COVID-19: THE PATHOGENESIS AND PATHOPHYSIOLOGY

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ABSTRACT

Recently, coronavirus disease-19 (COVID-19) considered as novel pulmonary diseases, and it is considered as emerging virus that led to the pandemic and considered a zoonotic that most commonly spreads direct contact through respiratory and mucosal membranes. COVID-19 especially affects the lungs and immune systems especially in an aged people. This review is aimed to understand the pathogenesis and pathophysiology that might help the clinicians and researchers for more effectiveness management to avoid future risks of COVID-19. The scientific information was collected from Medline of EBSCO, Science Direct, Scopus, and BioMedical. The main clinical symptoms of COVID-19 showed fever, chill, coughing, dyspnea, headache, sore throat, and chest pain. SARS-CoV-2 is more severe than SARS-CoV. The replication of the viral genome within the host cells is a pathway of infected stage of the SARS-CoV-2, which considered as viral life cycle with complex process involving translation of the viral polymerase and host proteins in order to perform RNA proofreading.

Keywords: Pathogenesis, Pathophysiology, COVID-19, SARS-CoV-2

I. INTRODUCTION

Pandemic of coronavirus disease-19 (COVID-19) recently consider as novel and outbreak coronavirus respiratory system and atypical pneumonia, first report of COVID-19 was in Wuhan, China in early December 2019, then it dramatically spread as a pandemic over the world with confirmed infections cases (1). Coronaviruses might consider as emerging and pandemic pathogens. Coronavirus disease 2019 (COVID-19) is considered a zoonotic disease that commonly spread through respiratory system transmission (2). The first cases of “an atypical pneumonia” appeared in the Guangdong Providence (China) in late 2002 (3). The early symptoms identification of pulmonary disease with a new respiratory illness was a severe acute respiratory syndrome (SARS) (4). A novel coronavirus pandemic recently diagnosed as the causative agent of the severe acute respiratory syndrome (SARS) outbreak worldwide. Many reports firmly the incidence of a Coronavirus outbreak given the estimation of a reproduction the Novel Coronavirus (COVID-19, named by WHO on Feb 11, 2020) (5). The first cases and outbreak of COVID-19 infections were reported on December 2019 (6). The severe clinical signs of COVID-19 are associated with an increasing the morbidity rate in the epidemic region of China, there was approximately cases have identified median age of the deaths (7). Although, COVID-19 especially affects the pulmonary and immune systems, cardiovascular, urinary, systems and nervous systems especially in the aged people (8). This review is aimed to understand the pathogenesis and pathophysiology that might help the clinicians and researchers for more effectiveness management to avoid future risks of COVID-19.
II. MATERIALS AND METHODS

Information Sources
Over the period of one year and a half, the researcher performed throughout of the articles review. The search included Medline of EBSCO, Science Direct, Google Scholar, PubMed, Scopus and Bio Medical. The terms that have searched were histopathology, pathogenesis and pathophysiology and lung pathology in COVID-19.

The research Criteria
The articles and publication that reported on histopathology, pathogenesis, and pathophysiology researchin patients with COVID-19 articles were used in the study. This article review was not obtained the ethical approval because the information’s were obtained from published data and information of human issues were not involved directly. On another hand, studies and publication with incomplete information were excluded.

Coronaviruses Outbreak
Coronaviruses consider a large group of enveloped virus with single-stranded polyadenylated largest viral RNA genomes classified in the Nidovirales order (9). Coronaviruses might infect different species of mammals and humans causing diseases of encephalitis, pneumonia to enteritis. These viruses infection caused a substantial morbidity and mortality, leading to major economic losses. These pathogens are transmissible porcine respiratory and infectious bronchitis and pneumonitis. These viruses might casus high morbidity but in a small percentage of cases, especially when the virus got mutation to become more virulent (10). Update, these viruses are highly pathogenic and deadly human coronaviruses, namely SARS-CoV, MERS-CoV and SARS-CoV-2. Moreover, the fast transmutation and spreading of transmission of the SARS-CoV-2 pandemic and causes more worldwide panic (11,12).

