Persistent neurological manifestations in long COVID-19 syndrome: A systematic review and meta-analysis

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Review

Persistent neurological manifestations in long COVID-19 syndrome: A systematic review and meta-analysis

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ABSTRACT

Background: Several studies have reported prolonged symptoms especially neurological symptoms following acute infection in patients with COVID-19, known as long COVID-19. There are only few studies investigating this population and relatively less known, including nervous system involvement. A systematic review and meta-analysis of these studies are required to understanding the prevalence of persistent neurological manifestations after COVID-19.
Objective: To conduct a systematic review and meta-analysis on the persistent neurological manifestations in COVID-19 survivors.
Methods: Authors conducted a literature search through PubMed and MedRxiv from January 1st, 2020 to October 2021 according to PRISMA guideline. Furthermore, the authors added additional sources by reviewing related references. Studies presenting the neurologic features of long COVID-19 patients in their data were included. Case reports and case series also included in this review. The quality of the studies was assessed based on the Oxford Centre for Evidence-Based Medicine guidelines. Selected studies were included in the meta-analysis of proportion and heterogeneity test.
Findings: From 128 identified studies, 36 were eligible, with 9944 participants included. Most of the included studies had mean duration of follow-up after COVID-19 onset of less than 6 months. Fatigue was the most common (52.8%, 95%CI 19.9 – 84.4) symptoms of long COVID, followed by cognitive disorder (35.4%, 95%CI 2.1 – 81.7); paresthesia (33.3%, 95%CI 2.7 – 76.6); sleep disorder (32.9%, 95%CI 6.5 – 67.4); musculoskeletal pain (27.8%, 95%CI 12.7 – 46); and dizziness (26.4%, 95%CI 4.6 – 57.9).
Conclusion: Neurological manifestations are prevalent and persisting in patients with long COVID. The duration of the symptoms are vary among literatures. However, the frequency are mostly observed during the first six months after the illness onset.

Contents

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Introduction

A newly emerging infectious disease caused by a novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a global pandemic, thus set a major burden around the world, with a jeopardize impact on healthcare and economic system with approximately > 270,000,000 confirmed cases globally [1].

Acute infection of SARS-CoV-2 varies from asymptomatic disease to respiratory tract symptoms, and multiorgan failure in severe disease. Fever, unproductive cough, and dyspnea are the most common clinical manifestations of coronavirus disease-2019 (COVID-19). Although the most commonly reported symptoms are respiratory symptom, several studies from Wuhan's major hospitals highlighted other organ involvement such as cardiovascular, digestive, and nervous symptoms [2,3,4]. The clinical manifestations of COVID-19 can be caused by the virus's direct effect, parainfectious complication, or as part of a multiple organ failure in critically ill patients [5].

Following hospital discharge, many patients reported persisting symptoms after the acute phase of COVID-19. These symptoms are varies, involving multiple organ systems, including respiratory (cough, dyspnea), muscle pain, fatigue, headache, taste or smell impairment, and brain fog. This group of sign and symptoms have been called “long COVID”.

In 36.4–82.3% of hospitalized COVID-19 patients worldwide, neurologic manifestations of varying severity have been reported [6–8]. However, these neurological symptoms may persist in the post-acute phase and constitute a “long Covid” syndrome [9,10]. "Long COVID" is a term used to describe persistent symptoms following a COVID-19 infection. [11–14] The onset of Long COVID is difficult to pinpoint, but it has been estimated to be anywhere between three and twelve weeks after infection [15].

In the United Kingdom, symptoms lasting four to twelve weeks after infection are referred to as "ongoing symptomatic COVID-19," and symptoms lasting longer than that are referred to as "post COVID-19 syndrome [16]. "Long COVID is a multi-system disorder with several distinct pathological mechanisms, regardless of how it is defined.[17–19]. The origin and pathogenesis of these symptoms remains unclear. However, it is likely to be a combination of a direct damage caused by the viral infection, comorbidities, immunological response, psychological and emotional factors [19].

Previous reports suggest a high prevalence of neurological manifestations after acute infection of COVID-19, but the full spectrum of post-discharge characteristics is still unclear. Furthermore, only few studies have reported neurological manifestations that persist after discharge. This review aims to determine the prevalence of persistent neurological symptoms in patients with Long COVID Syndrome.

Methods

We conducted a systematic review, followed by meta-analysis according to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [20].

Search strategy

We searched the available studies from PubMed and MedRxiv, published from 1st January 2020 to October 2021. The literature search was performed by using terms “Long COVID” OR “Persistent” OR “Post COVID-19” OR “Prolonged” OR “Neurological” OR “ Neurology”. The reference lists of selected papers as well as subsequent citations of these papers were also examined. To maximize our search and obtain more studies, the search strategy did not specify on neurological title only. We included observational studies as long as they contained neurological data of post-acute, persisting, or Long COVID-19. Furthermore, we examined the references of the articles that retrieved through the outlined search strategy for additional articles that were missed by the search strategy. As the condition is a newly emerging disease, we also included case reports or case series in the review.

Eligibility criteria

Studies were eligible when they reported persistent neurological symptoms in patients aged > 18 years, with a history of confirmed SARS-CoV-2 infection based on PCR test. The definition of “persistent” in our study was considered persistent symptoms as those still present after hospital discharge or at least four weeks after the onset of symptoms or a positive PCR test. We also included clinical characteristics studies to expand our search. The exclusion criteria were 1) non-original studies (e.g. review articles); 2) reported no post-hospital discharge data; 3) were not in the English language; 4) non-human subjects. In consideration to our main aim, studies were only eligible if they reported the prevalence of at least one persistent neurological symptom in post-discharge patients. On this basis, we excluded studies in which participants had pre-existing neurological conditions before the onset of SARS-CoV-2 infection (e.g., stroke, dementia). When data from the same cohort were reported in several papers, the study reporting the largest sample fitting our eligibility criteria was selected.

Screening and data extraction

Initially, screening of titles and abstracts was conducted by two authors independently for its eligibility. Then, two reviewers assessed the text articles that passed the first screening process to ensure their eligibility with inclusion and exclusion criteria. For each eligible study data were extracted to a customised spreadsheet by one reviewer. Additional articles were added based on the references of the articles collected through the outlined search strategy and were manually screened. Main author was consulted for any discrepancies. Any disagreement will be resolved by further discussion. The following data were recorded and tabulated from all reviewed articles: author names, study type, country location, study group, age, neurologic symptoms, and key findings.

Study Quality Assessment

The quality of each study was graded using the Oxford Center for Evidence-Based Medicine Quality ratings. The ratings ranged from 1 to

5, with 1 representing properly powered and adequate randomized controlled trial (RCT) and 5 representing opinions and case reports [21].

