

Long COVID: new perspectives and review of the literature

Georgios Pappas¹, Eleni Iasonidou²

¹*Institute of Continuing Medical Education of Ioannina, Greece*

²*Long Covid Greece patient society, Thessaloniki, Greece*



Summary

A major, but regrettably understudied, outcome of the pandemic is the significant percentage of patients exhibiting persisting symptoms, of varying localization and severity, for months after acute SARS-CoV-2 infection. These syndromes, collectively termed as Long Covid, may actually increase the pandemic burden for long after its end, leading to debilitation of previously healthy young individuals, in massive numbers. Long Covid as a term incorporates numerous syndromes, either systemic (as fatigue and expressions of dysautonomia) or localized (as residual lung damage or neurological complications). The etiology of Long Covid remains obscure, possibly attributed to viral persistence or continuous hyper-inflammatory reaction or even autoimmunity. Patient evaluation should be complex, extend to non-hospitalized pa-

tients, recognize the effect on the patient's quality of life, and the need for multi-task, but individualized, diagnostic and therapeutic approach. There are no specific pharmaceutical options at the time being, and the effect of vaccination on symptom alleviation has been inconsistent (although vaccination continues to reduce the odds of Long Covid development). Recognition of the medical and social burden of Long Covid remains a public health urgency.



Key words

Long Covid, SARS-CoV-2, orthostatic tachycardia syndrome, pulmonary fibrosis, dysautonomia

Corresponding author

Dr. Georgios Pappas, M.D.

*Institute of Continuing Medical Education
of Ioannina, Greece*

H. Trikoupi 10, 45333, Ioannina, Greece

Tel: +30 26510 28289

Email: gpele@otenet.gr

Introduction

When evaluating the burden of the pandemic caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), both science and society tend to focus strictly on the death toll and the significant economic losses. To a lesser extent, the burden of disrupted health practices irrelevant to SARS-CoV-2, such as regular vaccination campaigns and cancer screening/ early treatment, have also been addressed. What remains inadequately discussed though, both in scientific and social terms, is the burden of Long Covid.

Persisting syndromes post an acute infection are not novel: Numerous pathogens, either bacterial (as for example *Brucella*),¹ viral (HIV, Hepatitis B and C viruses, Epstein-Barr Virus recently implicated in multiple sclerosis pathogenesis, Varicella Zoster Virus),^{2,3} or parasitic (*Trypanosoma cruzi*),⁴ are potent, well-studied, chronic disease inducers. Yet, the sheer volume of patients infected from SARS-CoV-2 in a limited period, and with few certainties on their specific chronicity parameters, makes Long Covid a major public health emergency.⁵

In the UK, where a thorough follow up post acute disease is performed, recent estimates show that 2.8% of the population are Long Covid sufferers, with 57%

of these experiencing their acute infection more than a year ago.⁶

Nomenclature

Long Covid (hitherto LC) is an umbrella term encompassing various patterns of continuing morbidity, post acute SARS-CoV-2 infection. Other terms have been proposed for the description of (the whole or parts of) these syndromes, including Ongoing-Symptomatic-COVID-19, Post-Acute-Sequelae of COVID-19 Infection, or Post-Covid-19-Syndrome. Yet, LC was the term initially proposed by the first “long haulers”, and a term that seems to resonate with the patient community.⁷ The latter has been particularly active in bringing forth LC and in advocating the need for research on its etiology, diagnosis, and treatment, as well as its recognition by health and social security authorities as a chronic debilitation. Thus, the term LC will be used throughout this review.

LC refers to the presence of symptoms long after acute SARS-CoV-2 infection. These symptoms may persist, post acute infection, or may initially appear in the convalescence period. Obviously, regarding symptoms that persist, sequelae of severe acute infec-

tion are included in LC, for example residual pulmonary damage post intubation and Intensive Care Unit (ICU) stay. LC though is observed after mild disease also, one that may have never required hospitalization, or even emergency medical evaluation. LC may be further characterized by symptoms arising de novo in systems that were not involved in acute disease.

There is no consensus regarding the duration needed for a symptom to be characterized as part of LC, neither regarding the acceptable duration of the persistence of a symptom of acute disease, in order to be excluded from LC definition. Arbitrarily, both 4 weeks and 12 weeks have been used as cut-off points: Anything persisting (or initially manifesting) post 4 weeks can be considered as a "post-acute" syndrome, and anything persisting post 12 weeks can be safely considered as chronic, as LC. For example, the European Society of Clinical Microbiology and Infectious Diseases LC guidelines define LC as an entity post 12 weeks, while using the term post-acute COVID for the 4-12 week period.⁸ Duration of persisting symptoms is also incorporated in certain terminology approaches, with a minimal 2 month period considered as necessary.

