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The global challenges of the long COVID-19 in adults and children

During the last three and a half years (2020–2023), the coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), generated an international emergency, defined as a Public Health Emergency of International Concern (PHEIC) and was later declared a pandemic by the World Health Organization (WHO) [1–4]. In May 2023, the Emergency Committee of the WHO met for the 15th time and recommended to the WHO Director-General Dr. Tedros Adhanom Ghebreyesus, that COVID-19 should no longer be categorized as a PHEIC. Although the recommendation was adopted, COVID-19 is still considered a global health threat [5]. COVID-19 has caused more than 767 million cases and 6.94 million deaths up to June 2023 (https://covid19.who.int/), and these numbers could be significantly higher, potentially even three to four times the excess mortality associated with this disease [6–10]. Moreover, early during this pandemic (2020) [11–14], multiple studies began to recognize and understand that chronic consequences may occur in a significant proportion of patients [15,16], leading to various manifestations and affecting different systems and organs after the acute phase of the illness [17]. These chronic consequences have also been observed in other viral emerging and reemerging infectious diseases, such as chikungunya, Zika, Ebola, and even dengue [18–28].

Long COVID-19, post-COVID-19 syndrome or post-acute sequelae of SARS-CoV-2 infection (PASC) [29] occur in individuals with a history of probable or confirmed SARS-CoV-2 infection [30], usually three months from the onset of COVID-19, presenting symptoms that last for at least two months and cannot be explained by an alternative diagnosis, as defined by the WHO [31,32]. The U.S. Centers for Disease Control and Prevention (CDC) uses the term “Post-COVID Conditions” (PCC) as an umbrella term for the wide range of health consequences that can be present four or more weeks after infection with SARS-CoV-2 (https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/post-covid-conditions.html#print). Common clinical manifestations include fatigue, headache, attention disorder, dyspnea, cognitive dysfunction, and others (Fig. 1), which generally impact the patients’ daily functions [30]. The time frame of the symptoms in terms of onset and persistence is not the same for all presentations. Neurologic and cognitive symptoms tend to occur late and persist longer than gastrointestinal and respiratory symptoms [33,34].

New onset symptoms may occur after the initial recovery from an acute COVID-19 infection, or may persist from the initial disease [32]. Symptoms may also fluctuate or relapse over time. Some studies have found that the quality of life of long COVID-19 patients is significantly affected compared to controls. In addition to the multiple clinical findings, some associated conditions, or diseases may also be triggered, including autoimmune diseases or diabetes mellitus. Other studies suggest the existence in long COVID-19 patients of clusters of symptoms associated with functional impairments. Different authors also propose that different clinical phenotypes may be related to distinct underlying pathophysiologic mechanisms of disease [35,36]. The COVID-Home study performed in the Netherlands, and recently presented at the 33rd European Congress of Clinical Microbiology and Infectious Diseases (ECCMID 2023), organized its patients into three distinct phenotypes. The first one comprised by younger, healthier patients that had little to no persistent symptoms, the second one comprised of obese morbid women that had the highest burden of long COVID symptoms but showed little biological abnormalities and finally a third group made of middle-aged males with few lasting symptoms but with marked laboratory anomalies. According to this study, once the symptoms of prolonged COVID are established, they tend to remain stable and without much variation over time, the same can be said of those people who do not develop the condition immediately [37].

Long COVID-19 may affect patients with comorbidities, pregnant women, the elderly, and children and adolescents [32]. In fact, a new definition for pediatric long COVID-19 was released on February 16, 2023 by the WHO [38]. With this important step, a better characterization of the disease in the pediatric age would be possible and awareness improved.

According to systematic reviews, long COVID-19 is estimated to occur in 43%–80% of patients that develop an acute infection [39–41]. According to the WHO, 10–20% of people infected by SARS-CoV-2 may go on to develop its symptoms (https://www.who.int/europe/news-room/fact-sheets/item/post-covid-19-condition). However, available studies of long COVID-19 syndrome are highly heterogeneous [42]. Thus, we would consider that between 325 and 606 million people would probably live with long COVID-19. Nevertheless, a key aspect is to assess the evolution and make the proper follow-up of such patients with long COVID-19. Therefore, studies assessing the trajectories of the evolution of post-COVID-19 conditions in the long term are widely needed [43]. A recent study assessing more than 2000 patients found that 91% of patients with post COVID-19 condition improved slowly over a two-year course, 5% improved rapidly, and 4% had a persistent condition [43].

