

## Frontier Review

# Neurological post-acute sequelae of SARS-CoV-2 infection (PASC)

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Running title: Post-acute sequelae of COVID-19

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## Abstract

The novel corona virus infectious disease, COVID-19, caused by SARS-CoV-2, can have two phases: acute (generally 4 weeks after onset) and chronic (> 4 weeks after onset). Both phases include a wide variety of signs and symptoms including neurological and psychiatric symptoms. The signs and symptoms that are considered sequelae of COVID-19 are termed post-COVID condition, long COVID-19, and post-acute sequelae of SARS-CoV-2 infection (PASC). PASC symptoms include fatigue, dyspnea, palpitation, dysosmia, sub-fever, hypertension, alopecia, sleep problems, loss of concentration, amnesia, numbness, pain, gastrointestinal symptoms, depression, and anxiety. Because the specific pathophysiology of PASC has not yet been clarified, there are no definite criteria of the condition, hence the World Health Organization's definition is quite broad. Consequently, it is difficult to correctly diagnose PASC. Approximately 50% of patients may show at least one PASC symptom up to 12 months after COVID-19 infection; however, the exact prevalence of PASC has not been determined. Despite extensive research in progress worldwide, there are currently no clear diagnostic methodologies or treatments for PASC. In this review, we discuss the currently available information on PASC and highlight the neurological sequelae of COVID-19 infection. Furthermore, we provide clinical suggestions for diagnosing and caring for PASC patients based on our outpatient clinic experience.

## Key words

COVID-19, long COVID, Neurological Disorders, Post-acute COVID-19 Syndrome, SARS-CoV-2

## Introduction

Various neurological and psychiatric symptoms may be present in the acute phase of coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).<sup>1-11</sup> These symptoms include headache, dizziness, encephalopathy, anosmia, dysgeusia, stroke, seizure, peripheral neuropathy, and myopathy.<sup>2, 3, 12</sup> The rate of neuropsychiatric symptoms is reported to range from 3.5% to 84%.<sup>5, 12, 13</sup> However, this wide range may be owing to different methodologies and specialties of physicians caring for patients with COVID-19.

Clinical signs and symptoms that are considered sequelae among individuals who have had COVID-19 are receiving increasing attention in medical and scientific fields. The medical conditions involved include all organs of the body, such as the central and peripheral nervous systems, as well as respiratory, cardiovascular, gastrointestinal, renal, endocrine and metabolic, hematologic, and cutaneous systems.<sup>14</sup> These sequelae are also reported in cases of severe acute respiratory syndrome (SARS; 2002)<sup>15, 16</sup> and Middle East Respiratory Syndrome (MERS; (2012)).<sup>17</sup>

In accordance with the increasing number of affected individuals, these sequelae are becoming a social problem. The signs and symptoms involved include fatigue, dyspnea, palpitation, dysosmia, subclinical fever, hypertension, alopecia, sleep problems, loss of concentration, amnesia, numbness, pain, gastrointestinal symptoms, depression, and anxiety.<sup>14, 17-23</sup> These may develop as a constellation in one patient. Even in children, symptoms may be severe and cause serious clinical

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problems.<sup>24</sup> In some cases, persistent symptoms appear in patients after complete recovery from acute COVID-19 infection.<sup>25</sup> The condition is independently associated with severity of the initial illness.<sup>26</sup> It has been noted that mortality and the use of medical resources during the chronic phase are high.<sup>14</sup>

This group of signs and symptoms are referred to using various names (Table 1). The World Health Organization (WHO) refers to “post-COVID condition,” which is defined as various symptoms such as fatigue, shortness of breath, and cognitive dysfunction lasting more than 2 months within 3 months of COVID-19 onset.<sup>27</sup> The National Institutes of Health (NIH) has named the condition post-acute sequelae of SARS-CoV-2 infection (PASC).<sup>28</sup> Post-COVID-19 Neurological Syndrome (PCNS) is also used.<sup>29</sup> It remains unknown whether this condition is a continuing presentation of the acute phase of COVID-19 or a newly developed pathological condition associated with SARS-CoV-2 infection. In NICE guideline, the term ‘long COVID’ is commonly used to describe signs and symptoms that continue or develop after acute COVID-19. It includes both ongoing symptomatic COVID-19 (from 4 to 12 weeks) and post-COVID-19 syndrome (12 weeks or more) (<https://www.nice.org.uk/guidance/ng188/resources/covid19-rapid-guideline-managing-the-longterm-effects-of-covid19-pdf-51035515742>). We use the term PASC in the present review. Herein, the authors focus on the neurological manifestations of PASC and describe our experiences of PASC in an outpatient clinic at our hospital.<sup>30, 31</sup>

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### Acute central nervous system (CNS) complications

To understand the neurological symptoms of PASC, we summarize the acute neurological presentations of PASC. The clinical stage of COVID-19 is mainly divided into an acute phase (up to 4 weeks after onset) and a chronic phase (more than 4 weeks after onset).<sup>17</sup> In the acute phase, headache, dizziness, encephalopathy, olfactory and taste disorders, stroke, and convulsions have been reported. However, the frequency of clinical neurological complications varies widely, ranging from 3.5 to 84%.<sup>5, 12, 13</sup> In a hospital in Strasbourg, France, patients with COVID-19 who were admitted with ARDS had neurological complications in 84% of cases, with agitation (69%), signs of pyramidal tract dysfunction (67%), and executive dysfunction (36%).<sup>5</sup> Among 917 patients with COVID-19 in Wuhan, Chongqing, and Sichuan, China, only 32 (3.5%) had new neurological complications.<sup>13</sup> In a survey conducted by the European Academy of Neurology, the main CNS symptoms were headache (61.9%), loss of the senses of smell (49.2%) and taste (39.8%), disturbance of consciousness (29.3%), psychomotor excitement (26.7%), and encephalopathy and acute cerebral vascular disease (21.0%).<sup>9</sup> In a meta-analysis, headache (20.2%), loss of sense of smell (31.4%), loss of taste (28.1%), disturbance of consciousness (6.1%), and acute cerebrovascular disease (1.4%) were reported.<sup>32</sup>

Meningoencephalitis may be important to understand neurological symptoms in PASC, however, this is uncommon in the acute phase of COVID-19. In the Spanish ALBACOVID study, as many as 57.4% of 841 patients hospitalized with COVID-19 presented with neurological symptoms, but there was only one case of

encephalitis.<sup>33</sup> Although that case showed magnetic resonance imaging (MRI) abnormalities (fluid-attenuated inversion recovery [FLAIR] imaging), there were no abnormal findings in cerebrospinal fluid, and polymerase chain reaction (PCR) for SARS-CoV-2 was negative.<sup>33</sup> Similarly, in a prospective study at NYU Langone Medical Center among 4491 patients with COVID-19, 606 (13.5%) had neurological symptoms, but there were no cases of meningoencephalitis.<sup>12</sup> In a study of 509 patients with COVID-19 admitted to a hospital belonging to Northwestern Medicine Healthcare in Chicago, 42.2% had any neurological complications at COVID-19 onset; this proportion was 82.3% across the entire course of the disease. However, encephalitis occurred in one case (0.2%).<sup>34</sup>

