Clinical manifestation and disease progression in COVID-19 infection

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Abstract: Coronavirus disease 2019 (COVID-19) is mainly an infectious disease of the respiratory system transmitted through air droplets, and pulmonary symptoms constitute main presentations of this disease. However, COVID-19 demonstrates a clinically diverse manifestation ranging from asymptomatic presentation to critically illness with severe pneumonia, acute respiratory distress syndrome, respiratory failure, or multiple organ failure. Accumulating evidences demonstrated that COVID-19 has extrapulmonary involvement, including neurological, smelling sensation, cardiovascular, digestive, hepatobiliary, renal, endocrinologic, dermatologic system, and others. Over a third of COVID-19 patients manifest a wide range of neurological symptoms involving the central/peripheral nervous system. Underlying cardiovascular comorbidities were associated with detrimental outcomes, meanwhile the occurrence of cardiovascular complications correlate to poor survival. Gastrointestinal symptoms frequently occur and have been associated with a longer period of illness. Impaired hepatic functions were associated with the severity of the disease. Higher rate of acute kidney injury was reported in critically ill patients with COVID-19. Endocrinologic presentations of COVID-19 include exacerbating hyperglycemia, euglycemic ketosis, and diabetic ketoacidosis. The most common cutaneous manifestation was acro-cutaneous (pernio or chilblain-like) lesions, and other skin lesions consist of maculopapular rash, vesicular lesions, livedoid/necrotic lesions, exanthematous rashes, and petechiae. This review article summarized the general clinical signs and symptoms, radiologic features, and disease manifestation with progression in patients with COVID-19.

Keywords: Coronavirus; COVID-19; Severe acute respiratory syndrome coronavirus 2

1. INTRODUCTION

Coronaviruses with RNA club-shaped spikes on the viral surface are one of the largest among RNA viruses.[1] The structure of coronaviruses consists of enveloped surface, a nucleocapsid, and single-stranded RNA genome. In the 1930s, the first coronaviruses were discovered when infectious bronchitis virus caused an acute respiratory tract infection.[2] In the 1940s, mouse hepatitis virus and transmissible gastroenteritis virus were identified as the first coronaviruses in mammals. The first human coronaviruses were identified in the 1960s.[3] Two human coronaviruses, coronavirus 229E and OC43, cause upper respiratory tract infections, nasal symptoms, cough, and pharyngitis. According to previous reports, human coronavirus usually results in a low mortality rate and rarely causes critical illness.[4,5] Nonetheless, the severe acute respiratory syndrome coronavirus (SARS-CoV) may cause more severe symptoms which are not usually caused by known coronavirus. In 2003, SARS-CoV caused pulmonary infection, and the mortality rate reached approximately 10%.[4] Therefore, the World Health Organization (WHO) reported that SARS-CoV might cause severe acute infectious disease in the world. In 2012, another severe coronavirus infection was discovered in the Middle East. The discovery process was similar to SARS. A patient had severe unexplained pneumonia and was later found to be caused by a new type of coronavirus. The novel virus, Middle East respiratory syndrome coronavirus (MERS-CoV), was first found in a patient from Saudi Arabia with severe unexplained pneumonia.[4] The MERS-CoV outbreak in 2012-2015 affected 25 countries (mostly Saudi Arabia and South Korea) with 2506 cases and 862 deaths (34% fatality rate).[5] In December 2019, a new type of pneumonia with unknown cause occurred in Wuhan, China and started to spread rapidly. The Chinese government identified an extreme

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pathogenic coronavirus on January 9, 2020 when WHO named such novel SARS-CoV. People also called this disease of SARS-CoV-2 as COVID-19 or Wuhan pneumonia.[6] The number of cases increased significantly in January 2020, and the global statistics as of August 4 had 18 166 298 confirmed cases, and the death toll had reached 690 953 all of which exceeded the SARS record of that year. Although COVID-19 was initially limited to China, it has rapidly spread to >180 countries because of its highly contagious pathogen. This pandemic infection is continuously spreading across the world with exponentially increasing death toll. It is important to clarify and understand the clinical manifestation and disease progression in COVID-19 pandemic infection.

