Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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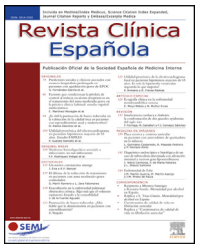

REVIEW

Persistent COVID-19 syndrome. A narrative review☆

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KEYWORDS
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Abstract As the coronavirus-2019 disease (COVID-19) pandemic, caused by the infection with severe acute respiratory syndrome (SARS-CoV-2) coronavirus type 2, has progressed, persistent COVID-19 syndrome is an increasingly recognized problem on which a significant volume of medical literature is developing. Symptoms may be persistent or appear, after an asymptomatic period, weeks or months after the initial infection. The clinical picture is as markedly heterogeneous and multisystemic as in the acute phase, so multidisciplinary management is required. In addition, their appearance is not related to the severity of the initial infection, so they can affect both mild patients, even asymptomatic, and seriously ill patients who have required hospitalization. Although it can affect people of any age, it is more common in middle-aged women. The sequelae can generate a high impact on the quality of life, and in the work and social environment. The objective of this paper is to review persistent COVID-19 syndrome, to know its clinical manifestations and the strategies for the management and follow-up of these patients.

PALABRAS CLAVE
COVID-19 persistente;
COVID-19 posagudo;
COVID de larga duración;
Secuelas COVID-19

Síndrome de COVID-19 persistente. Una revisión narrativa

Resumen A medida que ha avanzado la pandemia de la enfermedad por coronavirus 2019 (COVID-19), originada por la infección por el coronavirus de tipo 2, causante del síndrome respiratorio agudo severo (SARS-CoV-2), el síndrome de COVID-19 persistente es un problema cada vez más reconocido y sobre el que se está desarrollando un importante volumen de

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publicaciones. Los síntomas pueden ser persistentes o aparecer, tras un periodo asintomático, semanas o meses después de la infección inicial. El cuadro clínico es tan marcadamente heterogéneo y multisistémico como en la fase aguda, por lo que se requiere un manejo multidisciplinar. Además, su aparición no está relacionada con la gravedad de la infección inicial, por lo que pueden afectar tanto a pacientes leves, incluso asintomáticos, como a enfermos graves que han requerido hospitalización. Aunque puede afectar a personas de cualquier edad, es más frecuente en mujeres de edad media. Las secuelas pueden generar un elevado impacto en la calidad de vida, y en el ámbito laboral y social. El objetivo de este trabajo es hacer una revisión sobre el síndrome de COVID-19 persistente, conocer sus manifestaciones clínicas y las estrategias para el manejo y seguimiento de estos pacientes.

Introduction

In March 2020, the World Health Organization (WHO) declared a pandemic due to the illness caused by coronavirus 2019 (COVID-19), caused by the type 2 coronavirus infection responsible for severe acute respiratory syndrome (SARS-CoV-2). The clinical and epidemiological characteristics, pathogenesis, and complications of patients with COVID-19 in the acute phase have been widely reported, however the long-term consequences of the disease are yet not well defined[1,2].

As of early July 2021, over 191 million people had already been infected by SARS-CoV-2 around the world and the pandemic was still spreading widely in multiple countries. In its acute phase, severe COVID-19 is characterised by acute pulmonary disease that can manifest as pneumonia and with acute respiratory distress syndrome[3]. Numerous extrapulmonary manifestations have been described in multiple systems, including haematological, cardiovascular, renal, digestive, neurological, endocrine, ophthalmological and dermatological symptoms[3,4].

Mean symptom duration in the acute phase of the disease is 11.5 ± 5.7 days[5]. However, it has been observed that up to 10–15% of patients with COVID-19 can present persistent symptomatology weeks or even months after infection, though this percent may be even higher. The symptomatology reported after the acute phase is highly heterogeneous and includes fatigue, dyspnoea, chest pain, palpitations, gastrointestinal symptoms, mental confusion, anxiety, and depression, among many other associated symptoms[6].

