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Epidemiology, course and predictors of long-term COVID infection (long COVID): a review

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ABSTRACT

The COVID-19 pandemic has posed a serious challenge to the healthcare system in the 21st century. At present, over 771 million cases have been reported worldwide. Apart from the acute symptoms, many patients experience long-term consequences of the infection, which greatly affect their quality of life. The collection of these long-term effects is called "long COVID." Therefore, the consequences of COVID-19 must be studied to develop effective strategies for combating them. This review aimed to provide an overview of the history of long COVID and discuss the characteristics of contemporary terminology. This review also presents data on the prevalence of long COVID, primary symptoms, and risk factors and explores potential biomarkers, prognosis, and prospects for subsequent clinical trials.

Keywords: postacute COVID-19 syndrome; long COVID-19; COVID-19 complications.

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Эпидемиология, течение и прогностические признаки длительной COVID-инфекции (лонг-ковида): научный обзор

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АННОТАЦИЯ

Пандемия COVID-19 стала наиболее серьёзным вызовом для системы здравоохранения в XXI веке. Во всём мире на сегодняшний день зарегистрировано более 771 млн случаев заболевания. Помимо симптомов, характерных для острого периода заболевания, значительная часть пациентов сталкивается с долгосрочными последствиями перенесённой инфекции, которые значимо влияют на качество жизни. Долгосрочные последствия перенесённой инфекции COVID-19 были объединены под общим названием лонг-ковид. Их изучение необходимо для разработки профилактических мероприятий в целях предупреждения тяжёлых долгосрочных последствий, значительно влияющих на состояние здоровья населения. В данном литературном обзоре описана история появления термина «лонг-ковид», обсуждены особенности современной терминологии. Представлены данные о распространённости лонг-ковида, основных симптомах, факторах риска, а также обсуждены возможные биомаркеры, прогноз и перспективы для дальнейших клинических исследований.

Ключевые слова: долгий COVID-19; постковидный синдром; лонг-ковид.

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INTRODUCTION

Currently, amid reports of an increasing number of cases, more than 771 million cases of the novel coronavirus infection have been reported worldwide [1], including 23 million in the Russian Federation [2]. Despite unprecedented efforts by the scientific and medical community to detect, diagnose, treat, and prevent coronavirus disease 2019 (COVID-19), the long-term sequelae of the disease remain poorly understood.

The first and most notable publication describing post-acute COVID-19 syndrome (long COVID) came early in the pandemic, when the medical community was focused on treatment and containment of COVID-19 spread. The report was published in The Atlantic nonmedical journal on June 4, 2020. The author, Ed Yong, presented the case studies of nine patients who experienced prolonged symptoms and a reduction in quality-of-life following COVID-19 infection.

By August 2020, the article had been accessed online by over one million individuals, and Ed Yong was subsequently awarded a Pulitzer Prize for explanatory reporting and coverage of the COVID-19 pandemic [3]. This was the first case in which the patient community independently paid attention to the emergence of a new medical problem.

DEFINITIONS AND TERMINOLOGY

The lack of a single term to describe the effects of COVID-19 infection contributes to additional difficulties in long COVID research, preventing qualitative analysis of the information obtained by different research groups.

Accordingly, the World Health Organization (WHO) utilizes the term *post COVID-19 condition*, defining it as a condition manifesting in individuals with a probable or confirmed history of SARS-CoV-2 infection, typically three months following the onset of SARS-CoV-2 infection. The condition is characterized by symptoms persisting for at least two months, and the underlying cause remains unidentified [4].

The term *persistent symptoms/effects of COIVD*-19 is frequently used by researchers and is generally understood to refer to the persistence of signs and symptoms beyond the acute phase of the disease, regardless of the duration [5, 6].

The term *long COVID* was first proposed by patient researchers in March 2020 to cover in a wide sense a range of signs, symptoms, and sequelae that persist or develop after an acute infection with the COVID-19 virus. These effects may manifest at any point following the initial infection and are typically multisystemic in nature. Symptoms may manifest with a relapsing-remitting course and progression or worsening over time, with the possibility of developing severe and life-threatening conditions even months or years after infection [7].

Fernández-de-Las-Peñas et al. [8] proposed a classification to define the symptoms typical of long COVID.

- *Transitional phase* includes symptoms potentially associated with acute COVID-19 (lasting up to 4–5 weeks).
- *Phase 1* is characterized by acute symptoms after COVID-19 (Week 5 to Week 12).
- *Phase 2* includes long-term symptoms after COVID-19 (Week 12 to Week 24).
- *Phase 3* includes persistent symptoms after COVID-19 (lasting more than 24 weeks).

