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New Coronavirus Disease 2019 Pandemic: A Review on Epidemiology, Pathogenesis, and Global Scenario

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Abstract

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), a β-CoV, and a seventh member of family *Coronaviridae* causing infection in humans, are the causative agent of the new coronavirus disease 2019 (COVID-19). For the 1st time, the disease was reported as an outbreak on December 31, 2019 in Wuhan, Hubei Province, China, when patients with the symptoms of pneumonia were admitted in hospitals. Soon, the disease became epidemic and spread in 25 provinces in China with a total of 571 cases up to January 24, 2020. At present, COVID-19 has spread across 216 countries. As of July 18, 2020, the World Health Organization confirmed 13,876,441 cases and 593,087 deaths globally, despite rigorous containment and quarantine efforts. The main symptoms of COVID-19 include cough, fever, and fatigue and other symptoms such as headache, hemoptysis, sputum production, dyspnea, and diarrhea and lymphopenia may also arise. The diagnosis of COVID-19 is by demonstrating ribonucleic acid of SARS-CoV-2 in respiratory secretions by reverse transcription polymerase chain reaction. Treatment is supportive, and the role of antiviral agents is yet to be found. Preventive measures include regular and thorough cleaning of hands with soap and water for at least 20 s or an alcohol-based hand sanitizer and social distancing. It is important to develop simple, fast, and accurate technologies for the detection and treatment of COVID-19 to control the spread of the disease.

Keywords: Coronavirus disease 2019, Coronaviruses, Pathogenesis, Severe acute respiratory syndrome coronavirus-2, Transmission

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Introduction

Coronaviruses (CoV) are the group of viruses in the family *Coronaviridae*, causing sickness, which ranges from the common cold to deadly diseases such as Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS). CoV are zoonotic being transmitted between animals and humans, whereby MERS transmitted from Arabian camels (dromedary) to humans and SARS transmitted from civet cats to humans. Novel CoV (nCoV) has emerged as a new virus strain not previously reported in humans. SARS-COV-2, a beta-CoV is the seventh member of the Coronaviridae family infecting humans and the causative agent of the new CoV disease, (COVID-19).[1] MERS, SARS-CoV-1, and SARS-CoV-2 cause severe disease while four other viruses, namely, NL63, HKU1, 229E, and OC43, cause mild respiratory symptoms. The World Health Organization has declared new COVID-19, a Public Health Emergency of International concern.

The disease was reported on December 31, 2019, in Wuhan, Hubei Province, China, when 27 patients with the symptoms of pneumonia were admitted to hospitals. The clinical symptoms of the disease included dry cough, fever, and difficulty in breathing (dyspnea) and were related to Huanan Seafood Wholesale Market, Wuhan trading in wet animal and seafood including fish and live animals such as bats, poultry, marmots, and snakes.[2] On January 7, 2020, the causative agent was identified and named as SARS-CoV-2 by Chinese Centre for Disease Control and Prevention and disease named as new COVID-19 by the WHO on February 11, 2020.

Origin and Global Scenario

The cases of COVID-19 were reported first in December 2019 in Wuhan, Hubei Province, China.[3] Up to December 29, 2019, five patients with acute respiratory distress syndrome (ARDS) were hospitalized, out of which one died.[4] Forty-one admitted hospital-admitted patients were laboratory-confirmed for COVID-19 by January 2, 2020. Some of the admitted patients had underlying diseases such as diabetes and hypertension, and they were presumed to be infected due to nosocomial infection. Chinese research authorities announced the isolation of a new virus from seafood market in Wuhan on January 7, 2020, which was named as 2019-nCoV. On January 13, 2020, one patient imported from Wuhan city of China was reported by the Ministry of Public Health Thailand, and on January 15, 2020, first case was reported in Japan by the Ministry of health, Labor, and Welfare of Japan. Subsequently, COVID-19 infection was spread to 25 provinces of China with total cases of 571 and 17 deaths up to January 22 and 1975 confirmed cases and 56 deaths on January 25, 2020.[5] As of February 7, 2020, about 31,161 people have contracted the infection, and more than 630 people died in China, according to a report published in Nature (http://www.nature.com/articles/d41586-020-00154) of infection. It is worth mentioning that a paper published in the year 2007 predicting the re-emergence of these viruses warned "The presence of a large reservoir of SARS-CoV-like viruses in horseshoe bats, together with the culture of eating exotic mammals in Southern China, is a time bomb."[6] It also

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mentioned that "The possibility of the reemergence of SARS and other novel viruses from animals or laboratories and, therefore, the need for preparedness should not be ignored."

