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Global prevalence of persistent neuromuscular symptoms and the possible pathomechanisms in COVID-19 recovered individuals: A systematic review and meta-analysis

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Abstract

This study was conducted to determine the prevalence of prolonged neuromuscular symptoms, including fatigue, anosmia, headache, myalgia, and joint pain in COVID-19 survivors hospitalized with mild, moderate, or severe infections worldwide. The search was conducted up to January 30th, 2021 using three databases (PubMed, Scopus, and Web of Science) to identify potentially eligible studies. Data on study characteristics, follow-up characteristics, and severity of COVID-19 during hospitalization were collected in accordance with PRISMA guidelines. The Newcastle-Ottawa scale was used to assess the quality of relevant articles. The estimated prevalence of specific prolonged neuromuscular symptoms and the association between COVID-19 severity and occurrence of prolonged neuromuscular symptoms was analyzed wherever appropriate. Database search yielded 4,050 articles and 22 articles were included for meta-analysis. The estimated prevalence of prolonged fatigue was recorded in 21.2% (95%CI: 11.9%–34.8%) of 3,730 COVID-19 survivors. Persistent anosmia was recorded in 239 of 2,600 COVID-19 survivors (9.7%, 95%CI: 6.1%–15.2%). In 84 out of 2,412 COVID-19 survivors (8.9%, 95%CI: 3.2%–22.6%), prolonged headache was observed. A total of 53 out of 1,125 COVID-19 patients (5.6%, 95%CI: 2.1%–14.2%) complained of persistent myalgia even after being discharged from the hospital. The prevalence of prolonged joint pain was in 15.4% (95%CI: 8.2%–27.2%) of subjects. Due to data scarcity on COVID-19 severity and prolonged neuromuscular symptoms, association analysis could not be conducted. Widespread concern regarding long-term impacts of COVID-19 was raised

after several studies reported prolonged symptoms in COVID-19 survivors. Numerous theories have been proposed to address this concern; however, as the research on this pandemic is still ongoing, no explanation is definitive yet. Therefore, follow-up studies in COVID-19 survivors after recovery from COVID-19 are warranted to determine the pathogenesis of prolonged symptoms. PROSPERO registration: CRD42021242332.

Keywords: COVID-19, prolonged symptom, long-term effect, neuromuscular, systematic review

Introduction

*T*he pathophysiological extent of coronavirus disease 2019 (COVID-19) infection is yet to be assessed [1]. COVID-19, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared as a global pandemic on March 11, 2020. After more than a year, the end of COVID-19 pandemic is still uncertain although several 'return to normal' theories have been discussed since the beginning of the global COVID-19 vaccination program [2-4]. Not only the healthcare system [5-8] but the global economy and education [9, 10] have also been hit equally hard [11-13], particularly by the lockdown policies [9, 14]. Although numerous proposed treatments have been investigated [15-19] many failed to provide good efficacy to treat severe COVID-19.

SARS-CoV-2 infection mainly attacks the respiratory system. Involvement of other organs has also been reported [20-24]. Studies assessing the effects of COVID-19 on the cardiovascular system [25, 26], liver [27], and the central nervous system [28, 29] have been conducted. The prevalence of anosmia and dysgeusia [30], hemorrhagic and ischemic stroke [31], and gastrointestinal symptoms in COVID-19 patients have also been previously studied [32]. Currently, concerns about the persistence of COVID-19 symptoms even after recovery have been raised in several articles, particularly in the context of neurological manifestation such as fatigue [33, 34], headache [35], and anosmia [36]. Although no direct association of prolonged fatigue with laboratory markers and COVID-19 severity has been reported [33], persistent fatigue was the most common symptom experienced by 80% of COVID-19 patients even after six months of recovery [37]. Moreover, varying degrees of depression, sleep difficulties, and anxiety among healthcare workers post COVID-19 infection were published so far [38, 39].

The need for continuous monitoring of all COVID-19 cases irrespective of the clinical severity of the initial acute infection has been raised, particularly after prolonged symptoms such as dizziness, muscle pain, headache, fatigue, and anosmia were reported among asymptomatic or mildly symptomatic patients for months [40]. This systematic review was conducted to address (a) the global estimated prevalence of prolonged neuromuscular symptoms (fatigue, anosmia, headache, myalgia, and joint pain) in recovered COVID-19 patients and (b) the association of COVID-19 severity with prolonged neuromuscular symptoms.

Methods

Registration and protocol
The study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines for searching databases and reporting our findings [41], as presented in **Supplementary Material**. In addition, the study protocol was registered on PROSPERO registration (CRD42021242332) and no ethical approval was required. Partial results of this systematic review have been published elsewhere [39].

