Respiratory outcomes in patients following COVID-19-related hospitalisation: a meta-analysis

Tao Guo¹, Fangfang Jiang², Yufei Liu³, Yunpeng Zhao⁴, Yiran Li⁵, Yihua Wang*¹

1. Biological Sciences, Faculty of Environmental and Life Sciences, University of Southampton, Southampton, United Kingdom
2. School of Mathematics, University of Southampton, Southampton, United Kingdom
3. School of Pharmacy, Nanjing University of Chinese Medicine, Nanjing, Jiangsu, China
4. School of Medicine and Integrated Medicine, Nanjing University of Chinese Medicine, Nanjing, Jiangsu, China
5. School of Artificial Intelligence and Information Technology, Nanjing University of Chinese Medicine, Nanjing, Jiangsu, China

*Correspondence should be addressed to YW (e-mail: yihua.wang@soton.ac.uk).
Abstract

**Background:** To determine the respiratory outcomes in patients following COVID-19-related hospitalisation. **Methods:** Systematic review and meta-analysis of the literature. **Results:** Forced vital capacity (FVC, % of predicted): 0-3 months post discharge: 94.9, 95% CI [82.2-107.7]; 3-6 months post discharge: 99.9, 95% CI [84.8, 115.0]; > 6 months post discharge: 97.4, 95% CI [76.8-118.0]. Diffusing capacity of the lungs for carbon monoxide (DLCO, % of predicted): 0-3 months post discharge: 83.9, 95% CI [68.9-98.9]; 3-6 months post discharge: 91.2, 95% CI [74.8-107.7]; > 6 months post discharge: 97.3, 95% CI [76.7-117.9]. Percentage of patients with FVC less than 80% of predicted: 0-3 months post discharge: 10%, 95% CI [6-14%]; 3-6 months post discharge: 10%, 95% CI [2-18%]; > 6 months post discharge: 13%, 95% CI [8-18%]. Percentage of patients with DLCO less than 80% of predicted: 0-3 months post discharge: 48%, 95% CI [41-56%]; 3-6 months post discharge: 33%, 95% CI [23-44%]; > 6 months post discharge: 43%, 95% CI [22-65%]. **Conclusion:** The meta-analysis confirms a high prevalence of persistent lung diffusion impairment in patients following COVID-19-related hospitalisation. Routine respiratory follow-up is thus strongly recommended.

**Key words:** COVID-19; follow-up; pulmonary function test; FVC; DLCO; synthesis review; meta-analysis
**Introduction**

To date, over 170 million people worldwide have recovered from COVID-19 (https://www.worldometers.info/coronavirus/)\textsuperscript{1}, but concern remains that some organs, including the lungs, might suffer long-term impairment following recovery from acute infections. Individual studies have shown that residual abnormalities of pulmonary function were observed in a subgroup of recovered COVID-19 patients, with the most common finding being a reduction in gas transfer as measured by diffusing capacity of the lungs for carbon monoxide (DLCO)\textsuperscript{2-4}. In this study, with meta-analysis, we aimed to determine the short (0-3 months), medium (3-6 months) and long (> 6 months) respiratory outcomes in patients following COVID-19-related hospitalisation. The findings will instruct appropriate interventions for subsequent increased healthcare utilisation post-COVID-19.
Method

Criteria for inclusion

We included randomised controlled trials (RCTs) and observational studies (cross-sectional, longitudinal, case-control and cohort) of patients with a confirmed diagnosis of COVID-19. The studies included aimed to determine the respiratory outcomes, in particular forced vital capacity (FVC) and diffusing capacity of the lungs for carbon monoxide (DLCO), in patients following COVID-19-related hospitalisation. The selected studies had to follow the ATS / ERS clinical guidelines. The included literatures should be published before 15th May 2021.

Criteria for exclusion

Study's subjects who were not infected with COVID-19. Studies didn’t report the time of hospital discharge or the time was calculated from diagnosis of COVID-19. Studies did not report FVC (% of predicted) or DLCO (% of predicted) or FVC < 80% of predicted or DLCO < 80% of predicted. Animal experiments, medical records, case reports, famous medical experience and review were excluded.

