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Long covid: A comprehensive review of epidemiology, clinical manifestations and therapeutic approaches

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ABSTRACT

Long-COVID is a complex post-infection condition defined by symptoms that persist after an acute SARS-CoV-2 infection. These may include newly emerging symptoms or symptoms that persist and occur during recovery and result from the primary SARS-CoV-2 infection. This paper provides a synopsis of what is currently known about long-COVID using a summary of the last several years' literature. Specifically, focus is put on the variability of symptomatology, multiple organ system involvement, as well as the impact on the patient's functional status and overall quality of life. This review also describes the possible mechanisms involved in the persistence of symptoms, including viral persistence, immune system dysfunction, and mechanisms similar to those observed in myalgic encephalomyelitis/chronic fatigue syndrome. Additionally, this paper assesses existing treatment options and digital therapies for long-COVID symptoms, acknowledges the lack of evidence-based treatments for these patients, and identifies populations that may be at increased risk of long-term complications following SARS-CoV-2 infection. Finally, the entire review shows the heterogeneity of long-COVID and draws attention to the need for future studies to improve our knowledge of the biological mechanisms involved in this condition, as well as to develop evidence-based treatment options.

Keywords: Long COVID; post-COVID syndrome; post-acute sequelae of SARS-CoV-2 infection (PASC); SARS-CoV-2; post-viral fatigue

1. INTRODUCTION

Ever since Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) emerged at the end of 2019, clinicians have increasingly moved their focus from the acute presentations of Coronavirus Disease 2019 (COVID-19) to the long-term effects of the disease that continue long after the initial illness. There are many different terms for continuing symptoms experienced after a person has had COVID-19, such as "Long-COVID," "Post-COVID-19 Syndrome," and "Post-Acute

Sequelae of SARS-CoV-2 Infection (PASC)" (Taribagil et al., 2021; Boufidou et al., 2023).

The World Health Organization (WHO) defines post-COVID-19 condition as symptoms that happen in patients who have had a possible or confirmed SARS-CoV-2 infection. These symptoms usually start about three months after COVID-19 begins, last for at least two months, and cannot be explained by another illness (Rodriguez-Sanchez et al., 2022; Veronese et al., 2022). The National Institute for Health and Care Excellence (NICE) separates COVID-19 symptoms into ongoing symptoms (4–12 weeks) and post-COVID-19 syndrome (more than 12 weeks). The term "long COVID" is used to describe both of these conditions (Taribagil et al., 2021).

The number of long-COVID cases is different among epidemiological estimates. Systematic reviews show that approximately 10-20% of patients who contract SARS-CoV-2 will develop medium to long-term symptoms after the initial acute phase of COVID-19 (Veronese et al., 2022). Approximately one out of four questionnaire responders (25.4%) said that they had at least one symptom that lasted more than 2.5 months after their acute COVID-19 illness (Baruch et al., 2022). The clinical presentation of long-COVID is heterogeneous and multisystemic. Common symptoms include fatigue, dyspnea, myalgia, headache, cognitive dysfunction, anxiety, and mood disturbances (Rodriguez-Sanchez et al., 2022; Debie et al., 2024).

Given the variable prevalence of long-COVID, the need to identify risk factors for its development (such as gender or the severity of the acute phase of the disease), the potential cumulative impact of reinfection, and the lack of clearly established, effective treatment methods, a periodic review of the current state of knowledge is necessary. This review covers the epidemiology, clinical presentation, risk factors, pathophysiological mechanisms, and available treatment options for this syndrome. Therefore, the aim of this review is to summarize relevant peer-reviewed studies on the epidemiology, clinical symptoms, risk factors, pathophysiological mechanisms, and emerging treatment options for long-COVID-19.

