

A COMPREHENSIVE REVIEW ON COVID-19

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Abstract

Covid-19, a highly contagious disease with its epicentre in Wuhan, China, caused by coronavirus which is an enveloped RNA virus found diversely in human and wildlife. WHO has declared this outbreak as public health emergency of international concern. Almost 14,761,814 cases have been identified across the world as on 19 July 2020. The damage mechanism of disease is still unclear. This review will introduce and systematically summarizes the origin and spread of disease along with its epidemiology, pathogenesis, clinical characters with different stages, diagnosis and treatment strategies. This is expected that this review will be helpful for the public in recognising and deal with threatening disease and can also provide a reference for further studies. It will also provide a means to raise awareness about the pandemic among the public and healthcare.

Key words: World Health Organisation (WHO), CoVid: Corona Virus Disease, PRC (Prevention Research Centre), SARS-CoV-2 (Severe Acute Respiratory Syndrome Corona virus 2), ACE (Angiotensin Converting Enzyme), RAS (Renin Angiotensin System), SARS (Severe Acute Respiratory Syndrome).

Introduction

In last of December 2019, some cases of pneumonia were reported with an unidentified aetiology and most of these cases have a similar history of exposure to the Huanan Seafood wholesale market, Wuhan city, Hubei province, China and its clinical symptoms were relatively close to viral pneumonia.[1] After deep sequencing studies and investigation of respiratory samples by the experts at the PRC (prevention research centres) for disease control had declared the cause of pneumonia as a novel virus which was a strain of corona. It was initially reported to the WHO on December 31, 2019. On January 30, 2020, the WHO declared the COVID-19 outbreak a global health emergency. Later on, 11 Feb 2020, the International Committee of Taxonomy of Viruses named this virus as SARS-CoV-2 (Severe Acute Respiratory Syndrome Corona virus 2). Later SARS-CoV-2 was termed COVID-19 by WHO, the acronym derived from “corona virus disease 2019”.[2] The name was chosen to avoid stigmatizing the virus’s origins in terms of population, geography or animal association. From last of December till 5th March 2020, around 96000 cases were found across the world and approximately 3300 deaths were also reported due to this viral infection. In India, about 29 cases were reported till 5th March. Currently, Covid-19 has been declared as pandemic due to its wide spread infectivity as well as high contagion rate and become a Public Health emergency of International concern and WHO has also stated its threat status to “highest level”.[3]

Corona virus is not a single virus in itself, but it’s a large family of single stranded RNA positive viruses, belongs to Nidovirales order and beta (β)-corona family, which is accountable for 5-10% acute respiratory tract infections. There is an exponential increase in number of cases reflecting its human to human transmission. Infection is spread through droplets of symptomatic patients during cough and sneezing and the virus can keep on for approx 3 hours and can be detectable for 72 hours from the affected surface. Its transmission may also be possible through fecal excretion route of SARS-CoV and MERS.[4] This has been reported that SARS CoV-2 infected patients have gastrointestinal symptoms as well as viral RNA can be present in feces of some patients. In China, eight out of ten paediatric CoVid-19 patients found positive swabs for SARS-CoV-2 even after negative nasopharyngeal tests. [5] In another study, 39 patients out of 73 are also found for SARS-CoV-2 in stool samples. Among these 39, 17 patients are still found positive stool test even after a negative nasopharyngeal sample. [6] This ranges from 60 nm to 140 nm in diameter with spike like projections on its surface giving it crown like structure and hence named “corona virus”. The four main viruses from its family named as HKU1, NL63, 229E and OC43 generally responsible for causing mild respiratory disease. Since the last two decades, this is third time of emergence when beta corona has resulted in severe viral diseases. The first case of infection was traced in 2002 and 2003 when a new corona virus from beta family originated from bats crossed over to humans in China and declared as severe acute respiratory syndrome (SARS). Due to this corona virus, around 8422 people were affected with 916 deaths with a mortality rate of 11% across worldwide. Then in year 2012, Middle East Respiratory Syndrome corona virus (MERS CoV) emerged in Saudi Arabia that affected 2494 people and 858 deaths. This was also originated from bats. But this new corona virus (COVID-19) has become a world-wide health threat in just couple of months. [7], [3] The spike protein on SARS-CoV anchors to ACE 2 receptors, located in lungs, kidneys and vascular beds and through these sites can enter into the host cell. As SARS-CoV and SARS-CoV-2 both are initiated from China, due to which it can be hypothesized that Asians might be more prone to this infectious virus. This is also reported that ACE2 remains same among all Asians and other races, increases with increase of age but sex doesn’t matter in any manner. Thus, there is not any evidence for any relation between ethnicity and susceptibility of SARS-CoV infection. [8]

