



(REVIEW ARTICLE)



## Extra-pulmonary manifestations of COVID-19: A comprehensive review

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### Abstract

The COVID-19 pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has predominantly been recognized for its respiratory impact. However, as the pandemic has progressed, it has become evident that SARS-CoV-2 affects multiple organ systems beyond the lungs, resulting in a wide array of extra-pulmonary manifestations. These manifestations encompass cardiovascular, neurological, gastrointestinal, hepatic, renal, dermatological, hematological, endocrine, musculoskeletal, ocular, immunological, and psychiatric complications. This review aims to provide a comprehensive understanding of these extra-pulmonary manifestations, highlighting their clinical significance, underlying mechanisms, and implications for patient management. Recognizing these manifestations is critical for improving patient outcomes and informing ongoing research and therapeutic strategies.

**Keywords:** Chest; Bone; Muscle; COVID-19; Abdomen

### 1. Introduction

COVID-19 emerged as a significant global health crisis in late 2019, spreading rapidly and leading to high morbidity and mortality worldwide (1,2). While the respiratory system is the primary target of SARS-CoV-2, manifesting in symptoms such as cough, dyspnea, and acute respiratory distress syndrome (ARDS), the virus's impact extends far beyond the lungs. Early in the pandemic, it became clear that SARS-CoV-2 could lead to complications in multiple organ systems, including the cardiovascular, neurological, gastrointestinal, and renal systems, among others (3). These extra-pulmonary manifestations have been linked to increased morbidity and mortality, as well as prolonged recovery times. This paper seeks to provide an in-depth review of these manifestations, exploring their clinical presentations, underlying pathophysiology, and management strategies. Additionally, understanding these extra-pulmonary effects is vital for guiding public health responses and therapeutic interventions as the pandemic continues to evolve (4).

### 2. Cardiovascular Manifestations

COVID-19 has been associated with a spectrum of cardiovascular complications that significantly impact patient outcomes. Among the most concerning are myocardial injury, myocarditis, pericarditis, arrhythmias, and heart failure. The pathophysiology of these manifestations is multifactorial, involving direct viral invasion of cardiomyocytes, systemic inflammation, and the hypercoagulable state induced by the virus. Myocardial injury, often indicated by elevated cardiac biomarkers such as troponin, has been observed in a substantial proportion of hospitalized COVID-19 patients. This injury may be a consequence of direct viral invasion, as SARS-CoV-2 can bind to angiotensin-converting enzyme 2 (ACE2) receptors, which are highly expressed in cardiac tissue (5).

Myocarditis, an inflammation of the heart muscle, can lead to arrhythmias and heart failure, significantly worsening the prognosis of COVID-19 patients. The inflammatory response to SARS-CoV-2, characterized by a cytokine storm, further exacerbates cardiovascular conditions by contributing to vascular inflammation and endothelial dysfunction. This, in

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turn, increases the risk of acute coronary syndromes and thromboembolic events, including pulmonary embolism and stroke. The hypercoagulable state observed in COVID-19 is attributed to a combination of factors, including endothelial injury, platelet activation, and elevated levels of pro-inflammatory cytokines, which collectively increase the risk of venous thromboembolism (6).

Managing cardiovascular complications in COVID-19 patients requires a multidisciplinary approach. Anticoagulation therapy is often recommended to mitigate the risk of thromboembolic events, particularly in patients with elevated D-dimer levels. In cases of myocarditis and heart failure, treatment may include the use of beta-blockers, ACE inhibitors, and immunosuppressive therapies, although the specific management strategies are still evolving. Cardiac monitoring is essential for detecting arrhythmias and managing heart failure, particularly in critically ill patients. The long-term cardiovascular impact of COVID-19 remains an area of active investigation, with ongoing studies aiming to understand the potential for chronic cardiovascular sequelae in survivors (7).

