

A comprehensive review of aetiology of COVID-19, its pathogenesis, histopathological features and the current potential therapies to address it and its future on public health.

By

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**Introduction**

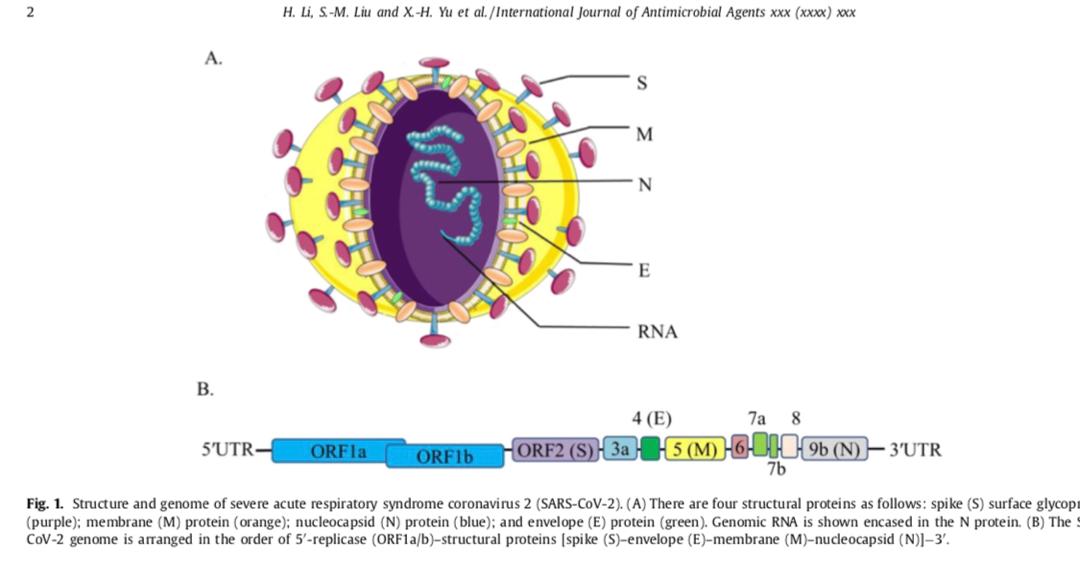
Novel coronavirus (2019-nCoV), officially known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (WHO, 2020), the etiological agent of the (Corona Virus Disease 2019) COVID-19, emerged in Wuhan, Hubei province, China. On 11th March 2020, The World Health Organization (WHO) declared this disease as pandemic (WHO, 2020). At the time of the writing of this review, the COVID-19 pandemic, caused by a novel coronavirus, has already affected over 2,347,875 people in 210 countries and territories, and killed over 161,402 people worldwide (WHO, 2020). The number of cases reported worldwide and in Nigeria increase daily at an alarming rate, in part as a consequence of more widespread testing. As the fears of a global coronavirus COVID-19 pandemic, a disease caused by the SARS-CoV2 virus continue to grow (Chen N *et al.,*2020), the biomedical researchers must also brace itself to continue to offer the best service to patients worldwide. The coronavirus disease 2019 (COVID-19) is a pandemic with the SARS-CoV-2 virus (Huang C *et al.,*2019). 2019-nCoV a large enveloped virus with a positive sense, single stranded RNA genome (Liu Y *et al.,*2020), is the third known coronavirus after SARS-CoV and MERS-CoV that was first identified in 2019 and causes severe respiratory illness and pneumonia-like infection in humans (Chen N *et al.,* 2020). The infection has predominantly respiratory transmission and is transmitted through large droplets or aerosols, and less commonly by contact with infected surfaces or fomites (Li Q, 2020). In both SARS-CoV and SARS-CoV-2 virus entry into the host cells is mediated by interaction of the receptor-binding domain (RBD) in S protein on virus outer-membrane and angiotensin-converting enzyme 2 (ACE2) on cell (Yang D *et al.,* 2015). The alarming spread of the infection and the severe clinical disease that it may cause, have led to the widespread institution of social distancing measures (Graham RL *et al.,* 2013). This review paper provides an assessment of the current state of knowledge about the disease and its pathology, histopathological features and the current potential to address it and its future on public health.

**Aetiology of COVID-19**

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a previously unknown (Nicholas *et al.,* 2020) beta coronavirus 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).

**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 high powered 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).



