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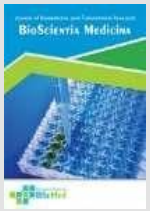

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Pathogenesis Coronavirus Disease 2019 (COVID-19): Narrative Literature Review

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A B S T R A C T

The pathogenesis of COVID-19 occurs in 3 phases according to the pathophysiology and clinical degree. The three phases are grouped into the initial phase of infection, the pulmonary phase, and the hyperinflammatory phase. The initial phase of infection begins with the inoculation of the virus into host cells. This virus infects cells in the airways that line the alveoli. SARS CoV-2 will bind to receptors found on the epithelium of the respiratory tract, gastrointestinal tract, and endothelium of blood vessels and make its way into cells. The second phase is the pulmonary phase. In this phase, there is viral multiplication and inflammation in the lungs. The binding of SARS-CoV-2 to the ACE2 receptor causes ACE2 deficiency and an imbalance of the renin-angiotensin system (RAS). In the third phase, namely hyper inflammation, excessive cytokine production after SARS-CoV-2 infection will increase the permeability of the capillary wall membrane around the infected alveoli, causing edema, pulmonary dyspnea, and hypoxemia. The presence of plasma fluid in the alveoli and loss of elasticity due to decreased surfactant function due to type 2 pneumocyte infection caused by SARS-CoV-2 infection causes acute respiratory distress syndrome in COVID-19 patients.

1. Introduction

Coronavirus Disease 2019 (COVID-19) is a new viral infectious disease that has become a pandemic since it was first discovered in Wuhan, China, at the end of 2019. The COVID-19 pandemic is a major problem in the world today, causing the deaths of millions of people and negatively impacting the global economy and health system. As of March 14, 2021, about 119 million people were infected with the SARS-CoV-2 virus, which caused the death of 2.6 million people worldwide. In Indonesia, as many as 1.4 million people suffer from COVID-19, with a death rate of 38,329 people as of March 14, 2021. The new Beta coronavirus strain known as severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) is the cause of COVID-19. The SARS-CoV-2 virus has a spherical morphology that looks like a solar corona with a diameter varying from about 60-140 nm and a spike around 9-12 nm. The SARS-CoV-2 virus contains a nucleocapsid protein (N), spike glycoprotein (S), membrane glycoprotein (M), and envelope glycoprotein (E) as structural components.[1-5]

Epidemiology

This 2019 coronavirus disease (COVID-19) was first reported to the World Health Organization (WHO) on December 31 2019. On March 11 2020, WHO declared the COVID-19 outbreak a global pandemic. Data from

WHO, until the second week of February 2021, the total number of COVID-19 cases worldwide has reached 107 million cases, with 54 million cases recovered and 2.7 million cases dying. Until now, the data has continued to increase. This indicates that this pandemic is not over.[6-9]

Pathogenesis

In general, the pathogenesis of COVID-19 occurs in 3 phases according to the pathophysiology and clinical degree. The three phases are grouped into the initial phase of infection, the pulmonary phase, and the hyperinflammatory phase, as described in the following figure:

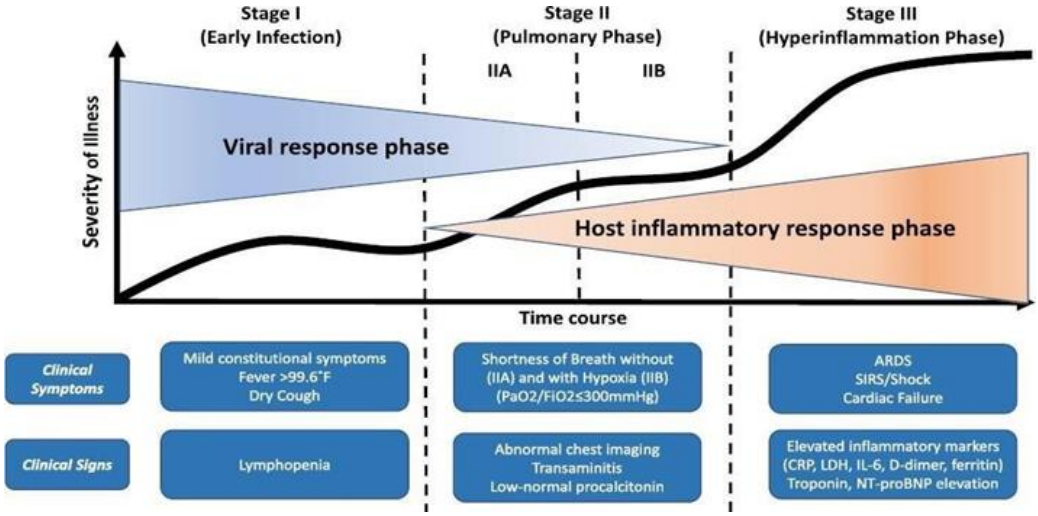

Figure 1. Classification of the clinical phase of COVID-19

The initial phase of infection begins with the inoculation of the virus into *host cells.* This virus infects cells in the airways that line the alveoli. SARS CoV-2 will bind to receptors found on the epithelium of the respiratory tract, gastrointestinal tract, and endothelium of blood vessels and make its way into the cell. The virus enters the host by recognizing the *angiotensin-converting enzyme 2* (ACE2) receptor via *spike* glycoprotein that induces membrane fusion, resulting in the release of the viral genome in the cytoplasm. Virus Ribonucleic Acid (RNA) is translated into a polyprotein which is then cleaved by the coronavirus protease enzyme (CLpro) to form non-structural such as RNA dependent RNA polymerase (RdRp) for viral RNA replication.RNA viruses' Positive sense then undergoes a translation into structural proteins (N, S, M, and E) where S, M, and E are processed in the endoplasmic reticulum (ER), while N proteins are processed in the cytoplasm where they are assembled with viral RNA replicas. All components are then combined in the ER-Golgi inter compartment (ERGIC), in which virions are released in vesicles and secreted outside the cell by exocytosis.[10-13]

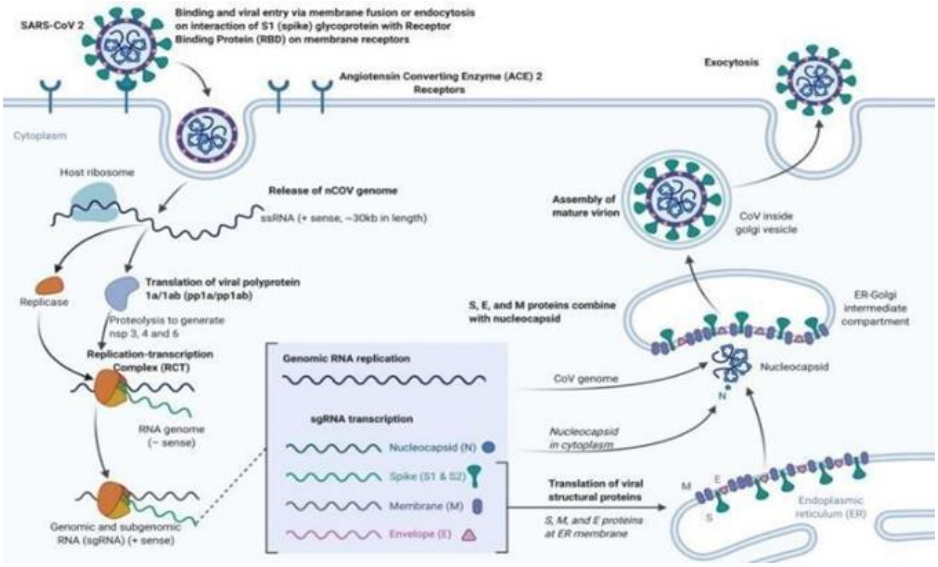

Figure 2. Mechanism of Coronavirus infecting cells

When the virus enters cells, its antigens are presented to Antigen Presenting Cells (APC) cells which are the center of the body's antiviral immunity. Antigenic peptides are represented by the major histocompatibility complex (MHC) and are then recognized by Cytotoxic T lymphocytes (CTL). The presentation of the SARS-CoV antigen is dependent on the MHC I molecule, but MHC II also contributes to its presentation. Antigen presentation further stimulates humoral and cellular immunity mediated by B and T cell viruses. The antibody response to the SARS-CoV virus has a characteristic pattern of production of Immunoglobulin M (IgM) and Immunoglobulin G (IgG). SARS-specific IgM antibodies disappeared at week 12, whereas IgG antibodies persisted for a long time.[14]

As a result of the above series of viral inoculation cycles against the affinity of the angiotensin-converting enzyme 2 in the lung, the infection presents in mild respiratory and systemic clinical forms. Diagnosis in this phase can be confirmed by examination of the polymerase chain reaction (PCR) of respiratory samples, chest X-ray, blood type count, and liver function. Examination of the blood type will reveal lymphopenia and neutrophilia without significant clinical abnormalities.[11-13]

