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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 21.1 – 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.

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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 a 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].
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, Netherlands, 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
| 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  | Kounpa 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              | 5                   |
|    |                             |                   |             |                                                                              |                                 |                                        | A week after extubation and transferred out of ICU, patient noticed left-sided tinnitus and sudden onset hearing loss. |                      |
| 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 | 5                   |
|    |                             |                   |             |                                                                              |                                 |                                        | – Workups showed elevated inflammatory markers, recurrence of a positive nasopharyngeal SARS-CoV-2 polymerase chain reaction, and hippocampal atrophy. |                      |
| 3  | Zito et al., 2020[25]       | Case Report       | Germany     | 57-year-old male presented with Guillain–Barré Syndrome                      | [case report]                  | The patient presented with:            | – GBS symptoms developed 12 days after resolution of COVID-19 symptoms                               | 5                   |
|    |                             |                   |             |                                                                              |                                 | – weakness in hand and finger extension | – SARS-CoV-2 (RT-PCR) was negative |                                                                              |                      |
|    |                             |                   |             |                                                                              |                                 | – gait ataxia                         |                                                                                           |                      |
|    |                             |                   |             |                                                                              |                                 | – loss of touch & vibration on feet and ankles |                                                                                           |                      |
| 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:            | – Thirteen days after admitted to hospital, the patient was intubated because of the worsening of overall clinical condition | 5                   |
|    |                             |                   |             |                                                                              |                                 | – dysphagia                          | – Date of negative PCR results was not mention on this study |                      |
|    |                             |                   |             |                                                                              |                                 | – impairment of lingual               | – On admission, RT-PCR to SARS-CoV-2 was negative, however IgG was tested positive through ELISA examination |                      |
|    |                             |                   |             |                                                                              |                                 | – cranial nerves number IX, X, and XII dysfunctions |                                                                                           |                      |
| 5  | Reyes-Bueno et al., 2020[27]| Case Report/Case Study | Spain    | 51-year-old female presented with Miller-Fisher syndrome                      | [case report]                  | The patient presented with:            | – Global areflexia                                                                      | 5                   |
|    |                             |                   |             |                                                                              |                                 | – paresis of the left external rectus muscle | – The patient experienced an episode of dry cough four weeks prior  |                      |
|    |                             |                   |             |                                                                              |                                 | – horizontal diplopia                 | – 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 |                      |
|    |                             |                   |             |                                                                              |                                 | – inferior bilateral facial paresis   | – The RT-PCR for SARS-CoV-2 was negative, however serum IgG antibodies for SARS-CoV2 were positive |                      |
|    |                             |                   |             |                                                                              |                                 | – symmetrical paraparesis             | – Radiology workups revealed cardiomegaly, mediastinal & left supraclavicular adenopathy, hepatomegaly, and ascites |                      |
|    |                             |                   |             |                                                                              |                                 | – global areflexia                    | – The patient had a history of flu-like symptoms for two weeks |                      |
|    |                             |                   |             |                                                                              |                                 | – and unsteady gait                   | – Two weeks after improvement of respiratory symptoms, the patients experienced severe bilateral leg pain, numbness, and weakness |                      |
