

Post-COVID and long-COVID manifestations in different organ systems: review

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

COVID-19, caused by SARS-CoV-2, has resulted in substantial acute morbidity and mortality worldwide. Beyond the acute phase, a growing number of individuals experience persistent or new symptoms, collectively described as post-COVID syndrome or long-COVID, now recognized as part of the post-acute sequelae of SARS-CoV-2 infection (PASC). These conditions pose a significant and ongoing challenge to healthcare systems.

Aim. This narrative review aims to summarize current evidence on post-COVID and long-COVID manifestations across multiple organ systems, explore underlying pathophysiological mechanisms, and highlight implications for long-term management and future research.

Materials and methods. A comprehensive literature search was conducted using PubMed, Scopus, and Web of Science databases, covering publications from 2020 to 2025, including original research articles, systematic reviews, meta-analyses, clinical cohort studies, and relevant consensus statements.

Results. A review of recent literature on clinical and morphological alterations across various organ systems in the late phase after COVID-19 reveals a wide spectrum of pathological states characterized by a heterogeneous clinical course. Such conditions may persist for months, substantially compromising the patients' quality of life. While it is established that the pathogenesis of post-COVID pathology is multifaceted, it remains to be fully elucidated. Effective clinical management requires a holistic, multidisciplinary strategy focusing on symptom-directed care, early rehabilitation, and psychosocial support.

Conclusions. Post-COVID multisystem damage is mediated by diverse pathological mechanisms, such as cellular alteration, chronic inflammation, impaired regeneration, immunopathology, and microvascular dysfunction. These manifestations span multiple systems, affecting the pulmonary, cardiovascular, endocrine, and integumentary systems, as well as the central and peripheral nervous systems. The pathogenesis of long-COVID involves a synergistic interplay between persistent viral reservoirs, cytokine dysregulation with subsequent autoimmunity, autonomic dysfunction, systemic endotheliopathy and mitochondrial dysfunction. Notably, the protracted treatment regimens required for SARS-CoV-2 can lead to medication-induced pathology, where long-term management strategies themselves may become a source of iatrogenic complications.

Keywords:

COVID-19, SARS-CoV-2, post-COVID syndrome, long-COVID, post acute sequelae of COVID-19 (PASC), multisystem involvement, immune dysregulation, endothelial dysfunction.

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Постковідний синдром і long-COVID: прояви у різних системах організму: огляд

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COVID-19, спричинений вірусом SARS-CoV-2, зумовив високий рівень захворюваності та смертності в усьому світі. У дедалі більшій кількості пацієнтів після гострої фази перебігу захворювання виявляють тривалі або нові симптоми, що разом визначають як постковідний синдром або long COVID (тривалий ковід). Нині ці стани класифіковано як частину постгострих наслідків інфекції SARS-CoV-2 (PASC). Вони є складним викликом для системи охорони здоров'я через тривалий вплив на здоров'я пацієнтів.

Мета роботи – узагальнити сучасні дані щодо проявів постковідного синдрому та long-COVID у різних системах організму, дослідити основні патофізіологічні механізми та висвітлити наслідки довгострокового лікування та перспективи для майбутніх досліджень.

Матеріали і методи. Проведено всебічний пошук наукової літератури з використанням наукометричних баз даних PubMed, Scopus і Web of Science. Включали публікації за 2020–2025 роки. Пошук включав оригінальні дослідницькі статті, систематичні огляди, метааналізи, клінічні когортні дослідження тощо.

Результати. Аналіз сучасної фахової літератури щодо клініко-морфологічних змін у різних органах і системах організму у віддаленому періоді після перенесеного COVID-19 дав змогу визначити різноманіття патологічних станів із гетерогенним клінічним перебігом. Прояви цієї патології можуть зберігатися протягом багатьох місяців і суттєво погіршувати якість життя пацієнтів. Показано, що патогенез постковідної патології складний і потребує продовження вивчення. Ведення таких пацієнтів передбачає застосування цілісного мультидисциплінарного підходу з акцентом на симптоматичну терапію, ранню реабілітацію та психосоціальну підтримку.

Висновки. Мультисистемні ураження після перенесеного COVID зумовлені такими численними загальнопатологічними процесами, як альтерація, запалення, дисрегенерация, імунопатологія, порушення мікроциркуляції, що виникають у

Ключові слова:

COVID-19, SARS-CoV-2, постковідний синдром, long-COVID, постгострі наслідки інфекції SARS-CoV-2 (PASC), мультисистемне ураження, імунна дисрегуляція, ендотеліальна дисфункція.

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різних органах: легенях, серці, центральній і периферичній нервовій системі, ендокринних залозах, шкірі. У патогенезі постковідного синдрому визначено поєднану дію багатьох факторів: персистенції вірусних резервуарів в органах-мішенях, цитокинової дисрегуляції з розвитком аутоімунних реакцій, вегетативної дисфункції, системної ендотеліопатії та мітохондріальної дисфункції. Встановлено, що тривале лікування інфекції SARS-CoV-2 може призводити до медикаментозно зумовленої патології, коли довготривала терапія сама стає причиною ятрогенних ускладнень.