**Structure of SARS-CoV-2**

The SARS-CoV-2 genome (30 kb in size) encodes a large, non-structural polyprotein (ORF1a/b) that is further proteolytically cleaved to generate 15/16 proteins, 4 structural proteins and 5 accessory proteins (ORF3a, ORF6, ORF7, ORF8 and ORF9) (Ramaiah A *et al.,* 2020; Chan JF *et al.,*2020; Wu A *et al.,* 2020) (Fig. 1). The four structural proteins consist of the spike (S) surface glycoprotein, the membrane (M) protein, the envelope (E) protein and the nucleocapsid (N) protein, which are essential for SARS-CoV-2 assembly and infection. The spike surface glycoprotein plays a key role in its attachment to host cells and can be further cleaved by host proteases into an N-terminal S1 subunit and a membrane-bound C-terminal S2 region (Yuan Y *et al.,* 2017) Binding of the S1 subunit to a host receptor can destabilise the prefusion trimer, leading to shedding of the S1 subunit and transition of the S2 subunit into a highly stable post fusion conformation (Walls AC et al., 2020 ). In order to engage a host receptor, the receptor-binding domain (RBD) of the S1 subunit undergoes hinge-like conformational movements, which transiently hide or expose the determinants of receptor binding (Wrapp D *et al.,* 2020; Li F, 2016). These two states of the S1 subunit can be regarded as the ‘down’ conformation and the ‘up’ conformation. The former represents an inaccessible state of the receptor, whereas the latter corresponds to an accessible state (Li F, 2016; Gui M *et al.,* 2017) Therefore, understanding the structure and function of the spike protein can help to develop monoclonal antibody drugs.

**Epidemiology**

Several measures are commonly used to quantify mortality (PFE, 2020) These numbers vary by region and over time and are influenced by the volume of testing, healthcare system quality, treatment options, time since initial outbreak and population characteristics such as age, sex and overall health. (Ritchie *et al*., 2020). In late 2019, WHO assigned the emergency ICD-10 disease codes U07.1 for deaths from lab-confirmed SARS-CoV-2 infection and U07.2 for deaths from clinically or epidemiologically diagnosed COVID-19 without lab-confirmed SARS-CoV-2 infection (WHO, 2020). The death-to-case ratio reflects the number of deaths divided by the number of diagnosed cases within a given time interval. Based on Johns Hopkins University statistics, the global death-to-case ratio is 6.0% (89,915/1,502,618) as of 9 April 2020 (CSSE, 2020). The number varies by region (Lazzerini *et al*., 2020).

Other measures include the case fatality rate (CFR), which reflects the percent of diagnosed individuals who die from a disease, and the infection fatality rate (IFR), which reflects the percent of infected individuals (diagnosed and undiagnosed) who die from a disease. These statistics are not time bound and follow a specific population from infection through case resolution. A number of academics have attempted to calculate these numbers for specific populations (Castiglione *et al.,* 2020). In the epicentre of the outbreak in Italy, Castiglione d'Adda, a small village of 4500, 80 (1.8%) are already dead. Most people in the village appear to have developed antibodies and plausible immunity, most did so without being diagnosed, and many did not have symptoms (Castiglione *et al*., 2020). An investigation is underway to test the entire population to learn more about the disease (Galli *et al.,* 2020).

**Histopathology 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 micro vesicular 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 edema 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).

**Pathogenesis and histopathological features**

Clinical features: Public Health England (PHE) has outlined criteria to assess possibility of COVID-19 infection in patients (HSE, 2020). These criteria are the same when the patient is deceased with the exception that the timelines given in the guidance refer to the time prior death or onset of relevant symptoms before death where known. If it is considered that COVID-19 may have been related to death by these criteria, the choice of either to perform a full postmortem or an examination is limited only to retrieving the samples required to verify COVID-19 infection. This decision must be made according to the individual case and should include the requirements of the coroner or any pertinent individuals. A staged postmortem may also be considered. This involves taking only diagnostic samples initially and later considering or a more complete autopsy after the results of these diagnostic tests are available. This staged technique is recommended if possible.

Macroscopic features: the macroscopic features of COVID-19 are likely to be in the chest and may include pleurisy, pericarditis, lung consolidation and pulmonary oedema. Lung weight may be increased above normal. It should be noted a secondary infection may be superimposed on the viral infection that can lead to purulent inflammation more typical of bacterial infection (Osborn *et al*., 2020).

