Review

Post-Covid-19 Syndrome: symptoms and stratified follow-up. A systematic review and meta-analysis

Sindrome post-Covid-19: sintomi e follow-up stratificato. Una revisione sistematica e una meta-analisi

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Key words: Post-Covid-19; syndrome; symptoms; follow-up.

ABSTRACT

Background: Post-COVID-19 syndrome has been found in patients admitted to a hospital with severe conditions of COVID-19 and in adults who initially presented a mild illness. The aim is to underline the available literature on post-COVID-19 follow-up until 12 months about symptoms reported by adults infected with Sars-Cov-2 from at least 12 weeks after disease onset.
Methods: The bibliographic search was conducted on PubMed, Embase, CINHAL, Scopus and the Cochrane Central Register of Controlled Studies.
Results: We found that 68% of patients had at least one symptom post-COVID-19 after 12 weeks and up to 24 weeks post-onset. The most frequent symptoms were fatigue and muscle weakness (26%), dizziness and mental clouding (15%) and taste disturbances (10%).
Conclusions: Health policy needs to prepare for a long-term management plan to address COVID-19, as there are significant needs beyond recovery from the acute infection.

Background: La sindrome post-COVID-19 è stata riscontrata in pazienti ricoverati in ospedale con gravi condizioni di COVID-19 e in adulti che inizialmente presentavano una malattia lieve. L'obiettivo è sottolineare la letteratura disponibile sul follow-up post-COVID-19 fino a 12 mesi sui sintomi riportati dagli adulti infetti da Sars-Cov-2 da almeno 12 settimane dopo l'insorgenza della malattia.
Metodi: La ricerca bibliografica è stata condotta su PubMed, Embase, CINHAL, Scopus e il Cochrane Central Register of Controlled Studies.
Risultati: L'analisi ha rilevato che il 68% dei pazienti presentava almeno un sintomo post-COVID-19 dopo 12 settimane e fino a 24 settimane dopo l'esordio. I sintomi più frequenti sono stati affaticamento e debolezza muscolare (26%), vertigini e annebbiamento mentale (15%) e disturbi del gusto (10%).
Conclusioni: La politica sanitaria deve prepararsi a un piano di gestione a lungo termine per affrontare la COVID-19 in quanto vi sono esigenze significative oltre la ripresa dall'infezione acuta.

BACKGROUND

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the pathogen responsible for coronavirus disease 2019 (COVID-19), has caused morbidity and mortality on an unprecedented scale.[1] Clinical characteristics vary from a mild asymptomatic state to a severe state with respiratory dysfunction, thrombotic complications and multi-organ failure.[2] SARS-CoV-2 is known to affect the respiratory tract. Still, the resulting viral replication and immune response may lead to cardiac, renal and hepatic risks and an acute systemic inflammatory response and subsequent cardio-circulatory shock.[3]

As of January 2022, the COVID-19 pandemic has killed more than 5.5 million people worldwide, while about 265 million people have survived;[4] however, it is unknown whether these patients have made a real recovery. Even though most COVID-19 patients recover completely, without consequences, many patients can continue to experience COVID-19 symptoms after recovery from the infection and others may even develop new symptoms.[5] Altogether, this clinical spectrum that arises after the acute infection is called post-COVID syndrome (PCS).[6] Different authors have used different terms to describe the prolonged symptoms following the COVID-19 disease including "long COVID-19", "post-acute COVID-19", "persistent COVID-19 symptoms",

"chronic COVID-19", "post-COVID-19 manifestations", "long-term COVID-19 effects", "post-COVID-19 syndrome", "ongoing COVID-19", "long-term sequelae" or "long-range" as synonyms.[7] The National Institute for Health and Care Excellence (NICE) guidelines propose the following classification:[8] acute COVID-19 infection (signs and symptoms up to 4 weeks), ongoing symptomatic COVID-19 (signs and symptoms of COVID-19 present from 4 weeks and up to 12 weeks), post-COVID-19 syndrome (signs and symptoms developing during or after a COVID-19 compatible infection, present for more than 12 weeks and not referable to alternative diagnoses).

