Lung Function In Discharged Patients After Coronavirus Infection (SARS, MERS, COVID-19): A Systemic Review And Meta-Analysis

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Abstract

Background: To date, coronaviruses have caused three pandemics. Fewer studies concentrated on the prognosis of lung function.

Objective: To summarize the lung function of the discharged after coronavirus infection.

Methods: We systematically searched PubMed, Cochrane Library, Web of Science, and EMBASE. Two authors independently screened articles and extracted data. On average, predicted values and damage rates of seven lung function indices were pooled by single-arm meta-analysis. And, in severe/critical vs. non-severe/critical and one-year follow-up, they were pooled by two-arm meta-analysis. The source of high heterogeneity was explored by meta-regression or subgroup analysis.

Results: Of the 7798 articles identified, 34 studies were included. On average, the pooled predicted values of the seven indices were within normal except for DLCO (79.2, 95% CI (76.2–82.2)). Damage of lung function indices accounted for 6.2–35.2% of the discharged with DLCO most, and 83–100% of the damage was mild. Meta-regression showed that different viruses, countries, disease settings, and measurement times were not the source of high heterogeneities. In severe/critical illness vs. non-severe/critical, predicted values of seven indices were significantly lower (largest gap in DLCO (WMD -11.60, 95% CI -14.23 –-8.98)). However, damage rates got rises only in DLCO (RR 1.74, 95% CI 1.46–2.07) and TLC, having no differences in the other indices. In one-year follow-up, predicted values were significantly improved in the severe/critical subgroup, while having no change in the non-severe/critical subgroup. Damage rates got no improvement in all indices.

Interpretation: A single predicted value or damage rate can't give a clear description of lung function after coronavirus infection, and the trends of the two are sometimes inconsistent. We suggest more prospective cohort or follow-up studies in the future to lessen the influence of differences in lung function measurements across studies.

Registration: PROSPERO (CRD42020192843)

Introduction

Coronaviruses have caused three pandemics worldwide in the first two decades of the 21st century (severe acute respiratory syndrome (SARS), middle east respiratory syndrome (MERS), and coronavirus disease 2019 (COVID-19)).[1-4] COVID-19, which began in December 2019, is still in an emerging, rapidly evolving situation and has caused more than 130 million infections and nearly three million deaths to date.[5] Furthermore, SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) has accumulated multiple mutations during its global circulation.[6] Researches state that COVID-19 may become a sustained epidemic as new flu.[1, 7]

During the outbreak of coronaviruses, plenty of articles have sprung up on pathogenesis, epidemiology, clinical features, treatments, and preventions. Studies have shown that the three coronaviruses share many similarities. They are spread through the respiratory tract and mainly cause lung disease.[8] The most common lung pathology is diffuse alveolar damage with the hyaline membrane, and some also have microvascular thrombosis.[9-11] Typical imagings are ground-glass opacity, consolidation, reticular pattern, and crazy paving pattern. [12, 13] So, these structural changes may have a similar impact on lung function.

Impaired lung function is generally confirmed to be related to decreased health-related quality of life (HRQL) in COPD,[14] ARDS,[15, 16] SARS,[2] and COVID-19 studies.[17] Some studies also reported that damaged forced expiratory volume in 1 second (EFV_1),[18] forced vital capacity (FVC), or diffusing capacity of the lung for carbon monoxide (DLCO)[19] is associated with increased mortality. Therefore, lung function is of great importance to the prognosis of patients infected with coronavirus. However, it is still unclear that how coronavirus would affect lung function until now. Because the relevant studies were insufficient[4, 20] and there were distinct differences between them.[2, 4, 17, 21-23] The only meta-analysis provided limited information on the prevalences of altered diffusion, restrictive, and obstructive pattern, with a small sample size of COVID-19 patients and a short observation.[24]

So, we conducted this systematic review, aiming to systematically describe the prognosis of lung function for the enormous number of patients with coronavirus infection. To our knowledge, it is the first relatively comprehensive meta-analysis on lung function after coronavirus infection (SARS, MERS, COVID-19) with seven indices (FVC, FEV_1, forced vital capacity/forced expiratory volume in 1 second (FEV_1/FVC), total lung capacity (TLC), residual volume (RV), DLCO, diffusion capacity for carbon monoxide per liter of alveolar volume (Kco)). It included the predicted value and damage rate of lung function on average, in severe/critical vs. non-severe/critical, and a one-year follow-up.

Methods

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA),[25] and the protocol was registered with PROSPERO (CRD42020192843).

Citation Search and Selection

The PubMed, EMBASE, Web of Science, and Cochrane Library databases were searched from January 01, 2002, to February 20, 2021, with no publication language limited, using the following search strategy: ("Severe Acute Respiratory Syndrome" OR "SARS" OR "Middle East Respiratory Syndrome" OR "MERS" OR "COVID-19" OR "Coronavirus Disease 2019" OR "2019-nCoV Disease" OR "2019-nCoV Infection" OR "SARS-CoV-2 Disease" OR "SARS-CoV-2 Infection") AND ("Respiratory Function Tests" OR "Lung Function Tests" OR "Pulmonary Function Tests" OR "Respiratory Function" OR "Lung Function" OR "Pulmonary Function"). The Medical Subject Headings (MeSH) and all variants were searched. Besides, the reference lists of reviews were manually screened to find all possible articles.

All retrieved articles were independently screened by two authors (YLC, WWC) based on the relevance of the title, abstract, or full text. The full-text articles that met the inclusion and exclusion criteria were included in this review. The inclusion criteria were as follows: (1) original cohort, case-control, case-series, or cross-sectional study; (2) human adults (≥ 18 years) with coronavirus infection and lung function tests (LFTs); (3) follow-up in one year; (4) if an institution published several similar studies, only the one with the largest sample size was included. Studies with the following designs were excluded: (1) reviews, case reports, letters, comments, meeting abstracts, or posters; (2) particular study population with coronavirus infection, such as children, pregnant women, cancer survivors, patients with clinical symptoms, or patients with medicine or rehabilitation training intervention; (3) the sample size of LFTs less than 10. Any disagreement on article inclusion was resolved by an arbitrator (ZMC).

