



Pulmonary function test and computed tomography features during follow-up after SARS, MERS and COVID-19: a systematic review and meta-analysis

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Shareable abstract (@ERSpublications)

A mild reduction in D_{LCO} , and ground-glass opacity, linear opacities and reticulation on CT may persist after #COVID19 at 6 months: severe/critical COVID-19 acute infection increases this risk. Similar patterns observed after SARS and MERS. <https://bit.ly/35u3ree>

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Abstract

Background The COVID-19 pandemic follows severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) coronavirus epidemics. Some survivors of COVID-19 infection experience persistent respiratory symptoms, yet their cause and natural history remain unclear. Follow-up after SARS and MERS may provide a model for predicting the long-term pulmonary consequences of COVID-19.

Methods This systematic review and meta-analysis aims to describe and compare the longitudinal pulmonary function test (PFT) and computed tomography (CT) features of patients recovering from SARS, MERS and COVID-19. Meta-analysis of PFT parameters (DerSimonian and Laird random-effects model) and proportion of CT features (Freeman-Tukey transformation random-effects model) were performed.

Findings Persistent reduction in the diffusing capacity for carbon monoxide following SARS and COVID-19 infection is seen at 6 months follow-up, and 12 months after MERS. Other PFT parameters recover in this time. 6 months after SARS and COVID-19, ground-glass opacity, linear opacities and reticulation persist in over 30% of patients; honeycombing and traction dilatation are reported less often. Severe/critical COVID-19 infection leads to greater CT and PFT abnormality compared to mild/moderate infection.

Interpretation Persistent diffusion defects suggestive of parenchymal lung injury occur after SARS, MERS and COVID-19 infection, but improve over time. After COVID-19 infection, CT features are suggestive of persistent parenchymal lung injury, in keeping with a post-COVID-19 interstitial lung syndrome. It is yet to be determined if this is a regressive or progressive disease.

Introduction

Coronaviruses are enveloped single-stranded RNA viruses (family Coronaviridae, order Nidovirales, genus *Betacoronavirus* [1, 2]) first identified in the 1960s and have historically caused avian and animal respiratory and gastrointestinal illness. Whilst traditionally associated with the human common cold [3], since the turn of the 21st century, three novel coronaviruses have emerged in humans (following zoonosis from animal reservoirs), resulting in significant morbidity and mortality: severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; also referred to as COVID-19) [4–6].



The clinical course of COVID-19 varies, ranging from asymptomatic or mild, self-limiting illness to severe pneumonia and multi-organ failure requiring intensivists' treatment. Patients who survive the acute phase of COVID-19 similarly experience a varied clinical recovery, with the natural history and long-term impact on the lungs unclear. It is, however, increasingly apparent that many individuals suffer from residual respiratory symptoms with functional impairment. These are often included under the umbrella term "long-COVID", which can be misleading or misinterpreted, as these symptoms more likely represent sequelae in the lungs following the acute infection. Prior to the UK COVID-19 vaccination programme, it was estimated that 20% of patients have persistent symptoms (related to any organ) at 5 weeks and 10% at 12 weeks after COVID-19 infection, respectively [7]. The estimated prevalence of persistent dyspnoea, cough and sputum production in the first 3 months after infection is 24%, 19% and 3%, respectively [8]. However, the underlying pathophysiology of these symptoms has yet to be defined, with concern surrounding the development of a post-COVID interstitial lung disease (ILD) [9, 10]. Likewise, reports of "pulmonary fibrosis" following SARS and MERS infection have previously been described [11, 12].

With similarities between SARS-CoV-2 and SARS-CoV and MERS-CoV lineage and genomic homology (79.5% and 50% respectively [13]) in mind, the primary aim of this systematic review and meta-analysis is to describe and compare the longitudinal pulmonary function and computed tomography (CT) features of patients recovering from SARS, MERS and COVID-19 during follow-up. A secondary aim is to assess whether the severity of the acute COVID-19 infection influences pulmonary function and CT features seen during follow-up. This systematic review and meta-analysis includes studies published in the first 20 months of the COVID-19 pandemic.

Methods

Meta-analyses and systematic review were performed in accordance with MOOSE guidelines and reported in concordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (PRISMA-P) [14, 15]. The protocol was registered and can be viewed in full on the PROSPERO international database (PROSPERO ID: CRD420202643). We present a summary of the methodology.

Studies were eligible for inclusion if they included adult patients (18 years and older) and met the eligibility criteria in given in supplementary table S1.

Search strategy

Medline (Ovid) and Embase (Ovid) electronic databases were searched for articles published between 1 January 2000 and 23 July 2021. Searches applied a combination of index terms and text words relating to SARS, MERS or COVID-19 coronaviruses, respiratory diseases, sequelae and outcome measures (supplementary table S2a,b). No study design or language restrictions were implemented.

Study selection, data extraction and quality assessment

Study selection against pre-determined inclusion and exclusion criteria (supplementary table S2) was performed independently by two reviewers (C.C.H., K.P., S.B.B., F.M., M.N.A., A.P., C.B.K., A.M., M.K., A.Z.M. or E.M.), reviewing the title and abstracts then the full texts of those eligible. Disagreements were resolved by discussion or review by a third independent reviewer (C.C.H., K.P. or G.I.W.).

Data were extracted from each eligible study using a pre-determined standardised, piloted data extraction sheet (which included a risk of bias tool) by two independent reviewers (all authors). A third reviewer checked the data extracted and risk of bias assessment and resolved any conflicts (C.C.H., K.P. or G.I.W.). For studies not in the English language, study selection and data extraction process was performed by one reviewer (A.M.T.) alongside a lay speaker of the language. Risk of bias and quality assessment was performed using the Newcastle-Ottawa scale for cohort and case-control studies and the Joanna Briggs Institute critical appraisal tool for analytical cross-sectional studies (longitudinal or cross-sectional studies). Authors of studies with incomplete or missing data or data reported in an alternative format were contacted to provide additional information and excluded if an unsatisfactory or no response was received.

Statistical analysis

Studies were grouped according to the outcomes they reported. For physiological results, the percentage of predicted values (% predicted) of the forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), diffusing capacity of the lung for carbon monoxide (D_{LCO}), carbon monoxide transfer coefficient (K_{CO}), total lung capacity (TLC) and/or residual volume (RV) were collected at time points reported after admission or discharge. Where the median and interquartile range (IQR) were reported, the mean \pm SD was estimated as per Hozo *et al.* [16]. The proportion of patients with various CT (CT pulmonary angiogram (CTPA), high-resolution CT (HRCT) and CT thorax +/- contrast) features was collected at specified time

points. If the follow-up time point was not reported, the corresponding author was contacted, and if unable to clarify, the study was excluded.

Follow-up time points were grouped ordinally into follow-up time periods to allow for minor variations in the follow-up reported as well as whether the study reported data from post-admission or post-discharge (supplementary table S3). If a study reported more than one timepoint in the same period (*e.g.* 1 month and 2 months) the later data set was included to avoid duplicate publication bias. Two expert physicians in ILD reviewed and categorised all terms reported due to variations observed in CT feature terminology between studies (supplementary table S4).

