COVID-19: A Review on Clinical Manifestations

Hamidreza Hasani1, Shayan Mardi2, Ghazale Molaverdi3, Reihane Yousefi4, Omid Kohandel5, Haniyeh Fathi6, Nooshin Taherzadeh-Ghahfarokhi7, Parham Mardi2, Sara Shamsoddini2

1Department of Ophthalmology, Shahid Madani Hospital, Alborz University of Medical Sciences, Karaj, Iran
2Student Research Committee, Arak University of Medical Sciences, Arak, Iran
3Student Research Committee, Alborz University of Medical Sciences, Karaj, Iran
4Radiologist, Tehran University of Medical Sciences, Tehran, Iran
5Shams Eye and Skin Infirmary, Tehran, Iran

Abstract
SARS-CoV-2 primarily targets the respiratory system, resulting in pulmonary complications. However, recent research has indicated that COVID-19 can exert broader systemic effects on various organs. This comprehensive paper, which synthesizes studies up until now, centers on the clinical characteristics and symptoms of COVID-19. It furnishes a detailed overview of prevalent symptoms, highlighting fever, cough, and fatigue as the most frequently reported symptoms. Moreover, it delves into the diverse manifestations impacting not only the respiratory system but also the eyes, nervous system, musculoskeletal system, and skin. In addition to symptomatology, this study offers a succinct exploration of patients’ clinical presentations, potential complications, incubation period, and outcomes. This compilation of knowledge serves as an invaluable tool for medical practitioners, providing them with essential insights to enhance the accuracy of diagnosis and optimize the treatment strategies for COVID-19 patients. It bridges the gap between the pulmonary-centric focus of the virus and the broader multi-organ implications, thereby empowering healthcare professionals in their comprehensive care approach.

Keywords: COVID-19, Clinical manifestations, Patients’ outcomes, Vulnerable groups

Pulmonary Manifestations
Respiratory Tract Manifestations
Recent studies have provided insights into the upper respiratory symptoms of COVID-19, which include common manifestations observed during medical visits.1 These symptoms bear resemblance to the outbreaks of severe acute respiratory syndrome (SARS) in 2003 and Middle East respiratory syndrome (MERS) in 2012, suggesting possible similarities in transmission routes.2 Patients typically exhibit signs of an upper respiratory infection (URI) such as dry cough, dyspnea, expectoration, sore throat, rhinorrhea, nasal congestion, sneezing, and pharyngalgia at the onset of the illness.3 However, sputum production, sore throat, and hemoptysis occur less frequently (in less than 5% of patients),4,5 and there are no indications of shock, shortness of breath, or dehydration.6 Notably, atypical symptoms (e.g., loss of hearing) and cutaneous manifestations are more common in elderly and immunosuppressed patients, while only a small fraction of patients manifest pronounced upper respiratory tract symptoms. The average time from the onset of illness to dyspnea is approximately 5 days.6

Pneumonia
Novel coronavirus-infected pneumonia (NCIP) emerged in December 2019 in Wuhan, Hubei province. Among the diverse array of manifestations associated with novel COVID-19 infection, pneumonia emerges as a prominent clinical feature. In the early stages, patients commonly exhibit symptoms akin to severe acute respiratory infection, and in certain instances, this progression leads to acute respiratory failure and other grave complications.7 It is noteworthy, however, that a majority of reported not been classified as severe.7 Chest computed tomography (CT) scans of patients with NCIP frequently reveal basilar ground-glass opacities, sometimes accompanied by consolidation, in the majority of cases. Notably, additional studies have also identified the presence of the “air bronchogram sign” and, to a lesser extent, the “crazy-paving pattern” as distinctive CT findings in COVID-19 patients.8 Bilateral lung involvement is commonly observed, while unilateral findings are more suggestive of the onset of pneumonia or indicative of milder cases.9,10 The opacities often assume a rounded morphology although streaky patterns or a reverse halo sign may be present in some instances. These opacities are typically located in the peripheral regions without axial involvement. Although pneumonia cases frequently encompass multiple lobes, the right lower lobe seems to be the most frequently affected region.8