Additionally, when patients have underlying chronic comorbidities, the outcomes would be worse. A recent large study of adult patients with chronic liver disease who were diagnosed with COVID-19 before May 2020, found that symptoms consistent with long-COVID-19 were present in 30% of patients with chronic liver disease [44]. Different studies have also demonstrated significant and long-lasting neurological manifestations [45,46]. It has been suggested that as many as 80% of patients who sustained COVID-19 will show one or several neurological symptoms

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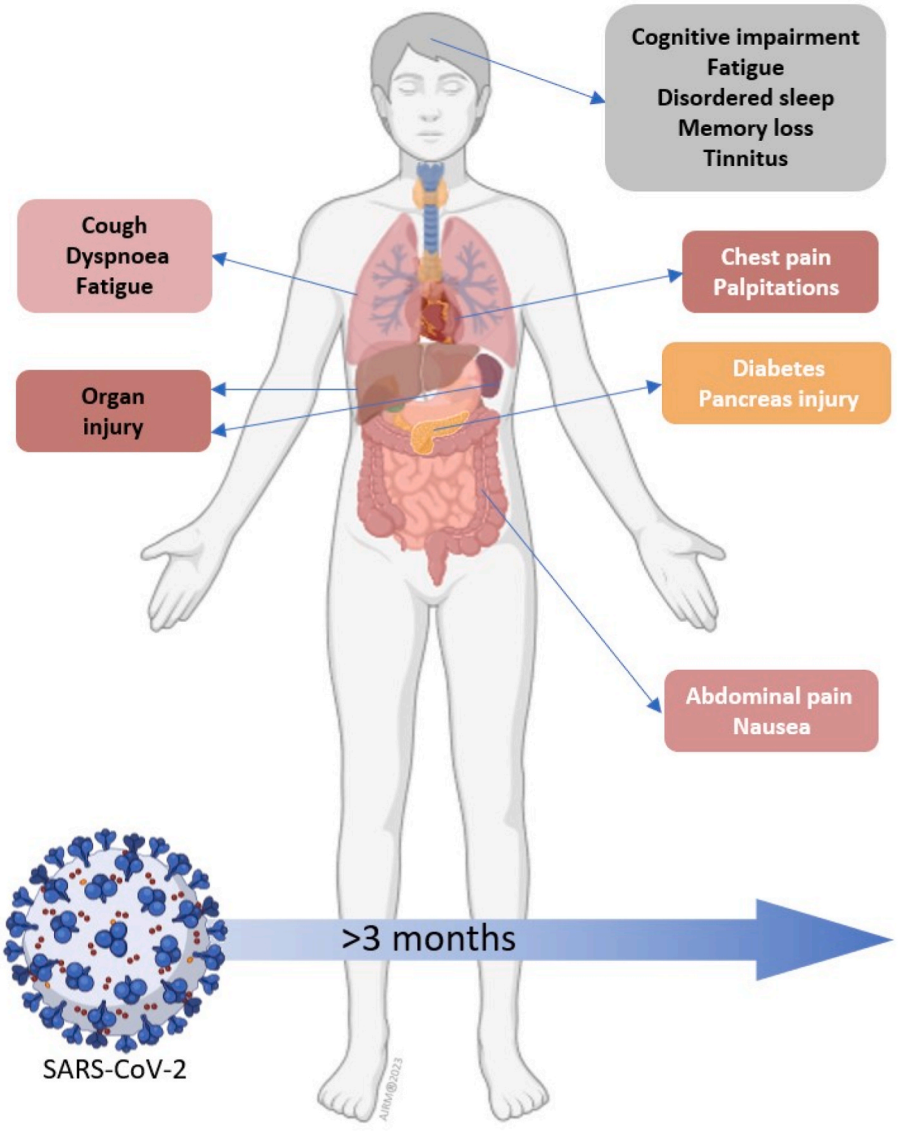


Fig. 1. Some of the clinical findings associated with long COVID-19, modified from Davis et al. [63].

that can last months after the acute infection. Neurological symptoms are most common in young adults, while encephalopathy is more common in older adults [45].