Discrepancies in LC definition further obstruct appropriate research on the subject. Vast differences exist between reported patient cohorts, in terms of age, disease severity, thoroughness and breadth and duration of follow-up, diagnostic tools and interventions. Given that LC appears to be common, and that the pandemic has resulted in hundreds of millions of cases, one understands that the burden of LC is, at least, in the range of tens of millions of patients, some of them in healthcare-challenged countries or communities. Thus, defining the syndrome, securing its recognition beyond hospitalized, severe patients, appropriately evaluating its individual and social burden, and tentatively seeking for research and therapeutic support, should become a public health priority today and in the years to follow.

Incidence

Syndromes compatible with LC have been described in varying percentages, often reaching >50% of the subjects evaluated. Methods of evaluation differ, and are often based on questionnaires of personal health evaluation.⁹ These studies are often biased, regarding LC incidence, since patients that tend to participate in such studies and self-report persisting symptoms are patients that DO have symptoms (an individual convalescing from a mild acute course of SARS-CoV-2

without sequelae, may not be interested or spirited to participate in such a study, while one experiencing persisting symptoms may be more prone to actively search for, and participate). Differences in incidence can also be attributed to the width of LC definition for each study (the number and variety of symptoms evaluated). A similar pattern has been observed in studies where medical practitioners evaluate LC in person, with different diagnostic tools used, of varying sensitivity or specificity.

LC incidence may further fluctuate through follow-up time. Many studies have recently surpassed the 12-month follow-up period, almost unanimously underlining that a significant percentage of LC patients continue to exhibit, often debilitating, or even relapsing symptoms,^{10,11} even when the population studied reported no hospitalization during the acute phase, as in a recent Danish study.¹²

The incidence of LC in childhood has been less thoroughly evaluated, partly due to the limited interest in childhood disease during the initial pandemic waves (since childhood disease was considered disproportionately mild). During the predominance of Delta and Omicron variants though, most of the pediatric population, particularly in severely hit countries such as the US and the UK, has been exposed to the virus in conjunction with enhanced diagnostic ability. Thus, pediatric LC series have emerged, demonstrating a less common, but nevertheless existing issue of residual post-infectious disability, that may accumulate particularly in adolescent females.^{13,14}

A large Greek study, with the assistance of the Long Covid Greek patient Society was recently pre-published,¹⁵ and outlined the burden of LC even in non-hospitalized patients (whose symptom severity and persistence was not different to hospitalized patients'), as well as the low medical and social awareness on LC.

Pathophysiology

A single pathophysiologic route leading to all LC symptoms does not exist.¹⁶ Obviously, a part of LC spectrum can be attributed to residual tissue damage that happened during acute disease, as for example pulmonary fibrosis. Numerous theories are actively investigated, including viral persistence, ongoing inflammatory response, autoimmunity and molecular mimicry, triggering of pre-existing subclinical pathology, and even conversion disorders. It should be noted though that the latter is a frivolous theory that may inadvertently discourage patients from seeking appropriate medical advice. Recognition of the patho-

physiologic pathways involved is of paramount importance, since these pathways will navigate towards appropriate diagnostic and therapeutic approaches.

Viral persistence has been demonstrated in the enteric lumen of a significant percentage of recovering patients. It has been proposed that this may serve as a continuous trigger of symptoms, although there is no consistent analogy between particular symptomatology and demonstration of virus in specific tissue.

Proponents of an ongoing inflammatory response as the cause of LC often use the example of hyper-inflammatory responses in acute SARS-CoV-2 infection as an argument. Admittedly, acute lung pathology is largely due to host inflammatory response. Moreover, a significant subset of patients exhibit an hyper-inflammatory systematic course during acute disease. Furthermore, a multi-inflammatory systemic syndrome has been typically observed in pediatric patients, weeks after acute, usually mild, infection. Recent studies have indeed demonstrated such an hyper-inflammatory persistence in LC patients, particularly regarding interferon sub-types.¹⁷

Autoimmunity could serve as the etiology of various LC symptoms. It has been repeatedly demonstrated that acute infection serves as an inducer of various auto-antibodies. Research needs to further outline that these autoantibodies correlate to compatible clinical syndromes, and whether individual parameters predispose to the development of autoimmune-related LC.^{18,19}

Any evaluation of LC symptoms need to take into account the possibility that acute infection simply brought forth a previously undiagnosed pathology. Not all patients with post-infectious Diabetes Mellitus for example, are aware of their pre-infectious blood glucose levels. Similarly, a middle-aged male smoker with non-diagnosed, and thus untreated hypertension and increased blood cholesterol levels, may suffer from acute ischemic heart events during or slightly after the acute phase of SARS-CoV-2: in such a case, the infection was purely a non-specific trigger of a pre-existing disease, one that could erroneously be included in the LC spectrum.

