Post-COVID-19 Tissue Remodeling and Multiorgan Damage: Pathogenetic Mechanisms, Structural Alterations, and Long-Term Clinical Consequences of SARS-CoV-2 Infection

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Abstract. Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is primarily recognized as an acute respiratory infection; however, accumulated evidence demonstrates that its biological effects extend far beyond the respiratory tract. Materials and Methods. A narrative analytical review of published scientific literature on post-COVID-19 tissue injury was performed. Particular attention was given to studies addressing persistent inflammation, viral persistence, endothelial and microvascular injury, fibrotic remodeling, skeletal muscle pathology, and multiorgan involvement. Publications from peer-reviewed journals and authoritative international sources were evaluated with emphasis on pulmonary, cardiovascular, renal, muscular, neurological, and vascular changes. Results. Post-COVID-19 tissue pathology appears to result from several interacting mechanisms, including residual injury from acute infection, dysregulated immune activation, endothelial damage, microcirculatory impairment, persistent or residual viral material in selected tissues, oxidative stress, mitochondrial dysfunction, and profibrotic signaling. Pulmonary interstitial abnormalities and fibrosis are particularly evident after severe disease, whereas endothelial and microvascular abnormalities may contribute to multisystem symptoms. Skeletal muscle abnormalities, inflammatory changes, impaired energy metabolism, and reduced exercise tolerance have also been reported. Persistent structural damage does not occur uniformly in all patients, and the extent of tissue injury depends on acute disease severity, pre-existing disorders, age, immunological response, and other host-related factors. Conclusion. SARS-CoV-2 infection may produce prolonged structural and functional changes in multiple tissues. Post-COVID-19 complications should therefore be considered a multisystem pathophysiological process rather than exclusively a respiratory sequela. Evaluation of tissue remodeling, endothelial dysfunction, inflammatory activation, and fibrosis may improve understanding of persistent symptoms and support individualized follow-up strategies.
Keywords: SARS-CoV-2, COVID-19, post-COVID-19 condition, long COVID, tissue damage, inflammation, fibrosis, endothelial dysfunction, microcirculation, pulmonary fibrosis, skeletal muscle, multiorgan injury.

Introduction.

The COVID-19 pandemic fundamentally changed the understanding of systemic viral infections. Although SARS-CoV-2 initially attracted attention because of its ability to produce viral pneumonia and acute respiratory distress syndrome, subsequent clinical and experimental observations demonstrated that COVID-19 may affect nearly every major organ system. The consequences of infection are determined not only by direct viral effects but also by an excessive or dysregulated host immune

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response, endothelial injury, coagulation abnormalities, hypoxia, oxidative stress, and disturbances of tissue repair.[1][2]

Most individuals recover from acute COVID-19 without major long-term structural complications. Nevertheless, a clinically important subgroup experiences persistent or newly developing symptoms after the acute infection. According to the World Health Organization, post-COVID-19 condition may include fatigue, dyspnea, cognitive impairment, muscle and joint pain, sleep disorders, and numerous other manifestations affecting daily functioning. WHO currently notes that the estimated proportion developing post-COVID-19 condition is lower than early-pandemic estimates but remains clinically significant.[3][4]

At the tissue level, the development of persistent symptoms appears to involve several overlapping pathological processes. A major contemporary hypothesis proposes that long-term manifestations can arise from persistence of viral antigens or reservoirs, altered innate and adaptive immune responses, autoimmunity, reactivation of latent viruses, endothelial dysfunction, abnormal coagulation, autonomic disturbances, and persistent organ injury.

Histopathological and molecular investigations have also demonstrated that SARS-CoV-2 can affect extrapulmonary tissues. Autopsy-based research has detected viral material in multiple organs, including respiratory and non-respiratory tissues, although such findings—especially from patients who died with severe disease—cannot automatically be generalized to all patients with long COVID. [5][6]

The clinical importance of tissue remodeling is particularly evident in the lungs, cardiovascular system, kidneys, skeletal muscles, nervous system, and vascular endothelium. Persistent structural abnormalities can contribute to reduced organ reserve, impaired oxygen delivery, exercise intolerance, chronic fatigue, shortness of breath, pain, and reduced quality of life.[7][8]

Aim of the study

The aim of this study was to analyze the major post-COVID-19 tissue complications, characterize their pathogenetic mechanisms, and summarize the structural and functional changes affecting major organs after SARS-CoV-2 infection.

