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Worldwide Threatening to Mankind-SARS-CoV-2 and It's Attributes

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Abstract:

The newly emerged pandemic causes massive fatality which was originated from Huanan sea food market in Hubei province in China. It closely resembles SARS-CoV and MERS-CoV. It was transmitted from infected animal host to human and it was suspected that bats are carrier as its genome is 96% similar to the new pandemic. Due to the close resemblance of COVID-19 with SARS-CoV it was named as SARS-CoV-2 by ICTV under orthocoronavirinae subfamily and genus betacoronaviruses. Through the droplets and fomites from the infected persons and close contact with them causes the transmission. SARS-COV-2 contains structural proteins, M, N, E, S and sixteen non-structural proteins. It enters the cell by binding with ACE2 receptor on the cell membrane of lungs with the help of S protein by endocytosis. The host innate and adaptive immunity effectively produce antiviral response by pro inflammatory cytokines, CD4 cells and CD 8+ cells. CTLS are activated by cytotoxic T cells. Due to the increased release of cytokines leads to cytokine storm and cause inflammatory-induced lung injury. RT-PCR, CT, and Serological methods are used to diagnose the COVID-19 which helps in isolation of infected patients and control of spread of the infection. Since there is no vaccines and proper medications for SARS-CoV-2 it is more vital to prevent our own selves from infection by following preventive measures like maintaining social distancing, washing hands, and practicing personal health hygiene.

Keywords: SARS-CoV-2, respiratory infection, ACE2 receptor, cytokine storm, RT-PCR.

INTRODUCTION

The newly emerging pandemic SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) gathers international attention towards it due to massive fatality among the human race globally[1]. Coronaviruses (zoonotic virus) have been reported as cause of mild and severe respiratory infections. It closely resembles to the structure of SARS (Sever Acute Respiratory Syndrome) and MERS (Middle East Respiratory Syndrome). When compared to other human coronaviruses like SARS and MERS, SARS-CoV-2 is more severe due to its mutational changes which causes rapid outbreak of pandemic[2]. It targets the respiratory system of the host and resembles pneumonia symptoms[3]. SARS-CoV-2 gains its entry by binding Receptor Binding Domain (RBD) of the virus to Angiotensin Converting Enzyme 2 (ACE2), a receptor in the cell membrane by endocytosis. After entering host cell by endocytosis it unleashes its genetic material (single stranded RNA) into cytoplasm. SARS-CoV-2 hijacks human machinery to replicate RNA and form its structural proteins (Membrane, Nucleocapsid, envelope, and spike proteins) and other nonstructural proteins. Then the virus gets assembled and it moves out of the cell and begins to infect the uninfected cells [4]. Body responds to viral infection with innate (non-specific) immunity. It is followed by adaptive immune response where B cells produce antibody binds to viral spike protein. Body makes T-cells that recognize and eliminate viral infected cells [5].

Aetiology

In December 2019, a cluster of patients with pneumonia of unknown etiology was identified in Wuhan city, China [6]. The epidemic (new coronavirus) originated from the Huanan sea food market in Hubei province in China where the animals, source of infection are suspected. Infection from the animal host to human is suspected to be transmitted through wildlife trade, transportation, and slaughter [7]. Inspite of its initial source, it is likely that nCoV2019 was introduced into a small cluster of humans from a cluster of infected animals and, from there, the virus acquired the capacity for human-to-human transmission [8]. The virus has been detected in environmental samples from the market, the origin of the virus has not been determined conclusively. Malayan pangolins (Manis javanica) illegally imported into Guangdong province contains coronaviruses similar to SARS-CoV-2[8][9]. The nucleotide sequence of SARS-CoV-2 is 96% and 79% similar to Bat coronavirus and SARS-CoV[10]. The WHO (World Health Organization) declared that the epidemic is a public health emergency of international concern on January31, 2020[11]. In 2003, SARS-CoV infected 8,098 individuals with mortality rate of 9% across 26 countries in the world. In 2012, another coronavirus was detected in Saudi Arabian nationals named MERS-CoV affected more than 2,428 individuals and 838 deaths [12]. The recent pandemic, COVID-19, has been spreading worldwide, causing over 9,277,214 cases and over 478,691 of deaths which is more severe than the early detected human coronaviruses (HCoV) [13].