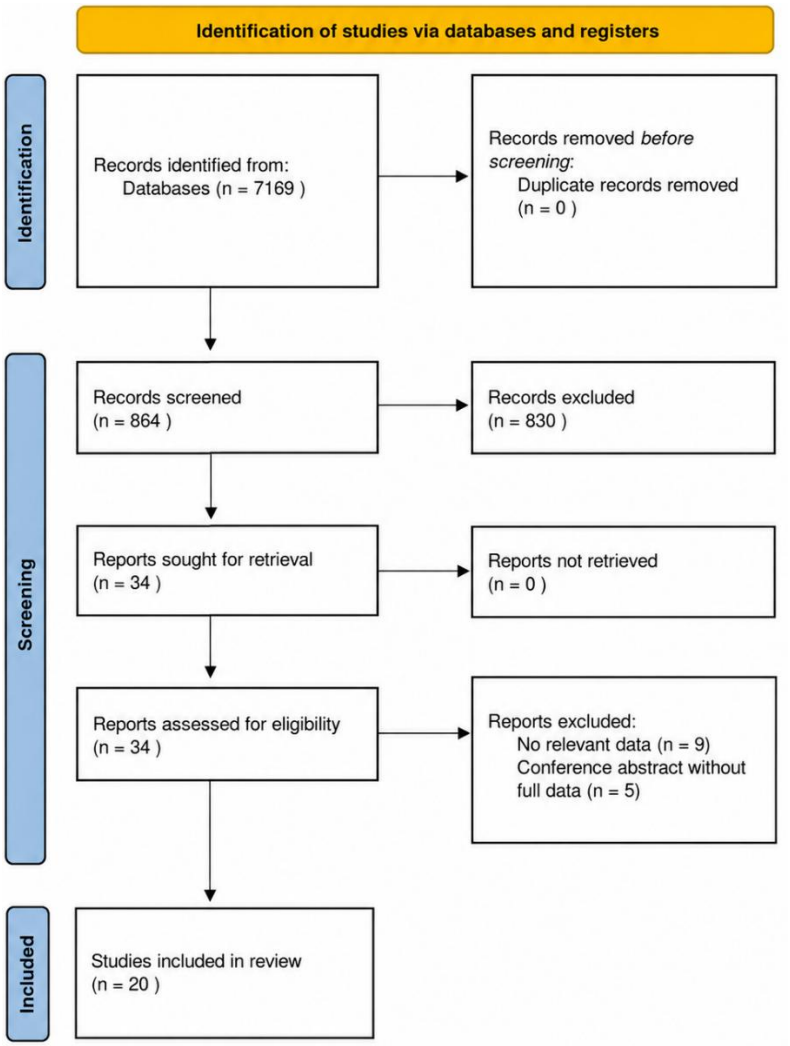

Figure 1. PRISMA flow chart.

2. REVIEW METHODS

A review of articles about long-COVID from the PubMed database was carried out. The search included studies published between 2020 and 2025. The keyword used to search for articles was “long-COVID”.

The study included peer-reviewed articles, clinical trials, and review papers about long-COVID, including its epidemiology, symptoms, causes, and treatment. Studies about specific symptom groups, such as memory and thinking problems, fatigue, dysautonomia, and problems with functioning, were also included.

The exclusion criteria included publications not written in English, case reports lacking sufficient methodological details, and conference abstracts for which the full text was not available. The study selection process is presented in Figure 1.

3. RESULTS & DISCUSSION

Epidemiology and Risk Factors

Prevalence and Population-Based Estimates

Long-COVID rates differ between studies depending on the type of study, how long patients were followed, and which groups of people were included. Some hospital-based studies found long-term symptoms in 30% to 90% of patients six months after infection, showing large differences between study results (Rodriguez-Sanchez et al., 2022).

In a population study with 2,696 adults (ages 18 – 55 years old) with confirmed COVID-19, 1,680 adults (62.3%) reported they had long-COVID at least three months after being in hospital. In the same study, 194 adults (7.2%) experienced "brain fog" at least three months after hospitalization (Asadi-Pooya et al., 2022).

Malta's national survey data provides additional epidemiologic knowledge of the burden of long-COVID. A total of 8,446 eligible PCR-confirmed COVID-19 cases occurred in 2020 and 2,665 of them completed a questionnaire approximately 3 – 6 months post-infection with an estimated 31.55% response rate. Based on responses to the questionnaire, it was determined that 25.4% of respondents reported experiencing at least one symptom after 2.5 months post-infection (Baruch et al., 2022).