Recent studies suggest that the so-called long COVID syndrome is emerging as a prevalent syndrome and refers to a highly diverse set of symptoms that persist long after a confirmed SARS-CoV-2 infection yet does not seem to have a clear association with the severity of the acute phase of COVID-19[7].

Definition of long COVID-19 syndrome

As of yet there is no consensus regarding the definition and timeline associated with the long-term symptoms of COVID-19. The terminology used to describe this clinical presentation varies widely in the literature and includes terms, among others, such as 'long haulers', 'late sequelae of COVID-19', 'chronic COVID-19 syndrome', 'post-acute COVID-19 syndrome' (PACS), and 'persistent COVID-19 syndrome'[8].

One of the most widely used terms is long COVID, collectively coined by patients themselves through social media, as the contraction of the long-term, cyclical, progressive, and multiphase disease[9]. The WHO currently recommends using the term 'post-COVID-19 condition' to refer to this clinical presentation, as it does not imply causality nor duration, and there are already specific ICD-10 (U09) and ICD-11 (RA02) codes to identify it[10].

With the aim of unifying criteria, the National Institute for Health and Care Excellence proposed the following definitions to describe the various symptomatic phases of SARS-CoV-2 infection[11]. Acute COVID-19 generally lasts up to 4 weeks from the onset of symptoms. When symptoms last longer than 4 weeks or late or long-term symptoms appear, then the term 'post-acute COVID-19' is used. The latter term encompasses both patients with long COVID (LC) and post-COVID-19 sequelae.

LC applies to symptoms that remain 4 or even 12 weeks beyond the acute infection, or that appear later on in the case of subjects with asymptomatic infection, but without the presence of irreversible organ damage. In terms of post-COVID-19 sequelae, patients tend to present a history of severe acute COVID-19 and symptoms resulting from structural damage secondary to complications suffered during the acute phase[12]. Making this distinction is important since these 2 sub-types of post-acute COVID-19 affect different patient profiles. While sequelae are predominant in older males, typically around 70 years-old and with associated comorbidities, LC tends to present in middle-aged women, around 40 years-old, without significant health issues.

Three clinical phenotypes within LC have been described: permanent (no changes during follow-up), relapsing/recurring (episodic and fluctuating course, with intervals of symptom exacerbation and remission), and slowly progressive improvement[13].

Pathophysiology

The fact that some patients with COVID-19 experience symptoms after recovering from acute infection is to be expected. Other infections, such as those caused by the Epstein-Barr virus, *Giardia lamblia, Coxiella burnetii, Borrelia burgdorferi* (Lyme disease) and the Ross River virus, as well as other coronaviruses such as SARS-CoV and MERS-CoV (causes of severe acute respiratory syndrome [SARS] and Middle East respiratory syndrome [MERS], respectively), are also associated with a higher risk of post-infectious sequelae.

These sequelae include long-term symptoms (months, even years) in the absence of active infection and include debilitating fatigue, musculoskeletal pain, neurocognitive difficulties, and mood disorders[14]. These acute, post-infection syndromes show a clear clinical and pathophysiological parallel with long COVID syndrome, particularly with SARS and MERS due to the phylogenetic similarities between the pathogenic coronaviruses responsible. The overlap of the genome sequence identity of SARS-CoV-2 is 79% with SARS-CoV-1 and 50% with MERS-CoV[15,16].

The potential mechanisms that contribute to the pathophysiology of LC are not yet clear, as numerous factors have been suggested (Fig. 1). A key element may be the presence of a state of chronic hyperinflammation[17]. The virus, in relation to the lungs, activates innate immunity, resulting in an inflammatory cytokine release cascade, including interleukin 6 (IL-6), IL-1, tumour necrosis factor alpha, and reactive oxygen species. This systemic cytokine elevation becomes involved in the development of pulmonary fibrosis[18] and cardiac and neurological lesions secondary to endothelial damage caused by the activation of fibroblasts with collagen and fibronectin deposition.

