

Covid-19-A Dreaded Pandemic Disease

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Abstract: *The emergence of new COVID-19 by the severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) create great public health crises in the world. Its genome sequence analysis indicated that the virus originated in bats and was transmitted to humans through yet unknown intermediary animals in Wuhan, Hubei province, China in December 2019. There have been millions of confirmed cases of Corona virus disease 2019 (COVID-19) and thousands of deaths have been reported. The disease is transmitted by inhalation or contact with infected droplets and the incubation period ranges from 2 to 14 days. The symptoms are usually fever, cough, sore throat, breathlessness, fatigue, malaise among others. The disease is mild, moderate and severe forms in different age group of immunocompromised people. It may progress to pneumonia, acute respiratory distress syndrome (ARDS) and multi organ dysfunction. Many people are asymptomatic. The case fatality rate is estimated to range from 2 to 3%. Diagnosis is by demonstration of the virus in nasal as well as throat secretions by special molecular tests. Common laboratory findings include normal/ low white cell counts with elevated C-reactive protein (CRP). The computerized tomographic chest scan is usually abnormal even in those with no symptoms or mild disease. Treatment is essentially supportive and role of antiviral agents is yet to be established. Prevention entails home isolation of suspected cases and those with mild illnesses and strict infection control measures at hospitals that include contact and droplet precautions. The virus spreads faster than its two ancestors the SARS-CoV and Middle East respiratory syndrome corona virus (MERS-CoV), but has lower fatality. The global impact of this new epidemic is yet uncertain.*

Keywords: COVID-19, origin, Phylogenetic relationship, SARS-CoV, MERS-CoV, Transmission, Symptoms, Therapeutics, Prevention and Control methods.

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I. Introduction

Whole world is facing a great challenge due to pandemic occurrence of Corona viral infection i.e; the disease called COVID-19. All the 209 affected countries are in Lockdown situation. Species jumped mutated SARS-CoV2 is such a dangerous viral agent which is completely novel in the sense that its pathogenesis, vaccine and treatment is not adequately understood. According to the World Health Organization, the first confirmed COVID-19 case in China was on December 8, but the global body does not track the disease itself but relies on nations to provide such information. Thousand of confirmed cases of Corona virus disease 2019 (COVID-19) and hundreds of deaths are being reported in world daily[1]. In India also several hundred active cases and deaths has been reported [2]. The human-to-human transmission of the SARS-CoV-2 created an alert with the increasing number of cases. The origin of this pandemic infection is in Wuhan city of Hubei province of China, from there the disease COVID-19 spread to the rest of the world and created global health crisis [3].

General characteristics of Corona viruses

Corona viruses (CoVs) are members of the family Coronaviridae, the enveloped helical viruses that possess extraordinarily large single-stranded RNA genomes ranging from 26 to 32 kilo bases in length [4]. Initially, the virus was associated with human and animal infections that caused intestinal as well as mild respiratory infections [5, 6]. Corona viruses have been detected in both avian hosts and various mammals, including bat, camels, dogs and masked palm civets. Earlier it was regarded as pathogens that only cause mild diseases in the immunocompetent people until the emergence of the corona virus causing severe acute respiratory syndrome (SARS-CoV) in 2002-03 [7-10]. Currently, at least seven corona virus species are known to cause diseases in humans. The viruses of 229E, OC43, NL63 and HKU1 only cause common cold symptoms, which are mild. Severe illness can be caused by the remaining three viruses, namely SARS-CoV, which resulted

in the outbreak of SARS in 2002 and 2003 [7, 8]; the corona viruses that are responsible for the Middle East respiratory syndrome (MERS-CoV), which emerged in 2012 and remains in the circulation in camels [11]; and SARS-CoV-2, the viruses emerged in December 2019 in Wuhan of China [6].