Acute necrotizing (hemorrhagic) encephalopathy and acute disseminated encephalomyelitis have been reported as acute complications of COVID-19.<sup>35-38</sup> Whether these pathologic conditions are caused by direct viral entry into the nervous system or systemic infection requires further research. As with meningoencephalitis, such complications are uncommon after COVID-19 infection. Although cerebrovascular disease is also a complication of acute COVID-19, it is not common, according to large studies.<sup>12, 33, 34</sup> Posterior reversible leukoencephalopathy has also been reported.<sup>39</sup> MRI studies show that cerebral infarcts, leukoencephalopathy, microhemorrhage, and leptomeningeal contrast enhancement are relatively common features.<sup>40</sup> Those findings are consistent with neuropathologic findings in COVID-19.<sup>41</sup>

## Definition of PASC

Although there are no definite criteria for PASC, the WHO definition is as follows:

*Post COVID-19 condition occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others\* and generally have an impact on everyday functioning. Symptoms may be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms may also fluctuate or relapse over time.*<sup>42</sup>

Based on this definition, the clinical presentation must last at least 1 month after COVID-19 infection. Therefore, clinical symptoms during the acute phase of COVID-19 must be excluded. However, it might be difficult to clearly separate PASC symptoms from those in the acute phase of illness. In fact, for patients who show continuing neurological symptoms lasting 1.5 months after COVID-19 onset, there are no scientific tools to discriminate whether each symptom is subacute or can be considered PASC. Therefore, the definition of PASC currently serves as an operational diagnostic criterion. In a recent report, a core outcome set for adults with post-COVID-19 condition (PASC) was proposed using the Delphi method (Figure 1).<sup>43</sup>

According to the WHO definition,<sup>42</sup> PASC may include individuals with probable COVID-19 infection. We consider that this definition may create difficulties in clinical scenarios. We have seen many patients complaining of PASC-like

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symptoms with no clear evidence of COVID-19 infection. One patient claimed to have been diagnosed with COVID-19 based on clinical symptoms but without laboratory confirmation, such as PCR. Most such cases were diagnosed during the early phase of the COVID-19 pandemic in 2020 when PCR testing was difficult because of a lack of diagnostic resources for SARS-CoV-2 in Japan. Additionally, some patients were diagnosed according to their clinical picture, such as symptoms or a history of close contact with a patient who had COVID-19 infection. However, PASC symptoms are non-specific and may be observed in other diseases. Therefore, we believe that caution is needed when diagnosing PASC without clear evidence of SARS-CoV-2 infection. According to a prospective PASC study, 13% individuals without SARS-CoV-2 infection had developed PASC symptoms at the time of study enrollment.<sup>44</sup>

In our outpatient clinic, we conduct SARS-CoV-2 antibody testing, including against spike (S) and nucleocapsid (N) proteins, to identify past infection (Table 2) (<https://diagnostics.roche.com/us/en/products/params/electsys-anti-sars-cov-2-s.html>). Although antibody tests are not perfect, the results are extremely important for treatment planning and discussing the clinical condition with the patient. If there is no evidence of SARS-CoV-2 infection, we immediately consider other clinical conditions and diseases. In recent analysis, anti-N antibody has around 80% sensitivity for identifying previous COVID-19 infection.<sup>45</sup> Therefore, we believe that it is important to evaluate the anti-S and -N antibodies in PASC cases.

## Diagnosis

As mentioned, there are no specific signs and symptoms of PASC. It is therefore important to carefully obtain the clinical history and carry out physical and neurological examinations. It is most important to confirm a history of SARS-CoV-2 infection. As mentioned previously, serological testing for antibodies against SARS-CoV-2 may be helpful in identifying PASC. We have used Elecsys Anti-SARS-CoV-2 S and Elecsys Anti-SARS-CoV-2 (cobas® Roche Diagnostics, Tokyo, Japan) to detect serum antibodies. The former is an antibody against the spike protein receptor binding domain and the latter is against SARS-CoV-2 nucleocapsid antigen. According to the manufacturer, the sensitivity and specificity are high for both antibodies (Table 2).

Laboratory confirmation of COVID-19 infection may provide an adequate medical approach for patients with various clinical symptoms. Because PASC is a heterogenous clinical condition, subclassification of PASC according to clinical and biological features might be important. A machine-learning approach may be a powerful tool for the diagnosis of PASC in the near future.<sup>46</sup>

In our outpatient clinic, we conduct blood examinations such as routine chemical analysis including zinc, hematologic assessment, D-dimer, C-reactive protein, rheumatoid factor, antinuclear antibody, and serum immunoglobulins. Those examination are relatively common and carried out in the study.<sup>44</sup> However, in most patients, there is no specific abnormality. Although we have identified abnormal immunological results in some cases, the interpretation of these results is usually inconclusive. A prospective study found no definite differences in routine

blood tests and autoantibodies between controls and patients with COVID-19.<sup>44</sup>

Robust diagnostic methodologies and biomarkers must be clarified.

## Epidemiology of PASC

According to a study using electronic medical records (TriNetX, a global clinical health care data service) of 273,618 COVID-19 survivors, 57% of patients who have PASC presented with one or more of the following nine symptoms (dyspnea, fatigue, chest and pharyngeal pain, headache, abdominal symptoms, myalgia, other pain, cognitive symptoms, and anxiety/depression) within 6 months after COVID-19 infection. Additionally, 36.55% individuals showed those symptoms between 3 and 6 months after COVID-19.<sup>18</sup> The incidence at each respective time point was reported for abnormal breathing (18.71%, 1- to 180-day period; 7.94%, 90- to 180-day period), fatigue/malaise (12.82%; 5.87%), chest/throat pain (12.60%; 5.71%), headache (8.67%; 4.63%), other pain (11.60%; 7.19%), abdominal symptoms (15.58%; 8.29%), myalgia (3.24%; 1.54%), cognitive symptoms (7.88%; 3.95%), and anxiety/depression (22.82%; 15.49%). All nine symptoms were more frequently present after COVID-19 than after influenza, with an overall excess incidence of 16.60% and hazard ratios between 1.44 and 2.04.<sup>18</sup>

