A prospective study of 3, 6, 9 and 12 month respiratory outcomes following COVID-19 related hospitalisation

Xiaojun Wu, MD[1,*]; Xiaofan Liu, MD[2,*]; Yilu Zhou, MSc[3,4,*]; Hongying Yu, MD[1,*]; Ruiyun Li, MD[1,*], Prof Qingyuan Zhan, MD[5,*]; Fang Ni, BM[2]; Si Fang, BM[2]; Yang Lu, MD[2]; Xuhong Ding, MD[1]; Hailing Liu, MD[1]; Rob M. Ewing, PhD[3,4]; Mark G. Jones, PhD[4,6,7,#,†]; Yi Hu, MD[2,#,†]; Prof Hanxiang Nie, MD[1,#,†]; Yihua Wang, PhD[3,4,7,#,†]

[1]Department of Respiratory & Critical Medicine, Renmin Hospital of Wuhan University, Wuhan 430060, Hubei, China;
[2]Department of Pulmonary and Critical Care Medicine, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China;
[3]Biological Sciences, Faculty of Environmental and Life Sciences, University of Southampton, Southampton SO17 1BJ, UK;
[4]Institute for Life Sciences, University of Southampton, Southampton, SO17 1BJ, UK;
[5]Department of Respiratory and Critical Care Medicine, China-Japan Friendship Hospital, Beijing, China;
[6]Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, Southampton, SO16 6YD, UK;
[7]NIHR Southampton Biomedical Research Centre, University Hospital Southampton, Southampton, SO16 6YD, UK

[*]These authors contributed equally to this work.
[#]Correspondence should be addressed to YW (e-mail: yihua.wang@soton.ac.uk), HN (e-mail: nhxbj@sohu.com), YH (email: huyi_pub@163.com) or MJ (email: mark.jones@soton.ac.uk).
[†]These senior authors contributed equally to this work.

Abstract

Background: The consequences of COVID-19 in those that recover from acute infection requiring hospitalisation have yet to be clearly defined. In this study, we aimed to describe the temporal trends in respiratory outcomes over 12 months of patients hospitalised for severe COVID-19 and to investigate the associated risk factors.

Methods: Patients hospitalised for severe COVID-19 who did not require mechanical ventilation were prospectively followed up at 3, 6, 9 and 12 months after discharge. During the follow-up visits, subjects were interviewed and underwent physical examination, pulmonary function tests, chest high-resolution computed tomography (HRCT), and 6-min walk distance (6MWD) test as well as evaluation with a modified Medical Research Council dyspnoea scale (mMRC).

Findings: Of those eligible, 83 patients participated in this study. Temporal improvement in pulmonary physiology and exercise capacity was observed in the majority of patients, however, persistent physiological and radiographic abnormalities remained in a proportion of COVID-19 patients at 12 months after discharge. There was a significant reduction in diffusing capacity of the lungs for carbon monoxide (DLCO) over the study period, with 77% of predicted (IQR 67 ~ 87), 76% of predicted (IQR 68 ~ 90) and 88% of predicted (IQR 78 ~ 101) at 3, 6 or 12 months after discharge, respectively. At 12 months after discharge, radiologic changes persisted in 24% of patients. Multivariate logistic regression showed increasing odds of impaired DLCO associated with female gender (Odds ratio/ 95% confidence interval: 8.61/ 2.83 ~ 26.2;

P = 0.0002), while radiologic abnormalities associated with peak HRCT pneumonia scores during hospitalisation (Odds ratio/ 95% CI: 1.36/ 1.13 ~ 1.62; P = 0.0009).

Interpretation: In the majority of recovered patients from severe COVID-19 dyspnoea scores and exercise capacity improve over time, however, in a sub-group of patients at 12 months there is evidence of persistent physiologic and radiographic change. A unified pathway for the respiratory follow-up of patients with COVID-19 is required.

Key words: COVID-19; Follow-up study; HRCT; Pulmonary function; FVC; DLCO; 6MWD; mMRC.

Research in the context

Evidence before this study

We searched PubMed without language restriction for studies published until 30 March 2021, using keywords “2019 novel coronavirus”, “2019-nCoV”, “SARS-CoV-2”, “COVID-19” AND “follow-up” OR “pulmonary function” OR “sequelae”. Although there are reports on outcomes up to 6 months following discharge for COVID-19 pneumonia hospitalisation, the temporal changes as well as 12-month outcomes have not previously been reported.

Added value of this study

We present the 3, 6, 9 and 12 month outcomes of a prospective cohort of 83 patients with severe COVID-19 who did not require mechanical ventilation. Serial pulmonary function, exercise capacity and chest radiographs were examined at 3, 6, 9 and 12 months after discharge. In the majority of recovered patients from severe COVID-19 exercise capacity improved over this time period however there was evidence of persistent physiologic and radiographic change in a subgroup of patients, with women having a higher risk of persistent lung diffusion impairment.

Implications of all the available evidence

Routine respiratory follow up of patients hospitalised with COVID-19 pneumonia is warranted. Investigation into potential sex-specific differences in longitudinal recovery and whether standardised pulmonary rehabilitation interventions improve the short-, medium-, and long-term outcome of patients hospitalised with COVID-19 pneumonia should be considered.

Introduction

The dramatic spread of the coronavirus disease 2019 (COVID-19) pandemic worldwide has placed an enormous burden on health authorities across the world. The symptoms associated with COVID-19 are diverse, ranging from mild upper respiratory tract symptoms to severe acute respiratory distress syndrome (ARDS). In addition, a number of non-respiratory presentations have been reported in the literature, including hematologic, gastroenterological, renal, dermatologic, neurologic, and psychiatric manifestations[1]. To date, over 100 million people worldwide have recovered from COVID-19 (https://www.worldometers.info/coronavirus/#countries), but there remains concern that some organs, including the lungs, might have long-term impairment following infection.

Although data to accurately estimate the extent of post-COVID-19 sequelae are missing, post-viral syndromes are well documented following other viral infections including previous coronavirus outbreaks such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). SARS resulted in significant impact on pulmonary function, chronic musculoskeletal pain and long-term mental disorders in survivors[2-5]. In MERS survivors, at a median follow-up point of 6 weeks, 36% of patients had residual chest radiographic changes, the vast majority of which were due to pulmonary fibrosis[6]. Moreover, data collected from the COVID Symptom Study suggest that while most people recover from COVID-19 within 2 weeks, about 10% of patients may still have symptoms after 3 weeks, and some may suffer for months (https://covid.joinzoe.com/post/covid-long-term). Post-COVID-19 sequelae have been reported to include pulmonary fibrosis, pulmonary and systemic vascular disease, bronchiectasis, chronic fatigue, mental disorders including post-traumatic stress disorder, depression and anxiety[7]. It is thus important to follow these patients to detect and manage pulmonary sequelae and functional impairment.

Here, we present the temporal trends in respiratory outcomes over 12 months in a prospective cohort of patients hospitalised with severe COVID-19 pneumonia without intubation. Serial pulmonary function, exercise capacity and chest radiographs were examined from 3 to 12 months after discharge.

Methods

Study design and participants

This is a prospective, longitudinal, follow-up study, approved by the Ethics Commission of Renmin Hospital of Wuhan University (No. WDRY2020-K143). Written informed consent was obtained from all study participants. In this study, adult (≥ 18 years old) patients with severe COVID-19 discharged from Renmin Hospital of Wuhan University between 1 February 2020 to 31 March 2020 were identified through electronic case note review and approached for study participation.

A diagnosis of severe COVID-19 pneumonia was based on the WHO interim guidance (https://www.who.int/publications/i/item/clinical-management-of-covid-19) and all patients had subsequent laboratory confirmation of SARS-CoV-2 using real-time RT-PCR with a standard protocol recommended by China Center for Disease Control and Prevention (CDC)[8,9]. Cases with any of the following features were categorized as severe: respiratory rate ≥30 breaths/min; oxygen saturation ≤93% at a rest state; arterial partial pressure of oxygen (PaO2)/oxygen concentration (FiO2) ≤300 mmHg; >50% progression of lesions on lung imaging within 24 to 48 hours. Patients with a prior history of hypertension, diabetes, cardiovascular diseases, cancer and chronic lung disease including asthma or chronic obstructive pulmonary disease (COPD) or a history of smoking documented at time of hospital admission were excluded (N = 136 co-morbidity and N = 117 smoking history) at time of electronic case note review. Patients who required intubation and mechanical ventilation were excluded given the potential for the consequences of mechanical ventilation itself to influence the factors under investigation. Twenty-four patients who had consented for study participation did not attend the first 3 month visit and so were excluded from the study.