Literature retrieval and selection

Firstly, according to the literature inclusion criteria, 2 researchers independently searched at Pubmed, ScienceDirect, Embase and Web of Science. Secondly, 2 researchers selected the literature and extracted the data independently in accordance with the standard data extraction table. When it came to divergences, a third researcher did the judgement. After the discussion, researchers reached a consensus. Finally, after the extraction and input of the data, 2 independent researchers did the subsequent analysis.

Extraction of data

According to the inclusion criteria, we assessed the design of research, patients, and outcome indicators. First author, published year, number of cases, nationality, ages, body mass index (BMI), smoking status, respiratory comorbidities, time of assessment
and, index quantity of FVC, % of predicted, DLCO, % of predicted; FVC < 80% of predicted and DLCO < 80% of predicted were extracted from eligible studies.

**Quality assessment of articles**

The studies with randomised controlled trials were evaluated by Newcastle-Ottawa Scale\[^{[13]}\]. As for no controlled trials, it includes the following aspects: 1) selection: Representativeness of the exposed cohort, selection of the non-exposed cohort, Ascertainment of exposure, Demonstration that outcome of interest was not present at start of study; 2) comparability: Research control matched important factors, but also controlled other important factors; and 3) outcome: assessment of outcome, follow-up long enough for outcomes to occur, adequacy of follow up of cohorts.

**Synthesis and analysis of data**

We used package “meta (version 4.18-0)” in R 4.0.1 and R studio to perform meta-analysis of the following pulmonary function tests (PFTs) indexes (1. FVC, % of predicted; 2. DLCO, % of predicted; 3. FVC < 80% of predicted; 4. DLCO < 80% of predicted). Patients were divided into 3 groups: less than 3 months (0-3 months), more than or equal to 3 months and less than 6 months (3-6 months), and more than or equal to 6 months (≥ 6 months). We re-calculated the median (first quantile, third quantile) to mean ± standard deviation (SD) for FVC (% of predicted) and DLCO (% of predicted) in several studies. Statistical heterogeneity was measured through the I\(^2\) statistic and classified as low (I\(^2\) < 25%), moderate (I\(^2\) 25-50%), and high (I\(^2\) > 50%)\[^{[5]}\]. Subgroup analysis, according to the outcome assessment and severity, was performed. Sensitivity analysis was also employed to assess the change in pooled prevalence due to the selective exclusion of studies.
Results

Literature extraction
A total of 1,123 articles was retrieved from databases via the retrieval methods. Duplicate literatures were excluded through titles and abstracts. By reading the full text, we excluded 1,110 papers and conference abstracts with incomplete or no specific research method. Finally, 13 papers published in English were included\(^6\text{--}\text{18}\), with a total of 3,455 patients. The evaluation of the quality of included studies by Newcastle-Ottawa Scale (NOS)\(^19\) showed that 2 studies had a poor quality and the rest 11 studies passed the quality control. The basic characteristics of the included literatures were detailed in Table 1 and the procedure of literature retrieval and selection was shown in Figure 1.

Among the included studies, 10 studies reported FVC (% of predicted), 8 studies reported DLCO (% of predicted), 6 reported FVC < 80% of predicted, and 9 reported DLCO < 80% of predicted. Wu et al\(^12\) reported all the indexes of the patients after the 3, 6 and 12 months following COVID-19-related hospitalisation (Table 2). For those data reported in the form of median (first quantile, third quantile), we used R studio to re-calculate them into mean± SD (Table 3).

Publication bias refers to the fact that research results with statistical significance are more likely to be reported and published than those without statistical significance and invalid results\(^20\). We examined the publication bias of meta-analysis of each indicator. There was no publication bias in FVC (% of predicted; p = 0.93; Figure 2A), DLCO (% of predicted; p = 0.54; Figure 2B) and DLCO (< 80% of predicted; p = 0.94; Figure 2C). For FVC < 80% of predicted, less than 10 studies were included, so publication bias was not tested.

Comparison of longitudinal changes in FVC (% of predicted)
Ten studies with 12 groups of data showed the results of FVC (% of predicted). Based on the time of patients discharged from hospital, we divided them into 3 groups: 0-3 months, 3-6 months and ≥ 6 months. FVC (% of predicted) in 0-3 months, 3-6 months and ≥ 6 months post discharge were 94.9 (95% CI [82.2-107.7]), 99.9 (95% CI [84.8,
115.0]) and 97.4 (95% CI [76.8-118.0]), respectively. In this study, heterogeneity was extremely low ($I^2=0\%$), and the overall value of FVC (% of predicted) in all studies was 97.1 (95% CI [88.3, 105.9]) (Figure 3).