In a meta-analysis, 70% of patients had at least one symptom 6 months after illness onset, and approximately 30% of those infected had neurological symptoms such as olfactory and memory impairment.<sup>47</sup> A recent large meta-analysis of 151 studies including 1,285,407 participants from 32 countries clarified that at least one PASC symptom occurred in 50.1% (95% confidence interval [CI] 45.4–54.8) of patients up to 12 months after COVID-19 infection.<sup>22</sup> The most common signs and

symptoms were abnormalities on lung computed tomography (CT; 56.9%, 95% CI 46.2–67.3) and abnormal pulmonary function tests (45.6%, 95% CI 36.3–55.0), followed by generalized symptoms such as fatigue, pain, and fever (28.7%, 95% CI 21.0–37.0).<sup>22</sup> For psychiatric symptoms including depression, post-traumatic stress disorder, anxiety, and sleep disturbance, the estimated prevalence was 25.7% (95% CI 21.4–30.2). Neurological symptoms including cognitive deficits, memory impairment, loss of taste, olfactory dysfunction, impaired concentration, headache, and dizziness occurred at a rate of 18.7% (95% CI 16.2–21.4).<sup>22</sup>

The prevalence of PASC may be affected by study design such as case selection, methods of analysis, and definitions of each clinical condition. Generally, patients show at least one symptom of PASC up to 12 months after COVID-19 infection.<sup>22</sup>

In a prospective study, PASC symptoms were observed in 13% of individuals without COVID-19 at the time of enrollment.<sup>44</sup> Therefore, careful diagnosis of each patient after COVID-19 infection is needed to detect PASC based on clinical signs and symptoms. We emphasize the importance of evaluating whether a patient's symptoms are associated with COVID-19 or appear without infection. In our personal experiences at our hospital, we identified rheumatoid arthritis in an individual who developed joint pain after COVID-19. Another patient was referred with cognitive decline after COVID-19, but the clinical and laboratory findings were consistent with Alzheimer-type dementia.

From June 2021 to May 2022, we saw 359 patients for PASC at our outpatient clinic. Among them, we identified 199 patients with PASC. The remainder complained of physical problems after COVID-19 vaccination. Patients comprised

99 male and 100 female individuals, with mean age 40 years. The most common chief complaint was olfactory and taste disorders, followed by fatigue, memory impairment, headache, hair loss, and sleep disorders.

The prognosis of PASC has not been clarified and there are no data on the long-term clinical course. According to a prospective longitudinal post-hospitalization cohort study in the United Kingdom (UK), half of patients (48.8%) did not feel fully recovered from COVID-19 at 1 year after infection.<sup>48</sup> At 14–15 months from COVID-19 onset, there is improvement in olfactory and taste disorders, but no change in higher brain dysfunction, brain fog, numbness, dizziness, or headache.<sup>49</sup> Physical and mental health problems in PASC may persist for a long time, with no specific treatment for PASC symptoms at present.<sup>48</sup> Independent risk factors associated with no recovery at 1 year were female sex (odds ratio [OR] 0.68), body mass index 30 kg/m<sup>2</sup> or greater (OR 0.50), and requiring mechanical ventilation (0.42).<sup>48</sup>

## Risks of PASC

Reported risk factors for PASC included severe COVID-19 such as cases requiring intensive care,<sup>19</sup> female sex,<sup>50</sup> and underlying anxiety disorders.<sup>44</sup> In particular, preexisting symptoms may be important in analyzing the risks of PASC. In a prospective study, 13% of controls without COVID-19 infection showed PASC features at the time of study enrollment.<sup>44</sup> Another study reported four risk factors of PASC: type 2 diabetes, SAR-CoV-2 RNAemia, Epstein–Barr virus viremia, and specific autoantibodies such as anti-Ro/SS-A, La/SS-B, Jo-1, P1, IGM-alpha2, and U1-snRNP in cases 2–3 months after COVID-19 infection.<sup>51</sup> In that study,

neurological manifestations of PASC were associated with higher levels of anti-SARS-CoV-2 nucleocapsid protein IgG.<sup>51</sup> The findings may be associated with chronic inflammation, which is one possible mechanism of PASC.

## Pathomechanism of PASC

The mechanism by which CNS symptoms occur in PASC is not yet clear.<sup>17</sup> As mentioned in the review article above,<sup>30</sup> coronaviruses are known to invade the CNS.<sup>52</sup> Porcine hemagglutinating encephalomyelitis virus invades the CNS from the nasal mucosa and tonsils via the trigeminal ganglia or the enteric plexus via the sensory and vagus nerves, resulting in encephalomyelitis.<sup>52, 53</sup> Murine hepatitis virus in rodents also infects the nervous system; strain JHM has a particularly high affinity for the nervous system.<sup>52, 53</sup> The virus replicates in the nasal mucosa and invades the CNS via the olfactory nerve, resulting in acute encephalitis. Demyelinating lesions also occur, and it has been reported that the virus can infect oligodendrocytes.<sup>53</sup> Therefore, it is possible that SARS-CoV-2 invades the CNS of humans and causes neurological disorders including PASC. Although virus detection in the brain is not common,<sup>41</sup> SARS-CoV-2 viral particles can infect the olfactory mucosa and bulbs, as well as the frontal lobes, where the virus may interact with neurons via angiotensin-converting enzyme 2 (ACE2) receptors.<sup>55, 56</sup> Viral particles may also reach the brain via capillary endothelial cells of the brain through systemic blood circulation; SARS-CoV-2 has been detected in capillary endothelial cells.<sup>57, 58</sup>

However, invasion of the brain by virus particles alone does not explain the etiology of PASC. Chronic inflammation may also be important.<sup>59, 60</sup> In fact, some

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cases of PASC have a clinical presentation similar to myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).<sup>59</sup> PASC may develop via similar mechanisms involving neuroinflammation owing to unique signaling pathways and blood–brain barrier dysfunction.<sup>61</sup> Increased interferon  $\gamma$ -induced protein in association with intestinal bacteria, ACE2 receptor-mediated disturbances of the hypothalamus–pituitary–adrenal (HPA) axis, and persistent brainstem disturbances are also postulated.<sup>62</sup> Because patients with PASC show various clinical symptoms in different organs, there may be numerous factors associated with PASC. These include viral persistence in the gastrointestinal tract and brain, persistent inflammation related to an altered homeostatic milieu and organs, persistence of proinflammatory cells, altered cytokine production, altered immunometabolic pathways, altered Fc-dependent signaling, autoimmunity, and hormonal imbalance.<sup>59, 60</sup> In addition to these physiological changes, acute organ injury, such as in cerebrovascular diseases and underlying neuropsychiatric disease, may be involved in the development of complex clinical conditions in PASC.