The estimated number of long-COVID cases is also different in specific patient groups. A one-year study followed 96 patients with cancer. In the study, 49 of the 96 patients (51.0%) were infected with SARS-CoV-2, of whom 39 (79.6%) developed long-COVID symptoms (Debie et al., 2024). This is significantly higher than in the general population, where long-COVID occurs in approximately 10–20% of people (Veronese et al., 2022).

These results show that long-COVID is more common in some groups of patients than in others. For example, this condition is more common in patients who were in hospital and those with a compromised immune system than in patients who were not hospitalized and have a properly functioning immune system (Rodriguez-Sanchez et al., 2022; Debie et al., 2024).

Identified Risk Factors

Several individual and group factors are associated with an increase in the chance of experiencing persistent symptoms after COVID19. Female sex was significantly associated with the development of “brain fog” (odds ratio [OR] = 1.4) in patients with chronic post-COVID syndrome (Asadi-Pooya et al., 2022). In addition, respiratory symptoms during the initial illness (OR = 1.9) and intensive care unit admission (OR = 1.7) were associated with persistent cognitive complaints (Asadi-Pooya et al., 2022). The Maltese national survey demonstrated that female sex, hospitalization for the acute illness, and presence of initial symptoms, were all associated with an increased likelihood of persistent fatigue, shortness of breath, cough, anxiety, sadness, and memory loss, compared to those who did not experience these symptoms at > 2.5 months (Baruch et al., 2022).

Age-related patterns vary. While evidence suggests that older people experience both greater acute morbidity/mortality from COVID-19 and greater disease severity during their acute illness, most case series regarding long-COVID (the condition formerly known as post-acute sequelae of SARS-CoV-2) report predominantly middle-aged women to be the demographic most frequently affected by this condition. Older people may also exhibit different presentations of COVID-19, including non-specific symptoms such as weakness, confusion, and mood changes (Rodriguez-Sanchez et al., 2022).

Another possible risk factor for developing long-COVID is reinfection. The number of previous SARS-CoV-2 infections appears to increase the risk of developing long-COVID and related cardiovascular, pulmonary, and neurologic complications. Although reinfection tends to be milder than the first infection, there is still a risk of developing long-COVID due to each subsequent infection (Boufidou et al., 2023).

The number of preexisting health conditions may also affect the likelihood of developing long-COVID symptoms. For instance, studies have shown that in the group of oncology patients, 79,6% developed long-haul COVID-19 and had pre-existing cancer diagnoses. It is reasonable to assume that these cancers contributed to lowered immune function and/or reduced physiologic reserves, which may have worsened the development of chronic symptoms (Debie et al., 2024).

Overall, current literature indicates that factors that play a role in a greater risk of developing ongoing symptoms post-COVID-19 include: female sex, the extent to which one experiences severe acute symptoms of COVID-19, the presence of severe respiratory symptoms (especially at onset), whether or not one requires hospitalization for COVID-19 treatment, the frequency of reinfection, and how many comorbidities an individual possesses.

Clinical Spectrum of Long-COVID

Fatigue and Post-Exertional Symptom Exacerbation

Fatigue is the most common manifestation of long-COVID across all populations. A total of 2,696 adults who had contracted COVID-19 found that 62.3% of them experienced some form of long-COVID (as defined by Asadi-Pooya et al.) for at least three months after they had left the hospital. While there was an emphasis on cognition in their study, the long-COVID group had the highest number of persistent symptoms due to the effects of COVID-19, which included fatigue as a symptom (Asadi-Pooya et al., 2022).

In a national survey of 2,665 people 3–6 months after PCR-confirmed infection, fatigue was one of the most common symptoms lasting more than 2.5 months. In this group, 25.4% of respondents reported persistence of at least one symptom beyond 2.5 months (Baruch et al., 2022).