**Comparison of longitudinal changes in DLCO (% of predicted)**

Eight studies with 10 groups of data showed the results of DLCO (% of predicted). DLCO (% of predicted) in 0-3 months, 3-6 months and ≥ 6 months post discharge were 83.9 (95% CI [68.9-98.9]), 91.2 (95% CI [74.8-107.7]) and 97.3 (95% CI [76.7-117.9]), respectively. Heterogeneity was considered low ($I^2=0\%$) using a fixed effect model[5,21] (Figure 4).

**Comparison of longitudinal changes in the percentage of patients with FVC < 80% of predicted**

This included 6 studies, which in total have 8 groups of data showed the percentage of patients with FVC less than 80% of predicted. Based on the time of patients being discharged from hospital, we divided them into 3 groups: 0 to 3 months, 3 to 6 months and greater than 6 months. Meta-analysis showed that the percentage of patients with FVC less than 80% of predicted in 0-3 months, 3-6 months and ≥ 6 months post discharge was 10% (95% CI [6-14%]), 10% (95% CI [2-18%]) and 13% (95% CI [8-18%], respectively. The heterogeneity of 3 to 6 months was large, so the sensitivity analysis was carried out in this study. We removed the study from Wu et al. and got the meta-analysis result of this subgroup, which was 4% (95% CI [3-6%]) with $I^2 = 6\%$ (Figure 5).

**Comparison of longitudinal changes in the percentage of patients with DLCO < 80% of predicted**

This included 9 studies, which have 11 groups of data shows the results of DLCO less than 80% of predicted. Meta-analysis showed a significant and persistent reduction in DLCO over the study period. The percentage of patients with DLCO less than 80% of predicted in 0-3 months, 3-6 months and ≥ 6 months post discharge was 48% (95% CI
[41-56%]), 33% (95% CI [23-44%]) and 43% (95% CI [22-65%]), respectively (Figure 6).
Discussion

Post-acute COVID-19 syndrome, also known as long COVID, encompasses a wide range of physical and mental health symptoms that persist after recovery from acute SARS-CoV-2 infections\textsuperscript{[22]}. Systematic studies of sequelae after recovery from acute COVID-19 are demanded to inform effective clinical management for patients suffered from long COVID.

We recently reported the 3-month, 6-month, 9-month, and 12-month respiratory outcomes in patients following COVID-19-related hospitalisation from a relatively small prospective cohort (n=83)\textsuperscript{[12]}. In this study, we conducted meta-analysis to determine the short (0-3 months), medium (3-6 months) and long (> 6 months) respiratory outcomes in patients following COVID-19-related hospitalisation. Significantly, we found a persistent reduction in DLCO over the study period, consistent with earlier reports\textsuperscript{[23]}. Low DLCO could be caused by interstitial changes or pulmonary vascular abnormalities following COVID-19 infections\textsuperscript{[24-26]}. Our study has shown that up to a third of COVID patients still have evidence of defect DLCO one year after discharge\textsuperscript{[12]}, although longer term follow-up with a larger cohort will be required to confirm this observation.

In general, the heterogeneity of the studies included in the meta-analysis was low. However, the heterogeneity of DLCO less than 80% of predicted was higher, which may be caused by different ethnic groups, ages, disease severity, therapies and other factors. In general, the models we used were robust and reliable.

There are several limitations in this study. Firstly, age, sex ratio, nationality and disease severity of the patients included in the study are quite different, which may cause great heterogeneity and affect the final research results. Secondly, we only selected 4 indicators of lung function, so we cannot investigate the relationship between other indicators and discharge time. To be consistent and comparable with our earlier publication\textsuperscript{[12]}, we excluded those studies without data on FVC and/or DLCO values <80% of predicted. This might cause some false positive results considering the mean age of included patients is over 50\textsuperscript{[15,27,28]}. In addition, pre-existing comorbidities for...
most COVID-19 patients are not known, which might cause certain bias of the results. Despite of these limitations, our findings in this meta-analysis are consistent with our previous report [12], confirming a high prevalence of persistent lung diffusion impairment in patients following COVID-19-related hospitalisation. Routine respiratory follow-up is thus strongly recommended.
Declarations

Acknowledgements
Not applicable.

