Analysis on the Dynamic Attributes of SARS-CoV-2 and COVID-19

Mohd Abass Dar*, Garima Charak, Suman Bala, Sudhanshu Shekhar, Muneeb Qadir

Department Physiology, Govt. Medical College Doda
*Corresponding author: aabvee191@gmail.com

Received November 05, 2021; Revised December 08, 2021; Accepted December 16, 2021

Abstract An eminently transmissible and dead-dealing pathogenic coronavirus come to light in late 2019, which was known as Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has caused a lethal pandemic of acute respiratory disease, named ‘Coronavirus disease 2019’ (COVID-19), which menace human health and public safety. Coronaviruses are RNA viruses that are phenotypically and genotypically myriad. In this Review, we light on the the basic virological concept of SARS-CoV-2, including genomic attributes and receptor use, highlighting its role key variance from previously known coronaviruses. The virus spreads faster than its two ancestors the SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), but has lower fatality. The global impact of this new epidemic is yet uncertain. CoV can lead to a range of conditions as mild as the common cold, fever and cough and as severe as pneumonia, respiratory distress kidney failure or even death. These viruses are zoonotic, that is, they are transmitted between animals and humans. A couple of coronaviruses were previously identified: MERS-CoV, which causes Middle East respiratory syndrome and was transmitted from dromedary camels to humans, and SARS-CoV, which causes severe acute respiratory syndrome and was transmitted from civet cats to humans. COVID-19 is believed to have been transmitted zoonotically, in a wet market in Wuhan where game animals and meat were sold. The Centers for Disease Control and Prevention (CDC), in collaboration with seven U.S. health care systems and research centers with integrated medical, laboratory, and vaccination records, established the VISION Network to assess the effectiveness of Covid-19 vaccines with respect to laboratory-confirmed SARS-CoV-2 infection-associated hospitalizations, ICU admissions, or visits to emergency departments or urgent care clinics from January 1 through June 22, 2021. We searched PubMed, LitCovid, and MedRxiv using the search terms coronavirus, severe acute respiratory syndrome coronavirus 2, 2019-nCoV, SARS-CoV-2, SARS-CoV, MERS-CoV, and COVID-19 for studies published from January 1, 2002, to November 23, 2021, and the references of select articles for additional relevant articles searched manually also. Ongoing or completed clinical trials were identified using the disease search term coronavirus infection on ClinicalTrials.gov, the Chinese Clinical Trial Registry, and the International Clinical Trials Registry Platform. We selected articles relevant and in close approach to a systematic reviews, clinical practice guidelines, general medicine readership, and prioritizing randomized clinical trials.

Keywords: Covid-19, SARS-CoV-19, MERS-CoV, REVIEW, CDC, CoV

Cite This Article: Mohd Abass Dar, Garima Charak, Suman Bala, Sudhanshu Shekhar, and Muneeb Qadir, “Analysis on the Dynamic Attributes of SARS-CoV-2 and COVID-19.” American Journal of Infectious Diseases and Microbiology, vol. 10, no. 1 (2022): 26-47. doi: 10.12691/ajidm-10-1-5.

1. Unveiling and Brisk Spread of COVID-19

Globally, as of 6:45 pm CET, 23 November 2021, there have been 257,469,528 confirmed cases of COVID-19, including 5,158,211 deaths, reported to WHO. As of 22 November 2021, Figure 1. A total of 7,408,870,760 vaccine doses have been administered. In India, from 3 January 2020 to 6:45pm CET, 23 November 2021, there have been 34,526,480 cumulative confirmed cases of COVID-19 with 466,147 cumulative deaths cases, reported to WHO. As of 16 November 2021, a total of 1,136,168,939 vaccine doses have been administered [1].

In December 2019, several pneumonia cases of unknown aetiology were identified in the city of Wuhan in central China. Towards the end of December 2019, patients headlining with symptoms of viral pneumonia including diverse critical presenting symptoms because of an unknown pathogenic agent were reported in Wuhan, China. A novel coronavirus was subsequently identified as the causative pathogen, provisionally named 2019-nCoV. WHO announced the swiftly rambling coronavirus disease as COVID-19 on 11th Feb-2020. As of 26th January 2020, more than 2000 cases of COVID-19 infection have been confirmed, most of which involved people living in or visiting Wuhan, and human-to-human transmission was confirmed. The initial infected individuals mostly were networked to divulging to a seafood market in Wuhan. The Chinese authorities reported 2835 confirmed cases in
mainland China in 2020, including 81 deaths. Additionally, 19 confirmed cases were pinpointed in Hong Kong, Macao and Taiwan, and 39 imported cases were identified in other myriad countries like Thailand, Japan, South Korea, United States, Vietnam, Singapore, Nepal, France, Australia and Canada. COVID-19 was closely related to Severe Acute Respiratory Syndrome CoV (SARS-CoV). The authorities of China officially announced a novel coronavirus, 2019-nCoV, as the causative agent [2].

Figure 1. Covid-19 cases reported by WHO Region and Global deaths, as of 21 November 2021

| DECEMBER | JANUARY | FEBRUARY | MARCH | OCTOBER | NOVEMBER |
|----------|---------|----------|-------|---------|----------|
| 8 December 2019 | Onset of the first recorded case in Wuhan. | 9 January 2020 | First confirmed death outside China (Philippines) of a Chinese man from Wuhan. | 11 March 2020 | 2 October 2020 |
| 31 December 2019 | First report of 27 cases of pneumonia with unknown cause in Wuhan, China. | 20 January 2020 | 11 February 2020 | WHO defined COVID-19 as a pandemic. | 34,000,000 cases and >1,000,000 deaths |
| | | Human-to-human transmission was confirmed | 14 February 2020 | | |
| | | Wuhan city was locked down | 28 February 2020 | | | Globally, as of 23 Nov 2021, there have been 257,469,528 confirmed cases of COVID-19, including 5,158,211 deaths, reported to WHO. As of 22 November 2021, a total of 7,418,870,760 vaccine doses have been administered. |
| | | 29 January 2020 | WHO reported 1,770 confirmed cases and 58 deaths | 18 March 2020 WHO launches International solidarity trial aiming to find the most effective treatments for COVID-19. | 28 Oct 2020 announced the following actions taken in its ongoing response effort to the COVID-19 pandemic: enforcement of non-invasive remote monitoring devices used to support patient monitoring during the COVID-19 public health emergency. |
| | | The coronavirus spread to all 34 provinces across China. | 28 February 2020 | WHO launched joint mission to China to investigate the origins of SARS-CoV-2 and to find effective treatment approaches. | 28 Oct 2020 | Approve two generic drugs indicated to facilitate tracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation: succinylcholine chloride injection and cisatracurium besylate injection. |
| | | 30 January 2020 | 21 Feb 2020 |More cases outside mainland China than within. | 25 November 2021, a total of 1,156,189,399 vaccine doses have been administered. |

Figure 2. Chronology of the chief events of the COVID-19 paroxysm. The first recorded cases were reported in December 2019 in Wuhan, China. Over the course of the following 10 months, more than 30 million cases have been confirmed worldwide. COVID-19, coronavirus disease 2019; ICTV, International Committee on Taxonomy of Viruses; PHEIC, public health emergency of international concern; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WHO, World Health Organization.
Betacoronavirus was identified the causative agent of this dead emerging disease by the independent team of Chinese scientists by means of metagenomic RNA sequencing and virus isolation from broncho-alveolar lavage fluid samples from patients with severe pneumonia [3]. The result of this etiological identification was publicly announced on 9 Jan-2020 (Figure 3). On 10 Jan 2020, the first genome sequence of the novel coronavirus was published on the Virological website and more nearly complete genome sequences determined by different research institutes were then released via the GISAID database on 12 January [4]. Later, cluster of patients with no history of openness to Huanan Seafood Wholesale Market were identified. Several familial clusters of infection were reported, and nosocomial infection also occurred in health-care facilities. All these cases bestowed clear evidence for human-to-human web transmission of the new virus [5]. As the outbreak coincided with the approach of the lunar New Year, travel between cities before the festival facilitated virus transmission in China. This novel coronavirus pneumonia soon spread to other cities in Hubei province and to diverse parts of China. Steadily and massively spread to all 34 provinces of China with in a month. The number of confirmed cases abruptly peaked, with thousands of new cases diagnosed daily during late January [6]. The WHO declared the novel coronavirus outbreak a public health emergency of international concern on 30th January [7]. The International Committee on Taxonomy of Viruses named the novel coronavirus ‘SARS- CoV-2’, and the WHO named the disease ‘COVID-19’ on 11th February [8]. The outbreak of COVID-19 in China reached an epidemic peak in February. According to the National Health Commission of China, the total number of cases continued to rise sharply in early February at an average rate of more than 3,000 newly confirmed cases per day. To control COVID-19, China implemented unprecedentedly strict public health measures. The city of Wuhan was shut down on 23 January, and all travel and transportation connecting the city was blocked. In the following couple of weeks, all outdoor activities and gatherings were restricted, and public facilities were closed in most cities as well as in countryside. Owing to these measures, the daily number of new cases in China started to decrease steadily. However, despite the declining trend in China, the international spread of COVID-19 accelerated from late February. Large clusters of infection have been reported from an increasing number of countries. The high transmission efficiency of SARS- CoV-2 and the abundance of international travel enabled rapid worldwide spread of COVID-19. On 11 March 2020, the WHO officially characterized the global COVID-19 outbreak as a pandemic. Since March, while COVID-19 in China has become effectively controlled, the case numbers in Europe, the USA and other regions have jumped sharply. According to the COVID-19 dashboard of the Center for System Science and Engineering at Johns Hopkins University, as of 11 August 2020, 216 countries and regions from all six continents had reported more than 20 million cases of COVID-19, and more than 733,000 patients had died. High mortality occurred especially when health-care resources were overwhelmed. The USA is the country with the largest number of cases so far. Although genetic evidence suggests that SARS-CoV-2 is a natural virus that likely originated in animals, there is no conclusion yet about when and where the virus first entered humans. As some of the first reported cases in Wuhan had no epidemological link to the seafood market, it has been suggested that the market may not be the initial source of human infection with SARS-CoV-2. France detected SARS- CoV-2 from one study by PCR in a stored sample from a patient who had pneumonia at the end of 2019, implying SARS- CoV-2 might have spread there much earlier than the generally known starting time of the outbreak in France. However, the origin and contamination of SARS-CoV-2 is still not aptly evident and thus cannot be excluded if the result is false positive. To-boot retrospective investigations involving a larger number of banked samples from patients, and environments, and last but not least animals need to be conducted globally with properly and well-validated assays, so that this highly controversial issue will be addressed adequately [9].