The coronavirus disease 2019 (COVID-19) pandemic has had a lasting and profound impact on global healthcare systems, not only because of the acute infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), but also due to the growing recognition of post-COVID conditions. SARS-CoV-2, the causative agent of COVID-19 combines with angiotensin-converting enzymes 2 (ACE2) on entry into the host cells and undergoes replication. This process leads to damage across multiple organs and tissues, resulting in a wide constellation of clinical manifestations. In comparison between SARS-CoV-2 and SARS-CoV-1, SARS-CoV-2 demonstrates a stronger affinity for ACE2, furthermore, the presence of an additional S1-S2 cleavage site in SARS-CoV-2 leads to more effective cleavage by the host proteases, this makes it easier for the virus to gain entry into the host cells and cause infection [1].

The terms post-COVID and long-COVID are often used interchangeably in clinical literature, but subtle distinctions exist. Post-COVID generally refers to persistent or new symptoms that remain beyond the acute phase which is typically >4 weeks after infection, whereas long-COVID is more specifically defined as symptoms lasting beyond 12 weeks, with no alternative diagnosis (Fig. 1). For this review, both terms are considered part of a spectrum of post-acute sequelae of SARS-CoV-2 infection (PASC) [2]. Reports of persistent symptoms first emerged in mid-2020, when patient cohorts in Italy, the UK, and the United States described ongoing symptoms weeks after recovery, even among those with mild or moderate acute disease. By late 2020, international health agencies such as the World Health Organization and the Centers for Disease Control and Prevention had formally recognized long-COVID as an emerging syndrome requiring systematic investigation [3,4].

Risk factors for developing long-COVID include pre-existing conditions associated with endothelial dysfunction and chronic inflammation, such as hypertension, diabetes mellitus, obesity, and cardiovascular disease. Higher risk is also seen in women, older adults, and individuals requiring hospitalization or intensive care during acute infection. However, persistent symptoms may also occur in young, previously healthy individuals, reflecting the complex pathogenesis of the condition [5,6,7].

Various recent studies suggest that mechanisms such as viral persistence, immune dysregulation, autoimmunity, and endothelial dysfunction may underlie these chronic complications [2].

Current criteria for diagnosing post-COVID syndrome include: prior confirmed or probable SARS-CoV-2 infection; persistent or new symptoms lasting beyond 4 weeks from acute infection onset; absence of an alternative diagnosis that explains these symptoms; evidence in some cases of objective abnormalities (e. g., imaging changes, lab markers, or functional testing); these criteria remain under refinement as global consensus develops.

Understanding the constellation of these symptoms that affect various organ systems such as the lungs, heart, brain, kidneys, endocrine glands, skin, and immune system is vital for the establishment of long-term management strategies, targeted interventions, and comprehensive rehabilitation programs [8]. The main hypotheses for the occurrence of post-COVID conditions include persistence of viral reservoirs or viral antigens, chronic immune dysregulation with autoimmunity, microvascular and endothelial injury, prolonged systemic inflammation and cytokines dysregulation, mitochondrial dysfunction and oxidative stress and reactivation of latent viruses such as Epstein–Barr virus [9]. These mechanisms may act independently or synergistically to drive the chronic sequelae of COVID-19.

Aim

This narrative review aims to summarize current evidence on post-COVID and long-COVID manifestations across multiple organ systems, explore underlying pathophysiological mechanisms, and highlight implications for long-term management and future research.

Materials and methods

During the preparation of this review, a comprehensive analysis of current scientific literature was carried out regarding the manifestations of post-COVID syndrome and long-COVID in different organ systems, with an emphasis on pathophysiological and morphogenetic mechanisms. In addition, scientific information on the consequences of long-term treatment of this condition was analyzed. The literature search was performed in international scientific databases, including PubMed, Scopus, Web of Science, and Google Scholar, as well as in national medical information resources of Ukraine. The following keywords were used: COVID-19, SARS-CoV-2, post-COVID syndrome, long-COVID, post-acute sequelae of SARS-CoV-2 infection (PASC), multisystem involvement, immune dysregulation, endothelial dysfunction, as well as these keywords in Ukrainian. Scientific publications from the last six years (2020–2025) were analyzed.

A total of approximately 120 articles were screened, and 58 were selected for inclusion in this review. Of these, 16 % were large-scale clinical cohort studies (with a total enrollment of over 10,000 patients), 37 % were original studies, 8 % were case reports, and 28 % were review articles featuring integrative analysis. The inclusion of review articles is explained by the fact that this study is aimed at providing a broad and maximally comprehensive overview of the pattern of post-COVID syndrome and long-COVID across organs of different body systems. Such a broad source base supports the representativeness of the conclusions, reflecting both clinical and mechanistic aspects of global scientific research.

