Outcomes of Recovered COVID-19 Patients: 6 Months of Sequential Observations at a Designated Tertiary Center

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Research

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Abstract

Objectives: An ongoing global pandemic of coronavirus disease 2019 (COVID-19) has affecting almost 100,000,000 cases with 2,100,000 deaths worldwide. However, the long-term outcomes of recovered patients remain to be defined.

Methods: This is a prospective observational study of patients with COVID-19 using sequential assessments after hospital discharge from a designated tertiary center in Hefei, China. We examined clinical symptom, chest CT imaging, pulmonary function, and 6-min walk distance (6-MWD).

Results: There were 62, 61 and 51 discharged patients enrolled the 1-month, 3-month and 6-month observations, respectively. Symptoms persisted in 24 (39%), 25 (41%) and 5 (10%) patients, mainly cough in 31%, 15% and 8% of them, respectively. Mild restrictive pulmonary impairment was detected in 11%, 10%, 12% of patients at 1, 3, 6-month follow-up. Although chest CT scores were overall gradually improved at 1 month (5.0±5.1), 3 months (3.0±4.5) and 6 months (2.0±3.3) compared with that during hospitalization (11.0±6.8), residual CT abnormalities were seen in 73%, 54% and 43% of them at 1, 3, 6 months. At 6-month follow-up, the 6MWD was 541±59 m in these recovered patients, which was significantly lower compared to healthy controls (589±75 m p<0.01). Only the steroid treatment during hospitalization (p=0.009, OR 12.091, 95% CI 1.882 to 77.678) was associated with abnormal CT score at 6 months.

Conclusions: At 6 months after hospital discharge, respiratory symptoms and pulmonary function were improved in most COVID-19 patients while residual impairments were still present in both chest CT images and exercise capacity.

Introduction

In December 2019, an outbreak of an unknown pneumonia occurred in Wuhan and spread rapidly to other parts of China and the world[1]. Later, it was named Coronavirus disease 2019 (COVID-19) and resulted in a global pandemic[2, 3]. Lung is the primarily affected organ and typical manifestations include acute fever, cough, dyspnea with rapid progression and ground glass opacities or consolidation on chest imaging[3]. As of 27 January 2021, COVID-19 has affected over 100,000,000 patients globally and led to 2,100,000 deaths[4], representing an unprecedented health care crisis in modern times.

Much of what has been learned about COVID-19, including its epidemiological, clinical features and treatments, has been derived from studies focused on the acute phase of this illness[5–9]. Remdesivir and dexamethasone has been proved effective in hospitalized patients with COVID-19 in recent clinical trials[7, 8]. As the number of recovered patients accumulate, there is a growing need to understand evolving aspects of clinical, radiological, and functional outcomes[10–12]

Post-illness outcome studies pertaining to other Coronavirus infections, Severe Acute Respiratory Syndrome (SARS) and Middle East respiratory syndrome (MERS), have demonstrated some patients to
experience long-term respiratory impairment in the recovery phase[13–15]. Recent studies showed some patients with COVID-19 pneumonia to manifest persistent symptoms and residual abnormalities on chest CT scans at 3–4 months after discharge[16–18]. However, knowledge about the 6-month clinical outcomes of recovered patients with COVID-19 remains rather limited[19].

In the current study, we conducted a prospective observational study to characterize the outcomes of patients with COVID-19 with sequential assessments at 1, 3 and 6 months after discharge from a tertiary COVID-19 designated hospital in Hefei, China. We evaluated clinical symptoms, chest CT imaging, pulmonary function, and exercise capacity.

**Methods**

**Subjects**

The initial study cohort comprised 84 patients discharged from The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China between January 22 and March 7, 2020. Our hospital is the largest hospital in Anhui Province, China, and is a designated referral center for critical/severely ill patients with COVID-19 for a region with nearly 20,000,000 population. One patient who died within 24 hours had been supported with mechanical ventilation due to a severe stroke complicating his disease course. Three patients were excluded due to age parameter including a 4-year-old child and two elderly men above 85 years of age. At 2 weeks, 1 month, 3 months and 6 months after discharge, all the discharged patients were contacted to undergo medical reassessments at post-COVID-19 clinic of Anhui Provincial Hospital, according to the study protocol (Fig. 1).

