**The Aetiology of COVID-19, its pathogenesis, histopathological features and the current potential therapies**

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**Table of Content**

* **Brief introduction to the virus (COVID-19)**
* **Aetiology of COVID-19**
* **Symptoms**
* **Pathogenesis of COVID-19**
* **Histopathological features of COVID-19**
* **Current Potential Therapies**
* **Antiviral agents**
* **Corticosteroids**
* **Antimicrobial therapy**
* **Anticoagulant**
* **Convalescent plasma therapy**
* **Conclusion**
* **References**

**Introduction**

 Wuhan City, Hubei province in China on 31st of December 2019 was the origin of a soon pandemic virus that lead to the death of thousands and the total shut down of all public and private organizations (Businesses, Schools of all levels, Markets, etc), eventually leading to the lock down of different countries across the globe restricting transportation and any form of social gathering was prohibited. Movements and physical interactions were asked to be limited to only the gathering of feeding and medicational resources, this virus at this time humbled the world in such a way it felt like a punishment from Mother Earth. What was the cause, how does it spread, what are its histopathological features and current therapies were the questions been asked, a virus that made the globe combine to battle a singular enemy we identified as the corona virus(COVID-19).

**Aetiology of COVID-19**

Wuhan, the most populous city in chain with a population of over 11 million people was the origin of the virus. Early cases involving the virus were all linked to a Wholesales Market called Wuhan’s Huanan Seafood which trades in fish and a variety of live animal species including poultry, bats, marmots, and snakes (Lu *et al*., 2020). The causative agent was identified from throat swab samples conducted by the Chinese Centre for Disease Control and Prevention (CCDC)on 7th of January 2020, and was subsequently named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The disease was named COVID-19 by the World Health Organization (WHO, 2020). To date, most SARS-CoV-2 infected patients have developed mild symptoms such as dry cough, sore throat, and fever. The majority of cases have spontaneously resolved. However, some have developed various fatal complications including organ failure, septic shock, pulmonary oedema, severe pneumonia, and Acute Respiratory Distress Syndrome (ARDS)(Chen *et al*., 2020). 54.3% of those infected with SARS-CoV-2 are male with a median age of 56 years. Notably, patients who required intensive care support were older and had multiple comorbidities including cardiovascular, cerebrovascular, endocrine, digestive, and respiratory disease. Those in intensive care were also more likely to report dyspnoea, dizziness, abdominal pain and anorexia(Wang *et al*., 2020)



**The chronological incidence of COVID-19 infections and death cases in China. Infections with COVID-19 appears in December 2019. At the time of preparing this manuscript, February 16, 2020 there have been 51,174 people who have contracted the infection in China, and more than 1666 people have died.**

**Symptoms**

The symptoms of COVID-19 infection appear after an incubation period of approximately 5.2 days(Li *et al*., 2020). The period from the onset of COVID-19 symptoms to death ranged from 6 to 41 days with a median of 14 days(Wang *et al*.,2020). This period is dependent on the age of the patient and status of the patient's immune system. It was shorter among patients >70-years old compared with those under the age of 70(Wang *et al*.,2020).  The most common symptoms at onset of COVID-19 illness are fever, cough, and fatigue, while other symptoms include sputum production, headache, haemoptysis, diarrhoea, dyspnoea, and lymphopenia(Huang *et al*., 2020). 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(Huang *et al*., 2020). In some cases, the multiple peripheral ground-glass opacities were observed in subpleural regions of both lungs(Lei et al.,2020)that likely induced both systemic and localized immune response that led to increased inflammation. Regrettably, treatment of some cases with interferon inhalation showed no clinical effect and instead appeared to worsen the condition by progressing pulmonary opacities(Lei et al.,2020).