Eligibility criteria of studies
The inclusion criteria were articles reporting at least one persistent neuromuscular symptom (fatigue, anosmia, headache, myalgia, and joint pain) in recovered COVID-19 hospitalized patients. All studies must have included real-time polymerase chain reaction (RT-PCR) results of SARS-COV-2 RNA from nasal or oropharyngeal swab samples for confirmation of COVID-19.

Recovered patients were defined as all COVID-19 patients who met the discharge criteria from the WHO or China National Health Commission [42, 43]. Data for prolonged neuromuscular symptoms was collected only in recovered patients with persistent symptoms for at least two weeks after discharge.

The exclusion criteria included editorials, commentaries, reviews, case reports, and case series. In addition, cases, where the diagnosis of COVID-19 was confirmed based on only radiology or symptoms were excluded. Finally, only articles written in English and published between 2019 to 2021 were included in this study.

Information sources and search strategy

The search was performed in three databases (PubMed, Scopus, and Web of Science) as of January 30, 2021 to identify potential studies. The keywords used were ("SARS-CoV-2" OR "COVID-19" OR "Wuhan coronavirus" OR "Wuhan virus" OR "novel coronavirus" OR "nCoV" OR "severe acute respiratory syndrome coronavirus 2" OR "coronavirus disease 2019" OR "2019-nCoV" OR "2019 novel coronavirus" OR "SARS 2") AND ("prolong*" OR "follow-up" OR "persistent" OR "sequelae" OR "consequen*" OR "prospective" OR "cohort" OR "long-term" OR "follow*" OR "longitudinal"). The details of the search strategy for each database have been published elsewhere [39].

Study selection and data extraction

Endnote X9 (Thompson Reuters, Philadelphia, PA, USA) was used as a reference manager where all studies were imported and duplicates were removed. The first screening was done on titles and abstracts of all references to identify eligible articles. The second screening was conducted on the full texts of potentially eligible studies and decided the eligibility of each study based on the inclusion criteria and the availability of the data. Data extraction included data from main articles and supplementary materials, whenever required. In addition, a list of references was also retrieved as explained in previous studies [30, 31, 44] to explore additional studies. The extracted data included study characteristics of eligible studies (author(s), publication year, location of the study, and study design) and follow-up characteristics (extent of follow-up conducted after discharge, number of COVID-19 patients, number of COVID-19 patients with prolonged neuromuscular symptoms, and severity of COVID-19 infection during admission to the hospital).

Outcomes

The two main outcomes of this study were as follows: (a) global prevalence of persistent neuromuscular symptoms: fatigue, anosmia, headache, myalgia, and joint pain and (b) association of COVID-19 severity with the presence of persistent neuromuscular symptoms (fatigue, anosmia, headache, myalgia, and joint pain).

Data synthesis

The prevalence of each persistent neuromuscular symptom (fatigue, anosmia, headache, myalgia, and joint pain) was calculated as the number of patients with a prolonged symptom divided by the total number of patients with COVID-19 with or without the specific neuromuscular symptom during the follow-up and expressed as frequency (%) with a 95% confidence interval (CI). The association of COVID-19 severity with risk of prolonged neuromuscular symptoms was also calculated using z-test and presented as odds ratio and 95% confidence interval (95%CI). Forest plots were used to visualize the data.

Risk of bias assessment

The quality appraisal of eligible studies was performed using the Newcastle-Ottawa scale (NOS) [45]. Nine characteristics of a study including four items for sample collection, one item for group comparison, and three items for the outcome was considered in NOS with the score range of 0 to 9. A high-quality article was defined as a study with a NOS score ≥7, while moderate and low-quality articles were studies with NOS scores between 5–6 and ≤4, respectively.

Statistical analysis

Data analysis was performed on Review Manager version 5.3 [46]. Heterogeneity of the pooled data was evaluated using the Q test and I2 statistic. Data were analyzed using a random-effect or fixed-effect model as appropriate. Publication bias was assessed using Egger's test, with p<0.05 considered as potentially having publication bias.