### Neuropathology of COVID-19

Neuropathological studies are important to understand CNS complications in COVID-19. However, autopsies are rarely performed in Japan. Therefore, it is extremely difficult to accumulate original data, and we must rely on data from other countries. In a study including a small number of cases, meningoencephalitis was observed as infiltration of the brain parenchyma and perivascular areas, mainly by T lymphocytes.<sup>63</sup> There were thrombi in the small vessels and small

infarcts in some cases. However, it is unclear whether these pathologic changes were derived from direct infiltration by a virus or indirectly via the immune system; further investigation is needed.<sup>63</sup> In 43 autopsy cases in Germany, an increased number of astrocytes and infiltration of cytotoxic T cells were observed in the brainstem and cerebellum.<sup>64</sup> In 32 pathological autopsy cases (29 of which were confirmed by PCR and 3 were suspected cases), the presence of SARS-CoV-2 was most frequently confirmed by PCR in the olfactory mucosa, olfactory bulb, oral mucosa, trigeminal ganglia, and medulla oblongata.<sup>55</sup> Electron microscopy findings were suggestive of virus particles in capillary endothelial cells of the brain as well as in the olfactory bulb.<sup>57, 58</sup> In other large autopsy studies, no meningoencephalitis, glial nodules, or viral inclusion bodies were found, including in the olfactory bulb and brainstem.<sup>65</sup> In our autopsy case report of acute COVID-19 infection, we found small infarcts in the brain; however, no viral particles were observed in the brain tissue.<sup>66</sup> A recent review of neuropathologic analyses of COVID-19 summarized that microglial activation, lymphoid infiltration, acute hypoxic–ischemic changes, astrocytosis, brain infarcts, hemorrhage, and microthrombi were relatively common findings.<sup>41</sup> Lee and colleagues suggested that antibody-mediated cytotoxicity directed against endothelial cells is the most likely initiating event leading to vascular leakage, platelet aggregation, neuroinflammation, and neuronal injury in the acute phase of COVID-19.<sup>67</sup>

Based on those reports, there are no definite neuropathologic changes that can explain neurological and psychiatric complications in COVID-19. Pathologic studies are limited and the results differ among reports. Additionally, most cases were in the acute phase of COVID-19, not PASC cases. The NIH established the RECOVER

(Researching COVID to Enhance Recovery) Initiative to analyze the long-term effects of COVID-19. In RECOVER, an autopsy research protocol was developed and published online (<https://recovercovid.org/>). This document describes the precise methodology for full body autopsy, including of the CNS. Future research may reveal the pathomechanism of PASC.

## Representative neurological symptoms of PASC

### General neurological and psychiatric conditions of PASC

A study using TriNetX showed that the incidence of various neurological and psychiatric syndromes such as mood disorders, anxiety, psychiatric disorders, or dementia within 6 months after COVID-19 onset was higher than that after influenza or other respiratory tract infections.<sup>19</sup> When the same data were examined in terms of long COVID, 57% of patients had one or more of nine symptoms (dyspnea, fatigue, chest/pharyngeal pain, headache, abdominal symptoms, myalgia, other pain, cognitive symptoms, anxiety, and depression) within 6 months after COVID-19 infection. Furthermore, 36.55% of patients had some symptoms, even if limited to 90 to 180 days.<sup>18</sup> The symptom frequency is clearly higher than in patients with influenza. It remains to be elucidated whether there is viral infiltration of the CNS in COVID-19 or whether the pathology is mediated by the immune system. In animal studies, transient influenza virus infection has been reported to affect long-term cognitive dysfunction and synapse-related gene expression.<sup>68</sup> Based on autopsy studies, brain pathological findings have not been established.<sup>30, 41, 66</sup> However, the fact that psychiatric and

neurological sequelae are more frequent than after influenza infection may indicate a unique characteristic of COVID-19 infection.

Taquet and colleagues reported additional data for neurological and psychiatric risk trajectories of 2-year retrospective cohort of 1,284,437 cases.<sup>69</sup> Based on the results, risk of the psychiatric disorders returned to baseline after 1-2 months, but cognitive deficit, dementia, psychotic disorders, and epilepsy and seizures increased after 2-year.<sup>69</sup>

### Cognitive dysfunction

Cognitive dysfunction in PASC has been increasingly reported. However, there are few long-term data approximately 2 years after the start of the COVID-19 pandemic. Higher brain function tests have been conducted in cross-sectional studies among hospitalized patients.<sup>70</sup> Attention, verbal fluency, semantic category fluency, and memory and recall were found to be impaired at a higher rate than in outpatients.<sup>70</sup> However, a telephone-based study used the Montreal Cognitive Assessment (a score of less than 18 on a 22-point scale is considered to indicate cognitive impairment) at 6 months after COVID-19 infection.<sup>71</sup> According to the results, less than 12 years of schooling before the onset of COVID-19, Black race, and unemployment were associated with the risk of cognitive impairment.<sup>71</sup> That study indicated that assessment in the pre-symptomatic state is important when examining cognitive status associated with COVID-19 infection.

A recent study revealed that after infection with COVID-19, the cortical thickness of the orbitofrontal cortex, the piriform lobe, or the whole brain showed atrophy compared with pre-onset brain MRI, which has also been associated with cognitive

decline.<sup>72</sup> Possible inflammation of the brain and nervous system degeneration via the olfactory bulb can be considered.

## Brain fog

We consider “brain fog” to be a generic term used to describe a subjective condition in which the patient perceives cognitive decline, lack of mental clarity, and poor concentration.<sup>28, 73, 74</sup> Brain fog is sometimes used to describe the subjective complaints of individuals with ME/CFS.<sup>75</sup> Although some have theorized that the brain pathologic alterations in both conditions are the same,<sup>59</sup> there is no strong evidence that the pathophysiology is identical in both conditions. Many patients who are referred to our outpatient clinic complain of brain fog. Therefore, we must clarify the condition of brain fog using objective methods.<sup>64</sup>

Currently, the specific pathology of the nervous systems, including brain pathology, has not been elucidated to explain cognitive dysfunction in PASC, including brain fog.<sup>41, 64</sup> Several factors may contribute to PASC clinical conditions. These include direct viral infiltration into the brain, damage to small blood vessels in the brain, and so-called inflammation such as microglial activation. According to neuropathologic analysis, the identification of SARS-CoV-2 in the brain is rare.<sup>58, 76</sup> Neuroinflammation in association with mast cells may be the cause of brain fog.<sup>77</sup> Although this condition is associated with mast cell activation syndrome (MCAS),<sup>78,</sup><sup>79</sup> MCAS itself is not a well-established concept. It is speculated that neurogenesis disorders, myelin damage, and inflammation may be a possible cause of PASC.<sup>77</sup>

COVID-19 infection may affect the HPA axis and reduce stress tolerance.<sup>77, 80</sup>

Based on pathological analysis of COVID-19, the adrenal glands show severe

inflammation, with inflammatory cell death as well as adrenal injury.<sup>80</sup> Although such severe cases may not well explain clinical conditions in PASC, dysregulation of the HPA system may be an important factor PASC. Some patients with PASC show low levels of serum cortisol.

