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Molecular Adaptation of SARS-CoV 2

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ABSTRACT

Novel disease called as COVID-19 is a highly transmittable and pathogenic viral infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which emerged in Wuhan, China, and spread around the world. Mostly Severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) are two highly transmissible and pathogenic viruses that emerged in humans at the beginning of the 21st century. Genomic analysis revealed that SARS-CoV-2 is phylogenetically related to severe acute respiratory syndrome-like (SARS-like) bat viruses; therefore, bats could be the possible primary reservoir. The intermediate source of origin and transfer to humans is not known, however, the rapid human to human transfer has been confirmed widely. Therefore, rapid and accurate identification of pathogenic viruses plays a vital role in selecting appropriate treatments, saving people's lives also preventing many epidemics. Hence it is the need of the hour by using PCR as a gold standard test for the molecular diagnosis of viral infection to prevent secondary transmission with high sensitivity and specificity. This pandemic presents an unprecedented challenge to identify effective drugs for prevention and treatment. Given the rapid pace of scientific discovery and clinical data therapeutic options including antimalarial, antivirals, and vaccines are under study. As there are currently no effective drugs targeting this virus, drug repurposing represents a short-term strategy to treat millions of infected patients at a low cost. The purpose of this brief is to provide timely insights into its origin, transmission, clinical features, and treatments which guide frontline medical staff in the clinical management of this outbreak.

INTRODUCTION

The day, December 31, 2019, hospitals reported a cluster of cases with pneumonia of unknown cause in Wuhan, Hubei, China, attracting great attention nationally and worldwide. On January 1, 2020, Wuhan public health authorities shut down the seafood wholesale market where wild and live animals were sold due to a suspected link with the emerging noval coronavirus outbreak[1]. Coronaviruses are members of the subfamily *Coronavirinae* in the family *Coronaviridae* and the order *Nidovirales* (International Committee on Taxonomy of Viruses). Corona represents crown-like spikes on the outer surface of the virus: thus it was abbreviated as COVID19. They are minute in size (65-125 nm in diameter) and contain a single-stranded RNA as a nucleic material, size ranging from 26 to 32kbs in length[2]. The subfamily consists of four genera – *Alpha, Beta, Gamma* and *Delta* virus based on their phylogenetic relationships and genomic structures. The α-coronaviruses and β-coronaviruses infect only mammals. The γ-coronaviruses and Δ-coronaviruses infect birds but some of them can also infect mammals. α--coronaviruses and β-coronaviruses usually cause respiratory illness in humans and gastroenteritis in animals[3]. Studies estimated the basic reproduction number (R_0) of SARS-CoV-2 to be around 2.2 or even more (range from 1.4 to 6.5) and familial clusters of pneumonia outbreaks add to evidence of the epidemic COVID-19 steadily growing by human-to-human transmission[4]. It shows that the transmission rate of SARS-CoV-2 is higher than SARS-CoV and the reason could be genetic recombination event at S protein in the binding domain of receptor (RBD) region of SARS-CoV-2 may have enhanced its transmission ability. Early diagnosis of SARS-CoV infection which involves viral detection is important for preventing future epidemics. Since culturing of SARS-CoV is difficult and insensitive, the reverse transcription-polymerase chain reaction (RT-PCR) and quantitative RT-PCR (qRT-PCR) were used as working standard in diagnosis[5]. Besides, several molecular tests employed non-PCR methods such as isothermal nucleic acid amplification (loop-mediated isothermal amplification (LAMP) and nucleic acid sequence-based detection methods for the detection of coronavirus RNA[6]. Recently studies reported the development of 2 stage sandwich enzyme-linked immunosorbent assays (ELISAs) for the detection of SARS-CoV from clinical specimens for SARS patients. However, no studies have shown the sensitiveness of the ELISA technique in literature used when compared with PCR. Rapidly expanding knowledge regarding SARS-CoV-2 virology provides a significant number of potential drug targets. The most promising is remedesivir but it is not approved by U.S. FDA and is currently being tested in coming andomized trials. Oseltamivir has not been

