**COVID-19, ITS AETIOLOGY, HISTOPATHOLOGICAL FEATURES AND CURRENT THERAPIES**

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**1.1: COVID-19**

Coronaviruses belong to the Coronaviridae family in the Nidovirales order. Corona represents crown-like spikes on the outer surface of the virus; thus, it was named as a coronavirus (Lupia *et al.,* 2020). Coronaviruses are minute in size (65–125 nm in diameter) and contain a single-stranded RNA as a nucleic material, size ranging from 26 to 32kbs in length. The subgroups of coronaviruses family are alpha (α), beta (β), gamma (y) and delta (∆) coronavirus (Shereen *et al.,* 2020). The severe acute respiratory syndrome coronavirus (SARS-CoV), H5N1 influenza A and Middle East respiratory syndrome coronavirus (MERS-CoV) cause acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) which leads to pulmonary failure and result in fatality (Lupia *et al.,* 2020). These viruses were thought to infect only animals until the world witnessed a severe acute respiratory syndrome (SARS) outbreak caused by SARS-CoV, 2002 in Guangdong, China. Only a decade later, another pathogenic coronavirus, known as Middle East respiratory syndrome coronavirus (MERS-CoV) caused an endemic in Middle Eastern countries Recently at the end of 2019, Wuhan an emerging business hub of China experienced an outbreak of a novel coronavirus that killed more than eighteen hundred and infected over seventy thousand individuals within the first fifty days of the epidemic (Lupia *et al.,* 2020). This virus was reported to be a member of the β group of coronaviruses. The novel virus was named as Wuhan coronavirus or 2019 novel coronavirus (2019-nCov) by the Chinese researchers (Shereen *et al.,* 2020). The International Committee on Taxonomy of Viruses (ICTV) named the virus as SARS-CoV-2 and the disease as COVID-19. In the history, SRAS-CoV (2003) infected 8098 individuals with mortality rate of 9%, across 26 countries in the world, on the other hand, novel corona virus (2019) infected 120,000 individuals with mortality rate of 2.9%, across 109 countries (Shereen *et al.,* 2020). **1.2: Aeitiology of COVID-19**

All coronaviruses contain specific genes in ORF1-Protein downstream regions that encode proteins for viral replication, nucleocapsid and spikes formation. The glycoprotein spikes on the outer surface of coronaviruses are responsible for the attachment and entry of the virus to host cells (Xu *et al.,* 2020). The receptor-binding domain (RBD) is loosely attached among virus, therefore, the virus may infect multiple hosts. Other coronaviruses mostly recognize aminopeptidases or carbohydrates as a key receptor for entry to human cells while SARS-CoV and MERS-CoV recognize exopeptidases (Bai *et al.,* 2020). The entry mechanism of a coronavirus depends upon cellular proteases which include, human airway trypsin-like protease (HAT), cathepsins and transmembrane protease serine 2 (TMPRSS2) that split the spike protein and establish further penetration changes (Xu *et al.,* 2020). MERS-coronavirus employs dipeptidyl peptidase 4 (DPP4), while HCoV-NL63 and SARS-coronavirus require angiotensin-converting enzyme 2 (ACE2) as a key receptor (Bai *et al.,* 2020). SARS-CoV-2 possesses the typical coronavirus structure with spike protein and also expressed other polyproteins, nucleoproteins, and membrane proteins, such as RNA polymerase, 3- chymotrypsin-like protease, papain-like protease, helicase, glycoprotein, and accessory proteins (Shereen *et al.,* 2020). The spike protein of SARS-CoV-2 contains a 3-D structure in the RBD region to maintain the van der Waals forces. The 394 glutamine residue in the RBD region of SARS-CoV-2 is recognized by the critical lysine 31 residue on the human ACE2 receptor (Shereen *et al.,* 2020).



Figure 1.1: Aetiology of COVID-19 (Shereen *et al.,* 2020).