2. CLINICAL SYMPTOM AND DISEASED MANIFESTATION IN COVID-19

In recent decades, two previous coronavirus outbreaks have been reported, and the clinical manifestations of SARS-CoV-2, in comparison with SARS-CoV and MERS-CoV, are summarized in the Table 1.[7–9] Pulmonary infectious diseases, such as SARS and MERS, present a major threat to public health.[10] In late December 2019, several new SARS-like pneumonia cases were reported in a Chinese city of Wuhan. A new coronavirus SARS-CoV-2 was rapidly identified as the etiologic pathogen leading to the outbreaks of COVID-19.[10] This novel coronavirus infection demonstrated human-to-human transmission of SARS-CoV-2 among healthcare practitioners in a Wuhan hospital.[11,12] The global spread and lethality of SARS-CoV-2 lead to primary challenges for the worldwide healthcare system. SARS-CoV-2 is highly contagious, and the incubation period of COVID-19 has been reported around 1 to 14 days (interquartile range [IQR], 2-7 days).[11,13–15]

The common symptoms of SARS-CoV-2 infection are fever (83%-98%), cough (50%-82%), fatigue (25%-44%), shortness of breath (19%-55%), and muscle soreness (11%-44%).[14,15] Some patients may suffer from sputum production, rhinorrhea, chest tightness, sore throat, nausea, vomiting, diarrhea, headache, ageusia, and anosmia a few days before the occurrence of fever, suggesting that fever is critical but not the only initial symptom of infection.[14] Some patients only had a mild fever, mild fatigue, or even no symptoms.[13,15–17]

Table 1

Characteristic comparison of SARS-CoV, SARS-CoV-2, and MERS-CoV

	SARS-CoV-2	SARS-CoV	MERS-CoV
Start time	December 2019	November 2002	June 2012
Initial area	Wuhan, China	Guangdong, China	Jedda, Saudi Arabia
Confirmed patients	214 894	8096	2494
Mean age (range)	47-56 (0.5-92)	39.9 (1-91)	56
Male	58%-75%	44%	76.70%
HCWs	2%-29%	23.10%	9.80%
Symptoms			
Fever	83%-98%	99%-100%	98%
Dry cough	59%-78%	29%-75%	47%
Dyspnea	19%-55%	40%-42%	72%
Diarrhea	2%-10%	20%-25%	...
Sore throat	5%-17%	13%-25%	...
Ventilator support	2%-12%	14%-20%	80%
ARDS	3%-29%	20%-30%	Case reports
Mortality	690 953 (3.8%)	744 (10%)	858 (37%)

ARDS = adult respiratory distress syndrome; HCWs = healthcare workers; MERS-CoV = Middle East respiratory syndrome coronavirus; SARS-CoV = severe acute respiratory syndrome coronavirus.

About 80% of SARS-CoV-2 infections in ambulatory patients manifest as a mild respiratory illness and could usually be managed by outpatient care. About 15% of patients need inpatient care for moderate to severe pneumonia.[18] Among the hospitalized patients, the median time from initial symptoms to the occurrence of dyspnea is five days (IQR, 1-10 days), and the median time to be hospitalized is 5 days (IQR, 4-8 days).[13] Disease course may show rapid progression to multiple organ failure and even death in severely ill patients.[11,13] Patients (3%-29%) may require admission to an intensive care unit (ICU) for the management of complications, including hypoxemic respiratory failure or hypotension. Overall mortality rate appears to be approximately 3.8%[11,13,14,16,19] (Table). Some patients with dyspnea and hypoxemia could quickly progress into acute respiratory distress syndrome (ARDS), septic shock, blood clotting dysfunction, and even multiple organ failure in 1 week.[16,20] The median time to ARDS is 8 days (IQR, 6-12 days). The high incidence of multiple organ failure is one of the features of COVID-19.[15] Most of the critically ill patients are related to comorbidities, including cardiovascular disease, hypertension, diabetes, and renal disease. Moreover, the mortality rates are relatively high in COVID-19 patients with these comorbidities.[21] The severity of COVID-19 patients is also related to age, and the death toll was concentrated among those aged ≥40. Studies have shown that morbidity rate is lower in children and infants than in adults.[22,23]

