Radiology

ORIGINAL RESEARCH • THORACIC IMAGING

Six-month Follow-up Chest CT Findings after Severe COVID-19 Pneumonia

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Conflicts of interest are listed at the end of this article.

See also the editorial by Wells et al in this issue.

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Background: Little is known about the long-term lung radiographic changes in patients who have recovered from coronavirus disease 2019 (COVID-19), especially those with severe disease.

Purpose: To prospectively assess pulmonary sequelae and explore the risk factors for fibrotic-like changes in the lung at 6-month follow-up chest CT of survivors of severe COVID-19 pneumonia.

Materials and Methods: A total of 114 patients (80 [70%] men; mean age, 54 years ± 12) were studied prospectively. Initial and follow-up CT scans were obtained a mean of 17 days ± 11 and 175 days ± 20, respectively, after symptom onset. Lung changes (opacification, consolidation, reticulation, and fibrotic-like changes) and CT extent scores (score per lobe, 0–5; maximum score, 25) were recorded. Participants were divided into two groups on the basis of their 6-month follow-up CT scan: those with CT evidence of fibrotic-like changes (traction bronchiectasis, parenchymal bands, and/or honeycombing) (group 1) and those without CT evidence of fibrotic-like changes (group 2). Between-group differences were assessed with the Fisher exact test, two-sample *t* test, or Mann-Whitney *U* test. Multiple logistic regression analyses were performed to identify the independent predictive factors of fibrotic-like changes.

Results: At follow-up CT, evidence of fibrotic-like changes was observed in 40 of the 114 participants (35%) (group 1), whereas the remaining 74 participants (65%) showed either complete radiologic resolution (43 of 114, 38%) or residual ground-glass opacification or interstitial thickening (31 of 114, 27%) (group 2). Multivariable analysis identified age of greater than 50 years (odds ratio [OR]: 8.5; 95% CI: 1.9, 38; $P = .01$), heart rate greater than 100 beats per minute at admission (OR: 5.6; 95% CI: 1.1, 29; $P = .04$), duration of hospital stay greater than or equal to 17 days (OR: 5.5; 95% CI: 1.5, 21; $P = .01$), acute respiratory distress syndrome (OR: 13; 95% CI: 3.3, 55; $P < .001$), noninvasive mechanical ventilation (OR: 6.3; 95% CI: 1.3, 30; $P = .02$), and total CT score of 18 or more (OR: 4.2; 95% CI: 1.2, 14; $P = .02$) at initial CT as independent predictors for fibrotic-like changes in the lung at 6 months.

Conclusion: Six-month follow-up CT showed fibrotic-like changes in the lung in more than one-third of patients who survived severe coronavirus disease 2019 pneumonia. These changes were associated with an older age, acute respiratory distress syndrome, longer hospital stays, tachycardia, noninvasive mechanical ventilation, and higher initial chest CT score.

Online supplemental material is available for this article.

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2, or SARS-CoV-2, has become a global pandemic. As of November 19, 2020, this disease has been found in more than 200 countries, with 55 659 785 confirmed cases and 1 338 769 deaths (1). Pathology studies (2,3) 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).

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 (4–7). Recent publications (8,9) 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. 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 (11–13). However, little is known about the long-term

Abbreviations

ARDS = acute respiratory distress syndrome, COVID-19 = coronavirus disease 2019, DLco = diffusing capacity of the lung for carbon monoxide, GGO = ground-glass opacities, IQR = interquartile range, OR = odds ratio

Summary

This prospective longitudinal study found that approximately one-third of participants showed chest CT findings with pulmonary fibrosis-like changes within 6 months of recovery from severe coronavirus disease 2019 pneumonia.

Key Results

- Approximately one-third of participants (40 of 114, 35%) recovered from severe coronavirus disease 2019 developed fibrotic-like changes in the lung within 6 months of disease onset.
- Older age (>50 years), acute respiratory distress syndrome, and higher baseline CT lung involvement score (≥18 out of a possible score of 25) were associated with fibrotic-like changes in the lung.
- Twenty-seven of 104 participants (26%) had an abnormal diffusing capacity of the lung for carbon monoxide, or DLco, at 6-month follow up, which more frequently occurred in participants with fibrotic-like changes in the lung than in those without fibrotic-like changes.

lung changes after COVID-19 infection. The purpose of this study was to evaluate pulmonary changes on 6-month follow-up chest CT scans and to explore the risk factors for fibrotic-like changes in the lung in patients who recovered from severe COVID-19 pneumonia.

Materials and Methods

Study Design and Participants

This prospective study obtained ethical approval from the ethics commissions of Wuhan Jinyintan Hospital and Wuhan Union Hospital. All participants remained anonymous, and written informed content was acquired. This trial was registered with the Chinese Clinical Trial Registry with identifier ChiCTR2000038609.

We prospectively enrolled 114 patients with severe COVID-19 who had been discharged from the hospital after treatment for COVID-19 as inpatients between December 25, 2019, and February 20, 2020, at our institutions (Wuhan Jinyintan Hospital, $n = 69$; Wuhan Union Hospital, $n = 45$) (Fig 1). Throat swab samples were collected for confirmation of severe acute respiratory syndrome coronavirus 2 with a reverse-transcription polymerase chain reaction test (Sansure Biotech) as previously described (14,15). The World Health Organization's interim guidance diagnostic criteria for adults with severe COVID-19 pneumonia were used (16). The discharge criteria were based on the sixth edition of the "Pneumonia Diagnosis and Treatment Plan for New Coronavirus Infection" in China (17).

The medical records of each participant were reviewed by one of four physicians (Y.L., X.H., N.L., or X.J., with 7, 5, 4, and 3 years of experience in thoracic radiology, respectively). Age, sex, underlying comorbidities, onset of symptoms, peak acute phase laboratory results, and the treatments received by individual patients were recorded. The durations from the onset of disease to hospital admission and chest CT were reviewed. The Berlin definition of acute respiratory distress syndrome (ARDS) was used (18).

