Pulmonary Dysfunction in Patients Recovered from COVID-19 Pneumonia: A 6-Month Follow-up Study

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Abstract

Objectives: This study investigates the clinical features and pulmonary functions of COVID-19 pneumonia survivors at 3 or 6 months after diagnosis in the Heilongjiang Province, China.

Methods: Forty-six patients with COVID-19 pneumonia diagnosed since February 2020 were enrolled in this study for follow-up in July 2020. These patients were categorized into three groups: Group A (n=24) and Group B (n=11) who were diagnosed with moderate or severe pneumonia and followed up at three months after diagnosis; Group C (n=11) who were diagnosed with severe pneumonia and followed up at six months after diagnosis. Data on pulmonary function, arterial blood gas analysis, chest CT, blood test, antibody test, and health-related quality of life during hospitalization and at the follow-up visits were collected and analyzed.

Results: Abnormal PO_2 (A-a) was more prevalent in severe cases (Group B and C) than in moderate cases (Group A). Pulmonary dysfunction was common in this cohort. Abnormal CT scores of severe cases (Group B and C) were significantly higher than that of moderate cases (Group A). During the follow-up, lung abnormalities gradually resolved in the first 3 months (Group A and B), however, further resolution was not significant from 3 months to 6 months (Group B and C).

Conclusion: Although pulmonary interstitial changes due to COVID-19 pneumonia gradually reverse over time, pulmonary dysfunction is common and appears to persist at least up to 6 months in patients recovered from COVID-19 pneumonia.

Introduction

The coronavirus disease 2019 (COVID-19) has evolved into a global pandemic since December 2019. Because of its high rates of transmission and mortality, more than 50 million patients have been infected globally among whom 1,250,000 have died from COVID-19 pneumonia or other complications since its outbreak. 5% of symptomatic patients were classified as critically ill and needed to be treated in the ICU; the mortality rate of such patients was as high as 53%[1, 2].

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) mainly attacks the lung and causes pneumonia. Patients often presented with fever and cough; severe cases may rapidly progress to acute respiratory distress syndrome (ARDS) and respiratory failure and need respiratory support. Although the long-term sequelae of COVID-19 are currently not fully understood, there is a possibility of pulmonary fibrosis based on previous experience with other coronaviral diseases such as the Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS)[3, 4]. Such sequelae often lead to severe pulmonary dysfunction that significantly affects the quality of life[5].

While there has been a surge in research aiming to gain a deeper insight into the clinical profile and pathophysiology of the disease, less is known regarding the long-term pulmonary function in survivors of COVID-19 pneumonia [6, 7]. This study aims to follow up on patients who have recovered from COVID-19

pneumonia for three or six months to understand the impact of disease severity and time on the pulmonary function and clinical characteristics after recovery from COVID19 pneumonia.

Methods

Patients

According to the COVID-19 treatment guidelines from China and the WHO[8, 9], the severity of COVID-19 pneumonia is categorized into four levels according to the condition at the time of admission: mild (no radiological evidence of pneumonia and mild clinical symptoms), moderate (pneumonia on chest radiograph with fever and evidence of respiratory symptoms), severe (pneumonia with any of the following indications: $PaO_2/FiO_2 \leq 300$mmHg, oxygen saturation$\leq$93% at rest, tachypnoea at RR$\geq$30/min or respiratory distress), and critical (patients who either developed organ failure requiring ICU monitoring or respiratory failure requiring mechanical ventilation).

Forty-six patients with COVID-19 pneumonia treated at the First Affiliated Hospital, Harbin Medical University since February 2020 were enrolled in this study for follow-up in July 2020. These patients were categorized into three groups: Group A (n=24) who were diagnosed with moderate pneumonia in April 2020 and were followed up at three months after diagnosis; Group B (n=11) who were diagnosed with severe pneumonia in April 2020 and were followed up at three months after diagnosis; Group C (n=11) who were diagnosed with severe pneumonia in February 2020 and were followed up at six months after diagnosis. During hospitalization, all patients were treated in accordance with the COVID-19 treatment guidelines of China[8]. Patients were given oxygen therapy, high-flow nasal cannula, non-invasive ventilator, or invasive ventilator according to their pulmonary conditions. They were discharged from our hospital when the following criteria were met: oropharyngeal swab SARS-CoV-2 nucleic acid was negative twice from tests done at least 24 hours apart; body temperature has returned to normal for more than 3 days; respiratory symptoms have improved significantly; lung radiograph shows significant improvement in acute exudative lesion.

These patients were all followed up in the outpatient clinic in July 2020. Figure 1 shows a flowchart of the study. They were assessed for their pulmonary function, chest high-resolution CT (HRCT), arterial blood gas analysis, blood tests, modified Medical Research Council (mMRC) dyspnea score, and health-related quality of life (HRQoL). The clinical research ethics committee of the First Affiliated Hospital, Harbin Medical University approved this study (Protocol No. IRB-AF/SC-04/01.0).

Blood tests

Blood analyses included blood cell counts, renal and liver function tests, coagulation profile, and immunoglobulin test for SARS-CoV-2. Serum SAR-CoV-2 IgG and IgM antibody titers (AU/mL) were analyzed with a chemiluminescent immunoassay (Shenzhen Yahuilong Biotechnology Co., Ltd, Shenzhen, China), with a reference level of 10 AU/mL. A blood gas analyzer (GEM Premier 3000; Instrumentation Laboratory, New York, USA) was used to quantify arterial oxygen partial pressure and the

alveolar-arterial oxygen pressure gradient (PO_2 (A-a)). Arterial blood gas analysis was not performed for two patients because of their disconsent.

