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NEUROLOGY OF SYSTEMIC DISEASES (J. BILLER, SECTION EDITOR)

The Neurological Manifestations of Post-Acute Sequelae of SARS-CoV-2 Infection

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Abstract

Purpose of Review Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a global health challenge. This review aims to summarize the incidence, risk factors, possible pathophysiology, and proposed management of neurological manifestations of post-acute sequelae of SARS-CoV-2 infection (PASC) or neuro-PASC based on the published literature.

Recent Findings The National Institutes of Health has noted that PASC is a multi-organ disorder ranging from mild symptoms to an incapacitating state that can last for weeks or longer following recovery from initial infection with SARS-CoV-2. Various pathophysiological mechanisms have been proposed as the culprit for the development of PASC. These include, but are not limited to, direct or indirect invasion of the virus into the brain, immune dysregulation, hormonal disturbances, elevated cytokine levels due to immune reaction leading to chronic inflammation, direct tissue damage to other organs, and persistent low-grade infection. A multidisciplinary approach for the treatment of neuro-PASC will be required to diagnose and address these symptoms. Tailored rehabilitation and novel cognitive therapy protocols are as important as pharmacological treatments to treat neuro-PASC effectively.

Summary With recognizing the growing numbers of COVID-19 patients suffering from neuro-PASC, there is an urgent need to identify affected individuals early to provide the most appropriate and efficient treatments. Awareness among the general population and health care professionals about PASC is rising, and more efforts are needed to understand and treat this new emerging challenge. In this review, we summarize the relevant scientific literature about neuro-PASC.

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Keywords COVID-19 · SARS-CoV-2 · Post-Acute Sequelae of SARS-CoV-2 infection · PASC · Chronic fatigue syndrome · Myalgic encephalomyelitis · Long COVID · Post-COVID syndrome

Introduction

With more than 177 million documented infected cases globally and more than 3.8 million deaths (https://covid19.who.int/, as of June 20, 2021), the coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has left a lasting global impact in unprecedented ways. With the increasing number of patients that have been infected, survivors of COVID-19 may be left with chronic post-viral complications similar to the previous severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome pandemics [1]. Systemic and neurocognitive deficits may last only weeks but can potentially lead to lifelong disability [2, 3]. Some studies indicate that disease severity correlates with worse and more prolonged neurological symptoms [4, 5•], while other studies have found no such correlation [6]. Chronic symptoms may affect multiple organs (see Fig. 1) including the brain, heart, lungs, musculoskeletal system, gastrointestinal tract, and kidneys [7–9]. The post-COVID symptoms, initially referred to as "long COVID" or "long-haul COVID," are now collectively referred to as "post-acute sequelae of SARS-CoV-2 infection" (PASC). These symptoms are expected to increase the burden on already overstretched health care systems worldwide. This review describes the incidence, risk factors, possible pathophysiology, and proposed management of neurological manifestations of PASC (neuro-PASC).

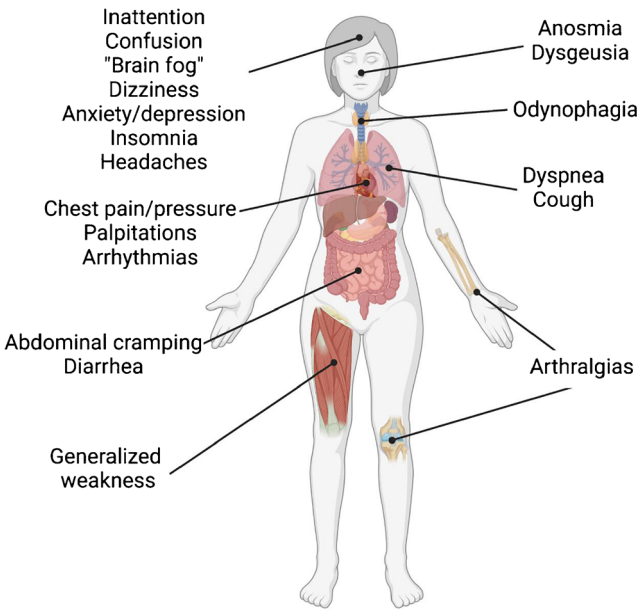

Fig. 1 Organ systems affected by PASC (the figure generated using biorender.com)

Lingering COVID-19 Symptoms and PASC

In 2021, the National Institutes of Health (NIH) noted that common symptoms of PASC include fatigue, shortness of breath, brain fog, sleep disorders, intermittent fevers, gastrointestinal symptoms, anxiety, and depression. The most commonly reported symptoms are fatigue, dyspnea, headaches, cough and chest tightness with myalgias, fever, palpitations, and other constitutional symptoms, although the list is growing [10•]. However, the lack of a standardized definition for PASC precludes effective epidemiologic assessment of the condition, incidence rates, the impact of the condition on long-term disability, and the health care cost. Table 1 outlines PASC symptoms that have been reported in the literature so far. These symptoms, ranging from mild to severe, can persist for months, with new symptoms arising well after the time of infection [11]. Post-infectious fatigue syndromes follow in the wake of various infectious processes. Patients with post-infectious fatigue syndromes share a group of symptoms in common with patients who have myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).

About 80% of COVID-19 cases are asymptomatic and mild, and many patients recover within 2–4 weeks. However, severe pneumonia and critical multi-organ failure occurs in 15% and 5% of cases, respectively, and can last for 3–6 weeks [12]. Many COVID-19 survivors suffer from PASC, with the number dramatically increasing as more are infected [13]. Studies have also found that PASC can affect young adults, children, and those who had only mild COVID-19 symptoms that needed neither respiratory support nor hospitalization [14••, 15]. PASC symptoms range from mild (e.g., slight fatigue) to severe disability (ongoing dyspnea, depression, lethargy), affecting the quality of life. Most studies have found that the severity of the disease can lead to worse or prolonged symptoms. However, one study found that this might not be the case, and more studies are needed to investigate this topic specifically [16].

