Post-COVID-19 syndrome: epidemiology, diagnostic criteria and the pathogenic mechanisms involved

Francisco J. Carod-Artal

Neurology Department; Raigmore Hospital; Inverness, United Kingdom. Universitat Internacional de Catalunya; Barcelona, Spain.

Correspondence:
Francisco Javier Carod Artal, MD. Neurology Department. Raigmore Hospital. Old Perth Road. IV2 3UJ, Inverness, UK.

E-mail:
javier.carodartal@nhs.scot

Accepted:
11.05.21.

How to cite this article:
Carod-Artal F.J. Post-COVID-19 syndrome: epidemiology, diagnostic, criteria and the pathogenic mechanisms involved. Rev Neurol 2021; 72: 384-96. doi: 10.33588/rn.7211.2021230.

Versión española disponible en www.neurologia.com

Introduction. Many patients with mild or severe COVID-19 do not make a full recovery and have a wide range of chronic symptoms for weeks or months after infection, often of a neurological, cognitive or psychiatric nature. The epidemiological evidence, diagnostic criteria and pathogenesis of post-COVID-19 syndrome are reviewed.

Development. Post-COVID-19 syndrome is defined by persistent clinical signs and symptoms that appear while or after suffering COVID-19, persist for more than 12 weeks and cannot be explained by an alternative diagnosis. The symptoms can fluctuate or cause relapses. It is a heterogeneous condition that includes post-viral chronic fatigue syndrome, sequelae in multiple organs and the effects of severe hospitalisation/post-intensive care syndrome. It has been reported in patients with mild or severe COVID-19 and irrespective of the severity of the symptoms in the acute phase. Between 10% and 65% of survivors who had mild/moderate COVID-19 present symptoms of post-COVID-19 syndrome for 12 weeks or more. At six months, subjects report an average of 14 persistent symptoms. The most common symptoms are fatigue, dyspnoea, anxiety, depression, and impaired attention, concentration, memory and sleep. The underlying biological mechanisms are unknown, although an abnormal or excessive autoimmune and inflammatory response may play an important role.

Conclusions. Clinical manifestations are diverse, fluctuating and variable, although fatigue and neurocognitive complaints predominate. There is no defined consensus on post-COVID-19 syndrome and its diagnostic criteria have not been subjected to adequate psychometric evaluation.

Key words. Chronic fatigue syndrome. Coronavirus. COVID-19. Persistent COVID. Post-COVID syndrome. SARS-CoV-2.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the agent that causes COVID-19 (coronavirus disease 2019) and was discovered in China in December 2019 [1]. At the time of writing, 18 months into the pandemic, more than 164 million confirmed cases have been reported and at least 3.4 million people have died [2].

The acute phase is accompanied by headache, fever, dyspnoea, non-productive cough, anosmia/ageusia and myalgia, although a considerable proportion of patients may have mild symptoms or be asymptomatic. The severe form may be complicated by severe acute respiratory distress syndrome, hypoxia, respiratory failure and multiple organ failure. Several neurological complications have been described in the acute phase, including encephalopathy, delirium, inflammatory syndromes of the central nervous system, encephalitis, Guillain-Barré syndrome and stroke, among others [3].

Descriptive studies during the first wave of the pandemic in 2020 indicated that at least 10-20% of subjects had not fully recovered after three weeks [4]. How long the convalescence period can last and the reasons for the remarkable variation in sequelae from one individual to another are currently unknown. However, this is not unique to COVID-19, as other viral diseases can also trigger chronic or persistent symptoms.

The disability associated with the symptoms of post-COVID-19 syndrome is one of its main features and it can have a considerable impact on care and rehabilitation units [5]. The chronic neurological symptoms and fatigue associated with post-COVID-19 syndrome differ from the neurological complications of the acute phase. The impact on mental health and cognition is notable [6], and at least 30% may have symptoms of anxiety and/or depression after recovery from the acute phase [6,7].

In the last year, a plethora of terms to define this new entity have emerged in the literature (persistent or prolonged COVID, sub-acute COVID syndrome, ongoing COVID, post-COVID syndrome, etc.). This article uses the term post-COVID syndrome and reviews the epidemiological evidence, the proposed diagnostic criteria, the possible pathogenic mechanisms involved and their clinical manifestations. A search was performed in PubMed (2 May 2021) using the descriptors '*post-COVID*

syndrome' (1,132 articles), '*long COVID*' (200 articles) and their combinations with the term '*neurological complications*' (88 and 19 articles, respectively).

Biological plausibility

A variety of infectious diseases can cause a wide range of chronic symptoms. Viral post-infectious syndromes have been described following infection with a number of viruses, including Epstein-Barr, herpes type 6, cytomegalovirus, dengue, West Nile, chikungunya, Ebola, influenza, Coxsackie, retrovirus and coronavirus, among others, as well as in bacterial, fungal and protozoal infections (*Borrelia, Mycoplasma, Clamidia,* etc.). Post-treatment Lyme disease syndrome, chronic fatigue syndrome and/or myalgic encephalitis, post-viral cerebellar ataxia or post-polio syndrome are examples that illustrate our limited knowledge about the interaction of the immune system in the convalescent phase after an infectious disease [8].

A viral aetiology has been implicated in chronic fatigue syndrome. The diagnostic criteria for this condition proposed by the National Academy of Medicine in 2015 [9] are summarised in Table I. The diagnosis of chronic fatigue syndrome requires that the three cardinal symptoms (fatigue, aggravation of symptoms with exercise, and unrefreshing sleep) be present for more than six months and be moderate or severe in severity for at least 50% of the time. The term 'systemic exercise intolerance disease' was proposed as an alternative to chronic fatigue syndrome.

Post-infectious syndromes have been described with other coronaviruses. Severe acute respiratory syndrome-associated coronavirus (SARS-CoV) caused an epidemic outbreak in 2002 that started in Guangdong, south-east China, with more than 8,000 reported cases and 774 deaths [10]. Follow-up studies of survivors of this epidemic revealed that 50% of them had fatigue and sleep disorders at 12 months [11], 50% had chronic fatigue syndrome at four years and 25% met criteria for myalgic encephalitis syndrome [12,13].

Clinical sequelae of multiple organ dysfunction have been reported in a systematic review and meta-analysis of survivors of SARS-CoV and Middle East respiratory syndrome-associated coronavirus (MERS-CoV) from previous pandemics. At six months post-infection, 27% of subjects had reduced lung diffusing capacity for carbon monoxide and decreased physical capacity. At 12 months, one third of patients had persistent symptoms of anxiety or depression, and 39% had post-traumatic stress disorder [14].

Table I. Chronic fatigue syndrome/myalgic encephalitis. Diagnostic criteria.

1. Chronic fatigue syndrome (essential criteria)
Substantial impairment in the ability to perform activities carried out prior to the disease for more than six months
Profound fatigue not relieved by rest
Discomfort or aggravation after physical exertion
Unrefreshing sleep
2. Chronic fatigue syndrome (at least one of the two additional criteria must be present)
Cognitive impairment (impairment of executive functions or thinking that worsens with exertion, stress or pressure)
Orthostatic intolerance (symptoms worsen when standing and improve when lying down or raising the lower limbs)

Patients who meet criteria for myalgic encephalitis must also have cognitive impairment.

