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REVIEW ARTICLE

Long COVID: Pathophysiology, Clinical Manifestations, Diagnosis, and Contemporary Management—An Evidence-Based Narrative Review

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Abstract: Background: Long COVID, also known as post-COVID-19 condition, is a heterogeneous chronic condition that can affect multiple organ systems following infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It may develop after severe or mild acute illness and can substantially impair physical functioning, cognition, mental well-being, and quality of life.Objective: This review summarizes current understanding of the definition, epidemiology, proposed pathophysiological mechanisms, clinical manifestations, diagnostic assessment, management, and future research priorities for Long COVID.Methods: A narrative review was developed using international clinical guidance, peer-reviewed reviews, consensus definitions, and relevant clinical research on post-COVID-19 condition. The review emphasizes clinically applicable evidence and distinguishes established observations from proposed mechanisms and treatments that remain under investigation.Discussion: Long COVID is characterized by persistent, fluctuating, or newly emerging symptoms that cannot be adequately explained by another diagnosis. Common manifestations include fatigue, post-exertional symptom exacerbation, dyspnoea, cognitive impairment, sleep disturbance, autonomic symptoms, and pain. Proposed mechanisms include persistent viral material, immune dysregulation, endothelial dysfunction, microvascular abnormalities, autonomic disturbance, and altered energy metabolism. These mechanisms may coexist, but no single explanation accounts for every patient. Diagnosis remains clinical because no validated laboratory test can independently confirm or exclude the condition. Management requires individualized assessment, treatment of identifiable complications, symptom-directed care, appropriate rehabilitation, and recognition of post-exertional symptom exacerbation. Evidence for a universally effective disease-modifying treatment remains insufficient.Conclusion: Long COVID requires a patient-centred, multidisciplinary approach supported by better diagnostic research, adequately powered clinical trials, equitable access to care, and longitudinal investigation of its biological mechanisms and long-term outcomes.

Keywords: Long COVID; post-COVID-19 condition; SARS-CoV-2; post-viral syndrome; fatigue; cognitive impairment; rehabilitation; autonomic dysfunction..

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Introduction

The clinical consequences of SARS-CoV-2 infection extend beyond the acute respiratory illness. Although many individuals recover within several weeks, others experience persistent symptoms, develop new health problems after apparent recovery, or experience relapsing episodes that interfere with daily functioning. This spectrum of post-acute illness is commonly referred to as Long COVID or post-COVID-19 condition.

The recognition of Long COVID has changed the understanding of recovery from COVID-19. Early clinical attention focused predominantly on pneumonia, respiratory failure, and complications requiring hospitalization. Subsequent observations established that prolonged illness can also occur after non-hospitalized infection and may involve

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neurological, cardiovascular, respiratory, gastrointestinal, musculoskeletal, and other systems. The absence of a single characteristic symptom or diagnostic biomarker has made the condition difficult to define, measure, and manage consistently [1,2].

The World Health Organization (WHO) developed an international clinical case definition through a Delphi consensus process involving patients, clinicians, researchers, and public health experts. In adults, post-COVID-19 condition usually occurs approximately three months after the onset of COVID-19, with symptoms lasting at least two months that cannot be explained by an alternative diagnosis. Symptoms may persist from the initial illness, emerge after initial recovery, or fluctuate or relapse over time [1]. Other clinical and research frameworks use different time thresholds, contributing to variation in reported prevalence and case identification.

Long COVID should not be regarded as a single uniform disease with an established mechanism. It is better understood as a heterogeneous clinical condition that may include several overlapping biological and functional patterns. Some patients have demonstrable pulmonary, cardiac, neurological, or other organ abnormalities; others have disabling symptoms despite routine investigations that are normal or inconclusive. The absence of an abnormal conventional test does not, by itself, establish that symptoms are psychological or exclude a clinically significant post-infectious disorder [2,3].

This review examines the current evidence concerning Long COVID, with emphasis on the mechanisms under investigation, practical diagnostic evaluation, symptom-directed treatment, rehabilitation, and priorities for clinical research.

Epidemiology and clinical burden

Estimating the prevalence of Long COVID is challenging because studies use different case definitions, follow-up periods, sampling strategies, and symptom criteria. Prevalence also varies according to the characteristics of the population, the severity and timing of the initial infection, vaccination status, viral variants, reinfection history, and access to healthcare. Studies conducted among hospitalized patients may report a different burden from community-based studies, while self-selected surveys can provide important patient-reported information but may not yield representative population estimates.