An online survey of 3762 patients was conducted between December 2019 and May 2020 among patients who experienced symptoms consistent with COVID-19 [17]. Seven months after the onset of COVID-19, symptoms of persistent fatigue, post-exertional malaise, and cognitive dysfunction were reported by 77.9%, 71.2%, 56.8%, and 67.5% of patients, respectively. Many were unable to work or required a reduced work schedule compared with prior to infection [17]. In an analysis of 1733 consecutive patients with laboratory-confirmed COVID-19 (see Table 1), 76% of patients reported at least one of the following symptoms 6 months after discharge: fatigue/muscle weakness (63%), difficulty sleeping

Table 1 Summary of reported PASC

Authors	Study setting	COVID-19 sample size (n) Groups (n)	Country/age: range or mean ± SD (years)	PASC (%)	Duration
Arnold et al. [4]	Prospective study of patients hospitalized with COVID-19	110	UK/32-71	Persistence of at least one symptom (74) Breathlessness (39) Fatigue (39) Insomnia (24)	8–12 weeks after admission
Halpin et al. [5•]	Prospective study of survivors discharged from hospital using telephone screening tool	100 - ICU group (32) - Ward group (68)	UK/20–93	Fatigue - ICU group (72) - Ward group (60.3) Breathlessness - ICU group (65.6) - Ward group (42.6) Psychological distress - ICU group (46.9) - Ward group (23.5) Swallowing problems - ICU group (12.5) - Ward group (5.9) Laryngeal sensitivity - ICU group (25) - Ward group (11.8) Decline in health status: EQ-5D - ICU group (8) - Ward group (45.6)	4–8 weeks after discharge
Moreno-Peréz et al. [6]	Prospective study of adult patients recovered from COVID-19	277	Spain/42–67.5	Persistence of at least one symptom (50.9) Dyspnea (34.4) Cough (21.3) Fatigue (34.8) Anosmia-dysgeusia (21.4) Myalgias-arthralgias (19.6) Neurological symptoms: headaches, memory disorders/cognitive deterioration (11.9)	10–14 weeks after symptom onset
Goertz et al. [10•]	Prospective questionnaire of two Facebook groups for COVID-19 patients with persistent complaints and panel of people who registered on Lung Foundation Netherlands	2113	Netherlands and Belgium/37–60	Fatigue (94.9) Dyspnea (89.5) Headaches (76) Chest tightness (75.2) Cough (68.1) Muscle pain (64.7) Sore throat (61.9) Increased body temp: 37–39C (61.2) Pain between shoulder blades (61) Pain/burning feeling in lungs (60.5) Heart palpitations (54.9) Increased resting heart rate (54.6) Dizziness (51.6)	8–14 weeks after symptom onset

Table 1 (continued)

Authors	Study setting	COVID-19 sample size (n) Groups (n)	Country/age: range or mean ± SD (years)	PASC (%)	Duration
				Nose cold (43.9) Burning feeling in the trachea (43.9) Fever (42.7) Ageusia (42.3) Diarrhea (41.1) Anosmia (39.7) Joint pain (38.2) Nausea (36.2) Mucus (36.2) Sneezing (31.6) Hot flushes (25.9)Eye problems (25.7) Ear pain (21.7) Sudden weight loss (18.4) Vomiting (9) Red spots on toes/feet (5.6)	
Carfi et al. [14••]	Prospective study of hospitalized patients upon follow-up	143	Italy/19–84	Persistence of at least one symptom (87.4) Fatigue (53.1) Dyspnea (43.4) Joint pain (27.3) Chest pain (21.7)	60.3 days after symptom onset 36.1 days after discharge
Mandal et al. [15]	Prospective study of hospitalized patients upon follow-up	384	UK/43.8–76	Persistent breathlessness (53) Cough (34) Fatigue (69) Depression (14.6)	52 days after discharge
Townsend et al. [16]	Prospective cross-sectional study of positive SARS-CoV-2 PCR patients	153	Ireland/35–59	Fatigue (48) Failure to feel back to full health (62)	75 days after diagnosis
Davis et al. [17]	Prospective online survey from confirmed or suspected COVID-19 patients from 56 countries with symptoms beyond 90 days	3762	56 countries/18+	Fatigue (77.91) Headaches and related symptoms (50.61) Brain fog (56.85) Palpitations (40.99) Insomnia (42.54) Joint pain (34.43) Memory issues (49.39) Muscle aches (40.71) Shortness of breath (37.94) Speech/language issues (35.17) Dizziness/vertigo/unsteadiness or balance issues (35.25) Tightness of chest (33.54) Breathing difficulty (27.10) Changes to sense of smell and taste (23.43) Chills/flushing/sweats (26)	7 months after symptom onset
Huang et al. [18••]	Prospective ambidirectional cohort study of discharged patients	1655	China/47–65	Persistence of at least one symptom (76) Fatigue or muscle weakness (63)	6 months after symptom onset

Table 1 (continued)