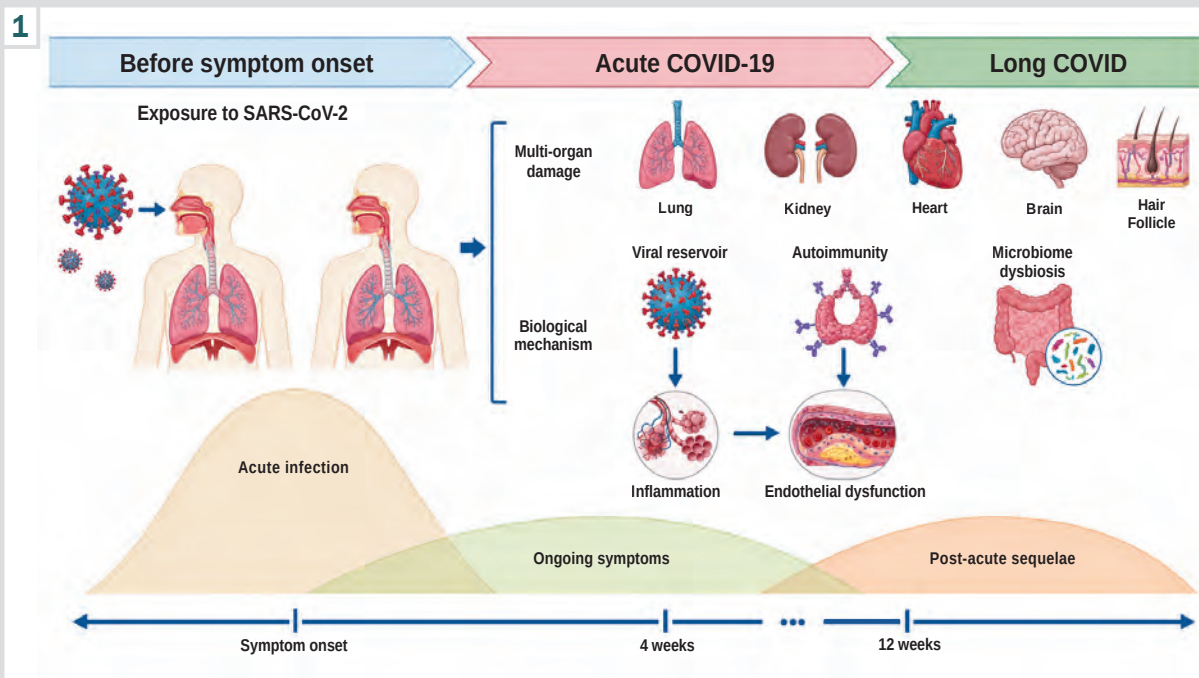


Fig. 1. Timeline of COVID-19 progression from acute infection to long-COVID (original composition).

Schematic representation showing the phases before symptom onset, acute COVID-19, and long-COVID, with associated biological mechanisms and organ involvement.

We used Canva software and personally created the images using the tools available on the platform to develop a pictorial representation of our text.

Results

Pulmonary sequelae after COVID-19. The lungs are known to be the primary site of SARS-CoV-2 infection, and clinical manifestation experience by many patients include dyspnoea, persistent cough, chest tightness and decreased exercise tolerance, these symptoms may persist even after viral clearance [4,10]. High-resolution computed tomography of the chest of post-COVID patients commonly shows various radiographical findings such as Ground-glass opacities, reticulations, interlobular septal thickening, bronchiectasis, parenchymal bands, and in some cases, evolving fibrotic change [11]. In patients with severe COVID-19 pneumonia, these radiographical findings can persist for months [12]. According to X. Han et al. (2021) [13], 35 % of recovered patients had radiologic abnormalities after 6 months, with approximately 25 % showing fibrotic-like lesions. The utilization of pulmonary function tests may reveal reduced diffusion capacity (DLCO), often with a restrictive pattern, and occasionally obstructive changes.

Pulmonary sequelae mechanism. As illustrated in Fig. 2, the mechanism of post-COVID conditions involves a complex interplay of persistent inflammation, immune dysregulation, tissue injury, and residual viral antigens. Sustained immune activation may result in chronic inflammation or autoimmunity, evidenced by prolonged elevation of inflammatory markers, such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- α), and interferons weeks after acute infection [5,14].

Endothelial injury result from SARS-CoV-2 binding to ACE2 receptors, leading to a widespread disruption of micro vessels, this results in the formation of thrombosis and long-term organ ischemia [15]. The development of pulmonary fibrosis is driven by various mediators, including cytokines, growth factors, and enzymes. Among these, TGF- β is recognized as having the most profound impact. Other significant mediators implicated in pulmonary fibrosis include legumain, osteopontin, IL-4, IL-6, IL-13, IL-17, TNF- α , Gal-1, Gal-3, PDGF, and FGFR-1. The high-risk cohort comprises patients requiring mechanical ventilation due to severe acute respiratory distress syndrome, individuals presenting with elevated D-dimer levels or hyperinflammatory syndrome, and those with a prior history of chronic interstitial lung diseases [16].

Additionally, even after months of the clearance of initial infection, studies report the persistence of SARS-CoV-2 RNA or protein antigens in various tissues, including the gastrointestinal tract, lymphoid organs, and even the brain, and possibly sustaining antigen-driven immune responses [17]. Additionally, post-intensive care syndrome, particularly in intensive care unit patients, contributes to long-term neuromuscular weakness, cognitive dysfunction, and psychiatric symptoms due to immobility, hypoxia, sedation, and critical illness itself. Together, these mechanisms may explain the diverse and sometimes disabling manifestations seen in post-acute COVID-19 syndrome [18,19].