Virus isolation and genomic characterization of the complete sequence of the virus through next-generation sequencing (NGS), identified it as a novel CoV, named 2019-nCoV [6]. The virus characterization revealed that it is an enveloped RNA virus with a genome size of 29,903 bp. The phylogenetic analysis of the sequence showed that it belonged to the *Sarbecovirus* subgenus of genus *Betacoronavirus* and the family *Coronaviridae*. The sequence was closely related (~87.5% sequence similarity) to two bat-derived SARS-like CoV strains (bat-SL-CoVZC45 and bat-SL-CoVZXC21) that are known to infect humans, including the virus which led to the 2003 SARS-CoV-1 outbreak [13]. Based on phylogeny, taxonomy and established practice, the Corona virus Study Group (CSG) of the International Committee on Taxonomy of Viruses (ICTV), formally recognizes this virus as a sister to severe acute respiratory syndrome corona viruses (SARS-CoVs) as species of Severe acute respiratory syndrome-related corona virus and designated it as severe acute respiratory syndrome corona virus 2 (SARS-CoV-2). Therefore, the 2019-nCoV is now named as SARS-CoV-2 virus [14]. Further, based on SimPlot analyses, it was demonstrated that SARS-CoV-2 was more closely related to the BatCoV RaTG13 sequence (~96.3% similarity) throughout the genome. The bat-SL-CoVZC45 and bat-SL-CoVZXC21 strains clustered differently from the group formed by SARS-CoV-2 and BatCoV RaTG13 in the region spanning the 3'-end of open reading frame (ORF)1a, the ORF1b and almost half of the spike region [15]. The receptor-binding domain (RBD) of the spike protein mediates interaction with the host cell receptor [16], and the angiotensin-converting enzyme 2 (ACE2) has been identified as the receptor for the SARS-CoVs [17]. Specific mutations in the RBD of the SARS-CoV-2 spike glycoprotein were found to have enhanced binding to the ACE2 [18]. As per WHO-CHINA joint mission on Covid 19 final report 16-24 February 2020 stated that virus was isolated by culturing in various cell lines such as human airway epithelial cells, Vero E6, and Huh-7. Cytopathic effects (CPE) were observed 96 hours after inoculation. Typical crown-like particles were observed under transmission electron microscope (TEM) with negative staining. The cellular infectivity of the isolated viruses could be completely neutralized by the sera collected from convalescent patients. Transgenic human ACE2 mice and Rhesus monkey intranasally challenged by this virus isolate induced multifocal pneumonia with interstitial hyperplasia. The COVID-19 virus was subsequently detected and isolated in the lung and intestinal tissues of the challenged animals [19].

Origin of Covid 19

In December 2019, adults in Wuhan, capital city of Hubei province and a major transportation hub of China started presenting to local hospitals with severe pneumonia of unknown cause. Many of the initial cases had a common exposure to the Huanan wholesale seafood market that also traded live animals. The surveillance system (put into place after the SARS outbreak) was activated and respiratory samples of patients were sent to reference labs for etiologic investigations. On December 31st 2019, China notified the outbreak to the World Health Organization and on 1st January the Huanan sea food market was closed. On 7th January the virus was identified as a corona virus that had >95% homology with the bat corona virus and > 70% similarity with the SARS-CoV. Environmental samples from the Huanan sea food market also tested positive, signifying that the virus originated from there. The number of cases started increasing exponentially, some of which did not have exposure to the live animal market, indicative of the fact that human-to-human transmission was occurring. The first fatal case was reported on 11th Jan 2020. The massive migration of Chinese during the Chinese New Year fuelled the epidemic. Cases in other provinces of China, other countries (Thailand, Japan and South Korea in quick succession) were reported in people who were returning from Wuhan. Transmission to healthcare workers caring for patients was described on 20th Jan, 2020. By 23rd January, the 11 million population of Wuhan was placed under lock down with restrictions of entry and exit from the region. Soon this lock down was extended to other cities of Hubei province. Cases of COVID-19 in countries outside China were reported in those with no history of travel to China suggesting that local human-to-human transmission was occurring in these countries. Airports in different countries including India put in thermal screening mechanisms to detect symptomatic people returning from China and placed them in isolation and testing them for COVID-19. Soon it was apparent that the infection could be transmitted from asymptomatic people and also before onset of symptoms. Therefore, countries including India who evacuated their citizens from Wuhan through special flights or had travelers returning from China placed all people symptomatic or otherwise in isolation for 14 days and screened them for the virus [20].

