**HALIRU MUHAMMAD MAHDI**

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**400LEVEL ANATOMY**

ANA. 404; INTRODUCTION TO HISTOPATHOLOGY

**A COMPREHENSIVE REVIEW OF THE AETIOLOGY OF COVID-19, ITS PATHOGENESIS, HISTOPATHOLOGICAL FEATURES AND THE CURRENT POTENTIAL THERAPIES TO ADDRESS IT. AND ALSO COMMENT ON THE FUTURE OF COVID-19 ON PUBLIC HEALTH.**

**LECTURER IN-CHARDE: MR. EDEM EDEM**

**AETIOLOGY**

**Virology**

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a previously unknown (Nicholas *et al.,* 2020) betacoronavirus that was discovered in bronchoalveolar lavage samples taken from clusters of patients who presented with pneumonia of unknown cause in Wuhan City, Hubei Province, China, in December 2019 (Nicholas *et al.,* 2020). Coronaviruses are a large family of enveloped RNA viruses, some of which cause illness in people (e.g., common cold, severe acute respiratory syndrome [SARS], Middle East respiratory syndrome [MERS]), and others that circulate among mammals and birds. Rarely, animal coronaviruses can spread to humans and subsequently spread between people, as was the case with SARS and MERS (Nicholas *et al.,* 2020)

SARS-CoV-2 belongs to the Sarbecovirus subgenus of the Coronaviridae family, and is the seventh coronavirus known to infect humans. The virus has been found to be similar to SARS-like coronaviruses from bats, but it is distinct from SARS-CoV and MERS-CoV. The full genome has been determined and published in GenBank (Nicholas *et al.,* 2020)

A preliminary study suggests that there are two major types (or strains) of the SARS-CoV-2 virus in China, designated L and S. The L type was found to be more prevalent during the early stages of the outbreak in Wuhan City and may be more aggressive (although this is speculative), but its frequency decreased after early January. The relevance of this finding is unknown at this stage and further research is required (Nicholas *et al.,* 2020)

**Origin of virus**

A majority of patients in the initial stages of this outbreak reported a link to the Huanan South China Seafood Market, a live animal or ‘wet’ market, suggesting a zoonotic origin of the virus (Nicholas *et al.,* 2020)

While the potential animal reservoir and intermediary host(s) are unknown at this point, studies suggest they may derive from a recombinant virus between the bat coronavirus and an origin-unknown coronavirus; however, this is yet to be confirmed. Pangolins have been suggested as an intermediate host as they have been found to be a natural reservoir of SARS-CoV-2-like coronaviruses. Transmission dynamics (Nicholas *et al.,* 2020)

Person-to-person spread has been confirmed in community and healthcare settings, with local transmission now occurring in many countries around the world (Nicholas *et al.,* 2020)

Coronavirus disease (COVID-19) is caused by SARS-COV2 and represents the causative agent of a potentially fatal disease that is of great global public health concern. Based on the large number of infected people that were exposed to the wet animal market in Wuhan City, China, it is suggested that this is likely the zoonotic origin of COVID-19. Person-to-person transmission of COVID-19 infection led to the isolation of patients that were subsequently administered a variety of treatments. Extensive measures to reduce person-to-person transmission of COVID-19 have been implemented to control the current outbreak ([Rothan and](https://www.ncbi.nlm.nih.gov/pubmed/?term=Rothan%20HA%5BAuthor%5D&cauthor=true&cauthor_uid=32113704) [Byrareddy,](https://www.ncbi.nlm.nih.gov/pubmed/?term=Byrareddy%20SN%5BAuthor%5D&cauthor=true&cauthor_uid=32113704) 2020)

An initial assessment of the transmission dynamics in the first 425 confirmed cases found that 55% of cases before 1 January 2020 were linked to the Huanan South China Seafood Market, whereas only 8.6% of cases after this date were linked to the market. This confirms that person-to-person spread occurred among close contacts since the middle of December 2019, including infections in healthcare workers (Nicholas *et al.,* 2020)

It is uncertain how easily the virus spreads between people, but transmission in chains involving several links is increasingly recognized. Available evidence indicates that human transmission occurs via close contact with respiratory droplets produced when a person exhales, sneezes, or coughs; via direct contact with infected people; or via contact with fomites. Airborne transmission has not been reported; however, it may be possible during aerosol-generating procedures performed in clinical care (Nicholas *et al.,* 2020)

The virus has been found to be more stable on plastic and stainless steel (up to 72 hours) compared with copper (up to 4 hours) and cardboard (up to 24 hours).[27] This study also found that the virus was viable in aerosol particles for up to 3 hours; however, aerosols were generated using highpowered apparatus that do not reflect normal human cough conditions or a clinical setting where aerosol-generating procedures are performed. The World Health Organization has confirmed that there have been no reports of airborne transmission (Nicholas *et al.,* 2020)