In addition, damage to the blood–brain barrier (BBB) has been observed with increased permeability for neurotoxic substances. Likewise, elevated levels of IL-6 can disrupt muscle metabolic homoeostasis[19] and exacerbate muscle loss, which is why some authors postulate that skeletal muscle may be impacted both by direct infection by SARS-CoV-2 of the myocytes, cells with elevated expression of the angiotensin-converting enzyme 2 receptor (ACE2), and indirectly through systemic cytokine release and subsequent muscle homoeostasis disruption, resulting in fatigue and muscle weakness.

Some studies[20] have aimed to detect the presence of T cells and NK lymphocytes in these patients and so it seems long COVID is characterised by alterations in the TCD4+ and TCD8+ cells, with two clinically important profiles distinguished: one that is more inflammatory (decrease in TCD4+ and increase in TCD8+) and another that is more immune (increase in TCD4+ and TCD8+).

Other suggested mechanisms include the autoimmune, via the existence of autoantibodies that act against modulator proteins which would disrupt immune function[21]. Another mechanism that may be involved is the hypercoagulability state associated with SARS-CoV-2 infection (thromboinflammatory state), responsible for the disproportionately high (20-30%) rates of thrombotic complications observed in patients with COVID-19[22].

In addition, a hypothesis has been proposed in which SARS-CoV-2 infection may affect the autonomic nervous system,[23] resulting in autonomic dysfunction mediated by the virus itself. This dysautonomia manifests as various syndromes of orthostatic intolerance including orthostatic hypotension, vasovagal syncope, and postural orthostatic tachycardia syndrome (POTS).

Another etiopathogenetic hypothesis may be the persistence of the virus in the body due to a weak or absent antibody response[24], relapses or reinfections, and other factors related to COVID-19 such as: immobilisation, nutrition disorders, mental disorders such as post-traumatic stress, or alterations in the intestinal microbiota[25].

Epidemiology and risk factors

Persistent symptoms following SARS-CoV-2 infection occur in both patients who required hospitalisation due to severe COVID-19 presentation and those who presented with mild paucisymptomatic disease, and even in subjects with asymptomatic infection[26].

Published studies have produced varying results on the prevalence of LC (Table 1). In the United Kingdom, around 10% of patients with documented SARS-CoV-2 infection remained symptomatic after 3 weeks, and a smaller proportion during months following acute infection[27].

An observational cohort study conducted in Michigan (United States)[28] which used a telephone survey to evaluate 488 patients discharged from hospital due to COVID-19 found that 32.6% of the patients reported persistent symptoms at 3 months, with 18.9% of the subjects with new or worsening symptoms; dyspnoea (23%) was the most prevalent symptom. A total of 38.5% of the patients were not able to return to their activities of daily living and 48.8% reported being emotionally affected by their health.

Other studies have reported even higher rates of prevalence. In Italy[29], 87.4% of 143 patients discharged from hospital due to COVID-19 presented persistent symptoms at mean follow-up of 2 months after the onset of symptoms, with the most common symptoms being fatigue (53.1%), dyspnoea (43.4%), joint pain (27.3%), and chest pain (21.7%). In a study conducted in France[30], 66% of patients still had symptoms at 60 days of follow-up. In a prospective cohort study conducted in Wuhan (China)[31] which evaluated 1,733 subjects 6 months after onset of COVID-19 symptoms, the majority of the patients (76%) reported at least one symptom, the most common being fatigue/muscle weakness (63%), sleep difficulties (26%), and anxiety/depression (23%).

There are 2 studies in Spain that stand out[32,33]. One retrospective multicentre cohort study conducted at 4 centres in Andalusia[32] analysed symptom prevalence in 962 patients who required hospitalisation during the acute phase: up to 63.9% presented symptoms after 6 months of follow-up, predominantly respiratory symptoms (42%), followed by systemic (36.1%), neurological (20.8%), and psychological (12.2%). Another national study conducted in the Primary Care service[33] via an online survey with 2,120 individual participants with a history of COVID-19 concluded that 5% of patients presented at least one symptom after an average of 185 days post-acute infection.

