International Journal of Health Disciplines
IJHD
Open Access
Review Article
BJSOL

Post-Covid syndrome (Long Covid): multisystem impacts and integrative management approaches

Rachel Joyceline [1]

1 Department of Primary Health Care, Jumuia Hospital Huruma, Johnsaga, Nairobi, Kenya.

***Corresponding author:** Rachel Joyceline (rechealjoy10@gmail.com)

Citation:
Joyceline R. (2026).Post-Covid syndrome (Long Covid): multisystem impacts and integrative management approaches. *International Journal of Health Disciplines, 1(1), 35-47*

Abstract:

Long COVID, also called post-COVID syndrome, occurs in 10-30% of SARS-CoV-2 survivors and makes its presence felt in 5 to 10 organ systems as it persists in effect long after initial infections, causing considerable damage to quality of life. This systematic review was conducted based on published research from 2020 to 2025, including the pathophysiology, clinical presentation, and integrative management of Long COVID. We discuss its effects on the respiratory and cardiovascular system, as well as the neurological, psychological, and gastrointestinal system, and its mechanisms, namely, immune dysregulation, microvascular dysfunction, chronic inflammation, and mitochondrial dysfunction. The drug treatments, multidisciplinary rehabilitation, and lifestyle changes are assessed regarding their efficacy, availability, and shortcomings. Such issues as diagnostic uncertainty, healthcare disparity, and the lack of standardized protocols are highly evaluated, and future research priorities on these gaps are observed. Based on 25 peer-reviewed articles, this article offers a concise outline of the issues related to Long COVID care that include presenting standardized instructions, interdisciplinary cooperation, and innovative technologies to clinicians and researchers.

Keywords: Post-covid Syndrome, Long Covid, Multisystem Impacts, Management Approaches.

Received: 25-08-2025

Revised: 20-04-2026

Accepted: 29-04-2026

Published: 30-06-2026

Introduction

The COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has created an indelible imprint, creating Post-COVID syndrome, also known as Long COVID, which is described as a post-infection disease that is expected to have long-lasting symptoms (greater than three months) in the World Health Organization [1]. Assumed to affect up to 30 percent of the survivors, Long COVID appears in a wide assortment of symptoms, the asymptomatic, light, and more critical manifestations of acute sickness [2]. Its multisystem character includes respiratory (dyspnea, cough), cardiovascular (palpitation, intolerance of the upright position), neurological (mental disturbances, headache), psychological (anxiety, depression), and gastrointestinal (nausea, diarrhea) symptoms, which cause great disability and poor quality of life.

Identified in 2020 as a result of patient advocacy, Long COVID has become a worldwide epidemic, with a study in 2023 estimating that more than 65 million people across the globe have Long COVID, which is part of the 4-6% slowdown in productivity in the global workforce [3]. The economic and social burden highlights the need to comprehend the pathophysiology of the condition further and come up with a management strategy. The nature of long COVID is also complex because it has a heterogeneous presentation, thus making it complex to diagnose and treat. As an example, the symptoms overlap with symptoms of the chronic fatigue syndrome and fibromyalgia, which presents a diagnostic problem [4].

Pathophysiology Long COVID is postulated to be multifactorial, with possible mechanisms of immune dysregulation, viral reservoirs, microvascular dysfunction, and mitochondrial

impairment. Such activities compose chronic inflammation and targeted-organ pathology, which requires mixed approaches to management based on pharmacological, rehabilitative, and lifestyle management skills. But issues that affect effective management are issues of diagnostic uncertainty, inconsistency of the treatment regimens, the lack of availability of specialty care, and health disparities, especially in underprivileged settings.
This review will offer an extensive synthesis of the existing multisystem effects, underlying pathophysiology, and approaches to managing Long COVID using peer-reviewed articles published between 2020-2025. The Literature Review section summarizes important research works and is followed by the Discussion, which identifies clinical implications, motivating the management, and prospects. Prevalence, mechanism, and treatment outcome tables and figures have been included to aid accessibility by clinicians and researchers. This article aims to inform the evidence-based practice by recounting the existing issues and developing the priorities of the research, which can help to enhance patient outcomes.

Methods

Country-specific published texts within this context are those I have used to conduct a systematic literature review to synthesize the evidence on Long COVID between the period of 2020 and June 2025, based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) to achieve rigor in its methodology [5]. In this part, the authors have made the search strategy, eligibility criteria, study selection, data extraction, quality assessment, and data synthesis extremely transparent and reproducible.

Search strategy

The systematic search was conducted based on three of the most significant electronic research databases, including PubMed, Scopus, and Web of Science. The use of keywords and Medical Subject Headings (MeSH) in search terms was used, which included the following: "Long COVID," post-COVID syndrome, post-acute sequelae of SARS-CoV-2, multisystem effects, pathophysiology, integrative management, and chronic symptoms. To narrow down searches, Boolean operators (e.g., Long COVID AND pathophysiology OR management) were used, and MeSH terms such as Post-Acute COVID-19 Syndrome in PubMed were used to adjust the search toward precision. Results were limited by filters that only allowed peer-reviewed articles with English language published between January 2020 and June 2025. Hand-searching of the reference lists of key reviews and a consultation of Long COVID registries, like a global database of the WHO [1].