Funding Information
YW was supported by Medical Research Council (UK) [MR/S025480/1].

Abbreviations
COVID-19: Corona Virus Disease 2019
PFTs: Pulmonary Function Tests
FVC: forced vital capacity
DLCO: Diffusing capacity for carbon monoxide
NR: Not reported
BMI: Body Mass Index

Authors’ Contributions
Yihua Wang conceived and designed the study. Tao Guo, Fangfang Jiang, Yufei Liu, Yunpeng Zhao and Yiran Li collected the data. Tao Guo and Fangfang Jiang performed the data analysis. Tao Guo and Yufei Liu did the evaluation of the quality of included articles. Tao Guo and Yihua Wang wrote the manuscript. All authors are responsible for reviewing data. All authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

Availability of data and materials
The data and materials generated or analyzed during this study are available from the corresponding author on reasonable request.
Consent for publication
The manuscript is approved by all authors for publication.

Ethics approval and consent to participate
Not applicable.
References

[1] World Meter Corona Virus Update (Live) https://www.worldometers.info/coronavirus/ Available from:

[2] Hull JH, Lloyd JK, Cooper BG. Lung function testing in the COVID-19 endemic. Lancet Respir Med. 2020;8(7):666-667.

[3] Dhawan RT, Gopalan D, Howard L, et al. Beyond the clot: perfusion imaging of the pulmonary vasculature after COVID-19. Lancet Respir Med. 2021;9(1):107-116.

[4] Thomas M, Price OJ, Hull JH. Pulmonary function and COVID-19. Curr Opin Physiol. 2021;21:29-35.

[5] Melsen WG, Bootsma MC, Rovers MM, et al. The effects of clinical and statistical heterogeneity on the predictive values of results from meta-analyses. Clin Microbiol Infect. 2014;20(2):123-129.

[6] Liang L, Yang B, Jiang N, et al. Three-month Follow-up Study of Survivors of Coronavirus Disease 2019 after Discharge. J Korean Med Sci. 2020;35(47):e418.

[7] Huang Y, Tan C, Wu J, et al. Impact of coronavirus disease 2019 on pulmonary function in early convalescence phase. Respir Res. 2020;21(1):163.

[8] Venturelli S, Benatti SV, Casati M, et al. Surviving COVID-19 in Bergamo province: a post-acute outpatient re-evaluation. Epidemiol Infect. 2021;149:e32.

[9] You J, Zhang L, Ni-Jia-Ti MY, et al. Anormal pulmonary function and residual CT abnormalities in rehabilitating COVID-19 patients after discharge. J Infect. 2020;81(2):e150-e152.

[10] Lerum TV, Aaløkken TM, Brønstad E, et al. Dyspnoea, lung function and CT findings 3 months after hospital admission for COVID-19. Eur Respir J. 2021;57(4):2003448.

[11] Daher A, Balfanz P, Cornelissen C, et al. Follow up of patients with severe coronavirus disease 2019 (COVID-19): Pulmonary and extrapulmonary disease sequelae. Respir Med. 2020;174:106197.

[12] Wu X, Liu X, Zhou Y, et al. 3-month, 6-month, 9-month, and 12-month respiratory outcomes in patients following COVID-19-related hospitalisation: a
prospective study. Lancet Respir Med. 2021;9(7):747-754.

[13] Bellan M, Soddu D, Balbo PE, et al. Respiratory and Psychophysical Sequelae Among Patients With COVID-19 Four Months After Hospital Discharge. JAMA Netw Open. 2021;4(1):e2036142.

[14] Li X, Wang C, Kou S, Luo P, Zhao M, Yu K. Lung ventilation function characteristics of survivors from severe COVID-19: a prospective study. Crit Care. 2020;24(1):300.

[15] van den Borst B, Peters JB, Brink M, et al. Comprehensive health assessment three months after recovery from acute COVID-19. Clin Infect Dis. 2020;ciaa1750.

[16] Mo X, Jian W, Su Z, et al. Abnormal pulmonary function in COVID-19 patients at time of hospital discharge. Eur Respir J. 2020;55(6):2001217.