Analysis

The primary outcome was the pooled prevalence of each persistent neurological manifestations, using estimates of point prevalence where available. We pooled results based on random-effects meta-analysis to calculate weight proportion for each prevalence outcome, using the inverse variance method with the Freeman-Tukey double arcsine transformation analysis. Heterogeneity between assessed using the I2 statistic. Forest plots were used to interpreted the prevalence in each study and the combined estimated prevalence plots with 95% confidence intervals. The overall random-effects pooled estimate with its CI was reported. We limited the articles included in the meta-analysis to those manifestations that were present in more than one study and excluded the case reports. Statistical significance was declared at I2 > 50% and p < 0.05. We conducted the analysis using MedCalc V.19.2.0 software [22].

Results

Initially, our search identified 128 manuscripts related to the search strategies used. After applying the exclusion criteria, 58 articles were analysed for its eligibility. A total of 36 eligible studies were included in quantitative synthesis. The results of the search strategy are shown in a PRISMA flow chart in Fig. 1.

Nine prospective study [46,50,51,53–58] 3 retrospective studies [40,48,49], 1 cross-sectional [52] and 23 case report/series [23–39, 41–45,47] corresponding to a total of 9944 patients (sample size range 50 – 3762) with previous history of COVID-19 infection were included in this review. Patient data from the included studies were obtained from various countries, as follows: Australia, Bangladesh, China, Egypt, Germany, Japan, Morocco, Netherland, Italy, India, Japan, Pakistan, Spain, Thailand, United Kingdom, and the USA. The characteristics of the studies included in this meta-analysis and study quality ratings are shown in Table 1.

The duration of these persistence symptoms were various among studies. Most of the studies, excluding case report, reported duration of follow-up after symptom onset in the COVID-19 survivor was less than 6 months and the prevalence of long COVID symptom was highest in the earlier months after discharge. Only 2 studies had mean time from discharge to follow-up visit of more than 6 months [55,57]. Moreover, one prospective study observed up to 48.9% patients had at least one persistent symptom beyond 6 months after the COVID-19 diagnosis [57]. In a Long COVID cohort, the probability of symptoms lasting beyond 35 weeks was 91.8% (95% CI; 89.5–93.5), whereas at least 85.9% of

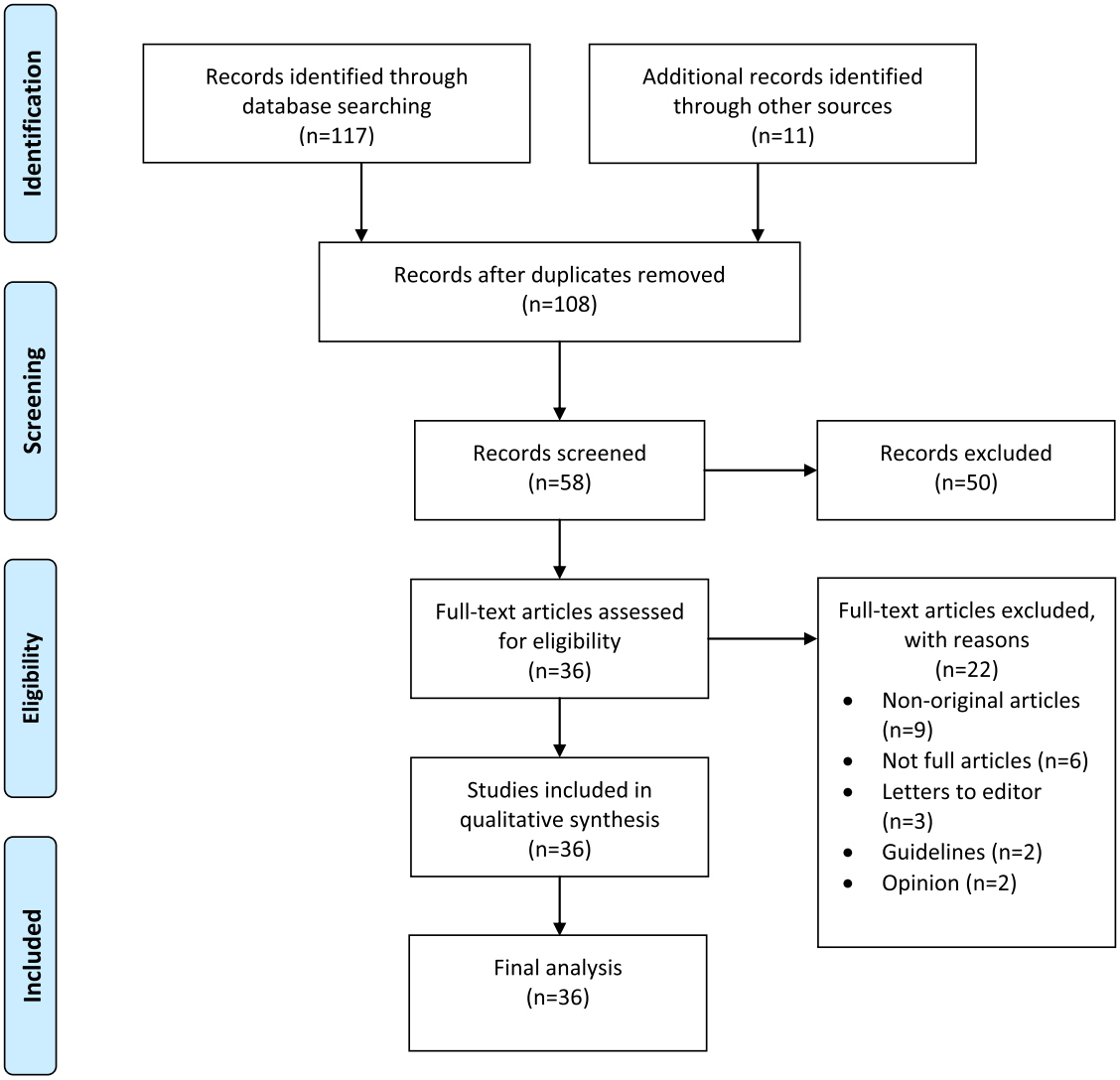

Fig. 1. Search Algorithm for Reviewed Articles.

Table 1
Studies Included in Systematic Review.