2. Bibliography of COVID-19

2.1. Phylo-Genetic Taxonomy

Scientists generously shared the SARS-CoV-2 coronavirus genomes at the Shanghai Public Health Clinical Center & School of Public Health, Fudan University (WH-Human_1), at the National Institute for Viral Disease Control and Prevention, China CDC, Beijing, China (Wuhan/IVDC-HB-01/2019, Wuhan/IVDC-HB-05/2019, IVDC-HB-04/2020) at the Institute of Pathogen Biology, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China (Wuhan/IPBCAMS-WH-01/2019), and at the Wuhan Institute of Virology, Chinese Academy of Sciences, Wuhan, China (Wuhan/WIV04/2019, bat/Yunnan/RaTG13/2013). Related SARS-like bat virus was shared by Zhu et al at the Wuhan Institute of Virology, Chinese Academy of Sciences, Wuhan, China (bat/Yunnan/RaTG13/2013). Related SARS-like pangolin viruses were shared by Lam, Cao et al at the State Key Laboratory of Pathogen and Biosecurity, Beijing Institute of Microbiology and Epidemiology, Beijing, China and at the State Key Laboratory of Emerging Infectious Diseases and Centre of Influenza Research, University of Hong Kong, Hong_Kong(pangolin/Guangdong/P2S/2019,pangolin/Guangxi/P1E/2017, pangolin/Guangxi/P2V/2017,pangolin/Guangxi/P3B/2017,pangolin/Guangxi/P4L/2017,pangolin/Guangxi/P5E/2017,pangolin/Guangxi/P5L/2017). Other related SARS-like pangolin viruses were shared by Shen, Xiao et al at the South China Agricultural University (pangolin/Guang- dong/1/2020) [10]. SARS-CoV shares 79% and MERS-CoV shares 50% genome sequence with a novel betacoronavirus, SARS-CoV-2. Its genome organization is shared with other betacoronaviruses. The six functional open reading frames (ORFs) are arranged in order from 5’ to 3’: replicase (ORF1a/ORF1b), spike (S), envelope (E), membrane (M) and nucleocapsid (N). further, seven putative ORFs encoding accessory proteins are interspersed between the structural genes. Most of the proteins encoded by SARS- CoV-2 have a similar length...
to the corresponding proteins in SARS-CoV. Of the four structural genes, SARS-CoV-2 shares more than 90% amino acid identity with SARS-CoV except for the S gene, which diverges. The replicase gene covers two thirds of the 3’ genome, and encodes a large polyprotein (pp1ab), which is proteolytically cleaved into 16 non-structural proteins that are involved in transcription and virus replication. Most of these SARS-CoV-2 non-structural proteins have greater than 85% amino acid sequence identity with SARS-CoV. The phylogenetic analysis for the whole genome shows that SARS-CoV-2 is clustered with SARS-CoV and SARS-related coronaviruses (SARSr-CoVs) found in bats, placing it in the subgenus Sarbecovirus of the genus Betacoronavirus. Within this clade, SARS-CoV-2 is grouped in a distinct lineage together with four horseshoe bat coronavirus isolates (RaTG13, RmYN02, ZC45 and ZXC21) as well as novel coronaviruses recently identified in pangolins, which group parallel to SARS-CoV and other SARSr-CoVs (Figure 3). Using sequences of five conserved replicative domains in pp1ab (3C-like protease (3CLpro), nidoivirus RNA-dependent RNA polymerase (RdRp)-associated nucleotidyltransferase (NiRAN), RdRp, zinc-binding domain (ZBD) and HEL1), the Coronaviridae Study Group of the International Committee on Taxonomy of Viruses estimated the pairwise patristic distances between SARS-CoV-2 and known coronaviruses, and assigned SARS-CoV-2 to the existing species SARSr-CoV. Although phylogenetically related, SARS-CoV-2 is distinct from all other coronaviruses from bats and pangolins in this species. The SARS-CoV-2 S protein has a full size of 1,273 amino acids, longer than that of SARS-CoV (1,255 amino acids) and known bat SARSr-CoVs (1,245-1,269 amino acids). It is distinct from the S proteins of most members in the subgenus Sarbecovirus, sharing amino acid sequence similarities of 76.7-77.0% with SARS-CoVs from civets and humans, 75-97.7% with bat coronaviruses in the same subgenus and 90.7-92.6% with pangolin coronaviruses. In the receptor-binding domain (RBD) of S protein, the amino acid similarity between SARS-CoV-2 and SARS-CoV is only 73% [9].

Figure 3. Phylogenetic tree of the full-length genome sequences of SARS-CoV-2, SARSr-CoVs and other betacoronaviruses. The construction was performed by the neighbour joining method with use of the program MEGA6 with bootstrap values being calculated from 1,000 trees. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) clusters with closely related viruses in bats and pangolins and together with SARS-CoV and bat SARS-related coronaviruses (SARSr-CoVs) forms the sarbecoviruses. The sequences were downloaded from the GISAID database and GenBank. MERS-CoV, Middle East respiratory syndrome coronavirus.
Figure 3. Phylogenetic analysis and homology modeling of the Receptor-binding domain of the 2019-nCoV, SARS-CoV, and MERS-CoV. (A) Phylogenetic analysis of the receptor-binding domain from various betacoronaviruses. The star highlights 2019-nCoV and the question marks mean that the receptor used by the viruses remains unknown. Structural comparison of the receptor-binding domain of SARS-CoV (B), 2019-nCoV (C), and MERS-CoV (D) binding to their own receptors. Core subdomains are magenta, and the external subdomains of SARS-CoV, 2019-nCoV, and MERS-CoV are orange, dark blue, and green, respectively. Variable residues between SARS-CoV and 2019-nCoV in the receptor-binding site are highlighted as sticks. CoV= coronavirus. 2019-nCoV=2019 novel coronavirus. SARS-CoV=severe acute respiratory syndrome coronavirus. MERS= Middle East respiratory syndrome coronavirus [9]

Figure 4. Key contrasts in the spike protein of SARS-CoV-2 related coronaviruses. Key differences in the spike protein of SARS-CoV-2 and related coronaviruses. a | Schematic diagram of the spike (S) protein of severe acute respiratory syndrome coronavirus (SARS-CoV) and SARS-CoV-2. The residue numbers of each region correspond to their positions in the S proteins of SARS-CoV and SARS-CoV-2. The dark blue blocks represent insertions in the S protein. The insertions at amino acids 675-691 of the SARS-CoV-2 S protein are shown in an enlargement at the bottom right and aligned with those of other coronaviruses in the same region. b | Alignment of the receptor-binding domain (RBD) in SARS-CoV-2, SARS-CoV BJ01, RaTG13, pangolin coronavirus reported from Guangdong, China (GD pangolin), pangolin coronavirus reported from Guangxi, China (GX pangolin) and bat SARS-related coronavirus (SARSr-CoV) WIV1. The receptor-binding motif (RBM) is shown in purple, and the five key residues that contact angiotensin-converting enzyme 2 (ACE2) directly are highlighted in green
Another specific genomic feature of SARS-CoV-2 is the insertion of four amino acid residues (PRRA) at the junction of subunits S1 and S2 of S protein (Figure 4). Mutations in contact residues of the SARS-CoV-2 spike protein. The spike protein of SARS-CoV-2 (red bar at top) was aligned against the most closely related SARS-CoV-like coronaviruses and SARS-CoV itself. Key residues in the spike protein that make contact to the ACE2 receptor are marked with blue boxes in both SARS-CoV-2 and related viruses, including SARS-CoV (Urbani strain). Acquisition of polybasic cleavage site and O-linked glycans. Both the polybasic cleavage site and the three adjacent predicted O-linked glycans are unique to SARS-CoV-2 and were not previously seen in lineage B betacoronaviruses. Sequences shown are from NCBI GenBank, accession codes MN908947, MN996532, AY278741, KY417146 and MK211376. The pangolin coronavirus sequences are a consensus generated from SRR10168377 and SRR10168378 (NCBI BioProject PRJNA573298).

