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Systematic review

Prevalence of post-acute COVID-19 syndrome symptoms at different follow-up periods: a systematic review and meta-analysis

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ABSTRACT

Background: Post-acute coronavirus 2019 (COVID-19) syndrome is now recognized as a complex systemic disease that is associated with substantial morbidity.
Objectives: To estimate the prevalence of persistent symptoms and signs at least 12 weeks after acute COVID-19 at different follow-up periods.
Data sources: Searches were conducted up to October 2021 in Ovid Embase, Ovid Medline, and PubMed.
Study eligibility criteria, participants and interventions: Articles in English that reported the prevalence of persistent symptoms among individuals with confirmed severe acute respiratory syndrome coronavirus 2 infection and included at least 50 patients with a follow-up of at least 12 weeks after acute illness.
Methods: Random-effect meta-analysis was performed to produce a pooled prevalence for each symptom at four different follow-up time intervals. Between-study heterogeneity was evaluated using the I2 statistic and was explored via meta-regression, considering several a priori study-level variables. Risk of bias was assessed using the Joanna Briggs Institute tool and the Newcastle-Ottawa Scale for prevalence studies and comparative studies, respectively.
Results: After screening 3209 studies, a total of 63 studies were eligible, with a total COVID-19 population of 257 348. The most commonly reported symptoms were fatigue, dyspnea, sleep disorder, and difficulty concentrating (32%, 25%, 24%, and 22%, respectively, at 3- to <6-month follow-up); effort intolerance, fatigue, sleep disorder, and dyspnea (45%, 36%, 29%, and 25%, respectively, at 6- to <9-month follow-up); fatigue (37%) and dyspnea (21%) at 9 to <12 months; and fatigue, dyspnea, sleep disorder, and myalgia (41%, 31%, 30%, and 22%, respectively, at >12-month follow-up). There was substantial between-study heterogeneity for all reported symptom prevalences. Meta-regressions identified statistically significant effect modifiers: world region, male sex, diabetes mellitus, disease severity, and overall study quality score. Five of six studies including a comparator group consisting of COVID-19–negative cases observed significant adjusted associations between COVID-19 and several long-term symptoms.
Conclusions: This systematic review found that a large proportion of patients experience post-acute COVID-19 syndrome 3 to 12 months after recovery from the acute phase of COVID-19. However, available studies of post-acute COVID-19 syndrome are highly heterogeneous. Future studies need to have

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appropriate comparator groups, standardized symptom definitions and measurements, and longer follow-up. **Mohamad Salim Alkodaymi, Clin Microbiol Infect 2022;28:657**

Introduction

A significant number of patients who have recovered from acute coronavirus disease 2019 (COVID-19) infection are reporting lasting symptoms resulting in impairment of everyday activities beyond the initial acute period. These post–COVID-19 patients suffer from a phenomenon known as 'long' or 'chronic' COVID-19, or more recently, post-acute sequelae of COVID-19 or post-acute COVID-19 Syndrome (PACS) [1,2].

The terms 'long COVID-19' and 'post-acute COVID-19 syndrome' lack a unified definition. The definition endorsed by the National Institute for Health and Care Excellence (NICE) and the WHO is a set of 'signs and symptoms that emerge during or after an infection consistent with COVID-19, persist for more than 12 weeks, and are not explained by an alternative diagnosis' [3,4]. Many experts, including the NICE panel, also agree with subdividing into two categories: a post–COVID-19 subacute phase of ongoing symptoms that lasts 4–12 weeks after the onset of illness, and a chronic-phase or long COVID-19, defined as symptoms and abnormalities that last more than 12 weeks after the onset of illness and are not explained by an alternative diagnosis [2,4].

This time-frame distinction is important because it differentiates between the acute illness and the possible sequelae of irreversible tissue damage, with varying degrees of dysfunction and symptoms involving several possible conditions as suggested by some experts: post–intensive care syndrome, post-thrombotic or haemorrhagic complications, acute-phase immune-mediated complications, and/or multisystemic inflammatory syndrome in children or adults [5]. Globally, the number of patients recovering from COVID-19 infection continues to grow at an unprecedented rate. Therefore, we sought to perform a systematic review and meta-analysis of the available literature to estimate the prevalence of persistent symptoms and signs at least 12 weeks after acute COVID-19 at different follow-up periods.

Methods

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline for study design, search protocol, screening, and reporting [6,7].

Literature search and study selection

The literature was searched by a medical librarian for studies of long-term symptoms in patients with COVID-19. Search strategies were created using a combination of keywords and standardized index terms. Searches were originally run in November 2020 and updated in January and September 2021 in Ovid Embase, Ovid Medline (including publication ahead of print, in-process, and other nonindexed citations), and PubMed.gov, which includes preprints. Results were limited to English-language and primarily adult studies. All citations were exported to EndNote, where 4539 duplicates were removed, leaving 3921 citations. Search strategies are provided in the supplementary material (Supplement 1).

Articles were considered eligible for inclusion if they (a) were written in the English language; (b) were peer-reviewed cohort, case-control, or cross-sectional studies that reported the prevalence of persistent symptoms among individuals with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection; (c) included at least 50 patients; (d) had follow-up of at least 3 months after symptom onset (as per the NICE definition); (e) included only patients with laboratory-confirmed COVID-19; and (f) reported follow-up as mean, median, or a set interval after symptom onset, diagnosis, acute illness, or initial CT chest imaging. Where studies had overlapping investigated populations, studies with larger sample sizes were prioritized, with the remainder excluded [8]. We subsequently identified a subgroup of these eligible studies that included studies with a comparator group consisting of non–COVID-19 cases.