Predisposing factors

Certain studies have attempted to evaluate a series of laboratory indices as potential markers of LC predisposition. The utility of these markers though, often measured strictly in research settings in limited numbers of patients, orientates only towards understanding of the cause of LC, and less towards developing a predicting test. Other studies have focused

on clinical characteristics of acute disease that may correlate with LC. Severe acute disease and ICU admittance are typically strong predictors of LC, although in these cases LC may simply describe the residual damage of severe disease, in need of pulmonary or systemic rehabilitation. Similarly, a severe acute complication as pulmonary embolism, myocardial infarction or myocarditis, any other major vascular disorder, or acute renal failure, will have long-standing consequences that can be, at least theoretically, considered as part of LC.

Varying factors have been implicated in studies: a large Fred Hutchinson Cancer Research patients series identified viral RNA-emia, Epstein Barr viremia, Diabetes Mellitus, and autoantibody patterns at the time of diagnosis, as predictors of evolution to LC.²⁰

Age and gender predispose to LC development, with most series underlining an increased incidence in females (contrary to the male predisposition for severe acute disease) and younger adults (contrary again to the vulnerability to severe disease of the elderly).²¹ Race on the other hand, has not been systematically demonstrated as a predisposing factor. The continuing diagnoses of LC after Omicron variant predominance, based on the systematic UK population follow-up,⁶ outline at the moment a lower LC risk for double-vaccinated individuals after Omicron BA.1 infections compared to Delta infections, but no such difference in triple-vaccinated individuals between Delta infections and either Omicron BA.1 infections or Omicron BA.2 infections. The latter might be more prone to reporting LC-related symptoms in the second month post acute disease, compared to Omicron BA.1- there were no differences in severity though.

Clinical Manifestations

Systemic: Fatigue remains the commonest symptom attributed to LC, and one of the most persistent.²² Varying in magnitude, it can be debilitating or relapsing after exercise or strain. Whether fatigue can be attributed to any specific metabolic disarray, changes of micro-vasculature, or inadequate oxygen delivery to peripheral tissues, remains to be clarified.

Exercise intolerance can be also described as fatigue, and its hallmarks may include reduced peak exercise aerobic capacity associated with alterations in tissue oxygen extraction.²³ A recent study demonstrated a low aerobic threshold even in young adult patients, persisting at 6 months post acute infection.²⁴ There is no consensus even for the tissue level damage which induces it, some advocating that it is a result of viral or inflammatory effect on the skeletal

muscle, while others supporting inflammatory or vascular alterations in brain areas. A recent study suggested a microthrombotic local etiology, one that could further be monitored by the evaluation of a sophisticated blood marker (Factor (VWF) Antigen (Ag):ADAMTS13 ratio).²⁵ Alternative theories include a role for mast cell activation syndrome.

Non-specific pain is also reported, including chest pain, musculoskeletal, or headaches.

Cardiovascular: Large prospective studies of individuals infected with SARS-CoV-2 have demonstrated a subsequent increased risk for cardiovascular events and cardiac pathology in general, in the months following acute infection.²⁶ Initial concerns due to magnetic resonance imaging evidence of residual heart involvement even in young healthy athletes, has largely subsided. Nevertheless, numerous studies have shown residual pulmonary hypertension or diastolic dysfunction post acute disease, even in non-hospitalized patients. Cardiac manifestations can significantly affect quality of life in LC, either through dyspnea, in the case of pericarditis/ myocarditis and resulting heart failure/ ischemic heart episodes, or through arrhythmias that may further need major therapeutic interventions.

Orthostatic tachycardia syndrome and orthostatic hypotension are common LC manifestations that may be debilitating, particularly if not accurately diagnosed. These syndromes could also be considered as neurological complications, since they are manifestations of dysautonomia, autonomous nervous system dysregulation- an involvement though that is manifested through the vascular system. Both syndromes can be readily diagnosed by simple clinical examination.

Hypercoagulability and endothelial dysfunction indices have been described in certain series, (fan) possibly correlating with the increased incidence of thromboembolic events observed in patients with a SARS-CoV-2 history, long after acute infection.²⁷

Pulmonary: Dyspnea remains one of the commonest complaints, one that could also be classified as systematic or cardiovascular also. Dyspnea can persist even in patients with mild acute disease, and can be attributed to dysfunctional breathing and/or dysautonomia. Although many researchers suggest a psychological background for dysfunctional breathing, a more pragmatic approach would investigate the role of brainstem involvement, particularly of the nuclei of respiration regulation.

The commonest, strictly pulmonary, manifestation is that of pulmonary fibrosis, secondary to acute lung

involvement and respiratory distress syndrome. Pulmonary rehabilitation may be lengthy in such cases. Fibrotic changes may also be observed with mild/moderate disease that does not require hospitalization.

