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Editorial

COVID-19: Clinical and pathophysiological features and laboratory diagnosis

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In December 2019, a new coronavirus was detected in a series of mortal pneumonia cases in Wuhan, China, with a clinical picture that resembled viral pneumonia. This single-chain RNA virus from the Coronaviridae family caused a pandemic in the first quarter of 2020. The World Health Organization (WHO), named the virus Serious Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), and the disease was called COVID-19 (Coronavirus disease 2019). Seven types of coronavirus are known to infect humans and cause mild to moderate respiratory symptoms. The disease caused by the SARS-CoV-2 infection has some features that are similar to the Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS), but the global spread of COVID-19 has led to many more cases of serious illness that can lead to severe pneumonia and death. The common complications observed in severe cases of COVID-19 include acute respiratory distress syndrome (ARDS) and respiratory failure. Secondary infection, acute cardiac injury, hypoxic encephalopathy, acute kidney injury, shock, and acute liver injury are less common complications that have been seen among severe cases. Severe illness is associated with older age and the presence of underlying health conditions (such as diabetes, cardiovascular diseases, chronic kidney disease, inflammatory bowel disease, asthma, cancers, etc.) or smoking. The leading cause of death in patients with COVID-19 is respiratory failure [1-7].

The disease spread is primarily through infectious droplets and is transmitted through the respiratory system. It is also transmitted by people touching a virus-infected surface or object and then touching their own eyes, nose, or mouth. The virus has been detected in respiratory secretions of asymptomatic individuals, and these secretions have proven to be highly contagious. The contribution to transmission by the presence of the virus in other body fluids is unknown at present, but the virus has been detected in blood, saliva, tears, cerebrospinal fluid, and conjunctival secretions. Fecal-oral transmission may be possible. It is also unknown if perinatal transmission (including transmission via breastfeeding) is possible. Current estimates of the incubation period range from 1 to 14 days, according to the WHO and the US Centers for Disease Control and Prevention. The median incubation period has been estimated to be approximately 7 days for adults. The virus has been detected in sputum and feces for up to 39 days after pharyngeal swabs became negative. However, the full view of the transmission dynamics of COVID-19 remains unclear at present [8-12].

The pathophysiology of the unusually high pathogenicity of COVID-19 is not yet completely understood. The virus appears to bind to the angiotensin-converting enzyme-2 (ACE2) receptor in human cells. It has been reported that the coronavirus spike protein was a significant determinant of virus entry into host cells. It is thought that the inhaled SARS-CoV-2 virus likely binds to epithelial cells in the nasal cavity and begins to replicate. The spike glycoprotein of the coronavirus envelope binds to its cellular receptor, angiotensin-converting enzyme 2 (ACE2). ACE2 is the main receptor for both SARS-CoV2 and SARS-CoV. The organs considered

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more vulnerable to COVID-19 due to the ACE2 expression level include the lungs, heart, esophagus, kidneys, bladder, and the ileum. Ciliated cells are the primary cells infected in COVID-19. SARS-CoV-2 may downregulate ACE2, leading to a toxic over-accumulation of angiotensin-II, which may induce ARDS or fulminant myocarditis. ACE2 expression is thought to be high in the lungs, heart, ileum, kidney, and bladder. ACE2 has been seen to be highly expressed in lung epithelial cells. When the virus enters the cells, the virus antigen is recognized by the antigen-presenting cells. Antigen presentation subsequently stimulates the body's humoral and cellular immunity, which are mediated by virus-specific B and T cells. The virus propagates and migrates down the respiratory tract along the conducting airways, and a more robust, innate immune response is triggered. Little is known at present about the immune response of patients with COVID-19. Considering its similarity to SARS-CoV and MERS-CoV, the pathogenesis of COVID-19 may be associated with a high cytokine level. Severe COVID-19 infection is typically characterized by a massive, pro-inflammatory response, or cytokine storm, triggered by the immune system that results in ARDS and multi-organ dysfunction [13-19].

Molecular testing is required for diagnosis. The definitive COVID-19 test is a nucleic acid amplification test, such as a real-time, reverse-transcription, polymerase chain reaction (PCR) test, with confirmation by nucleic acid sequencing when necessary. The PCR technique is a molecular method used to obtain multiple copies of a very small portion of DNA to ensure that the virus is detectable, a process known as DNA amplification. Since COVID-19 is an RNA virus and RNA is a single-stranded nucleic acid molecule, it must be converted to DNA before it can be replicated. During testing, the reverse transcriptase enzyme binds to the single-stranded RNA of the virus and can be replicated by normal PCR processing. This is only possible if sufficient viral RNA is present in the sample and ensures that the test result is positive. If there is no viral RNA, the test will be negative. However, 1 or more negative test results do not rule out the possibility of COVID-19 virus infection. Several factors can lead to a negative result in an infected individual, including poor quality of the specimen, inadequate patient material, collection at late or very early stage infection, improper handling or shipment, or technical reasons inherent in the test, e.g., virus mutation or PCR inhibition. Virus whole-genome sequencing can also help molecular epidemiology studies. Virus isolation is not recommended as a routine diagnostic procedure [20-23].