Identification of studies

Six reviewers (OO, MSA, MO, NAF, RA, BAS) examined the titles and abstracts of articles in pairs, using the aforementioned predefined selection criteria. This was followed by a full text review of each article to confirm meeting the eligibility criteria. Disagreements regarding inclusion of a full-text article were discussed and resolved with the senior reviewer (IMT).

Data collection

Data were extracted simultaneously by six reviewers in duplicate (OO, NAF, BAS, RA, MSA, MO) into a prespecified data collection form, with any discrepancies resolved in consultation with the senior reviewer (IMT). Data were collected across the following domains: study characteristics, follow-up method, baseline demographics, and symptom prevalence. Full details of the data collation variables can be found in the supplementary material (Supplement 2).

Quality assessment

The reviewers independently assessed the risk of bias for each study using the Joanna Briggs Institute critical appraisal tool for prevalence studies. The critical appraisal checklist for studies reporting prevalence consists of nine topics: (a) sample frame suitability, (b) sampling method appropriateness, (c) sample size adequacy, (d) proper description of study subjects and setting, (e) sufficient coverage of the identified sample, (f) usage of valid methods for identification of the condition, (g) standard and reliable way of measuring the condition for all participants, (h) appropriate statistical analysis, and (i) adequate response rate [9]. Each study was assessed across each of these areas, with results reported as Yes, No, or Unclear. Studies were assigned an overall score, reflecting the number of questions with a Yes response.

Studies with a comparator group consisting of non–COVID-19 cases were assessed using the Newcastle-Ottawa Scale [10], which rates observational studies based on three parameters: selection, comparability between exposed and unexposed groups, and exposure and outcome assessment. These three domains can have a maximum score of 4, 2, and 3 stars, respectively. Studies with <5 stars are considered low quality, 5–7 stars moderate quality, and >7 stars high quality.

Data synthesis

Our outcome of interest was prevalence of symptoms at follow-up across four different intervals: 3 to <6 months, 6 to <9 months, 9 to <12 months, and ≥12 months. Due to varying definitions of 'day 0' across the literature, we accepted definitions that include COVID-19 symptom onset, COVID-19 diagnosis, or hospital discharge after acute illness. We further categorized studies according to the severity of COVID-19, which was defined in this context as patient setting during acute illness, including outpatient, general inpatient ward, or intensive care unit (ICU) settings. Where symptom prevalence at follow-up was not reported separately based on COVID-19 severity, studies were described as 'mixed' (e.g. 'mixed inpatient/ICU').

The range of persistent COVID-19 symptoms reported to date was then identified and categorized. Given the interchangeable terminology to refer to symptoms across studies, the following terms were grouped: 'sleep disturbance' to refer to insomnia, daytime sleepiness, sleep difficulties, and/or sleep disorders; 'concentration difficulties' to refer to confusion, change in level of consciousness, and/or concentration; 'cognitive impairment' to refer to cognitive dysfunction, brain fog, and/or cognition difficulties; 'loss of taste' to refer to taste dysfunction, alteration of taste, dysgeusia, and parageusia; and 'loss of smell' to refer to smell dysfunction, alteration of smell, anosmia, hyposmia, smell blindness, and olfactory disorders. Signs and symptoms were divided into seven main systems: mental health, respiratory system, cardiovascular system, musculoskeletal system, nervous system, gastrointestinal system, and other.

Statistical analyses

The total cohort number and the number of patients with different symptoms or complaints at different follow-up times were extracted from each study and sorted into four intervals: 3 to <6 months, 6 to <9 months, 9 to <12 months, and ≥12 months. We performed separate meta-analyses for the aforementioned follow-up intervals where ≥3 studies reported symptom prevalence at that follow-up interval. The arcsine transformation was used to obtain a pooled estimate of the prevalence of each symptom. Because conventional meta-analysis models assume normally distributed data, arcsine-based transformations are applied to the proportion data to yield better approximations to the normal distribution; they have the important advantage of stabilizing variances [11,12]. We used a DerSimonian and Laird random effect model with the inverse variance method to pool prevalence [13]. We performed subgroup meta-analyses by severity of acute COVID-19 in the included studies, allowing a visual display of heterogeneity due to differences in the severity of illness in reporting studies. We evaluated between-study heterogeneity using the I^2 statistic, which estimates the variability percentage in effect estimates that is due to heterogeneity rather than to chance [14]. Two-tailed $p < 0.05$ was considered statistically significant.

We performed meta-regression to explore between-study heterogeneity. We considered several a priori chosen study-level variables based on clinical plausibility (Supplement 3). Meta-regression was performed for each symptom where ≥10 studies reported prevalence at any given follow-up interval, as per the Cochrane Handbook for Systematic Reviews [15]. The regression coefficients obtained from the meta-regression analyses describe how the outcome variable (the pooled prevalence) changes with a unit increase in the continuous explanatory variable and changes for the category of interest compared to a reference category for a categorical variable. The statistical significance was $p < 0.01$ for the results of the meta-regression, and we reported if a variable was found to be a significant contributor to heterogeneity. All statistical analyses were performed using Stata 12 statistical software (StataCorp, College Station, TX, USA) [16].