United State of America confirmed the first case of COVID-19 in America on January 23, 2020. Vietnam reported the first case of human to human transmission of SARS-CoV-2 on January 24, 2020, and subsequently the second case was reported in Chicago on January 30, 2020 (WHO situation reports). On January 30, 2020, the WHO declared COVID-19 a Public Health Emergency of International concern.

The WHO confirmed 375,498 COVID-19 cases and 16,362 deaths on March 25, 2020, across 196 countries. The very next day, on March 26, 2020, 41,188 more confirmed cases were reported making it to 416,686 with 18,589 deaths across 197 countries, area, and territories including China, Italy, United States, Spain, Germany, Iran, France, South Korea, Switzerland, United Kingdom, The Netherlands, Austria, Belgium, Norway, Portugal, Sweden, Canada, Australia, Brazil, Denmark, Turkey, Malaysia, Israel, Czech Republic, Japan, Ireland, Ecuador, Luxembourg, Pakistan, Thailand, Poland, and India (WHO situation reports https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/). According to the WHO, the number of confirmed cases on March 25, 2020 was 3.5 times higher and the number of deaths 4.2 times higher than that reported 15 days earlier on March 11, 2020, globally [Figure 1]. As of now up to July 18, 2020, the World Health Organization (WHO) reported 13,876,441 confirmed cases and 593,087 deaths across 216 countries, area, and territories (WHO situation Report-180, https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/). At present, the highest COVID-19 infections are reported from the United States of America (3,544,143 confirmed cases and 137,674 deaths), followed by Brazil (2,012,151 cases and 76,688 deaths) and India (1,038,716 cases and 26,273 deaths). Despite rigorous containment and quarantine efforts, the number of COVID-19 cases is increasing at a fast rate globally.

Structure and Phylogenetic Analysis of SARS-CoV-2

SARS-CoV-2, causative agent of novel COVID-19, has been classified as a β-CoV of group 2B by World Health Organization.[7,8] SARS-COV-2 virion is spherical, enveloped and has spikes protruding from their surface like other CoV. The spike protein (S protein) of SARS-CoV-2 binds to the receptor angiotensin-converting enzyme 2 (ACE2).[9] It is likely to bind 10–20 times more than the spikes of SARS virus of 2002 to ACE2 (NIH Research Matters, March 3, 2020, www.nih.gov). Although, the structure of spikes of the two viruses is similar, the antibodies against SARS were failed to bind to the spike protein of SARS-CoV-2, suggesting the treatment strategy based on antibodies and vaccination needs to be unique to SARS-CoV-2. The highly variable spike protein of SARS-CoV-2 (COVID-19) has been found to have a polybasic cleavage site at S1 and S2 boundary through the insertion of 12 nucleotides, contributing to the prediction of three O-linked glycans around the cleavage site.[1]

The phylogenetic analysis indicates that SARS-CoV-2 (COVID-19) belongs to beta CoV genus, including SARS-CoV that infects humans, bats, and wild animals as it showed more than 80% similarity with SARS-CoV and 50% similarity with MERS-CoV.[4,10,11] Due to insufficient phylogenetic difference between SARS-CoV-2 and SARS-CoV, it can be considered as a new beta-CoV infecting humans. Genome sequences of SARS-CoV-2 (COVID-19) obtained

