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Review Article

Respiratory Symptoms, Pulmonary Function and Lung CT Findings in Patients with Post-COVID-19 Syndrome: A Systematic Review and Meta-Analysis

Abstract

Background: Post-COVID-19 syndrome is a recognized condition characterized by persisting and/or newly detected signs and symptoms 12 or more weeks after a laboratory-confirmed acute COVID-19 infection. Our objectives were to determine the prevalence of the most common respiratory symptoms, abnormal lung CT-scan patterns and abnormal lung function test results in patients experiencing post-COVID-19 syndrome, as well as the mean values of the parameters of respiratory function test results in the same patient group.

Methods: A systematic review was performed in four databases. Of the initial 13675 abstracts retrieved, 41 studies reporting on 17, 565 patients were included in the data synthesis.

Results: The most significant prevalence in our analysis was for: dyspnea 0.25 (0.19-0.31, p<0.01, I2=98%), cough 0.11 (CI 0.07–0.16, p <0.01, I^2 = 96%), increased and/or newly detected sputum production 0.07 (CI 0.02–0.16, p <0.01, I^2 = 95%), ground-glass opacities 0.42 (CI 0.30–0.54, p <0.01, I2 = 96%), fibrosis and/or fibrotic-like changes 0.31 (CI 0.16–0.49, p <0.01, I^2 = 96%), DLCO below 80% of predicted value 0.37 (CI 0.29–0.46, p <0.01, I^2 = 90%), RV below 80% of predicted value 0.25 (CI 0.05–0.52, p <0.01, I^2 = 97%).

Conclusion: A significant portion of patients in the post-COVID-19 period experience respiratory manifestations, chest CT-scan and PFTs abnormalities. The insight and understanding of the respiratory profile in post-COVID-19 syndrome could aid for its timely recognition and accurate diagnosis, as well as further research in terms of prevention and early mitigation of these sequelae, and improvement of quality of life.

Keywords: Post-COVID-19 syndrome, Respiratory symptoms, Pulmonary function tests (PFTs), chest CT-scan, Systematic review, Meta-analysis.

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Abbreviations

COPD, Chronic Obstructive Pulmonary Disease; **COVID-19**, Coronavirus disease 2019; **CT**, Computerized tomography; C- fibers, Group C nerve fiber; **DLCO**, Diffusion Capacity Of The Lungs For Carbon Monoxide; **DLCO/VA**, Diffusion Capacity Of The Lungs For Carbon Monoxide Divided By Alveolar Volume; **FEV1**, Forced Expiratory Volume In The First Second; **FEV6**, Forced Expiratory Volume In The First Six Seconds; **FEV1/FVC**, **FEV/1FVC** ratio= Forced Expiratory Volume In The First Second Divided By The Forced Vital Capacity; **FVC**, Forced Vital Capacity; **GRADE**, Grading Of Recommendations, Assessment, Development, And Evaluations; **KCO**, Carbon Monoxide Transfer Coefficient; **Long-COVID**, Long Term Sequelae Of Coronavirus 2019 Disease; **mMRC**, Modified Medical Research Council Dyspnea Scale; **MOOSE**, Meta-Analysis Of Observational Studies In Epidemiology; **NICE**, National Institute for Health and Care Excellence; Polymerase Chain Reaction; **PRISMA**, Reporting Items for Systematic Reviews and Meta-Analyses; post-COVID-19, Sequelae 12 or more weeks after acute Coronavirus 2019 disease; **PROSPERO**, International Prospective Register of Systematic Reviews; **REML**, Restricted Maximum Likelihood Model; **RV**, Residual Volume; **Sars-CoV-2**, Severe Acute Respiratory Syndrome Coronavirus 2; **TLC**, Total Lung Capacity; **VA**, Alveolar Volume; **VC**, Vital Capacity; **WHO**, World Health Organization.

Introduction

The global COVID-19 pandemic has had an unprecedented deleterious impact. According to the WHO, the novel SARS-CoV-2 virus is responsible for 6.97 million deaths worldwide, with more than 771 million cumulative cases reported so far [1]. Since the beginning of the pandemic at the end of 2019, "It has become increasingly clear that patients recovering from acute COVID-19 are developing persistent symptoms that are not explained by any other underlying conditions." A growing body

of evidence has shown that survivors of the acute illness of COVID-19 are experiencing symptoms and signs that cannot be explained by an alternative etiology or a previous illness. As early as 2020, many studies that supported this conclusion began to emerge [2,3]. The time of onset of these manifestations varied greatly, from 2 weeks after PCR-confirmed infection with COVID-19, to more than a year [4, 5]. Consequences included signs and symptoms following acute COVID-19 (or newly developed), usually long-term respiratory (dyspnea, cough, excessive sputum production), as well as various new non-respiratory complaints, most often neuropsychiatric, dermatological, and other less common manifestations [6,7,8]. Many healthcare regulatory authorities worldwide have attempted to classify these signs and symptoms by time of onset and duration, as well as other attributes. Despite this, there is no internationally agreed clinical definition or clear treatment pathway, and the evidence base on this topic is a living and evolving matter. The UK's National Institute for Health and Care Excellence (NICE), in collaboration with the Scottish Intercollegiate Guidelines Network (SIGN) and the Royal College of General Practitioners (RCGP), recognizes three separate entities associated with SARS-CoV-2 infection, formulated as clinical case definitions: acute COVID-19, ongoing symptomatic COVID-19 and post-COVID-19 syndrome [9]. According to previous guidelines, post-COVID-19 syndrome is recognized as "Signs and symptoms that develop during or after an infection consistent with COVID-19, persist for more than 12 weeks, and cannot be explained by an alternative diagnosis". Post-COVID-19 syndrome continues to be a challenge in determining the best practice standards of care due to evolving evidence, while can have significant impact on quality of life. Therefore, a summary of available evidence in the literature at a given time could be useful in further clarifying its nature and creating a strategy for management. In this context, we conducted a systematic review and meta-analysis to determine, with regard to the NICE clinical case definition, the respiratory profile of patients who experienced post-COVID-19 syndrome and had a previously laboratory-confirmed SARS-CoV-2 infection. The respiratory profile consisted of the prevalence of respiratory symptoms, the prevalence of abnormal Pulmonary Function Tests (PFTs) and Chest Computed Tomography (CT) findings, as well as the mean values of PFTs parameters.