In many cases of PASC, there are no specific abnormal findings on brain CT and MRI. Because there are reports of patients with PASC having acute stroke, demyelination, and encephalitis in the acute phase of COVID-19 infection,<sup>8, 12, 33, 34, 81-84</sup> these acute changes may partially become sequelae, or PASC.

Fluorodeoxyglucose–positron emission tomography has been reported to show hypometabolism of the cingulate gyrus in patients with brain fog.<sup>85</sup> Reduction of cerebral blood flow velocity is also reported in individuals with PASC.<sup>86</sup> In contrast, one report stated that cerebral vascular function was not affected in the post-acute phase of COVID-19.<sup>87</sup> In our personal experiences at our hospital, we sometimes see patients who have PASC and showed hypoperfusion in various anatomical areas, particularly the frontal lobes, using single-photon emission computed tomography (SPECT). Because we have no SPECT data for patients before COVID-19 infection, the precise meaning of the results remains unclear. Additional functional studies of the brain in patients with PASC are needed.

Interestingly, a similar brain condition is recognized as mild cognitive dysfunction in individuals with celiac disease and after chemotherapy (chemo brain).<sup>74, 77, 88, 89</sup> Chemo brain is a particularly important clinical condition in cancer survivors,<sup>90, 91</sup> with the condition observed in 17%–75% of survivors.<sup>90</sup> This clinical condition is characterized by dysfunction of short term memory, verbal abilities, and executive

function.<sup>92</sup> The role of chronic central inflammation, including astrocytic and microglial activation, may be important in chemo brain.<sup>92</sup> It is also hypothesized that cytokines and epigenetic reprogramming may be associated with chemo brain.<sup>93</sup> Scientific evidence regarding chemo brain may help with understanding brain fog in PASC.

At present, it is important to carefully evaluate patients who complain of brain fog using multidisciplinary approaches such as routine blood analysis, neuroimaging including functional imaging, and neuropsychological analysis. This includes obtaining a medical history, including psychiatric diseases that may cause so-called brain fog.

### Sleep disorders

Insomnia is a common and predominant symptom seen in PASC.<sup>94-97</sup> Few patients present with sleep disorders alone, and many present with various symptoms such as anxiety, depression, cognitive dysfunction, and olfactory dysfunction at the same time. The prevalence of sleep disturbance varies, and a recent meta-analysis showed that 12.3% of patients reported insomnia for 6 to 12 months after COVID-19 infection.<sup>22</sup> However, a low rate (1.4%) of insomnia in PASC has also been reported from a prospective study in India.<sup>98</sup>

The causes and risks of insomnia have not yet been clarified. One study indicated that the preexistence of hypertension may be associated with sleep disturbance in PASC.<sup>99</sup> The presence of hypothyroidism and hypoxia in the acute phase of COVID-19 are reported PASC risks, including insomnia.<sup>98</sup> Some of our patients showed cerebral hypoperfusion on SPECT images. However, the patterns of hypoperfusion

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vary among patients. Particularly in cases of cognitive dysfunction or brain fog, we cannot link hypoperfusion to insomnia without SPECT images from each patient before COVID-19 infection for comparison. In a study at least 3 weeks after COVID-19 infection, hypometabolism in the olfactory gyrus and connected limbic/paralimbic regions, including the brainstem and cerebellum, was associated with insomnia.<sup>100</sup>

Based on our experiences of our clinic, some of our patients improve quickly with the use of medication to improve sleep; others are resistant to treatment, and these patients may develop psychiatric symptoms such as anxiety and depression.

Preexisting psychiatric symptoms may worsen sleep disturbance after COVID-19 infection and may affect symptoms of PASC.<sup>101</sup> Collaboration between psychiatrists and neurologists is important in the care of patients with PASC.

### Olfactory dysfunction

It is well known that olfactory dysfunction such as anosmia and dysosmia is a common clinical presentation in the acute phase of COVID-19 as well as in PASC. Olfactory dysfunction or loss of taste or smell may be present in up to 15.8% and 17.1% of patients at 6 to 12 months after COVID-19 infection, respectively.<sup>22</sup> The above systematic review found that anosmia was seen in 23.6% of patients 6 months after COVID-19.<sup>47</sup>

For olfactory disorders, we use a T&T olfactometer (Daiichi Yakuhin Sangyo Co., Ltd. Tokyo, Japan). In the absence of a T&T olfactometer, an intravenous thiamine propyl disulfide (Alinamin) injection test is easy to carry out.<sup>102, 103</sup> A mercaptan (garlic) smell is released when it arrives at the olfactory epithelium via the

nasopharynx.<sup>103</sup> According to our experience, the test must be performed carefully, especially in patients with strong dysosmia, because they may experience a more uncomfortable smell. Patients with dysosmia frequently complain that their normal food smells like gasoline or other unpleasant substances. These patients show poorer improvement in olfaction tests with floral and sweet odors than with putrefaction and fecal odors.<sup>104</sup> We speculate that this difference may be a risk factor and a target for treatment in the future.

The mechanism of olfactory dysfunction remains unclear. Different mechanisms may be present in each patient because the rate of recovery from olfactory dysfunction is very different depending on the patient. These mechanisms include reversible inflammation within the olfactory clefts, downregulation of olfactory receptor proteins, and permanent lesions of the olfactory systems.<sup>105</sup> According to MRI analysis, individuals with olfactory dysfunction show reversible obstruction of the olfactory clefts.<sup>106</sup> These findings may be why some individuals with anosmia owing to COVID-19 can improve completely in a short period. SARS-CoV-2 may cause structural changes in the olfactory neurons and temporarily reduce receptor expression.<sup>107</sup>

MRI studies have reported abnormal signal and atrophy of the olfactory bulbs.<sup>108,</sup><sup>109</sup> However, these results remain controversial.<sup>110, 111</sup> Postmortem analysis shows a loss of myelinated fibers and endothelial injury of small vessels of the olfactory nerve in COVID-19 cases with olfactory dysfunction.<sup>112</sup> The presence of virus is rare in these cases. In these studies, most patients died during the acute phase and not owing to PASC.<sup>112</sup> The association between the olfactory neurons and olfactory

nerves in COVID-19, including inflammatory changes in the olfactory system, remains to be clarified.