shown to have efficacy and corticosteroids are currently not recommended. Clinical evidence does not support stopping ACE inhibitors or ARB in patients with COVID-19[7]. Various antiviral agents were included in the latest guidelines from the National Health Commission including interferon, lopinavir/ritonavir, chloroquine phosphate, ribavirin and arbidol. The treatment guidelines for COVID-19 vary between countries[8]. Meanwhile, the current epidemic has called a waking alarm of therapeutic tools to treat infectious diseases. Convalescent plasma (CP) constitutes the first option in the current situation since it has been successfully used in other coronaviruses outbreak[9]. Developing a safe and effective COVID-19 vaccine is a global priority to end this pandemic. Hence, therefore, it is ssential to develop a vaccine against SARS-CoV-2 including in areas such as genomics and structural biology that is supporting a new era in vaccine development[10]. In this review article, we will discuss the origin of coronavirus, notable features of SARS and MERS with a special focus on COVID-19, mutation in the receptor binding domain of SARS-CoV-2 and potential therapeutic strategies against COVID-19[2].

CLASSIFICATION OF CORONAVIRUS

The classification of novel virus consists of 39 species, 5 genera belonging to the *Coronaviridae* family (Nidovirales order). Classification of novel coronavirus was performed by Coronaviridae Study Group (CSG) along with International Committee on Taxonomy of Viruses (ICTV) group. They studied the whole classification of Nidovirales as they believed to understand the relationship between the genomic structure and virus it is necessary to know the full taxonomy of several coronaviruses. The CSG group picked the most conserved region of the genetic sequence i.e. ORF 1a and 1b of various coronaviruses to identify the common link or any similarity between them. From the analysis, it was seen that these novel coronaviruses converge with the family of SARS-CoV at one point of time in the family tree and belongs to the genera of β-coronaviruses.

History: The first human coronavirus named HCoV-229E was discovered and then SARS-CoV disease outbreak occurred byHCoV–229E and HCoV–OC43. These two known human coronaviruses came into existence. Nidovirales (Coronaviridae family) consists of two genera Coronaviruses and Toroviruses. Those infect humans and animals are recognized as Coronaviruses while cause only diarrhoeal disease in animals belong to the genus Toroviruses. It was also observed that Torovirus can also found in the excreta of humans but this possibility remains unsolved.

Types: Nidovirales have coronaviridiae family contain diversified genus and species described below.

α-coronavirus genus

Human coronavirus (HCoV 229E): HCoV 229E was found by Dorothy Hamre, a researcher in 1965 infecting bats and humans. The genetic material of consists of ss +ve sense RNA(+ssRNA); gain entry inside the host cell by binding to the aminopeptidase N receptor[11]. Together with HCoVOC43 (belongs to the genus of β coronaviruses) causes normal flu like symptoms. This virus transmits via aerosol and fomites and causing wide clinical symptoms from the less severe common cold to severe death resulting in pneumonia, bronchiolitis.

Human coronavirus (NL63): HCoV NL63 was found in a 7-month newborn child having some bronchiolitis issue in late 2004. This case occurred in the Netherlands. Like HCoV 229E, this genetic material was same as above which gains entry inside the host cell by binding to the ACE 2 receptor[12]. The virus causes problems in upper respiratory tract of the lungs causing a wide range of infections such as bronchiolitis.

Porcine transmissible gastroenteritis virus (TGEV): TGEV is a virus that harm pigs; enters the host cell with the help of receptor aminopeptidase N present inside the host cell. The viral genetic material is a positive-sense single-stranded RNA; a spreading virus characterized by diarrhea & vomiting[12].

Canine coronavirus (CCoV): CCoV was discovered in the guard dogs in Germany when a sudden outbreak takes place in 1971. The genetic material of this virus consists of a ss positive RNA strand which enters inside the host with the help of receptor of host cells i.e. aminopeptidase N. This virus causes disease in a wide variety of dogs in the intestine which is highly contagious.

Feline infectious peritonitis virus (FIPV): It is a viral disease occurring in wild and domestic cats and results in feline infectious peritonitis. The virus is shed in feces and cats become infected by ingesting or inhaling the virus; also transmitted via bodily fluids. Clinical manifestations include common cold-like symptoms and then later on ataxia, muscle weakness, shortness of breath, etc.

