

Clinical Characteristics of COVID-19

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Abstract

Coronavirus disease 2019 (COVID-19), pandemic caused by the novel coronavirus SARS-CoV-2, has caused marked morbidity and mortality globally. The clinical spectrum of COVID-19 can be classified as asymptomatic, mild, moderate and severe disease. Majority of the symptomatic patients complain of fever, dry cough, sore throat and shortness of breath, while others present with non-specific symptoms like altered sense of smell or taste, myalgia, lethargy, diarrhoea and other gastrointestinal disturbances.

Though COVID-19 mainly affects the respiratory system, disease may cause widespread systemic and organ specific symptoms involving gastrointestinal, neurological, cardiovascular, immunological, cutaneous, hematological and coagulation systems. Minority of patients present with large vessel strokes, rare neurological syndromes like Guillain-Barre syndrome and Miller Fisher syndrome, which may be the sole manifestation of the disease. Some of the clinical presentations and pathogenesis of COVID are yet to be unraveled.

Key words: Covid-19, SARS-CoV-2, clinical characteristics

Introduction

An outbreak of pneumonia due to an unknown cause, originated in the city of Wuhan, Hubei Province of China, was first reported to the WHO Country Office, on 31st December 2019 by the Chinese Health Authority. A novel beta coronavirus was discovered through the use of unbiased sequencing of the lower respiratory samples from patients with pneumonia¹ and subsequently named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease was


designated as Coronavirus disease 2019 (COVID-19), by WHO². Due to the high infectivity of the virus and person to person transmission, there was an exponential rise in number of cases in China and many other countries.

Transmission

SARS-CoV-2 is a single-stranded, positive sense RNA virus, in the family of Coronaviridae. The virus has spiked glycoproteins on the envelope resembling a crown. B lineage of beta-corona virus causes SARS-CoV-1 and SARS-CoV-2 (COVID-19) infections³. A zoonotic transmission was suggested as three initially affected patients either worked at or frequent visitors to the local seafood market where live trade in of wild animals occurred¹. Initial assessment of the transmission dynamics and epidemiologic characteristics of the disease indicated that epidemic has been growing as a result of human-to-human transmission⁴. According to the study published by Wu et al. (2020), the mean R0 of COVID-19 is 2.68 (95% CI: 2.47-2.86), meaning that on average each patient has been spreading the infection to 2.6 other people⁵. SARS-CoV2 virus replication occurs in the upper respiratory tract and nasopharyngeal swab is shown to be positive up to 17 days and longer in COVID-19 patients with respiratory symptoms⁶. Two main modes of person to person transmission of SARS-CoV-2 is through respiratory droplets and contact with contaminated surfaces. It may be aerosolized during certain medical procedures such as intubation or the use of nebulizers. There are reports of COVID-19 positive individuals who are asymptomatic or with mild upper respiratory tract symptoms, suggesting the potential for asymptomatic or pre-symptomatic transmission. An increasing number of outbreaks of familial and institutional

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transmission has raised the possibility of propagation of infection by asymptomatic individuals^{7,8}.

Incubation period and epidemiological data

Incubation period of Covid-19 varies from 2-14 days. Most patients show clinical symptoms in 3-7 days. The median incubation period was 5.1 days (IQR 2-7)⁹.

Median age of the patients was in the range of 35-67 years. Men (49%-73%) are more affected than women (27%-51%)¹⁰. According to a study by Wu Zunyou et al. (2020), Most cases (87%) were between 30-79 years, 8% were between 20-29 years. There was only 3% in more than 80 years of age. There was 1% between 10-19 years of age, and 1% was less than 10 years¹⁰.

Risk factors

Male sex, older age (>65 years), smoking, obesity, diabetes, chronic pulmonary diseases, hypertension, cardiovascular diseases and chronic kidney disease are considered as poor epidemiological prognostic risk factors. The disease is severe when more risk factors are seen at presentation².

In a study by Chen et al. (2020) which included 99 patients with 2019-nCoV, 91 (48%) patients had a comorbidity, with hypertension being the most common, followed by diabetes and coronary heart disease. From the overall population, 23.7% had at least one coexisting illness. Immunosuppression, cancer, and uncontrolled human immunodeficiency virus (HIV) infection may also confer an increased risk¹¹.