Cardiovascular sequelae after COVID-19. COVID-19 has been associated with a broad spectrum of cardiovascular complications during both the acute and post-acute phases. In the post-acute phase, patients may experience chest pain, palpitations, orthostatic intolerance, and signs of myocarditis or pericarditis. Cardiac magnetic resonance

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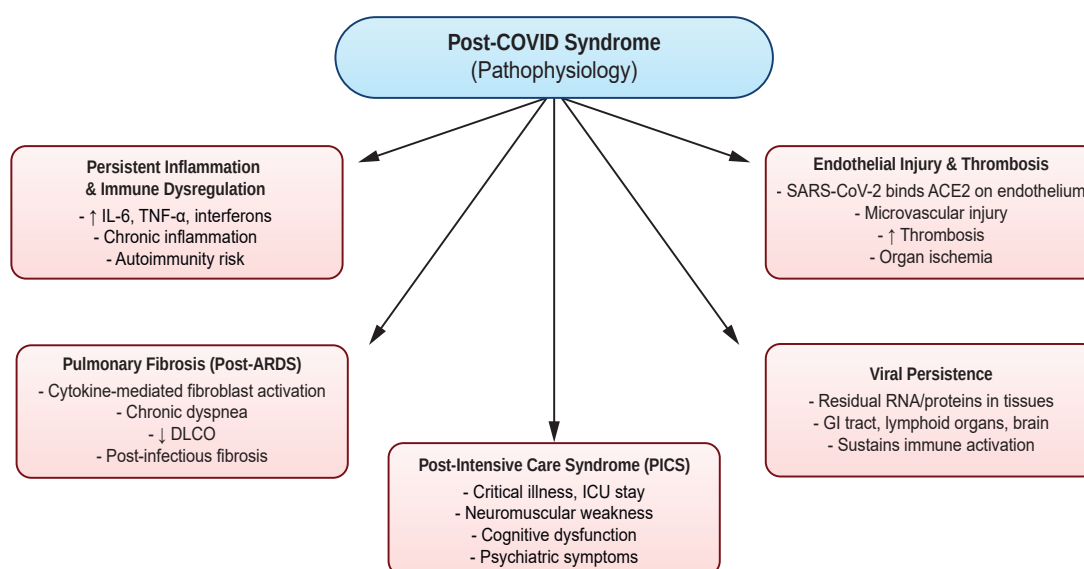


Fig. 2. Pathophysiology of post-COVID syndrome (original composition). Diagram summarizing major mechanisms contributing to post-COVID syndrome, including persistent inflammation, pulmonary fibrosis, endothelial injury, viral persistence, and post-intensive care syndrome.

imaging studies have demonstrated persistent myocardial inflammation in recovered patients, including those with initially mild symptoms [8,20]. Elevated troponin levels, arrhythmias, and heart failure have been reported as lingering effects in some survivors. In addition, postural orthostatic tachycardia syndrome (POTS) and other dysautonomias have emerged as post-COVID syndromes, particularly in young adults [8].

Mechanism of cardiovascular sequelae. The proposed mechanisms include direct viral injury to myocardial tissue through the virus binding to ACE2 receptors to enter the cells especially pericytes and myocytes. Viral entry leads to the downregulation of ACE2 receptor on cells, hindering its protective role in the heart and lungs [8]. Another mechanism via immune-mediated injury, due to the invasion of pericytes, this disrupts the stability of the blood vessel endothelium, this will lead to the pericyte dysfunction, this will lead to microthrombi formation in small muscular arteries, capillaries and arterioles causing ischemia and myocyte necrosis [1]. Another mechanism associated with endothelium damage is the upregulation of proinflammatory cytokines such as IL-6, IL-1, and tumor necrosis factor (TNF)- α aiding thrombosis formation and contributes to post-acute COVID-19 cardiac manifestations [1,21,22]. These mechanisms may act independently or synergistically to drive persistent cardiovascular symptoms in post-COVID patients.

Management of cardiac complication. It is essential for patients who experience cardiovascular complications during acute COVID-19 or those who have persistent cardiac symptoms such as chest pain, palpitations, fatigue, to have serial cardiac evaluation, such as ECG and echocardiogram at 4-12 weeks post-infection to assess ventricular function, identify structural change, and assess ongoing inflammation [23]. It is recommended for athletes known to have COVID-19-related myocarditis to refrain from intense exercise for 3–6 months until cardiac magnetic

resonance imaging reveals that myocardial inflammation is resolved and the troponin level is within its normal range [23]. Previously, RAAS inhibitors, such as ACE inhibitors or ARBs, were of concern, for fears that these drugs may aid the entry of the virus by causing an increase in expression of ACE2 [24]. But rather, recent observational studies have reported that there is no increase in the severity of COVID-19 infection among patients taking these medications; rather, abruptly stopping these drugs can be harmful, particularly in patients who are hypertensive or have heart failure [8]. Low-dose beta blockers, such as propranolol or metoprolol, are used to treat Postural Orthostatic Tachycardia Syndrome & Inappropriate Sinus Tachycardia. Caution should be taken with antiarrhythmics like amiodarone in patients with post-COVID fibrosis due to the risk of pulmonary toxicity.