Mild Cases
In mild cases of COVID-19 infection, patients frequently report symptoms such as a dry tickly cough, along with
feelings of fatigue, nausea, and occasional vomiting. Notably, they do not experience shortness of breath or chest discomfort. Their vital signs typically fall within the normal range, and chest radiographs show no discernible abnormalities. Moreover, clinical assessments often reveal signs of dehydration manifested through dry mucosal surfaces. Furthermore, in certain instances, an intermittent fever may emerge approximately five days after the onset of the disease, occasionally accompanied by episodes of tachycardia.11

**Mild to Moderate Cases**

Patients experiencing mild to moderate NCIP typically display non-severe pneumonia. While their symptoms may bear resemblance to those seen in patients with URIs, clinical indicators of pneumonia also emerge in chest imaging. Additionally, in specific cases, patients’ oxygen saturation may drop significantly even though their ventilation remains within normal limits, plummeting to levels as low as 90%. In children with mild pneumonia, respiratory distress becomes noticeable, accompanied by symptoms such as coughing, rapid breathing, and the presence of moist rales during auscultation. The swift respiratory rate varies based on the child’s age and encompasses distinct ranges when adjustments are made for the influence of fever and crying on breath count.12

**Severe Cases**

In adolescents and adults, the diagnosis of severe pneumonia is established when febrile pneumonia is coupled with decreased arterial oxygen saturation, falling below the critical threshold of 90%, along with evident signs of severe respiratory distress or a respiratory rate surpassing 30 breaths per minute. Confirmatory measures include conducting chest imaging to meticulously rule out alternative complications. In pregnant women, severe infection can precipitate maternal hypoxemia, potentially culminating in scenarios of intrauterine asphyxia and preterm labor, underscoring the critical importance of timely and vigilant medical intervention.13

**Acute Respiratory Distress Syndrome**

Studies indicate that approximately 3.4% of hospitalized patients may develop acute respiratory distress syndrome (ARDS).5 This syndrome typically emerges about a week after the onset of the illness, either through the appearance of new respiratory symptoms or the exacerbation of existing chronic respiratory conditions. Regrettably, the onset of ARDS is associated with an unfavorable prognosis as it often progresses swiftly to multiple organ failure, ultimately leading to fatal outcomes in most cases.14

**Cardiovascular Manifestations**

Acute cardiac injury is a prevalent complication observed in patients with severe and critical illness, often presenting as arrhythmia, acute myocardial injury, and atrial fibrillation. Elevated levels of creatine kinase, as indicated by abnormal myocardial zymograms, are frequently observed.15 Individuals with COVID-19 infection may also experience occurrences of arrhythmias, shock, cardiomegaly, severe pericardial effusion, generalized edema, and notable ST-T changes, all of which necessitate echocardiography.16 Previous studies have emphasized an increased incidence of thrombosis in terminal COVID-19 patients, even among those receiving anticoagulation prophylaxis.17,18 Notably, in a study involving patients from Wuhan, roughly 7% of all COVID-19 fatalities were attributed to myocardial injury.19

**Renal Manifestations**

A study on kidney function in 59 patients infected by COVID-19 has been conducted recently. The results revealed that 63% (32/51) of the patients exhibited proteinuria, while 19% (11/59) and 27% (16/59) of the patients had elevated levels of plasma creatinine and blood urea nitrogen, respectively.20 Furthermore, all (27/27) patients showed radiographic abnormalities in the kidneys on CT scans. Consequently, the study concluded that renal impairment is a common occurrence in COVID-19 patients, which could be one of the major contributors to the illness caused by the virus, potentially leading to multi-organ failure and death.21 Conversely, there are studies that suggest COVID-19 infection does not significantly damage the kidneys. For instance, Wang et al reported the clinical characteristics of 138 hospitalized COVID-19-confirmed cases in a previous study.22 The data indicated that both blood urea nitrogen and creatinine levels were within the normal range. Similarly, Guan et al presented data on the clinical characteristics of 1099 confirmed COVID-19 patients from 552 hospitals in 31 provinces or provincial municipalities in another study.23 According to this study, only 12 out of 752 patients (1.6%) exhibited creatinine levels ≥ 133 µmol/L. These findings suggest that acute renal impairment is relatively uncommon in COVID-19, and COVID-19 infection does not typically cause significant azotemia or acute kidney injury.

