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# A Primer on COVID-19 for Clinicians: Clinical Manifestation and Natural Course

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## Abstract

**Context:** COVID-19 is a new pandemic in the world and data in the various aspect of this disease are evolving. In this review, the authors tried to cover different aspects of clinical manifestations and the natural course of the disease.

**Evidence acquisition:** For data gathering, the authors searched through MEDLINE, Cochrane library, google scholar and Scopus. The key phrases for search were "clinical presentation of COVID-19", "clinical features of COVID-19", "natural course of COVID-19", "neurologic manifestation of COVID-19", "cardiovascular manifestation of COVID-19" and "gastrointestinal manifestation of COVID-19".

**Results:** After screening of titles and abstracts, the authors finally enrolled 55 articles. Then the full texts of the selected articles were read carefully to determine eligibility and extracting relevant information.

**Conclusion:** The most common presentations of COVID-19 patients were fever, non-producing cough and dyspnea but a considerable amount of patients may seek heath care without these complaints. Asymptomatic patients and patients with only gastrointestinal and neurologic symptoms remain a significant challenge for medical practitioners.

**Key words:** COVID-19; Disease Progression; Symptom Assessment

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## CONTEXT

Primary information about COVID-19 was provided back in December 2019 when physicians in Wuhan, China, encountered patients with manifestations of this viral pneumonia for the first time [1]. The highly contagious nature of this new disease, which helps it spread easily in the society, has attracted the attention of regional and international health related organizations. On 11 March 2020 the World Health Organization (WHO) declared the disease as a worldwide problem and pandemic [2]. By 10 April 2020 more than 1.5 million people in the world were affected by this virus and COVID-19 was reported in most countries [3, 4]. The clinical manifestations of COVID-19 make up a spectrum; at one extreme there are asymptomatic cases, and at the other, there are patients with severe respiratory distress syndrome (SARS-CoV-2) and shock who finally die [4-6]. Total fatality rate differs around the world, ranging from 3.8% in China to 9% in Italy [2, 7, 8]. The center for disease control and prevention (CDC) of China categorized the disease manifestations as mild and moderate (none or mild pneumonia), severe (dyspnea, respiratory rate (RR) ≥30, oxygen saturation (Spo2) ≤93%, Pao2/Fio2 ≤300 or pulmonary infiltration ≥50% in 24-48 hours) and critical (respiratory compromise, septic shock, multiple organ failure) [9, 10]. In this review, the authors tried to cover different aspects of clinical manifestations and the natural course of the disease.

## EVIDENCE ACQUISITION

To extract evidence, the authors searched for articles in Medline, Google Scholar, Cochrane data base for systematic reviews and Scopus. The key words were "clinical presentation of COVID-19", "clinical features of COVID-19", "natural course of COVID-19", "neurologic manifestation of COVID-19", "cardiovascular manifestation of COVID-19" and "gastrointestinal manifestation of COVID-19". All types of articles, such as reviews, originals, letters, and etc., were included in the study. Online articles that were not peer-reviewed and accepted to a specific journal were excluded from the study. In the next stage, the researchers read titles and abstracts of search engine results and selected related articles to probe their main text for more details in. Finally, articles that consisted of

confirmed cases of COVID-19 based on reverse transcription polymerase chain reaction (RT-PCR) test and included data related to the main research subject were chosen for data extraction.