Neurological and psychiatric sequelae of post-COVID syndrome. A wide spectrum of neurological and psychiatric symptoms is frequently experienced by patients recovering from acute COVID-19. The most reported neurological complaint is brain fog, affecting approximately 22 % of patients. Other commonly reported symptoms are headaches, anosmia, myalgia, and dizziness. In more severe situations, patients report ischemic or haemorrhagic stroke, encephalopathy, acute disseminated encephalomyelitis, Guillain-Barré syndrome, and critical illness-associated neuropathy or myopathy [12].

SARS-CoV-2 is capable of invading the nervous system by breaching the neural-mucosal barrier within the olfactory mucosa. This neuroinvasion exploits the close anatomical proximity of olfactory mucosal, endothelial, and neural tissues, including delicate olfactory and sensory nerve endings [25].

Neuroinflammation plays a key role in post-COVID cognitive dysfunction. Elevated inflammatory cytokines, such as CCL11, impair neurogenesis in the hippocampus and activate microglia [26]. Survivors of SARS-CoV-2

infection frequently experience persistent neurological symptoms, including impairments in attention, concentration, information processing speed, and memory. This long-COVID-associated cognitive syndrome shares numerous features with cancer therapy-related cognitive impairment (CRCI). Neuroinflammation, particularly microglial reactivity and the subsequent dysregulation of hippocampal neurogenesis and oligodendrocyte lineage cells, plays a central role in the pathogenesis of CRCI. Utilizing a mouse model of mild respiratory SARS-CoV-2 infection induced via intranasal viral delivery, the authors identified white matter-selective microglial reactivity, a pattern consistent with that observed in CRCI [27]. Magnetic resonance imaging in patients with SARS-CoV-2 infection revealed reduced grey matter thickness and tissue contrast in the orbitofrontal cortex and parahippocampal gyrus, alterations in markers of tissue damage in regions functionally connected to the primary olfactory cortex, and a reduction in overall brain volume [28].

A large-scale systematic meta-analysis of the prevalence and incidence of neuropsychiatric disorders in post-hospitalized COVID-19 patients in South America demonstrates that the estimated prevalence of all neurological disorders was 31.48 %. The pooled prevalence of depression, anxiety, insomnia, post-traumatic stress disorder, and memory alterations stood at 16.23 %. These neuropsychiatric disorders develop more frequently in individuals who were hospitalized with moderate-to-severe disease [29]. These findings suggest that both direct and indirect mechanisms, including viral neurotropism, inflammatory cascades, and psychosocial stress, contribute to prolonged neuropsychiatric morbidity in post-acute COVID-19. Overall, the persistence of these neuropsychiatric symptoms highlights the importance of long-term follow-up, early multidisciplinary intervention, and deeper investigation into the neuroinflammatory and neurodegenerative pathways triggered by SARS-CoV-2, to achieve better futuristic therapeutic strategies [29].

Endocrine and metabolic dysfunction. SARS-CoV-2 infection has significant effects on the endocrine and metabolic systems during both the acute and post-acute phases. The virus may disrupt hormonal regulation through direct viral invasion, inflammation-mediated injury, and immune dysregulation, resulting in new-onset endocrine disorders or worsening of pre-existing conditions [8].

One of the most concerning outcomes is the emergence of new-onset diabetes mellitus after COVID-19. Multiple large-scale cohort studies have reported higher incidence of diabetes in persons post-infection, even among patients without previous metabolic disease [30,31]. The proposed pathophysiological mechanism includes direct damage to pancreatic β -cells via ACE2 receptor-mediated entry, systemic inflammation, cytokine-induced insulin resistance, and glucocorticoid therapy during acute illness [32,33]. Similarly, thyroid dysfunction has been observed in the form of subacute thyroiditis, autoimmune thyroid diseases, and non-thyroidal illness syndrome. A study conducted in Italy identified thyroid hormone alterations in over 15 % of hospitalized COVID-19 patients, suggesting viral and cytokine-mediated damage to the thyroid gland [34,35]. The virus uses ACE2 receptors, which are highly expressed in thyroid

follicular cells. This allows direct viral entry, leading to inflammation of the thyroid gland.

At the same time, the cytokines storm in COVID-19 causes systemic inflammation, which may suppress thyroid hormone synthesis, trigger autoimmune responses in genetically susceptible individuals. Long-term follow-up data indicates that some patients continue to experience subclinical hypothyroidism, and this can explain ongoing fatigue, cold intolerance, and brain fog after recovery [36].

Adrenal gland involvement is another emerging area of interest. COVID-19 may precipitate or worsen adrenal insufficiency through direct viral infection of adrenal cortical cells expressing ACE2. In addition, microvascular damage and endothelial dysfunction may impair adrenal blood flow, or Inflammation may affect the HPA axis (hypothalamus- pituitary-adrenal), leading to reduced cortisol production [37,38]. In severe cases, especially those requiring intensive care, critical illness-related corticosteroid insufficiency has been reported, contributing to prolonged fatigue and weakness [39]. Symptoms experienced by patients are fatigue, hypotension, poor stress response. Imaging may reveal adrenal atrophy or haemorrhage in some patients.

Metabolic complications, including obesity, insulin resistance, and dyslipidaemia, may be exacerbated following COVID-19. Long-COVID has been associated with persistent dyslipidaemia, weight gain, and worsening insulin sensitivity, thereby perpetuating a cycle of metabolic dysfunction [18]. The persistence of these abnormalities highlights the need for routine endocrine and metabolic evaluation in patients recovering from COVID-19, especially those with prior endocrine disorders, critical illness, or long-COVID symptoms. Early identification and treatment may mitigate complications, improve recovery, and enhance quality of life [8].