The initial CT scans in each participant were obtained at admission. Within 1 week of the follow-up CT scans, 104 patients underwent standard pulmonary function testing for maximum vital capacity, forced expiratory volume in 1 second, forced vital capacity, diffusing capacity of the lung for carbon monoxide (DLco), and DLco divided by the alveolar volume measured in a single breath test. The results were compared with those in age- and sex-matched control participants and reported as percentages of predicted values. Pulmonary diffusion was regarded as abnormal when DLco was less than 80% of the predicted value.

CT Image Acquisition and Interpretation

The initial CT examinations were performed with the patient in the supine position with one of two CT scanners: Somatom Definition AS+ or Somatom Perspective (Siemens Healthineers). Nonenhanced chest CT was performed with the acquisition from the thoracic inlet to the diaphragm. The following parameters were used: detector collimation width of 64 × 0.6 mm or 128 × 0.6 mm and a tube voltage of 120 kV. The tube current was regulated by an automatic exposure control system (CARE Dose 4D, Siemens Healthineers). Images in 62 of the 114 patients (54%) were reconstructed with a section thickness of 5 mm and an interval of 5 mm. Images in 52 of the 114 patients (46%) were reconstructed with a section thickness of 1 mm and an interval of 1 mm. Images were reconstructed with a pulmonary B70f kernel and a mediastinal B30f kernel (Somatom Definition AS+) or a pulmonary B80s kernel and a mediastinal B30s kernel (Somatom Perspective).

All 114 patients underwent follow-up CT examinations using the same scanners used for the initial CT scans. Images in all patients were reconstructed with a section thickness of 1 mm and an interval of 1 mm. Before the prospectively planned 6-month follow-up examination, 83 of the 114 patients (73%) underwent CT 3 months after symptom onset to monitor the evolution of their lung disease.

All CT images were reviewed in random order by three senior cardiothoracic radiologists (H.S., Y.F., and J.G., with 31, 13, and 10 years of experience in thoracic radiology, respectively) who were not aware of any clinical or laboratory findings or patient outcomes. The readers independently assessed the CT features using axial and multiplanar reconstructed images. The mediastinal window (center, 50 HU; width, 350 HU) and lung window (center, −600 HU; width, 1200 HU) were obtained from the picture archiving and communication system (Vue PACS, version 11.3.5.8902; Carestream Health). After independent evaluation, the radiologists resolved any disagreement with discussion and consensus. For each patient with severe pneumonia, the predominant CT patterns according to the Fleischner Society glossary (19) were enumerated as follows: ground-glass opacities (GGO), consolidation, reticulation, emphysema, thickening of the adjacent pleura, pleural effusion, presence of nodules or masses, honeycombing, bronchiectasis, and interlobar pleural traction (retraction of the interlobar pleura toward the lesions). The CT evidence of fibrotic-like changes was defined as the

presence of traction bronchiectasis, parenchymal bands (12,20), and/or honeycombing (19) (Fig 2).

To quantify the extent of pulmonary abnormalities (total lesions, GGO, consolidation, reticulation, and fibrotic-like changes), a semiquantitative CT score (21) was assigned on the basis of the area involved in each of the five lung lobes, as follows: 0, no involvement; 1, less than 5% involvement; 2, 5%–25% involvement; 3, 26%–49% involvement; 4, 50%–75% involvement; and 5, greater than 75% involvement. The total CT severity score was calculated by summing the individual lobar scores, with possible scores ranging from 0 to 25.

Statistical Analysis

The analyses were performed using software (SAS, version 9.4; SAS Institute). The Kolmogorov-Smirnov test was used to assess the normality of continuous data. Normally and nonnormally distributed data and categorical variables are presented as means ± standard deviations, medians with interquartile ranges (IQRs), and numbers with percentages, respectively. Between-group differences in categorical variables were assessed using the Fisher exact test, and continuous variables with normally and nonnormally distributed data were assessed using the two-sample *t* test or Mann-Whitney *U* test, respectively. *P* values for multiple univariate testing on acute phase data were adjusted by using the Benjamini-Hochberg method. A cutoff CT score value of 18 was selected as suggested in a recent investigation (22), which indicated that a chest CT score of 18 or greater was correlated with disease severity and increased mortality risk in patients with COVID-19 pneumonia. Multiple logistic regression analyses were performed to identify the independent predictive factors of fibrotic-like changes. The final model was determined using stepwise logistic regression, with significance level for selection set at $P = .05$. Factors associated with the CT score of fibrotic-like changes were analyzed by calculating the Spearman correlation coefficient. Statistically significant difference was considered at $P < .05$ (two tailed).

Results

Demographic and Participant Characteristics

A total of 114 participants (80 men, 34 women; mean age, 54 years ± 12; age range, 24–82 years) were included (Table 1). The initial and follow-up scans were obtained a mean of 17 days ± 11 and 175 days ± 20 after disease onset, respectively. Evidence of fibrotic-like changes was observed on follow-up CT scans (Fig 3) in 40 of the 114 participants (35%) (group 1); 38 of those 40 participants (95%) had de novo fibrotic abnormalities. The remaining 74 participants (65%) (group 2) showed either complete radiologic resolution (43 of 114, 38%) (Fig 4) or residual GGO or interstitial thickening (31 of 114, 27%) (Fig 5).

After correction for multiple comparisons (Table 1), participants in group 1 were significantly older than those in group 2 (mean age, 60 years ± 12 vs 51 years ± 11, respectively; $P = .003$), had a higher heart rate at admission (mean, 96 beats per minute ± 16 vs 87 beats per minute ± 12; $P = .03$), and had a greater frequency of ARDS (63% [25 of 40 participants] vs 8.1% [six of 74 participants], $P < .001$) and other comorbidities (73% [29 of 40 of participants] vs 41% [30 of 74 participants], $P = .01$), particularly chronic pulmonary disease (28% [11 of 40 participants] vs 6.8% [five of 74 participants], $P = .02$). The median hospital stay was longer for participants in group 1 than those in group 2 (27 days [IQR, 26] vs 15 days [IQR, 8], $P < .001$). With regard to treatment, participants in group 1 were more likely to receive glucocorticosteroids (53% [21 of 40] vs 20% [15 of 74], $P = .01$) and noninvasive mechanical ventilation (45% [18 of 40] vs 8.1% [six of 74], $P < .001$) than participants in group 2.