Data Extraction

Two independent reviewers (DX, ZWM) extracted the data from each included study. The data involved authors, publication year, country, subject characteristics, study design, diagnostic methods of coronavirus infection, seven lung function indices (FVC, FEV_1, FEV_1/FVC, TLC, RV, DLCO, and Kco) reported as predicted value or damage rate, and details of follow-up. Most included studies performed LFTs under the American Thoracic Society (ATS) recommendations. [26] Therefore, the predicted value > 80% (FEV_1/FVC > 70%) was defined as a normal range, the predicted value in 60–80% was mild damage, in 40–60% was moderate damage, and < 40% was severe damage. If there were multiple LFTs within one-year follow-up, the lung function measurements of the third month (as the sample mode) after discharge were extracted. The follow-up changes of lung function were determined by the first and last test of LFTs within one year.

Risk of bias assessment

The risk of bias for the included studies was assessed by two reviewers (YLC, WWC) independently, using the NHLBI's quality assessment tool for observational cohort and cross-sectional studies or the quality assessment tool for Before-After (Pre-Post) studies with no control group.[27] The criteria which assess the internal validity and risk of bias were evaluated as "Yes", "No", or "Other". The overall rating was defined by the items rated with an affirmative answer: ≥ 75% = good, 50–75% = fair, < 50% = poor.

Statistical analysis

Single-arm meta-analysis was used to pool the estimated predicted values, damage rates, and extent of the damages with 95% confidence intervals (CI). Double arcsine transformation was used to stabilize the variance of the extremum for the dichotomous variable.[28] In the two-arm meta-analysis, weighted mean difference (WMD) and relative risk (RR)/odds ratio (OR) with 95% CI was the effect size of continuous and dichotomous variables, respectively. RR was chosen for the prospective cohort studies. All analyses were performed using Stata MP version 14.0 (Stata Corporation, College Station, TX, USA), with heterogeneities assessed by I^2.[29] I^2 of 25%, 50%, and 75% indicates low, moderate, and high heterogeneity, respectively. When $I^2 < 50\%$, the inverse variance weight (fixed-effect model) was used. Inversely, the DerSimonian-Laird procedure (random-effect model) was used. And at the same time, a further meta-regression (number of studies ≥ 10) or subgroup analysis (n < 10) was performed to explore the source of heterogeneity. Publication bias (studies ≥ 10) was evaluated by Egger's test.[30] $P < 0.05$ was considered as statistical significance.

Results

The search strategy generated 7798 records. After the exclusion of duplicates, 6820 articles were screened according to the inclusion and exclusion criteria. Then 106 articles were retrieved for full-text review. Finally, 34 articles were included in this study. (Figure 1)

Characteristics of included studies

Of the 34 included studies (Table 1),[2-4, 17, 20-23, 31-56] 8 were on SARS,[2, 20, 21, 31-35] 1 was on MERS,[3] and 25 were on COVID-19.[4, 17, 22, 23, 36-56] A total of 3230 coronavirus-infected patients underwent LFTs, including 905 SARS patients, 73 MERS patients and 2252 COVID-19 patients. Three articles published in Chinese,[21, 34, 35] one article published in Spanish,[41] and all others were in English. The majority of studies were from Asia (n=18) and Europe (n=14), including 16 from China,2, 4, 21, 23, 32-38, 40, 46, 48, 52, 56 one each from Singapore[20] and South Kore,[3] and 14 articles from 10 European countries. The other two studies were from Canada.[31, 43] The prospective cohort design[2-4, 17, 23, 31, 32, 36, 38, 42-45, 51-53] was most commonly used (n=16), followed by 9 prospective follow-up studies[20, 22, 33, 37, 39, 41, 49, 55, 56], 4 retrospective cohort studies[40, 46-48], 3 retrospective follow-up studies[21, 34, 35], and 2 cross-sectional study studies[50, 54]. Twenty-three studies were conducted on the entire hospital setting, 6 were on the severe/critical setting,[22, 37, 44, 45, 51, 55] and 5 were on the non-severe/critical setting.[17, 38, 41, 49, 50] 20 studies were evaluated as "good" in the quality assessment, and the risk of bias was judged as low.[2, 3, 20-23, 31-34, 40, 41, 43, 44, 46, 48, 49, 51, 53, 55] Another 14 studies had a moderate risk of bias.[4, 17, 35-39, 42, 45, 47, 50, 52, 54, 56]

Predicted values and damage rates of lung function on average

In total, 23 of the included studies reported the predicted value of lung function, involving seven indices.[2, 3, 17, 20-22, 31, 34, 36-39, 43-47, 49-53, 56] (Table 2) The overall pooled DLCO %-predicted (79.2 (95% CI, 76.2–82.2)) of 1428 patients in 19 studies was the lowest and the only one below the normal range. (Figure 2A) The pooled predicted values of the other 6 indices (FVC, FEV_1, FEV_1/FVC, TLC, RV, Kco) was 93.8 (95% CI, 91.2–96.4), 94.5 (95% CI, 91.7–97.2), 83.3 (95% CI, 81.3–85.2), 94.8 (95% CI, 91.7–97.9), 97.2 (95% CI, 90.7–103.7), and 90.2 (95% CI, 85.4–95.0), respectively. The heterogeneities of the seven indices were high, with I^2 ranging from 91.1% to 94.3%. To explore the source of heterogeneity, we performed meta-regression on the virus, country, disease setting, and measurement time for the seven indices, finding that there were no statistical differences across all the studies. And, publication bias was only found on the FEV_1/FVC index. ($P = 0.046$) (Table 2) Twenty-four studies were included in the meta-analyses to pool the damage rate of lung function in seven indices,[2-4, 17, 20, 22, 23, 32-34, 36, 38-41, 43, 46, 48, 51-56] and the DLCO got the highest rate with 35.2% (95% CI, 28.7–41.8%). (Figure 2B) The rate of the other six indices varied from 6.2% to 21.5%. (Table 2) Similarly, the heterogeneities of the seven indices were high, (I^2 = 79.6–96.4%) and no positive findings were found in the meta-regression. However, publication bias was the opposite that it existed in all but DLCO. (P = 0.052) (Table 2) Several studies also identified the extent of lung function damage, and the mild impairment accounted for most, with the pooled 83%–100% in FVC, FEV_1, TLC, DLCO, and Kco.[17, 20, 22, 23, 33, 39, 46, 56] (Table 2)