Results

Of the 3209 abstracts screened, 152 full-text articles were reviewed, with 63 included in the final analysis (Fig. 1) [17–49], [50–79]. After full article review, the most common reason for exclusion was absence of reported data on symptom prevalence at the stated follow-up ($n = 36$), followed by the inclusion of COVID-19 patients without laboratory-confirmed COVID-19 ($n = 23$). Of the 63 included studies (total COVID-19 population = 257 348), 6 were from North America (COVID-19 sample size = 237 261), 12 from East Asia (COVID-19 sample size = 10 162), 37 from Europe (COVID-19 sample size = 8998), and 8 from North Africa, the Middle East, or South Asia (COVID-19 sample size = 927) (Table 1).

The majority of included studies were single centre ($n = 43$), followed by multicentre ($n = 18$), with two nationwide studies. Only 4 studies included follow-up of ≥365 days (sample size = 1246), with 5 studies with follow-up of 270 to 364 days (sample size = 3758), 25 studies with follow-up of 180 to 269 days (sample size = 243 576), and the majority of studies with follow-up of 90 to 179 days ($n = 33$, sample size = 9323).

Meta-analyses of prevalence of symptoms at different follow-up periods

Meta-analysis highlighted the substantial heterogeneity in symptom prevalence reported across studies, with I^2 statistics ranging from 75.4% (difficulty concentrating at 3- to <6-month follow-up) to 99.4% (fatigue at 9- to <12-month follow-up), with the vast majority of symptoms across all follow-up intervals producing an $I^2 \geq 90\%$. The most commonly reported symptoms between 3 and < 6 months are fatigue (32%, 95% CI = 22%–44%, number of studies = 25, sample size = 7268), dyspnoea (25%, 95% CI = 17%–34%, number of studies = 28, sample size = 8132), sleep disorder (24%, 95% CI = 8%–44%, number of studies = 8, sample size = 4369), and concentration difficulty (22%, 95% CI = 15%–31%, number of studies = 5, sample size = 466).

At 6 to <9 months, the most common symptoms reported were effort intolerance (45%, 95% CI = 25%–67%, number of studies = 5, sample size = 850), fatigue (36%, 95% CI = 27%–46%, number of studies = 19, sample size 8191), sleep disorder (29%, 95% CI 15%–45%, number of studies = 12, sample size = 242 000), and dyspnoea (25%, 95% CI = 20%–30%, number of studies = 134 384).

In the 9- to <12-month period, the meta-analysis included nine symptoms, with the highest prevalence reported for fatigue (37%, 95% CI = 16%–62%, number of studies = 5, sample size = 3758) and dyspnoea (21%, 95% CI = 14%–28%, number of studies = 5, sample size = 3758), with loss of taste being the least reported (6%, 95% CI: 1%–13%, number of studies = 3, sample size = 1742). Similarly, fatigue was the most reported symptom (41%, 95% CI: 30%–53%, number of studies = 4, sample size = 1246) in the >12-month period. It is noteworthy that fatigue, dyspnoea, myalgia, and sleep disorder were most reported in the >12-month interval, while cough, headache, loss of taste, and loss of smell were most common at 6 to <9 months (Figs. 2A, B; Supplement 6, Panels C, D).

Exploring heterogeneity

Due to a limited number of studies reporting symptom prevalence at 9 to <12 months or ≥12 months, meta-regression was performed for symptom prevalence at 3 to <6 months and 6 to