Results

Study eligibility results

Database search resulted in 4,050 articles, of which 2,045 publications were duplicates. The remaining 2,005 studies underwent first screening on titles and abstracts, yielding 761 potentially eligible studies (**Figure 1**). The second screening excluded an additional 739 articles which did not meet the inclusion criteria. The final result included 22 articles for meta-analysis.
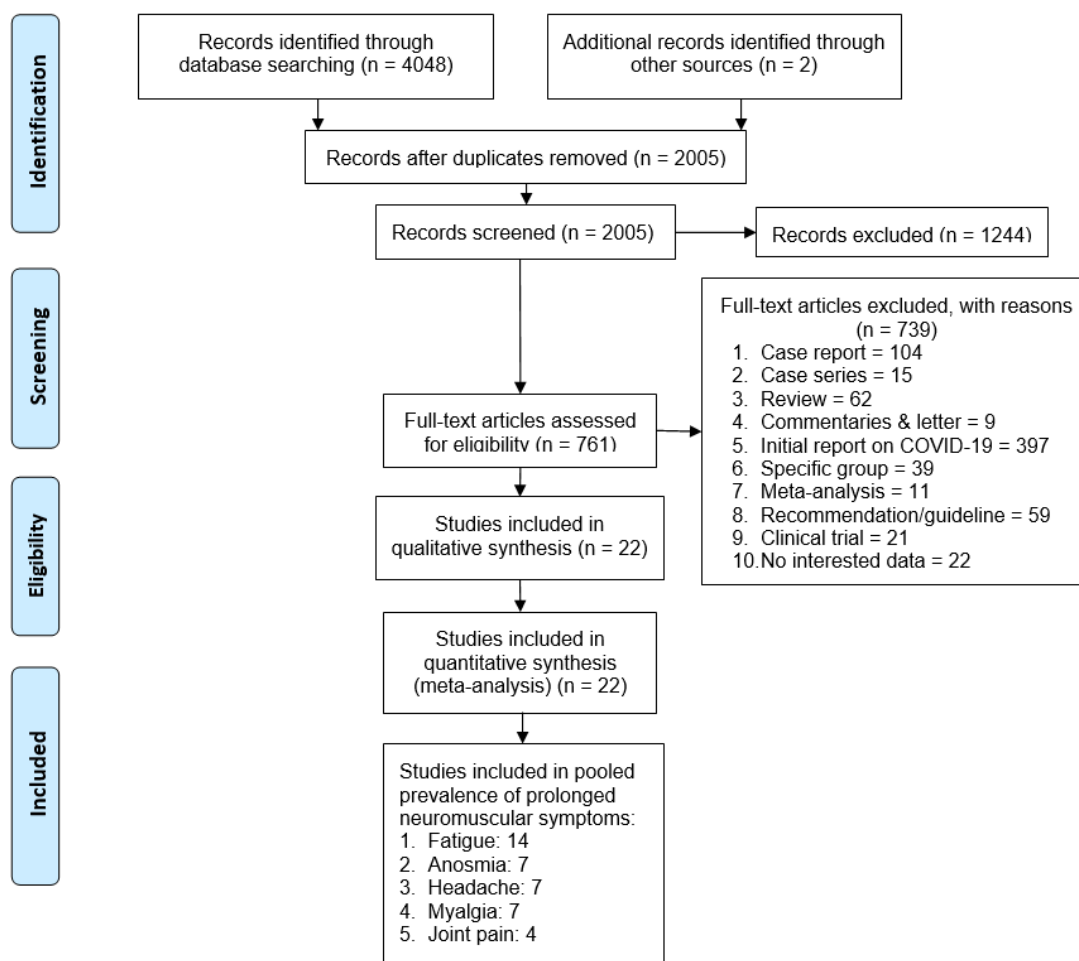

Figure 1. Flowchart of literature search according to PRISMA

The prevalence of persistent neuromuscular symptoms was calculated from 14 studies for fatigue [33, 47-59], 7 studies for anosmia [48-50, 52-54, 60], 7 studies for headache [48-50, 52, 54, 55, 57] and myalgia [48-50, 52, 55, 56, 58], and 4 studies for joint pain [47, 48, 50, 58]. The studies included for the meta-analysis of prevalence of prolonged neuromuscular symptoms are summarized in **Table 1**.

The information of COVID-19 severity on admission and the occurrence of prolonged neuromuscular symptoms were scarce. Therefore, no additional analysis could be performed.

Original Article

Table 1. The prevalence of prolonged neuromuscular symptoms among COVID-19 survivors

