International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 1 Jan - Feb 2025, pp: 1655-1664 www.ijprajournal.com ISSN: 2456-4494

Long COVID: Unraveling the Mystery of Persistent Symptoms

Abishek B, Benjamin J, C Fanie Rollex
Arulmigu Kalasalingam College of Pharmacy, Tamil Nadu, India – 626126.
corresponding author : Abishek B

Date of Submission: 25-02-2025 Date of Acceptance: 05-03-2025

ABSTRACT

Background: Long COVID, also known as post-acute sequelae of SARS-CoV-2 infection (PASC), is a complex condition characterized by persistent symptoms that continue for weeks or months after the initial infection. It affects multiple organ systems and significantly impacts patients' quality of life. Despite growing research efforts, the exact mechanisms underlying Long COVID remain poorly understood, making diagnosis and treatment challenging.

Objectives: This review aims to explore the common symptoms, variability in symptom duration and severity, impact on quality of life, potential mechanisms, diagnostic challenges, and future directions in Long COVID research.

Methods: A comprehensive analysis of recent literature was conducted, focusing on studies investigating the pathophysiology, clinical manifestations, and therapeutic strategies for Long COVID. Emerging research on viral persistence, immune dysregulation, and biomarkers was reviewed to provide insights into disease mechanisms and diagnostic advancements.

Results: Long COVID manifests through a wide range of symptoms, including fatigue, cognitive dysfunction, respiratory issues, cardiovascular complications, and psychological distress. The severity and duration of symptoms vary among individuals, influenced by factors such as age, gender, comorbidities, and initial infection severity. Proposed mechanisms include persistent viral reservoirs, immune system dysregulation, and endothelial dysfunction. Diagnosis remains a challenge due to symptom overlap with other conditions and the absence of standardized criteria, though biomarker research is showing promise.

Conclusion: Long COVID represents a pressing healthcare issue requiring multidisciplinary research and patient-centered management strategies. Ongoing clinical trials and long-term follow-up studies are essential to understanding disease progression and identifying effective treatments. Personalized medicine approaches may provide targeted therapeutic solutions, improving patient outcomes. A global collaborative effort is needed to address the long-term consequences of Long COVID and mitigate its impact on public health.

Keywords: Long COVID, post-acute sequelae of SARS-CoV-2, persistent symptoms, immune dysregulation, viral persistence, quality of life.

I. INTRODUCTION

Long COVID, also known as post-acute sequelae of SARS-CoV-2 infection (PASC), has emerged as a significant health concern in the wake of the COVID-19 pandemic. This condition is characterized by persistent symptoms that continue or develop after the acute phase of COVID-19 infection, lasting for weeks, months, or even years [1] . The World Health Organization (WHO) defines Long COVID as the continuation or development of new symptoms three months after the initial SARS-CoV-2 infection, with these symptoms lasting for at least two months and cannot be explained by an alternative diagnosis [2] . The significance and prevalence of Long COVID have become increasingly apparent as the pandemic has progressed. Studies suggest that approximately 10-30% of individuals who contract COVID-19 may experience Long COVID symptoms, regardless of the initial severity of their infection [3] . This high prevalence translates to millions of affected individuals worldwide, posing substantial challenges to healthcare systems and economies.

Long COVID presents a complex and multifaceted clinical picture, with patients reporting a wide array of symptoms affecting multiple organ systems. Common manifestations include fatigue, cognitive dysfunction (often referred to as "brain fog"), shortness of breath, and various neurological and cardiovascular symptoms [4] . The variability in symptom duration and severity among patients adds to the complexity of this condition, with some individuals experiencing mild, transient symptoms while others face debilitating effects that significantly impact their quality of life and ability to perform daily activities.

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 1 Jan - Feb 2025, pp: 1655-1664 www.ijprajournal.com ISSN: 2456-4494

This article aims to provide a comprehensive overview of Long COVID, exploring its clinical presentation, potential underlying mechanisms, diagnostic challenges, and current treatment approaches. By unraveling the mystery of these persistent symptoms, we hope to contribute to the growing body of knowledge on Long COVID and pave the way for improved patient care and targeted interventions. Furthermore, we will discuss future directions in Long COVID research, including ongoing clinical trials, the potential for personalized treatment strategies, and the critical importance of long-term follow-up studies in understanding the full spectrum and trajectory of this condition.