Autoimmune and inflammatory disorders in long-COVID. The prolonged and sometimes debilitating symptoms seen in long-COVID have raised concerns that these symptoms manifest due to immune dysregulation including autoimmunity and chronic inflammation. SARS-CoV-2 can disrupt immune tolerance, even after viral clearance, potentially leading to autoimmune responses and chronic inflammation. Following SARS-CoV-2 infection in adult populations, there is an increased risk of developing autoimmune diseases, including mixed connective tissue disease, Behçet's disease, rheumatoid arthritis, psoriasis, and dermatomyositis [8,40].

Immune dysregulation and autoimmunity. SARS-CoV-2 infection contributes persistent immune activation and is associated with prolonged elevation of inflammatory cytokines such as IL-6, TNF- α , and interferons. SARS-CoV-2 shares structural similarities with some human proteins. In some patients, this immune activation mimics autoimmune responses with the findings of certain markers that signifies the loss of immune tolerance, which could lead to the development of de novo autoimmune diseases or worsening of existing ones, such markers are; positive antinuclear antibodies (ANA) test, rheumatoid factor, antiphospholipid antibodies, anti-SSA/Ro antibodies that is linked to Sjögren's-like symptoms [41].

Several autoimmune conditions have been reported post-COVID like Guillain-Barré syndrome, autoimmune

thyroiditis, psoriasis flares, type 1 diabetes mellitus, multisystem inflammatory syndrome in children (MIS-C) and adults (MIS-A). Notably, Guillain-Barré syndrome is among the most frequent autoimmune neurological sequelae of SARS-CoV-2 infection, that usually presents with rapid-onset muscle weakness and areflexia [42].

Even in the absence of autoantibodies, many long-COVID patients exhibit low-grade chronic inflammation, which may contribute to persistent fatigue, myalgia, and cognitive dysfunction. Elevated C-reactive protein and ferritin levels have been observed months post-infection, and the persistent activation of monocytes and T-cells supports the notion of post-viral immune imbalance. This non-specific inflammation may sustain tissue damage and worsen comorbid conditions [23].

Dermatologic manifestations. Telogen effluvium a dermatologic manifestation, it is a form of hair loss, that is increasingly reported as part of post-acute sequelae of SARS-CoV-2 infection, especially among women. Other dermatologic presentations include rashes, urticaria, and chilblain-like lesions often called COVID toes [43,44]. Telogen effluvium is a non-scarring, diffuse hair shedding that is triggered by systemic stress. It occurs 2–3 months after the acute phase of COVID-19. Severe systemic stress or the cytokine storm may push many hair follicles into the telogen phase also known as the resting phase, which will result in noticeable hair shedding. Recovery is usually spontaneous within 6–9 months, but in some cases, recurrence or persistence can occur [24].

Urticarial rash and maculopapular eruptions can appear either during the acute infection or persist afterward. COVID toes are frequently seen in younger patients, potentially linked to microvascular damage or immune dysregulation. Due to systemic vascular inflammation or coagulopathy, vasculitis-like skin lesions have also been described [45].

Mechanisms of dermatologic sequelae. Microvascular injury and endothelial dysfunction may underlie many cutaneous signs. Immune complex deposition and persistent inflammation are also implicated to cause rashes and vasculitis [7,45]. Stress will trigger the release of stress hormone such as cortisol and catecholamines. These stress hormone causes the disruption of follicular proteoglycan metabolism and can trigger premature entry into the telogen phase. In addition, medication and nutritional deficiency during illness may exacerbate skin and hair conditions. Furthermore, SARS-CoV-2 may indirectly impact hair follicles through antibody-dependent enhancement, a process where virus-antibody complexes facilitate uptake into host cells, potentially affecting follicular cells. Microthrombi formation due to the hypercoagulable state induced by COVID-19 results in the compromise of the follicular blood supply [8].

Reassurance is often key for telogen effluvium. Topical minoxidil, nutritional support such as iron, zinc, and stress management may help. Chronic or unusual lesions may require dermatologic referral and skin biopsy [3].

Hematological and other systemic manifestations in long-COVID. Although respiratory and neurological effects dominate discussions, hematologic changes in long-COVID are significant and may drive multi-organ complications. Many patients remain in a pro-thrombotic

state weeks to months after infection. Possible mechanisms such as endothelial injury and platelet activation, persistent elevated D-dimer, ongoing microthrombi in the pulmonary and systemic circulation. Furthermore, increasing the risk of deep vein thrombosis, pulmonary embolism, and stroke even after mild COVID-19 [46]. Hypocellularity of the bone marrow in some patients may reflect marrow suppression from inflammation or viral effects. Reactive lymphocytosis or prolonged neutrophilia may persist in others. Autoimmune hemolytic anemia has been reported in post-COVID cases, likely from molecular mimicry and autoantibody formation [47].