Material and Methods

Protocol and registration

We performed a systematic review in accordance with the Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [10]. The meta-analysis was performed according to the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) [11]. This review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42022368236) [12].

Eligibility criteria

Inclusion criteria: We included only articles that met the following inclusion criteria:

Study design

1. Observational studies (cohort, cross-sectional, case control, prospective and retrospective, case series); 2. PCR confirmed (laboratory-confirmed) SARS-CoV-2 infection; 3. Length of participant's follow-up in according to NICE clinical case definition of post-COVID-19 syndrome (Signs and symptoms that develop during or after an infection consistent with COVID-19, and continue for more than 12 weeks [9]; 4. Participant's age ≥ 18 years; 5. Peer-reviewed articles and ethically approved clinical studies on humans that were reporting on: respiratory complications and outcomes after acute COVID-19 and/or respiratory symptoms and signs in patients with post-COVID-19 syndrome and/or results of PFTs (spirometry, 6MWD, DLCO) in patients with post-COVID-19 syndrome and/or chest CT scan findings in patients with post-COVID-19 syndrome.

Exclusion criteria: The exclusion criteria of this systematic review and meta-analysis were as follows: 1. Articles not written in English language; 2. Studies utilizing non-human methodology (i.e., lab simulation, in vitro studies, or animal models); 3. Studies with less than 30 participants and/or gender ratio > 80%:20% (male or female favorable); 4. Studies not focused on COVID-19 sequelae; 5. Studies that do not provide detailed information for further analysis.

Search strategy across databases

We systematically searched across four databases: PubMed, Google Scholar, Research Gate and Elsevier, to identify the studies that were conducted in the period January 2020 - June 2022. The search terms used as keywords in the databases search engines were: post-COVID-19 syndrome (and synonyms such as post-COVID syndrome, long-COVID-19 syndrome, long-COVID-19, Post-COVID, Long-COVID, Post SARS-CoV-2, Long SARS-CoV-2), respiratory symptoms (or respiratory sequelae, respiratory complications), dyspnea (or dyspnoea), cough, sputum (or sputum production), CT scan (or lung CT scan, chest CT scan, CT scan findings), ground glass opacifications, bronchiectasis, parenchymal bands, COPD, asthma, lung fibrosis (or pulmonary fibrosis), spirometry findings (or spirometry results), FEV1, FVC, FEV1/FVC ratio (or Tiffeneau index), RV, TLC, 6-minute walking distance test, DLCO (or lung diffusion capacity), mMRC (or mMRC score). The terms referring

to the post-COVID-19 entity were combined with the rest of the search terms using the Boolean Logical Operator (AND).

Study selection process and data extraction

The individual references were screened by three investigators (I.R., N.G. and N.M). All duplicate references were removed from the reference pool and the remaining references were first screened based on their abstract and title. If they were excluded by merit of the exclusion criteria of this systematic review and meta-analysis, they were subjected to a full text screening by the same three investigators. (I.R., N.G. and N.M). All disagreements and problems in the selection process were resolved through consultation and under the guidance of the fourth author (Z.N.). If all inclusion criteria were met, an individual study was included in the final draft of this systematic review and meta-analysis. For all the studies included quality assessment by one author (I.R.) was performed. Data extraction was performed by three authors. (I.R., N.G. and N.M). The data were then compared, and the extraction process was assessed by the three authors in consultation with and under the guidance of the fourth author (Z.N.). From the included studies we extracted outcome data and study characteristics in a standardized data collection form. The collection form for the statistical analysis of pooled prevalence for each separate outcome contained the total number of events (patients with the target outcome), the total number of participants and the percentage of outcomes among the study's participants. Studies without data on total events (outcomes) and/or total participants were excluded from the analysis for that particular outcome. If a study contained data on the total number of events (outcomes) and the total participants but not on the percentage of target outcomes among the study participants, the study was not excluded, and the percentage was calculated by dividing the total number of events (outcomes) by the total number of participants. If a study contained data on the total participants and the exact percentage of people with the target outcome, but not on the number of participants with the target event, the number of events was calculated by using the above data.

Methodological quality assessment

One review author (I.R.) conducted an independent risk of bias assessment for each study included in the review and meta-analysis using the "Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Studies Reporting Prevalence Data" [13]. Each study's full text and supplementary materials were submitted to analysis to answer the nine questions included in the questionnaire. Whenever needed, the review author consulted the three remaining authors to discuss the correct definitions and resolve issues. Each study's overall risk of bias was classified as low, medium, or high, based on the summation of the risk of bias for each individual category for that study. In addition, for each of the studies used for the synthesis of an outcome the results for each question of the checklist were pooled together and presented in the form of a graph to evaluate the risk of bias for each category of that particular outcome.

