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

**By**

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1. **Introduction**

The name “coronavirus,” coined in 1968, is derived from the “corona”-like or crown-like morphology observed for these viruses in the electron microscope (Tyrell *et al.,* 1968). Coronavirus disease 2019 (COVID-19) originated in the city of Wuhan, Hubei Province, Central China, and has spread quickly to 72 countries to date. COVID-19 is caused by a novel coronavirus, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [previously provisionally known as 2019 novel coronavirus (2019-nCoV)] (Li *et al.,* 2020).



FIG 1.0: Illustration of the SARS-CoV-2 virion (The Harvard Gazette 2020)

Firstly, Viruses are small obligate intracellular parasites, which by definition contain either a RNA or DNA genome surrounded by a protective, virus-coded protein coat. Viruses may be viewed as mobile genetic elements, most probably of cellular origin and characterized by a long co-evolution of virus and host. For propagation viruses depend on specialized host cells supplying the complex metabolic and biosynthetic machinery of eukaryotic or prokaryotic cells. A complete virus particle is called a virion. The main function of the virion is to deliver its DNA or RNA genome into the host cell so that the genome can be expressed (transcribed and translated) by the host cell. The viral genome, often with associated basic proteins, is packaged inside a symmetric protein capsid. The nucleic acid-associated protein, called nucleoprotein, together with the genome, forms the nucleocapsid. In enveloped viruses, the nucleocapsid is surrounded by a lipid bilayer derived from the modified host cell membrane and studded with an outer layer of virus envelope glycoproteins (Gelderblom, 1996).

 In 1975, the Coronaviridae family was established by the International Committee on the Taxonomy of Viruses. Recently, at the 10th International Nidovirus Symposium in Colorado Springs, Colo., in June 2005, it was proposed that the Coronaviridae family be divided into two subfamilies, the coronaviruses and the toroviruses, the latter of which cause enteric diseases in cattle and possibly in humans(Cowley *et al.,* 2000). The Coronaviridae family, along with the Arteviridae and Roniviridae families, form the Nidovirales order. The Arteviridae family includes swine and equine pathogens, and the Roniviridae family is composed of invertebrate viruses (Enjuanes *et al.,* 2000).

Coronaviruses (CoVs) belong to the subfamily Orthocoronavirinae in the family Coronaviridae, Order Nidovirales. There are four genera within the subfamily Orthocoronavirinae, namely Alphacoronavirus (α-CoV), Betacoronavirus (β-CoV), Gammacoronavirus (γ-CoV) and Deltacoronavirus (δ-CoV) (Banerjee *et al.,* 2019; Yang and Leibowitz, 2015). The CoV genome is an enveloped, positive-sense, single-stranded RNA with a size varying between 26 kb and 32 kb, the largest genome of known RNA viruses. Both α- and β-CoV genera are known to infect mammals, whilst δ- and γ-CoVs infect birds (Song *et al.,* 2019). Two recent outbreaks of viral pneumonia caused by β-CoVs are severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). In 2002, an outbreak of SARS was first reported in China and then spread quickly worldwide, resulting in hundreds of deaths with an 11% mortality rate (Graham *et al.,* 2013). In 2012, MERS first emerged in Saudi Arabia and subsequently spread to other countries, with a fatality rate of 37% (Zumla *et al.,* 2015; Hui *et al.,* 2018; Su *et al.,* 2015). In both of these epidemics, the viruses likely originated from bats and then infected humans through other intermediate animal hosts, e.g. the civet (Paguma larvata) for SARS-CoV and the camel for MERS-CoV (Reusken *et al.,* 2013; de Wit *et al.,* 2016; Lu *et al.,* 2015).

Beginning in December 2019, a number of patients with pneumonia of unknown aetiology emerged in Wuhan City, Hubei Province, Central China. Genome sequencing has demonstrated that this pneumonia, named coronavirus disease 2019 (COVID-19), is caused by a novel CoV, namely severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), previously known as 2019 novel coronavirus (2019-nCoV) (Xu *et al.,* 2020; Wong *et al.,* 2020; Li *et al.,* 2020). Like SARS-CoV and MERS-CoV, this newly emerged SARS-CoV-2 virus belongs to the B lineage of the β-CoVs.

To date, COVID-19 has spread rapidly in 72 countries, causing >90 000 confirmed cases and over 2946 deaths as of 3 March 2020. Considering the global threat, the World Health Organization (WHO) has declared COVID-19 a public health emergency of international concern (PHEIC). However, there are no vaccines against SARS-CoV-2 or specific therapeutic drugs for this communicable disease. Thus, a better understanding of SARS-CoV-2 is essential for exploring effective vaccines and drugs. In this review, we summarise recent progress in SARS-CoV-2 to provide a framework for the prevention and treatment of COVID-19 (Li *et al.,* 2020).

Coronaviruses infect many species of animals, including humans (Bailey *et al.,* 1949). Coronaviruses have been described for more than 50 years; the isolation of the prototype murine coronavirus strain JHM, for example, was reported in 1949 (Cheever *et al.,* 1949).The molecular mechanisms of replication as well as the pathogenesis of several coronaviruses have been actively studied since the 1970s. Some of the animal viruses, such as porcine transmissible gastroenteritis virus (TGEV), bovine coronavirus (BCoV), and avian infectious bronchitis viruses (IBV), are of veterinary importance. The murine coronavirus mouse hepatitis virus (MHV) is studied as a model for human disease. This family of viruses remained relatively obscure, probably because there were no severe human diseases that could definitely be attributed to coronaviruses; human coronaviruses caused only the common cold. However, in the spring of 2003, when it became clear that a new human coronavirus was responsible for severe acute respiratory syndrome (SARS), coronaviruses became much more recognized. With the occurrence of the SARS epidemic, coronaviruses may now be considered “emerging pathogens.” The origin of the SARS coronavirus (SARS-CoV) poses interesting questions about coronavirus evolution and species specificity. Since the SARS epidemic, two new human respiratory coronaviruses have been described(Weiss and Navas-Martin, 2005).

