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Review Article

A pandemic by novel corona virus, seventh member of human coronavirus

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ABSTRACT

Human coronavirus (HCoVs) pathogens are the cause of multiple respiratory epidemics since last 18 years, now has one more outbreak with novel evolution recognized in Wuhan, China in early December 2019. The novel corona virus 2019 is the most dangerous evolution of species SARS (severe acute respiratory syndrome) and MERS (Middle East respiratory syndrome) spread on 2003 and 2012 respectively, named "coronavirus disease 2019" (COVID-19) by the World health organization. The HCoVs have remarkably huge RNA genome, and an inimitable replication tactic. The current evolution COVID-19 has very high morbidity and mortality rate and has created world's biggest health emergency ever. The outbreak is now declared pandemic by WHO. In this review we highlight history of HCoVs, epidemiology, possible genetic evolution, pathogenesis, diagnosis and current prevention and treatment strategies for COVID-19.

1. History & Epidemiology

Human coronaviruses, first characterized in the 1960s, are responsible for a substantial proportion of upper respiratory tract infections. People around the world generally get infected by four common human coronaviruses are 229E (alpha coronavirus), NL63 (alpha coronavirus), OC43 (beta coronavirus), HKU1 (beta coronavirus). But after a large outbreak of severe pneumonia associated with human deaths occurred in late 2002 in Guangdong Province, China and in late February 2003, a similar illness was reported concurrently in Vietnam, Hong Kong, Canada, Singapore, and other countries, the fifth member was been introduced in HCoVs family named SARS-CoV (the beta coronavirus that causes severe acute respiratory syndrome, or SARS) The disease, was known as SARS, causes an influenza like illness with fever, cough, dyspnea, and headache.[1] Later, the infection rapidly spread throughout the world, and by July 2003, when the World Health Organization declared that the outbreak was contained, 8,437 cases and 813 deaths in 32 countries.[2]

The Middle East respiratory syndrome coronavirus (MERS-CoV) has been linked to severe human respiratory disease starting in September of 2012 was the sixth member of the group. As of 27 December 2013, a total of 170 laboratory-confirmed human cases of infection with MERS-CoV, including 72 deaths, are reported by the World Health Organization (WHO). Most cases originated in the Middle East, including Jordan, Kuwait, Qatar, Saudi Arabia, Oman and United Arab Emirates.[3] By that in May 2014 two cases were again observed in Florida and Indiana, United states of America and then again in 2015 in Korea and in 2019, 2468 were conformed of MARS CoV. During the second quarter of 2014 (April–May) there was an unusual increase in the number of reported cases from Saudi Arabia. From April 11 to June 9, 2014, a total of 515 cases of MERSCoV were reported to WHO. A total of 113 cases were reported on June 2, 2014 retrospectively to WHO.[4] In 2015, there was a

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large outbreak in South Korea.[5]

Since early December 2019 a new epidemic has begun from Wuhan, Hubei Province, China due to novel corona virus. By end of December 2019, the reported infected cases had risen to 266. On January 1, 2020 the numbers jumped to 381. The spread of these coronavirus disease 2019 (COVID-19) is very quick compare 2009 H1N1 influenza epidemic that took 132 days to spread in 262 Chinese cities compare to COVID 19 just in 28 days to be spread in same number of cities and it is now seventh member of HCoVs family.[6]

The spreading in between countries is even terrific. As per the situation reports released by WHO, on 20 January 2020 COVID 19 was limited to only 4 countries, China, Japan, Republic of Korea and Thailand with register number of cases 282, on 20 February that reaches to more than 26 countries with register number of cases 621, and on 20 March it covered 177 countries/territories with registered cases 234073 and 9840 deaths. and on 20 April the registered cases reach to 2314621 with number of total 157847 death from 213 countries/territories. Within ten-day on 30 April, the total registered cases number increases to 3090445 and 217769 deaths and increasing day by day. Figure 1 shows daily increasing infections among china and outside china registered at WHO for first 4 months.