Taxonomy

International Committee on Taxonomy of Viruses announced the name of virus causing COVID-19, a newly emerging pandemic as SARS-CoV-2 on 11 February 2020. Coronavirus has gained their name due to their projections on their outer surface. SARS-CoV-2 belongs to the family

Coronaviridae, suborder Cornidovirineae and order Nidovirales. The family Coronaviridae is classified to two subfamilies namely, Letovirinae and Orthocoronavirinae. The subfamily Orthocoronaviridae is again classified to four genera namely Alphacoronavirus, Betacoronavirus, Gamacoronavirus, and Deltacoronavirus based on the genome structure where the SARS-CoV2 comes under the genus Betacoronavirus [14][15]. Alpha and Betacoronaviruses infects mammals. Seven members of the Alpha and Betacoronaviruses cause human diseases namely HCov-HKU1, HCoV-OC43, HCoV-229E, HCoV-NL63, SARS-CoV, MERS-CoV and SARS-CoV-2. Human Coronaviruses are capable of causing diseases ranging from mild respiratory illness to mortality. HCoV-OC43, HCoV-229E are identified in mid-1960s. SARS-CoV, HCoV-NL63, HCoV-HKU1, and MERS are identified in 2003, 2004, 2005, and 2012 respectively [16][17][18]. Gamma Coronaviruses and Deltacoronaviruses are found in birds and mammals [19]. Deltacoronaviruses includes bulbul coronavirus HkU13, thrush coronavirus HKU12 and munia coronavirus HKU13 [20].

Transmission and Epidemiology

The transmission of COVID-19 with four data sets from within and outside of Wuhan [21]. The first case of nCoV-19 where it linked animals to human transmission was presumed as main mechanism. Later human to human transmission was confirmed through respiratory fomites [22]. Human to human transmission was mainly occurring between close contacts with infected individuals [10]. It is also found that infection may transfer through droplets spread by coughing or sneezing from an infected individual [23]. From the analyzed study it was estimated that 72.3% of infected patients have contact with people from Wuhan [24]. The most common symptoms of COVID-19 are fever, cough or sneeze. Other symptoms are headache, sore throat, and sputum production [25]. In some cases infected patient may be asymptomatic but actively involved in the transmission of virus [26]. The aerosol transmission is one of the aspects of viral transmission [27]. Faecal and urine samples have potential to serve as an alternative route of infection [28]. The international response to SARS-CoV-2 has been more efficient when compared to SARS and MERS outbreak [22]. The Spike gene of Coronavirus plays a major role in interspecies transmission [9]. Routes of transmission and subclinical infections of infected patients should be monitored for epidemiological changes [29]. The patients may affected by chronic disease, including cardiovascular and cerebrovascular diseases, endocrine system disease, digestive system disease, respiratory system disease and nervous system disease. It also causes organ function damage, acute respiratory injury, acute renal injury, ARDS (Acute Respiratory Distress Syndrome), ventilator-associated pneumonia [30]. From the report of WHO, on March 13, 2020 the confirmed cases were 4,179,479 and deaths were 5,362. On 25 June, 2020 confirmed cases were 9,277,214 and deaths were 478,691[31]. The medical history, fatality, and mortality of the patients had been increasingly livelihood of a virus outbreak [32].

Structure

SARS-CoV2 are pleomorphic or spherical in shape, contains positive sense single stranded RNA (+ssRNA) genome of 29.9 KB, the largest RNA genome and size ranging between 80-120nm. Virus particle has four structural proteins namely Spike (S), Membrane (M), Envelope (E), and Nucleocapsid (N) protein[33] [34]. S protein, a type I fusion protein vital for infection to human by binding to the receptors and fusion with cell membrane. S protein attached on the viral envelope is trimeric globular proteins which are 150Å in diameter. It comprises two subunits S1 and S2 subunits. S1subunit has RBD which binds to ACE2 receptor in host cell membrane. S2 subunit forms the stack of the spike [35]. M proteins are small (~25-30kDa) and most abundant structural protein of the virus. E proteins are found in small quantities and size ranges approximately from 8-12kDa. N proteins have two domains, N-terminal domain and C-terminal domain. It is the only protein present in nucleocapsid [36]. SARS-CoV-2 comprises 6-11 Open Reading Frame (ORF). The two third of RNA genome was occupied by first ORF, ORF1a/b translates polyprotein pp1a, pp1ab which encodes 16nsps (non structural proteins). The other ORFs which occupies remaining one-third of RNA genome encodes for other accessory and structural proteins. The non-structural proteins encoded by ORF1a/b include papin-like protease (nsp3), chymotrypsin-like 3C or main protease (nsp5), RNA-dependent RNA Polymerase (nsp12), helicase (nsp13), other non-structural proteins involved in transcription and replication of virus[37][38].