Meta-analyses were performed for each coronavirus infection (SARS, MERS, COVID-19). Pulmonary function test (PFT) parameters (FEV_1 , FVC, D_{LCO} , K_{CO} , TLC and RV % predicted) by follow-up time period were meta-analysed applying a DerSimonian Laird random-effects model, whilst meta-analyses of proportions of specific CT features by follow-up time period were performed by applying a Freeman–Tukey random-effects model. Subgroup analyses of COVID-19 PFT and CT outcomes by severity of the acute infection (as defined by the World Health Organisation COVID-19 clinical management guidelines; supplementary table S5 [17]) were performed when this information was available. Meta-analysis was conducted using STATA (Stata statistical software: Release 16; StataCorp LP, College Station, TX, USA).

Results

51 120 studies were identified from the search strategy, with 108 studies eligible for inclusion in the meta-analyses (figure 1). A summary of all included studies is shown in table 1. A list of the excluded studies at full-text review is available from the authors on request. All included studies were of adult patients who had required admission to hospital for SARS, MERS or COVID-19 infection. Measurement of the follow-up time varied among studies, commonly reporting from the time of hospital admission, coronavirus confirmation or discharge. All eligible studies had a risk of bias assessment completed by two reviewers independently (supplementary table S6a–c).

83 studies reporting PFT parameters and 58 studies reporting individual CT thorax features during follow-up were included. 7777 individual PFT tests and 5053 CT thorax examinations are included in these analyses. A total of 1496 (males $n=458$ (30.6%), females $n=790$ (52.8%), not reported $n=248$ (16.6%)), 73 (males $n=43$ (58.9%), females $n=30$ (41.1%)) and 9941 (males $n=5455$ (54.9%), females $n=4316$ (43.4%), not reported $n=170$ (1.7%)) patients have been included in the meta-analyses for SARS, MERS and COVID-19 infection, respectively. Individual forest plots of meta-analyses results are available in the supplementary material for each PFT parameter and CT feature by SARS, MERS and COVID-19 (including severity of infection subgroup analysis) infection (supplementary figures S1a to S9f). Many studies reported PFT by subgroups based on specific variables (*e.g.* severity of the acute coronavirus pneumonia or ventilation strategy) and are listed on the individual forest plots. Results of meta-analyses of PFTs are reported as mean % predicted value (95% confidence interval, I^2 estimate of heterogeneity). CT meta-analyses are reported as proportion (%) of participants (95% confidence interval, I^2 estimate of heterogeneity).

Pulmonary function tests

FEV_1 was 97.8% predicted (95% CI 89.2–106.3, I^2 97.8%) at 6 months after SARS infection, 98.84% predicted (95% CI 94.9–102.8, I^2 98.9%) at 6 months after COVID-19 infection and 90.7% predicted (95% CI 79.9–101.5, I^2 81.1%) at 12 months after MERS infection (figure 2). There was no difference between mild/moderate and severe/critical COVID-19 infection (figure 3).

FVC was 96.0% predicted (95% CI 93.5–102.6, I^2 94.3%) at 6 months after SARS infection, 96.0% predicted (95% CI 92.3–99.7, I^2 98.8%) at 6 months after COVID-19 infection and 92.8% predicted (95% CI 82.4–103.2, I^2 88.4%) at 12 months after MERS infection (figure 2). At 6 months after COVID-19 infection, severe/critical infection results in a lower FVC (89.1% predicted; 95% CI 85.4–92.9, I^2 82.6%) than after mild/moderate disease (102.3% predicted; 95% CI 95.2–109.5, I^2 92.8%) – this pattern is observed until 8–12 months follow-up (figure 3).

D_{LCO} was 82.5% predicted (95% CI 76.1–88.9, I^2 94.3%) and 82.3% predicted (95% CI 78.6–87.0, I^2 97.1%) after SARS and COVID-19 infection at 6 months, respectively, and 83.6% predicted (95% CI 79.3–88.0, I^2 89.6%) after MERS infection at 12 months (figure 2). At 6 months after COVID-19 infection, severe/critical infection results in a lower D_{LCO} (75.1% predicted; 95% CI 72.6–77.6, I^2 83.0%) than after mild/moderate disease (90.1% predicted; 95% CI 84.5–95.7, I^2 87.1%) – this pattern is observed until 8–12 months follow-up (figure 3). K_{CO} was 99.1% predicted (95% CI 85.3–113.0, I^2 98.0%) at

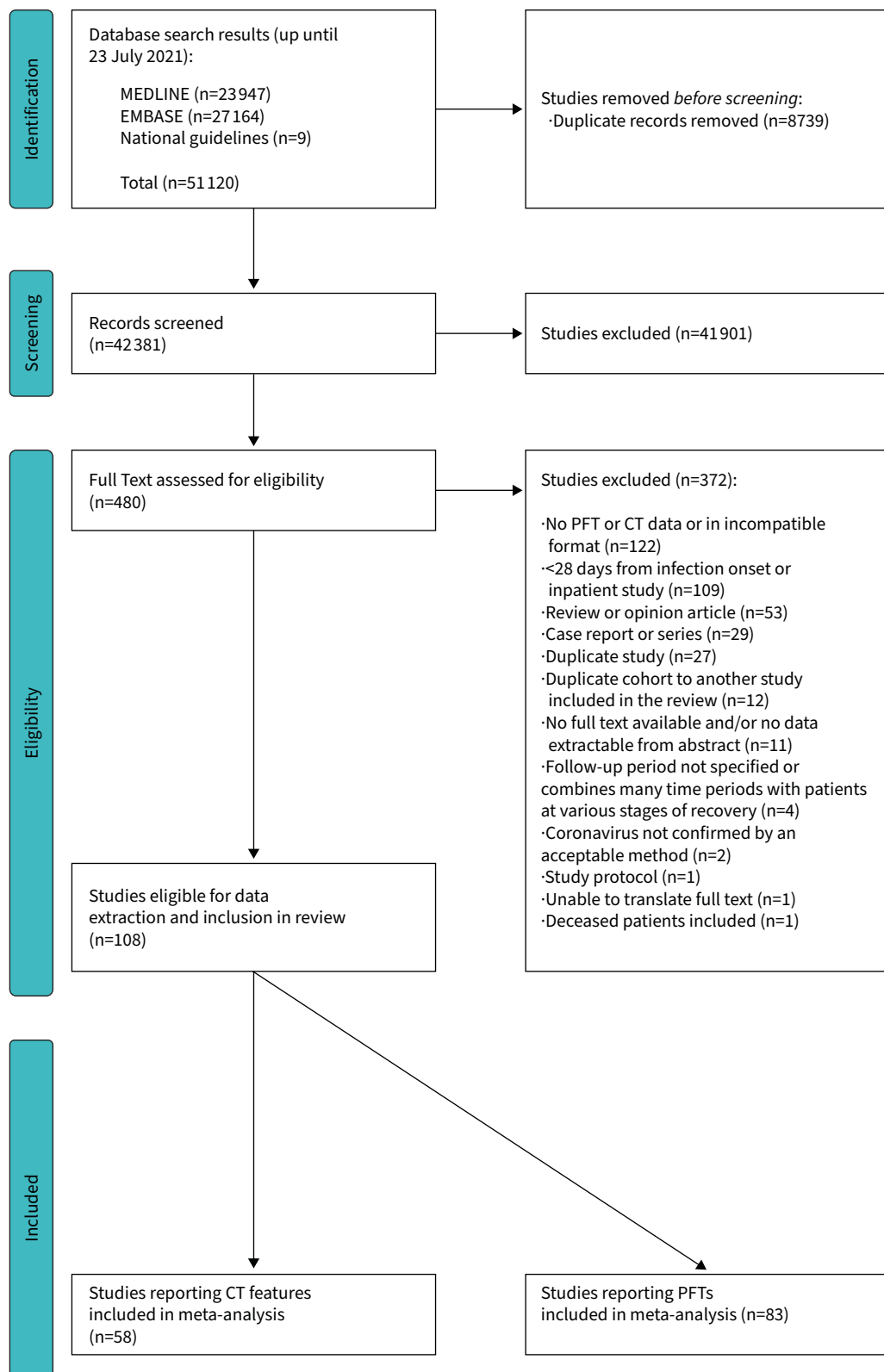


FIGURE 1 PRISMA-P flow diagram of study selection and inclusion process. CT: computed tomography; PFT: pulmonary function test.