Persistent cough may also be reported, although it may resemble post-infectious reactive cough of other entities. In a subset of patients though, persistent cough may actually reflect central nervous system pathology.²⁸

Neurologic: Brain fog is a popular, among patients, term, to describe extremes of cognitive disturbances and attention deficits, already observed as a syndrome in similar entities as other post-viral chronic neurologic sequelae, or chronic fatigue syndrome/ myalgic encephalomyelitis.²⁹ Paraclinical studies have demonstrated abnormalities in brain vasculature or magnetic resonance imaging in a considerable percentage of patients, with reduction of grey matter thickness and contrast as well as reduction in the overall brain size.³⁰ Central nervous system manifestations may also be attributed to changes in the blood brain barrier permeability, allowing for toxic substances to enter and injure parts of the brain. Recent studies have indicated myelin loss even after mild acute disease (in conjunction with increases in cytokine CCL11),³¹ and a role of SARS-CoV-2 in dementia pathology, striking in terms of speed of evolution and definitely more frequent than observed in other pneumonia patients.³²

Persistent involvement of cranial nerves is often described, either as anosmia/ parosmia³³ or as dysgeusia. The pathophysiology of these entities has been contested (whether it is a pure neurologic complication or a local, sensor, alteration); nevertheless, all these entities are troubling since they can often persist for months, without reliable therapeutic options, apart from extended behavioral approaches.

Involvement of the autonomous nervous system may manifest, apart from the aforementioned orthostatic syndromes, through persistent perspiration.

Mood disorders are often reported by patients; the clinician should differentiate between stress imposed by other, purely somatic, persisting symptoms, and typical psychological disorders.

Insomnia is a common complaint, attributed possibly to cortisol dysregulation or circadian sleep/ wake cycle disruption.

Gastrointestinal: Given that viral persistence, particularly in the gastrointestinal tract, has been proposed as one of the most probable mechanisms of LC, one would expect a significant amplitude of relevant

manifestations. Surprisingly, these have been scarce and non-specific, ranging from chronic diarrhea to vague gastrointestinal pain. The role of the gut microbiome disarray in LC development has also been contested: similarly though, one would expect more striking clinical manifestations from such a disarray.

Endocrine: Pancreatic involvement during acute SARS-CoV-2 infection has been repeatedly recognized, particularly regarding β -islet cells. Thus, one would expect new diagnoses of Diabetes Mellitus and worsening of pre-existing Diabetes Mellitus to be constant findings of LC series. A large pediatric series from the US has also implicated SARS-CoV-2 in the increased incidence of Type-1 Diabetes in children, in the year following acute infection.³⁴ Other endocrine disorders that are often reported include all kinds of thyroid disease (de novo or worsening hypo- or hyperthyroidism and thyroiditis).

Immune system: whether alterations of the immune system during LC is an effect and not a cause, remains a subject of debate. Spleen pathology has been observed in a minority of patients, and may contribute to lymphocyte-related immune deficits in LC.

Skin: The most annoying, and common, dermatologic LC manifestation is hair loss. Fortunately, it usually is due to telogen effluvium, meaning that it is transient and reversible. Despite a relative paucity of dermatologic LC symptom description in the literature, there is ample evidence from patient organizations and initiatives on such LC manifestations, including in pediatric LC.³⁵

Diagnosis

There are no single diagnostic tests that can set the diagnosis of LC. Similarly, not all that looks like LC can safely be attributed to LC. Thus initial diagnostic evaluation should: 1. outline all troublesome persisting manifestations and 2. specify whether these manifestations are actually part of the LC spectrum and not due to any underlying disorder. Another important parameter of the initial LC patient diagnostic evaluation is patient assurance that LC is indeed a clinical entity and not a conversion disorder, that they indeed suffer from something specific and it's not "all in their mind". Specifically developed validated questionnaires, such as the "symptom burden questionnaire for long covid" (SBQ-LC), may initially augment in approaching the patient.³⁶

Diagnostic approach should be individualized. A

broad range of laboratory tests are usually performed, both in terms of symptom etiology and LC mechanism clarification. Apart from the usual biochemical and inflammatory indices profile (the latter including C-Reactive Protein, serum protein electrophoresis, and serum ferritin, which tends to persist in significantly high levels in many new LC patients), this workup may include hormonal indices, cardiac markers (including B-type Natriuretic Peptide and Troponin-I) or Hemoglobin A1C for evaluation of prior diabetic predisposition and longitudinal evaluation of potential development or worsening of it. Studies demonstrating alterations of blood inflammatory markers of tissue damage and repair have recently emerged, indicating a correlation with certain LC patterns, these indices though cannot be widely performed.³⁷

Imaging diagnostic approach is of paramount importance for evaluation of pulmonary fibrosis resolution: a chest computed tomography scan and 3 months and repeatedly thereafter, is suggested by most specialist societies' guidelines. Pulmonary function tests may follow suit (with a restrictive pattern in diffusion capacity for carbon monoxide, DLCO, being the commonest abnormal result and analogous to acute disease severity) and indicate the necessity of any therapeutic intervention.