One of the main lines of investigation is the development of tools to be able to predict the likelihood of developing

Table 1 Principal studies of follow-up in patients with post-COVID-19 symptoms.

Authors	Country	Study type	n	Mean age (years)	Sex	Acute phase (H/NH)	Follow-up period	Persistence of symptoms (%)	Symptoms
Chopra et al.[28]	USA	Observational cohort	488	62	M: 51.8% F: 47.2%	H	2 months	32.6	Dyspnoea 23%; cough 15.3%; anosmia/ageusia 13.1%; chest pain 9.0%; inability to return to daily activities 32.4%; emotional impairment 38.5%
Carfi et al.[29]	Italy	Longitudinal prospective	143	56.5	M: 63% F: 37%	H	2 months	87.4	Fatigue 53.1%; dyspnoea 43.4%; joint pain 27.3%; chest pain 21.7%
Carvalho-Schneider et al.[30]	France	Longitudinal prospective	150	49	M: 46% F: 54%	H	2 months	66.0	Asthenia 40%; dyspnoea 30%; anosmia/ageusia 23%
Huang et al.[31]	China	Ambispective cohort	1,733	57	M: 52% F: 48%	H	6 months	76.0	Fatigue/muscle weakness 63%; insomnia 26%; anxiety/depression 23%; alopecia 22%; anosmia 11%; palpitations 9%; arthralgia 9%; loss of appetite 8%; dysgeusia 7%; dizziness 6%; diarrhoea 5%; chest pain 5%, and headache 2%
Romero-Duarte et al.[32]	Spain	Observational longitudinal	962	63	M: 46.3% F: 53.7%	H	6 months	63.9	Dyspnoea 28%; fatigue 22.1%; anosmia 20.8%; musculoskeletal pain 15.3%; diarrhoea 10.3%; dysgeusia 7.2%; fever 7%; anxiety 6.8%; chest pain 6%; abdominal pain 5.3%; headache 5.3%; insomnia 4.9%; anxiety 4.4%; paraesthesia 3.4%; movement disorder 3.4%, y disorientation/confusion 2.6%
Rodriguez-Ledo et al.[33]	Spain (online survey)	Observational cohort	2,120	43.3	M: 21% F: 79%	H NH	187 days	86.5	Asthenia 83.6%; general discomfort 79.3%; headache 63%; myalgia 60.7%; low mood 56.6%; arthralgia 56.4%; dyspnoea 56.2%, and chest pain 54.7%
Augustin et al.[35]	Germany	Longitudinal prospective	958	46	M: 46.4% F: 53.6%	H: 2.9% NH: 97.1%	4 months	27.8	Anosmia 12.4%; dysgeusia 11.1%; fatigue 9.7%, and dyspnoea 8.6%
Peghin et al.[36]	Italy	Ambispective cohort	559	53	M: 46.6% F: 53.4%	H NH	6 months	40.2	Fever 73.7%; anosmia/dysgeusia 60.3%; cough 47.9%, and fatigue 43.8%
Goërtz et al.[37]	Holland Belgium	Observational cohort	2,113	47	–	H: 5.3% NH: 94.7%	79 days	93.0	Fatigue 87%; dyspnoea 71%; chest pain 44%; headache 38%; muscle pain 36%; palpitations 32%, and cough 29%

F: female; H: hospitalisation; M: male; NH: no hospitalisation.

