

Coronavirus: The Silent Killer

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Abstract- The corona virus disease covid-19 is a highly transmittable and pathogenic viral infection caused by severe acute respiratory syndrome coronavirus 2 SARS-CoV-2), which emerged in Wuhan, China and spread around the world. Genomic analysis revealed that SARS-CoV-2 is phylogenetically related to severe acute respiratory syndrome like (SARS-like-viruses. It can be transferred from human to human has been confirmed widely. There is no clinically approved antiviral drug or vaccine available to be used against COVID-19 in clinical trials, resulted in clinical recovery. World health organisation (WHO) officially declared the COVID-19 epidemic as a public health emergency of international concern. According to the world health issue to public health its transmission via droplets, contaminated hands or surfaces. Early diagnosis, quarantine, and supportive treatments are essential to cure patients.

Index terms- Novel corona virus, COVID 19 outbreak Pathogenesis, pandemic, Diagnosis, Treatment

INTRODUCTION

There is a current worldwide outbreak of a new type of coronavirus (COVID-19), which originated from Wuhan, China and has now spread to 140 other countries, including Japan, Korea and Italy. The WHO declared that COVID-19 has become a global health concern, causing severe respiratory tract infections in humans. Current evidence suggests that SARS-CoV-2 spread to humans via transmission from wild animals illegally sold in the Huanan Seafood Wholesale Market. Phylogenetic analysis shows that SARS-CoV-2 is a new member of the Coronaviridae family but is distinct from SARS-CoV (identity of approximately 79%) and MERSCoV (identity of approximately 50%).[1,2] Knowing the origin of such a pathogen is critical to developing means to block further transmission and vaccines.

[3] Notably, SARS-CoV-2 shares a high level of genetic similarity (96.3%) with the bat coronavirus RaTG13, which was obtained from bats in Yunnan in 2013; however, bats are not the immediate source of SARS-CoV-2.[4] The typical symptoms of COVID-19 are fever, sore throat, fatigue, cough or dyspnea coupled with recent exposure. As of March 16 2020, the outbreak of COVID-19 generated 168, 826 confirmed cases, including 6, 503 deaths worldwide. In China during the outbreak of the pandemic 42,000 doctors and nurses from all over the country supported Wuhan. Moreover, the government shared the updated genome sequence of COVID-19 to the public, and scientists from China and overseas are working closely and efficiently on this public health emergency.[5,6] Due to interventions and control measures from the government (shutting down public transportation and implementing a treatment strategy) and the reaction of personal behaviours (wearing masks and reducing contact with others), the number of confirmed and suspected cases has started to decrease. However, the transmission of pneumonia associated with SARS-CoV-2 has not yet been completely eliminated. The COVID-19 outbreak is still a major challenge for clinicians. The aim of this article is to describe the epidemiology, diagnosis, isolation and treatment of COVID-19.

EPIDEMIOLOGY

Incubation period

Early spreading dynamics of COVID-19 declared that the intimated incubation period was 5.2 days (95% CI, 4.1 to 7.0), with the 95th percentile of the distribution at 12.5 days.[7] Another study later using the travel history and symptom onset of 88 confirmed cases had a similar mean incubation period, which was 6.4 days (95% CI: 5.6-7.7).[8] An unusual case

was reported, in which the incubation period was as long as 19 days.[9] Notably, a long incubation time means adjustments in screening and control policies.[10] The 19-day incubation period is a low probability event, and experts suggest 14 days for quarantine.

Basic reproductive number

The basic reproduction number is model-based and largely depends on the epidemiological setting and the most important parameter to determine the intrinsic transmissibility. The early outbreak data largely follow exponential growth. Different models based on the clinical progression of the disease were devised to estimate the basic reproductive number. In the early stages of corona, the pandemic twice in size every 7.4 days, and the basic reproductive number was estimated to be 2.2.[7] Another study estimated a similar reproductive number, which ranged from 2.24 to 3.58.[11] However, a deterministic compartmental model devised based on the likelihood and a model analysis showed that the control reproduction number may be as high as 6.47.[12] As noted in the paper, this basic reproductive number is higher because the estimation accounts for three to four generations of viral transmission and intensive social contacts. The basic reproductive number estimated by the majority of studies ranges from 2.24 to 3.58.[13] which is slightly higher than that of SARS.