Psychiatric manifestations also persist in the chronic phase. A systematic review and meta-analysis of psychiatric manifestations associated with illness due to SARS/MERS and SARS-CoV-2 concluded that post-traumatic stress disorder is highly prevalent in the acute phase (32%), followed by memory deficits (19%), irritability (12.8%), anxiety (12.3%), insomnia (12%) and depression (19.5%). In the convalescent phase, the meta-analysis showed that the prevalence of post-traumatic stress disorder was 32.2%, that of depression, 14.9%, and the prevalence of anxiety disorders was 14.8% [15].

Diagnostic criteria and categories. Case definition

There is no universal consensus definition of the post-acute period of COVID-19. Some authors [13,16] have suggested that the sub-acute period starts within three weeks of symptom onset, as the average duration of polymerase chain reaction (PCR) positivity in symptomatic subjects has been estimated at 24 days [17]. In hospitalised subjects, it has been proposed that the post-acute period begins at the time of hospital discharge [16].

Table II. Symptoms of post-COVID-19 syndrome classified by systems.

1. Respiratory symptoms	Cough
	Dyspnoea
2. Cardiovascular symptoms	Chest pain
	Oppression
	Palpitations
3. Neurological symptoms	Headache
	Dizziness
	Tinnitus
	Loss of taste and/or smell
	Sleep disorders
	Paraesthesia
	Muscle aches and pains
	Cognitive symptoms • 'Mental fog' • Memory problems • Concentration problems
	Psychiatric symptoms • Anxiety • Depression
4. Gastrointestinal symptoms	Abdominal pain
	Nausea
	Diarrhoea
	Anorexia
5. Systemic symptoms	Fatigue
	Fever
	Pain
	Arthralgia
	Earache and sore throat

Adapted from [19].

Amenta et al. proposed dividing post-acute COVID-19 manifestations into three categories: a) residual symptoms that persist after recovery from acute SARS-CoV-2 infection; b) symptoms due to single or multiple organ dysfunction that persists after initial recovery; and c) novel symptoms or syndromes that arise after mild or asymptomatic infection. Categories 1 and 2 would not be mutually exclusive [13].

The Cochrane 2020 systematic review on rehabilitation of persistent COVID-19 uses four different categories in relation to post-COVID-19 syndrome: a) symptoms persisting from the acute phase and their treatment; b) symptoms associated with a new disease; c) late-onset symptoms resulting from COVID-19 arising at the end of the acute phase; and d) impact on a previous pathology or disability [18].

In December 2020, the UK's National Institute for Health and Care Excellence (NICE) published guidance on the long-term consequences of COVID-19 [19]. This guidance distinguishes between acute COVID-19 (signs and symptoms of COVID-19 last up to four weeks), ongoing symptomatic COVID-19 (signs and symptoms of COVID-19 last from four to 12 weeks) and post-COVID-19 syndrome. The NICE guidance defines post-COVID-19 syndrome as the set of signs and symptoms that develop during or after an infection compatible with COVID-19 (a previous history of COVID-19 confirmed by PCR is not required for diagnosis), continue for more than 12 weeks and cannot be explained by an alternative diagnosis. Symptoms can often overlap each other and fluctuate and change over time, sometimes in the form of relapses. They can affect any body system, including the cardiovascular, respiratory, gastrointestinal, neurological, musculoskeletal, metabolic, renal, dermatological, ENT and haematological systems, as well as psychiatric problems, generalised pain, fatigue and persistent fever (Table II).

According to NICE, a diagnosis of post-COVID-19 syndrome may be considered before 12 weeks, while the possibility of an alternative underlying disease is being assessed [19]. The term 'long COVID' is commonly used to describe signs and symptoms that continue or develop after acute COVID-19, and includes both ongoing symptomatic COVID-19 syndrome and post-COVID-19 syndrome.

The US Center for Disease Control and Prevention uses the term 'post-COVID conditions' to describe any health disorder or disturbance that persists for more than four weeks after SARS-CoV-2 infection [20], and distinguishes three subtypes: a) persistent COVID, which is defined as a series of symptoms that occur in combination in varying proportions, last for weeks or months, and may also affect people who had mild COVID or even

those who were asymptomatic. The main symptoms are: fatigue, difficulty in thinking or concentrating (so-called brain fog), headache, loss of taste or smell, dizziness when standing upright, palpitations, dyspnoea, cough, muscle or joint pain, anxiety and/or depression, fever and symptoms that worsen after physical or mental activity; b) symptoms resulting from damage to multiple organs, such as the heart, lung, kidneys, skin and nervous system. This category also includes multisystem inflammatory syndrome and other autoimmune entities; and c) consequences of COVID-19 treatment or prolonged hospitalisation, including post-intensive care unit (post-ICU) or critical patient syndrome, in which a high percentage of patients present fatigue and severe muscle weakness, critical patient polyneuropathy, cognitive impairment (affecting sustained and divided attention, short-term memory, executive functions and slowed information processing), and symptoms of post-traumatic stress disorder, pain, anxiety and depression [20].

The categories proposed have received some criticism, such as: a) the natural history of the post-COVID syndrome is unknown; b) the pathogenic mechanisms of new symptoms that emerge months after infection are unknown; c) the definition of time of onset and/or persistence of clinical signs and symptoms is arbitrary; and d) neuropsychological aspects have not been assessed in a standardised or uniform way in many studies.

Epidemiological evidence

The Coronavirus Infection Survey published by the UK Office for National Statistics (ONS) has collected random data from representative samples of the population in the community [4]. According to this survey, 20% of people with COVID-19 had symptoms lasting more than five weeks, and 10% had symptoms lasting more than 12 weeks. Thus, 300,000 people had symptoms lasting between five and 12 weeks in December 2020 [4]. The ONS updated its data in March 2021 [21] and estimates that in the UK 1,100,000 people have presented with 'persistent COVID-19' symptoms lasting longer than four weeks. Symptoms lasted longer than 12 weeks in 65% and would have limited activities of daily living in 20% of subjects [21]. According to the British National Institute for Health Research, 20-30% of people who were not admitted to hospital in the acute phase had at least one symptom one month later, and 10% of them three months later [22]. In addition, 12% of children aged 2-11 years and 14.5% of those aged 12-16 years reported symptoms of fatigue, cough, headache, muscle pain or loss of taste or smell five weeks after developing COVID-19 [22].

A number of clinical studies on post-COVID-19 syndrome have been published, differing in sample size, time of analysis, methodology used, severity and diagnostic criteria employed. Table III summarises some of the most prominent descriptive studies from China, Europe and the United States [23-30].

Patients with mild COVID-19

Post-COVID-19 syndrome has been described in patients with both mild and severe COVID-19 and regardless of the severity of the symptoms in the acute phase. One study used a telephone survey to evaluate 292 young patients (mean age: 42.5 years) with mild COVID-19 16 days after diagnosis. Thirty-five per cent of symptomatic adults had not recovered within 2-3 weeks [23], and the main symptoms reported were cough, fatigue and dyspnoea. In another study of 150 patients with mild COVID-19 at two months, two-thirds had complaints, the most frequent being asthenia (40%), dyspnoea (30%) and anosmia/ageusia (23%) [24]. In a study of 153 patients, Townsend et al. found that 62% of patients had not fully recovered and 47% were fatigued 75 days after discharge [25]. These authors concluded that chronic health impairment after COVID-19 was not associated with the severity of the initial illness or the incidence of respiratory complications.

Patients requiring hospitalisation

Most of the patients who required hospitalisation report persistent symptoms over time. Garrigues et al. evaluated 120 patients who had been admitted to a COVID-19 unit 110 days afterwards. The most frequently described symptoms were fatigue (55%), dyspnoea (42%), memory loss (34%), difficulty falling asleep (31%), concentration problems (28%) and a significant impairment in their quality of life as measured by the *EuroQol-5D (European Quality of Life-5 Dimensions)* [26].

