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REVIEW

The long-term cardiovascular impairment of COVID 19: need for clarity in definition and terminology

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ABSTRACT

Clinical experience and several large studies in the field have found that SARS-CoV-2 infection can cause long-term persistent cardiovascular (CV) impairment beyond the acute phase of the disease. This has resulted in a major public health concern worldwide. Regarding COVID-related long-term involvement of various organs and systems, using specific definitions and terminology is crucial to point out time relationships, lingering damage, and outcome, mostly when symptoms and signs of CV disease persist beyond the acute phase. Due to a lack of a common standardized definition, investigators have used interchangeable terms such as "long COVID," "post-COVID," or "post-acute sequelae of COVID-19" to describe CV involvement, thus causing some confusion. For the sake of clarity, the aim of this paper is to discuss the definition and terminology used in defining sequelae after the acute phase of COVID-19, thus pointing out the meaning of definitions like acute cardiac injury, post-acute sequelae of COVID-19, long COVID syndrome, and increased risk of atherosclerotic cardiovascular disease.

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KEY WORDS: Heart injuries; Post-acute COVID-19 syndrome; Cardiovascular abnormalities.

Several large longitudinal studies on COVID-19 affected people have found that SARS-CoV-2 infection can result in long-term cardiovascular (CV) impairment beyond the acute phase. This has become a major public health concern.[1-3] Current knowledge of the pathophysiological mechanisms responsible for delayed complications is limited. Many symptoms (like breathlessness, chest pain, fatigue, headaches, brain fog, and palpitations) and signs of CV issues (like ventricular dysfunction and arrhythmias) are reported. Still, there are no definitive indicators that suggest that long-lasting cardiac involvement is developing.[4, 5] A new syndrome is emerging.

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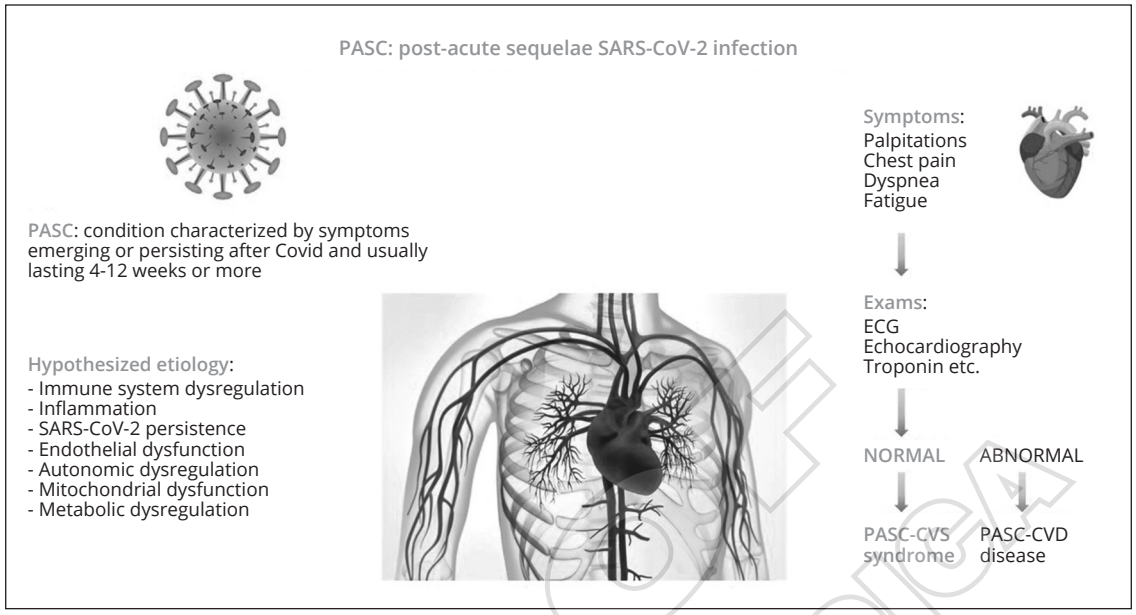


Figure 1.—Graphical abstract.

As such, developing specific definitions and appropriate terminology regarding time relationships, lingering damage, and the outcome is imperative, mainly when symptoms and signs of heart problems persist over time (Figure 1).[4-6]

Literature search

Due to a lack of a standard standardized definition of the syndrome regarding time relationship the most, recently a few investigators have published state for art papers on "long COVID," "post-COVID" or "post-acute sequelae of COVID-19" (PASC) in patients with CV involvement.

We have conducted a systematic search on the most frequent scientific information platforms to clarify how the above-stated terminology is used and which clinical picture and symptomatology it refers to.

Our search strategy has been designed to create this review relating to the terminology used to define the chronic post-COVID-19 syndrome. We have searched MEDLINE, Scopus, and Web of Science databases.