Pulmonary function

All patients first were assessed with an oropharyngeal swab SARS-CoV-2 nucleic acid test to exclude active viral infection. Standard single-breath pulmonary function testing (MasterScreen Body/Diff, Jaeger Co., Germany) was then carried out to determine total lung capacity (TLC), forced vital capacity (FVC), vital capacity (VC), forced expiratory volume at first second (FEV1), and diffusing lung capacity for carbon monoxide single-breath (DLCO SB). DLCO SB values were corrected for individual hemoglobin levels. A DLCO SB of less than 80% was interpreted as diffusion deficit, while all other results were depicted in terms of percentages of predicted normal values. Pulmonary function test was not done for one patient because of positive SARS-CoV-2 IgM.

Chest high-resolution CT Scan (HRCT)

All COVID-19 patients underwent chest HRCT with a 256-slice multi-detector CT scanner (Brilliance iCT, Philips Healthcare, Holland) when hospitalized, and chest HRCT at the follow-up visit was performed with a 40-row multi-detector CT scanner (uCT 528, Shanghai United Imaging Healthcare, Shanghai, China). Imaging parameters were set as follows: slice thickness, 1 mm; tube voltage, 100 kV; 125 mas; 0.30-second gantry rotation time, automatic. All images were analyzed with the Extended Brilliance Workspace V 4.0.2.145 (Philips Healthcare, Cleveland, OH, USA). For each patient, chest HRCT was performed at four stages: when the patient was admitted (Admission), when clinical condition reached its worst (Progression), at the time of hospital discharge (Discharge), and at the time of follow-up (Follow-up).

Two experienced radiologists without prior knowledge of the clinical profiles reviewed and graded CT images independently. A consensus had to be reached between these two radiologists about the abnormalities. When there was a disagreement, the final decision would be made by a third senior radiologist with more than 10 years of experience. A scoring system was adapted for this study[10]. Each image was assigned a score ranging from 0 to 5 based on the presence of air trapping, fibrosis, consolidation, and ground-glass opacity (GGO). Score 0 indicated a normal lung; Score 1 was scored if <5% of a lobe presented GGO; Score 2 if 6-25% was involved; Score 3 if 26-50% was involved; 4 points if 51-75% was involved; Score 5 if more than 75% was involved. All 5 lung lobes were scored and an abnormal CT score (range 0-25) was generated by adding scores of individual lobes.

Health-related quality of life (HRQoL) assessment and mMRC dyspnea score

The HRQoL of patients was determined using the St. George's Respiratory Questionnaire (SGRQ)[11]. This questionnaire encompassed information regarding symptom severity, activity tolerance, and impact on daily life. A higher score was indicative of worse overall functional status. The mMRC dyspnea scale was used to assess dyspnea (score 0–4, with 4 indicating the worst dyspnea)[12].

Statistical analysis

Statistical analysis was performed using SPSS 25.0, For normally distributed variables, the data were expressed as mean ± standard deviation (SD); the differences among these three groups were analyzed with one-way ANOVA and then Fisher's LSD tests. For variables that are not normally distributed, data were presented as medians (interquartile range) and analyzed with the Kruskal-Wallis H test and then Nemenyi tests. Categorical variables were presented as frequencies or percentages and statistically analyzed with the Chi-square test or Fisher's exact test. A p-value of <0.05 was taken to indicate statistical significance.

Results

Demographics and clinical characteristics of patients at the baseline

Forty-six COVID-19 pneumonia patients participated in this investigation. Our study cohort involved 24 moderate cases diagnosed for 3 months (Group A), 11 severe COVID-19 cases diagnosed for 3 months (Group B), and 11 severe COVID-19 cases diagnosed for 6 months (Group C). There were no differences among these three groups in major clinical characteristics such as body mass index (BMI), comorbidities, symptoms such as dyspnea, sputum, and fatigue, except that in contrast to moderate cases severe cases were older; the proportion of male cases in Group C were more than that in Group A (81.82% vs 25.00%, $p = 0.006$); Group B had more smokers than other groups. All patients had a negative result of SARS-CoV-2 nucleic acid oropharyngeal swab test, while all were positive for SARS-CoV-2 IgG and only one patient in Group C was positive for SARS-CoV-2 IgM (Table 1).

Table 1

Demographics and baseline clinical characteristics of patients with COVID-19 pneumonia. Data are depicted as mean ± SD or No. (%). One-way ANOVA, Kruskal-Wallis H rank-sum test and Fisher exact test were used to analyze the differences among these three groups. [a] $P < 0.05$, in contrast to Group B; "—", Fisher's exact test.

Characteristics	Group A (n = 24)	Group B (n = 11)	Group C (n = 11)	$c^2/F/H$	*P* value
Age, mean (SD), years	45.29 ± 14.22[a]	59.09 ± 7.54	61.73 ± 15.15	7.613	0.001
Male, n (%)	6 (25.00)	6 (54.55)	9 (81.82)	10.275	0.006
BMI, mean (SD)	24.54 ± 3.67	26.18 ± 2.76	24.94 ± 3.14	0.909	0.411
Smoking	2 (8.33) [a]	8 (72.73)	0 (0.00) [a]	—	< 0.001
Comorbidities, n (%)					
Hypertension	3 (12.50)	1 (9.09)	1 (9.09)	—	1.000
Diabetes	0 (0.00)	2 (18.18)	0 (0.00)	—	0.106
COPD	2 (8.33)	1 (9.09)	0 (0.00)	—	1.000
Cardiovascular disease	0 (0.00)	1 (9.09)	0 (0.00)	—	0.478
Cancer	0 (0.00)	2 (18.18)	1 (9.09)	—	0.101
Symptoms, n (%)					
Cough	1 (4.17)	1 (9.09)	1 (9.09)	—	0.599
Dyspnea	14 (58.33)	8 (72.73)	3 (27.27)	4.901	0.086
Sputum	0 (0.00)	0 (0.00)	0 (0.00)	—	1.000
Fatigue	8 (33.33)	4 (36.36)	5 (45.45)	—	0.919
SARS-CoV-2 nucleic acid test positivity, n (%)	0 (0.00)	0 (0.00)	0 (0.00)	—	1.000
SARS-CoV-2 IgG antibody positivity, n (%)	24 (100.00)	11 (100.00)	11 (100.00)	—	1.000
SARS-CoV-2 IgM antibody positivity, n (%)	1 (4.17)	0 (0.00)	0 (0.00)	—	1.000