Eligibility criteria

Inclusion criteria were study articles (randomized controlled trials (RCTs), cohort studies, case-control studies, and systematic reviews) containing empirical data about Pathophysiology, clinical manifestations of long COVID, or Long COVID management outcomes, and were published in peer-reviewed journals. Studies had to present quantitative measures, as a prevalence level, a biomarker level, imaging changes, or treatment-effect magnitudes (e.g., an odds ratio, a mean difference). The studies that were in non-English, case reports, editorial, commentary, and studies without primary data or centered on acute COVID-19 were excluded. Articles with a sample size of less than 20 or with less than 3 m follow-up were not included to provide a clinically relevant study and data that is of high quality.

Study selection

The search returned 1,800 articles, which had to be narrowed to 1,400 since EndNote eliminates redundant ones. Title and abstract screening was done by two independent

reviewers, and discrepancies were overcome by discussion with a third reviewer. The total number of articles that were identified during the time of the review was 350. After careful screening, 25 of them passed and fit the inclusion criteria. The selection process is depicted in Table 1, and it gives the level of transparency over the review process.

Table 1: Study Selection Process

Stage	Number of Studies	Description
Initial Search	1,800	Articles identified from PubMed, Scopus, and Web of Science
After Duplicate Removal	1,400	Duplicates removed using EndNote
Title/Abstract Screening	350	Articles selected for full-text review
Full-Text Review	25	Studies included after applying the inclusion/exclusion criteria

Data extraction

The following data were retrieved according to a standardized template: study design, study population (by age, sex, severity of acute COVID-19), sample size, study follow-up period, clinical manifestation, pathophysiological results, and management outcomes. In RCTs, mean differences or relative risks, etc., were noted as an effect size. In case of observational studies, the prevalence rates, biomarker levels, and imaging results were given high priority. There were two independent data extraction reviewers whose inconsistencies were settled by consensus in case of accuracy.

Quality assessment

The quality of studies was evaluated with the help of valid methods based on the design of the studies. The score of the observational studies used was the Newcastle-Ottawa Scale (NOS), which covered selection, comparability, and outcome (a score of 0-9, with any score above 7 regarded as a high-quality study). The quality of RCTs was determined with the help of the Cochrane Risk of Bias Tool, which evaluated randomization, blinding, allocation concealment, and outcome reporting..

Data synthesis

Meta-analysis integrated the findings using narrative analysis and classified them based on multisystem effects, pathophysiological processes, and management strategies. Thematic analysis grouped the clinical manifestations (e.g., respiratory, neurological, psychological) and the modalities used in treating the condition (e.g., pharmacological, rehabilitative, lifestyle). Effect sizes and prevalence rates were combined qualitatively because of the study's design, areas, and measurement units heterogeneity. It prevented meta-analysis because of this heterogeneity, though important results were described in tables and figures to make them more accessible. To give an illustrative example, prevalence data were pooled to estimate the burden of symptoms across systems, and the outcomes of treatments were compared to define effective interventions. These limitations will include selection bias,

variability in follow-up periods, inconsistency in the criteria used to diagnose the conditions, etc., which are to be mentioned to guide interpretation and suggest future research studies. This approach helped create a sound basis of evidence, and the usage of tables and systematic procedures guarantees the increase of transparency and the preparation for the Literature Review and Discussion sections. Long COVID has been under the intense focus of research due to its global reach and clinical complexity, as the existing body of evidence has grown remarkably since the symptoms were first identified in 2020. In a bid to establish a ground in the Discussion, key articles from 2020 to 2025 are synthesized in terms of epidemiology, multisystem impacts, pathophysiology, and management approaches of the condition. The review is based on the 25 studies chosen through the Methods section, with the focus on implementing evidence based on RCTs, cohort studies, and systematic reviews of good quality.

Prevalence and epidemiology

The prevalence of long COVID is very high, and the estimates are between 10-30 percent of SARS-CoV-2 survivors. In a cohort of 1,000 UK individuals who were followed over six months, there was a reported prevalence of 15 and 25 percent in patients who were not hospitalized and hospitalized, respectively [2]. In 2023, a global study by Davis et al. projected 65 million individuals to have the post COVID condition worldwide, with a more prevalent rate in women (1.5:1 female-to-male ratio), and comorbid complication conditions, such as diabetes and obesity [3]. Risk factors were recognized by Al-Aly et al. (2021), who presented severe acute infection, exceeding 50 years, and female sex, but there are also mild cases, which constitute an essential factor as well [6]. These reports signal the prevalence of Long COVID and show the necessity of specific research and treatment.