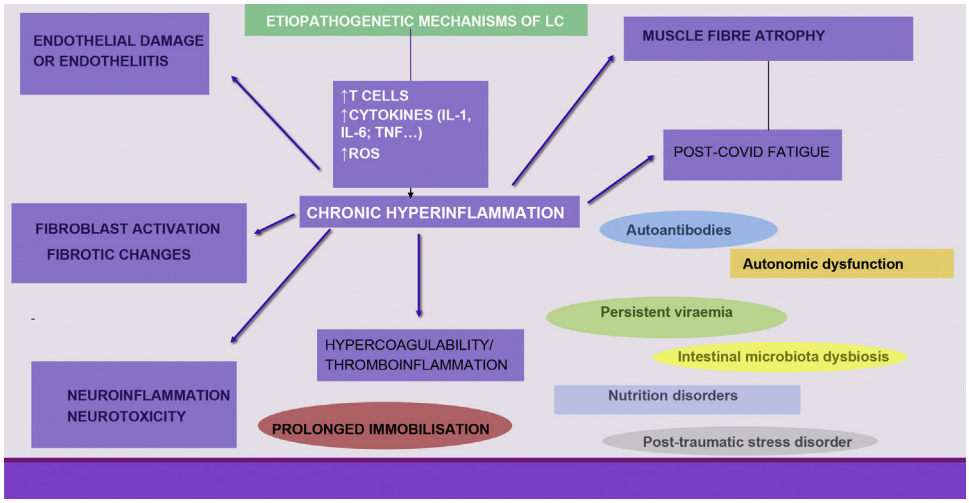

Figure 1 Etiopathogenetic mechanisms of long COVID-19.

LC. The risk factors related to LC have not been described in the majority of previous studies. It has been suggested that experiencing more than 5 symptoms in the first 7 days increases the risk of developing persistent symptoms[11]. Though the presence of anosmia, particularly in adults over the age of 70, has been related to a better prognosis in patients hospitalised due to COVID-19[34], it is considered to be the most predictive symptom for LC[12].

A German study[35], which included 958 non-hospitalised patients, found a significant association between the presence of long-term symptoms and a lower baseline level of IgG subclass antibodies, and the presence of anosmia and diarrhoea during acute COVID-19. Persistent symptoms have also been related to female sex, a larger number of symptoms at the start of the clinical picture, and admission to Intensive Care[36].

In summary, and in the absence of more rigorous studies, it is estimated that around 10–20% of subjects infected with SARS-CoV-2 will develop LC, although this prevalence varies due to the differences in methodology used and the populations analysed, particularly between studies including hospitalised patients and outpatient patients. What's more, in many cases no differentiation is made between true persistence of symptoms and sequelae of severe acute disease[12].

Symptomatology

The clinical presentation of patients with long COVID is highly heterogeneous. Over 200 associated symptoms affecting different organs and systems have been described[37] (Fig. 2). The most common long-term symptoms are fatigue (52%), cardiorespiratory symptoms (30–42%), and neurological symptoms (40%)[38], including symptoms of dysautonomia[39].

Symptoms and respiratory sequelae

The lung is the organ that is most affected by SARS-CoV-2 infection. Therefore, persistent respiratory symptoms and exercise limitations are common following severe COVID-19. The most common persistent respiratory symptom is dyspnoea,[28] followed by cough and chest pain[29,40]. The proportion of symptoms that are due to pulmonary sequelae is not well defined. Venous thromboembolism (VTE) and pulmonary fibrosis are the most significant pulmonary sequelae and, unlike other post-acute sequelae, present a clear association with the severity of the infection during its initial phase, and are more common in patients requiring admission to intensive care units and those in need of chronic home oxygen therapy.

The reported prevalence of VTE varies across the different studies (18–42%)[41]. It has been hypothesised that pulmonary artery occlusions could be caused by local pulmonary thrombi within the context of the inflammatory response (thromboinflammation)[42]. However, the long-term risks of chronic pulmonary embolism and consequent pulmonary hypertension are unknown.

Some studies in hospitalised patients report the onset of pulmonary fibrosis in up to 40% during subsequent follow-up[43,44]. The onset of pulmonary fibrosis is related to the duration and severity of the disease, as well as advanced age[43,44].

While descriptions of findings via high-resolution computed tomography (HRCT) remain scarce, after the acute phase 3 types of radiological patterns have been observed[45]: the first in which there is a predominance of ground-glass and organisational areas; a second pattern in which fibrosing changes in the septal thickening are observed, and a third pattern in which a combination of the 2 previous patterns occurs. The first pattern responds to low-dose corticosteroids over an extended period, while the response of the second is little to none.