Blood tests at follow-up

All blood test results (leucocytes, lymphocytes, coagulation function, liver, and kidney function) were in the normal range, and most were not markedly different among these three groups. However, the level of creatinine in Group C was significantly higher than that in Group B, while the level of lactic dehydrogenase (LDH) in Group B was higher than that in Group A (Table 2).

Table 2

Blood tests of patients with COVID-19 pneumonia at follow-up. Data are expressed as mean ± SD if it fits normal distribution, or median (IQR) if it does not. CRP: C-reactive protein; BUN: blood urea nitrogen; Cr: creatinine; ALT: alanine transaminase; AST: aspartate Transaminase; GGT: gamma glutamyl transferase; LDH: lactate dehydrogenase. [a] $P < 0.05$, in contrast to Group B;

Lab test	Group A (n = 24)	Group B (n = 11)	Group C (n = 11)
Leucocytes (× 10^9/L)	5.86 ± 1.21	5.28 ± 1.48	5.08 ± 1.46
Lymphocyte (× 10^9/L)	1.90 ± 0.50	1.77 ± 0.61	1.51 ± 0.50
Prothrombin time (sec)	10.82 ± 0.48	10.90 ± 1.13	10.95 ± 0.35
D-dimer (mg/L)	0.20 (0.13 ~ 0.35)	0.30 (0.17 ~ 0.37)	0.27 (0.17 ~ 0.40)
CRP (mg/L)	1.74 (1.23 ~ 2.65)	1.80 (1.41 ~ 2.59)	2.77 (1.57 ~ 6.32)
Creatinine kinase (U/L)	54.00 (44.50 ~ 73.50)	54.00 (36.50 ~ 77.50)	49.50 (41.00 ~ 73.00)
BUN (mmol/L)	5.24 ± 1.19	5.47 ± 1.82	7.15 ± 3.16
Cr (μmol/L)	54.80 (46.30 ~ 62.55)	48.60 (39.60 ~ 67.20)	78.95 (69.90 ~ 94.00) [a]
ALT (U/L)	19.65 (11.95 ~ 22.88)	21.90 (16.50 ~ 30.60)	17.90 (14.60 ~ 26.80)
AST (U/L)	23.15 (18.75 ~ 26.45)	25.60 (23.50 ~ 27.60)	22.20 (18.00 ~ 30.90)
GGT (U/L)	28.52 ± 18.56	53.84 ± 79.47	31.74 ± 12.53
LDH (U/L)	348.63 ± 65.83[a]	423.55 ± 47.73	371.55 ± 79.10

Blood level of SARS-CoV-2 IgG antibody during hospitalization and at follow-up

SARS-CoV-2 IgG antibody in blood was measured in all patients when hospitalized and at the follow-up visit. The level of SARS-CoV-2 IgG kept increasing significantly at 3 months (Group A and B; Fig. 2A and B). At 6 months, the level of SARS-CoV-2 IgG significantly dropped from 123.81 ± 15.02 to 58.84 ± 33.74 AU/ml (Group C; Fig. 2C).

Arterial blood gas analysis at follow-up

Forty-four patients underwent arterial blood gas analysis at follow-up (Table 3). Although the average oxygenation indexes of each group were within the normal range, severe cases (Group B and C) had significantly lower oxygenation indices compared to moderate cases (Group A). Group B had a higher

difference of PO_2 (A-a) than Group A, but this parameter was equivalent in Group B and Group C. 36.36% patients of Group A had their PO_2 (A-a) higher than the normal predicted value, while 45.46% in Group B and 54.55% in Group C had values higher than the normal predicted value. Severe cases (Group B and C) seemed to have higher hemoglobin than moderate cases (Group A) although the difference did not reach statistical significance. These data suggest that severe cases had worse blood oxygen exchange than moderate cases, and such damage in severe cases persisted up to 6 months at follow-up.

Table 3

Arterial blood gas analysis in patients with COVID-19 pneumonia at follow-up. Data are expressed as No. (%) or mean ± SD if it fits normal distribution, or median (IQR) if it does not. [a] $P < 0.05$, in contrast to Group B.

Arterial blood gas	Group A (n = 22)	Group B (n = 11)	Group C (n = 11)
PO_2 (a)/FO_2	442.14 ± 28.90 [a]	403.91 ± 51.70	404.64 ± 24.90
PO_2 (A-a)	8.60 (5.60 ~ 14.00) [a]	16.60 (10.40 ~ 19.70)	15.50 (12.30 ~ 18.10)
Abnormal PO_2 (A-a), N, (%)	8 (36.36)	5 (45.45)	6 (54.55)
Hemoglobin (g/L)	140.13 ± 15.84	147.55 ± 13.52	149.45 ± 11.63