Studies in literature explain the cytokine-driven evolution of the post-COVID-19 syndrome, but further research is needed to understand its pathogenesis.[9]

The most common late symptoms of the acute COVID-19 infection are fatigue, dyspnea, coughing, anosmia, mental cloudiness and dysgeusia. Still, there are also specific organ lesions involving the respiratory system (with symptoms such as coughing and shortness of breath), the cardiovascular system (with symptoms such as chest oppression, chest pain, palpitations), the neuropsychiatric system (stroke, encephalopathy, meningoencephalitis, convulsions, cognitive impairment, headaches, sleep disorders, dizziness, delirium), the gastrointestinal system (with symptoms such as abdominal pain, nausea, diarrhea, anorexia and reduced appetite), the musculoskeletal system (with symptoms such as joint pain, muscle pain), the immune system (with symptoms such as fatigue, fever, pain), non-specific symptoms (rashes, tinnitus, earache, sore throat, dizziness, loss of taste and/or sense of smell).[10] In a study conducted in Italy, 87% of individuals that had recovered from COVID-19 and were discharged after hospitalization showed persistence of at least one symptom 60 days after its onset.[11] In a prospective Chinese cohort study, the majority of previously hospitalized patients (76%) reported at least one symptom 6 months after symptom onset, of which fatigue was the main symptom (63%).[10]

PCS has been found in patients admitted to a hospital with severe conditions of COVID-19 , as well as in adults who initially presented a mild disease.[10,12] Symptom familiarity and their prevalence can guide research on measures for prevention and treatment to respond effectively to long-term post-COVID-19 outcomes.

This systematic review highlights the available literature on post-COVID-19 follow-up until 12 months about symptoms reported by adults infected with Sars-Cov-2 from at least 12 weeks after disease onset.

METHODS

The Prisma Statement guidelines 2020 were used to conduct the systematic review.

Eligibility criteria

Study types: all cohort, cross-sectional, case-control, case-report, case-series, qualitative studies that addressed post-COVID-19 follow-up with a timeframe greater than or equal to 12 weeks. No language, publication date or publication status restrictions were applied.

Type of participant: adults (aged 18 years or older) after at least 12 weeks from illness, including all levels of severity (severe to mild), admitted to any ward, or not admitted at all. Studies treating patients younger than 18 years, patients still hospitalized for COVID-19, follow-up before 12 weeks post-infection or lack of data on follow-up times and studies with clinical, radiological, histological and hematological findings were excluded.

Outcomes: Face-to-face and remote (online survey, telephone) follow-ups including subjective (patient self-reported) assessments were considered.

SOURCES OF INFORMATION AND RESEARCH STRATEGY

Studies were accessed through bibliographic references in electronic databases, or indirectly through the bibliography of articles. No limits on publication language were applied and articles in foreign languages were translated. The bibliographic search was conducted on PubMed, Embase, CINHAL, Scopus and the Cochrane Central Register of Controlled Studies (Central). The following keywords were searched as Mesh or Major and Emtree terms or as accessible terms and were variably associated according to the specific syntax of the databases consulted: post-acute COVID-19 syndrome, long COVID, follow-up, post COVID-19 symptoms.

The database search was conducted on 30/8/2021.

The review was registered on the International Prospective Register for Systematic Review (PROSPERO) (ID: CRD42021283689).

STUDY SELECTION

The screening of the citations identified by the bibliographic search was conducted by examining titles and abstracts to discard any duplicate studies and to select potentially relevant studies about the established eligibility criteria. Once eligible studies were identified, inclusion criteria were applied to the full texts. Four reviewers conducted each step of the selection process. The selection process is outlined in the Prism flow diagram (Figure 1).

RISK OF BIAS IN INDIVIDUAL STUDIES

The quality of the included studies was assessed independently by the four researchers to increase the reliability of the assessment.