TABLE 1 Characteristics of included studies

Study lead author, year of publication	Country	Study design	No. of participants (male/female)	Age of participants years	Follow-up time period(s)	Pulmonary function tests reported	CT thorax features reported	Report outcomes by acute infection severity
Severe acute respiratory syndrome (SARS)								
Antonio GE, <i>et al.</i> 2003 [11]	Hong Kong, China	Longitudinal	24 (10/14)	39± [#]	36.5 days		+	
Chang YC, <i>et al.</i> 2005 [18]	Taiwan, China	Longitudinal	40 (15/25)	42.8±12.3 [#]	51.8, 140.7 days		+	
Chen JH, <i>et al.</i> 2006 [19]	China	Longitudinal	111 (–/–)	–	3, 18 months		+	
Chiang CH, <i>et al.</i> 2004 [20]	Taiwan, China	Longitudinal	14 (3/11)	36.1±13.9 [#]	6 months	+	+	
Han Y, <i>et al.</i> 2003 [21]	China	Cross-sectional	69 (29/40)	–	59.7 days	+	+	
Hsu HH, <i>et al.</i> 2004 [22]	Taiwan, China	Cross-sectional	19 (6/13)	42.5±12.4 [#]	31.2 days	+	+	
Hui DS, <i>et al.</i> 2005 [23]	Hong Kong, China	Longitudinal	97 (39/58)	36.9±9.5 [#]	3, 6, 12 months	+		
Jin ZY, <i>et al.</i> 2003 [24]	China	Cross-sectional	100 (–/–)	–	2 months		+	
Li L, <i>et al.</i> 2015 [25]	China	Longitudinal	25 (3/22)	45.8±12.2 [#]	10 years	+		
Li TST, <i>et al.</i> 2006 [26]	China	Longitudinal	59 (34/25)	47±15.7 [#]	12 months	+		
Liu Y, <i>et al.</i> 2007 [27]	China	Longitudinal	37 (–/–)	–	1, 3, 12 months; 3 years	+		
Ngai JC, <i>et al.</i> 2010 [28]	China	Longitudinal	55 (19/36)	44.4±13.7 [#]	3, 6, 12, 18 months; 2 years	+		
Ong KC, <i>et al.</i> 2005 [29]	Singapore	Cross-sectional	94 (24/70)	37±12 [#]	1 year	+		
Ong KC, <i>et al.</i> 2004 [30]	Singapore	Cross-sectional	46 (12/34)	37.3±10.7 [#]	3 months	+		
Su MC, <i>et al.</i> 2007 [31]	Taiwan, China	Cross-sectional	13 (3/10)	31.4±4.8 [#]	14 months	+		
Tansey CM, <i>et al.</i> 2007 [32]	Canada	Longitudinal	117 (39/78)	42 (33–51) [¶]	3, 6, 12 months	+		
Wang CH, <i>et al.</i> 2005 [33]	Taiwan, China	Longitudinal	12 (3/9)	–	60, 90 days		+	
Wong KT, <i>et al.</i> 2004 [34]	China	Longitudinal	99 (41/58)	39.4±12.8 [#]	48 days; 3, 6 months		+	
Wu X, <i>et al.</i> 2016 [35]	China	Longitudinal	11 (3/8)	36.1±5.5 [#]	3, 6 months; 7 years		+	
Xie L, <i>et al.</i> 2005 [36]	China	Longitudinal	383 (160/223)	38.2±13.6 [#]	45 days; 2, 4, 6, 11 months	+		
Zhang P, <i>et al.</i> 2020 [37]	China	Longitudinal	71 (15/56)	–	3, 15 years	+		
Middle East respiratory syndrome (MERS)								
Park WB, <i>et al.</i> 2018 [38]	South Korea	Longitudinal	73 (43/30)	51±13 [#]	12 months	+		
Severe acute respiratory syndrome 2 (COVID-19)								
Anastasio F, <i>et al.</i> 2021 [39]	Italy	Cross-sectional	379 (174/205)	56 (49–63) [¶]	135 days	+		+
Aparisi A, <i>et al.</i> 2021 [40]	Spain	Cross-sectional	70 (25/45)	54.8±11.9 [#]	3 months	+		
Armange L, <i>et al.</i> 2021 [41]	France	Cross-sectional	23 (5/18)	44 (34–50) [¶]	6–8 weeks		+	

Continued

TABLE 1 Continued

Study lead author, year of publication	Country	Study design	No. of participants (male/female)	Age of participants years	Follow-up time period(s)	Pulmonary function tests reported	CT thorax features reported	Report outcomes by acute infection severity
Arnold DT, <i>et al.</i> 2020 [42]	UK	Cross-sectional	110 (68/42)	60 (44–76) [¶]	83 days	+	+	+
Balbi M, <i>et al.</i> 2021 [43]	Italy	Cross-sectional	91 (60/31)	66 (59–73) [¶]	105 days	+	+	+
Barisione G, <i>et al.</i> 2021 [44]	Italy	Cross-sectional	94 (65/29)	62±14 mild; 61±10 moderate; 60±11 severe [#]	117 days	+		+
Bellan M, <i>et al.</i> 2021 [45]	Italy	Cross-sectional	238 (142/96)	61 (50–71) [¶]	4 months	+		
Boari GEM, <i>et al.</i> 2021 [46]	Italy	Cross-sectional	94 (–/–)	–	4 months	+		+
Cao J, <i>et al.</i> 2021 [47]	China	Longitudinal	62 (35/27)	43.1±15.5 [#]	1 month		+	
Cortes-Telles A, <i>et al.</i> 2021 [48]	Mexico	Cross-sectional	186 (113/73)	47±13 [#]	2 months	+		+
Crisafulli E, <i>et al.</i> 2021 [49]	Italy	Cross-sectional	81 (54/27)	66.5±11.2 [#]	4 months	+		
D’Cruz RF, <i>et al.</i> 2021 [50]	UK	Cross-sectional	119 (74/45)	58.7±14.4 [#]	61 days		+	
Daher A, <i>et al.</i> 2021 [51]	Germany	Cross-sectional	18 (11/7)	61±7 [#]	6 months	+		+
Darley DR, <i>et al.</i> 2020 [52]	Australia	Cross-sectional	78 (51/27)	47±16 [#]	113 days	+		+
de Graaf MA, <i>et al.</i> 2021 [53]	Netherlands	Cross-sectional	81 (51/30)	60.8±13 [#]	6 weeks	+		+
Debeaumont D, <i>et al.</i> 2021 [54]	France	Cross-sectional	23 (12/11)	59±13 [#]	6 months	+		+
Dorelli G, <i>et al.</i> 2021 [55]	Italy	Cross-sectional	28 (22/6)	55.3 (52.3–61.9) [¶]	169 days	+		
Ego A, <i>et al.</i> 2021 [56]	Belgium	Cross-sectional	11 (8/3)	51.9±8.8 [#]	178 days	+		+
Frija-Masson J, <i>et al.</i> 2021a [57]	France	Cross-sectional	151 (91/55)	57 (49–67) [¶]	3 months	+		
Frija-Masson J, <i>et al.</i> 2021 [58]	France	Cross-sectional	137 (69/68)	59 (50–68) [¶]	3 months		+	
Froidure A, <i>et al.</i> 2021 [59]	Belgium	Cross-sectional	134 (79/55)	60 (53–68) [¶]	3 months	+	+	+
Gianella P, <i>et al.</i> 2021 [60]	Switzerland	Cross-sectional	39 (30/9)	62.5 (51.3–71) [¶]	3 months	+	+	
Gonzalez J, <i>et al.</i> 2021 [61]	Spain	Cross-sectional	62 (46/16)	60 (48–65) [¶]	3 months	+	+	+
Grist JT, <i>et al.</i> 2021 [62]	UK	Case-control	9 (6/3)	57±7 [#]	163 days	+		
Guler SA, <i>et al.</i> 2021 [63]	Switzerland	Cohort	113 (67/46)	60.3±12 severe; 52.9±11 mild [#]	128 days	+	+	+
Han X, <i>et al.</i> 2021 [64]	China	Longitudinal	114 (80/34)	54±12 [#]	175 days	+	+	
Huang C, <i>et al.</i> 2021 [65]	China	Cohort	1733 (897/836)	57 (47–65) [¶]	186 days		+	+
Huang Y, <i>et al.</i> 2020 [66]	China	Cross-sectional	57 (26/31)	46.7±13.8 [#]	1 month	+		
Jiang A, <i>et al.</i> 2021 [67]	Canada	Longitudinal	15 (12/3)	53±15 [#]	186 days	+		+
Joris M, <i>et al.</i> 2021 [68]	Belgium	Longitudinal	14 (10/4)	59 (52–62) [¶]	3 months	+		+

