Neurologic and neuropsychiatric symptoms in long-COVID 19 syndrome: a systematic review

Giovani Zocche Junior
BraIns https://orcid.org/0000-0001-6261-9392
Lia Fonseca Siqueira
BraIns https://orcid.org/0000-0003-1520-9803
Leonardo Bongiovani Loro
BraIns
Felipe Valles Fortes
BraIns
Gabriele Zanirati
BraIns https://orcid.org/0000-0002-1986-973X
Daniel Marinowic
BraIns https://orcid.org/0000-0002-1146-0745
Jaderson Costa da Costa (jcc@pucrs.br)
BraIns https://orcid.org/0000-0001-6776-1515

Systematic Review

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Abstract

Covid-19 pandemic globally impaired health care, basic assistance, and quality of life, even for those who recovered after SARS-CoV-2 infection. New questions arise regarding post infection and prolonged or new symptoms. This broad concept of COVID-19 long defined as symptoms occurring after infection is very relevant for health care taken together with patient complaints related to new emerging variants and prior infections. Therefore, establishing the relationship between neurological symptoms and COVID-19 is very important. For this review, we considered only neurologic or neuropsychiatric findings after a positive SARS-CoV-2 serological test and COVID-19 long symptoms after a negative PCR test, which resulted in 42 studies after exclusions. Our results demonstrated that the most relevant and frequent neurological complaints reported was fatigue, followed by attention or memory difficulties, including brain fog and smell and taste disturbances. This systematic literature review of long COVID-19 aims to enhance the current knowledge regarding symptoms after infection and to discuss long-term COVID-19 concept, given the possibility of new or persistent symptoms.

Introduction

In January 2020, the World Health Organization (WHO) declared an international public health emergency launched by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The world had never faced a global pandemic of this magnitude: 364.191.494 cases of COVID-19 have been confirmed, including 5.631.457 deaths reported to the WHO (https://covid19.who.int) to date (29 January 2022). The global COVID-19 pandemic crisis had a significant impact on health care in unprecedented ways. Due to this scenario, unraveling the mechanisms and possible treatments for this disease has been a challenge for the scientific community.

There is growing scientific and clinical evidence pointing towards subacute and long-term effects of COVID-19, which have multisystemic effects[1]. On the other hand, health care professionals and patients have reported symptoms long after recovering from the acute phase of COVID-19 infection [2 3], which can continue for several months after mild cases [4]. Notably, among these symptoms, many are neurological, including fatigue, headaches, brain fog and memory loss [5]. As the cases of persistent neurological symptoms have been increasing, numerous reports of patients with late-onset neurologic and neuropsychiatric symptoms are currently integrating scientific databases. Recent studies have named this new clinical entity "Long COVID Syndrome" or "Post COVID 19 Neurological Syndrome - PCNS", which has not yet been studied or completely elucidated.

Different descriptions of long COVID-19 have already been proposed, and the most common description include “symptoms lasting for more than three months after the first symptom onset” [6]. Here, we highlight that the term “long COVID-19” is often used to refer to symptoms that continue or develop after acute COVID-19 [7]. In this sense, because of the lack of separation of symptoms that start in the acute phase and persist for a given time from symptoms that appear after recovery from the acute phase and then

become chronic, diagnosing long COVID-19 is still a challenge due to the lack of biomarkers and long-term follow-up studies [7].

From this perspective, this systematic review aims to assess the presence, prevalence, clinical manifestations and the association of neurological and neuropsychiatric symptoms in patients with a clinical history of symptomatic SARS-CoV-2 infection, seeking to unravel this new entity named "Long COVID Syndrome" or "Post COVID 19 Neurological Syndrome - PCNS", which has not been completely elucidated.

Methods

Registration and protocol

Registration to the PROSPERO database was submitted and registered (ID CRD42021272151). This systematic review was correspondent to the PRISMA statement in its execution.

INFORMATION SOURCES AND SEARCH STRATEGY

We performed a systematic review of studies describing long-term neurological symptoms in patients with previous COVID-19 infection. From May to June 2021, we searched the Embase, Scopus and PubMed databases using the keywords “Long COVID”; “Neurological Symptoms”, “Post-COVID”; “Neuropsychiatric Symptoms” and “COVID Long-Haulers” as well as synonyms that were combined using the operators “AND” and “OR”.

ELIGIBILITY CRITERIA

The inclusion criteria were as follows: case reports, case series, cohort studies, case-control studies, short communications, and cross-sectional and follow-up studies discussing the prolongation or emergence of neuropsychic symptoms or manifestations after the acute phase of COVID-19. Systematic reviews, reviews, meta-analyses, letters to the editor, editorials, guidelines, nonhuman and *in vitro* research articles and inaccessible articles were excluded. Articles with only pediatric patients (< 18 years) were not included. Additionally, studies considering only with the acute phase of COVID-19 infection, limited to secondary impacts caused by SARS-CoV-2 infection, or emphasizing nonneuropsychiatric disorders or manifestations were excluded. Studies related only to methods of rehabilitation, therapies and treatments for post-COVID 19 manifestations were also excluded.

SELECTION PROCESS

Two reviewers independently selected studies and extracted data (GZJ and LFS), and a third-party judge (LBL) reviewed all articles with at least one positive vote and resolved any dispute. Articles with at least 2 of 3 positive votes were included.

DATA COLLECTION PROCESS

Data extraction was performed individually, and each reviewer worked independently in reviewing random relevant articles. We used Mendeley® and EndNote 20® software for data extraction.

We evaluated the following metrics: the number of patients (*n*), evaluation methods, study design, age, main symptoms during COVID-19 infection, comorbidities, previous neurological diseases, ICU stay and the main persistent neurological and neuropsychiatric symptoms.

Demographic Data

The number of patients, age (mean, range and standard deviation when available), location of the study, publication data and sex proportion were evaluated.

Evaluation Methods

We analyzed how each article assessed patient data (medical records review, history and physical examination, laboratory and imaging findings).

Main persistent neurological and neuropsychiatric symptoms

The main symptoms characterized by time, severity, activity, localization, therapeutic response and outcome were assessed. When available, standardized scales were preferred. Some symptoms, such as “brain fog”, have not yet been thoroughly described.

RISK OF BIAS ASSESSMENT

Due to the transversal character of most articles present in this review, reverse causality bias may interfere in the results, specially

Some articles applied non-validated scales or self-assessed scales to assess persistent symptoms, mainly “new-onset symptoms” like brain fog. These results can potentially lead to measurement bias and unspecific results.