To determine the validity of the non-randomized studies, the Newcastle-Ottawa scale[13] was used, according to which each study is judged on eight elements, classified into three groups: selection of study groups, comparability of groups and assessment of the exposure or outcome of interest for case-control or cohort studies respectively. In longitudinal cohort studies or case-control studies, a maximum of 9 stars can be assigned. In cross-sectional cohort studies, a maximum of 3 stars can be assigned. Studies with a score of 3 are of good quality, studies with a score of 2 are of fair quality and studies with a score of 1 are of poor quality. The methodological quality of the included studies was determined by two authors and differences, if any, were discussed. In the event of disagreement, a third researcher mediated a consensual decision.

DATA CHARACTERISTICS AND DATA EXTRACTION

From each of the included studies, the following data were extracted:

1) study characteristics (first author, publication date, country, study period, study design)
2) characteristics of the participants (age, gender, number of participants)
3) primary outcomes: time considered for follow-up, identifying method of reported symptoms

Data extraction was conducted in two groups of two reviewers who independently extracted data from all included studies. To ensure accurate data collection, data extracted independently by each reviewer were compared, and any differences were further discussed to nsure coherence between reviewers. Data was filled into a single bibliographic review software program, synthesized and then downloaded into a single Excel spreadsheet in Microsoft Excel software for validation and codification.

STATISTICAL ANALYSIS

The meta-analysis was conducted with the software Review Manager V.5.3 (The Cochrane Collaboration, Oxford, UK). An α-level of 0.05 was chosen to indicate statistical significance. Heterogeneity between studies was assessed using Cochran's chi-squared test and I 2. A random-effects model was used to calculate the mean effect size reported in 2 or more studies. Pooled prevalence was presented with a 95% confidence interval (CI). Publication bias was assessed by Egger's regression test ($p<0.10$). (MedCalc software - MedCalc Software Ltd).

RESULTS

Study selection

Six hundred and fifty-nine articles were identified initially, leaving 420 articles after removing duplicates. After screening for titles and abstracts, 43 articles remained for full-text evaluation, of which 37 were excluded for the following reasons: 7 studies addressed follow-up at <12 weeks after discharge, 6 studies addressed only respiratory outcomes (residual volume; total lung capacity; and vital capacity), high-resolution computed tomography (HRCT) of the chest and 6-minute walking distance test), 8 studies addressed neurological consequences, 2 studies addressed only magnetic resonance imaging (MRI) - based consequences, 3 studies were surveys without a follow-up timeline, 1 study lacked full text, 10 studies addressed outcomes related to the quality of life scales and did not indicate reported symptoms.

After completion, 6 studies with 5266 participants were eligible for synthesis (Figure 1).

CHARACTERISTICS OF THE INCLUDED STUDIES

Table 1 presents the characteristics of the included studies.

Four studies were from Europe, one from China and one from Russia. The number of patient cohorts followed in the studies ranged from 57 to 2649. Adults aged between 18 and 87 years were included. Patient follow-up time went from 84 to 180 days. Three studies[14-16] collected information from patients using self-reported online or telephone surveys; three studies[17-19] collected data during follow-up visits. Three studies[14,16,18] included only hospitalized patients for COVID-19; the rest of the studies treated both inpatients and outpatients.

The level of heterogeneity found was considerable Chi2=407.20, df=5 ($p<0.00001$), I2>75%. All studies included mild, moderate and severe mixed first-wave patients. The observation period was well established.

SYMPTOM PRESENCE

The analysis of the included studies found that 68% of patients had at least one symptom post-COVID-19 after 12 weeks from the onset and up to 24 weeks post-onset. The aggregated data show an odds ratio of 3.08 with a confidence interval of 1.23-7.69 and a p-value <0.00001. The combination of studies (overall) is significant, despite heterogeneity, favoring the presence of prolonged post-

COVID-19 symptoms (p=0.02). Three studies had significant positive results (Figure 2).