Figure 2 and Figure 3 shows how number of COVID 19 confirmed cases and total deaths respectively around the world increase based on 3 months of situation reports of WHO. In both figure sharp rise is observed after 2 months showing how pandemic COVID 19 is. Looking at increasing number of infectious cases, one can get idea about how dangerously the situation is evolving. It took 67 days, to reach one lac of the total number of confirmed cases; that reached 1 million just in the next 28 days (Figure 2). In 80 days of pandemic, the number of deaths crossed 10,000 that reaches to one lac in just 23 days.

Based on it seems that the death ratio is continuously increasing and may still increase as the infectious cases are still increases till date. These data also draw attention that for the first 24 days there was 0% death ratio, for almost next 25 days it remains in between 2-3% and for further next 25 days, it remains in between 3-4%; now after 75 days it has move beyond 4% and with no surprise it may move beyond 5% in total 100 days.[7]

2. Virology and Genetic Evolution

It is very important to know how genome and protein of 2019 n-CoV looks like. The protein differences in 2019-nCoV compare to SARV-CoV and MERV CoV may give idea why it is so virulent and transmissible in humans.

The COVID 19 viruses are enveloped viruses with a positive-sense single-stranded RNA genome and a nucleocapsid. The nucleocapsid has helical symmetry. The genome size of COVID-19 genome, it is 29,903 base pairs (~30k base pairs).[8] The corona name of coronavirus family is derived from the Latin corona, meaning "crown" or "halo", which refers to the characteristic appearance of the virus particles (virions): they have a fringe reminiscent of a crown or of a solar corona. The structure of corona virus is formed by protein which formed Envelope, membrane, nucleocapsid. the virus also contains spike protein which can be divided into an amino-proximal half (S1 subunit or domain) containing the receptor-binding domain, and a carboxyl-proximal half (S2 subunit or domain) containing elements involved in membrane fusion.[9] The S protein is an important target for T cell responses and is the major inducer of virus-neutralizing antibodies, which are elicited by epitopes located mostly in the molecule's S1 domain.[10,11] In the specific case of the SARS coronavirus, a defined receptor-binding domain on S mediates the attachment of the virus to its cellular receptor, angiotensin-converting enzyme 2 (ACE2).[12] Some coronaviruses (specifically the members of Beta coronavirus subgroup A) also have a shorter spike-like protein.[13]

The novel corona virus (Wuhan corona virus) has some different in structure (Figure 1) it had hemagglutinin esterase protein on lipid bilayer membrane in addition to that it had also glycoprotein spikes and RNA with nucleoprotein. It had Envelope small membrane protein E inner side of the lipid bilayer so, 2019 n-CoV had completely different structure from SARS CoV.[1]

Corona virus, classified in the subfamily Coronavirinae, family Coronaviridae, order Nidovirales. which were developed by the Coronavirus Study Group,[13,14] a working group of the International Committee on Taxonomy of Viruses CoVs are subdivided into four genera on the basis of genotypic and serological characterization: alpha and beta coronaviruses, which are found mainly in mammals; gamma coronaviruses, detected in birds and marine mammals; and delta coronaviruses found mainly in birds and swine.[15] In addition that Most viruses in the genus Gammacoronavirus are isolated from birds, including Galliformes (chicken, turkey, quail, guinea fowl, pheasant, and peafowl).[16] The evidence shows that the novel corona virus (SARS-2) has 90% matches to SARS CoV by their phylogenetic tree.[3] Both are belonging to same family, but both have different sub-family.

3. Replication of Coronaviruses

Replication of Coronavirus begins with entry to the cell takes place in the cytoplasm in a membrane-protected microenvironment, upon entry to the cell the virus particle is uncoated, and the RNA genome is deposited into the cytoplasm. The Coronavirus genome has a 5' methylated cap and a 3'polyadenylated-A tail to make it look as much like the host RNA as possible. This also allows the RNA to attach to ribosomes for translation. Coronaviruses also have a protein known as a replicase encoded in its genome which allows the RNA viral genome to be translated into RNA

