Clinical Research

COVID-19 potentially causes long-term deterioration of lung function: a systematic review and meta-analysis

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ABSTRACT

BACKGROUND The COVID-19 is an emerging disease that commonly involves respiratory complaints, including acute respiratory distress syndrome. The effect of COVID-19 on pulmonary function is still unclear and only based on sporadic reports with a small sample size. This study aimed to compile evidence on the pulmonary function of patients who have recovered from COVID-19.

METHODS Literature searching was conducted in PubMed, Embase, Google Scholar, Scopus, Web of Sciences, and CINAHL. Any types of studies published before June 26, 2020 and reported lung function tests of post-COVID-19 patients were included. Articles reporting data from early hospitalization were excluded. The risk of bias was measured using tools developed by the Joanna Briggs Institute. Meta-analysis was done using a meta statistical package in R and presented in the random effects model.

RESULTS 378 recovered COVID-19 patients in 7 studies were included. The lung function measurement periods were varied, ranging from 14 days after hospitalization to 10 weeks after receiving rehabilitation. Meta-analyses found that the pooled mean of diffusion capacity of carbon monoxide in recovered COVID-19 patients was lower than 80% predicted, whereas the other parameters were normal. The forced vital capacity and total lung capacity showing restrictive lung disorders were significantly lower in the severe COVID-19 survivors.

CONCLUSIONS COVID-19 has a negative impact on lung function for at least several weeks in the recovery period. Diffusion and restrictive problems could be the main long-term consequences of COVID-19.

KEYWORDS COVID-19, FEV1, pulmonary function test, SARS-CoV-2, spirometry

Coronavirus disease 2019 (COVID-19) is a newly emerging disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) firstly appeared in Wuhan, China, at the end of 2019. The disease spread very quickly worldwide and was declared a pandemic disease by World Health Organization (WHO).[1]

In contrast to the viral common cold that generally induces mild symptoms, COVID-19 shows a wide spectrum of disease severity ranging from mild symptoms such as dry cough to critical conditions requiring intensive care facilities or death.[1] Acute respiratory distress syndrome and pneumonia are the most common underlying causes of death in COVID-19 patients.[2] Pneumonia, a potentially sudden and severe lung inflammation, in COVID-19 patients occurs due to the invasion of the SARS-CoV-2 virus through the angiotensin-converting enzyme 2 (ACE2) receptors, which are highly expressed in the lung epithelial

cells.[3] The viral infection leads to the destruction of the alveolar lining, resulting in impaired diffusion of oxygen and carbon dioxide.[4] Lung injury then triggers a repair process to restore the alveolar architecture. A repair dysregulation may sometimes occur and result in fibrosis.[4] Ultimately, lung fibrosis causes reduced lung compliance.[5]

COVID-19 survivors often report some respiratory complaints, such as dyspnea.[6] In SARS and MERS cases, about 27% of the survivors had impaired diffusing capacity of the lungs for carbon monoxide (DLCO) (<80% predicted) at the first 6 months after recovery, suggesting a lung diffusion problem.[7] This prevalence decreased to 24% after 6 months. The prevalence of restrictive lung disorder was also considerably high (10–15%) and characterized by low forced vital capacity (FVC) (<80%) and total lung capacity (TLC) (<80%).[7] Pulmonary function impairment limits the patient's ability to engage in physical activities, leading to reduced work productivity and decreased quality of life. However, data on lung function of COVID-19 patients are very limited. Therefore, this rapid systematic review aimed to gather evidence on the pulmonary function of COVID-19 survivors.

METHODS

Searching strategy and selection criteria

A study protocol was developed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines.[8] This rapid review was pre-registered in the Open Science Framework (10.17605/OSF.IO/B73F5). Studies were searched in PubMed, Embase, Google Scholar, Scopus, Web of Sciences, and CINAHL. The keywords used were "novel coronavirus", "SARS-CoV", "COVID-19", "lung function test", "LFT", "respiratory function test", "FEV1", "FVC", and other related terms. These terms were optimized for each database.

The eligibility criteria were case reports, case series, cross-sectional, cohort, randomized controlled trials (RCTs), and letters to the editor, which reported lung function test data obtained from the recovered COVID-19 patients. Articles without pulmonary function examination or COVID-19 patients were excluded. Only articles written in English and published from January 1, 2019 to June 26, 2020 were retrieved for this review. The searching was conducted on June 26, 2020, and the screening was conducted in July.