3. Animal Host and Spillover

Natural imperious hosts of alpha-coronaviruses and beta-coronaviruses are bats. Till date The bat coronavirus is closest relative to SARS-CoV-2, detected in Rhinolophus affinis from Yunnan province, China, named ‘RaTG13’, whose full-length genome sequence is 96.2% identical to that of SARS-CoV-2. This bat virus shares more than 90% sequence identity with SARS-CoV-2 in all ORFs throughout the genome, including the highly variable S and ORF8. Phylogenetic analysis confirms that SARS-CoV-2 closely clusters with RaTG13 (Figure 3). The high genetic similarity between SARS-CoV-2 and RaTG13 supports the hypothesis that SARS-CoV-2 likely originated from bats. Another related coronavirus has been reported more recently in a Rhinolophus malayanus bat sampled in Yunnan. This novel bat virus, denoted ‘RmYN02’, is 93.3% identical to SARS-CoV-2 across the genome. In the long 1ab gene, it exhibits 97.2% identity to SARS-CoV-2, which is even higher than for RaTG13. In addition to RaTG13 and RmYN02, bat coronaviruses ZC45 and ZXC21 previously detected in Rhinolophus pusillus bats from eastern China also fall into the SARS-CoV-2 lineage of the subgenus Sarbecovirus as per the data of phylogenetic analysis (Figure 3). The treasure-trove of myriad bat coronaviruses closely related to SARS-CoV-2 suggests that bats are possible reservoirs of SARS-CoV-2. Nevertheless, on the basis of current findings, the divergence between SARS-CoV-2 and related bat coronaviruses likely speaks-for more than 20 years of sequence evolution, suggesting that these bat coronaviruses can be regarded only as the likely evolutionary precursor of SARS-CoV-2 but not as the direct progenitor of SARS-CoV-2 [9]. Another wildlife host pangolins beyond bats probably linked with SARS-CoV-2. Multiple SARS-CoV-2-related viruses have been identified in tissues of Malayan pangolins smuggled from Southeast Asia into southern China from 2017 to 2019. These viruses from pangolins independently seized by Guangxi and Guangdong provincial customs belong to two distinct sub-lineages. The Guangdong strains, which were isolated or sequenced by different research groups from smuggled pangolins, have 99.8% sequence identity with each other. They are meticulously related to SARS-CoV-2, exhibiting 92.4% sequence similarity. Notably, the RBD of Guangdong pangolin coronaviruses is highly kindred to that of SARS-CoV-2. The receptor-binding motif (RBM; which is part of the RBD) of these viruses has only one amino acid variation from SARS-CoV-2, and it is identical to that of SARS-CoV-2 in all five critical residues for receptor binding. The Guangdong comparability strains, pangolin coronaviruses reported from Guangxi are less akin to SARS-CoV-2, with 85.5% genome sequence identity. The repeated manifestation of SARS-CoV-2-related coronavirus infections in pangolins from diverse smuggling events suggests that these animals are possible hosts of the viruses. However, unlike bats, which carry coronaviruses healthily, the infected pangolins showed clinical signs and histopathological changes, including interstitial pneumonia and inflammatory cell infiltration in different organs. These abnormalities suggest that pangolins are unlikely to be the reservoir of these coronaviruses but more likely acquired the viruses after spillover from the natural hosts [9]. An intermediate host usually plays an vital role in the outbreak of bat-derived emerging corona viruses; for example, palm civets for SARS-CoV and dromedary camels for MERS-CoV. The virus strains carried by these two intermediate hosts were almost genetically identical to the corresponding viruses in humans (more than 99% genome sequence identity). Despise an RBD that is virtually identical to that of SARS-CoV-2, the pangolin coronaviruses known to date have no more than 92% genome identity with SARS-CoV-2. The till date available data are insufficient to interpret pangolins as the intermediate host of SARS-CoV-2. So far, no appreciating evidence has shown that pangolins were directly involved in the emergence of SARS-CoV-2. Currently, our knowledge on the animal origin of SARS-CoV-2 remains incomplete to a large part. The reservoir hosts of the virus have not been clearly proven. It is unknown whether SARS-CoV-2 was transmitted to humans through an intermediate host and which animals may act as its intermediate host. Detection of RaTG13, RmYN02 and pangolin coronaviruses implies that myriad coronaviruses analogous to SARS-CoV-2 are circulating in wildlife. The previous studies showed recombination as the potential origin of some sarbecoviruses such as SARS-CoV, it cannot be excluded that viral RNA recombination among different related coronaviruses was involved in the evolution of SARS-CoV-2. Extensive surveillance of SARS-CoV-2-related viruses in China, Southeast Asia and other regions targeting bats, wild and captured pangolins and other wildlife species will help us to better understand the zoonotic origin of SARS-CoV-2. Besides wildlife, researchers investigated the susceptibility of domesticated and laboratory animals to SARS-CoV-2 infection. The study demonstrated experimentally that SARS-CoV-2 replicates efficiently in cats and in the upper respiratory tract of ferrets, whereas dogs, pigs, chickens and ducks were not susceptible to SARS-CoV-2. Netherlands reports a documented susceptibility of minks, on an outbreak of SARS-CoV-2 infection in farmed minks. Most infected minks showed mild symptoms, some
developed severe respiratory distress and got died of because of interstitial pneumonia. Natural SARS-CoV-2 infection in two dogs from households with human cases of COVID-19 in Hong Kong, was found testimony by means of virological and serological testing, but the dogs appeared asymptomatic. After covid-19 flare-up a cat serum samples assembled in Wuhan demonstrated SARS-CoV-2 neutralizing antibodies under the umbrella of a serological study, despite the fact currently it is uncertain the potential of SARS-CoV-2 hauling from cats to human chain [9].

4. Pathophysiology

Viral Architecture of SARS-CoV-2 with Post-Fusion Divulged by Cry-EM:

The pathogen of the COVID-19, the native SARS-CoV-2, was isolated, amplified and purified in a BSL-3 laboratory. The whole viral architecture of SARS-CoV-2 was examined by transmission electron microscopy (both negative staining and cryo-EM), Figure 5. We observed that the virion particles are roughly spherical or moderately pleomorphic. Spikes have nail-like shape towards outside with a long body embedded in the envelope. The morphology of virion observed in our result indicates that the S protein of SARS-CoV-2 is in post-fusion state, with S1 disassociated. This state revealed by cryo-EM [Cryogenic electron microscopy], Figure 6, first time could provide an important information for the identification and relevant clinical research of this new coronavirus [11].

Humans and other mammals, such as dogs, cats, chicken, cattle, pigs, and birds are main source of large enveloped, single stranded RNA coronaviruses. Coronaviruses are very lethal to cause respiratory, neurological and gastrointestinal, disease. The most common coronaviruses in clinical practice are 229E, OC43, NL63, and HKU1, which typically cause common cold symptoms in immune competent individuals. SARS-CoV-2 is the third coronavirus that has caused severe disease in humans to spread globally in the past 2 decades. Severe acute respiratory syndrome (SARS) was first coronavirus that caused severe disease, which was thought to originate in Foshan, China, and resulted in the 2002-2003 SARS-CoV pandemic. The second was the coronavirus caused Middle East respiratory syndrome (MERS), which originated from the Arabian peninsula in 2012. SARS-CoV-2 has a diameter of 60 nm to 140 nm and distinctive spikes, ranging from 9 nm to 12 nm, giving the virions the appearance of a solar corona (Figure 7). Through genetic recombination and variation, coronaviruses can adapt to and infect new hosts. Bats are thought to be a natural reservoir for SARS-CoV-2, but it has been suggested that humans became infected with SARS-CoV-2 via an intermediate host, such as the pangolin [12].
5. The Host Defense against SARS-CoV-2

SARS-CoV-2 targets cells, such as nasal and bronchial epithelial cells and pneumocytes, through the viral structural spike (S) protein that binds to the angiotensin-converting enzyme 2 (ACE2) receptor-7 in early infection, (Figure 7). The type 2 trans-membrane serine protease (TMPRSS2), present in the host cell, promotes viral uptake by cleaving ACE2 and activating the SARS-CoV-2 S protein, which mediates coronavirus entry into host cells. 7-ACE2 and TMPRSS2 are expressed in host target cells, particularly alveolar epithelial type II cells. Similar to other respiratory viral diseases, such as influenza, profound lymphopenia may occur in individuals with COVID-19 when SARS-CoV-2 infects and kills T lymphocyte cells. In addition, the viral inflammatory response, consisting of both the innate and the adaptive immune response (comprising humoral and cell-mediated immunity), impairs lymphopoiesis and increases lymphocyte apoptosis. Although up regulation of ACE2 receptors from ACE inhibitor and angiotensin receptor blocker medications has been hypothesized to increase susceptibility to SARS-CoV-2 infection, large observational cohorts have not found an association between these medications and risk of infection or hospital mortality due to COVID-19 [13,14]. For example, in a study 4480 patients with COVID-19 from Denmark, previous treatment with ACE inhibitors or angiotensin receptor Blockers was not associated with mortality [14]. In later stages of infection, when viral replication accelerates, epithelial-endothelial barrier integrity is compromised. In addition to epithelial cells, SARS-CoV-2 infects pulmonary capillary endothelial cells, accentuating the inflammatory response and triggering an influx of monocytes and neutrophils. Autopsy studies have shown diffuse thickening of the alveolar wall with mononuclear cells and macrophages infiltrating air spaces in addition to endothelialitis. Interstitial mononuclear inflammatory infiltrates and edema develop and appear as ground-glass opacities on computed
Pulmonary edema filling the alveolar spaces with hyaline membrane formation follows, compatible with early-phase acute respiratory distress syndrome (ARDS). Bradykinin-dependent lung angioedema may contribute to disease. Collectively, endothelial barrier disruption, dysfunctional alveolar-capillary oxygen transmission, and impaired oxygen diffusion capacity are characteristic features of COVID-19 [15,16].

Figure 7. Immunopathogenesis of Coronavirus Disease 2019 (COVID-19): Current understanding of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-induced host immune response. SARS-CoV-2 targets cells through the viral structural spike (S) protein that binds to the angiotensin converting enzyme 2 (ACE2) receptor. The serine protease type 2 transmembrane serine protease (TMPRSS2) in the host cell further promotes viral uptake by cleaving ACE2 and activating the SARS-CoV-2 S protein. In the early stage, viral copy numbers can be high in the lower respiratory tract. Inflammatory signaling molecules are released by infected cells and alveolar macrophages in addition to recruited T lymphocytes, monocytes, and neutrophils. In the late stage, pulmonary edema can fill the alveolar spaces with hyaline membrane formation, compatible with early phase acute respiratory distress syndrome.