Porcine epidemic diarrhea virus (PEDV): PDEV was discovered in Europe belongs to the α-coronavirus genus. It is a virus which harm porcine epidemic diarrhea in the cell lining of the

stomach of pigs; characterized by severe diarrhea and dehydration. Transmission occurs via the fecal-oral route and often older hogs get a sock and lose weight after being infected whereas nekonatal pigs die within five days after being infected.

β-coronavirus genus

Human coronavirus (HCoV)OC43: HCoV-OC43 which belongs to the genus β coronavirus infecting humans and cattle. The virus gains entry inside the host cell through binding to the N-acetyl-9-O-acetylneuraminic acid. The genetic material of this virus consists of a single positive sensed RNA and along with HCoV 229E cause common cold in various species. Both the virus causes upper respiratory canal disease and that leads to pneumonia.

Human coronavirus (HKU1): HCoV-HKU1 genetic material consists of ss positive sensed RNA; originated from infected mice. In humans, it causes respiratory disease associated with the common cold but advances to pneumonia and bronchitis. It was discovered in Hong Kong in 2 patients in the year 2005 during a study an important gene,

SARS coronavirus: A species of coronavirus belongs to the β coronavirus genus. It also has positive sensed single-stranded RNA virus infecting humans, bats, and certain other mammals. The virus gains entry inside the host cell by binding to the ACE2 receptor present in the host. Two strains of the virus have been found; SARS-CoV1 which has caused SARS infection during 2002-04 and the other one is SARS-CoV 2 which has caused pandemic Coronavirus disease recently in the year 2019.

Rat sialodacroadenitis virus (SDAV): SDAV is found in rats; prevalence in wild rats transmitted via aerosol or contact with infected nasal or salivary secretions and is highly contagious. Symptoms associated with the disease are squinting, photophobia, blinking and eye rubbing followed by sneezing and cervical swelling within post 5 days of infection.

Porcine haemagglutinating encephalomyelitis virus (PHEV): PHEV is the causative agent of encephalomyelitis disease in pigs characterized by vomiting, constipation, and anorexia. The virus containing information is stored in the +ve sense ss RNA genetic material belonging to the genus β coronavirus. Pathogenicity of the virus occurs in the respiratory tract in pigs further spread to Central Nervous System via different pathways.

Bovine coronavirus (BCoV): BCoV belongs to the β coronavirus genus having genetic material consisting of ss positive sensed RNA which infects the respiratory canal of various

species like pigs, turkeys, humans, and chickens. The virus enters the host cell by binding to the N-acetyl-9-O-acetylneuraminic acid receptor. Transmission occurs via the oral-fecal route.

Mouse hepatitis virus (MHV): MHV belongs to the genus of beta coronavirus which infects mice and rats and enters the cells by binding to Carcinoembryonic antigen-related cell adhesion molecule 1 (biliary glycoprotein) (CEACAM 1) receptor. The genetic material of this virus consists of ss positive sensed RNA causing epidemic murine illness.

γ coronavirus genus

Avian infectious bronchitis virus (IBV): IBV; γ coronavirus genus infects chicken resulted in the malfunction of laying eggs. Replication takes place in the lower part of the respiratory canal tract of the alimentary canal, kidney, oviduct, and testis. This virus results in economic loss in the poultry farms hence, causing economic loss.

Turkey coronavirus (TCoV): TCoV is closely related to IBV as it also causes respiratory infections in turkey. The disease is characterized by causing diarrhea in little turkeys but fewer things were known about this virus, hence, less prevalent.

Δ coronavirus genus

Bulbul coronavirus HKU11 (BuCoV – HKU11): This virus belongs to the δ coronavirus genus which is positive single-stranded RNA found in Chinese bulbuls.

Origin and Transmission of Coronavirus (SARS-CoV-2)

The Chinese population was once infected with one of the infectious particles known as SARS-CoV (Severe Acute Respiratory Syndrome Coronavirus) in the Guangdong province in 2003. When the virus was analyzed, it was confirmed that it belongs to the genus of β coronavirus. The persons who were infected by this SARS show some flu-like symptoms like the common cold, cough, throat infection, *etc.* also infect the alveoli of the respiratory system and cause Acute Respiratory Distress Syndrome (ARDS). Similarly, another virus was found in Saudi Arabian in 2012 and diagnosed with Coronavirus family and named the Middle East Respiratory Syndrome Coronavirus (MERS-CoV). It shows similar symptoms like SARS-CoV, later on, it shows ARDS and kidney failure reaction.