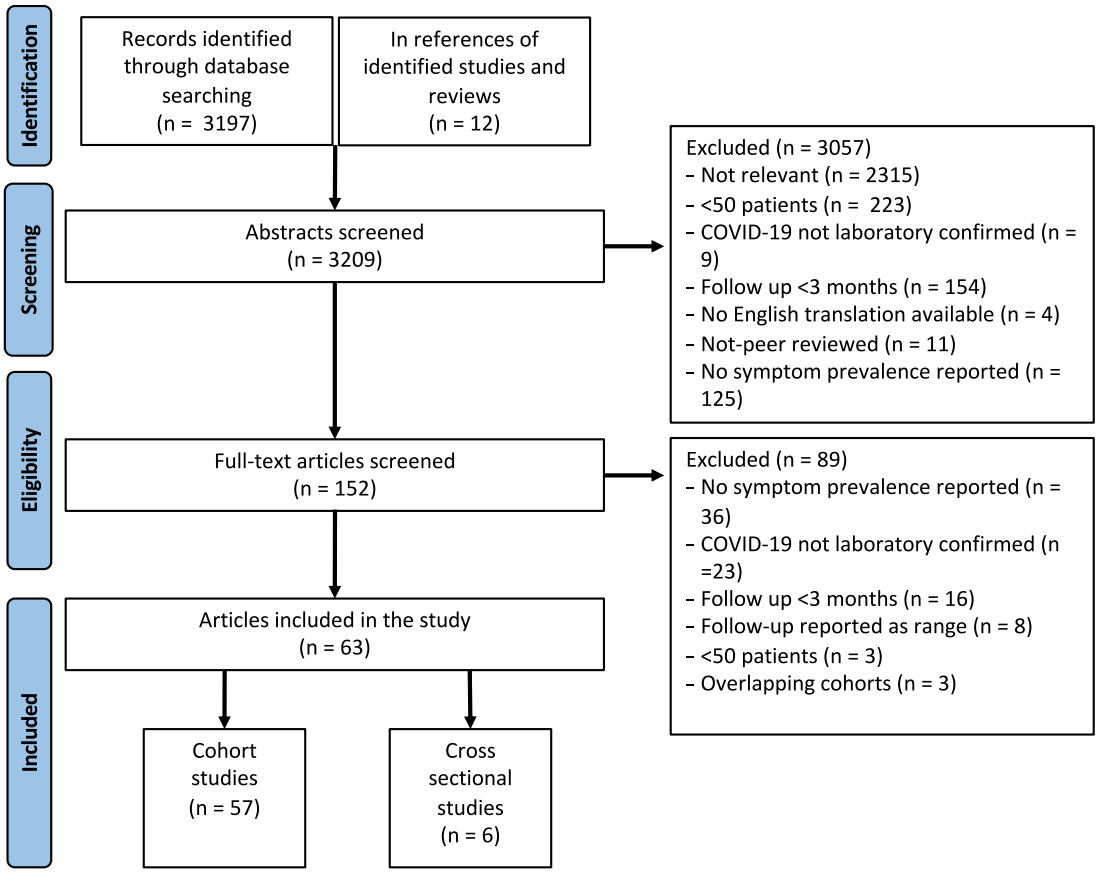

Fig. 1. PRISMA diagram.

<9 months (Supplement 6). Observed statistically significant effect modifiers included world region where the study was conducted; percentage of study participants who were male and those who had DM; disease severity categorym as defined earlier; and the overall study quality score.

Studies reporting results from Asian populations reported a lower prevalence of fatigue, dyspnoea, loss of smell, and loss of taste at 3–6-month follow-up and a lower prevalence of fatigue at 6–9-month follow-up. A higher proportion of male patients was found to be associated with a lower prevalence of cough and loss of smell at 6–9 months, whilst a higher proportion of diabetes mellitus as a comorbidity was associated with a lower prevalence of loss of smell and taste at 3–6 and 6–9 months. Studies investigating patients in ICUs were associated with a higher prevalence of dyspnoea compared to studies investigating an OP population at 3–6-month and 6–9-month follow-up intervals. Higher study quality was found to be associated with lower prevalence of dyspnoea at 3–6 months and cough at 6–9 months.

Studies with a COVID-19–negative comparator group

A total of six studies reporting symptom prevalence included a comparator group consisting of COVID-19–negative cases, with a summary of their findings presented in Table 2 [17,24,26,37,59,62]. Of these, two studies compared long-term symptom prevalence of COVID-19 cases to either influenza, pneumonia, or other respiratory tract infection cases [17,26]. Overall, all but one study reported a higher prevalence of symptoms or adverse events in cases after COVID-19 compared to respective comparator groups, with one negative study specifically assessing olfactory and gustatory dysfunction at 6 months [37]. Two of six studies were rigorously designed. One study observed that COVID-19 cases had a significantly higher hazard of mood disorder, anxiety, and insomnia when compared to matched cohorts with influenza or respiratory tract infection [26]. Another study observed that COVID-19 cases have a significantly higher prevalence of symptoms at 6- and 9-month follow-up when compared to community controls, including fatigue, sleep difficulties, hair loss, smell disorder, taste disorder, palpitations, chest pain, and headaches [45].

Quality assessment

Studies without comparator groups

The studies were generally assessed to have good quality, with a mean average critical appraisal score across all studies of 7.97 of 9. The question that affected the scores the most was 'Was the sample size adequate?'; few studies demonstrated appropriate sample size calculations or represented a large enough sample to provide high external validity (Table S1).

Studies with comparator groups

Study quality was assessed via the NOS as moderate to high, ranging from 5 to 9 (maximum 9), with a number of studies using a nonrepresentative sample of healthcare workers [37,59] or having comparability concerns by not adequately matching cases with the comparator group [17,37,59,62] (Table S2).