Symptoms	Year	Study design	City	Country	Day from discharge to follow-up Day (±SD) or Day (min-max)	Prevalence of prolonged neuromuscular symptoms over total followed COVID-19 survivors			NOS	Reference
						No patients	Total patients	Percentage		
Fatigue	2020	Prospective	Wuhan	China	14	7	131	5.3	7	[55]
	2020	Prospective	Isfahan	Iran	72 (62–87)	50	452	11.1	9	[54]
	2021	Cohort	Hubei	China	153 (146–160)	1038	1655	62.7	8	[50]
	2020	prospective	Fuyang	China	90	4	60	6.7	7	[52]
	2020	Cohort	Georgia	USA	38 (21–49)	17	26	65.4	8	[48]
	2021	Prospective	Wuhan	China	97 (95–102)	152	538	28.3	8	[58]
	2020	Prospective	Aachen	Germany	56 (48–71)	15	33	45.5	8	[49]
	2020	Prospective	Henan	China	90	9	55	16.4	7	[57]
	2020	Prospective	Wuhan	China	14	5	337	1.5	7	[56]
	2020	Prospective	Dublin	Ireland		22	128	17.2	9	[33]
	2020	Prospective	Rome	Italy	60.3 (±13.6)	76	143	53.1	7	[47]
	2020	Prospective	Tokyo	Japan	108 (±23)	10	58	17.2	7	[53]
	2020	Prospective	Wuhan	China	28	1	38	2.6	7	[59]
	2020	Prospective	Wuhan	China	90	45	76	59.2	8	[51]
	Total					1451	3730	38.9		
Anosmia	2020	Prospective	Isfahan	Iran	28	21	452	4.6	9	[54]
	2021	Cohort	Hubei	China	153 (146–160)	176	1655	10.6	8	[50]
	2020	Prospective	Fuyang	China	90	2	60	3.3	7	[52]
	2020	Cohort	Georgia	USA	38 (21–49)	8	26	30.8	8	[48]
	2020	Prospective	Aachen	Germany	56 (48–71)	4	33	12.1	8	[49]
	2020	Prospective	California	USA	9.4 (3.8–14.8)	18	316	5.7	8	[60]
	2020	Prospective	Tokyo	Japan	108 (±23)	10	58	17.2	7	[53]
	Total					239	2600	9.2		
Headache	2020	Prospective	Isfahan	Iran	28	12	452	2.7	9	[54]
	2020	Prospective	Wuhan	China	14	5	131	3.8	7	[55]
	2021	Cohort	Hubei	China	153 (146–160)	33	1655	2.0	8	[50]
	2020	Prospective	Fuyang	China	90	6	60	10.0	7	[52]
	2020	Cohort	Georgia	USA	38 (21–49)	13	26	50.0	8	[48]

Symptoms	Year	Study design	City	Country	Day from discharge to follow-up Day (±SD) or Day (min-max)	Prevalence of prolonged neuromuscular symptoms over total followed COVID-19 survivors			NOS	Reference
						No patients	Total patients	Percentage		
	2020	Prospective	Aachen	Germany	56 (48–71)	5	33	15.2	8	[49]
	2020	Prospective	Henan	China	90	10	55	18.2	7	[57]
	Total					84	2412	3.5		
Myalgia	2021	Cohort	Hubei	China	153 (146–160)	39	1655	2.4	8	[50]
	2020	Prospective	Wuhan	China	14	1	131	0.8	7	[55]
	2020	Prospective	Fuyang	China	90	15	60	25.0	7	[52]
	2020	Cohort	Georgia	USA	38 (21–49)	7	26	26.9	8	[48]
	2021	Prospective	Wuhan	China	97 (95–102)	24	538	4.5	8	[58]
	2020	Prospective	Aachen	Germany	56 (48–71)	5	33	15.2	8	[49]
	2020	Prospective	Wuhan	China	14	1	337	0.3	7	[56]
	Total					53	1125	4.7		
Joint pain	2021	Cohort	Hubei	China	153 (146–160)	154	1655	9.3	8	[50]
	2020	Cohort	Georgia	USA	38 (21–49)	8	26	30.8	8	[48]
	2021	Prospective	Wuhan	China	97 (95–102)	41	538	7.6	8	[58]
	2020	Prospective	Rome	Italy	60.3 (±13.6)	39	143	27.3	7	[47]
	Total					242	2362	10.2		