**1.1 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 and Arumugaswami, 2020; Chan *et al.,* 2020; Wu *et al.,* 2020). 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 *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 postfusion conformation (Walls *et al.,* 2019).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 *et al.,* 2020; Li, 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 (Wrapp *et al.,* 2020; Gui *et al.,* 2017). Therefore, understanding the structure and function of the spike protein can help to develop monoclonal antibody drugs and to guide the design and development of vaccines.



FIG 1.1: Structure and genome of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). (A) There are four structural proteins as follows: spike (S) surface glycoprotein (purple); membrane (M) protein (orange); nucleocapsid (N) protein (blue); and envelope (E) protein (green). Genomic RNA is shown encased in the N protein. (B) The SARS-CoV-2 genome is arranged in the order of 5′-replicase (ORF1a/b)–structural proteins [spike (S)–envelope (E)–membrane (M)–nucleocapsid (N)]−3′ (Li *et al.,* 2020).

1. **Aetiology of COVID-19**

SARS-CoV-2 is the seventh member of the family of CoVs that infect humans. Four human CoVs (HCoV-229E, HCoV-NL63, HCoV-OC43 and HCoV-HKU1) are able to cause a wide range of upper respiratory tract infections (common cold), whereas SARS-CoV and MERS-CoV are responsible for atypical pneumonia (Paules *et al.,* 2020S). The causes of different infection sites are likely related to the presence of dipeptidyl peptidase 4 (DPP4) and angiotensin-converting enzyme 2 (ACE2) in the lower respiratory tract, which are the major human receptors for the surface spike (S) glycoprotein of MERS-CoV and SARS-CoV, respectively (Raj *et al.,* 2013; Kuba *et al.,* 2005). The genetic sequence of SARS-CoV-2 is ≥70% similar to that SARS-CoV, and SARS-CoV-2 is capable of using the same cell entry receptor (ACE2) as SARS-CoV to infect humans (Hui *et al.,* 2020; Zhou *et al.,* 2020) . However, there are more differences in the key S proteins that the viruses use to interact with host cells. SARS-CoV-2 spike binds to human ACE2 with approximately 10–20-fold higher affinity than the SARS-CoV spike (Wrapp *et al.,* 2020), making it easier to spread from human to human.

CoVs are positive-stranded RNA viruses with a crown-like appearance under an electron microscope (*coronam* is the Latin term for crown) due to the presence of spike glycoproteins on the envelope. The subfamily *Orthocoronavirinae* of the *Coronaviridae* family (order *Nidovirales*) classifies into four genera of CoVs: Alphacoronavirus (alphaCoV), Betacoronavirus (betaCoV), Deltacoronavirus (deltaCoV), and Gammacoronavirus (gammaCoV). Furthermore, the betaCoV genus divides into five sub-genera or lineages (Chan *et al.,* 2013). Genomic characterization has shown that probably bats and rodents are the gene sources of alphaCoVs and betaCoVs. On the contrary, avian species seem to represent the gene sources of deltaCoVs and gammaCoVs (Cascella *et al.,* 2020).

Members of this large family of viruses can cause respiratory, enteric, hepatic, and neurological diseases in different animal species, including camels, cattle, cats, and bats. To date, seven human CoVs (HCoVs) — capable of infecting humans — have been identified. Some of HCoVs were identified in the mid-1960s, while others were only detected in the new millennium.

In general, estimates suggest that 2% of the population are healthy carriers of a CoV and that these viruses are responsible for about 5% to 10% of acute respiratory infections (Chen *et al.,* 2020).

* Common human CoVs: HCoV-OC43, and HCoV-HKU1 (betaCoVs of the A lineage); HCoV-229E, and HCoV-NL63 (alphaCoVs). They can cause common colds and self-limiting upper respiratory infections in immunocompetent individuals. In immunocompromised subjects and the elderly, lower respiratory tract infections can occur.
* Other human CoVs: SARS-CoV, SARS-CoV-2, and MERS-CoV (betaCoVs of the B and C lineage, respectively). These cause epidemics with variable clinical severity featuring respiratory and extra-respiratory manifestations. Concerning SARS-CoV, MERS-CoV, the mortality rates are up to 10% and 35%, respectively.

Thus, SARS-CoV-2 belongs to the betaCoVs category. It has round or elliptic and often pleomorphic form, and a diameter of approximately 60–140 nm. Like other CoVs, it is sensitive to ultraviolet rays and heat. Furthermore, these viruses can be effectively inactivated by lipid solvents including ether (75%), ethanol, chlorine-containing disinfectant, peroxyacetic acid and chloroform except for chlorhexidine.

In genetic terms, Chan et al. have proven that the genome of the new HCoV, isolated from a cluster-patient with atypical pneumonia after visiting Wuhan, had 89% nucleotide identity with bat SARS-like-CoVZXC21 and 82% with that of human SARS-CoV(Chan *et al.,* 2020). For this reason, the new virus was called SARS-CoV-2. Its single-stranded RNA genome contains 29891 nucleotides, encoding for 9860 amino acids. Although its origins are not entirely understood, these genomic analyses suggest that SARS-CoV-2 probably evolved from a strain found in bats. The potential amplifying mammalian host, intermediate between bats and humans, is, however, not known. Since the mutation in the original strain could have directly triggered virulence towards humans, it is not certain that this intermediary exists (Cascella *et al.,* 2020).

1. **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).