Table 1
Summary of all included studies in descending order by sample size

Study	Study design	Location	Sample size	Day zero	Follow-up (d)	Assessment method	Severity
Taquet et al. [26]	Nationwide	USA	236 379	Diagnosis date	180	EMR	Mixed IP/OP/ICU
Mei et al. [51]	Multicentre	China	3677	Hospital discharge	144	In person	IP
César Fernández-de-las-Peñas et al. [21]	Multicentre	Spain	1950	Hospital discharge	340	Telephone	Mixed IP/ICU
Chaolin Huang et al. [45]	Single centre	China	1733	Hospital discharge	186	In person	Mixed IP/ICU
Huang et al. [24]	Single centre	China	1276	Symptom onset	185, 349	In person	Mixed IP/ICU
Fernández-de-las-Peñas et al. [46]	Multicentre	Spain	1142	Hospital discharge	213	Telephone, EMR	Mixed IP/ICU
Kim et al. [42]	Single centre	South Korea	822	Symptom onset or diagnosis date	195	Online	Mixed IP/OP/ICU
Shang et al. [31]	Multicentre	China	796	Hospital discharge	180	Telephone	Mixed IP/ICU
Søraas et al. [62]	Multicentre	Norway	676	Diagnosis date	132	Online	OP
Qin et al. [49]	Single centre	China	647	Hospital discharge	90	In person	IP
Maestre-Muñiz et al. [20]	Single centre	Spain	543	Hospital discharge	365	In person	Mixed OP/IP
Qu et al. [54]	Multicentre	China	540	Hospital discharge	90	Telephone, online	IP
Knut Stavem et al. [55]	Multicentre	Norway	458	Symptom onset	117.5	Online, postal/mail	OP
Menges et al. [27]	Nationwide	Switzerland	431	Diagnosis date	220	Online	Mixed IP/OP/ICU
Shoucri et al. [28]	Single centre	USA	364	Diagnosis date	158	In person, telephone	Mixed IP/OP/ICU
Zayet et al. [18]	Single centre	France	354	Diagnosis date	289.1	Telephone, online	Mixed IP/OP/ICU
Augustin et al. [36]	Single centre	Germany	353	Symptom onset	207	In person	Mixed IP/ICU
Yin et al. [34]	Single centre	China	337	Symptom onset	203.4	In person	Mixed IP/ICU
Sigfrid et al. [33]	Multicentre	United Kingdom	327	Hospital discharge	222	Telephone, in person, postal	Mixed IP/ICU
Boscolo-Rizzo et al. [23]	Multicentre	Italy	304	Symptom onset	365	Telephone	OP
DM Lombrado et al. [22]	Single centre	Italy	303	Diagnosis date	371	Telephone, EMR	Mixed IP/OP/ICU
Sathyamurthy P et al. [68]	Single centre	India	279	Hospital discharge	90	Telephone	Mixed IP/ICU
Blomberg et al. [32]	Single centre	Norway	247	Diagnosis date	180	In person	OP
Clavario et al. [25]	Single centre	Italy	200	Hospital discharge	180	In person	IP
Darcis et al. [35]	Single centre	Belgium	199	Hospital discharge	94, 180	In person	Mixed IP/ICU
Riestra-Ayora et al. [37]	Single centre	Spain	195	Diagnosis date	180	Telephone	Mixed OP/IP
Jennifer A. Frontera et al. [41]	Multicentre	USA	192	Symptom onset	201	Telephone	Mixed IP/ICU
Pablo Parente-Arias et al. [58]	Multicentre	Spain	151	Symptom onset	100.5	Telephone, EMR	Mixed OP/IP
Han et al. [43]	Multicentre	China	144	Symptom onset	180	In person	Mixed IP/ICU
Sonnweber et al. [78]	Multicentre	Austria	135	Symptom onset	103	In person	Mixed IP/OP/ICU
Froidure et al. [52]	Single centre	Belgium	134	Hospital discharge	95	In person	Mixed IP/ICU
Suárez-Robles et al. [60]	Single centre	Spain	134	Hospital discharge	90	Telephone	Mixed IP/ICU
González-Hermosillo et al. [64]	Single centre	Mexico	130	Hospital discharge	90, 180	Telephone	Mixed IP/ICU
Nguyen et al. [47]	Single centre	France	125	Symptom onset	221.7	Telephone	IP
Garrigues et al. [74]	Single centre	France	120	Hospital admission	110.9	Telephone	IP/ICU*
Mattioli et al. [59]	Single centre	Italy	120	Diagnosis date	126	In person	Mixed OP/IP
Tawfik et al. [79]	Multicentre	Egypt	120	Diagnosis date	120	In person	Mixed OP/IP
Leila Simani et al. [40]	Single centre	Iran	120	Hospital discharge	180	In person	Mixed IP/ICU
Jacobson et al. [61]	Single centre	USA	118	Diagnosis date	119.3	In person	Mixed IP/OP/ICU
Caruso et al. [39]	Single centre	Italy	118	Initial CT chest	180	In person	Mixed IP/ICU
Motiejunaite et al. [69]	Single centre	France	114	Diagnosis date	90	In person	Mixed IP/OP/ICU
Schandl et al. [50]	Single centre	Sweden	113	ICU discharge	152	In person	ICU
Aranda et al. [38]	Single centre	Spain	113	Diagnosis date	240	In person	Mixed IP/ICU
Mechi et al. [19]	Single centre	Iraq	112	Diagnosis date	274	In person	OP
Skala et al. [65]	Multicentre	Czech Republic	102	Diagnosis date	90	In person	Mixed OP/IP
T. J. M. Wallis et al. [67]	Single centre	United Kingdom	101	Hospital admission	96	Telephone, in person	Mixed IP/ICU
Lindahl et al. [48]	Single centre	Finland	101	Hospital discharge	180	Online	Mixed IP/ICU
Biadsee et al. [29]	Single centre	Israel	97	Diagnosis date	231	Telephone	OP
Seeßle et al. [66]	Single centre	Germany	96	Symptom onset	152, 365	In person	Mixed OP/IP
Boari et al. [72]	Single centre	Italy	91	Hospital discharge	120	In person	Mixed IP/ICU
Taboada et al. [44]	Multicentre	Spain	91	ICU discharge	180	In person	ICU
Mumoli et al. [57]	Single centre	Italy	88	Hospital admission	91	In person	IP
Parry et al. [56]	Single centre	India	81	Initial CT chest	100.6	EMR	Mixed IP/OP/ICU
Wong et al. [73]	Multicentre	Canada	78	Symptom onset	91	In person	Mixed IP/ICU
Dieter Munker et al. [70]	Multicentre	Germany	76	Diagnosis date	120	In person	Mixed IP/OP/ICU
Liang et al. [71]	Single centre	China	76	Hospital discharge	90	In person	Mixed IP/ICU
Noel-Savina et al. [63]	Single centre	France	72	Diagnosis date	129	In person	Mixed IP/ICU
Elkan et al. [17]	Single centre	Israel	66	Hospital discharge	270	Online, telephone	IP
Jessica González et al. [53]	Single centre	Spain	62	Hospital discharge	90	In person, EMR	ICU
Yiping Lu et al. [75]	Single centre	China	60	Symptom onset	90	In-person	Mixed IP/ICU
Fortini et al. [77]	Single centre	Italy	59	Hospital discharge	123	In-person, telephone	IP
Wu et al. [30]	Single centre	China	54	Hospital discharge	180	In person	IP
Seyed Mohammad Hossein Tabatabaei et al. [76]	Single centre	Iran	52	Initial CT chest	91	EMR	Mixed IP/OP/ICU

IP, inpatient; OP, outpatient; ICU, intensive care unit; EMR, electronic medical records.
* ICU and IP results presented separately.