Multiple factors would affect such outcomes and were associated with reporting symptoms 12 weeks or more after infection [47]. Female sex, younger age, belonging to a an African-American, mixed ethnicity or another ethnic minority group, socioeconomic deprivation, smoking, high body mass index and the presence of a wide range of comorbidities were associated with increased risk of symptoms included in the WHO definition of long COVID-19, and they are statistically associated with SARS-CoV-2 infection reported 12 weeks or more after infection [48]. Several multi-organ symptoms have been described, and multiple adverse consequences have also been documented as new onset diseases including cardiovascular, thrombotic and cerebrovascular diseases, type 2 diabetes, myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and dysautonomias such as postural orthostatic tachycardia syndrome (POTS) [33].

Health care workers, and local and national health authorities should recognize the importance of long COVID-19, including its proper diagnosis and management, as part of the health agenda to address it [49]. There is also an urgent need to develop evidence-based guidelines at national and international levels [50] dealing comprehensively with long COVID-19 [51]. As occurred with COVID-19 acute infection, many therapeutic approaches for long COVID-19 that have been already suggested, and even applied, are not well studied. Further, international studies are needed to establish the best practice to help the multitude of patients currently suffering this condition. Considering the involvement of multiple clinical areas and other healthcare professionals, the approach should be multidisciplinary, given not just the clinical but also the social and mental consequences of this long-term event [52]. We believe surveillance of long COVID-19 should be globally implemented; and it must considered a notifiable condition. To improve the documentation of long or post–COVID-19, a new International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) diagnosis code (U09.9 Post COVID-19 condition, unspecified) (https://www.who.int/standards/classifications/classification-of-diseases/emergency-use-icd-codes-for-covid-19-disease-outbreak) (Fig. 2) was introduced on October 1, 2021 [53,54]. In addition, global and local health authorities should begin to think about laws or policies related to total or partial disability as result of long COVID-19 [55,56].

Compared to the acute phase of COVID-19, where there is evidence that several pharmacologic interventions may reduce the severity of infections, lessen morbidity, and lower mortality [57], there is an absence of evidence-based treatments in the post-viral syndrome, which

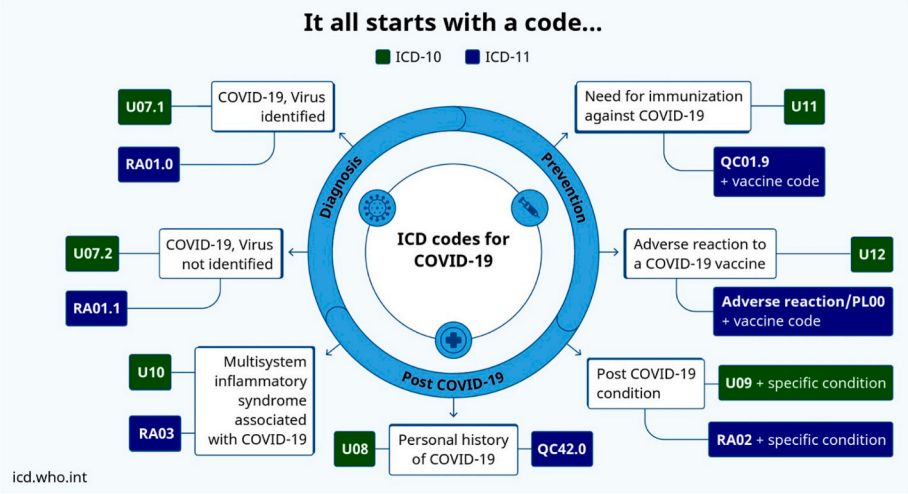


Fig. 2. ICD codes for COVID-19, according the WHO (https://www.who.int/standards/classifications/classification-of-diseases/emergency-use-icd-codes-for-covid-19-disease-outbreak).

further fuels the frustration of affected patients and their clinicians [58]. Add to these problems the disparities in healthcare systems, especially in the most affected and vulnerable countries, which impose a significant disease burden on this complex and multifaceted disorder [59]. Long COVID-19 prevention is also an important area of practice and research. It is worth mentioning that vaccination against SARS-CoV-2 decreases the risk of long COVID-19 [60]. Also, in two cohort studies, nirmatrelvir and molnupiravir treatment reduced the risk of long COVID-19 when initiated early in patients at risk of severe disease progression [47,61].