The confirmed cases of COVID-19 were defined as patients who tested positive by real-time reverse-transcription polymerase-chain-reaction (RT-PCR) assay on pharyngeal or sputum specimens. Following the Chinese guidance, disease severity was categorized as mild illness (mild symptoms without radiographic findings of pneumonia), pneumonia (presence of symptoms and radiographic evidence of pneumonia, with no requirement for supplemental oxygen), severe pneumonia (evidence of pneumonia with one of the following features: respiratory rate > 30 breaths/minute; severe respiratory distress; or SpO2 ≤ 93% on room air at rest), and critical cases (e.g., respiratory failure requiring mechanical ventilation, septic shock, other organ failure, or admission into the ICU). All the treatment decisions were made by a multi-specialist’s team according to the Chinese guidance. The criteria for discharge from the hospital included: (1) substantial improvement of respiratory symptoms (e.g. cough, chest discomfort and shortness of breath); (2) maintenance of normal body temperature for ≥ 3 days without the use of steroids or antipyretics; (3) improvement in radiological abnormalities on chest CT or radiography; (4) two consecutively negative RT-PCR test results separated by at least 24 hours[20].

**Assessment**
A special follow-up team including physicians (Drs. XH, JC, XC) and several experienced nurses conducted multiple on-site interviews with each patient according to predesigned follow-up protocols. All patients underwent clinical evaluations, chest CT scans and pulmonary function tests (PFTs) on the follow-up visits. We also conducted six-minute walk test (6MWT) according to the American Thoracic Society (ATS) guideline[21].

**Chest CT evaluation**

The main chest patterns were described in line with the terms defined by the Fleischner Society[22]. Chest CT findings were assessed using a scoring method similar to the one previously described[5]. In general, each lung was divided into 3 zones (upper, middle, lower); each zone was evaluated for percentage of lung involvement on a scale of 0–4. Overall CT score was the summation of scores from all 6 lung zones. All CT evaluations were blindly assessed by a chest radiologist with 20-years’ experience (Dr. WW) according to the published method.

**Pulmonary function test and 6MWT**

PFTs and 6MWTs were performed according to the ATS guidelines and supervised by a designated physician (Dr. JC). All PFTs were performed by a same physician at our follow-up clinic. The forced vital capacity (FVC) forced expiratory volume in one second (FEV₁), and maximum voluntary ventilation (MVV) were measured using the exclusive Spirolab III electronic spirometer manufactured by Medical International Research (MIR), Italy. The 6-min walk distances (6MWDs) were compared to normative reference data collected from a population survey of 106 normal healthy volunteers at our center.

**Statistical analysis**

All data are expressed as mean ± SD unless otherwise indicated. Comparisons between groups were performed with unpaired t-tests for normally distributed continuous variables and Mann-Whitney U-tests for non-normally distributed continuous variables, Mantel-Haenszel test for categorical variables. Univariate analyses were performed to explore the potential correlates of CT scores. With each statistical test, the level used to determine the significance was considered at a p value < 0.05.

**Results**

There were 62, 61 and 51 discharged patients enrolled the 1-month, 3-month and 6-month observation study, respectively (number of studied patients at follow-up was affected by their adherence and physical condition) (Fig. 1). Demographic details and comorbidities of this cohort are shown in Table 1. Only one patient received mechanical ventilation and died of a complicating severe cerebrovascular accident on hospital day 2. Eleven patients were admitted to the ICU. Oxygen therapy was required in 54 patients, 10 of whom received high-flow nasal cannula oxygen therapy (HFNC). At 1-month follow-up, the mean age of the patients was 43.1 years and 35 were male. There were 23 patients with at least one comorbidity and severe or critical patients accounted for 33% of them (27 patients). At 3-month follow-up, the mean
The age of the patients was 43.5 years and 25 of them with comorbidity. At 6-month follow-up, the mean age was 43.2 years and 22 patients with comorbidity. Among of them, 53% of patients need oxygen therapy during hospitalization and 45% of cases were administered steroid treatment during their hospitalization. There were no significant differences in the clinical features during hospitalization period among the different follow-up populations (Table 1).

Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Baseline (n = 81)</th>
<th>1 month (n = 62)</th>
<th>3 months (n = 61)</th>
<th>6 months (n = 51)</th>
<th>F/X2</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age-years, mean (± SD)</td>
<td>45 (15)</td>
<td>43.1 (15.5)</td>
<td>43.5 (15.9)</td>
<td>43.2 (14.6)</td>
<td>0.434</td>
<td>0.729</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>47 (58)</td>
<td>35 (56)</td>
<td>33 (54)</td>
<td>27 (53)</td>
<td>0.412</td>
<td>0.938</td>
</tr>
<tr>
<td>Current smoking history, n (%)</td>
<td>9 (11)</td>
<td>7 (11)</td>
<td>8 (13)</td>
<td>5 (10)</td>
<td>0.314</td>
<td>0.957</td>
</tr>
<tr>
<td>Comorbidities, n (%)</td>
<td>30 (37)</td>
<td>23 (37)</td>
<td>25 (41)</td>
<td>22 (43)</td>
<td>0.687</td>
<td>0.876</td>
</tr>
<tr>
<td>Severe/critical patients, n (%)</td>
<td>27 (33)</td>
<td>14 (23)</td>
<td>17 (28)</td>
<td>16 (31)</td>
<td>2.156</td>
<td>0.541</td>
</tr>
<tr>
<td>Oxygen therapy, n (%)</td>
<td>42 (52)</td>
<td>28 (45)</td>
<td>29 (47)</td>
<td>27 (53)</td>
<td>0.598</td>
<td>0.806</td>
</tr>
<tr>
<td>Steroid treatment, n (%)</td>
<td>32 (40)</td>
<td>24 (39)</td>
<td>25 (41)</td>
<td>23 (45)</td>
<td>0.559</td>
<td>0.906</td>
</tr>
<tr>
<td>WBC (²×10⁹/L), n (%)</td>
<td>18 (22)</td>
<td>14 (23)</td>
<td>16 (26)</td>
<td>6 (12)</td>
<td>3.752</td>
<td>0.290</td>
</tr>
<tr>
<td>Lymphocytes (¹×10⁹/L), n (%)</td>
<td>44 (54)</td>
<td>35 (56)</td>
<td>32 (52)</td>
<td>24 (47)</td>
<td>1.033</td>
<td>0.793</td>
</tr>
</tbody>
</table>

Clinical Presentation

During hospitalization, there were 65 patients (80%) who manifested fever; cough in 54 (67%); fatigue in 17 (21%) and dyspnea in 13 (16%). At 1 month after discharge, there were 28 patients (45%) who remained symptomatic while the SpO₂ % on room air at rest was normal in all subjects. At 3 months, 25 (41%) patients had symptoms; cough in 9 (15%), dyspnea in 11 (18%), fatigue in 5 (8%), and no one with fever. At 6-month follow-up, only 5 (10%) patients had symptoms; cough in 4 (8%) and fatigue in 1 (2%) but no one with fever or dyspnea (Table 2).
Table 2
—Clinical outcomes of patients with COVID-19 after discharge

