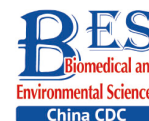


Review



The Epidemiology, Diagnosis and Prognosis of Long-COVID*

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INTRODUCTION

As of October 26, 2022, more than 625 million confirmed cases of COVID-19 and more than 6.56 million deaths have been reported to the World Health Organization (WHO), and the natural history, clinical course, and long-term consequences of this new disease are still not completely understood. After more than two years of fighting against the SARS-CoV-2 pandemic, the number of patients with long-term persistent COVID-19 symptoms after acute infection is noteworthy. This group of symptoms was called “long COVID” by WHO^[1]. Previous studies have shown that approximately 6.2%–79% of COVID-19 survivors may develop long COVID^[2-14], which was characterized by persistent symptoms lasting for 3 months or more after acute COVID-19^[15-17]. The reported prevalence of long COVID was likely overestimated because people with long COVID were perhaps more motivated to enroll.

The most common symptoms of long COVID-19 include fatigue, shortness of breath, cough, loss of taste or smell, myalgia, gastrointestinal disturbance, high heart rates, mood changes, anxiety, insomnia, headache, sore throat, chest pain, palpitations, diarrhea, nausea, joint pain, hair loss, skin rashes, and memory and cognitive dysfunction even several months after infection. Even home-isolated adults with mild COVID-19 were at risk of long-lasting dyspnea^[18]. These symptoms varied in prevalence, relapse pattern, duration and severity. The WHO and United Kingdom (UK) Office for National Statistics have estimated that 10% of COVID-19 cases will lead to long COVID, regardless of hospitalization history^[19-21]. Compared with nonserious diseases, persistent symptoms seemed to be more likely to appear after serious diseases, and people treated in intensive care units have the most obvious symptoms in the recovery period^[22].

DEFINITION AND DIAGNOSIS

Some people experienced long-term persistent COVID-19 symptoms after acute infection, usually called “long COVID”, “post-acute COVID-19 syndrome (PACS)”, “post COVID 19 condition” or “post-COVID-19 syndrome” (PCS). The long COVID was defined as “wide range of new, returning, or ongoing health problems people can experience four or more weeks after first being infected with the virus that causes COVID-19” by the United States of America Centers for Disease Control and Prevention^[23]. The UK National Institute for Health and Care Excellence (NICE) defined it as (1) ongoing symptomatic COVID-19 for people who still have symptoms between 4 and 12 weeks after the start of acute symptoms; and (2) long COVID for people who still have symptoms for more than 12 weeks after the start of acute symptoms^[24]. The WHO defined it as a condition characterized by symptoms impacting everyday life, such as fatigue, shortness of breath, and cognitive dysfunction, which occurred after a history of probable or confirmed SARS-CoV-2 infection^[25]. Usually, symptoms appear 3 months after the onset of acute COVID-19 symptoms, lasting at least 2 months, and cannot be explained by alternative diagnosis. An article proposed the classification of three different stages, the 5th–12th week, the 12th–24th week and the 24th week after diagnosis^[26]. NICE distinguished between COVID-19 syndrome and long COVID with persistent symptoms, aiming at those who have symptoms for 4–12 weeks and more than 12 weeks after the onset of acute diseases^[27].

SYMPTOMS AND PREVALENCE

A previous study showed that although it is common in patients with other viral infections (such

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as influenza), the symptoms of long COVID appear more frequently after novel coronavirus virus infection^[28]. Several systematic reviews showed that the most common symptoms are fatigue, shortness of breath, muscle pain, joint pain, headache, cough, chest pain, change of smell, change of taste, and diarrhea in hospitalized adults^[7,15,29-33]. Due to the lack of standardized research methods in various studies, the prevalence and duration of individual symptoms are still difficult to determine.

The population-based COVID-19 infection survey carried out by the British National Bureau of Statistics estimated that as of November 6, 2022, 2.2 million people living in private homes in the UK (3.4% of the population) were experiencing self-reported long COVID lasting for more than 4 weeks after the first confirmed or suspected COVID-19 infection that were not explained by something else, and 1.6 million people's (75% of them) day-to-day activities affected adversely. Fatigue, difficulty in concentration, shortness of breath, and muscle ache were the main symptoms reported. The prevalence of self-reported long COVID was greatest in people aged 35 to 69 years, females, those working in social care, and those with another activity-limiting health condition or disability^[34].

