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A Review of Severe Acute Respiratory Syndrome Coronavirus 2 and Pathological Disorders in Patients

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ABSTRACT

Firstly, a new coronavirus emerged in Wuhan, China, sparking a pandemic of acute respiratory syndrome in humans. Corona virus disease-19 (COVID-19) was declared as a pandemic after the infection spread globally and disease caused by the new type of coronavirus, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was named as COVID-19. The virus originated from bats and has been passed to humans. Initially, SARS-CoV-19 infects respiratory system an acute serious viral infection mainly developed with over a million people worldwide were transmitted rapidly in a few months. SARS-CoV-19, progress a moderate to serious severe respiratory symptoms such as headache, cough, and breathlessness. Also, digestive system symptoms include nausea, vomiting, and stomach pain. Although the precise of the mechanism of inflammation unclear but this virus firstly use the angiotensin converting enzyme 2 (ACE2) receptor of the alveolar cells of lung tissue causing inflammation and cell death. Then virus spreads and affects other important organ and tissues with complex pathophysiological alterations, the coronary disease, pulmonary disease, chronic kidney disease and chronic liver disease are the most prevalent comorbidities among patients. In COVID-19 infection therapy lots agents recommended. Unfortunately, there is no clear effective drug for treatment. This review presented potential pathogenic pathway of the SARS-CoV-19 infection and symptoms in the patients and given the information about the negative effects on different systems in the respiratory, cardiac system, nervous system, gastrointestinal system, and urinary tract.

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1. Introduction

The 2019 novel coronavirus (2019-nCoV) or as it is now referred to as the severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) originated in Wuhan City of Hubei Province of China and is rapidly spreading to the rest of the world (1). On March 11th 2019 World Health Organization declares the COVID-19 outbreak as pandemic. COVID-19 can be transmitted directly or indirectly by infected animals, directly from one person to another, or by droplets spread by infected persons through coughing or sneezing, and environmental contamination. Larger aerosols with higher transmission capacity may form indoors, causing the virus to last longer. Also possible on smooth surfaces transmission such as cardboard, stainless steel, and plastic surfaces survival between 24 to 72 hours. Additionally, SARS-CoV-19 virus, in sputum, blood, feces, saliva, and urine of infected individuals has been identified. Although, the initial cases of COVID-19 were diffused directly contact

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with infectious animals to humans through yet unknown intermediate animals in Wuhan, China (2).

In most people, the condition is mild; in others (usually the elderly and those with comorbidities) may be development to pneumonia, severe respirational distress disorder (2). Moreover, signs are nonspecific and the diagnosis of the disease can vary from no symptoms to COVID-19 extreme pneumonia and death (2). While COVID-19 often causes typical symptoms such as fever, cough, myalgia, weakness and sputum; It can also cause atypical symptoms such as hemoptysis, headache, and diarrhea. About half the patients have dyspnea and 63 percent of patients, lymphocytopenia was found (3). Diagnosis of COVID-19 needs specimen's collection from the anterior respiratory tract, nasopharyngeal and oropharyngeal sample and inferior oropharynx. The reverse polymerase chain reaction (RT-PCR) evaluation is common method for the detection of viral genomic sequences in the early stage of COVID-19. SARS-CoV-19 virus predominantly affects the pulmonary system. In addition, other organ involvement, septic shock and metabolic acidosis may occur (3). According to the pathological findings of autopsies and biopsies restriction, in addition to the lung SARS-CoV-19 can inter numerous tissues and organs, as the liver, spleen, heart, brain and kidney (4).

In this paper we will review the pathogenic features, pathways and mechanisms for the infection of SARS-CoV-19 are discussed in order to provide theoretic and clinical basis for diagnosis, classification and predictions and as well as any adverse effects on the circulatory system digestive system, urinary system and central nervous system.

2. History

The Coronaviridae are a large family of viruses, which were first discovered in 1960. They induce common cold in humans and animals, and crown-like thrones on the wall surfaces of viruses are important characterize. The genus Coronaviruses is a virus enveloped with a large plus-strand RNA genome with genomic RNA size is between 27–32 kb, capped or poly adenylated (5).