Study selection and data extraction

Two reviewers (RMS and YNP) independently screened the retrieved articles. The study quality was assessed by YNP using tools developed by Joanna Briggs Institute for case series[9] and RCT study.[10] Disagreements were resolved by discussion until consensus was reached. The main study outcomes were the means of several lung function test parameters including forced expiratory volume in 1 second (FEV1)% predicted and FVC% predicted. The secondary outcomes included the means of other lung function test parameters such as FEV1/FVC, TLC% predicted, maximal mid-expiratory flow (MMEF)% predicted, and DLCO% predicted. The severity of COVID-19 was also recorded, and meta-analysis was performed if more than one study provided usable data. Due to limited data availability for conducting a meta-analysis, we simplified the WHO's four degrees of COVID-19 severity[11] into two groups: the mild and moderate COVID-19 into the non-severe group, while the severe and critical COVID-19 into the severe group.

Data analysis

Meta-analysis was performed using the open-source meta statistical package in R (R project, New Zealand) and presented in the random effects model according to the previous studies.[12,13] We used the metamean statistical function to calculate the pooled mean from studies that reported a single mean. Metacont statistical function was used to generate the pooled mean difference between patients with a history of non-severe and severe COVID-19. The heterogeneity of the included studies was assessed using I^2 and Q statistics. Subgroup analysis was conducted when necessary. Fisher exact test was used to compare the difference in proportion, and an independent *t*-test was used in the mean comparison between the two groups. All the statistical analyses were performed in the 95% confidence interval (CI) with a *p*-value of <0.05 was considered significant.

RESULTS

Study selection and characteristics

Of 607 articles identified, 175 were removed due to duplication, and 394 were removed due to irrelevant title and abstract screening. The remaining 38 articles were proceeded to full-text assessment, resulting in seven eligible articles. The article selection process is presented in Figure 1.

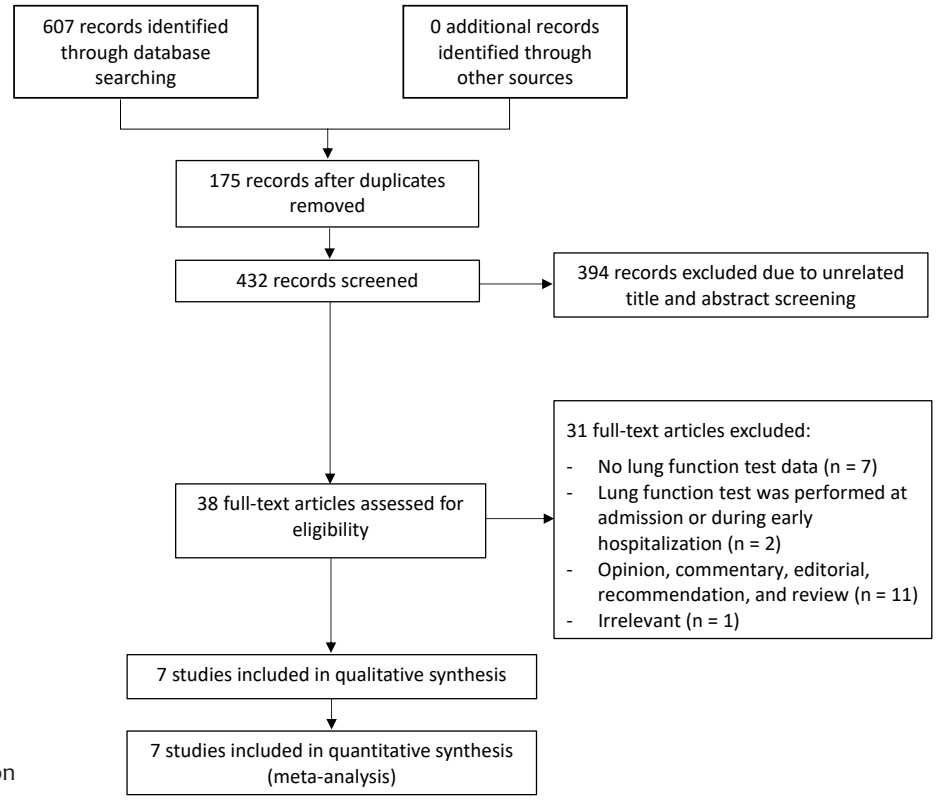


Figure 1. The eligible article selection process

The seven eligible studies from China consisted of four research letters, two case series, and one RCT (Table 1). One study involved only elderly subjects,[14] whereas the other six involved subjects with a wide range of age groups.[15–20] Six studies reported the clinical status of subjects during hospitalization. Lung imaging results were available in four studies with lung abnormalities appearing in most subjects.[14,15,19,20] Reports of comorbidities and smoking history were widely varied across studies; however, hypertension was the most common comorbidity found in the subjects.