Now, another mutated virus was detected in Wuhan, China in 2019; identified that it belongs to the Coronavirus family and was named SARS-CoV-2. The SARS-CoV-2, non-enveloped, non-segmented, β coronavirus (subgenus sarbecovirus, Orthocoronavirus subfamily) consisting of genetic material having ss positive sensed RNA. To study the whole genomic sequence, researchers obtained the virus from the infected patients through the techniques known as Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) most common and next-generation sequencing. Results showed that the genome structure of SARS-CoV-2 is 96.2% and 79.5% identical to the Bat CoV RaTG13 and SARS-CoV respectively.

The conclusion drawn from above was that the Bat can be a host from which the virus has been originated and came into humans via another host i.e. intermediate host that may be present or not. On comparing databases of each coronavirus family, it was found that the whole Coronaviruses genus shows link with an animal origin for example; SARS-CoV, MERS-CoV, HCoV-NL63, and HCoV-229E while HCoV-OC43 and HKU1 have origin from rodents.[13] Some research revealed the domestic animals also play a very important role as intermediate hosts in the transmission of the virus from host to human. There are 7 α coronaviruses species out of 11 and 4 β coronaviruses species out of 9 found in bats which may be rightly said, that Bats are likely to be the natural host of the viruses[13].

Also, the viral structure consists of spike proteins which may vary among species which plays an important role in an entry inside the host cell. It was seen that the SARS-CoV-2 uses an enzyme ACE i.e. Angiotensin-Converting zyme to enter inside the host cell which is similar to SRS-CoV which uses the same machinery to enter. More depth of knowledge is required to investigate the natural host of this novel virus as the exact mechanism of transmission is not clear.

SARS-CoV-2 emergence theories

It is hard to believe that SARS-CoV2 emerged by genetic manipulation or synthetic cultivation. The Receptor Binding Domain (RBD) present in SARS-CoV-2 having an affinity for ACE 2 domian binding is different from the earlier prediction. If this had happened, then one of the genetic system machinery used for β coronaviruses must have used. But when data was evaluated, it showed no evidence of manipulation or derived from using previously virus backbone. However, we have proposed some conclusions which can be drawn from the above analysis about the existence of the novel coronavirus (SARS-CoV-2) and these are as follows-

Natural selection happened in the animal host before transmission: -

As already stated, SARS-CoV-2 is 96% identical to Bats SARS-CoV coronaviruses so the bat can be a natural host reservoir of the virus. But gene RaTG13, present in bat diverges in the context of spike protein as the spike protein present in the virus do not bind optimally to the ACE 2 receptor present in the host cell. This shows that SARS-CoV-2 binding to ACE 2 receptor optimally had occurred due to a natural selection process and finding of polybasic cleavage site in the S1-S2 junction had occurred during revolutionary process by mutation, insertion, or deletion. Mostly these all become possible when the host (animal host) has large density pool to breed and a gene encoding ACE 2 receptor which should be similar to human origin.

Natural selection happened in humans after transmission:-

Progenitor cells of SARS-CoV-2 showed transposition into humans which helps in acquiring the genomic structure during transmission via human to human. The Receptor Binding Domain (RBD) present in a virus which is similar to humans implies that the virus may have jumped into a human during transmission. Insertion of the polybasic cleavage site in the genome also suggests that it might have happened during human-to-human transmission. Hence, it states that during some interval of time, transfer of some characters occurred in humans during zoonotic transfer.

Acquire of characters during the interval of time:-

SARS-CoV-2 acquired this Receptor Binding Domain (RBD) during their lifetime in cell culture via mutation or recombination gives strong evidence of how the genes have transferred. Further, hypothetically, the generation of SARS-CoV-2 requires progenitor cells in the cell culture which has not been mentioned in detail yet. The presence of polybasic cleavage site having ACE 2 receptors occurred during their lifetime which shows high similarity to humans. Lastly, O-linked glycans present might have occurred during their lifetime.