Pulmonary function at follow-up

No remarkable differences in FEV1, FEV1/FVC, MEF50, MEF25, MMEF75/25, and DLCO/VA were observed among the three groups (Table 4). However, on average, the DLCO SB of all three groups was less than the predicted 80%. The DLCO SB of Group B was slightly lower than that of Group A without statistical significance, yet the DLCO SB of Group C was significantly higher than that of Group B (75.56 ± 13.95 *vs* 61.01 ± 15.04 $P < 0.05$) (Table 4). The TLC of Group B was significantly lower that of Group A; but the TLC of Group C was higher than that of Group B (88.35 ± 9.48 *vs* 76.90 ± 11.46; P□0.05). Additionally, the FRC was markedly reduced in Group B compared to that in Group C. Abnormal ventilation (FEV1 < 80% predicted or FEV1/FVC < 70% predicted or MEF50, MEF25, MMEF75/25 < 70% predicted) were present in 52.17%, 72.73%, and 45.45% of the cases, in three groups, respectively. Abnormal diffusion (DLCO SB < 80% predicted or DLCO/VA < 80% predicted) was present in 65.22%, 81.82%, 72.73% of the cases. All together, pulmonary dysfunction (abnormal ventilation or diffusion) was observed in 82.61%, 81.82%, 72.73% of the cases in these three groups, respectively. These data suggest that at 3 and 6 months of follow-up, most patients still had pulmonary dysfunction.

Table 4

Pulmonary function of patients with COVID-19 pneumonia at follow-up. Data are expressed as mean ± SD if it fits normal distribution, or median (IQR) if it does not. DLCO SB: diffusing lung capacity for carbon monoxide single-breath; FEV1: forced expiratory volume at first second; FVC: forced vital capacity; TLC: total lung capacity; FRC: functional reserve capacity; MEF: maximal expiratory flow-volume; MMEF: Maximal mid-expiratory flow; VA: alveolar volume. [a] $P < 0.05$, in contrast to Group B.

Pulmonary Function	Group A (n = 23)	Group B (n = 11)	Group C (n = 11)
FEV1 (% predicted)	91.70 ± 18.91	83.30 ± 20.32	95.70 ± 15.89
FEV1/FVC (% predicted)	78.03 ± 10.34	79.03 ± 6.71	75.99 ± 12.00
MEF50 (% predicted)	90.65 (56.85 ~ 96.80)	66.30 (51.45 ~ 98.00)	70.20 (44.00 ~ 81.90)
MEF25 (% predicted)	60.85 (35.60 ~ 76.85)	39.90 (31.65 ~ 62.60)	40.80 (27.30 ~ 48.70)
MMEF75/25 (% predicted)	65.30 (51.505 ~ 88.35)	53.10 (42.55 ~ 73.70)	67.80 (48.65 ~ 90.90)
TLC-SB (% predicted)	90.70 ± 10.85 [a]	76.90 ± 11.46	88.35 ± 9.48
FRC-SB (% predicted)	85.99 ± 17.26	72.76 ± 10.76	91.04 ± 20.00 [a]
DLCO SB (% predicted)	72.41 ± 13.07	61.01 ± 15.04	75.56 ± 13.95 [a]
DLCO/VA (% predicted)	82.68 ± 12.95	81.71 ± 13.18	88.62 ± 16.58
Abnormal ventilation, n (%)	12 (52.17)	8 (72.73)	5 (45.45)
Abnormal diffusion, n (%)	15 (65.22)	9 (81.82)	8 (72.73)
Pulmonary dysfunction, n (%)	19 (82.61)	9 (81.82)	8 (72.73)

Dynamic changes of chest HRCT

Images and data of chest HRCT were available for each patient at four stages: admission, progression, discharge, and follow-up (Fig. 3A-L). Severe cases (Group B and C) had worse signs of pneumonia than moderate cases (Group A). While the HRCT image was exacerbated initially and then improved after the patients being discharged, severe cases (Group B and C) tended to have some residual changes in the lung at follow-up. The abnormal CT score at follow-up of each group was lower than that at the time of hospital discharge (Fig. 3M). At 3 months of follow-up, severe cases (Group B) had a higher score than moderate cases (Group A). For severe cases, the abnormal CT score remained high at 6 months of follow-up (Group C) as compared with 3 months of follow-up (Group B).

HRQoL score and mMRC dyspnea score

SGRQ scores of most patients remained abnormal at follow-up. Although there was no statistical difference among the SGRQ scores of these three groups at follow-up, severe cases at 6 months (Group C) had a better quality of life than moderate cases at 3 months (Group A) and severe cases at 3 months (Group B). Similarly, the mMRC apnea score of severe cases at 6 months (Group C) improved as compared with severe cases at 3 months (Group B) (Table 5).

Table 5
Health-related quality of life (HRQoL) in patients with COVID-19 pneumonia at follow-up. Data are expressed as median (IQR). SGRQ: St. George's respiratory questionnaire, mMRC: modified Medical Research Council. [a] $P < 0.05$, in contrast to Group B.

	Group A (n = 24)	Group B (n = 11)	Group C (n = 11)
SGRQ	18.00 (15.00 ~ 27.00)	17.00 (16.00 ~ 20.00)	9.00 (4.00 ~ 28.00)
mMRC	1.00 (0.00 ~ 2.00)	2.00 (0.00 ~ 3.00)	0.00 (0.00 ~ 1.00) [a]

Discussion

At present, SARS-CoV-2 is still in a global pandemic, infecting tens of millions of people and severely affecting global health and economy. The long-term consequences of COVID-19 pneumonia have not been fully documented. In this study, our data have shown that severe cases had worse pulmonary function than moderate cases at three months of follow-up, and severe cases had residual lesions in the lung even at six months of follow-up. This observation is reminiscent of SARS, MERS, and ARDS due to other causes. Pulmonary dysfunction due to residual pulmonary fibrosis persisted in these situations and caused high mortality after recovery[13] [14] [15]. COVID-19 pneumonia may present a similar pattern of disease progression.

