

Long COVID: long-term effects?

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KEYWORDS

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The term Long COVID (or Post COVID) describes a condition characterized by persistence of symptoms for at least 12 weeks after the onset of COVID-19. It may last several months but the duration is still matter of observation. The symptoms and the clinical manifestations are clinically heterogeneous and suggesting involvement of multi-organs/systems, including the cardiovascular system. The general recurrent symptoms include fatigue, breathlessness, myalgia, headache, loss of memory, and impaired concentration. Patients report loss of their previous psychophysical performance. Cardiovascular involvement manifests with common symptoms such as palpitations and chest pain, and, less commonly, with events such as late arterial and venous thromboembolisms, heart failure episodes, strokes or transient ischaemic attack, 'myo-pericarditis'. The diagnostic criteria are mainly based on the narrative of the patients. Measurable biomarkers or instrumental findings or clinical events are not yet framed in a shared diagnostic framework. The open question for clinicians and researchers is whether biomarkers, electrocardiogram, non-invasive imaging, and clinical monitoring should be included in a shared diagnostic protocol aimed at defining the diagnostic path and protecting patients at risk of unexpected events.

Introduction

Although severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes an acute respiratory disease, numerous patients who recovered from COVID-19 subsequently experience a constellation of late heterogeneous symptoms and events lasting for more than 3 months after the onset of the acute infection.¹ After an initial social media movement triggered by patients, the medical-scientific community recognized, in the spectrum of symptoms and late manifestations, a possible link with the COVID-19.

The condition was named LONG-COVID or POST-COVID (*Figure 1*). These terms were introduced to provide a common nosology suitable for coding all the symptoms and clinical evidence of organs/systems involvement. World Health Organization (WHO) acknowledged that 'Some people who have had COVID-19, irrespective of having been hospitalized, continue to experience symptoms, including fatigue, cardiovascular, respiratory and neurological symptoms'.² WHO specified the use of the term POST-COVID as follows: 'the need for disambiguation between acute disease, late effects or lengthy course led to the neutral formulation of Post-COVID'. The latest WHO update now includes a new ICD code for the post-COVID-19 condition (U09 + specific condition).

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CARDIOVASCULAR LONG COVID		
COVID 19: ACUTE	COVID 19: EVOLUTION	LONG COVID
CARDIOGENIC SHOCK ACUTE HEART FAILURE ACUTE ISCHEMIC SYNDROMES ACUTE THROMBOEMBOLIC EVENTS MYOCARDIAL DAMAGE MYOPERICARDITIS STROKE ARRHYTHMIAS	DEATH SURVIVAL WITH RESIDUAL ORGAN DAMAGE SURVIVAL WITH REPAIR OF THE ACUTE DAMAGE RECOVERY <ul style="list-style-type: none"> • CLINICAL • FUNCTIONAL • STRUCTURAL PERSISTENT CARDIOVASCULAR SYMPTOMS	CRITERIA <ul style="list-style-type: none"> - PERSISTENCE > 12 WEEKS FOLLOWING THE ACUTE PHASE - SYMPTOMS, CONSTITUTIONAL, CARDIOVASCULAR - BIOMARKERS <ul style="list-style-type: none"> - COAGULATION: FIBRINOGEN, D-DIMER, PLATELETS - MYOCYTE DAMAGE: HSTNI - SYSTEMIC INFLAMMATION, CRP, LEUKOCYTE COUNT - IMMUNITY/CYTOKINES (IL-6) - MYOCYTE LOAD/STRESS BNP, NTProBNP - DE NOVO ECG CHANGES AND IMAGING FINDINGS: ZDTTE, CMR, OTHERS (PET?) - DE NOVO EVENTS IN LOW-RISK SUBJECTS
CONTEXT OF OBSERVATION: HOSPITALIZATION IN ICU OR NON-ICU WARDS OR OUTPATIENT SETTING. FACTORS CONTRIBUTING TO THE RISK OF INFECTION: AGE, SEX, CHRONIC COMORBIDITIES/DISEASES.	CONTEXT OF OBSERVATION OF SURVIVORS: REHABILITATION CLINICS OR SERVICES FOR PATIENTS WHO WERE ADMITTED TO ICU OR OTHER HOSPITAL WARDS; FAMILY PHYSICIANS. SELF-MANAGED SYMPTOMS.	CONTEXT OF OBSERVATION OF SURVIVORS: LONG COVID CLINICS WITH MULTIDISCIPLINARY EVALUATION INCLUDING CARDIOLOGISTS. EITHER POST-ICU AND NON ICU WARDS OR NON HOSPITALIZED PATIENTS MAY COMPLAIN LONG COVID SYMPTOMS / MANIFESTATIONS