Outcomes

We report the prevalence of all primary outcomes: respiratory symptoms (dyspnea, cough, increased and/or new sputum production), mMRC scores (≥ 1, and ≥ 2), PFTs results that deviate from normal range of values (DLCO/VA(KCO), DLCO, TLC, RV, FEV1 and FVC below 80% of predicted value, FEV1/FVC ratio below 70% of predicted value), chest CT-scan findings (ground-glass opacities, consolidation, bronchiectasis and/or bronchial dilation, interlobular septal thickening, reticular pattern, fibrosis and/or fibrotic lung changes, atelectasis, pulmonary nodules, emphysema, honeycombing, mixed ground-glass opacities, sub-pleural lines, line-like and/or band-like opacities), as well as overall prevalence of abnormal chest CT findings. Pertaining to the secondary outcomes we report the mean values of PFTs [6-minute walking distance (6MWD) score value (in meters), DLCO as % of predicted value, FEV1 value (in liters), and FVC value (in liters)], as well as FEV1, FVC, FEV1/FVC ratio, RV, and TLC as % of predicted value.

Data synthesis and statistical analysis

Statistical analysis and the creation of plots were carried out by one author (I.R.).

For each of the primary and secondary outcomes a forest plot was constructed. We pooled the prevalence of each of the primary outcomes using the Freeman-Tukey double arcsine transformation method. We calculated the single means of each secondary outcome using a Restricted Maximum Likelihood Model (REML). The combined measurements of effect for each primary and secondary outcome were obtained under a random-effects model due to the expected heterogeneity between studies in prognostic reviews. Statistical heterogeneity was measured through the I^2 statistic and expressed as either low (I^2<25%), moderate (I^2=25-50%) or high (I^2>50%). All statistical analyses were carried out with a confidence interval (CI) of 95%. To assess the risk of publication bias, funnel plots were constructed and visually analyzed. The certainty of evidence for each of the reported outcomes was assessed using the Grading of Recommendations, Assessment, Development, And Evaluations (GRADE) system [14]. All the statistical analysis and the creation of plots were performed using the software program R Studio.

Addressing missing data

We conducted meta-analyses based on the available data on each outcome of each study. We tried to retrieve missing data where there was any. However, where missing data was not retrieved, it was not imputed either.

Patient and Public Involvement

There were no patients involved in the development of this protocol.

Ethics and dissemination

This review does not require ethics approval as this is a systematic review of other published studies and does not directly involve patients. The results of this review will be submitted to a peer-reviewed journal for publication and will be available on publicly accessible institutional websites.

Results

Study selection

The initial search identified 13675 potential studies from four databases: PubMed (n=6225), Google Scholar (n=3308), Research Gate (n=2605) and Scopus (n=1537). Out of these, 5812 publications were left after removing the duplicates (n=7003) and removing publications not written in English (n=860). The remaining 5812 abstracts were screened, and 4989 abstracts were excluded. Out of the remaining 823 abstracts, only two full texts could not be retrieved, so 821 studies full texts were assessed for eligibility. Out of them, 378 studies were excluded for having a follow-up period less than 12 weeks after an acute COVID-19 infection, 185 for not a having a PCR or laboratory-confirmed acute COVID-19 infection for all study's participants, 121 studies for having less than 30 participants, 51 studies for including patients with an ongoing acute COVID-19 infection in the participants at follow-up, 36 studies for not being adequate for this reviews purpose (letters to the editor and reviews), 8 studies for having an insufficient gender ratio (patient cohort being composed of mostly men or women) and one study was retracted by the publisher. Overall, 780 studies were excluded because they did not meet the criteria of the systematic review, and the remaining 41 studies were included in this systematic review and meta-analysis [Figure 1].

Characteristics of the included studies

Country of origin and design of included studies

The studies included in this systematic review and meta-analysis were conducted in 13 different countries: China (n=11) [18, 22, 27, 28, 30, 31, 40, 50 52, 54, 55], Spain (n=8) [23, 33, 38, 39, 41, 42, 44, 47], Italy (n=4) [15, 17, 19, 37], France (n=3) [20, 21, 53], India (n=3) [24, 36, 45], United Kingdom (n=2) [25, 49], Iran (n=2) [16,

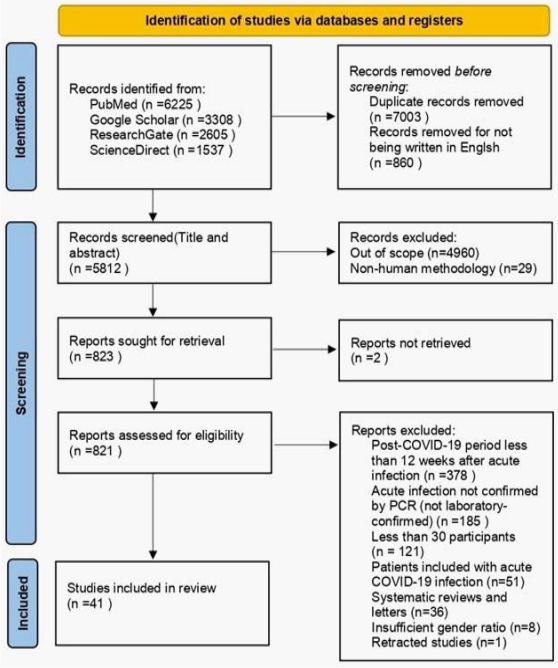

Figure 1: PRISMA flow diagram for the systematic review, detailing database searches, number of abstracts screened and full texts retrieved.

Table 1: Characteristics of the included studies.