Severe/critical vs. Non-Severe/critical

A total of 10 cohort studies detailed the predicted values of lung function in two groups of severe/critical and non-severe/critical. (283 vs. 531 patients)[2, 3, 17, 36, 38, 46, 47, 51-53] Differences between the two groups of the seven indices were summarized by meta-analyses. (Table 3) Predicted values in the severe/critical group were found to be worse than that in the non-severe/critical group (all $P < 0.013$), except for FEV_1/FVC (no difference between two groups, $P = 0.585$). And, DLCO got the largest gap, whose lung function in severe/critical decreased -11.6 (WMD, 95% CI -14.2 to -9.0) compared with non-severe/critical.[2, 3, 17, 38, 46, 47, 51-53] (Figure 3A) All the heterogeneities were acceptable. (I^2: 0 to 58.5%) (Table 3) Nine cohort studies[4, 17, 36, 38, 46, 47, 51-53] compared the damage rates of the seven indices between the two groups, two of which were retrospective cohort studies[46, 47] and the others were prospective studies. (483 vs. 492 patients) Meta-analyses found that the risk of lung function damage of DLCO and TLC in the severe/critical group was 1.74 (RR, 95% CI 1.46 to 2.07) (Figure 3B) and 2.00 (RR, 95% CI 1.38 to 2.90) times higher than that in the non-severe/critical group, respectively. ($P = 0.000$) However, there were no significant differences in the other five indices. ($P > 0.088$) Heterogeneities were low, with I^2 varied from 0 to 13.9%. (Table 3)

Follow-up Changes

Five articles reported the changes of lung function in predicted value during a one-year follow-up.[2, 22, 31, 37, 50] Meta-analyses showed improvements in FVC, FEV_1/FVC, and Kco. ($P < 0.049$) While there were no statistically significant changes in the other four indices. ($P > 0.074$) (Table 4) Given the high heterogeneity of most indices, we performed subgroup analyses. It showed that all indices got statistically improved in the severe/critical group, ($P < 0.049$) while they had no changes in the non-severe/critical group, except for Kco. ($P > 0.208$) (Supplementary Figure 1) Only three articles covered the damage rate changes of lung function.[2, 22, 55] Analyses showed that there was no statistically significant change in any of the seven indices. ($P > 0.182$) (Table 4) And except that DLCO had a high heterogeneity, ($I^2 = 84.6\%$) no heterogeneity was found in other indices. ($I^2 = 0\%$) (Table 4)

Discussion

The predicted value of lung function was the most widely reported in the included studies. They were normal on average (except for DLCO), worse in severe/critical illness, and might get improvements in a one-year follow-up. These trends were consistent with other COVID-19 studies,[57-60] and even H7N9[61] and ARDS studies,[16, 62, 63] for sharing a common pathological mechanism mediated by inflammatory factors.[64, 65] But these can't figure out more information about how much the coronaviruses may affect the individual's lung function or the situation of lung function impaired. The reason may be that although studies have corrected continuous lung function according to the local predicting formula, the span of the ATS recommendations for grading respiratory impairment is large. For example, mild respiratory impairment has a range of 60 to 80% of the predicted values. But in this study, even a difference in the predicted value of less than 10% was statistically significant. (severe/critical vs. non-severe/critical; follow-up) Also, this lead to some features of predicted value was quite different from those of damage rate. For example, they got different trends in severe/critical vs. non-severe/critical, and follow-up within one year.

Liking the meta-analysis authored by Torres-Castro R,[24] many studies reported a rate of respiratory impairment pattern (such as restrictive pattern) with different criteria.[35-37, 44, 46, 47, 54] To minimize the possible errors, we pooled the damage rate of seven indices in detail. On average, the pooled damage rate of FVC (TLC), FEV_1/FVC, and DLCO was similar to the percentage of restrictive, obstructive, and diffusing damage patterns reported in that meta-analysis authored by Torres-Castro R, respectively.[24] DLCO got the highest damage rate. It may be related to the most common abnormal CT pattern—interstitial pneumonia in coronavirus infection[13, 33] or pulmonary fibrosis caused by the activation of fibroblasts during recovery.[4, 66] Damages of seven indices were all mild, and this was consistent with that average predicted values were almost within the normal range. Severe/critical illness was a risk factor for damage only in DLCO and TLC. Several studies on predictors for DLCO damage also proved this,[4, 39, 51, 52] but no studies were conducted on other indices. We suppose they may be more easily affected by age, gender, smoking, or previous lung disease, et al.

Multiple meta-analyses were performed in this paper. Predicted value and damage rate got the highest heterogeneity on average. However, meta-regression showed that the possible sources of heterogeneity (virus, country, disease setting, measurement time) all had no statistical significance. One possibility is that the heterogeneous sources we chose were improper and they had no

statistical significance. But we preferred that the differences in lung function measurements across studies were so great that they obscured other differences. Cohort and follow-up studies confirmed our assumption that their heterogeneities were low or acceptable. Significant differences were found in predicted value and damage rate in severe/critical vs. non-severe/critical, indicating that different illness settings might be one source of heterogeneity. The meta-analysis by Torres-Castro R mainly pooled the rates of respiratory impairment pattern at discharge or one month after discharge,[24] and they proposed that inflammation during the acute phase may affect results, suggesting a follow-up to 3 months after discharge.[67] In this review, only predicted values in severe/critical subgroup got significant improvements within one-year follow-up, indicating that different measurement times might not be a source of heterogeneity. But given the small sample size, we consider that more evidence is needed. Therefore, we suggest more prospective cohort or follow-up designs on lung function to increase the credibility and comparability of the results.