## RESULS

### *General Considerations*

In the early stages of disease outbreak, most patients were related to a seafood market; but later, a huge number of patients visited medical facilities with symptoms and signs of COVID-19 and positive RT-PCR in china and all over the world. These new surges of the disease indicated that the source of the prevalence should be human to human transmission of the disease [2, 6]. Respiratory droplets are the main source of direct infection transmission in communities but virus could survive on different surfaces for considerable times and transfer to the others indirectly [2]. Studies have proved virus shedding in feces and now fecal-oral transmission is deemed a potential source of infection. Currently, there is no evidence suggesting airborne transmission of COVID-19 [2]. The disease is more common in males and also critical cases are more frequent in males (67% vs 33%) [11-13]. Incubation period of this disease is about 5.1 days (2 to 14 days) and the mean age of the patients is 59 years old (36 hours to 92 years) [2, 12-14]. The most prevalent symptoms and signs are fever and chill, cough, dyspnea, fatigue or myalgia, sore throat, headache, diarrhea, nausea and vomiting, sputum production, rhinorrhea and hemoptysis, respectively [15-22]. Hypertension, diabetes, chronic respiratory disease and cardiovascular disease are comorbidities that were present in about 50% of the patients [9, 15, 16]. Age ≥60 years, high sequential organ failure assessment (SOFA) Score on admission, male gender, d-dimer ≥1 micromol/L, and presence of comorbid diseases and malignancies are prognostic factors for poor outcome among patients with COVID-19 [6, 17-19].

### *Constitutional symptoms*

Fever is the most prevalent constitutional symptom reported in various studies. The other symptoms in this category are Myalgia, fatigue, weakness [20-25].

### *Respiratory tract manifestations*

Respiratory manifestations include some features of upper respiratory tract involvement such as: sore throat, rhinorrhea and nasal congestion but in more server cases patients may complain of lower respiratory tract involvements that include cough, chest tightness, hemoptysis, dyspnea and severe air hunger that could finally lead to refractory pneumonia and SARS [18, 21-25]. Mo et al. defined refractory pneumonia in COVID-19 patients as continuing and unrevealing symptoms and hospital stay of more than 10 days. They showed that these patients were older and male and had more comorbidity. In laboratory evaluation these patients had a higher level of neutrophils in complete blood count (CBC), Lactate dehydrogenase (LDH), C-reactive protein (CRP), ferritin, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and lower level of albumin and platelets. Bilateral lung involvements were more common in these patients [18]. In 80.9% of patients the clinical course of the disease is mild to moderate and consists of varying degrees of constitutional symptoms plus some of the respiratory tract manifestations [7]. In 13.8% of patients the disease progresses to the severe form with prominent respiratory symptom such as: severe dyspnea, RR ≥30, Spo2 ≤93% and Pao2/Fio2 <300 and involvement of more than 50% of lung parenchyma in imaging modalities. Unfortunately, in about 5% of cases, disease progresses to the critical stage, which presents with multi-organ dysfunction, septic shock and respiratory compromise [6, 7]. Based on the results of Pao2/Fio2, acute respiratory distress syndrome (ARDS) is categorized as mild, moderate and severe (>100, 100-200, 200-300 respectively). In critical forms, patients' mortality rate increases to 49% [6].

### *Gastrointestinal manifestations*

Gastrointestinal (GI) symptoms could be the only manifestation in COVID-19 patients [26-29]. There are some reasons for manifestation of gastrointestinal symptoms in these patients: First, the virus invades human cells via angiotensin converting enzyme 2 (ACE2) receptors and these receptors exist in the liver and intestine. Second, inflammatory response to the virus may cause some intestinal damage and consequently make changes to bowel flora, which could be a possible explanation for GI symptoms [28, 29]. GI features of COVID-19 include anorexia, nausea and vomiting, diarrhea, GI bleeding and abdominal pain. Prevalence of GI symptoms varied in different in studies, ranging from 3% in primary studies to 79% in latter ones [29]. In the study conducted by Zhou et al., there was no correlation between GI symptoms and disease severity [27]; but in the other studies performed by Jin et al. [26] and Pan et al [28], GI symptoms were more common in severe and critical cases. Alimentary tract symptoms may be the first presenting problem or may evolve during admission and disease progression. GI symptoms, mostly anorexia and abdominal pain, were more

prevalent in intensive care unit (ICU) admitted patients [29]. Virus could be shed in the feces and probably infect the others via fecal-oral transmission. Studies show that fecal shedding may commence 2-5 days after positive respiratory tests and will continue to be positive a few days after negative respiratory test [26, 29]. Family clustering of disease increased in patients with GI symptoms [26]. Liver involvement and rise in AST and ALT were more common in COVID-19 patients with GI symptoms [26, 28, 29].