The most frequent symptoms found in the population sample of the studies analysed were fatigue and muscle weakness (26%, 95% CI 2-63; Egger's test p=0.6665), followed by dizziness and mental clouding (15%, 2-35; Egger's test p=0.0873) and taste disturbances (10%, 1-24; Egger's test p=0.2148). Then dyspnea (9%, 1-27; Egger's

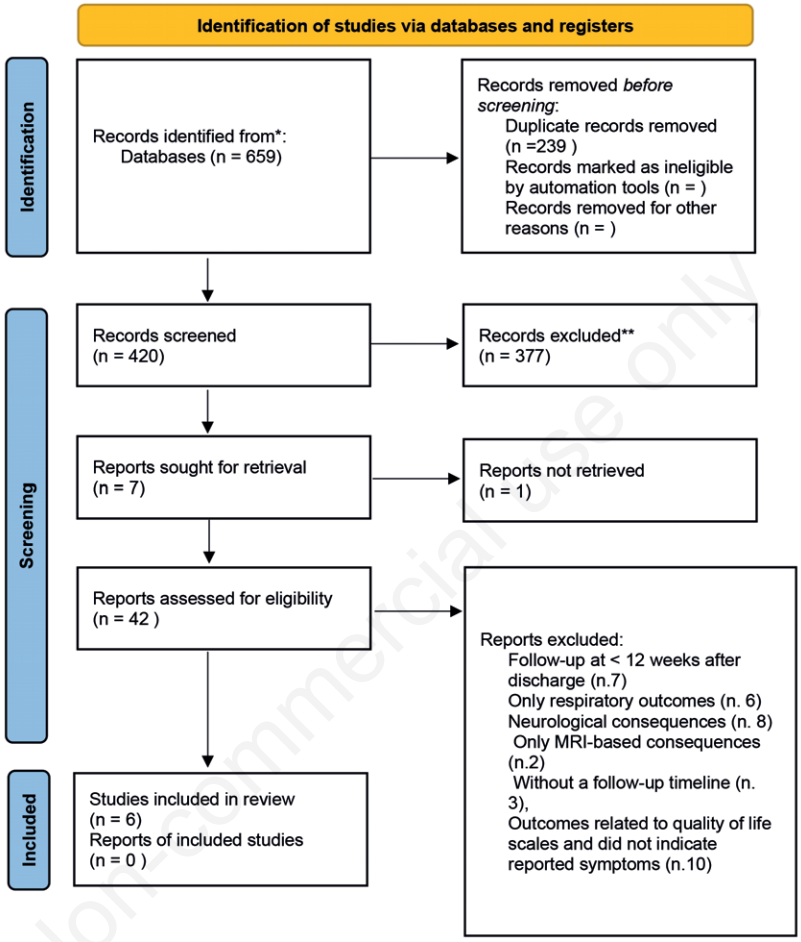

Figure 1. Prisma flowchart 2009.

Study or Subgroup	any symtoms Events	Total	no symtomps Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Bjørn Blomberg 2021 Norway	136	247	111	247	19.0%	1.50 [1.05, 2.14]
Daniel Munblit 2021 Russia	1534	2649	1115	2649	19.5%	1.89 [1.70, 2.11]
Huang Chaolin et al. January 2021, Wuhan, Cina	1265	1655	390	1655	19.4%	10.52 [8.96, 12.35]
Johnsen Stine et al. 2021 Danmark	57	57	0	57	4.2%	13225.00 [257.99, 677929.45]
Maria Skaalum Petersen	96	180	84	180	18.8%	1.31 [0.86, 1.98]
Morin L et al	244	478	234	478	19.2%	1.09 [0.84, 1.40]
Total (95% CI)		**5266**		**5266**	**100.0%**	**3.08 [1.23, 7.69]**
Total events	3332		1934			

Heterogeneity: Tau² = 1.12; Chi² = 407.20, df = 5 (P < 0.00001); I² = 99%
Test for overall effect: Z = 2.41 (P = 0.02)

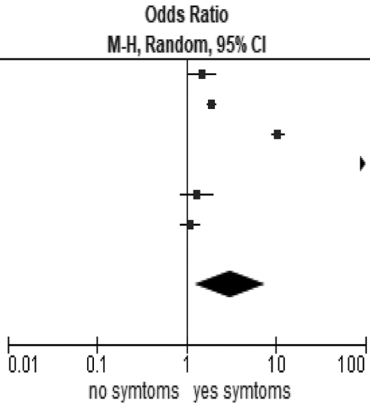

Figure 2. Forest plot presence/absence of symptoms post COVID-19.