According to the researchers, symptoms observed during the transitional phase should be cautiously interpreted as potentially related to COVID-19 infection before being considered as symptoms of long COVID. To improve the specificity of identifying long COVID symptoms, potential hospitalization-related complications should first be ruled out before making a diagnosis. After discharge, it is proposed that the next 4–5 weeks be considered as a clearing period to better determine whether symptoms are truly related to the course of long COVID [9].

EPIDEMIOLOGY AND CLINICAL MANIFESTATIONS

Early studies indicated that approximately 6.2% to 7.9% of patients may develop long COVID [10], which is characterized by persistent symptoms lasting for three months or more after the acute phase of COVID-19 [11]. Even patients with a mild course of the disease who were treated outpatiently were at risk of developing long-term symptoms, primarily dyspnea on exertion [12]. According to the WHO, at least 10% of COVID-19 cases will result in long COVID, irrespective of the severity of the initial infection and the need for hospitalization [13].

The data did not indicate a correlation between the severity of the acute infection and the probability of late persistent symptoms of long COVID. Accordingly, the data from the two-center prospective study by Dennis et al. indicate that 70% of patients with a low risk of mortality from COVID-19 infection exhibited at least one organ system dysfunction four months or more after infection, whereas only 19% of patients required hospitalization during the acute phase of the disease [14].

In a systematic review and meta-analysis, one of the first to include 57 studies involving 250,351 patients who experienced COVID-19 between December 2019 and March 2021, the authors described the incidence of various long COVID symptoms [15]. In the study population, 79% of patients required hospitalization due to the severity of COVID-19. Of these patients, more than half experienced long COVID symptoms six months after recovery. The most common symptoms were decreased functional activity, dyspnea, and psychological distress. On examination, participants were found to have persistent changes on chest imaging studies (62.2%; CI, 45.8%–76.5%), difficulty concentrating (23.8%: CI, 20.4%–25.9%), generalized anxiety disorder (29.6%: CI, 14.0–44.0%), generalized functional impairment (44.0%: CI, 23.4–62.6%), and fatigue or muscle weakness (37.5%; CI, 25.4%–54.5%). Other commonly reported symptoms included cardiovascular, dermatologic, gastrointestinal, and olfactory disorders.

Subsequently, the active participation of patients and the use of remote data collection technologies became a feature of long-COVID-related studies.

For example, according to a large population-based study conducted by the UK Office for National Statistics [16], as of November 6, 2022, 2.2 million people in the UK (3.4% of the population) self-reported long-term symptoms lasting more than four weeks after the first confirmed or suspected COVID-19 infection that were not attributed to other causes using the COVID Symptom Study mobile app. The most commonly reported symptoms were fatigue, difficulty concentrating, dyspnea, and muscle pain. The prevalence of long COVID was the highest among women aged 35 to 69 years, those working in social services, and those with health or disability limitations.

Subsequently, the considerable heterogeneity of the reported data necessitated the conduct of systematic reviews and meta-analyses focusing on lesions of individual organs and systems.

Thus, a systematic review and meta-analysis by Freedberg et al. of the gastrointestinal manifestations of acute COVID-19 and long COVID included 50 studies [17]. The incidence of gastrointestinal symptoms was 12% in patients with COVID-19 and 22% in patients with long COVID. The following symptoms were described: loss of appetite, dysgeusia, dyspepsia, and irritable bowel syndrome. The study authors suggest that gastrointestinal symptoms are associated with psychological disorders such as anxiety and depression and should be considered within a biopsychosocial model of disease.

In the meta-analysis by Pinzon et al. [18], which focused on neurological impairment with long COVID and included 36 studies and 9,944 participants, fatigue was the most common symptom of long COVID (52.8%; 95% CI, 19.9%–84.4%), followed by cognitive impairment (35.4%; 95% CI, 2.1%–81.7%), paresthesias (33.3%; 95% CI, 2.7%–76.6%), sleep disturbance (32.9%; 95% CI, 6.5%–67.4%), musculoskeletal pain (27.8%; 95% CI, 12.7%–46%), and dizziness (26.4%; 95% CI, 4.6%–57.9%). Neurological symptoms in long COVID are thought to be related to direct damage to the brain caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), as neuronal regeneration takes a long time, resulting in prolonged impairment of neuronal function. Another possible mechanism of neurological disorders is the alteration of the gut microbiome, which is involved in the production, transport, and function of neurotransmitters, with subsequent dysregulation of the microbiota-gut-brain axis. In addition, long COVID symptoms may be a form of so-called "sick behavior." This is a form of universal adaptive response to infectious pathogens that conserves the body's energy to increase the efficiency of the immune system and includes fever, loss of strength, and cognitive impairment [19].