The lung function test (LFT) parameters and the timing of LFT measurements were varied across all studies. However, most studies reported FVC% predicted, FEV1% predicted, FEV1/FVC, and MMEF% predicted (Table 1). Those studies reported restrictive lung disorders, diffusion lung problems, and small airway dysfunction as the main outcomes of recovered COVID-19 patients. The TLC% predicted and DLCO% predicted were reported in two and three studies, respectively. Two studies reported the lung function test data of individual subject,[15,20] and six studies reported the average mean values.[14–19] The timing of spirometry/LFT test were varied across studies, ranging from a day before discharge to more than a month after discharge.

The quality assessment showed a similar quality across the included studies (Table 2). Most studies used clearly defined subjects' inclusion and exclusion criteria and categorized the subjects based on the severity of COVID-19 history. Most studies recruited the subjects consecutively with unclear completeness of subject inclusion that might raise selection bias. The study outcomes (lung function parameters) were measured using standardized protocols. However, the variability of COVID-19 treatment during hospitalization was also not systematically reported, which might significantly influence the lung function outcomes.

Lung function test

Meta-analysis was performed on the reported mean values of the six LFT parameters (TLC, FVC% predicted, FEV1% predicted, FEV1/FVC, MMEF% predicted, and DLCO% predicted). This showed that the subjects' mean value of TLC% predicted, FVC% predicted, FEV1% predicted, FEV1/FVC, and MMEF% predicted were within normal range, whereas DLCO was lower than normal (73.3, 95% CI: 51.5 to 95.09) (Figure 2).

Table 1. The characteristics of the included studies and average LFT results

First author, year	Country/ study type	Clinical status	Age (years)	N (male/ female)	Period of LFT examination	LFT						The proportion of abnormal LFT parameters		
						FVC% predicted, mean (SD)	TLC% predicted, mean (SD)	FEV1% predicted, mean (SD)	FEV1/FVC (%), mean (SD)	MMEF% predicted, mean (SD)	DLCO% predicted, mean (SD)	FVC% predicted, mean <80%	FEV1% predicted, mean <80%	DLCO% predicted, mean <80%
Li,[16] 2020	China/ letter	Severe	NR	NR	Within 14 days after discharge	91.5 (17.3)	NR	89.4 (15.7)	80.5 (7.0)	73.6 (29.8)	NR	NR	NR	NR
Lv,[17] 2020	China/ case series	Non-severe	46 (13)	55/55	14 days after discharge	NR	NR	NR	83.1 (7.3)	NR	NR	16.40%	NR	NR
		Severe	52 (12)	16/11		NR	NR	NR	81.4 (7.9)	NR	NR	55.60%	NR	NR
Zha,[20] 2021	China/ letter	Severe	20	0/1	15 days after discharge	103.7	NR	NR	84.64	NR	NR	0%	0%	0%
		Severe	68	1/0	30 days after discharge	62.3	NR	NR	80.1	NR	NR	100%	0	100%
Mo,[18] 2020	China/ letter	Mild	46.8 (15.6)	11/13	20 (6) days from onset	94.06 (10.48)	87.13 (10.43)	94.26 (11.00)	81.84 (5.48)	99.77 (28.17)	87.13 (10.43)	7.46%	16.67%	30.43%
		Moderate	47.9 (13.7)	31/36	29 (8) days from onset	94.12 (12.31)	88.11 (10.72)	92.59 (11.87)	80.39 (6.12)	96.59 (26.51)	88.11 (10.72)	7.46%	13.43%	42.42%
		Severe	56.5 (11.0)	13/6	34 (7) days from onset	91.12 (14.30)	79.16 (12.13)	91.12 (11.58)	80.19 (5.15)	96.14 (23.82)	79.16 (12.13)	10.53%	10.53%	84.21%
Huang,[15] 2020	China/ case series	Non-severe	43.5 (13.9)	NR	30 days after discharge	103 (13.83)	96.22 (10.35)	99.57 (13.92)	81.49 (6.62)	NR	80.12 (10.56)	5.00%	5.00%	42.50%
		Severe	50.68 (15.9)	NR		95.92 (19.59)	88.72 (16.20)	93.93 (16.79)	80.58 (4.88)	NR	74.14 (18.85)	23.50%	17.60%	76.50%
You,[19] 2020	China/ letter	Non-severe	NR	7/5	40 (11.6) days	108.4 (22.5)	NR	102.3 (19.7)	75.8 (8.3)	73.2 (32.4)	NR	8.30%	8.30%	NR
		Severe	NR	3/3	34.7 (16.5) days	98.6 (25.6)	NR	98.6 (20.6)	82.0 (6.1)	94.3 (34.8)	NR	33.30%	33.30%	NR
Liu,[14] 2020	China/ RCT, open label	NR	68.9 (7.6)	25/11	6–10 weeks from onset	NR	NR	NR	61.23 (6.43)	NR	63.0 (13.4)	NR	NR	NR

