Fibrotic Interstitial Lung Abnormalities at 1-year Follow-up CT after Severe COVID-19

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

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Given the large scale of the COVID-19 pandemic worldwide, lung sequelae after COVID-19 are a major concern to all populations. Our previous study (1) showed that about one-third of survivors with severe COVID-19 had lung “fibrotic-like” changes (fibrotic interstitial lung abnormalities [ILAs]) according to Fleischner Society Glossary (2) at 6-month follow-up. However, whether these fibrotic ILAs changes are permanent, progressive, or reversible remained unclear and little is known about the 1-year sequela of COVID-19. The purpose of this study was to assess the chest CT changes of fibrotic ILAs at 1-year follow-up in survivors of COVID-19.

Materials and Methods

This prospective study was approved by the ethics commission of Wuhan Jin Yin-tan Hospital and Wuhan Union Hospital. All participants remained anonymous, and written informed consent was acquired by June 1st, 2020.

A total of 71 participants (41 men, 30 women; mean age ± standard deviation, 57 years ± 10) with lung sequelae (40 participants with fibrotic ILAs [previously described as fibrotic-like changes]; 31 participants without fibrotic ILAs, including ground-glass opacification, consolidation, or reticular abnormalities) at 6-month follow-up in our previous study (1) were invited to this 1-year follow-up study. Nine individuals were excluded due to refusal to participate in the study. Finally, 62 participants (34 men, 28 women; mean age, 57 years ± 10; 35 participants with fibrotic ILAs, 27 participants without fibrotic ILAs) were prospectively enrolled in this study. The flowchart of inclusion is shown in Figure E1 (online).

The World Health Organization’s interim guidance diagnostic criteria for adults with severe COVID-19 pneumonia were used (3). Within 1 week of the follow-up CT scans, 57 participants (32 men, 25 women; mean age, 57 years ± 10) underwent standard pulmonary function testing (PFT) at 6 months, whereas 53 participants (31 men, 21 women; mean age, 57 years ± 10) underwent PFT at 1 year. The severity of the diffusing lung capacity drop was assessed by using a standardized grading system (normal, >75%–140%; mild, 60%–75%; moderate, 40%–59%; and severe, <40%) (4).

All 62 participants underwent 1-year follow-up CT examinations using the same scanners (SOMATOM Definition AS+ or SOMATOM Perspective, Siemens Healthineers) as the 6-month CT scans. CT images obtained at 6 months and 1 year were reviewed side by side in random order by three senior cardiothoracic radiologists (H.S.S., Y.Q.F., and X.Z., with 31, 13 and 8 years of experience in thoracic radiology, respectively). After independent evaluation, discussion and consensus resolved any disagreement. For each patient, CT features according to the Fleischner Society Glossary were assessed and recorded (Appendix E1 [online]). A semiquantitative CT score (Appendix E1 [online]) was used to quantify the extent of pulmonary abnormalities (all lesions, ground-glass opacification, consolidation, ILAs, and fibrotic ILAs abnormalities and traction bronchiectasis).

Results

The final study group consisted of 62 participants (34 men, 28 women; mean age, 57 years ± 10; range, 34–84 years), of whom 35 of 62 (56%) participants (group 1) showed fibrotic ILAs and the remaining 27 of 62 (44%) participants (group 2) showed no fibrotic ILAs on 6-month follow-up CT scans. Six-month and 1-year follow-up CT scans were obtained at 182 days (interquartile range, 169–196 days) and 363 days (interquartile range, 355–372 days) after symptoms onset, respectively.

In group 1, all participants (35 of 35, 100%) demonstrated persistent fibrotic ILAs on 1-year follow-up CT scans. Specifically, 27 of 35 (77%) participants had stable lung fibrotic ILAs (Fig A, B), whereas the extent of fibrotic ILAs was slightly reduced in eight of 35 (23%) cases (Fig C). Seventeen of 27 (63%) participants in group 2 showed complete resolution at 1-year CT (Fig F), whereas the remaining 10 of 27 (37%) participants showed either partial resorption of the abnormalities (six of 27, 22%) (Fig D) or static radiologic changes (four of 27, 15%) (Fig E).
Images show changes in CT findings of lung abnormalities for six patients with COVID-19 at baseline (top row) during the acute illness, at 6 months (middle row), and 1 year (bottom row) after hospital discharge. Middle and bottom rows show (A) persisting traction cylindrical bronchiectasis; (B) persisting subpleural bronchiectasis; (C) persistent honeycombing with slightly reduced extension; (D) partial resorption of residual opacifications; (E) static radiologic changes; and (F) complete radiologic resolution. (Figure F [top and middle rows] reprinted, with permission, from reference 1.)