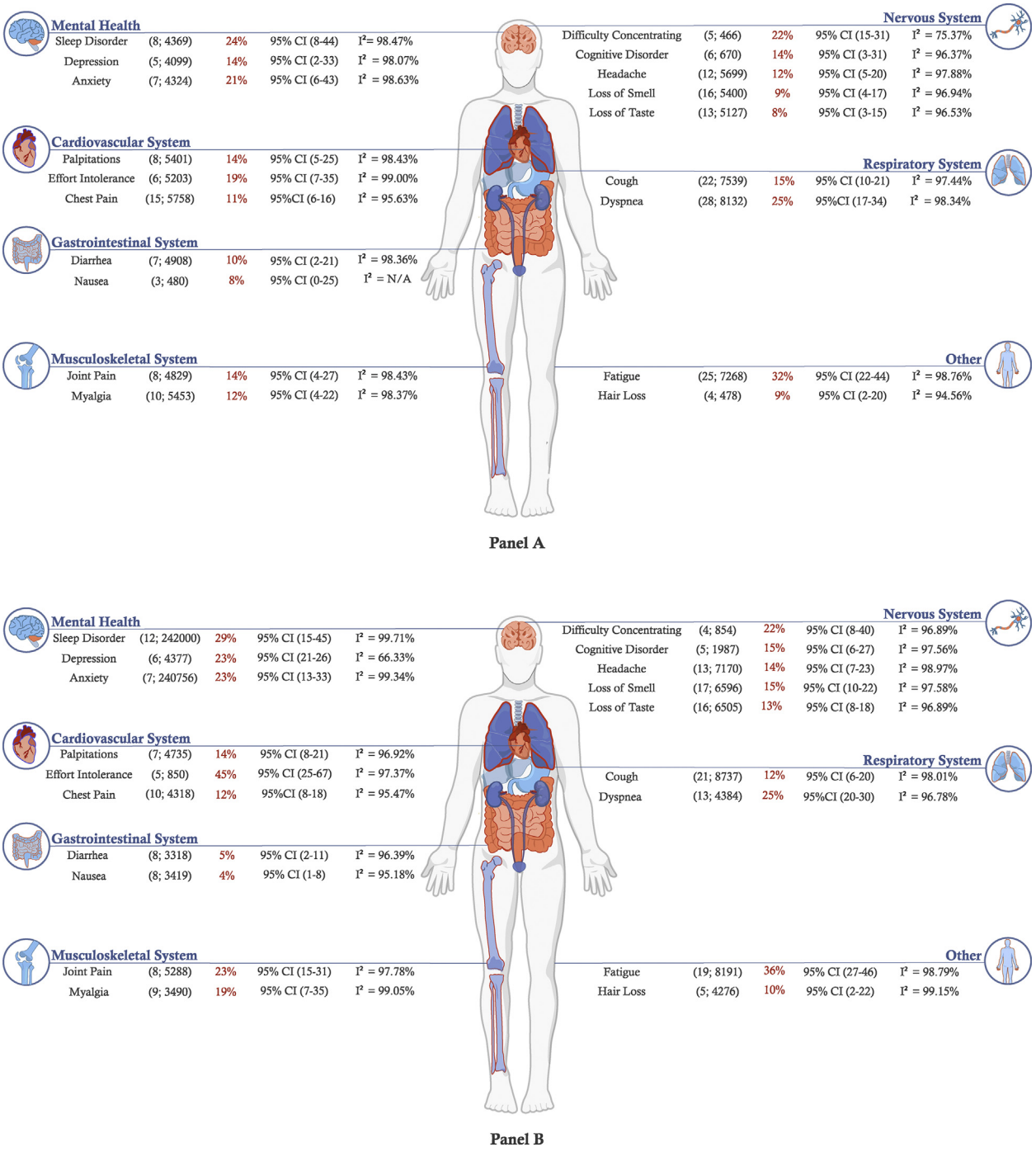

Fig. 2. Illustration of meta-analysis results with estimated prevalence of symptoms following acute COVID-19 infection across follow-up intervals of (A) 3 to <6 months and (B) 6 to <9 months (number of studies, size of population used to calculate point estimate).

Discussion

Summary of the findings

In this systematic review and meta-analysis of 63 studies with a total of 257 348 COVID-19 patients from different world regions, we observed that patients report several clinically significant symptoms across many organs systems 3 months after acute COVID-19. In addition, we observed that the high between-study heterogeneity of reported symptom prevalence could be at least partially explained by clinically plausible effect modifiers such as acute COVID-19 severity and certain patients' demographics and comorbidities [26,45,80,81].