No	Author	Study Type	Country	Study Group	Median (range) or Mean (SD) Age	Neurological Symptoms and/or % of Total	Key Findings/Summary	Study Quality Level
1	Koumpa et al., 2020[23]	Case Report	UK	45-year-old patient with sudden onset sensorineural hearing loss post COVID-19	*[case report]*	The patient had sensorineural hearing loss	– Patient admitted to hospital on 10th day of COVID-19 symptoms and required intubation A week after extubation and transferred out of ITU, patient noticed left-sided tinnitus and sudden onset hearing loss.	5
2	Carroll et al., 2020[24]	Case Report	USA	69-year-old patient with sudden onset sensorineural hearing loss post COVID-19	*[case report]*	The patient experienced seizure (refractory status epilepticus)	– Patient was admitted to hospital with severe SARS-CoV-2 and intubated for hypoxia – Workups showed elevated inflammatory markers, recurrence of a positive nasopharyngeal SARS-CoV-2 polymerase chain reaction, and hippocampal atrophy.	5
3	Zito et al., 2020[25]	Case Report	Germany	57-year-old male presented with Guillain–Barré Syndrome	*[case report]*	The patient presented with: – weakness in hand and finger extension – gait ataxia – loss of touch & vibration on feet and ankles	– GBS symptoms developed 12 days after resolution of COVID-19 symptoms – SARS-CoV-2 (RT-PCR) was negative	5
4	Calvagli et al., 2021[26]	Case report	Italy	69-year-old man presented with acquired weakness and dysphagia with clinical cranial nerves impairment of lingual, IX, X and XII post COVId − 19	*[case report]*	The patient presented with: – dysphagia – impairment of lingual – cranial nerves number IX, X, and XII dysfunction	– Thirteen days after admitted to hospital, the patient was intubated because of the worsening of overall clinical condition – Date of negative PCR results was not mention on this study	5
5	Reyes-Bueno et al., 2020[27]	Case Report	Spain	51-year-old female presented with Miller-Fisher syndrome	*[case report]*	The patient presented with: – paresis of the left external rectus muscle – horizontal diplopia – inferior bilateral facial paresis – symmetrical paraparesis – global areflexia	– On admission, RT-PCR to SARS-CoV-2 was negative, however IgG was tested positive through ELISA examination	5
6	Kilinc et al., 2020[28]	Case Report/ Case Study	Netherland	50-year-old male presented with Guillain–Barré Syndrome	*[case report]*	The patient presented with: – bilateral facial weakness – paresthesia of distal extremities – and unsteady gait	– The patient experienced an episode of dry cough four weeks prior – RT-PCR test for SARS-CoV-2 in the CSF was negative. Fecal PCR and serum IgM and IgG for SARS-CoV-2 were all positive	5
7	Mitry et al., 2021[29]	Case Report	USA	17-year-old female presented with Parsonage-turner syndrome	*[case report]*	The patient presented with multifocal joint pain prominent in the left shoulder and left hand	– The RT-PCR for SARS-CoV-2 was negative, however serum IgG antibodies for SARS-CoV2 were positive – Radiology workups revealed cardiomegaly, mediastinal & left supraclavicular adenopathy, hepatomegaly, and ascites	5
8	Bureau et al., 2020[30]	Case Report	USA	A 40-year-old Woman	*[case report]*	The patient experienced: – sudden severe bilateral leg pain (burning, stabbing, and aching) originated in the lower back and hips with radicular features numbness bilateral, symmetrical, non-ascending lower extremity weakness	– The patient had a history of flu-like symptoms for two weeks – Two weeks after improvement of respiratory symptoms, the patients experienced severe bilateral leg pain, numbness, and weakness – Workups showed mildly elevated serum lactate, borderline low serum copper and low vitamin B6	5
9	Wijeratne et al., 2020[31]	Case Report	Australia	A case of a 75-year-old man	*[case report]*	Patient presented with acute stroke-like symptoms, as well as elevated-intracranial pressure-related symptoms	– Day 26: the patient was stuporous (Glasgow Coma Scale fluctuating between 3 and 6) with no physical signs	5

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Table 1 (*continued*)

No	Author	Study Type	Country	Study Group	Median (range) or Mean (SD) Age	Neurological Symptoms and/or % of Total	Key Findings/Summary	Study Quality Level
							of cranial nerve involvement and positive meningeal signs Day 32: Brain MRI results showed generalized cortical diffusion restriction, which was also present in the supra- and infratentorial white matter, A few scattered micro bleeds in the frontal, parietal and temporal lobe were described along with a small volume subarachnoid hemorrhage in the right frontal lobe	
10	Ahsan et al., 2020[32]	Case Report	Pakistan	A 28-year-old married man with thalassemia minor was diagnosed with SARS-CoV-2 infection	*[case report]*	The patient experienced: • blurring of vision • intermittent diplopia on lateral gaze • unable to purse his lips	– Six days after being discharged from hospital, the patient experienced uncontrolled saliva dribbling, as well inability to purse his lips. The patient also complained blurring of vision and intermittent diplopia on lateral gaze – Patient's wife reported a change in behavior and personality, and difficulty in processing information	5
11	Raahimi M, et al., 2021[33]	Case Report	UK	46-year-old man	*[case report]*	The patient presented with: – sensory loss in his feet – gait unsteadiness – distal lower limb weakness (ascending weakness) – severe bilateral leg pain (shooting and burning) paraesthesia and clumsiness in his hands	– Fifty-three days prior the patient had a history of 7-day admission with COVID-19 pneumonitis (confirmed by nasopharyngeal swab PCR) – Cerebrospinal fluid (CSF) analysis, at day 1 of admission, showed raised CSF total protein	5
12	Roushdy T, et al., 2021[34]	Case Series	Egypt	– 59-year-old female – 80-year-old male – 73-year-old male – 59-year-old male	–	– A 59-year-old female presented with: • complete ophthalmoplegia • no perception of light • ptosis along the right eye • decreased sensation along maxillary division of trigeminal nerve – A 80-year-old male experienced reduced visual acuity on the right eye – A 73-year-old male experienced complete left ophthalmoplegia and ptosis – A 59-year-old male experienced right total ophthalmoplegia and ptosis	The case series represents four patients with mucormycosis post-COVID 19	5
13	Dono et al., 2020[35]	Case Report	Italy	A 81-year-old male	*[case report]*	The patient presented with: – mild confusion with mental status fluctuation – jerky myoclonic contractions of the abdomen and the right lower limb	– EEG recording showed continuous sharp waves and spike-and-slow-wave complexes at 2–2.5 Hz with superimposed fast activity predominantly lateralized over the left fronto-centro-temporal regions – According to Salzburg criteria, a diagnosis of non-convulsive status epilepticus with coma was made	5
14	Nuzzo et al., 2021[36]	Case Report	Italy	A 56-year-old male	*[case report]*	The patient experienced: – difficulty walking – weakness in the lower limbs	– These symptoms appeared 3 months after the patient's RT-PCR is declared negative	5

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Table 1 (*continued*)