Neurocognitive symptoms

It was initially thought that SARS-CoV-2 did not cross the BBB, but post-mortem studies have shown that the virus broadly attacks the central nervous system. The entry route for SARS-CoV-2 is the transmembrane enzyme protein ACE2, to which it binds with excellent affinity via the S spike pro-

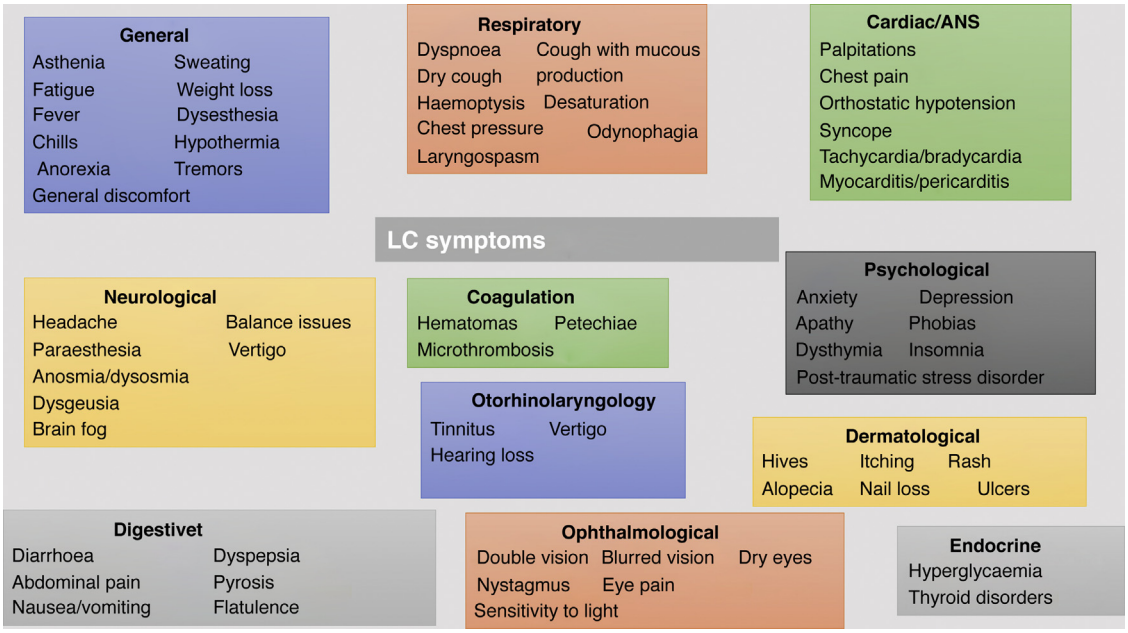

Figure 2 Symptomatology of long COVID-19.

tein. The ACE2 receptor expresses widely in the endothelial cells of the brain[46], and this S protein can directly damage the integrity of the BBB, and also induce a strong immune response generated by the cytokine release. In addition, it also seems that the virus affects the peripheral nervous system via the interaction with ACE2 receptors, which could result in neuromuscular complications[47].

During ongoing infection, around 36% of cases develop neurological symptoms[48], of which headache is the most frequent, both in the acute phase and in LC. These headaches are similar to migraines,48 and often refractory to typical analgesics, which is attributed to elevated levels of circulating cytokines. Cognitive impairment has also been observed, sometimes in a fluctuating manner, with symptoms such as 'brain fog' that can manifest as difficulty concentrating, memory loss, receptive language or impaired executive functions[49]. Anosmia and ageusia are also common and lingering, as are sleep disorders.

Cardiac symptoms and autonomic nervous system symptoms

Persistent chest pain has been reported in 20–30% of patients, though coronary artery disease must always be ruled out, particularly in patients with cardiovascular risk factors. In the event of persistent symptoms, the presence of myocarditis must be suspected, which has been reported via magnetic resonance imaging (MRI) in up to 60% of patients after 2 months of acute symptoms[50].