Additionally, disruption of iron metabolism with functional iron deficiency may contribute to post-viral fatigue. COVID-19-associated kidney injury can progress to chronic kidney disease due to microvascular damage, persistent inflammation, and renin – angiotensin – aldosterone system (RAAS) dysregulation. RAAS dysregulation also links kidney effects with cardiovascular and endocrine sequelae [24]. Some patients develop POTS and myalgic encephalomyelitis like symptoms with haematological contributions such as reduced plasma volume, micro-clots.

Mechanisms of disease formation in long-COVID.

The pathophysiology of long-COVID is multifactorial, involving viral persistence, immune dysregulation, endothelial damage, and metabolic changes (Fig. 3).

While some patients recover fully, others experience prolonged symptoms across various organ systems due to complex biological mechanisms that are still being unravelled. Key contributing mechanisms include:

Viral persistence. SARS-CoV-2 RNA and proteins have been detected in tissues such as the gut, brain, and lungs several months after initial infection, even in the absence of active viral replication. This persistent antigen presence may lead to chronic immune stimulation and contribute to sustained inflammatory responses [9].

Immune dysregulation and autoimmunity. Long-COVID is associated with altered immune profiles, including persistent T-cell activation and exhaustion, reduction in regulatory T-cells, development of autoantibodies (e. g., antinuclear antibodies, antiphospholipid antibodies, and anti-interferon antibodies) [48,49].

Mechanisms such as molecular mimicry, bystander activation, and epitope spreading may explain the post-viral autoimmunity observed in some patients, linking long-COVID to conditions like autoimmune thyroiditis and systemic lupus erythematosus-like flares [35].

Endothelial dysfunction and microvascular injury. SARS-CoV-2 infects cells expressing ACE2, including vascular endothelial cells. This leads to endothelial inflammation, microvascular inflammation, capillary leak syndrome, microthrombi formation, even in the absence of acute COVID symptoms, chronic vascular impairment that may underlie brain fog, fatigue, and dyspnoea [8,40,50].

Chronic inflammation and cytokine dysregulation. Many Long-COVID patients exhibit ongoing systemic inflammation with elevated levels of IL-6, TNF- α , CCL11, and IFN- γ , chemokine imbalances resulting in neuroinflammation, especially in the hippocampus. This prolonged pro-inflammatory state mimics that of post-chemotherapy cognitive dysfunction and may

contribute to impaired memory, concentration, and sleep disturbances [30].

Mitochondrial dysfunction and oxidative stress. SARS-CoV-2-associated inflammation interferes with mitochondrial bioenergetics, leading to ATP depletion, elevated reactive oxygen species, poor muscle endurance, exercise intolerance, and mental fatigue. This may explain symptoms of post-exertional malaise seen in many long-COVID cases [51].

Reactivation of latent viruses. Reactivation of Epstein-Barr virus, HHV-6, and other latent infections has been reported in long-COVID cohorts. These reactivations can worsen fatigue, trigger new autoantibodies, aggravate neuroinflammatory pathways [48,52].

Gut dysbiosis and the gut – lung – brain axis. Disruption of gut microbiota in COVID-19 alters immune regulation and may influence systemic inflammation through reduced short-chain fatty acid production, loss of protective commensals, increased gut permeability. This dysbiosis is also implicated in neuropsychiatric symptoms and autoimmunity [53,54].

Neuroinflammation. Chronic activation of microglia and astrocytes has been observed, especially in the hippocampus and olfactory bulb. This may stem from direct viral effects, cytokine spillover, loss of neuronal plasticity. These changes are linked to cognitive impairment, memory loss, and anosmia [8,55].

Management and follow-up considerations in long-COVID. The management of post-COVID symptoms requires a multidisciplinary and individualized approach that addresses persistent symptoms, monitors for late complications, and supports functional recovery [55]. Physical, social and psychological dimensions should be integrated in the patients care plans. Setting up a structured post-COVID follow-up, typically within 4–12 weeks post-infection, will aid in the early identification of persistent symptoms.

Multidisciplinary care teams involving primary care physicians, pulmonologists, cardiologists, neurologists, endocrinologists, rheumatologists, dermatologists, rehabilitation specialists, and mental health professionals to ensure a comprehensive post care for these patients [56]. Shared decision making with patients, and prioritization of patients most impactful symptoms is vital to improve the quality of life of patients. Pulmonary sequelae management benefits from a structured pulmonary rehabilitation program to improve dyspnea and exercise tolerance. It is required to repeat pulmonary function tests and high-resolution computed tomography in those patients with prolonged hypoxia or abnormal imaging, with antifibrotic therapy considered in progressive fibrotic changes under trial conditions [11,17].