Phylogenetic relationship of Covid-19 with other corona viruses-

COVID-19 represents the seventh member of the corona virus family that infects humans and has been classified under the orthocoronavirinae subfamily. The COVID-19 forms a clade within the subgenus sarbecovirus [12]. As per the WHO-China joint mission report Whole genome sequencing analysis of 104

strains of the COVID-19 virus isolated from patients in different localities with symptom onset between the end of December 2019 and mid-February 2020 showed 99.9% homology, without significant mutation. Bioinformatic analyses indicated that the virus had features typical of the corona virus family and belonged to the Betacoronavirus 2B lineage. Alignment of the full-length genome sequence of the COVID-19 virus and other available genomes of Betacoronavirus showed the closest relationship was with the bat SARS-like coronavirus strain BatCov RaTG13, identity 96%. Indian SARS-CoV-2 clustered with the *Sarbecovirus* subgenus of the *Betacoronavirus* genus and was closest to the BatCoV RaTG13 sequence (96.09% nt). The Indian SARS-CoV-2 viruses were positioned in different clusters. The phylogeny revealed emerging heterogeneity within the SARS-CoV-2 sequences globally [15,19, 21]. Based on the genetic sequence identity and the phylogenetic reports, COVID-19 is sufficiently different from SARS-CoV and it can thus be considered as a new betacoronavirus that infects humans. The COVID-19 most likely developed from bat origin coronaviruses. Another piece of evidence 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 [18]. Moreover, these viruses have a single intact open reading frame on gene 8, which is a further indicator of bat-origin CoVs. However, the amino acid sequence of the tentative receptor-binding domain resembles that of SARS-CoV, indicating that these viruses might use the same receptor [12].

Transmission

Finding of large number of infected people from the wet animal market of Wuhan City where live animals are routinely sold. It is suggested that this is the likely zoonotic origin of the COVID-19. Efforts have been made to search for a reservoir host or intermediate carriers from which the infection may have spread to humans. Initial reports identified two species of snakes that could be a possible reservoir of the COVID-19. However, to date, there has been no consistent evidence of corona virus reservoirs other than mammals and birds [22,23]. Genomic sequence analysis of COVID-19 showed 88% identity with two bat-derived severe acute respiratory syndrome (SARS)-like corona viruses [13,24], indicating that mammals are the most likely link between COVID-19 and humans. Several reports have suggested that person-to-person transmission is a likely route for spreading COVID-19 infection. This is supported by cases that occurred within families and among people who did not visit the wet animal market in Wuhan [13, 21]. Person-to-person and surface to person transmission occurs primarily via direct contact or through droplets spread by coughing or sneezing from an infected individual.

The binding of a receptor expressed by host cells is the first step of viral infection followed by fusion with the cell membrane. It is reasoned that the lung epithelial cells are the primary target of the virus. Thus, it has been reported that human-to-human transmissions of SARS-CoV occurs by the binding between the receptor-binding domain of virus spikes and the cellular receptor which has been identified as angiotensin-converting enzyme 2 (ACE2) receptor. Importantly, the sequence of the receptor-binding domain of COVID-19 spikes is similar to that of SARS-CoV. This data strongly suggests that entry into the host cells is most likely via the ACE2 receptor [24].

Maintenance of COVID-19

Cases of COVID-19 first reported from the Wuhan Metropolitan in People's Republic of China, in December 2019 and presently assumed the status of Pandemic. It is now observed that all ages are susceptible. Infection is transmitted through large droplets generated during coughing and sneezing by symptomatic patients but can also occur from asymptomatic people and before onset of symptoms [25]. Studies have shown higher viral loads in the nasal cavity as compared to the throat with no difference in viral burden between symptomatic and asymptomatic people [26]. Patients can be infectious for as long as the symptoms last and even on clinical recovery. Some people may act as super spreaders; a UK citizen who attended a conference in Singapore infected 11 other people while staying in a resort in the French Alps and upon return to the UK [1]. When asymptomatic affected people move from one place to another or address the large gathering/meeting, owing to these activities they spread the infectious disease very rapidly, for example increasing the number of covid-19 positive cases in India due to activities of Tableegi community people. These infected droplets can spread 1–2 m and deposit on surfaces. The human corona virus can remain viable on surfaces of fomites as Steel, Aluminum, Metal, Wood, Paper, Glass, Plastics, Surgical gloves, Disposable gown etc. for from 2 hours to 9 days in favourable atmospheric conditions (Temperature, relative humidity and the inocula) but are destroyed in less than a minute by common disinfectants like sodium hypochlorite, Ethanol, Benzalkonium chloride, hydrogen peroxide etc. [27]. Infection is acquired either by inhalation of these droplets or touching surfaces contaminated by them, handshake and then touching the nose, mouth and eyes. Extra-pulmonary detection of viral RNA does not mean infectious virus is present, further positive viral culture suggests the possibility of salivary gland infection and possible transmission. More recently, 2 independent laboratories from China declared that they