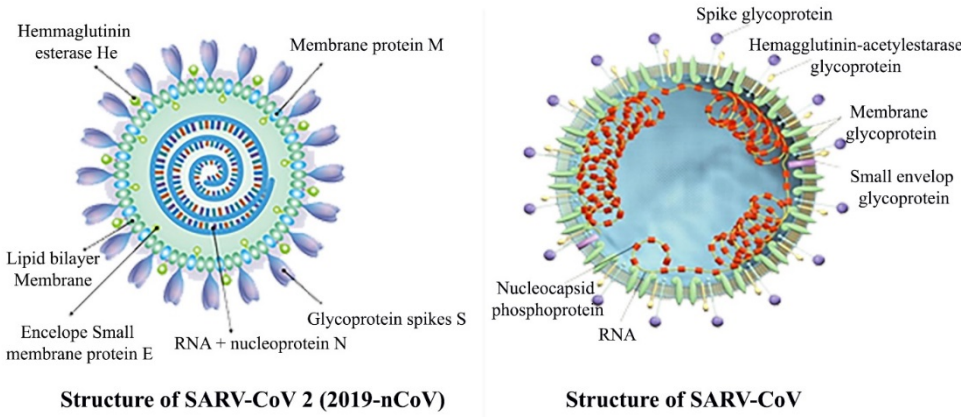

Figure 1: tructural difference between Novel 2019 corona and SARS corona virus Source: Cusabio technology, https://www.cusabio.com/2019-novel-coronavirus.html

Table 1: Comparison of SARV-CoV, MERV CoV and 2019-nCoV

Characteristics	**SARV-CoV**	**MERV-CoV**	**2019-nCov**
Pathogen	Corona virus	Corona virus	Corona virus
Period	2002-2004	2012-	2019-
Likely origin	china	Middle east	china
Intermediate host	civet cats	camels	Pangolin?
Human to human transmitter	Yes	yes	Yes
Incubation	2-10 days	2-14 days	2-14 days
Clinical manifestation	Fever, malaise, myalgia, headache, diarrhea, shivering, cough, shortness of breath	Fever, myalgia, diarrhea, cough, shortness of breath	Fever, myalgia, cough, shortness of breath
Major complication	Pneumonia, severe acute respiratory distress syndrome, death	Pneumonia, severe acute respiratory distress syndrome, death	Pneumonia, severe acute respiratory distress syndrome, death

by using the host cells machinery. The replicase is the first protein to be made as once the gene encoding the replicase is translated the translation is stopped by a stop codon. This is known as a nested transcript, where the transcript only encodes one gene- it is monoisotopic. The RNA genome is replicated, and a long polyprotein is formed, where all the proteins are attached. Coronaviruses have a non-structural protein called a protease which can separate the proteins in the chain. This is a form of genetic economy for the virus allowing it to encode the most amounts of genes in a small number of nucleotides.

Coronavirus transcription involves a discontinuous RNA synthesis (template switch) during the extension of a negative copy of the sub genomic mRNAs. Base pairing during transcription is a requirement. Coronavirus N protein is required for coronavirus RNA synthesis and has RNA chaperone activity that may be involved in template switch. Both viral and cellular proteins are required for replication and transcription. Coronaviruses initiate translation by cap-dependent and cap-independent mechanisms. Cell macromolecular synthesis may be controlled after Coronavirus infection by locating some virus proteins in the host cell nucleus. Infection by different coronaviruses cause in the host alteration in the transcription and translation patterns, in the cell cycle, the cytoskeleton, apoptosis and coagulation pathways, inflammation, and immune and stress responses.[9]

4. Clinical Manifestations

In humans, the incubation period from infection to symptom onset is ≈ 2-10 days.[3,16] From symptoms to death onset is 6-41 days Mainly all ages people are susceptible (geriatric to pediatric),[4] but the period of onset is shorter in geriatrics. It has similarity with the flu infection like symptoms, commonly reported symptoms like cough, fever, fatigue, difficulty in breathing, sore throat, Nasal congestion and some symptoms of malaises, muscle pain and headache. In case of severe pneumonia respiratory infection and