II. CLINICAL PRESENTATION OF LONG COVID

2.1 COMMON SYMPTOMS

Long COVID presents with a wide range of persistent symptoms affecting multiple organ systems. These symptoms vary in severity, fluctuate over time, and can significantly impact daily activities [4,5] . The table below categorizes the most commonly reported symptoms based on the affected organ system:

Table 1: Common Symptoms of Long COVID by Organ System

Organ System	Symptoms	Description
General	Fatigue	Persistent, unrelenting exhaustion not relieved by rest.
Neurological	Cognitive dysfunction ("brain fog")	Impaired memory, concentration, and mental clarity.
	Headaches	Recurring or chronic headaches, sometimes with light and sound sensitivity.
	Dizziness, numbness, tingling (paresthesia)	Possible autonomic nervous system involvement.
Respiratory	Shortness of breath (dyspnea)	Persistent breathing difficulties, even with mild exertion.
Musculoskeletal	Muscle and joint pain	Generalized or localized pain, fluctuating in intensity.
Cardiovascular	Palpitations, tachycardia, chest pain	May be linked to postural orthostatic tachycardia syndrome (POTS).
Gastrointestinal	Nausea, diarrhea, bloating, abdominal pain	Symptoms resembling irritable bowel syndrome (IBS).
Sleep-related	Insomnia, fragmented sleep, altered sleep-wake cycles	Contributing to fatigue and cognitive impairment.

Additional Considerations

- Some individuals also experience hair loss, skin rashes, or issues with temperature regulation.
- Symptoms often occur in clusters and may fluctuate over weeks or months.
- The unpredictable nature of Long COVID makes diagnosis and treatment challenging.

Understanding these diverse manifestations is crucial for early recognition, patient support, and developing effective management strategies [5] .

2.2 VARIABILITY IN SYMPTOM DURATION AND SEVERITY

The duration and severity of Long COVID symptoms vary significantly among affected individuals, making it a complex and unpredictable condition. While some individuals experience mild symptoms that resolve within weeks or months, others endure persistent, debilitating effects that can last a year or longer. A study by Sudre et al. (2021) highlighted that approximately 13.3% of patients reported symptoms persisting beyond 28 days, 4.5% experienced symptoms for more than eight weeks, and 2.3% continued to struggle with symptoms for over 12 weeks [3] . This variability suggests that Long COVID is not a uniform condition but rather a spectrum of post-viral complications influenced by multiple factors.Several factors have been identified as potential contributors to the duration and severity of Long COVID. Age plays a significant role, with older individuals generally experiencing more prolonged and severe symptoms. This may be due to age-related declines in immune function and a higher likelihood of pre-existing health conditions. However, younger adults and even children are not

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 1 Jan - Feb 2025, pp: 1655-1664 www.ijprajournal.com ISSN: 2456-4494

exempt from developing persistent symptoms, demonstrating that Long COVID affects individuals across all age groups [6].

Pre-existing health conditions also contribute to symptom variability. Individuals with chronic illnesses such as diabetes, cardiovascular disease, or respiratory conditions may experience an exacerbation of their underlying health issues, compounding the effects of Long COVID. Autoimmune conditions, in particular, appear to increase the risk of prolonged symptoms due to potential immune dysregulation following COVID-19 infection.Interestingly, the severity of the initial COVID-19 infection does not always predict Long COVID risk. While individuals who experienced severe acute infections are more likely to suffer prolonged complications, many cases of Long COVID arise in those who initially had mild or even asymptomatic infections. This suggests that Long COVID may be driven by immune system dysfunction, viral persistence, or other underlying mechanisms independent of initial disease severity [7] .