Davis and colleagues summarized the emerging evidence on Long COVID and highlighted its broad clinical spectrum, substantial functional effects, and multiple potential biological mechanisms [2]. Their review also emphasized that persistent illness can occur after infections of different initial severities and that patients may experience symptoms across several organ systems simultaneously.

The overall burden extends beyond the number of symptoms reported. Fatigue, reduced exercise tolerance, cognitive difficulties, sleep disturbance, and orthostatic intolerance can limit employment, education, household responsibilities, and social participation. Individuals with pre-existing conditions may experience worsening disability, while those without a history of substantial illness may develop new limitations following an infection that initially appeared mild. The unpredictability of symptoms can further complicate employment and rehabilitation planning.

Children and adolescents may also experience post-COVID-19 symptoms, although their presentation, functional consequences, and diagnostic considerations can differ from those of adults. Age-appropriate assessment should consider educational participation, physical activity, sleep, developmental needs, and family functioning. Clinical services should avoid assuming that adult symptom patterns or treatment approaches apply identically to younger populations.

The burden of Long COVID is also influenced by social determinants. Access to specialist assessment, rehabilitation, income support, and workplace adjustments varies substantially. Patients in rural areas and resource-limited health systems may have fewer opportunities for multidisciplinary care. In addition, under-recognition can delay evaluation for treatable complications and undermine confidence in healthcare services. Public health planning therefore requires both better epidemiological measurement and accessible clinical pathways.

Proposed pathophysiological mechanisms

The biological mechanisms underlying Long COVID remain incompletely established. Current evidence supports the possibility that multiple pathways contribute to different clinical phenotypes, with several mechanisms potentially operating in the same individual. The distinction between a plausible mechanism, an observed biological association, and a proven cause is essential when interpreting emerging research.

One proposed mechanism is the persistence of viral material or reservoirs following the acute infection. SARS-CoV-2 components have been detected in selected tissues or biological samples in some studies, raising the possibility that ongoing antigen

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exposure may contribute to sustained immune activation. However, findings differ by tissue, study design, assay, and patient population. Detection of viral material does not necessarily establish the presence of replication-competent virus, nor does it prove that persistent virus explains an individual's symptoms [2].

Immune dysregulation is another major research area. Studies have reported altered immune-cell populations, inflammatory signalling, and immune responses in some people with persistent post-COVID symptoms. Potential explanations include prolonged activation of immune pathways, impaired immune regulation, reactivation of latent viruses, or autoimmune processes. Nevertheless, these findings are not uniform across studies, and no single immune profile currently functions as a validated diagnostic test. Evidence of an immune abnormality in a subgroup should not be interpreted as proof that all patients have the same immune-mediated disease.

Endothelial dysfunction and microvascular abnormalities have also been proposed. SARS-CoV-2 infection can affect vascular biology, and disturbances in endothelial function, coagulation, and tissue perfusion may plausibly contribute to exertional intolerance or organ-specific symptoms. Some studies have identified microvascular or coagulation-related abnormalities in selected populations. However, the clinical significance of these findings and the extent to which they explain persistent symptoms remain under investigation. Treatments directed at coagulation or vascular pathways should not be prescribed solely on the basis of unconfirmed mechanistic hypotheses.

Autonomic dysfunction is particularly relevant to patients who experience palpitations, dizziness, presyncope, orthostatic intolerance, or disproportionate increases in heart rate on standing. Postural orthostatic tachycardia syndrome (POTS) and other forms of dysautonomia have been reported following COVID-19. Potential mechanisms include autonomic nerve dysfunction, altered vascular regulation, reduced circulating volume, and immune-mediated effects. A careful history, orthostatic vital signs, and selected cardiovascular or autonomic investigations can help identify clinically relevant abnormalities.

Altered energy metabolism and impaired physiological responses to exertion are additional areas of investigation. Some patients report a delayed worsening of fatigue, pain, cognitive symptoms, or flu-like symptoms after physical or mental activity. This phenomenon, known as post-exertional symptom exacerbation or post-exertional malaise, can differ from ordinary tiredness and may persist for hours or days after the triggering activity. Its mechanisms are not fully established, but the symptom pattern has important implications for rehabilitation and activity planning [2,3].