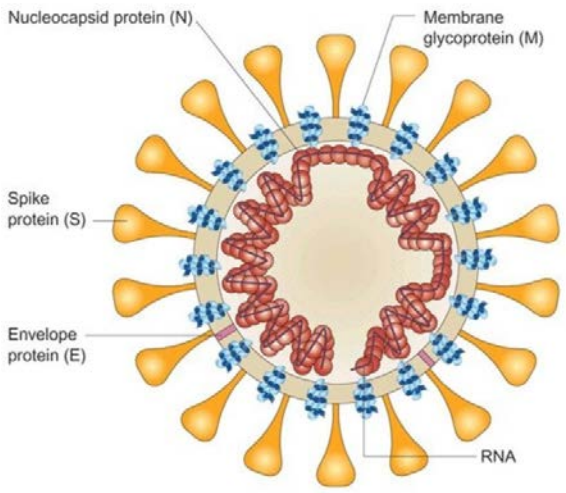

Figure 1: Structure of Coronavirus

Structure of Coronavirus is depicted with structural proteins namely Spike protein(S), Membrane protein (M), Envelope protein (E), Nucleocapsid protein (N) and Single stranded RNA.

Cell entry

Respiratory droplets are ingested or inhaled by individuals allows the entry of virus to human lungs. Touching eyes, nose, mouth subsequently after touching contaminated objects with virus and aerosol in air when inhaled may enter into lungs. Digestive system is also a potential transmission route for SARS-CoV-2 infection [39]. The ACE2 gene spans about 39.98 kb of human genomic DNA and encodes a type I cell-surface glycoprotein of about 100 kDa, composed by 805 amino acids and characterized by a N-terminal signal peptide of 17 amino acid residues, a peptidase domain (PD), and a C-terminal Collectrin -like domain (CLD12), that end with an hydrophobic transmembrane hydrophobic helix region of 22 amino acid residues followed by an intracellular segment of 43 amino acid residues[40]. COVID-19 uses the ACE2 as the receptor for the host cell entry [41]. ACE2 is negative regulator of RAS (Renin Angiotensin System), while RAS maintains homeostasis of blood pressure and the balance of fluid and salts. ACE2 degrades angiotensin II, a vasoconstrictor, pro inflammator into Angiotensin (1-7), which is a vasodilator, anti-pro liferator. ACE2 are highly distributed in the heart, kidneys, testes, lungs, liver, intestine and brain of the humans [42]. In lungs ACE2 expression is concentrated in type II alveolar cells, and in bronchial and tracheal epithelial cells [43]. Elevation of angiotensin II level is associated to viral infection and lungs injuries [44]. SARS-CoV-2 exhibits four-fold higher binding affinity to ACE2 than SARS-CoV[45]. SARS-CoV-2 utilizes the homotrimeric spike glycoprotein to bind to function ACE2 receptor. The Receptor Binding Domain (RBD) in S protein helps the binding of virus to host cells, which is a crucial step for virus to enter host cell [46]. The S protein is cleaved to subunit S1 and S2, subunit S1 has RBD binds to peptidase domain of ACE2. For entry to the cell, cellular serine proteases, TMPRSS2 priming S protein is involved, which is a critical step of viral infection. S2 site allows the fusion of viral and cellular membranes [47][48]. SARS-CoV-2 viruses are cleaved and enter cells by endocytosis [49].

Immune response and Adverse effects

Human immune response to SARS-CoV-2 infection that may help in designing for treatment, diagnosis and therapeutic vaccines against COVID-19[50]. The host innate and adaptive immunity effective antiviral responses including the production of various proinflammatory cytokines, the activation of T cells, CD4 and CD8+ T cells, are essential for controlling the viral replication and spread of virus, inflammation and cleaning the infected cells[51]. The S and N protein of SARS-CoV-2 were the most immunogenic expressed proteins during infection. Infected macrophages present CoV antigens to T cell that leads to activation and differentiation of T cells, includes the production of cytokines with the different T cells subsets (i.e. Th17), accompanied by a massive release of cytokines for immune response amplification. CTLS (cytokine T lymphocytes) are generated by immune activation of cytotoxic T cells. CTLS become activated by detecting the viral antigen presenting MHC-I complexes of the infected cell and generate immune response[52][53]. In COVID-19 patients with high-levels of pro inflammatory cytokines including IL-2, IL-6, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1A, and TNFα are seen in the severe cases[54]. Especially in severe infected patients they have high plasma IL-6 level which can be stimulated by SARS-CoV-2 or by other immune cells, secreted in peripheral blood. In fact, during CoV-2, CD4+ T lymphocytes are rapidly activated to differentiate into pathogenic Th1 cells, generating GM-CSF and other pro inflammatory cytokines, which induced activation of monocytes, with high expression of IL-6. IL-6 blockade reduce the immune response caused by SARS-CoV-2. It involves massive release of cytokines which leads to CRS (Cytokine Release Syndrome). Cytokines produce CD8+ cells very effective mediators to clear Beta coronaviruses[55]. CRS is common in immune system-related disease and systemic inflammatory response by infection. Presence of lymphocytopenia is seen in severe COVID-19 patients ,causes CRS by COVID-19 virus has to clear up by leucocytes than T cells. It's has characterized by increase in level of vast number of proinflammatory cytokines[56]. “Cytokines storm” may have a vital role in pathogenesis of COVID-19, this can initiate viral sepsis and inflammatory-induced lung injury with other supplements including respiratory failures, organ failure, ARDS and potentially death[57].