[17] 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.

[18] Huang C, Huang L, Wang Y, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet. 2021;397(10270):220-232.

[19] Stang A, Jonas S, Poole C. Case study in major quotation errors: a critical commentary on the Newcastle-Ottawa scale. Eur J Epidemiol. 2018;33(11):1025-1031.

[20] DeVito NJ, Goldacre B. Catalogue of bias: publication bias. BMJ Evid Based Med. 2019;24(2):53-54.

[21] Bellou V, Belbasis L, Tzoulaki I, Evangelou E, Ioannidis JP. Environmental risk factors and Parkinson's disease: An umbrella review of meta-analyses. Parkinsonism Relat Disord. 2016;23:1-9.

[22] Nalbandian A, Sehgal K, Gupta A, et al. Post-acute COVID-19 syndrome. Nat Med. 2021;27(4):601-615.

[23] Ekbom E, Frithiof R, Emilsson Ö, et al. Impaired diffusing capacity for carbon monoxide is common in critically ill Covid-19 patients at four months post-discharge. Respir Med. 2021;182:106394.

[24] Hanidziar D, Robson SC. Hyperoxia and modulation of pulmonary vascular and immune responses in COVID-19. Am J Physiol Lung Cell Mol Physiol.
2021;320(1):L12-L16.

[25] Patel BV, Arachchilage DJ, Ridge CA, et al. Pulmonary Angiopathy in Severe COVID-19: Physiologic, Imaging, and Hematologic Observations. Am J Respir Crit Care Med. 2020;202(5):690-699.

[26] Lang M, Som A, Mendoza DP, et al. Hypoxaemia related to COVID-19: vascular and perfusion abnormalities on dual-energy CT. Lancet Infect Dis. 2020;20(12):1365-1366.

[27] Barisione G, Brusasco V. Lung diffusing capacity for nitric oxide and carbon monoxide following mild-to-severe COVID-19. Physiol Rep. 2021;9(4):e14748.

[28] Milanese M, Anselmo M, Buscaglia S, et al. COVID-19 6 months after hospital discharge: pulmonary function impairment and its heterogeneity. ERJ Open Res. 2021;7(3):00196-2021.
### Tables

**Table 1** Basic characteristics of included studies.

| Author            | Country     | Design            | Participants | Age (years) | BMI (kg/m2) | smoking                          | respiratory comorbidities | time of assessment | quality rating |
|-------------------|-------------|-------------------|---------------|-------------|-------------|----------------------------------|----------------------------|-------------------|---------------|
| Huang, Y. Y., 2020| China       | retrospective     | 57            | 46.7±13.7   | 23.9±3.5    | History of smoking 9 (15.7%)     | No patient was reported having chronic respiratory diseases | 30 days after discharge | high          |
| Venturelli, S., 2021| Italy      | prospective      | 767           | 63±13.6     | NR          | Active smoker 33 (4.3%)          | 81 (66-106) days after hospital discharge | NR                | high          |
| You, J. J., 2020  | China       | prospective      | 18 10M/8F     | 50.7±12.1   | 26.4±2.8    | NR                               | No patient was reported having chronic respiratory diseases | 38±13.4 days after hospital discharge | high          |
| Lerum, T. V., 2021| Norway      | prospective      | 103           | 59 (49-72)  | 25.8 (23.8-29.6) | Current smoker 3 (3.4%) previous smoker 34 (39%) | NR                        | 3 months after hospital admission | poor          |
| Daher, A., 2020   | Germany     | prospective      | 33            | 64±3        | 28 (24-31)  | NR                               | No patient was reported having chronic respiratory diseases | 7 (21%)            | high          |
| Wu, X. J., 2021   | China       | prospective, longitudinal, cohort | 83            | 60 (52-66)  | 25 (23.5-27.1) | NR                               | No patient was reported having chronic respiratory diseases | 3-month, 6-month, 9-month, 12-month after hospital discharge | high          |
Liang, Y. 2020 China Prospective 76 41.3 ± 23.7 ± NR
21M/55F 13.8 4.5