Figure 1

Epidemiology

The early studies included only patients who had been hospitalized with acute COVID-19. Percentages of Long COVID in survivors ranged between 30% and 80%; patients reported at least one symptom lasting several months after the resolution of the acute phase of the disease.³ However, most patients with COVID-19 did not need hospitalization. Therefore, a global estimate can only rely on systematic follow-up of patients who have tested positive for the virus or demonstrated positive serology. The expected prevalence of post COVID-19 symptoms is around one-third of cases of the entire COVID-19 population.⁴ The burden is such that it has led to the activation of Long-COVID outpatients clinics in all countries affected by the pandemic.⁵ Patients who complain of persistent or new-onset symptoms can spontaneously refer to these centres; with greater epidemiological efficacy, the centres themselves can activate monitoring programmes for COVID-19 survivors, offering care and performing research on the mechanisms and causes of Long COVID, meeting the WHO objective of 'studying patients beyond the initial acute course of illness to understand the proportion of patients who have long-term effects, how long they persist, and why they occur'.

Diagnosis: symptoms and times

Symptoms

The heterogeneous clinical manifestations include both the constitutional symptoms such as fatigue, difficulty or loss of attention and memory disturbances, and the organ/system-related symptoms and events involving immunological, respiratory, cardiovascular, central and peripheral neurological, muscular, haematological, gastrointestinal, renal/urinary, endocrine and cardiometabolic systems.⁶ Generally, the diagnosis of Long COVID or Post-COVID syndrome is made in the presence of one or more symptoms commonly described by patients as unprecedented deterioration of the individual psycho-physical status. In itself, the narrative 'something has changed even if I can't

understand what it is' anticipates a multifaceted description of subjective perceptions, variously interpreted, but all traced back to COVID-19 as the most plausible cause.³ In this context, cardiovascular involvement calls for the identification of measurable biomarkers with diagnostic specificity.⁷

Long-lasting symptoms

Long COVID is diagnosed at least 12 weeks after the onset of COVID-19. Symptoms can represent a continuum with those of the acute phase, therefore suggesting persistence of symptoms; it has not yet been established whether a 'chronic' Long COVID does exist. The Long COVID has a beginning but not a precise end. The most recent studies now report prevalence data 1 year after the onset of infection: 'at month 12, only 22,9% of patients are completely free of symptoms'.⁹ Maintaining monitoring is essential to define temporal boundaries and, in particular, the end of symptoms.⁸ Individual symptoms can last for variable time intervals, some of them regressing, others persisting longer. For example, neurocognitive long COVID symptoms can persist at least for 1 year after COVID-19 symptom onset.⁹ Long recovery duration seems to be related to high severity but has also been reported independently of acute-phase severity, hospitalization, and admission to intensive care units.⁸

Who develops long COVID?

Long COVID seems to be more common in women than in men, but this could reflect greater severity of COVID-19 in males, who demonstrated higher hospitalization rates and risk of mortality. Therefore, the estimates concerning Long COVID do not reflect the epidemiology of COVID-19, but only that relating to COVID-19 survivors and excludes the high number of deceased patients, mainly males, old age. The distribution by age in Long COVID should be read from the perspective of survivors of the acute phase: this condition is in fact prevalent in middle-aged people. On the one hand, COVID-19 is less frequent in younger people, on the

other, many old people have died. A recent model that uses age, sex, and the number of symptoms reported in the first week, seems to successfully predict whether a person would get Long COVID.¹⁰ About the paediatric age, at least 10% of children who test positive for the virus still have persistent symptoms that deserve to be properly assessed.¹¹

Two main groups can be distinguished: (i) patients with pre-existing comorbidities, cardiovascular, respiratory, neurological, gastrointestinal, nephrological, endocrine, etc. (ii) patients without known comorbidities prior to COVID 19.

The analysis of the relationship between acute phase, need for hospitalization in the intensive care unit (ICU), non-ICU wards vs. no hospitalization, demonstrates that Long COVID can occur regardless of frailty or pre-existing morbidities.