Our findings lend more support to the initiatives of several countries and organizations that have started to fund more research and disseminate guidelines to better understand, diagnose, and treat PACS [8,82,83].

Mechanisms

It remains unknown what proportion of these lingering symptoms are true sequalae of COVID-19 vs. the effects of underlying

Table 2
Summary of studies reporting long COVID-19 symptom prevalence with a comparator group

Authors	Study design (average follow up in d)	COVID-19 group definition	Comparator group definition	Symptom/outcome assessment method	Newcastle-Ottawa scale	Summary of findings
Huang et al. [24]	Ambidirectional cohort (185 days and 349 days).	Patients with laboratory-confirmed COVID-19 discharged from Jin Yin-tan Hospital (Wuhan, China) ($n = 1164$)	Community adults without COVID-19 from two districts of Wuhan city, matched with cases 1:1 by age, sex and comorbidities[a] ($n = 1164$)	Interview, physical examination, questionnaires	7/9	COVID-19 patients had significantly higher prevalence of any of the following symptoms and for each individual symptom: fatigue or muscle weakness, sleep difficulties, hair loss, smell disorder, palpitations, joint pain, decreased appetite, taste disorder, dizziness, diarrhoea or vomiting, chest pain, sore throat or difficulty swallowing, skin rash, myalgia, headache, cough. COVID-19 patients had significantly higher mMRC dyspnoea scores and reported significantly more difficulty with mobility, personal care, pain or discomfort, anxiety or depression and overall quality of life.
Taquet et al. [26]	Retrospective cohort (180 d)	Patients with confirmed COVID-19 diagnosis, aged ≥10 y and alive at time of analysis; data collected using the TriNetX Analytics Network, consisting of anonymized data from 81 million patients, primarily in the USA (matched with influenza cases $n = 105\,579$, matched with other RTI $n = 236\,038$)	Propensity-matched patients from the same database, with COVID-19 cases matched separately with influenza or RTI, including influenza; matched for age, sex, race, ethnicity and co-morbidities[b] (influenza $n = 105\,579$, RTI $n = 236\,038$)	ICD-10 codes, EMR	9/9	COVID-19 had significantly higher hazard compared to both the matched influenza cohort and RTI cohort for mood disorder, anxiety disorder, psychotic disorder, substance use disorder, and insomnia
Riestra-Ayora et al. [37]	Prospective cohort[†] (180 d)	Health workers from a tertiary care hospital with suspected and symptomatic COVID-19, confirmed by PCR ($n = 195$)	Health workers from a tertiary care hospital with suspected COVID-19 with negative PCR, matched for sex and age ($n = 125$)	Interview	5/9	There was no statistically significant difference in the rate of recovery from olfactory dysfunction between those with positive PCR for COVID-19 and those with suspected COVID-19 with negative PCR
Mattioli et al. [59]	Prospective cohort (126 d)	Healthcare workers at University Hospital of Brescia (Italy) with previous confirmed diagnosis of mild-moderate COVID-19 ($n = 120$)	Healthcare workers from the same hospital not previously affected by COVID-19 ($n = 30$)	Interview, physical examination, questionnaires	5/9	COVID-19 cases did not differ significantly from non–COVID-19 controls in terms of neurological or cognitive deficits but had significantly higher scores for anxiety and depression
Elkan et al. [17]	Retrospective cohort[c] (270 d)	Adult patients discharged from Shamir Medical Center (Israel) with confirmed COVID-19 ($n = 42$)	Age- and sex-matched patients hospitalized during the same period as COVID-19 patients due to pneumonia or respiratory infection with negative COVID-19 PCR ($n = 42$)	Questionnaire	6/9	Although there are baseline differences between groups in terms of comorbidities, COVID-19 cases had significantly lower self-reported 'health change' compared to controls
Søraas et al. [62]	Prospective cohort (132 d)	Adults testing positive for COVID-19 across four laboratories in southeastern Norway, excluding participants later hospitalized ($n = 676$)	Adults testing negative for COVID-19 across the same sites, excluding participants later hospitalized ($n = 6006$)	Questionnaire	9/9	COVID-19–positive participants were significantly more likely to report a worsening of health compared to 1 y prior to follow-up when compared to COVID-19 –negative participants[d]

mMRC, modified Medical Research Council; RTI, respiratory tract infection.
[a] Cardiovascular disease, chronic respiratory disease, chronic kidney disease, hypertension, and diabetes.
[b] Obesity, hypertension, diabetes, chronic kidney disease, asthma, chronic lower respiratory diseases, nicotine dependence, substance use disorder, ischaemic heart disease and other forms of heart disease, socioeconomic deprivation, cancer, haematological cancer, chronic liver disease, stroke, dementia, organ transplant, rheumatoid arthritis, lupus, psoriasis, and disorders involving an immune mechanism.
[c] Study design was derived from manuscript method section and not author description.
[d] Multivariate regression model including age, sex, chronic diseases, smoking, health professional occupation, income level, fitness, and time from COVID-19 testing to follow-up.

chronic diseases or pandemic effects on individuals and societies [84,85]. Although most studies did not have a control group, the association of certain symptoms with COVID-19 infection among the six studies that had appropriate comparator groups supports our findings of a significant burden of PACS. Recent rigorously conducted comparative studies that examined the risk of new clinical sequalae rather than persistent symptoms at 6-month follow-up have shown a higher risk of long-term complications and incident diagnoses after acute COVID-19 infection among nonhospitalized cases when compared to a matched non–COVID-19 cohort and among hospitalized COVID-19 cases when compared to matched hospitalized influenza cases or other non–COVID-19 viral lower respiratory tract illnesses. An increasing risk gradient of new sequalae was observed with increasing COVID-19 severity [86,87].