On December 30, 2019, a cluster of patients with pneumonia of unknown etiology was observed in Wuhan, China, and reported to the World Health Organization (WHO)’s China bureau in Beijing. On January 7, 2020, a new coronavirus (SARS-CoV-2) was isolated from these patients. The virus was initially referred to as “novel coronavirus 2019” (2019-nCoV) by the WHO – but, on February 11, 2020, was given the official name of SARS-CoV-2 by the International Committee on Taxonomy of Viruses (Del Rio and Malani, 2020).



FIG 3.0: The structure of SARS-CoV-2. (Credit: Scientific Animations™, 2020).

SARS-CoV-2 is a betacoronavirus that shares 79 percent of its genetic sequence with SARS-CoV and has 96 percent homology with two coronaviruses in chrysanthemum bats. The pangolin is thought to the intermediate host between bats and humans. The virion contains four proteins (spike, envelope, membrane, and nucleocapsid) and single-stranded RNA

Upon entry into alveolar epithelial cells, SARS-CoV-2 replicates rapidly and triggers a strong immune response, resulting in cytokine storm syndromes and pulmonary tissue damage (Villar *et al.,* 2019). Cytokine storm syndromes, also known as hypercytokinaemia, are a group of disorders characterised by the uncontrolled production of pro-inflammatory cytokines and are important causes of acute respiratory distress syndrome (ARDS) and multiple organ failure (Channappanavar and Perlman, 2017; Wang and Ma, 2007). Analysis of the first 99 confirmed cases of SARS-CoV-2 infection revealed that cytokine storm syndromes occurred in patients with severe COVID-19; 17 patients (17%) had ARDS, among whom 11 (11%) deteriorated within a short period of time and died of multiple organ failure (Chen *et al.,* 2020) In addition, the numbers of total T-cells, CD4+ T-cells and CD8+ T-cells are decreased in patients with SARS-CoV-2 infection, and the surviving T-cells are functionally exhausted (Diao *et al.,* 2020) , suggesting a decreased immune function in SARS-CoV-2-infected patients. ARDS, decreased immune function and secondary infection further worsens respiratory failure.

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). The 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 (Huang *et al.,* 20200. 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).

The RNA genome consists of 29,900 nucleotides – larger than most other RNA viruses. One-third of the genome consists of genes for the four structural proteins and eight genes for accessory proteins that inhibit host defenses. Most of the remainder of the genome consists of the replicase gene, which encodes two large polyproteins that are cleaved into 15 or 16 nonstructural proteins (NSP) that assist in replicating and proofreading the viral genome (Plapp 2020).

**3.1 Transmission**

Because the first cases of the CoVID-19 disease were linked to direct exposure to the Huanan Seafood Wholesale Market of Wuhan, the animal-to-human transmission was presumed as the main mechanism. Nevertheless, subsequent cases were not associated with this exposure mechanism. Therefore, it was concluded that the virus could also be transmitted from human-to-human, and symptomatic people are the most frequent source of COVID-19 spread. The possibility of transmission before symptoms develop seems to be infrequent, although it cannot be excluded. Moreover, there are suggestions that individuals who remain asymptomatic could transmit the virus. This data suggests that the use of isolation is the best way to contain this epidemic (Cascella *et al.,* 2020).

As with other respiratory pathogens, including flu and rhinovirus, the transmission is believed to occur through respiratory droplets from coughing and sneezing. Aerosol transmission is also possible in case of protracted exposure to elevated aerosol concentrations in closed spaces. Analysis of data related to the spread of SARS-CoV-2 in China seems to indicate that close contact between individuals is necessary. The spread, in fact, is primarily limited to family members, healthcare professionals, and other close contacts (Cascella *et al.,* 2020).

Based on data from the first cases in Wuhan and investigations conducted by the China CDC and local CDCs, the incubation time could be generally within 3 to 7 days and up to 2 weeks as the longest time from infection to symptoms was 12.5 days (95% CI, 9.2 to 18) (Li *et al.,* 2020). This data also showed that this novel epidemic doubled about every seven days, whereas the basic reproduction number (R0 - R naught) is 2.2. In other words, on average, each patient transmits the infection to an additional 2.2 individuals. Of note, estimations of the R0 of the SARS-CoV epidemic in 2002-2003 were approximately 3 (Bauch *et al.,* 2005).

It must be emphasized that this information is the result of the first reports. Thus, further studies are needed to understand the mechanisms of transmission, the incubation times and the clinical course, and the duration of infectivity (Cascella *et al.,* 2020).

SARS-CoV-2 virions attach to human cells with their densely glycosylated spike protein and bind with high affinity to the angiotensin-converting enzyme 2 receptor on human alveolar type II cells. Once the virus has attached to these receptors, the TMPRSS2 protease cleaves the spike protein to expose a fusion peptide. Virions are then able to release their RNA into infected cells, where it is replicated and translated into new viral proteins. Nucleocapsid proteins bind to RNA molecules and are then covered by the envelope and membrane proteins. Infected cells can produce 100 to 1,000 virions per day (Plapp, 2020).

1. **Histopathological features of COVID-19**

(Tian et al.., 2020) and others reported 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.

Recently, Xu et al. reported the pathological features of the first patient known to have died from SARS-CoV-2 infection (Xu *et al.,* 2020). Biopsy samples were obtained from lung tissue of the patient and it was found that the pathological features of COVID-19 are related to ARDS. For example, evident desquamation of pneumocytes and hyaline membrane formation were seen in the lung tissue, indicating ARDS. Moreover, interstitial mononuclear inflammatory infiltration was observed in lung tissue. Multinucleated giant cells with atypical enlarged pneumocytes characterised by large nuclei, prominent nucleoli and amphophilic granular cytoplasm were observed in the intra-alveolar spaces, suggesting viral cytopathic-like change (Xu *et al.,* 2020). These pathological characteristics of COVID-19 are highly similar to those seen in SARS-CoV and MERS-CoV infection (Ng *et al.,* 2016; Chung *et al.,* 2020) Taken together, understanding the pathological characteristics of this severe case of COVID-19 could help to provide new insights into the pathogenesis of SARS-CoV-2-infected pneumonia, which may help physicians to formulate a timely strategy for the treatment of similar severe patients and to decrease mortality.