Continued

TABLE 1 Continued

Study lead author, year of publication	Country	Study design	No. of participants (male/female)	Age of participants years	Follow-up time period(s)	Pulmonary function tests reported	CT thorax features reported	Report outcomes by acute infection severity
Komici K, <i>et al.</i> 2021 [69]	Italy	Cross-sectional	24 (–/–)	23.5 (20–25.5) [¶]	1 month	+		+
Labaraca G, <i>et al.</i> 2021 [70]	Chile	Cross-sectional	60 (32/28)	39.2±14.3 mild; 47.4±11 moderate; 50±10.3 severe [#]	4 months	+	+	+
Lerum TV, <i>et al.</i> 2021 [71]	Norway	Cross-sectional	103 (54/49)	59 (49–72) [¶]	3 months	+	+	+
Li X, <i>et al.</i> 2021 [72]	China	Longitudinal	289 (141/148)	33.1±17.5 group A; 50.7±13.3 group B [#]	61–90 days		+	
Li H, <i>et al.</i> 2020 [73]	China	Cohort	13 (4/9)	35.8±– [#]	18.6, 24.6 days		+	
Liang L, <i>et al.</i> 2020 [74]	China	Cross-sectional	76 (21/55)	41.3±13.8 [#]	3 months	+	+	
Liu D, <i>et al.</i> 2020 [75]	China	Longitudinal	149 (67/82)	43±– [#]	7, 14, 21 days		+	
Liu C, <i>et al.</i> 2020 [76]	China	Longitudinal	51 (21/30)	46.9±14.9 male; 46.7±13.6 [#] female	10, 31 days		+	
Liu M, <i>et al.</i> 2021a [77]	China	Longitudinal	41 (22/19)	50±14 [#]	7 months		+	
Liu M, <i>et al.</i> 2021b [78]	China	Longitudinal	52 (26/26)	50.5 (41.3–57) [¶]	1 month		+	+
Lombardi F, <i>et al.</i> 2021 [79]	Italy	Cross-sectional	87 (58/29)	58±13 [#]	35 days	+		
Lopez-Romero S, <i>et al.</i> 2021 [80]	Mexico	Longitudinal	30 (16/14)	54 (40–62) [¶]	54, 120 days	+		
Marvisi M, <i>et al.</i> 2020 [81]	Italy	Cross-sectional	90 (60/30)	66±15 [#]	70 days	+	+	
McGroder CF, <i>et al.</i> 2021 [82]	USA	Cross-sectional	76 (45/31)	54±13.7 [#]	4 months	+	+	
Miwa M, <i>et al.</i> 2021 [83]	Japan	Cross-sectional	17 (14/3)	63 (59–57) [¶]	100 days	+	+	+
Mohr A, <i>et al.</i> 2021 [84]	Germany	Cross-sectional	10 (6/4)	50±13.1 [#]	115 days	+		
Myall KJ, <i>et al.</i> 2021 [85]	UK	Longitudinal	35 (25/10)	60.5±10.7 [#]	60 days	+		
Noel-Savina E, <i>et al.</i> 2021 [86]	France	Cross-sectional	72 (55/17)	60.5±12.8 [#]	4 months	+	+	
Nunez-Fernandez M, <i>et al.</i> 2021 [87]	Spain	Cross-sectional	225 (129/96)	62 (50–71) [¶]	12 weeks	+		
Pan M, <i>et al.</i> 2021 [88]	China	Cross-sectional	155 (87/68)	42.0±15.3 [#]	2 months	+		+
Parker AJ, <i>et al.</i> 2021 [89]	UK	Cross-sectional	36 (23/13)	52.5±11.4 [#]	10.9 weeks	+		+
Parry AH, <i>et al.</i> 2021 [90]	India	Cross-sectional	81 (50/31)	51.8±11.7 [#]	3 months		+	
Pasau T, <i>et al.</i> 2021 [91]	Belgium	Cross-sectional	32 (26/6)	59 (46–75) [¶]	3 months	+		+
Polese J, <i>et al.</i> 2021 [92]	Brazil	Cross-sectional	41 (30/11)	51±14 [#]	36 days	+		+
Qin W, <i>et al.</i> 2021 [93]	China	Cross-sectional	81 (34/47)	59±14 [#]	3 months	+	+	+
Raman B, <i>et al.</i> 2021 [94]	UK	Cohort	58 (34/24)	55.4±13.2 [#]	2.3 months	+		