DLCO=diffusing capacity of the lung for carbon monoxide; FEV1=forced expiratory volume 1; FVC=forced vital capacity; LFT=lung function test; MMEF=maximal mid-expiratory flow; NR=not recorded; SD=standard deviation; TLC=total lung capacity

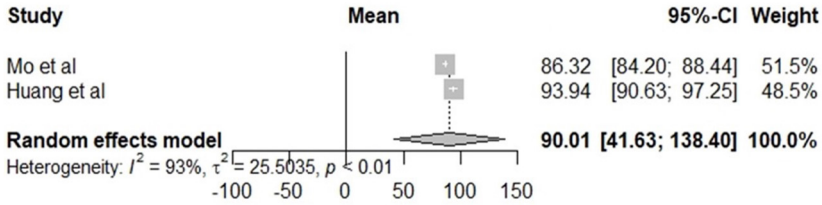
Table 2. Study quality assessment

Case series							
No	Questions	Li,[16] 2020 (research letter)	Lv,[17] 2020 (case series)	Mo,[18] 2020 (research letter)	Huang,[15] 2020 (case series)	You,[19] 2020 (research letter)	Zha,[20] 2021 (research letter)
1.	Were there clear criteria for inclusion in the case series?	×	✓	✓	✓	✓	×
2.	Was the condition measured in a standard, reliable way for all participants included in the case series?	✓	✓	✓	✓	✓	✓
3.	Were valid methods used for identification of the condition for all participants included in the case series?	✓	✓	✓	✓	✓	✓
4.	Did the case series have consecutive inclusion of the participants?	×	✓	✓	✓	✓	×
5.	Did the case series have complete inclusion of the participants?	?	?	?	×	?	×
6.	Was there clear reporting of the demographics of the participants in the study?	×	✓	✓	✓	✓	✓
7.	Was there clear reporting of clinical information of the participants?	×	✓	✓	✓	✓	✓
8.	Were the outcomes or follow-up results of cases clearly reported?	?	?	?	?	?	×
9.	Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	×	×	×	×	✓	×
10.	Was statistical analysis appropriate?	✓	✓	✓	✓	✓	N/A

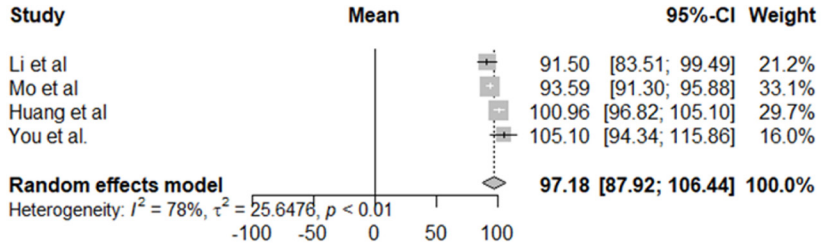
Randomized controlled trial		
No	Questions	Liu,[14] 2020
1.	Was true randomization used for assignment of participants to treatment groups?	✓
2.	Was allocation to treatment groups concealed?	×
3.	Were treatment groups similar at the baseline?	✓
4.	Were participants blind to treatment assignment?	×
5.	Were those delivering treatment blind to treatment assignment?	×
6.	Were outcomes assessors blind to treatment assignment?	?
7.	Were treatment groups treated identically other than the intervention of interest?	?
8.	Was follow-up complete and if not, were differences between groups in terms of their follow-up adequately described and analyzed?	✓
9.	Were participants analyzed in the groups to which they were randomized?	✓
10.	Were outcomes measured in the same way for treatment groups?	✓
11.	Were outcomes measured in a reliable way?	✓
12.	Was appropriate statistical analysis used?	✓
13.	Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?	✓