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### 3. Neurological Manifestations

Neurological complications of COVID-19 have been widely reported, with a broad spectrum of manifestations ranging from mild symptoms such as headache and anosmia (loss of smell) to severe conditions like encephalitis, stroke, and Guillain-Barré syndrome. The neurotropism of SARS-CoV-2 is believed to be mediated by its ability to invade the central nervous system (CNS) via multiple routes, including the olfactory nerve, hematogenous spread, and direct invasion of the blood-brain barrier (8).

Anosmia and ageusia (loss of taste) are among the most common early neurological symptoms and are often the first indicators of SARS-CoV-2 infection, even in the absence of respiratory symptoms. These symptoms are thought to result from viral invasion of the olfactory bulb, although the precise mechanisms remain under investigation. In more severe cases, COVID-19 has been associated with acute cerebrovascular events, including ischemic and hemorrhagic strokes. The hypercoagulable state induced by the virus, along with systemic inflammation and endothelial dysfunction, contributes to the increased risk of stroke in COVID-19 patients (9).

Encephalitis, an inflammation of the brain, has been reported in some COVID-19 patients and can present with altered mental status, seizures, and focal neurological deficits. Guillain-Barré syndrome, a rare autoimmune disorder characterized by ascending paralysis, has also been linked to COVID-19, with several case reports describing its occurrence following SARS-CoV-2 infection (10). The management of neurological manifestations in COVID-19 involves early recognition and treatment, with supportive care for stroke and encephalitis, and immunotherapy for Guillain-Barré syndrome. The long-term neurological impact of COVID-19 is a growing concern, with many patients reporting persistent symptoms such as cognitive impairment and fatigue, often referred to as "long COVID" or post-acute sequelae of SARS-CoV-2 infection (11).

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### 4. Gastrointestinal Manifestations

The gastrointestinal (GI) system is another key target of SARS-CoV-2, with a significant proportion of COVID-19 patients presenting with GI symptoms such as diarrhea, nausea, vomiting, and abdominal pain. These symptoms may appear alongside respiratory symptoms or, in some cases, may be the primary presentation of the disease (12). The GI tract is highly susceptible to SARS-CoV-2 due to the abundant expression of ACE2 receptors in the enterocytes of the small intestine. The binding of the virus to these receptors facilitates its entry into the GI cells, leading to direct viral damage and inflammation (13).

In addition to GI symptoms, COVID-19 has been associated with hepatic injury, as evidenced by elevated liver enzymes in some patients. The mechanisms underlying hepatic injury in COVID-19 are multifactorial, including direct viral invasion of hepatocytes, immune-mediated damage, and drug-induced liver injury from medications used to treat COVID-19. Hepatic dysfunction may complicate the clinical course of COVID-19, particularly in patients with pre-existing liver conditions, such as cirrhosis or non-alcoholic fatty liver disease (NAFLD) (14).

The management of GI and hepatic manifestations in COVID-19 involves supportive care, with a focus on maintaining hydration and electrolyte balance. In severe cases, particularly in patients with hepatic dysfunction, the use of antiviral and anti-inflammatory therapies may be considered. The potential for fecal-oral transmission of SARS-CoV-2, as suggested by the detection of viral RNA in stool samples, highlights the importance of infection control measures, particularly in healthcare settings. Further research is needed to fully understand the long-term impact of COVID-19 on

the GI and hepatic systems, including the potential for chronic liver disease and persistent GI symptoms in survivors (15).

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## 5. Renal Manifestations

Acute kidney injury (AKI) is a common complication in COVID-19, particularly in critically ill patients. The prevalence of AKI in COVID-19 varies widely depending on the severity of the disease and the patient population studied, with reports ranging from 0.5% in mild cases to over 50% in patients requiring intensive care. The pathophysiology of AKI in COVID-19 is complex and involves multiple mechanisms, including direct viral invasion of renal cells, systemic inflammation, and hemodynamic instability (16).