Assessments

Patients were evaluated at 3, 6, 9 and 12 months after discharge. During the visit, subjects were interviewed and underwent a physical examination, routine blood test, pulmonary function tests, chest high-resolution Computed Tomography (HRCT) scan, and a standardised 6-min walk distance (6MWD) test[10]. In addition, all cases were evaluated with a modified Medical Research Council dyspnoea scale (mMRC)[11,12] (Figure 1).

Pulmonary function test

Pulmonary function tests were performed according to ATS-ERS guidelines[13]. The following parameters were measured: DLCO, diffusing capacity of the lungs for carbon monoxide; $FEF_{25-75\%}$, forced expiratory flow between 25% and 75% of FVC; FRC, functional residual capacity; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; RV, residual volume; TLC, total lung capacity; VC, vital capacity. DLCO was measured by means of the single-breath test. The haemoglobin value was taken for correcting the DLCO. For spirometry, flow-volume curves were obtained through a dry spirometer (Vmax 229, United States Sensor-Medics, Yorba Linda) and the best volume of the three manoeuvres was expressed as the percentage of predicted normal and used for analysis. All pulmonary function test measurements were expressed as percentages of predicted normal values. Diffusion deficit was considered as DLCO < 80% of predicted values.

High-resolution Computed Tomography (HRCT) scans and image analysis

Patients underwent chest non-contrast enhanced CT examinations in the supine position and with breath-holding following inspiration (GE Healthcare Optima CT680). The technical parameters included a 64-section scanner with 1 mm collimation at 5 mm intervals. Images were obtained with both mediastinal (width 350 HU; level 50 HU) and parenchymal (width 1500 HU; level -700 HU) window settings. The follow-up patients completed HRCT scan testing every 3 months.

For imaging evaluations, 2 radiologists, with 5 and 27 years of thoracic radiology experience, respectively, reviewed the images independently, with a final finding reached by consensus when there was a discrepancy. They were blinded to the clinical information or clinical progress of the patients, except for the knowledge that these were cases of COVID-19 patients. The pneumonia CT scores of patients during hospitalisation were recorded with a method described previously[8]. The peak pneumonia CT score is the highest pneumonia CT score for a patient during COVID-related hospitalisation. To analyse follow-up HRCT scans, HRCT findings were initially evaluated based on key features[14] and then scored based on a method adapted from Ichikado and colleagues[15], here named HRCT follow-up score (see Supplementary Materials for details), which allowed us to evaluate interstitial changes in lungs[15].

Six-minute walk distance (6MWD) test

6MWD test was performed according to the ATS practical guidelines[10]. Each follow-up patient walked on the flat ground as fast as possible without oxygen inhalation and completed the 6-minute walk distance test independently. The results were expressed as meters and % of predicted values calculated using a method described by Enright and colleagues[16].

Measurement of dyspnea

In this study, the severity of dyspnea was measured by a modified Medical Research Council dyspnoea scale (mMRC)[11]. The mMRC scale is a self-rating tool to measure the degree of disability that breathlessness poses on day-to-day activities on a scale from 0 to 4. Details of this scoring system are: 0, no breathlessness except on strenuous exercise; 1, shortness of breath when hurrying on the level or walking up a slight hill; 2, walks slower than people of same age on the level because of breathlessness or has to stop to catch breath when walking at their own pace on the level; 3, stops for breath after walking ~100 m or after few minutes on the level; and 4, too breathless to leave the house, or breathless when dressing or undressing[12].

Statistical analysis

Continuous variables were expressed as median (interquartile range, IQR), and compared with Two Sample *t*-test, Welch Two Sample *t*-test, Mann-Whitney *U* test, one-way ANOVA, Kruskal–Wallis test or repeated measure ANOVA if appropriate; categorical variables were expressed as number (N) (%) and compared by $\chi 2$ test or Fisher's Exact Test if appropriate. Due to the sample size, measurable variables with significant differences between groups were considered in subsequent univariate and multivariate logistic regression analysis[17,18]. P values less than 0.05 were considered statistically significant. All data analyses and graphs were done in R (version 3.6.1) or SPSS (version 26).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. XW, XL, YH and HN had full access to all the data in the study.

Results

Of 135 hospitalised patients with severe COVID-19 who met the inclusion criteria, 83 patients were prospectively enrolled after discharge for follow-up at 3, 6, 9 and 12 months (Figure 1). The median (IQR) of days for follow-up after discharge at 3, 6, 9 and 12 months were 98 (9), 189 (10), 275 (12) and 348 (19), respectively. Forty-seven (57%) patients were male. The median (IQR) age was 60 (14) years. The median (IQR) body mass index (BMI) was 25 (3.2) in males and 24 (4.4) in females. All patients were never-smokers, and no patient had a prior history of hypertension, diabetes, cardiovascular diseases, cancer, asthma or COPD. During hospitalisation all patients received anti-viral drugs, including Oseltamivir (64%), Ribavirin (100%) and/or Ganciclovir (51%). No patient received treatment with corticosteroids. Thirty-seven (45%) patients received supplemental oxygen only via nasal cannula or mask, and forty-six (55%) patients required high-flow nasal cannula (HFNC) and/or non-invasive ventilation (NIV). The median (IQR) of length of hospital stay was 29 (10) days. These data are shown in Table 1.

Temporal changes in pulmonary function

Pulmonary function tests were completed in all patients at month 3, 6 and 12 following discharge. An overview of the serial pulmonary function test results for COVID-19 cohort is shown in Figure 2, and Table S1. As a consequence of changes in local aerosolisation guidance, pulmonary function tests were precluded at 9 months.

Diffusing capacity of the lungs for carbon monoxide (DLCO) was 77% (IQR 67 ~ 87) of predicted at 3 months, 76% (IQR 68 ~ 90) of predicted at 6 months and increased to 88% (IQR 78 ~ 101) of predicted at 12 months. Forced vital capacity (FVC) was 92% (IQR 81 ~ 99) of predicted at 3 months, 94% (IQR 85 ~ 104) of predicted at 6 months and increased to 98% (IQR 89 ~ 109) of predicted at 12 months.

The frequency of pulmonary function parameters below 80% of predicted values is shown in Table S2. Nine patients (11%) had reduced FVC measurements (< 80% predicted value) at 12 months, whilst 27 patients (33%) had impaired DLCO (< 80% predicted value). Correlations between impaired DLCO and demographics, disease severity and treatment during hospitalisation were examined. A higher percentage of patients with DLCO < 80% predicted at 12 months after discharge was observed in women when compared to men (Table 2; 20/36 (56%) *vs.* 7/47 (15%); P < 0.0001). Patients with impaired DLCO at 12 months after discharge also had increased peak HRCT pneumonia scores during hospitalisation (median 30 with IQR 13 *vs.* median 28 with IQR 12) however this was not statistically significant (Table 2).

To explore the risk factors associated with impaired DLCO at 12 months after discharge, univariate and multivariate logistic regression models were used. Multivariate logistic regression showed increasing odds of impaired DLCO associated with female gender (Odds ratio/ 95% confidence interval: 8.61/ 2.83 ~ 26.2; P = 0.0002), independent of age and peak HRCT pneumonia scores (Table S3).

6MWD test and mMRC

The median 6MWD increased significantly, from 535 m (IQR, 76 m) at 3 months to 585 m (IQR, 74 m) at 6 months ($P < 0.0001$). A further detectable increase was observed at 9 and 12 months (596 m with IQR 56 m and 615 m with IQR 50, respectively; $P = 0.044$ and < 0.0001, respectively) (Figure 3A). Similar results were obtained if normalised to predicted values calculated according to a method described by Enright and colleagues[16] (Figure S1).

To assess dyspnea, a modified Medical Research Council dyspnoea scale (mMRC) was used. Dyspnea symptom assessed by the mMRC scale was very frequent in subjects at 3 months with 81% (N = 67) of patients with a mMRC scale ≥ 1 and 6% (N = 5) of patients with a mMRC scale ≥ 2. The number of patients with various levels of dyspnoea symptom progressively and significantly reduced at 6, 9 and 12 months (Figure 3B). Four patients (5%) reported persistent symptoms of dyspnea at 12 months.

Temporal changes in HRCT scans

78% of individuals had residual changes on CT at 3 months post-discharge with ground-glass opacity (GGO) (78%), interlobular septal thickening (34%), reticular opacity (33%), and subpleural curvilinear opacity (11%) the most common CT features found (Figure S2; Table S4). At 6 months 48% of subjects still had abnormal chest radiographic scores, with GGO (46%), interlobular septal thickening (13%), reticular opacity (16%), subpleural curvilinear opacity (5%), mosaic attenuation (4%) and bronchiectasis (1%). Typical features such as interlobular septal thickening (5%), reticular opacity (4%) and subpleural curvilinear opacity (1%) were almost resolved at 9 months, but the radiological changes did not fully resolve in 27% of patients, predominantly with GGO (24%). No significant improvement at 12 months was identified when compared with 9 months (Figure S3; Table S4). There were 20 (24%) patients with abnormal HRCT at 12 months. None of the HRCT scans showed evidence of established fibrosis (Table S4), and none showed evidence of progressive interstitial changes (Figures S2 and S3).