have successfully isolated live 2019-nCoV from the stool of patients [48]. Taken together, a growing number of clinical evidence reminds us that digestive system other than respiratory system may serve as an alternative route of infection when people are in contact with infected wild animals or sufferers, and asymptomatic carriers or individuals with mild enteric symptoms at an early stage must have been neglected or underestimated in previous investigations. Clinicians should be careful to promptly identify the patients with initial gastrointestinal symptoms and explore the duration of infectivity with delayed viral conversion [20, 28]. As per current information, transplacental transmission from pregnant women to their fetus has not been described. However, neonatal disease due to post natal transmission is described [29]. The incubation period varies from 2 to 14 days [median 5 days]. Studies have identified angiotensin receptor 2 (ACE2) as the receptor through which the virus enters the respiratory mucosa. COVID-19 remains a highly infectious disease, with reproductive number (R0) estimates ranging from 1.4 to 3.5. The early WHO estimate of R0 was 1.4 to 2.5. Preliminary studies, conducted at the beginning of the outbreak, reported higher estimates of R0, in the range of 2.24-3.58 [1, 30, 31]

Symptoms and sign

The clinical symptoms of COVID-19 are varied, ranging from asymptomatic state to acute respiratory distress and multi organ dysfunctions. The symptoms of COVID-19 infection appear after an incubation period of approximately 5.2 days [32]. The period from the onset of COVID-19 symptoms to death ranged from 6 to 41 days with a median of 14 days. This period is dependent on the age of the patient and status of the patient's immune system. It was shorter among patients >70-years old compared with those under the age of 70 [33]. The most common symptoms at onset of COVID-19 illness are fever (not in all), cough, sore throat and fatigue, while other symptoms include sputum production, headache, haemoptysis, diarrhoea, dyspnoea, and lymphopenia [12,32-34,35]. Clinical features revealed by a chest CT scan presented as pneumonia, however, there were abnormal features such as RNAemia, acute respiratory distress syndrome (ARDS), acute cardiac injury, and incidence of multiple peripheral ground-glass opacities in the lungs that led to death. It is important to note that there are similarities in the symptoms between COVID-19 and earlier betacoronavirus such as fever, dry cough, dyspnea, and bilateral ground-glass opacities on chest CT scans. However, COVID-19 showed some unique clinical features that include the targeting of the lower airway as evident by upper respiratory tract symptoms like nasal congestion, runny nose, sneezing, and sore throat [36]. In addition, the chest radiographs upon admission, some of the cases show an infiltrate in the upper lobe of the lung that is associated with increasing dyspnoea with hypoxemia [37]. Importantly, whereas patients infected with COVID-19 developed gastrointestinal symptoms like diarrhoea, a low percentage of MERS-CoV or SARS-CoV patients experienced similar GI distress. Therefore, it is important to test faecal and urine samples to exclude a potential alternative route of transmission, specifically through health care workers, patients etc. Therefore, development of methods to identify the various modes of transmission such as faecal and urine samples are urgently warranted in order to develop strategies to inhibit and/or minimize transmission and to develop therapeutics to control the disease.