**Gastrointestinal Manifestations**

**GI Tract**

Less common symptoms associated with COVID-19 infection encompass gastrointestinal (GI) tract issues such as diarrhea, nausea, and vomiting. In certain instances, atypical early symptoms may manifest as diarrhea and nausea one to two days before the onset of fever or dyspnea, prompting hospitalization. Furthermore, individuals with milder presentations may encounter episodes of loose bowel movements and abdominal discomfort starting around the fifth day after the disease onset.24 Interestingly, a small subset of patients paradoxically experience constipation as the clinical course progresses. In general,
abdominal pain and GI symptoms are more frequently noted in patients requiring admission to the intensive care unit (ICU) compared to those with milder infections. Noteworthy is the detection of COVID-19 in stool tests of infected patients who exhibit abdominal manifestations, suggesting an alternative route for viral dissemination. Though most patients exhibit mild symptoms and a favorable prognosis, the emergence of symptoms such as abdominal pain, dyspnea, and anorexia may assist clinicians in identifying patients with a less favorable prognosis.24

Hepatobiliary System
Studies have indicated that patients with elevated liver enzymes are more likely to exhibit a moderate to high degree of fever, and this occurrence is significantly more common in male patients compared to those with normal liver function. Liver damage has been found to be more prevalent in patients with severe pneumonia, suspected to be associated with an inflammatory factor storm. However, this explanation does not fully account for the observed liver damage in mild cases of the disease.25 In drawing parallels between the outbreaks of COVID-19 and SARS-CoV, it is noteworthy to refer to autopsy analyses of patients who succumbed to SARS. These analyses revealed not only severe lung and immune system damage but also fatty degeneration, central lobular necrosis, and the detection of SARS-CoV in the liver. Consequently, the evidence suggests that COVID-19 can indeed affect the hepatobiliary system.25

Ocular Manifestations
COVID-19 has been reported in some patients with conjunctivitis as the herald sign occasionally accompanied by anterior non-granulomatosis uveitis (Figure 1). If the eye is not protected while in proximity to the infected person (despite the use of a protective suit and N95 respirator) or if an infected hand makes contact with the eye, the virus can enter the host's ocular system, which manifests itself as conjunctivitis (Figure 1). Fever can subsequently appear, but the first symptom of these patients was conjunctivitis. Although conjunctivitis is poorly associated with SARS-CoV-2, its accompanying respiratory symptoms or a history of recent international travel or working in a healthcare system without eye protection (face mask or goggles) raises this possibility.26,27

Neurological Manifestations
In addition to its impact on the respiratory tract, COVID-19 has demonstrated the potential to infiltrate the nervous system. Olfactory and gustatory disorders have been extensively observed in hospitalized patients, with prevalent rates ranging from 33% to 80% and a higher incidence among females. Interestingly, anosmia can occasionally stand as the sole clinical manifestation of an uncomplicated COVID-19 infection.28 In cases of severe infection, the likelihood of neurological involvement rises, culminating in conditions such as acute cerebrovascular diseases, altered consciousness, dizziness, and headaches. When the nervous system is affected, the prognosis tends to be less favorable, and clinical conditions may deteriorate, resulting in an elevated mortality rate.29 It is hence imperative for healthcare professionals to remain vigilant in monitoring and addressing neurological symptoms in COVID-19 patients to optimize outcomes.

Musculoskeletal Manifestations
Muscle symptoms are a prevalent feature of COVID-19 infection, affecting approximately 36% of patients during their illness.30 These symptoms are believed to stem from skeletal muscle injury, a hypothesis supported by elevated creatine kinase levels observed in affected individuals. Notably, severe infections exhibit significantly higher levels of creatine kinase and lactate dehydrogenase compared to milder cases, suggesting a potential correlation between illness severity and muscle injury.30 While it has been suggested that the ACE2 receptor in skeletal muscle might play a role in this injury, it is intriguing to note that post-mortem examinations of SARS-CoV, which also utilizes ACE2 as a receptor, did not detect the virus in skeletal muscle. An alternative explanation could be an infection-mediated harmful immune response leading to nervous system abnormalities. Furthermore, the marked increase in pro-inflammatory cytokines in the serum may contribute to the damage in skeletal muscles.29 Accordingly, a comprehensive understanding of the mechanisms underlying muscle symptoms in COVID-19 is essential for delivering appropriate management and care for affected individuals. Further research is also imperative to unravel the precise pathways and processes involved in the manifestation of muscle-related symptoms in this viral infection.
Cutaneous Manifestations
The most frequently observed cutaneous manifestation of COVID-19 is reported to be maculopapular exanthem, appearing in approximately 36.1% of patients in a case series study. Additionally, other manifestations include papulovesicular rash, urticaria, and red-purple papules, and less common manifestations are livedo reticularis lesions and petechiae. These skin lesions typically affect the trunk and are less likely to be found on the hands and feet. Interestingly, the development of skin lesions often occurs before the onset of respiratory symptoms in patients, adding an intriguing aspect to the presentation of the disease. It is worth noting that there appears to be no clear correlation between the severity of the disease and the occurrence of skin lesions. Further research is thus needed to fully understand the underlying mechanisms and implications of these cutaneous manifestations of COVID-19. Careful monitoring of skin changes could potentially aid in the early detection and appropriate management of the illness.