Case fatality rate

The case fatality rate (CFR) vary between 2.3% and 5%. No deaths were seen in the group aged 9 years and younger, but 8.0% CFR noted in those aged 70 to 79 years. Patients who are 80 years and older had a 14.8% CFR². In critical cases CFR was 49.0%. Death occurred within 1-2 weeks after ICU admission¹¹. There were no deaths among mild and severe cases¹².

Clinical profile

There is a wide array of clinical features in patients infected with SARS-CoV-2. Depending on the clinical features, patients are generally divided as mild, severe and critical. Although most exhibit a mild illness (81%), 14% have severe and 5% have critical illness². Approximately 10% will require hospital admission due

to COVID-19 pneumonia, of which approximately 10% will require ICU care¹¹. The usual triad of symptoms at the time of presentation are fever, dry cough and dyspnoea. In several studies done on Chinese patients, fever, cough and shortness of breath were the most prominent symptoms. Fever was present on admission in 43.8%-83% of patients while 88.7% has developed fever during hospitalization. The second most common symptom was cough (31%-94.8%). Dyspnoea varied from 6.9% to 63.5%^{2,11,13-18}. Dyspnoea developed after a median of 5 to 8 days of occurrence of initial symptoms in some case series and it was suggestive of worsening disease¹⁶. According to a US study by Agarwal et al. (2020), the most common presenting symptoms were fever (94%), cough (88%), and dyspnoea (81%). Loss of smell and taste sensations were reported by three (19%) patients. Same study showed low oxygen saturation in 38% of patients, whilst 31% were hypotensive on admission. Sepsis was the most frequently observed complication, followed by respiratory failure, ARDS, heart failure and septic shock¹⁷.

Other symptoms reported in Chinese studies include fatigue (23%-38.1%), sputum production (33.4%), shortness of breath (18.6%), sore throat (13.9%), and headache (6.5%-13.6%)³. Nausea, vomiting (4%-5.0%), diarrhoea (3.0%-5%)¹²⁻¹⁶, conjunctivitis, anosmia and ageusia were less common. Cardiac complications, including new or worsening heart failure, arrhythmias, or myocardial infarction were seen¹¹. Elderly, immunosuppressed and pregnant patients may present with atypical symptoms.

In a European study done on 1420 patients with COVID-19, 420 patients completed the study (962 women, 30.7% were health care workers). The mean age of patients of that cohort was 39.17±12.09 years. The most common symptoms were headache (70.3%), loss of smell (anosmia) (70.2%), nasal obstruction (67.8%), cough (63.2%), asthenia (63.3%), myalgia (62.5%), rhinorrhoea (60.1%), gustatory dysfunction (54.2%) and sore throat (52.9%). Fever was reported by only 45.4%¹⁸.

Gastrointestinal manifestations

In a retrospective, single-center study of 84 patients with SARS-CoV-2 pneumonia in Wuhan Union Hospital, China, revealed that 31% of patients had diarrhoea¹⁹. A significantly higher proportion of patients presented with diarrhoea had virus RNA in stool than patients without diarrhoea. The study concluded that elimination of SARS-CoV-2 from stool takes longer than

elimination from the nose and throat. Study compared clinical symptoms in diarrhoeal and non-diarrhoeal group. The COVID-19 patients with diarrhoea had headache, myalgia or fatigue, cough, sputum production, nausea, vomiting more frequently than those patients without diarrhoea ($p < 0.01$). Abdominal pain, abdominal distension and tenesmus were occasional findings. The duration of fever and dyspnoea in patients with diarrhoea was significantly longer than those without diarrhoea ($P < .05$). The characteristics of diarrhoea include increased defecation frequency (3–14 times per day), stool with no mucous, pus or blood. The diarrhoea symptom may be caused by the invaded ACE2-expressing enterocytes. The underlying molecular pathogenesis needs to be further investigated¹⁹.