The symptoms are frequent in patients who required admission to the ICU. In another study of 100 patients, numerous symptoms were described 7 weeks after discharge: fatigue, dyspnoea, pain, cough, dysphagia, anxiety/depression, post-traumatic stress symptoms and concentration/memory problems [27]. Thirty per cent of the patients had

Table III. Examples of descriptive studies on post-COVID-19 syndrome.

	n	Severity	Methodology	Time (days)	Prevalence	Most commonly reported symptoms
Halpin et al	100	30%, ICU	Telephone	48	60-72%	Fatigue (72%), dyspnoea (65%), stress (47%)
Garrigues et al	120	Hospital	Telephone	110	55%	Fatigue (55%), dyspnoea (42%), memory problems (34%)
Tenforde et al	292	Mild	Telephone	14-21	94%	Cough (43%), fatigue (35%), dyspnoea (29%)
Carvalho-Schneider et al	150	Mild	Telephone	30-60	66%	Asthenia (40%), dyspnoea (30%), anosmia (23%)
Carfi et al	143	Hospital	Clinic	60	87%	Fatigue (53%), dyspnoea (43%), arthralgia (22%)
D'Cruz et al	110	Pneumonia	Clinic	60	89%	Fatigue (68%), sleepiness (57%), dyspnoea (44%)
Townsend et al	153	Hospital	Clinic	75	62%	Fatigue (48%)
Moreno-Pérez et al	272	Hospital	Clinic	77	51%	Fatigue and dyspnoea (35%), anosmia (21%), arthralgia (20%)
Venturelli et al	767	Hospital	Clínica	81	51.4%	Fatigue and dyspnoea (51%), post-traumatic stress (30.5%)

n: number of patients studied; severity: mild vs. hospital admission, pneumonia or admission to intensive care unit (ICU); methodology: telephone survey vs. clinical assessment; time: average assessment in days after COVID-19; prevalence: percentage of patients with post-COVID syndrome; most commonly reported symptoms: main symptoms ordered by frequency.

been admitted to the ICU, and there were significant differences in their mean age (70.5 years in regular care (ward) versus 58.5 years in the ICU). The prevalence of post-COVID-19 symptoms was higher in ICU patients compared to ward patients: fatigue (72% vs. 60.3%), dyspnoea (65.6% vs. 42.6%), post-traumatic stress (46.9% vs. 23.5%), attention and memory disorders (52% vs. 33.8%), and swallowing and language disorders (68.7% vs. 42.6%).

In a prospective observational study, D'Cruz et al. analysed 119 patients who had been admitted for severe pneumonia 60 days after discharge, and only 11% were free of chronic symptoms [28]. Sixty-eight per cent had persistent fatigue; 57% had sleep disorders; 25% had post-traumatic stress symptoms; and 39% had persistent dyspnoea or cough. In another Italian study of 143 hospitalised patients with COVID-19, 87% of patients had symptoms two months after being discharged and 40% reported a decrease in their quality of life; fatigue persisted in over 50% more than 60 days after the onset of symptoms [29]. Another cross-sectional study conducted in Milan of 105 patients discharged from hospital after suffering from pneumonia due to COVID-19 found persistent physical symptoms (52%) 1-3 months after discharge, anxiety (29%) and cognitive complaints (17%) [7].

In a prospective Chinese study in Wuhan, 538 patients were evaluated at least three months after hospital discharge, and the most frequent chronic symptoms were alopecia (28.6%), fatigue (28%), sweating (23.6%) and sleep disorders (18%) [31].

In Spain, a study analysed 274 patients with COVID-19 (24%, mild; 65.7%, severe) at 10-14 weeks after disease onset [31]. Fifty-one per cent of the patients had post-COVID-19 syndrome, and the most common symptoms were dyspnoea and fatigue (35%) and neurological symptoms, headache and cognitive complaints (12%). Abnormalities in spirometry tests or the chest X-ray were present in 25% of the subjects studied [32].

In addition to physical or cognitive symptoms, post-COVID-19 syndrome affects quality of life [26,29], gives rise to significant disability and has financial and return-to-work implications [33]. The observational cohort of 38 hospitals in Michigan studied 1,648 patients 60 days after hospital discharge; one-third of the patients died in hospital or during follow-up and only 488 completed a telephone survey. Of these, 58% of survivors reported new or worsening difficulties in performing activities of daily living, as well as physical and emotional symptoms (97.5%) and financial loss (26.6%), and among those previously employed, 66.6% had not returned to work [33].

A recent systematic review of 15 clinical studies and 47,910 patients (age range 18-87 years) analysed the frequency of 55 symptoms or long-term complications after developing COVID-19 [33]. Follow-up time was very heterogeneous and ranged from 14 to 110 days after infection. Eighty per cent had experienced one or more symptoms and the five most prevalent symptoms were fatigue (58%), headache (44%), attention deficit (27%), alopecia (25%) and dyspnoea (24%). Other prevalent neurological and psychiatric symptoms were ageusia (23%), anosmia (21%), memory problems (16%), tinnitus (15%), anxiety (13%) and depression (12%) [34].

Studies at four and six months after COVID-19

The COVERSCAN study evaluated a prospective cohort of 201 low-risk subjects with severe COV-

ID-19 (mean age: 45 years; 32% were healthcare workers) [35]. At four months, the most common symptoms were fatigue (98%), muscle pain (87%), dyspnoea (88%) and headache (83%). Forty-two per cent had 10 or more symptoms and 60% reported having a severe post-COVID-19 syndrome.

The COMEBAC study, conducted at the Bicétre Hospital in Paris, analysed post-COVID-19 sequelae four months after hospital discharge [36]. In this cohort, 57% of the survivors (478/834) were assessed by telephone survey. Fifty per cent reported at least one new physical, emotional or cognitive symptom, the most frequent being fatigue (31%), cognitive difficulties (21%) and dyspnoea (16%). In addition, 174 patients were examined in person and in this subgroup 54% suffered from sleep disorders and 38% from cognitive impairment. In the subgroup of patients who had been admitted to the ICU (94), 23% reported symptoms of anxiety, 18% depression and 7% post-traumatic stress disorder [36].

Data are available on the outcome of COVID-19 at six months after hospital discharge. The original cohort of 1,733 patients (mean age: 57 years; 52% male) from Wuhan, China, was assessed by interview, quality-of-life questionnaires, physical examination and the six-minute test [37]. Seventy-six per cent of patients had at least one symptom of post-COVID-19 syndrome at six months, the most prevalent being fatigue and muscle weakness (63%), sleep disturbances (26%), alopecia (22%), anosmia (11%), ageusia (9%) and mobility disorders (7%). The most severe patients had lung diffusing abnormalities, fatigue and muscle weakness, and anxiety and depression [37].

The International Symptom Survey has collected information from 3,762 participants from 56 countries (79% female) who suffered from COVID-19. This study collected 205 symptoms of post-COVID-19 syndrome, and 96% of participants reported persistent symptoms for more than 90 days in nine organ systems. Subjects with symptoms continuing for more than six months had an average of 13.8 symptoms. The most frequently described symptoms were fatigue (77.7%), malaise after exertion (72%) and cognitive dysfunction (55%). Patients with persistent COVID-19 reported prolonged multisystem involvement and significant disability [38].