In severe COVID-19, fulminant activation of coagulation and consumption of clotting factors occur. A report from Wuhan, China, indicated that 71% of 183 individuals who died of COVID-19 met criteria for diffuse intravascular coagulation. Inflamed lung tissues and pulmonary endothelial cells may result in micro thrombi formation and contribute to the high incidence of thrombotic complications, such as deep venous thrombosis, pulmonary embolism, and thrombotic arterial complications (e.g., limb ischemia, ischemic stroke, myocardial infarction). In
critically ill patients. The development of viral sepsis, defined as life threatening organ dysfunction caused by a dysregulated host response to infection, may further contribute to multi organ failure [12].

6. SARS-CoV-2 Infection Transmission

Epidemiologic data suggest that droplets expelled during face-to-face exposure during talking, coughing, or sneezing is the most common mode of transmission (Box A). Prolonged exposure to an infected person (being within 6 feet for at least 15 minutes) and briefer exposures to individuals who are symptomatic (eg, coughing) are associated with higher risk for transmission, while brief exposures to asymptomatic contacts are less likely to result in transmission [17]. Contact surface spread (touching a surface with virus on it) is another possible mode of transmission. Transmission may also occur via aerosols (smaller droplets that remain suspended in air), but it is unclear if this is a significant source of infection in humans outside of a laboratory setting [18,19]. The existence of aerosols in physiological states (eg, coughing) or the detection of nucleic acid in the air does not mean that small airborne particles are infectious. Maternal COVID-19 is currently believed to be associated with low risk for vertical transmission.

In most reported series, the mothers’ infection with SARS-CoV-2 occurred in the third trimester of pregnancy, with no maternal deaths and a favorable clinical course in the neonates [20,21,22]. The clinical significance of SARS-CoV-2 transmission from inanimate surfaces is difficult to interpret without knowing the minimum dose of virus particles that can initiate infection. Viral load appears to persist at higher levels on impermeable surfaces, such as stainless steel and plastic, than permeable surfaces, such as cardboard. Virus has been identified on impermeable surfaces for up to 3 to 4 days after inoculation. Widespread viral contamination of hospital rooms has been documented. However, it is thought that the amount of virus detected on surfaces decays rapidly within 48 to 72 hours. Although the detection of virus on surfaces reinforces the potential for transmission via fomites (objects such as a doorknob, cutlery, or clothing that may be contaminated with SARS-CoV-2) and the need for adequate environmental hygiene, droplet spread via face-to-face contact remains the primary mode of transmission. Viral load in the upper respiratory tract appears to peak around the time of symptom onset and viral shedding begins approximately 2 to 3 days prior to the onset of symptoms. A symptomatic and presymptomatic carriers can transmit SARS-CoV-2. In Singapore, presymptomatic transmission has been described in clusters of patients with close contact (eg, through church going or singing class) approximately 1 to 3 days before the source patient developed symptoms. Presymptomatic transmission is thought to be a major contributor to the spread of SARS-CoV-2 [12]. Modeling studies from China and Singapore estimated the percentage of infections transmitted from a presymptomatic individual as 48% to 62%. Pharyngeal shedding is high during the first week of infection at a time in which symptoms are still mild, which might explain the efficient transmission of SARS-CoV-2, because infected individuals can be infectious before they realize they are ill. Although studies have described rates of asymptomatic infection, ranging from 4% to 32%, it is unclear whether these reports represent truly asymptomatic infection by individuals who never develop symptoms, transmission by individuals with very mild symptoms, or transmission by individuals who are asymptomatic at the time of transmission but subsequently develop symptoms. A systematic review on this topic suggested that true asymptomatic infection is probably uncommon. Although viral nucleic acid can be detectable in throat swabs for up to 6 weeks after the onset of illness, several studies suggest that viral cultures are generally negative for SARS-CoV-28 days after symptom onset. This is supported by epidemiological studies that have shown that transmission did not occur to contacts whose exposure to the index case started more than 5 days after the onset of symptoms. This case suggests that individuals can be released from isolation based on clinical improvement [12].

Box A. Perplexing Complications, Transmission, Symptoms of Coronavirus Disease 2019 (COVID-19)
The Centers for Disease Control and Prevention recommend isolating for at least 10 days after symptom onset and 3 days after improvement of symptoms. However, there remains uncertainty about whether serial testing is required for specific subgroups, such as immune suppressed patients or critically ill patients for whom symptom resolution may be delayed or older adults residing in short or long-term care facilities [12].

7. COVID-19 Clinical Manifestation

Approximately 5 (2-7) days is the mean (interquartile range) incubation period (the time from exposure to symptom onset) for COVID-19. Approximately 97.5% of individuals who develop symptoms will do so within 11.5 days of infection [27,28]. The median (inter-quartile range) interval from symptom onset to hospital admission is 7 (3-9) days. The median age of hospitalized patients varies between 47 and 73 years, with most cohorts having a male preponderance of approximately 60%. Among patients hospitalized with COVID-19, 74% to 86% are aged at least 50 years [29]. COVID-19 has various clinical manifestations (Box A and Box B). In a study of 44,672 patients with COVID-19 in China, 81% of patients had mild manifestations, 14% had severe manifestations, and 5% had critical manifestations (defined by respiratory failure, septic shock, and/or multiple organ dysfunction). [30] A study of 20,133 individuals hospitalized with COVID-19 in the UK reported that 17.1% were admitted to high-dependency or intensive care units (ICUs) [31].

**Box A. Commonly Asked Questions About Coronavirus Disease 2019 (COVID-19) [12]**

- **How is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) most commonly transmitted?**
  SARS-CoV-2 is most commonly spread via respiratory droplets (e.g., from coughing, sneezing, shouting) during face-to-face exposure or by surface contamination.

- **What are the most common symptoms of COVID-19?**
  The 3 most common symptoms are fever, cough, and shortness of breath. Additional symptoms include weakness, fatigue, muscle or body aches, headache, loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, diarrhea, new loss of smell or taste (anosmia). Myalgia and dyspnea are also common.

- **How is the diagnosis made?**
  Diagnosis of COVID-19 is typically made by polymerase chain reaction testing of a nasopharyngeal swab. However, given the possibility of false-negative test results, clinical, laboratory, and imaging findings may also be used to make a presumptive diagnosis.

- **What are current evidence-based treatments for individuals with COVID-19?**
  Supportive care, including supplemental oxygen, is generally the first line of treatment for most patients. Recent trials indicate that dexamethasone decreases mortality (subgroup analysis suggests benefit is limited to patients who require supplemental oxygen and who have symptoms for >7 d) and remdesivir improves time to recovery (subgroup analysis suggests benefit is limited to patients not receiving mechanical ventilation).

- **What percentage of people are asymptomatic carriers, and how important are they in transmitting the disease?**
  True asymptomatic infection is believed to be uncommon. The average time from exposure to symptoms onset is 5 days, and up to 62% of transmission may occur prior to the onset of symptoms.

- **Are masks effective at preventing spread?**
  Yes. Face masks reduce the spread of viral respiratory infection. N95 respirators and surgical masks both provide substantial protection (compared with no mask), and surgical masks provide greater protection than cloth masks. However, physical distancing is also associated with substantial reduction of viral transmission, with greater distances providing greater protection. Additional measures such as hand and environmental disinfection are also important.

Although only approximately 25% of infected patients have co-morbidities, 60% to 90% of hospitalized infected patients have comorbidities [29]. The most common comorbidities in hospitalized patients include hypertension (present in 48%-57% of patients), diabetes (17%-34%), cardiovascular disease (21%-28%), chronic pulmonary disease (4%-10%), chronic kidney disease (3%-13%), malignancy (6%-8%), and chronic liver disease (<5%). [32] The most common symptoms in hospitalized patients are fever (up to 90% of patients), dry cough (60%-86%), shortness of breath (53%-80%), fatigue (38%), nausea/vomiting or diarrhea (15%-39%), and myalgia (15%-44%). Patients can also present with non-classical symptoms, such as isolated gastrointestinal symptoms. Olfactory and/or gustatory dysfunctions have been reported in 64% to 80% of patients. Anosmia or ageusia may be the sole presenting symptom in approximately 3% of patients. Complications of COVID-19 include impaired function of the heart, brain, lung, liver, kidney, and coagulation system. COVID-19 can lead to myocarditis, cardiomyopathy, ventricular arrhythmias, and hemodynamic instability. Acute cerebrovascular disease and encephalitis are observed with severe illness (in up to 8% of patients). Venous and arterial thromboembolic events occur in 10% to 25% in hospitalized patients with COVID-19. In the ICU, venous and arterial thromboembolic events may occur in up to 31% to 59% of patients with COVID-19. Men older than 68 years had a higher risk of respiratory failure, acute cardiac injury and heart failure that led to death, regardless of a history of cardiovascular disease. (Figure 8). Most patients recovered enough to be released from hospital in 2 weeks [12] (Figure 8).
Approximately 17% to 35% of hospitalized patients with COVID-19 are treated in an ICU, most commonly due to hypoxemic respiratory failure. Among patients in the ICU with COVID-19, 29% to 91% require invasive mechanical ventilation. In addition to respiratory failure, hospitalized patients may develop acute kidney injury (9%), liver dysfunction (19%), bleeding and coagulation dysfunction (10%-25%), and septic shock (6%). Approximately 2% to 5% of individuals with laboratory-confirmed COVID-19 are younger than 18 years, with a median age of 11 years. Children with COVID-19 have milder symptoms that are pre-dominantly limited to the upper respiratory tract, and rarely require hospitalization. It is unclear why children are less susceptible to COVID-19. Potential explanations include that children have less robust immune responses (i.e., no cytokine storm), partial immunity from other viral exposures, and lower rates of exposure to SARS-CoV-2.

Although most pediatric cases are mild, a small percentage (<7%) of children admitted to the hospital for COVID-19 develop severe disease requiring mechanical ventilation. A rare multi system inflammatory syndrome similar to Kawasaki disease has recently been described in children in Europe and North America with SARS-CoV-2 infection. This multisystem inflammatory syndrome in children is uncommon (2 in 100 000 persons aged <21 years) [12].