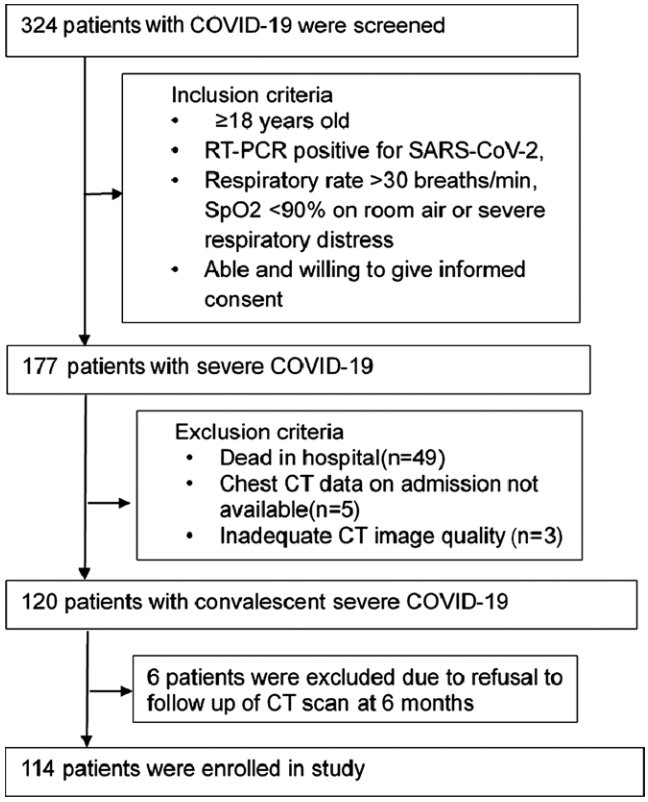

Figure 1: Participant flow diagram. COVID-19 = coronavirus disease 2019, RT-PCR = reverse-transcription polymerase chain reaction, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, SpO2 = oxygen saturation as measured by pulse oximetry.

Comparison of Peak Laboratory Findings

After correction for multiple comparisons (Table 2), the laboratory findings showed significantly higher peak levels of hypersensitive C-reactive protein (median, 80 mg/L [IQR, 124] vs 26 mg/L [IQR, 76], $P = .03$) and D-dimer (median, 8.7 mg/L [IQR, 33] vs 1.0 mg/L [IQR, 1.5], $P < .001$) in group 1 than in group 2.

Comparison of Initial CT Findings and Scores

The initial CT scans were obtained a mean of 17 days ± 11 after the onset of symptoms, with no difference between the two groups (19 days ± 11 for group 1 vs 16 days ± 11 for group 2; $P > .99$) (Table 3). The overall median total CT score was 15 (IQR, 9). After correction for multiple comparisons, participants in group 1 had significantly higher scores for total lesions

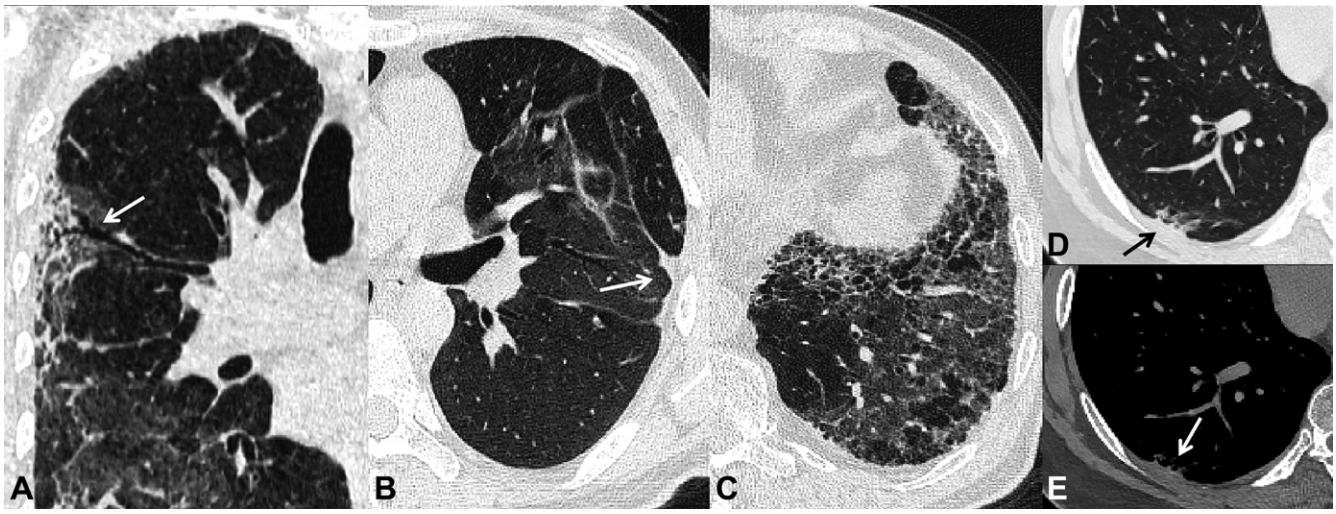

Figure 2: Follow-up chest CT findings of coronavirus disease 2019 pneumonia. Scans show, *A*, traction bronchiectasis (arrow), *B*, parenchymal bands (arrow), *C*, honeycombing, and, *D*, *E*, thickening of the adjacent pleura (arrow).

(median, 20 [IQR, 5.5] vs 13 [IQR, 7]; $P < .001$) and GGO (median, 16 [IQR, 10] vs 10 [IQR, 8]; $P = .02$) than participants in group 2 (Table 3). Thickening of the adjacent pleura was more common in group 1 than in group 2 (55% [22 of 40 participants] vs 24% [18 of 74 participants], $P = .02$) (Fig 2).