Risk factors and pathogenic mechanisms

Risk factors for post-COVID-19 syndrome that have been identified include severity of illness (need for hospital or ICU admission) or need for ventilatory support in the acute phase [27], age (over 50 years), gender (female) and comorbidities (asthma or previous respiratory disease, obesity and increased body mass index) [39]. Diabetes, hypertension, cancer and immunosuppression are risk factors for severity and mortality in the acute phase of COVID-19; however, there is no evidence of their association with post-COVID-19 syndrome.

An analysis of the prospective observational cohort of 4,182 subjects with COVID-19 who recorded their symptoms in the digital application 'Zoe' of the 'COVID Symptom Study' [39] has shown that having more than five COVID-19 symptoms during the first week of illness is associated with an increased risk of persistent COVID-19 (odds ratio = 3.53, confidence interval: 2.76-4.5). In this study, 13.3% of participants had symptoms for more than 28 days, 4.5% for more than eight weeks, and 2.3% for more than 12 weeks. Chronic symptoms affected 10% of individuals aged 18-49 years, but the proportion increased to 22% in individuals over the age of 70 years [39].

The aetiopathogenesis of post-COVID-19 syndrome is probably due to multiple causes, given the broad spectrum of clinical manifestations [40]. Post-COVID-19 syndrome is a complex and heterogeneous entity, in which multiple factors may trigger specific post-recovery syndromes (Table IV). Post-ICU syndrome has been related to ischaemia due to small vessel involvement, the effect of immobility, myopathy/neuropathy of the critically ill patient and metabolic disorders associated with critical illness.

A characteristic feature of post-COVID-19 syndrome is the emergence of new symptoms that may fluctuate over time. Several hypotheses have been put forward to explain this: (a) the presence of a defective immune response in the host, which would favour viral replication for a longer time; (b) the existence of systemic damage secondary to an excessive inflammatory response or an altered immune system (cytokine storm syndrome); c) the presence of physical (physical impairment) or mental/psychosocial sequelae (anxiety, depression, post-traumatic stress disorder, effects of confinement or social isolation); and, although more unlikely, d) reinfection with the same or a different variant of SARS-CoV-2 [40,41].

No virus particles have been detected replicating beyond three weeks after the onset of symptoms. Yet, the virus could persist in immune sanctuaries where the immune system would have difficulty eradicating it, resulting in latent or chronic infection, but so far there is no evidence to confirm

Table IV. Factors that could explain the heterogeneity of post-COVID-19 syndrome.

1. Residual symptoms persisting after the acute phase of infection
2. Multiple organ damage/sequelae persisting after initial recovery
Myocarditis/cardiac arrhythmias
Pneumonia/pulmonary fibrosis
Thromboembolism
Chronic kidney disease
Central nervous system compromise: stroke, encephalopathy, seizures
3. Consequence of prolonged hospitalisation or intubation
Post-intensive care syndrome
4. Consequence of residual inflammation
Vasculitis
Autoimmunity
5. Aggravation of previous comorbidities
6. Chronic fatigue syndrome/myalgic encephalitis
7. Post-traumatic stress disorder
8. Psychosocial effect of confinement/social isolation

this hypothesis. In a recent study, 25% of patients whose symptoms had lasted more than two months or had recurred had a positive PCR in samples from the oro- or nasopharyngeal region [41].

Effect of inflammation and immune response

The inflammatory response can affect the endothelium of vessels (endothelitis), the myocardium (myocarditis) and the central nervous system (neuroinflammation), among other systems [42]. An exacerbated inflammatory response can aggravate previous pathologies and also promote thrombotic complications. Post-mortem studies have confirmed the presence of severe endothelial damage, microangiopathy and thrombotic phenomena, and hence endothelial damage and endothelial dysfunction may play an additional role [43,44].

A deregulated immune system is relevant, and the effect caused by the immune response may make symptoms worse. Several factors have been associated with an excessive systemic inflammatory response, including exposure to a high viral load, the presence of comorbidities and the degree of immunocompetence of the person with COVID-19.

Several inflammatory markers, such as type 1 cytokines (interleukin 1β, interleukin 6, interferon-γ and tumour necrosis factor) and type 2 cytokines (interleukin 4 and interleukin 10), are found in elevated levels in the serum of patients with COVID-19. Cytokine storm syndrome is its most severe expression and is characterised by a marked release of interleukins 1, 6, 8 and 17, tumour necrosis factor α and monocyte-attractant protein 1β, among others [40].

Patients with post-COVID-19 syndrome develop a dysfunctional immune response, with increased interferon-γ, interleukin-2, B-cell, $CD4^+$ and $CD8^+$ T-cells, and appear to have effector T-cell activation with pro-inflammatory features. Some patients may also have an inadequate innate response to interferons and/or macrophage activity, and even a genetic predisposition [40].

The detection of inflammatory cytokines in the leptomeninges has been associated with the presence of neurological symptoms two months after SARS-CoV-2 infection. A study of 18 patients with cancer and neurological sequelae due to COVID-19 found elevated levels of metalloproteinase-10 in cerebrospinal fluid in the absence of viral invasion of the central nervous system, compared with cancer patients not infected with the coronavirus [45]. According to this hypothesis, the neuroinflammatory process would persist for weeks after convalescence from acute respiratory infection.

Alterations detected in brain MRI and decreased tolerance to exercise also correlate with serum markers of inflammation [46]. In a case-control study, 58 patients admitted due to COVID-19 and 30 controls were evaluated by multi-organ MRI (brain, lungs, heart, liver and kidneys), spirometry, cardiopulmonary and cognitive function tests. Two to three months after discharge, 55% had fatigue and 64% had dyspnoea. Signal disturbances detected in the thalamus and thalamic radiations, and impairment in executive and visuospatial domains predominated in the group of patients with post-COVID-19 syndrome [46].

Multiple organ damage or sequelae

Prolonged organ dysfunction after suffering from COVID-19 has been studied in several articles. The most frequent pulmonary symptom of post-COV-

ID-19 syndrome is dyspnoea, with a frequency of 30-72% at three months, while reduced diffusing capacity is the most common physiological impairment [23-30]. The frequency of pulmonary sequelae at discharge analysed by carbon monoxide diffusion technique in a series of 110 patients was 47.2% [47]. Fifty per cent of 349 COVID-19 survivors in a Chinese series had an abnormal radiological pattern with ground-glass opacity in chest CT at 6 months [37]. However, the prevalence of sequelae in the form of pulmonary embolism in these patients is unknown, as pulmonary angiography was not performed. Bronchiectasis and fibrotic pulmonary changes have been observed in 25% and 65% of patients admitted for mild-moderate and severe COVID-19, respectively, at three months after discharge [48].

Chest pain has been reported in 20% of COVID-19 survivors at 60 days of follow-up [24,29], and palpitations and chest pain were described in 9% and 5% of cases, respectively, at six months [37]. The inflammatory response may cause cardiomyocyte damage and death in the acute phase, but in the chronic phase, myocardial fibrosis and cardiomyopathy may favour the appearance of arrhythmias [42]. The prevalence of cardiac MRI abnormalities in a series of 100 patients studied 71 days after discharge was 78%; in addition, 60% had findings suggestive of myocardial inflammation [49].

The incidence of thromboembolic complications and thrombosis described in a series of 163 patients 30 days after discharge was 2.5%, including pulmonary embolism, intracardiac thrombus and ischaemic stroke [50]. Pulmonary micro- and macrothrombosis have been observed in 20-30% of patients with COVID-19 [42].