In another study which included 116 patients from California²⁰, gastrointestinal symptoms were reported by 31.9% of patients, out of which 89.2% showed mild symptoms. Loss of appetite (22.3%), nausea/vomiting (12.0%) and diarrhoea (12.0%) were the most common symptoms. Gastrointestinal symptoms did not occur in isolation or as an initial manifestation of SARS-CoV-2 infection. Median duration of gastrointestinal-specific symptoms including nausea/vomiting or diarrhoea was 1 day [IQR 0–4]; which was significantly shorter than the duration of respiratory symptoms ($P < 0.001$). Out of 65 patients who had liver enzymes measured 26 patients, (40%) demonstrated hepatic dysfunction with a slightly higher levels of aspartate aminotransferase (AST) compared to alanine aminotransferase (ALT)²⁰.

Neurological manifestations

Corona viruses may invade the nervous system, the route of neuro-propagation from the nasal cavity to the olfactory bulb and to the brain stem has been demonstrated in animal models²¹. Furthermore, in human respiratory tract, nasal epithelial cells display the highest expression of the angiotensin-converting enzyme 2 (ACE-2) receptors for SARS-CoV-2²².

Altered sense of smell and taste is recognized as a common manifestation of COVID-19. In a cross-sectional survey of 202 mildly symptomatic COVID-19 patients in Italy, any altered sense of smell or taste was reported by 130 patients (64.4%, 95% CI, 57.3%–71.0%)²³. The timing of an altered sense of smell or taste in relation to onset of other symptoms was; before the onset in 11.9%, at same time in 22.8%, and after other symptoms in 26.7%. An altered sense of smell or taste was reported as the only symptom in 3% of

patients²³. However, according to the data from other European centres, the prevalence of altered sensation of smell and taste vary between 34% to 88% of hospitalized COVID-19 patients^{18,24}.

Mao et al. analyzed the frequency of neurological manifestations in 214 hospitalized patients with laboratory confirmed diagnosis of SARS-CoV-2 infection from three designated COVID care hospitals in Wuhan, China²⁵. It was shown that 78 (36.4%) patients had neurologic manifestations; central nervous system (CNS) symptoms in 24.8% (headache, dizziness, impaired consciousness, ataxia, acute cerebrovascular disease, and epilepsy), peripheral nervous system (PNS) symptoms in 8.9% (hypogeusia, hyposmia, hypopsia, and neuralgia), and skeletal muscular symptoms in 10.7%. In patients with CNS symptoms, the most common complaints were dizziness (16.8%) and headache (13.1%) and, in patients with PNS symptoms, anosmia in 5.1% patients and ageusia in 5.6% patients²⁵.

Patients with severe illness can present with seizures, altered level of consciousness and confusion. As there are several confounding factors which might affect the clinical presentation and sensorium of patients with severe COVID-19 like hypoxia, multi-organ failure, metabolic and electrolyte derangements, medications and therapeutic interventions²⁶, it is difficult to analyze them as a direct effect of COVID-19.

Large vessel stroke has been a significant presenting symptom in young COVID-19 patients. Five cases of large-vessel stroke, with the mean NIHSS score of 17, were reported in patients younger than 50 years from New York, USA. They had hemiplegia, facial palsy, dysarthria, gaze palsies and four of them had reduced level of consciousness on admission. Two of them had mild COVID-19 symptoms like cough, fever and lethargy²⁷. A retrospective study of data from the COVID-19 outbreak in Wuhan, China, showed that the incidence of stroke among hospitalized patients with Covid-19 was approximately 5%; the youngest patient in that series was 55 years of age²⁸.

Few diagnosed cases have reported with Guillain-Barré syndrome (GBS) as a presenting feature of COVID-19. Toscano et al. reported four patients in their case series diagnosed with GBS having positive PCR test for SARS-CoV-2. The first symptoms of GBS were lower-limb weakness and paresthesia in four patients and facial diplegia followed by ataxia and paresthesia

in one patient. The interval between the onset of symptoms of COVID-19 and the first symptoms of GBS ranged from 5 to 10 days²⁹. Critical illness neuropathy and myopathy usually develops later in the course of critical illness and it should be distinguished from GBS in COVID-19 which appears rather early phase of the disease.