Min-max: minimum-maximum, NOS: Newcastle-Ottawa scale, SD: standard deviation

Prevalence of prolonged neuromuscular symptoms in patients with COVID-19

Prolonged fatigue was recorded in 1,451 out of 3,730 recovered COVID-19 patients, with an estimated prevalence of 21.2% (95%CI: 11.9%–34.8%) (**Figure 2**). Persistent anosmia was reported in 239 out of 2,600 COVID-19 survivors, corresponding to a pooled prevalence of 9.7% (95%CI: 6.1%–15.2%). Persistent headache was identified in seven studies that included 2,412 patients with COVID-19 out of which 84 patients were reported to have had the symptom, corresponding to an estimated prevalence of 8.9% (95%CI: 3.2%–22.6%) (**Figure 3**). Myalgia was reported in 53 out of 1,125 patients with COVID-19, with an estimated prevalence of 5.6% (95%CI: 2.1%–14.2%). The last four studies identified 242 cases of persistent joint pain out of a total of 2,362 COVID-19 survivors, which corresponds to an estimated prevalence of 15.4% (95%CI: 8.2 %–27.2%).
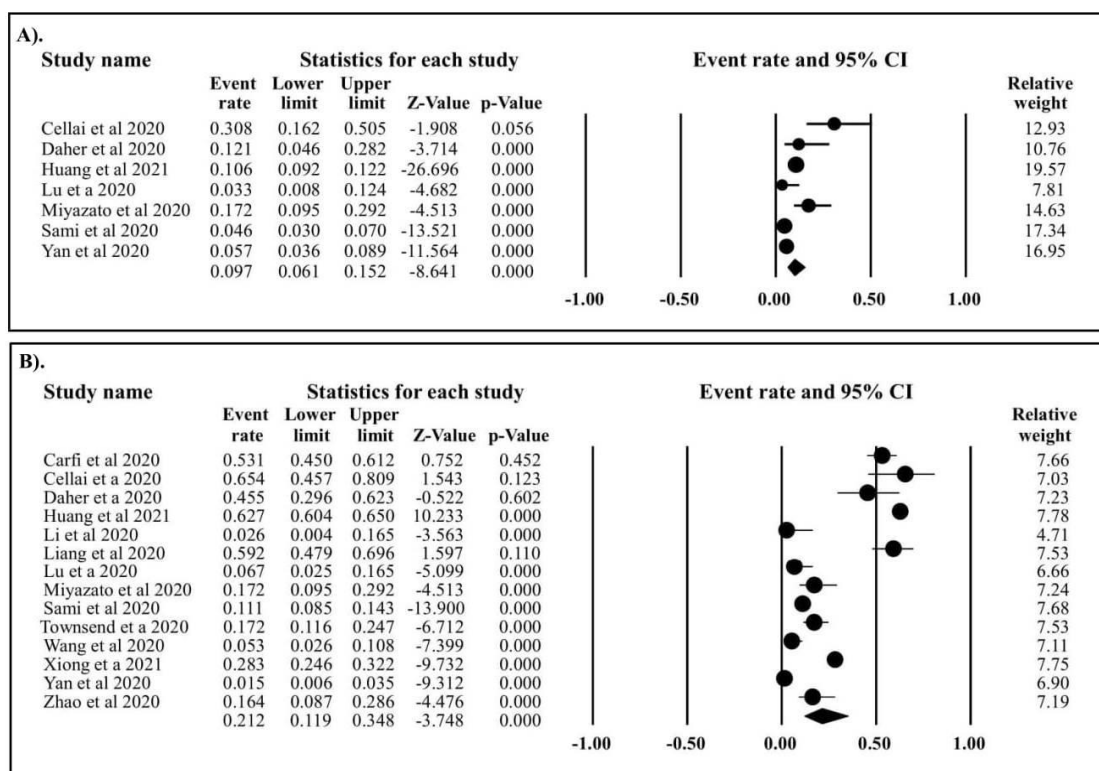

Figure 2. Forest plot of prolonged anosmia and fatigue in COVID-19 survivors. (A) Estimated prevalence of prolonged anosmia in COVID-19 survivor (event rate: 9.7%, 95%CI: 6.1%–15.2%, p<0.001, p Egger 0.577, p heterogeneity <0.0001. (B) Estimated prevalence of prolonged fatigue in COVID-19 survivor (event rate: 21.2%, 95%CI: 11.9%–34.8%, p<0.001, p Egger: 1.254, p heterogeneity <0.0001.

Association of COVID-19 severity and prolonged neuromuscular symptoms

The association of COVID-19 severity with persistent neuromuscular symptoms could not be analyzed due to insufficient data on prolonged neuromuscular symptoms in patients with mild to moderate and severe COVID-19.

Discussion

During the initial months of the pandemic, the primary focus of doctors and scientists worldwide was to improve the patient's condition, especially their respiratory and to help them overcome the disease mostly by repurposing drugs already in clinical use [61, 62]. The impact of COVID-19 on the respiratory system was well studied. However, its effects on the other organs were still limited. Around April, 2020, that the first studies reporting the effects of SARS-CoV-2 on the brain emerged [63]. Our study found that persistent neuromuscular symptoms were