Multi-organ involvement has also been assessed in low-risk patients who did not require hospitalisation. In the COVERSCAN study, single and multiple organ involvement was detected in 70% and 29%, respectively, four months after infection. Liver (28%), heart (26%), lungs (11%) and kidneys (4%) were the organs considered to be mildly compromised [35].

However, severe multi-organ involvement is associated with a 7-fold and 3.5-fold higher risk of mortality and hospital readmission, respectively, than in controls. A retrospective British case-control study analysed 47,780 patients hospitalised due to COVID-19 (mean age: 64.5 years) who were followed up for 140 days. Some 29.4% were readmitted, and the frequency of respiratory and cardiovascular complications and diabetes increased significantly during follow-up [51]. In another study of 1,775 veterans in the USA, 20% were readmitted within 60 days of discharge and mortality was 9%, again reflecting the impact of multiple organ sequelae in this population [52].

Other types of long-term sequelae following COVID-19 include those affecting the endocrine (sub-acute thyroiditis, thyroid dysfunction and new-onset diabetes have been reported), renal (reduced glomerular filtration rate), gastrointestinal (diarrhoea, dyspepsia, abdominal pain, nausea, dysphagia and intestinal microbiota involvement), dermatological (alopecia, perniosis, acral skin lesions, etc.) and locomotor system (bone and osteoarticular pain, myalgia and muscle spasms), among others [42].

Persistent neurological and cognitive symptoms

Neurological and psychiatric morbidity is substantial during the first six months after SARS-CoV-2 infection. A recent study published in *Lancet Psychiatry* in 2021 retrospectively analysed a cohort of 236,379 COVID-19 survivors and a control group of patients who had influenza or some other respiratory infection, but did not have COVID-19, and quantified the incidence of neurological or psychiatric complications in the following six months [53]. The incidence of any such complication in the COVID-19 group was 33.6%, including anxiety (17.4%), depression (13.7%), insomnia (5.4%), ischaemic stroke (2.1%), psychosis (1.4%), dementia (0.67%), cerebral haemorrhage (0.56%) and Parkinsonism (0.11%). The incidence of such complications was higher in patients who required admission to the ICU (46.4%) or who presented with encephalopathy in the acute phase. Likewise, it was also higher compared to patients with influenza or other respiratory infections [53].

Dementia was diagnosed in 2.6% of patients over 65 years of age and 4.7% of those with encephalopathy in the first six months after COVID-19. The incidence of cognitive and psychiatric complications was also increased in patients who did not require hospital admission. Substance abuse and sleep disorders/insomnia were also more frequent in the COVID-19 survivor group [53].

Cerebrovascular complications, encephalopathy and neuroinflammatory syndromes are more common in the acute phase. In contrast, symptoms such as chronic fatigue, headache, memory, attention and executive function problems are relatively common in post-COVID-19 syndrome. Salmon-Ceron et al. [41] described fatigue in 73% of patients with post-COVID-19 syndrome and an ag-

gregate of neurological symptoms in 77%, and stratified them into sensory disorders (paraesthesias and neurogenic pain; 56%), headache (41%), memory and attention disorders (37%), anosmia/ageusia (30%) and others (24%), such as language and thermoregulation disorders.

Persistent headache weeks after recovery from COVID-19 is common and some patients meet criteria for recent-onset daily persistent headache. The profile of a person suffering from this chronic daily headache is a subject who experienced COVID-19 with mild to moderate respiratory symptoms, with no history of primary headache, and who presents with a holocranial oppressive-type headache, with onset within two weeks after recovery from the respiratory symptoms. Neuroimaging studies showed no evidence of structural damage or cerebral venous occlusive pathology [54,55]. Loss of taste and smell persists after resolution of other symptoms in at least 10% at 6 month of follow-up [26,56].

Role of dysautonomia

The involvement of the autonomic nervous system, either immune-mediated or by direct action of the virus, could also explain part of the symptoms of post-COVID-19 syndrome. Autonomic instability may be exacerbated by hypovolaemia in the early phase of infection or by physical reconditioning after prolonged bed rest [56].

Postural orthostatic tachycardia syndrome can cause dizziness, unsteadiness and palpitations when a person changes from prone to standing, and infections are a triggering factor. Patients have been described as having persistent symptoms and orthostatic intolerance after COVID-19, including dysautonomia and postural tachycardia syndrome, exercise intolerance, chest tightness and palpitations [57-60].

The diagnostic criteria for postural orthostatic tachycardia syndrome are: a) excessive orthostatic tachycardia defined by an increase in heart rate of more than 30 beats per minute in adults (or > 40 beats per minute in patients aged 12-19 years) within 10 minutes of adopting an upright posture; b) absence of orthostatic hypotension; c) associated symptoms of orthostatic intolerance; and d) duration of at least three months [61].

However, no differences were found in autonomic function tests and 24-hour ambulatory blood pressure monitoring in patients with post-COVID-19 chronic fatigue compared to patients without fatigue in the convalescent phase. Symptoms of orthostatic intolerance were present in 70% of subjects with fatigue on standing up. These data are from a case-control study comparing 20 patients with post-COVID-19 fatigue and 20 without fatigue, who underwent the Ewing autonomic function battery, including deep breathing, active standing, Valsalva manoeuvre, and pressure and cold test, with electrocardiographic and blood pressure monitoring [62].

Neuropathogenesis and cortical hypometabolism

Proposed neuropathogenic mechanisms in the chronic phase include direct damage by the virus, and the effect of severe systemic inflammation, neuroinflammation, microvascular thrombosis and neurodegeneration. Necropsy studies have shown that SARS-CoV-2 causes changes in vessels and brain parenchyma, affects the blood-brain and blood-cerebrospinal fluid barriers, and induces neuronal, glia and brain vessel inflammation [42]. Nevertheless, there is no evidence of direct infection of neurons. Mechanisms implicated in neuropsychological sequelae include the immune response to SARS-CoV-2 infection in the host, stress before and during infection, and also a possible viral effect on the central nervous system [63].

It was initially thought that cognitive sequelae might be a consequence of the neuroinvasive capacity of SARS-CoV-2. However, this has not been reliably demonstrated and reported cases of SARS-CoV-2 encephalitis are rare, so other factors, such as toxic/metabolic/immune effects and cortical metabolic disorders following post-COVID-19 encephalopathy, may be relevant.

A case-control study of 35 patients with persistent neurological symptoms after COVID-19 submitted to positron emission tomography has shown a pattern of decreased fluorodeoxyglucose uptake in the cerebral cortex compared to 44 healthy subjects. Patients with persistent COVID-19 had a pattern of hypometabolism in the bilateral rectus and orbital sulci, and the olfactory sulcus, in the temporal lobe, amygdala and hippocampus, pons, brainstem and cerebellum at least three weeks after the initial infection. The most severe pattern of hypoenhancement was detected in patients with post-COVID-19 syndrome with cognitive problems, memory complaints and anosmia, pain and insomnia [64].

Critical analysis of epidemiological evidence

Persistent symptoms following COVID-19 have been identified in a large majority of patients, and

studies report a wide variation in frequency, ranging from 40-90% [65-67].