The existence of pericardial effusion, generally low in numbers, can be observed via MRI in 20% of the subjects during the acute phase, however symptomatic pericarditis is less frequent[51]. Palpitations are also common, though if recurrent these suggest a dysautonomia clinical picture such as inappropriate sinus tachycardia, or POTS if associated with symptoms of orthostatic hypotension.

Digestive symptoms

While some follow-up studies on patients hospitalised due to COVID-19 have not reported gastrointestinal or significant hepatobiliary sequelae[51], other authors have pointed out that digestive manifestations are present in over half of those affected by LC, including symptoms such as diarrhoea, meteorism, dyspepsia, abdominal pain, nausea, and vomiting. Some studies have reported the existence of changes to intestinal microbiota following acute infection, which remains in patients with LC[24]. In addition, it has been observed that the ileum is a preferred target of SARS-CoV-2, where it is able to remain for months[52].

Endocrine disorders

The acute phase of SARS-CoV-2 infection has been associated with stress hyperglycaemia in patients without known diabetes mellitus, as well as worse glycaemic control in those with prior diabetes[53]. Hyperglycaemia and the onset of diabetes mellitus also appear during follow-up of patients with LC[54]. Similarly, thyroid alterations have also been reported, such as Hashimoto's disease[55], Graves' disease[56], or subacute thyroiditis[57].

Dermatological symptoms

The most commonly reported sequela is hair loss which, according to a Chinese post-COVID-19 study, affected 20% of patients at 6 months follow-up[30,58]. This hair loss may be attributed to telogen effluvium resulting from a viral infection or a stress response[29].

Psychological symptoms

Individuals with COVID-19 may experience a series of psychiatric symptoms that persist or present after the

initial infection[59]. The most frequently reported symptoms are anxiety and depression (30–40%), followed by post-traumatic stress disorder, insomnia, and obsessive-compulsive symptomatology.

Follow-up and clinical-therapeutic approach

As we have seen, the symptoms of LC are just as heterogeneous as those observed in the acute phase of the disease and can manifest in an ongoing, fluctuating, or changing manner.

In the absence of a solid and standardised foundation for patients with long COVID, various clinical guidelines have been published with recommendations on long-term follow-up for said patients, both internationally[11] and nationally[12,60,61], and post-COVID-19 specialized consultation units have been set up in many hospitals.

These recommendations coincide in that, due to the complexity of this viral infection and the potential involvement of multiple systems and organs, a multidisciplinary assessment involving different medical specialists is needed to allow doctors to optimally monitor patient progress and offer the best possible care and management. Said recommendations suggest the need for an initial evaluation that includes a comprehensive physical examination, lab testing, and imaging tests. In addition, studying patient comorbidities and social and functional staus is also essential. All of this will enable doctors to perform a comprehensive assessment of the patient's baseline condition[23].

The proposed follow-up strategies recommend performing a basic analysis that includes a complete blood count, erythrocyte sedimentation rate, blood sugar, lipid profile, renal, ions, hepatic panel, albumin, lactate dehydrogenase, C-reactive protein, thyroid function tests, iron metabolism, vitamin B_{12}, folic acid, vitamin D, calcium, phosphorus, and coagulation tests as well as, in certain circumstances, and depending on the medical history and examination, other specific analytical assessments according to patient symptoms. In certain circumstances (persistent lymphopenia or altered lymphocyte count), it may be convenient to perform a basic cellular immunity study, including lymphocyte subpopulations (B cells, T cells, TCD4+, TCD8+), immunoglobulins, and a supplementary study to enable us to rule out other alternative illnesses[12].

The need to perform imaging studies in the follow-up of patients with COVID-19 remains a topic of controversy. The British Thoracic Society guidelines recommend performing a chest X-ray at 12 weeks in those patients who have experienced significant respiratory illness during the acute phase and, if alterations are observed, performing a chest CT with high-resolution reconstructions and contrast, according to the pulmonary thromboembolism protocol[62,63].

