



COVID-19, A CORONA VIRUS PANDEMIC OF 21ST CENTURY; A STORY SO FAR

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ABSTRACT

Coronavirus (COVID-19) disease 2019 is one of the major pathogens that primarily target the human respiratory system. This disease has emerged as pandemic in 2019. It is a kind of viral pneumonia which is caused by SARS-CoV-2 and represents the causative agent of a potentially fatal disease that is of great global public health concern now a day. Based on the large number of infected people that were exposed to the wet animal market in Wuhan City, China, it is suggested that origin of COVID-19 is likely to be zoonotic. Extensive measures to reduce person-to-person transmission of COVID-19 have been implemented to control the current outbreak. The transmission from mother to next generation is not confirmed as all the cases under observation gave birth through C section. Thousands of people died not only in China but also in European and American continent, and millions of people infected, as 2019-nCoV continues to spread around the world. An effective vaccine to cure this virus is not yet available, thus requires concerted efforts at various ways. Till to date, there is no effective specific antiviral therapy against COVID-19 but supportive medicines are working well against this viral disease. In this mini review, we provide a brief introduction of the general clinical symptoms of SARS-CoV-2 and discuss current knowledge of pathogenesis, etiology, transmission; phylogenetic analysis diagnosis and therapeutic options and future directions to control proliferate of this disaster disease.

KEYWORDS: COVID-19, SARS-CoV-2, coronaviruses, respiratory Syndrome, RT-PCR and Wuhan.

INTRODUCTION

Many pathogens attack humans, one of the major pathogens is corona viruses that primarily target the human respiratory system. Previous epidemic of corona viruses (CoVs) causes severe acute respiratory Syndrome (SARS)-CoV and the Middle East respiratory Syndrome (MERS)-CoV. This disease was previously characterized as agents that cause severe public health hazard. More than many patients were admitted to different health centers with an initial symptom of pneumonia of an unknown etiology in late December 2019. These affected patients were mutually linked with seafood and wet animal wholesale market in Wuhan, Hubei Province, China (Lu *et al.*, 2020; Bogoch *et al.*, 2020). Initial reports said the upcoming outbreak of a potential Coronavirus given the calculation of a propagation number for the 2019

Novel(New) Coronavirus (COVID-19, named by WHO on Feb, 2020) which was considered to be weightily larger than 1 (ranges from 2.24 to 3.58) (Zhao *et al.*, 2020). Several Infections of COVID-19 in china are as follows. An initial infection reports was submitted in December 2019 (Du, 2020). From December 18, 2019 to onward December 29, 2019, five patients were slightly unwell with severe respiratory agonizing syndrome and one of these patients died (Ren *et al.*, 2020). Forty-one admitted hospital patients were distinguished as having COVID-19 infection that is authenticated by laboratory techniques, less than half of these patients had latent diseases, including hypertension, diabetes, and heart disease until January 2, 2020 (Huang *et al.*, 2020). The patients were predicted to be infected in that hospital, likely due to nosocomial infection. It was resulted that the COVID-19 is

not a super-hot spreading virus (spread by one patient to many others), but it can be transmitted due to many infected persons that get infection from different places throughout the hospital by an unknown mechanism. In addition, some patients that got sick and come to hospitals were tested, thus there may be many other unknown untested patients infected by this virus. On January 22, 2020, 571 cases of the 2019-new coronavirus (COVID-19) were reported from 25 provinces (Lu, 2020). First 17 death reports were submitted by The China National Health Commission up to January 22, 2020. On January 25, 2020, a total of 1975 cases were reported as confirmed to be infected with the COVID-19 in mainland China with 56 deaths (Wang *et al.*, 2020). Another report was

submitted on January 24, 2020 that includes the cumulative incidence in China to be total of 5502 cases (Nishiura *et al.*, 2020). To January 30, 2020, cases were increased to 7734 in China and 90 more cases were also reported from other countries (Bassetti *et al.*, 2020). At the time of preparing this manuscript, the World Health Organization (WHO) reported 81,116 confirmed cases and 3231 death cases in China. Globally, the number of confirmed cases as of this writing (July 19, 2020) reached 14,043,176 confirmed case including 597,583 deaths more than 180 regions (Figure 1). The start of the viral outbreak till now many cases of COVID-19 has been reported in many countries, territories or areas throughout the world (Figure 2).