Authors and year	Sample size	Country	Study design	Median age of participants (mean ± SD or median (IQR) or median (range)	Gender distribution-m(%)/f(n%)	Weeks passed from acute COVID-19 onset to follow up	Hospitalization status during acute COVID-19 illness
Anastasio F. et al. 2021	379	Italy	Retrospective	median 56(49-63)	174(45.9%)/ 205(54.1%)	median 135 days (102-175)	All hospitalized
Asadi-Pooya A.A. et al .2021	4682	Iran	Retrospective	mean 52 ± 15	2478(52.9%)/ 2203(47.1%)	3-6 months	All hospitalized
Boscolo-Rizzo P. et al. 2021	304	Italy	Prospective	47 years (range, 18–76 years).	119 (39.1%)/ 185 (60.9%)	12 months	None hospitalized; all outpatients
Cao J. et al. Apr 2021	61	China	Prospective	mean 43.5 (15.9)	33(54%)/ 28(46%)	3 months	All hospitalized
Caruso D. et al. 2021	118	Italy	Prospective	65 ± 12	56 (47%)/ 62 (53%)	6 months ± 14days	All hospitalized
Chan Sui Ko A. et al. 2022	316	France	Prospective	64.1 ± 14.3	187(59.1%)/ 129(40.9%)	4 months	All hospitalized
Eberst G. et al. 2022	85	France	Prospective	median 68.4(60.1-72.9)	67(78.8%)/ 18(21.2%)	3 months, 6, 9	All hospitalized
Fang X. et al. 2021	1233	China	Prospective	median 68(64–73)	591(47.9%)/ 642(52.1%)	12 months	All hospitalized
Fernández-de-las-Peñas C. et al .2021	1950	Spain	Prospective	mean 61 ± 16	1035(53.1%)/ 915(46.9%)	11.2 ± 0.5 months	All hospitalized
Gaur R. et al. 2022	97	India	Cross-sectional	mean 48.68 ± 15.8(18-84)	62 (63.9%)/ 35 (36.1%)	15.5 ± 3.64 weeks (12-33)	47 (48.5%) hospitallized
Gautam N. et al. 2021	200	United Kingdom	Retrospective case series	mean 56.5 ± 13.2	125 (62.5%)/ 75 (37.5%)	143.3 ± 42.4 days (4-7 months)	All hospitalized
Gianella P. et al. 2021	39	Switzerland	Prospective	median 62.5 (51.3–71)	30(76.9%)/ 9(23.1%)	12 weeks (3 months)	All hospitalized
Han X. et al. 2021	114	China	Prospective	mean age, 54 years 6 12; age range, 24–82 years	80(70.1%)/ 34(29.9%)	175 ± 20 days	All hospitalized*
Huang L. et al. 2021	1733	China	Ambidirectional	median 59(49-67)	681(53%)/ 595(47%)	185 days (IQR 175-198 days)	All hospitalized
Labarca G. et al. 2021	60	Chile	Prospective	mild group: 39.2 (±14.3), moderate group: 47.4 (±11) and severe group:50.0 (±10.3)	32(53.3%)/ 28(46.7%)	4 months	All hospitalized
Li Y. et al.2021	141	China	Prospective	median 59.0 (51.0–66.0)	89 (63.1%)/ 52 (36.9%)	175 days [IQR, 154.5, 189.5]	All hospitalized
Liang L. at al. 2020	76	China	Prospective	mean 41.3 ± 13.8(24-76)	21(27.6%)/ 55(72.4%)	3 months	All hospitalized
Lindhal A. et al. 2021	101	Finland	Prospective	mean 60 ± 11	54(53.5%)/ 47(46.5%)	174 d (median 180 days)	All hospitalized
Méndez R. et a. 2021	171	Spain	Prospective	median 58 [50, 68]	99(57.9%)/ 72(42.1%)	12 months	All hospitalized
Menges D. et al. 2021	431	Switzerland	Prospective	median 47 (33 - 58)	217 (50.3%)/ 214 (49.7%)	6 to 8 months	All hospitalized
Nabahati M. et al. 2021	173	Iran	Prospective	mean 53.62 ± 13.67(18 - 93)	57(32.9%)/ 116 (67.1%)	3 months, 6 months	All hospitalized
Parry A.H. et al. 2021	81	India	Retrospective	mean 51.8 ± 11.7 years (32–69 years)	50 (61.7%)/ 31 (38.3%)	100.6 days (90–111 days)	65/81(80.2%) hospitallized
Peghin M. et al. 2021	599	Italy	Prospective	mean 53 ± 15.8(18-94)	279(46.6%)/ 320(53.4%)	187 ± 22 days	157/599(26.2%) hospitallized
Pérez-Catalán I. et al. 2021	76	Spain	Prospective	No steroids group: 61.5 (52.7–72.5) and steroids group: 68.5 (60.2-75.7)	57(75%)/ 19(25%)	12 months	All hospitalized
Pérez-González A. et al. 2022	248	Spain	Prospective	median 57 (46–68)	148 (59.7%)/ 100(40.3%)	6 months	172 (69.4%) hospitalized
Qin W. et al. 2021	647	China	Prospective	mean 58 ± 15	287 (44.4%)/ 360(55.6%)	3 months(90days)	All hospitalized
Rivera - Izquerdo M. et al. 2022	453	Spain	Prospective	mean 61.2 ± 14.3	260 (57.4%)/ 193 (42.6%)	12 months (post hospitall)	All hospitalized
Romero-Duarte Á. et al. 2021	797	Spain	Retrospective	mean 63 ± 14.4	428 (53.7%)/ 369(46.3%)	6 months	All hospitalized
Ross Darley D. et al. 2021	78	Australia	Prospective	mean 47 ± 16	51(65.4%)/ 27(34.6%)	113 days (IQR, 105–131 days)	9/65(13.8%) hospitalized
Safont B. et al. 2021	313	Spain	Prospective	mean 61.12 ± 12.26)	184 (58.8%)/ 129 (41.2%)	6 months	All hospitalized
Sathyamurthy P. et al. 2021	279	India	Prospective	mean 71 ± 5.56	178 (63.8%)/ 101 (36.2%)	90 days	All hospitalized