## Headache

Most acute-phase COVID-19 headaches are considered tension-type headaches, and many patients show improvement over time.<sup>113</sup> Clearly, we must rule out other acute conditions such as encephalitis, meningitis, and stroke. Prolonged headache is also common in PASC. In one study, the rate of headache was 47.1% at onset or hospital admission, 10.2% at 30 days, 16.5% at 60 days, 10.6% at 90 days, and 8.4% at  $\geq 180$  days after onset/hospital discharge.<sup>114</sup> A meta-analysis showed the rate of headache was 10.9% (3–6 months) and 9.5% (6–12 months).<sup>22</sup>

Inflammation via the trigeminal nerve has been postulated as a possible mechanism of headache.<sup>115</sup> SARS-CoV-2 has been detected in the trigeminal ganglion in autopsy studies.<sup>55</sup> However, there may be a variety of factors associated with headache in COVID-19 cases. If symptoms are prolonged, it may be necessary to confirm the absence of other diseases, including cerebrovascular diseases and brain tumors, rather than attributing these symptoms to PASC.

## Numbness and pain

Patients with PASC often complain of numbness and/or pain in the extremities. Most patients show no abnormal results on nerve conduction studies, and there are no abnormal findings on neurological examination.<sup>116</sup> These results support that large fiber neuropathy is not associated with the condition. In some cases with paresthesia or autonomic dysfunction, skin biopsy reveals the presence of small

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fiber neuropathy.<sup>116</sup> It is important to evaluate each patient for various aspects such as pre-existing diseases (e.g., diabetes mellitus), medications (e.g., anticancer drugs, antibiotics, and antiarrhythmic drugs), or incomplete recovery from autonomic involvement in Guillain–Barre syndrome.<sup>117</sup>

### Postural orthostatic tachycardia syndrome (POTS)

POTS is clinically characterized by lightheadedness, palpitation (“heart racing”), tremulousness, and atypical chest discomfort. Additionally, sleep disturbance, headache, chronic fatigue, exercise intolerance and deconditioning, perceived cognitive impairment, peripheral acrocyanosis (“POTS feet”), frequent nausea, mild diarrhea, constipation, and bloating, or non-specific abdominal pain (“irritable bowel syndrome”) may be present.<sup>118, 119</sup> It is important to confirm the following physical findings; sustained increase in heart rate  $\geq 30$  bpm (older than 19 years) or 40 bpm (younger than 19 years) within 10 minutes of standing when moving from a supine position to upright, and the absence of orthostatic hypotension (decrease in systolic blood pressure  $>20$  mm Hg or diastolic blood pressure  $>10$  mm Hg).<sup>118, 119</sup>

POTS is common terminology among pediatricians, referring to orthostatic dysregulation.<sup>120</sup>

The prevalence of POTS in PASC is unclear.<sup>121</sup> The estimated rate of POTS after COVID-19 infection may be 2-14%.<sup>122</sup> It may be that POTS is overlooked owing to its non-specific clinical symptoms. We must be careful to determine whether patients are experiencing dizziness, headache, fainting, or palpitations.

It is reported that at 6 months, 9% of patients with COVID-19 have palpitations.<sup>97</sup> Another study mentioned that approximately 25%–50% of patients at a tertiary post-COVID multidisciplinary clinic had tachycardia or palpitations lasting 12 weeks or longer.<sup>123</sup> Although not all patients complaining of palpitations have POTS, it is necessary to check blood pressure and pulse rate in the supine and standing positions.

Several etiologies are reported as causing POTS.<sup>119</sup> These include autonomic nerve dysfunction, hyperadrenergic condition, hypovolemic state, autoimmune disease, and physical and cardiovascular deconditioning.<sup>119</sup> The cause of POTS in PASC remains unclear. Autonomic nervous system dysfunction may be associated with SARS-CoV-2 infection.<sup>124, 125</sup> Five cases have been reported in which skin biopsies of young people with POTS after COVID-19 infection showed alpha-synuclein deposition in nerve fibers, as seen in Parkinson's disease.<sup>126</sup> These results may lead to further investigation of SARS-CoV-2 infection and protein accumulation associated with neurodegenerative disorders in the CNS.<sup>127</sup>

## Experiences for PASC clinic of National Center of Neurology and Psychiatry

It might be unusual way to provide our personal experiences in the review paper. Since there have been no rigorous methodologies for diagnosis and treatment for PASC, we believe that our experiences may help physicians to see PASC patients as well as raise the issues for future studies for PASC. PASC has been widely reported in the media. At our outpatient clinic, the number of patients with PASC

has increased. Although some information in the media is sensationalized, we must realize that the specific pathophysiology of PASC has not been clarified.<sup>128</sup> Because patients can obtain information about PASC themselves, clinicians must be careful to evaluate each patient without bias. There is no evidence-based approach for patients with PASC. Herein, we describe the experiences at our outpatient clinic. We usually accept patients at least 2 months after recovery from acute COVID-19 infection.

### Routine examinations

In the initial visit, we obtain patients' clinical history and perform general physical examination and neurological examination in all cases, even if the patient does not have a neurological complaint. It is important to conduct face-to-face examination, including neurological examination as well as listening to heart and respiratory sounds. When shortness of breath persists, it is essential to evaluate for anemia, signs of heart failure, hidden arrhythmias such as atrial fibrillation, and interstitial pneumonia, as well as to check for decreased oxygen saturation with exercise. When joint symptoms are reported, rheumatoid arthritis or other related disorders must be analyzed. For hair loss, we ask the patient to bring photographs of past hair loss; we then check the scalp, and confirm the amount of hair loss.

Patients sometimes complain of "brain fog." However, it is important to recognize that "brain fog" is not a diagnosis. Patients also report "poor concentration" and "poor memory." Patients' subjective symptoms and other findings on examination should be carefully evaluated on a case-by-case basis to determine the pathophysiology. We do not routinely carry out neuropsychological examination for

these patients. To exclude organic brain damage, we recommend brain MRI initially, including MR angiography. In our experience, there are rare cases with obvious abnormalities on head imaging, such as MRI, probably owing to the patient's young age. However, in older patients, we have detected abnormal findings suggesting Alzheimer disease or early changes of other types of neurodegenerative dementia on MRI. When such patients complain of memory impairment, it is important to determine whether the complaint is associated with existing brain diseases or PASC. It is possible that COVID-19 infection may enhance patients' preexisting symptoms. If ischemic or hemorrhagic stroke is observed on MRI, we must consider medical treatment to prevent stroke recurrence as well as treatment of risk factors. Accumulating brain MRI data from patients with PASC may help in understanding the pathomechanism of PASC from various perspectives.