Gender differences have also been observed, with some studies indicating a higher prevalence of Long COVID in females. Hormonal differences, immune response variations, and societal factors may contribute to this disparity, though further research is needed to understand the underlying mechanisms. Additionally, genetic factors are being explored as potential contributors, with ongoing studies investigating whether certain genetic predispositions make individuals more susceptible to prolonged symptoms.

Given the wide spectrum of symptom duration and severity, it is crucial to develop personalized treatment strategies tailored to individual patient needs. A multidisciplinary approach, including medical, psychological, and rehabilitative care, is essential to support recovery and improve quality of life for those affected by Long COVID. Understanding these variations will help refine diagnostic criteria, enhance treatment protocols, and guide future research efforts in managing this complex condition [8] .

2.3 IMPACT ON QUALITY OF LIFE

Long COVID significantly affects multiple aspects of life, including physical health, cognitive function, emotional well-being, financial stability, and social relationships. Unlike the acute phase of COVID-19, which primarily involves respiratory distress and systemic inflammation, Long COVID presents persistent and often debilitating symptoms that disrupt daily living [9].

Table 2 : Key Areas of Quality of Life Affected by Long COVID

Domain	Impact
Physical Limitations	Fatigue, reduced exercise tolerance, difficulty performing routine tasks, muscle weakness.
Cognitive Impairment	Memory lapses, difficulty concentrating, brain fog, reduced work or academic performance.
Emotional Well-being	Anxiety, depression, post-traumatic stress disorder (PTSD), frustration, social withdrawal.
Financial Strain	Reduced work hours, job loss, increased healthcare expenses, financial instability.
Social Relationships	Difficulty maintaining friendships, family strain, isolation due to persistent symptoms.

Figure 1: The Cycle of Long COVID's Impact on Quality of Life

Below is a flowchart illustrating how Long COVID symptoms contribute to a decline in quality of life, creating a vicious cycle of worsening health and social challenges.

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 1 Jan - Feb 2025, pp: 1655-1664 www.ijprajournal.com ISSN: 2456-4494

A study by Davis et al. (2021) found that 45% of Long COVID patients had to reduce their work hours, while 22% were unable to work at all due to their condition [10] . This loss of income, combined with ongoing healthcare expenses, creates economic strain that further worsens mental and physical health. The interplay between physical symptoms, cognitive dysfunction, and emotional distress leads to a self-perpetuating cycle where declining health exacerbates financial and social difficulties, which, in turn, further deteriorate overall well-being.

Addressing the impact of Long COVID requires a multidimensional approach that includes medical interventions, rehabilitation programs, psychological support, financial assistance, and workplace accommodations. Early diagnosis and comprehensive care can help break the cycle and improve recovery outcomes for those affected [11].

III. POTENTIAL MECHANISMS OF LONG COVID

The underlying causes of Long COVID remain an area of active research, with several hypotheses proposed to explain the persistence of symptoms. One prominent theory suggests that lingering viral components may continue to stimulate the immune system, leading to chronic inflammation and multi-organ dysfunction.

3.1 VIRAL PERSISTENCE

One of the key hypotheses behind Long COVID is the persistence of SARS-CoV-2 in certain tissues long after the acute phase of the infection has resolved. Unlike many viruses that are entirely cleared from the body after recovery, SARS-CoV-2 has been detected in multiple organs, including the lungs, heart, brain, intestines, and lymphatic system, months after the initial infection [12] . This ongoing presence of viral RNA or protein remnants may contribute to prolonged symptoms by continuously triggering immune responses and localized inflammation.

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 1 Jan - Feb 2025, pp: 1655-1664 www.ijprajournal.com ISSN: 2456-4494

Table 3: Evidence Supporting Viral Persistence in Long COVID

Organ/Tissue	Findings	Potential Consequences
Lungs	SARS-CoV-2 RNA detected in lung tissue months post-infection	Chronic respiratory symptoms, fibrosis, breathlessness
Heart	Viral RNA found in cardiac tissue	Palpitations, myocarditis, heart failure
Brain	Presence of viral remnants in cerebrospinal fluid	Brain fog, cognitive impairment, headaches
Gut	Viral particles detected in intestinal biopsies	Persistent nausea, diarrhea, gut inflammation
Lymph Nodes	Viral antigens persist in lymphatic tissues	Prolonged immune activation, fatigue