Authors	Study setting	COVID-19 sample size (n) Groups (n)	Country/age: range or mean ± SD (years)	PASC (%)	Duration
				Sleep difficulties (26) Hair loss (22) Smell disorder (11) Palpitations (9) Joint pain (9) Decreased appetite (8) Taste disorder (7) Dizziness (6) Diarrhea or vomiting (5) Sore throat or difficult to swallow (4) Skin rash (3) Myalgias (2) Headaches (2) Anxiety or depression (23, n=1617) Pain or discomfort (27, n=1616)	
Chopra et al. [19]	Prospective observational cohort study of discharged patients with telephone survey	488	USA/50–72	Persistence of at least one symptom (33) Persistent loss of taste or smell (13) Cough (15) Shortness of breath/chest tightness/wheezing (17) Difficulty ambulating due to chest problems (9) Breathlessness walking upstairs (23)	60 days after discharge
Carvalho-Schneider et al. [20]	Prospective follow-up of patients with noncritical COVID-19 with confirmed PCR	130	France/49 ± 15	Persistence of at least one symptom (55) Dyspnea/shortness of breath (7.7) Chest pain (13.1) Flulike symptoms (21.5) Diarrhea (33.3) Weight loss (17.2) Anosmia/ageusia (22.7) Palpitations (10.9) Arthralgia (16.3)	2 months after symptom onset
Garrigues et al. [21]	Prospective follow-up assessment of hospitalized COVID-19 patients	120	France/64.2 ± 15.7	Fatigue (55) Dyspnea (42) Loss of memory (34) Concentration disorders (28) Sleep disorders (30.8)	110.9 ±11.1 days after admission
Tenforde et al. [11]	Prospective follow-up of symptomatic outpatient COVID-19 with confirmed PCR	292	USA/31–54	Cough (43) Fatigue (35) Shortness of breath (29)	2–3 weeks after positive PCR test
Petersen et al. [46]	Prospective study of both hospitalized and outpatient PCR positive COVID-19	180	Faroe Islands/39.9 ± 19.4	Persistence of at least one symptom (53.1) Loss of smell (24.3) Loss of taste (16.4) Fatigue (23.9) Headaches (7.3)	45–153 days after symptom onset

Table 1 (continued)

Authors	Study setting	COVID-19 sample size (n) Groups (n)	Country/age: range or mean ± SD (years)	PASC (%)	Duration
Townsend et al. [113]	Prospective study of positive SARS-CoV-2 PCR patients	128	Ireland/49.5 ± 15	Persistent fatigue (52.3)	10 weeks after symptom onset

(26%), hair loss (22%), impaired smell and taste (11% and 9%, respectively), and trouble with mobility (7%) [18••]. There was higher risk of fatigue or muscle weakness, pulmonary diffusion abnormalities, and anxiety or depression in severely ill patients. Similar observations have been corroborated in multicenter studies in the USA [19] and other countries [20, 21]. Investigators from Italy [14••] and other countries have reported a high prevalence of lasting systemic symptoms following diagnosis with COVID-19, which have been observed more frequently among survivors who received ICU care.

In a telephone survey of 100 hospitalized COVID-19 patients discharged at least 4 weeks prior, most patients in the survey experienced persistent symptoms [5•]. About 72% of 32 patients who had been in the ICU reported fatigue compared with 60.3% in the non-ICU group. This suggests that PASC symptoms are not solely reflective of disease severity or ICU stay. Other common symptoms included dyspnea (65.6% in the ICU group and 42.6% in the non-ICU group) and psychological distress (46.9% in the ICU group and 23.5% in the non-ICU group). A decline in health status was reported by 8% of patients in the ICU group and 45.6% in the non-ICU group, as measured by the EQ-5D instrument [5•]. A multi-state telephone interview of 274 patients with mild SARS-CoV-2 also found that the majority had persistent symptoms [11]. The most common symptoms included cough (43%), fatigue (35%), and dyspnea (29%). About 57% of patients with ≥3 chronic conditions reported not returning to their baseline state of health and 47% of patients ≥50 years reported not returning to their normal state of health [11].

Post-COVID-19 Fatigue Syndrome and ME/CFS

There are concerns about possible long-term sequelae resembling ME/CFS among COVID-19 patients. Understanding the potential mechanisms of pathogenesis and management strategies in ME/CFS patients is essential for the development of preventive and early treatment methods for "post-COVID-19 fatigue syndrome" [22].

ME/CFS is defined as persistent or relapsing fatigue that cannot be explained by other medical or psychiatric conditions, which has been present for at least six months, is not alleviated by rest, and causes a substantial reduction in the activity of daily living (ADL) [23]. ME/CSF remains a puzzling disease after more than two decades of research [24]. Cognitive dysfunction, depression, and prolonged fatigue are related to ME/CFS [25]. Patients with post-viral fatigue syndromes share a group of symptoms with ME/CFS patients. Substantial evidence supports the role of infection as a trigger of ME/CFS [26, 27] and post-viral fatigue syndrome as a possible subset of ME/CFS [28]. Previous studies suggested that CFS might be due to a non-pathogenic virus gaining access to the brain [29].

Historically, the symptoms of ME/CFS have been reported during earlier pandemics, including the influenza pandemics of 1889 and 1892 (Russian flu), the Spanish flu pandemic (1918–1919), and diphtheria (1921) [30]. Post-infectious fatigue syndrome is described in different infectious agents including SARS [31], Epstein-Barr virus (EBV) [32, 33], parvovirus [34], West Nile virus [35], Enteroviruses [36], Coxiella burnetii [37], human herpesvirus-6 [38], Ross River virus [33], Dengue virus [39], Ebola virus [40], Mycoplasma pneumoniae [41], Borrelia burgdorferi [42], and even parasites such as Giardia lamblia [43]. According to the literature, ME/CFS prevalence in the USA is estimated to be between 800,000 and 3.4 million [44], and rates following viral infections vary by diagnostic techniques, population group, and case definitions [45].