Cardiac ultrasound can be easily performed at minimal cost in order to broadly assess cardiac function. Series of cardiac magnetic resonance imaging of representative LC patients are increasingly published:³⁸ a similar recent one, demonstrated that, at 12 months post acute infection, a significant percentage of LC patients, including non-hospitalized during the acute phase ones, still exhibited residual pathology.³⁹

Brain magnetic resonance imaging of patients with neurologic and cognitive disorders would shed light in underlying mechanisms of relevant LC symptoms and their evolution through time, as would any positron emission tomography scan in individuals with systemic complaints. Admittedly, these are procedures that cost and should be individually, initially, performed at research level. Their results though might help us better understand the mechanism of certain LC symptoms and syndromes, and clarify the subset of patients that do need these interventions and might benefit from them.

As already mentioned, certain clinical syndromes, as orthostatic tachycardia syndrome, can be accurately diagnosed by clinical examination. A similar evaluation of pulmonary reserves can be made with evaluation of oxygen saturation and sense of breathlessness post an exercise tolerance test: many patients erroneously consider their saturation adequate, when

measured at rest, failing to recognize potential dramatic decreases upon minimal stress.

Therapeutic approaches

The single most important intervention when treating an LC patient is reassurance that his symptoms refer to something defined, partially understood, and subject of intense scientific research. It remains an important step in the patient's self-awareness and increased willingness to participate in future research and therapeutic interventions. On the other hand, the clinician should inform the patient that certain symptoms may persist for an unknown period of time, and that "return to normal" dates cannot be reliably predicted. Furthermore, the patient should be informed that their symptoms may exhibit a remitting-relapsing course, with certain symptom relapse related to external stimuli, including medications, activities, and even hormonal factors.

Approaching an LC patient, one has to take into account that there are no available treatments at the moment. The patient should be re-educated in self-management, in the handling of a disability, for an indefinite period of time. This demands a multi-task collaboration of varying specialties. A coordinating role should be reserved for the patient's physician, and cardiologists, pulmonologists, neurologists, endocrinologists, rehabilitation specialists and physiotherapists should participate with individualized therapeutic approaches, while public health officials and specialized nurses may focus on the aftermath of the LC effect in the patient's everyday life: the patient may not be able to return to work full-term, or may even be unable to serve themselves.

Ideally, one-stop LC healthcare facilities should have already been developed. In practice, many existing "LC follow-up clinics" may only focus on patients that were hospitalized, or patients with specific respiratory residual disease.

Behavioral therapy and graded exercise have been advocated by many as therapeutic approaches to fatigue, but their utility and appropriateness has been extensively questioned by experts.⁴⁰ The latter, stratifying the patient's priorities in everyday life and pacing their fulfillment, is extensively being studied. Patients should be advised on the need of extremely slow gradual return to exercise, particularly due to the risk of fatigue relapse when extensively and disproportionately increasing exercise strain. Many specialist societies advocate a role for alternative therapeutic approaches, including yoga.

Expressions of dysautonomia may further be re-

versed with salt and volume repletion, before pursuing more aggressive approaches (including calcium channel blockers).

Breathing exercises and body positioning practices are an essential part of managing LC-related dyspnea. The patient should essentially be re-educated in breathing through respiratory physiotherapy.⁴¹

Speech therapy might be warranted for individuals with persisting, post-acute dysphonia (possibly attributed to vagus nerve involvement).

There are no available pharmaceutical therapeutic approaches to LC at the moment. Numerous small trials have evaluated the utility of a wide array of agents, ranging from immunomodulating monoclonal antibodies with a role in acute infection to re-purposing of asthma or allergy medications. Theoretical discussions about the potential role of novel antivirals, as the combination of nirmatrelvir/ritonavir, have not translated yet to large clinical trials. Approaches focusing on reversing theoretical vitamin and elemental deficiencies have not been fruitful, since such shortages have not been demonstrated.

Caution should be advised for certain over-zealous protocols suggested by research teams. For example, a proposed therapeutic approach targeting the creation of micro-thrombi, with a triple anti-coagulative pharmaceutical regimen, should balance the extreme risks of hemorrhage with the theoretical potential of LC remission.

The benefit of SARS-CoV-2 vaccination in relieving LC symptoms has been evaluated in certain small trials. Overall, the response was inconsistent, with a minority of patients exhibiting a positive response (often transient and repeated, again transiently, by booster doses), an even smaller minority exhibiting worsening of the symptoms, and the majority of patients reporting minor alterations of their symptoms.⁴² One has to underline though that vaccination reduces the risk of LC after breakthrough infection, both by reducing the odds of such an infection and by reducing LC odds after such an infection per se.

Prognosis

There are too many unknowns about a too broad term as LC, in order to discuss prognosis. Longitudinal series with 6-month and 12-month evaluations have shown that a considerable percentage of patients exhibit symptom regression post 6 months; yet, another considerable percentage continues to suffer, more than 12 months after acute disease. Progress, both in understanding disease and treating it, may be just around the corner. Alternatively, the entity's etiology may con-

tinue to remain obscure and, with SARS-CoV-2 achieving endemicity, we may have to deal with an increasing number of previously healthy patients, suffering severe debilitation post an infection, often of mild/moderate severity. Not exactly a return to normal.