Mechanisms of Viral Persistence and Impact on Health

The presence of viral RNA or proteins in tissues suggests that SARS-CoV-2 may evade complete immune clearance [13] . Several mechanisms have been proposed to explain how the virus may persist in the body:

1. **Immune Evasion**: The virus may evade immune detection by residing in **immune-privileged sites** such as the brain or lymphatic system.
2. **Viral Reservoirs**: Certain cells, such as **gut epithelial cells and alveolar macrophages**, may serve as long-term reservoirs for the virus.
3. **Reactivation of Dormant Virus**: Similar to other persistent viral infections (e.g., Epstein-Barr virus), SARS-CoV-2 components may become reactivated under stress or immune dysregulation.
4. **Chronic Inflammatory Response**: The continued presence of viral components may **stimulate low-grade inflammation**, leading to tissue damage and long-term symptoms [14] .

3.2 IMMUNE DYSREGULATION

Another proposed mechanism for Long COVID is **immune dysregulation**, where the body's immune response remains hyperactive or dysfunctional even after the acute infection has resolved [15] . This dysregulated immune activity can lead to chronic inflammation, tissue damage, and prolonged symptoms.

Table 4 :Key Immune Abnormalities in Long COVID

Immune Dysfunction	Description	Potential Consequences
Autoantibodies	The immune system mistakenly produces antibodies that target the body's own tissues	Autoimmune-like symptoms, joint pain, neurological issues
Cytokine Imbalance	Persistent elevation of pro-inflammatory cytokines (e.g., IL-6, TNF-α) leading to chronic inflammation	Fatigue, muscle weakness, prolonged fever
T-Cell Exhaustion	Virus-specific T-cells become dysfunctional and fail to clear residual viral components	Increased susceptibility to infections, persistent symptoms
Immune Dysfunction	**Description**	**Potential Consequences**

Mechanisms Contributing to Immune Dysregulation [16]

1. **Autoimmunity and Autoantibodies**

Studies have detected autoantibodies in Long COVID patients, suggesting that SARS-CoV-2 may trigger an autoimmune-like response. These autoantibodies can attack healthy tissues, leading to neurological symptoms, joint pain, and cardiovascular issues. This phenomenon has been observed in other viral infections, such as Epstein-Barr virus and influenza.

2. **Cytokine Storm and Persistent Inflammation**

The **cytokine storm** seen in severe COVID-19 cases can lead to long-term immune activation. Even after the acute infection resolves, certain pro-inflammatory cytokines (such as **IL-6, TNF-α, and IFN-γ**) remain elevated, contributing

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 1 Jan - Feb 2025, pp: 1655-1664 www.ijprajournal.com ISSN: 2456-4494

to symptoms like fatigue, muscle pain, and cognitive dysfunction. Chronic low-grade inflammation can also impact **vascular health, brain function, and metabolism**.

3. **T-Cell Dysfunction and Immune Exhaustion**

T-cells play a crucial role in clearing viral infections, but studies suggest that Long COVID patients may exhibit **T-cell exhaustion**, where virus-fighting T-cells lose their effectiveness over time. This can result in prolonged symptoms and an increased risk of secondary infections or reactivation of latent viruses like **Epstein-Barr virus (EBV)**.

IV. DIAGNOSTIC CHALLENGES

Diagnosing Long COVID remains a complex and evolving challenge due to the **lack of standardized criteria**, symptom overlap with other conditions, and the ongoing search for reliable **biomarkers**. The difficulty in distinguishing Long COVID from other post-viral syndromes complicates both clinical management and research efforts.

4.1 LACK OF STANDARDIZED DIAGNOSTIC CRITERIA

Currently, no universally accepted diagnostic criteria exist for Long COVID. Different healthcare organizations define it based on varying factors, such as symptom duration, severity, and organ involvement. Some definitions focus on **persistent symptoms beyond four weeks** post-infection, while others require symptoms to last **at least 12 weeks** for a confirmed diagnosis. The absence of a unified framework affects **treatment decisions, research outcomes, and patient care**, leading to inconsistencies in both clinical and epidemiological studies [17,18].