The virus (see Figure 4.0 ) appears to be transmitted primarily through large droplets, but it has also been found in stool and blood, raising questions about other potential modes of transmission. The incubation period was originally thought to range from one to 14 days with a median of five to six days, but recent case reports suggest that it may be as long as 24 days. Patients with COVID-19 have a median age of 59 years. They present with fever, dry cough, fatigue, myalgia, and shortness of breath. Patients may develop pneumonia towards the end of the first week of infection. The mean interval from onset of illness to hospitalization is between 9.1 and 12.5 days. Approximately 25 percent of patients have a severe course requiring intensive care, and approximately 10 percent require mechanical ventilation. The most severe cases develop pneumonia and acute respiratory distress syndrome. Children and younger adults have more benign disease



FIG 4.0: A coronavirus viewed under an electron microscope. (Credit: CDC/Fred Murphy, 2020).

One histopathological study of the lungs of a deceased patient reported the presence of hyaline membrane formation (see Figure 8), interstitial mononuclear inflammatory infiltrates, and multinucleated giant cells. These findings were consistent with acute respiratory distress syndrome.



FIG 4.1: Hyaline membrane formation in diffuse alveolar damage, the histological correlate of acute respiratory distress syndrome. (Credit: Wikimedia user Nephron, 2020).

There is no doubt that pathological examination is very important to elucidate the pathological changes, pathogenesis and the cause of death of COVID-19. However, up to now, its clinical pathology remains largely unknown (Xu *et al.,* 2020).

The following is a research conducted by (Luo *et al.,* 2020) in which the whole lungs of surgical critical patient of COVID-19 was described, therefore for the first time, described the main pathological changes of patient with critical type.

Pathological tissues of the whole lung organ were collected in P3 laboratory, fix all tissues with 4% neutral buffered formaldehyde (pH = 7.0) for 24h. Dehydrate the fixed tissues in an ethanol series (100%, 95%, 80% and 75%) for 1 min in each percentage, clear in xylene and then embed in paraffin wax. Finally, cut the slices and incubate for 40 min in 70℃ oven. Special histochemical stains, for example, Masson staining was used to detect pulmonary interstitial fibrosis, periodic acid Schiff (PAS) staining and silver methenamin staining were used to identify bacterial and fungal infections. Masson kit (iron hematoxylin, bright red acid fuchsin working fluid, aniline blue, phosphomolybdic acid). Periodic acid Schiff and sliver methenamine kit (periodate, borax solution, silver nitrate hexamethylenetetramine powder) (Luo *et al.,* 2020).

Immunohistochemical staining

The procedure of IHC was done as previously described.9 In brief, parafﬁn-embedded sections were deparafﬁnized in xylenes for 20 min and rehydrated in an ethanol gradient. The sections were submerged into EDTA buffer and boiled for 2 mins with high-pressure for antigenic retrieval. After natural cooling, the slides were treated with 3% H2O2 to quench endogenous peroxidase activity, followed by incubation with 1% bovine serum albumin (BSA). The slides were incubated with the primary antibodies including CD3, CD20, CD79a, CD4, CD8, CD5, CD68, CD38, CD31, TTF1, CK5/6, CK7, CK19, SMA, F VIII and Collagen IV (working dilution, Zymed, San Francisco, CA) overnight at 4 °C. The sections were reacted with the biotinylated secondary antibody (Zymed, San Francisco, CA) and visualized with 3,3′-diaminobenzidine (DAB) under the microscop(Luo *et al.,* 2020)

Special staining

Special staining includes Masson staining, sirius red staining, reticular fibers staining and PAS staining. According to Masson staining, the tissues were fixed immediately in 10% formalin after dissection, paraffin-embed and section at 1.5 µm thickness. The slices were deparaffinized in dimethylbenzene, oxidize the slices with 1% periodate for 30 min and rinse with distilled water. Fix the tissues with 3% sodium thiosulfate for 1 min, replenish by the bouin's solution (37℃ water bath for 4 h) and wash the sections by distilled water for 5 min. The sections was dyed by Mayer hematoxylin and put into hot water (45℃) for 30s. Stain the specimens by Masson solution (100 μl) for 30 min. Differentiate the sections by 1% phosphomolybdic acid (100μl). Remove phosphomolybdic acid and add the sections with 1% aniline blue (100 μl). Rinse the sections with distilled water, add 1% acetic acid. Dehydrate the sections lastly by 95% and 100% alcohol (10 s and 1 min, respectively) and seal (Luo *et al.,* 2020).

The results are as follows:



FIG 4.2: Gross morphology of the right lung. Haemorrhagic necrosis is obvious in the outer edge of pulmonary right lobe(Luo *et al.,* 2020).