Microscopic findings*:* a recent article described the early histopathological features in COVID-19 in two patients who underwent surgical resections for lung adenocarcinoma but were later discovered to have had COVID-19 at the time of the operation (Tian *et al.,* 2020). The findings were non-specific and included oedema, pneumocyte hyperplasia, focal inflammation and multinucleated giant cell formation while no hyaline membranes were seen (Tian *et al.,* 2020). Given that these patients were asymptomatic with respect to COVID-19 at the time of the operation, these are likely to reflect only early changes of acute lung injury in the infection In another case, a 50-year-old man died from severe COVID-19 infection and more marked histopathological findings were noted (Xu *et al.*, 2020). Samples were taken by postmortem biopsy, and a description of the gross postmortem findings is not given, although multiple ground glass opacities were noted on chest X-ray. The microscopic findings included diffuse alveolar damage with exudates (Xu *et al.,* 2020). The inflammation was predominantly lymphocytic, and multinucleated giant cells were seen alongside large atypical pneumocytes, although no definitive viral inclusions were noted. Micro vesicular steatosis with mild inflammation was noted in the liver, although it was unclear whether this was related to the virus or iatrogenic. The features are very similar to those seen in SARS and MERS-coronavirus infections (Ding *et al.,* 2020).

**Current potential therapies**

* **Antiviral western medicine treatment**

At present, the treatments of patients with SARS-CoV-2 infection are mainly symptomatic treatments. Remdesivir was recently reported as a promising antiviral drug against a wide array of RNA viruses. (Holshue *et al.,*2020). for the first time reported that treatment of a patient with COVID-19 used remdesivir and achieved good results (Holshue ML *et al.,*2020). Then, Xiao et al. findings reveal that remdesivir effectively in the control of 2019-nCoV infection in vitro. Meanwhile, also found that chloroquine has an immune-modulating activity and could effectively inhibit in this virus in vitro (Wang M *et al.,*2020). Clinical controlled trials have shown that Chloroquine was proved to be effective in the treatment of patients with COVID 19 (Gao J *et al.,* 2020). Remdesivir is undergoing a large number of clinical trials in several hospitals, and the final efficacy of the drug is uncertain. Arbidol, a small indole derivative molecule, was found to block viral fusion against influenza A and B viruses and hepatitis C viruses (Boriskin YS *et al.,* 2008) and confirmed to have antiviral effect on SARS-CoV in cell experiment (Khamitov RA *et al.,* 2008), so that it might be a choice for COVID-19 treatment. The randomized controlled study on treatment of novel coronavirus by Arbidol and Kaletra undertaken at present showed that Arbidol had better therapeutic effect than Kaletra did and could significantly reduce the incidence of severe cases. Apart from the above, lopinavir/ritonavir, nucleoside analogues, neuraminidase inhibitors, remdesivir, and peptide EK1 could also be the choices of antiviral drugs for COVID-19 treatment (Lu H, 2020).

* **Chinese medicine treatment**

Chinese medicine also played an important role in the treatment of SARS-CoV-2 infection. Local governments and medical institutions published a number of traditional Chinese medicine prescriptions. The Novel Coronavirus Pneumonia Diagnosis and Treatment Plan (6th trial version) suggested to use clearing lung and detoxification decoction in the clinical treatment (PRC NH Cot, 2020). A joint study made by Shanghai Institute of Materia Medica and Wuhan Institute of Virology. CAS found that Shuanghuanglian oral liquid could inhibit SARS-CoV-2. Previous studies have proved that baicalin, chlorogenic acid and forsythin in Shuanghuanglian oral liquid have certain inhibitory effects on a variety of viruses and bacteria (Li W, 2002; Lu HT, 2000). The mechanism might be that these components played a therapeutic role by effectively reducing the inflammatory response of the body caused by viruses and bacteria (Chen X *et al.,* 2002). Lianhuaqingwen capsule has been proven to have a wide-spectrum effect on a series of influenza viruses, including H7N9, and could regulate the immune response of the virus, reducing the level of inflammatory factors in the early stage of infection (Ding Y *et al.,* 2017).

* **Immunoenhancement therapy**

Synthetic recombinant interferon α has proven to be effective in treatment of SARS patients in clinic trials (Loutfy MR *et al.,*2003). Pulmonary X-ray abnormal remission time was reduced by 50% in the interferon-treated group compared with the glucocorticoid-treated group alone. Interferon was also found to be an effective inhibitor of MERS-CoV replication (Mustafa S. *et al.,*2018). Those findings suggested that interferon could be used in the treatment of COVID-19. Intravenous immunoglobulin might be the safest immunomodulator for long-term use in all ages, and could help to inhibit the production of proinflammatory cytokines and increase the production of anti-inflammatory mediators (Gilardin L, Bayry J, Kaveri SV. (2015). Moreover, Thymosin alpha-1 (Ta1) can be an immune booster for SARS patients, effectively controlling the spread of disease (Kumar V, Jung YS, Liang PH, 2013). Intravenous immunoglobulin and Ta1 may also be considered as therapeutics for COVID-19.