No	Author	Study Type	Country	Study Group	Median (range) or Mean (SD) Age	Neurological Symptoms and/or % of Total	Key Findings/Summary	Study Quality Level
						– lack of strength in the pelvic girdle muscles skin hyperalgesia seizure	Even after 5 months since negative RT-PCR result, the patient was still having a short epileptic seizures	
15	Sattar et al., 2020[37]	Case Report	USA	A 44-year-old male	*[case report]*	The patient experienced: – generalized tonic-clonic seizures – confusion diminished response from external factors	Two days post-extubation (day 20 after COVID-19 onset), the patient having an episode of generalized tonic-clonic seizures for a minute	5
16	Hara et al., 2021[38]	Case Report	Japan	A 65-year-old man	*[case report]*	The patient had confusion and verbal communication difficulties	The symptoms appeared one week after discharged from the hospital	5
17	Garg A et al., 2021[39]	Case Report	USA	A 54-year-old man	*[case report]*	The patient experienced: • repetitive flexion movement of head • cognitive impairment • frequent headaches • fatigue • sleeping disturbances • dizziness	• The symptoms appeared two months after discharged from hospital • Motoric symptom occurred while sitting or lying down, and did not occur wihen standing or walking	5
18	Romeo-Duarte et al., 2021[40]	Retrospective cohort	Spain	797 COVID-19 who were followed up in a period of 6 months after discharged	Mean 63 ± 14,4	– 176/797 (22.1%) had fatigue – 30/797 (3.8%) had muscle weakness – 122/797 (15.3%) had musculoskeletal pain – 25/797 (3.1%) had ICU-polyneuropathy – 42/797 (5.3%) had headache – 27/797 (3.4%) had paraesthesia – 27/797 (3.4%) had movement disturbances – 21/797 (2.6%) had disorientation/ confusion – 57/797 (7.2%) had persistent anosmia/ dysgeusia	– 160/797 (20.1%) returned to the Emergency Services, 35/797 (4.4%) required hospital readmission, and 8/ 797 (1.0%) died during follow-up	3
19	El Mezzeoui et al., 2021[41]	Case report	Morocco	A 3-year-old female patient presented with ascending paraesthesia, two weeks after COVID-19 infection	*[case report]*	The patient experienced progressive and ascending paraesthesia, decrease of limb muscle strength, loss of deep tendon reflexes, decrease in sensitivity in 4 members, and swallowing disability	– GBS post-COVID-19 infection in children remain rare and insufficient	5
20	Taribagil et al., 2021[42]	Case report	UK	A 28-year-old female patient who previously diagnosed with COVID-19 experienced variety of symptoms	*[case report]*	– The patient experienced reduction in concentration, poor memory, 'non-specific head buzzing', worsening anxiety, and brain fog. – Musculoskeletal symptoms included restless legs, non-specific paraesthesia across the patient's hands and feet, and generalised body ache	– Presentation can vary greatly between individuals, making diagnosis and treatment challenging. – Management of patients with 'long COVID' should include a multidisciplinary team	5
21	Shetty et al., 2021[43]	Case report	India	A 41-year-old male patient, with history of febrile illness, experienced involuntary movement and walking difficulty	*[case report]*	– After approximately 10 days after having symptoms of febrile illness, the patient had subtle jerky involuntary movement of the limb along with walking difficulty – The motoric symptoms peaked over the next 10 days, manifested as severe limb and truncal jerking at rest that worsened upon action. The patient also could not walk without support	– Myoclonus-ataxia syndrome appears to be a neurological manifestation of COVID-19 infection, and knowledge regarding this phenomenon should be increased among clinicians for better patient care in a pandemic situation.	5
22	Varadan et al., 2021[44]	Case report	India	A 46-year-old male patient, with prior history of COVID-19,	*[case report]*			5

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Table 1 (*continued*)

No	Author	Study Type	Country	Study Group	Median (range) or Mean (SD) Age	Neurological Symptoms and/or % of Total	Key Findings/Summary	Study Quality Level
				experienced with headache and altered mental status		Five weeks following discharge, the patient presented with headache and altered mental status	– The patient was diagnosed with COVID-19-related acute hemorrhagic leukoencephalitis (AHLE) – AHLE is a rare and often fatal neurological complication of COVID-19	
23	Zubair et al., 2021[45]	Case Report	USA	A 32-year-old male; A 61-year-old male	*[case report]*	Both patients had bilateral lower extremity weakness and abnormalities on nerve conduction study	– Two cases of GBS-associated COVID-19, which started approximately eight weeks after the earlier COVID-19 infection – CSF analysis showed albumino-cytological dissociation	5
24	Shahrvini et al., 2021[46]	Prospective Study	USA	67 COVID-19 patients with symptom of smell loss	NR	17/67 (25.4%) patients had persistent smell loss	– From 67 patients, 50 (74.6%) patients demonstrated objective smelling recovery – Seventeen (25.4%) patients had persistent smelling loss with an average follow-up period of 60 days (range, 30–189 days) for the persistent smelling loss group	3
25	El Aidouni et al., 2021[47]	Case report	Morocco	A 49-year-old man presented with GBS occurring 2 weeks post COVID-19 infection	*[case report]*	The patient experienced bilateral ascending symmetrical paresthesia and weakness	– The patient had no previous medical history – The onset of GBS symptoms occurred 2 weeks after COIVD-19 infection – Workups showed albumin-cytologic dissociation of CSF and abnormalities on nerve conduction study	5
26	Garrigues et al., 2020[48]	Retrospective Cohort	France	120 COVID-19 patients	63.2 (± 15.7)	• Ageusia, 13 (10.8%) • Anosmia, 16 (13.3%) • Attention disorder, 32 (26.7%) • Memory loss, 41 (34.2%) Sleep Disorder, 37 (30.8%0	• A single-centre study assessing post-discharge persistent symptoms between ward and ICU groups after a mean of 110.9 days after their admission for COVID-19 • There was no statistically significant difference between ward and ICU groups, but there was a non-significant trend towards a reduced proportion of patients returning to work amongst ICU patients (46.7% versus 77.5%, $P = 0.061$)	3
27	Goërtz et al., 2020[49]	Non-randomized controlled cohort/ follow-up study	Netherlands	2113 COVID-19 patients	47[39–54]	• Headache, 803 (38%) • Ageusia, 232 (11%) • Muscle Pain, 761 (36%) • Dizziness, 571 (27%) • Anosmia, 275 (13%) • Nausea, 254 (12%) • Vomiting, 21 (1%)	• Patients with persistent symptoms of COVID-19 in a mean period of 79 ± 17 days after the onset of the first symptoms • Headache (76%) and muscle pain (65%) were the two most prevalent neurologic symptoms at the beginning	3
28	Sykes et al., 2021[50]	Prospective cohort	United Kingdom	134 COVID-19 patients	59.6 (± 14.0)	• Muscular pain, 69 (51.5%) • Fatigue, 53 (39.6%) • Memory impairment, 50 (37.3%) • Sleep disturbance, 47 (35.1%) • Dysnosmia, 13 (9.7%) • Dysgeusia, 12 (9%)	• Eighty-six percent of patients reported at least one residual symptom at follow-up • No patients had persistent radiographic abnormalities. Patients were followed up at a median of 113 days (range = 46–167) post-discharge.	2
29	Huang et al., 2021[51]	Ambidirectional cohort	China	1655 COVID-19 patients	57[47–65]	• Fatigue, 1038 (63%) • Sleep disturbance, 437 (26%) • Dysnosmia, 176 (11%) • Muscular pain, 154 (9%) • Dysgeusia, 120 (7%)	• Fatigue or muscle weakness (1038 [63%] of 1655) and sleep difficulties (437 [26%] of 1655) were the most common symptoms after discharge	2