Seeßle J. et al. 2021	96	Germany	Prospective	median 57 (50–63)	43(44.8%) / 53(55.2%)	5 months (20–22 weeks post–symptom onset)	31(32.3%) hospitalized during acute COVID-19
Sibila O. et al. 2022	215	Spain	Prospective	mean 61.4 ± 11.8	142(66%)/ 73(34%)	6 months	All hospitalized
Titze-de-Almeida R. et al. 2022	236	Brazil	Prospective	mean 41.2 ± 12.8(19-81)	92(39%)/ 144(61%)	5-8 months	32/236(13.7%) hospitalized
Vijaykumar B. et al. 2021	80	United Kingdom	Prospective	mean 59 ± 13	53(66.3%)/ 27(33.7%)	3 months: 97 (86–121) days	All hospitalized
Wu X. et al. 2021	83	China	Prospective	median 60 (52–66)	47(56.6%)/ 36(43.4%)	3* , 6,9,12 months	All hospitalized
Yaksi N. et al. 2022	133	Turkey	Retrospective	mean 65.7 ± 13.1	69(51.9%)/ 64(48.1%)	approximately 4 months (126.5 ± 19.8 days)	All hospitalized
Yan X. et al. 2021	119	China	Prospective	mean 52.97 ± 12.17	49(41.2%)/ 70(58.8%)	1 year	All hospitalized
Zayet S. et al. 2021	354	France	Retrospective	mean 49.6 ± 18.7	131(37%)/ 223(63%)	9 months (mean 289.1 ± 24.5 days)	121/354(34.2%) hospitalized
Zhao Y. et al. 2021	94	China	Prospective	mean 48.11 ± 11.9	54 (57.5%)/ 40 (42.5%)	1-year (median 366.0 (355.0, 376.0) days)	All hospitalized
Zhou F. et al. 2021	120	China	Prospective	mean 51.6 ± 10.8	49 (40.8%)/ 71 (59.2%)	314.5 (IQR, 296–338) days	All hospitalized

35], Switzerland (n=2) [26, 34], Germany (n=1) [46], Finland (n=1) [32], Chile (n=1) [29], Australia (n=1) [43], Turkey (n=1) [51] and Brazil (n=1) [48].The final selection resulted with thirty-two prospective studies [17-23, 26, 27, 29-35, 37-41, 43-50, 52, 54, 55] six retrospective studies [15, 16, 36, 42, 51, 53], one cross-sectional study [24], one ambidirectional study [28] and one retrospective case-series [25] [Table 1].

Participants characteristics

A total of 17, 565 participants were enrolled in the selected studies. The smallest sample size was 39 [26] and the largest sample size was 4682 [16]. The studies included 50.9 % males (8938/17 565) and 49.1 % females (8, 655/17, 565), with a maximal male predominance of 78.8 % [21] and maximal female predominance of 72.4 % [31]. The age of the participants across the included studies varied from a mean of 41.2 ± 12.8 years [48] to a mean of 71 ± 5.56 years [45] [Table 1].

Results of the methodological quality assessment

The quality assessment of the studies according to the "Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Studies Reporting Prevalence Data" [13] was determined to be of low overall quality rating (high risk of bias) in seven studies, moderate overall quality rating (moderate risk of bias) in thirty-three studies and high overall quality rating (low risk of bias) in one study (Supplementary file S5). The risk of bias for each individual outcome is available in Supplementary file S6.

Results of the certainty of evidence assessment

All of the outcomes in this systematic review and meta-analysis were found to have very low certainty of evidence, predominantly because of the observational study designs, but also due to the very serious risk of bias (Supplementary file S7).

Results of sensitivity and subgroup analysis

The results of the sensitivity and subgroup analysis, along with the forest plots for each outcome are included in the database at the Mendeley Data Repository files [56].

Main findings

Prevalence of respiratory symptoms

For the purposes of this systematic review and meta-analysis, we included the three most common respiratory symptoms reported in the studies: dyspnea, cough, and increased/newly detected sputum production. In addition, we included the prevalence of mMRC values ≥ 1 and ≥ 2 to serve as a comparison with the subjectively reported prevalence of dyspnea [Table 2]. The most common symptom was dyspnea 0.25 (CI 0.19–0.31, p <0.01, I2 = 98%), followed by cough 0.11 (CI 0.07–0.16, p <0.01, I2 = 96%) and increased and/or newly detected sputum production 0.07 (CI 0.02–0.16, p <0.01, I2 = 95%). The mMRC scores ≥ 1 and ≥ 2 were 0.47 (CI 0.31–0.63, p <0.01, I2 = 96%) and 0.10 (CI 0.05–0.16, p <0.01, I2 = 90%) respectively.

Prevalence of abnormal lung findings on chest CT-scan

On the follow-up chest CT-scans of all patients in all studies included in this systematic review and meta-

Table 2: Prevalence of respiratory symptoms and mMRC score values ≥ 1 and ≥2.

Symptom	Events	Sample size	Prevalence % (95% CI)	p-value	I^2	Number of studies
Dyspnea	2486	12137	0.25(0.19-0.31)	<0.01	98%	29
mMRC score ≥ 1	550	1489	0.47(0.31-0.63)	<0.01	96%	9
mMRC score ≥ 2	134	1380	0.10(0.05-0.16)	<0.01	90%	8
Cough	956	11250	0.11(0.07-0.16)	<0.01	96%	25
Increased and/or new-found sputum production	302	5084	0.07(0.02-0.16)	<0.01	95%	8

Table 3: Prevalence of abnormal lung CT-scan findings and abnormal pulmonary function test results.