Diagnosis

A suspect case is defined as one with symptoms like fever, runny nose, sore throat and cough who has history of travel to China or affected countries or other areas of persistent local transmission or contact with patients with similar travel history or those with confirmed COVID-19 infection. However cases may be asymptomatic or even without fever. A confirmed case is a suspect case with a positive molecular test. Specific diagnosis is by specific molecular tests on respiratory samples (throat swab/ nasopharyngeal swab/ sputum/ endotracheal aspirates and bronchoalveolar lavage). Virus may also be detected in the stool and in severe cases, the blood. In a suspect case in India, the appropriate sample has to be sent to designated reference labs in India or the National Institute of Virology in Pune. As the epidemic progresses, commercial tests will become available. Other laboratory investigations are usually non specific. The white cell count is usually normal or low. There may be lymphopenia; a lymphocyte count <1000 has been associated with severe procalcitonin levels are usually normal. A high procalcitonin level may indicate a bacterial co-infection. The ALT/AST, prothrombin time, creatinine, D-dimer, CPK and LDH may be elevated and high levels are associated with severe disease. The chest X-ray (CXR) usually shows bilateral infiltrates but may be normal in early disease. The CT is more sensitive and specific. CT imaging generally shows infiltrates, ground glass opacities and sub segmental consolidation. It is also abnormal in asymptomatic patients/ patients with no clinical evidence of lower respiratory tract involvement. In fact, abnormal CT scans have been used to diagnose COVID-19 in suspect cases with negative molecular diagnosis; many of these patients had positive molecular tests on repeat testing [38-40]. The WHO and CDC have both issued guidance on key clinical and epidemiological findings suggestive of a COVID-19 infection. Extensive laboratory tests should be requested for patients with suspected infection. Patients may present with an elevated C-reactive protein, erythrocyte sedimentation rate, lactate dehydrogenase, creatinine, and a prolonged prothrombin time [41, 42]. Full genome sequencing and phylogenetic analysis on fluid from bronchoalveolar lavage can confirm COVID-2019 infection [6].

Investigations for other respiratory pathogens should also be performed. Under Differential Diagnosis covid-19 can be distinguished from other pneumonia causing viruses such as influenza, parainfluenza, respiratory syncytial virus, adenovirus, other corona viruses and also from mycoplasma pneumonia, chlamydia pneumonia, and bacterial pneumonia. CT scan, blood profile, laboratory findings, travel history etc may help to differentiate the Covid-19 patients.

Therapeutics

At present, no approved treatment is available for COVID-19 and only treatments are essentially supportive and symptomatic. The first step is to ensure adequate isolation to prevent transmission to other contacts, patients and healthcare workers. Mild illness should be managed at home with counseling about danger signs. The usual principles are maintaining hydration and nutrition and controlling fever and cough. In hypoxic patients, provision of oxygen through nasal prongs, face mask, high flow nasal cannula (HFNC) or non-invasive ventilation is indicated. Mechanical ventilation and even extra corporeal membrane oxygen support may be needed. This should be at 5 L/min to reach SpO₂ targets of $\geq 90\%$ in non-pregnant adults and children, and $\geq 92-95\%$ in pregnant women [30–32]. Detailed guidelines for critical care management for COVID-19 have been published by the WHO [43]. Antiviral drugs such as lopinavir/ritonavir combination therapy for laboratory-confirmed COVID-19 patients [44], Remdesivir, a broad spectrum anti RNA drug developed for Ebola in management of COVID-19 [45], arbidol (an antiviral drug available in Russia and China), and intravenous immunoglobulin, interferons, hydroxychloroquine and plasma of patients recovered from COVID-19. Herbal treatments against COVID-19 are used as per the affected countries own guidelines. More evidences are needed before these drugs are recommended for use against COVID-19.

Prevention and Control methods

Since there is no approved treatment available presently for Covid-19 disease, hence in that situation effective prevention and control measures are very crucial. Through Screening for suspected cases at individual or community level, Isolation and quarantine are followed as per the guideline of World Health Organization [46] as well as concerned authority of respective countries. Preventive measures such as maintaining social distancing for breaking human to human or surface to human chain of disease transmission may be implemented. For adopting social distancing complete lockdown is one of the important panacea for restriction of the infection spread, demarcation and containment of hot spot areas, categorization into three different zones- Red, Orange and Green zones as per government directives. Personal hygienic measures such as regular vigorous hand washing, sanitization with alcohol based sanitizers, wearing of suitable mask, and personal protective equipments especially for health workers, nurses, lab workers, doctors etc. should be followed. Since COVID-19 is an emerging disease, hence after the ending of outbreak the possibility of re-emergence cannot be ruled out. It may occur in another form.

II. Conclusions

Covid-19 disease outbreak has challenged the economic, medical and public health infrastructure. Scientists and researchers of the globe are working very hard to find out its appropriate mitigation methods including treatment and suitable vaccine. I hope very soon we will conquer on the enemy of mankind and may resume the normal situation till then preventive measures should be properly followed.

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