|    |                             |                   |             |                                                                              |                                 | – and unsteady gait                   | – Workups showed mildly elevated serum lactate, borderline low serum copper and low vitamin B6 |                      |
| 6  | Kilinc et al., 2020[28]     | Case Report/Case Study | Netherlands | 50-year-old male presented with Guillain–Barré Syndrome                      | [case report]                  | The patient presented with:            | – Day 26: the patient was stuporous                                                                  | 5                   |
|    |                             |                   |             |                                                                              |                                 | – bilateral facial weakness          | (Glasgow Coma Scale fluctuating between 3 and 6) with no physical signs                     |                      |
|    |                             |                   |             |                                                                              |                                 | – pain of distal extremities          |                                                                                           |                      |
|    |                             |                   |             |                                                                              |                                 | – and unsteady gait                   |                                                                                           |                      |
| 7  | Mitry et al., 2021[29]      | Case Report       | USA         | 17-year-old female presented with Parsonage-turner syndrome                   | [case report]                  | The patient presented with multilocal joint pain prominent in the left shoulder and left hand | – The patient had a history of flu-like symptoms for two weeks | 5                   |
|    |                             |                   |             |                                                                              |                                 | – sudden severe bilateral leg pain   | – Two weeks after improvement of respiratory symptoms, the patients experienced severe bilateral leg pain, numbness, and weakness |                      |
|    |                             |                   |             |                                                                              |                                 | (burning, stabbing, and aching)       | – Workups showed mildly elevated serum lactate, borderline low serum copper and low vitamin B6 |                      |
|    |                             |                   |             |                                                                              |                                 | originated in the lower back and hips with radicular features numbness                   |                                                                                           |                      |
|    |                             |                   |             |                                                                              |                                 | bilateral, symmetrical, non-ascending lower extremity weakness |                                                                                           |                      |
| 8  | Bureau et al., 2020[30]     | Case Report       | USA         | A 40-year-old Woman                                                          | [case report]                  | The patient described the symptoms    | – Day 26: the patient was stuporous                                                                  | 5                   |
|    |                             |                   |             |                                                                              |                                 | – acute stroke-like symptoms, as well as elevated-intracranial pressure-related symptoms | (Glasgow Coma Scale fluctuating between 3 and 6) with no physical signs                     |                      |
| 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                                                                  | 5                   |
| 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 |
|----|--------|------------|---------|-------------|---------------------------------|------------------------------------------|----------------------|-------------------|
| 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 | 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  
- 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 | Roushy T, et al., 2021 [34] | Case Series | Egypt | – 59-year-old female  
– 80-year-old male  
– 73-year-old male  
– 58-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  
- These symptoms appeared 3 months after the patient’s RT-PCR is declared negative | 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 |  | 5 |
| 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 |
|----|--------|------------|---------|-------------|--------------------------------|-------------------------------------------------------------|-------------------|
| 15 | Sattar et al., 2020 [37] | Case Report | USA | A 44-year-old male | [case report] | – lack of strength in the pelvic girdle muscles | ** | 5 |
| | | | | | | – skin hyperalgesia seizure | | |
| | | | | | – The patient experienced: | | |
| | | | | | – generalized tonic-clonic seizures | | |
| | | | | | – confusion | | |
| | | | | | – diminished response from external factors | | |
| | | | | | – The patient had confusion and verbal communication difficulties | | |
| 16 | Hara et al., 2021 [38] | Case Report | Japan | A 65-year-old man | [case report] | | | 5 |
| | | | | | | | | |
| 17 | Garg A et al., 2021 [39] | Case Report | USA | A 54-year-old man | [case report] | | | 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 | | | 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] | | | 5 |
| | | | | | | | | |
| 20 | Tarbagil 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] | | | 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] | | | 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 |