Correlations between radiographic abnormality and demographics, disease severity during hospitalisation and pulmonary function test parameters were examined. Patients with abnormal radiographic changes at 12 months had increased length of hospital stay (Table 3; $P = 0.027$) and increased peak HRCT pneumonia scores (Table 3; Figure S3D; $P < 0.0001$). Patients receiving HFNC/NIV tended to have abnormal radiographic changes at 12 months (Table 3; $P = 0.043$). There was a significant difference in pulmonary function test parameters (including DLCO, FRC, FVC, RV, TLC and VC) between patients with normal *vs.* abnormal HRCT scores at 12 months after discharge (Table 3; all P values less than 0.05).

To explore the risk factors associated with abnormal radiographic changes at 12 months after discharge, univariate and multivariate logistic regression models were used. In univariate analysis, length of hospital stay, peak HRCT pneumonia scores during hospitalisation and receiving HFNC/NIV were associated with abnormal HRCT at 12 months after discharge (Table S5; both P values less than 0.05). We then identified peak HRCT pneumonia score (Odds ratio/ 95% CI: 1.36/ 1.13 ~ 1.62; P = 0.0009) as an independent risk factor of abnormal HRCT at 12 months after discharge including in multivariate analysis with length of hospital stay and receiving HFNC/NIV (Table S5).

Discussion

The consequences of COVID-19 in those that recover from acute infection are uncertain despite a few reports on outcomes up to 6 months after discharge[19-24], although data from previous coronavirus outbreaks such as SARS and MERS suggests that some patients will experience long-term respiratory complications of the infection. In this study, we report serial pulmonary function, exercise capacity and chest radiographic changes in non-intubated patients hospitalised with severe COVID pneumonia at 3-, 6-, 9- and 12-month following hospital discharge. Whilst in the majority of patients exercise capacity improves over this time period, there is evidence of persistent physiologic and radiographic changes in a sub-group of patients.

At 12 months after discharge, residual abnormalities of pulmonary function were observed in one third of the population within this cohort (< 80% predicted value), with the most common finding being a reduction in gas transfer as measured by DLCO. It has recently been reported that gas-blood exchange is impaired in patients discharged following hospital admission with COVID-19 pneumonia[19,20,24-26], including a recent 6-month cohort study of COVID-19 in patients discharged from hospital[23]. Low DLCO could be the consequence of interstitial abnormalities or pulmonary vascular abnormalities caused by COVID-19[27-29]. Longer term follow-up will be required to confirm this observation. Consistent with our findings, in follow-up studies for patients recovering from SARS, impaired pulmonary function could last for months or even years[2-5]. We extend a recent report[23] to identify that female gender strongly predicts impaired DLCO at 12 months after discharge. Notably, female gender was not significantly associated with persistent HRCT abnormalities, suggesting distinct mechanisms may underlie the identified persistent radiologic abnormalities and gas-blood exchange abnormalities, and the underlying mechanisms merit further investigation.

At 12 months after discharge, the radiological changes did not resolve fully in 24% of patients, including findings potentially consistent with evolving fibrosis in a minority of patients with the presence of interstitial thickening and reticular opacity. Although none of the HRCT scans showed any development of definitive fibrosis nor progressive interstitial change, plausibly the burden of pulmonary fibrosis after COVID-19 recovery could be substantial given these observations and the huge numbers of individuals affected by COVID-19[30,31], and so ongoing longitudinal follow up is warranted to further understand the natural history of the identified radiological changes.

The prospective enrolment of patients enabled us to study the temporal pulmonary physiology, exercise capacity and radiographic abnormalities. To better understand the the consequences of COVID-19 pneumonia itself we selected patients meeting the criteria for severe COVID-19 pneumonia whilst excluding patients requiring intubation given the potential for mechanical ventilation itself to alter the natural history of the factors under investigation, in particular the potential for triggering mechanical ventilation-associated lung fibrosis in acute respiratory distress syndrome.

This study has a number of limitations. By choosing a cohort of patients with severe COVID-19 pneumonia, it does not fully define the potential long-term consequences for varying severities of disease. In addition, as a consequence of changes in local guidance pulmonary function tests were precluded at 9 months. The study was not designed to collect data on any medication prescriptions following hospital discharge. Lastly, we did not have pulmonary function, exercise capacity, or CT results prior to COVID-19 that would enable longitudinal assessment of impact of COVID-19. However, the studied cohort had no history of significant cardiovascular or respiratory disease and the temporal improvement observed suggests at least some changes are related to COVID-19 and/or hospitalisation[32,33].

Our findings highlight the importance of respiratory follow-up of patients with COVID-19, and that studies to mitigate the long-term consequences of COVID-19 pneumonia including pulmonary rehabilitation as well as novel therapeutic approaches are required[34].

Contributors

YW, HN, YH, MJ, XW and XL had the idea for and designed the study. YW, HN, YH, XW and XL had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. YW, MJ, HN, YH and RE drafted the paper. YZ, XW, XL, HY, RL, QZ and YW did the analysis, and all authors critically revised the manuscript for important intellectual content and gave final approval for the version to be published. XW, XL, HY, RL, QZ, FN, SF, YL, XD and HL collected the data. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Acknowledgments

This project was funded by the National Natural Science foundation of China [No 81970024]. YZ was supported by an Institute for Life Sciences (University of Southampton) PhD Studentship. YW was funded by Medical Research Council (UK) [MR/S025480/1]. MGJ and YW acknowledge the support of the NIHR Southampton Biomedical Research Centre. We acknowledge all the patients involved in this study and appreciate all the frontline medical and nursing staff involved in the diagnosis, treatment and follow-up of patients in Wuhan. We also thank Drs Yan Jiang and Tao Li for their support in HRCT imaging evaluations.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request and with permission of Renmin Hospital of Wuhan University, Hubei, China.

Ethics approval and consent to participate

This study was approved by the Ethics Commission of Renmin Hospital of Wuhan University (No. WDRY2020-K143). Written informed consent was obtained from all study participants.

Declaration of interests

The authors declare that they have no conflict of interest.

References:

1. AlSamman M, Caggiula A, Ganguli S, Misak M, Pourmand A. Non-respiratory presentations of COVID-19, a clinical review. *Am J Emerg Med* 2020; **38**(11): 2444-54.
2. Moldofsky H, Patcai J. Chronic widespread musculoskeletal pain, fatigue, depression and disordered sleep in chronic post-SARS syndrome; a case-controlled study. *BMC Neurol* 2011; **11**: 37.
3. Hui DS, Joynt GM, Wong KT, et al. Impact of severe acute respiratory syndrome (SARS) on pulmonary function, functional capacity and quality of life in a cohort of survivors. *Thorax* 2005; **60**(5): 401-9.
4. Hui DS, Wong KT, Ko FW, et al. The 1-year impact of severe acute respiratory syndrome on pulmonary function, exercise capacity, and quality of life in a cohort of survivors. *Chest* 2005; **128**(4): 2247-61.
5. Ngai JC, Ko FW, Ng SS, To KW, Tong M, Hui DS. The long-term impact of severe acute respiratory syndrome on pulmonary function, exercise capacity and health status. *Respirology* 2010; **15**(3): 543-50.
6. Das KM, Lee EY, Singh R, et al. Follow-up chest radiographic findings in patients with MERS-CoV after recovery. *Indian J Radiol Imaging* 2017; **27**(3): 342-9.
7. Sudre CH, Murray B, Varsavsky T, et al. Attributes and predictors of Long-COVID: analysis of COVID cases and their symptoms collected by the Covid Symptoms Study App. *medRxiv* 2020: 2020.10.19.20214494.
8. Liu X, Zhou H, Zhou Y, et al. Temporal radiographic changes in COVID-19 patients: relationship to disease severity and viral clearance. *Scientific Reports* 2020; **10**(1): 10263.
9. Liu X, Zhou H, Zhou Y, et al. Risk factors associated with disease severity and length of hospital stay in COVID-19 patients. *Journal of Infection* 2020; **81**(1): e95-e7.
10. Laboratories ATSCoPSfCPF. ATS statement: guidelines for the six-minute walk test. *American journal of respiratory and critical care medicine* 2002; **166**(1): 111-7.
11. Rajala K, Lehto JT, Sutinen E, Kautiainen H, Myllarniemi M, Saarto T. mMRC dyspnoea scale indicates impaired quality of life and increased pain in patients with idiopathic pulmonary fibrosis. *ERJ Open Res* 2017; **3**(4).
12. Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax* 1999; **54**(7): 581-6.
13. Graham BL, Steenbruggen I, Miller MR, et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory

Society Technical Statement. *American journal of respiratory and critical care medicine* 2019; **200**(8): e70-e88.