observed in COVID-19 survivors, such as fatigue (21.2%), anosmia (9.7%), headache (8.9%), joint pain (15.4%) and myalgia (5.6%). These results are in line with CDC that declared that persistent fatigue and headache (71% and 61%, respectively) as the most commonly reported prolonged neuromusculoskeletal symptoms of COVID-19 in the US [64]. One study reported inflammation in the brain tissues of a patient with meningoencephalitis associated with SARS-CoV-2 infection [65]. Another report provided evidence of persistent central nervous system (CNS) complications in COVID-19 patients, which included encephalopathy [63], psychosis [66], and stroke [67]. Long-term complications were also observed in the peripheral nervous system, such as the Guillain-Barré syndrome (GBS) [68] and brachial plexus neuropathy [69-71]. Recent studies have reported new-onset of myasthenia gravis (MG) in COVID-19 survivors without previous history of neurological and autoimmune disorders following recovery of initial infection [72], suggesting that COVID-19 can trigger autoimmune disease. Several reports on musculoskeletal manifestations of COVID-19 have also emerged with myalgia as the most commonly reported symptom [73-75].
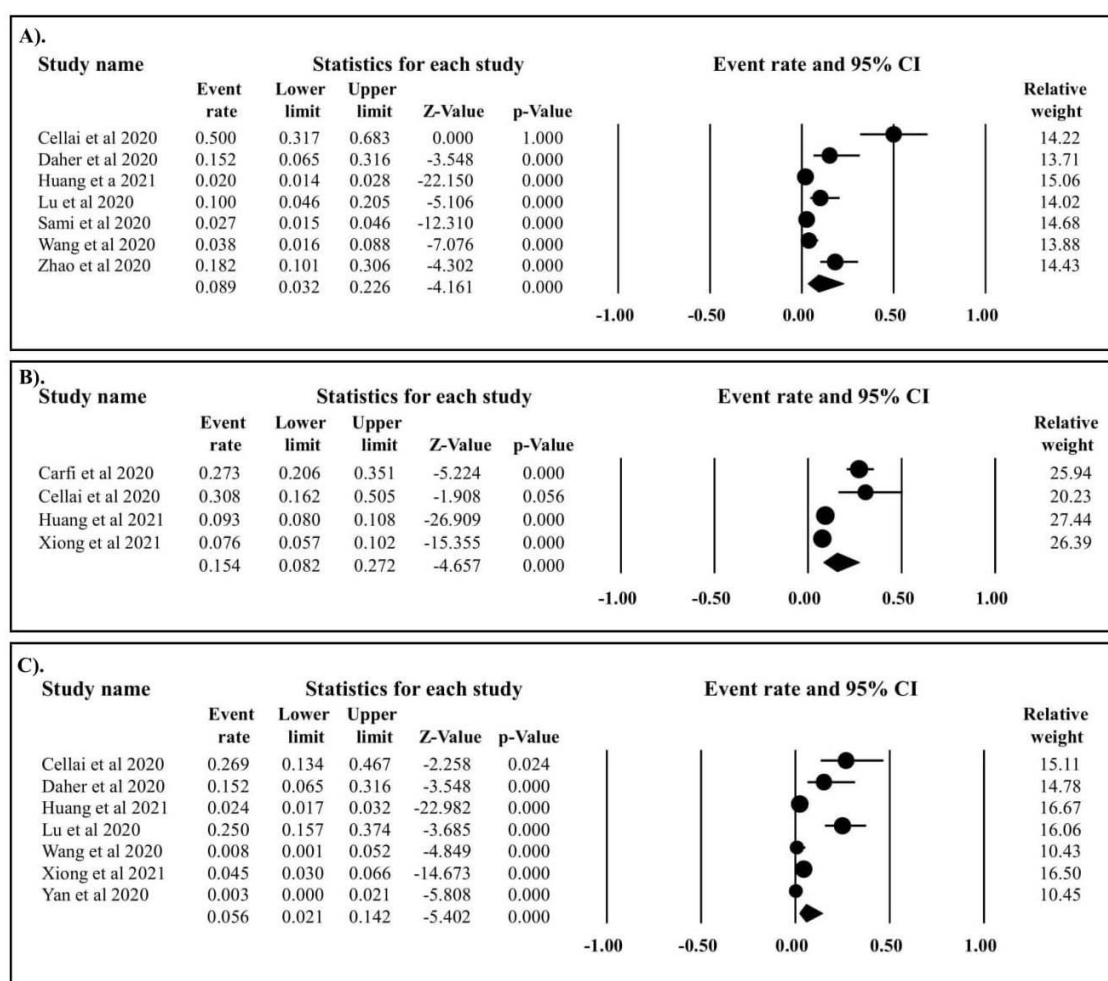

Figure 3. Forest plot of symptoms in COVID-19 survivors. (A) Estimated prevalence of prolonged headache in COVID-19 survivor (event rate: 8.9%, 95%CI: 3.2%–22.6%, p<0.001, p Egger 1.429, p heterogeneity <0.0001. (B) Estimated prevalence of prolonged joint pain in COVID-19 survivor (event rate: 15.4%, 95%CI: 8.2%–27.2%, p<0.001, p Egger 0.692, p heterogeneity <0.0001. (C) Estimated prevalence of prolonged myalgia in COVID-19 survivor (event rate: 5.6%, 95%CI: 2.1%–14.2%, p<0.001, p Egger 1.270, p heterogeneity <0.0001.