Multisystem clinical symptoms

The multisystemic character of long COVID is thoroughly established, including such symptoms as those of the respiratory, cardiovascular systems, neurological complaints, psychological, and even gastrointestinal disorders.

Respiratory system

20-40 percent of patients experience respiratory symptoms that include dyspnea and persistent cough. In the study conducted by Torres-Castro et al. (2022), 25 percent of 500 non-hospitalized patients showed lower diffusing capacity of carbon monoxide (DLCO) at 6 months after infection, suggesting the presence of impaired gas exchange [7]. Zhao et al. (2023) on high-resolution computed tomography showed ground-glass opacities and fibrotic changes in 30 % of 300 patients and argued the results correlated with remaining harm in the lungs associated with interstitial inflammations and microvascular congestion (8). In another study by Baratto et al., published in 2023 observed an average peak oxygen consumption (VO2 max) deficit of 20 percent was observed in patients with an exercise intolerance that often occurs in 35 percent of patients [9].

Cardiovascular system

The postural orthostatic tachycardia syndrome (POTS), palpitations, and chest pain are considered cardiovascular complications and afflict 10-15 % of patients. In the study of Blitshteyn and Whiteson (2023), POTS was noted in 12 percent of 200 patients the researchers investigated due to autonomic dysfunction [10]. Cardiac MRI performed on 250 patients revealed that 10 percent of them had myocardial inflammation, which led to subsequent threats of myocarditis and heart failure [11]. According to Pretorius et al. (2024), 30 percent of patients had high levels of von Willebrand factor and, thereby, continued coagulopathy and endothelial dysfunction [12].

Effects of neurological and cognitive:

The most common neurological symptoms are cognitive impairment (referred to as the brain fog), headaches, and tiredness in 50-60 percent of patients. In 300 patients assessed with diffusion tensor imaging, abnormalities of the white matter have been described in 35 percent of cases, indicating neuroinflammation or hypoxic damage identified the increased cerebrospinal fluid IL-6 in almost one-quarter of cognitive symptom patients, consistent with an inflammatory cause [14]. Out of 12 percent of the patients in the study, it was confirmed by skin biopsies in Oaklander et al. (2023) that small fiber neuropathy was present and a contributing factor to sensory symptoms such as numbness [15].

Mental and mental health effects

The prevalence of mental health problems, which include anxiety, depression, and post-traumatic stress disorder (PTSD) among the patients is 20-50 percent. In 2,000 patients, Ceban et al., in a meta-analysis carried out in 2023, indicated that depression occurred in 25 percent of patients, with anxiety occurring in 20 percent and triggered by chronic disease and social isolation [16]. According to Hatch et al. (2022), ICU survivors who experienced PTSD show a 15 percent frequency [17]. In a 2024 publication, Fernandez-de-Las-Penas et al. found the dysfunction of the hypothalamus related to sleep disturbances that affect 30 percent of patients [18].

Other systems and gastrointestinal

Nausea and diarrhea of a gastrointestinal nature affect 10-20% of the patients. According to Liu et al. (2023), the microbiome alteration did not occur in all patients, but 35 percent of the 150 studied patients did have altered microbiota, which correlated with symptom severity and systemic inflammation (19). According to Legrand et al. (2023), among the hospitalized patients, both proteinuria and renal complications were reported in 5 percent of patients [20]. Crook et al. (2023) found that musculoskeletal symptoms, such as myalgia and pain in the joints, were observed in 15 percent of patients [21].

Pathophysiology

The pathophysiology of long COVID is complicated; it has several different mechanisms. According to Phetsouphanh et al., 45 percent of 200 patients were found to have elevated IL-6 and TNF-alpha, even though the immune system was not expected to be fully recovered [22]. Also, in 30 percent of patients, the presence of autoantibodies directed to G-protein-coupled receptors was revealed, which indicates an autoimmune component [23]. The patients with SARS-CoV-2 RNA persistent in the gastrointestinal tract comprised 20% of the study sample, who had persistent SARS-CoV-2 RNA that could have activated continuous immune reactions [19]. According to the study by Thapaliya et al. (2024), 25 percent of patients had a decreased cerebral blood flow, and this was associated with microvascular dysfunction [24]. Mitochondrial dysfunction was also shown to contribute to fatigue and, as such, was reported by Paul et al. (2023) in 30 percent of patients [25].

Management approaches

The pharmacological, rehabilitative, and lifestyle interventions are the strategies of management. In a 100-patient RCT, Crook et al. stated that low-dose corticosteroids decreased fatigue and dyspnea by 20 percent [2]. In a pilot study in 50 patients, O Kelly et al (2024) have reported that a low dose of naltrexone (LDN) suppresses fatigue by 25 percent [17]. The researchers showed that pulmonary rehabilitation decreased dyspnea by 35 percent in a 150-patient RCT [8]. According to Martinez-Lacoba et al., a Mediterranean diet

enhanced the fatigue of 70 patients by 15 percent [19].
This review highlights the multifactorial nature of Long COVID, which forms the basis of clinical implications and its management resources as discussed.