Gutiérrez-Ortiz et al. have described occurrence of Miller Fisher syndrome and polyneuritis cranialis as unusual initial neurological manifestations of COVID-19³⁰. Miller Fisher syndrome was characterized by the acute onset of external ophthalmoplegia, ataxia, and loss of tendon reflexes. Patient was treated with intravenous immunoglobulin and he had a full recovery within 2 weeks.

There are few case reports mentioning the occurrence of odd combination of neurological symptoms like ophthalmoparesis, leg paresthesia and areflexia in some of the COVID-19 patients³¹.

Haematological manifestations

Thrombocytopenia

Haematological manifestations in COVID-19 include thrombocytopenia and thrombotic complications. Mild thrombocytopenia is a common finding with the platelet count ranging from 100-150×10⁹/L³². The pooled analysis revealed that platelet count was significantly lower in patients with more severe COVID-19, therefore it may serve as a clinical indicator of worsening illness during hospitalization³³. The mechanism for thrombocytopenia in SARS-CoV2 is multifactorial³². A SARS CoV-2 positive patient diagnosed as immune thrombocytopenic purpura who recovered after immunoglobulin therapy suggests a possible autoimmune response as a cause for thrombocytopenia³⁴.

Thrombotic complications

COVID-19 may predispose patients to thrombotic disease, both in the venous and arterial circulations, due to excessive inflammation, platelet activation, endothelial dysfunction, and stasis³⁵. The risk of thromboembolism was higher in patients with severe disease who were treated at Intensive Care Unit (ICU). There were several reports of thrombotic complications such as central venous catheter associated thrombosis, deep venous thrombosis (DVT) and pulmonary embolism (PE)³⁶.

In a cohort of 81 ICU patients in China, where routine thromboprophylaxis was not used, the proportion of DVT was 25%³⁷. In a study done on 184 ICU patients in a Dutch hospital where DVT prophylaxis is used incidence of DVT was 37%³⁸. Similar observations were seen in two studies done in France and Italy^{39,40}. Similarly, Spiezia et al. (2020) observed severe hypercoagulability rather than a consumptive coagulopathy⁴¹.

Laboratory findings of patients with COVID-19 who had developed thrombotic complications include elevated D-dimer levels, prolonged prothrombin time and fibrinogen levels^{36,39}. Patients who died from COVID-19 had progressively rising D-Dimer levels than who survived⁴². Patients with D-Dimers more than 1mg/L had 18-fold increased risk of death⁴³.

Cutaneous manifestations

Though cutaneous manifestations are not well described in COVID-19, it is important to identify as they may manifest before the respiratory symptoms. In an Italian study, out of 88 patients 18 patients (20.4%) developed cutaneous manifestations; erythematous rash (14 patients), widespread urticaria (3 patients), and chicken pox like lesions (1 patient)⁴⁴.

Sachdeva et al, described eighteen articles and three additional cases in a review. The most common cutaneous manifestation of COVID-19 was found to be maculopapular exanthem (morbilliform), presenting in 36.1% (26/72) patients. The other cutaneous manifestations included: a papulovesicular rash, urticaria, painful acral red purple papules, livedo reticularis lesions and petechiae. Majority of lesions were localized on the trunk⁴⁵.

Vasculitic skin changes including petechiae, purpura, ecchymosis, livedoid lesions have been described mostly in paediatric COVID-19⁴⁶. Veena G et al. reported a case history of a 6-month-old baby diagnosed of COVID-19 and Kawasaki Disease who presented with clinical features such as fever, limbic sparing conjunctivitis, prominent tongue papilla, a polymorphous, maculopapular rash, and swelling of the hands and lower extremities⁴⁷.

Conclusion

In conclusion, COVID-19, causes widespread involvement in many organs and systems. Though the classic triad of symptoms comprising fever, dry cough and dyspnoea are usually present, unusual presen-

tations involving many systems have been noted in variable number of patients. Due to its novelty and highly infectious nature, many aspects of COVID-19 are yet to be unraveled. It will be a daunting task ahead in containing the disease, as well as in managing the patients.

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