Other authors recommend performing a baseline pre-contrast high-resolution chest CT at 6 and 12 months and, if fibrotic alterations persist, to repeat this at 24 and 36 months[64]. One reasonable instruction would be to perform a chest CT in patients with persistent respiratory symptoms and alterations in their pulmonary function tests (PFT), or if anomalies persist in chest X-rays 3 months post-discharge or resolution of clinical pneumonia, this being a time when acute lesions should have resolved and would now be considered chronic[64].

Table 2 Clinical scales shown to be most useful for evaluating long COVID-19 based on symptomatology.

Quality of life	SF-36 survey
Dyspnoea	Medical Research Council modified scale
Pain	Spanish Graded Chronic Pain Scale
Fatigue	Modified Fatigue Impact Scale
Physical exercise	Global Physical Activity Questionnaire
Emotional disorders	Hospital Anxiety and Depression Scale
Sleep disorders	Pittsburgh Sleep Quality Index
Cognitive disorders	Modification to the Memory Failures of Everyday Questionnaire

Other supplementary tests that could be conducted depending on symptomatology include electrocardiogram, transthoracic echocardiogram, PFT, stress test, Holter monitor, ambulatory blood pressure monitoring or self-measured blood pressure monitoring, tilt table test for patients with dysautonomia symptomatology, and any other test considered necessary after conducting a thorough medical history and physical examination[12].

The guidelines recommend an initial consultation with patients who present persistent symptoms 4 weeks after acute COVID-19. This assessment may be in-person or over the phone depending on the warning signs, need to perform a physical examination, the patient's medical history, the severity and impact of the symptoms on their quality of life, or difficulties communicating. Follow-up strategies adhere to stricter protocols in hospitalised patients, with the recommendation being an initial telephone assessment at 4 weeks post-hospital discharge, followed by an in-person appointment at 12 weeks. If at that time the patient is asymptomatic, they will be given the all-clear; otherwise, they will be scheduled for follow-up[65].

The use of questionnaires or health measurement scales has been proposed as potentially useful in these patients since they allow doctors to make a comparison with their prior health status. It also enables follow-up of symptom evolution and helps determine the prognosis of the disease and standardise criteria among health professionals[66]. Diverse scales are currently used to evaluate the most frequent symptoms (Table 2), however there is a need to develop a specific measurement scale that globally reflects how these patients are affected[12].

In general, there is a trend towards spontaneous improvement of persistent post-COVID-19 symptoms, however it is difficult to determine the percent of patients who improve, and the time needed to achieve improvement, based on the heterogeneity of the studies published to date. Some prospective studies indicate that COVID-19 vaccination in patients with LC may significantly improve persistent symptoms, however more data are needed to confirm this theory[67].

Though various national and international clinical trials are currently under way, no specific treatment for LC is currently available. While we wait for results that can

guide us towards more effective and specific therapies, in the majority of cases symptomatic treatment is used, both pharmacological (analgesics, anti-inflammatory agents, bronchodilators, cough suppressants, antiemetic agents, antidepressants, anxiolytics, etc.) and non-pharmacological (food supplements, vitamin B_{12}, vitamin D, omega 3). Psychological and emotional support is also essential for these patients, and the need for multidisciplinary rehabilitation services must be considered (occupational therapy, physical therapy).

Conclusions

Persistent symptomatology and adverse events are frequent following SARS-CoV-2 infection, particularly, though not exclusively, after hospitalisation for severe COVID-19. Given the increase in cases and their potential impact on health care systems, there is a need to develop specific health plans and clinical follow-up programs with a multidisciplinary nature. This will help guarantee adequate care for this group, as achieving the quality care that these patients deserve may seem a challenge due to the excess demand on the national healthcare system at the current moment. Likewise, to improve clinical practice in this field, it is crucial to promote research strategies that make it possible to improve our knowledge of the pathophysiological aspects of the syndrome, harmonise diagnostic criteria, and develop effective therapies.

Data availability

Data will be made available on request.

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Conflicts of interest

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