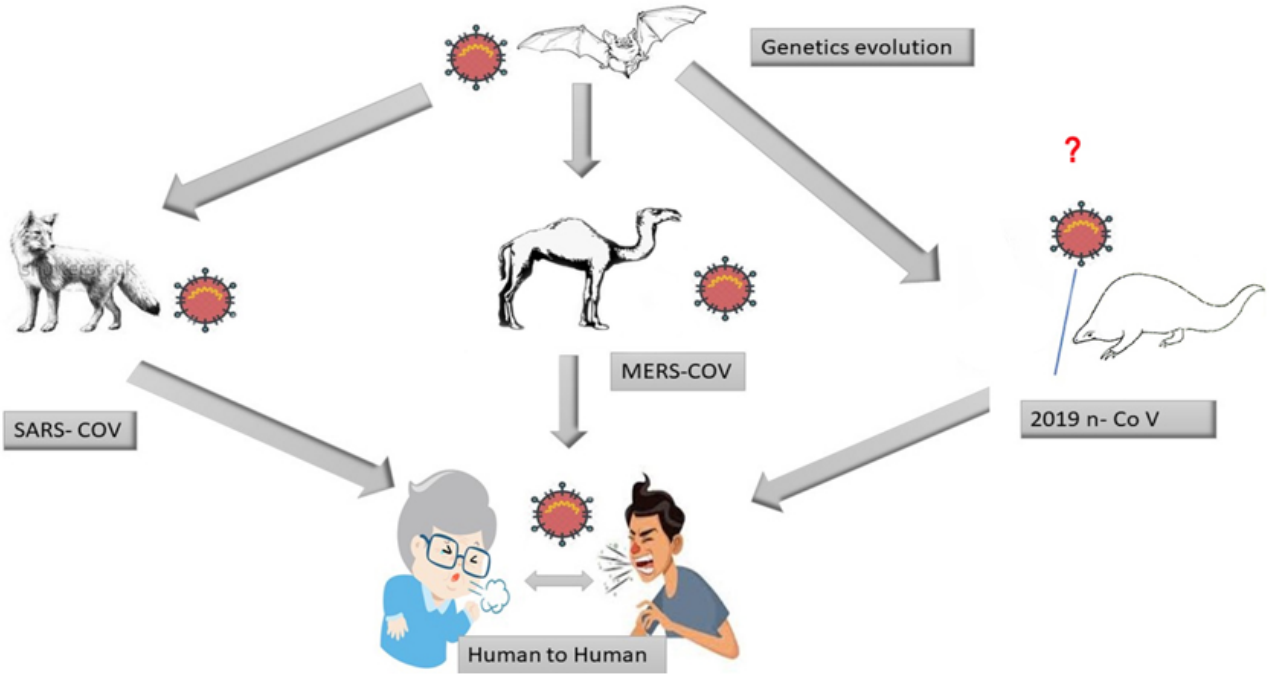

Figure 2: Transmission of various types of corona virus

also occurrence of convulsion is observed.[2] It has also some severe complication likes mild and severe pneumonia, acute respiratory distress syndrome (ARDS) and in some condition evidence of sepsis and septic shock is there. In sepsis life threatening organ dysfunction caused by a dysregulated host system response to be suspected and seen difficult or fast breathing, fast heart rate, skin mottling also occurs.[7] Just like that MERS- COV and SARS- COV have found that the greater number of males is infected as compared to female.[17]

5. Transmission

The high intensity of human to human transmission and infection of the novel corona virus is mainly due to direct contact with the body fluid of infected patients. This body fluid mainly salivary and respiratory secretion becomes free to air while coughing and sneezing play big role as contagious agent.[18] The place from where the pandemic begun, was seafood and wet animal wholesale market in Wuhan city. When the disease was just commenced, it was observed that all infected patients had history to visit that market so, it shows that the transmission of this virus strong and very quick. Similar like SARS COV transmitted from bat to fox and fox to human being and MERS COV transmitted from bat to camel and camel to human being, the 2019-nCoV can be possibly transmitted from bat to any mammalian sea creature available in market and it is said to be pangolin. The transmission of COVID 19 is so quick that during the pandemic many health care professionals and patients get cross infected.[19]