The results include;

Histopathological findings showed the main pulmonary pathological patterns were that extensive pulmonary interstitial fibrosis with partly hyaline degeneration, and pulmonary hemorrhagic infarct (figure 4.3A-C). Small vessels showed severe congestion, vessel wall thickening, and lumen stenosis and occlusion (figure 4.3D-E). Microthrombosis formations were present in the lumen (figure 4.3F-G). Focal interstitial infiltration of inflammatory cells including lymphocytes, plasma cells, macrophage and mononuclear cells (figure 2H-I)



FIG 4.3: Pulmonary interstitial histopathological changes. (A) The whole slide imaging (WSI) by HE staining. Extensive pulmonary hemorrhagic changes and focal hemorrhagic Infarction (B) Massive pulmonary interstitial fibrosis. (C) Pulmonary interstitial fibrosis accompanied with partly hyaline degeneration. (D) Vascular wall thickening, lumen stenosis and hemorrhagic changes. (E) Boangiitis obliterans are surround by inflammatory cells. (F and G) Microthrombosis formation. (H) Focal inflammatory cells in the interstitium (square indicates). (I) Interstitial plasma cells infiltrating (square indicates).

There was necrotizing bronchiolitis manifested necrosis of bronchiolar wall and epithelial cells were present in the lumen. Alveolitis with atrophy, proliferation, desquamation and various changes of squamous metaplasia of alveolar epithelial cells were observed (mainly typeⅡ) (figure 4.4A-D). The remaining pulmonary alveoli showed thickened septum, necrosis and desquamation of alveolar epithelial cells (figure 4.4E-F). In addition, massive fibrinous exudate, multinucleate giant cells and intracytoplasmic viral inclusion bodies were observed (figure 4.4G-I).



FIG 4.4: Pulmonary alveoli changes. (A) Necrotizing bronchiolitis, necrotic bronchial epithelial cells are present in the lumen. (B) Atrophy of alveolar epithelial cells and diffuse alveolar hemorrhage. (C) Squamous metaplasia of bronchiole epithelial cells (D) Squamous metaplasia of alveolar cells. (E) Widened alveolar septum. (F) Necrosis and desquamation of alveolar epithelial cells. (G) Inflammatory cells and massive fibrinous exudate in the lumen. (H) Multinucleate giant cell. (I) Intracytoplasmic viral inclusion body in alveolar epithelial cell (square frame indicates).

Special stain

On the other side, pulmonary interstitial fibrosis, as well as thickening of the vessel wall and fibrinous exudate were displayed by Masson staining (figure 4.5A-E). Enlarged and ruptured alveolar septum, massive pulmonary hemorrhage in alveolar cavity were found (figure 4.5F). In addition, extensive pulmonary interstitial fibrosis was also confirmed by

other special stains including sirius red staining (figure 4.5G), reticular fibers staining

(figure 4.5H) and PAS staining (figure 4.5I). No other bacterial and fungal infections were

detected by special staining.



FIG 4.5: Pulmonary changes by special stain. (A) The whole slide imaging (WSI) by Masson staining. (B) Interstitial fibrosis by Masson stain. (C) The thickening of the vessel wall by Masson staining. (D) Fibrotic walls of dilated bronchioles by Masson staining. Desquamation of epithelial cells and inflammatory cells including macrophages in the lumen. (E) Massive fibrinous exudate in the bronchiole lumen. (F) Enlarged alveolar septum, and partly ruptured septum. Massive pulmonary hemorrhage in alveolar cavity. (G) Interstitial fibrosis by sirius red staining. (H) Interstitial fibrosis by reticular fibers staining. (I) Fibrinous transudation by PAS staining.

Immunohistochemistry

Immunohistological findings showed positive for immunologic cells including CD3

(figure 4.6A), CD4 (figure 4.6B), CD8 (figure 4.6C), CD20 (figure 4.6D), CD79a (figure 4.6E), CD5 (figure 4.6F) and CD38 (figure 4.6G). Notably, we found that the positive expressions of immunologic cells were present focally in lung interstitium and near blood vessels. In addition, CD31, TTF1, CK5/6, CK7 (figure 4.6H), CK19, SMA, F VIII and Collagen IV (figure 4.6I) also exhibited positive (some data not shown). The HE image of these serial immunohistological sections as shown in figure 2H.

 

FIG 4.6: Immunohistological results in severe COVID-19. Serial sections showed the positive expressions of CD3 (A), CD4 (B), CD8 (C), CD20 (D), CD79a (E), CD5 (F), CD38 (G), CK7 (H) and collagen IV (I).

From the above research conducted it was further discovered that in this study, the surgical patient was diagnosed as critical case with COVID-19, and developed respiratory failure. In contrast, hyaline membrane formation was not detected, indicative of severe-phase ARDS and consistency with clinical diagnosis (Ding *et al.,* 2004).

 It was reported that the virus homology was over 85% between novel coronavirus pneumonia and severe acute respiratory syndrome (SARS). It means that the pathological changes of COVID-19 might be similar to SARS patient (Ding *et al.,* 2003). With regard to the pulmonary pathology of SARS, Ding and other research groups had found the pulmonary changes including localized haemorrhage and necrosis, pulmonary alveolitis and bronchitis, desquamation of alveolar epithelial cells (Nicholls *et al.,* 2020).

Results also showed the general pulmonary damages including alveolar edema with hemorrhage and bronchiolitis and alveolitis accompanied with inflammatory injury of epithelial cells. In the present study, one of the main pathological changes of critical COVID-19 was diffuse pulmonary interstitial fibrosis, suggestive of changes in late-stage disease. In addition, vascular wall thickening, lumen stenosis and occlusion occurred frequently under the microscopy, which might explain why some critical patients have pulmonary hypertension in later stage. However, the cause about vascular wall thickening and lumen stenosis need to be further investigated. Microthrombosis formation was also detected. These major changes might explain why late stage of critical patients develop severe hypoxaemia and respiratory failure (Zhou *et al.,* 2020). On the other side, gross detection found that haemorrhagic necrosis existed predominantly in outer edge of the right lower lung lobe. This observation brings us two following hints:

1) It could be one of the main causes of fatal death about critical patients.

2) The main lesions of COVID-19 might firstly originate from here.