There are several limitations in this present review. First, there were fewer studies on SARS, MERS, and follow-up research, although this study had included all relevant literature as much as possible. Second, through comprehensive analysis, we concluded that the greatest source of heterogeneity might be the differences in lung function measurements across studies. But, the differences can't be eliminated, for too many factors and difficult to unify. For example, maybe the effectiveness of predicting formula,[2, 20, 32] the criterion of severe illness,[3, 4, 37, 40] and the proportion of LFTs over all the discharged patients[2, 4, 51, 52] are different across studies. Moreover, various instruments, inspector's skill, patients' cooperation, environmental factors, or psychological factors might affect the LFTs. So we suggest more prospective cohort or follow-up researches. Third, no study provided the lung function condition before infected, and it is unreasonable in fact. So it is impossible to obtain the actual effect of coronavirus infection on lung function. While this review revealed the influences of severe illness and follow-up on lung function under coronavirus infection for the first time, with acceptable heterogeneities. Fourth, we reported the damage rates of seven lung function indices in detail, and one-third of the discharged patients had impaired DLCO. But the percentage of patients who got lung function impairment and the relationship between indices were unknown, for several indices can be injured in one patient. Fifth, for a large number of coronavirus infected, in particular COVID-19, the overall LFTs were laborious, costly, and risky of transmission.[68] So, it is a challenge to distinguish which and what extent indices were damaged cost-effectively, and it may affect the time for rehabilitation. Researches on the predictors of DLCO damage provided one method, but they were hard to pool for the distinct observation indices involved.[4, 39, 48, 51, 52] We suggest more studies on predictors or prediction models for lung function impairment.

Conclusion

Three coronaviruses had similar influences on the lung function of infected patients. The predicted value and damage rate of seven lung function indices were consistent on average damages of lung function indices were mild, with DLCO as the most vulnerable index. However, they had different features in severe/critical vs. non-severe/critical, and follow-up within one year. The dominating source of heterogeneity might be the differences in lung function measurements across studies. Meanwhile, given the previous lung function was unavailable, we suggest more prospective cohort or follow-up designs for further studies.

Abbreviations

SARS severe acute respiratory syndrome

MERS middle east respiratory syndrome

COVID-19 coronavirus disease 2019

SARS-CoV-2 severe acute respiratory syndrome coronavirus 2

FEV_1 forced expiratory volume in 1 second

FVC forced vital capacity

DLCO diffusing capacity of the lung for carbon monoxide

FEV_1/FVC forced vital capacity/forced expiratory volume in 1 second

TLC total lung capacity

RV residual volume

Kco diffusion capacity for carbon monoxide per liter of alveolar volume

LFTs lung function tests

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

Endnote is used for article screening, and Stata MP version 14.0 (Stata Corporation, College Station, TX, USA) is used for meta-analysis.

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Competing interests

The authors declare that they have no competing interests.

Authors' contributions

LYC and WWC were responsible for study design, screening, data extraction, data analysis, and writing the article. ZWM and DX helped extract and disposal data. SRS participated in the data analysis and revision of the article. ZMC designed and revised the article.

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Tables

Table 1
Characteristics of the included studies

Author, Year	Region, Country	Virus, Diagnosis method	Study Design	$N_{virus-infected}$ [a]	N_{LFTs} [b]	Age, years, Mean (SD)	Male Sex, (%)	Follow-up times, months (mo), years	Quality [c]
Hui DS, 2005[2]	Hongkong, China	SARS-Cov, laboratory +	prospective cohort	123 discharged	97	36.9 (9.5)	39 (40.2%)	3, 6, 12 mo	good
Ong KC, 2005[20]	Singapore	SARS-Cov, laboratory +	prospective follow-up	151 discharged	94	37 (12)	24 (26%)	12 mo	good
Li L, 2015[21]	TianJin, China	SARS-Cov, clinical/ laboratory +	retrospective follow-up	25 discharged	25	42.3 (11.9)	6 (24%)	discharge, 10 years	good
Tansey CM, 2007[31]	Canada	SARS-Cov, laboratory +	prospective cohort	198 discharged	103	42 (13.5)	39 (33.3%)	3, 6, 12 mo	good
Ng CK, 2004[32]	Hongkong, China	SARS-Cov, laboratory +	prospective cohort	93 discharged	57	38.1 (10.7)	22 (38.6%)	6 mo	good
Xie LX, 2005[33]	Beijing, China	SARS-Cov, laboratory +	prospective follow-up	208 discharged	51	–	–	3 mo	good
Liu T, 2003[34]	Beijing, China	SARS-Cov, clinical/ laboratory +	retrospective follow-up	119 discharged	72	–	–	1 mo	good
He ZY, 2005[35]	Beijing, China	SARS-Cov, –	retrospective follow-up	456 discharged	406	33 (9)	–	6 mo	fair
Park WB, 2018[3]	Korea	MERS-Cov, laboratory +	prospective cohort	146 discharged	73	51.2 (1 1.5)	43 (58.9%)	1 year	good
Huang CL, 2021[4]	Wuhan, China	2019-nCoV, laboratory +	prospective cohort	2436 discharged	349	–	–	6 mo	fair
van der S, 2021[17]	Breda, the Netherlands	2019-nCoV, laboratory +	prospective cohort	– non-critical	101	66.4 (12.6)	58 (57.4%)	1.5 mo	fair
Fumagalli A, 2021[22]	Lombardy, Italy	2019-nCoV, laboratory +	prospective follow-up	13 ICU	13	57.8 (10.0)	12 (92.3%)	discharge, 1.5 mo	good