Level of evidence

Author	Country	Study design	n	CEBM level of evidence
Huang C, et al.	China	Ambidirectional cohort	1733	1b
Romero-Duarte A, et al.	Spain	Retrospective multicentric observational follow-up	797	2b
El Sayed S., et al.	Egypt	Observational cross-sectional	200	4
Carroll E, et al.	United States	Case report	1	4
Zoghi A, et al.	Iran	Case report	1	4
Gedj E, et al.	France	Case report	2	4
Koumpa F, et al.	United Kingdom	Case report	1	4
Puchner B, et al.	Austria	Observational cohort	23*	3b
Tjin Lim S, et al.	United Kingdom	Case report	1	4
Needham E, et al.	United Kingdom	Case series	11	4
Whiteside D, et al.	United States	Case series	3	4
Sun B, et al.	United States	Case series	36	4
Graham E. L, et al.	United States	Observational cross-sectional	100	4
Nuzzo D, et al.	Italy	Case report	1	4
Ortelli P, et al.	Italy	Case series	12	4
Cavalagli A, et al.	Italy	Case report	1	4
Raahimi M, et al.	United Kingdom	Case report	1	4
Mattioli F, et al.	Italy	Cohort 4 months follow-up	150	3b
Islam M. S., et al.	Bangladesh	Cross-sectional survey	1002	4
Kincaid K. J., et al.	United States	Case report	1	4
Shetty K., et al.	India	Case report	1	4
Osikomaiya B., et al.	Nigeria	Retrospective study	274	2b
Taribagil P., et al.	United Kingdom	Case report	1	4
Aasfara J., et al.	Morocco	Case report	1	4
Sykes D., et al.	United Kingdom	Cohort study	134	2b

Author	Country	Study design	n	CEBM level of evidence
Cheng D., et al.	United Kingdom	Prospective cohort of patients invited for post discharge review	113	1b
Rangathan C., et al.	United States	Case report	1	4
Sergiu A., et al.	Spain	Cross-sectional observational study	30	4
Dani M., et al.	United Kingdom	Case report	1	4
Melegari G., et al.	Italy	Case report	1	4
Melegari G., et al.	Italy	Case report	1	4
Bierle D. M., et al.	United States	Retrospective study	42**	4
Omololu A., et al.	Nigeria	Case report	1	4
Alemanno F., et al.	Italy	Cohort	87	3b
Miskowiak K. W., et al.	Denmark	Cohort	29	2b
Przytula F., et al.	Poland	Case series	2	4
Frontera J. A., et al.	United States	Cohort	382	1b
Shouman K., et al.	United States	Case series	27	4
Vanichkachorn G., et al.	United States	Cohort	100	1b
Pistarini C., et al.	Italy	Cross-sectional	20	4
Makaronidis J., et al.	United Kingdom	Cohort	467	1b
Del Brutto O. H., et al.	Equator	Cohort-nested case-control***	93	1b

***13 patients did an additional neurologic evaluation**
****15 patients were COVID-19 confirmed**
*****despite being a case-control study, it contains a cohort-based population with pre-pandemic evaluation and exams.**

Results

A total of 353 studies initially matched the keywords (“Long COVID”, “Post-COVID 19”, “Neurological” and “Symptoms”), 73 of which were duplicates. A total of 229 articles were excluded, resulting in 51 articles after the initial screening. Within the data extraction process, 9 articles were excluded, resulting in 42 studies. We included 7 cohort studies ([8], [9], [10], [11], [12], [13], [14]), 6 cross-sectional studies ([15], [16], [17], [18], [19], [20]), 3 retrospective studies ([21], [22], [23]), 2 follow-ups ([24], [25]), 1 case-control study ([26]), 6 case series ([27], [28], [29], [30], [31], [32]) and 17 case reports ([33], [34], [35] [36], [37], [38], [39], [40], [41], [42], [43], [44], [45], [46], [47], [48], [49]), adding a total of 5888 patients. Unfortunately, 10 ([15], [9], [28], [17], [43], [45], [46], [47], [11], [26]) studies did not specify symptom onset in their

description of long COVID-19; that is, no clear distinction was evident regarding whether the symptoms had persisted from the acute phase or began to manifest after the acute phase.

The main neurological symptoms described were lower motor neuron-related disturbances (weakness, loss of strength, hypotonia, hyporeflexia), which were reported 26 times, followed by taste or smell disturbances (anosmia, ageusia, hyposmia, dysgeusia) and cognition-related disturbances (*brain fog*, attention difficulties, memory deficits, cognitive decline, cognitive impairment), which were cited 23 times each. Neuropsychiatric symptoms, such as depression, anhedonia, drowsiness, irritability and low mood, were also quoted 20 times. Other important manifestations included pain or aches, fatigue, movement disorders, anxiety symptoms, sleep disturbances and myalgia.

Among relevant patients, the mean age was 51.5 years old; the sample was 49.9% male and 50.1% female. A total of 806 patients (13.6%) required an ICU stay, with stays lasting from 1 to 73 days (some studies did not detail the need for and duration of ICU stay). The main comorbidities, when listed, were hypertension and diabetes, followed by depression and cardiovascular diseases.

We define long COVID-19 syndrome as the occurrence of residual symptoms after the acute COVID-19 infection, defined by a negative SARS-CoV-2 PCR test. In some isolated cases, the long symptoms started during the acute infection but persisted after the resolution of the respiratory tract infection.

Frequency of persistent neurological symptoms

Fatigue

A very important symptom observed was fatigue (including easy fatigue, extreme fatigue, easy fatigability and asthenia), which was reported in 15 articles [8 24 15 16 38 25 17 21 43 22 10 18 23 48 13]. Most studies describe fatigue as a self-assessed symptom, with no clinical evaluation of differential diagnosis. One particular study reporting a high rate of fatigue-related manifestations, found an 85% prevalence and noted that most patients reported impaired quality of life due to persistent fatigue[16]. Furthermore, prospective research focusing on neurologic findings pointed out that that fatigue symptoms starting in the acute phase that persist through the “long COVID” phase suggests direct peripheral nervous system involvement[25]. Moreover, a follow-up study from England with a total n > 100 patients found correlations between both female sex and higher body mass index (BMI) and higher rates of fatigue[22].

Pain or aches

In this section, we included symptoms described as: aches, pain or discomfort, headaches and retrosternal discomfort which were reported in 13 studies [8 24 16 38 25 17 21 43 18

46 23 48 13]. With a total “n” of 588 patients, “pain or discomfort” was reported by 26% of patients in a cohort from China[8] (n = 1733) and by 90% of patients in a retrospective analysis from the USA[23] (n = 42) along with a case series type study with 6 patients[46]. Headaches were reported in 12 studies but were not

specified in detail in terms of their type or location and were noted in more than two hundred patients across the analyzed studies. Retrosternal discomfort was reported in one study[43].

Taste and smell disturbances

In this section, were gathered: taste disorders, ageusia, anosmia, dysgeusia, loss or distortion of sense of taste or smell, loss of smell, residual smell disorder, hyposmia and hypogeusia. A total of 14 studies[8 24 35 9 16 38 30 25 21 22 18 47 48 14] reported some sort of alteration in the perception of smell or taste, and one particular study[47] illustrated by two case reports documented that the loss of smell and taste had little to no correlation with nasal obstruction and rhinorrhea as it is common in other respiratory conditions such as upper airway viral infections and it seems to have higher prevalence among the female population. Furthermore, a larger cohort study[8] documented that approximately 10% of its patients (approximately 176 individuals) had anosmia persisting for months after the acute phase.

Movement disturbances

Five articles[24 25 42 21 31] reported the occurrence of movement disturbances in a total of 33 patients. Described symptoms included dystonia, tremors, tremulousness, myoclonus, opsoclonus and ataxia. Curiously, two patients presented with Myoclonus-Ataxia Syndrome (MAS)[42 31] and one presented with Opsoclonus-Myoclonus-Ataxia Syndrome (OMAS)[31], suggesting inflammatory-mediated postinfectious neuronal injury. All patients had no previous history of primary autoimmune disease, or the use drugs that cause myoclonus.