14. Hansell DM, Bankier AA, MacMahon H, McLoud TC, Muller NL, Remy J. Fleischner Society: glossary of terms for thoracic imaging. *Radiology* 2008; **246**(3): 697-722.

15. Ichikado K, Suga M, Muller NL, et al. Acute interstitial pneumonia: comparison of high-resolution computed tomography findings between survivors and nonsurvivors. *American journal of respiratory and critical care medicine* 2002; **165**(11): 1551-6.

16. Enright PL, Sherrill DL. Reference equations for the six-minute walk in healthy adults. *American journal of respiratory and critical care medicine* 1998; **158**(5 Pt 1): 1384-7.

17. Courvoisier DS, Combescure C, Agoritsas T, Gayet-Ageron A, Perneger TV. Performance of logistic regression modeling: beyond the number of events per variable, the role of data structure. *J Clin Epidemiol* 2011; **64**(9): 993-1000.

18. Agoritsas T, Merglen A, Shah ND, O'Donnell M, Guyatt GH. Adjusted Analyses in Studies Addressing Therapy and Harm: Users' Guides to the Medical Literature. *Jama* 2017; **317**(7): 748-59.

19. Zhao YM, Shang YM, Song WB, et al. Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery. *EClinicalMedicine* 2020; **25**: 100463.

20. Shah AS, Wong AW, Hague CJ, et al. A prospective study of 12-week respiratory outcomes in COVID-19-related hospitalisations. *Thorax* 2020.

21. Liu C, Ye L, Xia R, et al. Chest Computed Tomography and Clinical Follow-Up of Discharged Patients with COVID-19 in Wenzhou City, Zhejiang, China. *Ann Am Thorac Soc* 2020; **17**(10): 1231-7.

22. Huang Y, Tan C, Wu J, et al. Impact of coronavirus disease 2019 on pulmonary function in early convalescence phase. *Respiratory research* 2020; **21**(1): 163.

23. Huang C, Huang L, Wang Y, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *The Lancet*.

24. Qin W, Chen S, Zhang Y, et al. Diffusion Capacity Abnormalities for Carbon Monoxide in Patients with COVID-19 At Three-Month Follow-up. *The European respiratory journal* 2021.

25. Mo X, Jian W, Su Z, et al. Abnormal pulmonary function in COVID-19 patients at time of hospital discharge. *The European respiratory journal* 2020; **55**(6).

26. Guler SA, Ebner L, Beigelman C, et al. Pulmonary function and radiological features four months after COVID-19: first results from the national prospective observational Swiss COVID-19 lung study. *The European respiratory journal* 2021.

27. Hanidziar D, Robson SC. Hyperoxia and modulation of pulmonary vascular and immune responses in COVID-19. *Am J Physiol Lung Cell Mol Physiol* 2020.

28. Patel BV, Arachchillage DJ, Ridge CA, et al. Pulmonary Angiopathy in Severe COVID-19: Physiologic, Imaging, and Hematologic Observations. *American journal of respiratory and critical care medicine* 2020; **202**(5): 690-9.

29. Lang M, Som A, Mendoza DP, et al. Hypoxaemia related to COVID-19: vascular and perfusion abnormalities on dual-energy CT. *The Lancet Infectious diseases* 2020; **20**(12): 1365-6.

30. George PM, Wells AU, Jenkins RG. Pulmonary fibrosis and COVID-19: the potential role for antifibrotic therapy. *The Lancet Respiratory medicine* 2020.

31. Spagnolo P, Balestro E, Aliberti S, et al. Pulmonary fibrosis secondary to COVID-19: a call to arms? *The Lancet Respiratory medicine* 2020.

32. Rogers JP, Chesney E, Oliver D, et al. Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. *Lancet Psychiatry* 2020; **7**(7): 611-27.

33. Pierce M, Hope H, Ford T, et al. Mental health before and during the COVID-19 pandemic: a longitudinal probability sample survey of the UK population. *Lancet Psychiatry* 2020; **7**(10): 883-92.

34. George PM, Barratt SL, Condliffe R, et al. Respiratory follow-up of patients with COVID-19 pneumonia. *Thorax* 2020; **75**(11): 1009-16.

Tables

Table 1. Characteristics of enrolled patients in this cohort (N = 83).

Table 2. Comparisons in severe COVID-19 patients with normal *vs.* abnormal DLCO at 12 months after discharge.

Table 3. Comparisons in severe COVID-19 patients with normal *vs.* abnormal HRCT at 12 months after discharge.

Table 1. Characteristics of enrolled patients in this cohort (N = 83).

	N = 83
Demographics	
Age, years	60 (14)
Gender	
Male	47 (57%)
Female	36 (43%)
BMI	25 (3.6)
Cigarette smoking	
Never-smoker	83 (100%)
Comorbidities*	0 (0%)
Hospitalisation	
Length of hospital stay (days)	29 (10)
Peak CT Pneumonia_score during hospitalization	30 (12)
Oxygen supply	
via nasal cannula or mask	37 (45%)
HFNC/NIV	46 (55%)
Antivirals	
Oseltamivir	53 (64%)
Ribavirin	83 (100%)
Ganciclovir	42 (51%)
Corticosteroids	0 (0%)
Follow-up visit (days)	
@ Month 3	98 (9)
@ Month 6	189 (10)
@ Month 9	275 (12)
@ Month 12	348 (19)

BMI, body mass index; HFNC, high-flow nasal cannula; NIV, non-invasive mechanical ventilation. Values are shown as median (interquartile range) or N (%). *Patients with a prior history of hypertension, diabetes, cardiovascular diseases, cancer and chronic lung disease including asthma or chronic obstructive pulmonary disease (COPD) at time of hospital admission were excluded at time of screening.

Table 2. Comparisons in severe COVID-19 patients with normal *vs.* abnormal DLCO at 12 months after discharge (N = 83).

	DLCO @ Month 12 ≥ 80% predicted value (N = 56)	**DLCO @ Month 12 < 80% predicted value (N = 27)**	**P - value**
Demographics			
Age, years	58 (15)	62 (9)	0.138
Gender			
Male (N = 47)	40 (71%)	7 (26%)	***< 0.0001***
Female (N = 36)	16 (29%)	20 (74%)	
BMI	25.1 (3.5)	24.4 (3.9)	0.808
Hospitalisation			
Length of hospital stay (days)	29 (9)	31 (11)	0.385
Peak CT Pneumonia_score during hospitalization	28 (12)	30 (13)	0.109
Oxygen supply			
via nasal cannula or mask (N = 37)	26 (46%)	11 (41%)	0.625
HFNC/NIV (N = 46)	30 (54%)	16 (59%)	
Antivirals			
Oseltamivir			
No (N = 30)	20 (36%)	10 (37%)	0.906
Yes (N = 53)	36 (64%)	17 (63%)	
Ganciclovir			
No (N = 41)	30 (54%)	11 (41%)	0.273
Yes (N = 42)	26 (46%)	16 (59%)	

BMI, body mass index; DLCO, diffusing capacity of the lungs for carbon monoxide. HFNC, high-flow nasal cannula; NIV, non-invasive mechanical ventilation. Values are shown as median (interquartile range) or N (%).

Table 3. Comparisons in severe COVID-19 patients with normal *vs.* abnormal HRCT at 12 months after discharge (N = 83).

	HRCT normal (N = 63)	**HRCT abnormal (N = 20)**	**P - value**
Demographics			
Age, years	59 (17)	61 (9)	0.271
Gender			
Male (N = 47)	38 (60%)	9 (45%)	0.228
Female (N = 36)	25 (40%)	11 (55%)	
BMI	25.3 (3.7)	24.2 (2.5)	0.361
Hospitalisation			
Length of hospital stay (days)	28 (9)	35 (8)	***0.027***
Peak CT Pneumonia_score during hospitalization	27 (8.5)	36 (14)	***< 0.0001***
Oxygen supply			
via nasal cannula or mask (N = 37)	32 (51%)	5 (25%)	***0.043***
HFNC/NIV (N = 46)	31 (49%)	15 (75%)	
Antivirals			
Oseltamivir			
No (N = 30)	25 (40%)	5 (25%)	0.234
Yes (N = 53)	38 (60%)	15 (75%)	
Ganciclovir			
No (N = 41)	33 (52%)	8 (40%)	0.335
Yes (N = 42)	30 (48%)	12 (60%)	
Pulmonary Function @ Month 12			
DLCO (% of predicted)	90 (21)	77 (15)	***< 0.0001***
FEF25-75% (% of predicted)	89 (33)	92 (50)	0.282
FEV1/FVC (% of predicted)	82 (7)	85 (6)	0.339
FRC (% of predicted)	107 (37)	99 (30)	***0.031***
FVC (% of predicted)	99 (21)	92 (22)	***0.012***
FEV1 (% of predicted)	97 (24)	88 (31)	0.054
RV (% of predicted)	88 (28)	75 (25)	***0.031***
TLC (% of predicted)	95 (16)	88 (22)	***0.007***
VC (% of predicted)	101 (21)	92 (22)	***0.004***

BMI, body mass index; DLCO, diffusing capacity of the lungs for carbon monoxide; $FEF_{25-75\%}$, forced expiratory flow between 25% and 75% of FVC; FRC, functional residual capacity; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; RV, residual volume; TLC, total lung capacity; VC, vital capacity; HFNC, high-flow nasal cannula; NIV, non-invasive mechanical ventilation. Values are shown as median (interquartile range) or N (%).

