# Clinical Features of SARS-CoV-2 Infection

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Ind J Car Dis Wom:2020;5:223–226

## Abstract

Viral diseases continue to emerge and represent a serious issue to public health. Since viral transmission occurs through respiratory droplets, most patients with coronavirus disease 2019 (COVID-19) predominantly have respiratory tract involvement. The clinical spectrum of COVID-19 ranges from asymptomatic to symptomatic with mild, moderate, and severe degrees of illnesses. There are no specific clinical features that can yet reliably distinguish COVID-19 from other viral respiratory infections. Unexplained worsening of underlying chronic illnesses and comorbidities should raise the suspicion of COVID-19. Beyond the life-threatening pulmonary complications of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the widespread organ-specific manifestations of COVID-19 are increasingly being appreciated. Given that angiotensin-converting enzyme 2, the entry receptor for the SARS-CoV-2, is expressed in multiple extrapulmonary tissues and that all might contribute to these extrapulmonary manifestations of COVID-19, here we review the pulmonary and extrapulmonary presentations for patients with COVID-19.

**Keywords**
- case
- cough
- COVID-19
- dyspnea
- respiratory
- viral

## Introduction

The group of cases of pneumonia seen in December 2019 in Wuhan, China, very rapidly became a "Public Health Emergency of International Concern" and then subsequently a worldwide pandemic as declared by the World Health Organization (WHO), engulfing the whole world.[1,2] The viral transmission occurs through respiratory route, through the formation of aerosols. The lung involvement is predominant but as the understanding of coronavirus disease 2019 (COVID-19) evolves, it is seen to involve various other organs. The main hypothesis was that there is high expression of angiotensin-converting enzyme 2 (ACE2) receptor, which are the main targets for viral entry.

## Case Definition

As per the WHO surveillance guidelines,[3] various case definitions have been proposed.

1. Confirmed case, with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms.
2. Probable case, when testing for the COVID-19 virus is inconclusive or for whom testing could not be performed for any reason.
3. Suspect case, when a patient has an acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath), has a history of travel to or residence in a location reporting community transmission of COVID-19 disease during the 14 days prior to symptom onset, or has been in contact with a confirmed or probable COVID-19 case in the last 14 days prior to symptom onset, or has severe acute respiratory illness with no alternative diagnosis.

## Clinical Characteristics

COVID-19 virus has an incubation period of ~14 days following exposure. The majority of the cases occur in ~4 to 5 days after exposure.[4] The clinical spectrum of COVID-19 ranges from asymptomatic to symptomatic. The illness is further classified as mild, moderate, and severe/critical in terms of degree of illness depending on the symptoms.[5]

**published online**
October 5, 2020

**DOI** https://doi.org/10.1055/s-0040-1717046.

- Asymptomatic infections have been well documented. The exact data on its prevalence are scanty.[6] The definition of "asymptomatic" is not uniform in literature as some have clinical and radiological abnormalities in spite of being asymptomatic. The classic examples of studies evaluating asymptomatic infections are (1) the outbreak on cruise ship where 58% of the 712 confirmed COVID-19 cases were asymptomatic at the time of diagnosis; 7 and (2) screening of all pregnant women at the time of delivery in New York, where 88% were asymptomatic.[8]
- Symptomatic COVID-19 patients have different presentations. Majority of infected people have mild to moderate disease and therefore, do not need hospitalization. The clinical symptoms include pyrexia, cough, and malaise. Other clinical symptoms include myalgias, diarrhea, sore throat, conjunctivitis, headache, loss of taste (ageusia) or smell (anosmia), a rash on skin, or bluish discoloration of fingers or toes.[5,9,10] The serious symptoms will include difficulty in breathing and chest pain. Atypical symptoms such as fatigue, reduced alertness, reduced mobility, loss of appetite, and delirium without fever are seen frequently in geriatric age group and those who are immune compromised.[11]
- Children usually report with milder symptoms.

The clinical manifestations can be further divided into pulmonary and extrapulmonary.

## Pulmonary Manifestations

The most common symptoms include fever, sore throat, and dry cough. Pneumonia appears to be the most frequent serious manifestation of the infection, characterized primarily by fever, cough, dyspnea, and bilateral infiltrates on chest imaging.[12,13] There are no specific clinical features that can yet reliably distinguish COVID-19 from other viral respiratory infections, although development of dyspnea several days after the onset of initial symptoms is suggestive.[14]

In a report from the Chinese Center for Disease Control and Prevention that included ~44,500 confirmed infections, mild infection (no or mild pneumonia) was reported in 81%, severe in 14%, and critical in 5% cases. The overall case fatality rate was 2.3%; no deaths were reported among noncritical cases.[5] Most of the fatal cases occurred with increasing age (>60 years) and underlying comorbidities such as diabetes mellitus, hypertension, cardiac disease, chronic lung disease, cerebrovascular disease, chronic liver and kidney diseases, immune suppression, and cancer.[15,16]