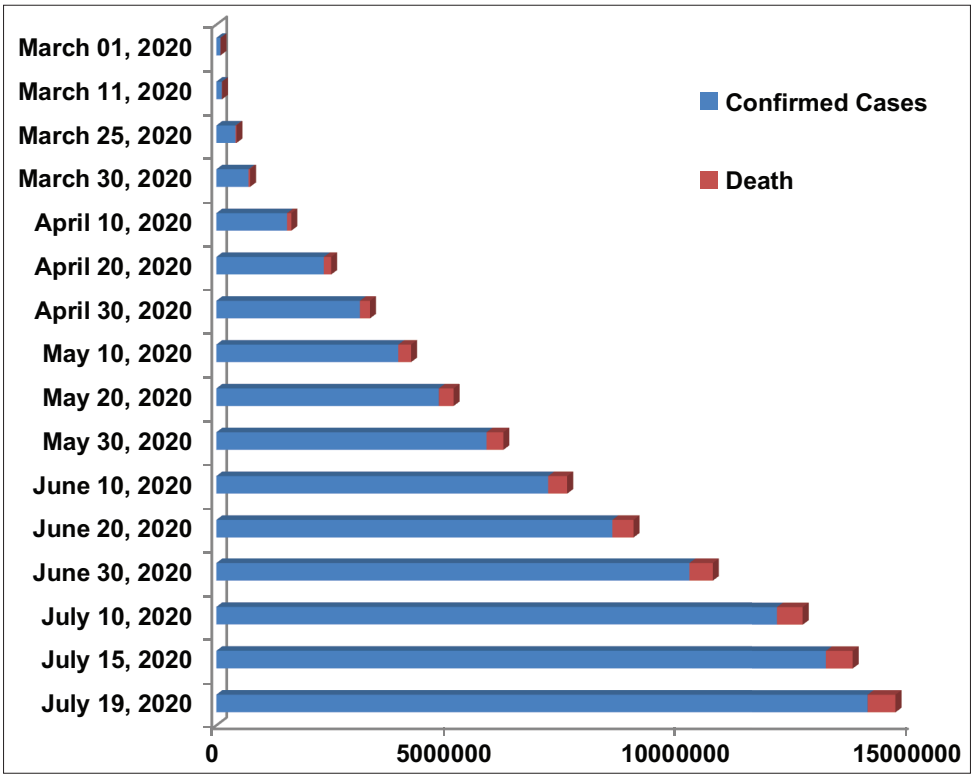

Figure 1: Coronavirus disease 19 confirmed cases and deaths globally during March-July, 2020. Further, there is tremendous increase in confirmed cases worldwide (Source: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports)

from nine patients showed a 99.98% sequence similarity.[10] In an another study, it was found that SARS-CoV-2 from five patients showed 99.8–99.9% nucleotide similarity revealing the presence of a new beta-CoV strain.[4] SARS-CoV-2 is the seventh member of the family Coronaviridae known to infect humans and falls under the subfamily Orthocoronavirinae. It forms a clade with the subgenus sarbecovirus.[11] SARS-CoV-2 is most likely to be of bat origin, as evident due to the presence of high degree of similarity of ACE2 receptor from a number of animal species, thereby implicating that these animals are the possible intermediate hosts for SARS-Cov-2.[12,13] Furthermore, on gene 8, the virus has a single intact open reading frame 8, indicative of the bat origin of the virus.

Transmission

COVID-19 is thought to be zoonotic in origin based on the reports on the infected persons exposed to the wet animal market in Wuhan City, China. Some initial reports have identified two snake species as a possible reservoir of the SARS-CoV-2; however, no consistent evidence for CoV reservoirs other than birds and mammals is available.[14,15] Reports suggest that SARS-CoV-2 spreads mainly through person to person either between people who are in close contact with one another or through respiratory droplets produced due to coughing and sneezing of an infected person.[16] The droplets may enter inside the nose or mouth of nearby people or possibly be inhaled into the lungs. The virus is also thought to spread due to contact with infected objects or surfaces. Virus enters inside when a person touches mouth, nose, or eyes after coming in contact with the infected surface or object. A person is thought to be most contagious when they are symptomatic, however, some spread might be possible before people show symptoms according to the information shared on CDC website (https://www.cdc.gov/coronavirus/2019-ncov/prepare/transmission.html).

A report also mentioned the detection of the ribonucleic acid (RNA) of SARS-CoV-2 in blood and stool specimens.[17] Although, live virus from stool samples has been cultured.,[18] the fecal-oral transmission does not seem to be a significant factor in the spread of infection according to a joint WHO-China report on joint Mission on COVID, February 16–24, 2019.

Two small studies provide evidence, though drawn from limited data that vertical transmission of COVID-19 did not occur. The first report mentioned that the nine mothers with COVID-19 delivered healthy infants through cesarean section.[19] The fluid surrounding infants in the womb as well as mother's breast milk were also tested negative for SARS-CoV-2. The second case study carried out in Wuhan, China, mentioned that the infants born to COVID-19 positive women were tested negative for the disease.[20] The infants did not develop serious symptoms of cough, fever, diarrhea, or abnormal radiologic or hematologic evidence.