Several studies were performed to investigate the prevalence of long COVID-19^[3,4,6,10-12,35-37] (Table 1). One systematic review and meta-analysis identified 57 studies with 250,351 survivors of COVID-19 from December 2019 to March 2021, and

79% were hospitalized during acute COVID-19, more than half of these survivors experienced PASC 6 months after recovery. The most common PASC involved functional mobility impairments, prevalent pulmonary sequelae, and mental health disorders. Among them, constitutional symptoms were chest imaging abnormalities (median [IQR], 62.2% [45.8%–76.5%]), difficulty concentrating (median [IQR], 23.8% [20.4%–25.9%]), generalized anxiety disorder (median [IQR], 29.6% [14.0%–44.0%]), general functional impairments (median [IQR], 44.0% [23.4%–62.6%]), and fatigue or muscle weakness (median [IQR], 37.5% [25.4%–54.5%]). Other frequently reported symptoms included cardiac, dermatologic, digestive, and ear, nose, and throat disorders^[29].

In one persistent neurological manifestation in long COVID systematic review analyses, 36 studies with 9,944 participants from January 2020 to October 2021 were included, and most of the included studies had a mean duration of follow-up after COVID-19 onset of less than 6 months. Before the wave of the Omicron variant, fatigue was the most common (52.8%) symptom of long COVID, followed by cognitive disorder (35.4%), parosmia (33.3%), sleep disorder (32.9%), musculoskeletal pain (27.8%), and dizziness (26.4%)^[38]. Another systematic review and meta-analysis on gastrointestinal (GI) manifestations of long COVID included 50 studies, and the frequencies of GI symptoms were 0.12 and 0.22 in patients with

Table 1. Prevalence and duration in patients with long COVID symptoms

System	Involved symptom (s)	Prevalence and duration*	Suggestion
Central and peripheral nervous system ^[15,17,70-75]	Fatigue, headache, stroke, Cognitive, mental health disorders, anosmia, ageusia, neuropathy	30%–80%, 6 months or more	Prompt diagnosis and intervention of any neuropsychiatric care is recommended for all patients recovering from COVID-19. An increase in mental health attention models in hospitals and communities is needed during and after the COVID-19 pandemic.
Respiratory ^[29,76,77]	Dyspnea, chest pain, cough, lung fibrosis	10%–70%, 6 months or more	In addition to symptomatic treatment, regular follow-up is needed.
Smell and taste ^[2,35,78-80]	Altered sense of smell, altered taste	10%–60%, 7 months or more	Early prevention, this must be seen as a frequent symptom of post-COVID-19 condition and might be partly due to a decreased central nervous amplification.
Gastrointestinal tract symptoms ^[15,33,81]	Disorders of GI tract motility	6%, 3 months or more	In addition to symptomatic treatment, regular follow-up is needed, specific focus directed to the GI tract need to be done.
Immune system ^[12,82]	Multisystem symptoms	3%–50%, 12 months or more	Regular monitoring of blood results and evaluation of the individualized thrombotic risk based on comorbidities and coagulation profile are essential for both post-acute and chronic COVID-19.

Note. *Prevalence is the intersection of all included studies, and the duration was the longest in all included studies.

COVID-19 and those with long COVID, respectively. Loss of appetite, dyspepsia, irritable bowel syndrome, loss of taste, and abdominal pain were the five most common GI symptoms of long COVID^[39].

A study led by the WHO and Global Burden of Disease Long COVID Collaborators included 1.2 million COVID-19 patients from 22 countries in 2020 and 2021 showed that, 6.2% of COVID-19 patients reported at least one symptom clusters of long COVID 3 months after acute infection onset, the risk of long COVID was greater in females and in those who needed hospitalization for the initial SARS-CoV-2 infection, particularly among those needing ICU care. The symptoms of sequela were not unique to COVID-19, similar symptoms were also occurred after other viral disease and bacteria disease^[40]. One large-scale study performed between March 2020 and August 2021 described long COVID symptoms after correcting the preinfectious symptoms of SARS-CoV-2 and distributed questionnaires to more than 75,000 adults in the Netherlands, with the aim of evaluating 23 physical symptoms. Researchers matched the respondents (5.5%) suffering from COVID-19 with the COVID-19 negative control group in age, sex and time period^[41]. 90 to 150 days after the diagnosis of COVID-19, the persistent symptoms (compared with those before diagnosis and those of the control group) included chest pain, dyspnea and pain, myalgia, loss of taste or smell, numbness of limbs, feeling hot and cold, and fatigue^[41]. Approximately 13% of these symptoms can be attributed to COVID-19, which suggests that 1/8 of COVID-19 patients have post-COVID-19 symptoms^[41].