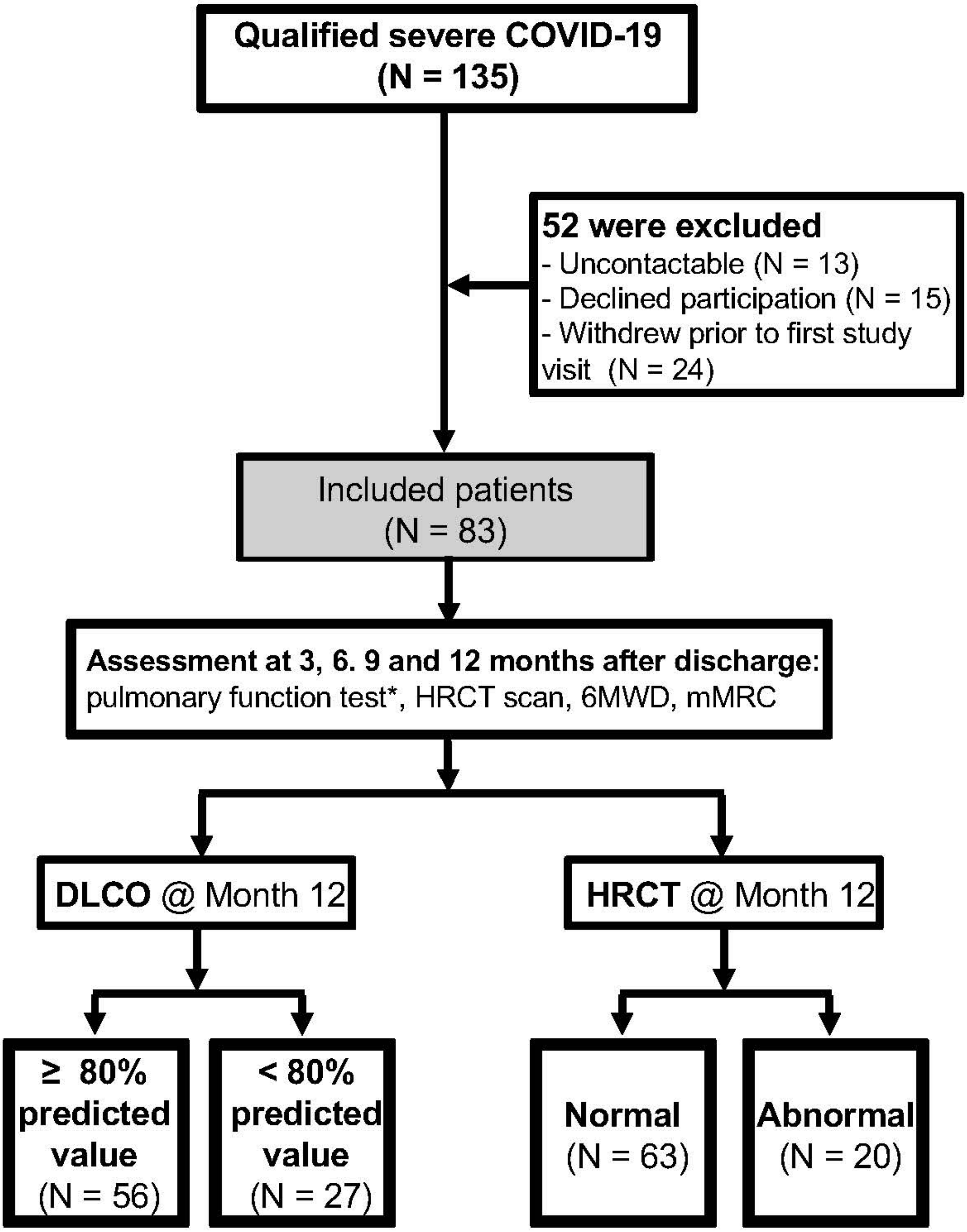
Figure Legends

Fig. 1 Enrolment of severe COVID-19 patients who did not require mechanical ventilation and follow-up at 3, 6, 9 and 12 months after hospital discharge. COVID-19: Coronavirus Disease 2019. HRCT: high-resolution Computed Tomography; 6MWD: 6-min walk distance test; mMRC: modified Medical Research Council dyspnoea scale; DLCO: diffusing capacity of the lungs for carbon monoxide.

Fig. 2 Temporal changes in pulmonary function following severe COVID-19 related hospitalisation. Graphs showing temporal changes in diffusing capacity of the lungs for carbon monoxide (DLCO) (**A**) or forced vital capacity (FVC) (**B**) at 3, 6 or 12 months after discharge in severe COVID-19 patients. Values in **A** and **B** are % of predicted. Median, IQR (interquartile range), P values and % of patients with abnormal DLCO or FVC are indicated. Horizontal dotted lines indicate the normal cut-off of 80%.

Fig. 3 Impact of severe COVID-19 on follow-up 6-minute walking distance (6MWD) test and modified Medical Research Council dyspnoea scale (mMRC). (**A**) Graph showing temporal changes in 6MWD at 3, 6, 9 and 12 months after discharge. Median, IQR (interquartile range) and P values are indicated. Values are in meter. (**B**) Graph showing the distributions of mMRC (modified Medical Research Council) dyspnea scores at 3, 6, 9 and 12 months after discharge. P values are indicated together with % of patients free of dyspnea.

Figure 1



*As a consequence of changes in local guidance, pulmonary function tests (PFT) were precluded at 9 months after discharge.

Figure 2

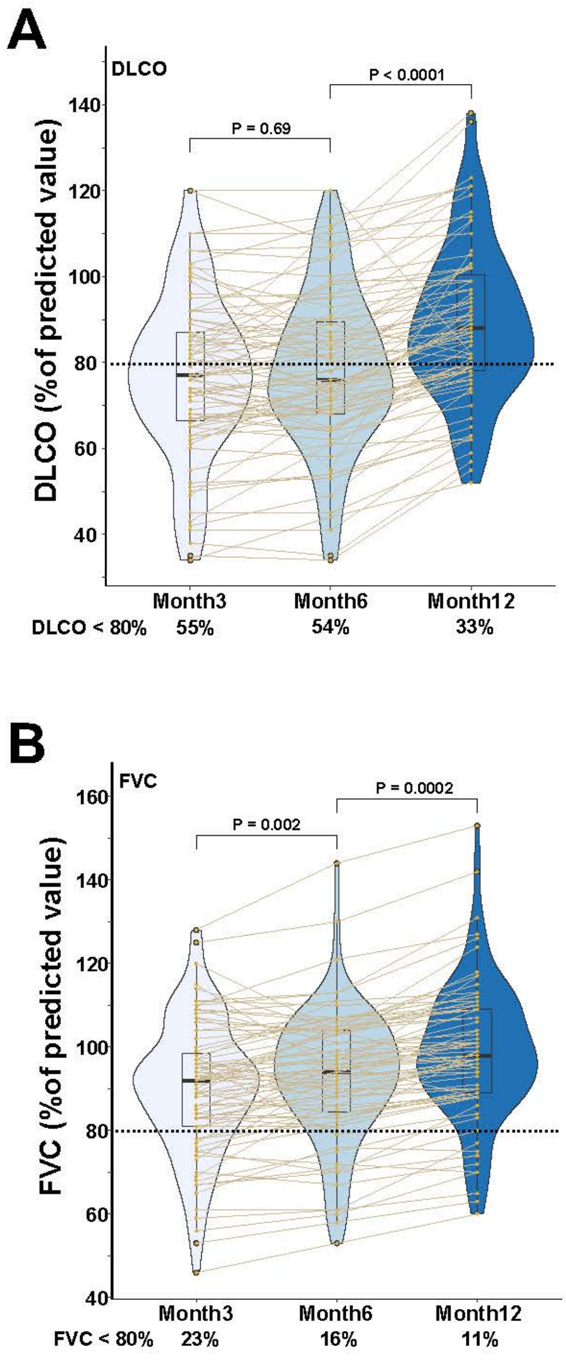
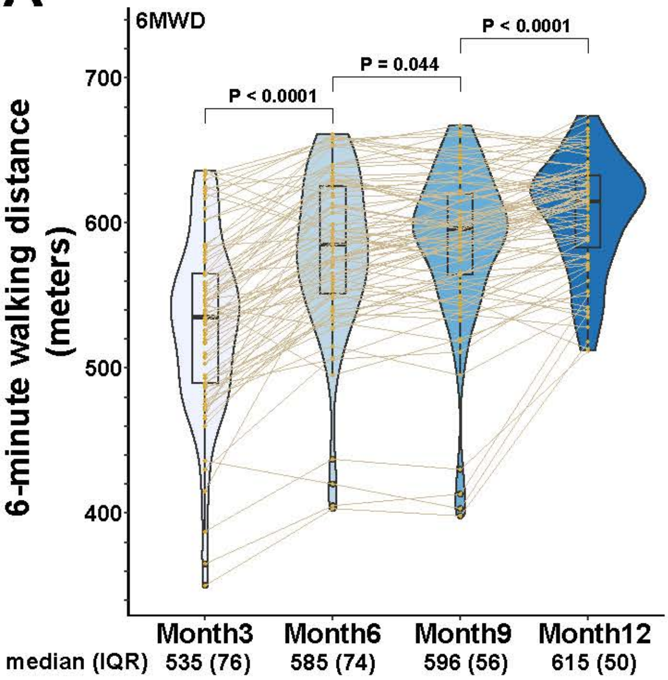