Author, Year	Region, Country	Virus, Diagnosis method	Study Design	$N_{virus-infected}$ [a]	N_{LFTs} [b]	Age, years, Mean (SD)	Male Sex, (%)	Follow-up times, months (mo), years	Quality [c]
Liang LM, 2020[23]	Wuhan, China	2019-nCoV, laboratory +	prospective cohort	134 discharged	76	41.3 (13.8)	21 (27.6%)	3 mo	good
You JJ, 2020[36]	Hubei, China	2019-nCoV, laboratory +	prospective cohort	–	18	10 (55.6)	50.7 (12.1%)	1 mo	fair
Li XY, 2020[37]	Haerbin, China	2019-nCoV, –	prospective follow-up	– severe	18	–	–	0.5, 1 mo	fair
Mo XN, 2020[38]	Guangzhou, China	2019-nCoV, laboratory +	prospective cohort	– non-critical	110	49.1 (14.0)	55 (50%)	discharge	fair
Bellan M, 2021[39]	Novara, Italy	2019-nCoV, laboratory +	prospective follow-up	732 discharged	224	60.6 (15.7)	142 (59.7%)	4 mo	fair
Lv DQ, 2020[40]	Taizhou, China	2019-nCoV, laboratory +	retrospective cohort	137 discharged	137	47 (13)	71 (51.8%)	discharge, 0.5 mo	good
Tabernero HE, 2021[41]	Spain	2019-nCoV, laboratory +	prospective follow-up	128 non-critial	104	58.1 (12.9)	54 (51.9%)	1-1.5 mo	good
Guler SA, 2021[42]	Swiss	2019-nCoV, –	prospective cohort	–	72	–	–	4 mo	fair
Shah AS, 2020[43]	Canada	2019-nCoV, laboratory +	prospective cohort	82 discharged	57	64.9 (15.2)	41 (68%)	3 mo	good
Truffaut L, 2021[44]	Brussels, Belgium	2019-nCoV, clinical/ laboratory +	prospective cohort	33 ICU	22	54.6 (10.9)	16 (72.7%)	3 mo	good
Anastasio F, 2021[45]	Sondalo, Italy	2019-nCoV, laboratory +	prospective cohort	61 ARDS	61	65.6 (11.4)	54 (83.1%)	4 mo	fair
Huang Y, 2020[46]	Zhuhai, China	2019-nCoV, laboratory +	retrospective cohort	70 discharged	57	46.7 (13.8)	26 (45.6%)	1 mo	good
Frija-Masson J, 2020[47]	Paris, France	2019-nCoV, laboratory +	retrospective cohort	–	50	54 (12.2)	28 (56%)	1 mo	fair

Author, Year	Region, Country	Virus, Diagnosis method	Study Design	$N_{virus-infected}$ [a]	N_{LFTs} [b]	Age, years, Mean (SD)	Male Sex, (%)	Follow-up times, months (mo), years	Quality [c]
Zhao YM, 2020[48]	Zhengzhou, China	2019-nCoV, laboratory +	retrospective cohort	74 non-critical	55	47.7 (15.5)	32 (58.2%)	3 mo	good
Daher A, 2020[49]	Aachen, Germany	2019-nCoV, laboratory +	prospective follow-up	33 non-critical	33	64 (3)	22 (66.7%)	1.5 mo	good
Bonnesen B, 2020[50]	Roskilde, Denmark	2019-nCoV, laboratory +	cross-sectional	16 critical	12	62 (8.4)	11 (91.7%)	1, 3 mo	fair
Lerum TV, 2020[51]	Norway	2019-nCoV, laboratory +	prospective cohort	103 discharged	103	60.1 (17.3)	54 (52%)	1.5, 3 mo	good
Qin W, 2021[52]	Wuhan, China	2019-nCoV, clinical/ laboratory +	prospective cohort	668 discharged	81	59 (14)	34 (42%)	3 mo	fair
Osman M, 2020[53]	Nijmegen, the Netherlands	2019-nCoV, clinical/ laboratory +	prospective cohort	170 discharged	124	59 (14)	74 (60%)	3 mo	good
Smet J, 2021[54]	Brussels, Belgium	2019-nCoV, –	cross-sectional	–	220	53 (13)	136 (62%)	2.5 mo	fair
Sonnweber T, 2020[55]	Innsbruck, Austria	2019-nCoV, laboratory +	prospective, follow-up	190 discharged	145	57 (14)	82 (56.6%)	2, 3 mo	good
Gao Y, 2021[56]	Guangzhou, China	2019-nCoV, –	prospective follow-up	–	10	50.7 (17.3)	7 (70%)	1 mo	fair

Abbreviations: SARS-CoV, SARS coronavirus; MERS-Cov, MERS coronavirus; 2019-nCoV, 2019 novel coronavirus; ICU, intensive care unit; ARDS, acute respiratory distress syndrome

[a] $N_{virus-infected}$, number of patients infected with coronavirus; [b] N_{LFTs}, number of patients underwent lung function tests; [c] Quality, studies were assessed by the NHLBI's quality assessment tool for observational cohort and cross-sectional studies or the quality assessment tool for Before-After (Pre-Post) studies with no control group; –, not available