Diagnosis

The number of suspected COVID-19 cases rise continuously, exceeds the capacity of many hospitals, many patients remained untested slow down efforts to the control the disease. Rapid, point-of-care diagnostics for the COVID-19 is needed intensively. nCoV-2019 laboratory test assay were based on the recommended by WHO[58]. Laboratory detection comprises genomic sequencing, Reverse Transcription Polymerase Chain Reaction (RT-PCR), Computer Tomography (CT) and serological methods [such as Enzyme-linked Immunoassay (ELISA)] [59]. In patients with suspected infection, conducting real-time fluorescence (RT-PCR) to detect SARS-CoV-2 has been suggested[60]. Sample should be collected from upper and lower respiratory tract of the patients[61]. Respiratory source including throat, nasal nasopharyngeal (NP), sputum, and bronchial fluid. Even though accurate and fast laboratory testing methods are available, the diagnosis of SARS-CoV-2 infection involves collecting the correct specimen from the patient at the right time[62]. RT-PCR is the accurate laboratory method for detecting, tracking, and studying the COVID-19. It is a nuclear-derived method for detecting the presence of specific genetic material from virus. This method uses radio isotope markers to detect the genetic materials, most frequently fluorescent dyes[63]. RT-PCR detects two different regions (ORF1b and N gene) of the viral genome. The amplicon size of ORF1b and N gene

assays are 132 bp and 110 bp respectively[64]. A cycle threshold value < 40 is interpreted as positive for viral RNA[65]. In the initial screening, for the auxiliary diagnosis Computed Tomography is needed[66]. In a study of more than thousand patients, chest CT outperformed lab testing in the diagnosis of COVID-19. CT investigation in COVID 19 patients involves the use of high-resolution technique (HRCT). It is most accurate technique used in identifying pathogenomic findings of interstitial pneumonia. The chest Computed Tomography with axial and coronal plains shows the absorption of both ground-glass opacities and organizing pneumonia[67][68]. Serology test is a screening of antibodies in blood. The doctors confirm the COVID-19 by detecting the presence of two antibodies namely IgM antibodies, which develop early in an infection and IgG antibodies, which are more likely to show up later after recovery.[69].

Prevention

Since vaccines or specific antiviral treatments are currently not available for SARS-CoV-2, the applications of preventive measures are the current strategy to limit the speed of the pandemic [70]. Preventive measures such as

- Frequent washing of hands with soap and water for minimum 20 seconds.
- Use hand sanitizers that contains at least 60% alcohol.
- Keep away unwashed hands from your eyes, nose and mouth.
- Avoid close contact with people who were sick.
- Put distance between yourself and other people from strangers.
- Stay at least six feet (about 2 arms length) from others [71].
- Practicing respiratory hygiene by coughing or sneezing into a bent elbow or tissue and dispose the tissue properly.
- Wearing a medical mask if you have respiratory symptoms.
- Routine cleaning and disinfection of environmental and other often handled surfaces[72].
- Don't share personal utensils(like phones, makeup, or combs)
- Avoid participating in public meetings includes religious places of worship, park or beaches.
- Avoid eating or drinking in public.
- Wash fresh groceries (soak all raw, whole fruits and vegetables in a solution of food grade hydrogen peroxide or with white vinegar [73].
- Avoid spitting in public places.
- Avoid physical contact while greeting.
- Stay home and self isolation even with minor symptoms such as cough, mild fever until recovery [74].

On 22 January 2020, the National Health Commission published national guidelines for the prevention and control of nCoV-2019 for medical institutes to prevent nosocomial infection such as:

- First-line health care providers should be highly aware of relevant infection prevention measures for suspected patients [39][75].
- Operation on patients with conformed or suspected SARS-CoV-2 infection must be carried out in designated room with necessary protection for medical staff members.
- The medical waste from confirmed or suspected patients with COVID-19 infection must be considered as a infectious medicinal waste and disposed accordingly [76].
- Early Screening, Diagnosis, isolation and treatment are necessary to prevent the spreading of the disease [77].

CONCLUSION

This study deals with the current outbreak, SARS-CoV-2. Many studies have been published with multiple scientific disciplines on COVID-19. This review discusses the genesis, taxonomy, transmission together with epidemiological knowledge also explores the structure followed by cell entry and figures out the immune response ad joint with diagnosis, as well as prevention and control of nCoV-2. In SARS-CoV-2, which has no approved vaccine or treatment, it is very important to prevent the spreading in the society. Preventive measures have been discussed as ways to reduce transmission. Many studies and researches are on going to have a complete understanding about SARS-CoV-2 and to eradicate the virus.

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