4.2 OVERLAP WITH OTHER CONDITIONS

Currently, no universally accepted diagnostic criteria exist for Long COVID. Different healthcare organizations define it based on varying factors, such as symptom duration, severity, and organ involvement. Some definitions focus on **persistent symptoms beyond four weeks** post-infection, while others require symptoms to last **at least 12 weeks** for a confirmed diagnosis [19] . The absence of a unified framework affects **treatment decisions, research outcomes, and patient care**, leading to inconsistencies in both clinical and epidemiological studies.

Table 5: diagnostic criteria by different organizations

Current Diagnostic Criteria by Organizations	**Definition of Long COVID**
World Health Organization (WHO)	Symptoms persisting **12+ weeks** after acute infection, with no alternative explanation.
Centers for Disease Control (CDC)	Symptoms lasting **4+ weeks** post-COVID-19 infection.
National Institute for Health and Care Excellence (NICE)	Symptoms persisting beyond **12 weeks**, with fluctuating severity.

A standardized definition is crucial for improving **clinical diagnosis, patient management, and research reproducibility [20]**.

4.3 THE ROLE OF BIOMARKERS

The identification of **biological markers** could significantly improve the diagnosis of Long COVID by providing objective indicators of **ongoing inflammation, immune dysfunction, or neurological damage [21-24]**. Several biomarkers are currently under investigation:

Table 6: Potential Biomarkers for Long COVID

Category	**Biomarkers**	**Clinical Relevance**
Inflammatory Markers	C-reactive protein (CRP), Interleukin-6 (IL-6), Tumor Necrosis Factor-alpha (TNF-α)	Indicate **chronic inflammation** and immune activation
Autoimmune Markers	Autoantibodies targeting self-antigens	Suggest potential **autoimmune involvement**

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 1 Jan - Feb 2025, pp: 1655-1664 www.ijprajournal.com ISSN: 2456-4494

Endothelial Dysfunction Markers	Von Willebrand Factor, Thrombomodulin	Associated with **vascular complications** and microclots
Neurological Markers	Neurofilament light chain (NfL), Glial fibrillary acidic protein (GFAP)	Indicate **nerve damage and neuroinflammation**
Category	**Biomarkers**	**Clinical Relevance**

While these biomarkers show promise, they are **not yet widely used in clinical practice**. More **large-scale studies** are needed to validate their effectiveness for **diagnosis, prognosis, and treatment monitoring** in Long COVID [23-25].

V. FUTURE DIRECTIONS IN LONG COVID RESEARCH

As the global burden of Long COVID continues to rise, research efforts are intensifying to understand its mechanisms, improve diagnosis, and develop effective treatments. Future research is focusing on clinical trials, personalized treatment approaches, and long-term patient follow-ups to address the complexity of this condition.

5.1 ONGOING CLINICAL TRIALS

Several clinical trials are currently underway to evaluate potential therapies for Long COVID, exploring a range of interventions such as anti-inflammatory drugs, antiviral therapies, immune modulators, and rehabilitation programs. Antiviral agents like Paxlovid and Molnupiravir are being investigated for their ability to reduce viral persistence, while anti-inflammatory drugs such as corticosteroids and colchicine aim to control chronic inflammation. Additionally, immune-modulating therapies, including monoclonal antibodies and intravenous immunoglobulin (IVIG), are being tested to restore immune balance [26] . Treatments targeting autonomic nervous system dysfunction, such as beta-blockers and Mestinon, are also under investigation, particularly for patients experiencing postural orthostatic tachycardia syndrome (POTS). Furthermore, rehabilitation programs focused on pulmonary and neurological recovery are being explored to improve respiratory function, cognitive impairment, and overall well-being. The findings from these clinical trials will be crucial in shaping evidence-based treatment protocols for Long COVID [27] .