GGO or grid-like changes are typical changes on HRCT of COVID-19 pneumonia. The lung parenchyma of severe cases may be extensively exuded; 25% of patients still had fiber-stripe shadows and bronchial structural distortions after discharge[16]. This is similar to CT changes in SARS patients during recovery. Such structural changes may remain for a long period, resulting in pulmonary dysfunction in ventilation and diffusion. We have reported previously that the rate of abnormal ventilation in COVID-19 pneumonia was high at the time of hospital discharge, with restrictive ventilatory defect and small airway dysfunction in 50% of the cases[17]. Zhao *et al.* indicated that 25.45% of recovered COVID-19 patients still had significantly impaired pulmonary function at 3 months after discharge[18]. But so far, there is no follow-up study on the pulmonary function of COVID-19 pneumonia at 6 months of follow-up. It also remains unknown whether initial disease severity and follow-up time may have significant impacts on pulmonary function during the recovery of COVID-19 pneumonia.

Previous studies have noted that impaired DLCO SB and reduced total lung capacity appeared to persist for months or even years in survivors of coronaviral pulmonary infections[19–21]. Some studies also reported that SARS and H1N1 patients also had small airway dysfunction during recovery [22, 23]. In our

study, we observed that the value of PO_2 (A-a) in severe cases at 3 months of follow-up (Group B) was higher than that in moderate cases at 3 months of follow-up (Group A), but was not different from that in severe cases at 6 months of follow-up (Group C). The proportions of patients with abnormal PO_2 (A-a) in Groups A, B, and C were 36.36%, 45.46%, and 54.55%, respectively (Table 3). Obviously, PO_2 (A-a) increased with the severity of the disease; it did not recover at 6 months of follow-up. Pulmonary dysfunction was common in our cases, and pulmonary function data matched the arterial gas analysis data, for example, DLCO SB in severe cases at 3 months of follow-up (Group B) was lower than that in moderate cases at 3 months of follow-up (Group A). In severe cases, DLCO SB at 6 months of follow-up (Group C) was higher than that at 3 months (Table 4). These results suggest that decreased diffusion and restrictive ventilatory defect are common in patients recovered from COVID-19 pneumonia, and the severity of pulmonary dysfunction is related to the severity of the initial disease. Although pulmonary function improved over time, at 6 months many severe cases still had pulmonary dysfunction.

In this study, chest HRCT of COVID-19 pneumonia at admission was significant with GGO and interstitial changes. As the disease progressed, consolidations occurred in some patients (Fig. 3), a development that corresponded with disease severity. Lung lesions appeared to gradually resolve on subsequent chest HRCT images taken at follow-up, with a decrease in density (Fig. 3M). Evidence from patients with other coronavirus infections such as SARS and MERS has shown that interstitial lung damage is followed by parenchymal lesions and then pulmonary fibrosis that causes significantly reduced pulmonary function lasting months to years after hospital discharge[4, 24, 25]. CT findings of COVID-19 pneumonia were similar to those noted in MERS and SARS which were all related to inflammatory damage of the lower respiratory tract and alveoli. The first change that occurs at the early stage was excessive inflammatory exudate and edema in the pulmonary interstitium manifested as GGO. ‘Crazy-paving’ was seen on later CT images, a feature due to increased exudate and thickened interlobular septum. At the most severe stage, cellular fibrous mucus-like organizing exudates appeared in the alveolar cavity and the density of the lesions increased, showing paving stone-like changes combined with consolidation[26, 27]. Subsequent follow-up of chest HRCT during recovery was significant with partial resolution of the lung lesions[28]. As expected, at the time of follow-up, the abnormal CT score was significantly lower than that at discharge. At 3 months of follow-up, severe cases (Group B) had higher abnormal CT scores than moderate cases (Group A), but their scores did not further improve at 6 months of follow-up (Group C) (Fig. 3M). Pathological studies of SARS, MERS, and COVID-19 have confirmed these changes[29]. These previous studies and our follow-up results suggest that COVID-19 lesions may involve the formation of thickened alveolar sacs and alveolar walls, rather than complete pulmonary fibrosis.

Given the key role of IgG in modulating the immune response, further efforts in developing vaccines and preventing reinfection are dependent on a better understanding of IgG changes in patients who have recovered from COVID-19 infection. Liu *et al.* tested 484 patients for SARS-CoV-2 IgG antibodies at 100 days after symptom onset and noted that 18% were tested negative[30]. In our study, the level of SARS-CoV-2 IgG rose significantly in patients at 3 months of follow-up (Group A and B) (Fig. 2A and B). However, the level of SARS-CoV-2 IgG at 6 months of follow-up (Group C) dropped significantly from

123.81 ± 15.02 AU/ml (at hospital admission) to 58.84 ± 33.74 AU/ml (Fig. 2C). The underlying factors and mechanisms contributing to the dynamics of IgG level in COVID-19 require further investigation.

Pulmonary dysfunction, fatigue, anxiety, and depression are associated with the decline of patient's quality of life[22, 31]. In our study, SGRQ and mMRC scores deteriorated with the severity of the initial disease, but as time goes by, they tended to improve (Table 5).

While several reports have delineated the outcomes of COVID-19 pneumonia at 3 months after diagnosis[18], ours is the first to correlate clinical features, HRCT imaging, and pulmonary function at 3 and 6 months of follow-up. Additionally, there appears to be a permanent impairment in pulmonary function despite apparent resolution of lung pathology seen on sequential HRCT images, resulting in poorer quality of life. Long-term follow-up of a larger cohort of COVID-19 pneumonia is warranted in future efforts to tackle this debilitating condition.