## Extrapulmonary Manifestations

### Gastrointestinal and Liver

Gastrointestinal (GI) symptoms were noted only in minority of patients; the presenting symptoms may be nausea and diarrhea, anorexia, vomiting, and pain abdomen.[17,18] In some patients, isolated GI symptoms may precede the respiratory symptoms. There is some evidence to suggest that GI symptoms may be associated with severe disease and poorer prognosis although a recent meta-analysis does not support this observation.[19] Hepatic involvement in COVID-19 is also not uncommon and is reflected by abnormal liver enzymes on biochemistry and development of acute hepatitis clinically. The GI and hepatic involvement in COVID-19 is postulated to be due to ACE2 receptor expression on intestinal cells, cholangiocytes, and hepatocytes.[20] For patients with an existing diagnosis of chronic GI or liver disease (e.g., Crohn's disease, ulcerative colitis, cirrhosis, autoimmune hepatitis), the clinician needs to be vary of disease flare due to superadded COVID-19 infection.[21]

### Cardiovascular System

In patients with coronavirus infection, cardiac involvement is demonstrated by a rise in specific markers of myocardial necrosis. Myocarditis, myocardial infarction, heart failure, and increased incidence of cardiac arrhythmias have also been reported.[22,23] The most likely causative hypotheses include myocardial damage related to hypoxia, cytokine storm, coagulation abnormalities, direct viral damage, or electrolyte imbalance. Also, many drugs used to treat COVID-19 may result in prolonged ventricular repolarization and hence arrhythmias.[24]

In severe cases of COVID-19, deep venous thrombosis and pulmonary embolism are seen, but the true prevalence remains unknown.[25]

### Kidney

Various renal abnormalities found in COVID-19 patients include proteinuria, hematuria, and elevated blood urea nitrogen and serum creatinine. Also, the mortality rate is higher in patients with COVID-19 with acute kidney injury.[26] The renal involvement is related to expression of ACE2 and dipeptidyl peptidase 4 on renal tubular cells, which are the binding receptors for SARS-CoV-2 infection.[27,28]

### Dermatology

Various dermatologic findings reported in patients with COVID-19 include erythematous rash, generalized urticaria, chicken-pox-like vesicles, exanthema, lymphocytic vasculitis, transient acantholytic dermatosis (Grover's disease), and livedo reticularis. Reddish-purple nodules on the distal digits (COVID toes) similar in appearance to pernio (chilblains) have also been described.[29] Skin lesions could possibly be related to virus, post viral immunological reaction, or consequences of use of drugs and disinfectants.[30]

### Central Nervous System

Like other coronaviruses, neurological involvement may occur through hematogenous or retrograde neuronal route.[31,32] The neurological symptoms include dizziness, headache, disturbed consciousness, febrile seizures, encephalitis, and cerebrovascular diseases. In some patients, hypogeusia and hyposmia have been reported. Paresthesia and skeletal muscle injury have also been reported.[33] The neurological involvement is confirmed by the presence of virus in cerebrospinal fluid and also brain tissue on autopsy.[34]

### Ocular

Ocular manifestations seen with COVID-19 include conjunctival hyperemia, chemosis, epiphora, and increased secretions.[35]

### Coagulation Abnormalities

The most common abnormalities are elevation of fibrinogen and D-dimer levels. The defect in coagulation parameters is in sync with rise in markers of inflammation (e.g., C-reactive protein). Unlike the pattern seen in classic disseminated intravascular coagulation (DIC) from bacterial sepsis or trauma, prolongation of the activated partial thromboplastin time and/or prothrombin time is not seen. Thrombocytopenia is mild (platelet count ~100 × $10^9$/L), and laboratory results supporting microangiopathy are uncommon. Rarely, patients with severe COVID-19 infection and multiorgan failure progress to a coagulopathy meeting criterion for overt DIC as per the International Society on Thrombosis and Haemostasis criteria.[36,37]

### Psychiatric Abnormalities

COVID-19 appears to be frequently associated with neuropsychiatric symptoms in the acute phase of the illness such as confusion, aggression, irritability, and impaired consciousness. In addition, COVID-19 may be associated with anxiety, impaired attention, depression, insomnia, irritability, memory impairment, and posttraumatic stress disorder (PTSD). Among patients with pre-existing psychiatric illness, COVID-19 may either exacerbate/flare the pre-existing symptoms or lead to development of new symptoms.[38,39]

Adverse psychological outcomes such as anger, anxiety, boredom, confusion, fear, depression, emotional exhaustion, frustration, irritability, and stress may be seen in individuals in quarantine. Other adverse outcomes include avoidance behaviors, detachment from others, subthreshold symptoms of alcohol use disorder and PTSD, excessive preoccupation with distressing somatic symptoms, and stigma, as well as domestic violence and suicidal ideation. These may stem from inconsistent messages and directives regarding public health measures, continuous media reporting, physical and social distancing, home confinement and quarantine, economic hardships, and insecurity.[40,41]

## Gender Variation

In terms of gender-based differences among patients with COVID-19, it has been observed that there is no difference in the males and females as far as disease prevalence is concerned. However, mortality is reportedly higher in males possibly due to immunological or gendered differences and behavioral differences such as smoking.[42,43]

## Conclusion

COVID-19 pandemic has affected the global health care in an unprecedented way. It is important to recognize the myriad presentations of the disease so as to suspect and isolate/quarantine the cases/contacts in time to prevent the spread of infection. Although the most common presenting features are the respiratory symptoms of cough and dyspnea, involvement of other organ systems is not uncommon and needs to be considered. Unexplained worsening of underlying chronic illnesses and comorbidities should raise the suspicion of COVID-19. Suspecting and identifying the cases/contacts early in the course of disease is the only way to limit the burden on already overwhelmed health care systems.

**Conflict of Interest**

None.

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