SARS-CoV-2 can infect renal tubular epithelial cells and podocytes, leading to acute tubular necrosis and proteinuria. The expression of ACE2 receptors in the kidneys facilitates the entry of the virus into renal cells, contributing to renal injury. In addition to direct viral damage, the systemic inflammatory response in COVID-19 can lead to cytokine-induced injury to the kidneys. Hemodynamic factors, such as hypotension and shock, further exacerbate renal dysfunction in critically ill patients (17).

Management of AKI in COVID-19 includes supportive care with careful fluid management, electrolyte monitoring, and, in severe cases, renal replacement therapy. Early identification and treatment of AKI are crucial for preventing long-term renal complications, which may include chronic kidney disease (CKD). The long-term renal outcomes in COVID-19 survivors remain uncertain, with ongoing studies investigating the potential for persistent renal dysfunction and the need for long-term monitoring of kidney function in these patients (18).

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## 6. Dermatological Manifestations

Cutaneous manifestations of COVID-19 have been increasingly recognized, with a variety of skin lesions reported in patients with the disease. These manifestations include maculopapular rashes, urticaria, vesicular eruptions, livedo reticularis, and chilblain-like lesions, often referred to as "COVID toes." The skin findings in COVID-19 are thought to result from a combination of direct viral invasion of the skin, immune-mediated responses, and the effects of systemic inflammation (19).

Maculopapular rashes, which resemble those seen in viral exanthems, are among the most commonly reported skin manifestations of COVID-19. Urticaria, or hives, has also been observed in some patients, often in association with other allergic-like symptoms. Vesicular eruptions, similar to those seen in varicella (chickenpox), have been reported in a subset of patients, typically appearing on the trunk and extremities. Livedo reticularis, a lace-like purplish discoloration of the skin, may indicate vascular involvement and has been associated with more severe disease (20).

Chilblain-like lesions, or "COVID toes," are characterized by erythematous, swollen, and sometimes painful lesions on the toes and fingers. These lesions have been observed primarily in younger patients and may reflect a localized inflammatory response to the virus. The management of dermatological manifestations in COVID-19 is generally supportive, with topical corticosteroids and antihistamines used to relieve symptoms (21). In some cases, skin manifestations may provide clues to the severity of the disease, warranting closer monitoring of the patient. The long-term dermatological effects of COVID-19 are not yet fully understood, and further research is needed to elucidate the potential for chronic skin conditions in survivors (22).

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## 7. Hematological Manifestations

Hematological abnormalities are common in COVID-19 and include lymphopenia, thrombocytopenia, elevated D-dimer levels, and a hypercoagulable state. Lymphopenia, or a reduction in the number of lymphocytes, is a characteristic finding in COVID-19 and has been associated with more severe disease and worse outcomes. The mechanisms underlying lymphopenia in COVID-19 are thought to involve direct viral infection of lymphocytes, as well as immune-mediated destruction of these cells (23).

Thrombocytopenia, or a low platelet count, has also been observed in COVID-19 patients, particularly in those with severe disease. The reduction in platelet count may be due to increased platelet destruction, decreased platelet production, or increased platelet consumption as a result of disseminated intravascular coagulation (DIC). Elevated D-dimer levels, which indicate increased fibrinolysis, are commonly seen in COVID-19 and have been associated with an increased risk of thromboembolic events (24).

The hypercoagulable state in COVID-19 is a major contributor to the increased risk of venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE). This hypercoagulable state is believed to result from a combination of endothelial injury, platelet activation, and increased levels of pro-inflammatory cytokines. The management of hematological abnormalities in COVID-19 includes the use of anticoagulation therapy, particularly in patients with elevated D-dimer levels or a high risk of thromboembolic events (25). The role of prophylactic anticoagulation in preventing VTE in COVID-19 patients is an area of active research, with ongoing studies aimed at determining the optimal anticoagulation strategies for these patients (26).