Nevertheless, the mechanisms that explain these chronic symptoms after COVID-19 are not yet fully understood. In addition to the direct effects of SARS-CoV-2, the immune response to the virus is believed to be partly responsible for the appearance of these lasting symptoms, possibly through facilitating an ongoing hyperinflammatory process [88]. Several hypotheses have been proposed to explain the long-term outcomes of COVID-19 infection: (a) sequalae of COVID-19 organ involvement during acute infection; (b) COVID-19 patients with chronic symptoms may harbour the virus in several potential tissue reservoirs across the body, which may not be identified by nasopharyngeal swabs; (c) cross-reactivity of SARS-CoV-2–specific antibodies with host proteins resulting in autoimmunity; (d) delayed viral clearance due to immune exhaustion resulting in chronic inflammation and impaired tissue repair; (e) mitochondrial dysfunction and impaired immunometabolism; and (f) alterations in microbiome leading to long-term health consequences of COVID-19 [88–91].

Comparison to other studies

Our systematic review provides a rigorous and unique update of previous attempts by other investigators. First, a number of previous reviews either did not assess the included studies for risk of bias or used an inappropriate assessment tool, such as the Newcastle-Ottawa Scale for noncomparative studies. We observed the quality of included studies to be a significant contributor to heterogeneity of reported symptoms prevalence, with lower-quality studies reporting higher prevalence of certain symptoms [92,93]. Second, other systematic reviews have included studies with short follow-up periods between 1 and 3 months after acute illness and hence do not provide an indication of persistent and chronic symptoms that are defined beyond 12 weeks as per NICE [92–95]. Third, although previous studies have performed meta-analyses, with Michelen et al. performing meta-regression for variables of ICU admission and proportion of female patients and Iqbal et al. performing thorough subgroup analysis, no previous systematic review has separated symptom prevalence across different follow-up intervals or considered other important effect modifiers for meta-regression [96,97]. Finally, and importantly, we present the first attempt to identify and assess studies including an appropriate non–COVID-19 group to provide additional evidence on the association between COVID-19 and the high prevalence of symptoms at follow-up.

Although our review included the most recent eligible studies with the largest sample size, there is a degree of consistency between the findings of symptom prevalence in our meta-analyses and others. We report a prevalence of fatigue of 32%, 36%, 47%, and 41% across follow-up periods from 3 to <6 months, 6 to <9 months, 9 to <12 months, and >12 months respectively, which is comparable to the findings of Michelen et al. [96] (30.1%) and Iqbal et al. [97] (37%). This similarity is also the case for dyspnoea, with previous meta-analysis reporting estimates of prevalence between 25% and 35%, as well as myalgia and hair loss.

Strengths and limitations

Our study is the largest and most comprehensive systematic review of persistent symptoms after acute COVID-19 to date. However, it has a number of limitations inherent to the included studies and study design. As noted by previous systematic reviews on this topic, studies included in our review lacked uniform symptom terminology, standardized recording methods, and grouping of multiple symptoms under umbrella terms. This limited our ability to compare prevalence and frequency of these symptoms across the studies. Severity of illness was not described in numerous studies, with results presented for whole cohorts and not presented as subgroups. Thus, grouping all symptoms of various disease severity yield inaccurate estimates of symptom frequencies. The high observed statistical heterogeneity as measured by I^2 limits the interpretation of the pooled frequencies, although our extensive meta-regression illuminates significant contributors to this heterogeneity, namely, severity as defined by highest level of medical care, geographic location, prevalence of diabetes, and method of assessing symptom at follow-up [98].

We agree with Nasserie et al. [94] in their recommendations about areas of improvement in future research of PACS, whether in the conduct of studies or reporting of the various characteristics of symptoms for such conditions, including the use of a standardized definition for symptoms and time-zero and including an objective measure of symptom severity and duration. There is a need for further rigorously conducted cohort studies to quantify the relative risk of developing long-term symptoms after acute COVID-19 infection in comparison to a non–COVID-19 comparator group, including healthy controls and those with other acute respiratory infections [94,97,99].

Conclusion

In this large systematic review, we observed, with high degree of between-study heterogeneity, that a large proportion of COVID-19 patients have persisting and varying symptoms for several months after the acute infection. Although many unanswered questions about PACS remain, our study brings more evidence from a large number of patients and across different worldwide populations on the prevalence of the long-term effects of COVID-19. Our data support the recent global efforts to conduct additional research to address the underlying mechanisms, epidemiology, diagnosis, and treatment of PACS.

Transparency declaration

The authors declare no conflicts of interest. EFB receives a UTD honorarium <5 k per year and is a member of the advisory board for Debiopharm International S.A. No funding was received for this work.

Author contribution

MSA and OAO contributed equally as first authors. NAF, BAS, RA, and MR contributed equally as second authors. Conceptualization: IMT and TK; supervision: IMT and KMT; project administration: MSA and OAO; formal analysis: MR; data curation: BAS, DG, MSA, MO, NAF, OAO, RA, YO, and ZK; visualization: MR, and RMT; writing—original draft: BAS, MSA, NAF, OAO, and RA; writing—review and editing: EFB and IMT.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2022.01.014.

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