There are certain epidemiological limitations in interpreting data from observational studies published in the literature, namely: a) non-systematic analyses and studies; b) short-term follow-up and evaluation; c) presence of heterogeneous samples in relation to age (young versus older age groups), severity of COVID-19 (mild forms versus hospital or ICU inpatients), follow-up time (6-8 weeks versus 4-6 months versus > 6 months), type of clinical assessment (telephone interview vs. face-to-face assessment in the outpatient clinic), type of studies (cross-sectional vs. prospective cohort), recruitment method (support groups, patients discharged from hospital, self-referred patients in digital application studies, etc.) and sample size ($n < 50$, $n < 100$ or $n < 1{,}000$); d) absence of a non-COVID control group in many publications; e) the fact that some studies were conducted in the early phase of the pandemic, where corticosteroids, anticoagulants or immunomodulators were not used routinely; f) a high percentage of patients declined to participate in telephone surveys; g) variable definitions of post-COVID-19 syndrome; and h) heterogeneous inclusion criteria, defined by the persistence of at least one clinically relevant symptom or a spirometric or radiological lung abnormality.

Furthermore, the incidence of mental illness has increased during the pandemic in the general population, regardless of COVID-19 infection, due to other factors such as social isolation, confinement, increased unemployment, and increased use of drugs and stimulants [53].

When patients with multiple organ sequelae are excluded, a specific post-COVID-19 syndrome profile emerges in the absence of previous comorbidities, affecting a younger population (50% of those affected are in the 35-50 years age range) that is predominantly female [38]. However, some studies on post-COVID-19 syndrome may not be representative of the general population. This is the case for studies in which patients recorded their symptoms in online digital applications, as subjects older than 70 years are under-represented [39].

Specific vulnerable groups, such as the elderly, children and adolescents, people with learning disabilities or residing in assisted living facilities, are usually under-represented. App-based studies have enrolled a significant percentage of patients without a confirmatory laboratory test, and in one study only 27% had a confirmed diagnosis [38]. Therefore, estimates of the prevalence of post-COVID-19 syndrome in patients discharged from hospital offer more robust clinical data than surveys of non-admitted patients. However, criteria for hospital admission differ by country, region, resource level and pandemic situation.

Numerous articles describe the percentage of individual symptoms but, in contrast, the analysis of specific symptom aggregates is rarely discussed. The COVID Symptom Study, using the 'Zoe' application, describes two different patterns of symptoms: one group of patients reported a syndrome characterised by fatigue, headache, dyspnoea, persistent cough and anosmia, while the other group reported multisystem complaints, fever and gastrointestinal symptoms [39].

The fluctuating or relapsing nature of post-COVID-19 syndrome has not been thoroughly evaluated. In a French study, 43% of a series of 70 discharged patients had a symptom-free period of 25 days before relapse [41] and 76% reported new symptoms that were not present during the acute phase. In the international survey of patients with persistent COVID-19, 86% of participants had experienced relapses in an irregular pattern or as a result of triggers such as stress, heat, alcohol consumption, exercise or performance of a physical or mental activity [38].

The natural history of post-COVID-19 syndrome, the duration of symptoms and the most likely amount of time required for recovery are unknown. For this reason, some authors and many patients even disagree with the term 'post-COVID-19', as it suggests that there is no active disease.

Conclusions

Post-COVID-19 syndrome is neither a homogeneous nor a unique entity, and wide variation in estimates of its incidence and prevalence has been reported. Chronic fatigue is the most frequently described symptom and often occurs in the absence of objective respiratory function abnormalities or fibrosing lung lesions.

There are differences in study populations, recruitment methods, assessment and follow-up periods and sample size, and the absence of a control group stands out in many studies. Most studies have focused on analysing the prevalence of post-COVID-19 syndrome symptoms rather than on the objective involvement of organs. The absence of a standard and accepted definition limits the comparison of findings across epidemiological studies.

Post-COVID-19 'recovery' cannot be based solely on a negative PCR or hospital discharge. There is

remarkable variation in the duration, severity and fluctuation of symptoms, which can affect survivors' quality of life, functional status, cognition and mood, and lead to severe disability.

There is a need for epidemiological studies on the determinants and predictors of post-COVID-19 syndrome, and to identify both risk groups and specific categories that differentiate chronic fatigue syndrome, multiple organ sequelae or post-ICU syndrome from post-COVID-19 syndrome.

The role that both the host and its immune system and the virus itself play in the persistence of symptoms is another challenge that needs to be clarified. Future studies should evaluate biomarkers that can be used in clinical practice and specific therapies. As an example, the Yale University 'COVID Mind' study is a prospective study that will evaluate COVID-19 survivors with persistent neurological symptoms using positron emission tomography, MRI and biomarkers in cerebrospinal fluid and peripheral blood [68].

Population-based research on post-COVID-19 syndrome is critical to: a) quantify the burden of the disease and its sequelae; b) measure the impact on public health systems and demand for care, and the need to reallocate resources and implement specific rehabilitation units for these patients; and c) plan and develop appropriate clinical trials.

References

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020; 382: 727-33.
2. Coronavirus disease (COVID-19) Pandemic. Geneva: World Health Organization, May 2, 2021. URL: https: //www.who.int/emergencies/diseases/novel-coronavirus-2019. Last consultation date: 04.05.2021.
3. Carod-Artal FJ. Complicaciones neurológicas por coronavirus y COVID-19. Rev Neurol 2020; 70: 311-22.
4. Office for National Statistics (ONS). The prevalence of long COVID symptoms and COVID-19 complications. URL: https: //www.ons.gov.uk/news/statementsandletters/theprevalenceoflongcovidsymptomsandcovid19complications. Last consultation date: 30.04.2021.
5. Ladds E, Rushforth A, Wieringa S, Taylor S, Rayner C, Husain L, et al. Persistent symptoms after COVID-19: qualitative study of 114 'long COVID' patients and draft quality principles for services. BMC Health Serv Res 2020; 20: 1144.
6. Amsalem D, Dixon LB, Neria Y. The coronavirus disease 2019 (COVID-19) outbreak and mental health: current risks and recommended actions. JAMA Psychiatry 2021; 78: 9-10.
7. Tomasoni D, Bai F, Castoldi R, Barbanotti D, Falcinella C, Mulè G, et al. Anxiety and depression symptoms after virological clearance of COVID-19: a cross-sectional study in Milan, Italy. J Med Virol 2021; 93: 1175-9.
8. Cortes Rivera M, Mastronardi C, Silva-Aldana CT, Arcos-Burgos M, Lidbury BA. Myalgic encephalomyelitis/chronic fatigue syndrome: A comprehensive review. Diagnostics (Basel) 2019; 9: 91.
9. Institute of Medicine (US), Committee on the diagnostic criteria for myalgic encephalomyelitis/chronic fatigue syndrome. Beyond myalgic encephalomyelitis/chronic fatigue syndrome-Redefining an illness: report guide for clinicians. 2015. URL: https: //www.nap.edu/resource/19012/MECFScliniciansguide.pdf. Last consultation date: 30.04.2021.
10. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 2020; 395: 565-74.
11. Tansey CM, Louie M, Loeb M, Gold WL, Muller MP, de Jager J, et al. One-year outcomes and health care utilization in survivors of severe acute respiratory syndrome. Arch Intern Med 2007; 167: 1312-20.
12. Lam MH, Wing YK, Yu MW, Leung CM, Ma RC, Kong AP, et al. Mental morbidities and chronic fatigue in severe acute respiratory syndrome survivors: long-term follow-up. Arch Intern Med 2009; 169: 2142-7.
13. Amenta EM, Spallone A, Rodriguez-Barradas MC, El Sahly HM, Atmar RL, Kulkarni PA. Postacute COVID-19: an overview and approach to classification. Open Forum Infect Dis 2020; 7: ofaa509.
14. Ahmed H, Patel K, Greenwood DC, Halpin S, Lewthwaite P, Salawu A, et al. Long-term clinical outcomes in survivors of severe acute respiratory syndrome and Middle East respiratory syndrome coronavirus outbreaks after hospitalisation or ICU admission: a systematic review and meta-analysis. J Rehab Med 2020; 52: jrm00063.
15. Rogers JP, Chesney E, Oliver D, Pollak TA, McGuire P, Fusar-Poli P, et al. Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. Lancet Psychiatry 2020; 7: 611-27.
16. Greenhalgh T, Knight M, Buxton M, Husain L. Management of post-acute COVID-19 in primary care. BMJ 2020; 370: 3026.
17. Xiao AT, Tong YX, Zhang S. Profile of RT-PCR for SARS-CoV-2: a preliminary study from 56 COVID-19 patients. Clin Infect Dis 2020; 71: 2249-51.
18. Ceravolo MG, Arienti C, De Sire A, Andrenelli E, Negrini F, Lazzarini SG, et al. Rehabilitation and COVID-19: the Cochrane Rehabilitation 2020 rapid living systematic review. Eur J Phys Rehabil Med 2020; 56: 642-51.
19. National Institute for Health and Care Excellence (NICE). COVID-19 rapid guideline: managing the long-term effects of COVID-19 (NG188). URL: https: //www.nice.org.uk/guidance/ng188. Last consultation date: 30.04.2021.
20. Centers for Disease Control and Prevention. Post-COVID Conditions. URL: https: //www.cdc.gov/coronavirus/2019-ncov/long-term-effects.html. Last consultation date: 30.04.2021.
21. Office for National Statistics (ONS). Coronavirus (COVID-19). Infection Survey, UK Statistical bulletins. URL: https: //www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/coronaviruscovid19infectionsurveypilot/previousReleases. Last consultation date: 30.04.2021.
22. National Institute for Health Research (NIHR). Living with COVID–second review. March 2021. URL: https: //evidence.nihr.ac.uk/themedreview/living-with-covid19-second-review/. Last consultation date: 04.05.2021.
23. Tenforde MW, Kim SS, Lindsell CJ, Billig Rose E, Shapiro NI, Files DC, et al; IVY Network Investigators; CDC COVID-19 Response Team. Symptom duration and risk factors for delayed return to usual health among outpatients with COVID-19 in a multistate health care systems network: United States, March-June 2020. MMWR Morb Mortal Wkly Rep 2020; 69: 993-8.
24. Carvalho-Schneider C, Laurent E, Lemaignen A, Beaufils E, Bourbao-Tournois C, Laribi S, et al. Follow-up of adults with non-critical COVID-19 two months after symptoms' onset. Clin Microbiol Infect 2021; 27: 258-63.