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Περίληψη

“Long COVID”: νεότερα δεδομένα και ανασκόπηση βιβλιογραφίας

Γεώργιος Παππάς^{*1}, Ελένη Ιασιωνίδου²

¹Ινστιτούτο Συνεχιζόμενης Εκπαίδευσης, Ιωάννινα, Ελλάδα

²Εταιρία Ασθενών “Long Covid”, Θεσσαλονίκη, Ελλάδα

*Υπεύθυνος αλληλογραφίας

Ένα μείζον, και δυστυχώς ανεπαρκώς μελετημένο, επακόλουθο της πανδημίας, παραμένει το σημαντικό ποσοστό ασθενών που εμφανίζουν επιμένοντα συμπτώματα, ποικίλης εντόπισης και βαρύτητας, μήνες μετά από την οξεία SARS-CoV-2 λοίμωξη. Τα σύνδρομα αυτά, που συλλογικά περιγράφονται ως Long Covid, μπορούν εν τέλει να αυξήσουν το φορτίο της πανδημίας επί μακρόν μετά το τέλος της, επάγοντας περιορισμούς στην ικανότητα εργασίας και την ποιότητα ζωής σε πολλούς, μέχρι πρότινος υγιείς, νέους ασθενείς. Το Long Covid ως όρος περιλαμβάνει πολλά σύνδρομα, είτε συστηματικά (όπως η κόπωση ή οι εκδηλώσεις της δυσавтоνομίας) ή εντοπισμένα (όπως οι υπολειμματικές πνευμονικές βλάβες ή οι νευρολογικές επιπλοκές). Η αιτιολογία του Long Covid παραμένει ασαφής, αποδιδόμενη πιθανώς σε κρυπτική παραμονή του ιού, ή συνεχιζόμενη υπερφλεγμονώδη αντίδραση, ή μηχανισμούς αυτοανοσίας. Η εκτίμηση του ασθενούς οφείλει να είναι σύνθετη, να επεκτείνεται και σε ήπια νοσήσαντες ασθενείς της κοινότητας, να αναγνωρίζει την επίδραση του συνδρόμου στην ποιότητα ζωής και την ανάγκη πολυπαραγοντικής, μα εξατομικευμένης, διαγνωστικής και θεραπευτικής προσέγγισης. Δεν υπάρχουν επί του παρόντος συγκεκριμένες θεραπευτικές φαρμακευτικές επιλογές, και η επίδραση του εμβολιασμού στην ύφεση των συμπτωμάτων έχει αποδειχθεί περιορισμένη (αν και ο προηγηθείς εμβολιασμός συνεχίζει να ελαττώνει τον κίνδυνο εμφάνισης Long Covid). Η αναγνώριση του ιατρικού και κοινωνικού φορτίου που συσσωρεύει το Long Covid αποτελεί ένα επείγον ζήτημα Δημόσιας Υγείας.



Λέξεις κλειδιά

Long Covid, SARS-CoV-2, σύνδρομο ορθοστατικής ταχυκαρδίας, πνευμονική ίνωση, δυσавтоνομία