Factors Associated with Fibrotic-Like Changes in the Lung

The multivariable analysis identified an age of older than 50 years (odds ratio [OR]: 8.5; 95% CI: 1.9, 38; $P = .01$), heart rate greater than 100 beats per minute at admission (OR: 5.6; 95% CI: 1.1, 29; $P = .04$), hospital stay of 17 days or more (OR: 5.5; 95% CI: 1.5, 21; $P = .01$), ARDS (OR: 13; 95% CI: 3.3, 55; $P < .001$), noninvasive mechanical ventilation (OR: 6.3; 95% CI: 1.3, 30; $P = .02$), and total CT score of 18 or greater on initial CT scans (OR: 4.2; 95% CI: 1.2, 14; $P = .02$) as independent predictors of fibrotic-like changes in the lung (Table 4).

Scores for Fibrotic-Like Changes

According to the Spearman correlation analysis (Table E1 [online]), the score for fibrotic-like changes was correlated with age ($r = 0.32$, $P < .001$), heart rate at admission ($r = 0.24$, $P = .01$), hospital stay ($r = 0.49$, $P < .001$), ARDS ($r = 0.57$, $P < .001$), peak hypersensitive C-reactive protein level ($r = 0.37$, $P < .001$), peak D-dimer level ($r = 0.59$, $P < .001$), noninvasive mechanical ventilation ($r = 0.49$, $P < .001$), total CT score ($r = 0.47$, $P < .001$), and CT score for GGO ($r = 0.38$, $P < .001$). In all participants, the CT score for fibrotic-like changes at 6-month follow-up CT was significantly increased from that at initial CT (median, 0 [range, 0–4; IQR, 0] vs 0 [range, 0–18; IQR, 4]; $P < .001$) (Table E2 [online]). In addition, the median score for fibrotic-like changes in participants in group 1 at 6-month follow-up CT was 6 (range, 2–18; IQR, 5).

Comparison of CT Findings and Scores between Initial and Follow-up Scans

A significant decrease in the CT scores for total lesions ($P < .001$), GGO ($P < .001$), and consolidation ($P < .001$) was observed in all participants (Table E2 [online]). Compared with the initial CT scans, follow-up scans had a significantly higher frequency of nodules or masses (1.8% [two of 114] vs 17% [19 of 114], $P < .001$), interlobar pleural traction (7.9% [nine of 144] vs 17% [19 of 114], $P = .04$) (Fig 6), pulmonary atelectasis (3.5% [four of 114] vs 11% [13 of 114], $P = .02$) (Fig E1 [online]), and bronchiectasis (7.0% [eight of 114] vs 24% [27 of 114], $P < .001$), whereas pleural effusion was completely resorbed (6.1% [seven of 114] vs 0% [0 of 114], $P = .01$).

Time Points of Occurrence of Fibrotic-Like Changes or Complete Resolution

In group 1 (participants who exhibited fibrotic-like lung changes), two of the 40 participants (5%) showed the fibrotic-like changes on initial CT scans. Fibrotic-like changes were seen on follow-up scans in 16 of the 37 participants (43%) who presented for 3-month follow-up and 22 of the 40 participants (55%) who presented for 6-month follow-up. In group 2, of the 43 participants (58%) who demonstrated complete resolution of CT abnormalities, 20 of the 34 participants (59%) who presented for follow-up showed resolution at 3 months, and the remaining 23 of 43 (53%) showed resolution at the 6-month follow-up (Table E3 [online]).

Follow-up Findings

At 6-month follow-up (Table E4 [online]), seven of the 114 participants (6.1%) were still reporting dry cough, 11 (10%) had expectoration, and 16 (14%) experienced slight dyspnea on exertion. Participants in group 1 with fibrotic-like changes in the lung more commonly experienced dry cough ($P = .03$) than participants in group 2. Of the 104 participants who underwent pulmonary function testing, 27 (26%) presented with abnormal pulmonary diffusion (DLco <80% predicted), with participants in group 1 more frequently presenting with diffusion abnormalities than those in group 2 (50% [18 of 36] vs 13% [nine of 68], respectively; $P < .001$).

Table 1: Comparison of Demographic and Clinical Characteristics between Groups

Characteristic	All Patients (n = 114)	Group 1 (n = 40)	Group 2 (n = 74)	P Value	Adjusted P Value*
Age (y)†	54 ± 12	60 ± 12	51 ± 11	<.001	.003
≤50	46 (40)	9 (23)	37 (50)	.004	.09
>50	68 (60)	31 (77)	37 (50)		
Sex					
F	34 (30)	10 (25)	24 (32)	.41	>.99
M	80 (70)	30 (75)	50 (68)		
Smoking history	16 (14)	9 (23)	7 (9.5)	.05	.97
History of alcohol consumption	29 (25)	11 (28)	18 (24)	.65	>.99
Maximum temperature (°C)‡	38.5 (1)	38.6 (1)	38.5 (1.1)	.63	>.99
<38	15/101 (15)	5/32 (16)	10/69 (14)	.88	>.99
≥38	86/101 (85)	27/32 (84)	59/69 (86)		
Heart rate (beats/min)†	90 ± 14	96 ± 16	87 ± 12	.002	.03
Respiratory rate at hospital admission†	23 ± 4	23 ± 4	23 ± 4	.96	>.99
SBP (mm Hg)†	124 ± 23	129 ± 26	121 ± 20	.08	>.99
DBP (mm Hg)†	85 ± 15	84 ± 13	85 ± 16	.61	>.99
Oxygen saturation on room air (%)†	93 ± 7	92 ± 7	94 ± 7	.06	>.99
Comorbidity	59 (52)	29 (73)	30 (41)	.001	.01
Diabetes	13 (11)	9 (23)	4 (5.4)	.01	.10
Hypertension	32 (28)	17 (43)	15 (20)	.01	.18
Chronic pulmonary disease	16 (14)	11 (28)	5 (6.8)	.001	.02
Bacterial infection	17 (15)	10 (25)	7 (9.5)	.03	.52
Hospital stay duration (d)‡	17 (14)	27 (26)	15 (8)	<.001	<.001
ARDS	31 (27)	25 (63)	6 (8.1)	<.001	<.001
Treatment					
Mechanical ventilation					
Noninvasive	24 (21)	18 (45)	6 (8.1)	<.001	<.001
Duration of noninvasive mechanical ventilation (d)‡	9.5 (8.5)	11 (9.0)	7.5 (5.0)	.42	>.99
Invasive	4 (3.5)	4 (10)	0 (0)	.01	.12
Duration of invasive mechanical ventilation (d)‡	20 (9.5)	20 (9.5)	…	…	…
Antiviral agents	80 (70)	28 (70)	52 (70)	.87	>.99
NSAID treatment	30 (26)	12 (30)	18 (24)	.51	>.99
Antibacterial agents	62 (54)	20 (50)	42 (57)	.38	>.99
Glucocorticosteroids	36 (32)	21 (53)	15 (20)	<.001	.01

