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## Commentary

## Post-acute COVID-19 syndrome: a new tsunami requiring a universal case definition

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The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has led to severe socio-economic and health impacts with few comparable precedents in the contemporary era. In addition to the acute and dramatic outcomes, the longer-term consequences have become a challenge. According to current data, 80% of coronavirus disease 2019 (COVID-19) patients develop mild or moderate disease [1], 15% severe disease, and 5% critical disease with different complications such as acute respiratory distress syndrome, sepsis, and septic shock, thromboembolism and multi-organ failure. When compared with influenza, there are many differences in terms of clinical features, morbidity, and mortality [2], and more so when comparing the case fatality rate of COVID-19 (0.1%–25%) [3] with that of the more recent pandemic of influenza A H1N1 of 2009 (0.001%–0.011%) [4]. Individuals with cancer and transplant recipients have an increased risk of worse outcomes, but no evidence for worse prognosis has been demonstrated in people with primary immunodeficiencies and human immunodeficiency virus infection [5,6]. However, individuals with systemic autoimmune diseases and those receiving high doses of corticosteroids or rituximab seem to be associated with more unfavourable outcomes [7].

Although it was expected for severely affected patients to require to follow-up after recovery, the healthcare system is now overburdened by patients with persistent and disabling symptoms, after mild or asymptomatic SARS-CoV-2 infections. Around 10%–15% of patients may present persistent symptoms after acute infection [8]. For example, in Catalonia (Spain, with a population

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of 7.5 million), 669 510 cases of COVID-19 have been confirmed and 22 060 deaths have been reported as of 15 May 2021 [9]. Assuming 75% of hospitalized [10] and 10% of non-hospitalized [11] patients have persistent symptoms, we speculate that over 90 000 confirmed COVID-19 patients might have had or might still have persistent symptoms or sequelae at the time of writing this report, adding an enormous burden to the health-care system. This prevalence is significantly higher if we compare long-term symptoms after influenza, where more than 90% of patients recover in approximately two weeks [12], and other severe conditions different from COVID-19 that are associated with acute respiratory distress syndrome and intensive care unit admission [13]. Improving the handling of these patients requires the contextualization and categorization of the long-term symptoms. To date, however, there are different nomenclatures and time ranges (3, 4, or 12 weeks) used to define the syndrome, insufficient knowledge on its aetiology, and an absence of evidence on potential treatments. This ambiguity, together with a lack of a necessary coding system to identify the syndrome adequately, obscures persistent COVID-19 symptoms and hinders the necessary classification.

No consensus has yet been reached on the definition and chronology associated with persistent COVID-19 symptoms until the latest WHO document of 6 October 2021 [14], where the term 'post-COVID-19 condition' has been proposed to describe 'individuals with a history of probable or confirmed SARS-CoV-2 infection, usually three months from the onset of COVID-19 with symptoms and that last for at least two months and cannot be explained by an alternative diagnosis. Despite this suggestion and many others previously ('prolonged COVID-19', 'prolonged sequelae', 'post-acute COVID-19', 'post-acute COVID-19 syndrome' (PACS), 'persistent COVID-19 symptoms', 'post-COVID-19 manifestations', 'long-term COVID-19 effects', 'post-COVID-19 syndrome', 'post-acute COVID-19 sequelae', 'chronic COVID syndrome'), we have considered the formulation of a final wording of the case definition as part of the consensus of the Spanish-based Multidisciplinary Collaborative Group for the Scientific Monitoring of COVID-19 (GCMSC), which provides a comprehensive overview of the symptoms associated with SARS-CoV-2 after the acute phase [15].

We support the term Post-Acute-COVID-19 Syndrome (or PACS) as the best approach to defining the clinical situation in which symptoms persist beyond four weeks. However, two scenarios should be differentiated: Long COVID and Sequelae (see Supplementary material, Fig. S1).

- The first includes the persistence of symptoms (present or not at the onset of the infection) four weeks after a COVID-19 diagnosis with a permanent, relapsing/remitting, or progressively improving the course.
- Sequelae refer to the presence of irreversible tissue damage 12 weeks after diagnosis with varying degrees of dysfunction and permanent symptoms potentially involving four conditions: post-intensive care syndrome, sequelae arising from post-thrombotic or haemorrhagic complications, sequelae from acute-phase immune-mediated phenomena, and/or multi-systemic inflammatory syndrome in children or adults.

The two scenarios are not mutually exclusive: the same patient may present both Long COVID and Sequelae. Although most patients in the Sequelae group have had severe COVID-19, there are also patients who have had more indolent courses. On the other hand, Long COVID usually concerns those who have had asymptomatic or mild courses [16,17]. Still, some manifestations, for example, fatigue, may also be present in those who have had severe COVID-19.

Numerous cohorts and systematic literature reviews have reported an increasingly detailed description of persistent clinical manifestations, highlighting fatigue, respiratory symptoms, and neurological manifestations as the most prevalent and disabling symptoms. This symptomatology is reminiscent of another chronic disease: myalgic encephalomyelitis/chronic fatigue syndrome, as some authors have already pointed out.