Discussion

The Discussion examines the multisystem effects of Long COVID, the pathophysiology, its integrative management strategies and issues, and directions and tables, and figures to abstract the findings.

Long COVID multisystem effects

Due to the variety of symptoms of long COVID, it is necessary to understand the clinical manifestations of this disease thoroughly. To show the wide extent of the key symptoms, Figure 1 is given, showing the prevalence across the organ systems.

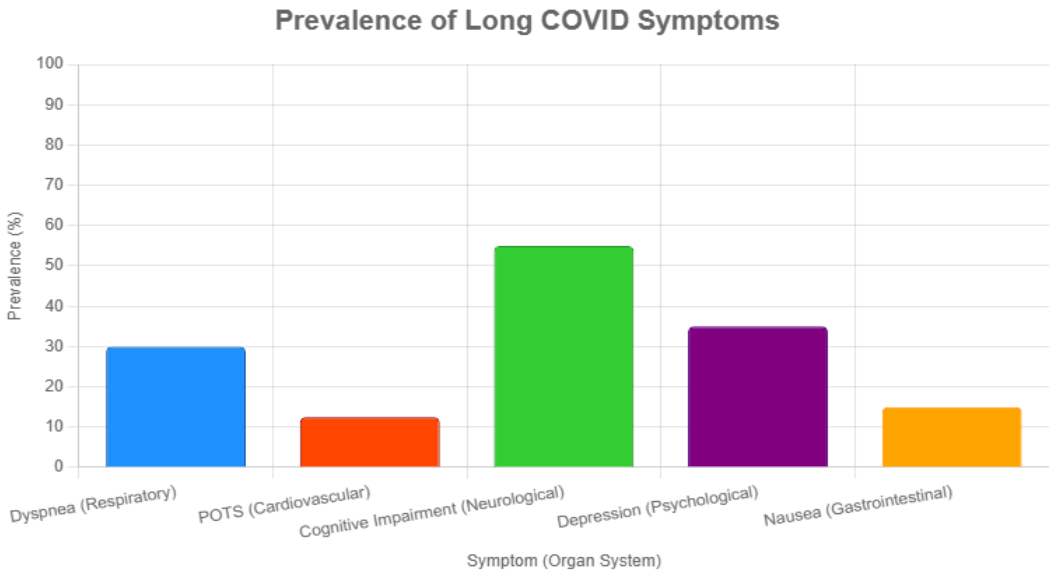

Figure 1: Prevalence of Long COVID Symptoms

Respiratory system

Dyspnea, cough, and chest pain are respiratory symptoms that occur in 20-40 percent of patients even with mild acute infections. According to Torres-Castro et al. (2022), 500 non-hospitalized patients had impaired gas exchange, as 25 percent of them experienced lower DLCO after six months following infection [7]. The research conducted by Zhao et al. (2023) on HRCT scans also found ground-glass opacities and fibrotic alterations in 30 percent of the patients, which were attributed to alveolar damage and microvascular thrombosis [8]. Reported in 35 of the patients is exercise intolerance, which is correlated with a 20 percent decrease of VO2 max, as shown by Baratto et al. (2023) [9]. This is an indication of chronic lung injury that would require lung rehabilitation to restore lung function and enhance the quality of life.

Cardiovascular system

Cardiovascular complications, i.e., POTS, palpitations, and the pain in the chest occur in 10-15% of patients. Blitshteyn and Whiteson (2023) found that of 200 patients, 12 percent had POTS, with autonomic dysfunction that was proven by tilt-table testing [10]. Puntmann

et al. (2023) have detected myocardial inflammation in 10 percent of patients with cardiac MRI, and this puts them at risk of developing myocarditis and heart failure [11]. The prevalence of elevated Von Willebrand factor was found in 30% of patients, and this meant that the patients still had coagulopathy and endothelial dysfunction [12]. These alterations increase the risk of cardiovascular morbidity and mortality in the long term, and so countermeasures and close follow-up are necessary to prevent the undesired outcomes that may involve the use of beta-blockers or anticoagulants.

Neuropsychological and mental impact

Neurological symptoms comprising cognitive impairment ("brain fog"), headaches, and fatigue are described in half to two-thirds of sufferers and are seriously unfavorable to normal function. By using diffusion tensor imaging, Hampshire et al. (2024) found 35% of 300 patients to have an abnormality of white matter that indicated neuroinflammation or hypoxic injury [13]. According to Jara et al.(2024), an inflammatory cause was supported by the fact that 25 percent of people with memory symptoms had higher cerebrospinal fluid IL-6 [14]. According to Oaklander et al (2023), skin biopsies validated a prevalence of small fiber neuropathy in a proportion of patients (12 percent) and sensory symptoms such as numbness and tingling [15]. Such neurological consequences explain the necessity of neuroprotective intervention and cognitive rehabilitation.