The contribution to transmission by the presence of the virus in other body fluids is unknown; however, the virus has been detected in blood, cerebrospinal fluid, saliva, tears, and conjunctival secretions. Faecal-oral transmission may be possible (virus has been detected in the stool samples of almost half of the patients in one meta-analysis), although it has not been reported yet (Nicholas *et al.,* 2020)

Nosocomial transmission in healthcare workers and patients has been reported in 41% of patients in one case series (Nicholas *et al.,* 2020). Widespread transmission has been reported in long-term care facilities and on cruise ships (19% of 3700 passengers and crew were infected aboard the Diamond Princess) (Nicholas *et al.,* 2020)

**Presymptomatic transmission**

A small number of studies suggest that some people can be contagious during the incubation period, the time between exposure to the virus and the onset of symptoms. The incubation period is estimated to be between 1 and 14 days, with a median of 5 to 7 days (possibly longer in children). Approximately 97.5% of patients develop symptoms within 11.5 days of infection (Nicholas *et al.,* 2020)

Presymptomatic transmission has been reported in 12.6% of cases in China. A study in Singapore identified 6.4% of patients among seven clusters of cases in which presymptomatic transmission was likely to have occurred 1 to 3 days before symptom onset.

Presymptomatic transmission still requires the virus to be spread by infectious droplets or contact with fomites.

**Asymptomatic transmission**

An asymptomatic case is a laboratory-confirmed case who does not develop symptoms. There is some evidence that spread from asymptomatic carriers is possible, although it is thought that transmission is greatest when people are symptomatic (especially around the time of symptom onset) (Nicholas *et al.,* 2020)

Estimating the prevalence of asymptomatic cases in the population is difficult. The best evidence so far comes from the Diamond Princess cruise ship, which was quarantined with all passengers and crew members repeatedly tested and closely monitored. A modelling study found that approximately 700 people with confirmed infection (18%) were asymptomatic. However, a Japanese study of citizens evacuated from Wuhan City estimates the rate to be closer to 31%. Data from a longterm care facility in the US found that 30% of patients with positive test results were asymptomatic (or presymptomatic) on the day of testing. Early data from an isolated village of 3000 people in Italy estimates the figure to be higher at 50% to 75%. Other studies ranged from 4% to 80% (Nicholas *et al.,* 2020)

The proportion of asymptomatic cases in children is thought to be significant, and children may play a role in community spread (Nicholas *et al.,* 2020)

**PATHOGENESIS OF COVID-19**

Patients with COVID-19 show clinical manifestations include fever, nonproductive cough, dyspnea, myalgia, fatigue, normal or decreased leukocyte counts, and radiographic evidence of pneumonia (Xiaowei *et al.,* 2020). which are similar to the symptoms of SARS-CoV and MERS-CoV infections (Xiaowei *et al.,* 2020). Hence, although the pathogenesis of COVID-19 is poorly understood, the similar mechanisms of SARS-CoV and MERS-CoV still can give us a lot of information on the pathogenesis of SARS-CoV-2 infection to facilitate our recognition of COVID-19 (Xiaowei *et al.,* 2020)

**Coronavirus entry and replication**

Coronavirus S protein has been reported as a significant determinant of virus entry into host cells. The envelope spike glycoprotein binds to its cellular receptor, ACE2 for SARS-CoV and SARS-CoV-2, CD209L a C-type lectin, also called L-SIGN) for SARS-CoV, DPP4 for MERS CoV(Xiaowei *et al.,* 2020). The entry of SARS-CoV into cells was initially identiﬁed to be accomplished two-step furin activation for membrane fusion. Besides membrane fusion, the clathrin-dependent and -independent endocytosis mediated SARS-CoV entry too. After the virus enters the cells, the viral RNA genome is releaseed into the cytoplasm and is translated into two polyproteins and structural proteins, after which the viral genome begins to replicate. The newly formed envelope glycoproteins are inserted into the membrane of the endoplasmic reticulum or Golgi, and the nucleocapsid is formed by the combination of genomic RNA and nucleocapsid protein. Then, viral particles germinate into the endoplasmic reticulum-Golgi intermediate compartment (ERGIC). At last, the vesicles containing the virus particles then fuse with the plasma membrane to release the virus (Xiaowei *et al.,* 2020)