Recent study indicates that SARS-CoV-2 has the same cell entry receptor ACE2 as SARS-CoV (Li *et al.,* 2003). Generally, ACE2 protein is expressed in alveolar cells, bronchial epithelium and vascular endothelium, therefore SARS-CoV-2 protein binds to ACE2 would result in acute lung injury and pulmonary edema (Puellman *et al.,* 2006). It was observed that abundant pulmonary edema and hemorrhage, desquamated bronchial and alveolar epithelial cells (Harrison, 2010; Alcaraz-Quiles *et al.,* 2018)

On the other side, cytokine storm links to an excessively exaggerated immune response, and uncontrolled proinflammatory responses, which causes severe organ diseases including lung damages. Several representative cytokines have been identified including IL-1β, IL-18, TNF-α, IL-6, IL-8 and IL-10, which are produced and regulated by various immunological cells including CD4 T cells and CD8 T cells (Savarin and Bergmann, 2018). Interestingly, we observed that lymphocytes including CD3 T cells 4 T cells and CD8 T cells , monocytes and plasma cells infiltrating into pulmonary interstitium, and these various types of inflammatory cells were confirmed by immunohistological method. It should be noted that local haemorrhagic necrosis occurred preferentially in outer edge of the right lower lung on gross detection. We suggest that the cytokine storm released by these inflammatory cells including CD4 and CD8 T cells could eventually lead to hemorrhagic necrosis, and ultimately result in severe and even fatal respiratory dysfunction of patients. More rigorous studies including experimental tests are needed to prove this prediction (Luo *et al.,* 2020).

1. **Current potential therapies to address COVID-19**

There is no specific antiviral treatment recommended for COVID-19, and no vaccine is currently available. The treatment is symptomatic, and oxygen therapy represents the major treatment intervention for patients with severe infection. Mechanical ventilation may be necessary in cases of respiratory failure refractory to oxygen therapy, whereas hemodynamic supsport is essential for managing septic shock(Cascella *et al.,* 2020).

1)General treatments

General treatment strategies include bed rest and supportive treatments, ensuring sufficient energy intake, maintaining a constant internal environment (water, electrolytes and other internal environment factors) and monitoring vital signs (heart rate, pulse, blood pressure, oxygen saturation, respiratory rate, etc.).

2)Antiviral therapy

a) Interferon-alpha (IFNα):IFNα is a member of the family of type I IFNs that plays an important role in host resistance to viral infection. IFNα suppresses viral infection by directly interfering with replication of the virus and by promoting both innate and adaptive immune responses (Ströher *et al.,* 2004). In vitro experiments showed that IFNα effectively inhibits the replication of SARS-CoV (Zorzitto *et al.,* 2006). It has also been reported that cynomolgus monkeys are protected from infection with SARS CoV by treatment with IFNα (Haagmans *et al.,* 2006). Moreover, the therapeutic benefit of synthetic recombinant IFNα for patients with SARS was demonstrated in a pilot clinical trial (Loutfy *et al.,* 2003). Thus, IFNα should be considered a candidate drug for COVID-19 therapy.

b) Lopinavir/ritonavir (Kaletra):Lopinavir/ritonavir was first known as a protease inhibitor that interferes with the replication and synthesis of human immunodeficiency virus (HIV), leading to the production of immature, non-infectious virus particles (Walmsley *et al.,* 2003; Pulido *et al.,* 2008). It has been reported that ritonavir and lopinavir can bind to the endopeptidase C30 of SARS-CoV-2 protease as evaluated by molecular models (Lin *et al.,* 2020). This suggests that lopinavir/ritonavir may exert an antiviral effect by inhibiting protein synthesis of SARS-CoV-2 (Chu *et al.,* 2004). In addition, several lines of evidence showed that treatment with lopinavir/ritonavir alone or in combination with other antiviral drugs was shown to improve the outcome of severe patients with SARS or MERS by ameliorating ARDS (Sheahan *et al.,* 2020; Zumla *et al.,* 2016). Given that SARS-CoV-2 is similar to these two viruses, lopinavir/ritonavir may have a beneficial effect on COVID-19. Future studies are needed to test this possibility.

c) Ribavirin:Ribavirin is a nucleoside analogue with broad antiviral activity. It can prevent the replication of RNA and DNA viruses by suppressing the activity of inosine monophosphate dehydrogenase, which is required for the synthesis of guanosine triphosphate (GTP) (Wenzel and Edmond, 2003). Ribavirin was widely used to treat SARS patients with or without concomitant use of steroids during the outbreak of SARS in Hong Kong (Jones *et al.,* 2004; Peiris *et al.,* 2003). Thus, ribavirin could be considered as a treatment option for COVID-19 patients.

d) Chloroquine:Chloroquine is a widely used antimalarial and autoimmune disease drug. Recently, chloroquine has been reported as a potential broad-spectrum antiviral drug(Savarino *et al.,* 2006; Yan *et al.,* 2013). Wang et al. found that chloroquine effectively suppresses the recently emerged novel CoV (SARS-CoV-2) in vitro (Wang *et al.,* 2020). Chloroquine is a cheap and safe drug that has been used for more than 70 years and thus it is potentially clinically applicable against COVID-19.

e) Arbidol (umifenovir):Arbidol is an antiviral drug against influenza infection that is widely used in Russia and China. Arbidol and arbidol mesylate were shown to have a potent inhibitory effect in reducing the reproduction of SARS-CoV in vitro (Khamitov *et al.,* 2008).Low-level evidence including a retrospective cohort study, case reports and case series revealed that arbidol alone or combined with antiviral drugs produced certain benefits in the treatment of COVID-19 pneumonia (Wang *et al.,* 2020; Zhang *et al.,* 2020; Xu *et al.,* 2020).Currently, many randomised clinical controlled trials are being carried out studying the efficacy of Arbidol on COVID-19 pneumonia in China.

f)Remdesivir:The nucleoside analogue remdesivir (GS-5734) was reported to inhibit SARS-CoV and MERS-CoV in vivo (de Wit *et al.,* 2020; Agostini *et al.,* 2018; Hammer *et al.,* 2018). More recently, an in vitro study showed that remdesivir potently blocked SARS-CoV-2 infection at low-micromolar concentrations and showed a high selectivity index (Wang *et al.,* 2020).In addition, the first case of SARS-CoV-2 infection in the USA was treated with intravenous remdesivir when the patient's condition deteriorated (Holshue et al 2020).Although remdesivir has some benefits for the treatment of COVID-19 pneumonia, randomised controlled trials are still required to determine its efficacy and safety.