Cardiac follow up entails monitoring for myocarditis, arrhythmias, and POTS. With treatment option for POTS with medications like beta-blockers, ivabradine, or midodrine, as appropriate, alongside thromboprophylaxis guided by risk assessment. The management of neurological/psychiatric clinical features require cognitive rehabilitation, graded activity pacing, and sleep optimization, also psychotherapy or pharmacotherapy management of mood disorders. Autonomic dysfunction can be addressed through hydration, salt supplementation, and compression garments. Endocrine / metabolic symptoms

3

THE RESPIRATORY SYSTEM

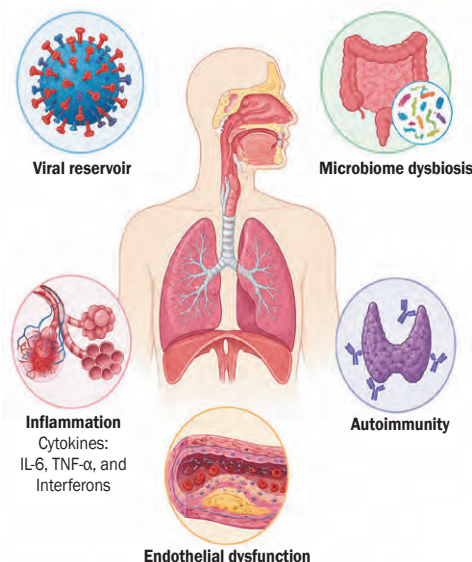


Fig. 3. Key biological mechanisms underlying long-COVID (original composition). Illustration showing viral reservoir formation, microbiome dysbiosis, autoimmunity, endothelial dysfunction, and cytokine-mediated inflammation.

warrant screening for thyroiditis, adrenal insufficiency, and new-onset diabetes, with lifestyle modifications and pharmacologic management for metabolic disturbances applied as needed. Autoimmune / inflammatory symptoms necessitate Immunomodulatory therapy in selected autoimmune flare cases, alongside longitudinal monitoring for evolving autoimmune diseases. Telogen effluvium a dermatological complication is typically self-limiting, usually most patients experience spontaneous hair regrowth within 6–12 months [8,44].

To support recovery, patients should prioritize nutritional optimization by ensuring sufficient intake of essential minerals like iron and zinc, alongside vitamin D. Should these supportive measures fail to address hair loss, clinical options such as minoxidil or laser therapy remain viable alternatives. From a hematological perspective, it is vital to screen for ongoing clotting issues and micro-pathologies, utilizing D-dimer tests and imaging to determine if long-term anticoagulation is necessary for at-risk patients. Lastly, physical rehabilitation must be approached with caution; while graded exercise is beneficial, it must be carefully paced to avoid the debilitating effects of post-exertional malaise [8,57].

Also, occupational therapy strategies should be considered to aid patients adapt to work demands and daily tasks. It is also important to address emotional and mental stress burden through psychological support like cognitive behavioural therapy or peer support groups. Ongoing surveillance for post-COVID organ dysfunction is recommended for at least 12 months, and participation in patient registries or clinical trials remains essential to advancing knowledge and improving management outcomes [58].

Conclusions

1. Post-COVID-19 multisystemic lesions are mediated by complex pathological mechanisms such as alteration, inflammation, dysregeneration, immunopathology, and microvascular dysfunction. Organ-specific consequences include pulmonary persistent inflammation and progressive fibrosis; cardiac myocarditis and arrhythmia; neurological symptoms like “brain fog”, headache, and anosmia; and endocrine disorders, including diabetes mellitus, subacute and autoimmune thyroiditis, hypothyroidism, and adrenal insufficiency, alongside various autoimmune conditions, dermatitis, and alopecia.

2. The pathogenesis of post-COVID syndrome and long-COVID involves the synergistic interplay of multiple factors: the persistence of viral reservoirs in target organs; chronic immune and cytokine dysregulation leading to autoimmune responses; autonomic dysfunction; systemic endothelial damage within the microcirculatory bed; and mitochondrial dysfunction. Furthermore, the consequences of prolonged SARS-CoV-2 therapy and the subsequent development of medication-induced pathologies contribute significantly to the clinical progression.

3. Prolonged therapy for long-COVID patients carries the risk of iatrogenic complications: antiarrhythmic administration in the context of post-COVID pulmonary fibrosis heightens pulmonary toxicity, and glucocorticoid use is associated with new-onset metabolic disturbances, such as steroid-induced diabetes and insulin resistance. Additionally, patients with a prothrombotic state face a persistently high risk of thromboembolic events. The fact that the mechanisms of post-COVID conditions are not yet fully elucidated continues to complicate both therapeutic strategies and preventive measures.

Future perspectives. The generalization of published results of already conducted studies on post-COVID pathologies allows us to suggest some directions for future research. In particular, studies involving the creation of global patient registries are promising for investigating the relationship between long-COVID and pre-existing chronic diseases. Of special interest is the experimental modelling of such situations in laboratory animals, with a detailed study of the mechanisms of the onset and progression of organ damage after recovery from COVID. Ultimately, overcoming the gap between understanding mechanisms and clinical application will be key to improving treatment outcomes of post-COVID conditions. Early treatment, applied immediately after recovery from COVID, can be especially promising, in a sense with a preventive purpose, specifically regarding post-COVID pathological conditions and diseases. Research on identifying biomarkers of post-COVID pathological conditions may help in patient risk stratification, in developing personalized treatment strategies, and in predicting recovery patterns.

AI statement

During the literature search and screening phase, generative artificial intelligence (AI) tools were utilized in strict accordance with the boundaries set by the GAIDeT Taxonomy (2025). Specifically, ChatGPT v5 (OpenAI) and Gemini (Google) were employed to identify relevant thematic clusters, summarize high-volume text, and assist with translation quality assessment, stylistic refinement, and copyediting

of the manuscript. Exclusively the authors performed the final selection, critical evaluation of all cited sources, and validation of the academic English translation.

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