Lung CT-scan finding/ Abnormal pulmonary function test prevalence	Events	Sample size	Prevalence % (95% CI)	p- value	I^2	Number of studies
Abnormal lung CT-scan findings	757	1269	0.62(0.49-0.75)	<0.01	96%	13
Ground-glass opacities (GGO)	641	1461	0.42(0.30-0.54)	<0.01	96%	16
Fibrosis and/or fibrotic changes	310	874	0.31(0.16-0.49)	<0.01	96%	10
Pulmonary nodules	147	506	0.30(0.17-0.44)	<0.01	92%	5
Line-like and/or band-like opacities	262	1013	0.25(0.17-0.34)	<0.01	88%	8
Interlobular septal thickening	187	798	0.20(0.10-0.33)	<0.01	95%	8
Reticular pattern	228	1044	0.20(0.08-0.37)	<0.01	97%	10
Sub-pleural line	54	350	0.18(0.05-0.37)	<0.01	91%	4
Bronchiectasis and/or bronchial dilation	243	1291	0.17(0.09-0.27)	<0.01	93%	12
Pulmonary atelectasis	43	315	0.14(0.10-0.18)	0.50	0%	3
Emphysema	27	340	0.07(0.01-0.18)	<0.01	87%	3
Mixed ground-glass opacities	12	162	0.07(0.03-0.12)	0.41	0%	3
Consolidations	31	812	0.03(0.02-0.05)	0.26	20%	9
Honeycombing	13	372	0.03(0.01-0.06)	0.19	40%	3
DLCO below 80% of predicted value	586	1448	0.37(0.29-0.46)	<0.01	90%	11
RV below 80% of predicted value	153	566	0.25(0.05-0.52)	<0.01	97%	4
DLCO/VA(KCO) below 80% of predicted value	103	551	0.18(0.08-0.32)	<0.01	89%	4
TLC below 80% of predicted value	141	756	0.16(0.08-0.26)	<0.01	91%	7
FEV1 below 80% of predicted value	133	1057	0.12(0.07-0.17)	<0.01	83%	9
FVC below 80% of predicted value	148	1280	0.11(0.07-0.17)	<0.01	88%	9
FEV1/FVC ratio below 70% of predicted value	59	805	0.07(0.03-0.12)	<0.01	77%	7

analysis, findings typical of pneumonia and COVID-19 were observed. The pooled prevalence of participants with pathological/abnormal lung findings on chest CT-scan was 0.62 (CI 0.49–0.75, p <0.01, I^2 = 96%). The most common finding was ground-glass opacity (GGO) with a pooled prevalence of 0.42 (CI 0.30–0.54, p <0.01, I^2 = 96%), followed by fibrosis and/or fibrotic-like changes 0.31 (CI 0.16–0.49, p <0.01, I^2 = 96%), pulmonary nodules 0.30 (CI 0.17–0.44, p <0.01, I^2 = 92%), line-like and/or band-like opacities 0.25 (CI 0.17–0.34, p <0.01, I^2 = 88%), interlobular septal thickening 0.20 (CI 0.10–0.33, p <0.01, I^2 = 95%), reticular pattern 0.20 (CI 0.08–0.37, p <0.01, I^2 = 97%), sub-pleural line 0.18 (CI 0.05–0.37, p <0.01, I^2 = 91%), bronchiectasis and/or bronchial dilation 0.17 (CI 0.09–0.27, p <0.01, I^2 = 93%), pulmonary atelectasis 0.14 (CI 0.10–0.18, p = 0.50, I^2 = 0%), emphysema 0.07 (CI 0.01–0.18, p <0.01, I^2 = 87%), mixed ground-glass opacities 0.07 (CI 0.03–0.12, p =0.41, I^2 = 0%), consolidations 0.03 (CI 0.02–0.05, p = 0.26, I^2 = 20%), and honeycombing 0.03 (CI 0.01–0.06, p = 0.19, I^2 = 40%) [Table 3].

Table 4: Mean values of pulmonary function test (PFTs) results.

Respiratory function test parameter means	Mean value (95% CI)	Sample size	p-value	I^2	Number of studies
DLCO % of predicted value	85.77(80.02-91.51)	917	<0.01	95%	8
DLCO/VA(KCO) % of predicted value	95.41(90.96-99.86)	823	<0.01	92%	6
FEV1 % of predicted value	98.50(95.75-101.25)	858	<0.01	84%	7
FVC % of predicted value	101.82(96.80-106.84)	909	<0.01	95%	7
FEV1/FVC ratio % of predicted value	81.78(76.49-87.06)	770	<0.01	99%	6
RV % of predicted value	100.90(70.79-131.02)	627	<0.01	99%	4
TLC % of predicted value	94.98(89.44-100.52)	774	<0.01	98%	6
VC % of predicted value	106.00(104.43-107.58)	306	0.51	0%	3
FEV1 mean value (in liters)	2.85(2.77-2.92)	428	0.49	0%	3
FVC mean value (in liters)	3.62(3.50-3.74)	428	0.29	18%	3
6MWD test mean value (in meters)	531.04(510.90-551.18)	471	<0.01	82%	3

Prevalence of abnormal pulmonary function tests (PFTs)

The highest prevalence of all outcomes associated with abnormal PFTs findings was found in DLCO below 80% predicted value, being 0.37 (CI 0.29–0.46, p<0.01, I^2=90%). The prevalence of other deviations in PFTs below 80 % predicted value were as follows: RV being 0.25 (CI 0.05–0.52, p <0.01, I^2 = 97%), DLCO/VA (KCO) being 0.18 (CI 0.08–0.32, p <0.01, I^2 =89%), TLC being 0.16 (CI 0.08–0.26, p <0.01, I^2 = 91%), FEV1 being 0.12 (CI 0.07–0.17, p <0.01, I^2 = 83%), FVC being 0.11 (CI 0.07–0.17, p <0.01, I^2 = 88%) and FEV1/FVC being 0.07 (CI 0.03–0.12, p <0.01, I^2 = 77%) [Table 3].