Reservoir and transmission

The source of origination and transmission are important in order to know preventive strategies to contain the infection. Initially, a group of researchers suggested snakes be the possible host, however, similar karyotype findings of novel coronavirus with SARS-like bat

viruses supported the statement that not snakes but only bats could be the key reservoirs. Furthermore, analysis of homologous recombination revealed that receptor binding spike glycoprotein of novel coronavirus is developed from SARS-CoV (CoVZXC21 or CoVZC45) and a yet unknown Beta-CoV[2]. Human-to-human transmission of SARS-CoV-2 occurs mainly between family members including relatives and friends who share an intimate bond contacted with patients or incubation carriers. By contrast, the transmission of SARS-CoV and MERS-CoV is reported to occur mainly through nosocomial transmission. Direct contact with intermediate host animals or consumption of wild animals was suspected to be the main route of SARS-CoV-2 transmission. However, the source(s) and transmission routine(s) of SARS-CoV-2 remain elusive[4].

The preliminary estimate of R_0 (the expected number of cases directly produced by one person in a population susceptible to infection) for COVID-19 is 22. Fomites are suspected as the main source of infectious particles though some uncertainty remains. Other coronaviruses have been shown to persist for days on a gross surface. Recently, SARS-CoV-2 was isolated from a swab sample of a confirmed patient's stool by Chinese researchers to show that it has the potential for fecal-oral route transmission of 2019-nCoV. Transmission can also occur via the ocular surface so eye protection should also be used[1].

Structure & Genomic variation of Coronavirus: The viral structure consists of spike (S) protein, membrane (M) and nucleocapsid (N) proteins; on basis of this, they were grouped into α-coronaviruses (HCoV - 229E and HCoV – NL63), β-coronavirus (HCoV OC43 and HCoV HKU - 1), γ-coronavirus (Coronaviruses belonging to this have no human origin and found in avian species) and δ-coronavirus.

SARS CoV2 was isolated from a COVID-19 patient, a worker in the Wuhan seafood market, the complete genome of Wuhan-Hu-1 coronavirus (WHCV), one strain of SARS-CoV-2 is 29.9 kb. It has been shown that the genome of CoVs contains a variable number (6-11) of open reading frames (ORFs). Two-thirds of viral RNA mainly located in the first ORF (ORF1a/b) translates two polyproteins, pp1a and pp1ab, and encodes 16 non-structural proteins (NSP) while the remaining ORFs encode accessory and structural proteins[4] (fig. 1).

The structural proteins are encoded by four structural genes including spike (S), envelope (E), membrane (M), and nucleocapsid (N) genes. Recent studies have indicated notable variations in SARS-CoV and SARS-CoV-2 such as the absence of 8a protein and fluctuation in the number of amino acids in 8b and 3c protein in SARS-Cov-2[2]. Compared with the known

SARS-CoV and MERS-CoV genome, SARS-CoV-2 is closer to the SARS-like bat CoVs in terms of the whole genome sequence.

At the protein level, there are no amino acid substitutions that occurred in NSP7, NSP13, envelope, matrix, or accessory proteins p6 and 8b except in NSP2, NSP3, spike protein, and underpinning subdomain i.e. RBD[4]. It is reported that Receptor Binding Domain (RBD) in the spike glycoprotein of the Wuhan coronavirus is modified via homologous recombination[13]. The spike glycoprotein of SARS-CoV-2 is the mixture of bat SARS-CoV-2 and a not known β-CoV. Six RBD AAs are crucial for binding to ACE2 inhibitor receptors. With coordinates, based on SARS-CoV, they are Y442, L472, N479, D480, T487, and Y491 which correspond to L455, F486, Q493, S494, N501, and Y505 in SARS-CoV-2[12]. Five of these six residues differ between SARS-CoV and SARS-CoV-2 which shows that SARS-CoV-2 binds with high affinity to ACE2. In a fluorescent microscopic study, it was confirmed that the SARS-CoV-2 also uses the same ACE2 (Angiotensin Converting Enzyme 2) cell receptor and mechanism for the entry to the host cell which is previously used by the SARS-CoV-2[13]. Another research suggested that the mutation in NSP2 and NSP3 plays a vital role in the infectious capability and differentiation mechanism of SARS-CoV-2. Polybasic cleavage site (RRAR) at the junction of S1 and S2, the two subunits of the spike. This allows effective cleavage by furin and other proteases and has a role in determining viral infectivity and host range. A leading proline is inserted at this site in SARS-CoV-2, thus, the inserted sequence is PRRA. This shown that insertion of a furin cleavage site at S1-S2 junction enhances cell-cell fusion without affecting viral entry[13]. It provokes people to explore the difference of the host tropism and transmission between SARS-CoV-2 and SARS-CoV or conduct further investigations on the potential therapeutic targets[4] (fig. 2).