Role of RAS (Renin Angiotensin System) Inhibitors in COVID:

Like SARS-CoV, SARS-CoV-2 also binds to ACE2 receptors in epithelial cells of lung, kidney, intestine and blood vessels and enters in host cell. Most of the diabetic or hypertensive patients in India are either on ACE inhibitors or on ARBs (Angiotensin receptor blockers) and hence may lead to modulation of ACE2. Hence, this would boost up the infection with COVID-19, but there is no strong authentication of COVID-19 susceptibility and ACE inhibitors.^[8] Contrary, a study reported that RAS inhibitors improve the clinical outcomes in COVID-19 hypertensive patients. As per this study, ACE inhibitors and angiotensin receptor blockers weaken the inflammation due to IL-16 reduction. Also there is an increase in CD3 and CD8 T cell counts in peripheral blood. [9]

Severe complications are observed in patients with diabetes, hypertension, chronic kidney disease and coronary artery disease, who were on ACE inhibitors and ARBs. [1] Hence, exact conclusion of role of these drugs cannot be made with current evidences.

Origin and spread

First Covid-19 clusters were reported in a metropolitan city of China, Wuhan in late December 2019, which spread very quickly in the other parts of the China as well as spread worldwide. During early stages, more than half patients had the contact history of Huanan seafood wholesale market and so the virus is thought to have a zoonotic origin. Later it was postulated that the origin of Covid-19 in Wuhan was closely related to bat corona viruses, pangolin corona viruses and SARS CoV. [10]

The scientific consensus is that COVID-19 has a natural origin. The probable bat-to-human infection may have been among processing bat carcasses and guano in the production of traditional Chinese medicines.^[10]

Later the numbers of positive cases grew exponentially, some of which didn't even have any visiting history to seafood market that symbolic the transmission of this virus through human to human. The first fatal case was reported on 11th Jan 2020. Immense movement of Chinese people on Chinese New Year works as a fuel for the epidemic, followed by quick succession of positive cases in other countries (Thailand, Italy, France and South Korea etc.) as well from the people returning from Wuhan.[11]

Initial transmissions to healthcare workers were reported on 20th Jan 2020 and then by 23rd Jan, about 11 million population of Wuhan was kept under restrictions and not allowed to enter or exit from their region. These lockdown restrictions were then extended to other cities of China too and soon to other countries as well. The airports of different countries put forward to the screening procedure as there were the risk of human to human transmission and the people were kept under quarantine. [10] Positive cases were increasing exponentially leading to almost 15000 new cases worldwide each day, 96000 total confirmed cases among which 80000 cases were from China only as on 03rd March 2020. Lately the numbers of cases in China were reduced but still increasing exponentially in other countries. India has reported only 3 cases till 2nd March 2020 but a sudden growth was seen and most of the cases were highlighted from Jaipur, Delhi and Agra those who came in contact with the foreign tourists. [11]