In ME/CFS, a well-defined identification of a viral agent has not been made. In the case of COVID-19, we can actually try to trace the biology to get clues that will help us understand and treat patients with PASC and, potentially, people with ME/CFS. In the case of SARS-CoV-2, we have a well-identified etiologic agent that should be very helpful in allowing us to understand ME/CFS pathophysiology. Like other viral agents, it is not surprising that SARS-CoV-2 may lead to post-infectious syndromes such as chronic fatigue. However, the rate of post-COVID fatigue appears much higher than those previously reported for EBV, Q-fever, and Ross River virus infection at a similar interval [33], with 1 in 4 post-COVID patients meeting CFS diagnostic criteria at 1 year [31, 46, 47]. The earlier post-H1N1 pandemic studies had similar findings [48]. A study by Magnus et al. about the H1N1 pandemic in Norway suggested that H1N1 infection was associated with a more than a twofold risk of CFS/EM [48].

Following SARS infection in 2009, Lam et al. reported a 27.1% incidence of ME/CFS among SARS survivors [47]. Tansey et al. confirmed high risk, long-term fatigue, and sleep disturbances among SARS survivors [49]. SARS-CoV-2 has a 79% genetic similarity to the SARS virus [50], where fatigue incidence could reach up to 80% in the first month and 53% about 2 months after infection [49].

What Causes Post-Infectious Fatigue Syndromes and ME/CFS in COVID19 patients?

Understanding the etiology and pathophysiology of classic ME/CSF is complicated by its broad heterogeneity but might share similar characteristics with COVID-19 induced ME/CSF [51, 52]. Multiple models have been proposed to explain the pathogenesis of ME/CFS [26, 53, 54]. The literature suggests several potential contributing factors that may play a role in the pathophysiology of the disorder, including the persistence of viral infection, immune dysregulation, mitochondria dysfunction, changes in microbiome composition, autonomic nervous system imbalance, and alterations of neuroendocrine and brain function [55, 56]. At present, however, none of these models has been proven to be accurate, and attempts to treat ME/CFS with antiviral drugs have been uniformly unsuccessful [57]. There might be some changes in the immune system in patients with ME/CFS; for instance, it is observed that in this group of patients, the function of NK (Natural killer cells) is impaired [58] and it is also reported the number of CD8+ T cells and B cells are increased [59, 60]. There are inconsistent reports on cytokine levels [61, 62]. In one observational study on adolescents with EBV infection, elevated levels of interleukin (IL)-2, IL-6, IL-8, IL-23, and interferon (IFN)γ were seen in patients with CFS. Still, these cytokines were not elevated in patients without ME/CFS [27]. CFS patients also had a significantly higher level of IL-8 and a lower level of IL-23. Several investigators hypothesized an immune signature could be detected by antibody profiling in ME/CFS patients [63, 64]. Few studies showed that in most cases with ME/CFS, especially in the early stages of the disease, T cells and cytokines levels are higher than the control group [61, 65], which could be the hallmark of CFS. It is essential to distinguish ME/CFS from the broader mix of related and unrelated conditions. Some conditions like fibromyalgia (FM) and postural orthostatic tachycardia syndrome (POTS) have substantial symptomatic overlap with ME/CFS [66, 67]. However, there is no evidence to indicate that approved FM and POTS drugs such as pregabalin, duloxetine, and milnacipran effectively treat ME/CFS [68]. This supports the notion that ME/CFS has unique pathophysiology.

The immune response to COVID-19 shares several characteristics with the classic pattern seen in ME/CFS [69]. Loss of plasmacytoid dendritic cells and basophils and T cell depletion, mainly CD8+ and γδT cells, are important features of the COVID-19 immune response. The expressions of cytokines, mainly IL-6-, IL-10-, and IFNγ-induced protein 10 (IP-10, previously CXCL10), are increased, and their expression is closely correlated with disease progression [70]. IP-10 is of particular interest because its concentrations frequently remain elevated throughout the COVID-19 response similar to in ME/CFS patients [61]. Higher levels may indicate that the immune system is dealing with a greater challenge that is more likely to result in severe symptoms. However, with the lack of large and long-term longitudinal studies in COVID-19 patients, it is impossible to establish whether the reported immunological responses in the acute phase evolve over time or are correlated with long-term sequelae. The inflammatory state seen in COVID-19 patients might persist, unabated, for decades. Adipokines (leptin and resistin) have been proposed as mediators and perpetrators of chronic inflammatory diseases [71]. Several studies show that COVID-19 patients show higher levels of leptin [72, 73] and resistin [74, 75], which were identified as being important biomarkers of the immune

response during COVID-19 infection. Thus, it is biologically plausible that changes in adipocyte tissue (in the bone marrow and/or peripheral tissues) linked to increased production of these adipokines may be a factor in the propagation of an inflammatory state in PASC.

Mitochondrial dysfunction, metabolic alterations with an increase in glycolysis, and high cytokine levels in peripheral blood mononuclear cells were demonstrated in patients with COVID-19 [76]. This is similar to other independent studies that identified ME/CFS as a hypometabolic state with impairment in multiple metabolic pathways [77] and potentially as a mitochondrial disease due to the increased mitochondrial damage, reductions in ATP production, and impaired oxidative phosphorylation [78]. Mitochondrial function in COVID-19 infected patients is impaired, and these patients cannot produce their required energy by this pathway. Therefore, glycolysis is increased to compensate for high energy demands. This is associated with a higher inflammatory response [76]. Inflammasome activation leads to the production of pro-inflammatory cytokines (IL-1β and IL-12) and predisposition to pyroptosis [79]. Cell-free mitochondrial DNA released after pyroptosis further aggravates local and systemic inflammation [80]. Further research in this area could also provide new insights into the understanding of post-COVID-19 chronic fatigue.