During a study on the stability of SARS-CoV-2 in aerosol and different surfaces, it was found that the virus is more stable on plastics and stainless steel compared to cardboard or copper.[21] The virus remained viable in air for the entire 3 h experiment while no viable virus was detected on the cardboard surface after 24 h and on the copper surface after 4 h. The virus was detected even after 72 h on stainless steel and plastic surfaces.

Symptoms and Diagnosis

Most common symptoms of COVID-19 include cough, fever, and fatigue and other symptoms such as headache, hemoptysis, sputum production, dyspnea, and diarrhea and lymphopenia.[4,18,22] According to CDC, the symptoms generally appear after an incubation period of approximately 2–14 days after exposure. The time period from the onset disease symptoms to death generally ranges from 6 to 41 days, being dependent on the age and immune status of the patient.[18] In general, this time period is short in patients aged more than 70 years. In a study, it was found that clinical feature of COVID-19 by chest computed tomography scan is presented as pneumonia, however, some other features including ARDS, acute cardiac injury, RNAaemia, and grand-glass opacities incidence were also observed.[22] It was also shown that COVID-19 exhibits unique clinical features like targeting of the lower airway as evident by the symptoms of sneezing, rhinorrhea, and sore throat. In addition, some cases showed an infiltrate in the upper lobe of the lungs associated with dyspnea as evident from the chest radiographs.[23]

COVID-19 possibility should be considered primarily in patients with new-onset of fever and/or cough and dyspnea. In addition, it should also be important to consider the patients with lower respiratory tract illness without any clear cause. The likelihood of COVID-19 increases if the patient resides in or has traveled to a location where there is community transmission of SARS-Cov-2 prior 14 days; or had a close contact with a COVID-19 suspected or confirmed case prior 14 days. The patients with the highest priority for testing include: Critically ill patients with unexplained pneumonia or respiratory failure; individuals in close contact with COVID-19 laboratory-confirmed patients within 14 days of symptoms; individuals traveled within 14 days of symptoms onset to areas with sustained community transmission; immune-compromised individuals with fever or lower respiratory tract illness; and individuals critical to the pandemic response, including healthcare workers, public health officials, and other essential leaders with symptoms of fever or lower respiratory tract illness. A nasopharyngeal swab specimen is collected for testing SARS-CoV-2 as recommended by the CDC. RNA of SARS-CoV-2 is detected by reverse transcription-polymerase chain reaction (RT-PCR) and a positive test generally confirms the diagnosis of COVID-19, though false-positive tests are also possible. WHO recommends re-sampling, if the test is negative, but suspicion of COVID-19 is there (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/surveillance-and-case-definitions).

Pathogenesis

COVID-19 patients exhibit clinical manifestations similar to SARS-CoV and MERS-CoV, including non-productive cough, fever, dyspnea (shortness of breath), myalgia (muscle pains), fatigue, normal or decreased leukocyte counts, and pneumonia.[22,24] In a case study, a female patient with a 5 days fever history presented with cough, coarse breathing sounds, and fever (39.0°C) was found positive for COVID-19 infection after carrying out the RT-PCR of patient's sputum.[25] Leukopenia with white blood cell count of 2.91×10^9 cells/L was observed in laboratory studies. In addition, C-reactive protein level of 16.16 mg/L in blood and high erythrocyte sedimentation rate was observed. In another study, it was found that in 41 laboratory-confirmed COVID-19 patients, complications mainly included ARDS in 29% patients, RNAaemia in 15% patients, acute cardiac injury in 12%, and secondary infection in 10% patients.[22] The report showed ARDS as the main death cause of COVID-19 patients. Uncontrolled systemic inflammatory response

due to the release of large amounts of pro-inflammatory cytokines and chemokines by immune effector cells on SARS-CoV infection is one of the main mechanisms for ARDS.[22,26,27] Likewise, a 50-year-old man admitted to hospital presented with cough, fever, chills, fatigue, and shortness of breath with a travel history to Wuhan, China, was confirmed with COVID-19 by RT-PCR.[28] Histological examination revealed bilateral diffuse alveolar damage and ARDS indicating that the COVID-19 pathological features resemble SARS-CoV and MERS-CoV infection.[28] The pathogenesis of new COVID-19 is not understood fully yet, the mechanisms of SARS-CoV and MERS-CoV could provide information on SARS-CoV-2 pathogenesis to give an insight into COVID-19.