Comparative exploration of origin and spreading of corona viruses

The Chinese population were infected with SARS (Severe Acute Respiratory Syndrome) in 2003 in Guangdong. The virus was detected as member of beta coronavirus and was named as SARS-CoV. The infected patients have revealed the pneumonia like symptoms along with presence of alveolar injury that leads to acute respiratory distress syndrome (ARDS). SARS was initially originated in Guangdong and then spread widely with more than 8000 infected cases and 776 deceased. [12], [13] Within ten years of SARS, in 2012, some Arabian countries were found infected with another type of coronavirus. The virus was detected as the Middle East Respiratory Syndrome (MERS-CoV). As per WHO, 2428 individuals were infected and 838 were deceased with the virus. MERS-CoV originates from a mild upper respiratory inflammation, which leads to severe respiratory disease. Symptoms of MERS- CoV are also similar to SARS-CoV, as both shows pneumonia, followed by ARDS and renal failure. [14] Now, in the end of 2019, Chinese government informed about cases of pneumonia with an unknown etiology. Further, on 12 January National Health Commission of China gave details of epidemic regarding viral pneumonia. The virus was analysed as a novel coronavirus. Moreover, the investigations showed that some infected individuals even don't have any history of visiting seafood market, from where this virus was originated. [15] The figure given below shows the global outbreaks of SARS-CoV, MERS-CoV and COVID-19.



Epidemiology

Generally, all age groups are susceptible with this pathogen that primarily targets the human respiratory system. But 25-50% of COVID infected patients has one or more underlying diseases, including hypertension, diabetes, chronic obstructive pulmonary disease, cardiovascular diseases and has low immunity. Infections are generally transmitted person to person through small droplets from the nose or mouth which is expelled when a person with COVID-19 coughs, sneezes, speaks or direct contact. These droplets are relatively heavy, do not travel far and quickly sink to the ground. These droplets can land on objects and surfaces around the person such as tables, doorknobs and handrails. People can also infect by touching these objects or surfaces, then touching their eyes, nose or mouth. In addition, several studies reported faecal-mouth pathway may also potential way for the transmission. But trans-placental transmission from pregnant women to their foetus is not proved yet. [16], [17]

According to the research, during the first stage virus is present in nasal cavity and throat and there is not any difference in viral burden in symptomatic and asymptomatic peoples. A patient can infect other peoples as long as their symptoms last and even till complete its clinical recovery. Some people can turn as upper spreader whereas, some are not. The virus present in the droplets can be active for many days if the atmospheric conditions are favourable to them but, can be demolished in less than a minute in presence of disinfectants. [17][18]

Pathogenesis

COVID-19 can be divided into three phases on the basis on the cells that likely infected have different clinical stages of the disease.

- Stage 1: asymptomatic state (initial 1-2 days of the infection):** this inhaled virus binds the epithelial cells in the nasal cavity and starts replicating. ACE₂ is the main receptor which is conducting airway cells. In this stage the virus can be detected by nasal swab, where the viral burden may low.[19]
- Stage2: upper airway and conducting airway response (next few days):** this virus propagates and migrates down the respiratory tract along conducting airways, and a more robust innate immune response is triggered. Nasal swabs or sputum should yield the virus as well as early markers of the innate immune response. About 8-% of the infected patients have mild and mostly restricted to the upper conducting airways.[20]
- Stage 3: hypoxia, ground glass infiltrates, and progression to ARDS:** about 20% of the infected person will progress to stage 3 disease and develop infiltrates and some of these will develop very severe disease. The fatality and morbidity rate of mild and asymptomatic cases is better defined. The virus reaches the gas exchange units of the lungs and infects alveolar type II cells, which results alveolar damage with fibrin rich hyaline. [20], [21]

Case definitions

Different types of cases are defined by WHO as per the interim guidance documents. The types of cases generally diagnosed worldwide are given below:

- SARI:** An acute respiratory infection with a history of fever $\geq 38^{\circ}\text{C}$ and cough; onset within the last for 10 days and patient requiring hospitalization.[22]
- Surveillance case:** Any patient with SARI with history of fever and cough remaining admission to hospital with no other aetiology, either travel history to Wuhan, China in last 14 days or patient is a health care worker (HCW), caring for SARI patients.[23]
- Acute respiratory illness:** Any patient either having close contact with confirmed or probable case of COVID-19 in last 14 days or worked or attended a health care facility in 14 days before onset of symptoms where confirmed cases are hospitalized.[24]

- Community based surveillance:** The outcome is yet to be ascertained systematically. These are patients without any travel history and symptoms as well. [25]

Clinical presentation

COVID-19 manifests a broad range of clinical spectrum that lies from asymptomatic state to acute respiratory syndrome, septic shock or even multiorgan failure. On the basis of severity of disease COVID-19 is classified as:

- Mild:** This covers the patients with upper respiratory tract viral infection. Symptoms include dry cough, mild fever, sore throat, nasal congestion, and headache and muscle pain. Mild patients can quickly deteriorate into severe or critical cases. Majority (81%) of cases are mild in severity.[26]
- Moderate:** These are patients with respiratory symptoms of cough, shortness of breath and tachypnoea.
- Severe:** This category covers the patients with severe pneumonia, acute respiratory distress syndrome (ARDS), septic shock, severe dyspnoea, tachypnoea (respiratory rate >30/minute). Fever can be absent or moderate. 5% of patients can develop to critical stage with symptoms like respiratory failure, RNAaemia, cardiac injury or multiple organ failure. According to studies, case fatality rate for critical patients is approx. 49%. [27], [28]
- Acute respiratory distress Syndrome (ARDS):** This category indicates onset of worsening respiratory distress or even failure. Radiograph features (CT scan, Xray or lungs ultrasound) can be used for diagnosis. Multiorgan failure may take place with symptoms include severe dyspnoea, low oxygen saturation, reduced urine output, tachycardia, cold extremities, hypotension and altered mutation.[29] Apart from the above categories and symptoms of each class, other common clinical manifestations are also there that we should keep in mind. Conjunctivitis has also been observed in some cases. In some mild cases, by the end of first week of disease pneumonia progression, respiratory failure and death can also be seen. This progression is associated with sudden increase in inflammatory cytokines like IL-2, IL-7, IL-10 and TNF- α . [30], [31]

Diagnosis

Basically, the standard procedure for diagnosis of COVID-19 is to detect the presence of viral nucleic acid. The virus has low sensitivity and hence there are chances false negative results. So, the novel coronavirus diagnosis and treatment plan considers the suspected cases and takes the essential steps for prevention and diagnosis. The suspected cases are then observed and tested and those cases whose reports will come positive will be considered as confirmed cases. Specific molecular tests on respiratory samples are carried out like throat swab, nasopharyngeal swab, sputum and bronchoalveolar lavage etc. In severe cases virus may be detected in stool also.[22] The clinical samples collected from suspected cases are then labelled (with demographic details, date, time and anatomical site) and evaluated viral RNA by polymerase chain reaction (PCR). The test is recommended to repeat in case of negative result with a strong clinical suspicion. As per WHO recommendation, culture tests are to be done in BSL-3 labs and the PCR must be done in BSL-2 labs. Charite Berlin was the first to develop the assay of PCR as well the standardisation of protocol. Lungs imaging is also considered in severe cases with a specific progression of > 50% lesions in 24-48 hours.[32]

Disease management

Management of COVID-19 basically consists of prevention and treatment phase.

Preventive measures

There is not approved treatment for this infection till date and that's why, its prevention is very crucial. SARS-CoV-2 generally spreads from respiratory droplets and physical contact. So, to prevent the transmission, precautionary measure such as hand hygiene, personal protective equipment (PPE) along with cough and sneezing etiquettes are must. Hand hygiene must be carried out with alcohol-based hand rubs having 60-80 % ethanol.[33] Timely handwash is to be done by following the correct steps with soap and water. Cloth towel should be avoided for drying of hands and disposable tissue papers are to be preferred. For droplet and physical contact transmission, masks with head straps should be used. Face shields and shoe covers should be used by all health care workers (HCWs). Isolation of confirmed or suspected cases with mild disease is recommended. Enough ventilation must be there for destruction of virus. At community level, people must avoid handshake, crowded areas and non-essential travel to places where transmission has been already present. [34], [35]

Drug Treatment

As there is no registered anti-viral medication or vaccine till date for treatment this infection. Therefore, the treatment generally includes symptomatic and supportive care. First step to be taken is to ensure proper isolation to prevent the further transmission to other people like HCWs, patients and family members. Along with the suspected cases, entire population must minimize the social contacts and the time spent outside. [36] To ensure the availability of beds for severe cases, mild cases must be isolated at home only, maintaining proper hydration and nutrition and symptomatic treatment like fever, sore throat and cough. Several clinical trials are underway for the treatments possible on the basis of immunomodulatory drugs, anti-inflammatory drugs, antivirals, antioxidants and cell therapies etc. As there are no evidences found for steroids and antibiotics against COVID-19.[37],[38] Main categories of drugs that are proved to be useful both *in vitro* as well as *in vivo* animal models are given below:

- Antiviral drugs:** On the basis of studies from SARS-CoV and MERS-CoV, antiviral drugs such as remdesivir, ritonavir-lopinavir combination, Vitamin C infusion, darunavir, cobicistat, unifenovir and hydroxy chloroquine for pneumonia can be used. Among all the above-mentioned antivirals, remdesivir has been reported as most active in preclinical studies and is successfully used in several patients in China, which acts through incorporation into RNA chain of the virus and leads to premature termination. [34] The widely available ritonavir-lopinavir combination inhibits viral protease and its

efficacy has been demonstrated against SARS-CoV and can reduce the viral load in COVID-19. However, there are limited clinical evidences for the combination.[39]

- **Hydroxychloroquine:** Chloroquine and hydroxychloroquine are antimalarial drugs, but various studies have shown their activity against SARS-CoV. Their antiviral efficacy is due to an increase in endosomal pH needed for fusion between the virus and host cell and also interfere with ACE2 cell receptor and also have immunomodulatory activity also. 500 mg BID dosage is suggested for chloroquine and 200 mg BID for hydroxychloroquine. [38]. Yao et al. has proved from *in vitro* studies that hydroxychloroquine is more potent than chloroquine in inhibition of SARS-CoV-2.[39]
- **Respiration therapy:** Requirement of oxygen therapy may be there in case of hypoxia ($\text{SatO}_2 < 93\%$) or if respiratory distress symptoms are present. Oxygen is generally given with the help of a nasal cannula and a face mask. Arterial SatO_2 must be monitored constantly during the therapy.[40], [41]
- **Anti-inflammatory drugs:** Specific drugs like tocilizumab, a monoclonal antibody against IL-6R were also used in Wuhan to treat 272 patients and a clinical trial is also ongoing in Italy. But still clinical data is too limited to show any type of efficacy and can't draw any conclusion about the therapy.[42], [43]

Vaccine

There is no vaccine available against COVID-19 since now. These days SARS-CoV vaccine is being used for development for vaccine and treatment strategies for COVID-19. Recombinant protein from Urbani (AY278741) strain of SARS-CoV was given to mice and hamsters, which leads in the production of neutralising antibodies and provides protection against SARS-CoV.[44], [45], The DNA fragment along with its inactivated whole virus or live vectored strain of SARS-CoV (AY278741) is shown to reduce the viral infection in various animal models.[46-48] However, there are few vaccines that are still in pipeline for SARS-CoV-2. The mRNA based vaccine designed by US national institute of Allergy and Infectious Diseases against SARS-CoV-2 is under phase 1 trial.[49] GeoVax-BravoVax is working for development of a vaccine based on modified vaccine Ankara (MVA). While Clover Biopharmaceuticals is developing a recombinant 2019-nCoV S protein subunit trimer based vaccine.[50]The WHO R & D blueprint along with its working group has conveyed an informal consultation on prioritization of vaccine against SARS-CoV-2 on 30th January 2020. Among different candidates in the vaccine pipeline, nucleic acid and viral vectored vaccine are being tried. One of the leading candidates is INO-4800, which is developed by Inovio pharmaceuticals and Beijing Ad vaccine Biotechnology. [11] All the vaccine studies are currently in preclinical phase.

Conclusion

The public, economic, medical, and financial and health consequences of pandemic COVID-19 are challenging. It has caused more infections and deaths as compared to SARS and MERS. Even though, many therapies and precautions are suggested but none of them is capable of treating and preventing spread of infection. Current treatment strategies focus on symptomatic care and oxygen therapy. Now, only time will how the virus affect our lives here in India. We urgently need specific clinical trials to find out most appropriate evidence-based treatment for turning the spread down and to prevent the load of future outbreak.

Disclosure

There is no conflict of interest among the authors.

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