Limitations

This study has several limitations. Firstly, a relatively small cohort of 46 patients with COVID-19 pneumonia was enrolled in this study. Secondly, due to the sudden outbreak of the epidemic, we were unable to evaluate those early severe cases (Group C) at the 3 months of follow-up; thus we were not able to produce longitudinal data of this group. The comparison between severe cases at 3 months of follow-up (Group B) and those at six months (Group C) was not ideal. Further longitudinal follow-up of a larger cohort would be necessary to increase our knowledge about pulmonary dysfunction after recovery from COVID-19 pneumonia.

Conclusions

To our best knowledge, this is the first follow-up study to describe the pulmonary function and clinical characteristics of COVID-19 pneumonia at 3 and 6 months. Our data indicated that pulmonary dysfunction was common at these time points, particularly in those severe cases. Although pulmonary interstitial changes due to COVID-19 pneumonia gradually reversed over time, pulmonary dysfunction appears to persist at least up to 6 months and such patients require further follow-up and treatment.

Abbreviations

ARDS, acute respiratory distress syndrome; BMI, Body Mass Index; COVID-19, coronavirus disease 2019; DLCO SB, diffusing lung capacity for carbon monoxide single-breath; FEV1, forced expiratory volume at first second; FRC, functional reserve capacity; FVC, forced vital capacity; GGO, ground-glass opacity; HRCT, chest high-resolution CT; HRQoL, health-related quality of life; IQR, interquartile range; LDH, lactic dehydrogenase; MEF, maximal expiratory flow-volume; MMEF, maximal mid-expiratory flow; mMRC, modified Medical Research Council; MERS, middle east respiratory syndrome; SARS, severe acute

respiratory syndrome; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SGRQ, St. George's respiratory questionnaire; SD, standard deviation; TLC: total lung capacity; VA, alveolar volume.

Declarations

Ethical Approval and Consent to participate:

the clinical research ethics committee of the First Affiliated Hospital, Harbin Medical University approved this study (Protocol No. IRB-AF/SC-04/01.0).

Consent for publication:

written informed consent for publication was obtained from all participants.

Availability of supporting data:

the authors confirm that the data supporting the findings of this study are available within the article.

Competing interests:

the authors have no competing interests to declare.

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Authors' contributions:

XLM wrote the manuscript; KK and XLM designed the study; YG, DSF, WY, SLY, MLZ, BTL, SSM, XYL, WL, SGJ, WLK, YC carried out the blood test and questionnaire survey; HLW carried out pulmonary function test; XG carried out immunoglobulin test for SARS-CoV-2; CYS performed HRCT scan; YL did statistical analysis; MYZ and KJY conceived the study, participated in its design and are guarantors of the paper. All authors approved the final manuscript.

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Figures

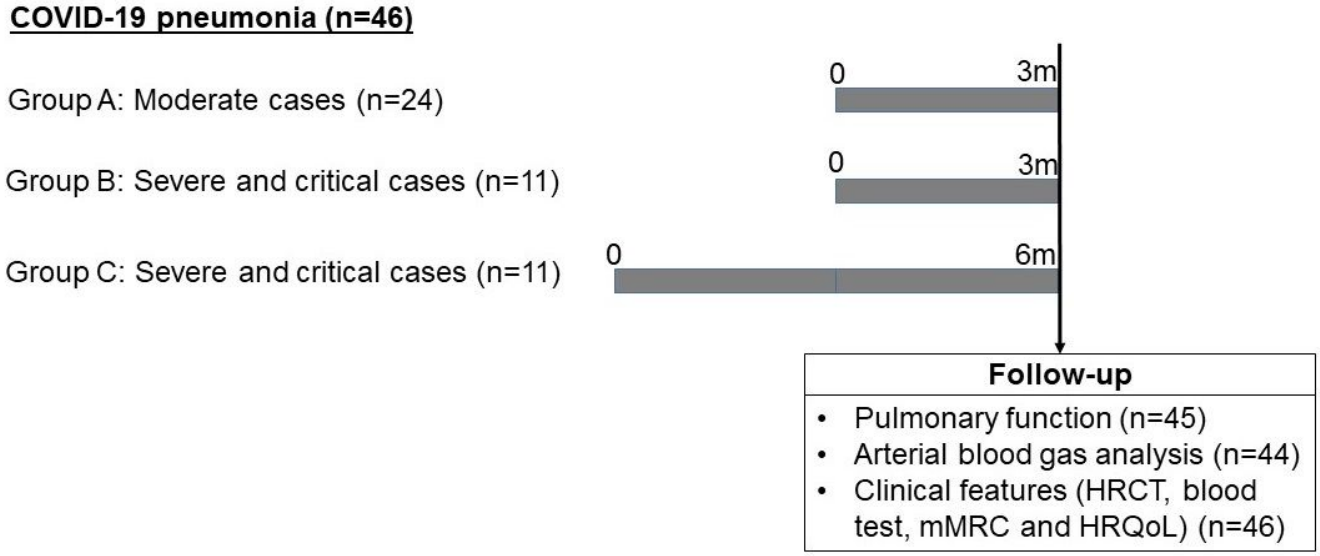
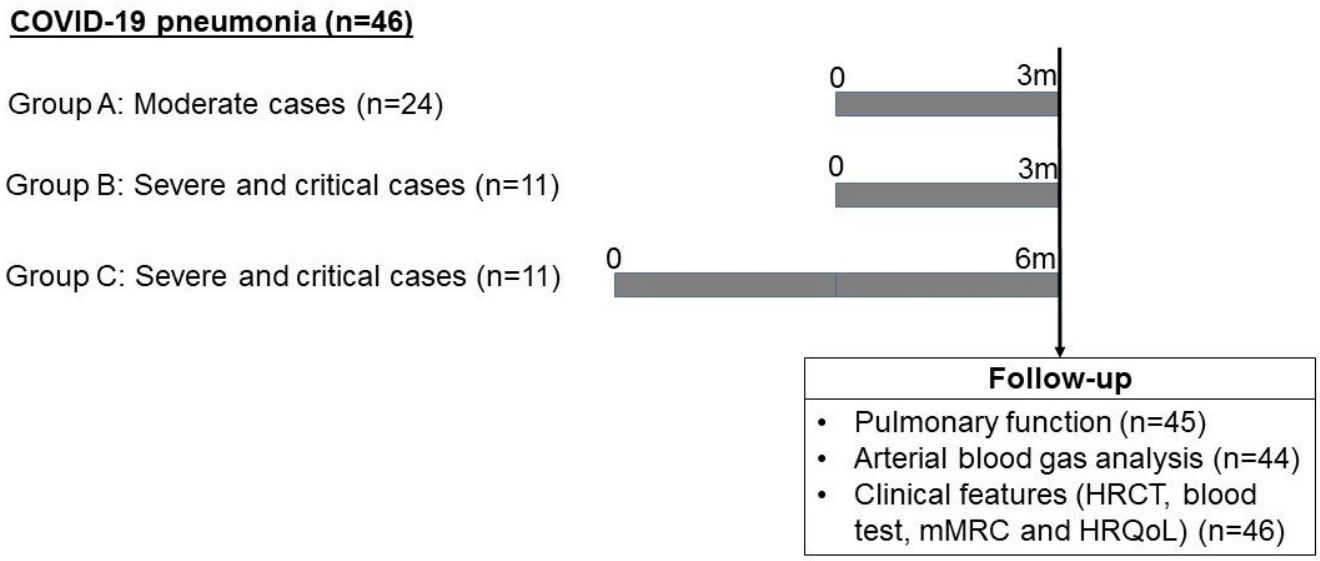