Cranial and peripheral nerves involvement

A wide range of persistent motor symptoms involving the peripheral nervous system were described, as follows: loss of strength in the lower limbs, weakness or muscle weakness, critical illness neuropathy, ICU-related polyneuropathy, ulnar or peroneal nerve lesions, mononeuritis multiplex, difficulty walking, lack of strength in the pelvic muscles, hypotonia, tetraparesis, hemiparesis or paraparesis, hyporeflexia or areflexia, abnormal neuromuscular fatigue, Tapia syndrome (with IX, X and XII cranial nerve deficits), bifacial weakness and paraesthesia, acute motor or sensory neurological deficits and muscle atrophy. The large spectrum of motor peripheral nervous system related symptoms affirms the already described neurotropism of SARS-CoV-2. Several studies described those symptoms[24 34 27 29 38 30 39 40 42 44 18 23 48 31], including two cohortsClique ou toque aqui para inserir o texto.[8 9] and one prospective study[25]. Although some studies described weakness as a subjective symptom[48], others reported objective paresis or plegy in the neurological exam, as well as electrophysiological study findings[30].

Depressive symptoms

Low mood, anhedonia, drowsy, lethargy, irritability, general malaise and lack of appetite were all grouped to summarize depressive manifestations. Across many studies[8 24 50 15 33 34 16 38 40 25 17 21 43 22 10 48 11

through self-applied questionnaires or medical interviews, patients reported depressive symptoms or some sort of distress that fit common depression markers such as lethargy or irritability. In particular, in one article the prevalence reached 48% which corresponded to 481 people[17] while an Italian cohort study found a 40% prevalence using validated questionnaires such as the Mini Mental State Evaluation (MMSE) and the Hamilton Scale for Depression[11].

Sleep disturbances

Sleep disorders and insomnia were reported in studies [8 24 37 9],[22] and in studies [16 30 25 21 48], respectively. Sleep difficulties were one of the most common symptoms described in postacute COVID-19[851] which were mentioned by 437 of 1655 and 19 of 23 patients, respectively. Moreover, sleep disturbances were common even at 6 months after symptom onset[8]. However, most studies describe sleep disturbances as a self-assessed symptom, with no consideration of differential diagnosis.

Anxiety symptoms

Worsening anxiety, anxiety and agitation were noted to be more prevalent and intense with more severe infection in the acute phase and to have higher prevalence among the female population, as reported in a large cohort article[8]. Among the studies reporting these types of psychological disturbances[8 24 37 28 16 25 43 22 10 18] we noticed that the overall percentage of findings varied extensively, sometimes not reaching 7% of patients[24], and others reaching more than 40% of patients[16 22]. In total, more than five hundred individuals presented these symptoms across all studies.

Paresthesia

A total of 5 studies described paraesthesia as a persistent symptom of long COVID-19[24 38 40 43 23]. Numbness and tingling were added to the paresthesia group, as described in studies[16 44], with [44] a case report in which the author specified “distal numbness in the lower limbs and left fingers”, while [16] was an observational cross-sectional study. Paresthesias tended to be more common in men than women[23]. However, the cohort articles[8 51 10 11 12 13 14] did not report these symptoms among their main findings.

Seizures and status epilepticus

Seizures and *status epilepticus* are infrequent conditions related to long-COVID syndrome. Three articles[33 41 49] reported the occurrence of unexplainable new-onset seizures in nonepileptic patients, one of whom presented with refractory *status epilepticus*[33]. In this case[33], the patient had a prepandemic routine brain MRI and EEG with no signs of epileptic activity or tumor/inflammation in the image, but after the infection, he developed tonic movements and shaking with bilateral discharges on EEG. In the other two cases[41 49], patients presented with frontal and temporal lobe discharges. The elementary mechanism for seizures associated with COVID-19 is not clarified. Although some hypotheses have been proposed, such as direct SARS-CoV-2 neurotropism via olfactory neuron axonal transport and

hematogenous spread via disruption of the blood brain barrier, with indirect factors such as hypoxia, multiorgan failure and metabolic derangements, as observed in several diseases[41].

Auditory disturbances

Vestibulocochlear neuritis, tinnitus, sudden hearing loss and hearing loss were included in auditory disturbances. These manifestations were reported by 4 studies [44 36 16 44 36 25 44]. Hearing loss and tinnitus have been seen in patients with both COVID-19 and influenza virus but have not been highlighted[36]. In Study [16], the 10 most frequent neurologic symptoms were nonspecific cognitive complaints such as tinnitus (29%)[16]. Aasfara et al.[44] in which a patient presenting unilateral sensorineural hearing loss along with vestibular areflexia that mimicked each of two: labyrinthitis and retro-cochlear hearing loss, was reported, which was not the first case report of an acute vestibular neuritis secondary to SARS-CoV-2. Malayala et al. reported a case of infection in which the pathophysiology was likely akin to those of other viral infections which cause damage to the vestibular nerve[43].

Psychiatric disturbances

Psychosis, paranoia and hallucinations were the most common psychiatric disturbances. Studies [29] and [37] documented 1 case of hallucinations and reported 1 case of psychotic symptoms consisting of persecutory delusion and complex visual and auditory hallucinations post COVID-19 infection[37] respectively. The patient reported by Study [37]also described paranoid delusions.

Cognition-related disturbances

Cognitive impairment, memory deficits, attention difficulty, poor memory and cognitive decline, as well as formal neuropsychological test score reductions were cited by 18 articles [24 34 37 51 28 29 16 30 40 25 43 22 10 18 23 19 12 26]. Despite the difficulty of standardizing the symptom evaluation in these cases, the high prevalence of neuropsychiatric cognitive-related disturbances found in our study requires more directed studies to assess the prevalence, the main clinical presentations and the outcome of the symptoms.

“Brain fog” is a novel term used by some patients to illustrate their cognition-related symptoms and seems to have a different meaning from classical cognitive-related complaints. Interestingly, in a recent study, “brain fog” was reported by 81% of “ long-term” patients[16]. In this particular study, the researchers theorized that “brain fog” could be “*a mild form of post COVID-19 encephalopathy”*. Furthermore, memory and attention complaints are a common report in post-COVID syndrome, with at least one cohort study reporting a high prevalence (50%)[12] and a lower percentage in other studies[16 43]. Additionally, a prospective study from England reported a prevalence of memory impairment and attention deficit geater than 25%[22].

Quality of life and daily living activities impairment

Three articles[8 51 12] with two cohorts[8 51] assessed the impact of long-COVID symptoms on daily living activities and quality of life of patients. Huang et al.[8] submitted 1733 patients to the EQ-5D-5-L questionnaire and found that 2% had problems with usual activity, while 7% reported mobility impairment. Another study[12] found that patients with neurological complications associated with COVID-19 had more abnormal activities of daily living than the control group (measured by Barthel Index, p = 0.002), and, among those working premorbidly, neurological patients were less likely to return to work than controls (p = 0.004)

Myalgia

Myalgia was reported by 9 studies[8 24 16 30 25 17 21 22 23], one of which was a cohort study[8]. Notably, this symptom is often reported during acute disease, suggesting, together with the very frequent symptoms of anosmia and ageusia, affecting, directly, the central nervous system (CNS) and peripheral nervous system (PNS)[25]. Sykes et al. reported that females were significantly more likely than males to experience myalgia (p = 0.022)[22].