Treatment Strategies and Precautions

The US Food and Drug Administration has not approved any drug, so far, for treating the patients with COVID-19. According to the Centers for Disease Control and Prevention, clinical management comprises: Prevention of infection, control measures, and supportive care, including supplementary oxygen and mechanical ventilator support.

Treatment is based on multiple principals, including fusion inhibitors, replication disruption, suppressing the excessive inflammatory response, plasma treatment. Multiple drug candidates are presently being used and need further investigation.

A trial of lopinavir and ritonavir to treat COVID-19 adult patients was carried out, where out of 199 patients 99 were included in lopinavir–ritonavir group and the other 100 in the standard-care group.[29] It was observed that no benefit was found with lopinavir–ritonavir treatment compared to standard care as the mortality at 28 days was similar in both the groups. Lopinavir-ritonavir is under investigation in one of the World Health Organization study.

Hydroxychloroquine and chloroquine, antimalarial oral drugs have shown *in vitro* activity against SARS-CoV-2, and other CoV, with relatively higher potency shown by hydroxychloroquine against SARS-CoV-2.[30-32] In China, chloroquine was used as a recommended antiviral for treating COVID-19 patients after a study reporting the clinical and virologic benefits of the drug.[33] Chloroquine or hydroxychloroquine are being used currently in treating hospitalized COVID-19 patients in many countries, based on *in vitro* and anecdotal data. Both the drugs have been reported to be well tolerated by COVID-19 patients. Hydroxychloroquine has been administered to COVID-19 hospitalized patients in many countries because of its higher *in vitro* activity against SARS-CoV-2 and availability compared to chloroquine. A study reported that with the use of hydroxychloroquine in combination with azithromycin or alone has decreased the detection of RNA of SARS-CoV-2 in the upper respiratory tract specimens as compared to a control group.[34] A caution is being advised in using hydroxychloroquine and azithromycin in patients with chronic conditions including renal failure and hepatic disease or those receiving medications that might interact to cause arrhythmias. At present, hydroxychloroquine is under testing in clinical trials for pre-exposure or post-exposure prophylaxis of SARS-CoV-2 infection, and treating patients with mild, moderate, and severe COVID-19.

In addition, remdesivir, an intravenous drug having broad-spectrum antiviral activity due to the premature termination of RNA transcription leading to the inhibition of viral replication, has found to have *in vitro* activity against SARS-CoV-2 and *in vitro* and *in vivo* activity against related beta CoV.[32,35] Likewise, many other drugs are currently being considered for clinical trials or under investigation in clinical trials for the treatment of COVID-19 worldwide. However, the main focus is on remdesivir; chloroquine and hydroxychloroquine; two HIV drugs, lopinavir and ritonavir; and the same combination along with interferon-beta (https://www.sciencemag.org/news/2020/03/who-launches-global-megatrial-four-most-promising-coronavirus-treatments). More laboratory and clinical evidence still need to be explored. World Health Organization is working to launch more than 80 clinical trials for the potential treatment of COVID-19.

In the present CoV pandemic, the use of convalescent plasma transfusion seems a promising treatment strategy until other treatment methods and vaccines are successfully evaluated. The administration of the convalescent plasma from a recovered patient within 14 days of onset of symptoms is the most promising. Clinical testing of the vaccine candidates against SARS-CoV2 is in progress.

The precautions include: Regular and thorough cleaning of hands with soap and water for at least 20 s or an alcohol-based hand sanitizer; covering nose and mouth with tissue during coughing and sneezing, maintain a social distance of at least 1 m when a person is coughing or sneezing, and self-isolation or staying at home if one feels unwell. A person should not touch his eyes, mouth, or nose if the hands are not clean.

Conclusion

SARS-CoV-2, the causative agent of the new COVID-19, has become a pandemic affecting 211 countries and territories. SARS-CoV-2 is highly infectious being transmitted by close contact and droplets. The disease has posed a serious threat to mankind globally. Stringent measures are required to control its spread by reducing person to person transmission mainly in children, elderly people, and healthcare workers. It is important to develop simple, fast, and accurate technologies for the detection and treatment of COVID-19 to control the spread of the disease. Many countries have now implemented major prevention and control measures including travel screenings to control further spread of the virus. The World Health Organization is working to assess the current level of knowledge about the new virus, provide advice, coordinate with partners, help countries prepare, increase supplies, and manage expert networks.

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