Cardiovascular involvement: symptoms

Palpitations

Palpitations are commonly complained by patients potentially affected by Long COVID; they may correspond to simple sinus tachycardias or supraventricular or ventricular arrhythmias. These manifestations have no diagnostic specificity, but must be carefully considered as they are a frequent cause of requests for medical assistance.¹² However, *de novo* electrocardiographic changes, absent before COVID-19, and even absent at the time of recovery, are rarely described. In fact, these changes should be considered *de novo* only when a baseline pre-COVID electrocardiogram (ECG) is available.¹³

Chest pain

Chest pain is another symptom commonly complained of by patients with Long COVID. These pains often do not correspond to instrumental findings useful for a correct interpretation.⁷

Postural tachycardia syndrome

When excessive orthostatic tachycardia and symptoms of orthostatic intolerance for at least 3 months are part of long COVID syndrome, they may lead to a diagnosis of post-COVID-19 postural tachycardia syndrome (POTS). The diagnosis is made in presence of an increase of >30 b.p.m. in adults (>40 b.p.m. in patients aged 12-19 years) within 10 min of assuming the upright position in the absence of orthostatic hypotension with associated symptoms of orthostatic intolerance. A number of case reports have recently described patients who developed POTS after SARS-CoV-2 infection. Currently, little is known about the pathophysiology and the natural history of long-COVID POTS.¹³

Cardiovascular involvement: findings and events

Heart failure

Although many review articles include heart failure (HF) amongst the possible clinical manifestations of the Long COVID syndrome, studies that have documented the onset of *de novo* HF in patients recovered from COVID-19 are

rare. In most studies, data on patients with pre-existing HF possibly worsening after COVID-19 are reported along with the few cases of *de novo* HF. This limits the ability to identify those cases in which HF is indeed a clinical manifestation of Long COVID. Maestre-Muñiz *et al.*¹⁴ report HF onset in 11 of the patients (2.0%) who recovered from COVID-19. Another seven patients with previously known chronic HF required treatment augmentation after suffering from COVID-19. Other studies comparing cardiovascular manifestations in COVID-19 and Long COVID reveal the absence of HF among the *de novo* manifestations of Long COVID.¹²

The venous thrombotic manifestations

The thromboembolic events recorded in Long COVID within the first year after recovering from acute COVID-19 include deep vein thrombosis (2.4%) and pulmonary thromboembolism (1.7%).¹⁴ A follow-up strategy to evaluate the burden of residual risk, small vessel injury and potential haemodynamic sequelae has been proposed looking at the state of lung perfusion.¹⁵

Arterial thrombosis

Arterial thrombosis in subjects without known vascular pathology is often described as occasional in case reports or small clinical series. In addition to the coronary arteries, with manifestations of acute coronary syndromes in subjects at low risk and without significant coronary artery disease on angiography,¹⁶ unexplained thrombotic/thromboembolic events continue to be described at the peripheral/cerebral/splanchnic level.¹⁷ The severity of acute infection, the need for hospitalization in ICU or non-ICU wards, as well as the management of infections in the non-hospitalized setting, do not correlate with these *de novo* thromboses.

De novo arrhythmias

Although establishing the timing of the onset of arrhythmic episodes is difficult, supraventricular and ventricular arrhythmias together with conduction disturbances have been reported among the possible manifestations of long COVID.¹³

Myocarditis, pericarditis, myopericarditis

Myocarditis is a debated issue in both COVID-19 and Long COVID mainly due to diagnostic incompleteness and therefore lack of certainty, in particular pathological evidence. In several studies, the diagnosis of myocarditis is based either on the levels of isolated hypertroponinaemia or on the combination of hypertroponinaemia and signs of myocardial oedema on CMR.¹⁸ It would be correct to describe persistent hypertroponinaemia and/or oedema, without forcing its interpretation into myocarditis.

Cardiometabolic conditions

Diabetes, both type 1 and type 2, is associated with severe COVID-19 and Long COVID. Interventions to target multiple risk factors, combined with the use of novel glucose-lowering agents that improve metabolic function and the key processes that are impaired in COVID-19, should be the

preferred therapeutic options for the management of people with long COVID.¹⁹

Measurable markers and findings

The diagnosis of Long COVID requires a paradigm shift in the physician's aptitude to accept only descriptive reports for the diagnosis; the clinical epidemiology data largely based on the narrative of the symptoms show such high percentages that the condition is perceived as a real 'pathology', to which WHO has assigned the formal recognition in the ICD10 U09 code. However, this code is rarely used in clinical practice, limiting its possible role in epidemiological studies. In addition, many countries are still adopting ICD-9 system. Two major diagnostic contributions should be highlighted: biomarkers and instrumental and imaging evidence, particularly useful if it is possible to demonstrate their absence in the pre-COVID phase.