Four corona viruses have been circulating in humans, namely HKU1, NL63, 229E and OC43, and usually cause mild respiratory disorders (2). Additionally, the severe acute respiratory syndrome caused by the SARS coronavirus (SARS-CoV), emerged in Asia and then expanded worldwide 2002 to 2003. In 2012, following by the Middle East respiratory syndrome (MERS), induced by the MERS coronavirus (MERS-CoV). At the end of December 2019, some local medical center documented patients with pneumonia of unknown epidemiologically linked to seafood and wet animal wholesale market in Wuhan, Hubei Province (6). On 31st December a team in the Chinese Center for Disease Control and Prevention with collaboration with Hubei Provincial Health Commission deployed the epidemiological and etiological underlying of the disease.

After a number of Chinese scientists isolated the virus from lower respiratory tract samples, deep genome sequencing analysis isolated the virus as a new beta-coronavirus. Then WHO was named this virus as the 2019 novel coronavirus. Symptoms such as fever, dry cough, chills, shortness of breath, and muscle pain have been related to this acute pneumonia. The epidemic of SARS-CoV-19 quickly spread worldwide. As of 20 July 2020, it has killed more than 14 million people and resulted in over 500,000 deaths (7). This virus looks circular and has an envelope. It has spike proteins (S1 and S2) and conjugated proteins itself on envelope (glycoproteins). Spike proteins are needed in coupling infected cells receptors to ACE2 receptors to enter the cell by endocytosis. The membrane protein (M) located on the envelope determines the virus's shape. Envelope (E) glycoprotein association with M protein generates the viral envelope. SARS-CoV-2 has a singular, non-segmented RNA strand with molecular weight about 30kb (8). It directs the cellular machinery of the body for its replication. The genomes comprise papain sequences like proteases, helicases, ribonuclease, replicases and Spike proteins. The spike proteins found in SARS-CoV-2 are distinct from SARS-CoV-2 proteins (9).

3. Clinical Features and Symptoms

After an incubation period of approximately 5.2 days appear the symptoms of COVID-19 infection (10). The period from the beginning with average of 14 days is expected for COVID-19 symptoms. The patient's immune system response and average of the age of the patient effect on the period. This time shorter among patients, those under the age of 70 years compared those more than 70-years old (1). Fever, tiredness, cough and sore throat are typical signs at the onset of COVID-19 infection, while other symptoms include diarrhea, production of sputum, headache, dyspnea, hemoptysis, shortness of breath, and leukopenia (3).

4. Diagnosis

The diagnostic approaches for corona virus diagnosis are basic molecular experiments on respiratory samples (esophagus swab/nasopharyngeal swab/saliva/ bronchoalveolar lavage and endotracheal extracts). In addition, the virus can also be differentiated in the stool and blood. Other laboratory investigations are usually nonspecific. The white cell count is usually normal or low. There may be lymphopenia; a lymphocyte count <1000 has been associated with severe disease. The platelet count is usually normal or mildly low. The CRP and ESR are generally elevated but procalcitonin levels are usually normal. A high procalcitonin level may indicate a bacterial co-infection. The ALT/AST, prothrombin time, creatinine, D-dimer, CPK and LDH may be elevated and high levels are associated with severe disease. Chest computer tomography scan presented as indicator for pneumonia is important clinical assay (2).
Other experimental experiments are normally non-specific.

The number of white cells is decline. Significant diseases have been associated with a lymphocyte count of less 1000. Lymphopenia may occur; typically, the platelet count is average poor. Normally, the CRP and ESR are raised up. ALT/AST, prothrombin period, D-dimer, creatinine, Creatinine Phosphokinase and Lactate dehydrogenase may be rising and extreme in severe disease status (3).