Note.—Except where indicated, data are numbers of participants, with percentages in parentheses. P values comparing participants with fibrotic-like changes in the lung at CT (group 1) and participants without fibrotic-like changes in the lung at CT (group 2) were determined with the χ^2 test, Fisher exact test, independent-samples t test, or Mann-Whitney U test. ARDS = acute respiratory distress syndrome, DBP = diastolic blood pressure, NSAID = nonsteroidal anti-inflammatory drug, SBP = systolic blood pressure.

* P values were adjusted for 51 variables by using the Benjamini-Hochberg method.

† Data are means ± standard deviations.

‡ Data are medians, with interquartile ranges in parentheses.

Discussion

In our study, 40 of 114 participants (35%) who recovered from severe coronavirus disease 2019 pneumonia developed fibrotic-like changes in the lung within 6 months; in this group, most of the fibrotic-like changes (22 of 40 [55%]) manifested at 6-month follow-up CT. Using multivariable analysis, we found that age older than 50 years (odds ratio [OR]: 8.5; 95% CI: 1.9, 38; P = .01), heart rate greater than 100 beats per minute at admission (OR: 5.6; 95% CI: 1.1, 29; P = .04), hospital stay of 17 days or more (OR: 5.5; 95% CI: 1.5, 21; P = .01), acute respiratory distress syndrome (OR: 13; 95% CI: 3.3, 55; P < .001), noninvasive mechanical ventilation (OR: 6.3; 95% CI: 1.3, 30; P = .02), and a total chest CT score of 18 or greater on initial CT scans (OR: 4.2; 95% CI: 1.2, 14; P = .02) were independent predictors of the subsequent development of fibrotic-like changes in the lung after 6-month follow-up.

Participants with fibrotic-like changes in the lung showed a higher frequency of ARDS (25 of 40 [63%]), which was also a predictor of fibrotic-like changes. Previous studies (23,24) have demonstrated that a substantial proportion of patients who survive ARDS may develop progressive fibrotic-like changes on CT scans. Nevertheless, it remains uncertain whether the