Taken together, these antiviral drugs may be promising treatment options for the treatment of COVID-19. However, there are also a few points worth noting here: (i) the potential interaction of these antiviral drugs with other therapeutic drugs should be considered; (ii) adverse reactions caused by lopinavir/ritonavir, such as diarrhoea, nausea, vomiting and liver damage, should be also considered; (iii) it is not recommended to use three or more antiviral drugs at the same time, and the use of related drugs should be stopped when there are intolerable side effects; and (iv) further evaluation of the efficacy of current antiviral drugs in clinical applications is needed(Li *et al.,* 2020).

3)Cellular therapy

a)Natural killer (NK) cells:NK cells are important immune cells necessary for defence against microbe-infected, stressed or malignant cells. Human NK cells lyse antibody-coated virus-infected cells via the process of antibody-dependent cellular cytotoxicity (ADCC) (Hammer *et al.,* 2018). In this way, NK cells are specific to almost all virus-infected cells. Several studies have shown that NK cells can exert antiviral activity by mediating ADCC against SARS-CoV, herpes simplex virus type 1 (HSV-1), cytomegalovirus and HIV (Dai and Caligiuri 2018; Arase et al 2002). Umbilical cord blood is a promising source of allogeneic NK cells. Recently, Sorrento and Celularity have announced the launch of a clinical collaboration aimed at extending the use of CYNK-001, an allogeneic, off-the-shelf, umbilical cord blood-derived NK cell therapy, to the treatment of the newly emerged SARS-CoV-2 infection. Whilst developing new drugs, new vaccines or clinical trials of old drugs, carrying out NK cell therapy to enhance immunity is currently a very feasible strategy for the treatment and prevention of COVID-19 pneumonia (Li *et al.,* 2020).

b) Mesenchymal stem cells (MSCs):It is well known that MSCs have strong anti-inflammatory and immunomodulatory functions (Ortiz *et al.,* 2007). Umbilical cord blood and placenta are good sources of MSCs (Gupta *et al.,* 2007). Numerous studies have shown that treatment with MSCs can ameliorate acute/chronic lung injury and ARDS by suppressing the infiltration of immune cells to pulmonary tissues and pro-inflammatory cytokine secretion (Moodley *et al.,* 2007; Matthay *et al.,* 2007). In addition, MSCs contribute to reducing lung fibrosis and enhancing tissue repair (Kumamoto *et al.,* 2009; El Agha *et al.,* 2017). Besides routine antiviral treatment, it is important to treat cytokine storm syndromes, ARDS and acute lung injury in patients with severe COVID-19 to prevent progression of the disease and to reduce mortality. Thus, MSCs may be a promising therapeutic option.

4) Immunotherapy

a)Convalescent plasma therapy:Antiviral antibodies (IgG, IgA, IgM, IgE and IgD) found in convalescent plasma from recovered patients can effectively treat patients with viral infections (Zhou *et al.,* 2017). Convalescent plasma therapy has been widely used in infectious diseases such as poliomyelitis, influenza A (H5N1) and Ebola (van Griensven wt al., 2016; Rinaldo, 2005). In addition, such passive immunisation can also be achieved by using convalescent plasma from patients with SARS-CoV infection (Cheng *et al.,* 2005). It has been reported that a small number of SARS-CoV-infected patients in Taiwan and Hong Kong received treatment with convalescent plasma during the early course of the disease with certain clinical benefits, including a reduction of plasma viral load from ~105 copies/mL to undetectable levels 24 h after plasma transfusion(Wong and Yuen, 2008; Yeh *et al.,* 2005). Thus, convalescent plasma could, theoretically, be a promising option for the treatment and prevention of SARS-CoV-2 infection, although this has not been tested clinically.

b) Monoclonal antibodies**:** Remission of the SARS-CoV-2 epidemic may depend on the development of monoclonal antibodies (ter Meulen *et al.,* 2004). Previous studies have identified a number of effective monoclonal antibodies that target the SARS-CoV spike protein to prevent the virus from entering host cells (ter Meulen *et al.,* 2006; Traggiai *et al.,* 2004). The 193-amino acid (residues 318–510) receptor-binding domain (RBD) of the spike protein is the key target of neutralising monoclonal antibodies (Wong *et al.,* 2004). The SARS-CoV neutralising monoclonal antibodies CR3014 and CR3022 were found to bind non-competitively to the SARS-CoV RBD and neutralised the virus in a synergistic manner (ter Meulen *et al.,* 2006). A recent study showed that CR3022 could combine effectively with SARS-CoV-2 RBD (KD of 6.3 nM) (Tian *et al.,*2020 ). Moreover, the epitope of CR3022 does not overlap with the binding site of ACE2 in the SARS-CoV-2 RBD (Tian *et al.,* 2020). Thus, CR3022 could be a promising therapeutic candidate, alone or in combination with other neutralising monoclonal antibodies, for the treatment of COVID-19 pneumonia.