Table 2

Predicted value and damage rate of lung function on average

Variables	$N_{studies}$ [a]	N_{LFTs}, n/N [b]	% of pred, rate (95% CI)	I^2	Egger's	P_{Virus} [c]	$P_{Country}$ [d]	$P_{Setting}$ [e]	P_{Time} [f]
FVC % of pred [g]	20	1309	93.8 (91.2-96.4)	93.7%	0.055	0.800	0.593	0.187	0.999
FVC < 80% of pred [h]	14	159/1331	15.9% (9.8-22.0)	93.2%	0.011	0.979	0.106	0.372	0.904
FVC mild damage [i]	4	25/30	86.3% (74.2-98.3)	0.0%	–	–	–	–	–
FEV_1 % of pred	22	1538	94.5 (91.7-97.2)	91.1%	0.179	0.567	0.818	0.144	0.610
FEV_1 < 80% of pred	15	155/1398	11.6% (7.8-15.3)	82.6%	0.004	0.649	0.081	0.148	0.658
FEV_1 mild damage	5	35/39	96.8% (73.1-96.8)	80.5%	–	–	–	–	–
FEV_1/FVC % of pred	19	1010	83.3 (81.3-85.2)	94.3%	0.046	0.653	0.311	0.676	0.726
FEV_1/FVC < 70% of pred	12	84/1104	6.2% (3.3-9.1)	79.6%	0.022	0.135	0.065	0.082	0.126
TLC % of pred	15	1105	94.8 (91.7-97.9)	91.6%	0.463	0.193	0.535	0.551	0.857
TLC < 80% of pred	12	266/1487	15.6% (9.5-21.7)	93.2%	0.012	0.729	0.491	0.163	0.920
TLC mild damage	4	36/37	99% (95-99)	22.5%	–	–	–	–	–
RV % of pred	13	906	97.2 (90.7-103.7)	94.3%	0.162	0.539	0.464	0.684	0.703
RV < 80% of pred	2	97/457	17.1% (-0.6-34.8)	96.4%	–	–	–	–	–
DLCO % of pred	19	1428	79.2 (76.2-82.2)	92.6%	0.241	0.293	0.645	0.050	0.895
DLCO < 80% of pred	21	822/2435	35.2% (28.7-41.8)	92.4%	0.052	0.959	0.784	0.861	0.706
DLCO mild damage	7	218/287	82.9% (72.0-93.9)	85.1%	–	–	–	–	–
Kco % of pred	11	763	90.2 (85.4-95.0)	94.2%	0.370	0.209	0.698	0.403	0.183
Kco < 80% of pred	4	64/298	21.5% (1.3-41.6)	95.6%	–	–	–	–	–
Kco mild damage	1	2/2	100.0%	–	–	–	–	–	–

Abbreviations: CI, confidence intervals; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second, FEV_1/FVC, forced vital capacity/forced expiratory volume in 1 second; TLC, total lung capacity; RV, residual volume; DLCO, diffusing capacity of the lung for carbon monoxide; Kco, diffusion capacity for carbon monoxide per liter of alveolar volume

[a] $N_{studies}$, number of studies included; [b] N_{LFTs}, n/N, number of patients underwent lung function tests, the lung function damage rate or the ratio of mild damage; [c] P_{Virus}, the *P* value of meta regression in different coronavirus; [d] $P_{Country}$, the *P* value of meta regression in different countries; [e] $P_{Setting}$, the *P* value of meta regression in different illness settings; [f] P_{Time}, the *P* value of meta regression in different measurement times; [g] FVC % of pred, the predicted value of FVC; [h] FVC < 80% of pred, damage rate of FVC; [i] FVC mild damage, the mild damage ratio of FVC (60 ≤ FVC < 80% of pred); I^2, index for the degree of heterogeneity; *P* value, significant at $P < 0.05$ and present in bold; Egger's, index for the degree of publication bias; –, not available

Table 3

Differences of predicted value and damage rate of lung function in severe/critical vs. non-severe/critical

Variables	$N_{studies}$ [a]	$N_{severe/critical}$, $n/N_{severe/critical}$ [b]	$N_{non-severe/critical}$, $n/N_{non-severe/critical}$ [c]	WMD, RR	95% CI	I^2	P
FVC % of pred [d]	9	237	453	-6.21	-8.76--3.66	24.5%	0.000
FVC < 80% of pred [e]	6	29/357	28/361	1.48	0.88-2.47	0.0%	0.138
FEV_1 % of pred	10	283	531	-3.50	-5.86--1.14	0.0%	0.004
FEV_1 < 80% of pred	7	31/402	42/437	1.07	0.66-1.74	0.0%	0.776
FEV_1/FVC % of pred	7	133	359	0.57	-1.47-2.61	55.8%	0.585
FEV_1/FVC < 70% of pred	5	38/398	21/261	0.99	0.58-1.69	0.0%	0.968
TLC % of pred	8	262	431	-7.97	-10.52--5.43	7.3%	0.000
TLC < 80% of pred	6	91/445	43/355	2.00	1.38-2.90	0.0%	0.000
RV % of pred	5	153	316	-10.43	-15.86--5.01	0.0%	0.000
RV < 80% of pred	2	74/288	22/156	1.40	0.89-2.20	0.0%	0.146
DLCO % of pred	9	277	519	-11.60	-14.23--8.98	29.0%	0.000
DLCO < 80% of pred	8	237/477	146/480	1.74	1.46-2.07	6.4%	0.000
Kco % of pred	5	179	260	-5.97	-9.22--2.72	0.0%	0.000
Kco < 80% of pred	2	25/59	35/132	1.44	0.95-2.20	0.0%	0.088

Abbreviations: WMD, weighted mean difference; RR, relative risk; CI, confidence intervals; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; FEV_1/FVC, forced vital capacity/forced expiratory volume in 1 second; TLC, total lung capacity; RV, residual volume; DLCO, diffusing capacity of the lung for carbon monoxide; Kco, diffusion capacity for carbon monoxide per liter of alveolar volume

[a] $N_{studies}$, number of studies included; [b] $N_{severe/critical}$, $n/N_{severe/critical}$, number of severe/critical patients, the damage rate of lung function in severe/critical; [c] $N_{non\text{-}severe/critical}$, $n/N_{non\text{-}severe/critical}$, number of non-severe/critical patients, the damage rate of lung

function in non-severe/critical; [d] FVC % of pred, the predicted value of FVC; [e] FVC < 80% of pred , damage rate of FVC; I^2, index for the degree of heterogeneity; *P* value, significant at $P < 0.05$ and present in bold

Table 4
Changes of predicted value and damage rate of lung function within one-year follow-up

Variables	$N_{studies}$ [a]	n_{first} [b]	n_{last} [c]	WMD, OR	95% CI	I^2	P
FVC % of pred [d]	5	223	243	-5.95	-10.52–1.38	54.2%	0.011
FVC < 80% of pred [e]	3	53/236	45/242	1.38	0.83-2.31	0.0%	0.219
FEV_1 % of pred	5	223	243	-5.27	-11.05-0.52	67.2%	0.074
FEV_1 < 80% of pred	3	43/237	45/246	1.00	0.59-1.69	0.0%	0.998
FEV_1/FVC % of pred	3	43	43	2.77	0.01-5.53	30.4%	0.049
TLC % of pred	3	192	212	-6.79	-15.54-1.95	88.3%	0.128
TLC < 80% of pred	2	21/224	20/233	1.11	0.59-2.12	0.0%	0.743
RV % of pred	3	192	212	-7.25	-16.90-2.40	76.7%	0.141
DLCO % of pred	3	192	212	-4.43	-14.52-5.67	92.6%	0.390
DLCO < 80% of pred	2	21/224	20/233	1.07	0.69-1.66	84.6%	0.754
Kco % of pred	2	109	109	-7.76	-11.58–3.93	31.4%	0.000
Kco < 80% of pred	1	2/97	0/97	5.11	0.24-107.73	–	0.295