**Comparison of Clinical Characteristics and CT Findings between Two Follow-ups in Convalescent Patients with Severe COVID-19**

| Characteristic                        | 6 Months (n = 62) | 1 Year (n = 62) | P Value |
|---------------------------------------|-------------------|-----------------|---------|
| Respiratory symptoms                  |                   |                 |         |
| Dry cough                             | 5/62 (8.1)        | 3/62 (4.8)      | .45     |
| Expectoration                         | 9/62 (15)         | 3/62 (4.8)      | .07     |
| Exertional dyspnea                    | 13/62 (21)        | 9/62 (15)       | .33     |
| Pulmonary function (%)                |                   |                 |         |
| Maximum VC*                           | 105 ± 18          | 108 ± 20        | .42     |
| Forced VC*                            | 107 ± 19          | 110 ± 20        | .38     |
| FEV₁*                                 | 105 ± 20          | 107 ± 22        | .35     |
| DLco*                                 | 85 ± 12           | 89 ± 19         | .23     |
| <75 for predicted                     | 18/57 (32)        | 13/53 (25)      | .41     |
| Severity grade (%)                    |                   |                 | .70     |
| Normal (75–140)                       | 39/57 (68)        | 40/53 (75)      |         |
| Mild (60–75)                          | 13/57 (23)        | 9/53 (17)       |         |
| Moderate (40–59)                      | 5/57 (8.8)        | 4/53 (7.5)      |         |
| Severe (<40)                          | 0                 | 0               |         |
| Lung radiographic changes             |                   |                 | <.001   |
| Fibrotic ILAs                         | 35/62 (56)        | 35/62 (56)      |         |

**Discussion**

This study shows that fibrotic ILAs were a common and persistent sequela at 1-year follow-up CT after severe COVID-19.
### Table (continued): Comparison of Clinical Characteristics and CT Findings between Two Follow-ups in Convalescent Patients with Severe COVID-19

| Characteristic | 6 Months ($n = 62$) | 1 Year ($n = 62$) | $P$ Value |
|---------------|---------------------|------------------|-----------|
| Without fibrotic ILAs | 27/62 (44) | 10/62 (16) | 0.001 |
| Normal | 0/62 (0) | 17/62 (27) | 0.001 |
| Major distribution of opacities | <0.001 | <0.001 | <0.001 |
| Normal | 0/62 (0) | 17/62 (27) | 0.001 |
| Septal or subpleural | 36/62 (58) | 19/62 (31) | 0.001 |
| Peribronchovascular | 17/62 (27) | 17/62 (27) | 0.001 |
| Random | 9/62 (15) | 9/62 (15) | 0.001 |
| Traction bronchiectasis | 3.4 | 3.3 | 0.90 |
| GGO | 5.9 | 4.7 | 0.47 |
| Normal | 0/62 (0) | 17/62 (27) | 0.001 |
| GGO | 20/62 (32) | 7/62 (11) | 0.001 |
| Consolidation | 6/62 (9.7) | 6/62 (10) | 0.001 |
| Reticular abnormalities | 36/62 (58) | 32/62 (52) | 0.001 |
| Pulmonary atelectasis | 12/62 (19) | 21/62 (34) | 0.001 |
| CT score* | 7.6 ± 4.9 | 4.7 ± 4.2 | <0.001 |
| All lesions | 5.9 ± 5.4 | 2.9 ± 4.3 | <0.001 |
| GGO | 0.6 ± 2.3 | 0.3 ± 0.9 | 0.28 |
| Reticular pattern | 5.1 ± 3.4 | 3.3 ± 3.4 | 0.04 |
| ILAs | 5.8 ± 3.7 | 4.4 ± 3.9 | 0.04 |
| Fibrotic ILAs | 3.1 ± 3.8 | 2.6 ± 2.9 | 0.40 |
| Traction bronchiectasis | 2.4 ± 2.6 | 2.3 ± 2.3 | 0.75 |

Note.—Unless otherwise specified, data are numerators and denominators, with percentages in parentheses. $P$ values comparing 6-month follow-up and 1-year follow-up are from $\chi^2$, Fisher exact test, and independent samples $T$ test. Pulmonary diffusion was regarded as abnormal when diffusion capacity of the lung for carbon monoxide (DLCO) was less than or equal to $6$.

* Data are means $\pm$ standard deviation.

Recent autopsy studies found that diffuse alveolar damage is the primary pathologic finding in patients with fatal COVID-19, which is indistinguishable from other causes of diffuse alveolar damage (5). Since the fibrotic phase of diffuse alveolar damage could occur in the process of lung injury due to the failure of removal of alveolar collagen (6), the fibrotic ILAs detected in our study could be part of diffuse alveolar damage, which could also be similar to other forms of postviral fibrotic changes such as those occurring after SARS-CoV infection. Although reversible CT evidence of lung fibrosis was noted in the early convalescence stage of SARS-CoV infection (7), lung fibrotic changes on CT images persisted in survivors of SARS-CoV until 1 year after discharge (8). Furthermore, a long-term follow-up SARS-CoV study (9) found that the proportion of lung fibrosis could remain stable from 1-year to 15-year follow-up. Similarly, our results confirmed that fibrotic ILAs were persisting at 1-year follow-up, which indicate that fibrotic diseases in late stage might be irreversible, although whether the findings represent actual pathologic fibrosis remain to be confirmed with lung biopsy.

There were some limitations to this study, including the small sample size and the lack of confirmatory pathologic testing, as well as the lack of quantitative analyses of lung parenchyma.

We conclude that interstitial lung abnormalities were found to be persistent on 1-year follow-up CT scans in survivors of severe COVID-19, which were correlated with a reduction in the diffusion capacity of carbon monoxide. These findings need to be confirmed by further investigations on a larger population.

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