Sepsis and Septic Shock
Life-threatening multi-organ failure in COVID-19 is characterized by a range of symptoms indicating the involvement of various systems in the body. These symptoms include decreased urine output, acidosis, or increased creatinine, indicating potential kidney dysfunction. Altered mental status signals central nervous system involvement. Furthermore, decreased blood pressure, cold extremities, low heart rate, and tachycardia suggest the involvement of the cardiovascular system, while low oxygen saturation and hard or fast breathing indicate respiratory system involvement. Alongside these symptoms, specific laboratory test results showing underlying coagulopathy, decreased platelets, high lactate, or elevated bilirubin indicate possible liver involvement, which may be indicative of sepsis in the patient if combined. Patients with a serum lactate level higher than 2 mmol/L and persistent hypotension despite volume resuscitation may progress to septic shock, which necessitates prompt and intensive medical intervention. Therefore, recognizing and promptly addressing these symptoms and laboratory findings are crucial for the early identification and management of sepsis in COVID-19 patients, ultimately aiding in improving patient outcomes.

Incubation Period and R0
Earlier investigations into COVID-19 suggested an average incubation period in China ranging from approximately 5 to a maximum of 7 days, as documented in previous research. However, more recent studies have presented divergent findings, with some reporting even longer incubation periods, reaching up to approximately 10 days. Given this variability in study results and the complexity of the disease, it is noteworthy that both the World Health Organization (WHO) and numerous countries have taken proactive measures since the early stages of the pandemic by recommending a quarantine period of 14 days for suspected cases (Table 1). Meanwhile, as evidence of human-to-human transmission of the disease emerged alongside the onset of the pandemic, several studies were conducted to determine the basic reproduction number (R0) of the COVID-19 virus. R0 “R naught” indicates how contagious COVID-19 is and depends on several factors such as contact rate, infectious period, and the mode of transmission. In the initial report by the WHO, the estimated R0 for COVID-19 ranged from 1.7 to 2.5. However, different research groups, considering various parameters and study populations, arrived at disparate estimates. For instance, a study conducted in January 2020 by Tang et al estimated an R0 of 6.49, while Shen et al reported a similar estimate of 6.49. In contrast, many studies reported a lower range for the R0 of COVID-19, falling between 1.95 and 3.58. The comprehensive findings of these studies are summarized in Table 2. These variations in incubation periods and R0 estimates underscore the complexity of the COVID-19 virus and the importance of ongoing research to refine our understanding of its epidemiological characteristics.

Disease Progression in Vulnerable Groups
Pregnant Cases
In general, pregnant women tend to follow a similar clinical course as the general population when infected...
with COVID-19. The majority of pregnant women experience only mild or moderate cold/flu-like symptoms. Recent case series data published by Chen et al4 and Zhu et al5 involving 18 women along with 19 infants infected in the third trimester of pregnancy with COVID-19 showed no laboratory evidence of viral transmission. These findings provide reassurance that the virus is unlikely to pass from mother to child during pregnancy. On the other hand, some studies have reported a significant increase in the incidence of hydatidiform moles with the onset of the pandemic, and an immune-based mechanism activated by COVID-19 has been suggested as a potential cause. Further research is needed to explore the potential relationship between the virus and hydatidiform moles and to better understand the underlying involved mechanisms. Nonetheless, it is essential to monitor and support pregnant women during this time to ensure their health and the well-being of their babies.