In a prospective cohort of 96 patients who had cancer, 49 patients (51.0%) developed SARS-CoV-2 infection, and 39 of them (79.6%) reported long-COVID symptoms. Of those patients who reported developing long-COVID symptoms, some reported experiencing fatigue, myalgia, and some reported having a problem sleeping (Debie et al., 2024).

Older adults who develop long-COVID often report weakness and functional decline. In a geriatric-focused review, 8.9% of patients in the cohort reported fatigue; however, symptom frequency depended on the severity of the patients' acute illness (Rodriguez-Sanchez et al., 2022). Symptoms of chronic fatigue that develop after infections are similar in many ways to those of long-COVID. A study comparing patients with ME/CFS and those with long-COVID-19 showed that post-exertional malaise (PEM) occurred in 79.4% of patients with long-COVID-19 and in 89.7% of patients with ME/CFS (Eckey et al., 2025).

These data show that one of the main symptoms of long-COVID is fatigue and exacerbated symptoms following physical exertion. These symptoms may occur in various patient groups—including the general population, older adults, cancer patients, and individuals with symptoms similar to ME/CFS (Asadi-Pooya et al., 2022; Debie et al., 2024; Eckey et al., 2025).

Neurocognitive Dysfunction ("Brain Fog")

Neurocognitive impairment is an ongoing aspect of the long-COVID syndrome. In a cohort of 2,696 adult patients, 194 individuals (7.2%) reported chronic post-COVID "brain fog" at least three months after acute infection. Female sex (OR 1.4), respiratory symptoms at disease onset (OR 1.9), and intensive care unit admission (OR 1.7) were associated with persistent brain fog in this study. Symptoms included decreased ability to concentrate, difficulty remembering things, and diminished mental clarity (Asadi-Pooya et al., 2022).

Oncology patients were evaluated for cognitive function by use of standardized tools, such as the Cognitive Failures Questionnaire (CFQ). They showed a reduction in quality of life and measurable cognitive performance due to long-COVID (Debie et al., 2024).

Data collected in the study on patient-reported outcomes of 3,925 participants showed that cognitive impairment and "brain fog" were commonly reported by both long-COVID and ME/CFS groups. The results also showed a strong relationship in how both groups responded to treatment ($R^2 = 0.68$) (Eckey et al., 2025).

Dysautonomia

Current evidence suggests that autonomic nervous system dysfunction contributes to persistent symptoms in long-COVID. In a prospective study including 39 participants (12 with COVID-19 and fatigue, 15 with COVID-19 without fatigue, and 12 control participants), heart rate variability was assessed using the Nociception Level (NOL) index. A significant dissociation in NOL index over time was observed between long-COVID participants with fatigue and control participants ($p = 0.046$). Additionally, no statistically significant differences in NOL scores were observed at different times between long-COVID patients with fatigue and those without

fatigue (p= .904). Some of the clinical manifestations of the dysautonomic symptoms included fatigue, orthostatic symptoms, fluctuations in blood pressure, and disturbances in heart rate variability (Barizien et al., 2021).

Musculoskeletal Manifestations and Functional Limitation

A significant number of people who experience long-COVID report musculoskeletal issues and a loss of function. In the oncology cohort, myalgia was reported in 46.2% of infected patients with long-COVID, fatigue in 38.5%, and disturbed sleep in 35.9% (Debie et al., 2024).

Older adults can develop sarcopenia and lose functional ability when they become acutely ill, bedridden, or inactive. It has been suggested that early detection of decreasing functional ability should be accomplished by performing a comprehensive geriatric assessment in these cases (Rodriguez-Sanchez et al., 2022).

A large study (including 3,925 participants), which asked patients about their self-assessed function in comparison to before they became ill, found that on average, long-COVID patients had 50.6% ± 20.4% of their former functional capacity, while ME/CFS patients had 41.0% ± 18.5% of their former functional capacity. In addition, 10.1% of long-COVID patients stated that their illness was at least moderate (15–25% capacity) to extremely severe (<15% capacity), while 20.4% of the ME/CFS cohort stated the same (Eckey et al., 2025).