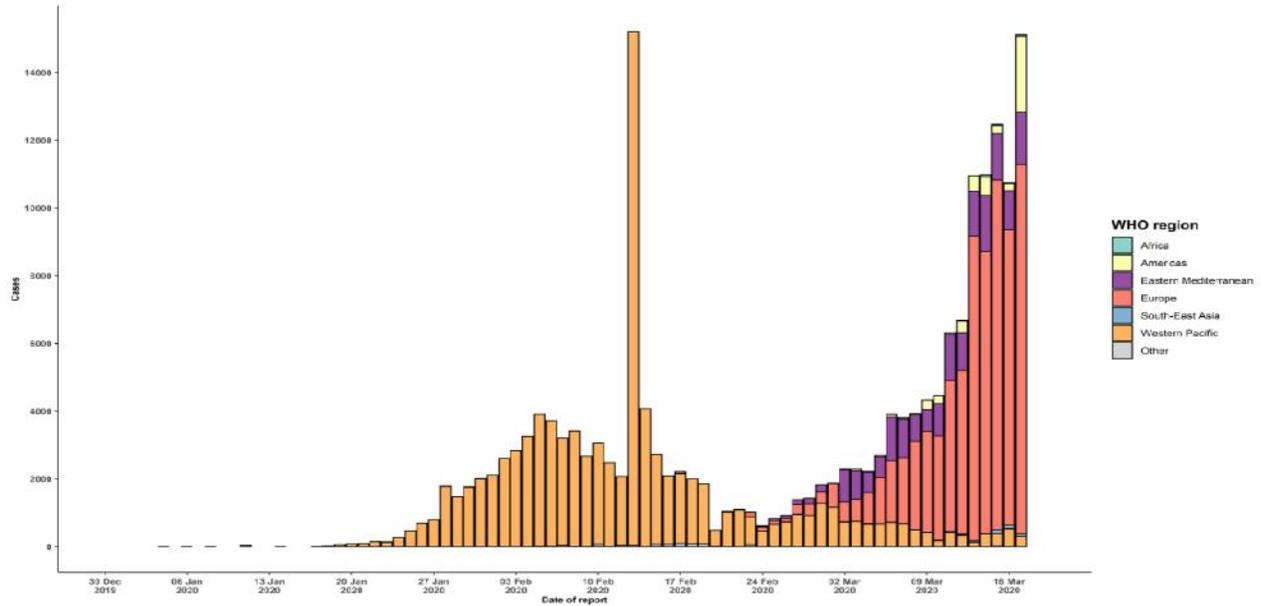


FIGURE 1: Epidemic curve of confirmed COVID-19, by date of report and cases in WHO region

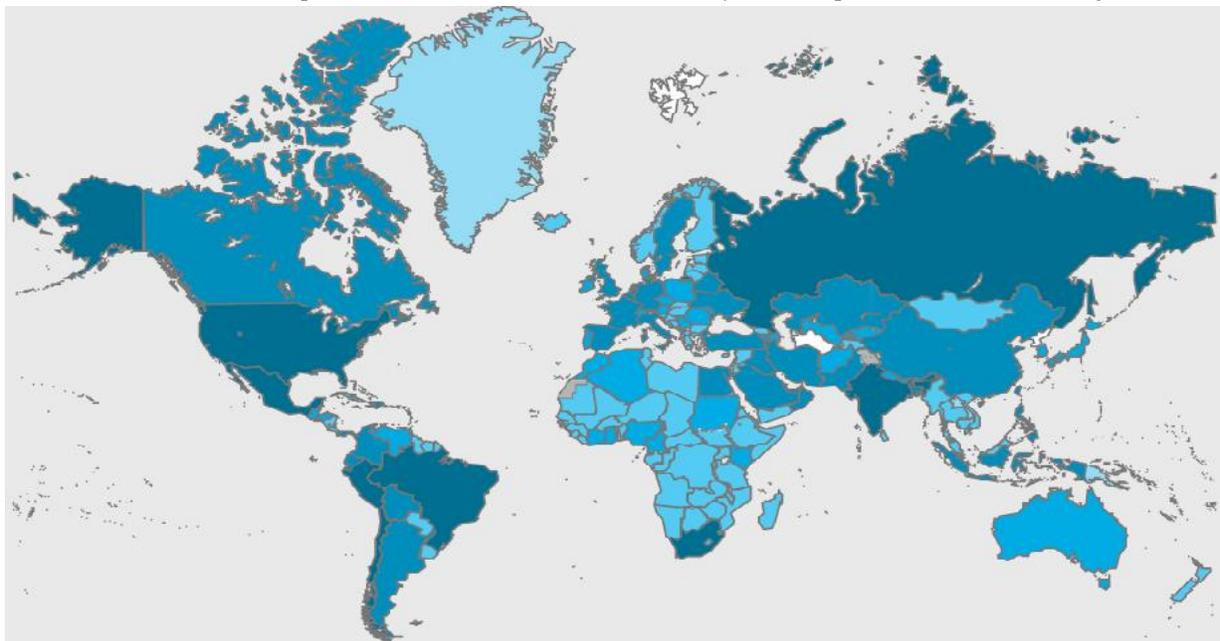


FIGURE 2: Cases of COVID-19 have been reported in many countries, territories or areas throughout the world