Firstly, we have searched the single MESH terms: "long COVID," "post-COVID" and "post-acute sequelae of COVID-19" (PASC). Second, we have used their combination.

We included papers published last year up to December 4th, 2022. For studies to be included in this review, they have had to report on primary research, be published in peer-reviewed journals, and be written in English. The present review briefly analyses terminology and the related clinical symptoms.

Search for the term "long COVID" has identified 188 articles, of whom 36 have been classified as review. Search for the term "post-COVID" has identified 1140 documents, of whom 124 have been classified as review. A search for "post-acute sequelae of COVID-19" (PASC) has identified 104 articles, and 20 of them have been classified as review.[7-10] Interestingly, in some manuscripts, the terms Long COVID and Post-COVID have been used to describe the same patients, clinical conditions, and symptoms, thus highlighting some confusion. Recently, a state-of-the-art paper on 'long-COVID: Post-acute sequelae of COVID-19 with a cardiovascular focus' has been published. The American College of Cardiology released a 2022 ACC Expert Consensus Decision Pathway on Cardiovascular Sequelae of COVID-19 in Adults as guidance on the evaluation of cardiovascular symptoms after covid-19 to help clinicians diagnose and manage PASC.[4, 5] Other manuscripts have emphasized

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Reported symptoms	%
Fever	8-16
Cough	10-14
Headache	13-27
Myalgia/fatigue	10-20
Sore throat/rhinorrhea	11-26
Dysgeusia/anosmia	4-15
Cardiovascular symptoms	4-8
Neurological symptoms	2-4
Gastro-intestinal symptoms	2-16



Figure 2.—Main aspects of the SARS-CoV-2 pandemic in terms of symptoms in Italy.

that persistent cardiac injury and COVID-19-related increased CV risk need further comments.[11]

Our understanding of long COVID needs to be continuously updated to provide timely information for public policy and guidance for post-COVID-19 care since the latter is a distinct entity compared to the acute phase of SARS-CoV-2 infection[5, 11-14] (Figure 2).[15, 16]

Many words are shared: "persistent," "sequelae," "long COVID," and "risk factor" In terms of terminology, all of them are linked to different concepts.

Definition of COVID 19 in the chronic phase

At the pandemic's beginning, scientists addressed critical knowledge gaps around COVID-19. They needed to learn about long COVID. One of the first reports was from Italy. The authors stated, "We assessed persistent symptoms in patients discharged from the hospital after recovery from COVID-19. Common symptoms included cough, fever, dyspnea, musculoskeletal symptoms (myalgia, joint pain, and fatigue), gastrointestinal symptoms, and anosmia/dysgeusia. However, information is lacking on symptoms that persist after recovery."[17, 18] These patients were called 'long haulers.' The term was initially coined by a patient and inspired several people to study long COVID, also known as post-COVID conditions.[19]

Several definitions have subsequently been introduced. The Centers for Disease Control and Prevention has defined "post-COVID conditions" as a broad range of symptoms presents 4 or more weeks after the first infection, which include LC (symptoms lasting weeks to months) and persistent post-COVID syndrome.[2] Based on the chronicity of symptoms post COVID-19 infection, Nalbandian *et al.* classified post-acute COVID-19 as follows: "post-acute COVID-19 syndrome" (presence of subacute or persistent symptoms up to 12 weeks from the initial episode) and "chronic post-COVID syndrome" (symptoms present beyond 12 weeks).[19]

According to the report in the literature, the post-acute sequelae of SARS-CoV-2 infection (PASC) represent a heterogeneous clinical disorder without an unanimously accepted definition for its widely varying presentations. Patients with PASC have symptoms after SARS-CoV-2 infection, usually persisting over 4-12 weeks (without ACI) in the post-acute period (in the past, the latter was called "convalescence").[4, 5, 11] Twelve weeks after the acute phase of infection,

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the 'chronic period' starts, and patients with symptoms not explained by an alternative diagnosis should have long COVID syndrome. This distinction is important and is related to several complex underlying mechanisms. These patients should be evaluated on an individual basis.[4, 5, 11] Irrespective of the definition used by different medical societies or health organizations, it is essential to remember that even individuals with mild form may still develop PASC in the days or weeks after infection and even chronic long COVID.[2, 4, 5, 20-22]

PASC into two groups: those with objectively distinguishable cardiovascular disease (PASC-cardiovascular disease, PASC-CVD) and those with test results normal or unable to fully explain reported symptoms (PASC-cardiovascular syndrome, PASC-CVS). Cardiovascular manifestations of PASC are frequent[23] and mainly affect non-elderly individuals.[24] Many patients, including those with cardiovascular diagnoses, suffered from exercise intolerance, describing fatigue even during activities of daily living and severe post-exertional dyspnea. However, in patients with cardiopulmonary symptoms suspected of having a cardiac etiology, tests led to a cardiovascular diagnosis in only 23% of cases. Specifically, the diagnosis included new cardiomyopathy, ischemia, arrhythmias, and myocardial involvement. On the contrary, in most cases (77%), no cardiovascular disease was found.[25]