Neurological mechanisms may include neuroinflammation, altered neurovascular function, autonomic disturbance, sleep disruption, and the consequences of systemic illness. Cognitive symptoms can arise from overlapping contributors rather than a single identifiable lesion. Similarly, respiratory symptoms may reflect residual lung injury, impaired gas exchange, dysfunctional breathing, deconditioning, cardiac disease, or other causes. Comprehensive clinical assessment is therefore preferable to assuming that all persistent symptoms share a common pathophysiology.

Overall, current research suggests that Long COVID may comprise several overlapping syndromes rather than one mechanistically uniform condition. Future studies should characterize patients using reproducible clinical phenotypes and validated biological measures, enabling more precise investigation of cause and treatment response.

Clinical manifestations

Long COVID may affect nearly every major organ system. Common symptoms include fatigue, dyspnoea, cognitive difficulties, headache, sleep disturbance, palpitations, dizziness, muscle or joint pain, altered smell or taste, gastrointestinal symptoms, and mood-related difficulties. Symptoms may persist continuously, appear intermittently, or recur after periods of improvement. The number and severity of symptoms vary substantially between individuals [2,3].

Fatigue is among the most frequently reported manifestations. It may be accompanied by reduced stamina, difficulty completing routine tasks, and a need for prolonged recovery after activity. Assessment should distinguish persistent fatigue from breathlessness, anaemia, sleep disorders, medication effects, depression, endocrine disease, and other potentially treatable contributors. A normal basic investigation does not negate the functional impact of fatigue, but it should prompt a careful, structured assessment rather than premature diagnostic closure.

Post-exertional symptom exacerbation is a particularly important feature because it changes how activity should be managed. Some patients experience delayed worsening after exertion that previously seemed tolerable. Repeatedly pushing through these episodes may worsen symptoms and reduce functional capacity. Clinicians should ask

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specifically about the timing and duration of symptom worsening after physical, cognitive, and emotional activity. This pattern should be distinguished from uncomplicated deconditioning, in which carefully graded exercise may be beneficial.

Respiratory manifestations include breathlessness, cough, chest discomfort, and reduced exercise tolerance. Patients with severe acute COVID-19 may have residual parenchymal lung abnormalities, but persistent respiratory symptoms also occur in individuals whose initial illness was mild. Evaluation should consider pulmonary disease, thromboembolic complications when clinically indicated, asthma, cardiac dysfunction, dysfunctional breathing, and other diagnoses. Pulse oximetry, spirometry, chest imaging, or exercise testing may be appropriate depending on the clinical presentation.

Cardiovascular symptoms include chest pain, palpitations, tachycardia, exercise intolerance, and orthostatic dizziness. These symptoms can arise from dysautonomia, arrhythmia, myocarditis, ischaemic disease, pulmonary embolism, or other causes. New or severe chest pain, syncope, marked breathlessness, or persistent tachycardia requires appropriate evaluation rather than automatic attribution to Long COVID. Diagnostic testing should be selected according to the history, examination, and suspected underlying condition.

Cognitive symptoms commonly described as brain fog may include impaired concentration, slowed information processing, word-finding difficulties, memory problems, and reduced ability to manage complex tasks. These symptoms can affect education and employment even when routine neurological examination is unremarkable.

Sleep disruption, pain, fatigue, mood symptoms, autonomic dysfunction, and medication effects may contribute. Persistent or progressive cognitive impairment warrants evaluation for alternative neurological and medical causes.

Musculoskeletal symptoms include myalgia, arthralgia, weakness, and reduced physical endurance. Headache, altered smell or taste, gastrointestinal disturbance, and sleep difficulties may further reduce quality of life. Anxiety, depressive symptoms, and distress may develop in response to prolonged illness, uncertainty, financial pressure, and social isolation. These psychological consequences deserve assessment and treatment in their own right; their presence does not imply that the underlying physical symptoms are imaginary or exclusively psychological.

Diagnosis and clinical assessment

There is currently no single laboratory test, imaging finding, or biomarker that definitively confirms or excludes Long COVID. The US Centers for Disease Control and Prevention (CDC) states that diagnosis may be based on the patient's history and physical examination, supplemented by directed investigations where indicated. A documented positive viral test is not always necessary because testing may not have been available during the initial infection [3].

The initial assessment should establish the timing of the suspected infection, the nature and duration of symptoms, the pattern of recovery, functional limitations, previous medical conditions, medication use, and the presence of new or worsening symptoms. The clinician should assess whether symptoms are persistent, fluctuating, relapsing, or newly emerging and identify their effects on mobility, self-care, cognition, work, education, and social participation.