5. Pathological Mechanism of Coronavirus Disease

The pandemic of COVID-19 has emerged as a major health crisis, with more than a million people around the world infected by SARS-CoV-19 within a few months of its identification as a human pathogen. First, cells in the respiratory system become infected with SARS-CoV-19 and inflammation begins, after which clinical symptoms are observed. Later, the infection spreads and causes complex pathophysiological changes in various vital organs (10). In the early stages of COVID-19, the lungs are the primary organ affected. Although the mechanism of infection is unclear, many studies reveal that the virus uses the ACE2 receptor to enter cells that are abundant in the lower respiratory tract. Importantly, it can be stated that ACE2 receptor targets all these organs in the brain, heart, intestinal epithelium, vascular endothelium and kidneys (11). Infection with SARS-CoV-19 is accompanied by the binding of the virus's spike protein to ACE2, which is strongly expressed in the lungs. SARS-CoV-19 primarily invades alveolar epithelial cells, allowing to be released into other cells (12). The role of ACE2 and the SARS-CoV-19 cellular binding site has been approved (13).

ACE2 is an amino peptidase enzyme, which changes Angiotensin (Ang) II into Ang (1-7). It is well known that function Ang II as major role in contraction blood vessel, pro-inflammatory and pro-fibrotic, effects. In contrast, Ang (1-7), is a potent vasodilator, inhibitor of the apoptotic, and inhibitor of the proliferative agent. In almost all the pathological conditions, especially those of the cardiovascular system, ACE enzyme prevent ACE2 enzyme in your body which producing Ang II. Furthermore, the two enzymes ACE/ACE2 play a major role in the renin-angiotensin system homeostasis which regulation blood pressure as well as equilibrium of the fluid and salt in the body. In some metabolic disorder increase in the ACE/ACE2 ratio within the organs and systems. This ACE/ACE2 imbalance is very often due to a decrease the expression of ACE2 levels, and followed imbalance ratio by disruption in renin-angiotensin system, regulation blood pressure and fluid and electrolyte balance. Overall, it resultant that when patient have SARS-CoV-19 decrease the ACE2 levels or activity and the ACE/ACE2 ratio rises, patients appear to be in trouble and may be higher risk to having a worse outcome in COVID-19 infection (14).

5.1. SARS-Cov-19 and the Digestive System

The digestive system is second system which virus affected following the respiratory epithelial cells and alveolar cells. Evidence from previous studies about SARS established tendency coronavirus for the digestive tract. In stool specimens of patients who were contaminated with SARS, viral nucleic acid may be readily identified. Reports from China reported that up to 50% of patients in hospitalized and maybe perhaps more COVID-19 outpatients would have at least one stage of the disease have commonly diarrhea or anorexia. In these patients, diarrhea is the most frequent gastrointestinal manifestation that may occur in the absence of signs of respiration disorders or before taken treatment (15). The particular cause of diarrhea associated with COVID-19 remains unknown, although multiple theories have been suggested. Viral infection can disturbance intestinal permeability, which resulting in malabsorption of enterocytes. Mucosa ACE2 receptor and transmembrane serine protease 2 receptors are key proteins in the digestive system for entry virus like the receptor for the respiratory like ACE2. Other gastrointestinal signs may be related to the nervous system anosmia and ageusia are considered important indicators of COVID-19 although less commonly presented. Both symptoms particularly predictive as compared with other symptoms and accomplishment of these study in the diagnostic criteria have proven (16). In patients with serious COVID-19 disorder, the ratio of liver damage was also higher. Although the cause of liver damage is not known exactly, it may be due to immune response damage, hepatotoxicity of drugs or direct hepatocyte viral invasion (4). Elevations of serum liver enzymes were also observed. One cohort data in Wuhan reported 99 patients, 43 patients had increased ALT or AST; one patient with vital COVID-19 had increased serum ALT extreme hepatitis up to 7590 U/LL (17) (Table 1).