* **Convalescent plasma therapy**

When there are no sufficient vaccines and specific drugs, convalescent plasma therapy could be an effective way to alleviate the course of disease for severely infected patients (Mair-Jenkins J *et al.,* 2015). In a retrospective analysis, convalescent plasma therapy is more effective than severe doses of hormonal shock in patients with severe SARS, reducing mortality and shortening hospital stays (Soo Yoo *et al.,*2004). A prospective cohort study by Hung and colleagues showed that for patients with pandemic H1N1 influenza virus infection in 2009, the relative risk of death was significantly lower in patients treated with convalescent plasma (Hung IF *et al.,* 2011). Moreover, from the perspective of immunology, most of the patients recovered from COVID-19 would produce specific antibodies against the SARS-CoV-2, and their serum could be used to prevent reinfection. At the same time, antibodies can limit the virus reproduction in the acute phase of infection and help clear the virus, which is conducive to the rapid recovery of the disease (GR K,1996). Theoretically, viremia peaks during the first week of most viral infections, and it should be more effective to give recovery plasma early in the disease (Cheng Y *et al.,* 2005). Therefore, the plasma of some patients recovered from COVID-19 could be collected to prepare plasma globulin specific to SARS-CoV-2. However, the safety of plasma globulin products specific to SARS-CoV-2 deserves further consideration.

* **Auxiliary blood purification treatment**

At present, extracorporeal blood purification technology in the treatment of severe NCP patients ((PRC NH Cot, 2020)). According to the latest studies (Li Z *et al.,* 2020) ACE2, the key receptor of SARS-CoV-2, is highly expressed in human kidney (nearly 100 times higher than that in lung). Kidney might be main target of attack for novel coronavirus. Early continuous blood purification treatment could reduce renal workload and help to promote the recovery of renal function (Zarbock A *et al.,* 2016). Most of the severe patients with novel coronavirus might suffer from cytokine storm. The imbalance of pro-inflammatory factors and anti-inflammatory factors might cause immune damage. Therefore, blood purification technology could be used to remove inflammatory factors, eliminate cytokine storm, correct electrolyte imbalance, and maintain acid-base balance, to control patient’s capacity load in an effective manner (Lim CC *et al.,* 2015). In this logic, the patient's symptoms could be improved and the blood oxygen saturation could be increased. In summary, the drug treatment for COVID-19 mainly comprised four ways, i.e., antiviral Western medicine, Chinese medicine, immunoenhancement therapy, and viral specific plasma globulin. Machines could be used as auxiliary therapy. However, randomized double-blind large sample clinical trial should be served as the standard to determine whether the antiviral drugs could be used in clinical practice.

**Conclusion and future directions**

SARS-CoV first appeared in 2002 and rapidly spread to 32 countries and regions, after which the world then experienced the outbreak of MERS-CoV in 2012. Recently, the newly emerged SARSCoV-2 is undoubtedly a warning. It has been confirmed that SARSCoV-2 enters lung cells by binding to ACE2. Besides pulmonary tissue, ACE2 is also highly expressed in other tissues including bile duct, liver, gastrointestinal organs (small intestine, duodenum), oesophagus, testis and kidney (Zhang H *et al.,* 2020; Chai X *et al.,*2020). Thus, these organs may also be damaged by SARS-CoV-2. Currently, SARS-CoV-2 has spread rapidly in multiple countries, caused severe illness and sustained human-to-human transmission, making it a concerning and serious public-health threat. Considering the global threat to health caused by SARS-CoV-2, effective prevention and treatment of COVID-19 pneumonia will be urgently needed. However, the development of drugs for pathogenic SARS-CoV-2 is still a major problem for humans, and there are currently no officially approved drugs to treat COVID-19. In view of the epidemiological characteristics of SARSCoV-2, it is crucial to interrupt the spread of the virus through epidemic prevention and control methods, such as isolating infected patients and controlling the source of infection. At the same time, wild animal trafficking must be banned to reduce the spread of CoVs. In addition, it is necessary to make full use of the currently limited evidence for therapeutic drugs to develop strategies of drug application to prevent and control the transmission of SARS-CoV2. It has been confirmed that the genome sequence of SARS-CoV2 shares high identity with that of bat and human SARS-CoVs. A number of antiviral drugs and treatment methods for SARS-CoV infection have also been considered for the treatment and prevention of COVID-19 pneumonia. We have been warned three times in recent years. CoVs are highly vulnerable to public-health intervention strategies, but the increasing incidence of CoV emergence in livestock animal populations and the identification of novel CoVs in reservoir species do not support this view. Therefore, in addition to developing new drugs and clinical trials of old drugs, the design and development of vaccines for SARS-CoV-2 is also needed. Lessons from SARS-CoV and MERS-CoV suggest that SARS-CoV-2 research should focus on the establishment of animal models that recapitulate the various aspects of human disease and determinants of vaccine safety and efficacy (Heng Li *et al.,* 2020).

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