Coronavirus Replication and Pathogenesis
The mechanism of disease in the simplest way just tries to swallow this one. It believes that the beneficial of understanding how the disease COVID-19 starts and ends in a humans and so here is a simplified explanation of it. The virus only comes from an infected living organism of man or animals (13), it jumps to another human thru the mucus membranes of the eye, nose, mouth, and throat as it is contaminated unconsciously by way of aerosol, droplets or directly through dirty hands (14). Then the virus attaches to the cells of the mucus membranes and enters the cells by a process called endocytosis where the cell creates an invagination that carries the virus inside. Then the virus which is now covered by the cell membrane is taken into the nucleus of the cell and there multiplies and destroys the host cell while releasing multitude of its kind. Perico et al. (15) reported, the host cells and tissue injured mechanism caused by SARS-CoV infection might propose and containing of three different phases that included the viral replication, host immune hyperactivity, and the host pulmonary inflammation. SARS pathogenesis of the pulmonary was associated with diffuse alveolar destruction, and an increase of inflammatory cells infiltration of macrophage or epithelial origin. Pro-inflammatory cytokines of inflammatory mediators released and stimulated the active macrophages in the alveoli, which have a pathogenesis role of SARS (16).

When the patient is asymptomatic after several days being confined and cared for in the hospital, will a negative PCR test declare the patient recovered. PCR has low sensitivity and studies have shown based on its test done with different samples i.e. nasopharyngeal swab, bronchial lavage, sputum etc. taken at different stages of the disease, sensitivity which is the ability of the test to detect a positive, range from 54% to 75% which leaves a lot of possible negative tests. Therefore, a patient declared negative by PCR, may not be very free of the virus and there still are possibilities of the patient harboring viruses and retaining its capacity to transmit it. However, Gao et al. (17) reported there is an evidence of COVID-19 patients with asymptomatic or mild symptoms, but it may have a chance to transfer the virus to other contact persons, delay in screening for asymptomatic of cases, which leads to difficult for treatment, prevention and control of the outbreak, therefore it needs more consideration and efficiently management system. A positive PCR test during this time eliminates the possibility of being completely recovered and the patient remains infectious, while a negative PCR test will not be an assurance of the patient being completely free of the virus due to its low sensitivity. Previous study by Wang (18) reported that a correlation with antibody test would complement the PCR and the clinical findings. This alteration might support the roles of the combined method for identification of SARS-COV-2 with a high level of sensitivity, specificity, accurate diagnosis methods, with more suspected treatment and management patients, epidemiological studies, which are more important for monitoring current outbreaks of with SARS-COV-2 infections.
The highest pathogenesis of COVID-19 infection of pulmonary system was targeting by virus with severe pulmonary pneumonitis, RNAaemiacombined and incidencethe acute cardiac injury (19). More interestingly, the highest levels of cytokines and other inflammatory mediators were presented in cases infected with COVID-19 that involved IL1-β, IL1RA, IL7, IL8, IL9, IL10, basic FGF2, GCSF, GMCSF, IFNγ, IP10, MCP1, MIP1α, MIP1β, PDGFB, TNFa, and VEGFA. On another hand, some patients with severe condition that were admitted to the hospitals and intensive care unit present high blood levels of pro-inflammatory cytokines including IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1α, and TNFa that might cause and promote more severity (19, 20). The specific spike protein the virus binds to specific host receptors that called receptor-binding domains (RBDs) of angiotensin-converting enzyme 2 (ACE2). The replication of the viral genome within the host cells is a pathway of infected stage of the SARS-CoV-2, which considered as viral life cycle with complex process involving translation of viral polymerase protein and host cells proteins in order to perform RNAof final capping (Figure 1). The ACE2 protein has been identified in various human organs, including the pulmonary system, GI tract, lymph nodes, thymus, haemopoietic tissues, and central never system (21). Using cryoelectron microscopy of Chinese scientists discovered the attachment of the virus to the ACE2 receptors of angiotensin converting enzyme 2 that present in the vascular endothelium and in various organs. Primed by proteolytic enzymes like TMPRSS2, the virus starts to enter the cell wall. Assisted by furins, the virus enters inside the cell and travels within the cells as vesicles, goes to the endosomes where it loses its glycoprotein coat and the naked viral RNA enters the nucleus. In the nucleus, it replicates and the thousands of new copies. The new viruses leave the dead cells in huge numbers and are primed while leaving the cells, thus are ready to infect other cells or spread in the environment as highly infectious microdroplets during coughing, sneezing or even breathing or talking. Wu et al. (22) reported angiotensin converting enzyme 2 (ACE2) roles as a functional receptor for SARS-CoV that appears more likely to mediate the 2019-nCoV intracellular into human systems. The roles of ACE2 as an enzymatic catalyst onto the receptor of coronavirus might invade the host cells, viral binding, expression, and virus transmission into susceptibility population. Therefore, the researchers have been recently speculated on the pathogenesis of COVID-19 and that might make available and suitable therapeutic management against the virus.

