Impaired Diffusion Capacity and Pulmonary Fibrosis after Recovery from COVID-19: A Systematic Review and Meta-Analysis

Jong Hyuk Lee

Seoul National University Hospital

Jae-Joon Yim

Seoul National University College of Medicine

Jimyung Park (✉ drjimyung@gmail.com)

Seoul National University Hospital <https://orcid.org/0000-0003-2655-5517>

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Abstract

Background: The medium- to long-term pulmonary consequences of coronavirus disease 2019 (COVID-19) after recovery from acute infection remain unclear. Several studies have examined this issue and reported heterogeneous results.

Methods: We conducted a systematic review and meta-analysis using a random-effects model to estimate the pooled prevalence of pulmonary sequelae after COVID-19, namely impaired diffusion capacity and pulmonary fibrosis, at least 1 month after the initial infection. PubMed, Embase, and Cochrane Library were searched from January 1, 2020, to February 15, 2021 to identify related studies. We also assessed whether the initial severity of infection was associated with impaired diffusion capacity in the recovery phase.

Results: Of the 8159 studies identified, 29 met our eligibility criteria. Among these studies, 25 and 20 had data on follow-up pulmonary function testing and chest computed tomography (CT), respectively. Impaired diffusion capacity (<80% of predicted values or lower limit of normal) was the most common pulmonary abnormality (pooled prevalence 34%, 95% CI 27%–41%). When classified according to the severity of index infection, patients with severe COVID-19 were more likely to display impaired diffusion capacity than those with non-severe COVID-19 (pooled odds ratio 2.97, 95% CI 2.10–4.20). On follow-up chest CT, pulmonary fibrosis was found in 26% (95% CI 17%–36%) of the patients.

Conclusions: A substantial number of patients recovering from COVID-19 displayed impaired diffusion capacity and pulmonary fibrosis. The severity of index COVID-19 was associated with impaired diffusion capacity, highlighting the importance of respiratory follow-up in patients recovering from severe COVID-19.

Systematic review registration number: PROSPERO CRD42021234357

Background

Since its first detection in Wuhan, China in December 2019, coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome (SARS) coronavirus 2 (SARS-CoV-2), has become a major health threat to the global population (1). The pandemic is still ongoing, and as of April 2021, more than 150 million people have been diagnosed with COVID-19 worldwide, resulting in more than 3 million deaths (2). Although the case fatality rate varies between countries according to several factors, the rate is believed to be lower than that of the initial phase of the pandemic (3). However, some COVID-19 survivors experience prolonged and various symptoms, a condition termed “long COVID” or “post COVID-19 syndrome” (4).

The most representative symptom of long COVID is dyspnea, which may be attributed to the direct consequence of lung damage by the virus. Furthermore, pulmonary fibrosis can develop as a sequela among the survivors of COVID-19 (5). Long-term sequelae after viral pneumonia have been documented among patients infected by other strains of the coronavirus family, including SARS-CoV-1 (SARS) and Middle East respiratory syndrome coronavirus (MERS) (6-8). Majority of survivors of H1N1 influenza-related acute respiratory distress syndrome (ARDS) also displayed impaired diffusion capacity (9).

Given the increasing and huge number of individuals affected by COVID-19, information about the actual prevalence and risk factors of pulmonary sequelae after initial recovery is needed for further follow-up planning. Several studies examined this issue, and in these studies, regular follow-up with pulmonary function testing (PFT)

and chest computed tomography (CT) was performed in patients recovering from acute infection (10-14). Among several pulmonary function parameters, impairment of diffusion capacity was reported to be the most common abnormality after recovery from acute infection (15). However, the actual prevalence of such clinically significant pulmonary sequelae of COVID-19 remains speculative because of the highly heterogeneous results between different studies. Therefore, we conducted a systematic review and meta-analysis to pool available data from studies and estimate the prevalence of lung function impairment and fibrotic changes on chest CT in the medium-term of period after COVID-19.