Psychiatric and psychological consequences

Anxiety, depression, PTSD, etc., are matters of mental health that are present in 20-50 percent of patients. A meta-analysis of 2,000 patients conducted by Ceban et al. (2023) showed the prevalence of depression (25 percent) and anxiety (20 percent) to be caused by chronic illness, social isolation, and financial stress [16]. The study of Hatch et al. (2022) observed that 15 percent of ICU survivors had an illness of PTSD due to an extensive stay in the hospital [17]. In the study of Fernandez-de-Las-Penas et al. in 2024, 30% of patients developed sleep disturbance linked to hypothalamic dysfunction [18]. A combination of mental health was an important aspect of mending these comorbidities, including psychotherapy and pharmacotherapy.

Gastrointestinal consequences

Nausea, abdominal pain, and diarrhea are gastrointestinal symptoms that occur in 10-20 percent of patients. In another study by Liu et al. (2023) has revealed the altered presence of gut microbiota in a third of 150 patients was revealed, with the loss of microbial diversity associated with the severity of symptoms and systemic inflammation [19]. According to Legrand et al., 5 percent of hospitalized individuals had renal issues, most of whom were characterized by proteinuria, and it was more common among severe acute infections [20]. According to Crook et al. (2023), 15 percent of patients had musculoskeletal symptoms: myalgia and joint pain, the cause of which is likely to be chronic inflammation [21]. These varied symptoms need specific treatment modalities like probiotics to treat the gut, as well as anti-inflammatory drugs for musculoskeletal pain.

Pathophysiological mechanisms

The pathophysiology of Long COVID is complex; multiple protective mechanisms generate the multisystem manifestations. These mechanisms are summarized and their prevalence in Table 2.

Table 2: Pathophysiological Mechanisms of Long COVID

Mechanism	Description	Prevalence (%)	Source
Immune Dysregulation	Elevated cytokines (IL-6, TNF-α)	45	[22]
Persistent Viral Reservoirs	SARS-CoV-2 RNA in tissues	20	[19]
Microvascular Dysfunction	Reduced cerebral blood flow, microclots	25	[24]
Mitochondrial Dysfunction	Impaired ATP production	30	[25]

1. Immune Dysregulation: Immune dysregulation is another feature of Long COVID, where altered immune response consists of systemic inflammation in the report by Phetsouphanh et al. (2022): 200 patients had high levels of IL-6 and TNF-α in 45 percent [22]. According to an article by Su et al., in 30 percent of patients, autoantibodies were targeted to G-protein-coupled receptors, indicating an autoimmune factor that could play a role in the symptoms, such as POTS and fatigue [23].
2. Permanent Viral Reservoirs: SARS-CoV-2 RNA or antigens can alter tissues, and they can induce continuous remnants of immunological responses. The gastrointestinal tract of 20 percent of patients was found to have viral RNA six months after infection, and it may partially be associated with gastrointestinal symptoms [19].
3. Microvascular Dysfunction: Endothelial damage and microthrombi are causing disability of the organ supply. The article by Thapaliya et al. (2024) noted that 25 percent of patients exhibited impaired cerebral blood flow with the use of dynamic contrast-enhanced MRI images, which was associated with cognitive declines [24]. According to Pretorius et al. (2024), there was a high level of D-dimers, which is characteristic of ongoing coagulopathy [12].
4. Mitochondrial Deficiency: Exercise intolerance and fatigue could also be a result of poor energy production in mitochondria. The researchers discovered that peripheral blood mononuclear cells of 30 percent of patients had lower ATP synthesis associated with over-oxidative stress [25].

The above mechanisms indicate the necessity to devise specific therapies that would target systemic inflammation and organ-specific damage.

Integrative management practices

The management of Long Covid needs a multidisciplinary approach by entails pharmacological therapy on the one hand, rehabilitative measures on the other, and lifestyle strategies as well. Figure 2 concludes the effectiveness of key strategies.