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Baseline (n = 81)</th>
<th>1 month (n = 62)</th>
<th>3 months (n = 61)</th>
<th>6 months (n = 51)</th>
<th>F/X2</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptom</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>54</td>
<td>8</td>
<td>9</td>
<td>4</td>
<td>80.0</td>
<td>0.000</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>13</td>
<td>13</td>
<td>11</td>
<td>0</td>
<td>11.5</td>
<td>0.009</td>
</tr>
<tr>
<td>Fatigue</td>
<td>17</td>
<td>7</td>
<td>5</td>
<td>1</td>
<td>12.1</td>
<td>0.007</td>
</tr>
<tr>
<td><strong>PFT, mean, (SD)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVC%</td>
<td>NA</td>
<td>95 (13.4)</td>
<td>96.4 (12.1)</td>
<td>96.2 (11.7)</td>
<td>0.55</td>
<td>0.577</td>
</tr>
<tr>
<td>FEV₁%</td>
<td>NA</td>
<td>95.2 (11.9)</td>
<td>95.6 (11.6)</td>
<td>95.7 (11.9)</td>
<td>0.30</td>
<td>0.738</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>NA</td>
<td>84.4 (5.2)</td>
<td>82.9 (4.9)</td>
<td>83.4 (4.7)</td>
<td>1.26</td>
<td>0.286</td>
</tr>
<tr>
<td>MVV%</td>
<td>NA</td>
<td>105.1 (21.1)</td>
<td>99.0 (16.7)</td>
<td>102.3 (16.0)</td>
<td>0.26</td>
<td>0.774</td>
</tr>
<tr>
<td><strong>Chest abnormalities</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GGO</td>
<td>11</td>
<td>10</td>
<td>9</td>
<td>4</td>
<td>48.80</td>
<td>0.000</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>6</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GGO + Fibrosis</td>
<td>58</td>
<td>27</td>
<td>19</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Chest CT scores, mean (SD)</strong></td>
<td>11.0 (6.8)</td>
<td>4.8 (5.1)</td>
<td>3.0 (4.5)</td>
<td>2.0 (3.3)</td>
<td>43.92</td>
<td>0.000</td>
</tr>
<tr>
<td>6MWD, mean ± SD, m</td>
<td>589 ± 75#</td>
<td>506 ± 72</td>
<td>544 ± 61</td>
<td>541 ± 59</td>
<td>1.68</td>
<td>0.002</td>
</tr>
</tbody>
</table>

# normal control group.

**Chest CT study**

At 6-month follow-up, CT findings included bilateral patchy areas of GGO alone in 4 patients (8%) or accompanied by septal thickening in 15 patients (29%) or associated with superimposed areas of fibrosis in 3 patients (6%). Twenty-nine patients (57%) manifested no relevant abnormalities. Chest CT scores significantly and gradually improved by the time of 6-month follow-up (2.0 ± 3.3) vs. 3-month follow-up (3.0 ± 4.5) vs. 1-month follow-up (5.0 ± 5.1, p<0.01), and compared with the in-hospital CT study (11 ± 6.8, p < 0.01). There were no significant differences in the clinical parameters and outcome measures of recovered COVID-19 patients at 1, 3, and 6-month follow-up assessments when analyzed by disease severity categories (Table 3). Comparison of the characteristics of 51 patients at 6-month follow-up showed there were significant differences in age (over 40 year), oxygen therapy, steroid treatment,
critically ill patient (including critical and severe patients), and underlying disorder when comparing those with persistent abnormalities on chest CT vs, those without (Table 4). Only Steroid treatment (p = 0.009, OR 12.091, 95% CI 1.882 to 77.678) during hospitalization was independently associated with abnormal CT score (Table 5).

Table 3
—Clinical characteristics of patients with COVID-19 at follow-up assessments according to disease severity categories.