Table 1. Characteristics of the studies included.

Author, date, Country	Study Design, study period	Number of participants	Avarage age (DS-range)	Gender M/F	Patient conditions during covid-19	Hospitalisation yes/no	Follow-up times	Symptom reporting methods
Huang Chaolin *et al.* January 2021, Wuhan, Cina	Prospective, observational cohort study Period: admissions from 7 January 2020 to 29 May 2020	1733	57.0 (47.0-65.0)	897/836	439=did not require supplementary oxygen; 1172 required oxygen supplement; 122 required HFNC, NIV o IMV	Jin Yin-tan Hospital	6 months from discharge	In-person visit Responding to questionnaire
Bliddal Sofie *et al.* June 2021. Denmark	Prospective, observational cohort study between 24 June and 15 August 2020	445	46.0 (16.1)	191/254	No need for hospitalization	Not hospitalized	At 4 weeks and >12 weeks	Online questionnaire
Johnsen Stine *et al.* July 2021 Denmark	Cross-sectional study	57	51.0 (13.0)		21 of the 34 patients required oxygen therapy, and about half of all patients received high-flow oxygen. The average length of hospital stay was 13 days	In-patient and out-patient	Follow up 3 months after discharge (hospitalized patients) or sent by the attending physician for persistent symptoms (out-patients)	At the respiratory outpatient clinic
Morin L. *et al.* March 2021. France	Prospective cohort study Patients admitted to a university hospital in France between 1 March and 29 May 2020	478	60.9 (16.1)	277/201	142 patients admitted to intensive care, of whom 72 were intubated. 336 were not admitted to intensive care	Adult patients admitted to the Bicêtre hospital (University hospitals of Paris-Saclay) in France	4 months after hospital discharge or after discharge from the intensive care unit (ICU) for patients admitted to ICU	Telephone interview
Daniel Munblit. August 2021 Russia	Prospective cohort study. Patients admitted between 8 April and 10 July 2020	2649	56.0 (46.0-66.0)	863/1353	1679 (63.4%) mild requiring no oxygen therapy; 902 (34%) moderate requiring supplemental oxygen; 68 (2.6%) requiring NIV or invasive ventilation or admission to ICU	Sechenov University Hospital Network (four tertiary hospitals) in Moscow, Russia	Follow-up between 2 December 2020 and 14 January 2021 (2 to 6 months after discharge)	Telephone interview using an ISARIC Long-term Follow-up Study questionnaire
Bjørn Blomberg. June 2021. Norway	Prospective cohort study 28 February to 4 April 2020	312	46.0 (30.0-58.0)	152/160		247 isolated at home and 65 admitted to hospital	Follow up at 6 months	In attendance
Maria Skaalum Petersen 2020 Denmark	Longitudinal study from April to August 2020	180	39.9 (19.4)	82/98	Symptomatic and asymptomatic patients without oxygen support	8 patients hospitalized with an average admittance period of 2 days and 179 not hospitalized	Follow up at 3 and 5 months. From 22 April to 16 August	Telephone interview

[Working Paper of Public Health 2022; 10:9540]

test p=0.1960), sleep disturbances (9%, 0-33; Egger's test p=0.8733), hair loss (8%, 1-38; Egger's test p<0. 0001), olfactory disturbances (8%, 1-20; Egger's test p=0.3902), paresthesia (5%, 1-11; Egger's test p=0.5161), palpitations (5%, 0-14; Egger's test p=0.7328). (Table 2 and Figure 3).