#### Examinations for specific symptoms

In some instances, cerebral perfusion studies may reveal non-specific but predominant frontal or temporal lobe hypoperfusion. It is difficult to judge whether these changes are important owing to a lack of pre-symptomatic data. Although there is no established treatment for this problem, some medications that improve cerebral blood flow may help to improve the condition. At the present, we consider cerebral perfusion study (single photon emission computed tomography) for patients having cognitive problems or brain fog. However, further well-designed studies are required.

Neuropsychological examination is occasionally performed. In some cases, there is no abnormality at all, but in others, some cognitive dysfunction is noted and frontal lobe dysfunction may be present. However, it is well known that even in critically ill patients receiving intensive care, cognitive dysfunction can occur after recovery,<sup>129</sup> so it is always necessary to carefully assess the sequelae of COVID-19.

In addition to basic blood tests, we assess thyroid hormones, zinc, ferritin, antinuclear antibody, rheumatoid factor, and blood sedimentation rate in nearly all patients. Patients with PASC may have electrolyte abnormalities, anemia, thrombocytopenia, low albumin, lipid abnormalities, and abnormal glucose metabolism.<sup>60</sup> However, careful judgment is needed to determine whether an abnormal laboratory test result can explain the symptoms of PASC.

Medical care for anosmia and dysosmia is challenging. Additionally, dysosmia leads to decreased appetite and affects mental conditions. We should first evaluate the level of olfactory dysfunction in all cases having anosmia or dysosmia. Even if patients believe that they have strong olfactory disturbance, the condition may not be severe upon examination. In such cases, explaining the objective results to patients often helps them overcome any anxieties and they can return to normal daily activities.

According to the statement of the Clinical Olfactory Working Group, olfactory training (OT) may be the best methodology according to evidence regarding postinfectious olfactory dysfunction.<sup>130</sup> A classic OT protocol involves twice-daily 5-minute exposure to four intense odors (phenyl ethyl alcohol: rose, eucalyptol: eucalyptus, citronellal: lemon, and eugenol: clove) over a period of 12 weeks.<sup>131-133</sup>

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However, it may be difficult carry out this exact protocol. The classic OT protocol should be modified as needed or the patient referred to an ear, nose, and throat specialist. If the patient is a smoker, stopping smoking should be suggested. There is also some evidence regarding oral and nasal steroid administration.<sup>130, 132, 133</sup> However, systemic steroids may cause serious complications. Nasal steroids can sometimes be used, with administration in the Kaiteki position.<sup>134</sup> Vitamin A drops, sodium citrate, theophylline, and alpha lipoic acid are other possible choices for anosmia or dysosmia; however, the clinical evidence for these options is limited.<sup>130</sup> There is no evidence for the use of minocycline, zinc sulphate, vitamin B, and caroverine.<sup>130, 135</sup> There is no strong evidence that zinc sulfate is beneficial for the prevention and treatment of COVID-19.<sup>136</sup> It is also well known that long-term administration of zinc can cause anemia and neurological disorders owing to copper deficiency, although the frequency is not high.<sup>137, 138</sup> In real-world clinical scenarios, zinc is used for olfactory and taste disorders. When prescribing zinc, patients' serum zinc levels should be measured and their condition evaluated on a case-by-case basis.

Hair loss is another common PASC symptom; however, we are not specialists in hair loss so we refer patients with severe cases to a dermatologist. Hair loss associated with COVID-19 may be temporary telogen effluvium, with a high likelihood of improvement.<sup>139-141</sup> We ask patients to bring photographs to compare the previous and present hair conditions. Although the hair loss is self-limiting, the condition may cause emotional distress in patients. Trichodynia, a painful sensation of the scalp, is also reported in patients with COVID-19 and might be a

PASC symptom.<sup>142, 143</sup> This may be associated with peripheral neuropathology in PASC.

Standard treatment of POTS is well described and established.<sup>144</sup> With a diagnosis of POTS, we first recommend fluid replacement (2–3 liters of water per day, avoiding caffeine and alcohol). Additionally, we try saline infusion, 1–2 liters per day. However, those methods are ineffective in many cases. Beta-blockers, such as propranolol or atenolol, are also used at low doses. It is important to monitor heart rate and blood pressure because many patients with POTS are female individuals whose resting blood pressure is sometimes low.<sup>124</sup>

## Vaccination

According to the US Department of Veterans Affairs national health care database, people with breakthrough SARS-CoV-2 infection exhibit a 15% reduced likelihood of PASC development compared with unvaccinated people.<sup>145</sup> In a prospective study in the UK, one or two doses of vaccine reduced the risk of PASC development.<sup>146</sup> Similarly, a first vaccination was associated with an initial 12.8% decreased odds of PASC and a second shot with an initial 8.8% decreased odds, with a subsequent decrease by 0.8% per week.<sup>147</sup> Another study reported that two or three doses of BNT162b2 vaccine reduced the prevalence of PASC (17.45% for two doses, 16.0% for three doses) compared with no vaccination (41.8%) and one dose (30.0%).<sup>148</sup> One-dose vaccination does not affect PASC symptoms, but two doses reduces symptoms.<sup>149</sup> In contrast, there is no evidence of an effect of SARS-CoV-2 vaccination in PASC symptoms.<sup>150</sup> The effect of vaccination is primarily evident among patients aged <60 years.<sup>149</sup> In a prospective registry study, there

was no difference in the rate of PASC between one and two doses of vaccine and unvaccinated participants.<sup>151</sup>

Our patients with PASC sometimes ask whether they should be vaccinated. These patients are concerned that additional vaccination may worsen their PASC symptoms or believe that additional vaccination is not recommended after COVID-19 infection. We usually recommend additional vaccination in patients with PASC symptoms that are mild and improving. However, we carefully discuss additional vaccination in patients with PASC who are in poor clinical condition. One study reported that vaccination did not worsen PASC symptoms<sup>152</sup> In a study including 380 patients with PASC at the time of vaccination, there was improvement in 21.8% and worsening in 31%,<sup>153</sup> with no differences according to the type of vaccine received.<sup>153</sup> If viral persistence is associated with PASC, additional vaccination for patients with PASC may be effective in improving PASC symptoms.<sup>153</sup>

## Conclusion

Despite the growing evidence regarding the sequelae of COVID-19 infection, a major problem remaining is that specific biomarkers for the diagnosis of PASC have not yet been identified. In many cases, patients are referred from one medical facility to another. Some patients improve after a few months of treatment, but others do not improve and actually worsen. Because many patients present with more than one symptom, a medical system is needed that can care for these patients comprehensively. It is also important to clarify the pathogenesis of this disease by examining a large number of patients. As mentioned, the RECOVER study supported by NIH may provide important information about PASC.