<table>
<thead>
<tr>
<th>Phase</th>
<th>Characteristic</th>
<th>Mild illness</th>
<th>Pneumonia</th>
<th>Severe pneumonia</th>
<th>Critical illness</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td>Number of cases</td>
<td>5</td>
<td>50</td>
<td>23</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Hospital stay, mean ± SD, d</td>
<td>20.8 ± 7.7</td>
<td>18.1 ± 6.6</td>
<td>15.0 ± 5.6</td>
<td>14.3 ± 1.5</td>
</tr>
<tr>
<td></td>
<td>Chest CT score</td>
<td>0</td>
<td>9.4 ± 5.4</td>
<td>16.6 ± 4.3</td>
<td>22 ± 2.6</td>
</tr>
<tr>
<td><strong>1M F/U</strong></td>
<td>Number of cases</td>
<td>4</td>
<td>44</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Chest CT score, mean ± SD</td>
<td>0</td>
<td>3.9 ± 4.1</td>
<td>9.5 ± 5.5</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>6MWD, mean ± SD, m</td>
<td>541 ± 42.8</td>
<td>509 ± 68.8</td>
<td>476 ± 78.5</td>
<td>480</td>
</tr>
<tr>
<td></td>
<td>Abnormal PFT patients</td>
<td>1</td>
<td>5</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>SF-36 scores</td>
<td>707 ± 78.5</td>
<td>578 ± 171.6</td>
<td>532 ± 215.8</td>
<td>624</td>
</tr>
<tr>
<td><strong>3M F/U</strong></td>
<td>Number of cases</td>
<td>4</td>
<td>40</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Chest CT score, mean ± SD</td>
<td>0</td>
<td>2 ± 2.5</td>
<td>6 ± 5.6</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>6MWD, mean ± SD, m</td>
<td>580 ± 26.9</td>
<td>552 ± 54.7</td>
<td>520 ± 66.5</td>
<td>508</td>
</tr>
<tr>
<td></td>
<td>Abnormal PFT patients</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>SF-36 scores</td>
<td>707 ± 78.5</td>
<td>581 ± 134.8</td>
<td>436 ± 159.7</td>
<td>365</td>
</tr>
<tr>
<td><strong>6M F/U</strong></td>
<td>Number of cases</td>
<td>4</td>
<td>32</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Chest CT score, mean ± SD</td>
<td>0</td>
<td>1.1 ± 1.8</td>
<td>3.7 ± 3.9</td>
<td>10 ± 7.1</td>
</tr>
<tr>
<td></td>
<td>6MWD, m</td>
<td>489 ± 47</td>
<td>556 ± 55</td>
<td>510 ± 59</td>
<td>572 ± 37</td>
</tr>
<tr>
<td></td>
<td>Abnormal PFT, n</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>SF-36 scores</td>
<td>549 ± 165</td>
<td>573 ± 55</td>
<td>507 ± 151</td>
<td>469 ± 37</td>
</tr>
</tbody>
</table>
Table 4
—Comparison of the characteristics of 51 patients with COVID-19 at 6-month follow-up

<table>
<thead>
<tr>
<th></th>
<th>CT 6M 80 (N = 22)</th>
<th>CT 6M = 0 (N = 29)</th>
<th>( \chi^2 )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, %</td>
<td></td>
<td></td>
<td>7.181</td>
<td>0.010</td>
</tr>
<tr>
<td>( \leq 40 )</td>
<td>4</td>
<td>16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( &gt;40 )</td>
<td>18</td>
<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender, %female</td>
<td>11</td>
<td>16</td>
<td>0.134</td>
<td>0.782</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>1</td>
<td>4</td>
<td>1.21</td>
<td>0.375</td>
</tr>
<tr>
<td>Lymphocyte count, %</td>
<td></td>
<td></td>
<td>4.268</td>
<td>0.051</td>
</tr>
<tr>
<td>( \geq 1.1 )</td>
<td>8</td>
<td>19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( &lt;1.1 )</td>
<td>14</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC, %</td>
<td></td>
<td></td>
<td>1.535</td>
<td>0.383</td>
</tr>
<tr>
<td>( \geq 4.0 )</td>
<td>18</td>
<td>27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( &lt;4.0 )</td>
<td>4</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxygen therapy, %</td>
<td>17</td>
<td>10</td>
<td>9.194</td>
<td>0.004</td>
</tr>
<tr>
<td>Steroid treatment, %</td>
<td>16</td>
<td>7</td>
<td>11.929</td>
<td>0.001</td>
</tr>
<tr>
<td>Underlying disorder, %</td>
<td>14</td>
<td>8</td>
<td>6.628</td>
<td>0.021</td>
</tr>
<tr>
<td>Critically ill patients, %</td>
<td>7</td>
<td>2</td>
<td>5.346</td>
<td>0.029</td>
</tr>
</tbody>
</table>