Although serological blood tests have recently been developed to detect antibodies produced by the immune system in response to a SARS-CoV-2 infection, the validated serological tests are limited. Serum samples can be stored to retrospectively define cases when validated serology tests become available. Presently, there are 2 potential serology tests for COVID-19. One determines viral proteins (likely a Western blot), while the other is an enzyme-linked immunoassay (ELISA) that detects the patient's antibodies to the virus. ELISA tests are based on the detection of immunoglobulin (Ig) G and IgM antibodies. IgM test positivity indicates that the infection exists (demonstrating prolonged virus replication in infected patients), and high levels of IgM during the acute phase of infection can last more than 1 month. IgG test positivity indicates that the individual had a previous infection and/or the immune response has begun. IgG responds later than IgM. Therefore, these tests are useful in identifying those who have an active COVID-19 infection or were previously infected, or those who have developed an immune response to the infection. Serological tests are not useful in detecting recently infected asymptomatic patients because it can take days for antibodies to multiply and reach a detectable level in the blood. This increases the risk of the virus spreading to the environment from people who have a negative test but who are, in fact, infected. The reliability of these tests is still not at the desired level [23, 24].

All imaging procedures should be performed according to local infection prevention and control procedures in order to prevent transmission. A chest X-ray should be ordered for patients with suspected pneumonia. Unilateral lung infiltrates or bilateral lung infiltrates are found in the majority of patients. A computed tomography scan of the chest is ordered for clinically suspected COVID-19 persons who are seriously ill with an uncertain or normal chest X-ray. Multiple bilateral lobular and subsegmental areas with ground-glass opacity or consolidation, crazy-paving pattern, air bronchograms, or a reverse halo/perilobular pattern are classic findings. Atypical features, such as interlobular or septal thickening (smooth or irregular) or thickening of the adjacent pleura or subpleural involvement, appear to be more common in the later stages of the disease, or on disease progression [25-28].

A group of biochemical tests is performed for the diagnosis, follow-up, and treatment of COVID-19. A complete blood count; lymphocyte count; measurement of the levels of C-reactive protein (CRP), procalcitonin, kidney and liver parameters, creatinine, transaminases, cardiac troponin, lactate dehydrogenase (LDH), and ferritin; as well as coagulation tests (prothrombin time, fibrinogen, D-dimer), and arterial blood gas analysis are widely used in the follow-up and treatment monitoring, the evaluation of the clinical course, and to support the diagnosis of the disease (Table 1). Compared with moderate cases, severe cases more frequently have dyspnea, lymphopenia, and hypoalbuminemia, with higher levels of alanine aminotransferase, lactate dehydrogenase, CRP, ferritin, and D-dimer. A decreased serum albumin level and elevated transaminases and bilirubin levels indicate liver injury. Elevated serum creatinine and urea levels can indicate kidney

Table 1. Blood test

Test	Diagnostic criteria
Complete blood count	Leukopenia, lymphopenia, and leukocytosis
	Neutrophilia, thrombocytopenia, and decreased hemoglobin levels
	Lymphopenia and thrombocytopenia have been associated with
	increased risk of severe disease and are clinical indicators for monitoring disease progression
Coagulation tests	Elevated D-dimer: D-dimer level >1 microgram/L is associated with
	a poor prognosis, including high Sequential Organ Failure Assessment Scores
	Elevated prolonged prothrombin time
	Elevated fibrinogen level (acute phase reactant)
Liver function test	Elevated transaminases
	Decreased albumin level (prognostic factor)
	Serum lactate dehydrogenase level might be elevated in patients with severe illness
	Elevated serum lactate dehydrogenase level might be indicated by lysis of blood erythrocytes (hemolysis)
Renal impairment test	Elevated creatinine
Serum procalcitonin	May be elevated in patients with a secondary bacterial infection
Serum C-reactive protein	May be elevated in patients with a secondary bacterial infection
	A prognostic factor
Serum creatine kinase	May be elevated in patients with muscle or myocardium injury
Serum troponin level	May be elevated in patients with myocardium injury
Serum ferritin	May be elevated
	Indicates acute inflammation response
Arterial blood gases (ABG)	May show low partial oxygen pressure
	May show low oxygen saturation (SpO_2<90%)
	ABG is ordered for patients with respiratory distress and cyanosis

injury, and increased serum troponin and creatinine kinase levels are associated with cardiac damage. Increased counts of white blood cells and neutrophils and elevated serum procalcitonin levels are related to the bacterial infection. A decreased immunological response to the virus is seen in decreased lymphocyte counts. An increased D-dimer level and prothrombin time are associated with the activation of blood coagulation and/or disseminated coagulopathy. In severe viral infection, sepsis or viremia, serum CRP levels are elevated. An elevated serum ferritin level is a laboratory sign of acute inflammation response [5, 29-36].

Testing on clinical specimens from patients meeting the suspected case definition should be performed in appropriately equipped laboratories by staff trained in the relevant technical and safety procedures. National guidelines on laboratory biosafety should be followed in all circumstances. There is still limited information on the risk posed by COVID-19, but all procedures should be undertaken based on a risk assessment. Specimen handling for molecular testing requires biosafety level 2 facilities or the equivalent [13, 37, 38].

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