The potential pathophysiological mechanisms of PASC remain unknown. However, the mechanisms implicated in PACS have been hypothesized to be consequences of altered physiological pathways and mechanical/anatomical damage to the cardiac system during the acute phase of COVID-19. These mechanisms include impaired regulatory mechanisms of the immune system, residual post-inflammatory damage, and inadequate and underlying antibody response during acute infection.[26, 27]

Pandemic-induced stress was included among the possible pathophysiological mechanisms and triggers.[28]

Stress induces several effects on the cardiovascular system: endothelial dysfunction, vasoconstriction, increased sympathetic activity, plaque activation, increased atrioventricular conduction velocity, platelets activation, increased systemic inflammation, and reduce immune system function.[28] All these factors have been called into question to explain the pathophysiological mechanism leading to the development of PASC. Furthermore, systemic vascular involvement may explain nearly all patients' fatigue. The mechanisms involved in PASC are like those of the acute phase. Still, vascular systemic involvement can determine different symptoms and slow and insidious disease evolution.[27, 28]

Anxiety has been associated with neurocognitive-PASC (neuro-PASC); a syndrome characterized by persistent neurocognitive symptoms.[29]

Several studies found females significantly more likely to report persistent neurocognitive symptoms following SARS-CoV2 infection. Discrepancies in sex hormones related to inflammatory processes may contribute to this difference. However, non-biological factors may also be associated with female sex and contribute to the observed associations.[30]

CV outcomes and COVID 19

Acute cardiac injury (ACI) is a known major complication of the infection. However, until the study's publication by Lu *et al.*, it was unknown whether ACI acquired during COVID-19 recovers or not.[6] The authors investigated the incidence of ACI over a follow-up period of 2.5 months following hospitalization. ACI was defined as serum troponin-T (TNT) level >99th percentile upper reference limit during hospitalization, and recovery was defined as TNT below this cut-off 2.5 months after admission. ACI incidence rate was 39.7% among hospitalized patients. Among the survivors, 55.8% exhibited persistent cardiac dysfunction. Predicting ACI recovery post-discharge using the top predictors (TNT, creatinine, lymphocyte, sodium, lactate dehydrogenase, lymphocytes, and hematocrit) at discharge yielded 63.73-75.73% accuracy. Although 2.5 months is a short definition, the term long-COVID (cardiac) condition may be applied to this setting.[6] Researchers from Washington University and the Veterans Administration Health Care System in St. Louis have reported that one year after COVID-19 infection some

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patients were still at higher risk of CV disease, including ischemic heart disease, myocarditis, pericarditis, heart failure, arrhythmias, cerebrovascular disorders, and thromboembolic disease.[11] Patients with mild COVID-19 infection who had not been hospitalized were also at risk, and the risk increased with the severity of the infection. Patients with a diagnosis of COVID-19 disease had a 72% increased risk of developing heart failure, a 63% increased risk of myocardial infarction, and a 52% increased risk of stroke compared with healthy controls. This was regardless of age, race, sex, and other cardiovascular risk factors, including obesity, hypertension, diabetes, chronic kidney disease, and hyperlipidemia, even in individuals without any underlying CV disease.[11]

The mechanism by which the virus causes long-term damage to the heart and blood vessels is the subject of debate and research. Potential tools include persistent damage from a previous direct viral invasion of endothelium and cardiac tissue; elevated levels of proinflammatory chemical messengers called cytokines that lead to heart scarring due to chronic infection; depression of the immune system; loneliness in quarantine; and genetic predisposition.[31, 32]

The distinction between the persistence of an ACI condition and PASC is simple if the two are separated by complete healing. Still, it is not simple if symptoms and complications continue soon after the infection and then persist.[4-7] Again, distinguishing between long-term CV consequences and increased risk of atherosclerotic cardiovascular disease (ASCVD) following COVID-19 infection is also difficult.

Some individuals with CV risk factors such as obesity and chronic kidney disease may have an increased risk of acquiring SARS-CoV-2 infection leading to worse CV outcomes after COVID-19.[33] However, Al-Aly *et al.* have noted that disease severity and related outcomes are similar across study subgroups suggesting that SARS-CoV-2 infection leads to *de-novo* CV disease due to a chronic latent inflammatory trigger.[11] The authors of this study have not compared symptomatic versus asymptomatic infections, a potential area for further research.[11]

Similarly, Kuehn has reported that young patients with COVID-19 were 166% more likely to receive a new diagnosis of diabetes than were age- and sex-matched patients without COVID-19.[34]

Without a standard definition and the lack of specific guidance on how to manage patients recovering from the acute phase of the illness and the wide range of similar symptoms as well, it is certainly challenging to distinguish among the different conditions and assign the label of persistent ACI, PASC, long COVID and increased risks of ASCVD.