The results of the studies mentioned above demonstrate that long-COVID causes measurable decreases in functional capacity in different patient groups (Debie et al., 2022; Eckey et al., 2025).

Pathophysiological Mechanisms

The literature included in this review defines long-COVID in various ways. Regardless of these differences, most definitions suggest that multiple biological processes add to long-COVID, although researchers do not yet fully understand these mechanisms. Several of the mechanisms described in the literature referenced in this report include viral persistence, immune dysfunction, and characteristics of immune exhaustion (Boufidou et al., 2023; Eaton-Fitch et al., 2024).

Viral Persistence

There have been reports of patients who have developed long-COVID and have had persistent levels of SARS-CoV-2 detectable after the acute phase of infection.

Levels of spike protein have been found to be present in the plasma of patients who have developed long-COVID between 2 and 12 months after they were infected with the virus. Similarly, studies detected SARS-CoV-2 RNA in stool samples over prolonged periods of time, suggesting continued viral RNA shedding from the gastrointestinal tract (Boufidou et al., 2023).

Researchers have found viral genetic material and proteins in many different tissues, including cardiovascular tissue, cerebrospinal fluid, brain, skeletal muscle, lymph nodes, appendix, liver, lung, and urine. However, it is not well understood how the virus can stay in the body in people with long-COVID. It is also not clear whether this means the virus is still active or whether only inactive pieces of the virus remain (Boufidou et al., 2023).

Viral Reactivation

Besides being present for a prolonged time after the initial illness, reactivating latent infections is another mechanism that could contribute to long-COVID. SARS-CoV-2 can possibly disrupt the immune system's homeostasis which could allow for reactivation of latent viruses such as Epstein–Barr virus (EBV), cytomegalovirus (CMV), herpes simplex virus (HSV), varicella-zoster virus (VZV), and human herpesviruses 6 and 7 due to an inability of the immune system to regulate the infection properly.

The reviewed literature points out many similarities between long-COVID, ME/CFS, and other post-infectious illnesses in which viral causes have been implicated. Nevertheless, it remains unclear what role viral reactivation plays in the persistence of symptoms (Boufidou et al., 2023).

Immune Dysregulation

Current evidence supports a key role of immune dysfunction in the pathogenesis of long-COVID and other post-infectious syndromes. Several studies have examined the immune systems of individuals who experience symptoms associated with long-COVID. These studies show differences in how their immune cells present antigens, signal through cytokines, and otherwise function compared to those of healthy control subjects. The gene expression of the immune cells from individuals experiencing long-COVID has

demonstrated dysregulation of gene expression related to antigen presentation, B cell development, macrophage function, and cytokine signaling (Eaton-Fitch et al., 2024).

Other studies have identified immune system dysfunction in individuals with long-COVID, including overexpression of MHC class II molecules on immune cells and increased proportions of "exhausted" CD4+ and CD8+ T lymphocytes. In addition, cytokine profiles were altered in these individuals. The authors point out that the immune dysfunction seen in long-COVID has similarities with the immune dysfunction seen in ME/CFS, specifically in terms of adaptive and innate immune dysfunction (Eaton-Fitch et al., 2024).

Immune Exhaustion

Immune exhaustion has been studied extensively in patients with long-COVID and ME/CFS. In a study that used peripheral blood mononuclear cells from 15 participants with long-COVID, 14 participants with ME/CFS, and 18 healthy controls to compare the differential gene expression of immune exhaustion-related genes in each group (Eaton-Fitch et al., 2024). The results showed dysregulated immune exhaustion-related gene expression in both the long-COVID and ME/CFS groups.

In patients with long-COVID, dysregulated gene expression correlated with pathways involved in antigen presentation, cytokine signaling, and immune activation. For patients with ME/CFS, there was downregulation of interferon signaling and immunoglobulin-related genes, indicating some degree of immune suppression (Eaton-Fitch et al., 2024).