Dysphagia

Dysphagia was reported by 1 study[39] which is a case report. Article[8] reported difficulty swallowing and sore throat in the same category. Sore throat was also included in this session and was reported by 4 studies: 1 cohort study[8] and [17 21 48], which are a cross-sectional survey, a retrospective observational study and a case report, respectively. Osikomaiya et al. described sore throat as a less common symptom in acute symptomatic COVID 19[21].

Vision-related disturbances

Double vision, blurred vision and visual blurring were reported by 3 studies: [29 16] and [21], respectively. Study [29] had one patient with double vision symptoms. On the other hand, Graham et al. reported 21/50 (42%) patients with blurred vision[16], while Osikomaiya et al. reported 6/274 patients with vision symptoms described as visual blurring[21].

Discussion

This systematic review searched for predominant symptoms during long COVID and demonstrated the main persistent symptoms after SARS-CoV-2 infection cognition-related disturbances (42.85%; 18/42), cranial and peripheral nerve involvement symptoms (40.47%; 17/42), depressive symptoms or low mood (40.47%; /42), fatigue (35.71%; 15/42), anosmia, taste or smell disturbances (33.33%;14/42), pain or aches (30.95%; 13/42), anxiety symptoms (23.8%; 10/42), sleep disturbances (23.80%; 10/42), myalgia (21.4%;9/42), paraesthesia (16.66%; 7/42), auditory disturbances (16.66%; 7/42), dysphagia (11.9%; 5/42) and movement disturbances (11.9%;5/42). On the other hand, seizures and status epilepticus are infrequent conditions related to long-COVID syndrome (7.14%; 3/42). Vision related disturbances were

mentioned by (7.14%; 3/42) of the authors. Regarding psychiatric disturbances, in this section, symptoms such as psychosis, paranoia and hallucinations were reported by (4.76%; 2/42) of studies. However, symptoms regarding quality of life and daily living activity impairment were reported by (7.14%; 3/42) of studies.

Symptoms of long Covid

Fatigue was the most frequently reported symptom and included easy fatigue, extreme fatigue, easy fatigability, and asthenia. These symptoms were reported by 15 studies although only one study[38] described asthenia. Accordingly, fatigue was the most frequently reported symptom (35.71%;15/42), but not the most frequent section, which corroborates a recent prospective cohort emphasizing the high prevalence of persistent fatigue in patients with COVID-19. In addition, the study highlights that this symptom appears to be more common in patients who had COVID-19 than after common infections, such as influenza, Epstein–Barr virus mononucleosis and dengue[52]. Furthermore, in a prospective multicenter cohort study from the UK Sigfrid et al. found that the most frequently reported symptom was fatigue 82,8% (255/308)[53].

The most common category was cognition-related disturbances which are related to attention and memory difficulties and cognitive impairment. The most reported symptoms were those related to attention difficulties (19.04%;8/42) described as cognitive deficits of concentration, attention difficulties, reduced concentration, difficulty focusing, deficits in formal neuropsychological function, and deficient attention and impulse control. On the other hand, the findings related to memory and cognitive dysfunctions were very similar to those related to attention difficulties: both were reported by (16.66%;7/42). Blomberg et al.´s findings were similar to ours; 26% of patients who had COVID-19 noted difficulty concentrating and 24% noticed memory problems. Notably “brain fog” was reported by 2 studies (4.47%)[16 43], which may manifest as difficulties with concentration, memory, receptive language and/or executive function[54]. Therefore, because the term is minimally used and unspecific, the number of patients may not be reliable.

The category “cranial and peripheral nerve involvement” was mentioned by 17 studies. The most prominent symptom was “weakness or muscle weakness” which reported by (11.9%;5/42) studies. Additionally in this group, fewer incidents of loss of strength in the lower limbs (7.14%;3/42), difficulty walking (7.14%;3/42) and other symptoms were described. Notably some authors include fatigue and muscle weakness in the same category, which can interfere with the results. Therefore, analyzing these symptoms separately is important, as fatigue can have different causes. Here we separate fatigue and muscle weakness into different sections to differentiate the frequency of these findings. Huang et al. reported fatigue or muscle weakness in 1038 of 1655 patients, however we cannot distinguish which was the most common symptom of the two[55].

Tase or smell disturbances were reported among 14 studies (33.33%;14/42). In this category, taste disorders, ageusia, anosmia, dysgeusia, loss or distortion of sense of taste or smell, loss of smell, residual smell disorder, hyposmia and hypogeusia were identified; across these symptoms, the most commonly reported was anosmia, loss of smell or residual smelling disorder (23.8%;10/42). In many studies, as well as in this review, changes in taste or smell seem to be one of the most reported issues, as noted by Blomberg et al. in their prospective cohort study in which 27% of the total patient population (n=189) analyzed had symptoms involving these senses[52].

Headache predominated in the category “pain or aches” and was reported by (26.19%;11/42) of the studies. Orrù et al. observed subjects (n=448) who were swab-positive for COVID-19 but had been negative for less than a month, for more than a month, for more than 2 months and for at least 3 months: in all these scenarios, except for patients who had been negative for at least 3 months, headache was present in 53%, 54% and 49% of the participants[56]. Additionally, in this study, the authors found higher levels of anxiety and/or depression in patients with long COVID-19 than in those who never had COVID-19[56]. Here, we observed that low mood, anhedonia, drowsiness, lethargy, irritability, general malaise and lack of appetite, which were all grouped to reflect depressive manifestations, were reported across 17 studies (40.47%;17/43). On the other hand, whether these symptoms preceded the SARS-CoV-2 infection was not analyzed in most studies.

Anxiety symptoms and worsening anxiety were reported by 23.8% (10/42) of patients who tested positive for COVID-19. On the other hand, Santabárbara et al. affirmed that in the general population, the rates of anxiety could more than triple if compared to the ones during the COVID-19 outbreak[57]. In this sense, we cannot assume a correlation between anxiety and COVID-19 pathophysiology which also holds true for sleep disorders, which were reported by 23.8% (10/42) studies, since other factors may have affected sleep quality apart from the pandemic itself. Targa et al. observed a decrease in sleep quality during the COVID-19 outbreak according to the Pittsburgh Sleep Quality Index (PSQI)[58].

Finally, myalgia was a frequent symptom among the findings and was reported by 21.42% (9/43) of the studies. This symptom has been frequently reported in COVID-19 patients with a prevalence ranging from 11 to 50% in large cohort studies; therefore, it should be studied in more detail[59]. Myalgia is an important symptom in patients who have had SARS-CoV-2 infection: 61% of the patient population reported this symptom even after 3 months of testing negative for COVID-19[56].

Timeline of long COVID

We observed different ways to address the timeline of long COVID syndrome. Some studies evaluated the time between acute infection and long symptom onset, while others assigned more value to the duration of the symptoms. We faced some difficulties determining what is ‘long COVID’ and what is part of acute clinical characteristics, which may be explained because of the pandemic character of the disease, our still limited knowledge about the clinical course and atypical manifestations, besides the variability of molecular tests. Thus, we consider ‘long COVID symptoms’ any neurological or neuropsychiatric

manifestation first presenting after a serological documented (PCR, IgG/IgM) SARS-CoV-2 infection. We consider both symptoms starting during the acute infection but persistinged for 3 or more weeks (mainly smell and taste disturbances, such as anosmia, ageusia and dysgeusia) and those presenting after negative serological tests. Because most of the patients included in our study were unvaccinated during long symptom onset, we do not believe that any described symptom associated with a positive IgG titer may be significantly related to vaccination.