Mean values of the pulmonary function test parameters

Mean values for various pulmonary function tests and parameters are given in Table 4 (all values are given as percentages of predicted values, except the values for FEV1 in liters, FVC in liters, and 6MWD in meters). The lowest mean value was calculated for DLCO 85.77 (CI 80.02–91.51, p <0.01, I^2 = 95%) and FEV1/FVC ratio 81.78 (CI 76.49–87.06, p <0.01, I^2 = 99%), and the highest mean value was calculated for FVC 100.72 (CI 95.86–105.58, p <0.01, I^2 = 95%), RV 100 .90 (CI 70.79–131.02, p < 0.01, I^2 = 99%) and VC 106.00 (CI 104.43-107.58, p = 0.51, I^2 = 0%). The mean value for FEV1 was 98.50 (CI 95.75-101.25, p <0.01, I^2 = 84%) and for FVC 101.82 (CI 96.80-106.84, p <0.01, I^2 = 95%). The mean value for FEV1 and FVC in liters was 2.85 (CI 2.77–2.92, p = 0.49, I^2 = 0%) and 3.62 (CI 3.50–3.74, p = 0.29, I^2 = 18%), respectively, and for 6MWD in meters 531.04 (CI 510.90-551.18, p <0.01, I^2 = 82%).

Discussion

In our systematic review and meta-analysis, a significant proportion of patients experienced dyspnea as a manifestation of post-COVID-19 syndrome. Dyspnea as part of the post-COVID-19 syndrome has been reported not only in patients with severe forms of acute COVID-19 but also in those with mild COVID-19 [57]. Mechanisms of dyspnea are very complex and include reflex stimulation of chemoreceptors, afferent signals through C-fibers of the vagal nerve and activation in the limbic system of the brain [58]. Afferent information from reflex stimulation of peripheral sensors in the form of chemoreceptors and/or vagal C-fibers is processed centrally in the limbic system and the sensorimotor cortex, resulting in increased neural output to the respiratory muscles. Dysfunction in the ventilatory response caused by paralysis, muscle weakness, as well as increased mechanical load in the muscle, generates an afferent impulse from the lungs vagal receptors (and possibly mechanoreceptors in the respiratory muscles) to the sensorimotor cortex, which then results in the sensation of dyspnea [58]. In the case of a COVID-19 in infection, this dysfunction of the ventilatory response could be caused by vascular damage to the respiratory chest muscles, as SARS-CoV-2 has been shown to cause vascular and endothelial damage and thereby compromise tissue perfusion in the body [59]. Potential hypoxia of the respiratory muscles could reduce the number of respirations per minute, which would lead to the accumulation of carbon dioxide, which could than stimulate the C-fibers of the vagal nerve and, through the action of the previously mentioned cascade, lead to a feeling of dyspnea. However, a primary origin in the central nervous system cannot be ruled out, as it has been proven that SARS-CoV-2 disrupts the blood-brain barrier and thereby allows entry into the central nervous system [60]. Cough had the second highest prevalence of all the respiratory symptoms in our systematic review and meta-analysis, ranging from 2% [37] to 61.3% [32]. The hypothesized mechanisms of cough in the post-COVID-19 syndrome are similar to those of post-COVID-19 dyspnea, and include viral neuro-tropism, neuro-inflammation, and neuro-immune responses [61]. Interactions between the vagal nerve and the airway vagus, precipitated by