RCT=randomized controlled trial

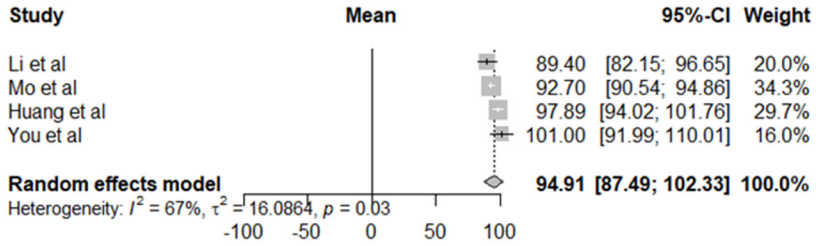
a. TLC% predicted



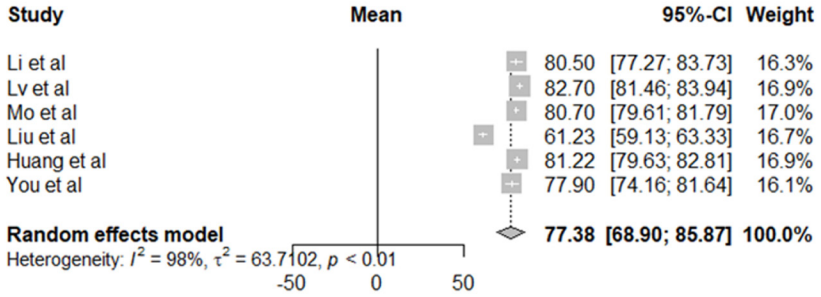
b. FVC% predicted



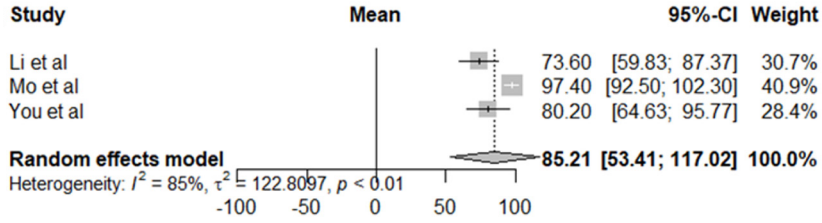
c. FEV1% predicted



d. FEV1/FVC



e. MMEF% predicted



f. DLCO% predicted

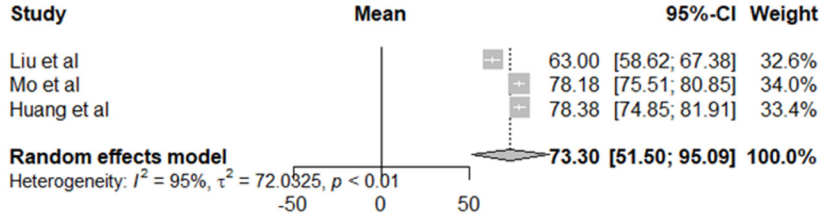
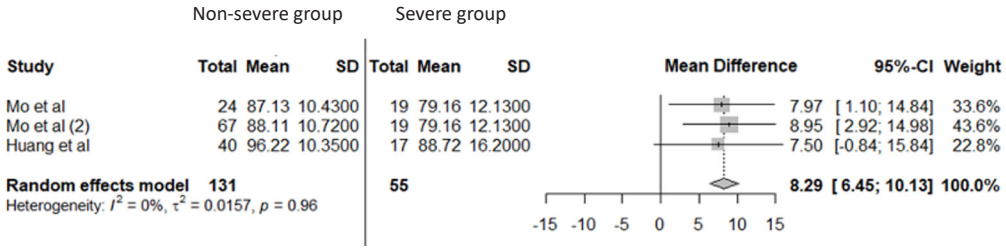
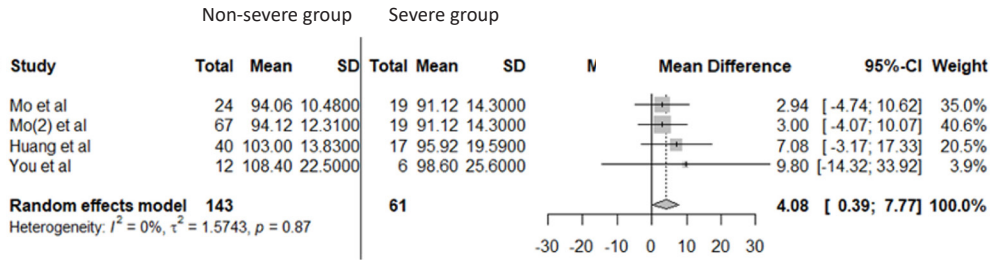