References

1. Castaño MJ, Solera J. Chronic brucellosis and persistence of *Brucella melitensis* DNA. *J Clin Microbiol* 2009; 47:2084-2089.
2. Fung J, Lai CL, Yuen MF. Hepatitis B and C virus-related carcinogenesis. *Clin Microbiol Infect* 2009; 15:964-970.
3. Bjornevik K, Cortese M, Healy BC, Kuhle J, Mina MJ, Leng Y, *et al.* Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis. *Science* 2022; 37:296-301.
4. Bern C, Kjos S, Yabsley MJ, Montgomery SP. Trypanosoma cruzi and Chagas' Disease in the United States. *Clin Microbiol Rev* 2011; 24:655-681.
5. Groff D, Sun A, Ssentongo AE, Ba DM, Parsons N, Poudel GR, *et al.* Short-term and Long-term Rates of Postacute Sequelae of SARS-CoV-2 Infection: A Systematic Review. *JAMA Netw Open* 2021; 4:e2128568.
6. Office for National Statistics. Prevalence of ongoing symptoms following coronavirus (COVID-19) infection in the UK: 6 May 2022. Available at <https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/prevalenceofongoingsymptomsfollowingcoronaviruscovid19infectionintheuk/6may2022>. Accessed May 12, 2022
7. Munblit D, O'Hara ME, Akrami A, Perego E, Olhario P, Needham DM. Long COVID: aiming for a consensus. *Lancet Respir Med* 2022; S2213-2600:00135-00137.
8. Yelin D, Moschopoulos CD, Margalit I, Gkrania-Klatsas E, Landi F, Stahl JP, *et al.* ESCMID rapid guidelines for assessment and management of long COVID. *Clin Microbiol Infect* 2022; S1198-743X:00092-1.
9. Crook H, Raza S, Nowell J, Young M, Edison P. Long covid-mechanisms, risk factors, and management. *BMJ* 2021; 374:n1648.
10. Tran VT, Porcher R, Pane I, Ravaud P. Course of post COVID-19 disease symptoms over time in the ComPaRe long COVID prospective e-cohort. *Nat Commun* 2022; 13:1812.
11. Huang L, Yao Q, Gu X, Wang Q, Ren L, Wang Y, *et al.* 1-year outcomes in hospital survivors with COVID-19: a longitudinal cohort study. *Lancet* 2021; 398:747-758.
12. Sørensen AIV, Spiliopoulos L, Bager P, Nielsen NM, Hansen JV, Koch A, *et al.* Post-acute symptoms, new onset diagnoses and health problems 6 to 12 months after SARS-CoV-2 infection: a nationwide questionnaire study in the adult Danish population. *medRxiv* 2022.02.27.22271328; doi: <https://doi.org/10.1101/2022.02.27.22271328>
13. Haddad A, Janda A, Renk H, Stich M, Frieh P, Kaier K, *et al.* Long COVID Symptoms in a Prospective Cohort of Exposed and Infected Children and Adolescents and Their Parents One Year After SARS-CoV-2 Infection. Available at SSRN: <https://ssrn.com/abstract=4048831> or <http://dx.doi.org/10.2139/ssrn.4048831>
14. Roessler M, Tesch F, Batram M, Jacob J, Loser F, Weidinger O, *et al.* Post COVID-19 in children, adolescents, and adults: results of a matched cohort study including more than 150,000 individuals with COVID-19. *medRxiv* 2021.10.21.21265133; doi: <https://doi.org/10.1101/2021.10.21.21265133>
15. Katsarou MS, Iasonidou E, Osarogue A, Kalafatis E, Gatzonis S, Pappa S, *et al.* Collaborative Research for Long COVID Haulers in Greece (Characteristics, Clinical Assessment and Rehabilitation). Non-hospitalized and Hospitalized Long COVID Patients Share Similar Symptom Patterns. Preprints 2022, 2022030277 (doi: 10.20944/preprints202203.0277.v1).
16. Thompson RC, Simons NW, Wilkins L, Cheng E, Del Valle DM, Hoffman GE, *et al.* Acute COVID-19 gene-expression profiles show multiple etiologies of long-term sequelae. *medRxiv* [Preprint]. 2021 Oct 5:2021.10.04.21264434. doi: 10.1101/2021.10.04.21264434.
17. Phetsouphanh C, Darley DR, Wilson DB, Howe A, Munier CML, Patel SK, *et al.* Immunological dysfunction persists for 8 months following initial mild-to-moderate SARS-CoV-2 infection. *Nat Immunol* 2022; 23:210-216.
18. Baiocchi GC, Vojdani A, Rosenberg AZ, Vojdani E, Halpert G, Ostrinski Y, *et al.* Autoantibodies linked to autoimmune diseases associate with COVID-19 outcomes. *medRxiv* 2022.02.17.22271057; doi: <https://doi.org/10.1101/2022.02.17.22271057>
19. Woodruff MC, Walker TA, Truong AD, Dixit AN, Han JE, Ramonell RP, *et al.* Evidence of Persisting Autoreactivity in Post-Acute Sequelae of SARS-CoV-2 Infection. *medRxiv* 2021.09.21.21263845; doi: <https://doi.org/10.1101/2021.09.21.21263845>
20. Su Y, Yuan D, Chen DG, Ng RH, Wang K, Choi J, *et al.* Multiple early factors anticipate post-acute COVID-19 sequelae. *Cell* 2022; 185:881-895
21. Pérez-González A, Araújo-Ameijeiras A, Fernández-Villar A, Crespo M, Poveda E, Cohort COVID-19 of the Galicia Sur Health Research Institute. Long COVID in hospitalized and non-hospitalized patients in a large cohort in Northwest Spain, a prospective cohort study. *Sci Rep* 2022; 12:3369.
22. Verveen A, Wynberg E, van Willigen HDG, Boyd A, de Jong MD, de Bree G, *et al.* Severe Fatigue in the First Year Following SARS-CoV-2 Infection: A Prospective Cohort Study. *Open Forum Infect Dis* 2022; 9:ofac127.