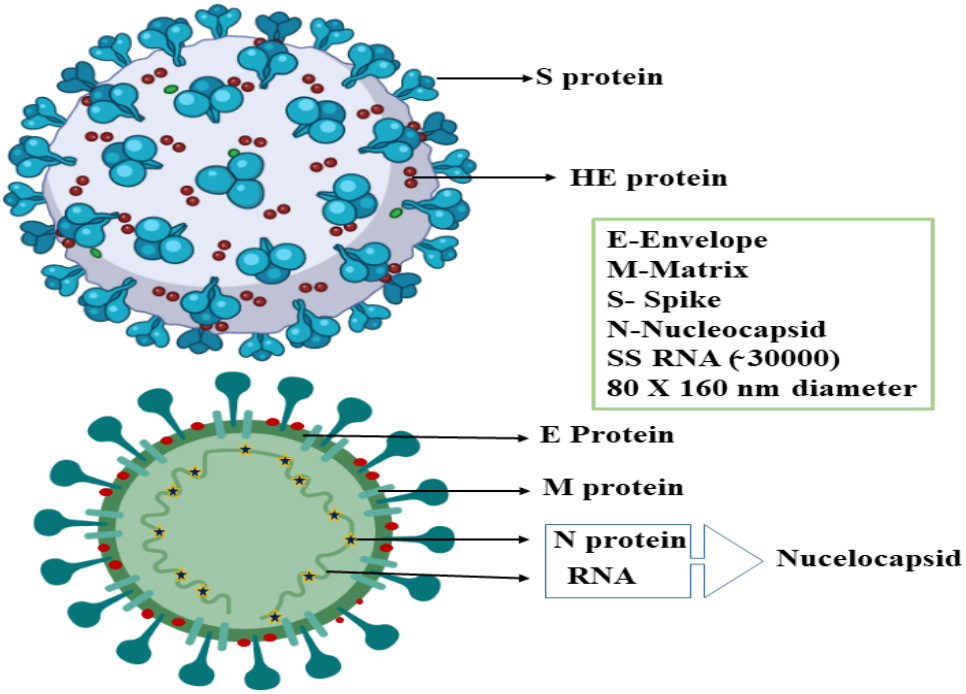

Figure No. 1. Structure of SARS - CoV 2

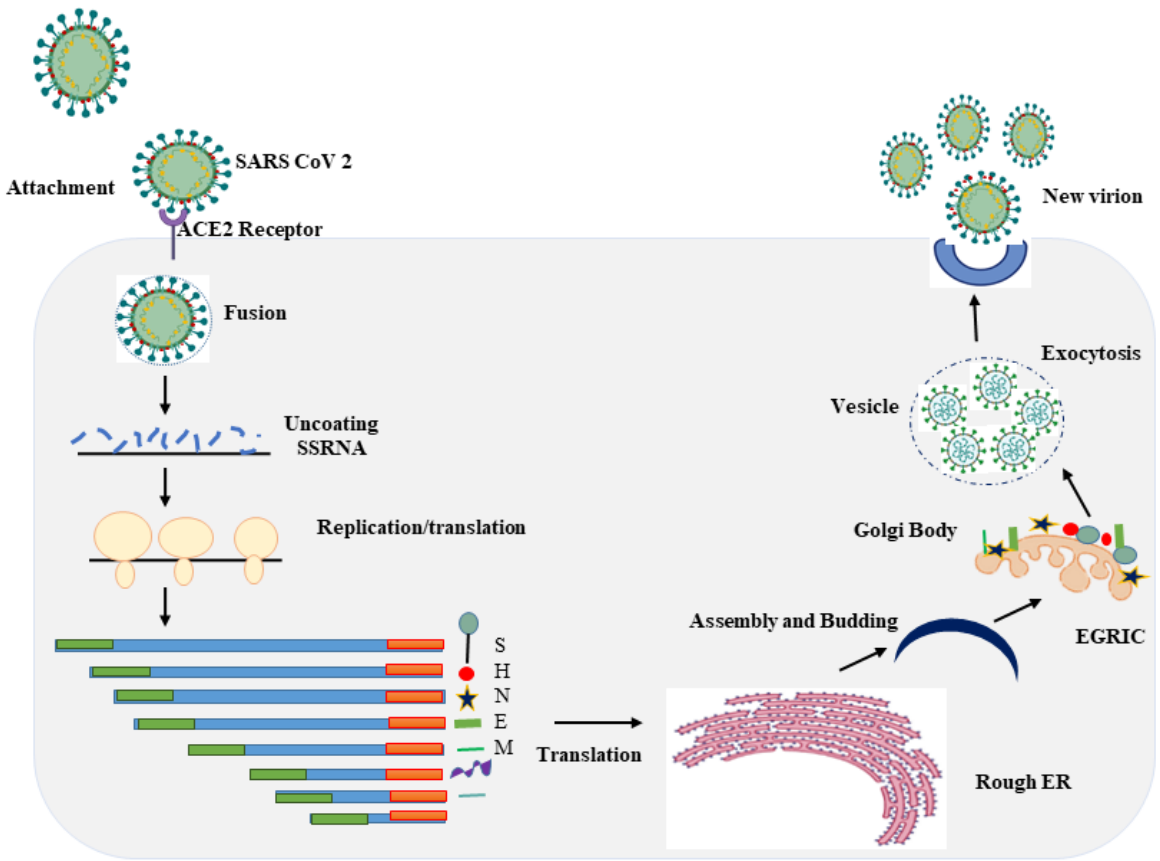

Figure No. 2. Replication and Translation of SARS- CoV 2

Clinical Manifestations associated with COVID-19

As an emerging acute respiratory infectious disease, COVID-19 primarily spreads through the respiratory tract by droplets, respiratory secretions, and direct contact for a low effective dose. ACE2 protein presents in abundance on lung alveolar epithelial cells and enterocytes of the small intestine which may help understand the routes of infection and disease manifestations. Based on current epidemiological investigation, the incubation period is 1-14 days, mostly 3-7 days[4]. This suggests that one can get infected contagiously before symptoms present (about 2.5 days earlier from the start of symptoms). About 18% of the cases remain asymptomatic. They can be asymptomatic and contagious regardless of lab or CT scan findings. Younger patients tend to remain asymptomatic (even if constantly around an infected individual) while the elderly usually show symptoms[14].

Age

Most cases present between ages 30-79 years. Table 1 shows the prevalence based on age ranges as witnessed by mainland China[4].

Table No. 1: Occurrence of COVID-19 related to age