25. Townsend L, Dowds J, O'Brien K, Sheill G, Dyer AH, O'Kelly B, et al. Persistent poor health post-COVID-19 is not associated with respiratory complications or initial disease severity. Ann Am Thorac Soc 2021 Jan 8. [Epub ahead of print].
26. Garrigues E, Janvier P, Kherabi Y, Le Bot A, Hamon A, Gouze H, et al. Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. J Infect 2020; 81: e4-6.
27. Halpin SJ, McIvor C, Whyatt G, Adams A, Harvey O, McLean L, et al. Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: a cross-sectional evaluation. J Med Virol 2021; 93: 1013-22.
28. D'Cruz RF, Waller MD, Perrin F, Periselneris J, Norton S, Smith LJ, et al. Chest radiography is a poor predictor of respiratory symptoms and functional impairment in survivors of severe COVID-19 pneumonia. ERJ Open Res 2021; 7: 00655-2020.
29. Carfì A, Bernabei R, Landi F. Persistent symptoms in patients after acute COVID19. JAMA 2020; 324: 603-5.
30. Venturelli S, Benatti SV, Casati M, Binda F, Zuglian G, Imeri G, et al. Surviving COVID-19 in Bergamo province: a post-acute outpatient re-evaluation. Epidemiol Infect 2021; 149: e32.
31. Xiong Q, Xu M, Li J, Liu Y, Zhang J, Xu Y, et al. Clinical sequelae of COVID-19 survivors in Wuhan, China: a single-centre longitudinal study. Clin Microbiol Infect 2021; 27: 89-95.
32. Moreno-Pérez O, Merino E, Leon-Ramirez JM, Andres M, Ramos JM, Arenas-Jiménez J, et al; COVID19-ALC research group. Post-acute COVID-19 syndrome. Incidence and risk factors: a Mediterranean cohort study. J Infect 2021; 82: 378-83.
33. Chopra V, Flanders SA, O'Malley M, Malani AN, Prescott HC. Sixty-day outcomes among patients hospitalized with COVID-19. Ann Intern Med 2021; 174: 576-8.
34. Lopez-Leon S, Wegman-Ostrosky T, Perelman C, Sepulveda R, Rebolledo PA, Cuapio A, et al. More than 50 Long-term effects of COVID-19: a systematic review and meta-analysis. medRxiv [Preprint]. 2021 Jan 30: 2021.01.27.21250617.
35. Dennis A, Wamil M, Alberts J, Oben J, Cuthbertson DJ, Wootton D, et al; COVERSCAN study investigators. Multiorgan impairment in low-risk individuals with post-COVID-19 syndrome: a prospective, community-based study. BMJ Open 2021; 11: e048391.
36. Morin L, Savale L, Pham T, Colle R, Figueiredo S, Harrois A, et al. Writing committee for the COMEBAC Study Group. Four-month clinical status of a cohort of patients after hospitalization for COVID-19. JAMA 2021; 325: 1525-34.
37. Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet 2021; 397: 220-32.
38. Davis HE, Assaf GS, McCorkell L, Wei H, Low RJ, Re'em Y, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. medRxiv preprint. https: //doi.org/10.1101/2020.12.24.20248802v2.full.pdf. Last consultation date: 08/05/2021.
39. Sudre CH, Murray B, Varsavsky T, Graham MS, Penfold RS, Bowyer RC, et al. Attributes and predictors of Long-COVID: analysis of COVID cases and their symptoms collected by the Covid Symptoms Study App. Nat Med 2021; 27: 626-31.
40. Oronsky B, Larson C, Hammond TC, Oronsky A, Kesari S, Lybeck M, et al. A review of persistent post-COVID syndrome (PPCS). Clin Rev Allergy Immunol 2021 Feb 20: 1-9. [Epub ahead of print].
41. Salmon-Ceron D, Slama D, De Broucker T, Karmochkine M, Pavie J, Sorbets E, et al; APHP COVID-19 research collaboration. Clinical, virological and imaging profile in patients with prolonged forms of COVID-19: a cross-sectional study. J Infect 2021; 82: e1-4.
42. Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, et al. Post-acute COVID-19 syndrome. Nat Med 2021; 27: 601-15.
43. Remmelink M, De Mendonça R, D'Haene N, De Clercq S, Verocq C, Lebrun L, et al. Unspecific post-mortem findings despite multiorgan viral spread in COVID-19 patients. Crit Care 2020; 24: 495.
44. Eapen MS, Lu W, Gaikwad AV, Bhattarai P, Chia C, Hardikar A, et al. Endothelial to mesenchymal transition: a precursor to post-COVID-19 interstitial pulmonary fibrosis and vascular obliteration? Eur Respir J 2020; 56: 2003167.
45. Remsik J, Wilcox JA, Babady NE, McMillen TA, Vachha BA, Halpern NA, et al. Inflammatory leptomeningeal cytokines mediate COVID-19 neurologic symptoms in cancer patients. Cancer Cell 2021; 39: 276-83.e3.
46. Raman B, Cassar MP, Tunnicliffe EM, Filippini N, Griffanti L, Alfaro-Almagro F, et al. Medium-term effects of SARS-CoV-2 infection on multiple vital organs, exercise capacity, cognition, quality of life and mental health, post-hospital discharge. EClinicalMedicine 2021; 31: 100683.
47. Mo X, Jian W, Su Z, Chen M, Peng H, Peng P, et al. Abnormal pulmonary function in COVID-19 patients at time of hospital discharge. Eur Respir J 2020; 55: 2001217.
48. Shah AS, Wong AW, Hague CJ, Murphy DT, Johnston JC, Ryerson CJ, et al. A prospective study of 12-week respiratory outcomes in COVID-19-related hospitalisations. Thorax 2021; 76: 402-4.
49. Puntmann VO, Carerj ML, Wieters I, Fahim M, Arendt C, Hoffmann J, et al. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). JAMA Cardiol 2020; 5: 1265-73.
50. Patell R, Bogue T, Koshy A, Bindal P, Merrill M, Aird WC, et al. Postdischarge thrombosis and hemorrhage in patients with COVID-19. Blood 2020; 136: 1342-6.
51. Ayoubkhani D, Khunti K, Nafilyan V, Maddox T, Humberstone B, Diamond I, et al. Post-COVID syndrome in individuals admitted to hospital with COVID-19: retrospective cohort study. BMJ 2021; 372: n693.
52. Donnelly JP, Wang XQ, Iwashyna TJ, Prescott HC. Readmission and death after initial hospital discharge among patients with COVID-19 in a large multihospital system. JAMA 2021; 325: 304-6.
53. Taquet M, Geddes JR, Husain M, Luciano S, Harrison PJ. 6-month neurological and psychiatric outcomes in 236379 survivors of COVID-19: a retrospective cohort study using electronic health records. Lancet Psychiatry 2021; 8: 416-27.
54. Sampaio Rocha-Filho PA, Voss L. Persistent headache and persistent anosmia associated with COVID-19. Headache 2020; 60: 1797-9.
55. Liu JWTW, de Luca RD, Mello Neto HO, Barcellos I. Post-COVID-19 syndrome? New daily persistent headache in the aftermath of COVID-19. Arq Neuropsiquiatr 2020; 78: 753-4.
56. Arnold DT, Hamilton FW, Milne A, Morley AJ, Viner J, Attwood M, et al. Patient outcomes after hospitalisation with COVID-19 and implications for follow-up: results from a prospective UK cohort. Thorax 2021; 76: 399-401.
57. Dani M, Dirksen A, Taraborrelli P, Torocastro M, Panagopoulos D, Sutton R, et al. Autonomic dysfunction in 'long COVID': rationale, physiology and management strategies. Clin Med (Lond) 2021; 21: e63-7.
58. Goldstein DS. The possible association between COVID-19 and postural tachycardia syndrome. Heart Rhythm 2021; 18: 508-9.
59. Kanjwal K, Jamal S, Kichloo A, Grubb BP. New-onset postural orthostatic tachycardia syndrome following coronavirus disease 2019 infection. J Innov Card Rhythm Manag 2020; 11: 4302-4.
60. Miglis MG, Prieto T, Shaik R, Muppidi S, Sinn DI, Jaradeh S. A case report of postural tachycardia syndrome after COVID-19. Clin Auton Res 2020; 30: 449-51.
61. Raj SR, Arnold AC, Barboi A, Claydon VE, Limberg JK, Lucci VM, et al; American Autonomic Society. Long-COVID postural tachycardia syndrome: an American Autonomic Society statement. Clin Auton Res 2021 Mar 19: 1-4. [Epub ahead of print].