These analyses accounted for symptomatic SARS-CoV-2 infections through the end of 2021 and therefore did not cover the Omicron variant wave. One case-control observational study between December 2021 and March 2022 reported that among omicron cases, 4.5% of people (2,501/56,003) experienced long COVID, and among delta cases, 10.8% of people (4,469/41,361) experienced long COVID. Omicron cases were less likely to experience long COVID for all vaccine timings, with an odds ratio ranging from 0.24 to 0.50^[42]. Another cross-sectional study with a cohort of 16,091 adults found that, between February 2021 and July 2022 in the US, 14.7% individuals reported long COVID-19 symptoms more than 2 months after acute illness, and compared with ancestral COVID-19, infection during periods when the Omicron variant (*OR*, 0.77; 95% *CI*, 0.64–0.92) predominated

in the US was associated with diminished likelihood of long COVID, completion of the primary vaccine series prior to acute illness was associated with diminished risk for long COVID (*OR*, 0.72; 95% *CI*, 0.60–0.86)^[43]. The same result was also found in a retrospective cohort study from Eastern India^[14]. These researches were mainly conducted in adult subjects, and the evidence of COVID-19 in children was very limited. The current proportion of long COVID among children was lower, and older age was not an independent predictor^[26,27,44,45]. Unfortunately, the variability in long COVID prevalence was heterogeneous, and there was a lack of standardization among the different long COVID studies, mainly for the different definitions of long COVID and different populations and settings that have been studied.

RISK FACTORS

Long COVID may occur independently of the acute degree of initial infection, hospitalization status, age or preexisting complications^[46]. Risk factors may include female sex, age gradient, hospitalization during acute COVID-19 (including oxygen therapy), ethnic minorities, socioeconomic deprivation, smoking, obesity, various complications, and potential respiratory, mental illness and unvaccinated^[13,47-53]. The sequelae after infection were common, not unique to COVID-19, and the risk of long-term sequelae after COVID-19 infection was related to the severity of the disease, that is, the more severe the illness is, the higher the risk of sequelae^[40]. The unified case definition and shared research methods will help to further clarify the prevalence of this disease and its long-term health consequences.

BIOMARKERS FOR LONG COVID DIAGNOSIS

Because of the heterogeneity of the pathogenesis and manifestations of long COVID, it is urgent to establish a standardized disease definition based on biomarkers.

After the first epidemic wave in Germany, prospective observation and research on long COVID chronic fatigue syndrome and biomarker reports related to symptom severity showed that early biomarkers provide a unique opportunity to identify patients and apply intervention measures at the very early stage of the disease^[54-56]. Another prospective longitudinal study with a 12-month follow-up of hospitalized patients with COVID-19 showed that

patients with long COVID who lasted for 1 year had unique immunological phenotype, including poor novel coronavirus antibody response, low-grade chronic inflammation tending to be in remission and autoimmunity^[12]. The plasma proteomic signature has been shown to be able to predict who will develop persistent symptoms following SARS-CoV-2 infection, according to one nested longitudinal case-control study and targeted analysis of the plasma proteome of 156 healthcare workers with and without laboratory-confirmed SARS-CoV-2 infection^[57]. This proteomic panel consists of proteins associated with the immune response enriched for neuroinflammatory biomarkers, which have been widely investigated thus far. A study on cytokine profiles related to long COVID found that high serum levels of IL-17 and IL-2 and low levels of IL-4 and IL-10 seemed to constitute the cytokine profiles (molecular characteristics) of pneumonia^[36]. Predictive markers of long-term sequelae of COVID-19 should be determined, including those existing before infection, during acute diseases and during the early recovery period. These biomarkers will allow clinicians to directly intervene in people with the greatest risk of long COVID.