Methods

Study protocol and outcome

This study was conducted in accordance with the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines, and the MOOSE checklist was used to standardize the reporting form (16). The primary outcome of this study was the prevalence of medium-term sequelae after COVID-19, mainly focusing on lung function (particularly diffusion capacity) and chest CT findings. First, we estimated the rates of impaired diffusion capacity and pulmonary fibrosis evident on follow-up PFT and chest CT after recovery from COVID-19. Second, we examined potential factors that could be associated with the impairment of diffusion capacity. The study protocol was registered with PROSPERO (CRD42021234357).

Eligibility criteria

Studies that met the following inclusion criteria were considered eligible for this systematic review and meta-analysis: 1) inclusion of patients who recovered from COVID-19 and underwent follow-up for at least 1 month after the index infection, and 2) inclusion of the results of objective assessments of pulmonary function (PFT and/or chest CT). Index infection was defined as an infection by SARS-CoV-2 as confirmed using real-time RT-PCR. Given the limited available data on this issue, both prospective and retrospective studies were considered eligible for this study. Case reports or small case series were excluded, and studies including only patients with critical COVID-19 were also excluded to minimize selection bias.

Information source and search strategy

Two experienced investigators (JHL and JP) performed the systematic literature search using the database of PubMed, EMBASE, and Cochrane Library. Studies published between January 1, 2020 and February 15, 2021 were identified. We also manually checked the reference lists of the relevant articles. Unpublished studies including preprinted forms that were not peer-reviewed were excluded. There were no language restrictions. The details of the search strategy are described in Appendix 1.

Study selection

The process of study selection was performed according to the Preferred Reporting Items of Systematic reviews and Meta-Analyses (PRISMA) flowchart (17). After removing duplicates, two investigators (JHL and JP) independently reviewed the titles and abstracts of the identified studies to decide whether they should be included for further full-text review. After full-text review, the studies that met our full eligibility criteria were finally selected. Any disagreement regarding study selection was resolved by discussion with a third author (JJY).

Data extraction and data items

Data on the prespecified variables were extracted from the selected studies. The extracted data included study design, study region, study period, follow-up interval after index infection, inclusion criteria of the study, demographics of the study patients, sample size, data on the index infection including COVID-19 severity, details of the patient assessment tools used (PFT and/or chest CT) during follow-up, and the results of patient assessments. Study authors were contacted to obtain additional information if needed.

Disease severity was determined according to the current global guideline with slight modification for the purpose of our study (18). Because the included studies did not employ universal disease severity criteria and some studies did not clearly present data on disease severity using predefined criteria, we regarded patients who needed supplemental oxygen therapy as having severe COVID-19. Patients who required intensive care unit admission and/or mechanical ventilation were regarded as having critical COVID-19.

Regarding PFT data, we first extracted the percent predicted diffusion capacity for carbon monoxide (DLCO). Then, we obtained data on the prevalence of impairment of diffusion capacity using the cutoff of 80% of the predicted values or the lower limit of normal (LLN), as presented in the searched studies. Data on other pulmonary function parameters including forced expiratory volume in 1 second (FEV₁) and forced vital capacity (FVC) were also reviewed.

For the searched studies with follow-up chest CT data, we estimated the prevalence of pulmonary fibrosis as a sequela of COVID-19. Although most studies clearly presented the number of patients who developed pulmonary fibrosis, some studies only reported the prevalence of various individual CT findings (e.g., ground-glass opacity [GGO], reticulation, traction bronchiectasis, interstitial thickening, parenchymal band, or consolidation). For studies in which pulmonary fibrosis was not clearly defined, one author (JHL, 9 years of experience in thoracic radiology) adjudicated the presence of pulmonary fibrosis based on the nomenclature and definition of the Fleischner Society (19). CT findings such as reticular opacity, architectural distortion, traction bronchiectasis, and honeycombing were considered indicative of pulmonary fibrosis. By contrast, GGO and consolidation were considered unrelated to pulmonary fibrosis. In addition to pulmonary fibrosis, we estimated the prevalence of persistent GGO given that GGO is the most common finding in the acute phase (20). The proportion of patients without any residual abnormal findings (complete radiologic resolution) on follow-up CT was also reviewed.