**Antigen presentation in coronavirus infection**.

While the virus enters the cells, its antigen will be presented to the antigen presentation cells (APC), which is a central part of the body's anti-viral immunity (Xiaowei *et al.,* 2020). Antigenic peptides are presented by major histocompatibility complex (MHC; or human leukocyte antigen (HLA) in humans) and then recognized by virus-specific cytotoxic T lymphocytes (CTLs). Hence, the understanding of antigen presentation of SARS-CoV-2 will help our comprehension of COVID-19 pathogenesis. Unfortunately, there is still lack of any report about it, and we can only get some information from previous researches on SARS CoV and MERS-CoV (Xiaowei *et al.,* 2020) The antigen presentation of SARS-CoV mainly depends on MHC I molecules, but MHC II also contributes to its presentation. Previous research shows numerous HLA polymorphisms correlate to the susceptibility of SARS-CoV, such as HLA-B 4601, HLA-B 0703, HLA-DR B1 and HLA-Cw0801, whereas the HLA-DR0301, HLA-Cw1502 and HLA-A 0201 alleles are related to the protection from SARS infection. In MERS-CoV infection, MHC II molecules, such as HLA-DRB111:01 and HLA-DQB102:0, are associated with the susceptibility to MERS-CoV infection. Besides, gene polymorphisms of MBL (mannose-binding lectin) associated with antigen presentation are related to the risk of SARS-CoV infection. These researches will provide valuable clues for the prevention, treatment, and mechanism of COVID-19 (Xiaowei *et al.,* 2020)

**Humoral and cellular immunity**

Antigen presentation subsequently stimulates the body's humoral and cellular immunity, which are mediated by virus-specific B and T cells (Xiaowei *et al.,* 2020). Similar to common acute viral infections, the antibody profile against SARS-CoV virus has a typical pattern of IgM and IgG production. The SARS-specific IgM antibodies disappeared at the end of week 12, while the IgG antibody can last for a long time, which indicates IgG antibody may mainly play a protective role, and the SARS-specific IgG antibodies primarily are S-specific and N-specific antibodies.Comparing to humoral responses, there are more researches on the cellular immunity of coronavirus. The latest report shows the number of CD4 + and CD8+ T cells in the peripheral blood of SARS-CoV-2-infected patients significantly is reduced whereas its status is excessive activation, as evidenced by high proportions of HLA-DR (CD4 3.47%) and CD38 (CD8 39.4%) double-positive fractions. Similarly, the acute phase response in patients with SARS-CoV is SARS-CoV infection, specific T-cell memory responses to the SARS-CoV S peptide library could still be identified in 14 of 23 recovered SARS patients. The specific CD8 + T cells also show a similar effect on MERS-CoV clearance in mice. These findings may provide valuable information for the rational design of vaccines against SARS-CoV-2.

**Cytokine storm in COVID-19**

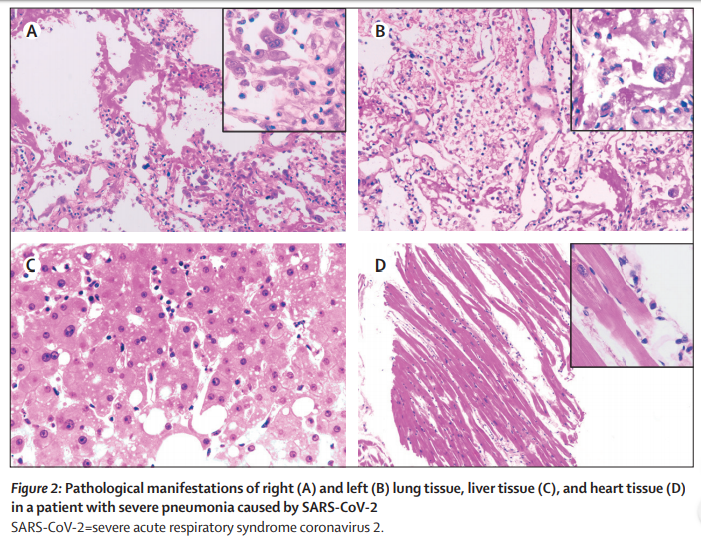
The report in Lancet shows ARDS is the main death cause of COVID-19. Of the 41 SARS-CoV-2-infected patients admitted in the early stages of the outbreak, six died from ARDS (Xiaowei *et al.,* 2020). ARDS is the common immunopathological event for SARS-CoV-2, SARS-CoV and MERS-CoV infections. One of the main mechanisms for ARDS is the cytokine storm, the deadly uncontrolled systemic inflammatory response resulting from the release of large amounts of pro-inflammatory cytokines (IFN-α, IFN-γ, IL-1β, IL-6, IL-12, IL-18, IL-33, TNF-α, TGFβ, etc.) and chemokines (CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10, etc.) by immune effector cells in SARS-CoV infection. Similar to those with SARS-CoV, individuals with severe MERS-CoV infection show elevated levels of IL-6, IFN-α, and CCL5, CXCL8, CXCL-10 in serum compared to those with the mild-moderate disease. The cytokine storm will trigger a violent attack by the immune system to the body, cause ARDS and multiple organ failure, and finally lead to death in severe cases of SARS-CoV-2 infection, just like what occurs in SARS-CoV and MERS-CoV infection (Xiaowei *et al.,* 2020)