5.2. SARS-Cov-19 and the Cardiovascular System

SARS-CoV-2 involves the respiratory system, but effects on cardiovascular system, either indirectly or directly, have been seen (18). Those with severe COVID-19, elderly, male gender, obese, and comorbid diseases are at high risk for cardiovascular involvement (19). Myocardial damage, myocarditis, acute coronary syndrome, acute myocardial infarction, cardiac arrhythmia, cardiac arrest, venous thromboembolic disease, and heart failure have been identified in patients with COVID-19 (20). It was found that an average of 12% of COVID-19 patients suffered from acute heart injury (3). An increase in cardiac markers troponin I, creatine kinase, C-reactive protein and N-terminal probrain natriuretic peptide (NT-proBNP) were observed in COVID-19 patients (3, 18). In COVID-19, there may be direct involvement of the cardiovascular system or a secondary response to systemic inflammation and hypoxic acute respiratory distress syndrome. Direct cardiovascular system effects can be seen via ACE2 in COVID-19 patients (21). However, it may affect blood vessels and heart indirectly through immune response to SARS-CoV-2. It is one of the different mechanisms in drug-induced heart damage with the use of antiviral drugs used in the treatment of COVID-19 (22).

It is understood that cardiovascular cells express ACE2 at elevated levels, which central regulator of blood pressure and heart contractility. The virus may preference this tissue and organ as target tissue which has numerous ACE2

ACE2 expression receptors virus binds to human ACE2 with high binding capacity and entry then invade target cells. SARS-CoV-19 may activate ACE2 and ACE2 signal transduction downstream activate pro inflammatory signal. Consequently, this may cause inflammation in myocardial tissue and fibrosis and dysfunction of cardiac (17). In myocardium and vascular endothelial cells, the widespread expression of ACE2 may be due to the existence of SARS-CoV-19, which may cause direct cardiovascular injury (23) (Table 1).

Hypertension

Individuals with COVID-19 requiring hospitalization, hypertension is the most frequent comorbidity. In a case-series study, 5.700 patients (average of 63 years; 39.7% female), the most frequent comorbidities hypertension (56.6%), obesity (41.7%) and diabetes (33.8%) were included (23). In overall, recent studies proved that patients with COVID-19 and hypertension have a higher risk of mortality relative with non- hypertensive. Hypertension may enhance the inflammatory profile in patients which have SARS-CoV-19 infection, concluding that hypertension perhaps increases even high risk for a more acute illness, these patients present higher levels of pro inflammatory biomarkers such as TNF-α and IL-6 level were demonstrated (24).

Myocardial injury

SARS-CoV-2 has been shown to cause myocarditis (4). However, myocardium is damaged due to hypoxia caused by lung involvement. An increase in troponin level is seen due to myocardial damage (20, 25, 26). Severe cases of myocarditis with reduced systolic function have been seen in COVID-19 patients. Increased levels of biomarkers such as serum troponin and natriuretic peptides have been reported (25, 27). Patients with COVID-19 have an increased risk of mortality with acute cardiac injury (28). Heart damage causes increased morbidity and mortality in COVID-19 disease (1, 29). Chronic or acute cardiac damage occurs in COVID-19 infection (30). Myocardial markers can predict COVID-19 mortality. There is not enough information about the mechanism of how COVID-19 results in the myocardial injuries. There are no data showing the presence of SARS-CoV-2 in myocardial tissue. Acute myocardial damage caused by COVID-19 infection can be associated with ACE2 (30). Other pathophysiological mechanisms of myocardial damage can be explained by hypoxia that begins with cytokine storm and respiratory dysfunction (30). The resulting myocardial inflammation can cause a decrease in cardiac contraction, inotropic deficiency, increased filling pressures, and acute heart failure. Myocarditis seen in COVID-19 shows acute ventricular dysfunction due to widespread myocardial edema. Pericarditis, pericardial effusion, and cardiac tamponade may occur with myocarditis (31). Myocardial damage is associated with a poor prognosis in COVID-19. Troponin levels, electrocardiography and echocardiography are mandatory in patients with signs of severe infection (18,28,32).