23. Singh I, Joseph P, Heerdt PM, Cullinan M, Lutchman-singh DD, Gulati M, *et al.* Persistent Exertional Intolerance After COVID-19: Insights From Invasive Cardiopulmonary Exercise Testing. *Chest* 2022; 161:54-63.
24. Deuel JW, Lauria E, Lovey T, Zweifel S, Meier MI, Züst R, *et al.* Persistence, prevalence, and polymorphism of sequelae after COVID-19 in young adults. *medRxiv* 2022.02.11.22270836; doi: <https://doi.org/10.1101/2022.02.11.22270836>
25. Prasannan N, Heigtman M, Hillman T, Wall E, Bell R, Kessler A, *et al.* Impaired exercise capacity in post-COVID syndrome: the role of VWF-ADAMTS13 axis. *Blood Adv* 2022; <https://doi.org/10.1182/blood-advances.2021006944>
26. Xie Y, Xu E, Bowe B, Al-Aly Z. Long-term cardiovascular outcomes of COVID-19. *Nat Med* 2022; 28:583-590.
27. Fan BE, Wong SW, Sum CLL, Lim GH, Leung BP, Tan CW, *et al.* Hypercoagulability, endotheliopathy, and inflammation approximating 1 year after recovery: Assessing the long-term outcomes in COVID-19 patients. *Am J Hematol* 2022;10.1002/ajh.26575.
28. Song WJ, Hui CKM, Hull JH, Birring SS, McGarvey L, Mazzone SB, *et al.* Confronting COVID-19-associated cough and the post-COVID syndrome: role of viral neurotropism, neuroinflammation, and neuroimmune responses. *Lancet Respir Med* 2021; 9:533-544.
29. Guo P, Benito Ballesteros A, Yeung SP, Liu R, Saha A, Curtis L, *et al.* COVCOG 2: Cognitive and Memory Deficits in Long COVID: A Second Publication From the COVID and Cognition Study. *Front Aging Neurosci* 2022; 14:804937.
30. Douaud G, Lee S, Alfaro-Almagro F, Arthofer C, Wang C, McCarthy P, *et al.* SARS-CoV-2 is associated with changes in brain structure in UK Biobank. *Nature* 2022; 604:697-707.
31. Fernández-Castañeda A, Lu P, Geraghty AC, Song E, Lee MH, Wood J, *et al.* Mild respiratory SARS-CoV-2 infection can cause multi-lineage cellular dysregulation and myelin loss in the brain. *bioRxiv* [Preprint]. 2022 Jan 10:2022.01.07.475453. doi: 10.1101/2022.01.07.475453.
32. Qureshi AI, Baskett WI, Huang W, Naqvi SH, Shyu CR. New-Onset Dementia Among Survivors of Pneumonia Associated With Severe Acute Respiratory Syndrome Coronavirus 2 Infection. *Open Forum Infect Dis* 2022; 9:ofac115.
33. Walker A, Kelly C, Pottinger G, Hopkins C. Parosmia-a common consequence of covid-19. *BMJ* 2022; 377:e069860.
34. Barrett CE, Koyama AK, Alvarez P, Chow W, Lundeen EA, Perrine CG, *et al.* Risk for Newly Diagnosed Diabetes >30 Days After SARS-CoV-2 Infection Among Persons Aged <18 Years - United States, March 1, 2020-June 28, 2021. *MMWR Morb Mortal Wkly Rep* 2022; 71:59-65.
35. Long Covid Kids. Symptom Gallery. Available at <https://el.longcovidkids.org/long-covid-kids-symptom-gallery> Accessed May 15, 2022
36. Hughes SE, Haroon S, Subramanian A, McMullan C, Aiyegbusi OL, Turner GM, *et al.* Development and validation of the symptom burden questionnaire for long covid (SBQ-LC): Rasch analysis. *BMJ* 2022; 377:e070230.
37. PHOSP-COVID Collaborative Group. Clinical characteristics with inflammation profiling of long COVID and association with 1-year recovery following hospitalisation in the UK: a prospective observational study [published online ahead of print, 2022 Apr 22]. *Lancet Respir Med* 2022;S2213-2600:00127-00128.
38. Borlotti A, Thomaides-Brears H, Georgiopoulos G, Banerjee R, Robson MD, Fusco DN, *et al.* The Additive Value of Cardiovascular Magnetic Resonance in Convalescent COVID-19 Patients. *Front Cardiovasc Med* 2022; 9:854750.
39. Roca-Fernández A, Wamil M, Telford A, Carapella V, Borlotti A, Monteiro D, *et al.* Cardiac impairment in Long Covid 1-year post-SARS-CoV-2 infection. *medRxiv* 2022.04.03.22272610; doi: <https://doi.org/10.1101/2022.04.03.22272610>
40. Herrera JE, Niehaus WN, Whiteson J, Azola A, Barratta JM, Fleming TK, *et al.* Multidisciplinary collaborative consensus guidance statement on the assessment and treatment of fatigue in postacute sequelae of SARS-CoV-2 infection (PASC) patients. *PM R* 2021; 13:1027-1043.
41. Montani D, Savale L, Noel N, Meyrignac O, Colle R, Gasnier M, *et al.* Post-acute COVID-19 syndrome. *Eur Respir Rev* 2022; 31:210185.
42. UK Health Security Agency. The effectiveness of vaccination against long COVID. Available at <https://www.pslhub.org/learn/coronavirus-covid19/data-and-statistics/the-effectiveness-of-vaccination-against-long-covid-a-rapid-evidence-briefing-february-2022-r6159/>, Accessed May 12, 2022