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Table 1 (*continued*)

No	Author	Study Type	Country	Study Group	Median (range) or Mean (SD) Age	Neurological Symptoms and/or % of Total	Key Findings/Summary	Study Quality Level
						• Dizziness, 101 (6%) • Headache, 33 (2%)	• The median time from discharge to follow-up visit is 153.0 (146.0–160.0) days	
30	Tomasoni et al., 2020[52]	Cross-sectional study	Italy	105 COVID-19 Patients	55[43–65]	• Anosmia, 6 (5,7%) • Dysguesia, 6 (5,7%) • Burning Pain, 11 (10,5%) • Asthenia, 33 (31,4%) Cognitive deficits (memory disorder): 18 (17,1%)	• All patients displayed interstitial pneumonia at hospital admission • Cross-sectional study including patients with documented clinical recovery and virological clearance after hospitalization • Asthenia or weakness is the most common symptoms after recovery from COVID-19	4
31	Jacobs et al., 2020[53]	Prospective cohort	Italy	183 COVID-19 patients	57[48–68]	• Fatigue, 149 (83.2%) • Muscular pain, 77 (43.0%) • Lack of smell, 65 (36.7%) • Headache, 59 (33.2%) • Joint pain, 53 (29.8) • Confusion, 37 (21.1%)	• The reported duration of symptoms were persisting from hospital discharge to 35 days in COVID-19 patients • The most frequent symptoms from hospital discharge until 35 days are Muscular pain: 77 (43%) and Lack of smell 65 (36,7%)	2
32	Graham et al., 2021[54]	Prospective	USA	50 COVID-19 patients	43.7 ± 11.8	• Brain fog, 43/50 (86%) • Headache, 41/50 (82%) • Numbness, 29/50 (58%) • Dysgeusia, 32/50 (64%) • Anosmia, 37/50 (74%) • Myalgia, 30/50 (60%) • Dizziness, 20/50 (40%) • Fatigue, 42/50 (84%)	• Mean duration of follow-up after symptom onset in the SARS-CoV-2 group was 4.72 months. • Most of the patients reported a median of five neurologic symptoms related to Covid-19%, and 85% reported at least four symptoms, with no difference between the two groups.	2
33	Boscolo-Rizzo et al., 2021[55]	Prospective cohort	Italy	304 COVID-19 patients	47[18–76]	• 83/304 (27,3%) patients had fatigue • 62/304 (20,4%) patients had dysnosmia • 46/304 (15,1%) patients had dysgeusia • 28/304 (9,2%) patients had musculoskeletal pain • 10/304 (3,2%) patients had dizziness • 10/304 (3,2%) patients had headache	• More than half of the subjects (53%) with previous mild-to-moderate symptomatic SARS-CoV-2 infection complained at least 1 persistence symptom 12-months after the onset of the illness. • These persistent symptoms are associated with impact on quality of life and depression	2
34	Hossain et al., 2021[56]	Prospective cohort	Bangladesh	356 patients had long covid syndrome 12 weeks after diagnosed COVID-19	38.07 (± 11.4)	• 295/356 (82,9%) had fatigue • 60/356 (16,9%) had musculoskeletal pain • 18/356 (5,1%) had dysnosmia • 8/356 (2,2%) had headache	• At 31 weeks post diagnosis, the prevalence of long covid symptoms was 16.1%. • Overall duration period of 21.8 ± 5.2 weeks.	2
35	Pérez-González et al., 2021[57]	Prospective Cohort	Spain	248 COVID-19 patients	57[46–68]	• Headache, 12 (4.8%) • Brain fog, 9 (3.6%) • Anosmia, 17 (6.9%) • Ageusia, 10 (4%) • Fatigue, 40 (16.1%) • Sleep disorder, 9 (3.6%) • Musculoskeletal pain, 18 (7.3%)	• Six months after the COVID-19 diagnosis, 119 patients (48.9%) reported at least one symptom • Previous history of chronic obstructive pulmonary disease (OR=5) and female gender (OR=2.7) were the main risk factors of long COVID.	2

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Table 1 (*continued*)

No	Author	Study Type	Country	Study Group	Median (range) or Mean (SD) Age	Neurological Symptoms and/or % of Total	Key Findings/Summary	Study Quality Level
36	Davis et al., 2021[58]	Prospective Cohort	International	3762 COVID-19 patients	Age group 40–49 (31%)	• Dysnosmia, 1352 (35,9%) • Musculoskeletal pain, 2601 (69%) • Headache, 2887 (76%) • Dysgeusia, 1267 (33%) • Fatigue, 3699 (98%) • Dizziness, 2531 (67%) • Cognitive impairment, 3212 (85%) • Paresthesia, 1852 (49%) • Sleep disorder, 2955 (78%)	• Of the 3762 respondents, 2454 experienced symptoms for at least 180 days (6 months) • The mean duration of followup was 77 days (range 14–182 days).	2

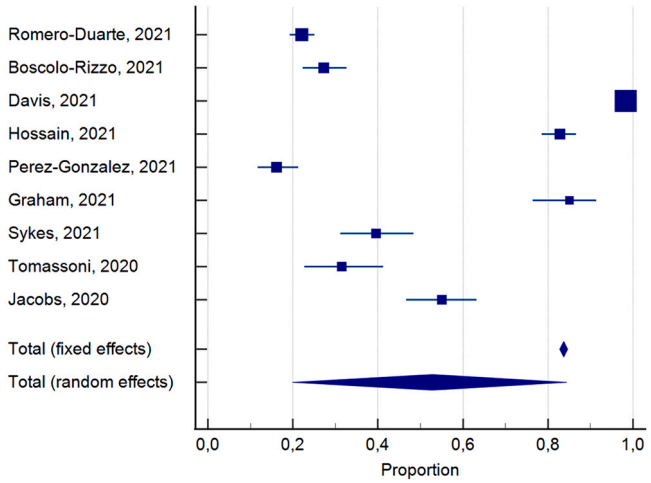

Fig. 2. Proportion estimates of Fatigue in long COVID-19 patients.

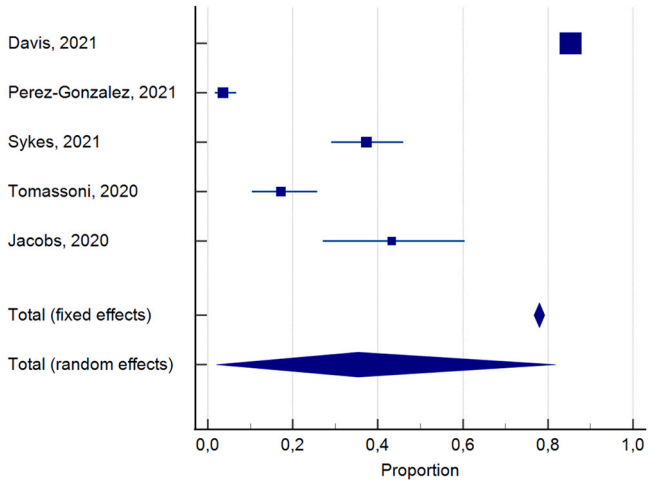

Fig. 3. Proportion estimates of Cognitive disorder in long COVID-19 patients.

respondents reported experiencing relapses of their symptoms [58].