5.2 POTENTIAL FOR PERSONALIZED TREATMENT

Given the diverse nature of Long COVID symptoms and underlying mechanisms, a one-size-fits-all treatment approach is unlikely to be effective. Personalized medicine, which tailors treatments to individual patient characteristics, has the potential to significantly improve outcomes [28] . Biomarker-based treatment strategies are being developed to identify patient-specific indicators, such as immune markers, viral load, and neurological abnormalities, which can help guide therapy selection [29] . Genetic profiling is also being explored to determine whether certain individuals have a genetic predisposition to Long COVID and how their genetic makeup influences treatment response. In addition, symptom-based therapeutic approaches are being refined to ensure that interventions are targeted based on dominant symptom clusters, such as cognitive dysfunction, cardiovascular issues, or respiratory impairment. Artificial intelligence and machine learning models are increasingly being used to analyze patient data and predict the most effective treatment strategies for different subgroups of Long COVID patients. These advancements in personalized medicine will play a crucial role in optimizing treatment strategies and improving patient outcomes [30] .

5.3 THE IMPORTANCE OF LONG-TERM FOLLOW-UP STUDIES

Long-term follow-up studies are essential for understanding the natural history of Long COVID, disease progression, and long-term complications. Many patients experience relapsing-remitting symptoms, making ongoing monitoring crucial for identifying persistent or fluctuating patterns. Follow-up studies will help assess the long-term impact of Long COVID on vital organ functions, including cardiovascular, neurological, and pulmonary health, which remain areas of significant concern [31] . Researchers are also investigating potential risk factors that may predict the severity and duration of Long COVID, allowing for early identification and intervention in high-risk individuals. Additionally, long-term observational studies will evaluate the effectiveness of different treatment strategies over extended periods, providing valuable insights into which approaches yield the most sustainable benefits. Large-scale cohort studies tracking Long COVID patients over

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 1 Jan - Feb 2025, pp: 1655-1664 www.ijprajournal.com ISSN: 2456-4494

multiple years will provide critical data to refine diagnostic criteria, predict long-term patient outcomes, and develop preventive and therapeutic strategies [32] .

VI. CONCLUSION

Long COVID remains a significant and evolving global health challenge, affecting millions of individuals worldwide. Its complex and heterogeneous nature, involving multiple organ systems, underscores the need for a deeper understanding of its underlying mechanisms, accurate diagnostic strategies, and effective treatment options. The persistence of symptoms—ranging from fatigue and cognitive dysfunction to cardiovascular and neurological complications—demands a multidisciplinary approach that integrates clinical research, personalized medicine, and long-term patient monitoring.

Despite significant progress, numerous gaps remain in our knowledge of Long COVID, particularly regarding its pathophysiology, risk factors, and long-term consequences. Ongoing research into viral persistence, immune dysregulation, and biomarkers holds promise for refining diagnostic criteria and identifying targeted therapies. Clinical trials investigating anti-inflammatory agents, immune modulators, and rehabilitation programs are paving the way for evidence-based treatment protocols, while advances in personalized medicine may enable tailored therapeutic approaches for different patient subgroups.The importance of long-term follow-up studies cannot be overstated, as they will provide valuable insights into disease progression, potential complications, and the effectiveness of interventions over time. A collaborative global effort involving researchers, healthcare professionals, and policymakers is essential to ensure that Long COVID patients receive the care and support they need.

As we continue to unravel the mysteries of Long COVID, a proactive and patient-centered approach will be key to mitigating its long-term impact. By bridging the gaps in research, refining treatment strategies, and fostering awareness, we can improve patient outcomes and enhance the quality of life for those affected by this debilitating condition.

REFERENCE

[1]. Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, Cook JR, Nordvig AS, Shalev D, Sehrawat TS, Ahluwalia N. Post-acute COVID-19 syndrome. Nature medicine. 2021 Apr;27(4):601-15.

[2]. World Health Organization. (2021). A clinical case definition of post COVID-19 condition by a Delphi consensus. https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1

[3]. Sudre CH, Murray B, Varsavsky T, Graham MS, Penfold RS, Bowyer RC, Pujol JC, Klaser K, Antonelli M, Canas LS, Molteni E. Attributes and predictors of long COVID. Nature medicine. 2021 Apr;27(4):626-31.