8. Diagnosis and Value Judgement

IN VITRO DIAGNOSTIC PROCEDURES: COVID-19 - Pandemic-Emergency Use Listing Procedure (EUL) open for IVDs: The Director-General declared on 30th Jan-2020 that the outbreak of COVID-19 caused by SARS-CoV2 constitutes a Public Health Emergency of International Concern (PHEIC) and it was characterized as a pandemic on 11th March-2020. In Vitro Diagnostics (IVDs) of assured quality, safety and performance are a critical component of an overall strategy to control the pandemic.

The WHO Emergency Use Listing procedure was developed to expedite the availability of IVDs needed in public health emergency situations. It is intended to assist procurement agencies and Member States with their decisions regarding the suitability for use of a specific IVD, based on a minimum set of available quality, safety, and performance data.

The procedure is currently open to candidate IVDs to detect SARS-CoV-2 (previously called 2019-nCoV) [1].

Prime concern cataloging of applications for prequalification and Emergency Use Listing (EUL) assessment of IVDs: Applications are currently prioritized as follows:

HIGH PRIORITY:
- EUL applications for SARS-CoV-2 antigen detection tests
- EUL applications for SARS-CoV-2 nucleic acid detection tests intended to be used at a point of care.

MEDIUM PRIORITY:
- Prequalification applications
- EUL applications for SARS-CoV-2 nucleic acid detection tests.
- All other submissions/requests are currently assigned a lower priority. Change notifications are prioritized on a case-by-case basis. Due to the current peak in applications under assessment that the Prequalification Unit is only accepting EUL pre-submission call requests and new expressions of interest in EUL assessment for the above high- and medium-priority applications.

IVDs eligible for EUL Submission: Currently, the following IVDs are eligible for EUL submission:
- ASSAYS for the detection of SARS-CoV-2 nucleic acid (multiplex assays, detecting more than one viral target).
- Rapid Diagnostic Tests for the detection of SARS-CoV-2 antigens; other platforms to detect SARS-CoV-2 antigen will be considered on a case-by-case basis [1].

WHO procedure:
WHO will review all documentation submitted in order to assess available evidence in support of the product’s safety, quality and performance.

Currently, several performance evaluations of SARS-CoV-2 IVDs are being carried out by regulatory authorities, reference laboratories and other stakeholders in various regions. Manufacturers are strongly encouraged to participate in initiatives which generate evidence that can be used to support their EUL submission. However, participation in external evaluations does not replace the EUL submission, nor is participation in such studies mandatory for submission for WHO EUL [2].

Early diagnosis is crucial for controlling the spread of COVID-19. Molecular detection of SARS-CoV-2 nucleic acid is the gold standard. Many viral nucleic acid detection kits targeting ORF1b (including RdRp), N, E or S genes are commercially available. The detection time ranges from several minutes to hours depending on the technology [33]. The molecular detection can be affected by many factors. Although SARS-CoV-2 has been detected from a variety of respiratory sources, including throat swabs, posterior oropharyngeal saliva, nasopharyngeal swabs, sputum and bronchial fluid, the viral load is higher in lower respiratory tract samples [34]. Diagnosis of COVID-19 is typically made using polymerase chain reaction testing via nasal swab (Box B). However, because of false-negative test result rates of SARS-CoV-2 PCR testing of nasal swabs, clinical, laboratory, and imaging findings may also be used to make a presumptive diagnosis.

Polymerase Chain Reaction and Serology as a Diagnostic Testing:
The standard for diagnosis is Reverse Transcript Polymerase Chain Reaction-based SARS-CoV-2 RNA detection from respiratory samples (e.g., nasopharynx). However, the sensitivity of testing varies with timing of testing relative to exposure. One modeling study estimated sensitivity at 33% 4 days after exposure, 62% on the day of symptom onset, and 80% 3 days after symptom onset [35,36,37]. Factors contributing to false-negative test results include the adequacy of the specimen collection technique, time from exposure, and specimen source. Lower respiratory samples, such as bronchoalveolar lavage fluid, are more sensitive than upper respiratory samples. Among 1070 specimens collected from 205 patients with COVID-19 in China, bronchoalveolar lavage fluid specimens had the highest positive rates of SARS-CoV-2 PCR testing results (93%), followed by sputum (72%), nasal swabs (63%), and pharyngeal swabs (32%). SARS-CoV-2 can also be detected in feces, but not in urine [35]. Saliva may be an alternative specimen source that requires less personal protective equipment and fewer swabs, but requires further validation [38]. Several serological tests can also aid in the diagnosis and measurement of responses to novel vaccines. However, the presence of antibodies may not confer immunity because not all antibodies produced in response to infection are neutralizing. Whether and how frequently second infections with SARS-CoV-2 occur remain unknown. Whether presence of antibody changes susceptibility to subsequent infection or how long antibody protection lasts are unknown. IgM antibodies are detectable within 5 days of infection, with higher IgM levels during weeks 2 to 3 of illness, while an IgG response is first seen approximately 14 days after symptom onset. Higher antibody titers occur with more severe disease. Available serological assays include point-of-care assays and high throughput enzyme immunoassays. However, test performance, accuracy, and validity are variable [39,40,41].

COVID-19, Laboratory Findings:
A systematic review of 19 studies of 2874 patients who were mostly from China (mean age, 52 years), of whom 88% were hospitalized, reported the typical range of laboratory abnormalities seen in COVID-19, including elevated serum C-reactive protein (increased in >60% of patients), lactate dehydrogenase (increased in approximately 50%-60%), alanine aminotransferase (elevated in approximately 25%), and aspartate aminotransferase (approximately 33%). Approximately 75% of patients had low albumin [24]. The most common hematological abnormality is lymphopenia (absolute lymphocyte count < 1.0 x 10^9/L), which is present in up to 83% of hospitalized patients with COVID-19 [43]. In conjunction with coagulopathy, modest prolongation of prothrombin times (prolonged > 5% of patients), mild thrombocytopenia (present in approximately 30% of patients) and elevated D-dimer values (present in 43%-60% of patients) are common. However, most of these laboratory characteristics are non specific and are common in pneumonia. More severe laboratory abnormalities have been associated with more severe infection [43]. D-dimer and, to a lesser extent, lymphopenia seem to have the largest prognostic associations.

Revealed Imaging For COVID-19:
The COVID-19 discourses the characteristic chest computed tomographic imaging abnormalities as diffuse, peripheral ground-glass opacities (Figure 9). Ground-glass opacities have ill-defined margins, air bronchograms, smooth or irregular interlobular or septal thickening, and thickening of the adjacent pleura [44]. Chest computed tomographic imaging findings in approximately 15% of individuals and chest radiograph findings in approximately 40% of individuals can be normal in early disease [45].
Rapid evolution of abnormalities can occur in the first 2 weeks after symptom onset, after which they subside gradually. Chest computed tomographic imaging findings are non specific and overlap with other infections, so the diagnostic value of chest computed tomographic imaging for COVID-19 is limited. Some patients admitted to the hospital with polymerase chain reaction testing-confirmed SARS-CoV-2 infection have normal computed tomographic imaging findings, while abnormal chest computed tomographic imaging findings compatible with COVID-19 occur days before detection of SARS-CoV-2 RNA in other patients [47,48].
9. Therapeutics and COVID-19

To date, there are no generally proven effective therapies for COVID-19 or antivirals against SARS-CoV-2, although some treatments have shown some benefits in certain subpopulations of patients or for certain end points. Researchers and manufacturers are conducting large-scale clinical trials to evaluate various therapies for COVID-19. As of 2 October 2020, there were about 405 therapeutic drugs in development for COVID-19, and nearly 318 in human clinical trials (COVID-19 vaccine and therapeutics tracker). In the following sections, we summarize potential therapeutics against SARS-CoV-2 on the basis of published clinical data and experience.

**Virus Entry Inhibition:**

Drugs that interfere with entry may be a potential treatment for COVID-19 because SARS-CoV-2 uses ACE2 as the receptor and human proteases as entry activators; subsequently it fuses the viral membrane with the cell membrane and achieves invasion. Umifenovir (Arbidol) is a drug approved in Russia and China for the treatment of influenza and other respiratory viral infections. It can target the interaction between the S protein and ACE2 and inhibit membrane fusion (Figure 10). In vitro experiments showed that it has activity against SARS-CoV-2, and current clinical data revealed it may be more effective than lopinavir and ritonavir in treating COVID-19 [49,50]. However, other clinical studies showed umifenovir might not improve the prognosis of or accelerate SARS-CoV-2 clearance in patients with mild to moderate COVID-19 [51,52]. Yet some ongoing clinical trials are evaluating its efficacy for COVID-19 treatment. Camostat mesylate is approved in Japan for the treatment of pancreatitis and postoperative reflux oesophagitis. Previous studies showed that it can prevent SARS-CoV from entering cells by blocking TMPRSS2 activity and protect mice from lethal infection with SARS-CoV in a pathogenic mouse model (wild type mice infected with a mouse-adapted SARS-CoV strain) [53,54]. Recently, a study revealed that camostat mesylate blocks the entry of SARS-CoV-2 into human lung cells [55]. Thus, it can be a potential antiviral drug against SARS-CoV-2 infection, although so far there are not sufficient clinical data to support its efficacy.
Figure 10. Replication and Potential Therapeutic Targets for SARS-CoV-2: Potential antivirals target the different steps of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) replication, ranging from receptor binding, entry and fusion to replication. Furthermore, immunoglobulin-based and immunomodulatory drugs are potential therapeutics as well. Note that robust data on clinical efficacy are lacking for most of these treatments so far. 3CLpro, 3C-like protease; ACE2, angiotensin-converting enzyme 2; CR3022, a SARS-CoV-specific human monoclonal antibody; E, envelope protein; EK1C4, lipopeptide derived from EK1 which is a pan-coronavirus fusion inhibitor targeting the HR1 domain of the spike protein; ER, endoplasmic reticulum; gRNA, genomic RNA; HR2P, heptad repeat 2-derived peptides of SARS-CoV-2 spike protein; IL-6, interleukin-6; ISG, interferon-stimulated gene; M, membrane protein; RdRp, RNA-dependent RNA polymerases; sgRNA, subgenomic RNA; S, spike protein; TMPRSS2, transmembrane protease serine protease 2.