*(continued on next page)*
| No | Author et al., 2021 | Study Type | Country | Study Group | Median (range or Mean (SD) Age) | Neurological Symptoms and/or % of Total | Key Findings/Summary | Study Quality Level |
|----|-------------------|------------|---------|-------------|--------------------------------|----------------------------------------|---------------------|-------------------|
| 23 | Zubair et al. | Case Report | USA | A 32-year-old male; A 61-year-old male | [case report] | Headache and altered mental status | Five weeks following discharge, the patient presented with headache and altered mental status | 5 |
| 24 | Shahrvin et al., 2021 | Prospective Study | USA | 67 COVID-19 patients with symptom of smell loss | NR | 17/67 (25.4%) patients had persistent smell loss | - The patient was diagnosed with COVID-19-related acute hemorrhagic leukoencephalitis (AHLE) - AHLE is a rare and often fatal neurological complication of COVID-19 | 3 |
| 25 | El Aidouni et al., 2021 | 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 COVID-19 infection - Workups showed albumino-cytological dissociation | 5 |
| 26 | Garrigues et al., 2020 | Retrospective Cohort | France | 120 COVID-19 patients | 63.2 (± 15.7) | • Aguesia, 13 (10.8%) • Anosmia, 16 (13.3%) • Attention disorder, 32 (26.7%) • Memory loss, 41 (34.2%) • Sleep Disorder, 37 (30.8%) | - 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 among ICU patients (46.7% versus 77.5%, P = 0.061) - 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 |
| 27 | Goertz et al., 2020 | Non-randomized controlled cohort/follow-up study | Netherlands | 2113 COVID-19 patients | 47[39–54] | • Headache, 803 (38.8%) • 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 | 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%) • Dysosmia, 13 (9.7%) • Dysguesia, 12 (9%) • Fatigue, 1038 (63%) • Sleep disturbance, 437 (26%) • Dysosmia, 176 (11%) • Muscular pain, 154 (9%) • Dysguesia, 120 (7%) | - 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. - Fatigue or muscle weakness (1038 [63%] of 1655) and sleep difficulties (437 [26%] of 1655) were the most common symptoms after discharge | 2 |
| 29 | Huang et al., 2021 | Ambidirectional cohort | China | 1655 COVID-19 patients | 57[47–65] | | | (continued on next page)
| 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 |
|----|--------|------------|---------|-------------|--------------------------------|--------------------------------------|----------------------|-------------------|
| 30 | Tomasoni et al., 2020 [52] | Cross-sectional study | Italy | 105 COVID-19 Patients | 55 [43–65] | • Dizziness, 101 (6%)<br>• Headache, 33 (2%)<br>• Anosmia, 6 (5.7%)<br>• Dysgeusia, 6 (5.7%)<br>• Burning Pain, 11 (10.5%)<br>• Asthenia, 33 (31.4%)<br>Cognitive deficits (memory disorder): 18 (17.1%) | • The median time from discharge to follow-up visit is 153.0 (1460–160.0) days<br>• All patients displayed interstitial pneumonia at hospital admission<br>• Cross-sectional study including patients with documented clinical recovery and virological clearance after hospitalization<br>• 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%)<br>• Muscular pain, 77 (43.0%)<br>• Lack of smell, 65 (36.7%)<br>• Headache, 59 (33.2%)<br>• Joint pain, 53 (29.8%)<br>• Confusion, 37 (21.1%) | • The reported duration of symptoms were persisting from hospital discharge to 35 days in COVID-19 patients<br>• 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%)<br>• Headache, 41/50 (82%)<br>• Numbness, 29/50 (58%)<br>• Dysgeusia, 32/50 (64%)<br>• Anosmia, 37/50 (74%)<br>• Myalgia, 30/50 (60%)<br>• Dizziness, 20/50 (40%)<br>• Fatigue, 42/50 (84%)<br>• 83/304 (27.3%) patients had fatigue<br>• 62/304 (20.4%) patients had dysnosmia<br>• 40/304 (13.1%) patients had dysgeusia<br>• 28/304 (9.2%) patients had musculoskeletal pain<br>• 10/304 (3.2%) patients had dizziness<br>• 10/304 (3.2%) patients had headache | • Mean duration of follow-up after symptom onset in the SARS-CoV-2 group was 4.7 ± 2 months.<br>• 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.<br>• 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.<br>• These persistent symptoms are associated with impact on quality of life and depression | 2 |
| 33 | Boscolo-Rizzo et al., 2021 [55] | Prospective cohort | Italy | 304 COVID-19 patients | 47 [18–76] | • 295/356 (82.9%) had fatigue<br>• 60/356 (16.9%) had musculoskeletal pain<br>• 18/356 (5.1%) had dysnosmia<br>• 8/356 (2.2%) had headache | • Six months post diagnosis, the prevalence of long covid symptoms was 16.1%.<br>• Overall duration period of 21.8 ± 5.2 weeks. | 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) | • Headache, 12 (4.8%)<br>• Brain fog, 9 (3.6%)<br>• Anosmia, 17 (6.5%)<br>• Ageusia, 10 (4.3%)<br>• Fatigue, 40 (16.1%)<br>• Sleep disorder, 9 (3.6%)<br>• Musculoskeletal pain, 18 (7.3%) | • Six months after the COVID-19 diagnosis, 119 patients (48.9%) reported at least one symptom<br>• Previous history of chronic obstructive pulmonary disease (OR=5) and female gender (OR=2.7) were the main risk factors of long COVID. | 2 |

(continued on next page)
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: 21.1–81.7) 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.
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), “dysosmia” (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.

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         | I² (%) | p value |
|---------------------|-------------------|--------------------|------------------------|----------------|--------|---------|
| Paresthesia         | 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. 5. Proportion estimates of Sleep disorder in long COVID-19 patients.

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

Fig. 7. Proportion estimates of Dizziness 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 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–subscales 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 circuits 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 assessed the cognitive dysfunction after COVID-19 [77]. 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 management, analysis and interpretation. AA: full text review, analysis and interpretation. RB: 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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