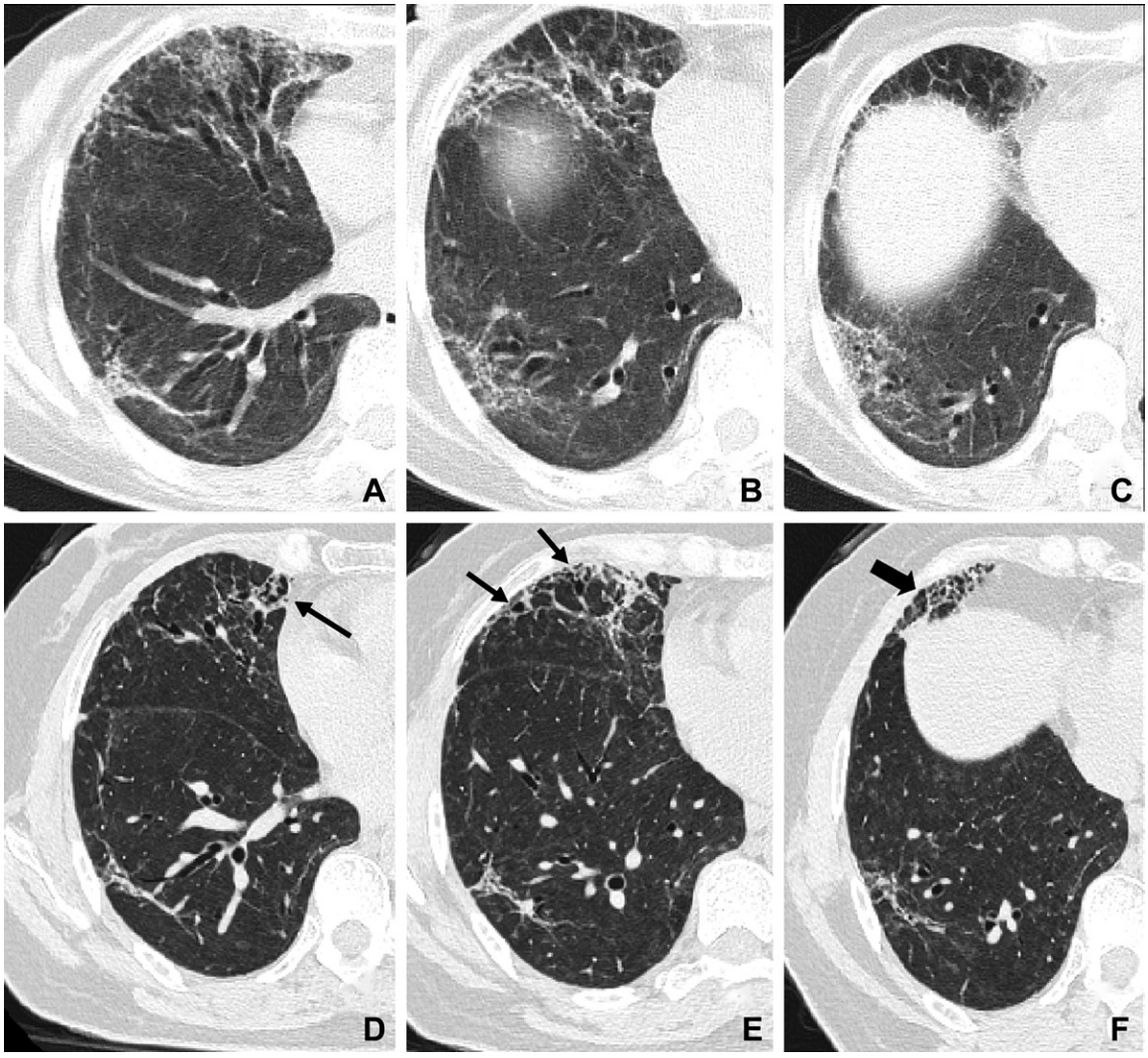

Figure 3: Serial CT scans in a 46-year-old woman with severe coronavirus disease 2019 pneumonia. *A–C*, Scans obtained on day 32 after symptom onset show multiple ground-glass opacities and interstitial thickening with mild cylindrical traction bronchiectasis involving the middle lobe and lower lobe of the right lung. *D–F*, Scans obtained on day 198 show partial absorption of the abnormalities, reduced extension, traction bronchiectasis (arrows in *D* and *E*), and localized "honeycombing" (arrow in *F*) in the subpleural region of the right middle lobe.

fibrotic-like changes observed in this study represent true fibrotic lung disease (eg, at pathologic examination or longer-term follow-up CT). Whether or not these fibrotic-like changes, found at 6 months, reflect permanent change in the lung remains to be investigated. Additionally, in our study, the high frequency of noninvasive mechanical ventilation is another risk factor for the development of fibrotic-like changes at 6 months. On the basis of previously published data (24), mechanical ventilation is strongly related to fibrotic-like changes observed after ARDS. Likewise, the fibrotic-like changes in the lung in our patients may also be associated with ventilator-induced lung injury. The laboratory results also demonstrated higher D-dimer and hypersensitive C-reactive protein levels in patients with pulmonary fibrotic-like changes. Emerging evidence of coagulopathy and an overexuberant inflammatory response has been reported in patients with severe COVID-19 (25,26); these findings are associated with disease severity and may also lead to greater damage to the pulmonary parenchyma.

We found that a higher CT score (≥18) at the initial CT examination was an independent prognostic factor for the presence of fibrotic-like changes at the 6-month follow-up examination. According to a previous study on idiopathic pulmonary fibrosis (27), CT score is correlated with the degree of pulmonary fibrosis in pathologic specimens. Moreover, a recent publication revealed an association between a CT score of 18 or greater and an increased mortality risk in patients with COVID-19 (22). Therefore, a greater extent of lung injury in the acute phase may be associated with a higher mortality rate and more severe pulmonary sequelae in survivors. In addition, the correlations of scores for fibrotic-like changes with the aforementioned risk factors were also confirmed in our study.

At 6-month follow-up, a few patients still reported ongoing respiratory symptoms, and 26% of patients had pulmonary diffusion abnormalities, which more frequently occurred in patients with fibrotic-like changes. Thus, both structural and functional lung impairments may simultaneously occur

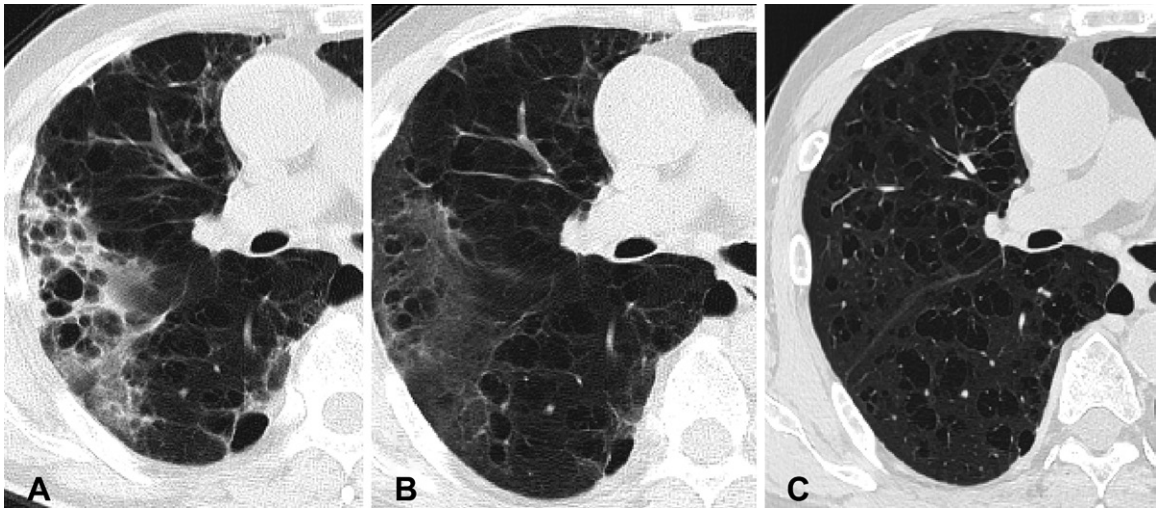

Figure 4: Serial CT scans in a 63-year-old man with emphysema and severe coronavirus disease 2019 pneumonia. *A*, Axial CT scan obtained on day 27 after onset of symptoms shows multiple ground-glass opacities in the subpleural right lung. *B*, Scan obtained on day 72 shows obvious absorption of the abnormalities. *C*, Scan obtained on day 164 shows complete resolution.