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## 8. Endocrine Manifestations

COVID-19 has been associated with several endocrine manifestations, including new-onset diabetes, thyroid dysfunction, and adrenal insufficiency. The virus's impact on the endocrine system is thought to be mediated by direct viral invasion of endocrine glands, as well as the systemic inflammatory response and the effects of critical illness (27).

New-onset diabetes has been reported in COVID-19 patients, with some studies suggesting that SARS-CoV-2 may trigger hyperglycemia and insulin resistance. The mechanisms underlying this association are not fully understood but may involve direct viral damage to pancreatic beta cells, which express ACE2 receptors, leading to impaired insulin secretion. Additionally, the systemic inflammatory response and the use of corticosteroids in the treatment of COVID-19 may contribute to the development of hyperglycemia and diabetes (28).

Thyroid dysfunction, including both hypothyroidism and hyperthyroidism, has also been observed in COVID-19 patients. The virus may directly infect thyroid cells, leading to thyroiditis and subsequent alterations in thyroid hormone levels. Adrenal insufficiency, although less commonly reported, may occur as a result of direct viral damage to the adrenal glands or as a consequence of the systemic inflammatory response (28).

The management of endocrine manifestations in COVID-19 involves the use of glucose-lowering therapies for hyperglycemia, hormone replacement therapy for thyroid dysfunction, and corticosteroid therapy for adrenal insufficiency. Early recognition and treatment of these endocrine abnormalities are crucial for preventing complications and improving patient outcomes. The long-term endocrine impact of COVID-19 is an area of ongoing research, with studies investigating the potential for persistent endocrine dysfunction in survivors (29).

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## 9. Musculoskeletal Manifestations

Musculoskeletal symptoms, including myalgia, arthralgia, and fatigue, are common in COVID-19 and can significantly impact patients' quality of life. These symptoms may persist for weeks to months after the acute phase of the disease, contributing to the phenomenon known as "long COVID" (30).

Myalgia, or muscle pain, is one of the most frequently reported symptoms of COVID-19 and may result from direct viral invasion of muscle tissue, systemic inflammation, or the effects of critical illness. Arthralgia, or joint pain, has also been observed in COVID-19 patients, with some reports suggesting that the virus may trigger an inflammatory response in the joints (31).

Fatigue is a hallmark of long COVID and can be debilitating for many patients. The mechanisms underlying post-COVID fatigue are not fully understood but may involve a combination of factors, including persistent inflammation, autonomic dysfunction, and the effects of prolonged bed rest during hospitalization (32).

The management of musculoskeletal symptoms in COVID-19 involves supportive care, including the use of analgesics, anti-inflammatory medications, and physical therapy. Early mobilization and rehabilitation are essential for preventing deconditioning and improving functional outcomes in COVID-19 patients. The long-term musculoskeletal impact of COVID-19 remains an area of active investigation, with ongoing studies aimed at understanding the potential for chronic pain and fatigue in survivors (33).

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## 10. Ocular Manifestations

Ocular involvement in COVID-19 has been increasingly recognized, with reports of conjunctivitis, uveitis, and retinal involvement in some patients. The ocular manifestations of COVID-19 may result from direct viral invasion of ocular tissues, as well as the effects of the systemic inflammatory response (34).

Conjunctivitis, or inflammation of the conjunctiva, is one of the most common ocular manifestations of COVID-19 and may present with symptoms such as redness, tearing, and photophobia. Uveitis, an inflammation of the uveal tract, has also been reported in some COVID-19 patients and may result in blurred vision and eye pain. Retinal involvement, including cotton wool spots and retinal hemorrhages, has been observed in a subset of patients, raising concerns about the potential for long-term ocular complications (35).

The management of ocular manifestations in COVID-19 involves supportive care, including the use of topical corticosteroids for conjunctivitis and uveitis. In cases of retinal involvement, close monitoring and referral to an ophthalmologist may be necessary. The potential for ocular transmission of SARS-CoV-2 highlights the importance of eye protection in healthcare settings, particularly for frontline workers. Further research is needed to understand the long-term ocular impact of COVID-19 and the potential for persistent visual disturbances in survivors (36).