III. PATHOLOGY AND PATHOPHYSIOLOGY

The factors are involved to differentiate case scenario of the clinical outcome is dependent on two main factors which is the virus and the other is the host. Factors involving the virus include the viral load that the host gets initially. Repeated exposure will result in increasing capability of the virus to multiply inside the cells in different stages, which in turn results in heavy load of viruses in the initial phase of the disease. On the other hand, factors of the host include his physical condition i.e. good immunity, well rested and less exposed to the source of the virus. Therefore, if the patient is infected but with little amount of virus, the immune system will take care of the condition and the virus just go away and disintegrates. It becomes "self-limited" but if the host is constantly exposed, and the patient is infected many times and the immune system gets overwhelmed, then the disease progresses on its full course. In a host with weak immune system, a small viral load will cause a serious disease such as in the elderly, people with co-existing diseases and the very young. Once the lungs considered the primary organ affected and the inflammation of the lung is called pneumonitis but when consolidation (lung becoming solid) occurs, it is called pneumonia. The inflammation in the lungs will be focused in the walls of the air sacs with thickening of the walls due to fluid accumulation within the walls (interstitial edema). Now, shortness of breath is evident because the rest of the body receives reduced oxygen from the blood (hypoxemia-low blood oxygen) and increased effort in breathing is manifested by the patient. Exchange of gases (Oxygen: Carbon dioxide) in the lungs is blocked due to the thickening of its wall (alveolo-capillary block) resulting in low oxygen levels in the blood. As the inflammation progresses, fluid seeps into the air sacs (alveoli) and fill it up with fluid. At this point, the breathing becomes more vigorous extremely shortness of breath or air hunger. Because the fluid is protein rich, as it stagnates within the air sacs, it forms into gel and x ray will show the "ground glass" pattern. Mechanical respirators are required to assist the breathing this time or else the patient will drown. Fluid in the lungs (non-cardiac cause), low oxygen in the blood which is not corrected with oxygenation, and inability of the lung to expand and an acute respiratory distress syndrome condition might be next sequences occur (23, 24).