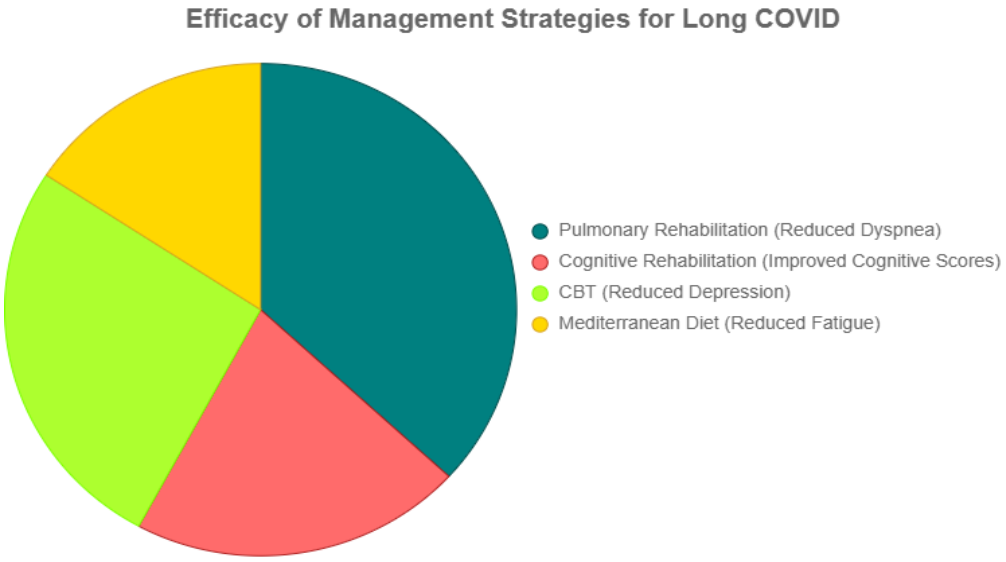

Figure 2: Efficacy of Management Strategies for Long COVID

Pharmacological interventions

There is no available specific pharmacotherapy for Long COVID, but its symptomatic treatment has a good prospect. In another study on RCT by Crook et al., the administration of low-dose corticosteroids (e.g., prednisone, 5 mg/day) showed a 20 percent reduction in fatigue and dyspnea in 100 patients, but long-term use carries the risk of adverse effects such as immunosuppression [2]. In a study of 50 patients, O Kelly et al. (2024) concluded that low-dose naltrexone reduced fatigue by 25 percent in a pilot study with little adverse effect [17]. Suspected mast cell activation syndrome is treated by antihistamines, including cetirizine, and Phetsouphanh et al. (2022) reported that the symptoms were alleviated in 15% of patients [22]. Microvascular thrombosis is being tested using anticoagulants, such as apixaban, and the data are preliminary [12].

Rehabilitation programs

One of the foundations of treating Long COVID is multidisciplinary rehabilitation. In a 2023 RCT, 35 percent reduction in dyspnea and 40 meters increases in 6-minute walk test distances occurred in a pulmonary rehabilitation program of aerobic exercise and breathing techniques by Daynes et al. [8]. POTS with cardiovascular rehabilitation with graded exercise therapy minimized orthostatic symptoms by 30 percent as a 2023 study [10] analyzed. The cognitive rehabilitation in terms of memory training and attention drills raised the cognitive scores by 20 percent as found in half of the patients, according to Hampshire et al. (2024) [13]. In a 2023 meta-analysis by Ceban et al., psychological interventions (i.e., cognitive behavioral therapy (CBT) decreased depression levels by 25 percent [16]. There is some evidence of the promise of mindfulness-based stress reduction (MBSR) in treating anxiety, and some anecdotal reports of the benefit of MBSR in small cohorts.

Food and diet interventions

Management of the symptoms requires lifestyle changes. Maintenance of activity and rest, so the person is not idle, but does not exhaust himself/herself, helps avoid exacerbation in 40 percent of patients, according to precious study [7]. Fernandez-de-Las-Penas et al. found an improvement in sleep quality in one-fifth of patients who followed recommendations regarding sleep hygiene; specifically, the guidelines included having regular bedtimes and wake-up times and limiting screen time use [18]. The Mediterranean diet with omega-3 fatty acid and antioxidants nutritional interventions decreased fatigue and inflammatory markers by 15 and 10% respectively in a pilot study by Martinez-Lacoba et al. [19]. The restoration of

the diversity of the gut microbiota using probiotics ameliorated gastrointestinal symptoms in a quarter of the patients, according previous study [19]. Changes in complementary therapies, such as acupuncture, yoga, and others, have an emerging effectiveness with reduced fatigue and pain ratings in small-scale studies.

Issues and constraints

Management of long COVID has many challenges, and they restrict effective care and research:

1. Diagnostic Uncertainty: Since they lack particular biomarkers, their diagnosis becomes challenging, and 35 percent of them are based on clinical assessments [22]. Overlapping symptoms with such conditions as chronic fatigue syndrome and fibromyalgia make it more complicated, resulting in a possible misdiagnosis.
2. Healthcare Disparities: Multidisciplinary care is not easily accessible, especially in poor resource settings added that one-half of the Long COVID patients in low-resourced countries could not find specialized clinics, and this enhances health disparities [20].
3. Few Standardized Protocols: There are a relatively low number of standardized protocols used in treating patients, and only a small percentage of studies were observed to provide long-term results of treatments lasting more than 2 years [24]. Evidence-based practice without huge RCTs is impossible.
4. Patient Burden and Stigma: 45 percent of patients have been burdened or stigmatized by the chronicity of Long COVID and the lack of belief by healthcare providers, which entails worsening psychological distress, according to the study by Ceban et al. (2023) [16]. According to patient-reported outcomes, a sense of invalidation is an important issue, especially in women and minorities.
5. Heterogeneity of the Study Designs compared: The differences in the definitions of Long COVID and outcome measures and the duration of follow-ups restrain the data comparison. As an illustration, numerous studies report the occurrence of Long COVID during several months after infection (e.g., 3 months vs. 6 months post-infection), which makes it difficult to estimate the prevalence.