**1.3: Pathogenesis of COVID-19**

The severe symptoms of COVID-19 are associated with an increasing numbers and rate of fatalities especially in the epidemic region of China. On January 22, 2020, the China National Health Commission reported the details of the first 17 deaths and on January 25, 2020 to 56 deaths (Rothan & Byrareddy, 2020). The percentage of death among the reported 2684 cases of COVID-19 was approximately 2.84% as of Jan 25, 2020 and the median age of the deaths was 75 (range 48–89) years. Patients infected with COVID-19 showed higher leukocyte numbers, abnormal respiratory findings, and increased levels of plasma pro-inflammatory cytokines (Rothan & Byrareddy, 2020). One of the COVID-19 case reports showed a patient at 5 days of fever presented with a cough, coarse breathing sounds of both lungs, and a body temperature of 39.0 °C. The patient's sputum showed positive real-time polymerase chain reaction results that confirmed COVID-19 infection. The laboratory studies showed leucopenia with leukocyte counts of 2.91 × 10^9 cells/L of which 70.0% were neutrophils (Rothan & Byrareddy, 2020). Additionally, a value of 16.16 mg/L of blood C-reactive protein was noted which is above the normal range (0–10 mg/L). High erythrocyte sedimentation rate and D-dimer were also observed. The main pathogenesis of COVID-19 infection as a respiratory system targeting virus was severe pneumonia combined with the incidence of ground-glass opacities, and acute cardiac injury (Chen *et al.,* 2020). Significantly high blood levels of cytokines and chemokines were noted in patients with COVID-19 infection that included Interleukins IL1-β, IL1RA, IL7, IL8, IL9, IL10, basic FGF2, GCSF, GMCSF, IFNγ, IP10, MCP1, MIP1α, MIP1β, PDGFB, TNFα, and VEGFA. Some of the severe cases that were admitted to the intensive care unit showed high levels of pro-inflammatory cytokines including IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1α, and TNFα that are reasoned to promote disease severity (Chen *et al.,* 2020).

**1.4: Histopathological Features of COVID-19**

The pathological features of COVID-19 greatly resemble those seen in SARS and Middle Eastern respiratory syndrome (MERS) coronavirus infection. In addition, the liver biopsy specimens of the patient with COVID-19 showed moderate micro vesicular steatosis and mild lobular and portal activity, indicating the injury could have been caused by either SARS-CoV-2 infection or drug-induced liver injury (Gao *et al.,* 2020). There were a few interstitial mononuclear inflammatory infiltrates, but no other substantial damage in the heart tissue. Peripheral blood was prepared for flow cytometry analysis. We found that the counts of peripheral CD4 and CD8 T cells were substantially reduced, while their status was hyper activated, as evidenced by the high proportions of HLA-DR (CD4 3·47%) and CD38 (CD8 39·4%) double-positive fractions (Gao *et al.,* 2020). Moreover, there was an increased concentration of highly proinflammatory CCR6+ Th17 in CD4 T cells. Additionally, CD8 T cells were found to harbor high concentrations of cytotoxic granules, in which 31·6% cells were performing positive, 64·2% cells were granulysin positive, and 30·5% cells were granulysin and performing double-positive (Gao *et al.,* 2020). Test results imply that over-activation of T cells, manifested by increase of Th17 and high cytotoxicity of CD8 T cells, accounts for, in part, the severe immune injury in this patient. X-ray images showed rapid progression of pneumonia and some differences between the left and right lung (Gao *et al.,* 2020). In addition, the liver tissue showed moderate micro vesicular steatosis and mild lobular activity, but there was no conclusive evidence to support SARS-CoV-2 infection or drug-induced liver injury as the cause (Gao *et al.,* 2020).

**1.5: Symptoms of COVID-19**

The symptoms of COVID-19 infection appear after an incubation period of approximately 5.2 days. The period from the onset of COVID-19 symptoms to death ranged from 6 to 41 days with a median of 14 days. This period is dependent on the age of the patient and status of the patient's immune system (Lupia *et al.,* 2020). It was shorter among patients over 70-years old compared with those under the age of 70. The most common symptoms at onset of COVID-19 illness are fever, cough, and fatigue, while other symptoms include sputum production, headache, hemoptysis, diarrhea, dyspnea, and lymphopenia. Clinical features revealed by a chest CT scan presented as pneumonia, however, there were abnormal features such as RNAaemia, acute respiratory distress syndrome, acute cardiac injury, and incidence of grand-glass opacities that led to death. In some cases, the multiple peripheral ground-glass opacities were observed in sub pleural regions of both lungs that likely induced both systemic and localized immune response that led to increased inflammation (Lupia *et al.,* 2020). Regrettably, treatment of some cases with interferon inhalation showed no clinical effect and instead appeared to worsen the condition by progressing pulmonary opacities. It is important to note that there are similarities in the symptoms between COVID-19 and earlier beta-coronavirus such as fever, dry cough, dyspnea, and bilateral ground-glass opacities on chest CT scans. However, COVID-19 showed some unique clinical features that include the targeting of the lower airway as evident by upper respiratory tract symptoms like rhinorrhea, sneezing, and sore throat (Lupia *et al.,* 2020). In addition, based on results from chest radiographs upon admission, some of the cases show an infiltrate in the upper lobe of the lung that is associated with increasing dyspnea with hypoxemia (Shereen *et al.,* 2020). Importantly, whereas patients infected with COVID-19 developed gastrointestinal symptoms like diarrhea, a low percentage of MERS-CoV or SARS-CoV patients experienced similar GI distress. Therefore, it is important to test fecal and urine samples to exclude a potential alternative route of transmission, specifically through health care workers, patients etc. (Shereen *et al.,* 2020). Therefore, development of methods to identify the various modes of transmission such as fecal and urine samples are urgently warranted in order to develop strategies to inhibit and/or minimize transmission and to develop therapeutics to control the disease (Shereen *et al.,* 2020).