Meanwhile, the virus continues to multiply and overwhelms the entire body system, the heart starts to fail and also the kidneys and the rest of the organs. The blood clotting mechanism is activated during this time and hence massive small clots occur in the circulation, which consumes all of its components, and hemorrhages may occur. Remember, all of these events are sequential, overlapping, and sometimes simultaneous. All of these resulting from the inflammatory reaction with the key role of chemicals produced by various cells (white blood cells) called Cytokines. Cytokines are protein substances produced by cells to activate other cells, very commonly the white
blood cells. This triggers a sequence of events calling on and calling off different cells to get involved or stop working. Some cells are inhibited while some cells are stimulated and unfortunately, some important cells are inhibited abnormally and thereby promote the multiplication and propagation of the virus and hence when this happens the condition worsens as described above. Finally, when cytokines are massively elaborated a complex inflammatory sequel called Cytokine Storm occurs which causes demise of the patient, this is the grim fullness of the course of the disease. These pathological events have been highlight by another researcher, which confirmed the haemodynamic finding of COVID-19 cases necessitating mechanical of ventilation and combined cardiopulmonary alterations. The pulmonary vascular disorders that reduced hypoxic vasoconstriction is associated with high post-capillary pulmonary and cardiac output with rickety hypertension that could eventually contribute to pulmonary stiffness and promote a vicious circle between the pulmonary and cardiovascular system (23).

Multiplication of the virus takes place in many cells reaching other cells directly and through the body fluids and blood and the body reacts by activating the immune system and the result is inflammation of various organs. In the sneezing, the cells in the nose and in the throat get involved and swelling produces oozing of fluid that stimulates the sneeze. This is what it called as runny nose and dry cough initially, the cough is dry not really due to the involvement of the lungs but rather due to a condition that call "post nasal drip" where the fluid that exudes from the nose drips to throat and causes itchiness and a dry cough. The virus continues to multiply and more cells are produced in many tissues. They may be found even in the saliva and in the glands of the respiratory passages, that is why this is where they get a swab and sometimes saliva spit for a PCR test. There may be viruses now in the lungs attached to the cells of the air sacs (alveoli). As more virus are produced, more cells are infected and then it goes to the blood they call this as viremia. At this time of viremia, fever becomes a prominent sign, could have started as a slight increase in body temperature, which may be missed. But during this viremic stage, fever is definite. May also be accompanied by dry cough that is more pronounced and may be associated with some degree of shortness of breath (SOB). The virus has an affinity to the cells of the lungs, so the lungs are infected not only directly during the initial stage but also via the blood during the viremic phase. Chaolin et al (25) has been reported the clinical condition at this stage is progressive and the viremia will allow the virus to reach to all organs of the body including the heart causing carditis, gastro intestinal system causing diarrhea, liver, brain and virtually into all possible areas of the body. Infected cases with COVID-19 appeared with increasing of leukocyte numbers, respiratory disorders, and in elevation levels of plasma pro-inflammatory cytokines. Previous study of COVID-19 patients showed high fever presented with a cough, pulmonary disorders. The patient's sputum showed positive molecular test confirmed COVID-19 infection (26).

Clinical Findings

The patients showed hyperthermia with temperatures of 38.9 °C. Molecular investigation of nasopharyngeal swab was showed positive in the patients, while who achieved different tests during the hospitalization. Some patients ultimately showed elevated white blood cells (WBC) over time are including neutrophil, and lymphocyte counts with the prominent of lymphocytopenia. Extra clinical finding are represented specific corresponding of organ tissue and cells injuries, increasing the pro-BNP, hypertensive of cardiac troponin (hs-cTnI) and LDH in myocardial patients. An aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), and total bilirubin tests were showed within normal rates in some patients (26).