Egger's test (p=0.8270) did not suggest a significant presence of publication bias for the data on the long-term persistence of post-COVID symptoms (Table 3).

Based on the data presented in the meta-analysis we can consider it likely that publication bias exists for the data referring to the symptoms of dizziness, hair loss, headache, joint pain, cough, diarrhea or vomiting, sore throat, myalgia, rash and low fever.

DISCUSSION

This systematic review and meta-analysis show that 68% (95% CI 56-79) of individuals with a confirmed diagnosis of COVID-19 would continue to have at least one symptom beyond the 12 weeks after acute infection. The choice of follow-up time is in line with the definition of the NICE guidelines:[8] persistence of symptoms in the first 4-8 weeks post-infection is expected, with multifactorial causes and a tendency towards progressive resolution, whereas the 12-week time frame enables a more differentiated and COVID-19-related clinical picture to be established.

The most frequent symptom was fatigue, a figure that is slightly lower but in agreement with the results found in the literature, where it is found that between 30% and 60% of patients admitted and treated on an outpatient basis reported fatigue at least up to six months after the acute infection.[20]

The underlying trigger for these long-term symptoms in post-COVID-19 patients is not well understood and is cur-

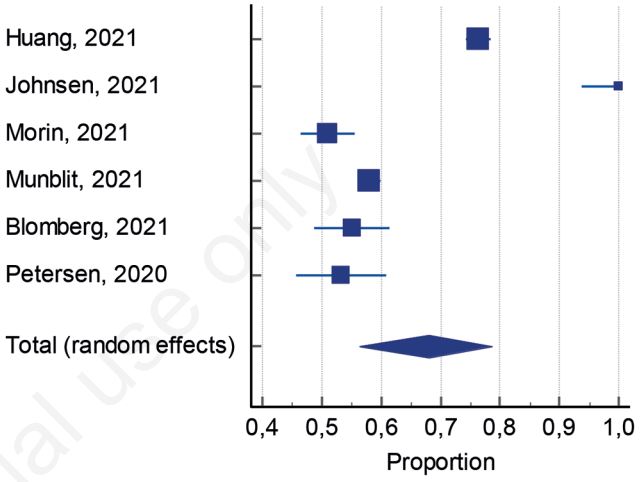

Figure 3. Aggregate prevalence of post-COVID-19 symptoms.

Table 2. Pooled prevalence of post-COVID-19 symptoms.

	Studies	Cases	Sample size	Pooled Prevalence % (95% CI)	
1 or > symptoms	6	3332	5266	68	(56 to 79)
Fatigue or muscle weakness	5	1336	5209	26	(2 to 63)
Dizziness/mental confusion/difficulty concentrating	3	272	4551	15	(2 to 35)
Taste disorder	4	221	4731	10	(1 to 24)
Dyspnea	3	151	3374	9	(1 to 27)
Sleeping difficulties	3	486	4551	9	(0 to 33)
Hair loss	2	385	4304	8	(1 to 38)
Olfactory disorder	4	253	4962	8	(1 to 20)
Paresthesia	3	127	3374	5	(1 to 11)
Palpitations	3	188	4551	5	(0 to 14)
Headache	5	115	5209	4	(2 to 8)
Reduced appetite	3	180	4782	4	(0 to 14)
Joint pains	2	179	4304	4	(0 to 16)
Chest pain	3	118	4782	3	(0 to 9)
Cough	3	53	3374	3	(0 to 8)
Diarrhea or vomiting	2	96	4304	2	(0 to 8)
Sore throat or difficulty swallowing	2	73	4304	2	(0 to 8)
Myalgia	2	58	4304	1	(0 to 3)
Skin rash	2	54	4304	1	(0 to 5)
Low fever	2	6	1902	1	(0 to 3)
Disturbed mood	1	73	Insufficient data for Meta-analysis		

rently an area of investigation. One cause could be traced to an inflammatory response following infection.[21] In addition, the coronavirus can spread through nerves to the central nervous system (CNS), as evidenced by autopsies that found viral proteins in the brainstem and cranial nerves. The cytokine storm (inflammatory response) and virus entry into the CNS could cause neuroinflammation resulting in prolonged generalized symptoms including fatigue, headaches, myalgias and dyspnea.[22]