***Cardiovascular manifestations***

Cardiovascular diseases are common comorbidities in COVID-19 patients [30-36]. ICU admission rates and severe forms of disease are more frequent in patients with cardiovascular diseases such as hypertension and coronary artery disease. Similarly, risk of death due to COVID-19 is higher in these patients [33, 35]. In some cases of COVID-19, cardiac complaints such as palpitation and chest discomfort were the first reasons that brought the patients to a clinic [32]. Currently, there are a few hypotheses to explain the cardiac effects of COVID-19 on infected patients. One of them is direct cytotoxic effect of virus, secondary to entrance to cardiac cells after binding to ACE2. Binding of the virus to ACE2 leads to down regulation of this receptor, which could generate imbalance in renin angiotensin system and increase in the level of angiotensin 2. Increased level of angiotensin 2 is responsible for cardiac hypertrophy, diastolic dysfunction, and cardiac fibrosis [36]. In addition, hypoxia generated as a result of pulmonary involvement and ARDS may also lead to cardiac injury [31, 33]. Inflammatory cytokines released in the circulation due to cellular reaction to virus such as: CRP, IL-6, TNF- α and $IFN_{\gamma}$ are another possible mechanism of cardiac injuries [35]. Elevation of ST segment and chest discomfort as well as decline in ejection fraction have been reported in COVID-19 patients with normal coronary vessels in angiography, which improved with corticosteroid therapy. This this may indicate to inflammatory nature of the problem [33]. Electrolyte imbalance and adverse effects of antiviral drugs may lead to some degree of cardiac injury [31]. Cardiac injury, new electrocardiogram (ECG) and echocardiographic changes have been reported in 22% of ICU admitted patients but the overall rate of these involvements among all COVID-19 patients was 7.2% [33]. Elevated level of cardiac troponin I or T (cTnI, cTnT), as a sign of cardiac injury, and myocarditis have been reported in several studies [31, 34]. A considerable rise in cTnI has been reported in 8 to 12 % of COVID-19 patients [31]. A high level of these markers correlated with more severe forms of COVID-19 infection and higher mortality rate of the patients [30-36]. Mortality rate in patients with elevated level of cTnT and no history of cardiac disease was higher than patients with normal level of cTnT and previous history of cardiovascular disease [34]. Incidence of heart failure was 52% in patients that eventually died of COVID-19 infection but only 12% of the survivors showed signs of heart failure. Tachyarrhythmias and bradyarrhythmias were observed in these patients and were more prevalent in ICU admitted (44.4%) patients compared to non-ICU patients (8.9%) [31].

***Genitourinary manifestations***

Renal function abnormalities and acute kidney injury are common in patients with COVID-19. The mechanism of renal injury may be related to sepsis mediated inflammatory response or the direct toxic effect of virus on renal cells via ACE2, which exists on nephrocytes. The virus was also extracted from urine sample of the infected patients [30, 37]. In a study that was conducted on 710 hospital-admitted patients, rate of proteinuria and hematuria was 44%; and 27% of these patients had hematuria on admission. In evaluation of renal function tests, rises in serum creatinine and blood urea nitrogen have been reported in 15.5% and 14.4% of the patients, respectively. In radiologic evaluation of kidneys, inflammation and edema have been reported [37]. Acute kidney injury is more prevalent in ICU admitted patients with COVID-19 and is an independent risk factor of death [30, 37]. Orchitis has been reported in the previous coronavirus outbreaks and there is also the possibility of testis inflammation in COVID-19, but currently, there are not enough data in this regard. ACE2 is also presented on the surface of leydig cells in the testes [30].