Possible pathomechanisms of neuromuscular manifestations
With evidence of prolonged neuromuscular manifestations of COVID-19 infection rapidly accumulating, COVID-19 has now been acknowledged as a threat to the nervous system as well [76]. Questions such as "Who are at risk of developing neuromuscular complications?", "Why do

these symptoms appear?", and "Are these symptoms are a lifelong consequence of COVID-19?" remain to be elucidated. Although theories of direct viral infection to the CNS, post-infection immune-mediated processes, and viral infection-induced hyperinflammation and hypercoagulability have been discussed, a definitive explanation for the pathogenesis of neuromusculoskeletal involvement is still due [76]. The elucidation of the molecular mechanisms underlying these symptoms is critical for the further development of treatment strategies. Moreover, the scenario for each of the different symptoms might be different or even contradictory. Olfactory cleft opacification and olfactory nerve inflammation have been observed, suggesting direct entry of the virus into the CNS from the olfactory bulb [77] and, therefore, direct brain infection of SARS-CoV-2 which requires antiviral therapy. A study using 'organoid', a miniature brain tissue model, has shown that SARS-CoV-2 can directly infect and kill neural cells [78]. Supporting this finding, another study that used mice expressing human ACE2 under the K18 promoter (K18-hACE2) reported neurotropism of SARS-CoV-2 [79]. However, another study in COVID-19 patients with peripheral nervous system involvement, such as acute inflammatory demyelinating polyradiculoneuropathy, reported elevated proinflammatory cytokines IL-6 and IL-8, indicating viral infection-induced hyperinflammatory response [80] which would require anti-inflammatory therapy. Therefore, knowledge of pathogenesis is crucial as administering anti-inflammatory drugs to patients with brain infection might lead to a contradictory and fatal outcome [81, 82].

Several studies have reported the presence of SARS-CoV-2 in the CNS [83, 84] indicating a neurotropic tendency of the virus. This is further supported by a study which showing that neurons and glial cells widely express ACE2 [85], thereby facilitating the entry of the SARS-CoV-2 virus into the cell. Following CNS infection, several neurological symptoms emerge. Among various vulnerable targets, the neuromuscular network is one such target to be attacked by the virus. Impairment of the neuromuscular network ultimately leads to the emergence of neuromuscular symptoms such as fatigue, anosmia, muscle weakness, headache, myalgia, and joint pain [86]. The presence of neuromuscular symptoms indicates damage to either the motor nerves controlling voluntary muscular functions (such as in neuromuscular junction leading to disturbances in neuromuscular transmission) or the sensory nerves [87].

It has been found that excessive production of proinflammatory cytokines has pathological roles in the development of some neuromuscular disorders. For example, deposition of intraneuronal α-synuclein and transactive DNA binding protein-43 (TDP-43) in Parkinson's disease and amyotrophic lateral sclerosis, respectively, is sensed by microglia leading to subsequent activation of NF-κB and AP-1 signaling pathways [88]. Activating signaling pathways culminates in the production of several pro-inflammatory cytokines (e.g., TNF-α and IL-1β) that attack dopaminergic neurons in PD and motor neurons in amyotrophic lateral sclerosis, leading to the emergence of some motoric disturbances, such as rigidity, tremor, and bradykinesia [88].

According to the aforementioned cases, several neuromuscular symptoms displayed by COVID-19 patients could also be associated with the overproduction of proinflammatory cytokines. This hypothesis is particularly convincing as 'cytokine storm' has been reported in many COVID-19 patients [89]. Headache, for example, has been linked to high levels of proinflammatory cytokines. Specifically, this symptom is caused by the activation of the trigeminovascular system which leads to excessive production of some neuropeptides, such as calcitonin gene-related peptide (CGRP), substance P, and pituitary adenylate cyclase-activating polypeptide (PACAP) [90]. Although several mechanisms are involved in the activation of the trigeminovascular system and release of neuropeptides, proinflammatory cytokines, especially IL-1, IL-6, and TNF-α, are strongly suspected of playing an important role in these mechanisms [91, 92].