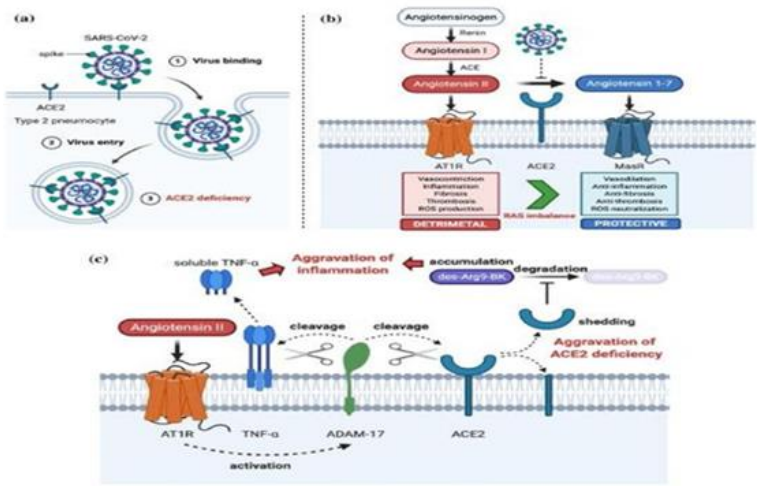

Figure 3. The pulmonary phase of COVID-19

The second phase is the pulmonary phase. In this phase, there is viral multiplication and inflammation in the lungs. The binding of SARS-CoV-2 to the ACE2 receptor causes ACE2 deficiency and an imbalance in the Renin-Angiotensin System (RAS). RAS has been known as a system that plays a role in controlling the work of the cardiovascular system through the modulation of blood pressure. In RAS, angiotensin I will be converted to angiotensin II by ACE, which will then bind to the angiotensin II type 1 receptor (AT1R) to carry out its function in vasoconstriction, inflammation, fibrosis, thrombosis and produce Reactive Oxygen Species (ROS). Angiotensin I will be degraded to angiotensin 1-7. Angiotensin 1-7 then binds to a receptor called masR so that it has the opposite effect to the binding between angiotensin I and AT1R. The imbalance of the RAS system above causes overactivity, inflammation, fibrosis, thrombosis, and the production of Reactive Oxygen Species (ROS), thus triggering a pro-inflammatory condition. During this phase, the patient clinically developed viral pneumonia, presenting with cough, fever, and hypoxia. Radiological examination of the chest, bilateral infiltrates, or ground-glass opacity. Lymphopenia was found on blood tests. Inflammatory markers are elevated. In this phase, the patient usually requires treatment in the hospital.[12-14]

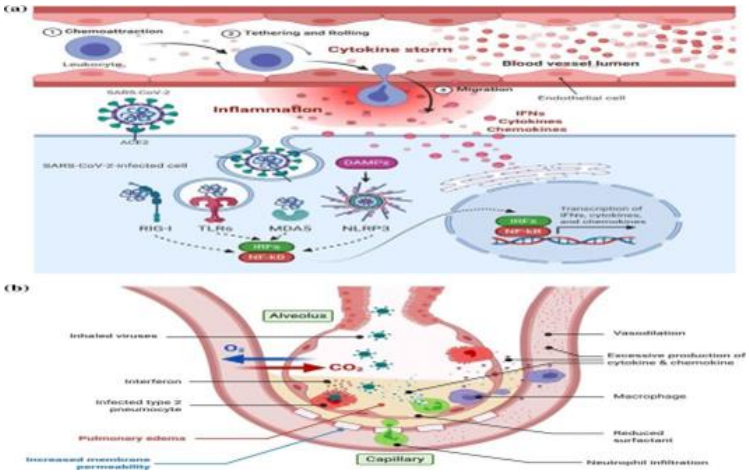

Figure 4. The hyperinflammatory phase of COVID-19

In the third phase of hyper inflammation, excessive cytokine production after SARS-CoV-2 infection will increase the permeability of the capillary wall membrane around the infected alveoli, causing edema, pulmonary dyspnea, and hypoxemia. The presence of plasma fluid in the alveoli and loss of elasticity due to decreased surfactant function due to type 2 pneumocyte infection caused by SARS-CoV-2 infection resulted in Acute Respiratory Distress Syndrome in COVID-19 patients.[11] The large amounts of cytokines released into the blood can also promote systemic inflammatory reactions. This results in vasodilation and a decrease in blood pressure, which will lead to plasma loss in the cardiovascular system, followed by circulatory collapse. These proinflammatory cytokines will increase the expression of cell adhesion molecules on the surface of neutrophils and endothelial. This will increase intracellular interactions between neutrophils and endothelial cells, as well as increase the permeability of the pulmonary endothelium and decreases barrier protection by attracting neutrophils to be infected through the endothelium. This dysregulation of the inflammatory immune response activates the adaptive immune system. As a

consequence of this abnormal immune system caused by SARS-CoV-2, microbial infection, septic shock, and severe multi-organ dysfunction can occur.[15,16]

2. Conclusion

The pathogenesis of COVID-19 consists of 3 main phases, namely early infection, pulmonary phase, and hyper inflammation phase.

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