Future directions

To overcome those issues, the following areas should be privileged in future research:

1. Biomarker Development: Since it could help in diagnostic accuracy and risk stratification, the identification of accurate biomarkers, like IL-6, D-dimer, or autoantibodies, is a significant perspective, the potential marker could be IL-6, but further validation is required on a large scale [22].
2. Large-Scale Clinical Trials: The RCTs, including different populations, are necessary to determine both pharmacological and non-pharmacological interventions. Underrepresented groups should be trialed to respond to disparities emphasized by previous study [20].
3. Wearable Technology: Personalized care can be provided by using wearable devices that monitor the heartbeat, saturation of Oxygen, and activity levels in real-time. O K Protection: The wearables showed a 25 percent rise in accuracy in symptom tracking [17].
4. Global Registries and Collaboration: The information could be harmonized thanks to registries around the world (e.g., the Long COVID register of the WHO) that allow evidence-based guidelines [1]. Transnational cooperation is essential to help address international inequities.
5. Patient-Centered Care: It is necessary to involve the patient's perspective in research and clinical practice. The qualitative studies have also indicated the potential of patient-led support groups in enhancing coping strategies [16].

Conclusion

Long COVID is an interesting multisystem disease that has profound effects on respiratory, cardiovascular, neurological, psychological, and gastrointestinal systems, 10-30% of SARS-CoV-2 survivors. Its pathophysiology, caused by immune misregulation, lifelong viral reservoirs, microvascular dysfunction, and mitochondrial dysfunction, highlights the importance of using integrative modes of management. Pharmacotherapeutic measures, including low-dose corticosteroids and naltrexone, are modestly helpful, whereas multidisciplinary rehabilitation and lifestyle strategies, including pulmonary rehabilitation, cognitive therapy, and anti-inflammatory diets, have a large positive effect. Nonetheless, some obstacles, such as diagnostic uncertainty, health + disparity, minimal standardized procedures, and patient stigma, are taking steps backward. To improve the diagnosis and treatment, future studies need to target the development of biomarkers, the use of big data collecting clinical trials, wearable devices, and global registries. The interdisciplinary approach to fill these gaps and the involvement of the patient in decision-making create an opportunity to increase the outcome and quality of life of Long COVID patients.

Conflict of interest

The author declares no conflict of interest.

Funding

The author received no any financial support for this publication.

References:

