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Update on Long COVID-19

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Long COVID-19 (also called 'post-acute sequelae of COVID-19' as a multisystemic disease has severe symptoms following a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. It affects 65 million people worldwide, considering a conservative estimated rate of 10% of infected cases and over 651 million recorded COVID-19 cases all over the world; the rate is possibly more than estimated because of several undocumented cases. The prevalence is appraised at 10 - 30% of non-hospitalized patients, 50 - 70% of hospitalized patients, and 10–12% of vaccinated patients (1-4). The disease affects all age groups and is accompanied by acute phase disease severities, and those aged 36 - 50 years are more affected. Most cases are non-hospitalized cases that have a mild acute illness, which represents the majority of overall COVID-19 patients. In this review, many research challenges and open questions, especially related to pathophysiology, risk factors, and effective treatments, are presented (1-4).

Several biomedical findings and many patients are suffering from symptoms in multiple organ systems (1). Long COVID-19 has different adverse outcomes, with common new-onset conditions, such as cerebrovascular, cardiovascular, and thrombotic disease (5), myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), type 2 diabetes (6), and dysautonomia, particularly postural orthostatic tachycardia syndrome (POTS). Symptoms may persist for years, and especially in cases of new-onset ME/CFS and dysautonomia, are expected to be lifelong. Given that a significant proportion of people with long COVID-19 are unable to return to work, the scale of newly disabled people contributes to the workforce shortage. No validated effective treatments are currently available (1, 7).

Long COVID-19 has possibly many potentially overlapping causes. There are several hypotheses for its pathogenesis, such as SARS-CoV-2 persisting reservoirs in tissues, immune dysregulation with, without reactivation of the pathogens, like herpesviruses, such as human herpesvirus 6 (HHV-6) and Epstein–Barr virus (EBV) among others effects of SARS-CoV-2 on the microbiota, such as the virome, microvascular blood clotting with endothelial dysfunction, the immune system autoimmunity and priming from molecular mimicry, and dysfunctional signaling in the vagus nerve and/or brainstem (1, 8).

Mechanistic investigations are at an early phase, and despite some theories obtained from research on postviral illnesses, such as ME/CFS, there are many unanswered questions. Risk factors are female gender, EBV reactivation, type 2 diabetes, connective tissue disorders, the existence of specific autoantibodies, chronic urticarial, attention deficit hyperactivity disorder, and allergic rhinitis; however, one-third of cases with long COVID-19 were found with no pre-existing conditions (5, 9).

Those with certain ethnicities, such as cases with Hispanic or Latino heritage, were found with a higher prevalence of long COVID-19. Socio-economic risk factors are being unable to rest in the early weeks after developing COVID-19 and lower income. Before the SARS-CoV-2 emergence, different bacterial and viral infections have caused postinfectious illnesses, like ME/CFS1, and long COVID-19 shares their phenotypic and mechanistic characteristics. In addition, dysautonomia has been found in other postviral diseases and more frequently in long COVID (1, 6, 10).

Therefore, we used the major finding of a review written by Davis et al. (7), who assessed the existing knowledge base of long COVID-19 and misconceptions surrounding long COVID-19 in Iranian guidelines of long

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COVID-19. Using this guideline, we hope that all medical settings and Iranian physicians can overcome the major issue of long COVID-19 and post-COVID-19 problems.

Footnote

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