Heart Failure

Heart failure is an important cause of death in patients with COVID-19 and occurs due different mechanisms of the myocardial aggression such as direct myocardial injury, indirect inflammatory damage pathway, imbalance of the O2 supply. Increasing of atherothrombotic cases as a result of inflammatory atheromatous plaque destabilization happen due to acute myocardial dysfunction (18,13,33). In the study 23.0% of COVID-19 patients had heart failure (26). In the study performed, it was observed that patients with heart failure exhibited higher ACE2 expression (17). Severe heart failure is seen in patients with COVID-19 infection (17). Heart failure, which can be caused by cardiomyopathy and myocarditis, is seen in COVID-19 patients (34). Imbalance in ventilation and perfusion occurs due to lung involvement of COVID-19 patients. With the increase in pulmonary vascular resistance, pulmonary hypertension develops and the associated right heart failure occurs (35).

Acute coronary syndrome

The incidence in patients with acute coronary syndrome COVID-19 is not clearly known. It may be associated with increased thrombotic tendency and endothelial dysfunction in patients (21, 36). With inflammation, it results in hypoxemia, immobility, and a prothrombotic state. Therefore, coronary thrombosis occurs with instability of the atherosclerotic plaque (37).

Cardiac arrhythmia

Many types of cardiac arrhythmias, ranging from tachycardia and bradycardia to asystole, are seen in COVID-19 patients (20). Causes of arrhythmias can be attributed to hypoxia, metabolic disorders, systemic inflammation, or myocarditis (21,38). Ventricular arrhythmias and acute myocarditis may present as the first clinical manifestation (39).

Thromboembolic disease

Patients with COVID-19 are at high risk of venous thromboembolism due to hypercoagulopathy. Abnormal coagulation parameters have been demonstrated in hospitalized patients with severe COVID-19 (8). D-dimer height has been shown to be highly correlated with mortality (25). ACE2 dysfunction causes systemic endothelialitis, leading to abnormal coagulation. Abnormal coagulation is responsible for mortality in COVID-19 patients (1). Coagulation screening tests are recommended for all COVID-19 patients. Atallah et al., recommends a patient-specific algorithm for patient-specific anticoagulation therapy for hospitalized COVID-19 patients (40).

5.3. SARS-Cov-19 and the Central Nervous System

SARS-CoV-2 has the ability to infect the central nervous system (CNS). The olfactory tract is an essential channel for virus transfer to the brain in the early stages of SARS-CoV-19 respiratory system infection. Olfactory tract becomes a main passage for virus spread to brain. In addition to the above studies, found that coronavirus would invade the

CNS via neuronal pathways from the periphery nerve system (11). A wide variety of neurological manifestations can occur in these patients, including encephalopathy, epilepsy, cerebrovascular events, encephalitis, acute polyneuropathy, fever, hypogeus, hyposmia, and some non-specific symptoms. Furthermore, the brainstem, as the life center of the human body, regulates essential processes such as beating of heart, maintenance of blood pressure and ventilation. Studies have shown that certain coronaviruses from the lungs and airways can invade the brain stem through a synapse-connected pathway. One source of acute respiratory failure may be the possible penetration of SARS-CoV-19 into the CNS. It is also importance for the treatment of serious patients to scientifically explain the disease process of patients with respiratory failure whether it is caused by pulmonary lesions or by viral brain stem infections. In a study of 58 COVID-19 patients, the most frequent of neurological interference found in 14 percent at ICU admission and 67 percent of anxiety and confusion. In eight patients, neuroradiological characteristics associated with meningoencephalitis were seen and acute ischemic stroke and sub-acute ischemic stroke were reported (10) (Table 1).

5.4. SARS-Cov-19 and Urinary System

Acute renal failure caused by extreme acute respiratory syndrome of coronavirus 2 can be seen with COVID-19 (SARS-CoV-2). The symptoms of the kidneys vary from simple urinalysis anomalies to extreme acute kidney injury that involves renal replacement therapy. Sometime higher mortality in people with COVID-19 develop in the Acute renal failure (1). Acute renal dysfunction in critically ill patients with COVID-19 can be secondary to hemodynamic instability-related acute tubular injury, although the cause of proteinuria is not well defined (41) (Table 1).