Figure 1

Follow-up of 46 cases of COVID-19 pneumonia. In this cohort of 46 cases, 24 cases with moderate pneumonia (Group A) were followed at 3 months after being diagnosed in April 2020, 11 cases with severe pneumonia (Group B) at 3 months after being diagnosed in April 2020, and 11 cases with severe pneumonia (Group C) at 6 months after being diagnosed in February 2020. Time 0 indicates the time of diagnosis. All follow-up was carried out in July 2020. Pulmonary function test and arterial blood gas analysis were performed in 45 cases and 44 cases, respectively.



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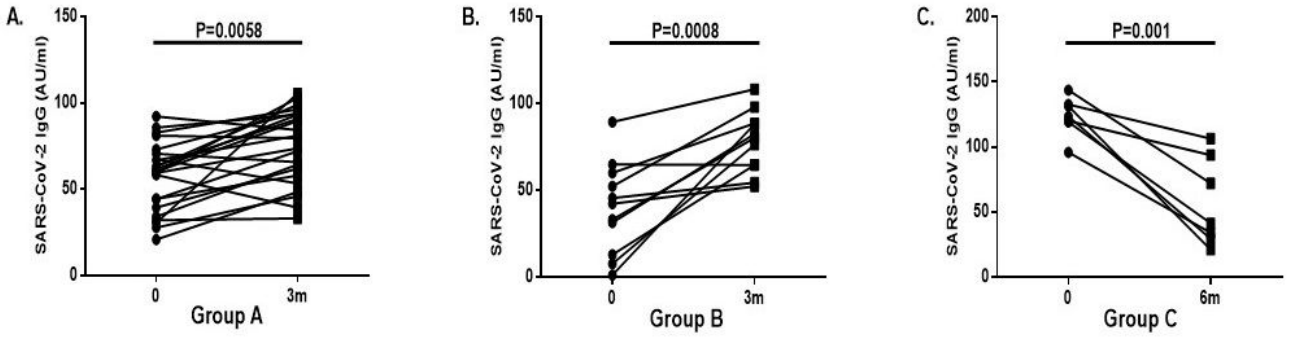
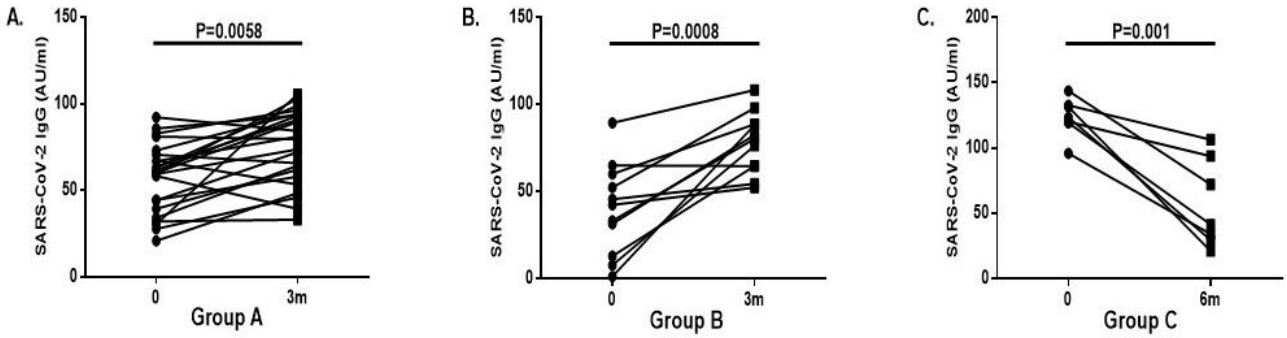


Figure 2

Blood level of SARS-CoV-2 IgG antibody during hospitalization and during follow-up. SARS-CoV-2 IgG antibody in blood was measured during hospitalization and at 3 months of follow-up for Group A (A), during hospitalization and 3 months of follow-up for Group B (B), and during hospitalization and at 6 months of follow-up for Group C (C).