[4]. Crook, H., Raza, S., Nowell, J., Young, M., & Edison, P. (2021). Long covid—mechanisms, risk factors, and management. BMJ, 374, n1648. https://doi.org/10.1136/bmj.n1648

[5]. Aiyegbusi OL, Hughes SE, Turner G, Rivera SC, McMullan C, Chandan JS, Haroon S, Price G, Davies EH, Nirantharakumar K, Sapey E. Symptoms, complications and management of long COVID: a review. Journal of the Royal Society of Medicine. 2021 Sep;114(9):428-42.

[6]. Mińko A, Turoń-Skrzypińska A, Rył A, Tomska N, Bereda Z, Rotter I. Searching for factors influencing the severity of the symptoms of long COVID. International Journal of Environmental Research and Public Health. 2022 Jun 30;19(13):8013.

[7]. Onieva AR, Castro CS, Morales VG, Vacas MA, Requena AH. Long COVID: Factors influencing persistent symptoms and the impact of gender. Medicina de Familia. SEMERGEN. 2024 Jul 1;50(5):102208.

[8]. Astin R, Banerjee A, Baker MR, Dani M, Ford E, Hull JH, Lim PB, McNarry M, Morten K, O'Sullivan O, Pretorius E. Long COVID: mechanisms, risk factors and recovery. Experimental physiology. 2023 Jan;108(1):12-27.

[9]. O'Mahony L, Buwalda T, Blair M, Forde B, Lunjani N, Ambikan A, Neogi U, Barrett P, Geary E, O'Connor N, Dineen J. Impact of Long COVID on health and quality of life. HRB open research. 2022 Apr 22;5:31.

[10]. Davis HE, Assaf GS, McCorkell L, Wei H, Low RJ, Re'em Y, Redfield S, Austin JP,

Akrami A. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. EClinicalMedicine. 2021 Aug 1;38.

[11]. Poudel AN, Zhu S, Cooper N, Roderick P, Alwan N, Tarrant C, Ziauddeen N, Yao GL. Impact of Covid-19 on health-related quality of life of patients: A structured review. PloS one. 2021 Oct 28;16(10):e0259164.

[12]. Puelles VG, Lütgehetmann M, Lindenmeyer MT, Sperhake JP, Wong MN, Allweiss L, Chilla S, Heinemann A, Wanner N, Liu S, Braun F. Multiorgan and renal tropism of SARS-CoV-2. New England Journal of Medicine. 2020 Aug 6;383(6):590-2.

[13]. Chen B, Julg B, Mohandas S, Bradfute SB. Viral persistence, reactivation, and mechanisms of long COVID. Elife. 2023 May 4;12:e86015.

[14]. Desimmie BA, Raru YY, Awadh HM, He P, Teka S, Willenburg KS. Insights into SARS-CoV-2 persistence and its relevance. Viruses. 2021 May 29;13(6):1025.

[15]. Wong LY, Perlman S. Immune dysregulation and immunopathology induced by SARS-CoV-2 and related coronaviruses—are we our own worst enemy?. Nature Reviews Immunology. 2022 Jan;22(1):47-56.

[16]. Proal AD, VanElzakker MB. Long COVID or post-acute sequelae of COVID-19 (PASC): an overview of biological factors that may contribute to persistent symptoms. Frontiers in microbiology. 2021 Jun 23;12:698169.

[17]. Raveendran AV, Jayadevan R, Sashidharan S. Long COVID: an overview. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2021 May 1;15(3):869-75.

[18]. Sisó-Almirall A, Brito-Zerón P, ConanglaFerrín L, Kostov B, Moragas Moreno A, Mestres J, Sellarès J, Galindo G, Morera R, Basora J, Trilla A. Long Covid-19: proposed primary care clinical guidelines for diagnosis and disease management. International journal of environmental research and public health. 2021 Apr 20;18(8):4350.