Virology-pathogenesis

Coronaviruses are viruses whose genome structure is well known among all RNA viruses. Two-thirds of RNA they have encodes viral polymerase (RdRp), RNA synthesis materials, and two large nonstructural polyproteins that are not involved in host response modulation (ORF1a-ORF1b). The other one-third of the genome encodes four structural proteins (spike (S), envelope (E), membrane (M) ve nucleocapsid (N), and the other helper proteins.[52,53] Although the length of the CoV genome shows high variability for ORF1a/ORF1b and four structural proteins, it is mostly associated with the number and size of accessory proteins.[52,53]The first step in virus infection is the interaction of sensitive human cells with Spike Protein. Genome encoding occurs after entering to the cell and facilitates the expression of the genes,that encode useful accessory proteins, which advance the adaptation of CoVs to their human

host.[53] Genome changes resulting from recombination, gene exchange, gene insertion, or deletion are frequent among CoVs, and this will take place in future outbreaks as in past epidemics. As a result of the studies, the CoV subfamily is rapidly expanding with new generation sequencing applications that improve the detection and definition of novel CoV species. In conclusion, CoV classification is continually changing. According to the most recent classification of The International Committee on Taxonomy of Viruses (ICTV), there are four genera of thirty-eight unique species.[54] SARS-CoV and MERS-CoV that attach to the host cell respectively bind to cellular receptor angiotensin-converting enzyme 2 (SARS-CoV associated) and cellular receptor of dipeptidyl peptidase 4 (MERS-CoV associated).[55] After entering the cell, the viral RNA manifest itself in the cytoplasm. Genomic RNA is encapsulated and polyadenylated, and encodes different structural and non-structural polypeptide genes. These polyproteins are split by proteases that exhibit chymotrypsin-like activity.[53,55] The resulting complex drives (-) RNA production through both replication and transcription. During replication, full-length (-) RNA copies of the genome are produced and used as a template for full-length (+) RNA genomes.[52,53] During transcription, a subset of 7-9 sub-genomic RNAs, including those encoding all structural proteins, are produced by discontinuous transcription. Viral nucleocapsids are combined from genomic RNA and R protein in the cytoplasm and then are budded into the lumen of the endoplasmic reticulum. Virions are then released from the affected cell through exocytosis. The released viruses can infect kidney cells, liver cells, intestines, and T lymphocytes, as well as the lower respiratory tract, where they form the main symptoms and signs.[55] Remarkably, CDT lymphocytes were found to be lower than 200 cells/mm³ in three patients with SARS-CoV infection. MERS-CoV is able to infect human dendritic cells and macrophages in-vitro. T lymphocytes are also a target for the pathogen due to the properties CD26 rosettes. This virus can make the antiviral T-cell response irregular due to the stimulation of T-cell apoptosis, thus causing a collapse of the immune system.[56,57]

Sources & Modes of transmission

CoVs is also known as a novel respiratory tract virus in the samples collected from the individuals who present symptoms of respiratory tract infection in 1962.[63] This is a huge family of viruses that are commonly present in many animal categories, including cattle, cats, and bats. Rarely, animal CoVs can affect on humans and, as a result, may spread among humans during epidemics such as MERS, SARS, and COVID-19.[61-62] At the onset of major outbreaks caused by CoVs, palm cats have been proposed to be a natural reservoir of Human CoVs for SARS and dromedary camels for MERS.[58] However, more advanced virological and genetic studies have shown that bats are reservoir hosts of both SARS-CoV and MERS- CoV and before these viruses spread to humans, they use the other responsible animals as intermediate hosts. Studies have reported that most of the bat CoVs are the gene source of alpha-CoV and beta-CoVs, while most of the bird CoVs are the gene source of gamma-CoVs and delta-CoVs.[58] In recent studies, it has been seen that the novel virus causing epidemics coincides with the CoV isolated in bats. Presence of wild animal trade in Huanan Seafoods Market where the first cases appeared, supports this finding.[59,60] After the first outbreak, secondary cases began to be reported after approximately ten days. Moreover, while these new patients had no link with the marketplace, they had a history of link with humans there. Confirmed recent reports from many infected healthcare workers in Wuhan show that human- to-human transmission can occur. As in SARS and MERS epidemics in the past, human- to human transmission has accelerated the spread of the outbreak and case reports have also started from other states of China. The first non-Chinese case of the infection, which spread to the Chinese provinces, and then to the Asian continent, was reported from Thailand on January 13, 2020. The case reported being a Chinese tourist who has traveled to Thailand and had no epidemiologic connection with the marketplace.[64] Other cases from oversea countries such as the USA and France have continued to be reported.[65] Often, the human-to-human transmission occurs with close contact. The transmission primarily occurs when an infected person sneezes and through the respiratory droplets produced just as the spread of influenza and other respiratory pathogens. These droplets can settle in the

mouth or nasal mucosa and lungs of people with inhaled air. Currently, it remains unclear whether a person can be infected by COVID-19 by touching an infected surface or object and then touching their mouth, nose, or possibly eyes.[66] Typically, like most respiratory viruses, it is considered to be the most contagious when people are most symptomatic. However, cases, who were infected from an asymptomatic person in the prodrome period of COVID-19, were also reported. Sufficient data are not available on infectiousness of the disease and research is ongoing.[67]