Taste and smell disturbances, such as anosmia, ageusia, dysgeusia, hyposmia and hypogeusia, are correlated with direct olfactory bulb and gyrus neuroinvasion by SARS-CoV-2, as well as the stem cells present therein.

We can note that cognitive, neurological and neuropsychiatric symptoms had a more insidious onset, as [13] demonstrated in his cohort, with a 93-day mean time between SARS-CoV-2 diagnosis and presentation to rehabilitation service.

Otherwise, movement disturbances (myoclonus, ataxia) and peripheral nervous system symptoms (weakness, polyneuropathy) had a more acute onset, with an 11-day interval between acute infection and postinfectious symptoms[31]

Main outcomes and evaluated parameters

In this section highlight the most impactful groups of symptoms regarding morbidity and quality of life, due to the objetive of this review, that is, to evaluate long-term COVID-19 disturbances across both neurological and psychological domains. According to a prospective study included in this review[16], assessing fatigue through the Patient Reported Outcome Measurement Information System (PROMIS), a high percentage (85%) of patients reported that fatigue impaired their quality of life to some degree, which has also been reported in other studies such as[25 4 8] which together encompass a greater number of individuals; thus fatigue-related complaints seem to impose a significant burden on daily life activities for a long period after the acute infection, with particularly described by *Hung et al.* showing its effects in as long as 6 months of evolution[8].

Continuing in the neurological aspect of symptoms, taste and smell related disturbances have been vastly reported across many articles. Although primarily associated with a differentiation aspect of the diagnosis of COVID-19's acute infection, these sensitivity related complaints seem to endure in many patients causing a significant alteration of their lives. Contrary to other respiratory infections that also affect the upper airways, such as sinusitis or rhinitis, COVID-19-related smell and taste impairment seems to have low to no correlation with nasal edema and mucus overproduction, as noted in our results section, according to[47]. This specific fact may point to a coronavirus' nervous tissue tropism, which is also extensively detailed in postmortem anatomopathological study by [60] who suggests that viral neuroinvasion occurs via axonal transport. With all these topics in mind, we may be starting to identify

the complete physiological pathway through which this pathogen reaches the central nervous system (CNS) and causes many peripheral manifestations.

Another aspect related to the peripheral and central nervous systems (PNS and CNS) is the wide range of movement disorders, weakness, paresthesia and disphagya found across many studies, which reflect electrophysiological findings[30] that objectively explained peripheral motor disorders as possibly a originating from post infectious nervous tissue inflammation. On another note[9], also adds to the topic of neuromotor manifestations and also points to a central etiology, which may then lead this discussion to a divergent point when the main cause of these mainly peripheral nervous functions is considered. However, the important aspect regarding these topics is that the burden of peripheral complaints in long-haulers is real, and although it may be still obscured by seemingly different methods of assessment, this aspect requires specific investigation.

Apart from these less clear topics, some auditory related disturbances warrant some attention since they actually have more involvement in other respiratory tract infections and more importantly because the impact of hearing related disturbances is devastating to patients' quality of life[61]. As such disturbances are more common in other viral infections such, as influenza virus infection, the pathophysiological mechanism causing hearing loss, in COVID-19, cases is likely similar.

Considering the topic of psychological-related disturbances, and starting with cognition-related disturbances, we found a high prevalence of patients with some cognitive impairment in the post-COVID scenario. One manifestation in particular deserves special attention, which is described as "brain fog" by two studies. This form of confusion and disorientation appears to be mild but very objectively reported by patients as being different from a lack of attention and difficulty focusing as well as memory-related problems[16]. In a prospective study theorized an origin for the complaint in the form of encephalopathy, which deepen the relationship between COVID-19 and CNS effects if confirmed in future research. The rate with which patients reported imparied cognition, was noted to be as high as 50% at 6 months in one study[12], rerendering the long-term effects of this condition in psychological processes even higher than the known rate of cognitive disorders in the normal population[62]. Regarding the overall understanding of cognitive disorders related to long-term COVID-19 [22] points out that in this field mental and biopsychosocial effects should not be taken lightly. Depressive and anxiety related symptoms such as worsening of these conditions due to the social aspect of the pandemic (isolation, death toll) have been high in prevalence post COVID and again point to a different outcome of worldwide epidemics, such as this one. Accordingly we may theorize that the burden of cognition-related symptoms in long-haulers may be a larger phenomenon than simply persistent set of mental alterations at the individual level but rather a larger collective manifestation that affects our whole species given the impact that this pandemic has had on us.

We identified a high overall prevalence of both neurological and psychological manifestations in long COVID patients through by analyzing different studies from different parts of the world, which was partly due to the scale of this pandemic. From the whole set of data obtained, the most impactful neurological

disorders were fatigue, anosmia and ageusia, with the main psychological disorders being impaired cognition, anxiety and depression. Given the process with which we conducted this study, these two areas could be differentiated because they are organic and mental in nature, but this has only been executed in a methodological and procedural capacity. The full scope of long-haulers burden is a complex and intricate matter and its aspects cannot be separately addressed on an individual level.

Management considerations/Interdisciplinarity considerations

As COVID-19 is a multiorgan disease, multidisciplinary management is urgently required during the long COVID-19 period. Some studies have reported that special care of individuals infected with COVID-19 extends beyond the period of acute infection[63 54]. Comprehensive and multidisciplinary care of these patients after hospital discharge is necessary, especially for patients with severe COVID-19 requiring hospitalization in the ICU remained with permanent sequelae. Within the current scenario, a new strain has emerged (B.1.1.529 - Omicron), as a variant of SARS-CoV-2 that the World Health Organization (WHO) has identified in real concerns [64 65]. The damage that COVID-19 can cause to the global population and the efficacy of the vaccines against this new mutation are still unknown and the number of cases with enduring damage caused by severe COVID-19 is expected to continue to rise. Thus, hospitals and clinics must have multidisciplinary teams prepared to monitor these post-COVID patients in the long term to enhance screening time and patient diagnosis.

LIMITATIONS

This review's limitations are pointed out as follows. Most of the included studies were of low quality, probably because COVID-19 is a very new diagnosis including many symptoms related to many pathologies. Furthermore, the overall impact of COVID-19 consequences is under debate. We must also state that the study design among the included papers and the general symptom descriptions, prevented us from addressing important issues. Including: the duration of persistent symptoms, the past histories of patients with similar symptoms, which possible therapeutic options were applied in the patients and the impact on quality of life. As symptoms were not captured uniformly in all papers, the comparison between symptom severity and the interconnection between symptoms was ultimately unclear. Some patient symptoms and descriptions may also fit as in more than one diagnosis. The heterogeneity of the study design highlights the importance of using international standards to standardize the studies, diagnostic criteria and severity scores. Notably, as mentioned in the results, ten[15 9 28 17 43 45 46 47 11 26] studies did not symptoms in terms of whether: they were persistent from the acute phase or if they began to manifest after the acute phase. From this perspective, because we did not have this clear distinction of symptoms, we were unable to distinguish long COVID from other postviral syndromes[7].