6. Pathogenicity

The reports of two COVID19 patient's pulmonary pathology revealed important information about pathology of COVID 19. The autopsy of COVID 19 patients showed similar exudative and proliferative phases of acute lung injury as was observed in autopsy of SARS, These include edema, inflammatory infiltrate, type II pneumocyte hyperplasia, and organization but without obvious hyaline membrane formation and other long-term processes, such as squamous metaplasia. It was also observed that patient also showed high WBC counts and lymphocytopenia.[19]

In an another COVID-19 patient's report showed at 5 days of fever existing with a cough, coarse breathing sounds of both lungs, and a body temperature of 39.0 °C. The patient's sputum showed positive real-time polymerase chain reaction results that verified COVID-19.[20] In all cases the CT scan showed lesions in lunges.

The biopsy of one more patient who had died due to sudden cardiac arrest on 14 day of COVID-19 illness and was receiving high-flow nasal cannula (HFNC) oxygen therapy, showed desquamation of pneumocytes and hyaline membrane formation. The report also suggested early phase acute respiratory distress syndrome but no evidence found to prove direct deficiency of heart due to COVID 19.[21]

In all above patients, it was observed that Lymphocytopenia is a common feature that may well be a critical factor linked with disease harshness and death.

7. Diagnosis

Real time reverse-transcription polymerase chain reaction (RT-PCR) diagnostic panels are the only confirmatory method to diagnose COVID 19 till date. The test process involves collection of respiratory specimens both from upper and lower respiratory tract. The specimens are subjected to extract RNA and then tested by real time PCR using specific primers and probe. The genome can be identified by one of two methods: Sanger sequencing, Illumina sequencing, or nanopore sequencing. The test is conducted on RNA if the open reading frame 1a or 1b and nucleocapsid each target is positive by specific Real time PCR so; the case is considered as laboratory conformed case. If the value of PCR cycle threshold value is less than 37, the case is as positive result of RT-PCR. If there is cycle threshold (CT value) is 40 or more, it is defined as negative result. When the CT value is medium load like 37 and less than 40 the case required for reconfirmation by retesting of the specimen.[22,23]

7.1. Currently available treatment

COVID 19 infection treatment is symptomatic, no specific treatment is available, and no vaccine is available till date as per WHO and Centers for Disease Control. The first and foremost requirement for the infected patients is immediately they need to isolate in specified isolation ward of designated hospitals. Favipiravir approved in japan to treat influenza is inhibiting the RNA dependent-RNA polymerase enzymes so; it is stopped replication cycle of virus.[24] Lopinavir and Ritonavir showed potential benefit in some patients but on further study they failed to claim effective treatment drug candidate. Remdesivir is still under clinical trial. Chloroquine and hydro-chloroquine are also been suggested but only with limited clinical data. Based on theoretical possibility of COVID 19 treatment, an antibiotic Azithromycin and an immunosuppressant Tocilizumab showed positive results as adjunct therapy on limited preliminary investigations.[25] One another investigation still under progress for treatment using COVID-19 convalescent plasma. Corticosteroids usually not recommended for viral pneumonia but such practice is required together with ventilator support for the severe patients to prevent ARDS development. Even use of NSAIDS are also under investigation.[25,26]

8. Precaution

The data provided here has showed the intensity of COVID 19 infection. Moreover there are no drug therapy available for the disease. So, the only way to break the chain of infection is to take several precautions. For now, several province and countries have lock down themselves to avoid cross territorial infection and same has been implemented to plenty of cities also. Even one has to lockdown himself and need to avoid unwanted travelling in such contagious condition. Avoid unwanted contact. Cover mouth and nose while coughing and sneezing or wear medical mask. Avoid direct contact with body fluids, particularly oral and respiratory secretion. Avoid unnecessary touching to mouth, eyes and nose with naked hand and contaminated hand. Wash your hand with soap and sanitizer frequently and alcohol based hand rub can be used. If any symptoms show meet immediately health care professional. Patient should be in separated area with required ventilation. Keep distance from patients or other (1 meter).[2,7]

9. Source of Funding

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10. Conflict of Interest

None.

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