Figure 2. Forest plots of the pooled mean values of all cases in all subjects with a history of COVID-19. COVID-19=coronavirus disease 2019; DLCO=diffusing capacity of the lungs for carbon monoxide; FEV1=forced expiratory volume in 1 second; FVC=forced vital capacity; MMEF=maximal mid-expiratory flow; TLC=total lung capacity

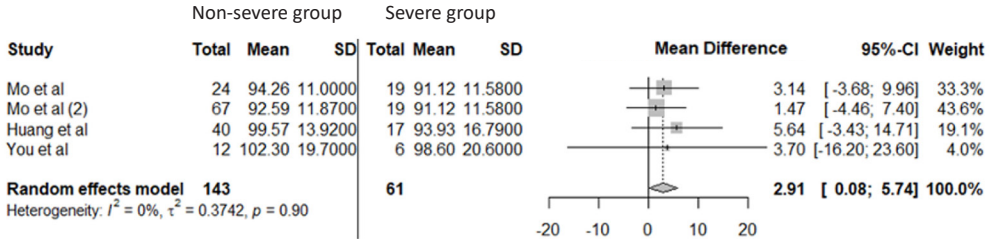
a. TLC% predicted



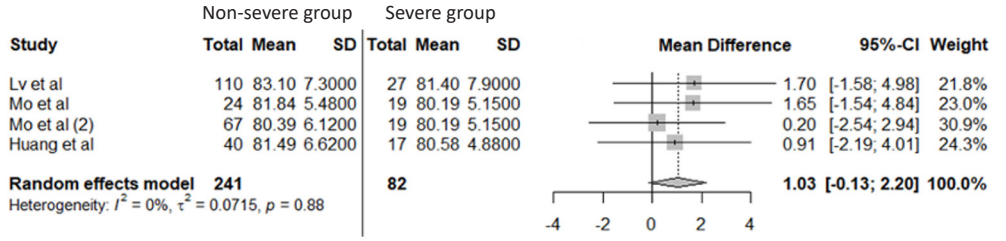
b. FVC% predicted



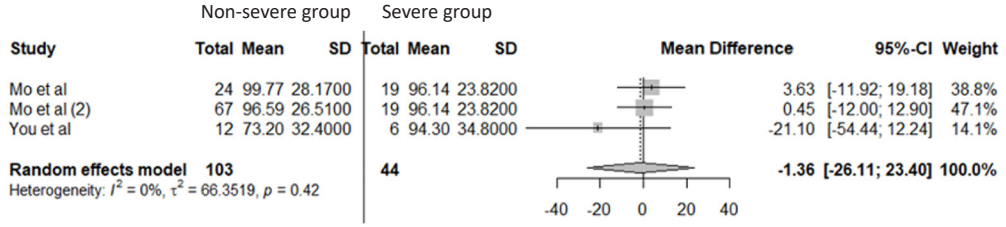
c. FEV1% predicted



d. FEV1/FVC



e. MMEF % predicted



f. DLCO% predicted

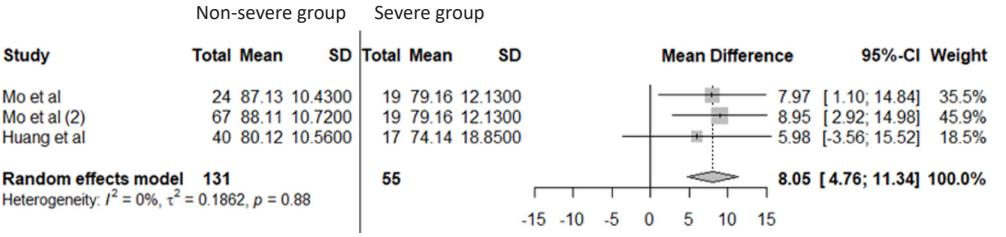


Figure 3. Forest plots of the pooled mean values between non-severe group (left) and severe group (right). DLCO=diffusing capacity of the lungs for carbon monoxide; FEV1=forced expiratory volume in 1 second; FVC=forced vital capacity; MMEF=maximal mid-expiratory flow; TLC=total lung capacity

Lung function test in severe *versus* non-severe COVID-19 cases

We divided the clinical status into non-severe and severe groups, with non-severe groups consisting of mild and moderate COVID-19 cases. The results showed that the mean of each LFT parameter was within normal limits except for the DLCO% predicted in the severe group (77.56, 95% CI: 47.83–107.29), suggesting that the severe COVID-19 caused lung diffusion problem (Figure 3).