**The systemic and respiratory disorders caused by COVID-19 infection. The incubation period of COVID-19 infection is approximately 5.2 days. There are general similarities in the symptoms between COVID-19 and previous betacoronavirus. However, COVID-19 showed some unique clinical features that include the targeting of the lower airway as evident by upper respiratory tract symptoms like rhinorrhoea, sneezing, and sore throat. Additionally, patients infected with COVID-19 developed intestinal symptoms like diarrhoea only a low percentage of MERS-CoV or SARS-CoV patients exhibited diarrhoea.**

It is important to note that there are similarities in the symptoms between COVID-19 and earlier betacoronavirus such as fever, dry cough, dyspnea, and bilateral ground-glass opacities on chest CT scans(Huang *et al*., 2020). However, COVID-19 showed some unique clinical features that include the targeting of the lower airway as evident by upper respiratory tract symptoms like rhinorrhoea, sneezing, and sore throat. 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(Phan *et al*.,2020). Importantly, whereas patients infected with COVID-19 developed gastrointestinal symptoms like diarrhoea, a low percentage of MERS-CoV or SARS-CoV patients experienced similar GI distress. Therefore, it is important to test faecal and urine samples to exclude a potential alternative route of transmission, specifically through health care workers, patients etc(Lee *et al*., 2003).

**Pathogenesis of COVID-19**

The severe symptoms of COVID-19 are associated with an increasing numbers and rate of fatalities specially 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 the death cases increased to 56 deaths(Wang *et al*.,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(Wang *et al*.,2020).

Patients infected with COVID-19 showed higher leukocyte numbers, abnormal respiratory findings, and increased levels of plasma pro-inflammatory cytokines. 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(Lei et al.,2020). Laboratory studies showed leucopenia with leukocyte counts of 2.91 × 10^9 cells/L of which 70.0% were neutrophils. 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(Lei et al.,2020).  The main pathogenesis of COVID-19 infection as a respiratory system targeting virus was severe pneumonia, RNAaemia, combined with the incidence of ground-glass opacities, and acute cardiac injury. Significantly high blood levels of cytokines and chemokines were noted in patients with COVID-19 infection that included 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(Huang *et al*., 2020).

**Histopathology of COVID-19**

Biopsy samples were taken from the lung, liver, and heart tissue of a patient. Histological examination showed bilateral diffuse alveolar damage with cellular fibromyxoid exudates. The right lung showed evident desquamation of pneumocytes and hyaline membrane formation, indicating acute respiratory distress syndrome. The left lung tissue displayed pulmonary oedema with hyaline membrane formation, suggestive of early-phase ARDS Interstitial mononuclear inflammatory infiltrates, dominated by lymphocytes, were seen in both lungs. Multinucleated syncytial cells with atypical enlarged pneumocytes characterized by large nuclei, amphophilic granular cytoplasm, and prominent nucleoli were identified in the intra-alveolar spaces, showing viral cytopathic-like changes. No obvious intranuclear or intracytoplasmic viral inclusions were identified.

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**Pathological manifestations of right (A) and left (B) lung tissue, liver tissue (C), and heart tissue (D) in a patient with severe pneumonia caused by SARS-CoV-2**

The pathological features of COVID-19 greatly resemble those seen in SARS and Middle Eastern respiratory syndrome (MERS) coronavirus infection(Ding *et al.,* 2003). In addition, the liver biopsy specimens of the patient with COVID-19 showed moderate microvesicular 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. There were a few interstitial mononuclear inflammatory infiltrates, but no other substantial damage in the heart tissue.

Other researches reports histopathological data obtained on the lungs of two patients who underwent lung lobectomies for adenocarcinoma and retrospectively found to have had the infection at the time of surgery. Apart from the tumors, the lungs of both 'accidental' cases showed edema and important proteinaceous exudates as large protein globules. The authors also reported vascular congestion combined with inflammatory clusters of fibrinoid material and multinucleated giant cells and hyperplasia of pneumocytes(Tian *et al.,* 2020)

**Current Potential Therapies**

* **Antimicrobial therapy**

It is widely recognized that many patients, especially critically ill patients were susceptible to secondary infections. Patients receiving corticosteroids had increased risks of developing HAP due to the immunosuppression effects, and those who received mechanical ventilation were susceptible to VAP. The latest guidelines issued by National Health Commission of China for the diagnosis and treatment of COVID-19 infection(NHC, 2020) advise against inappropriate and unnecessary use of antimicrobial therapy, especially combination of broad-spectrum antibiotics. If the sputum or blood specimens showed a clear evidence of etiology or the PCT levels increased, administration of antimicrobial agents should be considered.