Risk of bias assessment

We assessed the risk of bias of the included studies using a tool developed and validated for prevalence studies (21). The detailed items of questions included in this tool are described in Appendix 2. Briefly, four and six items were used to evaluate external and internal validity, respectively. Because the studies of interest were those reporting the results of objective and direct assessments of the patients (PFT and/or chest CT), the overall risk of bias was mostly determined according to the external validity of individual studies rather than internal validity. In particular, we assessed whether the included study patients could represent the entire target population of patients with COVID-19 in the real world. For example, studies in which only a small and selected subgroup of patients underwent PFT and/or chest CT were regarded as having a high risk of bias in terms of external validity.

Statistical analysis

Considering the heterogeneity between the included studies such as that related to the severity of index infection, the DerSimonian and Laird random-effects model was used for our meta-analysis (22). First, the results of PFT (DLCO, FEV₁, and FVC) were pooled using the “metan” command (23). For studies providing summary statistics as the median and interquartile range (IQR), opposed to the mean and standard deviation (SD), the mean and SD were estimated (24). Then, our primary study outcome, namely the pooled prevalence (and 95% confidence interval [CI]) of impaired diffusion capacity (less than 80% of predicted values or LLN), was calculated using the “metaprop” command (25). A similar approach was used to calculate the pooled prevalence of impairment of other pulmonary function parameters (FEV₁ and FVC). The pooled prevalence of chest CT abnormalities (pulmonary fibrosis and persistent GGO) was also analyzed.

To identify potential factors associated with the development of impaired diffusion capacity, meta-regression was performed using candidate variables including age, smoking history, the severity of index infection, the follow-up interval after the index infection, and sample size, using the “metareg” command (26). Furthermore, for included studies that reported the prevalence of impaired diffusion capacity according to the disease severity (severe vs. non-severe or critical vs. non-critical), odds ratios (ORs) were calculated by estimating the risk of development of lung function sequelae according to initial disease severity, and these data were then used to calculate the pooled OR. For all meta-analyses, the heterogeneity among the studies was statistically investigated using the Q-test and I^2 index. We visually inspected funnel plots and employed Egger’s regression to assess possible publication bias (27). All statistical analyses were performed with STATA software version 14.0 (StataCorp LP, College Station, TX, USA).

Results

Search findings and study characteristics

In total, 8159 studies were identified through the literature search after removing duplicates. Among them, the full texts of 185 studies were reviewed, and 29 studies were finally included in our meta-analysis (Figure 1) (12, 14, 28-54). The details of the included studies are described in Tables 1 and E1. The studies were mainly conducted in Europe (19, 65.5%) and Asia (9, 31.0%), and 18 studies (62.1%) were prospective. Among the 29 studies, 25 (86.2%) had follow-up PFT data (12, 14, 28-30, 32-39, 41-47, 49-52, 54), and 20 (69.0%) had follow-up chest CT data (12, 14, 29, 32, 34-41, 45-50, 53, 54). However, more than 80% of study patients underwent follow-up chest CT in only 13 studies (Table 1). The eligibility criteria varied between the studies, but most studies included patients with confirmed COVID-19 who were successfully treated and discharged from the study hospitals.