5) Chinese medicine:Glycyrrhizin, an active component of liquorice roots used in Chinese medicine, could effectively inhibit the replication of SARS-associated CoV in vitro (Cinatl *et al.,* 2006; Hoever *et al.,* 2005). Furthermore, high doses of glycyrrhizin have been used in clinical trials and the compound was reported to be clinically effective for the treatment of SARS at that time (Lu *et al.,* 2006; Wu *et al.,* 2004). Recently, glycyrrhizin was predicted to have the ability to bind ACE2 with potential anti-COVID-19 effects (Chen and Du, 2020). Hesperetin, a well-known traditional Chinese medicine, is a natural predominant flavonoid found in citrus fruits. Hesperetin dose-dependently suppresses the cleavage activity of the 3C-like protease (3CLpro) of SARS-CoV in cell-free and cell-based assays (Lin *et al.,* 2005). Hesperetin was also reported to have the potential to inhibit ACE2 and therefore block infection with SARS-CoV-2 (Chen and Du, 2020). Baicalin, another traditional Chinese herbal medicine, is a flavone isolated from *Scutellaria baicalensis*. It has been shown that baicalin has antiviral activity against 10 clinical isolates of SARS-CoV by neutralisation tests (Chen *et al.,* 2004).In addition, quercetin is a plant flavone that is widely used in traditional Chinese medicine and botanical medicine. Quercetin was reported to exert antiviral effects by inhibiting the 3CLpro of SARS-CoV (Chen *et al.,* 2006) and blocking the entry of SARS-CoV into host cells (Yi *et al.,* 2004 ). Therefore, these studies suggest that Chinese medicine also plays a key role in the prevention and treatment of COVID-19 pneumonia.

As of January 22, 2020, a total of 571 cases of the 2019-new coronavirus (2019-nCoV) have been reported in 25 provinces (districts and cities) in China. At present, there is no vaccine or antiviral treatment for human and animal coronavirus, so that identifying the drug treatment options as soon as possible is critical for the response to the 2019-nCoV outbreak. Three general methods, which include existing broad-spectrum antiviral drugs using standard assays, screening of a chemical library containing many existing compounds or databases, and the redevelopment of new specific drugs based on the genome and biophysical understanding of individual coronaviruses, are used to discover the potential antiviral treatment of human pathogen coronavirus. Lopinavir /Ritonavir, Nucleoside analogues, Neuraminidase inhibitors, Remdesivir, peptide (EK1), abidol, RNA synthesis inhibitors (such as TDF, 3TC), anti-inflammatory drugs (such as hormones and other molecules), Chinese traditional medicine, such ShuFengJieDu Capsules and Lianhuaqingwen Capsule, could be the drug treatment options for 2019-nCoV. However, the efficacy and safety of these drugs for 2019- nCoV still need to be further confirmed by clinical experiments(Lu, 2020).



FIG 5.0: “Flattening the curve,” a mitigation approach to lower and delay the epidemic peak. (Credit: Esther Kim and Carl T. Bergstrom, 2020).

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

The onset of the novel Coronavirus Disease 2019 (COVID-19) out-break in Wuhan, China, suggests animal-to-person spread and laterperson-to-person spread. . The complete clinical picture following COVID-19 infection is not yet fully understood.

The WHO's declaration of COVID-19 to be a Public Health Emergency of International Concern is attributable to the high case fatality rates in China and the global economic effect of COVID-19,which may compound the current ongoing influenza epidemic Furthermore, there is the potential for higher death rates in countries with vulnerable health systems in resource limited regions (WHO, 2020). The ability to control local transmission depends on the application of the principles of rapid identification, prevention, and control, followed by patient isolation, rapid diagnosis, and contact tracing. Some countries remain ill equipped with limited diagnostic capacity, resulting in delays from suspected case identification to vector confirmation and patient isolation, which increases the risk of disease transmission (Gilbert *et al.,* 2020). Though, 74% of countries in Africa have an influenza pandemic preparedness plan; however, most are outdated and inadequate to deal with a global pandemic such as COVID-19 (Sambala *et al.,* 2018).

Conclusion

According to the World Health Organization (WHO), viral diseases continue to emerge and represent a serious issue to public health. In the last twenty years, several viral epidemics such as the severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002 to 2003, and H1N1 influenza in 2009, have been recorded. Most recently, the Middle East respiratory syndrome coronavirus (MERS-CoV) was first identified in Saudi Arabia in 2012(Cascella *et al.,* 2020).



-A linear scale showing total cases of COVID-19 as of April 18, (WHO, 2020)



-A linear scale showing total number of deaths of COVID-19 as of April 18, (WHO, 2020)

The 2019 novel coronavirus pneumonia was officially named by the World Health Organization (WHO) as COVID-19. COVID-19 caused by SARS-CoV-2 was firstly emerged in December 2019, Wuhan city, and resulted in other cities including Shenzhen in China and other counties (Chen *et al.,* 2020;Wu *et al.,* 2020). The world is experiencing a global viral epidemic of COVID-19. Reports regarding epidemiological and clinical characteristics of COVID-19 are accumulating (Zhu *et al.,* 2020; Li *et al.,* 2020; Wang *et al.,* 2020).

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(Zhang *et al.,* 2020). Recently, the newly emerged SARS-CoV-2 is undoubtedly a warning (Chai *et al.,* 2020). It has been confirmed that SARS-CoV-2 enters lung cells by binding to ACE2 (Li *et al.,* 2020). Besides pulmonary tissue, ACE2 is also highly expressed in other tissues including bile duct, liver, gastrointestinal organs (small intestine, duodenum), oesophagus, testis and kidney(Fan *et al.,* 2020).

Although there are several theories about how COVID-19 came to be, any of them is still yet to be proved.

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