Governments and health systems worldwide

TABLE I.—*Definitions and clinical presentation of COVID-19.*[45-49]

Definitions and clinical presentation of COVID-19
• Asymptomatic (or paucisymptomatic): it refers to an individual who tests positive for SARS-CoV-2 infection but has no symptoms or non-specific symptoms consistent with COVID-19
• Mild illness: it refers to an individual who has symptoms or signs of COVID-19 (*e.g.* fever, cough, sore throat, and malaise), without dyspnoea or abnormal chest imaging
• Moderate illness: individual who has lower respiratory disease (*e.g.* pneumonia) with oxygen saturation equal to or over 94% on room air at sea level
• Severe illness: individual who has lower respiratory disease with oxygen saturation <94% on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <300 mmHg, a respiratory rate >30 breaths per minute, or infiltrates involving >50% of the lung fields on chest imaging
• Critical illness: individual who has lower respiratory disease with respiratory failure, septic shock, and/or multiple organ dysfunction, without or with different heart participation
• Myocarditis: condition defined by the presence of cardiac symptoms (*e.g.* chest pain, dyspnoea, palpitations, syncope), elevated cardiac troponin, and abnormal electrocardiographic, echocardiographic, CMR, and/or histopathological findings on biopsy or post-mortem evaluation in the absence of flow-limiting coronary artery disease
• Myocardial involvement: condition defined by abnormal myocardium as elicited by electrocardiographic, echocardiographic, CMR and/or histopathological findings, with or without symptoms and with or without an elevated troponin
• Myocardial injury: condition defined by a troponin level above the 99th percentile upper reference limit
• Post-acute sequelae COVID of (PASC): condition defined by a collection of symptoms that emerge or persist after recovery from COVID-19, usually lasting for 4-12 weeks and beyond

TABLE II.—*Definitions of different form of PASC*.[27, 38-41]

Definitions of different form of PASC
• Neuro-PASC: persistence of neurocognitive symptoms
• PASC-cardiovascular disease (PASC-CVD): subjects with objectively distinguishable cardiovascular disease
• PASC-cardiovascular syndrome (PASC-CVS) subjects in which test results normal or unable to fully explain reported cardiovascular symptoms

should be prepared to deal with the likely significant contribution of the COVID-19 pandemic to a rise in the burden of CV diseases.[35-38]

Researchers have been steadily gathering important insights into the effects of two years of the COVID-19 pandemic on long-term direct and indirect lingering damage of biological processes and are raising concerns about the deterioration of many organs, CV system included.[27, 39-41] Long COVID-19 is a vast area that involves many different fields of medicine, and different viral variants may cause various long COVID-19 manifestations.[42, 43]

Given the large number of people with COVID-19 globally, multi-omics approaches to the disease might help understand the multifaceted expression of SARS-CoV-2 disease. Integrating different omics data types is often used to elucidate potential causative changes that lead to different phenotypes, diseases, and/or treatment targets.[44]

In conclusion, COVID-19 represents a complex entity not only regarding its acute phase but also concerning its consequences in the short and long term. The present paper tries to shed some light on the aftermaths of COVID-19 in terms of terminology to tackle confusion around them (Table I,[45-49] Table II).[27, 38-41]

Key messages

• COVID-related long-term involvement of various organs and systems, using specific definitions and terminology is crucial to point out time relationships, lingering damage, and outcome, mostly when symptoms and signs of CV disease persist beyond the acute phase.

• PASC into two groups: those with objectively distinguishable cardiovascular disease (PASC-cardiovascular disease, PASC-CVD) and those with test results normal or unable and those with test results normal or unable to fully explain reported symptoms (PASC-cardiovascular syndrome, PASC-CVS).

• The mechanism by which the virus causes long-term damage to the heart and blood vessels is the subject of debate and research.

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Conflicts of interest
The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions
Giuseppe Calcaterra and Pier P. Bassareo contributed equally to the paper. Conceptualization: Giuseppe Calcaterra, Pier P. Bassareo. Methodology: Anna V. Mattioli, Susanna Sciomer. Resources: Anna V. Mattioli. Writing — original draft preparation: Giuseppe Calcaterra, Pier P. Bassareo, Carmen A. Spaccarotella, Francesco Barillà, Giuseppe Vadalà, Cesare de Gregorio. Writing — review and editing: Francesco Romeo, Jawahar L. Mehta, Anna V. Mattioli. All authors have read and agreed to the published version of the manuscript.

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