Infected patients may have lymphopenia which is the most common laboratory manifestation, normal or lower white blood cell counts, or thrombocytopenia, with elevated C-reactive protein level.[11,13,14,16] Fever, lymphopenia, or leukopenia with the symptoms of upper respiratory tract is highly suspected to be the manifestations of patients with COVID-19, which is supported by the traveling history to the endemic area or close exposure history. The asymptomatic individuals in incubation period are critical sources of infection, which results in difficulties in the epidemic prevention and disease control.[24,25]

Currently, respiratory droplets are believed to be the primary route of transmission; however, transmission via the ocular surface should also be carefully prevented because the conjunctival epithelium is vulnerable to the infectious droplets and body fluid.[26] The fecal-oral route is suspected due to the identification of SARS-CoV-2 nucleic acids in the stool specimens from COVID-19 patients with pneumonia and abdominal symptoms.[27] Additionally, vertical transmission between mothers and infants has been reported as a potential transmission route according to the finding of a 30-hour-old newborn tested positive for SARS-CoV-2 infection. Despite tremendous efforts on investigating this pathogen, the contagious period of SARS-CoV-2 still varies in different reports.[19] Furthermore, the incidental hosts of SARS-CoV-2 are not yet clear to researcher. The unconfirmed incidental hosts may lead to repeated zoonotic transmission and the potentially underestimated contagious period also constitutes a significant challenge to the epidemic prevention. Additionally, the human-to-human transmission of SARS-CoV-2 occurs mainly in communities and between family members, suggesting that this pathogen could rapidly spread before the occurrence of symptoms. Another report showed that patients who have recovered from COVID-19 after two consecutive real-time reverse transcriptase-polymerase chain reaction tests turned out to demonstrate positive results a few days later.[28] Therefore, infected patients could be contagious before the onset of symptoms and after treatment of COVID-19. Besides, the optimal strategy for hospital discharge and cessation of quarantine remains to be elucidated in order to achieve superior disease control.

3. RADIOLOGICAL FEATURES IN COVID-19

Chest X-ray (CXR) and computed tomography (CT) scan are necessary radiological examinations for early identification of

COVID-19.[29] The radiological features of COVID-19 pneumonia are similar to influenza, SARS-CoV, and MERS-CoV pneumonia.[30–34] CXR of patients with COVID-19 pneumonia may reveal unilateral, bilateral, peripheral, and patchy opacities. In the early stage of COVID-19 pneumonia, CXR may not be able to detect abnormal findings, because CXR is not sensitive for ground-glass opacity (GGO).[35]

Severe COVID-19 cases may show the bilateral multiple consolidative lesion in the CXR radiograph. Besides, CT-scan radiograph can provide more information to assist the COVID-19 diagnosis. According to the experience on CT scan, COVID-19 patients exhibit bilateral pulmonary GGOs and consolidative lesions in the lung parenchyma. In addition, CT scan detects the feature of multiple pulmonary nodules, pleural effusion, lymphadenopathy, and absence of pulmonary cavitary lesion. Clinical doctors can efficiently catch pneumonia from early stage of COVID-19 patient according to CT scans.[15] Hence, CT scan provides a rapid evaluation of progression and severity of COVID-19. However, COVID-19 pneumonia and other pulmonary infectious diseases are sometimes difficult to distinguish from CT findings. Moreover, the early stage of COVID-19 patients might present no significant difference in the pulmonary image. Even nucleic acid detection sometimes show a false negative result due to the low virus abundance or inefficient sampling. As a result, the combination of nucleic acid detection assay and CT imaging is useful for the precise identification of COVID-19.[36–40]