A
DLCO
P = 0.69
P < 0.0001
DLCO (%of predicted value)
140
120
100
80
60
40
Month3
Month6
Month12
DLCO < 80%
55%
54%
33%
B
FVC
P = 0.002
P = 0.0002
FVC (%of predicted value)
160
140
120
100
80
60
40
Month3
Month6
Month12
FVC < 80%
23%
16%
11%

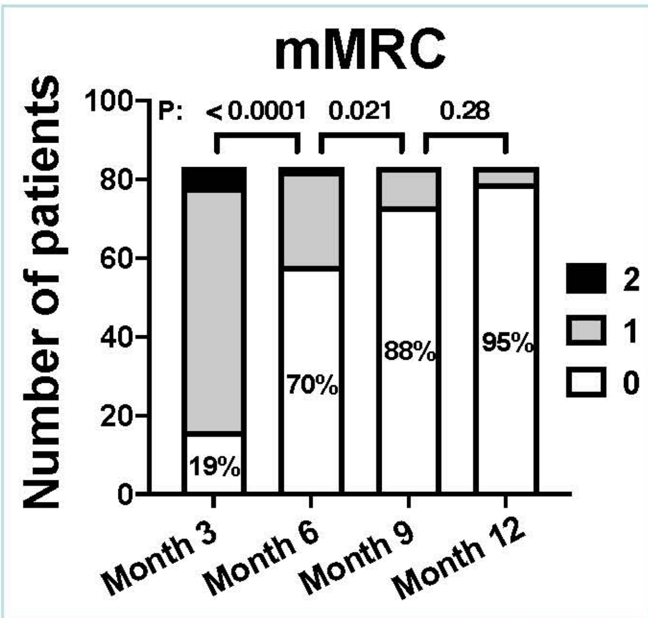
Figure 3

A



6MWD
P < 0.0001
P = 0.044
P < 0.0001
6-minute walking distance (meters)
700
600
500
400
Month3
Month6
Month9
Month12
median (IQR)
535 (76)
585 (74)
596 (56)
615 (50)

B



mMRC
P:
< 0.0001
0.021
0.28
Number of patients
100
80
60
40
20
0
19%
70%
88%
95%
2
1
0
Month 3
Month 6
Month 9
Month 12

Supplementary Methods

High-resolution Computed Tomography (HRCT) scans and image analysis

Patients underwent chest non-contrast enhanced CT examinations in the supine position and with breath-holding following inspiration (GE Healthcare Optima CT680). The technical parameters included a 64-section scanner with 1 mm collimation at 5 mm intervals. Images were obtained with both mediastinal (width 350 HU; level 50 HU) and parenchymal (width 1500 HU; level -700 HU) window settings. The follow-up patients completed HRCT scan testing every 3 months.

For imaging evaluations, 2 radiologists, with 5 and 27 years of thoracic radiology experience, respectively, reviewed the images independently, with a final finding reached by consensus when there was a discrepancy. They were blinded to the clinical information or clinical progress of the patients, except for the knowledge that these were cases of COVID-19 patients.

The pneumonia CT scores of patients during hospitalisation were recorded with a method described previously[1]. In brief, the CT features in hospitalised COVID-19 patients included ground glass opacity (GGO), consolidation, air bronchogram, nodular opacities and pleural effusion. The CT scans were scored on the axial images. The extent of involvement of each abnormality was assessed independently for each of 3 zones: upper (above the carina), middle (below the carina and above the inferior pulmonary vein), and lower (below the inferior pulmonary vein). The CT findings were graded on a 3-point scale: normal attenuation (1), GGO (2), and consolidation (3). Each lung zone, with a total of 6 lung zones in each patient, was assigned a following scale according to distribution of the affected lung parenchyma: normal (0), <25% abnormality (1), 25–50% abnormality (2), 50–75% abnormality (3), and >75% abnormality (4). The 4-point scale of the lung parenchyma distribution was then multiplied by the radiologic scale described above. Points from all zones were added for a final total cumulative score (HRCT pneumonia score during hospitalisation), with value ranging from 0 to 72. The peak pneumonia CT score is the highest pneumonia CT score for a patient during COVID-related hospitalisation.

To analyse follow-up HRCT scans, HRCT findings were initially evaluated based on key features[2] and then scored based on a method adapted from Ichikado and colleagues[3], here named HRCT follow-up score, which allowed us to evaluate interstitial changes in lungs[3]. Briefly, the lungs were divided into 6 zones (upper, middle, and lower on both sides), each zone was evaluated separately and for each zone the CT findings were graded on a 6-point scale: areas with (1) normal attenuation, (2) GGO without traction bronchiectasis or bronchiolectasis, (3) consolidation without traction bronchiectasis or bronchiolectasis, (4) GGO with traction bronchiectasis or bronchiolectasis, (5) consolidation with traction bronchiectasis or bronchiolectasis, and (6) honeycombing. The upper lung zone was defined as the area of the lung above the level of the tracheal carina, the lower lung zone was defined as the area of the lung below the level of the inferior pulmonary vein, and the middle lung zone was defined as the area of the lung between the upper and lower zones. Abnormal findings and the extent of lung involvement was evaluated visually and independently for each of the 6 zones. The scores were based on the percentage of the lung parenchyma that showed evidence of the abnormality and were estimated to the nearest 5 % of parenchymal involvement. Scores from all zones were added for a final total cumulative score, with value ranging from 6 to 36.

References:

1. Liu X, Zhou H, Zhou Y, et al. Temporal radiographic changes in COVID-19 patients: relationship to disease severity and viral clearance. *Scientific Reports* 2020; **10**(1): 10263.
2. Hansell DM, Bankier AA, MacMahon H, McLoud TC, Muller NL, Remy J. Fleischner Society: glossary of terms for thoracic imaging. *Radiology* 2008; **246**(3): 697-722.
3. Ichikado K, Suga M, Muller NL, et al. Acute interstitial pneumonia: comparison of high-resolution computed tomography findings between survivors and nonsurvivors. *American journal of respiratory and critical care medicine* 2002; **165**(11): 1551-6.