Abbreviations: WMD, weighted mean difference; OR, odds ratio; CI, confidence intervals; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; FEV_1/FVC, forced vital capacity/forced expiratory volume in 1 second; TLC, total lung capacity; RV, residual volume; DLCO, diffusing capacity of the lung for carbon monoxide; Kco, diffusion capacity for carbon monoxide per liter of alveolar volume

[a] $N_{studies}$, number of studies included; [b] n_{first}, number of patients underwent lung function tests at the first measurement time; [c] n_{last}, number of patients underwent lung function tests at the last measurement time; [d] FVC % of pred, the predicted value of FVC; [e] FVC < 80% of pred, damage rate of FVC; I^2, index for the degree of heterogeneity; *P* value, significant at $P < 0.05$ and present in bold; –, not available

Figures

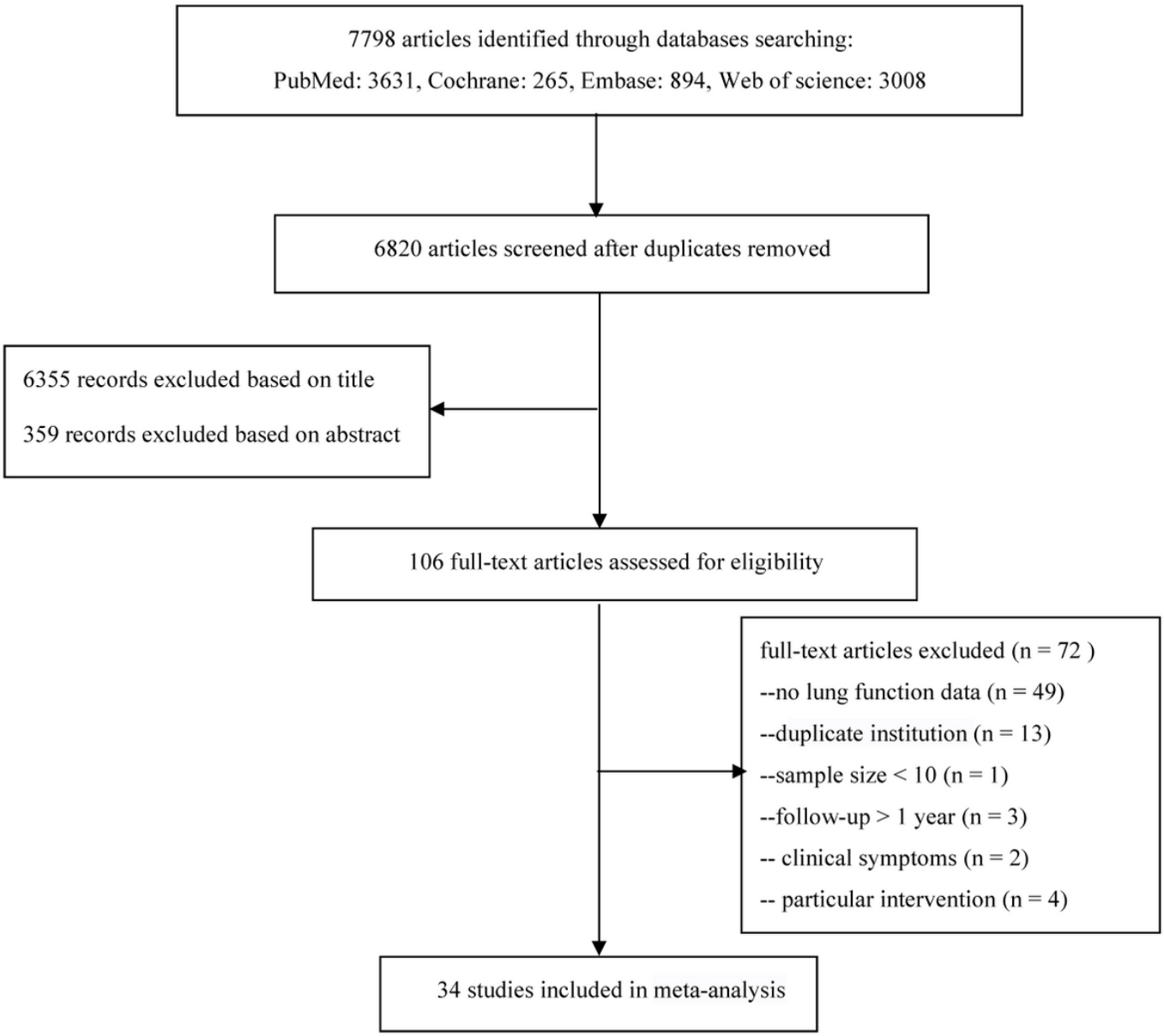

Figure 1

Flow chart of article selection.