The pathophysiology of long COVID-19 remains elusive partly because of the multiple possible signs, symptoms, and organ systems involved. A lack of understanding of long COVID-19 inevitably complicates care [59]. Then, more comprehensive and multidisciplinary research on these consequences is of utmost importance [62,63]. Even viral persistence beyond three months has also been reported, as well as identification of RNA or isolation of the virus itself from different organs and systems [64,65]. In a 2022 study, the expression of SARS-CoV-2 RNA in the gut mucosa ~7 months after mild acute COVID-19 was observed in 32 of 46 patients with inflammatory bowel disease [66]. Viral nucleocapsid protein persisted in 24 of 46 patients in gut epithelium and $CD8^+$ T cells. Expression of SARS-CoV-2 antigens was not detectable in stool, and viral antigen persistence was unrelated to the severity of acute COVID-19, immunosuppressive therapy, or gut inflammation. Authors could not culture SARS-CoV-2 from the gut tissue of patients with viral antigen persistence [66]. Post-acute sequelae of COVID-19 were reported from most patients with viral antigen persistence but not from patients without viral antigen persistence [66]. Different long-term gastrointestinal consequences of COVID-19 have been reported, including motility disorders, acid-related disorders (dyspepsia, gastroesophageal reflux disease, peptic ulcer disease), functional intestinal disorders, acute pancreatitis, hepatic and biliary disease [67]. Even more, long detection of SARS-CoV-2 in other organs and tissues has been reported in different publications [68], in some reaching up to more than a year post-infection [69–72], mainly in immunocompromised patients. Most studies focus on the clinical consequences of long COVID-19, but few assess viral persistence in different organs and tissues and the immunological profile of such conditions [73–76]. In the acute infection, studies have associated COVID-19 clinical evolution with the microbiome [77]. A recent study among recovered COVID-19 patients, found that the relative abundance of some specific primarily opportunistic pathogens, such as bacteria and fungi, was decreased in recovered patients, while the abundance of butyrate-producing organisms was increased in these patients. Moreover, these differences were still present for some organisms at 12 months after recovery, indicating the need for long-term monitoring of COVID-19 patients after virus clearance [78].

Immune system dysregulation [79,80] with or without reactivation of latent pathogens such as Epstein-Barr virus (EBV) and human herpesvirus 6 (HHV-6) [81,82] has also been described. Other authors have explored the effects of SARS-CoV-2 on the microbiota, including the virome [83]. Other possible factors include autoimmunity [84,85], immune system dysfunction through molecular mimicry [86], microvascular blood clotting with endothelial dysfunction [87,88], and dysfunctional signaling in the brainstem or vagus nerve [86,89].

As occurred after COVID-19 cases rose in 2020, when healthcare and academic centers prepared to attend population with this emerging disease [90–95]; it is prime time to have a rapid response to this threatening growing long COVID-19 pandemic. Institutions need to be prepared for the long COVID-19 consequences and to provide evidence-based health care to those thousands or millions affected by this sequela of the pandemic. At the same time, at the community level, the population needs to be educated and understand the potential long impact of COVID-19 and the situation regarding the status of knowledge on the problem, including the evolving approaches to diagnosis and management of its clinical consequences [96].

In countries where health authorities manage targeted resources and create control programs, these should integrally include long COVID-19 [97], with the idea to incorporate this into the regular surveillance and management at the population level to mitigate and decrease the long-term impacts of the post-COVID-19 syndrome [63].

As of today, the most effective preventive strategy to prevent post-COVID syndromes, long COVID, and associated long-term impact, is vaccination of adults and children [98–100]. It is crucial to decrease sequelae, societal costs, and economic impact of long COVID-19 to healthcare systems and societies. In the era of vaccine hesitancy, motivating vaccination of individuals is essential to prevent these problems, particularly in children who remain at much lower vaccination rates than adults. The consequences of reinfection of patients with different SARS-CoV2 variants and the impact of vaccination in preventing long COVID-19, remains unknown and should be subject to continuous monitoring and research. Finally, we consider that the creation of research networks should be encouraged to guide future long COVID-19 policies, including the impact of vaccination, long-term clinical impact, and burden on health systems, among others.

Declaration of competing interest

None.

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