ETIOLOGY

In preliminary report, complete viral genome sequence analysis shows that the virus account for 88% sequence similarity with two bat-derived severe acute respiratory syndromes (SARS)-like coronaviruses, but are more distant from severe acute respiratory syndrome coronavirus (SARS-CoV) (Lu *et al.*, 2020). Due to this fact, it was temporarily known as 2019-novel coronavirus (2019-nCoV). Coronavirus genome is enveloped positive sense, single-stranded ribonucleic acid (ssRNA) that named for its solar corona like appearance due to 9-12 nm long surface spikes (Zu *et al.*, 2020). The genome of coronavirus can code for four structural proteins on the protein envelope, as spike protein which binds with angiotensin-converting enzyme 2 (ACE2) receptor and help subsequent fusion between viral envelope and attacked host cell membranes to facilitate entry of virus in host cell (Kirchdoerfer *et al.*, 2016; Xu *et al.*, 2020). On February 11, 2020, the Coronavirus Study Group (CSG) of the International Committee on Taxonomy of Viruses announce it as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on the basis of phylogeny, taxonomy and established practice (Gorbalenya, 2020). Soon later, WHO named this disease as Coronavirus Disease 2019 (COVID-19) due to its causal agent Coronavirus (WHO, 2020).

CLINICAL SYMPTOM

The defined symptoms of COVID-19 infection will appear after an incubation period of almost 5.2 days (Li *et al.*, 2020). The time duration between the establishment and appearance of symptom of the virus to death of patient ranges from 6 to 41 days with a median of 14 days. The duration depends upon status of immune system and age of patient. This time period is recorded as shorter among patients more than 70-years old as compared to those who are under the age of 70 (Wang *et al.*, 2020). Some common and initial symptoms are fever, cough, and fatigue, and other symptoms include sputum production, headache, hemoptysis, diarrhea, dyspnea, and lymphopenia (Huang *et al.*, 2020; Wang *et al.*, 2020) (Carlos *et al.*, 2020; Ren *et al.*, 2020). Clinical tests showed by a chest CT scan presented as pneumonia, however, there were also unusual features such as RNAemia, acute respiratory distress syndrome, acute cardiac injury, and incidence of ground-glass opacities that is lethal (Huang *et al.*, 2020). In some patients, multiple peripheral ground-glass opacities were observed in subpleural regions of both lungs (Lei *et al.*, 2020) that likely induced both systemic and localized immune response that results in high inflammation. It is good to know that there is likeness between the symptoms of COVID-19 to earlier betacoronavirus. These similarities

are as dry cough, fever, dyspnea, and bilateral ground-glass opacities on chest CT scans (Huang *et al.*, 2020). But, COVID-19 has also showed some unique clinical features including the targeting of the lower airway as evident by upper respiratory tract symptoms like rhinorrhea, sore throat and sneezing (Lee *et al.*, 2003; Assiri *et al.*, 2013). In addition, on the basis of chest radiographs of patients, some of them show an infiltrate in the upper lobe of the lung which is associated with increasing dyspnea with hypoxemia (Phan *et al.*, 2020). More importantly, the patients infected with COVID-19 developed gastrointestinal symptoms like diarrhea, a low percentage of MERS-CoV or SARS-CoV patients experienced similar GI distress (Lee *et al.*, 2003; Assiri *et al.*, 2013). So, increase in the development of identifying techniques of transmission and spread such as fecal and urine samples are urgently warranted to develop measurement to control or lower transmission and to develop therapeutics and chemicals to control the disease (Rothan and Byrareddy, 2020).