Recently, CFS/ME was correlated with microbial signatures of dysbiosis in the intestinal microbiota [81]. In COVID-19 patients with lower post-convalescence richness, microbiota status was not restored to normal levels 6 months post-COVID-19 [82]. There is growing evidence that gut dysbiosis is associated with the recovery process of COVID-19. Targeted manipulation to promote microbial diversity could be an important strategy for treating PASC and enhancing recovery [82]. Similar to ME/CFS [54], it has been hypothesized that COVID-19 affects the autonomic nervous system [83]. The cytokine storm response of COVID-19 results from sympathetic activation inducing pro-inflammatory cytokine release [84, 85]. On the other hand, COVID-19-related autonomic dysfunction could be mediated by the virus itself into an immune-mediated neurological syndrome associated with autoantibodies (i.e., α-/β-adrenoceptors and muscarinic receptors autoantibodies) [86].

It is known that SARS-CoV-2 is a neurotropic virus that can infect and replicate in neuronal cell cultures, brain organoids, and murine brains [87–89]. Edema and neuronal degeneration along with the SARS-CoV-2 genome have been identified in the hypothalamus and pituitary tissues on autopsy studies [90]. COVID-19 has a high affinity for angiotensin-converting enzyme 2 (ACE2) receptors and potentially targets any tissue expressing ACE2, including hypothalamic and pituitary glands. Therefore, the hypothalamic-pituitary-adrenal (HPA) axis could be affected by SARS-CoV-2. Biochemical evidence of a high percentage of HPA axis involvement with central hypocortisolism and low dehydroepiandrosterone sulfate, most of which resolved within a year, was first reported by Leow et al. in SARS patients [91]. Based on this observation, the authors suggested a transient hypothalamo-pituitary dysfunction as the result of hypophysitis or direct hypothalamic damage [91].

COVID-19 patients have many different neuropsychiatric and neurological complaints such as headaches, changes in the smell and taste senses, fatigue, and myalgia. Cognitive and mood impairments are also frequently seen in these patients [92••, 93]. These neurological signs and symptoms are even seen in patients with mild COVID-19 symptoms, which suggests brain involvement happens in the early stages of COVID-19 [94]. Islam et al. suggested that the increase in cytokine levels such as IL-2, granulocyte-colony stimulating factor, and IP-10 may contribute to the development of long-term fatigue [95].

The brainstem has a relatively high expression of ACE2 receptors, and possibly neuropilin-1, a protein that SARS-CoV-2 exploits for cell infection [96]. Young et al. hypothesized that long COVID might be related to persistent brain stem dysfunction and may be an overlooked aspect of PASC [96]. The brainstem may be affected in the early disease phase causing a compromise in respiratory, cardiovascular, gastrointestinal, and neurological function. Brainstem dysfunction has also been implicated in other chronic disorders such as migraine, chronic pain, and ME/CFS [96].

Psychological Impact of COVID-19

Social isolation, separation from loved ones, freedom loss, and helplessness have affected the global population during the pandemic [97], potentially leading to dramatic consequences such as the rise of suicides. An increasing number of young and previously fit and healthy people who did not require hospitalization continue to have symptoms months after mild COVID-19 cases. A recent survey administered during the COVID-19 pandemic has shown children and young adults are particularly at risk of developing anxiety [98–100]. Health care workers are another group particularly affected by the pandemic and stress [101]. Women are more likely to be affected by anxiety, depression, and distress [102] related to childcare issues, job loss, etc. Patients' cognitive and behavioral responses to COVID-19 and its persistent symptoms are important risk factors of long-term health issues. Therefore, pharmacological and non-pharmacological interventions for cognitive enhancement should be considered [103]. These interventions should help COVID-19 patients learn how to efficiently save energy during their routine activities, to understand their physical limitations before experiencing a worsening of their symptoms, to have better relaxation techniques, and to improve their quality of rest [104].

COVID-19 and dementia have many risk factors in common, including possession of *APOE* ε4, age, gender, hypertension, diabetes, and obesity [105]. Cognitive follow-up of COVID-19 patients will be important, especially in patients who develop neurological complications during the acute phase.

A Proposal for PASC Diagnostic Criteria in Patients with Long-term Neurological Manifestations (Neuro-PASC)

To refine guidelines for the management of patients with PASC and to characterize the long-term neurological manifestations, large-scale and multidisciplinary collaborations are needed [106]. Many have been already initiated worldwide, such as those funded by the European Academy of Neurology, the National Institute of Neurological Disorders and Stroke, the Environmental Neurology Specialty Group of the World Federation of Neurology, and Neurocritical Care Society [106–109]. However, their approaches need to be standardized, and case definitions should be used consistently across studies. Unfortunately, the clinical characterization of PASC is inadequate and, therefore, to refine guidelines for the management of COVID-19 patients with long-term neurological complications and to characterize their long-term neurological manifestations, we need a unique operational case definition to use consistently across large-scale and multidisciplinary studies.

To determine if COVID-19 is the main cause of PASC, the symptoms should appear after a confirmatory diagnosis of SARS-CoV-2 infection. However, the prevailing problem is that millions infected by SARS-CoV-2 never received a positive diagnosis due to various reasons, such as lack of access to health care or not seeking health care due to mild or no symptoms from acute infection. In neuro-PASC, we suggest including patients with the persistence of neurological symptoms beyond 3 or 4 weeks from the onset of acute symptoms of COVID-19, as replication-competent SARS-CoV-2 approaches zero after 3 to 4 weeks [56, 110, 111]. We propose the following diagnostic criteria, as summarized in Fig. 2, for an operational diagnosis of neuro-PASC. The persistence of neurological symptoms or development of sequelae due to SARS-CoV-2 infection should persist beyond 4 weeks from the onset of acute symptoms. The neurological symptoms and abnormalities present from 4 to 12 weeks beyond the acute phase of COVID-19 represent subacute neuro-PASC, while neurological symptoms and abnormalities persisting or present beyond 12 weeks and not attributable to alternative diagnoses represent chronic neuro-PACS [110, 111].