Materials and Methods

This work was designed as a narrative analytical review structured according to the general IMRD model. Scientific publications concerning tissue and organ alterations after acute SARS-CoV-2 infection were evaluated.

The literature assessment focused on the following major domains: pulmonary tissue remodeling, cardiovascular and myocardial alterations, endothelial and microvascular abnormalities, kidney injury, skeletal muscle pathology, neurological tissue involvement, systemic inflammation, oxidative stress, and fibrotic processes.[9][10]

Priority was given to peer-reviewed studies and reviews describing histological, radiological, molecular, biochemical, and functional abnormalities after COVID-19. Publications from authoritative international health organizations were additionally used to define post-COVID-19 condition and its clinical relevance.[11][12]

The principal pathogenetic mechanisms evaluated included persistent inflammatory activation, endothelial dysfunction, immune dysregulation, microvascular thrombosis, tissue hypoxia, mitochondrial dysfunction, extracellular matrix deposition, fibroblast activation, and potential persistence of viral components.

Because this review did not involve primary patient recruitment or experimental intervention, no original numerical clinical dataset was generated. The findings presented below therefore represent a structured synthesis of published evidence rather than newly collected patient outcomes.

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Results

1. General mechanisms of post-COVID-19 tissue injury

Post-COVID-19 tissue complications appear to develop through a combination of direct and indirect biological mechanisms. During acute infection, epithelial cells, endothelial cells, immune cells, and surrounding stromal structures may undergo inflammatory or hypoxic injury. In severe disease, this process can be amplified by systemic cytokine activation, microvascular thrombosis, prolonged immobilization, intensive-care-related complications, and multiorgan dysfunction.

After viral clearance from the respiratory tract, tissue recovery may remain incomplete. In some individuals, persistent inflammatory signaling, endothelial dysfunction, altered immune responses, or residual viral material may sustain pathological processes beyond the acute phase. Contemporary reviews emphasize that long COVID is heterogeneous and probably does not result from one universal mechanism.

Table 1. Major pathogenetic mechanisms contributing to post-COVID-19 tissue complications

Pathogenetic mechanism	Main tissue effect	Possible clinical consequence
Persistent inflammation	Cellular injury and delayed repair	Fatigue, pain, organ dysfunction
Endothelial dysfunction	Impaired vasodilation and microcirculation	Dyspnea, exercise intolerance
Microvascular coagulation abnormalities	Reduced tissue perfusion	Hypoxia-related symptoms
Fibroblast activation	Extracellular matrix accumulation	Fibrosis and tissue stiffness
Oxidative stress	Membrane and mitochondrial injury	Reduced cellular energy production
Immune dysregulation	Chronic inflammatory signaling	Multisystem symptoms
Possible viral persistence	Continued antigenic stimulation	Persistent immune activation
Mitochondrial dysfunction	Reduced ATP generation	Muscle weakness and fatigue

2. Pulmonary tissue alterations

The lungs remain among the most extensively studied organs after COVID-19. Severe SARS-CoV-2 infection can cause diffuse alveolar injury, inflammatory exudation, endothelial damage, microthrombi, and disruption of the alveolar–capillary barrier.

During recovery, normal tissue repair involves elimination of inflammatory debris and restoration of alveolar architecture. In some patients, however, repair may become dysregulated and promote fibroblast activation, collagen deposition, and persistent interstitial abnormalities.

Post-COVID imaging studies have demonstrated residual ground-glass opacities, reticular changes, parenchymal bands, traction bronchiectasis, and fibrotic-like abnormalities, particularly among individuals previously hospitalized with severe pneumonia.

A review of post-COVID interstitial lung abnormalities reported that up to approximately 30% of previously hospitalized patients may show persistent interstitial abnormalities during follow-up, although many abnormalities improve with time. Modeling within that literature suggested that irreversible fibrotic features may occur in a smaller subset.

At the molecular level, prolonged activation of transforming growth factor-beta signaling, fibroblast proliferation, myofibroblast differentiation, and excessive extracellular matrix production may contribute to fibrotic remodeling.

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These changes can reduce pulmonary compliance and impair diffusion capacity, leading to persistent dyspnea, reduced exercise tolerance, and decreased oxygen-transfer efficiency.[13]

3. Vascular and endothelial complications

The vascular endothelium plays a central role in regulation of blood flow, coagulation, inflammatory signaling, and tissue oxygen delivery. SARS-CoV-2-associated inflammation can disrupt these functions.