Table 1. Clinical manifestation of COVID-19.

Organ system involved	Symptoms	Diseases	Diagnostic Signs
Respiratory System	Cough, rhinorrhea, sneezing, dry cough	Pneumonia Acute respiratory distress syndrome (ARDS)	Decreased % pO2 Chest X-rays show ground glass opacities
Digestive System	Nausea, vomiting, diarrhea, loss of appetite	Gastrointestinal bleeding Gastroinstestinal viral dissemt ination	Elevated liver enzymes and bilirubins SARS-CoV-2 detection in stool samples
Cardiovascular System	Chest pain, tachycardia, dyspnea	Hypertension Arrhytmia Cardiac injury Heart failure Acute coronary syndrome Thromboembolic diseases	Elevated cardiac enzymes Abnormal EKG Elevated cardiac-specific troponin and brain natriuretic peptide Elevated D-dimer
Central Nervous System	Hyposmia- anosmia, hypogeusia-ageusia, visual disturbance, fatigue, somnolence	Headaches Encephalopathy Meningoencephalitis Neuropathy Guillain Barre Syndrome	Brain MRI show hyperintensities in regions with infarction or encephalitis SARS-CoV-2 detection in cerebrospinal fluid or brain tissues in some patients
Urinary System	Proteinuria, hematuria	Acute renal injury Renal failure	Tubular necrosis and SARS- CoV-2 detection in kidney

6. COVID-19 and treatment recommedations

Protocols based on scientific data have been developed to fight the virus all over the world. The strategies against COVID-19 are by preventing adhesion of coronavirus to the target cells, by killing free virus with antivirals like Tocilizumab or Favipiravir or Remdesivir other antivirals and treatment with anticoagulants and antibiotics if required, by strengthening the immune system with antioxidants & high doses of vitamin C, micronutrients like magnesium, zinc, vitamin D, and vitamin A to eliminate the virus. General prophylactic protocol consists of vitamin C, magnesium, zinc, vitamin D and selenium (Table 2).

Table 2. COVID-19 prophylactic agents.

AGENTS	ORAL DOSE
Vitamin C	1.5 – 2 grams daily
Zinc	30 – 40mg daily
Magnesium	400mg daily
Vitamin D	5000IU daily for 2 weeks then 2000IU daily till advised
Selenium	55µg daily
NOTE: These can be bought from any pharmacy	

In treatment of COVID-19 contains antiviral agents, passive immunity or antibodies therapy and immunity boosters. For antiviral therapy remdesivir and tocilizumab are recommended. Passive immunity is a therapy where plasma of the recovered patient containing specific antibodies is infused to the patient suffering from COVID-19 infection. Vitamin D and high dose vitamin C are using for immunity boosters. They are not COVID-19 specific agents (42).

Conclusion

Infection of Coronavirus 2019 has become one of the most severe worldwide outbreaks in recent years, with major public health risk. Todays, overcome to mortality and morbidity of patient needs to be solved clinically. Coronavirus 2019 disease use the ACE2 receptors in many types of cells in the body, which might provide potential ways for SARS-CoV-2 infection. ACE/ACE2 ratio is increased in a number of pathologies and conditions, especially abnormal metabolism or cardiovascular diseases. The virus usually uses ACE2 receptors for tissue invasion. The major pathophysiology of this fatal illness is primary pulmonary injury and associated digestive and coronary complication. Coronaviruses from the lungs and airways can passing through ACE2 receptor in nasal tissue reach the brain invade brain stem, which important role in control of blood pressure. Viral infection affect permeability of digestive system produce many abnormalities such as diarrhea. Furthermore, in all this abnormality decrease the functional levels of ACE2 or activity and the increase the ACE/ACE2 ratio. So the increase proinflammatory, pro-apoptosis macromolecule in the body, following induce inflammation in the many organs like respiratory system digestive system, cardiovascular system such hypertension as heart failure. ACE2 became the first stage in the entrance into and infection of cells and control and regulation of ACE2 is the best candidate treatment for medicinal disease.

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