Even mild COVID-19 can result in PASC, specifically post-viral fatigue in about 30–80% of cases. Although post-viral fatigue is mostly a self-limited condition, cognitive, biological, and social risk factors can put these patients at risk of having chronic conditions. Previous studies showed that the severity and duration of the acute viral infection were the main biological determinants of the risk of chronicity [104, 112]. However, recent studies on COVID-19 show a lack of association with the severity of initial infection [6, 16, 113]. This has notable implications on identifying the potential PASC and the burden on public health systems [16, 113]. It also further emphasizes the need for screening all patients diagnosed with COVID-19 for PASC.

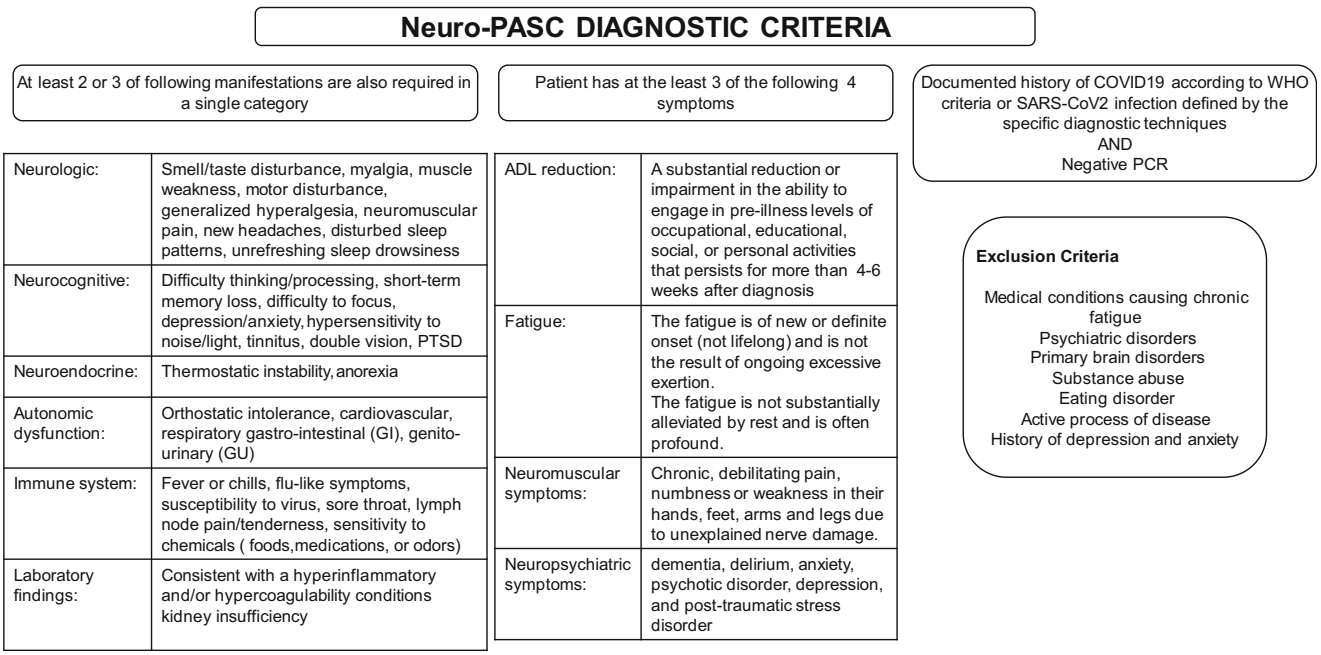

Fig. 2 Proposed neuro-PASC diagnostic criteria

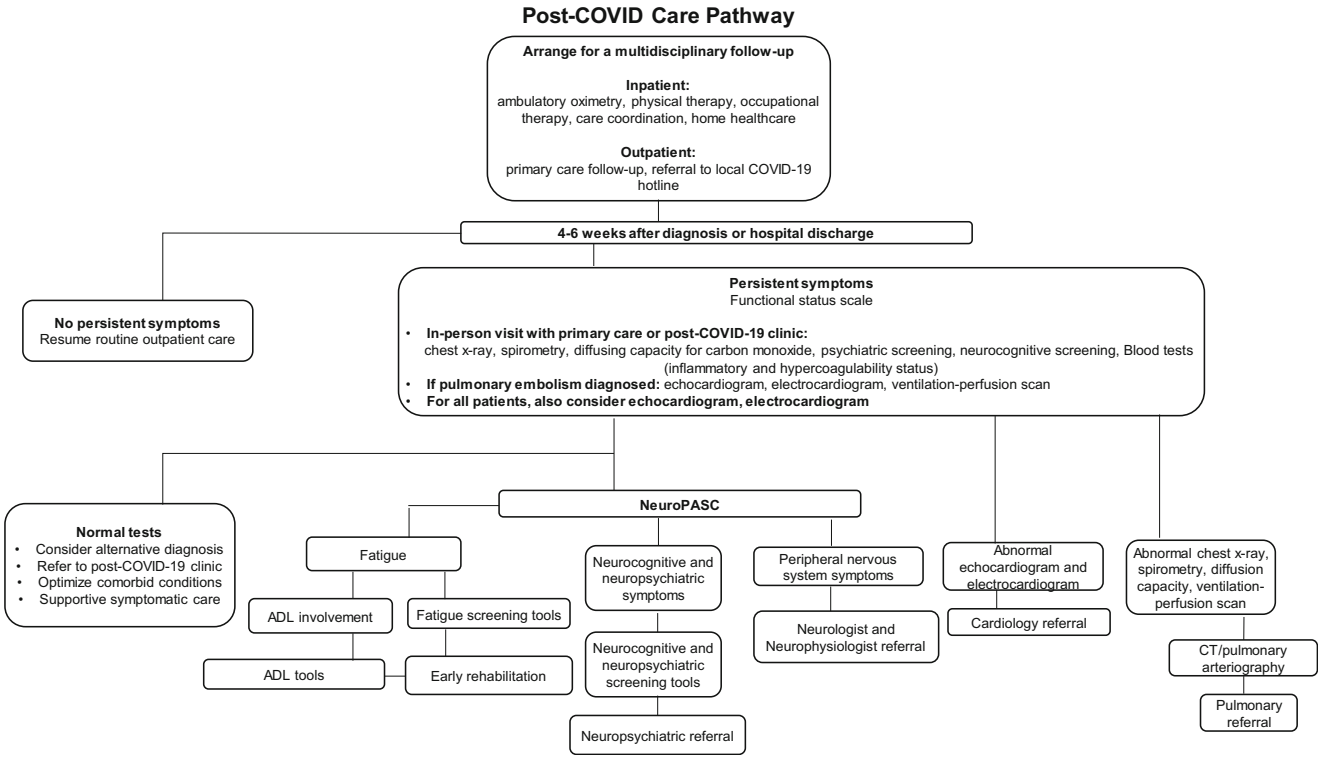

Fig. 3 A proposed post-COVID care pathway for patients with suspected neuro-PASC

In some patients with persistent fatigue following COVID-19, damage of the kidney, lung, and heart may be a sufficient explanation for their chronic fatigue [114]. A chronic low-grade neuroinflammatory response could explain post-COVID fatigue in some patients even in the absence of underlying cardiac, renal, and pulmonary conditions [108]. Advanced age is associated with increased fatigue and higher rates of chronic inflammation, often termed *inflammaging* [115, 116]. Clinical outcomes of COVID-19 are significantly worse in older patients and those with comorbidities such as cardiovascular disease, pulmonary disease, diabetes, hypertension, malignancy, and immunosuppression [117, 118]. Tenforde and collaborators have also shown the same aforementioned risk factors were associated with prolonged illness in an outpatient population [11]. Nearly one out of five young adults (18–34 years old) reported they could not return to their previous routine and normal life 14–21 days after their COVID-19 test was positive. This number was significantly different in influenza survivals as 90% of patients returned to their previous state of health 2 weeks after the positive test [119]. There is also some evidence supporting a weak genetic linkage indicating the potential for offspring of classic ME/CFS patients to be at elevated risk for the disease, which might help in understanding the possible genetic potential in COVID-19 induced ME/CSF in some patients [120].

Although some studies show the association between previous history of depression and development of severe fatigue [113, 121], other studies did not show any correlation [33]. Another strong risk factor for long-term fatigue is psychological distress during the acute and subacute phases of the viral infection [122]. Social distancing and isolation, social and economic challenges including anxiety, childcare issues, and job security, as well as elderly relatives' health concerns, etc. during COVID-19, could potentially cause more physical and psychological stress and fatigue compared to other infections [104, 123].