Genome structure of coronaviruses

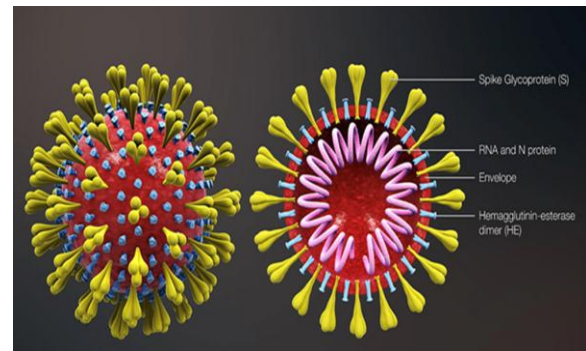


Figure 1: Coronavirus virion structure shown with structural proteins.

N: Nucleocapsid protein;
S: Spike protein,
HE: Hemagglutinin-Esterase
E: Envelope protein [68]

DIAGNOSIS

Rapid and accurate detection of COVID-19 is crucial to control outbreaks in the community and in hospitals [14]. Current diagnostic tests for coronavirus include reverse-transcription polymerase chain reaction (RT-PCR), real-time RT-PCR (rRT-PCR), and reverse transcription loop-mediated isothermal amplification (RT-LAMP) [15,16]. RT-LAMP has similar sensitivity to rRT-PCR, is highly specific and is used to detect MERS-CoV [17,18]. According to current diagnostic criteria founded by the China.

TREATMENT

Currently, no medication is recommended to treat COVID-19, and no cure is available. Antibiotics aren't effective against viral infections such as

COVID-19. Researchers are testing a variety of possible treatments. The U.S. Food and Drug Administration granted permission for some medications approved for other diseases to be used to treat severe COVID-19 when no other options are available. Two malaria drugs — hydroxychloroquine and chloroquine — and an antiviral drug, remdesivir, have been approved for this use.

Chloroquine and hydroxychloroquine

Chloroquine is a widely-used antimalarial and autoimmune disease drug that has been reported to be a potential broad-spectrum antiviral drug [56], [57], [58]. Chloroquine is known to block virus infection by increasing endosomal pH required for virus/cell fusion, as well as interfering with the glycosylation of cellular receptors of SARS-CoV [59]. The first results obtained from more than 100 patients showed the apparent efficacy of chloroquine in terms of reduction of exacerbation of pneumonia, duration of symptoms and delay of viral clearance, all in the absence of severe side effects [60]. Chloroquine was included in the recommendations for the prevention and treatment of COVID-19 pneumonia [60,61]. The optimal dosage of chloroquine for SARS-CoV-2 will need to be assessed in future trials [62].

Hydroxychloroquine is a chloroquine analog for which there are fewer concerns about drug-drug interactions [63]. In the previous SARS outbreak, hydroxychloroquine was reported to have anti-SARS-CoV activity in vitro [64]. Using physiologically-based pharmacokinetic (PBPK) models, hydroxychloroquine was found to be more potent than chloroquine in SARS-CoV-2-infected Vero cells [65]. Cytokines IL-6 and IL-10 have been reported to be increased in response to SARS-CoV-2 infection [66,67]. This may progress to a cytokine storm, followed by multiorgan failure and death. Both chloroquine and hydroxychloroquine have immunomodulatory effects and can suppress the immune response [68,69]. Therefore, 21 clinical studies were launched by Chinese hospitals and the University of Oxford to evaluate the efficacy of these agents in COVID-19 infection (Table 2). It is also necessary to determine whether the benefit of chloroquine therapy depends on the age of the patient and the clinical presentation or stage of the disease [70]. If clinical data confirm the biological results, chloroquine and hydroxychloroquine may be used in

prophylaxis as well as curative treatment for individuals exposed to SARS-CoV-2 [71].

Symptoms of COVID-19 ^[51]	
Symptom	Range
Fever	83–99%
Cough	59–82%
Loss of appetite	40–84%
Fatigue	44–70%
Shortness of breath	31–40%
Coughing up sputum	28–33%
Muscle aches and pains	11–35%

CONCLUSIONS

There has been a rapid surge in research in response to the outbreak of COVID-19. During this early period, published research primarily explored the epidemiology, causes, clinical manifestation and diagnosis, as well as prevention and control of the novel coronavirus. Although these studies are relevant to control the current public emergency, more high-quality research is needed to provide valid and reliable ways to manage this kind of public health emergency in both the short- and long-term.

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