Histopathological Findings

Clinical examination of the chest CT scan showed a pneumonia of an acute respiratory distress syndrome (19). Histopathological findings showed a major changing in the pulmonary tissue that involved the alveolar wall epithelial damage, hyaline degeneration, and hyperplasia of type II pneumocytes. Then in the advance cases, most of components of pulmonary tissue presented diffuse alveolar damage. Fibroblastic hyperplasia with extracellular matrix, fibrin forming and debrismassin the alveolar spaces were evidenced (27). Multifocal of peripheral ground-glass opacities were observed in subpleural regions of the lungs. Microscopic findings of the pulmonary showed multifocal or diffuse alveolar damage (DAD). Hyaline degeneration and bleed vessels congestion that presented as an acute inflammation (Fig. 2A–C), these finding were associated with scant of inflammatory cells such as pneumocyte necrosis with multifocal sloughing and formation of syncytial giant cells (Fig. 2A). 2B showed proliferation of large rich protein deposition, 2C intra-alveolar fibrin with organization, lymphocytes, active macrophages, and multinucleated giant cells, 2D) hyperplastic pneumocytes, some with suspected viral inclusions (27, 28).
There are exhibited focal interstitial thickening and lymphocytic cellular infiltration (Fig. 3A). In an advance cases, the more changes are the hyaline membranes in the alveolar paces, intra-alveolar hemorrhages and congestion, is same time there was scanty fibrin formation observed (Fig. 3B). The pulmonary alveolar wall showed fibrin formation with infiltration of mononuclear inflammatory cells and hyperplasia of stromal cells and type II pneumocyte. It was clearly noted the alveolar interstitial thickening and the fibrinoid degeneration of the small vessels (Fig. 3C, inset). On another hand, there was an indication of multifocal association of intra-alveolar inflammatory cells such as neutrophil that showed as a bronchitis or bronchopneumonia might because of secondary bacterial infection (Fig. 3D) (28).

This review article is considered on investigation of promptly advancing information and updated knowledge of COVID-19 on the pulmonary pathology and pathophysiology. However, the ARDS might associate with COVID-19 appeared to existent the major two principal distinct phenotypes: type L and type H. There "L" refers to low elastance, ventilation ratio, lung capacity, and recruits ability, and "H" refers to high pulmonary elastance, edema, and recruits ability.

IV. CONCLUSION
Pathophysiology mechanisms might lead to changes in pulmonary perfusion that might cause by more than one factors. These combination factors are 1) renin-angiotensin system dysregulation, 2) thrombosis and hemorrhage that caused blood vessels endothelium cell damages, 3) hypoxia pulmonary vasoconstriction led to endothelial dysfunction, and 4) collapsed of the pulmonary tissue led to the hyperperfusion. The pathologic changes pneumonia varied among the patients but consistent with diffuse alveolar damage caused by COVID-19. Early pathological changes were noted without fibrosis formation, while in advance cases there were hyperplasia of stromal cells led to interstitial thickening of alveolar walls.

Conflict of Interest
The authors have declared no conflicts of interest.

Ethical Approval
This article review was not obtained the ethical approval because the information’s were obtained from published data and information of human issues were not involved directly.

Authors’ Contributions
KAJ and his coauthors were contributed equally to this manuscript.

REFERENCES

Figure 1: SARS COV2- Replication pathway of the virus that enclosed by the host membrane, releasing the genome within the host cells, then translation of viral polymerase protein to release of virion.

Figure 2: Histolopathological changes of the lung infected with COVID-19 showed (2A) Proteinaceous exudates in alveolar spaces, with granules; (2B) scattered large protein globules (arrows); (2C) intra-alveolar fibrin with early organization, mononuclear inflammatory cells, and multinucleated giant cells; (2D) type II pneumocyte hyperplasia, and mild interstitial thickening, some with suspected viral inclusions (arrow)(27).
Figure 3: Histopathological changes of the lung infected with COVID-19 showed focal hyaline membrane, type II pneumocyte hyperplasia, and mild interstitial thickening (3A); alveolar spaces were filled with red blood cell exudation, and small fibrin plugs seen in adjacent alveoli (3B) Organization with intra-alveolar fibroblasts mixed with fibrin and inflammatory cellular infiltration. Diffuse type II pneumocyte hyperplasia in the background (inset: fibrinoid vascular necrosis, arrowheads) (3C). Changes of bronchopneumonia with prominent neutrophilic infiltration filling up alveolar spaces (3D)(28).