A Follow-up Clinical Pathway for PASC Patients with Long-term Neurological Manifestations

We propose a clinical-care pathway for patients with PASC (shown in Fig. 3). COVID-19 patients with long-term neurological manifestations should be referred to a multidisciplinary clinic. Ancillary blood tests should be ordered selectively. For example, anemia should be excluded in a patient with breathing difficulty. The British Thoracic Society proposed guideline on follow-up for COVID-19 patients with significant respiratory illness recommends a follow-up chest X-ray at 12 weeks and referral for new, persistent, or progressive symptoms (see https://www.brit-thoracic.org.uk/document-library/quality-improvement/covid-19/resp-follow-up-guidance-post-covid-pneumonia/). A post-COVID-19 functional status scale has been developed pragmatically but not formally validated [124]. Pulse oximeters may be extremely

useful for assessing and monitoring respiratory symptoms after COVID-19 with no evidence that their home use leads to increased anxiety [125]. Close to 50% of COVID-19 patients who required hospital admission had hypoxia on exertion without subjective dyspnea at the time of discharge. Some of these patients even did not have chronic lung disease. One-third of patients who were unable to complete the 6-Minute Walk Test had pulmonary embolism [126]. The 6MWT represents a useful tool for the evaluation of silent hypoxia to assess the cardiopulmonary reserve and to predict the anaerobic threshold representing a marker for combined efficiency of the lungs, heart, and circulation and marks the onset of anaerobic metabolism as a result of inadequate oxygen delivery. Ortelli et al. proposed fatigue assessment in post-COVID-19 patients by using neuropsychological and neurophysiological scales, including the Fatigue Severity Scale (FSS), Fatigue Rating Scale, Beck Depression Inventory, Apathy Evaluation Scale, cognitive tests, and computerized tasks [127]. Workup for chest pain on COVID-19 patients should be the same as other patients present with chest pain: a complete and comprehensive history including past medical history, personal and family risk factor assessment for cardiovascular events, physical examination, electrocardiography, echocardiography, chest computed tomography, and other imaging modalities such as cardiac magnetic resonance if clinically indicated [128].

What Can Be Done?

The United States Congress recently appropriated $1.15 billion to the NIH over the next 4 years for research and clinical studies related to the long-term effect of COVID-19. Patients experiencing long-term symptoms following acute COVID-19 infection are increasingly meeting criteria for ME/CFS suggestive of similar pathological processes. Furthermore, the potential benefits of the scientific insights gathered from years of treating ME/CFS for the emerging PASC have been discussed in the literature [129].