On the other hand, sleep disturbance could be explained by the fact that patients with PCS demonstrate higher levels of stress and/or psychological problems, such as post-traumatic stress disorder, which can impair rest and sleep.[23]

The review examines the different severities of the disease as gravity (*e.g.* based on admission to general wards or intensive care units) could depend on multiple factors, including local admission protocols.

Three studies[14,18,19] included in the meta-analysis show an association between the female gender and the risk of presenting persistent symptoms, whereas one study[15] found no difference due to gender.

According to the literature, there seems to be a tendency for the elderly to present PCS.[24] This may be because increasing age leads to a weakening of the immune system. Moreover, many of the studies conducted on PCS use data from hospitalized patients who tend to be older. The average age of the patients included in this meta-analysis is about 60 years; However, age is likely a risk factor for PCS. Further investigation in younger populations is needed before concluding.

Table 3. Publication bias. Calculated from the data published by the meta-analysis, p values below. Zero point ten express the possibility of publication bias.

	Publication bias (Egger test*) p
1 or > symptoms	0,8270
Fatigue/muscle weakness	0,6665
Dizziness/mental confusion/difficulty concentrating	0,0873
Taste disorder	0,2148
Dyspnea	0,1960
Sleeping difficulties	0,8733
Hair loss alopecia	<0,0001
Olfactory disorder	0,3902
Paresthesia	0,5161
Palpitations	0,7328
Tension-type Headache Migraine or Cluster headache	0,0158
Reduced appetite	0,5904
Joint pains	<0,0001
Chest pain	0,4384
Cough	0,0913
Diarrhea o vomiting	<0,0001
Sore throat or difficulty swallowing	<0,0001
Myalgia	<0,0001
Skin rash	<0,0001
Low fever	<0,0001
Disturbed mood	-