The most prevalent symptom in patients with long COVID-19 was fatigue, occurred in more than half of the subjects. The overall pooled prevalence of fatigue was 52.8% (95% CI: 19.9–84.4) from 9 studies [40,50–51,53–58] with a total of 4546 subjects with a high level of heterogeneity (I^2 = 99.8%). A forest plot of prevalence (%) of fatigue is included in Fig. 2. In a prospective, international study with 3762 subjects described the prevalence of fatigue (98.3%) as the most common symptom in patients with long COVID, with 80% (95% CI: 78.5–81.6) of the subjects still experienced this symptom for at least 6 months [58].

We included any symptoms related to cognitive disorder that were reported as brain fog, difficult thinking, poor attention, memory impairment and other cognitive impairment issues. The overall pooled prevalence of cognitive disorder was 35.4% (95% CI: 2.1–81.7) from 5 studies [48,50,52,57,58] with a total of 3305 subjects with a high level of heterogeneity (I^2 = 99.7%). A forest plot of prevalence (%) of cognitive disorder is included in Fig. 3. In a large cohort study, up to 85.1% of respondents reported experiencing brain fog and cognitive dysfunction, including poor attention, executive functioning, problem solving, and decision making. Interestingly, over one third of the respondents, the onset of brain fog/ cognitive dysfunction occurred in the first week of symptoms and increased over the first three months, then decreased in the following months

Table 2
Results of meta-analysis of prevalence based on each neurological manifestation in patients with long-covid.

Symptoms	Number of studies	Pooled sample size	Pooled prevalence (%)	95% CI	I^2	p value
Dysnosmia	11	2024	17,7	10,3 to 26,7	98,82%	< 0,0001
Musculoskeletal pain	11	3918	27,8	12,7 to 45,9	99,67%	< 0,0001
Headache	9	3886	21,3	3,3 to 48,9	99,86%	< 0,0001
Dysgeusia	9	1783	16,5	8,3 to 27,0	99,10%	< 0,0001
Fatigue	9	4546	52,8	19,9 to 84,4	99,80%	< 0,0001
Dizziness	5	3260	26,4	4,6 to 57,9	99,86%	< 0,0001
Cognitive disorder	5	3305	35,4	2,08 to 81,7	99,67%	< 0,0001
Sleep disorder	5	3485	32,9	6,5 to 67,4	99,80%	< 0,0001
Paresthesia	3	1939	33,3	2,7 to 76,6	99,79%	< 0,0001
Movement disorder	2	32	3,6	2,5 to 4,9	0,00%	0,3576

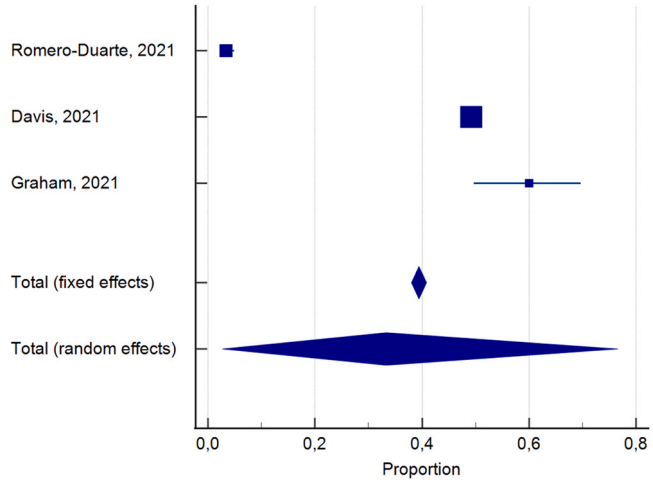

Fig. 4. Proportion estimates of Paresthesia in long COVID-19 patients.

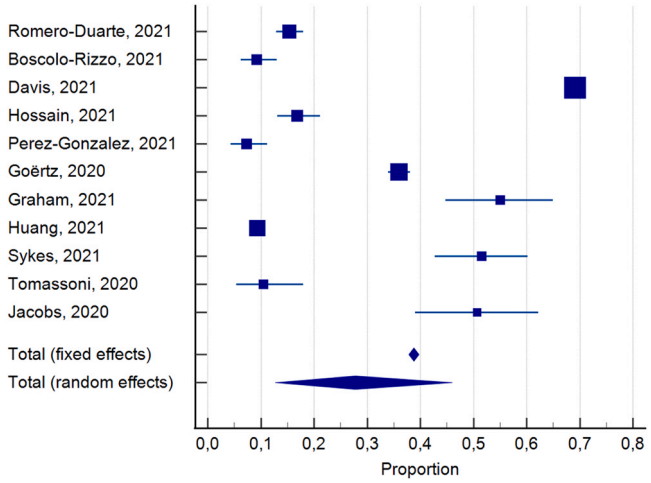

Fig. 6. Proportion estimates of Musculoskeletal Pain in long COVID-19 patients.

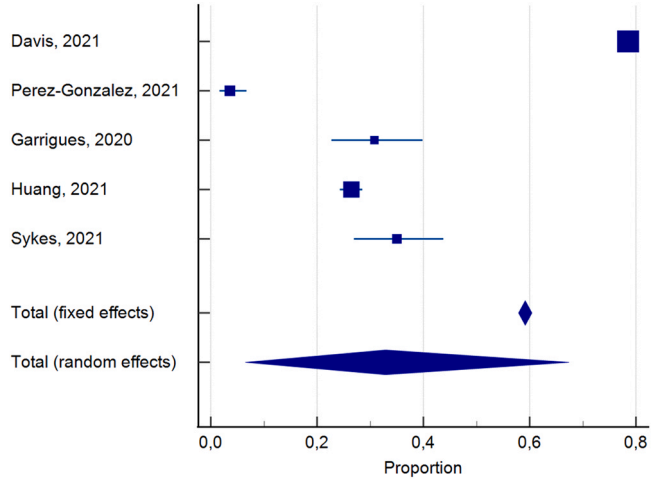

Fig. 5. Proportion estimates of Sleep disorder in long COVID-19 patients.