Some possible pathogenesis of anosmia seen in COVID-19 patients has been described elsewhere [93]. Impairment in either peripheral olfactory nerves or the olfactory center in the brain is suspected as the primary contributing factors in the pathogenesis of anosmia [94]. However, damage to the olfactory supporting cells called sustentacular cells has been attracting bigger interest because these cells express higher levels of ACE2 and TMPRSS than the other

cells involved in olfactory processes and are also located near the external environment [95, 96]. Nonetheless, dysfunctionalities in either olfactory nerves or olfactory supporting cells are closely related to the action of proinflammatory cytokines. TNF-α and IL-6 seem to be the major cytokines involved in the impairment of olfactory-related cells, both in peripheral and central nervous systems [97].

COVID-19-related neuromuscular symptoms could also be due to hypoxic conditions. However, in the end, it is the inflammation and oxidative stress caused as a result of hypoxia that underlies the emergence of these symptoms. Damage to the respiratory system during the course of COVID-19 leads to decreased oxygen supply in the body [98]. The insufficient oxygen levels eventually disturb energy production in many cells, including neuronal cells innervating the muscle cells. In hypoxic conditions, cells will produce energy by the anaerobic mechanism resulting in excessive by-products generation, including succinate and lactate [99-101]. The accumulation of these metabolites, particularly lactate, is attributed to fatigue conditions [102].

Furthermore, these by-products can promote the secretion of proinflammatory mediators, such as cytokines and reactive oxygen species (ROS). Succinate activates macrophages causing them to release IL-1β [103]. A study found that increased levels of lactic acid secreted by tumor cells activate the IL-23/IL-17 proinflammatory pathway [104]. In contrast, another study confirmed that lactate production played an important role in initiating IL-6 release [105]. Therefore, the presence of these metabolites from anaerobic mechanism of energy production could aggravate fatigue conditions in COVID-19 patients.

Indeed, the expression levels of all biomarkers related to fatigue have been detected to be out of the normal range in COVID-19 patients. Lactate level, as one of the adenosine triphosphates (ATP) metabolism biomarkers, has been reported to be elevated by some studies [89, 106, 107]. The levels of the other fatigue biomarkers have also been reported to be imbalanced in COVID-19 patients, for example, oxidative stress biomarkers (elevated level of ROS and reduced level of antioxidants) and inflammation biomarkers (increased levels of proinflammatory cytokines such as IL-6 and TNF-α) [107-109].

Furthermore, oxygen deficiency activates transcriptional factors called hypoxia-inducible factors (HIFs), including HIF-1α [110]. Following HIF-1α activation, the expression of genes responsible for physiological processes such as angiogenesis, erythropoiesis, cell proliferation as well as inflammation is upregulated under oxygen-deprived conditions [111].

In addition to oxygen-dependent activation, HIF-1α activation is also induced by proinflammatory cytokines, growth factors, and exogenous toxins [111]. Interestingly, this induction can take place even under normal oxygen levels according to some studies that have reported that TNF-α and IL-1β promoted the expression and activity of HIF-1α via NF-κB signaling pathway in cells even in the presence of sufficient oxygen supply [112-114].

COVID-19-induced hypoxia could lead to the overproduction of oxygen free radicals resulting in increased oxidative stress. Several studies have demonstrated that oxidative stress is positively correlated with incidents of neuromuscular symptoms such as fatigue, myalgia, and joint pain [101, 115, 116]. The excessive production of ROS could be caused by disturbances in the electron transport chain in mitochondria, various enzymatic systems (e.g., NADPH oxidase, xanthine oxidase, and nitric oxide synthase), or endoplasmic reticulum [101] as oxygen supply to these systems are diminished in hypoxic conditions. As a result, this can lead to the oxidation of lipids, proteins, and DNA followed by the triggering of inflammatory events. Intriguingly, oxidative stress and inflammatory cells have a reciprocal correlation. The excessive production of ROS promotes inflammation, and inflammatory cells also enhance the release of ROS at sites of inflammation [101].

Conclusion

The prolonged neuromuscular symptoms are concerning as the estimated prevalence of these symptoms is still high even after two weeks of recovery. Although proposed molecular mechanisms underlying the pathophysiology are yet to be addressed, this study adds new insights to the long-term impact of COVID-19 in recovered patients. How COVID-19 affects the

quality of life in recovered patients is necessary to be determined in global follow-up cohort studies.

Ethics approval

Not required.

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Conflict of interest

The authors declare that they have no competing interests.

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Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

Supplementary Material

PRISMA checklist is available from: https://doi.org/10.6084/m9.figshare.14235287.

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