Reinfection and Cumulative Risk

Studies have examined the possible impact of reinfection on long-term pathophysiology in the context of the post-Omicron phase of the pandemic. In older adults, the cumulative risk of long-COVID and its associated cardiac, pulmonary, or neurological complications appears to increase proportionally with the number of SARS-CoV-2 infections. Despite the fact that subsequent infections are typically less severe than the initial infection, the risk of developing long-COVID does not diminish (Boufidou et al., 2023).

The reviewed studies suggest that repeated SARS-CoV-2 infections may cause increasing problems in the immune system and could lead to more long-term health effects. However, it is still not clear exactly how this happens and research is ongoing (Boufidou et al., 2023).

Therapeutic Strategies and Interventions

Currently, there is no treatment that can change the course of long-COVID. Most of the available research includes small treatment studies, digital health programs, and large surveys based on patient-reported outcomes (Veronese et al., 2022; Rinn et al., 2023; Eckey et al., 2025).

Interventional Studies

A systematic review of treatments for long-COVID found only two randomized controlled trials (RCTs) that met the criteria for inclusion. The first trial assessed the effectiveness of using olfactory training with oral palmitoylethanolamide and luteolin in patients with prolonged olfactory dysfunction after COVID-19. Patients who received the intervention had better improvements in their olfactory functions when compared to those in the control group; however, the number of studies used to meet inclusion criteria for this review was only two RCTs, and thus the body of evidence supporting interventional treatments in long-COVID was determined to be very weak (Veronese et al., 2022).

The second RCT used in the review addressed the use of aromatherapy as an intervention to treat fatigue in post-COVID patients. Due to the small number of RCTs and the small sample size of each, the authors concluded that the quality of evidence for interventional treatments in long-COVID was poor. The authors highlight the need for better randomized controlled trials to develop standard treatments for long-COVID (Veronese et al., 2022).

Digital Interventions

A review of digital treatments for post-COVID or long-COVID symptoms found eight studies on telehealth or other digital therapy methods. These studies looked at treatments such as remote rehabilitation programs, online monitoring, and online cognitive behavioral therapy. Many of them reported improvements in fatigue, mental health, and physical function in post-COVID patients, but most did not include control groups and used very different study designs. The review also points out problems such as differences in methods, small study sizes, and a lack of standard ways to measure results (Rinn et al., 2023).

Patient-Reported Treatment Outcomes

A large patient-reported survey analyzed treatment experiences in 3,925 individuals, including 2,125 patients with ME/CFS and 1,800 with long-COVID. Participants reported using more than 150 supplements, over-the-counter medications, prescription medications, and non-pharmacologic interventions. Symptom profiles in the ME/CFS and long-COVID groups were similar, and the responses to the different treatments among the two groups correlated at a level of $R^2 = .68$ (Eckey et al., 2025).

The survey found that different groups of symptoms responded in different ways to treatment. For example, people with mainly postural orthostatic tachycardia syndrome (POTS) symptoms said they improved with drugs that affect the autonomic nervous system, while a cognitive-dysfunction cluster reported benefit from central nervous system stimulants. The authors also point out that self-reported data has some limits, including possible memory errors and a lack of standard ways to measure outcomes (Eckey et al., 2025).

Vaccination and Long-COVID

Researchers have examined the impact of COVID-19 vaccination on long-COVID symptoms. In a study involving 1,236 patients with long-COVID, the prevalence of persistent symptoms varied between the vaccinated and unvaccinated. Unvaccinated patients reported a lower rate of persistent symptoms (29.4%) than vaccinated patients (44.6%, $p = 0.032$). The authors note that these results should be interpreted carefully because the study was observational and other factors may have influenced the results (Asadi-Pooya et al., 2024).

Special Populations

Long-COVID does not affect all people equally. The studies show that some groups are more vulnerable, including older adults, patients with cancer, and people who have been infected more than once.

Older Adults

Older adults had higher death rates and more severe illness during the acute phase of COVID-19. However, the clinical expression of long-COVID in this population may differ from that observed in younger age groups. Symptoms of long-COVID in older adults often include weakness, decreased function, disorientation, and mood changes. In one study included in this review, 8.9% of older patients reported fatigue, but the incidence of fatigue depended on the severity of the acute disease (Rodriguez-Sanchez et al., 2022).