Chloroquine and hydroxychloroquine are other potential but controversial drugs that interfere with the entry of SARS-CoV-2. They have been used in the prevention and treatment of malaria and autoimmune diseases, including systemic lupus erythematosus and rheumatoid arthritis. They can inhibit the glycosylation of cellular receptors and interfere with virus-host receptor binding, as well as increase the endosomal pH and inhibit membrane fusion. Currently, no scientific consensus has been reached for their efficacy in the treatment of COVID-19. Some studies showed they can inhibit SARS-CoV-2 infection in vitro, but the clinical data are insufficient. Two clinical studies indicated no association with death rates in patients receiving chloroquine or hydroxychloroquine compared with those not receiving the drug and even suggest it may increase the risk of dying as a higher risk of cardiac arrest was found in the treated patients. On 15 June 2020, owing to the side effects...
observed in clinical trials, the US Food and Drug Administration (FDA) revoked the emergency use authorization for chloroquine and hydroxychloroquine for the treatment of COVID-19. Another potential therapeutic strategy is to block binding of the S protein to ACE2 through soluble recombinant hACE2, specific monoclonal antibodies or fusion inhibitors that target the SARS-CoV-2 S protein (Figure 10). The safety and efficacy of these strategies need to be assessed in future clinical trials [9].

**Virus Replication Inhibition:**

Replication inhibitors include remdesivir (GS-5734), favilavir (T-705), ribavirin, lopinavir and ritonavir. Except for lopinavir and ritonavir, which inhibit 3CLpro, the other three all target (Figure 10). Remdesivir has shown activity against SARS-CoV-2 in vitro and in vivo [56]. A clinical study revealed a lower need for oxygen support in patients with COVID-19 [57]. Preliminary results of the Adaptive COVID-19 Treatment Trial (ACTT) clinical trial by the National Institute of Allergy and Infectious Diseases (NIAID) reported that remdesivir can shorten the recovery time in hospitalized adults with COVID-19 by a couple days compared with placebo, but the difference in mortality was not statistically significant [58]. The FDA has issued an emergency use authorization for remdesivir for the treatment of hospitalized patients with severe COVID-19. It is also the first approved option by the European Union for treatment of adults and adolescents with pneumonia requiring supplemental oxygen.

Several international phase III clinical trials are continuing to evaluate the safety and efficacy of remdesivir for the treatment of COVID-19. Favilavir (T-705), which is an antiviral drug developed in Japan to treat influenza, has been approved in China, Russia and India for the treatment of COVID-19. A clinical study in China showed that favilavir significantly reduced the signs of improved disease signs on chest imaging and shortened the time to viral clearance. A preliminary report in Japan showed rates of clinical improvement of 73.8% and 87.8% from the start of favilavir therapy in patients with mild COVID-19 at 7 and 14 days, respectively, and 40.1% and 60.3% in patients with severe COVID-19 at 7 and 14 days, respectively. However, this study did not include a control arm, and most of the trials of favilavir were based on a small sample size. For more reliable assessment of the effectiveness of favilavir for treating COVID-19, large-scale randomized controlled trials should be conducted. Lopinavir and ritonavir were reported to have in vitro inhibitory activity against SARS-CoV and MERS-CoV. Alone, the combination of lopinavir and ritonavir had little therapeutic benefit in patients with COVID-19, but appeared more effective when used in combination with other drugs, including ribavirin and interferon beta-1b143. The Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial, a national clinical trial programme in the UK, has stopped treatment with lopinavir and ritonavir as no significant beneficial effect was observed in a randomized trial established in March 2020 with a total of 1,596 patients. Nevertheless, other clinical trials in different phases are still ongoing elsewhere [9].

![Network Map from the living network meta-analysis informing this guideline](image)

Figure 11. Network Map from the living network meta-analysis informing this guideline
**Immunomodulatory Agents:**

The Immunomodulatory agents that inhibit the excessive inflammatory response may be a potential adjunctive therapy for COVID-19 because SARS-CoV-2 triggers a strong immune response which may cause cytokine storm syndrome [59,60]. Dexamethasone is a corticosteroid often used in a wide range of conditions to relieve inflammation through its anti-inflammatory and immunosuppressant effects. Recently, the Recovery trial found dexamethasone reduced mortality by about one third in hospitalized patients with COVID-19 who received invasive mechanical ventilation and by one fifth in patients receiving oxygen. By contrast, no benefit was found in patients without respiratory support [61]. Tocilizumab and sarilumab, two types of interleukin-6 (IL-6) receptor-specific antibodies previously used to treat various types of arthritis, including rheumatoid arthritis, and cytokine release syndrome, showed effectiveness in the treatment of severe COVID-19 by attenuating the cytokine storm in a small uncontrolled trial [62]. Bevacizumab is an anti-vascular endothelial growth factor (VEGF) medication that could potentially reduce pulmonary oedema in patients with severe COVID-19. Eculizumab is a specific monoclonal antibody that inhibits the proinflammatory complement protein C5. Preliminary results showed that it induced a drop of inflammatory markers and C-reactive protein levels, suggesting its potential to be an option for the treatment of severe COVID-19 [63]. The interferon response is one of the major innate immunity defenses against virus invasion. Interferons induce the expression of diverse interferon-stimulated genes, which can interfere with every step of virus replication. Previous studies identified type I interferons as a promising therapeutic candidate for SARS [64]. In vitro data showed SARS-CoV-2 is even more sensitive to type I interferons than SARS-CoV.

**Therapy with Immunoglobulin:**

Convalescent plasma treatment is another potential adjunctive therapy for COVID-19. Preliminary findings have suggested improved clinical status after the treatment. The FDA has provided guidance for the use of COVID-19 convalescent plasma under an emergency investigational new drug application. However, this treatment may have adverse effects by causing antibody-mediated enhancement of infection, transfusion- associated acute lung injury and allergic transfusion reactions. Monoclonal antibody therapy is an effective immunotherapy for the treatment of some viral infections in select patients. Recent studies reported specific monoclonal antibodies neutralizing SARS-CoV-2 infection in vitro and in vivo [68,69,70,71]. Compared with convalescent plasma, which has limited availability and cannot be amplified, monoclonal antibodies can be developed in larger quantities to meet clinical requirements. Hence, they provide the possibility for the treatment and prevention of COVID-19. The neutralizing epitopes of these monoclonal antibodies also offer important information for vaccine design. However, the high cost and limited capacity of manufacturing, as well as the problem of bioavailability, may restrict the wide application of monoclonal antibody therapy [1].

**10. Vaccine Development and Prevention**

Many different vaccine platforms against SARS-CoV-2 are in development, the strategies of which include recombinant vectors, DNA, mRNA in lipid nanoparticles, inactivated viruses, live attenuated viruses and protein subunits. Vaccination is the most effective method for a long-term strategy for prevention and control of COVID-19 in the future. [72,73,74]. As of 2 October 2020, ~174 vaccine candidates for COVID-19 had been reported and 51 were in human clinical trials (COVID-19 vaccine and therapeutics tracker). Many of these vaccine candidates are in phase II testing, and some have already advanced to phase III trials. A randomized double-blind phase II trial of an adenovirus type 5- vectored vaccine expressing the SARS-CoV-2 S protein, developed by CanSino Biologics and the Academy of Military Medical Sciences of China, was conducted in 603 adult volunteers in Wuhan. The vaccine has proved to be safe and induced considerable humoral and cellular immune response in most recipients after a single immunization [75]. Another vectored vaccine, ChAdOx1, was developed on the basis of chimpanzee adenovirus by the University of Oxford. In a randomized controlled phase I/II trial, it induced neutralizing antibodies against SARS-CoV-2 in all 1,077 participants after a second vaccine dose, while its safety profile was acceptable as well [76]. The NIAID and Moderna co-manufactured mRNA-1273, a lipid nanoparticle- formulated mRNA vaccine candidate that encodes the stabilized prefusion SARS-CoV-2 S protein. Its immunogenicity has been confirmed by a phase I trial in which robust neutralizing antibody responses were induced in a dose-dependent manner and increased after a second dose [77]. Regarding inactivated vaccines, a successful phase I/II trial involving 320 participants has been reported in China. The whole-virus COVID-19 vaccine had a low rate of adverse reactions and effectively induced neutralizing antibody production [78]. The verified safety and immunogenicity support advancement of these vaccine candidates to phase III clinical trials, which will evaluate their efficacy in protecting healthy populations from SARS-CoV-2 infection.
11. Prognosis of COVID-19:

Mortality — Several retrospective studies have reported variable mortality from COVID-19-related acute respiratory distress syndrome (ARDS). Mortality appears lower than that in patients with severe acute respiratory syndrome (SARS-CoV-1) or Middle East respiratory syndrome (MERS). The mortality from COVID-19 appears driven by the presence of severe ARDS, and ranges widely, from 12% to 78% with an average of 25% to 50%. However, death can occur from several other conditions including cardiac arrhythmia, cardiac arrest, and pulmonary embolism.

In resource-limited settings, mortality may be on the higher end of this range. One study of nearly 4000 patients from 64 intensive care units (ICUs) in 10 African countries reported a 30-day mortality of 48%. Mortality ranged from 43% for patients referred from the emergency department to 51% in patients transferred from another facility.