The severe group tended to have a lower mean value of the six LFT parameters, suggesting lung function reduction. Therefore, we performed a meta-analysis on each LFT parameter to compare the mean between the non-severe and severe cases using a mean difference as the point estimate. Only studies that reported the mean values of each LFT parameter in both non-severe and severe groups were included in the meta-analysis. The TLC% predicted, FVC% predicted, FEV1% predicted, and DLCO% predicted in severe cases were significantly lower than in the non-severe group, indicating that history of severe COVID-19 caused more reduced pulmonary function. The FEV1/FVC and MMEF% predicted were not statistically different between the two groups (Figure 3).

Individual subject data analysis

Two studies provided 59 individual subject data and performed a descriptive statistical analysis. Out of 59 subjects, 19 of them had a history of severe COVID-19. Subjects in the severe group had a similar mean of age to the non-severe group (43.5 years old and 50.68 years old, respectively; $p>0.05$). The proportions of subjects with low FVC, low FEV1%, or low DLCO were not statistically different between the two groups. Interestingly, more than 50% of subjects in both groups had DLCO <80%. However, the proportion of subjects in the severe group with TLC <80% was significantly higher than in the non-severe group (29.4% *versus* 5%, respectively; $p<0.05$).

DISCUSSION

In this systematic review and meta-analysis, we collected and analyzed the lung function examination results from patients with a history of COVID-19. The lung function evaluation included FVC% predicted, TLC% predicted, FEV1 predicted, FEV1/FVC, MMEF% predicted, and DLCO% (Figure 3). TLC is the maximal amount of air volume in the lungs after maximal inspiration. A decrease in TLC is often accompanied by a decrease in FVC, suggesting a restrictive lung disorder.[21] In contrast, FEV1%, FEV1/FVC, and MMEF% indicate the presence or absence of airway obstruction. FEV1 indicates the amount of air that can be exhaled quickly and maximally in the first 1 sec. A decrease to <70% in FVE1% and/or FEV1/FVC indicates airway obstruction.[22] Airway obstruction is also indicated by a decrease of MMEF% to <80%. MMEF indicates the airflow velocity in the middle of forced expiration; thus, MMEF% indicates the presence or absence of obstruction in the airways, especially the small airways.[22]

The mean values of TLC, FVC%, FEV%, FEV1/FVC, and MMEF% were normal in post-COVID-19 patients, indicating the absence of restrictive, obstructive, or mixed disorders. However, some studies reported that some recovered COVID-19 patients had restrictive, obstructive, or mixed lung disorders,[16–18] and the proportion of restrictive cases was higher in patients with a history of severe COVID-19.[17,18] This difference may be due to the small number of subjects and the very large variation in the measurement results, resulting in normal pulmonary function examination results although some patients had lung function below the normal values. In addition, the individual subject data analysis found that the proportion of subjects with low TLC was significantly higher in subjects with severe COVID-19 history. This indicates that the development of restrictive lung disorders is related to the severity of COVID-19.

Restrictive disorders in COVID-19 patients are relevant to the natural course of COVID-19 where the SARS-CoV-2 target and ACE2 receptor-expressing cells are more abundant in the epithelial type I and II, compared with the airway epithelium.[3] The viral infection and replication could cause the destruction of type I and II pneumocytes.[23] Post-inflammation remodeling and abnormal regeneration of those damaged parenchyma may lead to fibrotic changes of the lung,[24] resulting in a fibrotic lung appearance shown in pulmonary computed tomography (CT) scans of the discharged COVID-19 patients.[14,19] A recent study showed that more than 70% of recovered COVID-19 patients showed lung CT scans abnormalities. The most common abnormalities observed within a 3-month recovery were ground-

glass opacity (7.27%), crazy paving (5.45%), and interstitial thickening (27.27%).[6] This interstitial thickening is the characteristic of lung fibrosis that will cause decreased lung compliance and clinically manifests into restrictive lung disorders.

Restrictive lung conditions could also be related to decreased surfactant production. Surfactant is important in lowering the surface tension of the alveolus, hence maintaining lung compliance.[25] Since the high expression of ACE2 receptors found in type II pneumocyte, a type of cell that plays a major role in surfactant production, the viral infection and replication in these cells may result in decreased surfactant production. Hence, a low level of surfactant causes alveoli to collapse, resulting in a low lung compliance. Although studies of surfactant in COVID-19 patients are very limited, administering surfactant to COVID-19 patients as an alternative COVID-19 treatment has already been proposed.[26]