Table 1
Patient characteristics of the included studies

Study	Total patients included (n)	Patients with PFT (n, %)	Patients with chest CT (n, %)	Mean age (year)	Male sex	Ever smoker	Chronic respiratory disease	Severe COVID-19	Critical COVID-19
Anastasio et al.	379	379 (100%)	0	56	46%	34%	8%	36%	9%
Arnold et al.	110	110 (100%)	9 (8%)	60	61%	N.A.	25%	75%	16%
Bellan et al.	238	238 (100%)	0	61	60%	42%	6%	72%	12%
Daher et al.	33	33 (100%)	0	64	67%	N.A.	22%	82%	0%
D'Cruz et al.	119	0	56 (47%)	59	62%	25%	11%	100%	34%
de Graaf et al.	81	81 (100%)	0	61	63%	11%	21%	N.A.	42%
Guler et al.	113	113 (100%)	52 (46%)	57	59%	48%	8%	58%	35%
Han et al.	114	114 (100%)	114 (100%)	54	70%	14%	14%	100%	27%
Huang C et al.	1733	349 (20%)	353 (20%)	56	52%	8%	2%	75%	25%
Huang Y et al.	57	57 (100%)	57 (100%)	47	46%	16%	0%	30%	N.A.
Lerum et al.	103	103 (100%)	100 (97%)	60	52%	35%	N.A.	66%	15%
Liang et al.	76	76 (100%)	61 (80%)	41	28%	0%	14%	9%	9%
Liu et al.	51	0	51 (100%)	47	41%	6%	N.A.	0%	0%
Marvisi et al.	90	90 (100%)	90 (100%)	66	66%	47%	10%	90%	N.A.
Méndez et al.	215	215 (100%)	0	56	61%	30%	13%	52%	19%
Moreno-Pérez et al.	277	269 (97%)	0	55	53%	N.A.	18%	66%	9%
Qin et al.	647	81 (13%)	45 (7%)	59	42%	N.A.	7%	49%	30%

COVID-19, coronavirus disease 2019; CT, computed tomography; PFT, pulmonary function test

Study	Total patients included (n)	Patients with PFT (n, %)	Patients with chest CT (n, %)	Mean age (year)	Male sex	Ever smoker	Chronic respiratory disease	Severe COVID-19	Critical COVID-19
Raman et al.	58	54 (93%)	0	55	59%	35%	40%	55%	36%
Rogliani et al.	27	27 (100%)	27 (100%)	61	74%	N.A.	N.A.	48%	11%
Shah et al.	60	57 (95%)	60 (100%)	65	68%	38%	13%	77%	20%
Smet et al.	220	220 (100%)	220 (100%)	53	62%	22%	N.A.	100%	19%
Sonnweber et al.	145	133 (92%)	133 (92%)	57	57%	39%	19%	50%	22%
Tabatabaei et al.	52	0	52 (100%)	50	62%	15%	4%	N.A.	21%
Trinkmann et al.	246	246 (100%)	17 (7%)	48	44%	N.A.	10%	9%	1%
van den Borst et al.	124	124 (100%)	84 (68%)	59	60%	61%	19%	37%	16%
van der Sar et al.	101	101 (100%)	0	66	57%	55%	35%	72%	0%
Venturelli et al.	767	716 (93%)	0	63	67%	28%	5%	79%	9%
Yang et al.	166	0	166 (100%)	57	42%	N.A.	N.A.	77%	8%
Zhao et al.	55	55 (100%)	55 (100%)	48	58%	7%	N.A.	7%	0%
COVID-19, coronavirus disease 2019; CT, computed tomography; PFT, pulmonary function test									

Study population

In total, 6457 patients (mean age, 57 ± 6 years) were included, and 56.5% of the patients were men. Smoking history data were presented in 22 studies, and approximately $28 \pm 17\%$ of the patients were ever-smokers. The severity of index COVID-19 was also highly various. The proportions of patients with severe and critical COVID-19 were $58 \pm 29\%$ and $16 \pm 12\%$, respectively. The median follow-up interval after the index infection was approximately 3 months (range 1–6 months, Table S1).