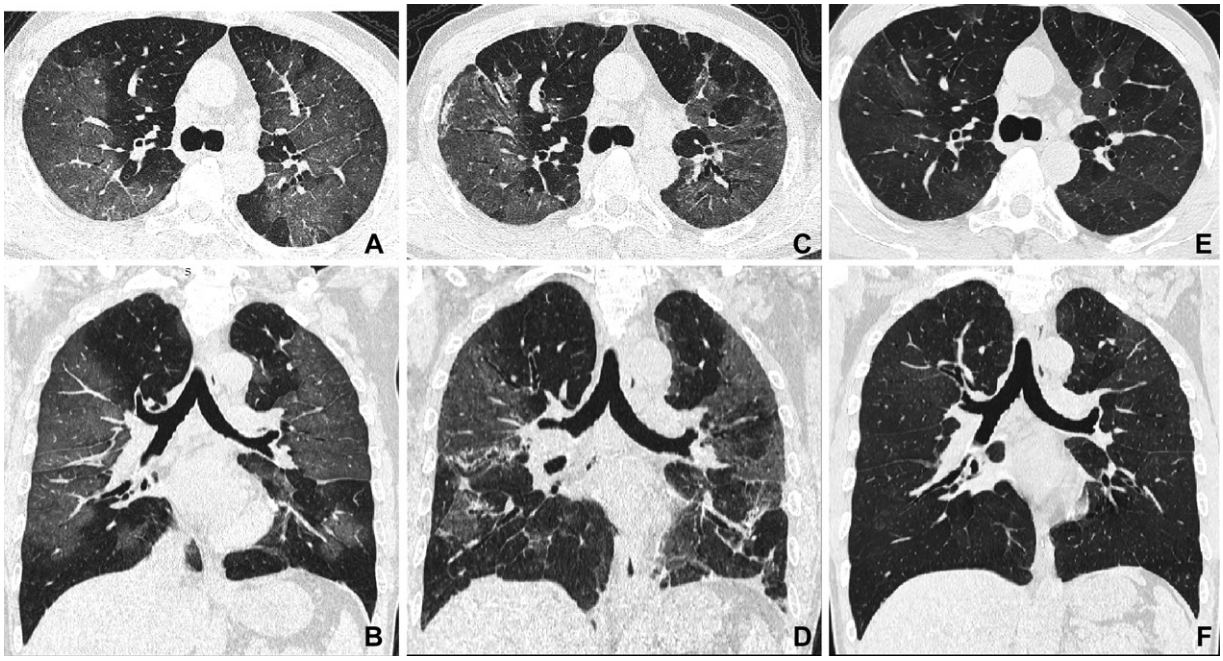

Figure 5: Serial thin-section CT scans in a 57-year-old man with severe coronavirus disease 2019 pneumonia. *A*, Axial and, *B*, coronal CT scans obtained on day 9 after the onset of symptoms show extensive ground-glass opacities (GGO) and interstitial thickening bilaterally. *C*, Axial and, *D*, coronal scans obtained on day 46 show evolution to a mixed pattern of GGO and consolidation with almost the same extent of lesions. *E*, Axial and, *F*, coronal scans obtained on day 159 show a marked decrease in the attenuation of GGO, with a slightly increased extension of the GGO ("tinted" sign or "melting sugar" sign, which is defined as an imaging appearance of increased extension of the GGO or consolidation and decreased attenuation).

in patients who survive severe COVID-19 pneumonia. Significant decreases in CT scores for total lesions, GGO, and consolidation were observed at follow-up CT compared with the initial CT. Although the predominant CT pattern at follow-up CT was still GGO, the densities had visually decreased, which might follow the "tinted" sign (10) or "melting sugar" sign (28), defined as an imaging appearance of increased extension of the GGO or consolidation and decreased attenuation. Two studies (10,28) reported an increased extension of the GGO or consolidation and a decreased attenuation at follow-up CT of COVID-19 pneumonia, which may indicate the gradual regression of the inflammation and re-expansion of the alveoli. GGO in the acute phase of COVID-19 pneumonia may represent the inflammatory infiltrates, edema, or hemorrhaging (2,3). Moreover, increased D-dimer levels in the acute phase were associated with pulmonary embolism in patients with COVID-19, which might also account for GGO appearance on the chest CT scans (29,30); however, CT pulmonary angiography was not routinely performed in our patients to clarify this point. The pathophysiology underlying GGO in

Table 2: Comparison of Peak Laboratory Findings between Groups

Parameter	All Patients (n = 114)	Group 1 (n = 40)	Group 2 (n = 74)	Normal Range*	P Value	Adjusted P Value†
Leukocyte count ($\times 10^9$/L)	6.4 (6.4)	6.2 (7.3)	6.6 (5.3)	4–10	.46	>.99
Lymphocyte count ($\times 10^9$/L)	0.8 (0.7)	0.7 (1)	0.9 (0.6)	1.1–3.2	.37	>.99
Hypersensitive C-reactive protein level (mg/L)	50 (99)	80 (124)	26 (76)	<25	.001	.03
ESR (mm/h)	50 (36)	49 (37)	50 (35)	0–15	.74	>.99
Interleukin-6 level (pg/mL)	8.8 (5.1)	10 (5.8)	8.3 (5)	0.1–2.9	.14	>.99
ALT level (U/L)	44 (37)	51 (42)	39 (29)	8–40	.004	.09
AST level (U/L)	61 (55)	72 (51)	52 (52)	5–40	.01	.11
Lactate dehydrogenase level (U/L)	352 (232)	399 (342)	324 (180)	109–254	.01	.27
Glucose level (mmol/L)	7.8 (3.5)	9 (3.9)	7.2 (3.2)	3.9–6.1	.01	.18
D-dimer level (mg/L)	1.9 (9)	8.7 (33)	1.0 (1.5)	<0.5	<.001	<.001

Note.—Except where indicated, data are medians, with interquartile ranges in parentheses. P values comparing participants with fibrotic-like changes in the lung at CT (group 1) and participants without fibrotic-like changes in the lung (group 2) were obtained with the Mann-Whitney U test. ALT = alanine aminotransferase, AST = aspartate aminotransferase, ESR = erythrocyte sedimentation rate.

* All values are approximate.

† P values were adjusted for 51 variables by using the Benjamini-Hochberg method.