[19]. Yong SJ. Long COVID or post-COVID-19 syndrome: putative pathophysiology, risk factors, and treatments. Infectious diseases. 2021 Oct 3;53(10):737-54.

[20]. O'Hare AM, Vig EK, Iwashyna TJ, Fox A, Taylor JS, Viglianti EM, Butler CR, Vranas KC, Helfand M, Tuepker A, Nugent SM. Complexity and challenges of the clinical diagnosis and management of long COVID. JAMA network open. 2022 Nov 1;5(11):e2240332-.

[21]. Lai YJ, Liu SH, Manachevakul S, Lee TA, Kuo CT, Bello D. Biomarkers in long COVID-19: A systematic review. Frontiers in medicine. 2023 Jan 20;10:1085988.

[22]. Phetsouphanh C, Darley DR, Wilson DB, Howe A, Munier CM, Patel SK, Juno JA, Burrell LM, Kent SJ, Dore GJ, Kelleher AD. Immunological dysfunction persists for 8 months following initial mild-to-moderate SARS-CoV-2 infection. Nature immunology. 2022 Feb;23(2):210-6.

[23]. Kermali M, Khalsa RK, Pillai K, Ismail Z, Harky A. The role of biomarkers in diagnosis of COVID-19–A systematic review. Life sciences. 2020 Aug 1;254:117788.

[24]. Ponti G, Maccaferri M, Ruini C, Tomasi A, Ozben T. Biomarkers associated with COVID-19 disease progression. Critical reviews in clinical laboratory sciences. 2020 Aug 17;57(6):389-99.

[25]. Mandal S, Barnett J, Brill SE, Brown JS, Denneny EK, Hare SS, Heightman M, Hillman TE, Jacob J, Jarvis HC, Lipman MC. 'Long-COVID': a cross-sectional study of persisting symptoms, biomarker and imaging abnormalities following hospitalisation for COVID-19. Thorax. 2021 Apr 1;76(4):396-8.

[26]. Wang L, Berger NA, Davis PB, Kaelber DC, Volkow ND, Xu R. COVID-19 rebound after Paxlovid and Molnupiravir during January-June 2022. MedRxiv. 2022 Jun 22.

[27]. Chee YJ, Fan BE, Young BE, Dalan R, Lye DC. Clinical trials on the pharmacological treatment of long COVID: A systematic review. Journal of medical virology. 2023 Jan;95(1):e28289.

[28]. Potter C, Leggat F, Lowe R, Pallmann P, Riaz M, Barlow C, Edwards A, Siriwardena AN, Sevdalis N, Sewell B, McRae J. Effectiveness and cost-effectiveness of a personalised self-management intervention for living with long COVID: protocol for the LISTEN randomised controlled trial. Trials. 2023 Feb 1;24(1):75.

[29]. Torres A, Motos A, Cillóniz C, Ceccato A, Fernández-Barat L, Gabarrús A, Bermejo-Martin J, Ferrer R, Riera J, Pérez-Arnal R, García-Gasulla D. Major candidate variables to guide personalised treatment with steroids in critically ill patients with COVID-19: CIBERESUCICOVID study. Intensive care medicine. 2022 Jul;48(7):850-64.

[30]. Bello B, Bundey YN, Bhave R, Khotimchenko M, Baran SW, Chakravarty K, Varshney J. Integrating AI/ML models for patient stratification leveraging omics dataset and clinical biomarkers from COVID-19 patients: A promising approach to personalized medicine. International Journal of Molecular Sciences. 2023 Mar 26;24(7):6250.

[31]. Han Q, Zheng B, Daines L, Sheikh A. Long-term sequelae of COVID-19: a systematic review and meta-analysis of one-year follow-up studies on post-COVID symptoms. Pathogens. 2022 Feb 19;11(2):269.

[32]. De Graaf MA, Antoni ML, Ter Kuile MM, Arbous MS, Duinisveld AJ, Feltkamp MC, Groeneveld GH, Hinnen SC, Janssen VR, Lijfering WM, Omara S. Short-term outpatient follow-up of COVID-19 patients: A multidisciplinary approach. EClinicalMedicine. 2021 Feb 1;32.