Deterioration of lung function on follow-up PFT

The most common abnormal finding on follow-up PFT was impaired diffusion capacity. The mean percent predicted DLCO was estimated as 81.4% (95% CI 73.3–89.5%), and the pooled estimate of the prevalence of impaired diffusion capacity was 34% (95% CI 27–41%) with considerable statistical heterogeneity ($I^2 = 94.9\%$, $P <$

0.01, Figure 2). Impairment of FEV1 and FVC was less frequent, with pooled rates of 10% (95% CI 7–13%, Figure S1) and 11% (95% CI 8–14%, Figure S2), respectively. The funnel plots of DLCO, FEV1, and FVC analyses all exhibited significant asymmetry, suggesting possible publication bias (Figure S3A–S3C).

Several meta-regression analyses were performed to evaluate factors contributing to the between-study heterogeneity in the prevalence of impaired diffusion capacity (Figure 3). Older age was marginally associated with a higher prevalence of impaired diffusion capacity ($P = 0.065$, Figure 3A). Otherwise, we found no factors associated with the development of diffusion impairment (Figure 3B–3F). Subgroup analysis also failed to identify definitive factors explaining the heterogeneity between the studies (Table 2).

Table 2
Subgroup analysis to explore heterogeneity in the estimate of the pooled prevalence of impaired diffusion capacity

	Studies (k)	Patients (n)	Pooled prevalence (95% CI)	I^2 (%)	<i>P</i> value
Overall	17	3009	0.34 (0.27–0.41)	94.92	
Study Design					0.252
Prospective cohort	11	2002	0.36 (0.27–0.46)	95.46	
Not prospective cohort	6	1007	0.28 (0.19–0.38)	92.27	
Risk of bias of study					0.297
High	8	1561	0.27 (0.18–0.36)	94.20	
Intermediate	5	1119	0.38 (0.24–0.52)	94.97	
Low	4	329	0.42 (0.17–0.67)	96.19	
Median follow-up interval after initial presentation					0.277
≥ 3 months	11	2242	0.30 (0.23–0.38)	94.45	
< 3 months	6	767	0.40 (0.25–0.55)	95.59	
Mean age					0.112
≥ 60 years	6	1231	0.44 (0.26–0.62)	97.46	
< 60 years	11	1778	0.28 (0.22–0.35)	90.47	
Proportion of patients with severe COVID-19					0.729
≥ 50%	10	2156	0.34 (0.25–0.43)	95.51	
< 50%	6	772	0.31 (0.18–0.45)	94.03	
Proportion of patients with critical COVID-19					0.194
≥ 20%	6	790	0.38 (0.28–0.48)	88.47	
< 20%	10	2162	0.29 (0.20–0.38)	95.92	
COVID-19, coronavirus disease 2019					

Nine studies presented the prevalence of impaired diffusion capacity according to the severity of index COVID-19 (12, 28, 30, 36–38, 42, 50, 51). Using these studies, the pooled OR for impaired diffusion capacity according to disease severity (severe vs. non-severe or critical vs. non-critical) was estimated. Patients with severe COVID-19 were more likely to exhibit impaired diffusion capacity (pooled OR 2.97, 95% CI 2.10–4.20, Figure 4A). Similarly, patients with critical COVID-19 were more likely to display impaired diffusion capacity (pooled OR 3.79, 95% CI 2.61–5.50, Figure 4B). There was no significant between-study heterogeneity regarding the pooled ORs.

Radiologic sequelae on follow-up CT

Of the 20 studies reporting the results of follow-up chest CT, we were able to pool the prevalence of pulmonary fibrosis from 15 studies (12, 14, 29, 31, 35-39, 41, 48-50, 53, 54). Among these 15 studies, the prevalence of pulmonary fibrosis was clearly described in 12 studies according to the CT interpretation by the study authors (12, 29, 31, 35, 37-39, 41, 48, 50, 53, 54), whereas we estimated the prevalence based on the individual CT findings in the remaining studies as described above (14, 36, 49). The pooled prevalence of pulmonary fibrosis was 26% (95% CI 17–36%, Figure 5A). However, there was a considerable statistical heterogeneity ($I^2 = 95.5\%$, $P < 0.01$), and the funnel plot also displayed significant asymmetry (Figure S3D).