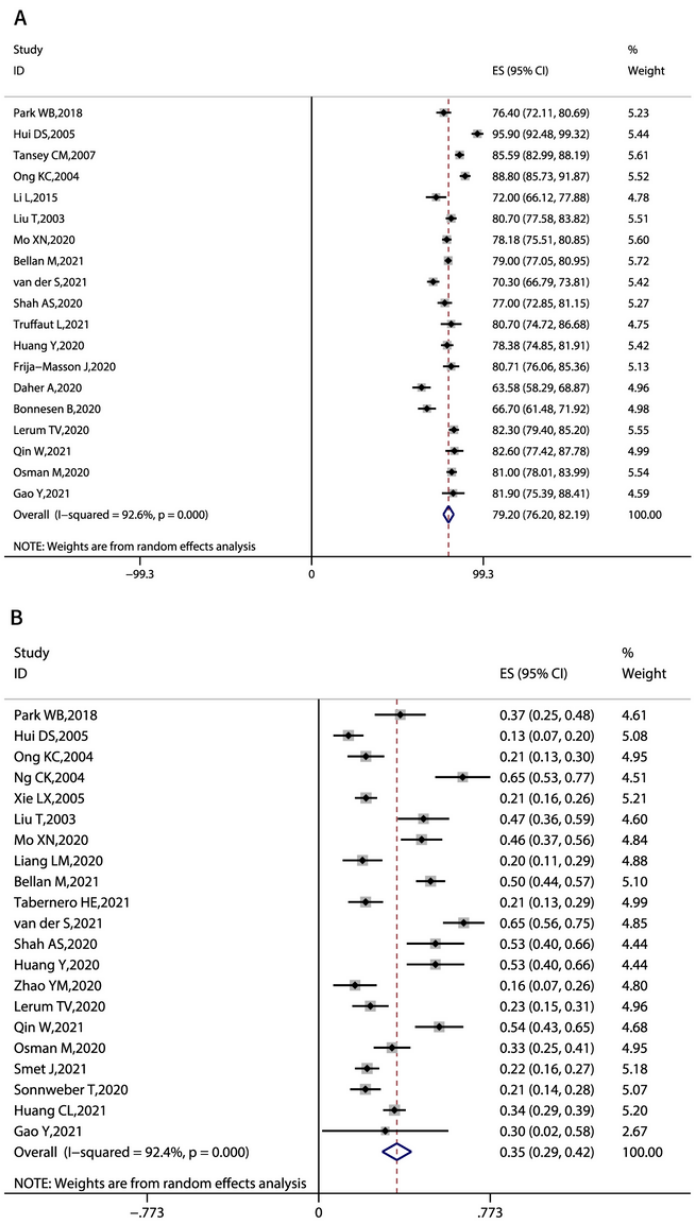

Figure 2

Meta-analysis of DLCO on average. A, predicted value of DLCO; B, damage rate of DLCO. Abbreviations: DLCO, diffusing capacity of the lung for carbon monoxide.

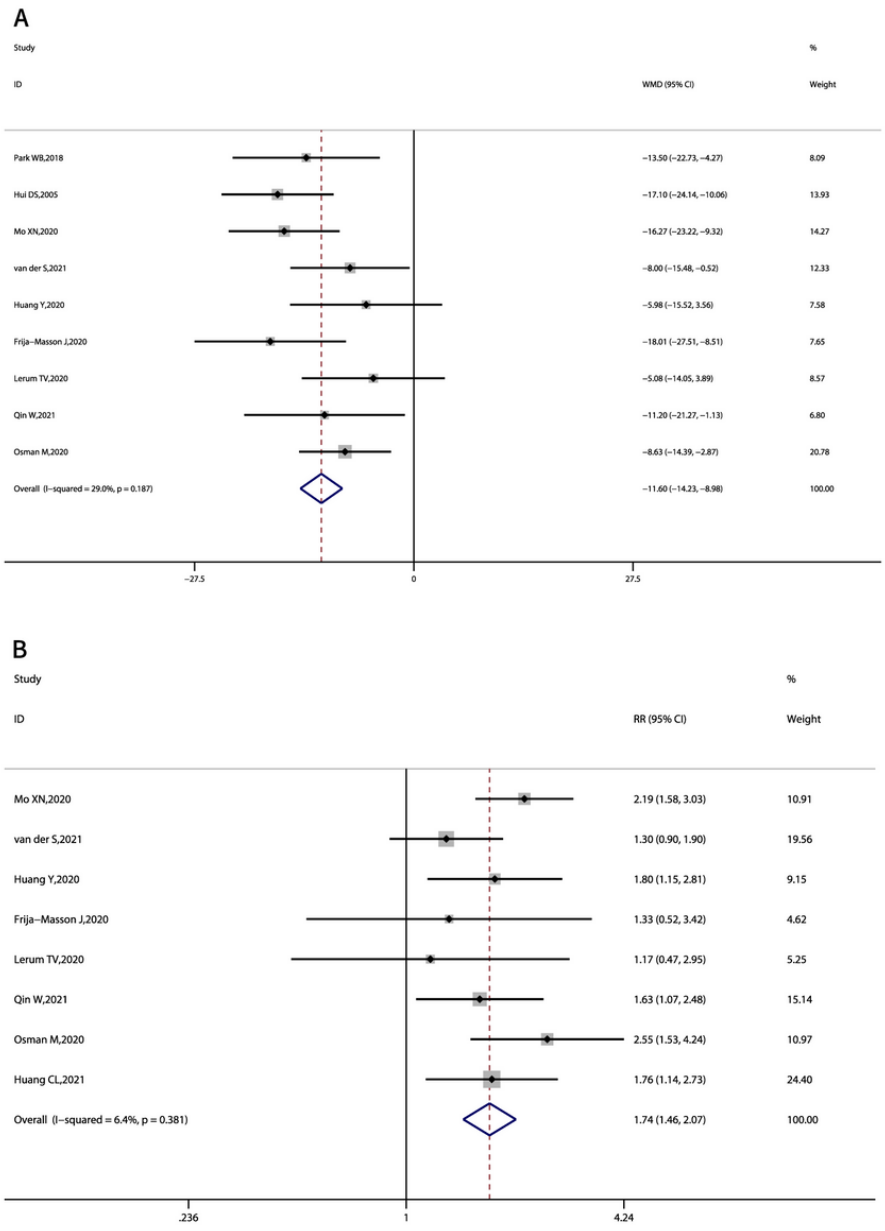

Figure 3

Meta-analysis of DLCO in severe/critical vs. non-severe/critical. A, predicted value of DLCO; B, damage rate of DLCO. Abbreviations: DLCO, diffusing capacity of the lung for carbon monoxide.

Supplementary Files

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- SupplementaryFigure1.tif