Mortality may be decreasing as the pandemic progressed. In an analysis of patients during a resurgence of COVID-19 in Houston, Texas, in-hospital mortality was lower during the second surge compared with the first surge (5% versus 12%) but the difference in ICU mortality was not significant (23% versus 28%). In another French cohort of over 4000 critically-ill patients, mortality decreased from 42% to 25% over a four-month period during the pandemic [2]. In a United States analysis of 468 patients with COVID-19-related critical illness from March 1, 2020 to May 11, 2020, the mortality decreased from 44% to 19%. Reducing mortality may be reflective of a patient population that is younger and has a lower comorbidity burden during the second surge, reduced burden of institutions, and/or growing expertise with COVID-19 care. However, reported rates may not accurately reflect differences in practice patterns over the course of the pandemic (eg, early versus late timing of intubation, increasing use of noninvasive modalities).

Risk factors for death — Globally, the consistent major risk factor associated with death in critically ill patients with COVID-19 is older age ≥64 years [1].

12. Future Perspectives

Till date the third highly pathogenic human coronavirus disease is COVID-19. Although less deadly than SARS and MERS, the rapid spreading of this highly contagious disease has posed the severest threat to global health in this century. The SARS-CoV-2 outbreak has lasted for more than half a year now, and it is likely that this emerging virus will establish a niche in humans and coexist with us for a long time [78]. Before clinically approved vaccines are widely available, there is no better way to protect us from SARS-CoV-2 than personal preventive behaviours such as social distancing and wearing masks, and public health measures, including active testing, case tracing and restrictions on social gatherings. Despite a flood of SARS-CoV-2 research published every week, current knowledge of this novel coronavirus is just the tip of the iceberg. The animal origin and cross-species infection route of SARS-CoV-2 are yet to be uncovered. The molecular mechanisms of SARS-CoV-2 infection pathogenesis and virus-host interactions remain largely unclear. Intensive studies on these virological profiles of SARS-CoV-2 will provide the basis for the development of preventive and therapeutic strategies against COVID-19. Moreover, continued genomic monitoring of SARS-CoV-2 in new cases is needed worldwide, as it is important to promptly identify any mutation that may result in phenotypic changes of the virus [9].

On 26 November 2021, WHO designated the variant B.1.1.529 a variant of concern, named Omicron, on the advice of WHO’s Technical Advisory Group on Virus Evolution (TAG-VE). This decision was based on the evidence presented to the TAG-VE that Omicron has several mutations that may have an impact on how it behaves, for example, on how easily it spreads or the severity of illness it causes. Here is a summary of what is currently known.

Current Knowledge about Omicron:
Researchers in South Africa and around the world are conducting studies to better understand many aspects of Omicron and will continue to share the findings of these studies as they become available.

Transmissibility:
It is not yet clear whether Omicron is more transmissible (e.g., more easily spread from person to person) compared to other variants, including Delta. The number of people testing positive has risen in areas of South Africa affected by this variant, but epidemiologic studies are underway to understand if it is because of Omicron or other factors.

Severity of Disease:
It is not yet clear whether infection with Omicron causes more severe disease compared to infections with other variants, including Delta. Preliminary data suggests that there are increasing rates of hospitalization in South Africa, but this may be due to increasing overall numbers of people becoming infected, rather than a result of specific infection with Omicron. There is currently no information to suggest that symptoms associated with Omicron are different from those from other variants. Initial reported infections were among university students—younger individuals who tend to have more mild disease—but understanding the level of severity of the Omicron variant will take days to several weeks. All variants of COVID-19, including the Delta variant that is dominant worldwide, can cause severe disease or death, in particular for the most vulnerable people, and thus prevention is always key [1].

Effectiveness of Prior SARS-CoV-2 Infection:
Preliminary evidence suggests there may be an increased risk of reinfection with Omicron (ie, people who have previously had COVID-19 could become reinfected more easily with Omicron), as compared to other variants of concern, but information is limited. More information on this will become available in the coming days and weeks.

Effectiveness of vaccines:
WHO is working with technical partners to understand the potential impact of this variant on our existing countermeasures, including vaccines. Vaccines remain critical to reducing severe disease and death, including...
against the dominant circulating variant, Delta. Current vaccines remain effective against severe disease and death. Effectiveness of current tests:

The widely used PCR tests continue to detect infection, including infection with Omicron, as we have seen with other variants as well. Studies are ongoing to determine whether there is any impact on other types of tests, including rapid antigen detection tests.

Effectiveness of current treatments:

Corticosteroids and IL6 Receptor Blockers will still be effective for managing patients with severe COVID-19. Other treatments will be assessed to see if they are still as effective given the changes to parts of the virus in the Omicron variant.

STUDIES UNDERWAY: At the present time, WHO is coordinating with a large number of researchers around the world to better understand Omicron. Studies currently underway or underway shortly include assessments of transmissibility, severity of infection (including symptoms), performance of vaccines and diagnostic tests, and effectiveness of treatments. WHO encourages countries to contribute the collection and sharing of hospitalized patient data through the WHO COVID-19 Clinical Data Platform to rapidly describe clinical characteristics and patient outcomes. More information will emerge in the coming future. WHO’s TAG-VE will continue to monitor and evaluate the data as it becomes available and assess how mutations in Omicron alter the behavior of the virus [1]. Finally, COVID-19 is challenging all human beings. Tackling this epidemic is a long-term job which requires efforts of every individual and international collaborations by scientists, authorities and the public.

13. Conclusion

About 25746952.8 million people worldwide had been infected with SARS-CoV-2 as of 23, November, 2021, Myraid aspects of transmission, infection, and treatment remain unclear non-obvious. The first line and advances in prevention and effective management of COVID-19 will require basic and clinical investigation and public health and clinical interventions. Time alone will tell how the virus will impact our lives cosmopolitanly. More so, future outbreaks of viruses and pathogens of zoonotic origin are likely to continue. Therefore, apart from curbing this outbreak, efforts should be made to devise comprehensive measures to prevent future outbreaks of zoonotic origin.

Abbreviations

COVID-19 = Coronavirus Disease 19
SARS-CoV-2 = Severe Respiratory Syndrome
Coronavirus-2
MERS-CoV = Middle East Respiratory Syndrome
Coronavirus
WHO = World Health Organization
ICTV = International Committee On Taxonomy Of Virus
PHEIC = Public Health Emergency Of International Concern
GISAID = Global Initiative On Sharing All Influenza Data
PCR = Polymerase Chain Reaction
CDC = Centers For Drug Control And Prevention.
ORFs = Observe Research Foundations
RdRp = RNA dependent RNA polymerase
NiRAN = Nucleotidyltransferase
ZBD = Zinc binding domain
RBD = Receptor binding domain
COV = Coronavirus
ACE2 = Angiotensin converting enzyme
RBM = Receptor binding motif
CRYO-EM = Cryogenic electron microscopy
TMPRSS2 = Serine protease type 2 transmembrane serine protease
PHEIC = Public health emergency of international concern
EUL = Emergency Use Listing
IVD = In Vitro Diagnostics
NIAID = National institute of allergy and infectious diseases
TAG-VE = Technical advisory group on virus evolution

AIM

In the current review study, we performed a literature review on Coronavirus flare-up to encapsulated current evidence regarding the clinical, pathophysiology, transmission mode, diagnosis. We also discuss the zoonotic origin and potential wildlife hosts of these come to light virus in detail and Management strategies for the disease control (covid-19).

References

[1] WHO Coronavirus (COVID-19), Dashboard, www.who.int/news-topics.
[2] Review on the (COVID-19) pandemic paper-3; WHO COVID-19, weekly epidemiological update edition 67, published 23 Nov.2021.
[3] Zhu, N. et al. A Novel Coronavirus from patients with pneumonia in China, 2019. N. Engl. J. Med. 382, 727-733 (2020).
[4] Gralinski, L. E. & Menachery, V. D. Return of the coronavirus: 2019-nCoV. Viruses 12, 135 (2020).
[5] Deng, S. Q. & Peng, H. J. Characteristics of and public health responses to the coronavirus disease 2019 outbreak in China. J. Clin. Med. 9, 575 (2020).
[6] National Health Commission of the People’s Republic of China. Briefing on the latest situation of the novel coronavirus pneumonia epidemic. http://www.nhc.gov.cn/xcs/yqtb/list_gzbd.shtml (2020).
[7] Eurosurveillance Editorial Team. Note from the editors: World Health Organization declares novel coronavirus (2019-nCoV) sixth public health emergency of international concern. Euro. Surveill. 25, 200131e (2020).
[8] Coronaviridae Study Group of the International Committee on Taxonomy of Viruses. The species severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat. Microbiol. 5, 356-544 (2020).
[9] Ben Hu, Hua Guo, Peng Zho and Zheng-Li Shi: Characteristics of SARS-CoV-2 and COVID-19, https://doi.org/10.1038/s41579-020-00459-7.
[10] PFISTER, Rodo (2020). [Bibliography] Coronaviruses • SARS • MERS • COVID-19 (Version5). <https://www.researchgate.net/publication/340514305>, <https://www.academia.edu/42128715/>. 
[11] Liu Shan-Lu & SAIF Lainda-2020; emerging Viruses without Borders: the wuhan coronavirus, (editorial) in viruses 2020, 12(2), no.130, 47-50. Issue Pathogenesis of Human and Animals Coronaviruses.

[12] W. Joost Wiersinga, MD, PhD; Andrew Rhodes, MD, PhD; Allen C. Cheng, MD, PhD; Sharon J. Peacock, PhD; Hallie C. Prescott, MD, MSc, Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19)A Review in JAMA, Patient Page-816.

[13] Mancia G, Rea F, Ludergnani M, Apolone G, Corrao G. Renin-angiotensin-aldosterone system blockers and the risk of COVID-19. N Engl J Med. 2020; 382(25): 2431-2440.

[14] Fosbol EL, Butt JH, Östergaard L, et al. Association of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker treatment with COVID-19 diagnosis and mortality. JAMA. Published online June 19, 2020.

[15] Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med. 2020, 8(4): 420-422.