Rather than fibrotic changes, persistent GGO was more common on follow-up CT, with pooled prevalence of 39% (95% CI 27–51%, Figure 5B), and there was no evidence of publication bias on the funnel plot (Figure S3E). The proportion of patients with no residual abnormality on follow-up CT, which indicates complete radiologic resolution, was also estimated. Overall, 39% of the patients (95% CI 25–52%) displayed no residual chest CT abnormalities (Figure 5C). Although there was significant between-study heterogeneity ($I^2 = 95.6\%$, $P < 0.01$), the funnel plot did not display asymmetry (Figure S3F).

Risk of bias assessment

The assessment of risk of bias of the included studies is summarized in Table S2. Among the 29 included studies, 13, 9, and 7 studies were regarded as having low, moderate, and high risks of bias, respectively. However, the risk of bias of individual studies was not associated with the estimated prevalence of impaired diffusion capacity (Table 2).

Discussion

Given the enormous number of patients affected by COVID-19 during the pandemic, the long-term consequences of COVID-19 are attracting increasing attention. The persistence of symptoms and signs that continue or develop 4 weeks after acute COVID-19 is described as “long COVID” (4, 55). Dyspnea is the most representative respiratory symptom of long COVID, and it is usually accompanied by other non-specific constitutional symptoms such as fatigue (56-58). Although long COVID is mainly defined by subjective symptoms, it is also important to assess patients with more objective tools, such as PFT and chest imaging, to comprehend the clinical impact of long COVID more accurately.

In this context, several observational studies, which were included in this meta-analysis, evaluated survivors of COVID-19 via follow-up PFT and/or chest CT (12, 14, 28-54), but most of these studies were single-center studies with limited sample sizes and statistical power. Two meta-analysis studies with similar study designs have been published. These studies included 15 and 7 individual studies, respectively (59, 60). However, more results from several other studies have become available and we were able to identify a substantially larger number of studies (29 studies including approximately 6500 patients).

In this systematic review and meta-analysis, we estimated the medium-term respiratory effect of COVID-19 in patients who recovered from acute infection. Abnormal diffusion as indicated by impaired diffusion capacity was the most common sequela with a pooled prevalence of 34%, albeit with considerable between-study heterogeneity. Severe index COVID-19 was associated with a higher prevalence of impaired diffusion capacity.

The most common radiographic sequela on follow-up chest CT was persistent GGO (pooled prevalence of 39%), followed by fibrotic changes (pooled prevalence of 26%). These findings suggest that a subset of patients recovering from acute COVID-19 may have persistent physiological pulmonary and radiographic sequelae.

A growing body of evidence shows that acute pneumonia can also be associated with chronic complications. SARS was revealed to result in long-term complications in some patients (6, 8, 61-63), and childhood pneumonia of various etiologies also has been reported to be associated with impaired lung growth and subsequently reduced lung function (64). ARDS, which is commonly caused by pneumonia, also results in long-term pulmonary dysfunction. In survivors of ARDS, diffusion capacity is the single most compromised functional variable (65), which is in line with our finding in patients with COVID-19. These long-term pulmonary sequelae may be caused by inappropriate host immune responses and dysregulated repair processes (66), but further studies are needed to better understand the pathophysiology and identify therapeutic options.