**Coronavirus immune evasion**

To better survive in host cells, SARS-CoV and MERS-CoV use multiple strategies to avoid immune responses. The evolutionarily conserved microbial structures called pathogen-associated molecular patterns (PAMPs) can be recognized by pattern recognition receptors (PRRs) (Xiaowei *et al.,* 2020). However, SARS-CoV and MERS-CoV can induce the production of double-membrane vesicles that lack PRRs and then replicate in these vesicles, thereby avoiding the host detection of their dsRNA. IFN-I (IFN-α and IFN-β) has a protective effect on SARS-CoV and MERS-CoV infection, but the IFN-I pathway is inhibited in infected mice. Accessory protein 4a of MERS-CoV may block the induction of IFN at the level of MDA5 activation through direct interaction with double-stranded RNA. Besides, ORF4a, ORF4b, ORF5, and membrane proteins of MERS-CoV inhibit nuclear transport of IFN regulatory factor 3 (IRF3) and activation of IFN β promoter (Xiaowei *et al.,* 2020). The antigen presentation can also be affected by the coronavirus. For example, gene expression related to antigen presentation is down-regulated after MERS-CoV infection. Therefore, destroying the immune evasion of SARS-CoV-2 is imperative in its treatment and specific drug development (Xiaowei *et al.,* 2020)

**HISTOPATTHOLOGY OF COVID-19**

The pathological features of COVID-19 greatly resemble those seen in SARS and Middle Eastern respiratory syndrome (MERS) coronavirus infection (Zhe Xu *et al.,* 2020). In addition, the liver biopsy specimens of the patient with COVID-19 showed moderate microvesicular steatosis and mild lobular and portal activity (Zhe Xu *et al.,* 2020), indicating the injury could have been caused by either SARS-CoV-2 infection or drug-induced liver injury (Zhe Xu *et al.,* 2020).



There was a reduction in the counts of peripheral CD4 and CD8 T cells, while their status was hyperactivated, as evidenced by the high proportions of HLA-DR (CD4 3·47%) and CD38 (CD8 39·4%) double-positive fractions (Zhe Xu *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 harbour high concentrations of cytotoxic granules, in which 31·6% cells were perforin positive, 64·2% cells were granulysin positive, and 30·5% cells were granulysin and perforin double-positive (Zhe Xu *et al.,* 2020) Our results imply that overactivation 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.

Although corticosteroid treatment is not routinely recommended to be used for SARS-CoV-2 pneumonia (Zhe Xu *et al.,* 2020), according to our pathological findings of pulmonary oedema and hyaline membrane formation, timely and appropriate use of corticosteroids together with ventilator support should be considered for the severe patients to prevent ARDS development. Lymphopenia is a common feature in the patients with COVID-19 and might be a critical factor associated with disease severity and mortality (Zhe Xu *et al.,* 2020). Our clinical and pathological findings in this severe case of COVID-19 can not only help to identify a cause of death, but also provide new insights into the pathogenesis of SARS-CoV-2-related pneumonia, which might help physicians to formulate a timely therapeutic strategy for similar severe patients and reduce mortality (Zhe Xu *et al.,* 2020).

**CURRENT POTENTIAL THERAPIES AND THE FUTURE OF COVID-19**

There is [no proof that any drug can cure or prevent infection](https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html) with the coronavirus (Denise et al., 2020). But in the face of an exploding pandemic with a frightening death toll, people are desperate for a bit of hope, a chance to believe there is something that will help (Denise et al., 2020).

The drug that has received the most attention is hydroxychloroquine, which [President Trump has recommended repeatedly](https://www.nytimes.com/2020/04/06/us/politics/coronavirus-trump-malaria-drug.html), despite warnings from his own health officials that there is little data to support its widespread use as a treatment against the virus (Denise et al., 2020)

Drug companies across the world have begun donating tens of millions of doses of hydroxychloroquine to the United States, and the president said on April 4 that 29 million doses had been added to the National Strategic Stockpile, a cache of medical supplies maintained by the government to respond to emergencies (Denise et al., 2020)

It has been reported that Chloroquine can be used to treat COVID-19, however, the cure is not yet found. People have been dying especially the elderly and children, but the adults have more chance of survival, and only those whose immune system is functioning accurately survive. Bill Gates predicted virus as the future of war because it has no cure for now, but only treatment (Denise et al., 2020)

The second is that healthcare systems will be the heroes in this. Already this year we have called them out as the sector that is [taking advantage of technology](https://disruptive.asia/5g-wanes-healthcare-kicking-off/) at a rate that should make us look to the future and be a little embarrassed. Already there are vaccines in early stages of testing. Just a few years ago a vaccine would still be years in the future (Denise et al., 2020)

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