Conclusions

The systematic review presented here reveals important findings related to symptoms in patients recovered from COVID-19. We used the term long COVID-19 to describe the period after confirmation of negative PCR for SARS-CoV-2 in patients who developed COVID-19. Several symptoms have been described in this postinfection period, including weakness, loss of strength, hypotonia and fatigue. Symptoms reported in the medical literature such as anosmia, ageusia, and dysgeusia were also quite relevant and warrant attention for confirmation of this relationship through this systematic review. We highlight some uncommon findings for patients recovered from COVID-19, such as movement disorders, motor symptoms related to cranial and peripheral nerves, depressive symptoms, and sleep disorders, among others, which are related to this post recovery period following the most acute phase of the disease. This systematic review can substantiqally the elucidation of clinical symptoms of patients who have recovered from SARS-CoV-2 infection and the development of strategies against COVID-19 by assisting medical teams, which are often in need of scientific support to determine the outcomes and clinical results of patients with this profile. In addition, a large number of those recovered from COVID-19 will need follow-ups and outpatient care given the spread that occurred during the pandemic or due to the circulation of new virus variants.

Declarations

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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Tables

Sections	Citations (n)	References
PAIN OR ACHES		
Pain or discomfort/ aches	5	55,16,46
Headache	11	55,24,38,25,17,21,18,23,48,13,16
TASTE OR SMELL DISTURBANCES		
Taste desordeer	2	55,13
Ageusia	3	35,25,47
Anosmia or dysgeusia/ loss of distortion of sense of smell and taste	3	55,24,14
Anosmia/ loss of smeel/ Residual smelling disorder	10	16,18,21,25,30,35,47,48,51,66
Dysgeusia	3	16,21,18
Hyposmia	1	38
Hypogeusia/ loss of taste	1	38
FATIGUE RELATED SYMPTOMS		
Fatigue/ Easy fatigability/ Extreme fatigue/ Athenia	15	55,24,15,16,38,25,17,21,43,66,10,18,23,48,13
MOVEMENT DISTURBANCES		
Dystonia	1	24
Tremors/ tremulousness	3	24,25,21
Opsoclonus/Myoclonus/Ataxia Syndrome (Kinsbourne Syndrome)	2	42, 31
Myoclonus	2	31,42
Ataxia	2	31,42
CRANIAL AND PERIPHERAL NERVE INVOLVEMENT		

Loss of strenght on lower limbs	3	38,34,40
Weakness or muscle weakness	5	23,30,34,51,48
Critical illness neuropathy/ ICU-related polyneuropathy	2	24,51
Ulnar or peroneal nerve lesion	1	51
Mononeuritis multiplex	1	27
Difficulty walking	3	42,38,55
Lack of strenght in pelvic muscles	1	38
Hypotonia	1	38
Tetraparesis, hemiparesis or paraparesis	1	30
Hyporreflexia or arreflexia	2	38, 30
Abnormal neuromuscular fatigue	1	30
Tapia Syndrome with IX, XII and X CNs deficit	1	39
Bifacial weakness and paraesthesia (BFP)	1	44
Acute motor or sensory neurological deficits	1	40
Muscle atrophy	2	38,30
DEPRESSIVE SYMPTOMS		
Depressive symptoms/ low mood	9	55,24,28,16,38,10,11,66,48
Anhedonia	1	15
Drowsy	2	34,38
Lethargy	4	38,33,40,43
Irritability	1	25
General malaise	1	21
Lack of appetite	2	17,21
SLEEP DISTURBANCES		
Sleep desorder/insomnia/ sleep disturbances	10	55,24,16,,25,21,37,51,66,48

ANXIETY SYMPTOMS		
Anxiety symptoms/ worsening anxiety	10	55,24,16,25,10,18,28,37,43,66
Agitation	1	37
PARAESTHESIA		
Paraesthesia	5	24,38,23,40,43
Nubmness or tingling	2	16,44
SEIZURE AND STATUS EPILEPTICUS		
Status epileticus	1	33
Seizures	2	41,49
AUDITORY DISTURBANCES		
Sudden hearing loss/ hearing loss	3	25,36,44
Tinnitus	3	16,36,44
Vestibulocochlear neuritis	1	44
PSYCHIATRIC DISTURBANCES		
Psychosis/ paranoid	1	37
Hallucinations	2	29,37
QUALITY OF LIFE AND DAILY LIVING ACTIVITY IMPAIRMENT		
Problems with washing or dishing/ probelms with usual activity	3	55,12,51
VISION-RELATED DISTURBANCES		
Double vision/ blurred vision/ visual blurring	3	16,21,29
MYALGIA		
Myalgia	9	55,24,16,25,17,21,23,66

DYSPHAGIA		
Dysphagia	1	55
Sore throat/ difficult to swallow	4	55,17,21,48
COGNITION-RELATED DISTURBANCES		
Brain fog	2	16,43
Cognitive deficts of concentration/ attention difficulties/ reduction in concentration/ difficulty focusing/deficits on formal neuropsychological/ deficit attention and impulsive control	7	24,34,37,10,28,40
Memory deficts/ memory difficulties/ poor memory	7	16,25,10,29,43,51,66
Cognitive impairment/ altered cognition/ cognitive dysfunction/ abnormal cognition/ cognitive deficits/ cognitive decline	7	12,18,19,23,26,29,30

Table 1: Frequency of finds divided by sections.
Cohort ([8 9 10 11 12 13 14])

Country	Study design	n	Age (avg, range, SD)	Sex (M:F)	Outcome Assessment	Main persistent symptom(s)	Time of symptoms onset after COVID infection	Comments
China	ambidirectional cohort	1733	57 (47-65)	897M : 836F	Medical records analysis, follow-up consultation (self-reported symptom questionnaire), mMRC, dyspnea scale, EQ-5D-5L, EQ-VAS, blood analysis, pulmonary function anaylsis	Fatigue/ muscle weakness (63%), Sleep difficulties (26%), dizzines, sore throat or difficult to swallow, myalgia, depression or anxiety, Anosmya or dysgeusia (11%), Headache (2%), problems with walking around, problems with washing or dishing, problems with usual activity, Pain or discomfort,	6.2 months (5.8- 6.6)	-
Spain	retrospective multicentric observational follow-up	797	63	428M : 369F	Hospitalization records analysis, primary care records,	Fatigue (22.1%), myalgia (15.3%), persistent anosmia or dysgeusia (7.2%), headache (5.3%), paresthesia (3.4%), movement disorders (3.4%), disorientation or confusion (2.6%), ICU-related polyneuropathya, Depressive symptoms, Anxiety symptoms, Sleep disturbances	6 months	-
Egypt	observational cross-section	200	36.58 (+-9.85)	114M : 86F	Self-assessment anhedonia scale, Fatigue Assessment Scale	Anhedonia and fatigue	Scaleless data	Self-assessed scales, no control group
United States	case report	1	69	F	Clinical examination, laboratory (inflammatory biomarkers), brain MRI, electroencephalogram, lumbar puncture and CSF analysis, autoimmune encephalitis panel	New onset refractory status epilepticus, lethargy	13 days (first episode)	Complex case, several potential confounding variables, no final diagnosis
Iran	case report	1	21	M	Clinical examination, laboratory, imaging, antibody panel	Weakness and paresthesia in lower limbs, urinary retention and drowsy	2 weeks	Serologictests for COVID-19 were requested, which revealed a negative result forIgM, but the IgG level was 1.6 (positive >1.1).
France	case report	2	54, 62	M	Clinical evaluation, FDG PET/MRI scan	Ageusia, anosmia, dyspnea	symptoms started	hypometabolism in