[16] Van de Veen Donk FL, Nete MG, van Deuren M, et al. Kalikrein-kinin blockade in patients with COVID-19 to prevent acute respiratory distress syndrome. Elife. Published online April 27, 2020.

[17] Chu DK, Akl EA, Duda S, et al; COVID-19 Systematic Urgent Review Group Effort (SURE) study authors. Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis. Lancet. 2020; 395(10242): 1973-1987.

[18] Bourouiba L. Turbulent gas clouds and respiratory pathogen emissions: potential implications for reducing transmission of COVID-19. JAMA. Published online March 26, 2020.

[19] Lewis D. Is the coronavirus airborne? experts can’t agree. Nature. 2020; 580(7802): 175.

[20] Dashraath P, Wong JLJ, Lim MXK, et al. Coronavirus disease 2019 (COVID-19) pandemic and pregnancy. Am J Obstet Gynecol. 2020; 222(6): 521-531.

[21] Chen H, Guo J, Wang C, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. Lancet. 2020; 395(10266): 809-815.

[22] Zeng L, Xia S, Yuan W, et al. Neonatal early-onset infection with SARS-CoV-2 in 33 neonates born to mothers with COVID-19 in Wuhan, China. JAMA Pediatr. Published online March 26, 2020. doi:10.1001/jamapediatrics.2020.0878.

[23] Ganyani T, Kremer C, Chen D, et al. Estimating the generation interval for coronavirus disease (COVID-19) based on symptom onset data, March 2020. Euro Surveill. 2020; 25(17).

[24] Mao R, Qiu Y, He JS, et al. Manifestations and prognosis of gastrointestinal and liver involvement in patients with COVID-19: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2020, 5(7): 667-678.

[25] Levi M, Thachil J, Iba T, Levy JH. Coagulation abnormalities and thrombosis in patients with COVID-19. Lancet Haematol. 2020; 7(6): e438-e440.

[26] Mao R, Qiu Y, He JS, et al. Manifestations and prognosis of gastrointestinal and liver involvement in patients with COVID-19: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2020, 5(7): 667-678.

[27] Lauer SA, Grantz KH, Bi Q, et al. The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application. Ann Intern Med. 2020; 172(9): 577-582.

[28] Guan WJ, Ni ZY, Hu Y, et al; China Medical Treatment Expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020; 382(18): 1708-1720.

[29] Zhou P, Huang B, Liang W, et al; China Chest CT findings in patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. Lancet Infect Dis. 2020; 20(4): 411-417.

[30] Lian, N. et al. Umifenovir treatment is not associated with severe acute respiratory syndrome coronavirus infection. Radiology. 2020; 295 (3):200463.

[31] Zeng, Z. et al. Pulmonary pathology of early phase COVID-19 pneumonia in a patient with a Benign lung lesion. Histopathology. (2020).

[32] Liu, R. et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 395, 565-574 (2020).

[33] Oreshkova, N. et al. SARS-CoV-2 infection in fermented minks, the Netherlands, April and May 2020. Euro Surveill. 25, 2001005 (2020).

[34] Shi H, Han X, Jiang N, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. Lancet 395, 565-574 (2020).

[35] Wu, C. et al. Risk factors associated with acute respiratory distress syndrome and death in patients with Coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern. Med. 180, 934-943 (2020).

[36] Liu, Y. et al. Association between age and clinical characteristics and outcomes of COVID-19. Eur. Respir. J. 55, 2001112 (2020).

[37] Tian, J. et al. Clinical characteristics and risk factors associated with COVID-19 disease severity in patients with cancer in Wuhan, China: a multicentre, retrospective, cohort study. Lancet Oncol. 21, 893-903 (2020).

[38] Yao, X. H. et al. [A pathological report of three COVID-19 cases by minimal invasive autopsies]. Zhonghua Bing Li Xue Za Zhi 49, 411-417 (2020).

[39] Martines, R. B. et al. Pathology and pathogenesis of SARS-CoV-2 associated with coronavirus disease, United States. Emerg. Infect. Dis. 26, 2005-2015 (2020).

[40] Zeng, Z. et al. Pulmonary pathology of early phase COVID-19 pneumonia in a patient with a Benign lung lesion. Histopathology. (2020).

[41] Lu, R. et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 395, 565-574 (2020).

[42] R. et al. Pulmonary pathology of early phase COVID-19 pneumonia in a patient with a Benign lung lesion. Histopathology. (2020).

[43] Wu, C. et al. Risk factors associated with acute respiratory distress syndrome and death in patients with Coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern. Med. 180, 934-943 (2020).

[44] Liu, Y. et al. Association between age and clinical characteristics and outcomes of COVID-19. Eur. Respir. J. 55, 2001112 (2020).

[45] Tian, J. et al. Clinical characteristics and risk factors associated with COVID-19 disease severity in patients with cancer in Wuhan, China: a multicentre, retrospective, cohort study. Lancet Oncol. 21, 893-903 (2020).

[46] Yao, X. H. et al. [A pathological report of three COVID-19 cases by minimal invasive autopsies]. Zhonghua Bing Li Xue Za Zhi 49, 411-417 (2020).

[47] Martines, R. B. et al. Pathology and pathogenesis of SARS-CoV-2 associated with coronavirus disease, United States. Emerg. Infect. Dis. 26, 2005-2015 (2020).

[48] Zeng, Z. et al. Pulmonary pathology of early phase COVID-19 pneumonia in a patient with a Benign lung lesion. Histopathology. (2020).

[49] Lu, R. et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 395, 565-574 (2020).

[50] Oreshkova, N. et al. SARS-CoV-2 infection in fermented minks, the Netherlands, April and May 2020. Euro Surveill. 25, 2001005 (2020).

[51] Shi H, Han X, Jiang N, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. Lancet 395, 565-574 (2020).

[52] Wu, C. et al. Risk factors associated with acute respiratory distress syndrome and death in patients with Coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern. Med. 180, 934-943 (2020).

[53] Liu, Y. et al. Association between age and clinical characteristics and outcomes of COVID-19. Eur. Respir. J. 55, 2001112 (2020).

[54] Tian, J. et al. Clinical characteristics and risk factors associated with COVID-19 disease severity in patients with cancer in Wuhan, China: a multicentre, retrospective, cohort study. Lancet Oncol. 21, 893-903 (2020).
[56] Grein, J. et al. Compassionate use of remdesivir for patients with severe Covid-19. *N. Engl. J. Med.* 382, 2327-2336 (2020).

[57] Beigel, J. H. et al. Remdesivir for the treatment of Covid-19 - preliminary report. *N. Engl. J. Med.* (2020).

[58] Huang, C. et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 395, 497-506 (2020).

[59] Mehta, P. et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 395, 1033-1034 (2020).

[60] Recovery Collaborative Group, et al. Dexamethasone in hospitalized patients with Covid-19 - preliminary report. *N. Engl. J. Med.* (2020).

[61] Xu, X. et al. Effective treatment of severe COVID-19 patients with tocilizumab. *Proc. Natl Acad. Sci. USA* 117, 10970-10975 (2020).

[62] Diurno, F. et al. Eculizumab treatment in patients with COVID-19: preliminary results from real life ASL Napoli 2 Nord experience. *Eur. Rev. Med. Pharmacol. Sci.* 24, 4040-4047 (2020).

[63] Stockman, L. J., Bellamy, R. & Garner, P. SARS: systematic review of treatment effects. *PLoS Med.* 3, e343 (2006).

[64] Mantlo, E., Bukreyeva, N., Maruyama, J., Paessler, S. & Huang, C. Antiviral activities of type I interferons to SARS-CoV-2 infection. *Antiviral Res.* 179, 104811 (2020).

[65] Sallard, E., Lescure, F. X., Yazdanpanah, Y., Mentre, F. & Peiffer-Smadja, N. Type I interferons as a potential treatment against COVID-19. *Antiviral Res.* 178, 104791 (2020).

[66] Park, A., Iwashiki, A. & Type, I and Type III interferons - induction, signaling, evasion, and application to combat COVID-19. *Cell Host Microbe* 27, 870-878 (2020).

[67] Wang, C. et al. A human monoclonal antibody blocking SARS-CoV-2 infection. *Nat. Commun.* 11, 2251 (2020).

[68] Wu, Y. et al. A noncompeting pair of human neutralizing antibodies block COVID-19 virus binding to its receptor ACE2. *Science* 368, 1274-1278 (2020).

[69] Zost, S. J. et al. Potently neutralizing and protective human antibodies against SARS-CoV-2. *Nature* 584, 443-449 (2020).

[70] Shi, R. et al. A human neutralizing antibody targets the receptor-binding site of SARS-CoV-2. *Nature* 584, 120-124 (2020).

[71] Smith, T. R. F. et al. Immunogenicity of a DNA vaccine candidate for COVID-19. *Nat. Commun.* 11, 2601 (2020).

[72] Zhu, F. C. et al. Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a dose-escalation, open-label, non-randomised, first-in-human trial. *Lancet* 395, 1845-1854 (2020).

[73] Gao, Q. et al. Development of an inactivated vaccine candidate for SARS-CoV-2. *Science* 369, 77-81 (2020).

[74] Zou, F. C. et al. Immunogenicity and safety of a recombinant adenovirus type-5 vectored COVID-19 vaccine in healthy adults aged 18 years or older: a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet* 396, 479-488 (2020).

[75] Folegatti, P. M. et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. *Lancet* 396, 467-478 (2020).

[76] Jackson, L. A. et al. An mRNA vaccine against SARS-CoV-2 - preliminary report. *N. Engl. J. Med.* (2020).

[77] Xia, S. et al. Effect of an inactivated vaccine against SARS-CoV-2 on safety and immunogenicity outcomes: interim analysis of 2 randomized clinical trials. *JAMA* 324, 1-10 (2020).

[78] Tang, D., Comish, P. & Kang, R. The hallmarks of COVID-19 disease. *PLoS Pathog.* 16, e1008536 (2020).