:202-207
9. Shi H, Han X, Zheng C. Evolution of CT manifestations in a patient recovered from 2019 novel coronavirus (2019-nCoV) pneumonia in Wuhan, China. *Radiology* 2020;295:20
10. Duan YN, Qin J. Pre- and posttreatment chest CT findings: 2019 novel coronavirus (2019-nCoV) pneumonia. *Radiology* 2020;295:21
11. Wong KT, Antonio GE, Hui DS, Lee N, Yuen EH, Wu A, et al. Thin-section CT of severe acute respiratory syndrome: evaluation of 73 patients exposed to or with the disease. *Radiology* 2003;228:395-400
12. Zerhouni EA, Naidich DP, Stitik FP, Khouri NF, Siegelman SS. Computed tomography of the pulmonary parenchyma. Part 2: interstitial disease. *J Thorac Imaging* 1985;1:54-64
13. Antonio GE, Wong KT, Hui DS, Wu A, Lee N, Yuen EH, et al. Thin-section CT in patients with severe acute respiratory syndrome following hospital discharge: preliminary experience. *Radiology* 2003;228:810-815
14. Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, et al. Diagnosis of idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med* 2018;198:e44-e68
15. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020;395:507-513
16. Cameron MJ, Bermejo-Martin JF, Danesh A, Muller MP, Kelvin DJ. Human immunopathogenesis of severe acute respiratory syndrome (SARS). *Virus Res* 2008;133:13-19
17. Winterbauer RH, Ludwig WR, Hammar SP. Clinical course, management, and long-term sequelae of respiratory failure due to influenza viral pneumonia. *Johns Hopkins Med J* 1977;141:148-155
18. Becroft DM. Bronchiolitis obliterans, bronchiectasis, and other sequelae of adenovirus type 21 infection in young children. *J Clin Pathol* 1971;24:72-82
19. Pan F, Ye T, Sun P, Gui S, Liang B, Li L, et al. Time course of lung changes on chest CT during recovery from 2019 novel coronavirus (COVID-19) pneumonia. *Radiology* 2020 Feb 13 [Epub]. https://doi.org/10.1148/radiol.2020200370
20. Ward PA, Hunninghake GW. Lung inflammation and fibrosis. *Am J Respir Crit Care Med* 1998;157(4 Pt 2):S123-S129

 https://doi.org/10.3348/kjr.2020.0215 