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## 11. Immunological Manifestations

The immune response to SARS-CoV-2 plays a critical role in determining the severity and outcome of COVID-19. In some cases, the immune response can become dysregulated, leading to an excessive release of pro-inflammatory cytokines, commonly referred to as a "cytokine storm." This hyperinflammatory state is associated with multi-organ failure and increased mortality in severe COVID-19 cases (37).

In addition to the cytokine storm, COVID-19 has been linked to the development of autoimmune conditions, such as Guillain-Barré syndrome and multisystem inflammatory syndrome in children (MIS-C). MIS-C is a rare but severe condition that occurs in children and adolescents following SARS-CoV-2 infection, characterized by widespread inflammation and multi-organ involvement (38).

The management of immunological manifestations in COVID-19 involves the use of immunomodulatory agents, such as corticosteroids, tocilizumab (an IL-6 receptor antagonist), and intravenous immunoglobulin (IVIG), as well as supportive care for organ dysfunction. Early recognition and treatment of these immunological abnormalities are crucial for preventing complications and improving patient outcomes. Understanding the role of the immune system in COVID-19 is essential for the development of targeted therapies and vaccines, as well as for guiding public health interventions aimed at controlling the spread of the virus (39).

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## 12. Psychiatric Manifestations

The psychiatric impact of COVID-19 has been profound, with patients experiencing a range of mental health conditions, including anxiety, depression, post-traumatic stress disorder (PTSD), and delirium. The psychological stress of the pandemic, combined with the neuroinflammatory effects of SARS-CoV-2, may contribute to the development of these conditions. Additionally, the social isolation, economic impact, and uncertainty associated with the pandemic have exacerbated mental health issues in the general population (40).

Anxiety and depression are among the most common psychiatric manifestations of COVID-19, affecting both patients and the general population. The neuroinflammatory response to SARS-CoV-2, characterized by the release of pro-inflammatory cytokines, may contribute to the development of mood disorders. PTSD has also been reported in some COVID-19 patients, particularly those who have experienced severe illness or prolonged hospitalization. Delirium, a state of acute confusion and altered consciousness, has been observed in critically ill COVID-19 patients, particularly those requiring intensive care (41).

The management of psychiatric manifestations in COVID-19 involves a multidisciplinary approach, including psychotherapy, pharmacotherapy, and social support. Addressing the mental health consequences of the pandemic is crucial for overall public health, particularly as the long-term psychological impact of COVID-19 continues to unfold. Ongoing research is needed to understand the full extent of the psychiatric impact of COVID-19 and to develop effective interventions for preventing and treating mental health conditions associated with the pandemic (42).

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## 13. Conclusion

COVID-19 is a multisystem disease with significant extra-pulmonary manifestations that can affect virtually every organ system. The recognition of these manifestations is critical for the comprehensive management of COVID-19 patients, as they can contribute to increased morbidity and mortality. Understanding the underlying mechanisms of these manifestations, including the role of the immune response, direct viral invasion, and the hypercoagulable state, is

essential for guiding therapeutic strategies and improving patient outcomes. As the pandemic continues, ongoing research is needed to further elucidate the long-term impact of COVID-19 on extra-pulmonary systems and to develop targeted interventions for mitigating these effects.

The management of extra-pulmonary manifestations requires a multidisciplinary approach, with early recognition and treatment essential for preventing complications and improving outcomes. The potential for long-term sequelae, including chronic cardiovascular, neurological, and psychiatric conditions, underscores the importance of ongoing monitoring and support for COVID-19 survivors. As our understanding of the full spectrum of COVID-19's impact continues to evolve, it is crucial to remain vigilant in recognizing and addressing the diverse manifestations of this complex disease.

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## Compliance with ethical standards

### *Disclosure of conflict of interest*

No conflict of interest to be disclosed.

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