4. EXTRAPULMONARY MANIFESTATIONS OF COVID-19

Although many COVID-19 patients suffered from respiratory symptoms, SARS-CoV-2 can also lead to several extrapulmonary manifestations, including thromboembolic complications, cardiac injury and arrhythmia, acute coronary syndromes, acute renal injury, gastrointestinal (GI) symptoms, liver function impairment, hyperglycemia and diabetic ketosis, neurologic deficits, and dermatologic complications.[41] We summarized the extrapulmonary organ-specific manifestation and pathophysiology for patients with COVID-19 to facilitate the understanding and monitoring of various manifestations in COVID-19 patients.

4.1. Neurologic manifestations

Neurologic presentations in COVID-19 patients are shown in the Fig. 1. Neurologic symptoms were reported in 36% of the patients with severe COVID-19.[42] The mild neurological symptoms in COVID-19 patients include headache, dizziness,

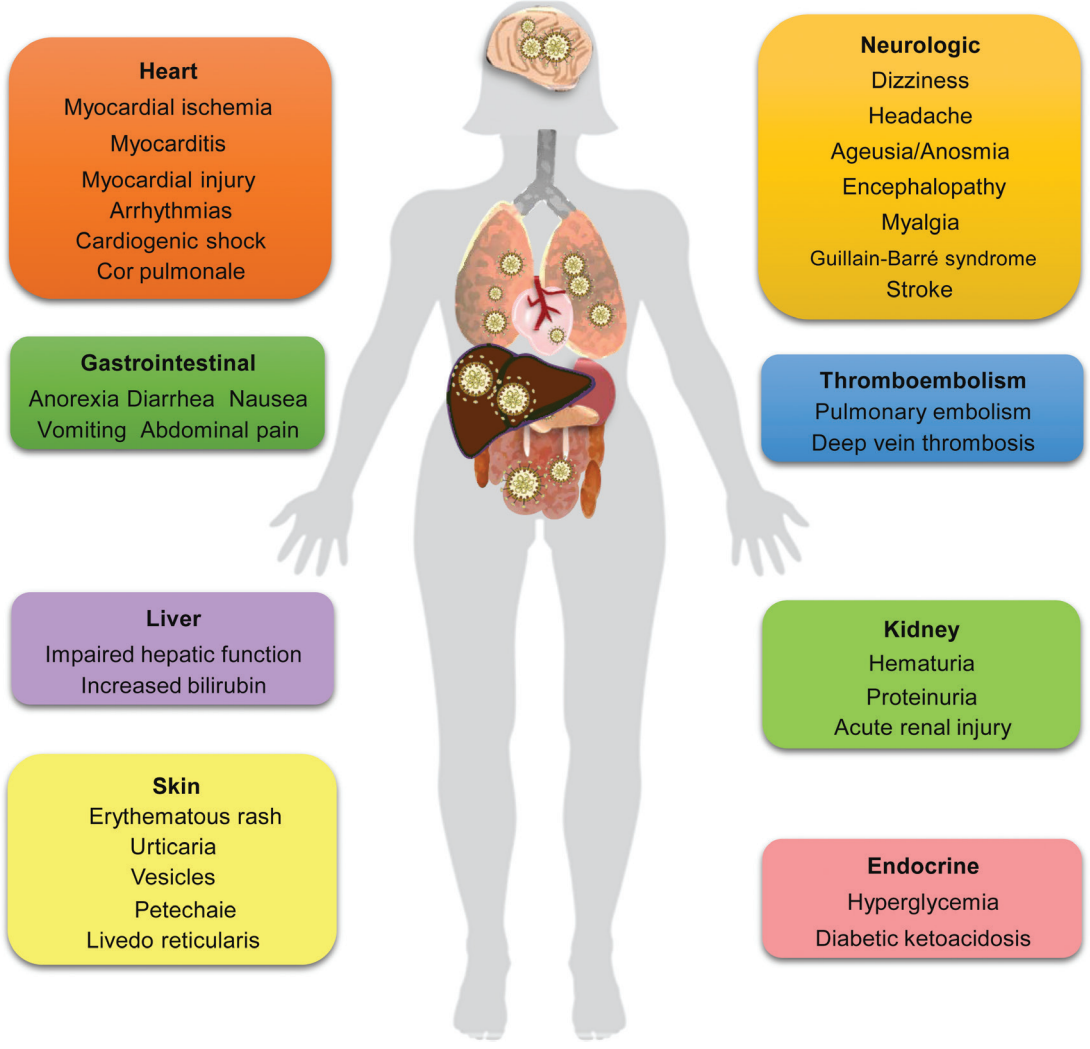

Fig. 1 Extrapulmonary involvements in patients with coronavirus disease 2019 (COVID-19).

anorexia, anosmia, myalgia/fatigue, and ageusia.[11,13,14] More-severe manifestations consist of acute stroke,[43,44] confusion or impaired consciousness,[42,45] acute inflammatory demyelinating polyneuropathy (Guillain-Barré syndrome),[46,47] meningoencephalitis, acute necrotizing encephalopathy including the brainstem and basal ganglia.[48,49]

4.2. Thromboembolic manifestations

The thromboembolic manifestations of COVID-19 are shown in the Fig. 1. Thromboembolic complications were reported in up to 30% of patients from ICUs.[50,51] Emerging evidence revealed the occurrence of thrombosis in intravenous catheters and extracorporeal circuits, acute myocardial infarction, acute limb ischemia, and cerebral vascular events, in patients with severe disease.