DIAGNOSIS OF COVID-19 INFECTION

The initial step for the clinical diagnostic work-flow is to confirm Wuhan city exposure history or make a close contact with people from Wuhan or confirmed reported patients during the past two or three weeks. However, the amount of the infected patients having unknown exposure history is increasing day by day due to the rapid and wide spread of the infection. The National Health Commission of China (Ai *et al.*, 2020) produced the Diagnosis and Treatment Program of 2019 New Coronavirus Pneumonia (trial sixth version) on the basis of recommendations of the World Health Organization (WHO) on severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) (WHO, 2004; Arabi *et al.*, 2017) (Azhar *et al.*, 2014). On the basis of the fifth trial edition (Committee), chest CT results of viral pneumonia are known as evidence of clinical diagnosis of COVID-19 infection. However, the WHO do not accept CT results without RT-PCR results until February, 17, 2020 (Bernheim *et al.*, 2020) and the most recently published Diagnosis result and Treatment Program of 2019 New Coronavirus Pneumonia (trial sixth version) has deleted the term of *clinical diagnosis* (Committee). The final reported *etiology diagnosis* of COVID-19 is important, that can be further confirmed by positive real-time (RT-PCR) assay for COVID-19 by respiratory samples or blood samples or by viral genome sequencing of respiratory or blood samples that are highly similar to COVID-19. According to the clinical manifestations, confirmed infected patients were divided into mild, moderate, severe, and critical disease stage (Table 1) (Committee, 2020; Zu *et al.*, 2020).

TABLE 1: Criteria for Clinical Severity of Confirmed Coronavirus COVID-19

Types	Mild	Moderate	Severe	Critical
Findings	Mild clinical symptoms [fever <38 (quelled without treatment), with or without cough, no dyspnea, no gasping, no chronic disease] No imaging findings of pneumonia	Fever, respiratory symptoms, imaging findings of pneumonia	Meet any of the followings: a. Respiratory distress, RR 30 times/min b. SpO ₂ <93% at rest c. PaO ₂ /FiO ₂ 300 mmHg* Patients showing a rapid progression (>50%) on CT imaging within 24- 48 hours should be managed as severe (added in the trial sixth edition)	Meet any of the followings: a. Respiratory failure, need mechanical assistance b. Shock c. Extra pulmonary organ failure, intensive care unit is needed.

Panel is adapted from WHO and data from (Jiang *et al.*, 2020) Abbreviations: RR: respiratory rate; SpO₂: oxygen saturation; PaO₂: partial pressure off oxygen; FiO₂: fraction of inspired oxygen

TRANSMISSION

On the basis of high number of patients that were exposed to the wet animal market in Wuhan City, where animals are routinely sold, it suggests that the virus have a zoonotic origin. Many efforts have been made to identify a reservoir host or intermediate carriers that spread the infection to the humans. Initial reports suggested two snake species that possibly can serve as a carrier host of the COVID-19. Up to date, there is no consistent prove of coronavirus carrier other than birds and mammals (Bassetti *et al.*, 2020; Ji *et al.*, 2020). Genomic sequencing of COVID-19 showed 88% similarity with two bat-derived severe acute respiratory syndrome (SARS)- like coronaviruses (Lu *et al.*, 2020; Wan *et al.*, 2020), it indicates that mammals are carrier link between COVID-19 and humans. Some reports have suggested that person-to-person spread is a route for spreading COVID-19 infection. This is supported by reports that occurred within families and between people who did not visit the wet animal market in Wuhan city (Carlos *et al.*, 2020; Wu *et al.*, 2020). Man, to man spread takes place primarily by direct contact or through droplets spread produced during coughing or sneezing from an infected person. In a survey conducted with women in their third trimester who were confirmed as a patient of coronavirus, there was no prove that there is transmission from mother to the next generation. However, all pregnant mothers give birth by cesarean sections, so it is still unclear whether transmission can occur during vaginal birth. This factor is important because pregnant mothers are relatively more sensitive to viral infection by respiratory pathogens and severe pneumonia. The first step of infection onset is binding of a receptor expressed by host cells followed by fusion with the cell membrane. It is reasoned that the epithelial cells of lung are the first target of the virus. Thus, it has been confirmed that person to person transmissions of SARS-CoV occurs with the successful attachment between the receptor-binding domain of virus spikes and the host cellular receptor which has been identified as angiotensin- converting enzyme 2 (ACE2) receptor (Jaimes *et al.*, 2020; Wan *et al.*, 2020). It is important that the sequence of the receptor-binding domain of COVID-19 spikes is similar to that of SARS-CoV. This report strongly suggests that entry to the host cells is most likely via the ACE2 receptor (Wan *et al.*, 2020).