Our study found that the pooled mean of all cases of DLCO% predicted was lower than 80%. In addition, individual subject data analysis showed that more than 50% of subjects recovered from COVID-19 had DLCO% predicted less than 80%. Moreover, the DLCO% predicted in the subjects with a history of severe COVID-19 was significantly lower than subjects with a history of non-severe COVID-19. These findings indicate that COVID-19, especially the severe cases, could potentially cause long-term lung diffusion disturbance. In line with our findings, a recent study showed that low DLCO% predicted is the most common lung function finding in patients recovered from COVID-19.[6]

Gas diffusion or transfer process from the alveoli to capillaries can occur with adequate pressure gradient between the alveoli and capillaries. Accordingly, a sufficient gas exchange area occurs with adequate perfusion in the pulmonary capillaries and without thickening of the respiratory membrane.[27] Fibrosis that occurs in COVID-19 causes not only pulmonary restrictions but also disruption of gas diffusion due to thickening of the respiratory membrane. Additionally, histological examination of the lungs of patients who had died from COVID-19 showed diffuse alveolar damage, thickening of the alveolar wall, pulmonary edema, and hyaline membrane formation in the lungs.[28] Alveolar damage can decrease the area of gas diffusion, while thickening of the alveolar wall, pulmonary edema, and hyaline membrane formation can increase the thickness of the respiratory membrane. These two conditions lead to the reduction in the rate of diffusion of oxygen into the capillaries. A significant fraction of cardiac output perfuses non-aerated lung tissue, causing pulmonary shunt formation which leads to hypoxemia. Numerous blockages in the pulmonary capillaries were also found in some COVID-19 patients,[29] causing a dead space in the alveoli. These conditions may eventually lead to an inefficient gas diffusion between alveolar space and bloodstreams, indicated by the low DLCO% predicted. Interestingly, recovered COVID-19 patients that are likely to suffer from hypoxemia might not experience dyspnea.[30] Therefore, clinical monitoring on DLCO% predicted or oxygen saturation is important, especially in high-risk patients such as the elderly and patients with severe comorbidities.

Longitudinal examinations were conducted by Li et al[16] and Liu et al[14]. Initially, Li et al[16] measured lung function within 2 weeks after the discharge and about 12 days after the first measurement. In the follow-up, spontaneous improvement of lung function was reported in patients with a history of severe COVID-19. However, Liu et al,[14] who explored elderly patients with COVID-19, found no spontaneous improvement between the first day of hospitalization and 6 weeks after the first examination. The improvement only occurs after the rehabilitative measures. This discrepancy may be caused by the difference in the subject characteristics and treatments given during hospitalization. Nonetheless, both studies showed that lung function improvement could occur in post-COVID-19 patients.

Prospective studies on MERS or SARS patients showed impaired pulmonary function in some patients with a history of severe diseases.[7] Recovered SARS patients showed persistent DLCO impairment.[31] Improvement of FVC and DLCO% predicted within 6 months after the infection was found only in recovered SARS patients with normal pulmonary CT scan. However, no significant improvement of the 32 pulmonary lesions was found between 1 and 15 years,[32] suggesting that the reduced lung function, particularly diffusion problem, was less reversible, especially in severe cases. In MERS cases, the presence of lung fibrosis was reported, and the improvement of pulmonary lesion occured 1 year after infection.[33] Since the causative agent of COVID-19 belongs to the same virus family that causes SARS and MERS, COVID-19

could potentially have similar long-term impacts on the pulmonary functions to the SARS and MERS.

This systematic review and meta-analysis has several weaknesses. The main weakness is the small number of samples included in the selected studies, which may lead to the high variability of baseline characteristics of the study subjects, especially the patient's lung function before getting COVID-19. The difference in the patient's lung function before getting COVID-19, the timing of pulmonary function examinations, and the various treatment received by the subjects during hospitalization may influence the lung function outcome. The limited data also restrict the subgroup analysis. However, this study has provided important information on the pulmonary function following COVID-19 based on the best available studies selected from multiple databases.

In conclusion, COVID-19 could potentially cause long-term deterioration of lung function. Diffusion and restrictive lung impairments could be the main lung abnormalities caused by COVID-19. Since the risk of hypoxemia due to impaired diffusion can still be found in patients who have been discharged from the hospital, it is very important to encourage patients to monitor oxygen saturation on a daily basis. Although obtained from limited data, lung function of the COVID-19 survivors can be improved. Rehabilitative measures could be a potential measure to achieve optimal recovery of lung function. Therefore, research on effective rehabilitation therapy to improve lung function in post-COVID-19 patients is needed. Additionally, a prospective longitudinal study involving a larger sample size is needed to evaluate the long-term impact of COVID-19 on lung function.

Conflict of Interest

The authors affirm no conflict of interest in this study.

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