[43,52–55] High rates of thromboembolic events were reported in severely ill patients with COVID-19 (17%-22%) who had received prophylactic anticoagulant therapies.[54,56–58] The rates of pulmonary emboli were reported to be notably higher in ICU patients with COVID-19 than those without (20.6% vs 6.1%, respectively).[59] Moreover, several studies demonstrated high rates of thromboembolic complications in critically ill patients with COVID-19 who were routinely screened for the thrombotic disease, ranging from 69% to 85%, despite prophylactic anticoagulant therapies.[41]

4.3. Cardiovascular manifestations

Clinical manifestations of COVID-19 pertaining to the cardiovascular system are shown in the Figure. COVID-19 can lead to direct and indirect cardiovascular injury, including acute coronary syndrome, myocardial injury, cardiomyopathy, cardiac arrhythmias, cor pulmonale, cardiogenic shock, and thromboembolic complications.[60,61] Around 20% to 30% of inpatients with COVID-19 were reported to have myocardial injury,[62] and higher degree of troponin elevations was associated with more severe complications and worse outcomes.[62,63] Biventricular cardiomyopathy occurred in approximately 7% to 33% of critically ill patients.[64,65] Hospitalized patients (17%-44%) with COVID-19 were reported to have cardiac arrhythmias, including atrial fibrillation, ventricular arrhythmias, and heart block.[13] Prolonged QTc was found in 6% of COVID-19 patients in a multicenter study. In an Italian cohort, the rate of out-of-hospital cardiac arrest increased by around 60% during COVID-19 pandemic compared with the similar period in 2019.