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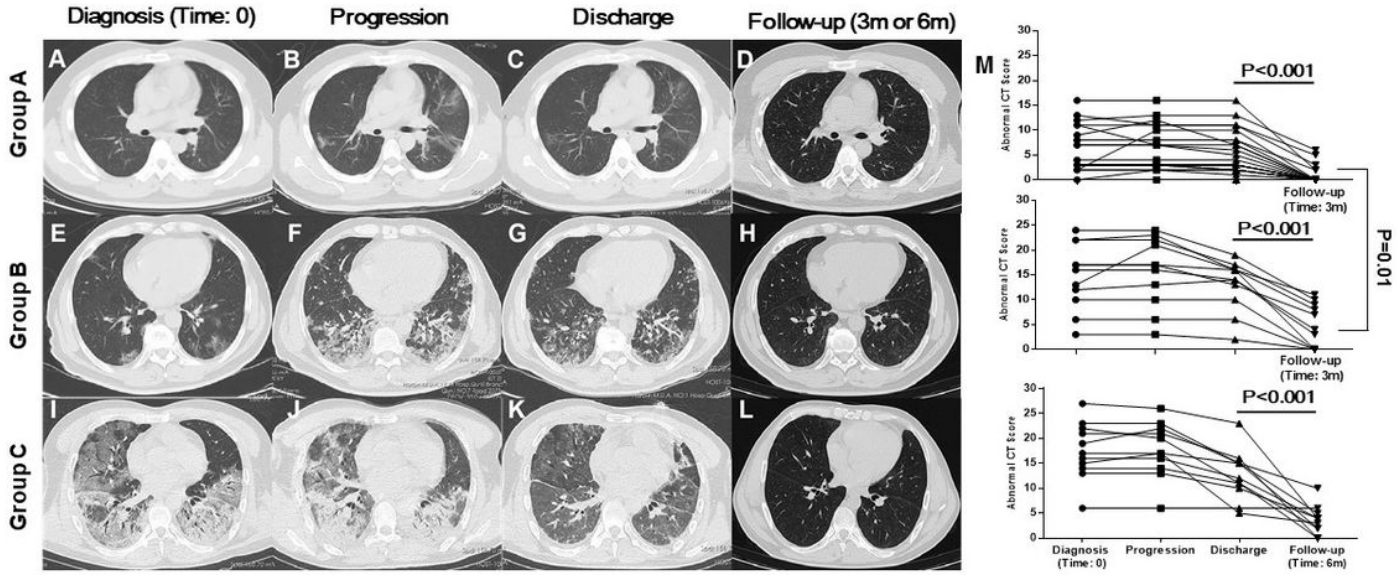
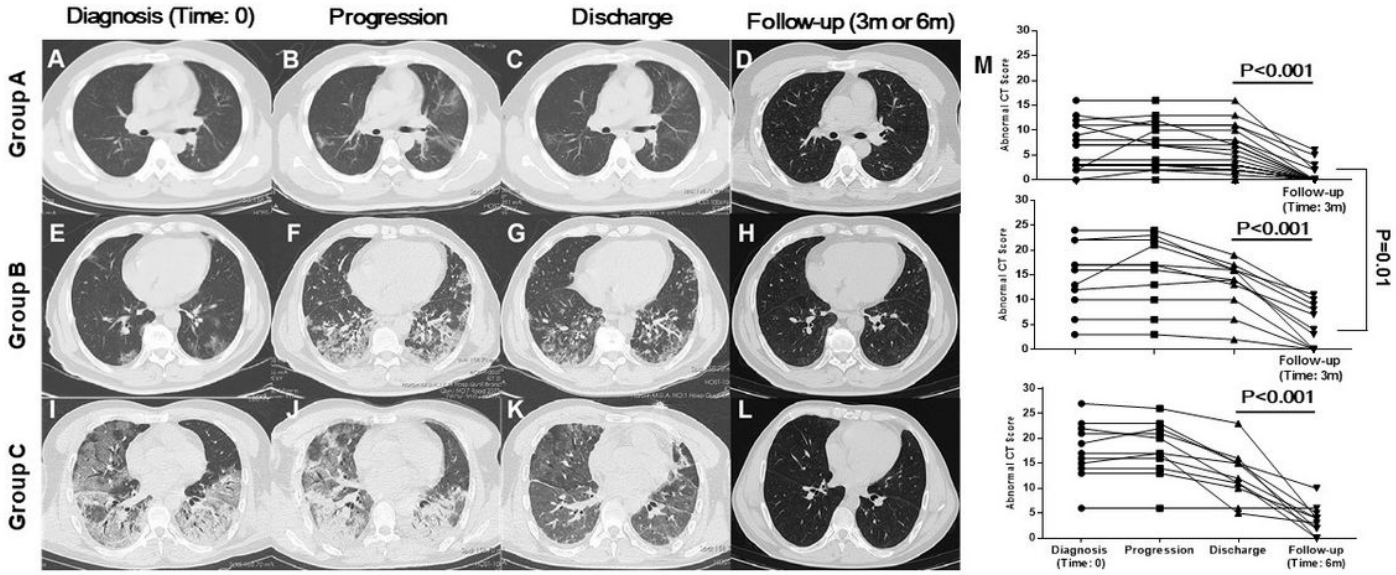


Figure 3

Dynamic changes of HRCT scan in patients with COVID-19 pneumonia. Series of HRCT were shown for three representative cases, one case of Group A (A, B, C, D), one case of Group B (E, F, G, H) and one case of Group C (I, J, K, L). These images were captured at the time of diagnosis (A, E, I), progression (B, F, J), hospital discharge (C, G, K), and at follow-up (D, H, L). Abnormal CT scores were determined for each case at these time points (M).



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