

A literature review in understanding the Physio-Pathological facet of Covid-19.

Abstract:

In December 2019, a novel coronavirus, now named as SARS-CoV-2, caused a series of acute atypical respiratory diseases in Wuhan, Hubei Province, China. The disease caused by this virus was termed as COVID-19 and is transmittable between humans that has caused a pandemic worldwide. An early clinical report showed that fever, cough, fatigue, sputum production, and myalgia were initial symptoms, with the development of pneumonia as the disease progressed. COVID-19 basically involved the pulmonary system at the onset, thereby involving the other organs like gastrointestinal system, cardiovascular System and nervous system is based on virulence. Increases in the level of serum liver enzymes D-dimer, cardiac troponin I, and creatinine have been observed in severely ill patients, indicating that multiple organ failure had occurred in these cases. Here, we review the current knowledge about this disease in relation to its various aspects and make comparison systemic-wise for better understanding of the systemic physio pathological aspect of Covid-19 that may help in contributing towards finding the solution that is needed at present.

Keywords: Covid-19, SARS-CoV-2, Physio-Pathology.

Introduction:

In December 2019, an outbreak of Covid-19 disease caused by Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) occurred in Wuhan, China, which rapidly led to a global pandemic.¹ Following the outbreak in China, SARS-CoV-2 has spread worldwide. As of early April 2020, the reported number of Covid-19 patients was highest in the U.S., followed by Spain, Italy, Germany, France and China.² Covid-19 affects people of all age groups but the following population sub-groups are at greater risk of developing severe disease with complications:

1. Elderly People
2. People having other co-morbidities
3. People who are immunocompromised.¹

As we are striving towards finding a solution for Covid-19, this present review focuses on comparing and evaluating different aspects of Covid-19 as there is a profound need to understand the Physio-Pathological Aspects of the disease with the aim to contribute in tackling the ongoing pandemic.

Comparison of Epidemiology of SARS-CoV-2 with SARS and MERS:

In two initial studies in Shanghai, China and Germany, it was observed that Covid-19 was infectious during the incubation period. Identification of the infected was extremely difficult in early stages. In the absence of identification, there would remain a constant threat of the exponential spread of the disease. SARS and MERS infected the intrapulmonary epithelial cells more than the cells in the upper respiratory tract while SARS-CoV-2 is capable of infecting even the upper respiratory tract making it easier to spread through nasal droplets. It has 10-20 times higher affinity as compared to SARS-CoV virus. The virus has the capability of surviving in various environmental conditions, thus making it even more dangerous for transmission³.

Genera of Corona Virus:

Corona viruses are single-stranded RNA viruses. They infect a wide variety of host species. Corona viruses are largely divided into four genera; α , β , γ , and δ based on their genomic structure. α and β corona viruses infect the mammals. SARS-CoV, Middle East Respiratory Syndrome corona virus (MERS-CoV) and SARS-CoV-2 are classified to β corona viruses²

The life cycle of the virus with the host consists of the following 5 steps; attachment, penetration, biosynthesis, maturation and release. Once the viruses bind to the host receptors (attachment), they enter the host cells through endocytosis or membrane fusion (penetration). Once viral contents are released inside the host cells, viral RNA enters the nucleus for replication. Viral mRNA is used to make viral proteins (biosynthesis). Then, new viral particles are made (maturation) and released. Coronaviruses consist of four structural proteins; Spike (S), Membrane (M), Envelop (E) and Nucleocapsid (N)⁴. Spike is composed of a transmembrane trimetric glycoprotein protruding from the viral surface, which determines the diversity of coronaviruses and host tropism. Spike comprises of two functional subunits; S₁ subunit which is responsible for binding to the host cell receptor and S₂ subunit which is for the fusion of the viral and cellular membranes. Angiotensin Converting Enzyme 2 (ACE2) was identified as a functional receptor for SARS-CoV⁵.