RISK FACTORS

Long COVID may develop regardless of the severity of the primary infection, the presence, or absence of hospitalization, age, and preexisting complications [20]. Several studies demonstrated that there is no association between the severity of acute COVID-19 and the probability of long COVID and the severity of symptoms [21–25]. However, there are studies showing that patients who experience severe COVID-19 and require ventilatory support, admission to an intensive care unit (ICU), or prolonged hospitalization are more likely to suffer from symptoms of long COVID [26–28]. In a study by Taboada et al. [26], a significant number of ICU patients reported a subjective worsening of their functional status compared with patients not requiring ICU care (81.3% vs. 40.4%, $p < 0.001$). Limitations in activities of daily living (2–4 points on the PCSF [The Post-COVID Functional Status] scale) were reported by 56.4% of ICU patients, compared with 17.9% of non-ICU patients ($p < 0.001$) [26]. Persistent symptoms were reported to be more common in women [27–29], and the risk of these symptoms was also linearly related to age. Other risk factors include smoking, obesity, multiple comorbidities, and respiratory and psychiatric diseases [30].

The study by Antonelli et al. [31] evaluated the prevalence and risk of long COVID according to the circulating strain. The researchers used the data collected from users of the COVID Symptom Study app, where patients reported their symptoms during the acute period and after COVID-19.

This case-control study included 97,364 patients. To be included in the study, patients had to meet the following criteria: a positive polymerase chain reaction or rapid antigen test for SARS-CoV-2 after vaccination, entry into the app at least once a week for at least 28 days after a positive test for SARS-CoV-2, and no previous infection with SARS-CoV-2 prior to vaccination.

The first sample comprised 56,003 patients with positive tests for SARS-CoV-2 between December 20, 2021, and March 9, 2022. These cases were attributed to the Omicron variant, as this was the cause of >70% of all cases of COVID-19 in the UK during this period. The second sample included 41,361 patients with positive tests for SARS-CoV-2 between June 6, 2021, and November 27, 2021, when the Delta strain was the predominant variant.

Among the cases of patients from the sample infected with the Omicron strain, 2,501 patients (4.5%) reported symptoms of long COVID, and 4,469 patients (10.8%) from the Delta strain sample exhibited similar symptoms. The authors used a logistic regression model to ascertain the significance of the circulating strain in the occurrence of long COVID, which also considered other potential risk factors, such as sex, age, body mass index, social status (on a scale from 1 to 10), vaccine status (1, 2, or 3 doses), and the presence of comorbidities. The probability of long COVID associated with the Omicron strain in comparison with the Delta variant was found to be between 0.24 and 0.50. Furthermore, age and time since vaccination were identified as significant factors.

LONG COVID BIOMARKERS

The search for biomarkers of long COVID is essential for timely diagnosis and treatment. There are many hypotheses

for the pathogenesis of long COVID, including persistence of SARS-CoV-2 virus or its remnants, activation of autoimmune processes, disruption of the gut microbiome, reactivation of other latent viruses in the body, and irreversible tissue damage due to inflammation.

In the article by Klein et al. [32], which is aimed at determining diagnostic criteria for long COVID by the formation of the immune profile of patients, in addition to changes in various groups of lymphocyte populations, a decrease in cortisol from two loci was detected, even after adjustment for demographic features and the time of sample collection. A compensatory increase in adrenocorticotropic hormone (ACTH) levels did not appear to occur with the decrease in cortisol observed in the study group of patients with long-COVID symptoms. This suggested that the response of the hypothalamic-pituitary axis to cortisol regulation may be reduced. As cortisol plays a central role in several homeostatic and stress responses, these findings require further investigation. Importantly, ACTH has an extremely short half-life in plasma, which may complicate accurate detection of changes. Further studies are needed to confirm these preliminary findings. In addition, this study showed that individuals with long COVID have an increased antibody response to non-SARS CoV-2 viral antigens, particularly Epstein-Barr virus (EBV) antigens.

As stated by Su et al. [33], the occurrence of EBV viremia during acute COVID-19 in hospitalized patients is a predictor of persistent symptoms in the post-infection period. The observation of elevated IgG levels against EBV antigens suggests that recent reactivation of latent herpesviruses (EBV, varicella-zoster virus) may be a common feature of long COVID.