A differential diagnosis remains essential. Depending on the presentation, relevant alternatives may include anaemia, thyroid disease, diabetes, sleep apnoea, medication adverse effects, primary cardiac or pulmonary disease, pulmonary embolism, inflammatory disorders, and neurological conditions. Coexisting diseases should not be overlooked merely because symptoms began after COVID-19. Conversely, extensive testing without a clinical rationale can produce incidental findings, increase patient burden, and delay appropriate symptom management.

Testing should be guided by clinical features. Initial investigations may include a complete blood count, renal and liver function, electrolytes, inflammatory markers, glucose assessment, thyroid function, or other basic tests when indicated. ECG, chest radiography, pulmonary function tests, echocardiography, ambulatory rhythm monitoring, or imaging may be appropriate for selected respiratory or cardiovascular presentations. Orthostatic blood pressure and heart rate measurements can help assess suspected autonomic dysfunction.

Normal investigations should be interpreted carefully. They may reduce the probability of certain organ-specific conditions but do not establish that a patient's symptoms are insignificant. Conversely, nonspecific abnormalities should not automatically be considered proof of Long COVID. Diagnostic reasoning should integrate symptom chronology, examination, relevant tests, alternative explanations, and functional impact. Assessment tools and symptom diaries may help

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document fluctuation, activity-related worsening, sleep, heart rate, and daily functioning. Follow-up is important because the clinical picture may evolve over time. The goals are to identify treatable complications, recognize red flags, establish realistic care priorities, and support patients even when no single pathophysiological explanation is available.

Contemporary management and rehabilitation

There is no universally effective disease-modifying treatment established for Long COVID. Management should therefore be individualized, guided by the patient's most burdensome symptoms, demonstrable complications, functional needs, and preferences. The CDC recommends patient-centred assessment, shared decision-making, optimization of underlying conditions, and symptom-directed care [3]. The WHO's living guidance also emphasizes individualized rehabilitation when symptoms and impairments limit daily functioning [4].

A comprehensive management plan begins with validation of the patient's experience and explanation of the uncertainty surrounding the condition. Clear communication helps avoid both therapeutic nihilism and unsupported promises of cure. Treatment goals should focus on symptom relief, safety, improved daily functioning, and quality of life, with periodic review of progress and adverse effects.

Fatigue management may include pacing, prioritization of essential activities, planned rest, sleep optimization, and adjustment of work or household demands. Pacing aims to keep activity within a tolerable range and reduce repeated cycles of overexertion followed by symptom exacerbation. It is not synonymous with permanent inactivity; rather, activity is adjusted according to symptoms and individual capacity. Where post-exertional symptom exacerbation is present, fixed incremental exercise programmes should not be imposed without careful assessment.

For patients without post-exertional symptom exacerbation or relevant contraindications, individualized physical rehabilitation may help address weakness, impaired mobility, respiratory limitations, and deconditioning.

Rehabilitation should be adapted to cardiovascular and respiratory status, orthostatic symptoms, and the patient's response to exertion. Clinicians should monitor delayed symptom worsening as well as immediate tolerance. A one-size-fits-all graded exercise prescription is inappropriate for a heterogeneous condition in which exertion may worsen symptoms in a subgroup.

Breathlessness management depends on the underlying cause. Patients may benefit from assessment of pulmonary function, breathing-pattern abnormalities, cardiac disease, or other conditions before a rehabilitation programme is designed. Selected patients may benefit from breathing retraining, occupational therapy, or supervised pulmonary rehabilitation. Oxygen therapy is appropriate only when clinically indicated, not simply because a patient reports breathlessness.

Orthostatic intolerance requires assessment of heart rate, blood pressure, hydration, medication effects, and possible autonomic disorders. Management may include individualized fluid intake, physical counter-manoeuvres, compression garments, and other measures according to the clinical situation. Increased salt intake or medications intended to influence heart rate or blood pressure require particular caution in patients with hypertension, kidney disease, heart failure, or other contraindications. Persistent or severe symptoms may justify specialist evaluation.

Cognitive difficulties may be addressed through management of sleep disturbance, fatigue, pain, and mood symptoms, along with practical strategies such as structured routines, written reminders, task simplification, and planned breaks. Occupational therapy and neuropsychological assessment may be helpful when symptoms substantially impair daily functioning. The evidence for specific cognitive rehabilitation protocols in Long COVID continues to develop, so interventions should be evaluated according to meaningful functional outcomes.