* **Anticoagulant**

In clinical practice, nearly 20% of patients with COVID-19 are found to have abnormal coagulation function, and almost all severely and critically ill patients presented coagulation disorders(Chen *et al.,* 2020). In view of no relevant experience for reference, anticoagulation should be given with great caution in patients with DIC though micro thrombosis was observed in lung, liver, and other organs by autopsy. When patients exhibit a bleeding tendency or when surgical treatment is needed, platelet transfusion or administration of fresh-frozen plasma is recommended to correct coagulopathies analogs(Nishida *et al*., 2018). Low molecular weigh heparin (LMWH)can be used for drug prevention. As for subjects with clinical manifestations, clinicians need to be alert to the occurrence of PTE, initiate the diagnostic procedures, and develop corresponding treatment strategies based on risk stratiﬁcation. Considering the risk of disease transmission and the false positive results caused by the presence of lung lesions, the diagnosis of PTE by pulmonary ventilation-perfusion imaging is not recommended. If the critically ill patients cannot take examination due to speciﬁc conditions and the infectivity ofCOVID-19, it is recommended to perform anticoagulant therapy for patients without contraindications. If the condition is life threatening and bedside echocardiography indicates new onset of right ventricular volume overload or pulmonary hypertension, thrombolytic therapy or other cardiopulmonary support treatments, such as extracorporeal membrane oxygenation (ECMO) can be initiated with the patient’s full informed consent

* **Oxygen therapy**

For mild to moderate patients with hypoxemia, nasal catheters and masks and even high-ﬂow nasal cannula oxygen therapy (HFNC) are advised. While for severe and critical patients with respiratory distress, HFNC, noninvasive mechanical ventilation (NIV) or invasive mechanical ventilation, and even ECMO should be considered.

**HFNC (High-Flow Nasal Cannula Oxygen Therapy)**

HFNC can provide accurate oxygen concentration and a certain positive airway pressure to promote alveolar expansion to improve oxygenation and respiratory distress(Lee *et al.,* 2015) However, according to expert consensus on the use of HFNC for COVID-19, patients with cardiac arrest, weak spontaneous breathing, PaO2/FiO2 < 100 mmHg, PaCO2 > 45 mmHg and pH < 7.25 and upper airway obstruction are contraindicated.

**NIV or invasive mechanical ventilation**

For severe patients with respiratory distress or hypoxemia that cannot be alleviated after standard oxygen therapy, NIV can also be considered with close surveillance(Wang et al., 2020). Dangers et al. considered that changes in dyspnea could be used as a variable to predict the failure of noninvasive ventilation(Dangers *et al.,* 2018). If the patient continuously deteriorates or the respiratory rate cannot be improved after a short time (about 1–2 h), timely tracheal intubation and invasive ventilation are required. Notably, patients with hemodynamic instability, multiple organ failure or abnormal mental status should not receive noninvasive ventilation. Lung protection ventilation strategies (small tidal volume, limited plateau pressure, and permissive hypercapnia) are suggested to be adopted in invasive mechanical ventilation to reduce ventilator-related lung injury(Fan *et al*., 2018). Compared with NIV, invasive mechanical ventilation can more effectively improve the pulmonary ventilation function and respiratory mechanics of patients with acute respiratory failure. It can effectively increase the SaO2 level and is more conducive to lower the plasma BNP level. However, invasive mechanical ventilation requires tracheotomy, or oral/nasal tracheal intubation to establish an artiﬁcial airway, which is very likely to cause damage to patients, such as mediastinal emphysema, ventilator related lung injury, and other related complications, such as reduced swallowing function, gastroesophageal reﬂux, infections, etc

* **Continuous renal replacement therapy (CRRT)**

For critical patients, CRRT can support organ function, reduce cytokine storms and maintain internal environment stability. Three clinical studies showed that the incidence of AKI in patients with COVID-19 was 3% to 7%, and 7% to 9.0% were treated with CRRT. In ICU, the rate of CRRT application was 5.6% to 23.0% and reached as high as 66.7% to 100% in patients with AKI(Chen *et al*.,2020). CRRT is recommended for patients who exhibit AKI indications (hyperkalemia, acidosis, pulmonary edema, severe sodium ion disorders) or patients with CKD who have not undergone hemodialysis. During septic shock, CRRT can effectively remove inﬂammatory mediators and signiﬁcantly improve hemodynamics. When ARDS appears in combination with multiple organ dysfunction syndrome (MODS), early CRRT is recommended(Träger *et al.,* 2016). CRRT combined with the treatment of ECMO may remove cytokines, reduce the activity of macrophages and monocytes, and better preserve lung parenchyma.