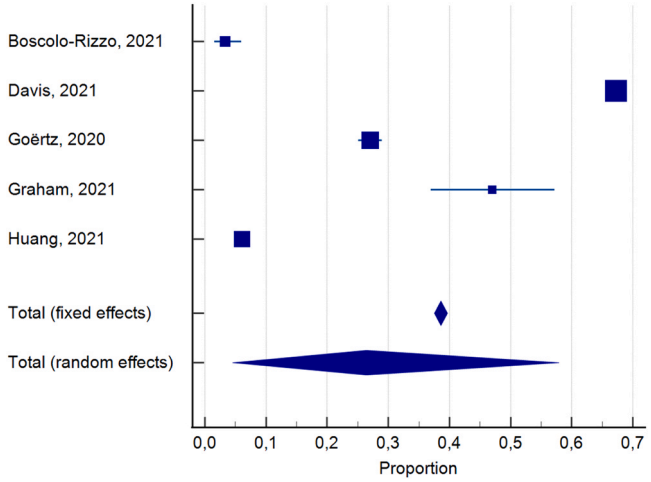

Fig. 7. Proportion estimates of Dizziness in long COVID-19 patients.

[58]. This finding may be an indicative of cognitive disorder as one of the earliest neurological manifestation of long covid syndrome.

The random-effects analysis for other persistent neurological symptom reported in post-discharge COVID-19 patients showed the following overall pooled prevalence with corresponding 95% CI, number of studies assessed, forest plot of the prevalence, and the overall number patients with the neurological symptom, respectively (see Table 2): “paresthesia” (33.3%, 95% CI: 2.7–76.6; 3 studies; Fig. 4; 1939 subjects), “sleep disorder” (32.9%, 95% CI: 6.5–67.4; 5 studies; Fig. 5; 3485 subjects), “musculoskeletal pain” (27.8%, 95% CI: 12.7–45.9; 3 studies; Fig. 6; 3918 subjects), “dizziness” (26.4%, 95% CI 4.6–57.9; 5 studies; Fig. 7; 1783), “headache” (21.3%, 95% CI 3.3–48.9; 9 studies; Fig. 8; 3886), “dysnosmia” (17.7%, 95% CI 10.3–26.7; 11 studies; Fig. 8; 2024), “dysgeusia” (16.5%, 95% CI 8.3–27.0; 9 studies; Fig. 9; 1783), and “movement disorder” (3.6%, 95% CI 2.5–4.9; 2 studies; Fig. 10; 32). Nearly all symptom analyses detected statistically significant. Fig. 11.

heterogeneity (p-value < 0.005) with a high degree of heterogeneity (I2 > 75%) excluding the symptom of “movement disorder” (p-value = 0.36; I2 = 0%) (see Table 2).

A total of 23 case studies were identified that described new-onset neurological disorders/complications linked to post-acute COVID-19 infection. Cranial and peripheral nerve disorders were noted as the most frequent that presented as Guillain-Barre

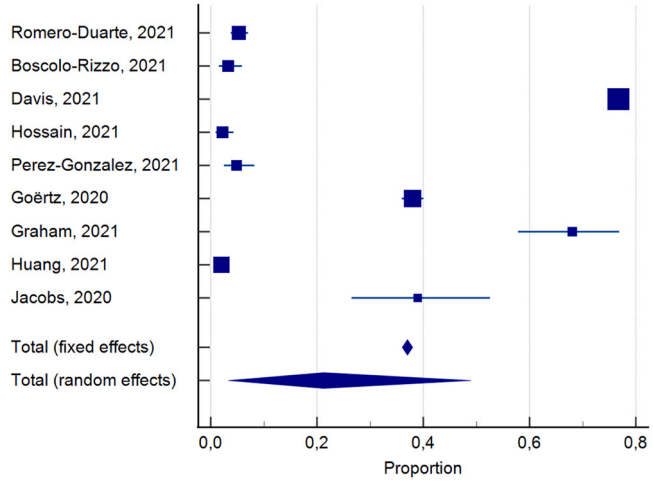

Fig. 8. Proportion estimates of Headache in long COVID-19 patients.

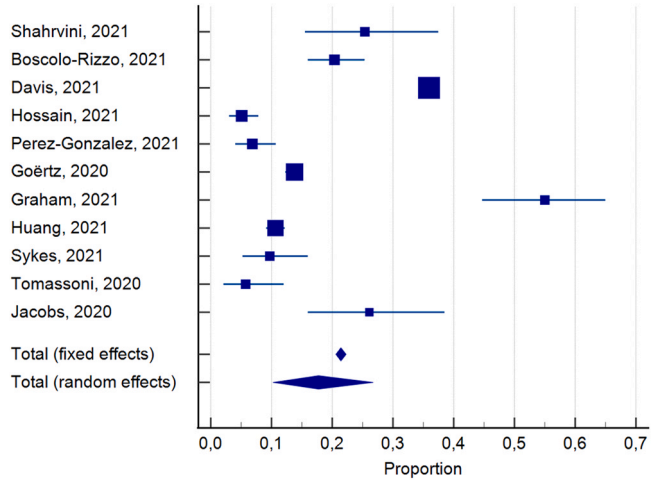

Fig. 9. Proportion estimates of Dysnosmia in long COVID-19 patients.

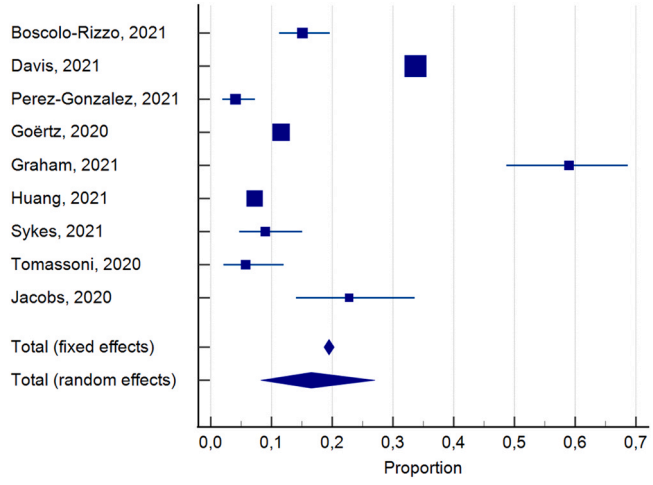

Fig. 10. Proportion estimates of Dysgeusia in long COVID-19 patients.

syndrome (n = 6) [25,28,33,41,45,47], Miller-Fisher syndrome [27], hearing loss [23], Parsonage-turner syndrome [29]. Most of these patients manifested in the form of acute neuropathies or polyneuropathies [26,30,46]. Cranial nerves were also affected by an unusual case of mucormycosis as an opportunistic fungal infection

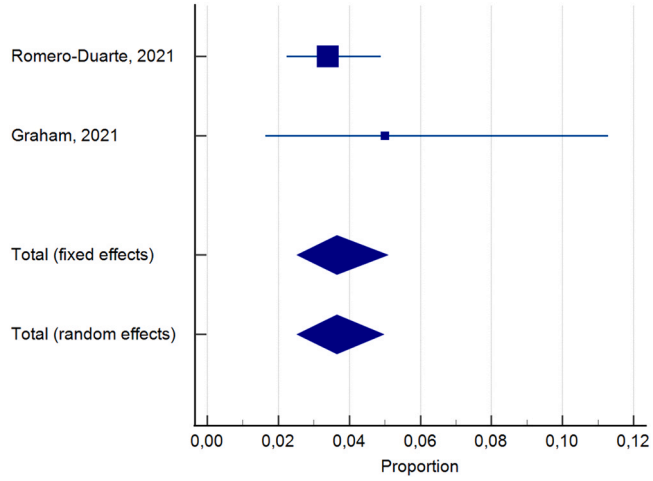

Fig. 11. Proportion estimates of Movement disorder in long COVID-19 patients.

post-COVID-19 infection, which involved 4 cases presented with ophthalmoplegia [34].