Research shows that older people can lose more muscle strength and function during illness and long periods of inactivity, especially when physical activity is reduced due to pandemic restrictions. Geriatric extensive assessments and early intervention through rehabilitation programs are proposed as two methods to improve post-COVID recovery in older adults. Although older adults represented the largest burden of acute disease cases, long-COVID case studies have primarily consisted of middle-aged women, which could indicate a possible lack of recognition and/or reporting of long-COVID cases in older adults (Rodriguez-Sanchez et al., 2022).

Patients with Cancer

Patients with cancer represent a population with elevated vulnerability to both acute COVID-19 as well as its long-term consequences. In a prospective cohort of 96 patients with cancer followed from March 2022 to March 2023, 49 individuals contracted SARS-CoV-2 during the study period, and of those 49 patients, 39 reported long-COVID symptoms such as myalgia, fatigue, and disturbed sleep (Debie et al., 2024).

In addition to the physical symptoms, patients with cancer reported negative emotional and psychological consequences caused by the pandemic-related restrictions. The study used standardized tools to measure these effects, including the EORTC QLQ-C30, the Hospital Anxiety and Depression Scale (HADS), and the Cognitive Failures Questionnaire (CFQ). The authors suggest that the higher rate of long-COVID in patients with cancer is possibly due to a decrease in the physiological reserve and a compromise of the immune system (Debie et al., 2024).

Reinfection and the Post-Omicron Phase

The literature stresses the impact of reinfection in the context of evolving SARS-CoV-2 variants. A review discussing the reinfection and long-COVID in the post-Omicron phase indicated that the likelihood of developing long-COVID and the associated cardiac, pulmonary, and neurological complications after each reinfection increases proportionately to the number of reinfections. This effect is described as most significant in older adults (Boufidou et al., 2023).

Although reinfection is usually milder than the initial infection, there is still a risk of developing long-COVID after each new infection. These findings suggest that repeated exposure to SARS-CoV-2 may lead to more long-term health problems in some groups of people (Boufidou et al., 2023). The study summary are mentioned in table 1.

Table 1. Characteristics and main findings of studies included in this review.

Author, year	Study design	Population/sample	Main findings
(Asadi-Pooya et al., 2022)	Population-based cohort study	2,696 adult patients with confirmed COVID-19	62.3% of patients reported long COVID symptoms; 7.2% reported persistent "brain fog". Female sex, respiratory symptoms at onset, and ICU admission were associated with cognitive complaints.
(Baruch et al., 2022)	National survey	2,665 respondents with PCR-confirmed COVID-19	Persistent symptoms beyond 2.5 months were reported in 25.4% of participants. Fatigue and respiratory symptoms were common long-term manifestations.
(Debie et al., 2024)	Prospective cohort study	96 oncology patients	Long COVID symptoms were reported in 79.6% of infected patients. Common manifestations included fatigue, myalgia, and disturbed sleep.
(Rodriguez-Sanchez et al., 2023)	Review article	Older adults with COVID-19	Long COVID in older adults was associated with weakness, functional decline, mood alterations, and sarcopenia.
(Boufidou et al., 2023)	Narrative review	Post-Omicron and reinfection-related cohorts	Reinfections may increase cumulative risk of long COVID and associated cardiac, pulmonary, and neurological complications.
(Eaton-Fitch et al., 2024)	Mechanistic study	Long COVID patients, ME/CFS patients, and healthy controls	Evidence of immune dysregulation and immune exhaustion involving cytokine signaling and antigen presentation pathways.
(Eckey et al., 2024)	Patient-reported outcomes survey	3,925 participants with long COVID or ME/CFS	Significant overlap between long COVID and ME/CFS symptom profiles, including post-exertional malaise and reduced functional capacity.
(Barizien et al., 2023)	Prospective observational study	39 participants	Autonomic dysfunction and altered heart rate variability were associated with fatigue in long COVID patients.
(Veronese et al., 2022)	Systematic review	Interventional studies in long COVID	Limited evidence for therapeutic interventions; only two randomized controlled trials met inclusion criteria.
(Rinn et al., 2024)	Scoping review	Digital intervention studies	Digital and telehealth interventions showed potential benefit in fatigue, psychological symptoms, and physical functioning, although evidence remained heterogeneous.