Supplementary Figure Legends

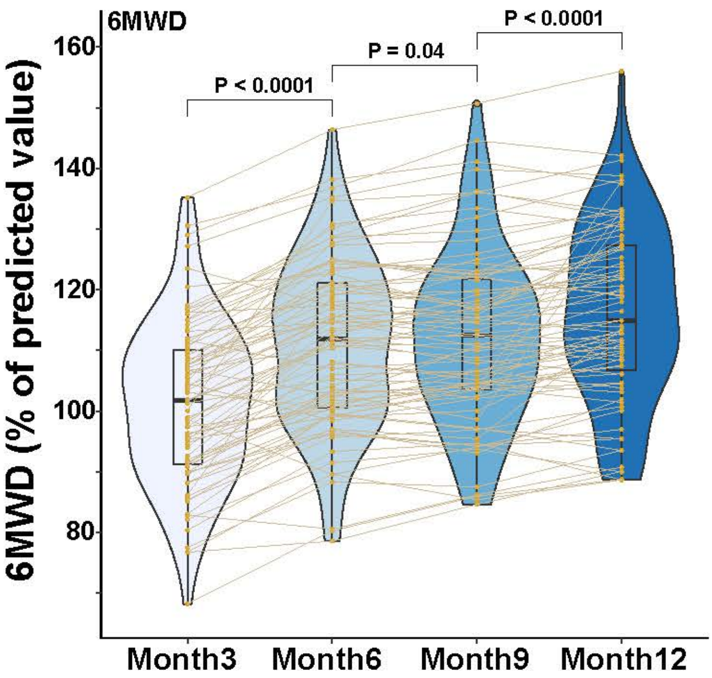
Supplementary Figure 1. Impact of severe COVID-19 on follow-up 6-minute walking distance (6MWD) test. Graph showing temporal changes in 6MWD at 3, 6, 9 and 12 months after discharge. Median, IQR (interquartile range) and P values are indicated. Values are % of predicted.

Supplementary Figure 2. Radiographic features of HRCT scans following severe COVID-19 related hospitalisation. Representative HRCT images showing (**A**) ground-glass opacity; (**B**) interlobular septal thickening; (**C**) reticular opacity; (**D**) subpleural curvilinear opacity; (**E**) mosaic attenuation; and (**F**) bronchiectasis, highlighted with red arrows.

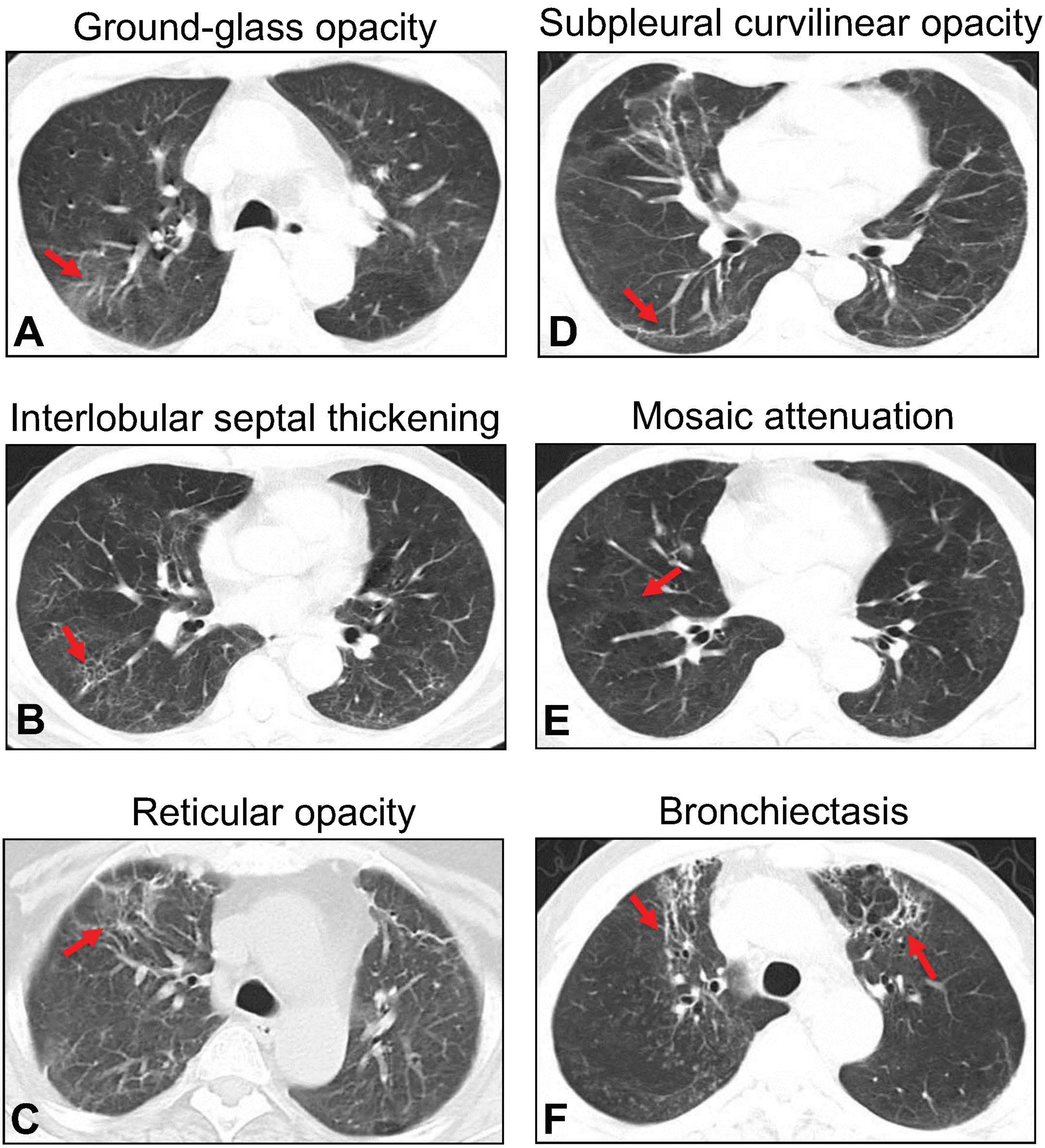
Supplementary Figure 3. Temporal changes in HRCT scans following severe COVID-19 related hospitalisation. Representative temporal radiographic changes in a 50 male patient with severe COVID-19 with all radiographic changes resolving by 6 months in (**A**); whilst in (**B**) a 54 male patient with severe COVID-19 where radiographic changes persist at 12 months. (**C**) Graph showing temporal HRCT Follow-up score changes in patients with normal (score = 6, blue) or abnormal (score ≥ 7, red) HRCT scans at 12 months after discharge. P values are indicated. (**D**) Graph showing peak HRCT Pneumonia score during hospitalisation in patients with normal *vs.*

abnormal HRCT scans at 12 months after discharge. Data are median and IQR (interquartile range) with P values indicated.