Age (in years)	Percentage of occurrence
<10 yrs	1 (%)
10-19 yrs	1 (%)
20-29 yrs	8 (%)
30-79 yrs	87 (%)
>80 yrs	3 (%)

Symptoms

Researchers reported clinical features of patients confirmed to be infected with the COVID-19 (Table 2). Almost all the patients had bilateral lung ground-glass opacity on CT imaging. The initial symptoms include fever (98%), cough (76%), dyspnoea (55%), myalgia or fatigue (44%), sputum production (28%), headache (8%), hemoptysis (5%), and diarrhea (3%)[1].

Also, a part of the patients manifested gastrointestinal symptoms with diarrhea (3.8%) and vomiting (5.0%). Fever and cough were the dominant symptoms whereas upper respiratory

symptoms and gastrointestinal symptoms were rare suggesting the differences in viral tropism as compared with SARS-CoV[4].

Table No. 2: Representation of symptoms at various rates

Clinical manifestations	Percent (%)
Pyrexia	82.2
Wheeze	61.7
Exhaustion	44.0
Shortness of breath	41.0
Starvation	40.0
Froth	27.7
Muscle pain	22.7
Pharyngitis	15.1
Vomiting	9.4
Vertigo	9.4
Trots	8.4
Migraine	6.7
Heave	3.6
Dyspepsia	2.2

Co-morbidities

Table 3 presents the co-morbidity rate seen with COVID-19 cases. The most common co-morbidity is hypertension (30.7%). This is followed by diabetes mellitus (14.3%) and cardiovascular diseases (11.9%).