Two case reports described patients who manifested with altered mental status, which was later diagnosed as encephalitis [37,38]. Movement disorder was also reported in some cases as unspecific jerky movements [39] and myoclonus-ataxia syndrome [43]. Neuroimaging of a patient with post-acute COVID-19 using computed tomography showed an appearance of acute hemorrhagic leukoencephalitis [44]. Electroencephalography (EEG) showed some specific changes in post-COVID-19 patients with new-onset of seizure [24] and non-convulsive status epilepticus [35].

Discussion

This review found out that neurological symptoms were prevalent among patients with Long COVID-19 symptoms. Fatigue was the most prevalent neurological symptom, with more than half of pooled sample size experiencing it. Other neurological symptoms such as cognitive disorder, sleep disorder, and paresthesia also seem particularly prevalent, affecting one-third of pooled sample size. Movement disorder was a less common neurological symptom we found among other symptoms. However, the pooled size of movement disorder was limited to only two studies and may be increased in the future along with the increasing study of neurological symptoms in long COVID.

Several past studies found fatigue was common among long COVID patients. Single center study in Ireland reported that more than half of subjects experienced fatigue at a median of 10 weeks after initial COVID-19 infection [59]. Web-Based Quantitative follow-up study in Netherland conducting a survey with The Checklist Individual Strength–subscale subjective fatigue (CIS-Fatigue) to 239 subjects, in week 10 and 23 after the onset of COVID-19 infection.

The results show that 85,4% of subjects experienced fatigue in the first survey and 78,8% in the second survey [60]. Mechanism behind fatigue in long COVID could be related to unresolved inflammation after the initial infection caused by viral persistence, gut dysbiosis, and lymphopenia [61]. Study by Li Q et al. found post COVID − 19 patients still shedding viral RNA for over three months [62]. Another recent study also reported that SARS-CoV-2 nucleic acids and proteins were discovered in 50% of asymptomatic patients four months after infection [63]. These findings showed evidence of SARS-CoV-2 viral persistence, which may contribute to immune activation, leading to unresolved inflammation.

Gut dysbiosis among COVID-19 patients was reported in several studies and could persist up to 30 days after disease resolution [64,65]. Recent study suggested gut dysbiosis may cause correlation with COVID-19 severity, prolonged fecal SARS-CoV-2 shedding, and

elevated inflammatory biomarkers that contributed to unresolved inflammation [66]. Evidence shows that severe COVID-19 causes lymphopenia. Lymphocytes, particularly T-cells, hold a significant role in infection resolution. Thus, lymphopenia leads to prolonged infection resolution that causes hyperinflammation. [67,68,69].

Other recent case-control studies also reported elevated levels of vascular-related proinflammatory biomarkers three months after discharge, thus strengthening the previous evidence of unresolved inflammation's role on fatigue symptoms. [4] However, unresolved inflammation may not be the only mechanism of fatigue symptoms in Long COVID − 19. Previous study suggested that six routine laboratory measures of cell turnover and inflammation had no relationship with fatigue [59]. Hence, we need to consider other factors such as autonomic nervous system dysfunction and inadequate cerebral perfusion [71,72].

Neurological symptoms in Long COVID may be related to long-term tissue damage caused by COVID-19 infection [61]. The SARS-CoV-2 virus might affect the central nervous system through the Olfactory bulb, causing neuroinflammation that damages the neuron, and because neuron rarely regenerates, leading to long-lasting neuron dysfunction that may underlie neurological symptoms in Long COVID [73,74]. The prospective MRI based study by Lu Y et al. reported the finding of abnormalities in brain structure and metabolic three months post-discharge among COVID-19 survivors, which correlated with neurological symptoms such as fatigue, memory loss and loss of smell [75]. Another mechanism that may cause neurological symptoms is the disruption of the gut microbiome, which play a role in modulating neurotransmitter circuitries in the gut and brain via the microbiota-gut-brain axis. [76].

Several past systematic reviews on long COVID also reported the neurological symptoms [77,78]. A recent review by Daroische et al. assessed the cognitive dysfunction after COVID-19 [77]. Patients with post-acute SARS-CoV-2 infection tend to experience global cognitive impairment, memory impairment, attention and executive function, and in particular verbal fluency, regardless of the disease severity [77]. Nasserie et al. also reported shortness of breath or dyspnea, fatigue or exhaustion, and sleep disorders or insomnia are the most frequent symptoms of long COVID-19 [78].

Long COVID symptoms might be also a form of a sickness behavior. Sickness behavior is a form of universal adaptive response to infectious pathogens that conserves body energy to enhance the immune system's efficiency. Sickness response includes fever, lethargy, and cognitive disturbance. Conversely, immune dysregulation caused by SARS-CoV-2 may disrupt microbiome balance and cytokine responses. Any ongoing infectious or inflammatory response that drives afferent vagus nerve neuroimmune signaling can activate a mirror response of glial activation in the dorsal. [79] This may be related to the persistent symptoms that do not resolve over the course of many months.

There are some limitations regarding this review. Most of the studies included in this review were various among duration of follow-up, thus making it difficult to track the trajectory of the disease. Another limitation was the weight of the studied population. There may be a difference between the studied patients whose data was collected through hospital-based data vs population-based data, where patients were recruited through survey invitation, long covid associations, or social networks. A future well-designed prospective study with a longer follow-up duration is required to support the finding of this study. The relationship between these persistent symptoms and the risk factors of initial COVID-19 infection (e.g. comorbidity, severity) also needs to be studied.

Conclusion

Patients with Long COVID may report persistent and multiorgan involvement, including a high prevalence of nervous system manifestations. Early diagnosis and management can help relieving the burden and further deterioration of the disease. Further long-term longitudinal studies are needed to observed these symptoms trajectory and the effect on quality of life.

This review may be a reference for physicians in management and detection of neurological manifestations in COVID-19 survivors.

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Conflict of Interest

Authors have no conflict of interest to disclose, including personal relationships, financial or otherwise.

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Contribution Statement

RP: study concept and design, supervision and final revision. VW: Study concept and design, writing of the initial draft, data extraction, analysis and interpretation. AA: full text review, analysis and interpretation, manuscript preparation. PN: abstract screening, data extraction, analysis and interpretation. RB: full text review, analysis and interpretation, manuscript preparation.

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