Although long COVID is not uncommon in even low-risk patients with mild COVID-19 (67), data are lacking on the risk factors or predictors of long COVID (68). Knowledge on the risk factors of long COVID would be helpful for identifying patients at risk of long COVID and providing close follow-up after acute infection. In this study, we revealed that the severity of index COVID-19 was associated with impaired diffusion capacity. Older age was also marginally associated with a higher prevalence of impaired diffusion capacity in meta-regression, but this finding may have been confounded by the fact that older age is usually associated with more severe manifestations of COVID-19 (69). Taking these findings together, in planning follow-up for patients with COVID-19, it can be suggested that patients recovering from more severe forms of COVID-19 should be more carefully followed up with regular PFT, particularly with DLCO measurements.

Our study also had limitations. First, most meta-analyses featured considerable statistical heterogeneity. This problem is believed to arise from the heterogeneity of study design and patient characteristics among the included studies. Furthermore, most studies were single-center analyses with small sample sizes. We attempted to assess the source of this heterogeneity via several meta-regression and subgroup analyses but failed to identify a definitive causative factor. Second, we focused on diffusion capacity as our primary outcome, but DLCO measurements can be influenced by several factors, which could result in variability between different laboratory units (70). Similarly, the presence of pulmonary fibrosis was determined by the investigators of each study, but this could not be adjudicated in this study, which may have also contributed to heterogeneity between the studies. Third, most studies did not report data on the baseline lung function of study patients before the index COVID-19 diagnosis. Therefore, some patients with underlying lung disease and impaired lung function may have been counted as exhibiting pulmonary sequelae in this study. Additionally, most of the studies included hospitalized patients and a substantial proportion of patients had severe COVID-19. Thus, the pooled prevalence of pulmonary sequelae from our meta-analysis may have been overestimated. Fourth, because the included studies had follow-up durations of 6 months or less after index COVID-19, we cannot conclude whether these pulmonary sequelae after COVID-19 would improve over time. Longer follow-up data are currently extremely limited, but it is expected that more information will be available in the near future (10).

Conclusions

In conclusion, a substantial number of patients recovering from COVID-19 appear to exhibit pulmonary sequelae as demonstrated by impaired diffusion capacity (34%) and pulmonary fibrosis on chest CT (26%). The severity of

index COVID-19 was associated with the development of impaired diffusion. Careful respiratory follow-up is warranted, especially for patients recovering from severe and critical COVID-19.

Declarations

Ethics approval and consent to participate: Not applicable.

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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

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Authors' contributions: All the authors contributed to study design, data interpretation, and writing of the manuscript. Specifically, Dr. Jong Hyuk Lee and Jimyung Park contributed to establishing search strategy and searching the database for literatures. They were also responsible for review of the searched literatures, data collection and review, statistical analysis, and generation of the figures. Dr. Jae-Joon Yim also contributed to selection of relevant studies and additional data acquisition. Dr. Jae-Joon Yim supervised the whole study process and contributed to critical revision of the manuscript. Dr. Jong Hyuk Lee wrote the first draft of this paper and Dr. Jimyung park critically revised it. All authors have read the final version of manuscript and approved it to be submitted for publication.

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Figures

Figure 1

Preferred Reporting Items of Systematic reviews and Meta-Analyses (PRISMA) flowchart for this systematic review and meta-analysis

A

B

Figure 2

Forest plot presenting the pooled estimate of the diffusion capacity of carbon monoxide (DLCO) in patients recovering from COVID-19 A) Percent predicted value B) Prevalence of impaired DLCO

Figure 3

Meta-regression plots presenting the effect of patient characteristics on the prevalence of impaired diffusion capacity A) Age B) Smoking history C) Number of study patients D) Proportion of patients with severe COVID-19 E) Proportion of patients with critical COVID-19 F) Follow-up interval

A

B

Figure 4

Forest plot presenting the association between the severity of index COVID-19 and impairment of diffusion capacity A) Severe vs. Non-severe B) Critical vs. Non-critical

A

B

C

Figure 5

Forest plot presenting the pooled estimate of abnormal findings in chest computed tomography (CT) in patients recovering from COVID-19 A) Pulmonary fibrosis B) Ground-glass opacity C) Normal (complete resolution)

Supplementary Files

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