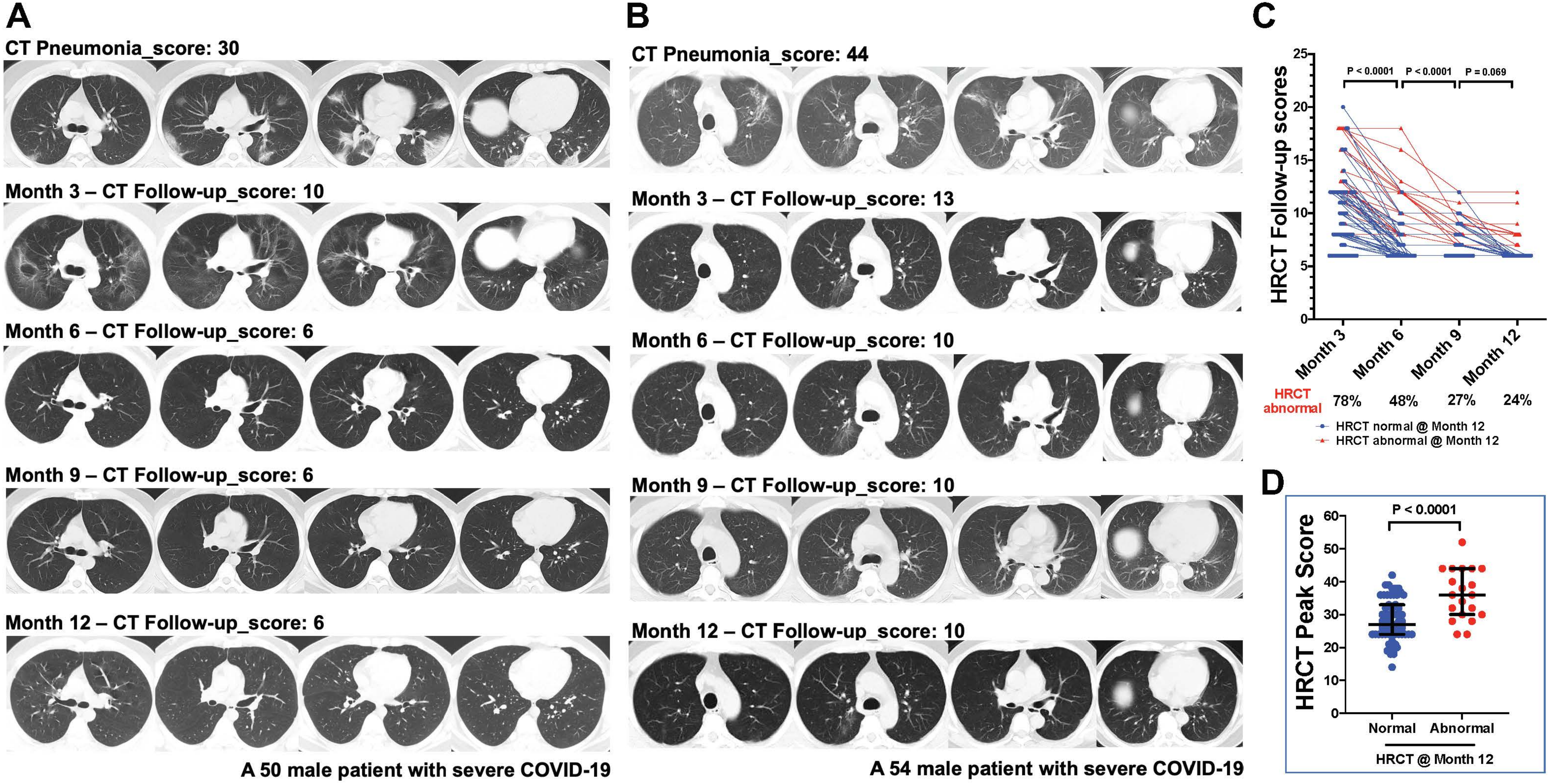
Supplementary Figure 1



Supplementary Figure 2



Supplementary Figure 3



Supplementary Tables

Supplementary Table 1. Results of serial pulmonary function tests among recovered severe COVID-19 patients who did not require mechanical ventilation.

Supplementary Table 2. Frequency of pulmonary function parameters below normal range in recovered severe COVID-19 patients who did not require mechanical ventilation.

Supplementary Table 3. Univariate and multivariate logistic regression analysis in severe COVID-19 patients who did not require mechanical ventilation for risk factors associated with diffusion deficit at 12 months after discharge.

Supplementary Table 4. HRCT features among recovered severe COVID-19 patients who did not require mechanical ventilation.

Supplementary Table 5. Univariate and multivariate logistic regression analysis in severe COVID-19 patients who did not require mechanical ventilation for risk factors associated with abnormal HRCT at 12 months after discharge.

Table S1. Results of serial pulmonary function tests among recovered severe COVID-19 patients who did not require mechanical ventilation (N = 83).

Parameter	@ Month 3	@ Month 6	@ Month 12	P value[a]	P value[b]
DLCO (% of predicted)	77 (67 ~ 87)	76 (68 ~ 90)	88 (78 ~ 101)	0.691	***< 0.0001***
FEF25-75% (% of predicted)	91 (64 ~ 109)	89 (67 ~ 103)	89 (76 ~ 111)	1	***0.032***
FEV1/FVC (% of predicted)	81 (77 ~ 84)	81 (78 ~ 84)	82 (79 ~ 86)	1	0.099
FRC (% of predicted)	89 (78 ~ 104)	89 (81 ~ 106)	102 (87 ~ 118)	1	***< 0.0001***
FVC (% of predicted)	92 (81 ~ 99)	94 (85 ~ 104)	98 (89 ~ 109)	***0.002***	***< 0.0001***
FEV1 (% of predicted)	90 (76 ~ 100)	92 (80 ~ 101)	96 (85 ~ 110)	0.206	***< 0.0001***
RV (% of predicted)	81 (69 ~ 97)	81 (72 ~ 100)	85 (72 ~ 99)	0.963	1
TLC (% of predicted)	87 (77 ~ 98)	91 (82 ~ 98)	92 (87 ~ 100)	***0.004***	***< 0.0001***
VC (% of predicted)	91 (81 ~ 103)	95 (83 ~ 104)	98 (90 ~ 111)	***0.006***	***< 0.0001***

DLCO, diffusing capacity of the lungs for carbon monoxide; $FEF_{25-75\%}$, forced expiratory flow between 25% and 75% of FVC; FRC, functional residual capacity; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; RV, residual volume; TLC, total lung capacity; VC, vital capacity. Values are expressed as median (interquartile range). [a]Month 6 *vs.* 3. [b]Month 12 *vs.* 6.

Table S2. Frequency of pulmonary function parameters below normal range in recovered severe COVID-19 patients who did not require mechanical ventilation (N = 83).

	< 60% predicted value			< 80% predicted value		
	@ Month 3	**@ Month 6**	**@ Month 12**	**@ Month 3**	**@ Month 6**	**@ Month 12**
DLCO	12 (15%)	11 (13%)	4 (5%)	46 (55%)	45 (54%)	27 (33%)
FRC	6 (7%)	6 (7%)	2 (2%)	23 (28%)	18 (22%)	10 (12%)
FVC	4 (5%)	2 (2%)	0 (0%)	19 (23%)	13 (16%)	9 (11%)
FEV1	6 (7%)	4 (5%)	3 (4%)	25 (30%)	20 (24%)	13 (16%)
RV	12 (15%)	9 (11%)	11 (13%)	38 (46%)	35 (42%)	32 (39%)
TLC	9 (11%)	4 (5%)	3 (4%)	22 (27%)	16 (19%)	12 (15%)
VC	4 (5%)	2 (2%)	1 (1%)	20 (24%)	15 (18%)	9 (11%)

DLCO, diffusing capacity of the lungs for carbon monoxide; FRC, functional residual capacity; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; RV, residual volume; TLC, total lung capacity; VC, vital capacity. Values are N (%).

Table S3. Univariate and multivariate logistic regression analysis in severe COVID-19 patients who did not require mechanical ventilation for risk factors associated with diffusion deficit at 12 months after discharge (N = 83).

	OR (odds ratio)	95% CI (confidence interval)	P - value
Univariate			
Age	1.03	0.99 ~ 1.08	0.140
Gender (Female)	7.14	2.53 ~ 20.16	***0.0002***
BMI	0.94	0.80 ~ 1.10	0.429
Length of hospital stay	1.00	0.93 ~ 1.07	0.952
Peak CT Pneumonia_score during hospitalization	1.00	0.94 ~ 1.06	0.876
HFNC/NIV	1.58	0.62 ~ 4.06	0.339
Oseltamivir	0.75	0.29 ~ 1.92	0.546
Ganciclovir	1.34	0.53 ~ 3.38	0.531
Multivariate			
Age	1.06	1.00 ~ 1.12	0.063
Gender (Female)	8.61	2.83 ~ 26.2	***0.0002***
Peak CT Pneumonia_score during hospitalization	0.98	0.91 ~ 1.05	0.521

BMI, body mass index; HFNC, high-flow nasal cannula; NIV, non-invasive mechanical ventilation.

Table S4. HRCT features among recovered severe COVID-19 patients who did not require mechanical ventilation (N = 83).

	@ Month 3	@ Month 6	@ Month 9	@ Month 12	P value[a]	P value[b]	P value[c]
Ground-glass opacity	65 (78%)	38 (46%)	20 (24%)	19 (23%)	***< 0.0001***	***0.010***	1
Interlobular septal thickening	28 (34%)	11 (13%)	4 (5%)	4 (5%)	***0.006***	0.174	1
Reticular opacity	27 (33%)	13 (16%)	3 (4%)	3 (4%)	***0.033***	***0.026***	1
Subpleural curvilinear opacity	9 (11%)	4 (5%)	1 (1%)	1 (1%)	0.446	1	1
Mosaic attenuation	2 (2%)	3 (4%)	3 (4%)	3 (4%)	1	1	1
Bronchiectasis	1 (1%)	1 (1%)	1 (1%)	1 (1%)	1	1	1

[a]Month 6 *vs.* 3. [b]Month 9 *vs.*6. [c]Month 12 *vs.*9. Values are N (%).

Table S5. Univariate and multivariate logistic regression analysis in severe COVID-19 patients who did not require mechanical ventilation for risk factors associated with abnormal HRCT at 12 months after discharge (N = 83).

	OR (odds ratio)	95% CI (confidence interval)	P - value
Univariate			
Age	1.02	0.97 ~ 1.07	0.401
Gender	1.86	0.67 ~ 5.13	0.232
BMI	0.92	0.77 ~ 1.10	0.357
Length of hospital stay	1.09	1.01 ~ 1.19	***0.031***
Peak CT Pneumonia_score during hospitalization	1.18	1.08 ~ 1.29	***0.0002***
HFNC/NIV	3.10	1.00 ~ 9.55	***0.049***
Oseltamivir	1.97	0.64 ~ 6.12	0.239
Ganciclovir	1.65	0.59 ~ 4.59	0.337
Multivariate			
Peak CT Pneumonia_score during hospitalization	1.36	1.13 ~ 1.62	***0.0009***
Length of hospital stay	0.92	0.81 ~ 1.04	0.180
HFNC/NIV	0.24	0.04 ~ 1.63	0.146

BMI, body mass index. HFNC, high-flow nasal cannula; NIV, non-invasive mechanical ventilation.