PHYLOGENETIC ANALYSIS

The World Health Organization (WHO) has classified COVID-19 as a CoV of group 2B (Hui *et al.*, 2020). With the examination of nine patients, ten genome sequences of COVID-19 that exhibited 99.98% sequence identity (Lu *et al.*, 2020). Another report revealed that there is 99.8-99.9% nucleotide sequence similarity between the isolates from five different patients and the sequence results showed that the presence of a new beta-CoV strain (Ren *et al.*, 2020). The genome sequence of the COVID- 19 showed more than 80% similarity to SARS-CoV and 50% to the MERSCoV (Lu *et al.*, 2020; Ren *et al.*, 2020), and both SARS-CoV and MERS-CoV have been originated in bats (Cui *et al.*, 2019). So, the proves from the phylogenetic analysis shows that the COVID-19 belongs to the genus beta coronavirus, which includes SARS-CoV, that infects humans, bats, and wild animals. COVID-19 represents the seventh member of the coronavirus family, it infects humans and subfamily is orthocoronavirinae. The COVID-19 produce a clade within the subgenus sarbecovirus (Zhu *et al.*, 2020). On the basis of genome sequence identity and the phylogenetic reports, COVID-19 is different enough from SARS-CoV-2 and it can be known as a new beta coronavirus that attack humans. The COVID-19 has bat origin coronaviruses. With the aid of another prove that supports the COVID-19 is of bat origin is the existence of a high degree of homology of the ACE2 receptor from a diversity of animal species, thus implicating these animal species as possible intermediate hosts or animal models for COVID-19 infections (Wan *et al.*, 2020). Moreover, these viruses have one intact open reading frame located on gene 8, that is also an indicator of bat-origin CoVs. The sequence of amino acid of the tentative receptor-binding domain resembles that of SARS-CoV-2, also shows that these viruses might use the same receptor (Ren *et al.*, 2020).

THERAPEUTICS/TREATMENT OPTIONS

The man to man spread of COVID-19 infection led to the isolation of patients that were administered a variety of treatments (Lu, 2020). Till the date, we have no single specific antiviral therapy for CoVs and the main treatments are supportive. Recombination of IFN with ribavirin has limited effects against CoVs infection (Cinatl *et al.*, 2003). After the epidemics of SARS and MERS,

many great efforts have been devoted for the synthesis of new antivirals targeting CoVs proteases, polymerases, MTases, and entry proteins, however, none of them has been shown to be efficacious in clinical trials (Chan *et al.*, 2013; Cheng *et al.*, 2015; Wang *et al.*, 2015) antibodies and plasma that are obtained from the convalescent patients have been proposed for use in treatment (Mair *et al.*, 2015). In addition, various kinds of antiviral vaccine strategies, such as using subunit vaccines inactivated viruses, live-attenuated viruses, viral vector-based vaccines, recombinant proteins, and DNA vaccines, have been developed but they are tested only on animals so far (Graham *et al.*, 2013; Wit *et al.*, 2016). A report showed that the broad-spectrum antiviral remdesivir and chloroquine are very effective for the control of 2019-nCoV infection in vitro. These antiviral compounds have been evaluated in human patients with a safety track record. So, these therapeutic agents can be considered to treat COVID-19 infection (Wang *et al.*, 2020). As we have no effective therapy or vaccine, the best way now is to control or inhibit the source of virus spread, do early diagnosis, reporting, isolation, supportive treatments, and timely publishing epidemic information to avoid unnecessary panic. For us, good personal hygiene, good fitted mask, ventilation, and avoiding to go out in crowded places will help to prevent CoVs infection (Chen *et al.*, 2020). Many groups of good scientists are currently working hard to synthesize a nonhuman primate model to study COVID-19 infection to establish fast track novel therapeutics and for the evaluation of potential vaccines in addition to providing a better understanding of virus-human host interactions (Rothan and Byrareddy, 2020).

FUTURE CHALLENGES

The extensive precautions to inhibit man to man transmission of COVID-19 to control the current epidemic. We should make special attention and efforts to inhibit or reduce spread in susceptible populations including mainly children, health care providers, and old people (Jin *et al.*, 2020). The early cases of death due to COVID-19 epidemic occurred initially in old age people, because of having a weak immune system that allow faster establishment of viral infection (Li *et al.*, 2020; Wang *et al.*, 2020). Public services and facilities should provide decontaminating reagents for cleaning hands more often than normal routine. Moreover, physical contact with contaminated things should be considered in dealing with the virus, such as fecal and urine material which are potential sources of virus spread (Lee *et al.*, 2003; Assiri *et al.*, 2013). Whole world including China and US have implemented major precautions and inhibitory measures including travel screenings to control further spread of the virus (Carlos *et al.*, 2020). COVID-19 has not only created major health issues, but also created virtual boundaries that isolated China from rest of the world. This disease has been created medical emergency in the whole world, thus badly affected the international travelling, tourism and trade. The efficient and quick responses were taken by centers for disease control as a preventive measure to restrict and overcome this novel disease (Ji *et al.*, 2020).

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