							during acute infection, but persisted for 4 weeks	olfactory/rectal gyrus, medial temporal lobe and brainstem
United Kingdom	case report	1	45	M	Clinical examination, laboratorial tests, Rinne and Weber tests, pure tone audiogram	Left-sided tinnitus and sudden hearing loss	1 week after extubation	-
Austria	observational cohort	23*	57 (+-10)	16M : 7F	-	Em 13 testados: Critical illness neuropathy, defined as decreased vibration sensation and hyporeflexia of knee and ankle jerks, ulnar or peroneal nerve lesion. A residual smelling disorder was present in only one patient. Em 14 testados, cognitive deficits of concentration, memory, and/or executive functions. Em 19 testados, sleeping disorder	-	-

Country	Study design	n	Age (avg, range, SD)	Sex (M:F)	Outcome Assessment	Main persistent symptom(s)	Time of symptoms onset after COVID infection	Comments
United Kingdom	case report	1	55	M	Clinical, laboratory, neurophysiological and neuroradiological evaluation	Psychotic symptoms with florid visual hallucinations, paranoid, agitation, anxiety and sleep disturbance	2 weeks	After this point there was gradual improvement and by day 52 no psychotic symptoms had been made known.
United Kingdom	case series	11	58 (50-77)	8M : 3F	Clinical examination, MRI, CT scan, ultrasound, elecroneuromyography, laboratory tests	Mononeuritis multiplex with 11 different patterns	The neuropathies were noted following withdrawal of sedation	Patients weren't tested at the neuropathic symptomts onset
United States	case series	3	70 (62-75)	2M : 1F	Telehealth neuropsychological evaluation, medical records analysis	The three patients all demonstrated deficits on formal neuropsychological testing, ranging from mild to severe. Two patients endorsed new depressiveand/or anxiety symptoms.	no data	Due to telehealth modality, a limited selection of tests was employed. There's no control data collected before the COVID-19 infection
United States	case series	36	45.3 (+-12.7)	14M : 22F	Self-reported neurological symptoms, peripheral blood sample - APOE4 genotyping, SARS-CoV-2 IgG antibody test, plasma multiplex cytokine analysis, nEV isolation, characterization and analysis, bioinformatics	Memory/cognition (25%), hallucinations (4,1%), double vision (4,1%)	Median 60 days (30-103)	Self-assessed and not padronized neurological symptoms
United States	observational cross-section	100	43.2 (+-11.3)	30M : 70F	Clinical evaluation, brain MRI, EMG, CSF analysis. PROMIS and NIH toolbox were applied. 48% televisits, 52% in-person	"Brain fog" (81%), headache (68%), numbness/tingling (60%), dysgeusia (59%), anosmia (55%) and myalgias (55%) dizziness (47%), pain (43%), blurred	Median 4.72 months (positive test) and 5.82	Patients with negative SARS-CoV 2 PCR and sorology were included as 'control group'.

						vision(30%), and tinnitus (29%), fatigue (85%), depression/anxiety(47%), insomnia (33%), short termmemory deficit by 4-item recall (32%) and attention deficit by serial 7s (27%)	months (negative test)	Some symptoms ('headache') were previous described as patient commorbities
Italy	case report	1	56	M	Clinical evaluation, laboratorial studies, chest CT, brain MRI, CSF analysis, EMG	Lower limbs weakness, difficulty walking, hypotonia, hyporreflexia, lethargy, chronic fatigue, headache, depression, paresthesia, hyposmia, hypogeusia, asthenia	3 months	Patient developed weakness and hypotonia immediatly after ICU discharge. Despite the brain MRI findings, critical illness neuropathy and myopathy could be overlaped another syndrome
Italy	case series	12	67 (+-9.56)	10M : 2F	Clinical evaluation, Neurophysiological assessment: Fatigue Rating Scale, Fatigue Severity Scale, Beck Depression Inventory, Apathy Evaluation Scale, cognitive tests and computerized tasks	Tetraparesis, hemiparesis, muscle atrophy, cognitive impairment, myalgia, anosmia, insomnia, areflexia, deep sensory disturbances in lower limbs, hyporeflexia, dysphagia, deficit in attentional processes and impulse control	Mean 11.5 (9-13 weeks)	-

Country	Study design	n	Age (avg, range, SD)	Sex (M:F)	Outcome Assessment	Main persistent symptom(s)	Time of symptoms onset after COVID infection	Comments
United States of America	Case report	1	71	M	Computed tomography (CT) angiography with perfusion imaging, MRI, radiographic and electrographic, Electroencephalogram (EEG), stroke labs, echocardiography, and cardiac telemetry	Seizure	6 days	-
India	Case report	1	41	M	Clinical examination, CT, EEG, MRI, Mini-Mental Status Examination (MMSE)	Subtle jerky involuntary movements of the limb along with difficulty while walking and gait ataxia.	10 days	-
Nigeria	Retrospective study	274	41.8 years (SD ± 11.8)	M (66.1%), F (33.9)	The study used a retrospective study design	Fever 17 (6.2); Easy fatigability 35 (12.8)Malaise 15 (5.5); Myalgia 24 (8.8); Excessive night sweat 10 (3.7); Cough 25 (9.2); Dysgeusia 7 (2.6); Anosmia 5 (1.8); Loss of appetite 24 (8.8); Nausea 6 (2.2); Headache 35 (12.8); Insomnia 27 (9.8); Attention or memory deficit 14 (5.2);Dizziness 8 (2.9);Visual blurring 6 (2.2);Tremulousness 2 (0.7)	15 days [mean: 15.6; SD ± 6.6]	-
United Kingdom	Case report	1	28	F	Blood tests, Chest X-ray, CT scan, ECG	fatigue, lethargy, intermittent dizziness, and persistent dyspnea, reduction in concentration, poor memory, 'non-specific head buzzing', worsening anxiety, and brain fog, non-specific paraesthesia across her hands and feet, and generalised body ache	The symptoms appeared to fluctuate unpredictably over the weeks with no aggravating or alleviating factors identified.	-
Morocco	Case report	1	36	F	Clinical presentation, neurophysiological, audiometry and videonystagmography workup and CSF	One day prior to admission convoluted by fullness of the right ear and left-sided facial weakness with tinnitus, right peripheral facial palsy and asymmetric distal numbness in the lower limbs and left	SARS-CoV-2 positive 6 weeks before admission	Pregnant at 37 weeks