Continued

TABLE 1 Continued

Study lead author, year of publication	Country	Study design	No. of participants (male/female)	Age of participants years	Follow-up time period(s)	Pulmonary function tests reported	CT thorax features reported	Report outcomes by acute infection severity
Remy-Jardin M, <i>et al.</i> 2021 [95]	France	Cross-sectional	55 (42/13)	59.7±13.7 [#]	3 months	+	+	
Riou N, <i>et al.</i> 2021 [96]	France	Longitudinal	81 (59/22)	61 (51–68) [¶]	3, 6 months	+	+	+
Salem AM, <i>et al.</i> 2021 [97]	Saudi Arabia	Case-control	20 (13/7)	47.1±11.6 [#]	3 months	+		
Santus P, <i>et al.</i> 2021 [98]	Italy	Longitudinal	20 (14/6)	58.2±15.5 [#]	6 weeks	+	+	+
Shah AS, <i>et al.</i> 2020 [99]	Canada	Cross-sectional	60 (41/19)	67 (54–74) [¶]	12 weeks	+	+	
Sibila O, <i>et al.</i> 2021 [100]	Spain	Cross-sectional	172 (98/74)	56.1±19.8 [#]	3 months	+		
Sonnweber T, <i>et al.</i> 2021 [101]	Austria	Longitudinal	145 (82/63)	57±14 [#]	60, 100 days		+	
Strumiliene E, <i>et al.</i> 2021 [102]	Lithuania	Cross-sectional	51 (25/26)	56±11.7 [#]	2 months	+	+	
Tabatabaei SMH, <i>et al.</i> 2020 [103]	Iran	Cross-sectional	52 (32/20)	50.2±13.1 [#]	3 months		+	
Trinkmann F, <i>et al.</i> 2021 [104]	Germany	Cross-sectional	246 (108/138)	48±15 [#]	2 months	+	+	
Truffaut L, <i>et al.</i> 2021 [105]	France	Cross-sectional	22 (16/6)	54.6±10.9 [#]	3 months	+	+	+
van den Borst B, <i>et al.</i> 2020 [106]	Netherlands	Cross-sectional	124 (74/50)	59±14 [#]	3 months	+	+	+
van der Sar-van der Brugge S, <i>et al.</i> 2021 [107]	Netherlands	Cross-sectional	101 (58/43)	66.4±12.6 [#]	6 weeks	+		+
Van Gassel RJJ, <i>et al.</i> 2021a [108]	Netherlands	Longitudinal	46 (32/14)	62 (55–68) [¶]	3, 7 months	+		+
Van Gassel RJJ, <i>et al.</i> 2021b [109]	Netherlands	Longitudinal	46 (32/14)	62 (55–68) [¶]	3 months	+	+	+
Varughese RA, <i>et al.</i> 2021 [110]	Canada	Case-control	7 (0/7)	53±4 [#]	158 days	+		
Venturelli S, <i>et al.</i> 2021 [111]	Italy	Cross-sectional	767 (515/252)	63±13.6 [#]	81 days	+		
Van Zeller C, <i>et al.</i> 2021 [112]	UK	Cross-sectional	15 (13/2)	51.1±16.1 [#]	3 months	+	+	+
Wang Z, <i>et al.</i> 2021 [113]	China	Longitudinal	25 (13/12)	43 (18–58) [¶]	8 weeks		+	
Writing committee for the COMEBAC study group. 2021 [114]	France	Cross-sectional	478 (277/201)	60.9±16.1 [#]	4 months	+	+	+
Wu Q, <i>et al.</i> 2021 [115]	China	Cross-sectional	54 (32/22)	43.4±15 moderate; 54.4±13.6 severe [#]	6 months	+	+	+
Wu X, <i>et al.</i> 2021 [116]	China	Longitudinal	83 (47/36)	60 (52–66) [¶]	3 months	+	+	+
Xu J, <i>et al.</i> 2021 [117]	China	Cohort	103 (46/57)	56 (44.75–63.25) RM group; 61 (55–68) RC group [¶]	3 months	+		+
Yan X, <i>et al.</i> 2021 [118]	China	Cross-sectional	119 (49/70)	53.0±12.2 [#]	12 months	+		+

Continued

TABLE 1 Continued

Study lead author, year of publication	Country	Study design	No. of participants (male/female)	Age of participants years	Follow-up time period(s)	Pulmonary function tests reported	CT thorax features reported	Report outcomes by acute infection severity
Yang ZL, <i>et al.</i> 2021 [119]	China	Cross-sectional	166 (69/97)	57±15 [#]	56 days		+	
Zampogna E, <i>et al.</i> 2021 [120]	Italy	Cross-sectional	30 (21/9)	63.6±12.2 [#]	1 months	+		
Zhang S, <i>et al.</i> 2021 [121]	China	Cross-sectional	40 (19/21)	57 (40–68) [¶]	8 months	+	+	+
Zhong L, <i>et al.</i> 2020 [122]	China	Cross-sectional	52 (–/–)	43.3±13.6 [#] moderate; 49.2±13.5 [#] severe	19.7 days		+	+
Zhou M, <i>et al.</i> 2021 [123]	China	Cohort	175 (75/100)	46 (39.5–56.75) asymptomatic; 56 (47.5–63) mild/moderate; 63 (56–69) severe [¶]	3 months	+	+	+
Zou JN, <i>et al.</i> 2021 [124]	China	Longitudinal	284 (122/162)	55.9±1.0 fibrosis group; 47.3±2.9 no fibrosis group [#]	30, 60, 90 days		+	+

CT: computed tomography; MRI: magnetic resonance imaging; USS: ultrasound; 6MWD: 6-min walk distance; CPET: cardiopulmonary exercise test; PET-CT: positive emission tomography-CT. +: present in study text; #: mean±SD; ¶: median (interquartile range).

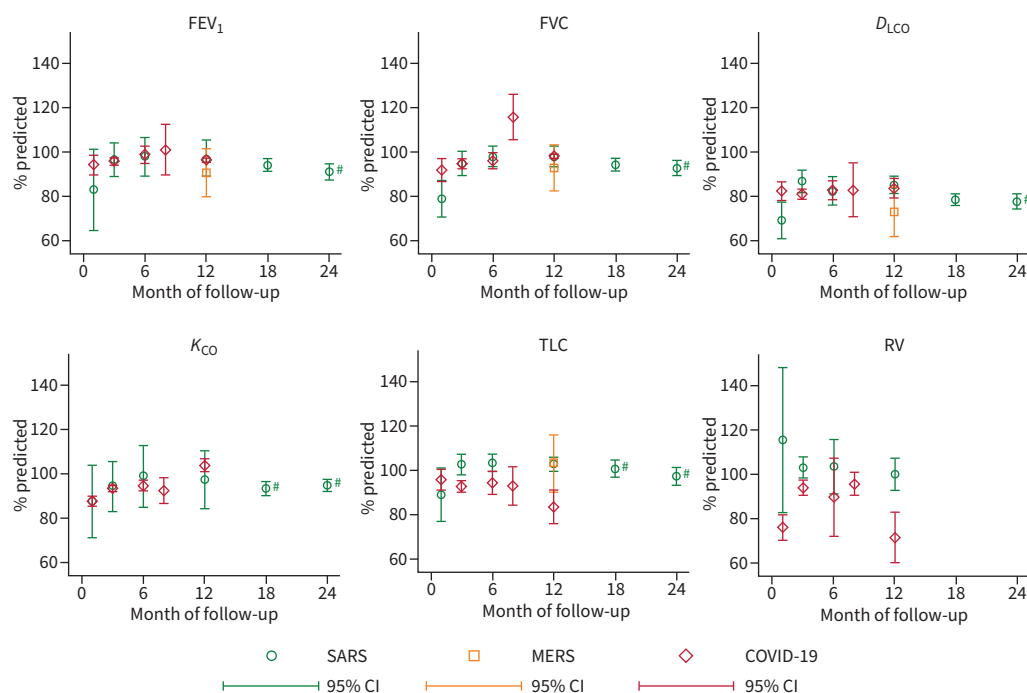


FIGURE 2 Meta-analysis results of pulmonary function parameters during the first 2 years of follow-up after SARS, MERS and COVID-19 infection. FEV₁: forced expiratory volume in 1 s; FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for uptake of carbon monoxide; K_{CO}: carbon monoxide transfer coefficient; TLC: total lung capacity; RV: residual volume; SARS: severe acute respiratory syndrome; MERS: Middle East respiratory syndrome; COVID-19: severe acute respiratory syndrome coronavirus 2; 95% CI: 95% confidence interval. #: one study only reporting data for this time period.