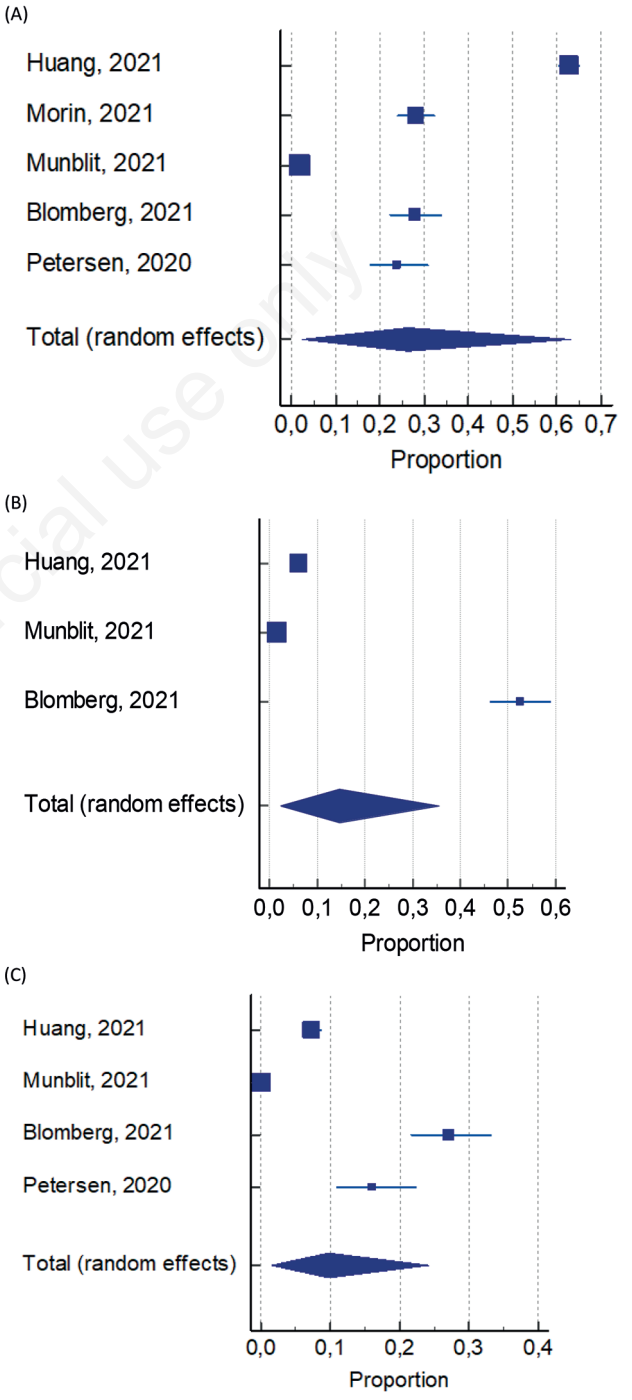

Figure 4. Forest plot of aggregate prevalence of muscle fatigue/weakness (A), dizziness/mental confusion/difficulty concentration (B), taste disorder (C).

LIMITATIONS

The results were influenced by significant heterogeneity in study design, duration, population, and method of symptom assessment.

In particular, social isolation and population demographics, such as patient ethnicity, can affect physical[25] and mental health, and were found to be associated with different outcomes in the context of COVID-19.[26] Data on the risk of fatigue as a function of ethnicity within socially diverse populations were not reported in the meta-analysis studies; such data would have added information on potential associations between fatigue and racial disparities among COVID-19 survivors. The sudden restrictions imposed on most of the world's population may also impact on the expression of physical symptoms. Our review could not separate the influence of these factors due to data limitations and the absence of appropriate controls.

Symptom causality remains unknown as studies do not allow a clear correlation of symptoms to disease or other factors associated with the pandemic. For example, pandemic-related restrictions or reduced physical activity may have played a role in the incidence of some symptoms.

Limitations of the study include the lack of information on the symptomatic pattern before the acute COVID-19 infection and the lack of detail on symptom severity.

The data reported refer to patients' self-assessment and not to an assessment with appropriate scales; therefore, data should be cautiously considered.

One study[17] included in the meta-analysis did not specify the frequency of all symptoms, but they are recorded by rating scale scores. In contrast, another study reported only the most frequently presented symptoms.[15]

Despite these limitations, our meta-analysis of 5266 patients presented persistent symptoms 12 weeks after disease onset. These results may help to develop a better management plan for the post-recovery of COVID-19 patients through the definition of guidelines for the treatment of patients with post COVID-19 syndrome.

CONCLUSIONS

Health policy needs to prepare for a long-term management plan to address COVID-19, as there are significant needs beyond recovery from the acute infection. Symptoms experienced at a distance from the acute infection could affect people's physical and working capacities with substantial economic consequences.

Future research should focus on more objective assessments of symptoms and standardized follow-up of patients post-COVID-19 by extending observation times. In public health, it should be possible to share anonymous individual data on persistent post-COVID-19 symptoms. New variants of the coronavirus may cause varied symptomatology and this merits further research.

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Authors' contributions: RDM, TB Substantial contributions to the conception, design of the work, acquisition, analysis and interpretation of data for the work, drafting of the work and revising it critically for important intellectual content, final approval of the version to be published, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. DG: Interpretation of data for the work, drafting of the work and revising it critically for important intellectual content, final approval of the version to be published, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. MG, AC: Acquisition, analysis and interpretation of data for the work, drafting of the work and revising it critically for important intellectual content, final approval of the version to be published, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. AM: Substantial contributions to the conception, design of the work, acquisition, analysis and interpretation of data for the work, drafting of the work and revising it critically for important intellectual content, final approval of the version to be published, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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