62. Townsend L, Moloney D, Finucane C, McCarthy K, Bergin C, Bannan C, et al. Fatigue following COVID-19 infection is not associated with autonomic dysfunction. PLoS One 2021; 16: e0247280.
63. Mazza MG, Palladini M, De Lorenzo R, Magnaghi C, Poletti S, Furlan R, et al; COVID-19 BioB outpatient clinic study group. Persistent psychopathology and neurocognitive impairment in COVID-19 survivors: effect of inflammatory biomarkers at three-month follow-up. Brain Behav Immun 2021; 94: 138-47.
64. Guedj E, Campion JY, Dudouet P, Kaphan E, Bregeon F, Tissot-Dupont H, et al. 18F-FDG brain PET hypometabolism in patients with long COVID. Eur J Nucl Med Mol Imaging 2021: 1-11. [Epub ahead of print].
65. Del Rio C, Collins LF, Malani P. Long-term health consequences of COVID-19. JAMA 2020; 324: 1723-4.
66. Stavem K, Ghanima W, Olsen MK, Gilboe HM, Einvik G. Persistent symptoms 1.5-6 months after COVID-19 in non-hospitalised subjects: a population-based cohort study. Thorax 2020; 76: 405-7.
67. COVID Symptom Study. How long does COVID-19 last? Kings College London 2020. URL: https: //covid19.joinzoe.com/post/covid-long-term?fbclid=IwAR1RxIcmmdL-EFjh_aI-. Last consultation date: 30.04.2021.
68. The COVID Mind Study. URL: https: //medicine.yale.edu/neurology/research/covid-mind-study/. Last consultation date: 30.04.2021.

Síndrome post-COVID-19: epidemiología, criterios diagnósticos y mecanismos patogénicos implicados

Introducción. Numerosos pacientes con COVID-19 leve o grave no tienen una recuperación completa y presentan una gran variedad de síntomas crónicos durante semanas o meses tras la infección, con frecuencia de carácter neurológico, cognitivo o psiquiátrico. Se revisan las evidencias epidemiológicas, los criterios diagnósticos y la patogenia del síndrome post-COVID-19.

Desarrollo. El síndrome post-COVID-19 se define por la persistencia de signos y síntomas clínicos que surgen durante o después de padecer la COVID-19, permanecen más de 12 semanas y no se explican por un diagnóstico alternativo. Los síntomas pueden fluctuar o causar brotes. Es una entidad heterogénea que incluye el síndrome de fatiga crónica posvírica, la secuela de múltiples órganos y los efectos de la hospitalización grave/síndrome poscuidados intensivos. Se ha descrito en pacientes con COVID-19 leve o grave y con independencia de la gravedad de los síntomas en la fase aguda. Un 10-65% de los supervivientes que padeció COVID-19 leve/moderada presenta síntomas de síndrome post-COVID-19 durante 12 semanas o más. A los seis meses, los sujetos relatan un promedio de 14 síntomas persistentes. Los síntomas más frecuentes son fatiga, disnea, alteración de la atención, de la concentración, de la memoria y del sueño, ansiedad y depresión. Se desconocen los mecanismos biológicos que subyacen, aunque una respuesta autoinmunitaria e inflamatoria anómala o excesiva puede tener un papel importante.

Conclusiones. Las manifestaciones clínicas son diversas, fluctuantes y variables, aunque predominan la fatiga y las quejas neurocognitivas. No existe un consenso definido sobre el síndrome post-COVID-19 y sus criterios diagnósticos no se han sometido a una evaluación psicométrica adecuada.

Palabras clave. Coronavirus. COVID-19. COVID persistente. SARS-CoV-2. Síndrome de fatiga crónica. Síndrome post-COVID.