*Continuous variables were compared using Wilcoxon scores (Mann-Whitney test), and categorical variables were compared using the Mantel-Haenszel test

Table 5
—Multivariate analysis of predictors of abnormal CT score on 6-month follow-up

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR</th>
<th>95 CI%</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 40 yrs</td>
<td>3.616</td>
<td>[0.808,16.180]</td>
<td>0.093</td>
</tr>
<tr>
<td>Lymphocyte &lt; 1.1×10⁹/L</td>
<td>0.884</td>
<td>[0.180,4.356]</td>
<td>0.880</td>
</tr>
<tr>
<td>Oxygen therapy</td>
<td>3.231</td>
<td>[0.521,20.053]</td>
<td>0.208</td>
</tr>
<tr>
<td>Steroid treatment</td>
<td>12.091</td>
<td>[1.882,77.678]</td>
<td>0.009</td>
</tr>
<tr>
<td>Critical ill patients</td>
<td>0.407</td>
<td>[0.047,3.495]</td>
<td>0.413</td>
</tr>
<tr>
<td>Underlying disorder</td>
<td>3.211</td>
<td>[0.657,15.704]</td>
<td>0.150</td>
</tr>
</tbody>
</table>
6MWT and PFT

At 6 months, results of 6MWD of discharged patient were still significantly lower compared to that of healthy control group (541 ± 59m, 589 ± 75m, p<0.01). The mean 6MWD was significantly reduced at 1 month when compared to the corresponding normal subjects, and gradually improved after the acute illness (506 ± 72m, 589 ± 75m, p<0.01). However, the 6MWD of recovery patients at 6 months was not significantly improved compared to the result at 3 months (541 ± 59m, 544 ± 61m, p > 0.05, shown in Table 2). Overall, pulmonary function parameters were well recovered at 1-month follow-up except for 1 patient who failed to perform the test due to chest discomfort. At 6 months, there were 6 patients (12%) who manifested abnormal pulmonary function measures; the portion of discharged patients with lung function parameters < 80% of predicted values were as follows: FEV$_1$ (3 [6%]), FVC (5 [10%]), MVV (4[8%]). No significant differences of pulmonary function measures were identified between patients with CT score0 and those with CT score 0 at 6-month follow-up (shown in Table 4).

Discussions

To the best of our knowledge, this is the first prospective study that sequentially evaluated respiratory symptoms, pulmonary function measures, chest CT findings, and exercise capacity in patients with COVID-19 from 1- to 6- month after hospital discharge. This cohort study shows the respiratory symptoms and pulmonary function to gradually improve in most patients after COVID-19 infection. But chest CT images and 6MWD were still impaired compared to healthy control subjects. Abnormal CT scores at 6-month follow-up were independently associated with steroid administration during hospitalization.

Same as the other pneumonias, fever, cough and dyspnea are the main presenting symptoms among those who become hospitalized. In general, these symptoms gradually improved as patients recovered from the acute illness. Similar results were demonstrated in other pneumonia and ARDS follow-up studies[23, 24]. In a retrospective cohort, 26% of 51 patients with common COVID-19 had cough (8), throat discomfort (3) and sputum (2) at 4-weeks after hospital discharge[25]. Our study cohort showed higher portion of discharged patients to have respiratory symptoms at 1 month, which decreased to 30% at 3 months and still present at 6 months. However, higher prevalence of persistent symptoms was reported at 3 months after mild SARS-CoV-2 infection[18]. Fatigue or muscle weakness were reported in more than 60% of 1733 survivors in Jin Yin-tan Hospital at 6 months; anxiety or depression was reported nearly 25% of them[19]. The significant differences between our observations and these other studies might reflect psychosocial effects associated with COVID-19 and its aftermath, which are issues that warrant for further investigations and follow-up studies.