Unfortunately, the majority of patients with ME/CFS may not fully recover and do not return to their previous state of health. Also, one-third of patients may become bedridden or housebound [130]. The economic burden of ME/CFS is substantial, with unemployment rates in the range of 35–69%. The annual cost of ME/CFS is estimated at $18–$24 billion in the USA [131, 132]. Currently, there is no definitive treatment for ME/CFS [52, 57]. Therapeutic approaches to ME/CFS can be categorized into central nervous system drugs, antivirals, immunomodulators, analgesics, and nutritional supplements [132]. Antidepressants remain one of the most commonly prescribed classes of medication for ME/CFS [132]. The monoamine oxidase inhibitor moclobemide in a randomized clinical trial (RCT) showed improvement in symptoms, but the difference was not statistically significant [133]. Using methylphenidate (Ritalin) in another double-blinded study provided statistically significant improvement in fatigue score [134]. Ongoing studies assess the benefits of low-dose methylphenidate and mitochondrial support nutrients (called KPAX002), including acetyl-L-carnitine, α-lipoic acid, and *N*-acetyl-cysteine [135]. Studies of antivirals treatment of ME/CFS can be found dating as far back as 1988 [136]. Unfortunately, none of the studies had an adequate sample size [68]. Rintatolimod (a restricted toll-like receptor 3 [TLR3] agonist) has been found to increase the function of NK cells in ME/CFS patients [137, 138]. The anti-IL6 antibody anakinra [139] and the anti-CD20 B cell depleting antibody rituximab failed to show effective response in large clinical trials [140]. Prospective cyclophosphamide trials have been reported as a potential role of autoimmunity in ME/CFS [141]. The use of steroids for treatment of ME/CSF has been shown to be ineffective [68, 142, 143]. Opioids and their derivatives such as morphine and naloxone are minimally effective [144]. Gabapentin and pregabalin could be helpful in the management of neuropathic pain in ME/CFS patients [145]. Daily doses of NADH + CoQ10 for 8 weeks showed improved Fatigue Impact Scale total score [146]. In light of new treatments of other autoimmune diseases, Tolle and colleagues' study of immune adsorption/IgG depletion treatment in a small cohort of ME/CFS patients improved symptoms in 7 of 10 patients [147]. Understanding the potential treatment for ME/CFS patients is essential for the early pharmacological treatment methods and future research in post-COVID-19 fatigue syndrome.

The non-pharmacological approaches, such as cognitive-behavioral therapy (CBT), in non-severe ME/CFS patients show limited efficacy. In some patients undergoing CBT report lower fatigue however, the overall physical activity does not increase [148]. The UK National Institute for Care and Health Excellence (NICE) recently indicates that graded exercise therapy (GET) should no longer be considered a treatment for ME/CFS [149]. The current advancement in treating ME/CFS will be helpful in further research in the treatment of patients with PASC, specifically patients with lingering chronic fatigue. Young suggests using pharmaceutical and non-pharmaceutical treatments currently used for similar conditions such as ME/CFS, postural orthostatic tachycardia syndrome, and mast cell activation syndrome to treat PASC [150]. We propose a summary of supplements that might be helpful in PASC (see Table 2). However, further research is required to see if these supplements are helpful in PASC to arrive at a definite treatment plan. In many cases, it appears that psychotropic drugs can be safely prescribed to patients receiving pharmacotherapy for COVID-19. For example, antidepressants (e.g., escitalopram), antipsychotics (e.g., olanzapine), benzodiazepines (lorazepam), and valproate do not seem to interact with antiviral agents such as interferon, lopinavir-ritonavir, and ribavirin [151].

Table 2 Proposed supplementations treatments for PASC

Drug	Dose (adults)	Remarks
Coenzyme Q10 (It is available in reduced form called ubiquinol and oxidized form ubiquinone. Reduced form has better bioavailability and is preferred)	Ubiquinol, 60–600 mg daily in 2 divided doses; ubiquinone, 300–2400 mg in 2–3 divided doses	Co Q10 is integral part of the mitochondrial electron transport chain; CoQ10 supplements are considered to enhance the efficiency of the electron transport chain.
Riboflavin (vitamin B_2)	50–400 mg daily in 2–3 divided doses	Riboflavin is precursor of flavoprotein, which is one of the building blocks of complexes I and II.
Alpha lipoic acid	300–600 mg/day	Alpha lipoic acid acts as an antioxidant scavenging the toxic ROS formed in excess in mitochondrial dysfunction.
Vitamin E	100–200 IU daily	Vitamin E acts as an antioxidant scavenging the toxic ROS formed in excess in mitochondrial dysfunction.
Vitamin C	50–200 mg daily	Vitamin C acts as an antioxidant scavenging the toxic ROS formed in excess in mitochondrial dysfunction.
L-carnitine	1000–3000 mg per day in 2–3 divided doses	L-carnitine facilitates entry of long chain fatty acid in mitochondria for oxidation and removes toxic acyl compounds.
L-creatine	2–10 g daily divided in 3 doses	Creatine phosphate acts as intracellular buffer for ATP.

Conclusion

The COVID-19 pandemic has been a tragedy and has devastated the health and financial well-being of many around the world. An unprecedented effort is underway to understand, prevent, and treat PASC. Non-hospitalized young adults and patients with no or few chronic underlying medical conditions might not perceive COVID-19 as a prolonged disease. Therefore, public health educational protocols should also target these populations. People experiencing PASC symptoms are increasingly meeting the criteria for ME/CFS. Approaches to ME/CFS therapy under investigation targeting specific molecular or cellular irregularities associated with ME/CFS, such as autoantibodies, immune dysregulation (e.g., NK cell function), or mitochondrial dysfunction, could potentially help in treating patients with PASC.

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Declarations

Conflict of Interest Narges Moghimi, Mario Di Napoli, José Biller, James E. Siegler, Rahul Shekhar, Louise D McCullough, Michelle S Harkins, Emily Hong, Danielle A Alaouieh, Gelsomina Mansueto, and Afshin A. Divani each declare no potential conflicts of interest.

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- • Of importance
- •• Of major importance

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