The neurological manifestations, which are possibly the most challenging, include the prolongation of disturbances in smell and taste, persistent headaches, and more complex symptomatology related to autonomic dysfunction and neurocognitive impairment. The latter has become one of the main complaints in terms of having the greatest impact on patients' quality of life. Suddenly they experience difficulties in carrying out otherwise routine tasks, performing work-related tasks, or memorizing information. Consequently, many have been forced to leave their employment, facing the additional aggravating uncertainty of unknown duration of symptoms.

The underlying cause of the persistence of symptoms has yet to be established, but many theories have been put forward. They mainly address virus-specific pathophysiological changes, aberrant immune responses, and inflammatory damage in response to the acute infection [18] and mechanisms of viral persistence [19,20]. More recently, the roles of exosomes [21] and the intervention of mast cells [22] have also come under consideration. These potential underlying aetiological causes must be explored if we are to improve our understanding of the mechanisms contributing to the pathophysiology of PACS. The ambiguity regarding PACS risk factors, due to variations in reporting, study design, and clinical and demographic characteristics of participants, is currently the main problem. However, female sex, high numbers of symptoms, and antibodies to SARS-CoV-2 may play a role in pathogenesis, although some studies have found no significant differences. New lines of research are investigating specific biomarkers to establish clusters for both severe COVID-19 and PACS using machine-learning techniques to resolve the discrepancies addressed above [23]. We must ensure the follow up of these patients, with a view to finding out how long these symptoms persist and whether they develop into chronic disorders. These conditions can lead to hospital re-admission, estimated at around 3.6%–4.5% in the first 30 days [24,25] and up to 27% after 6 months [26], resulting in a dramatic impact on communities and healthcare systems.

To date, there is no definitive treatment for managing the prolonged symptoms of PACS, although there are options for specific symptoms. Surprisingly, case reports, case series and some recent studies suggest that COVID-19 vaccines may improve or resolve long-term symptoms [27]. However, effective antiviral treatment from the early stage of infection may be the best way to minimize the likelihood of developing PACS. Unfortunately, symptoms such as fatigue, are difficult to tackle, but suitable rehabilitation programmes may bring enormous benefit to 'long-haulers' for pulmonary, cardiological, or neurological sequelae. Furthermore, appropriate psychological support should be considered as an additional treatment.

To address the clinical impact of PACS, some countries have created specialized units. In the USA, the National Institutes of Health are seeking to create a single initiative worth US\$1.15 billion in grant funding over the course of 4 years for the research and development of effective treatments. Likewise, the UK's National Health Service Commissioning Board (NHS England) has allocated £10 million to create a network of clinics across the country bringing together doctors, nurses, physiotherapists, and occupational therapists, with a view to offering both physical and psychological assessments and referring patients to appropriate

treatment and rehabilitation services. Medical specialties, e.g. infectious diseases, internal medicine, primary care medicine, infectious diseases specialists, cardiology, neurology, psychiatry, and rehabilitation, should be part of the multidisciplinary team and holistic approach [28,29]. We need to be able to share and compare health financing data across time and country. In addition to the US and UK policies, development assistance for health had reached \$40.4 billion in 2019 and increased to \$54.8 billion in 2020 because of the additional resources provided in response to COVID-19 but with only \$13.7 billion being disbursed to address the health-related effects of COVID-19 in low-income and middle-income countries [30]. The bulk of contributions should be allocated to where help is most needed, and it is therefore imperative that international collaborative programmes be established if we are to avoid inequality and non-homogenous access to care.

Although we can look forward to these advances, we must first identify patients with these persisting symptoms, and foster adequate monitoring and follow-up. We need to advocate the establishment of a clear, standardized set of definitions and an associated code, i.e. using the International Classification of Diseases or equivalent, and be able to establish well-defined and consensual referral circuits between primary and hospital care through a framework that allows for a dynamic, coordinated and transverse flow of patients according to the severity of symptoms and sequelae. Depending on a country's resources, it may be necessary to create new and complementary multidisciplinary units to provide support, as in the UK and US examples, but estimating the cost is difficult because each country has its own health system and its own budget. Furthermore, harmonized national and international registries will be essential, which in turn will facilitate the identification and eventual inclusion of patients in future clinical trials and research projects. The collaborative participation of patients will help them to feel accompanied and not abandoned by the health system. Finally, the full involvement of national health institutions will also be indispensable in this fundamental task.

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#### Author contributions

GML, JS, CB and MS conceptualized the document, searched for the documentation, prepared the first draft, and finalized the document. JM DA, JB, and Q conceptualized the document and reviewed all the different drafts and the final document. ASS conceptualized the document, searched for the documentation, prepared the visualization, and finalized the document. JMM and

SdS conceptualized the document, reviewed all the different drafts and the final document, and supervised the overall process.

#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.cmi.2021.11.015>.

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