Similar to previous SARS reports, mild pulmonary function abnormalities and residual CT abnormalities were seen in 10%-40% of our patients at 6-month follow-up. This might explain the persistent cough and dyspnea noted in these patients after discharge. A recent study reported 110 discharged patients with COVID-19 including 17% severe disease patients [26], pulmonary function defects were detected in FEV$_1$ %
in 15 (13.6%), FVC% in 10 (9.1%), which is similar to our findings. Furthermore, that study showed impairment of DLco in nearly 50% of patients and a significant difference in diffusing-capacity measurements among the different groups of disease severity. There were no significant differences among the survivors with different severity pneumonias in regard to other pulmonary function measures (e.g. FEV\(_1\), FVC, FEV\(_1\)/FVC). Similarly, about 15% of 55 SARS patients in Hong Kong were found to have a restrictive defect and 50% of them manifested impaired diffusion capacity after 2-year recovery period[14]. Compared to the study on SARS, pulmonary function impairment was less affected in our cohort of COVID-19 patients.

Recent autopsy study found that include diffuse alveolar damage, hyaline membrane formation, thrombi within the small pulmonary arteries, alveolar septal fibrous proliferation, and organizing pneumonia with fibrosis to be involved in pathogenesis of COVID-19 infection[27, 28]. Therefore, regarding to the secondary pulmonary fibrosis resulting from this injury, diffusion capacity would be expected to be more affected compared to lung volume in most patients[26]. Thus, it would be preferable to combine FEV\(_1\) with DLCO in detecting pulmonary function impairment in recovered COVID-19 patients.

The importance of chest CT images for the diagnosis of COVID-19 infection at early stage and assessment the treatment effects has been widely reported[29]. Liu et al. found that the pulmonary parenchymal abnormalities on CT scans due to COVID-19 could be reversible for the common COVID-19 patients after 4-week discharge[25]. Although most patients in this study manifested significantly improved CT scores, pulmonary abnormalities were still present in almost 40% of them at 6 months. The lung damage in COVID-19 was reported to be associated with a cytokine storm induced by SARS-CoV-2, which might be similar to that of SARS-CoV[30]. Wang et al investigated 12 recovered patients with SARS in Taiwan, over 80% of whom still manifested HRCT abnormalities at 60 days after discharge. Moreover, the HRCT scores were increased and correlated with increased cellularity of bronchoalveolar lavage fluid (BALF)[31]. Thus, persistence of lung inflammation during the early recovery period might be associated with the delayed resolution of SARS. As several studies on SARS reported, radiologic abnormalities were rather common among the survivors, accounting for about 80% and 30% of patients at 6-months and 1-year follow-up, respectively[32–34]. Compared with SARS, COVID-19 appears to be associated with a more prompt resolution? on chest CT images during the recovery phase in this study. According to a recent observation, 30 patients with post-COVID-19 interstitial lung changes received steroid treatment, resulting in relative increase in transfer factor and FVC with significant symptomatic and radiological improvement[35]. However, the residual lung damage as well as fibrosis of severe post-COVID-19 patients are still challenging for physicians in the setting of increasing numbers of survivors worldwide.

Previous studies have shown that 6MWD was substantially lower among ARDS and SARS survivors[36, 37]. The 6MWD of 97 survivors in Hong Kong was 464 m (SD, 87 m) at 3 months and 502m (SD 97 m) [37]. The 6MWD was significantly reduced in our patients at 1 month when compared to the corresponding matched healthy subjects, and gradually recovered at 3-month follow-up. The performance in our cohort was better than that of SARS survivors in Hong Kong. The 500m distance of our 6MWD at 1 month was similar as that of SARS at 6 months after discharge. These observations seem to indicate
relatively prompt recovery of COVID-19 patients compared to those with SARS. But there was no significant improvement in 6MWD after that until 6 months. Given the relatively well-preserved lung function in most of our patients, the reduced 6MWD may be related to extrapulmonary factors such as physical deconditioning and psychological effects[19]. It appears that post-COVID-19 clinic and rehabilitation program might be urgently needed in the pandemic area of COVID-19.