					polymerase chain reaction assay (PCR) for several viruses	fingers, severe right sensorineural on pure tone audiometry, complete right vestibular areflexia on caloric examination with left-beating spontaneous horizontal and torsional nystagmus (vestibulocochlear neuritis)		
United Kingdom	Retrospective observational	134	59.6 (SD ± 14.0)	88 M, 46 F	A standard dataset was collected for each patient / validated questionnaires were used to quantify dyspnoea (MRC dyspnoea scale) and quality of life (5- level EuroQol-5 Dimension also known as EQ-5D-5L) / anamnesis	myalgia, fatigue; low mood, anxiety, sleep disturbance; memory impairment, attention deficit, anosmia, taste deficiency, and cognitive impairment.	Patients were followed up at a median of 113 days (range = 46–167) post-discharge	All patients included in this cohort had RT-PCR confirmed COVID 19 pneumonia
United Kingdom	A prospective cohort of patients invited for postdischarge review	113	73	-	Anamnesis, PHQ-2 scores, GAD-2 scores, imaging performed, exams retrospectively assessed.	Fatigue, memory impairment, speech and language issues, hair-loss, depression and anxiety symptoms	6–12 weeks after discharge	-
Country	Study design	n	Age (avg, range, SD)	Sex (M:F)	Outcome Assessment	Main persistent symptom(s)	Time of symptoms onset after COVID infection	Comments
Spain	Cross-sectional observational study	30	54 (43.8–26.2)	19M:11F	Validated questionnaires, medical, Physical and respiratory and neurological evaluation,	Anosmia, fatigue, altered cognitivon, dysgeusia, anxiety, muscle and joint pain	Patients in the non-ICU subgroup started the rehabilitation 110.5 (89–124) days from the beginning of acute COVID-19 symptoms and 79 (64–90) days after discharge from conventional	-

							hospital unit, whereas in the ICU subgroup patients started the rehabilitation at 98 (95–112) days from the beginning of symptoms and 42 (8–64) days after hospital discharge.	
United States of America	Case report	1	69	F	Clinical examinations, laboratory tests, imaging	Severe persistent encephalopathy post COVID-19's acute phase.	-	
			66	M				
			62	M				
United Kingdom	Case report	1	30	F	Clinical evaluation, Tilt table test	Aches, dizziness, orthostatic intolerance	-	-
Italy	Case report	1	31	F	Clinical examinations, laboratory tests, imaging	Anosmia and ageusia	Anosmia and ageusia started with active infection, but persisted during 90 days (anosmia with mild improvement in sense of taste)	-

	Country	Study design	n	Age (avg, range, SD)	Sex (M:F)	Outcome Assessment	Main persistent symptom(s)	Time of symptoms onset after COVID infection	Comments
G.,	Italy	Case report	1	55	F	Clinical examinations, laboratory tests, imaging	One day before ICU planned discharge, the patient presented mydriasis, a sudden loss of consciousness and coma.	-	They discovered "acute ischemia with wide hemorrhagic infarction in the absence of vascular malformation with the acute quote of cerebral edema".
et	EUA	Retrospectivo (analise de registros de pacientes)	42**	46.2 (Mean) 46.5 (Median)	14M : 28F	Clinical symptoms	pain (90.2%), fatigue (73.8%), dyspnea (42.9%), orthostatic intolerance (38.1%), paresthesias, headache, weakness, cognitive dysfunction, myalgia	4-22 weeks (11 m)	Paresthesias and chest pain tended to be more common in men than women, while headache, anorexia, and joint pain were more common in women
et	Nigeria	Case report	1	22	F	Clinical examinations, laboratory tests	low grade fever, generalized body weakness, sore throat, anosmia, headache, fatigue, insomnia, easy fatigability	1 week on average per symptom	easy fatigability and exertional dyspnea persited
F,	Italy	Cohort	87	62 (±13)	62M : 25F	Neuropsychological evaluation (MMSE, MOCA, Hamilton, FIM), neurological evaluation	Regarding the inquiry of the MoCA scores : 74.2% of severe patients, 94.4% of critical patients, 89.6% of moderate patients and 77.8% of mild patients presented with deficits, as noted in the total	-	Subacute phase (disease onset between 5 to 20 days). No data about pre-pandemic neuropsychological scores

							score' scrutiny. 40% of patients had reported mild or moderate depression. The rates of depression were akin across all groups. 1- month follow-up showed all groups with persistent MoCA-scale deficits, despite significantly higher than at admission		
k	Denmark	Cross-sectional	29	56.2 (±10.6)	17M : 12F	Physical examination, blood tests, chest CT, ECG, COPD assessment test, MRC dyspnea assessment, asthma control questionnaire, work productivity and activity impairment questionnaire, EQ-5D-5L quality of life assessment, cognitive assessments (Scores: TMT-B, SCIP-D, CFQ)	Global and selective cognitive impairment (59-65%, according to score cut-off)	Data obtained 3-4 months after COVID-19 hospitalization discharge	No healthy controls inclusion criteria
et	Poland	Case series	2	49; 62	M	Neurological examination, brain CT and MRI, chest and abdomen CT, CSF analysis, EEG, antibody panel, viral neurological panel, onconeural antibodies, tumour markers	Myoclonus, ataxia, opsoclonus	11 days after	Case 1 infectious symptoms may be confounding factors. IgG titers increase substantially and overcome IgM approximately 20-25 days after symptoms onset (Galipeau, et al).
A,	USA	Cohort	382	68 (Median of	128M : 68F (neurological	Modified Rankins Scale, daily living	Limited activities of	2 days	Subacute manifestations (the

				neurological symptoms group)	symptoms group)	activities and neuropsychiatric symptoms's assessment	daily living, impaired cognition, inability to work, worsening of neuro-quality of life score. 6-month modified Rankin Score worse in patients with neurological complications than controls		median time from general COVID 19 symptom onset to neurological complication was 2 days), self report health measures
	Country	Study design	n	Age (avg, range, SD)	Sex (M:F)	Outcome Assessment	Main persistent symptom(s)	Time of symptoms onset after COVID infection	Comments
et	USA	Case series	27	30 (Median)	11M : 16F	Medical records review. Autonomic function testing, composite autonomic severity score (CASS).	Lightheadedness, orthostatic headache, syncope, hyperhidrosis, postural tachycardia syndrome (POTS) and burning pain, cough-associated syncope (vasovagal)	Avg 22.8 days (0- 122)	Some patients had the neurological symptoms during acute infection (41%)
orn	USA	Cohort	100	45 (Mean)	32M : 68F	Clinical symptoms, laboratory tests	Fatigue and headache (20%)	93 days after infection (mean)	-
et	Italy	Cross-sectional	20	65.4 (±11.5)	13M : 7F	Neuropsychological assessment (mini mental state evaluation, montreal cognitive assessment, hamilton rating scale for depression and impact of event scale-revised)	Cognitive deficits, depression, psychological distress.	25.14 ± 10.39 days after the last negative swab.	The majority of sample developed a severe form of COVID19. Data wasn't compared to controls or people with matching age/education years
s J,	UK	Cohort	467	39.7 (Mean)	139 M : 327F	Self-applied validated questionnaire	Loss or distortion of sense of smell and taste	21 weeks +- 4.5	All symptoms started during acute infection

)	Equator	Nested case-control	93	62.6 (±11)	34 M : 59F	Clinical interview, evaluation of cognitive performance (MOCA), EEG, MRI	Cognitive decline	No data	This is a really good study who had pre-pandemic cognitive assessment data of a cohort. Small sample size and asymptomatic infection may affect results.

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ts was COVID confirmed