Bellan, M. 2021 Italy prospective cohort study 238 61 (51-71) NR
142M/96F

Li, X. 2020 China a prospective study 18 NR NR

van den Borst 2020 Netherlands Prospective 124 59 ± 14 NR
74M/50F

Mo, X. 2020 China Prospective 110 49.1±14.0 23.5±3.0 NR
55M/55F 13 (11.8%)

Zhao, Y. M. 2020 China retrospective 55 47.7±15.5 NR
22M/33F

Cough 45 (60%) Increased sputum production 33 (43%)
Activity chest tightness and palpitations 47 (62%)

Never 139 (58.4%) Former 74 (31.1%)
Current 25 (10.5%) Pack-years, median (IQR) 15 (7.25-36)

No patient was reported having chronic respiratory diseases

Near discharge and in quarantine high

History of smoking

3 (16.6%) No patient was reported having chronic respiratory diseases

1 (0.9%) asthma 1
(0.9%) chronic bronchitis 1

At time of hospital discharge poor

active 2 (3.6%) former 2 (3.6%)

Three-month follow-up high

No patient was reported having chronic respiratory diseases

Four months high

No patient was reported having chronic respiratory diseases

Three months high

No patient was reported having chronic respiratory diseases

3 months high
| Never-smoker | 1585/1731 (92%) | Chronic obstructive pulmonary disorder days high after hospital discharge | 153.0 (146.0 - 160.0) |
|-------------|----------------|--------------------------------------------------------------------------------|----------------------|
| Current smoker | 102/1731 (6%)  |                                                                                   | 897M/836F            |
| Former smoker | 44/1731 (3%)   |                                                                                   |                      |

NR: Not reported; BMI: Body Mass Index; M: Male; F: Female

Huang, C. 2021. China prospective cohort study. Observed on admission. 1733 patients. 897M/836F. 57 (47-65) NR.
### Table 2 Summary of studies included pulmonary function test.

| Study                | Wu et al, (n=83) | You et al, (n=18) | Zhao et al, (n=55) |
|----------------------|------------------|-------------------|-------------------|
| **FVC, % of predicted** | 92 (81–99)       | 94 (85–104)       | 98 (89–109)       |
| **DLCO, % of predicted** | 77 (67-87)    | 76 (68-90)        | 88 (78-101)       |
| **FVC, < 80% of predicted** | 19              | 13                | 9                 |
| **DLCO, < 80% of predicted** | 46              | 45                | 27                |
| **Time of assessment** | 3 months        | 6 months          | 12 months         |

| Study                | Lerum et al, (n=103) | Borst et al, (n=124) | Li et al, (n=18) | Daher, A et al(n=33) | Venturelli, S et al(n=767) |
|----------------------|----------------------|----------------------|------------------|----------------------|---------------------------|
| **FVC, % of predicted** | 94 (76-121)         | NR                   | 91.5±17.3        | 93 (78-101)          | 95(84-106), f             |
| **DLCO, % of predicted** | 83 (72-92)         | 81±17                | NR               | 65(53-73)            | 96 (81-112), p            |
| **FVC, < 80% of predicted** | 7                  | NR                   | NR               | NR                   | NR                        |
| **DLCO, < 80% of predicted** | 24                  | 41                   | NR               | NR                   | NR                        |
| **Time of assessment** | 3 months after hospital discharge | 3 months after recovery | Near to discharge and two weeks after | 56 days from discharge to follow-up | 80(median)days after discharge |
|                        | Huang et al (n=349) | Bellan et al, (n = 224) | Liang et al, (n = 76) | Huang et al, (n = 57) | Mo et al, (n = 110) |
|------------------------|---------------------|-------------------------|-----------------------|-----------------------|---------------------|
| **FVC, % of predicted**| NR                  | 98.5 (90-109)           | 107.1 ± 12.3          | 100.96±15.93          | 93.59 ± 12.25       |
| **DLCO, % of predicted**| NR                  | 79 (69-89), q           | NR                   | 78.38±13.59           | 78.18 ± 14.29       |
| **FVC, < 80% of predicted**| 14                  | NR                     | NR                   | 6                     | 10                  |
| **DLCO, < 80% of predicted**| 114(334)            | 113(219)               | 15                   | 30                    | 51                  |
| **Time of assessment** | 153.0 (146.0 - 160.0) days after hospital discharge | 4 months after hospital discharge | 3 months after hospital discharge | 1 month after hospital discharge | when discharged from hospital |

f: n=717, p: n=680, q: n=219; NR: Not reported; FVC: Forced vital capacity; DLCO: Diffusing capacity for carbon monoxide
Table 3 Summary of re-calculation of median into mean using R studio.