According to a systematic review by Lai et al. [34], which included 28 studies, 113 biomarkers significantly associated with the long-term course of COVID were identified, which the authors divided into six groups: 1) cytokines/chemokines (38, or 33.6%); 2) biochemical markers (24, or 21.2%); 3) vascular markers (20, or 17.7%); 4) neurological markers (6, or 5.3%); 5) acute phase proteins (5, or 4.4%); and 6) others (20, or 17.7%).

The analysis included the markers that were hypothesized to be associated with pulmonary, neurological, and multiple symptoms.

Serum levels of neurofilaments (NFL) and glial fibrillary acidic protein (GFAP) were elevated in patients with neurologic symptoms of long COVID. These are skeletal proteins that maintain the stability of neuronal axons and astrocytes. Determination of these proteins in patients' blood may serve as biomarkers associated with neuronal degeneration and damage. Patients with long COVID and elevated serum levels of NFL and GFAP were found to have worsening headaches and persistent neuropathic pain. In addition, Peluso et al. [35] reported that serum NFL and GFAP levels in patients with acute COVID-19 are positively correlated with levels of interleukin 6 (IL-6), tumor necrosis factor alpha, and C-C motif ligand 2, which may activate immune cells and induce neuroinflammation. This indirect mechanism demonstrates that proinflammatory cytokines and chemokines can exacerbate significant neuronal damage.

However, the authors point out that the medical history of a particular patient should be considered in each individual case. For example, NFL may serve as a marker both for neurological manifestations of long COVID and for neurodegeneration in general, being elevated at the onset of Alzheimer's disease, Parkinson's disease, and others [34, 35].

Pulmonary fibrosis is one of the complications of severe COVID-19 cases. Elevated levels of IL-6, CRP, and transforming growth factor beta (TGF-β) were found in the patients with long COVID accompanied by pulmonary symptoms. However, CRP and IL-6 were already well known in COVID-19 studies. Therefore, TGF-β attracted the attention of researchers [36].

TGF-β is a multifunctional cytokine that plays a critical role in tissue repair after injury. In pulmonary viral infection, epithelial cell injury may cause activation of M2 macrophages to secrete TGF-β, which stimulates fibroblast proliferation and collagen synthesis, leading to fibrosis [37, 38]. Recently, Zhou et al. demonstrated that the Food and Drug Administration-approved pirfenidone, a TGF-β and a collagen-targeting drug, attenuated the manifestations of pulmonary fibrosis after COVID-19 [39]. Therefore, combination therapy targeting anti-inflammatory (e.g., IL-6 blockade) [40] and antifibrotic pathways (e.g., pirfenidone) [39] may be a potential therapeutic strategy for long COVID with pulmonary fibrosis.

PROGNOSIS

An outcome study of patients in China who required hospitalization for COVID-19 showed that even two years after hospital discharge, 55% of patients (650/1190) still had symptoms of acute disease [41].

A study conducted in Switzerland [42] revealed that fatigue, pain, and sleep or wake disturbances associated with long COVID had a detrimental impact on the quality of life and work capacity of most patients. These effects reduced significantly by Month 12. It became evident that Month 7, many patients had not yet recovered, with systemic and neurological or cognitive symptoms persisting. Consequently, they were unable to resume their previous level of performance and continued to experience significant impairment due to these symptoms.

A two-year retrospective cohort study of individuals diagnosed with COVID-19 showed that the increased incidence of mood and anxiety disorders was transient, whereas the increased risk of psychiatric disorders, cognitive deficits, and dementia persisted throughout the follow-up period [43].

A systematic review and meta-analysis of pulmonary function abnormalities and chest computed tomography 6–12 months after recovery from COVID-19 showed that the prevalence of complications did not decrease one year after initial infection [44].

PROSPECTS (CONCLUSION)

The Omicron strain and its quasispecies were found to cause a less severe course of COVID-19 than previous variants, reducing the likelihood of long COVID [45]. Data from this meta-analysis showed that the people who were vaccinated but infected with COVID-19 were less likely to report symptoms of long COVID compared with those unvaccinated. Consequently, a strategy to prevent persistent COVID-19 now appears to be the timely organization of vaccination-based prophylaxis against infection.

Furthermore, vaccination, timely diagnosis, and treatment to reduce the severity of COVID-19 if infected may potentially reduce the risk of complications.

Currently, long COVID remains a significant challenge for some patients. Once other possible causes unrelated to long COVID have been ruled out, symptomatic and supportive therapy for symptom relief remains the primary treatment method. Therefore, large-scale, well-designed research, and interdisciplinary approaches are needed to understand the medical and social consequences of these persistent symptoms, support the patients living with the long-term effects of COVID-19, and develop targeted treatments.

ADDITIONAL INFORMATION

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