**1.6: Current Therapies of COVID-19**

The person-to-person transmission of COVID-19 infection led to the isolation of patients that were administered a variety of treatments. At present, there are no specific antiviral drugs or vaccine against COVID19 infection for potential therapy of humans (Xu *et al.,* 2020). The only option available is using broad-spectrum antiviral drugs like Nucleoside analogues and also HIV-protease inhibitors that could attenuate virus infection until the specific antiviral becomes available. The treatment that have so far been attempted showed that 75 patients were administrated existing antiviral drugs (Xu *et al.,* 2020). The course of treatment included twice a day oral administration of 75 mg oseltamivir, 500 mg lopinavir, 500 mg ritonavir and the intravenous administration of 0·25 g ganciclovir for 3–14 days. Another report showed that the broad-spectrum antiviral remdesivir and chloroquine are highly effective in the control of 2019- nCoV infection in vitro (Xu *et al.,* 2020). These antiviral compounds have been used in human patients with a safety track record. Thus, these therapeutic agents can be considered to treat COVID-19 infection (Bai *et al.,* 2020). Furthermore, there are a number of other compounds that are in development. These include the clinical candidate EIDD-2801 compound that has shown high therapeutic potential against seasonal and pandemic influenza virus infections and this represents another potential drug to be considered for the treatment of COVID-19 infection (Bai *et al.,* 2020). Along those lines, until more specific therapeutics become available, it is reasonable to consider more broad-spectrum antivirals that provide drug treatment options for COVID-19 infection include Lopinavir/Ritonavir, Neuraminidase inhibitors, peptide (EK1), and RNA synthesis inhibitors (Bai *et al.,* 2020). It is clear however, that more research is urgently needed to identify novel chemotherapeutic drugs for treating COVID-19 infections. In order to develop pre-and post-exposure prophylaxis against COVID-19, there is an urgent need to establish an animal model to replicate the severe disease currently observed in humans (Xu *et al.,* 2020). Several groups of scientists are currently working hard to develop a nonhuman primate model to study COVID19 infection to establish fast track novel therapeutics and for the testing of potential vaccines in addition to providing a better understanding of virus-host interaction (Bai *et al.,* 2020).

**1.7 Future of COVID-19**

Extensive measures to reduce person-to-person transmission of COVID-19 are required to control the current outbreak. Special attention and efforts to protect or reduce transmission should be applied in susceptible populations including children, health care providers, and elderly people (Lupia *et al.,* 2020). A guideline was published for the medical staff, healthcare providers, and, public health individuals and researchers who are interested in the 2019-nCoV (Lupia *et al.,* 2020). The early death cases of COVID-19 outbreak occurred primarily in elderly people, possibly due to a weak immune system that permits faster progression of viral infection (Lupia *et al.,* 2020). The public services and facilities should provide decontaminating reagents for cleaning hands on a routine basis. Physical contact with wet and contaminated objects should be considered in dealing with the virus, especially agents such as fecal and urine samples that can potentially serve as an alternative route of transmission (Rothan & Byrareddy, 2020). China and other countries including the US have implemented major prevention and control measures including travel screenings to control further spread of the virus (Rothan & Byrareddy, 2020). Epidemiological changes in COVID-19 infection should be monitored taking into account potential routes of transmission and subclinical infections, in addition to the adaptation, evolution, and virus spread among humans and possible intermediate animals and reservoirs (Rothan & Byrareddy, 2020).

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