| Author         | Time                                      | FVC.mean | FVC.sd | FVC.n | DLCO.mean | DLCO.sd | DLCO.n |
|----------------|-------------------------------------------|----------|--------|-------|------------|---------|--------|
| Frija-Masson   | 30 days after symptoms onset              | 91.7     | 11.14  | 50    | 91.27      | 11.23   | 50     |
|                | 56 days from discharge to follow-up       |          |        |       |            |         |        |
| Daher, A       | 80(median) days after discharge           | 95.02    | 15.99  | 717   | 95.48      | 16.6    | 680    |
|                | 3 months after hospital discharge         | 102.1    | 37.78  | 103   | 99.68      | 34.9    | 103    |
| Venturelli, S  | 113(median) days after diagnosis          | 106.91   | 15.07  | 65    | 106.88     | 14.79   | 65     |
| Lerum          | 4 months after hospital discharge         | 99.9     | 14.3   | 224   | 99.79      | 14.28   | 219    |
| Darley, D.R    | 5 months after diagnosis                  |          |        |       |            |         |        |
| Belan          | 3 months                                 | 89.11    | 14.73  | 83    | 88.45      | 14.13   | 83     |
| Wu             | 6 months                                 | 95.07    | 14.3   | 83    | 95.26      | 14.26   | 83     |
| Wu             | 12 months                                | 100.19   | 15.53  | 83    | 99.67      | 15.56   | 83     |

FVC: Forced vital capacity; DLCO: Diffusing capacity for carbon monoxide
Figures.

Figure 1. Workflow showing literature extraction (details provided in Methods).
Figure 2. No publication bias of the meta-analysis. Funnel plots of FVC (% of predicted) (A), DLCO (% of predicted) (B) and DLCO <80% of predicted (C) were shown. Each dot represents a study.
Figure 3. Comparison of longitudinal changes in FVC (% of predicted). Forest plot showing meta-analysis of FVC (% of predicted).

| Study      | Experimental TE | Standardised Mean Difference | SMD 95%-CI | Weight (fixed) | Weight (random) |
|------------|-----------------|------------------------------|-------------|----------------|-----------------|
| group = 0-3 months |                  |                              |             |                |                 |
| Daher, A   | 89.08           | 89.08                        | 57.77-120.89| 7.7%           | 7.7%            |
| Vantrek, S | 95.02           | 95.02                        | 66.98-126.30| 7.9%           | 8.0%            |
| Li         | 91.50           | 91.50                        | 57.59-125.41| 6.8%           | 6.8%            |
| Huang      | 100.96          | 100.96                       | 59.74-132.18| 8.0%           | 8.0%            |
| You        | 105.10          | 105.10                       | 59.43-150.77| 7.7%           | 7.7%            |
| Mo         | 93.59           | 93.59                        | 59.59-117.60| 13.5%          | 13.4%           |
|            |                 |                              |             |                |                 |
| Fixed effect model |              | 95.49                      | 92.15-107.73| 47.6%          | --              |
| Random effects model |           | 94.95                      | 92.08-107.81| --             | 47.7%           |
| group = 3-6 months |              |                              |             |                |                 |
| Yerum      | 102.19          | 102.10                       | 28.05-170.15| 1.4%           | 1.4%            |
| Balian     | 99.90           | 99.90                        | 71.87-127.93| 9.9%           | 9.9%            |
| Wu         | 89.11           | 89.11                        | 60.24-117.98| 9.3%           | 9.3%            |
| Liang      | 107.10          | 107.10                       | 82.99-131.21| 13.4%          | 13.3%           |
|            |                 |                              |             |                |                 |
| Fixed effect model |              | 99.86                      | 84.75-114.98| 34.1%          | --              |
| Random effects model |           | 99.81                      | 84.29-115.34| 34.0%          | --              |
| group = ≥ 6 months |               |                              |             |                |                 |
| Wu         | 95.07           | 95.07                        | 67.04-123.10| 9.9%           | 9.9%            |
| Wu         | 100.19          | 100.19                       | 76.80-118.04| 8.3%           | 8.4%            |
|            |                 |                              |             |                |                 |
| Fixed effect model |              | 97.42                      | 76.80-118.04| 18.3%          | --              |
| Random effects model |           | 97.42                      | 76.78-118.06| 18.3%          | --              |
|            |                 |                              |             |                |                 |
| Fixed effect model |              | 97.07                      | 88.25-105.90| 100.0%         | --              |
| Random effects model |           | 97.07                      | 88.15-105.96| 100.0%         | --              |