**Pediatric Cases**

In pediatric cases, COVID-19 can be manifested across a spectrum of clinical features, ranging from mild to severe presentations. While some children may experience a rapidly progressive form of the disease leading to respiratory failure, it is important to note that not all pediatric cases follow this pattern. To diagnose severe pneumonia in children experiencing difficulty breathing or persistent coughing, one of the following conditions should be met:

(A) Oxygen saturation drops to below or equals 93% (in premature infants, below 90%). Alternatively, the child exhibits signs such as grunting, central cyanosis, apnea, subcostal, intercostal, and suprasternal retractions (indicative of severe respiratory distress), nasal flaring, and other related symptoms.

(B) Pneumonia symptoms are presented with general dangerous signs, including systemic toxin syndromes, the infant's inability to breastfeed or drink, poor appetite, malaise, dehydration, consciousness disorders, restlessness, lethargy, anesthesia, or seizures.

(C) PaO2 levels fall below 60 mm Hg, while PaCO2 rises above 50 mm Hg.

(D) Additional pneumonia symptoms emerge such as chest indrawing or rapid breathing (for children under 2 months ≥ 60 breaths/minute, 2-11 months ≥ 50 breaths/minute, and 1-5 years ≥ 50 breaths/minute).

(E) Severe manifestations of the disease include coagulopathy, metabolic acidosis, rhabdomyolysis, persistent bleeding, myocardial injury, GI dysfunction, elevated liver enzymes, and septic shock.

The prompt identification and timely addressing of these severe symptoms in children are crucial for providing appropriate medical interventions. This proactive approach can significantly influence patient outcomes and contribute to their recovery.

**Intensive Care Unit and the Risk of Death**

Despite the belief that COVID-19 has a 5% ICU admission rate, several studies have reported a higher rate of 16% of positively tested individuals during the early days of the outbreak in Italy. The large infection rate in different populations has necessitated an increase in ICU surge capacity.5,24 The need for ICU admission and increased risk of death in patients have been associated with multiple factors, including comorbidities such as cardiovascular disease, diabetes, cerebrovascular disease, obesity (body mass index > 40), hypertension, smoking, and old age (median > 55 years). Other factors contributing to higher risk include refractory hypoxemia, lymphopenia, hemodynamic instability, hypercapnia, immunodeficiency, bacterial coinfection, decreased consciousness, and multilobar infiltration. In addition, the ABC-GOALScl scale is useful for predicting admission to ICU in COVID-19 patients over 60 years old.55 Patients with critical illness are more likely to experience multi-organ involvement and require ICU admissions as compared to those with mild symptoms. Among the common causes of death are cardiac arrest, severe bilateral pneumonia, acute respiratory ARDS, lymphopenia, and sepsis.39 These findings highlight the importance of risk stratification and targeted care for vulnerable populations to optimize patient outcomes in managing COVID-19 cases. In the respiratory ICU of COVID-19, superinfections were an independent mortality predictor. Therefore, regulatory infection control is extremely crucial to decrease the spread of multidrug-resistant organisms.56 Therefore, healthcare professionals should remain vigilant and consider these factors when determining the appropriate level of care for patients with COVID-19.

**Acknowledgments**

We thank Sepehr Aghajanian (MD) for comments that greatly improved the manuscript.

**Authors’ Contribution**

Data curation: Hamidreza Hasani.
Formal analysis: Hamidreza Hasani, Shayan Mardi.
Funding acquisition: No funding acquitted.
Investigation: Ghazale Molaverdi, Reihane Yousefi, Omid Kohandel.
Methodology: Hamidreza Hasani, Haniyeh Fathi.
Project administration: Hamidreza Hasani.
Resources: Nooshin Taherzadeh-ghahfarokhi, Parham Mardi, Sara Shamsoddini.
Software: Hamidreza Hasani, Shayan Mardi, Ghazale Molaverdi.
Supervision: Hamidreza Hasani.
Validation: Hamidreza Hasani, Reihane Yousefi.
Visualization: Parham Mardi, Sara Shamsoddini.
Writing—original draft: Hamidreza Hasani.
Writing—review & editing: Hamidreza Hasani.

**Competing Interests**

All authors declare no conflict of interests.
Consent for Publication
Not applicable.

Data Availability Statement
No data have been submitted to any open-access databases.
All data supporting the study are presented in the manuscript or available upon request.

Ethical Approval
Not applicable.

Funding
None.

References
Hasani et al