Table No. 3:Co-morbidities associated with COVID-19 and their occurrence

Other illness	Rate of occurrence (%)
Blood pressure	30.7
Diabetes	14.3
Heart disease	11.9
Disease of liver	2.8
Disease of lung	2.4
Disease of kidney	2.1
HIV-AIDS	1.4
Immune system disorders	0.2

There is suspicion regarding whether ACE (Angiotensin-converting Enzyme) inhibitors and ARB (Angiotensin Receptor Blocker) increase the risk of COVID-19 infection and severity. Similar to SARS, COVID-19 binds to ACE2 to infiltrate cells and therefore, increases the level of ACE2 and hence, increases the infectivity of COVID-19. However, animal models have shown that ACE2 inhibitors and ARB modulate the level of ACE2 and decrease the severity of SARS pneumonia. While the question remains unanswered, therefore, experts recommend continuing the medications for COVID-19 patients[4].

Taken together, these studies indicate the main clinical manifestations of COVID-19 are fever (90% or more), cough (75%), and dyspnoea (upto 50%). A small but significant subset has gastrointestinal symptoms[1].

Complications with COVID-19

Acute Kidney Injury

Acute kidney injury presents with elevated urea and cystatin-C levels in severe COVID-19 infection. There are two hypotheses regarding the cause of acute kidney injury. One is that kidneys harbor more ACE2 levels than the lung or heart especially in the proximal convoluted tubules and the other is injury via a cytokine storm.

Myocardial Injury

The most common causes of COVID-19 related deaths are associated with the lungs and heart. This was supported by the evidence explaining the mechanim of myocardial injury. One is the heart having similar ACE2 levels as lungs allowing viral entry into myocardial cells and the other is a cytokine storm.

Acute Respiratory Distress Syndrome (ARDS)

Alveolar cells in the lung contain abundant amounts of ACE2 allowing COVID-19 to harbor within the alveoli. Diabetes mellitus is a factor associated with the development of ARDS. Other associated co-morbidities include hypertension, cardiovascular disease, and chronic kidney disease[4]. In laboratory results, most patients had normal or decreased WBCs and Lymphocytopenia. But in severe patients, the neutrophil count, D-dimer, blood urea, and creatinine levels were higher significantly and the lymphocyte counts continued to decrease. Additionally, inflammatory factors (IL-6. IL-10, tumor necrosis factor-α) increases indicating the immune status of patients[4].

Symptoms tend to resolve after 10 days. However, viral shedding continues despite symptoms disappearing. COVID-19 RNA viral shedding persists for about 18 days (by nasopharyngeal swab) or 19 days (via feces). Severe cases continue shredding up to 25 days after initial symptoms arise. Due to these findings, the Chinese Municipal Health Commission has recommended against discharging patients until the patient has remained afebrile for 3 days and RT-PCR becomes negative[14].

CONCLUSION

The novel coronaviruses originated from the Hunan seafood market at Wuhan, China where bats, snakes, raccoon dogs, palm civets, and other animals are sold and rapidly spread to 109 countries. The zoonotic source of SARS-CoV-2 is not confirmed, however, sequence-based analysis suggested bats are the key reservoir. DNA recombination was thought to be involved at spike glycoprotein which assorted SARS-CoV (CoVZXC21 and CoVZC45) with the RBD of another Beta-CoV, thus, could be the reason for cross-species transmission and rapid infection. The COVID-19 pandemic is rapidly spreading. Case rates and CFRs continue to change. Identifying clinical characteristics, developing and identifying pertinent diagnostic criteria, and providing effective treatment and care are vital for overcoming the pandemic. The speed and volume of CTs launched to investigate potential therapies for COVID-19 highlight both the need and capability to produce high-quality evidence even in the middle of the pandemic. Until now, no promising clinical treatments or prevention strategies have been developed against human coronaviruses. There are various pharmaceutical companies such as Moderna Therapeutics, Inovio Pharmaceuticals, Novavax, Johnson and Johnson, *etc*. working for the development of effective SARS-CoV-2 vaccines. But still some are some questions which left unveil and require thorough research like the origin of coronavirus with more scientific proof, their transmission from one species to other maybe answer underlying within the genomic structure and its mutation rate and last question which is whether this coronavirus infects other species (R_0), if yes, then at what rate and its re-occurrence in a world.

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