Mechanism of Infection:

The mechanism of infection is supported by the virus gaining entry to the host cell via the spike glycoprotein (S) that attaches to the ACE2 (angiotensin-converting enzyme 2) to enter the cell. After SARS-CoV-2 attached to the target cell, the virion release RNA into the cell, which further disseminate to infect cells. SARS-CoV-2 produces severe virulence factors that promote shedding of new Virion from host cell and Inhibit immune response⁶.

Target cells:

The target cells of SARS-CoV-2 are those that express the angiotensin-converting enzyme 2 (ACE-2): type II alveolar cells, upper respiratory epithelial cells, absorptive

enterocytes from ileum and colon, myocardial cells, proximal tubule cells of kidney and bladder, glial cells and neurons, oral tissues cells (especially epithelial cells of the tongue), and nasal epithelial cells, which display the highest expression of ACE-2 receptor in the respiratory tree⁷.

Specificity of SARS-CoV-2:

Following the binding of SARS-CoV-2 to the host protein, the spike protein undergoes protease cleavage. The corona virus spike is unusual among viruses because a range of different proteases can cleave and activate. The characteristics unique to SARS-CoV-2 among corona viruses is the existence of furin cleavage site at the S1/S2 site⁸.

Common Symptoms in Patients:

Infection can be spread by asymptomatic, pre-symptomatic, and symptomatic carriers. The average time from exposure to symptom onset is 5 days, and 97.5% of people who developed symptoms do so within 11.5 days. The most common symptoms are fever (up to 90% of patients), dry cough (60% - 86%), shortness of breath (53% - 80%), fatigue (38%), nausea / vomiting / diarrhea (15% - 39%), and myalgia (15% - 44%). Patients can also present with non-classical symptoms, such as isolated gastrointestinal symptoms. Olfactory and/or gustatory dysfunctions have been reported in 64% to 80% of patients⁹.

Pathophysiological Background of Pulmonary Involvement:

Lung involvement is the main pathological feature of Covid-19, and is responsible for respiratory failure, which is the leading cause of death. The lung injury produced by SARS-CoV-2 started with viral attachment to angiotensin converting enzyme 2 (ACE2) receptors, present on the apical surface of respiratory epithelial cells in the conductive airways. The infected respiratory epithelial cells are the source of the local and systemic (to distant organs) viral spread, a process which is facilitated by inflammation and alveolar-capillary damage¹⁰.

Hypoxia:¹¹

- SARS-CoV-2 enters the type II alveolar epithelial cells following binding of its spike protein to the ACE-2 receptor.

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- Down regulation of ACE-2 on pulmonary epithelium results in unopposed effects of ACE on the pulmonary capillary endothelial cells.

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- Level of ACE2-Ang 1-7-mas-R activity is reduced, while the level ACE -Ang II-AT1-R activity is increased.

↓

Pulmonary Vasoconstriction developed

↓

Hypoxia

Cardiovascular Involvement:

Evidence of myocardial injury in patients with Covid-19 has been a remarkable finding. ACE2 expression is significantly elevated in cardiac tissue and may potentially facilitate direct myocardial damage induced by viral infection¹².

ACE2 plays an important role in the renin-angiotensin system by catalyzing the conversion of angiotensin II to angiotensin 1-7, which exerts a protective effect on the cardiovascular system. Due to binding of SARS-CoV-2 to ACE2 is expected to result in loss of the external ACE2 catalytic effect, consequently the downregulation of ACE2 and the diminution in angiotensin 1-7 levels in patients with COVID-19 may also compromise heart function¹³. In addition to the above, some patients with COVID-19 have been reported to experience a hyper inflammatory state, in which inflammatory cytokines and other markers of systemic inflammation are markedly increased¹⁴.