***Laboratory findings***

There are a few laboratory abnormalities in hospital admitted COVID-19 patients and some of these derangements have prognostic properties. Leukopenia was one of the most reported abnormalities in the studies [12, 14, 16-19, 22]. The other common laboratory abnormalities included increase in AST, ALT, CRP, LDH, erythrocyte sedimentation rate (ESR), d-dimer and prothrombin time (PT) [14]. Pro-inflammatory cytokines including ferritin, IL2, IL7, IL10, GSCF, IP10, MCP1, MIP1A and TNF-α levels are high in COVID-19 patients and these levels significantly increase in severe cases and ICU admitted patients [17]. Procalcitonin is usually normal on admission, but in some cases it increases during

hospitalization, which may be due to possible super infections [12, 14]. In the severe form of this disease, platelet counts and albumin level may decrease significantly. Patients with refractory pneumonia had higher levels of neutrophils, AST, CRP and lower levels of albumin [18]. Abnormal renal function test and increase in cardiac troponin may be found in some COVID-19 patients and these abnormalities also are correlated with poor prognosis in these patients [31, 37]. In general, existence of laboratory derangements and degree of severity are more common in severe and critical forms of the disease.

***Neurologic manifestations***

SARS-CoV-2 may enter the brain via the hematogenous route or direct invasion through cribriform palate, which may explain loss of the sense of smell in some COVID-19 patients. Anosmia may occur in some COVID-19 patients in the first days of infection. ACE2, a receptor for SARS-CoV-2, is present in the nervous system and brain autopsies have shown some degree of neuronal destruction. These may explain the possible neurologic manifestations of COVID-19 [38, 39]. Central nervous system (CNS) invasion and causing encephalitis have been reported in other members of the coronavirus family and SARS-CoV-2 may have similar abilities. In previous outbreaks of coronaviruses, these viruses were detected in the cerebrospinal fluid of infected patients. Neurologic manifestations of COVID-19 could be classified into CNS and peripheral nervous system (PNS) manifestations. CNS presentations include headache, dizziness, seizure, decreased level of consciousness, cerebrovascular accident and PNS involvements are decrease taste and smell sensation and neuralgia [40]. In a research by Mao et al. on 217 COVID-19 patients, 36.4% had neurologic symptoms. The most prevalent CNS and PNS symptoms were dizziness and anosmia, respectively. CNS complications were more common in the severe form of COVID-19 infection and such cases had lower levels of platelets and lymphocytes and a higher level of blood urea nitrogen in comparison to patients without CNS symptoms. With regards to PNS involvement, there were no significant laboratory discrepancies between patients with and without PNS manifestations. They also showed that patients may come to healthcare facilities only with neurologic manifestations. One of the important issues in COVID-19 patients with neurologic dysfunction is difficulty to exclude hypoxia, metabolic and electrolyte abnormalities as potential causes of these disorders [41].

***Special populations***

- **Pregnant patients**

Based on available data, clinical manifestations of COVID-19 infection in pregnant women are similar to non-pregnant patients and fever, cough and dyspnea are the most prevalent complaints of these patients [1, 13, 42-45]. The clinical spectrum of this disease ranges from asymptomatic infection to severe pneumonia and ARDS with multiple organ failure [42]. Physiologic changes in cardiovascular, respiratory and immune systems during pregnancy increase the susceptibility of pregnant women to severe infection, which consequently leads to hypoxic insult in the fetus. Dominance of T helper 2 (Th2) lymphocyte is an explanation for vulnerability of pregnant women to intracellular pathogens. In pregnant women infected with COVID-19, anti-inflammatory cytokines (IL-4, IL-10) that are generated by Th2 play an important role in modulating immune system activities and may counter the effect of inflammatory cytokines (IL-6, IL-12, INF γ), which could lead to a decline in the severity of infection in these patients in comparison to non-pregnant women [43, 44]. In a study conducted by Liu et al. 46% of patients had preterm labor and 38% of them went to the operating room for cesarean section secondary to pregnancy related complications such as premature rupture of membrane and fetal distress. There was also one case of stillbirth. In the mentioned study, only one patient was admitted to ICU as a result of severe respiratory distress but was finally discharged in good clinical condition. Effects of COVID-19 infection on the fetus were miscarriage (2%), intrauterine growth retardation (10%) and preterm labor (38%) [45]. Chen et al. showed that vertical transmission of COVID-19 does not occur during pregnancy and labor. In this small study, they collected samples from amniotic fluid, placenta, umbilical cord and neonatal throat swab in the operating room and analyzed them for SARS-CoV2 virus. They also evaluate breast milk for virus. All results were negative [43]. In another study on seven pregnant patients with COVID-19 admitted to hospital for delivery, in one neonate, throat swab tested positive for SARS-CoV2 36 hours after the delivery [1]. Current data are against vertical transmission of COVID-19 [13, 43].