* **Convalescent plasma therapy for COVID-19**

Some studies reported that early convalescent plasma treatment for inﬂuenza and SARS-CoV infection is associated with decreased viral load and reduction in mortality(Mair-Jenkins *et al.,* 2015), however, the studies were heterogeneous and of low quality. The WHO deemed convalescent plasma transfusion as the most promising therapy for MERS-CoV infection, while the efﬁcacy remained inconclusive, with a lack of adequate clinical trials(Mair-Jenkins *et al.,* 2015). Since the virological and clinical characteristics among SARS, MERS, and COVID-19 were comparable(Lee *et al.*, 2020), convalescent plasma could have immunotherapeutic potential in COVID-19 treatment and further investigations are needed to prove its safety and efﬁcacy. One possible explanation for the efﬁcacy of convalescent plasma therapy is that the neutralizing antibodies from convalescent plasma might suppress viremia(Chen *et al*., 2020), so understanding the antibody response during SARS-CoV-2 infection could provide strong empirical support for the application of convalescent plasma therapy. A study reported that on day 5 after treatment, an increase of viral antibodies can be seen in nearly all patients, IgM positive rate increased to 81%, whereas IgG positive rate increased to 100%, which was considered as a transition from earlier to later period of infection(Zhang *et al.,* 2020). Preliminary study has showed that patients who have recovered from COVID-19 with a high neutralizing antibody titer and could provide a valuable source of the convalescent plasma. Plasma transfusion may cause adverse effects, so convalescent plasma therapy is recommended as a last resort to improve the survival rate of severe patients with COVID-19. The optimal dose and treatment time point, as well as the therapeutic indications of convalescent blood products in COVID-19 remain uncertain, which need to be further investigated in randomized clinical studies

**Future of COVID-19 on public health**

The COVID-19 pandemic has created unprecedented disruption for the global health and development community. Organizations fighting infectious disease, supporting health workers, delivering social services, and protecting livelihoods have moved to the very center of the world’s attention. But they find their work complicated by challenges of access, safety, supply chain logistics, and financial stress like never before. The short-term implications of this global challenge are evident everywhere, but the long-term consequences of the pandemic — how it will reshape health and development institutions, occupations, and priorities — are still difficult to imagine.

The COVID-19 pandemic will transform the global health community’s acceptance and use of digital health technologies. As health systems around the world are overwhelmed responding to COVID-19 while continuing to provide health care services, leaders are adopting technologies that only three months ago were on the sidelines of most health care systems.

As doctors, patients and home care providers turn to telemedicine to reduce exposure to COVID-19, they are discovering these virtual consultations are effective for triaging care, sharing critical guidance, and providing emotional support.

Dashboards for logistic management systems are improving the efficient deployment of essential resources — from hospital beds to PPE to, ultimately, vaccines. More advanced technologies including AI are being employed to provide insights into complex questions of how individual behaviors impact transmission and identifying which policies are effective for specific groups.

As the saying goes, “you can’t put the genie back in the bottle.” Once deployed, the use of these technologies will only expand as we revert back to solving the challenges problems that preoccupied us prior to COVID-19 — too few health personnel, inadequate budgets, and weak health systems. Maybe these technologies will be what helps us get closer to our shared goal of universal health coverage.

*“COVID-19 could be what makes us finally deliver on the promises of remote learning and support, impacts that will serve health workers — particularly in rural areas — long after this pandemic ends.”*

**Conclusion**

In this assignment, I gave an overview of epidemiological, etiological, clinical, pathological, and imaging characteristics of COVID-19 and introduced the latest advancements in the treatment. This virus spreads mainly through respiratory droplets and close personal contact. A series of complications tend to develop during disease progression, especially in critically ill patients. Pathological studies of autopsy showed typical presentations of acute respiratory distress syndrome and involvement of multiple organs. Apart from supportive care, no speciﬁc treatment has been established for COVID-19

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