Endothelial activation may increase vascular permeability, leukocyte adhesion, platelet activation, and procoagulant activity. Even after resolution of the acute illness, some studies have described persistent markers of endothelial dysfunction and altered coagulation.

Abnormal microvascular perfusion may theoretically contribute to symptoms involving multiple organs because adequate tissue oxygenation depends on intact capillary circulation.

Evidence on persistent “microclots” is still evolving, and their precise diagnostic and causal significance in long COVID has not been fully established. Nonetheless, abnormal coagulation, platelet activation, and endothelial dysfunction remain active areas of investigation.[14]

4. Myocardial and cardiovascular tissue changes

Cardiovascular involvement during acute COVID-19 may include myocardial injury, myocarditis-like inflammatory changes, microvascular dysfunction, thromboembolic complications, and stress-related myocardial damage.

In the post-acute period, some patients demonstrate persistent palpitations, chest discomfort, reduced exercise tolerance, or autonomic symptoms. Structural cardiac injury, however, is not present in all symptomatic individuals.

Possible mechanisms include residual myocardial inflammation, endothelial dysfunction, altered autonomic control, microvascular impairment, and systemic inflammatory signaling.

Fibrotic myocardial remodeling, when present after substantial myocardial injury, may alter ventricular relaxation, electrical conduction, and contractile reserve. Therefore, cardiac symptoms after COVID-19 require differential diagnosis rather than automatic attribution to one specific post-viral mechanism.

5. Skeletal muscle abnormalities

Skeletal muscle is increasingly recognized as an important target of post-COVID pathophysiology. Persistent muscle weakness, myalgia, exercise intolerance, and post-exertional symptom exacerbation are frequently described in long COVID.

Mechanisms may include systemic inflammation, physical deconditioning, microvascular impairment, mitochondrial dysfunction, altered substrate utilization, denervation, and direct consequences of critical illness.

A 2024 muscle-biopsy study of individuals with long COVID and post-exertional malaise reported skeletal muscle abnormalities and further pathological changes following exercise. These findings support the possibility that, in at least some patients, post-exertional symptoms have measurable biological correlates rather than representing simple physical inactivity alone.

Mitochondrial abnormalities may decrease oxidative phosphorylation and ATP availability, producing early fatigue during physical activity. Impaired microvascular oxygen delivery may further limit muscular performance.

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Table 2. Major post-COVID tissue alterations according to organ system

Organ/tissue	Main reported alterations	Potential consequences
Lungs	Interstitial abnormalities, fibrotic-like remodeling, alveolar injury	Dyspnea, impaired diffusion
Vascular endothelium	Endothelial activation and dysfunction	Reduced microvascular perfusion
Heart	Inflammatory or ischemic injury, possible remodeling	Palpitations, reduced cardiac reserve
Skeletal muscle	Mitochondrial and structural abnormalities	Weakness, exercise intolerance
Kidneys	Tubular and microvascular injury	Reduced renal functional reserve
Nervous system	Neuroinflammatory and vascular alterations	Cognitive and neurological symptoms
Liver	Inflammatory and metabolic injury	Altered biochemical function
Connective tissue	Excess extracellular matrix deposition	Fibrotic remodeling

6. Renal tissue complications

The kidneys may be affected during acute COVID-19 through hemodynamic instability, inflammation, endothelial injury, microthrombosis, tubular damage, nephrotoxic exposure, and systemic hypoxia.

Acute kidney injury during severe COVID-19 is particularly relevant because incomplete renal recovery may contribute to subsequent chronic kidney disease or accelerated decline of pre-existing kidney dysfunction.

Histopathological studies have described acute tubular injury as one of the major renal findings in severe COVID-19. Endothelial and microcirculatory abnormalities may additionally impair renal perfusion.

The long-term renal consequences are heterogeneous. Patients with severe acute kidney injury, diabetes, hypertension, pre-existing chronic kidney disease, or advanced age may require closer monitoring of serum creatinine, estimated glomerular filtration rate, and urinary protein excretion.

7. Nervous tissue and neurovascular alterations

Neurological manifestations of post-COVID-19 condition include cognitive dysfunction, impaired concentration, headaches, sleep disturbances, sensory abnormalities, dysautonomia, and fatigue.

Potential mechanisms include neuroinflammation, blood–brain barrier dysfunction, microvascular abnormalities, autonomic nervous system disturbance, immune-mediated injury, and systemic metabolic changes.

Autopsy research has detected SARS-CoV-2 material in multiple tissues, including the central nervous system, particularly in severe fatal cases. However, such evidence does not establish that ongoing viral replication in the brain is responsible for all neurological long-COVID symptoms.