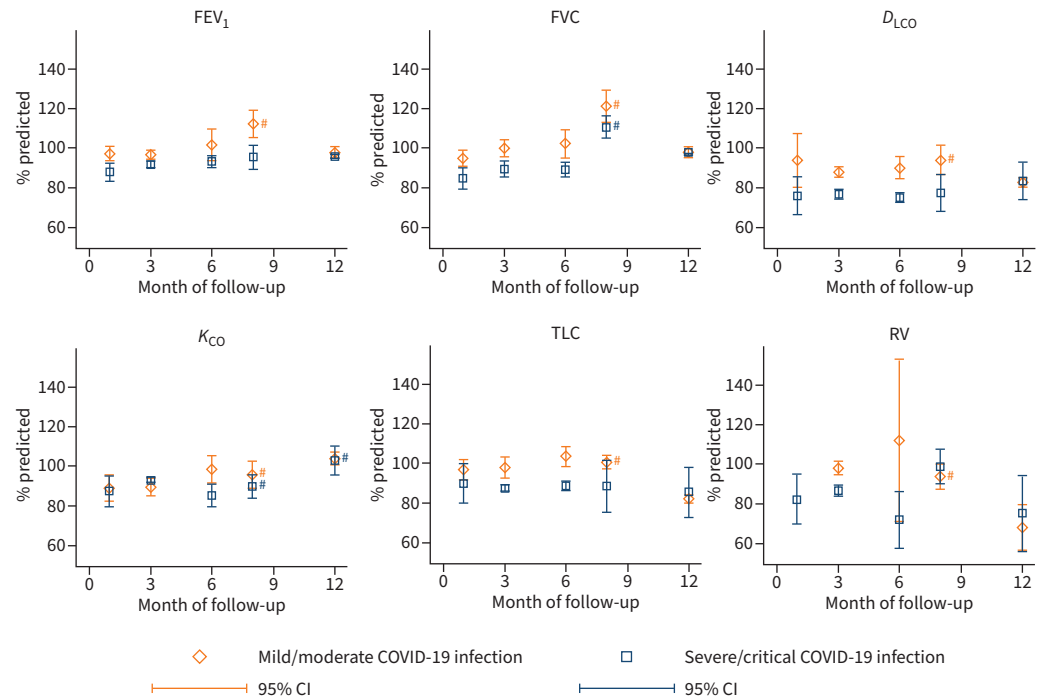


FIGURE 3 Subgroup meta-analysis results of pulmonary function parameters during the first year of follow-up after COVID-19 infection. FEV₁: forced expiratory volume in 1 s; FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for uptake of carbon monoxide; K_{CO}: carbon monoxide transfer coefficient; TLC: total lung capacity; RV: residual volume; COVID-19: severe acute respiratory syndrome coronavirus 2; 95% CI: 95% confidence interval. #: one study only reporting data for this time period.

6 months after SARS infection and 94.9% predicted (95% CI 92.4–97.4, I² 93.6%) 6 months after COVID-19 infection (figure 2). There was no difference between mild/moderate and severe/critical COVID-19 infection (figure 3).

TLC was 103.5% predicted (95% CI 99.8–107.3, I² 80.5%) at 6 months after SARS infection, 94.5% predicted (95% CI 89.3–99.7, I² 99.6%) 6 months after COVID-19 infection and 103.3% predicted (95% CI 90.3–116.3, I² 89.5%) 12 months after MERS infection (figure 2). At 6 months after COVID-19 infection, severe/critical infection results in a lower TLC (88.8% predicted; 95% CI 86.2–91.4, I² 83.8%) than after mild/moderate disease (103.8% predicted; 95% CI 98.6–108.9, I² 94.6%) – this pattern is observed until 8–12 months follow-up (figure 3). RV was 103.3% predicted (95% CI 98.5–108.1, I² 40.0%) at 3 months after SARS infection and 94.1% predicted (95% CI 90.7–97.6, I² 98.2%) 3 months after COVID-19 infection (figure 2).

Thoracic CT

At 6 months after SARS infection, 76% (95% CI 45–97%, I² 86.7%) of patients had ground-glass opacity (GGO), 59% (30–85%) had linear opacities, 71% (50–89%) had reticulation and 3% (0–9%) had consolidation present on CT. 6% (1–14%) of CTs at 6 months after SARS featured honeycombing and 18% (10–28%) had traction bronchiectasis and bronchiolectasis (figure 4). At 18 months after SARS infection, 21% (14–29%) of CTs showed persisting GGO and 25% (17–34%) had linear opacities. There were no data available following MERS infection.

At 6 months after COVID-19 infection, 32% (95% CI 16–50%, I² 93.1%) of patients had GGO, 34% (95% CI 14–57%, I² 93.9%) had linear opacities, 15% (95% CI 6–27%, I² 86.2%) had reticulation and 5% (95% CI 0–15%, I² 82.2%) had consolidation present on CT. 1% (95% CI 0–5%, I² 45.4%) of CTs featured honeycombing and 15% (95% CI 6–26%, I² 88.0%) had traction bronchiectasis and bronchiolectasis (figure 4). Early data reported at 12 months after COVID-19 suggests that linear opacities and GGO are the commonest persisting CT features, although at lower proportions than seen at 6 months.