The most frequently tested biomarkers are those related to (i) systemic inflammation such as e.g. C-reactive protein, neutrophil, lymphocyte, and platelet counts; (ii) immunological activation such as the dosage of cytokines [typically interleukin (IL) 6]; (iii) hypercoagulability markers, such as levels of fibrinogen, D-Dimer, or functional tests of platelet hyperactivity; (iv) myocyte damage, such as plasma levels of high-sensitivity troponin I; (v) myocardial stress/load such as natriuretic peptides. Less frequent is the dosage of alarmins (HMGB1; HSP; IL-1 α ; IL-33; LL-37; S100; defensins), investigated both in the acute phase and in Long COVID.²⁰

Instrumental evidence of persistent and non-pre-existing damage is difficult to demonstrate because it should be based on the absence of the finding in the pre-COVID phase. However, imaging studies, including cardiac magnetic resonance, are on the rise and provide information that is insufficient to assign the findings to Long COVID with certainty. Between seropositive and seronegative groups, there may be no differences in cardiac structure (left ventricular volumes, mass, atrial area), function (ejection fraction, global longitudinal shortening, aortic distensibility), tissue characterization (T1, T2, extracellular volume fraction mapping, late gadolinium enhancement).²¹

Pathogenetic hypotheses

The pathogenesis of Long COVID is unknown. The wide heterogeneity of the symptoms suggests that it is a multisystem disorder. The hypothesis of a direct role of the virus and its possible persistence must be carefully considered, also because there is no direct evidence of viral persistence with replication properties. Conversely, the possibility exists that fragments of the viral genome or viral antigens, lacking infectious capacity, persist over time. A very recent study reports the possibility that the viral genome is retrotranscribed and integrated into the DNA, thus becoming a driver and source of the synthesis of RNA and antigens of viral origin. On the one hand, the authors plausibly suggest that this phenomenon is the basis of persistently positive tests in patients recovered from COVID-19²²; on the other

hand, these molecules may keep the immune-inflammatory-procoagulant cascade active, potentially explaining e.g. late thrombotic events. The immunological/immune-mediated hypothesis could also be linked to this possibility. This hypothesis is supported both by the pathogenetic mechanisms of COVID-19, with cytokine storm induced by the inflammatory-immune reaction to the infection, and by early studies reporting an increase in autoantibodies, e.g. ANA titer elevations,⁹ which however do not have diagnostic specificity. A common research front pursued by several teams explores the persistence of both viral genome/peptides and inflammation, assessing the possibility that, among the immunomodulating factors/cytokines, substances with neuromodulator effects could be at the basis of common neurological symptoms in these patients. The heterogeneity of symptoms, however, in particular mental-health difficulties, anxiety, panic crises, and cognitive and memory impairments, must keep open the possibility of pursuing research objectives different from those more plausible.

Treatment

The treatment of patients whose diagnosis is only based on symptoms reflects the lack of measurable markers of the disease, making the treatment empirical and oriented to the sole purpose of controlling subjective symptoms. Although biochemical tests or non-invasive instrumental evaluations are regularly performed, there may be no diagnostic contribution of biomarkers, or instrumental data demonstrating organ or tissue damage. Vice versa, when symptoms are associated with evidence of organ damage [increased levels of biomarkers (e.g. of myocyte damage), or ECG changes, or imaging findings, or acute events] the treatments are guided by the clinical phenotypes.²³

Impact

The global impact of Long COVID cannot be ignored: it concerns individual psychophysical performance, the social, productive, and economic spheres in the medical, financial, and working context. The loss of efficiency at work, the need for medical support, the diagnostic demand make this condition worthy of a new vision of investments in the health sector, also aimed at containing the societal consequences of the outbreak and manage occupational health.²⁴

In fact, the SARS-CoV-2 pandemic shifted the attention away from return-to-work after health problems to resuming work during an outbreak, dealing with lockdown, and taking special account of workers with vulnerabilities.

Conclusions

Long COVID is a still not completely understood entity comprising a constellation of heterogeneous symptoms of uncertain aetiology and uncertain direct causality of SARS-CoV-2 infection. Most of this uncertainty is attributable to the largely retrospective data published to date. The systematic and prospective collection of clinical follow-up

data, facilitated by the opening of Post-COVID outpatient clinics, together with an accurate comparison of pre- and post-SARS-CoV-2 clinical characteristics of patients, may help substantiate their consistency. Moreover, to reach the therapeutic goal, many questions on SARS-CoV-2 pathogenetic mechanisms are still to be answered.

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