PROGNOSIS

A Swiss survey study found that fatigue, pain, and sleep-wake disturbance symptoms of the long COVID had an impact on the quality of life and ability to work in a majority of patients and had a significant reduction in symptoms over 12 months^[58]. A one-year follow-up cohort study reported that at 12 months after acute infection, COVID-19 survivors were still suffering from symptoms identified at shorter follow-up, and the most frequent symptoms included fatigue, pain, and sleep disorders^[59]. An international cohort reported that by seven months, many patients have not yet recovered (mainly from systemic and neurological/cognitive symptoms), have not returned to previous levels of work, and continue to experience significant symptom burden^[3].

An analysis of a 2-year retrospective cohort study of individuals diagnosed with COVID-19 showed that the increased incidence of mood and anxiety disorders was transient, and the increased risk of psychotic disorder, cognitive deficit, dementia, and epilepsy or seizures persisted throughout^[60]. Another two-year health outcome cohort study in hospitalized COVID-19 survivors in China reported that at 2 years after hospital discharge, 19.8% of

patients (370/1,864) still had symptoms, including 224 (12.0%) with persistent symptoms, and the most common symptoms were fatigue, chest tightness, anxiety, dyspnea, and myalgia^[31]. In early infection research, patients with long COVID reported prolonged multisystem involvement and significant disability. By 7 months, many patients have not yet recovered (mainly from systemic and neurological/cognitive symptoms), have not returned to previous levels of work, and continue to experience significant symptom burden^[3].

A meta-analysis of mid- and long-term neurological and neuropsychiatric manifestations of long COVID found that the prevalence of neurological and neuropsychiatric symptoms of long COVID was higher when assessed at or beyond six months (long-term) than when assessed between three and six months (mid-term)^[61]. Another systematic review and meta-analysis on pulmonary function and chest computed tomography abnormalities 6–12 months after recovery from COVID-19 showed that the prevalence of sequelae did not decrease until 1 year after initial infection^[62].

Although many studies have reported long COVID^[10,61,63], there are few studies on the prognosis and outcome of long COVID at present, and more follow-up studies are needed in the later stage to determine the harm. At the same time, it is also necessary to distinguish symptom research unrelated to COVID-19. Supportive therapy to relieve symptoms is still the main treatment. Thankfully, the symptoms of most patients were relieved within 1 year^[3,58]. Research suggested that people who are vaccinated but experience a breakthrough infection are less likely to report post-COVID conditions, compared to people who are unvaccinated^[23,42,43]. Therefore, the strategy to prevent long COVID was very clear: prevention of infection is the most important way to prevent long COVID. Vaccination, timely diagnosis and treatment to reduce the severity of the disease in case of infection also reduce the risk of sequelae.

PROSPECTIVE

Although studies suggested that long COVID is prevalent, omicron appears to cause less severe acute illness than previous variants^[64-66], there was also a reduction in odds of long COVID with the omicron variant since vaccination, and the estimated risk of long COVID at 3 months was lower in individuals who were not hospitalized^[14,42]. Early vaccine intervention minimized the effect of long

COVID and contributed to preventing syndrome altogether^[42,43].

Long COVID still remains a major challenge, further research is urgently needed to determine the characteristics of this syndrome and explore the treatment scheme. Additional research is also needed to describe the natural history of long COVID, characterize long COVID symptom clusters, and identify risk factors, underlying etiologies and their pathophysiology and clinical outcomes to inform prevention, rehabilitation, clinical and public health management to improve recovery and long-term COVID-19 outcomes^[67]. In the UK, a five-point national health service plan has allocated 10 million pounds to support long-term COVID patients through specialist clinics and online rehabilitation services, while allocating 20 million pounds for research funded by the National Institute of Health^[68]. There is also a need to better understand the risk factors leading to the development of long COVID, which is the research focus highlighted in the recently updated NICE COVID-19 Long-term Effect Management Guide^[69]. Large-scale, well-designed research and interdisciplinary approaches are also needed to understand the health and social impacts of these persistent symptoms, to support patients living with long-term sequelae and to develop targeted treatments.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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