The COVID-19 pandemic is the most devastating and serious since the 1918 influenza pandemic.<sup>154, 155</sup> Although there is no definite evidence of a correlation between the so-called Spanish flu of 1918 and encephalitis lethargica,<sup>156, 157</sup> there is a possibility that autoimmune triggers may be associated with encephalitis lethargica after influenza infection.<sup>156</sup> Similar symptoms of PASC were reported in patients with the so-called Russian flu (1889 and 1892).<sup>158, 159</sup> PASC symptoms occur as sequelae in various viral infections; however, the rate of such conditions is reported to be higher in COVID-19.<sup>62</sup> Although the precise mechanisms are different in each disorder, persistent viral infection of the CNS has long been a focus of attention, i.e., subacute sclerosing panencephalitis with measles virus,<sup>160</sup> progressive multifocal leukoencephalopathy with John Cunningham virus,<sup>161, 162</sup> and human T-lymphotropic virus type 1 (HTLV-1)-associated myelopathy.<sup>163</sup>

Knowledge of PASC increased day by day. Recent studies mentioned SARS-CoV-2 infection in golden hamsters develop inflammatory reaction in the olfactory bulb and epithelium without viral particles.<sup>164</sup> In similar, hamsters and patients deceased from COVID-19 showed microglial activation and expression of interleukin (IL)-1 $\beta$  and IL-6, especially within the hippocampus and the medulla oblongata.<sup>165</sup> Large number and well organized human brain study showed that COVID-19 brain changes are more likely due to blood-borne immune mediators and trans-synaptic gene expression changes arising from the olfactory bulb deafferentation.<sup>166</sup> Further research may clarify the mechanism of PASC and aid in the development of effective treatment strategies.

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## Disclosure Statement

The authors declare no conflict of interest.

## Authors' contributions

MT and MO: conception and design of the study, and drafting and revising the manuscript.

## Figure legend

Figure 1. A core outcome set for adults with post-COVID-19 condition (PASC) using the Delphi method and possible clinical presentations of PASC. Modified from the panel<sup>43</sup> and Table 1<sup>60</sup>.

COVID-19, coronavirus disease 2019; PTSD, post-traumatic stress disorder; POTS, postural orthostatic tachycardia syndrome; GFR, globular filtration rate.

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Core outcome set for adults with post-COVID-19 condition (PASC)

Physiological or clinical outcomes  
 Cardiovascular functioning, symptoms, and conditions  
 Fatigue or exhaustion  
 Pain  
 Nervous system functioning, symptoms, and conditions  
 Cognitive functioning, symptoms, and conditions  
 Mental functioning, symptoms, and conditions  
 Respiratory functioning, symptoms, and conditions  
 Post exertion symptoms

Life impact outcomes  
 Social functioning, symptoms, and conditions  
 Work or occupational and study changes

Representative signs and symptoms

|   |   |
|---|---|
| <p><b>Neuropsychiatric symptoms</b></p> <ul style="list-style-type: none"> <li>Sleep disorders</li> <li>Chronic headaches</li> <li>Olfactory and taste disorders</li> <li>Brain fog</li> <li>Memory loss</li> <li>Decreased concentration</li> <li>Depression</li> <li>Anxiety</li> <li>PTSD</li> <li>Dizziness</li> <li>Vertigo</li> <li>Tinnitus</li> <li>Hearing loss</li> <li>Instability</li> <li>Delirium</li> <li>Hallucinations</li> <li>Small fiber neuropathy</li> <li>Postural tremor</li> <li>Chronic pain</li> <li>Neurodegeneration</li> <li>Myalgia</li> </ul> | <p><b>Cardiovascular symptoms</b></p> <ul style="list-style-type: none"> <li>Nonspecific chest pain</li> <li>Tightness in the chest</li> <li>Palpitations</li> <li>Tachycardia</li> <li>Conduction disturbances</li> <li>Rhythm disorders</li> <li>Orthostatic hypotension</li> <li>Vasovagal syncope</li> <li>POTS</li> <li>Phlebitis</li> <li>Thrombophlebitis</li> </ul> |
|   | <p><b>Respiratory symptoms</b></p> <ul style="list-style-type: none"> <li>Dyspnea</li> <li>Persistent cough</li> <li>Worsening of asthma</li> <li>Decreased pulmonary diffusion capacity</li> <li>Persistent abnormal imaging findings</li> <li>Pleuritis</li> <li>Cough, sore throat</li> </ul>  |
| <p><b>Musculoskeletal symptoms</b></p> <ul style="list-style-type: none"> <li>Arthritis</li> <li>Joint pain</li> </ul>  | <p><b>Endocrinological diseases</b></p> <ul style="list-style-type: none"> <li>Impaired glucose metabolism</li> <li>Subacute thyrotoxicosis</li> <li>Hashimoto's disease</li> <li>Graves' disease</li> <li>Dyslipidemia</li> </ul>  |
| <p><b>Skin diseases</b></p> <ul style="list-style-type: none"> <li>Eruption</li> <li>Urticaria</li> <li>Telogen effluvium</li> <li>Nail changes</li> <li>Trichodynia</li> </ul>   | <p><b>Kidney diseases</b></p> <ul style="list-style-type: none"> <li>Decreased GFR</li> <li>Microscopic hematuria</li> </ul>  |

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Table 1. Nomenclature of post-COVID condition

|  |
|--|
| Post-COVID condition (WHO, CDC)                    |
| Long COVID syndrome                                |
| Long COVID   |
| Long-haul COVID                                    |
| Post-acute COVID-19                                |
| Long-term effects of COVID                         |
| Chronic COVID                                      |
| Post-acute sequelae of SARS-CoV-2 infection (PASC) |
| Post-COVID Neurological Syndrome (PCNS)            |

COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WHO, World Health Organization; CDC, Centers for Disease Control and Prevention.

Table 2. Antibody tests for SARS-CoV-2 used in our outpatient clinic

(<https://diagnostics.roche.com/us/en/products/params/electsys-anti-sars-cov-2-s.html>)

|                      | Sensitivity<br><br>(14 or more than<br>14 days after<br>diagnosis of<br>COVID-19, with<br>positive PCR) | Specificity | PPV and NPV if<br>the test is carried<br>out in a cohort<br>with 5%<br>prevalence |
|----------------------|---|-------------|---|
| Anti-SARS-CoV-2<br>S | 98.8  | 100         | 99.7 and 99.8   |
| Anti-SARS-CoV-2      | 100%  | 99.8        | 96.5 and 100  |

COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; PCR, polymerase chain reaction; PPV, positive predictive value; NPV, negative predictive value.