Steroids have been widely prescribed in patients with severe viral pneumonias in recent decades although the role of this treatment remains controversial[38–40]. During the 2003 SARS outbreak in Hong Kong, steroids were associated with better prognosis but associated with a higher rate of secondary infections[39]. In a controlled, open-label trial in 6,425 UK patients hospitalized with COVID-19, the use of low-dose dexamethasone resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone[7]. However, there was still concern that anti-inflammatory effects of steroids might lead to slower resolution of pneumonia as reflected in our results. Thus, it would be of interest to perform additional studies on the long-term outcome to determine the optimal timing, duration, and dose of steroid therapy in the treatment of patients with COVID-19.

There are several limitations of this study. Firstly, the number of patients in this cohort enrolled from a single center was relatively modest which might cause potential bias. Secondly, diffusing capacity was not measured in this study due to concerns regarding potential transmission during PFT performance. However, significantly decreased pulmonary gas exchange can be assessed by pulse oxygen oximetry. In this case-series, all the patients underwent 6MWT successfully and manifested oxygen saturation above 93% at room air at 3 months and 6 months. In addition, psychological evaluations were not performed to assess psycho-behavioral problems of anxiety and/or depression in this cohort. Investigating of the long-term sequelae of COVID-19 survivors in the physical and psychological domains will provide additional insights.

Conclusions

At 6 months after discharge, respiratory symptoms and pulmonary function were significantly improved in most patients with COVID-19 while residual abnormalities were still noted in both chest CT images and exercise capacity. Further follow-up study and appropriate support program should be provided to post-COVID-19 patients in the physical and psychological domains.

Abbreviations

COVID-19
Coronavirus disease 2019
6MWD
6-minute walk distance
6MWT
6-minute walk test
PFTs
pulmonary function tests
CI
Confidence interval
OR
Odds ratio
SD
Standard Deviation
RT-PCR
Real-time reverse-transcription polymerase-chain-reaction
SARS
Severe Acute Respiratory Syndrome
MERS
Middle East Respiratory Syndrome
ICU
Intensive Care Unit
SpO2
Percutaneous oxygen saturation,
FVC
Forced vital capacity
FEV1
Forced expiratory volume in one second
MVV
Maximum voluntary ventilation
HFNC
High-flow nasal cannula oxygen therapy
BALF
Cellularity of bronchoalveolar lavage fluid
HRCT
High-Resolution Computed tomography
SARS-CoV-2
Severe Acute Respiratory Syndrome Coronavirus 2
ATS
American Thoracic Society
USTC
University of Science and Technology of China

Declarations

Availability of data and materials
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Competing interests

The authors declare that they have no competing interests.

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**Author contributions:** Jie Cao, Xianmeng Chen and Xiaowen Hu conceived the idea, designed, and underwent the study, wrote the draft manuscript, and had full access to all the data and took responsibility for the integrity of the data. Jie Cao, Xianmeng Chen and Wei Wei collected and analyzed data and performed statistical analysis. Xiaowen Hu and Jay Ryu edited the study protocol and supervised the study and edited the manuscript. All the authors reviewed and approved the final version of the manuscript.

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**Ethics declarations**

**Ethics approval and consent to participate**

The Ethics Committee of The First Affiliation Hospital of University of Science and Technology (Anhui Provincial Hospital) approved the collection of clinical data from the enrolled patients with COVID-19 infections (No.2020-XG (H)-007). Written informed consent was obtained from all the patients.

**Consent for publication**

Yes.

**References**


Figures
Figure 1

Flow chart of 6-month outcome of discharged patients with COVID-19

85 cases of COVID-19

1 died and 3 excluded due to age

Patients (n=81)

14 F/U at local hospital; 5 refused

Patients (n=62) at 1 month

7 F/U at local hospital; 14 refused

Patients (n=61) at 3 months

12 F/U at local hospital; 18 refused

Patients (n=51) at 6 months