Limitations of Current Evidence

The currently available literature on long-COVID shows heterogeneity in study design, case definitions, outcome measures, and follow-up duration. There are different definitions of long-COVID, which vary depending on the institution, organization, or guideline considered. The World Health Organization defines post-COVID-19 condition as symptoms that appear after COVID-19, usually within three months after infection, and last for at least two months (Rodriguez-Sanchez et al., 2022; Veronese et al., 2022). Estimates of how common long-COVID is vary a lot, from 10–20% in the general population (Veronese et al., 2022) to 30–90% in hospital patients (Rodriguez-Sanchez et al., 2022), and up to 79.6% in cancer patients (Debie et al., 2024). These differences may be due to how studies

are done, who is included, and how many people respond. For example, in a Maltese survey, only 31.55% of eligible people responded, meaning 2,665 out of 8,446 (Baruch et al., 2022).

The authors noted that this low response rate may have affected the results. There are a few large-scale and high-quality studies of interventions for long-COVID. In fact, a systematic review of long-COVID interventions found only two randomized controlled trials that met the inclusion criteria. The authors concluded that, in general, there is limited evidence to support treatments for long-COVID and, therefore more high-quality randomized trials are needed (Veronese et al., 2022).

Similar problems are seen in studies of digital treatments for long-COVID. These studies often do not include a control group (Rinn et al., 2023). Because of this, they usually have small sample sizes and use different ways of measuring results, which makes it hard to compare them.

Patient-reported outcome surveys provide large amounts of real-world data on conditions such as long-COVID. However, they have an inherent issue with recall bias, and there is no clinically standard method of verifying the accuracy of patient responses. The authors of this article specifically indicate that their results were derived from self-reporting methods and therefore should be viewed in light of those methods (Eckey et al., 2025).

There have been relatively few mechanistic studies of long-COVID. For example, researchers performed immune exhaustion profiling using samples from 15 patients diagnosed with long-COVID, 14 with ME/CFS, and 18 healthy volunteers. Although these types of studies may help identify potential immunological changes associated with long-COVID, the number of participants involved in these studies limits the generalizability of the findings (Eaton-Fitch et al., 2025).

Therefore, in summary, the body of literature currently available regarding post-COVID is characterized by variable definitions of what constitutes post-COVID-19, a wide range of estimates of the prevalence of post-COVID-19, limited availability of randomized trials evaluating treatment options for post-COVID-19, reliance upon self-reporting of symptoms, and generally much smaller sized cohorts evaluating mechanisms underlying post-COVID-19 (Veronese et al., 2022; Rinn et al., 2023; Eckey et al., 2025; Eaton-Fitch et al., 2024).

4. CONCLUSION

Long-COVID represents a broad spectrum of conditions that may affect multiple organ systems and greatly impair functional capacity and quality of life in affected individuals. Recent studies have shown that the combination of the numerous systemic complications resulting from prolonged symptomatology of SARS-CoV-2 infection includes a variety of manifestations, such as chronic fatigue, neurocognitive deficits, autonomic nervous system dysfunction, and musculoskeletal complaints. Although awareness of long-COVID is increasing, the exact biological reasons why it develops are still not well understood. It is thought to involve a mix of viral persistence, immune system problems, and changes in the body that happen after recovery from the acute infection. Currently, the mainstay of therapy for long-COVID remains symptomatic support, and as such, evidence-based therapeutic options are still severely limited. Therefore, due to the large clinical and social burden of long-COVID, additional research is necessary to better understand its pathophysiologic basis, improve methods for diagnosis, and develop therapeutic options that will help to improve long-term outcomes for patients diagnosed with long-COVID.

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Conflict of interest

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Data and materials availability

All data associated with this study will be available based on the reasonable request to corresponding author.

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