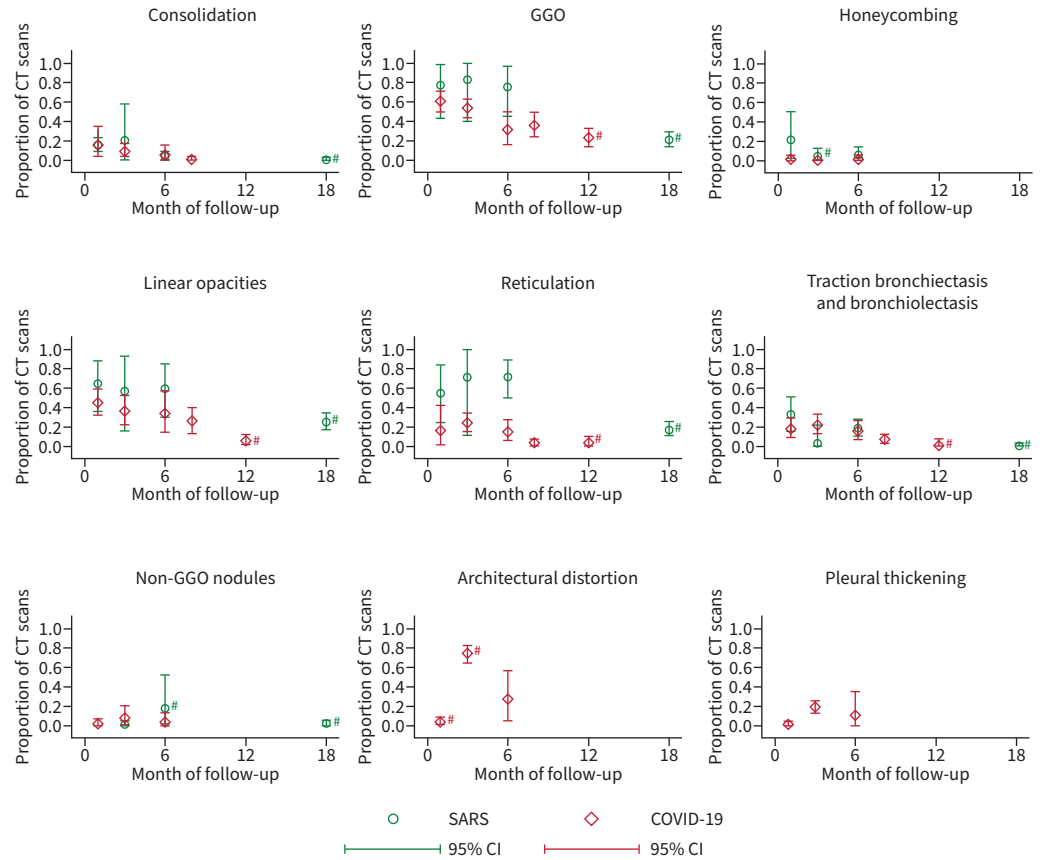


FIGURE 4 Meta-proportion results of computed tomography (CT) features during the first 18 months of follow-up after SARS and COVID-19 infection. SARS: severe acute respiratory syndrome; COVID-19: severe acute respiratory syndrome coronavirus 2; 95% CI: 95% confidence interval; GGO: ground-glass opacity. #: one study only reporting data for this time period.

All CT features were present at lower proportions in the first 6 months after mild/moderate acute COVID-19 infection compared with severe/critical COVID-19 infection (figure 5). GGO (43%; 95% CI 30–56%, I^2 54.2%), linear opacities (34%; 95% CI 16–55%, I^2 85.7%), traction bronchiectasis and bronchiolectasis (25%; 95% CI 3–56%, I^2 94.3%) and reticulation (28%; 95% CI 9–52%, I^2 88.6%) were present at 6 months after severe/critical COVID-19 infection. CT features are reported at lower proportions at each sequential time point in both groups.

Discussion

To the authors’ knowledge, this is the first systematic review and meta-analysis of PFT and CT features following infection with SARS, MERS and COVID-19. Following SARS and COVID-19 infection, a mild reduction in the FVC and TLC suggest a transient restrictive defect in the first 3 months of follow-up, with a return to the normal limits for an individual’s lung volumes noted at 6 months onwards. The most significant physiological abnormality seen in SARS, MERS and COVID-19 is a persistent reduction in the D_{LCO} . Considering this, one can deduce that in the follow-up period after SARS and COVID-19, microvascular abnormalities, reduced alveolar membrane diffusion and/or extrapulmonary restriction may be present in some patients. There was no physiological evidence of obstructive lung disease during follow-up of SARS, MERS or COVID-19 infection.

Whilst direct parenchymal injury is likely responsible for most physiological findings in recovery, it is important for physicians to consider the presence of respiratory muscle weakness, similar to that seen in post-intensive care syndrome and critical illness myopathy [125–127]. It is estimated that respiratory muscle weakness is two times that of limb muscle weakness after 1 day of invasive mechanical ventilation [128]. This may in part explain the observations seen in these meta-analyses when comparing mild/moderate and severe/critical disease outcomes, although it is more probable that this is the result of greater interstitial

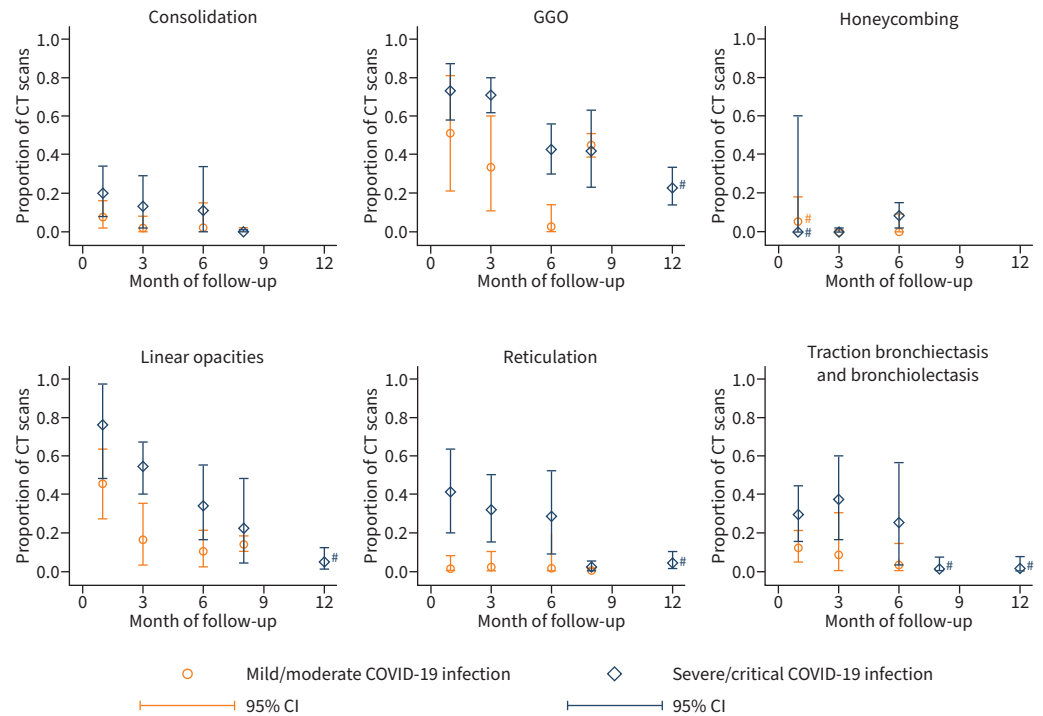


FIGURE 5 Meta-proportion results of computed tomography (CT) features during the first 12 months of follow-up after COVID-19 infection by severity of acute infection. COVID-19: severe acute respiratory syndrome coronavirus 2; 95% CI: 95% confidence interval; GGO: ground-glass opacity. #: one study only reporting data for this time period.

injury acquired in worse infection. To date, the prevalence of respiratory muscle weakness is unknown post-COVID-19 infection; however, small studies demonstrate inspiratory muscle training has physiological benefits during the recovery phase [129, 130]. Furthermore, studies assessing the role of pulmonary rehabilitation in COVID-19 survivors have demonstrated similar benefits [131]. Respiratory muscle weakness is an important additional factor to consider, especially in patients with severe or critical acute disease when prolonged intubation and intensivists support was required, and may contribute to the abnormalities seen physiologically, complicating interpretation.

Other studies have compared the D_{LCO} and transfer factor of the lung for nitric oxide (T_{LNO}) during follow-up after COVID-19 infection – the D_{LCO} is more sensitive to microvascular alterations, whilst T_{LNO} is more indicative of alveolar membrane diffusive conductance [132, 133]. Both studies demonstrate that greater proportions of patients have reduced T_{LNO} than D_{LCO} during follow-up at 3 months [87] and 8 months [44] which correlates with persistent symptoms and CT abnormalities. This is suggestive that an alveolar membrane abnormality persists after infection, causing reduced oxygen diffusion rather than a microvascular disease, supporting the presence of a post-COVID-19 interstitial lung abnormality or disease. In addition, there are sparse reports of pulmonary embolism months after COVID-19 infection.