Table 3: Comparison of Initial CT Findings and Scores between Groups

Characteristic	All Patients (n = 114)	Group 1 (n = 40)	Group 2 (n = 74)	P Value	Adjusted P Value*
Time from symptom onset to CT (d)†	17 ± 11	19 ± 11	16 ± 11	.16	>.99
Lung involvement					
Unilateral	2 (1.8)	0 (0)	2 (2.7)	.29	>.99
Bilateral	112 (98)	40 (100)	72 (97)		
Predominant CT pattern					
Ground-glass opacities	71 (62)	25 (63)	46 (62)	.97	>.99
Consolidation	27 (24)	9 (23)	18 (24)		
Reticulation	16 (14)	6 (15)	10 (14)		
Presence of nodule or mass	3 (2.6)	2 (5)	1 (1.4)	.28	>.99
Pleural effusion	10 (8.8)	6 (15)	4 (5.4)	.10	>.99
Emphysema	2 (1.8)	2 (5)	0 (0)	.12	>.99
Thickening of the adjacent pleura	40 (35)	22 (55)	18 (24)	.001	.02
Interlobar pleural traction	27 (24)	14 (35)	13 (18)	.06	>.99
Honeycombing	2 (1.8)	2 (5)	0 (0)	.12	>.99
Bronchiectasis	12 (11)	9 (23)	3 (4.1)	.004	.07
CT score					
All lesions‡	15 (9)	20 (5.5)	13 (7)	<.001	<.001
≥18	76 (67)	17 (43)	59 (80)	<.001	.001
<18	38 (33)	23 (58)	15 (20)		
Ground-glass opacities‡	10 (10)	16 (10)	10 (8)	.001	.02
Consolidation‡	5 (8)	7 (5.5)	4 (8)	.004	.07
Reticular‡	5 (7)	5 (6.5)	3.5 (6)	.01	.16

Note.—Except where indicated, data are numbers of participants, with percentages in parentheses. P values comparing participants with fibrotic-like changes in the lung at CT (group 1) and participants without fibrotic-like changes in the lung at CT (group 2) were obtained with the χ^2 test, Fisher exact test, independent-samples t test, or Wilcoxon rank-sum test.

* P values were adjusted for 51 variables by using the Benjamini-Hochberg method.

† Data are means ± standard deviations.

‡ Data are medians, with interquartile ranges in parentheses.

the convalescent phase of COVID-19 pneumonia and the correlation with fibrosis is worthy of further investigation.

Our study has several limitations. First, sample size was small, and follow-up was conducted for only 6 months. Patients with fibrotic-like changes require longer follow-up to determine whether the fibrotic-like changes are permanent, progressive, or reversible. Second, the extent of fibrotic-like changes in the lung was not quantified with a computer-based analysis as described

Table 4: Univariable and Multivariable Analysis of Predictors of Fibrotic-Like Changes in the Lung in Survivors of Severe Coronavirus Disease 2019

	Univariable Analysis (n = 114)			Multivariable Analysis (n = 114)		
Parameter	Odds Ratio	95% CI	P Value	Odds Ratio	95% CI	P Value
Age >50 years	3.4	1.4, 8.2	.005	8.5	1.9, 38	.01
Heart rate >100 beats/min	2.7	0.99, 7.6	.053	5.6	1.1,29	.04
Hospital stay ≥17 days	6.0	2.5, 14	<.001	5.5	1.5, 21	.01
ARDS	19	6.6, 56	<.001	13	3.3, 55	<.001
Noninvasive mechanical ventilation	9.3	3.3, 26	<.001	6.3	1.3, 30	.02
Lesions with CT score ≥18	6.5	2.8, 15	<.001	4.2	1.2, 14	.02

Note.—At follow-up CT, evidence of fibrotic-like changes was observed in 40 of the 114 participants. The R^2 of the final model was 0.47.
ARDS = acute respiratory distress syndrome.

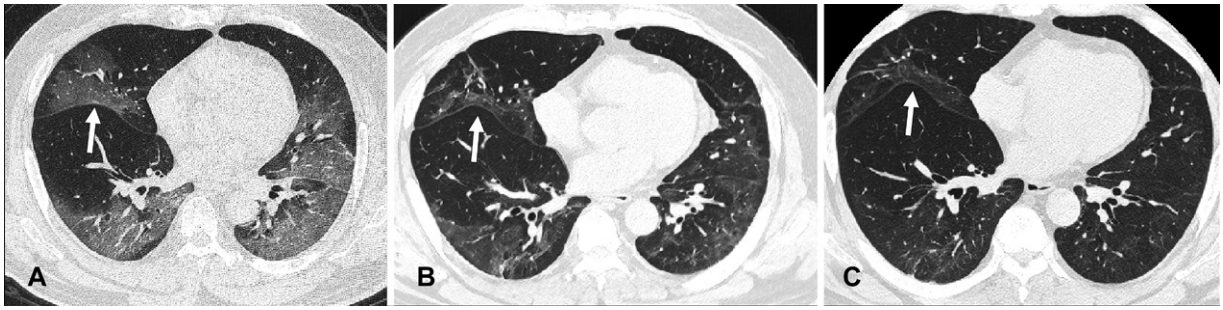

Figure 6: Serial thin-section CT scans in a 52-year-old man with severe coronavirus disease 2019 pneumonia. *A*, Axial CT scan obtained on day 8 after symptom onset shows multiple ground-glass opacities bilaterally, with a slight traction of the right interlobar pleural (arrow). *B*, *C*, Scans obtained on days 79 and 149, respectively, show continuous absorption of previous opacifications, with the progression of interlobar pleural traction.

in previous research (31). However, we have supplied the semiquantitative scores for the fibrotic-like changes, which were shown to be correlated with the degree of pulmonary fibrosis in pathologic specimens. Third, inter- and intrareader comparison of CT grading was not performed. Fourth, the number of years of smoking was not evaluated in the present study. Fifth, 62 of 114 participants (54%) had a section thickness of 5 mm on the initial scan, in which case subtle findings may be occult or overlooked. However, all follow-up CT scans were obtained with thin sections of 1 mm to assess lung abnormalities. Finally, the lack of a histologic correlation is a limitation. Further studies are warranted to explore whether fibrotic-like changes on CT scans represent true pathologic fibrosis.

In summary, follow-up CT scans obtained within 6 months of disease onset showed fibrotic-like changes in the lung in more than one-third of patients who survived severe coronavirus disease 2019 pneumonia. These patients were older and had more severe disease during the acute phase. However, the long-term lung sequelae of these CT findings are still largely unknown. This report serves as a basis for new, prospective, large-scale, long-term investigations analyzing these high-risk patients.

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