4.4. Renal manifestations

Clinical features pertaining to the kidney damage are shown in the Figure. The incidence of acute kidney injury (AKI) in hospitalized patients ranged from 0.5% to 37% with a median onset time of 7 to 14 days during admission.[16,66–69] Higher rate of AKI, ranging from 78% to 90%, was reported in critically ill patients in New York City; an 31% of ICU patients with COVID-19 required renal replacement therapy.[69–73] Up to 87% of critically ill patients had proteinuria in study.[71] Higher mortality rate of COVID-19 was also reported in patients with end-stage renal disease and kidney transplant recipients compared with those without.[74–76]

4.5. GI manifestations

GI symptoms occur in some patients with COVID-19 (Figure). GI symptoms in COVID-19 patients have been associated with a longer duration of illness, with the incidence of 12% to 61%.[77–80] The reported GI manifestations include anorexia (21%-35%), nausea/vomiting (7%-26%), diarrhea (9%-34%), and abdominal pain (3%).[79,80] The occurrence of GI symptoms has been associated with a 70% increased risk of identification of COVID-19 in a research,[81] and GI bleeding was rare in patients with prolonged mechanical ventilation or thrombocytopenia.[81]

4.6. Hepatobiliary manifestations

Clinical presentations of COVID-19 regarding the hepatobiliary system are shown in the Figure. In a systemic review, the prevalence of liver function impairment is around 19% (95% CI, 9%-32%) and associated with the severity of disease.[79] Patients usually have elevated transaminases which are less than five times the upper limit of normal and severe acute hepatitis is rarely reported.[82,83] Critically ill patients (14%-53%) with COVID-19 was reported to have hepatocellular injury.[16,65–67,84] Some studies reported that elevated bilirubin was associated with the severity of disease and deterioration to critical illness.[85,86]

4.7. Endocrinologic manifestations

Endocrinologic presentations in COVID-19 patients are shown in the Figure. The abnormalities of glycemic metabolism in hospitalized patients with COVID-19 include exacerbating hyperglycemia, euglycemic ketosis, and diabetic ketoacidosis.[16,18,87] A study in China reported that 6.4% of hospitalized patients had ketosis without the presence of fever or diarrhea.[88]

4.8. Dermatologic manifestations

Dermatologic manifestations of COVID-19 are shown in the Figure. A single-center study reported that 20% of hospitalized patients presented with dermatologic symptoms, including erythematous rash, urticaria, and chickenpox-like vesicles, and around 44% of dermatological findings occurred at disease onset.[89] The most common cutaneous manifestation was acrocutaneous (pernio or chilblain-like) lesions in a systemic review, and other skin lesions consist of maculopapular rash, vesicular lesions, livedoid/necrotic lesions, exanthematous rashes, and petechiae in patients with COVID-19.[90–93]

In conclusion, this review introduces the current status of knowledge on the global pandemic and clinical features of COVID-19. Given that SARS-CoV-2 is the third introduction of a deadly coronavirus into human society, after SARS-CoV in 2003 and MERS-CoV in 2012, respectively, various clinical manifestations of these three viruses were compared. Whereas SARS-CoV-2 is featured by relatively lower lethality compared with SARS-CoV and MERS-CoV, it has demonstrated significantly broader range of clinical presentation and apparent higher contagiousness. The COVID-19 outbreak started from China and then spread to other countries all over the world. Currently, the persistent pandemic still locates in Europe and North America. We also summarized the image findings for COVID-19.

Beside the deadly pulmonary complications of SARS-CoV-2, extrapulmonary spread, including neurological, smelling sensation, cardiovascular, digestive, hepatobiliary, renal, endocrinologic, and dermatologic system, are increasingly being appreciated. SARS-CoV-2 has undoubtedly catched the world's attention at the beginning of 2020 by posing a significant challenge toward the public health system. Still, despite the rapid development of countermeasures looming on the horizon, further investigation and development of drugs and vaccines are in urgent need, as according to our current knowledge of coronaviruses, where and when the next outbreak would take place is unpredictable. Therefore, only by equipping ourselves with adequate understanding and diverse treatment modalities can we devise appropriate strategies against the constantly changing nature of novel coronaviruses.

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