Persistent activation of glial cells and altered neuroimmune communication are among the mechanisms currently being investigated.

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8. Fibrosis as a common pathway of chronic tissue remodeling

Fibrosis represents one of the most important potential long-term consequences of tissue injury. It occurs when normal wound-healing mechanisms become excessive or persistent.

Following tissue damage, cytokines and growth factors activate fibroblasts. These cells differentiate into myofibroblasts and produce extracellular matrix proteins, particularly collagen and fibronectin. If regulatory mechanisms fail to terminate this process, normal tissue architecture may be progressively replaced by fibrotic tissue.

The lung provides the clearest clinical example of post-COVID fibrotic remodeling, particularly after severe pneumonia and acute respiratory distress syndrome. The effectiveness of routine antifibrotic therapy for post-COVID pulmonary fibrosis remains uncertain, and systematic reviews have emphasized that available evidence is not yet sufficient to support indiscriminate use. [15]

Discussion

The results of the reviewed literature indicate that post-COVID-19 complications should be considered within the framework of a multisystem tissue disorder. Although pulmonary damage is clinically prominent, the pathophysiological process can extend to vascular, cardiac, renal, muscular, and neurological tissues.

One of the central features connecting these organ systems is endothelial dysfunction. Endothelial cells regulate tissue perfusion, coagulation, leukocyte migration, and vascular tone. Persistent endothelial abnormalities may therefore create a common pathway linking systemic inflammation, impaired oxygen delivery, and organ dysfunction.

A second important mechanism is immune dysregulation. Studies summarized in major reviews have reported alterations in T-cell populations, B-cell activity, interferon signaling, monocyte phenotypes, and inflammatory mediators in subsets of patients with long COVID.

Another biologically plausible mechanism is persistence of viral components in selected anatomical compartments. Autopsy investigations demonstrated broad tissue distribution of SARS-CoV-2 during severe infection and persistence of viral material for extended periods in some cases. These observations support further investigation of viral persistence but do not mean that persistent virus is present in every patient with post-COVID-19 symptoms.

Fibrosis represents the structural endpoint of prolonged tissue injury in some organs. Following inflammatory damage, excessive activation of fibroblasts and deposition of extracellular matrix can reduce normal tissue elasticity and functional capacity. This mechanism is particularly relevant to post-COVID pulmonary disease.

Skeletal muscle pathology is also clinically important because fatigue and exercise intolerance are among the most disabling post-COVID manifestations. Recent muscle studies suggest that altered muscle bioenergetics, capillary function, and structural changes may contribute to persistent symptoms in some patients.

At the same time, an important limitation of post-COVID research is heterogeneity. Patients differ substantially in age, vaccination status, viral variant, acute disease severity, comorbidities, treatment exposure, and time since infection. Therefore, structural abnormalities described in hospitalized or critically ill cohorts should not automatically be extrapolated to all individuals after SARS-CoV-2 infection.

Another methodological problem is the distinction between tissue damage caused directly by SARS-CoV-2 and damage resulting from critical illness, prolonged mechanical ventilation, hypoxia, thromboembolism, secondary infection, or pre-existing disease. Future prospective investigations should therefore include appropriately matched control groups and longitudinal assessments before and after infection whenever possible.

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Conclusion

Post-COVID-19 complications may involve persistent structural, metabolic, vascular, and inflammatory alterations in multiple tissues. The lungs, vascular endothelium, heart, kidneys, skeletal muscles, and nervous system represent major sites of potential post-infectious dysfunction.

The principal mechanisms include prolonged inflammatory activation, endothelial dysfunction, microcirculatory disturbances, immune dysregulation, oxidative stress, mitochondrial impairment, profibrotic signaling, and, in selected patients, possible persistence of viral components.

Pulmonary interstitial abnormalities and fibrotic remodeling are more commonly documented after severe COVID-19, whereas endothelial and metabolic disturbances may contribute to persistent symptoms even in patients without major residual radiological changes. Current evidence therefore supports a personalized, organ-oriented approach to patients with persistent symptoms rather than assuming a single universal pathological mechanism.

Further prospective clinical, histological, molecular, and imaging studies are required to identify reliable biomarkers of post-COVID tissue injury, distinguish reversible abnormalities from irreversible remodeling, and determine which patients may benefit from targeted anti-inflammatory, vascular, metabolic, rehabilitative, or antifibrotic interventions.

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