neuro-inflammation, may play a key role in the initiation and maintenance of cough [62]. Newly detected and/or increased sputum production had the lowest prevalence among respiratory symptoms in our analysis. An interesting finding in patients with severe COVID-19 infections requiring intubation is the production of sputum with thicker consistency due to greater solid and protein contents, a finding that bears more similarity with sputum in patients with cystic fibrosis than it does with sputum in healthy control subjects [63]. A hypothetical explanation of the thicker respiratory secretions in severe acute forms of COVID-19 is the dysregulation of neutrophil extracellular traps and neutrophil elastase that occurs during the hyper-inflammatory immune response [64]. Spirometry is a very useful diagnostic and prognostic tool in the evaluation of a number of respiratory diseases. By quantifying the respiratory volumes, capacities and flows, such as Forced Vital Capacity (FVC) and Forced Expiratory Volume at First and Sixth second (FEV1 and FEV6, respectfully), and the relationship between some of these parameters (FEV1/FVC ratio), the obstructive ventilatory defect can be detected with high sensitivity and specificity, and it is possible to classify the severity in response to inhaled bronchodilator [65]. The reference values of the parameters measured with spirometry (and body-plethysmography, accordingly), when expressed in percentages of predicted values, are in the range of 80-120% for FEV1, FVC, and TLC, 75%-120% for RV, and 75%-120% for FRC [66]. The single mean values for each of the spirometry parameters in our systematic review and meta-analysis fell well within the normal expected range, while the results of pooled prevalence varied from approximately 9% for some of the parameters (FEV1, FVC) to one third for some of the other parameters (RV). Our finding is in accordance with previous studies of spirometry in patients during and after viral pneumonia. Reversible airflow limitation has been demonstrated in patients with acute respiratory infections, with a strong association between symptoms, such as cough and dyspnea, and low FEV1 in patients without previous asthma and COPD [67]. The Six-Minute Walking Distance (6MWD) is a sub-maximal exercise test to assess aerobic capacity and endurance in individuals. The distance walked is affected by the function of many organ systems, thus the 6MWD cannot be exclusively classified as a PFT. Nevertheless, it has a wide range of applicability in the assessment of lung function. In our meta-analysis the average value for walking distance was within the range predicted for healthy individuals (400 to 700 meters) [68]. The recommended reference values for DLCO, a measurement that quantifies the ability of the lungs to transfer carbon monoxide from inspired air into the bloodstream, are in the range of 75-140 % of predicted values [69, 70]. In the studies included in our systematic review and meta-analysis the prevalence of DLCO values varied across studies from 25%[29] to 58.1% [47]. This difference may be due to different follow-up periods between the studies, the characteristics of the patient populations, and/or the presence of previous undiagnosed respiratory illnesses that decrease DLCO. It is well known that DLCO can be decreased in interstitial lung diseases and pulmonary fibrosis due to the thickening of alveolar-capillary membrane or destruction of the alveoli [71]. Both mechanisms may be implicated for the decreased DLCO values in patients with post-COVID-19 syndrome, especially in patients with radiological lung changes at follow-up. The three most common changes in lung CT scans at ≥ 12 months after the initial PCR- confirmed COVID-19 infection were ground-glass opacities, fibrosis, and/or fibrotic-like changes and pulmonary nodules. When the lungs were involved during acute COVID-19 infection, the most common CT findings within the first five days of diagnosis were ground-glass opacities or mixed findings of ground-glass opacities and consolidation with peripheral and sub-pleural distribution [72]. A parallel could be drawn between the similarity of lung CT scan changes found in acute COVID-19 infection and those found in the post-COVID-19 period, implying that the post-COVID-19 lung CT changes could be a continuum of the changes during an acute COVID-19 infection. This continuation has already been demonstrated in studies examining follow up CT-scans after other types of viral pneumonia, with some persistence of acute radiologic findings during the resolution/improvement or worsening of the initial lesions [73,74]. In our systematic review, the major limitations in some of the studies were: the lack of baseline lung CT scan to be compared with the follow-up CT scans, and the lack of evidence if the patients experienced any other viral pneumonia in the window between acute COVID-19 and the follow-up period, or have had alternative pre-existing lung disease to which the lung CT scan changes could be attributed to. Regarding comparison with other systematic review and/or meta-analyses, several parallels can be drawn. To the best of our knowledge, this is the first systematic review and meta-analysis that combines the prevalence of most common respiratory symptoms experienced in post-COVID-19 syndrome with the most common lung CT findings and PFTs results. In similar systematic reviews and/or meta-analyses, the pooled prevalence of dyspnea among post-COVID-19 patients was, in ascending order, 18% [75], 24% [76], 26% [77], and 32% [78]. Cough, the second most common symptom in our meta-analysis, had a prevalence in other systematic reviews of 13% [78], 19% [76], and 25% [79]. In terms of residual lung changes on CT-scans in post-COVID-19 patients, the two most common findings in other meta-analyses were ground glass opacities and fibrotic like changes [80, 81], which is similar to findings in our systematic review and meta-analysis. Systematic reviews and/or meta-analyses examining PFTs revealed that 39% of post-COVID-19 patients experienced an altered DLCO, while 15% and 7% had a restrictive or obstructive ventilatory pattern, respectively [82].

Limitations

The main limitations of this systematic review and meta-analysis arose mainly from different follow-up

times, uneven sample sizes, and variations in the definition and criteria for some of the outcomes in different studies, as well as the unavailability of patients' baseline chest CT scans. As for the first two issues, there is very little space left for correction, because they are influenced by factors that are not even related to the disease (e.g. the impossibility of conducting the same time monitoring for all participants due to patient unavailability and/or uncooperativeness, scarce resources and financing, lack of logistics, etc.). The same could be said about the different definitions and measurements of each outcome in the included studies. The symptom reporting is subjective; however, we attempted to correct the dyspnea outcome by including mMRC scores for comparison. The lack of available information on whether the patients had previous lung changes on lung CT scans and history of previous respiratory diseases (including those that can cause lung changes visible on CT scan) is another limitation of this systematic review, as it is uncertain what percentage of the recorded CT scan outcomes can be attributed to COVID-19 and post-COVID-19 syndrome versus other viral illnesses and other pre-existing conditions.

Conclusion

Patients with post-COVID-19 syndrome show persistent or newly developed respiratory symptoms, altered pulmonary function test findings and abnormal lung CT scan patterns. The most common respiratory symptom is dyspnea, the most prevalent abnormal PFT parameter is RV, and the most common abnormal lung CT scan finding are ground glass opacities. The results of this systematic review must be analyzed with caution as they may be influenced by previous respiratory comorbidities, alternative viral illnesses during the follow-up period and the severity of the acute COVID-19 infection. Future research on post-COVID-19 syndrome should be focused on the early recognition and adequate treatment of post-COVID-19 syndrome and other associated comorbidities. The data collected in this systematic review could serve as a good starting point for that purpose. We believe that the insight and understanding of the health status and respiratory profile in post-COVID-19 syndrome could aid for its timely recognition and accurate diagnosis, as well as further research in terms of prevention and early mitigation of these sequelae, and improvement of quality of life.

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Data Availability Statement

The datasets, as well as forest plots and funnel plots of this systematic review and meta-analysis are available on Datasets and supplementary files for Respiratory symptoms, pulmonary function and lung CT findings in patients with post-COVID-19 syndrome: a systematic review and meta-analysis - Mendeley Data.

Conflicts of Interest

The authors declare no conflict of interest.

Author Contributions

All authors contributed equally in all aspects of the creation of this systematic review, unless stated otherwise in the full text. All writers approved the final manuscript.

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