Thoracic CT scans after SARS and COVID-19 demonstrate similar patterns: there is a significant burden of GGO, linear opacities, reticulation and architectural distortion (after COVID-19). This indicates a persistent abnormality in the interstitium and suggests an explanation for the observed reduction of the diffusion capacity of the lung physiologically. Considering the low proportions of honeycombing and traction bronchiectasis reported throughout the follow-up periods of both infections to date, it is likely the CT pattern does not represent usual interstitial pneumonia. Organising pneumonia is a feature of acute COVID-19 infection [134, 135] and has been reported during follow-up after COVID-19 infection [85]. It is likely that a subgroup of patients develop this post-COVID-19 interstitial pattern, although whether it is the dominant pattern is yet to be determined. When interpreting individual CT features, it is important to consider undiagnosed premorbid interstitial disease and acknowledge that some features can be indicative of non-ILD pathology (such as reticulation and GGO in isolation) – unfortunately this information was not clear in many studies. Therefore, the role of ILD specialist teams is paramount in the assessment of these patients.

Advances in imaging modalities between the SARS epidemic and COVID-19 pandemic have enabled attempts to assess pulmonary physiology and radiology in synchrony. Hyperpolarised [129] Xenon gas MRI of the thorax is an emerging research imaging modality and evaluates both pulmonary gas-exchange function and the lung microstructure. Li *et al.* [73] have demonstrated patients recovering from COVID-19 have reduced gas-exchange function with an average higher percentage of ventilation defects compared with healthy controls, whilst areas of GGO that have been reabsorbed on CT demonstrate a persistent reduction in ventilation. This suggests the presence of interstitial thickening and perfusion defects in the post-COVID-19 recovery phase is caused by alveolitis and possible early fibrosis.

This review highlights that the severity of acute infection determines the risk of persistent physiological and CT abnormalities in follow-up after COVID-19. Those with severe or critical acute COVID-19 (*i.e.* a greater acute lung parenchymal injury) have a greater severity of physiological and CT abnormalities compared with mild and moderate infection during follow-up. Those who have survived severe and critical illness still demonstrate improvement over time, and at 8–12 months show a similar degree of CT and physiological abnormality compared with mild/moderate infections. These sequelae may therefore represent a regressive interstitial syndrome [136] and not a diffuse progressive ILD. Considering this, in the interim, the term post-COVID-19 interstitial lung syndrome (PCOILS) may be more appropriate than post-COVID-19 ILD. For physicians managing these patients, we would advocate surveillance of these patients until clinical (symptom), radiological and physiological resolution has occurred – although this should be individualised to each patient based on their acute disease and comorbidities. In SARS studies, it was not possible to differentiate and perform subgroup analysis by acute infection severity as we have with COVID-19. It is estimated that 20–36% of patients infected with SARS required intensive care treatment [137], which is higher than estimates in COVID-19 infection [138], suggesting that SARS may have led to more severe disease – this could explain the differences in proportions of CT features observed between SARS and COVID-19 in the early recovery phase.

The main limitation of this systematic review and meta-analysis of PFTs and CT features concerns the high level of heterogeneity seen. Some variation occurs due to an inability to control analysis for confounders such as premorbid comorbidity and functional status, ethnicity and acute treatments received (this would require individual participant data meta-analysis). It was unclear from many studies whether a pre-existing ILD or chronic respiratory disease might explain some of the PFT and CT findings. Both PFT and CT studies (especially when retrospective) are vulnerable to a variety of selection, investigator, publication and reporting biases, as evidenced in risk of bias assessments (supplementary table S6a–c). Only a single retrospective study of PFTs was available at 12 months' follow-up following MERS infection, which is vulnerable to bias and requires caution when interpreting – no other data were available at other time points for MERS.

Some heterogeneity arising in the COVID-19 subgroup analysis will have resulted from inter-study variation in the classification of acute COVID-19 severity. Challenges arose in differentiating acute moderate and severe COVID-19 disease as per the World Health Organisation guidelines [17] – often studies determined severity by an oxygen requirement instead of oxygen saturation on air. Whilst we attempted to differentiate COVID-19 severity from the information provided, some studies were not included in subgroup analysis due to uncertainty arising over severity classification. Almost all COVID-19 studies select participants from patients admitted to hospital during their infection, with mild acute COVID-19 infection in the community (the majority of total COVID-19 cases) disproportionately under-represented in studies – these results likely over-represent sequelae after COVID-19.

It is important to recognise that each time period analysed in this review refers to a different cohort of patients, meaning longitudinal analysis between time periods is not possible and focus on single time points in turn should be applied. Furthermore, we have not been able to identify or quantify the proportion of lung parenchyma affected by CT features during recovery, nor identify the proportion of patients who experience complete CT resolution. Limited studies have included CT severity scores during recovery from COVID-19 [64, 139], with one demonstrating median CT score declines steadily over time [139]. This correlates with our earlier suggestion of a potentially regressive interstitial lung syndrome – future studies should consider the use of CT quantification methods, alongside describing which specific CT features arise during the recovery period.

The evidence base on the long-term respiratory impact of COVID-19 is ever increasing, and it is important to recognise that this review represents the evidence available from the first 20 months of the COVID-19 pandemic. The authors are aware that since the searches were performed, additional studies (of large scale) have been released [140, 141]. Larger research studies will continue to report in time, with focus on the

natural history, histopathological findings and treatment options of persistent post-COVID-19 pulmonary disease required. Studies such as the UKILD-Long COVID study [142] with sub-studies POSTCODE (POST COvid-19 interstitial lung Disease) and XMAS (Xenon MRI investigation of Alveolar dysfunction) and PCOILS [143] are eagerly anticipated. The emergence of COVID-19 variants and the utilisation of vaccination also require consideration in future studies of post-COVID-19 sequelae.

Conclusion

A significant proportion of patients recovering from SARS and MERS have experienced persistent pulmonary physiological and radiographic abnormalities during the follow-up period. A similar pattern has emerged in COVID-19 survivors. Physiological parameters suggest a persistent alveolar diffusion defect due to persisting interstitial injury with or without respiratory muscle weakness. Thoracic CT demonstrates persisting GGO, linear opacities and reticulation and may be indicative of a post-COVID-19 interstitial lung syndrome. CT features decline at subsequent time points but are present in significant proportions of survivors at 6 months. Severe and critical acute COVID-19 infection causes greater pulmonary physiological impairment and greater proportions of CT abnormality.

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Author contributors: C.C. Huntley and K. Patel conceived the idea for the study. C.C. Huntley, K. Patel, A.M. Turner, P.S. Burge and G.I. Walters designed the study and wrote the protocol. C.C. Huntley and K. Patel conducted initial database searches. C.C. Huntley, K. Patel, S. Bil Bushra, F. Mobeen, M.N. Armitage, A. Pye, C.B. Knight, A. Mostafa, M. Kershaw, A.Z. Mughal and E. McKemey conducted the initial review of search results against eligibility criteria, with all authors involved with full-text review and data extraction (ensuring two authors independently extracted data from each included study). All authors had full access to the data. C.C. Huntley conducted the data analysis and verified the data. G.I. Walters verified the data and the analysis. All authors reviewed the analysis results. C.C. Huntley wrote the original and final version of the manuscript with editing and review by all co-authors. A.M. Turner, P.S. Burge and G.I. Walters supervised the study.

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