- **Elderly patients**

Old patients with COVID-19 infection need special attention, because these patients usually suffer from many comorbidities such as hypertension, diabetes, cardiovascular diseases and chronic pulmonary disease that makes them susceptible to progressive and fatal complications [9, 15, 46, 47]. On

the other hand, old age is an independent risk factor of death and severe adverse events in COVID-19 infection [46, 47]. Wang et al. evaluated 339 patients (mean age: 71 years) with COVID-19 and followed them for four weeks. They found that 71% of patients had severe and critical forms of infection and finally, 19% of these patients died. In the general population, only 18.5% of patients experience severe or critical forms of the disease and fatality is significantly lower than old age groups. They also showed that in the elderly group, mortality rate rises with increase in age [46]. In another study by Lian et al. on 788 proved COVID-19 cases, mortality and disease severity were higher in patients with age ≥60 years in comparison those aged ≤60 years. Lymphocytopenia and lower rates of hemoglobin and albumin, and rise in AST, CRP, LDH and creatine phosphokinase (CPK) were significantly more prevalent in older ages [47].

- **Pediatric Patients**

Based on current data, the prevalence of COVID-19 in children is lower than adults and the nature of the infection is milder in the pediatric population [48-50]. COVID-19 has been reported in all pediatric age groups and the youngest patient was a 36-hour neonate in China [1, 51]. The most prevalent symptoms are fever, cough and weakness, which are similar to adult patients. Some patients may be afebrile and some others may first present with gastrointestinal symptoms such as diarrhea, nausea and vomiting and abdominal pain without any respiratory symptoms on presentation [29, 51]. In a study on 36 pediatric patients with COVID-19, Qiu et al. showed that all patients had mild or moderate form of the disease. Laboratory derangements such as decrease in lymphocytes and increase in CPK, pro-calcitonin and D-dimer were more common in moderate cases [48].

- **Immunosuppressed and cancer patients**

Pro-inflammatory reaction of the immune system and production of T cell-mediated inflammatory cytokines such as IL2, IL7, IL10, GSCF, IP10, MCP1, MIP1A and TNF α plays a central role in most complications of COVID-19 infection, specially severe respiratory presentations [17, 42]. Therefore, it is no surprise that patients under treatment with immunosuppressive agents including organ transplant patients may show milder and atypical forms of COVID-19 infection [52]. In a study on 320 rheumatoid arthritis patients, Monti et al. found 4 confirmed case of COVID-19 and 5 patients with symptoms suggestive of the disease and followed them for 2 weeks. Only one of them required hospital admission and only developed the need for low dose oxygen [53]. There is also a case report of COVID-19 infection in two heart transplant patients under immune suppressive therapy with final improvement of both of them [42]. Zhang et al. reported 28 cancer patients infected with COVID-19, all of which had a history of cancer therapy in the previous 2 weeks. 53.6% of these patients showed severe clinical manifestations and eventually, 28.6% died. ARDS, septic shock and myocardial infarction were the most prevalent complications. Severe clinical manifestations were significantly more prevalent in cancer patients who had undergone anti-cancer therapy in the previous 14 days compared to cancer patients without this history [54].

## Conclusions

In summary, although the most common presentations in COVID-19 patients are fever, non-producing cough and dyspnea, a considerable number of patients may seek healthcare without these complains. Asymptomatic patients and patients with only gastrointestinal and neurologic symptoms remain a significant challenge for medical practitioners. Special groups of patients may need more attention. They may need special evaluation strategies and protocols due to the difference in presentation, clinical course, severity, and disease progression in these patients compared to the general population.

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## Authors' contribution

The author met the standards of authorship based on the recommendations of the International Committee of Medical Journal Editors.

## Conflict of interest

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