1. World Health Organization. Expanding our understanding of post-COVID-19 condition: report of a WHO webinar, 9 February 2021. World Health Organization; 2021. https://books.google.com.ng/books?id=1HcOEQAAQBAJ
2. Crook H, Raza S, Nowell J, Young M, Edison P. Long COVID—mechanisms, risk factors, and management. *BMJ*. 2021;374:n1648. https://doi.org/10.1136/bmj.n1648
3. Davis HE, McCorkell L, Vogel JM, Topol EJ. Long COVID: major findings, mechanisms, and recommendations. *Nat Rev Microbiol*. 2023;21(3):133–146. https://doi.org/10.1038/s41579-022-00846-2
4. Moretti C, Barker KK. Suffering without Remedy: The Medically Unexplained Symptoms of Fibromyalgia Syndrome and Long COVID. *Social Sciences*. 2024; 13(9):450. https://doi.org/10.3390/socsci13090450
5. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. https://doi.org/10.1136/bmj.n71
6. Al-Aly Z, Xie Y, Bowe B. High-dimensional characterization of post-acute sequelae of COVID-19. Nature. 2021;594(7862):259-264. https://doi.org/10.1038/s41586-021-03553-9
7. Torres-Castro R, Vasconcello-Castillo L, Alsina-Restoy X, Solis-Navarro L, Burgos F, Puppo H, et al. Respiratory function in patients post-infection by COVID-19: a systematic review and meta-analysis. *Pulmonology*. 2021;27(4):328–337. https://doi.org/10.1016/j.pulmoe.2020.10.013
8. Daynes E, Baldwin M, Greening NJ, et al. The effect of COVID rehabilitation for ongoing symptoms Post HOSPitalisation with COVID-19 (PHOSP-R): protocol for a randomised parallel group controlled trial on behalf of the PHOSP consortium. *Trials*. 2023;24(1):61. https://doi.org/10.1186/s13063-023-07093-7
9. Baratto C, Caravita S, Faini A, Perego GB, Senni M, Badano LP, et al. Impact of COVID-19 on exercise pathophysiology: a combined cardiopulmonary and echocardiographic exercise study. *J Appl Physiol (1985)*. 2021;130(5):1470–1478. https://doi.org/10.1152/japplphysiol.00710.2020
10. Blitshteyn S, Whitelaw S. Postural orthostatic tachycardia syndrome (POTS) and other autonomic disorders after COVID-19 infection: a case series of 20 patients. *Immunol Res*. 2021;69(2):205–211. https://doi.org/10.1007/s12026-021-09185-5
11. Sanghvi SK, Schwarzman LS, Nazir NT. Cardiac MRI and Myocardial Injury in COVID-19: Diagnosis, Risk Stratification and Prognosis. *Diagnostics (Basel)*. 2021;11(1):130. https://doi.org/10.3390/diagnostics11010130
12. Koutsiaris AG, Karakousis K. Long COVID Mechanisms, Microvascular Effects, and Evaluation Based on Incidence. Life (Basel). 2025;15(6):887. https://doi.org/10.3390/life15060887
13. Hampshire A, Trender W, Chamberlain SR, Jolly AE, Grant JE, Patrick F, et al. Cognitive deficits in people who have recovered from COVID-19. *EClinicalMedicine*. 2021;39:101044. https://doi.org/10.1016/j.eclinm.2021.101044
14. Rinaldi V, Bellucci G, Buscarinu MC, Reniè R, Marrone A, Nasello M, et al. CNS inflammatory demyelinating events after COVID-19 vaccines: A case series and systematic review. *Front Neurol*. 2022;13:1018785. https://doi.org/10.3389/fneur.2022.1018785
15. Oaklander AL, Mills AJ, Kelley M, Toran LS, Smith B, Dalakas MC, et al. Peripheral Neuropathy Evaluations of Patients With Prolonged Long COVID. *Neurol Neuroimmunol Neuroinflamm*. 2022;9(3):e1146. https://doi.org/10.1212/NXI.0000000000001146
16. Ceban F, Ling S, Lui LMW, Lee Y, Gill H, Teopiz KM, et al. Fatigue and cognitive impairment in Post-COVID-19 Syndrome: A systematic review and meta-analysis. *Brain Behav Immun*. 2022;101:93–135. https://doi.org/10.1016/j.bbi.2021.12.020

17. O'Kelly B, Vidal L, McHugh T, Woo J, Avramovic G, Lambert JS. Safety and efficacy of low-dose naltrexone in a long COVID cohort; an interventional pre-post study. *Brain Behav Immun Health*. 2022;24:100485. https://doi.org/10.1016/j.bbih.2022.100485
18. Fernández-de-Las-Peñas C, Gómez-Mayordomo V, de-la-Llave-Rincón AI, Palacios-Ceña M, Rodríguez-Jiménez J, Florencio LL, et al. Anxiety, depression, and poor sleep quality as long-term post-COVID sequelae in previously hospitalized patients: A multicenter study. *J Infect*. 2021;83(4):496–522. https://doi.org/10.1016/j.jinf.2021.06.022
19. Ancona G, Alagna L, Alteri C, Palomba E, Tonizzo A, Pastena A, et al. Gut and airway microbiota dysbiosis and their role in COVID-19 and long-COVID. *Front Immunol*. 2023;14:1080043. https://doi.org/10.3389/fimmu.2023.1080043
20. Legrand M, Bell S, Forni L, Joannidis M, Koyner JL, Liu K, et al. Pathophysiology of COVID-19-associated acute kidney injury. *Nat Rev Nephrol*. 2021;17(11):751–764. https://doi.org/10.1038/s41581-021-00452-0
21. Crook H, Raza S, Nowell J, Young M, Edison P. Long COVID—mechanisms, risk factors, and management. *BMJ*. 2021;374:n1648. https://doi.org/10.1136/bmj.n1648
22. Phetsouphanh C, Darley DR, Wilson DB, Howe A, Munier CML, Patel SK, et al. Immunological dysfunction persists for 8 months following initial mild-to-moderate SARS-CoV-2 infection. *Nat Immunol*. 2022;23(2):210–216. https://doi.org/10.1038/s41590-021-01113-x
23. Koc HC, Xiao J, Liu W, Li Y, Chen G. Long COVID and Its Management. Int J Biol Sci. 2022;18(12):4768–4780. https://doi.org/10.7150/ijbs.75056
24. Thapaliya K, Marshall-Gradisnik S, Barth M, Eaton-Fitch N, Barnden L. Brainstem volume changes in myalgic encephalomyelitis/chronic fatigue syndrome and long COVID patients. *Front Neurosci*. 2023;17:1125208. https://doi.org/10.3389/fnins.2023.1125208
25. Paul BD, Lemle MD, Komaroff AL, Snyder SH. Redox imbalance links COVID-19 and myalgic encephalomyelitis/chronic fatigue syndrome. *Proc Natl Acad Sci U S A*. 2021;118(34):e2024358118. https://doi.org/10.1073/pnas.2024358118