Sleep disturbance, pain, anxiety, and depression should be assessed and treated using established clinical approaches where appropriate. Psychological support may assist coping and adjustment, but it should not be presented as proof that Long COVID is a psychological disorder. Medication should be selected for a defined indication, with attention to drug interactions, adverse effects, and the possibility that some symptoms overlap with medication-related problems.

Patients with persistent or severe symptoms may benefit from multidisciplinary care involving primary care, rehabilitation, respiratory medicine, cardiology, neurology, occupational therapy, mental health services, and other specialties according to need. Multidisciplinary care does not require every patient to attend every specialty; coordinated, targeted referral is preferable to fragmented investigations.

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Table 1. Clinical assessment and management of common Long COVID presentations

Presentation	Key assessment priorities	Potential management approach
Fatigue and post-exertional symptom exacerbation	Activity-related symptom pattern, sleep, anaemia and other treatable causes	Pacing, energy management, individualized support
Breathlessness	Oxygenation where indicated, pulmonary and cardiac assessment, alternative diagnoses	Cause-specific treatment, selected breathing support or rehabilitation
Palpitations and dizziness	ECG, medication review, orthostatic heart rate and blood pressure	Treat identified cause; consider autonomic assessment
Cognitive difficulties	Functional history, sleep, medication, neurological red flags	Practical cognitive strategies, occupational therapy, treatment of contributors
Musculoskeletal pain	Examination, functional impact, inflammatory or other causes when suspected	Symptom-directed treatment and adapted rehabilitation
Sleep and mood symptoms	Sleep history, psychosocial impact, mental health assessment	Evidence-based sleep and mental health interventions
Persistent multisystem impairment	Overall functional assessment and review of prior investigations	Coordinated, multidisciplinary, patient-centred care

Prevention, prognosis, and future research

Prevention of Long COVID remains an important public health objective. COVID-19 vaccination reduces the risk of severe acute disease and may reduce the risk of developing Long COVID, although protection against post-acute illness is not absolute and varies with the population, variant, vaccination history, and outcome definition. The CDC identifies vaccination as an important preventive measure [3]. Prevention also requires appropriate management of acute infection and continued research into the relationship between reinfection and long-term outcomes.

Prognosis varies considerably. Some individuals improve over time, while others experience persistent or relapsing symptoms that require prolonged support. Recovery may be nonlinear, and symptom improvement does not always occur uniformly across organ systems. Clinical follow-up should therefore consider functional capacity, symptom burden, participation in daily life, and the patient's own goals rather than relying exclusively on conventional laboratory results.

Future research should prioritize well-characterized patient cohorts, consistent case definitions, representative sampling, and longitudinal follow-up. Studies should distinguish post-hospitalization complications from broader post-infectious illness and examine differences by age, sex, comorbidity, vaccination, viral variant, and reinfection history. Biomarker studies require independent validation and should demonstrate clinical usefulness before proposed tests are adopted in routine practice.

Randomized clinical trials are needed to evaluate candidate disease-modifying therapies and symptom-specific interventions. Trials should use clearly defined patient populations, appropriate control groups, transparent reporting of adverse events, and outcomes that reflect function and quality of life. Mechanistic studies should test whether particular biological findings predict treatment response rather than assuming that a plausible pathway establishes a therapeutic target. Patient involvement is important in selecting meaningful outcomes and designing studies that reflect the realities of fluctuating illness.

Equity also requires attention. Clinical pathways should be accessible to people who lack documentation of their original infection, live far from specialist services, have limited financial resources, or experience difficulties obtaining workplace accommodations. Primary care clinicians need practical guidance for assessment and follow-up, while referral systems should support patients with complex or severe presentations. The objective is not merely to identify a syndrome but to reduce disability and improve the quality of life of affected individuals.

Conclusion

Long COVID is a heterogeneous post-infectious condition that can produce persistent and fluctuating symptoms across multiple organ systems. Its pathophysiology remains incompletely understood, and current evidence supports several possible mechanisms rather than one universal explanation. Diagnosis relies on clinical history, examination, appropriate investigation, and consideration of alternative conditions because no single validated test can confirm or exclude the

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syndrome. Management should prioritize patient-defined goals, treatment of identifiable complications, symptom-directed care, and individualized rehabilitation. Particular care is required when post-exertional symptom exacerbation is present. Progress will depend on rigorous clinical trials, better phenotyping, validated biomarkers, accessible multidisciplinary services, and sustained engagement with patients and communities affected by the condition.

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