Gastro Intestinal Tract Involvement:

The reported gastrointestinal manifestations of Covid-19 include diarrhea, nausea, vomiting and abdominal pain. ACE2 are found in the epithelial cells of the gastrointestinal tract,

signifying virus entry through the ACE2 receptors and its replication causing inflammatory changes and the patient's symptoms.

Diarrhea:

It is postulated that SARS-CoV-2 binds to host ACE 2 receptors (ACE2) on target cells to gain entry, possibly with the assistance of trans-membrane serine protease. ACE2 is recognized as an important regulator of intestinal inflammation, ACE2 is also necessary for the surface expression of amino acid transporters of the small intestine. Tryptophan amino acids regulate the secretion of antimicrobial peptides by Paneth cells via mTOR pathway activation. Antimicrobial peptides effect the configuration and diversity of the microbiota. Disturbance of this pathway could drive inflammation (enteritis) and eventually leads diarrhea¹⁵.

Nervous System:

A number of mechanisms have been proposed to describe the link between SARS-CoV-2 infection and nervous system injury.

It has been demonstrated that human corona viruses invade the central nervous system through the olfactory neuroepithelium and spread to the olfactory bulb using a mode of neuron-to-neuron propagation. Furthermore, SARS-CoV-2 can damage the blood-brain barrier, invade the nervous system through the slow cerebral microcirculation, which facilitates the interaction between the protein S (spike) and the ACE-2 receptors expressed on the capillary endothelium, and interact with the ACE-2 receptors expressed in neuronal cells¹⁶.

Nervous tissue damage might be possible due to direct viral infections by different ways. SARS-CoV-2 may enter the CNS through the retrograde neuronal or hemato-genous route. Infection of olfactory neurons in the nose may permit the virus to pass in the brain trans-neuronally and spread directly from the respiratory tract to the brain¹⁷. Cytokines can directly pass through the blood brain barrier causing considerable damage¹⁸.

In the serum of hyposmia patients increased IL-6 have been found. Experiments have confirmed that virus-infected microglial cells and astrocytes secrete IL6 and primary glial cells

cultured in vitro secrete a large number of inflammatory factors, such as IL-6, IL-12, IL-15, and TNF- α after being infected with coronaviruses. Because of regulation of neural and glial cell activity, IL-6 may act as an endogenous substance regulating olfactory neural activity. In addition, IL-6 can directly inhibit smell function through activating apoptotic pathways using TNF- α or through neuropoietin (NP)¹⁹.

Mutations in Novel Covid-19: makes it more dangerous.

The high infectivity of the virus is related to mutations in the receptor binding domain and acquisition of a furan cleavage site in the S spike protein. The virus interaction with ACE2 may downregulate the anti-inflammatory function and heighten angiotensin II effects in predisposed patient²⁰.

Potential explanation for the difference between children and adults in COVID-19:

The expression level of ACE2 may differ between adults and children. A study showed that ACE2 was more abundantly expressed on well-differentiated ciliated epithelial cells. Human lung and epithelial cells continue to develop following birth. ACE2 expression may be lower in pediatric population².

Preventive and Therapeutic measures:

Due to absence of complete and specific treatment regime, early diagnosis, timely reporting, Isolation and supportive treatment are significant strategies against covid-19 infection. Maintenance of physical distancing, improving personal hygiene, wearing masks, adequate rest and keeping rooms well ventilated are impotent measures against covid-19 pandemic. Since ARDS, followed by secondary infection, antiviral therapy, antibiotics, corticosteroids and anti-inflammatory drugs are generally used in treatment of Covid-19 infections.²¹ Covid-19 basically involved the pulmonary system, yoga and aerobic exercise may play important role in maintenance of health in post covid infection cases.

Conclusion:

Covid-19 affects people worldwide since 2020. While vaccination have been the main intervention that can help contain the spread of the virus, we are yet to find a permanent cure for

the disease. Hence, understanding the systemic physio pathological aspect of Covid-19 may help in contributing towards finding the solution that is needed at present and developing a treatment module in this regard.

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