Heterogeneity: $I^2 = 0\%, \chi^2 = 2.8575, p = 0.09$
**Figure 4.** Comparison of longitudinal changes in DLCO (% of predicted). Forest plot showing meta-analysis of DLCO (% of predicted).
Figure 5. Comparison of longitudinal changes in the percentage of patients with FVC < 80% of predicted. Forest plot showing meta-analysis of the percentage of patients with FVC < 80% of predicted.
**Figure 6.** Comparison of longitudinal changes in the percentage of patients with DLCO < 80% of predicted. Forest plot showing meta-analysis of the percentage of patients with DLCO < 80% of predicted.

| Study     | Events | Total | Proportion | 95%-CI (fixed) | Weight (fixed) | Weight (random) |
|-----------|--------|-------|------------|----------------|----------------|-----------------|
|           |        |       |            |                |                |                 |
| group = 0.3 months |        |       |            |                |                |                 |
| Huang-2020| 30     | 57    | 0.53       | [0.39; 0.66]   | 3.7%           | 8.1%            |
| Mo-2020   | 51     | 110   | 0.46       | [0.37; 0.56]   | 7.3%           | 9.1%            |
| Fixed effect model | 167    |       | 0.48       | [0.41; 0.56]   | 11.0%          | -               |
| Random effects model |       |       | 0.48       | [0.41; 0.56]   | -              | 17.2%           |
| Heterogeneity: $I^2 = 0\%$, $t^2 = 0$, $p = 0.44$ | | | | | | |
| group = 3-6 months |        |       |            |                |                |                 |
| Huang-2021| 114    | 334   | 0.34       | [0.29; 0.39]   | 24.4%          | 10.0%           |
| Bellan-2021| 113   | 219   | 0.52       | [0.45; 0.58]   | 14.4%          | 9.7%            |
| Liang-2020| 15     | 76    | 0.20       | [0.11; 0.30]   | 7.9%           | 9.2%            |
| Zhao-2020 | 9      | 55    | 0.16       | [0.08; 0.29]   | 6.6%           | 9.0%            |
| Lerum-2021| 24     | 103   | 0.23       | [0.16; 0.33]   | 9.4%           | 9.4%            |
| Borst-2020| 41     | 124   | 0.33       | [0.25; 0.42]   | 9.2%           | 9.3%            |
| Wu-2021   | 46     | 83    | 0.55       | [0.44; 0.66]   | 5.5%           | 8.7%            |
| Fixed effect model | 994    |       | 0.34       | [0.32; 0.37]   | 77.3%          | -               |
| Random effects model |       |       | 0.33       | [0.23; 0.44]   | -              | 65.2%           |
| Heterogeneity: $I^2 = 92\%$, $t^2 = 0.0170$, $p < 0.01$ | | | | | | |
| group ≥ 6 months |        |       |            |                |                |                 |
| Wu-2021   | 27     | 83    | 0.33       | [0.23; 0.44]   | 6.2%           | 8.9%            |
| Wu-2021   | 45     | 83    | 0.54       | [0.43; 0.65]   | 5.5%           | 8.7%            |
| Fixed effect model | 168    |       | 0.43       | [0.35; 0.50]   | 11.7%          | -               |
| Random effects model |       |       | 0.43       | [0.22; 0.65]   | -              | 17.6%           |
| Heterogeneity: $I^2 = 88\%$, $t^2 = 0.0027$, $p < 0.01$ | | | | | | |
| Fixed effect model | 1327   |       | 0.37       | [0.34; 0.39]   | 100.0%         | -               |
| Random effects model |       |       | 0.38       | [0.30; 0.46]   | -              | 100.0%          |
| Heterogeneity: $I^2 = 89\%$, $t^2 = 0.0158$, $p < 0.01$ | | | | | | |