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COVID 19: A RE-EMERGING PUBLIC HEALTH CHALLENGE

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ABSTARCT

The corona virus is named as a COVID-19 (Co-corona, vi-Virus, d-Disease), which is easily transmitted from person to person. The main symptoms of corona virus is sore throat, Runny nose, Headache, Difficulty in breathing, etc. The corona virus majorly affects the respiratory system and cardiovascular system. Corona viruses (CoVs) are a large family of viruses that causes illness ranging from the common cold to more sever disease such as Middle East Respiratory (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS-CoV). A novel corona virus (nCoV) is a new strain that has not been previously identified in humans. Corona viruses are zoonotic, meaning they are transmitted between animals and people. Corona viruses are large, enveloped, positive-stranded RNA viruses. They are the largest genome among all RNA viruses. The corona viruses spread from person to person among close contacts. Currently, there is no specific medicine or vaccine for COVID-19 and no medicines vaccines have been fully tested for safety and efficacy. At present, antiviral therapy is mainly used, as well as symptomatic and supportive treatment based on clinical condition of the patient. Avoid the meeting to infected person, leave from the infected area are the some measures to control the viral infection.

KEYWORDS: COVID-19, SARS, Novel corona virus, MERS, Zoonotic.

INTRODUCTION

The corona virus was firstly described in detail in 1960's. The corona virus get its name due to its distinctive corona or 'crown', which is made up of sugary protein the forms an envelope around the complete structure. The SARS-CoV-2 is novel strain of corona virus that was first detected in the city of Wuhan, in the province of Hubei, in the People's Republic of China – a city with a population of 11 million. The outbreak started as pneumonia of unknown causal agent at the end of December.

On 30 January 2020, the World Health Organization (WHO) declared the outbreak a Public Health Emergency of International Concern. The WHO recommended that the interim name of the disease causing the current outbreak should be 2019-nCoV acute respiratory disease. In the 2019-nCoV acronym, "2019" is the year the virus war first detected, "n" means "new", and "CoV" corresponds to the corona virus to the corona virus family.

On 11 February 2020, the International committee on Taxonomy of Viruses (ICTV) decide the name of virus as severe acute respiratory syndrome corona virus 2 (SARS-CoV-2), and the WHO finally decided to name the disease caused by the virus as COID-19 (for Corona virus disease identified in 2019).

Following large outbreak of the disease in multiple countries, with thousands of deaths around the world, on 11 March 2020 the WHO declared the outbreak to be a pandemic.

2019-nCoV belongs to subgenus Sarbecovirus of the genus Betacoronavirus of the family Coronaviridae possess a single strand, positive-sense RNA genome ranging from 26 to 32 kb in length. Next generation sequencing and phylogenetic analysis of the genome revealed 2019-nCoV was closely related (88% identical) to two bat-derived SARS- like corona virus and more distant from SARS-CoV (79%) and MERS-CoV (50%). Structural analysis suggested that 2019-nCoV might be able to bind to the angiotensin-converting enzyme 2 receptor in humans similar to SARS CoV which was confirmed by Zhou et al.

Up till now 6 human corona virus species known. HCoV-22E, HCoV-OC43, HCoV-NL63 and HKU1 cause only mild upper respiratory disease, and in rare cases cause severe infections at extreme age. In 2002-2003, an unusual atypical pneumonia emerged in

mainland China called severe acute respiratory syndrome (SARS) caused by new SARS CoV. It was transmitted in health care and hospital settings, generally five or more days after the onset of disease and from patients who were severely ill. Infected persons presented with fever, myalgia, malaise and chills or rigor, cough. Shortness of breath, tachypnea, or pleurisy developed later in the course of the illness. 20 to 30 percent of patients required admission to an intensive care unit requiring mechanical ventilation.

Structure of coronavirus (virion structure)

Corona virus virions are spherical with diameters of approximately 125 nm as depicted in recent studies by cryo-electron tomography and cryo-electron microscopy. The most prominent feature of corona viruses is the club-shaped spike projections emanating from the surface of the virion. These spikes are a defining feature of the virion and give them the appearance of a solar corona, prompting the name, corona viruses. Within the envelop of the virion is the nucleocapsid. Corona viruses have helically symmetrical nucleocapsids, which is uncommon among positive –sense RNA viruses, but far more common for negative –sense RNA viruses.

Corona viruses particles contain four main structural proteins. These are the spikes (S), membrane(M), envelop(E) and nucleocapsid(N) proteins, all of which are encoded within the 3' end of the viral genome. The S protein (~150 kDa), utilizes an N-terminal signal sequence to gain access to the ER, and is heavily N-linked glycosylated. Homotrimers of the virus encoded S protein make up the distinctive spike structure on the surface of virus. The trimeric S glycoprotein is a class I fusion protein and medicates attachment to the host receptor. In most, corona viruses, S is cleaved by a host cell furin-like protease into two separate polypeptides noted S1 and S2. S1 make up the larger receptor binding domain of the S protein, While S2 forms the stalk of the spike molecule.

The M protein is the most abundant structural protein in the virion. It is small (~25-30kDa) protein with three transmembrane domains and is thought to give the virion its shape. It has a small N-terminal glycosylated ectodomain and a much larger C-terminal endodomain the extend 6-8 nm into the viral particle. Despite being co-translationally inserted in the ER membrane, most M proteins do not contain a signal sequence. Recent studies suggest the M protein exists as a dimer in the virion, and may adapt two different confirmations, allowing it to promote membrane curvature as well as to bind to the nucleocapsid.

The E protein (~8-12kDa) is found in small quantities within the virion. The corona viruses E protein is highly divergent but have common architecture. The membrane topology of E protein is not completely resolved but most data suggest that it is a transmembrane protein. The E protein has an N-terminal ectodomain and C-terminal endodomain and has ion channel activity. As opposed to other structural protein, recombinant viruses lacking the E protein are not always lethal, although this is virus type dependent. The E protein facilitates assembly and release of the virus, but also has other functions. For instance, the ion channel activity in SARS-CoV E protein is not required for viral replication but is required for pathogenesis.

The N protein constitutes the only protein present in the nucleocapsid.it is composed of two separate domains, an N-terminal domain (NTD) and a C-terminal domain (CTD), both capable of binding RNA in vitro, but each domain uses different mechanism to bind RNA. It has been suggested that optimal RNA binding requires contributions from both domain. N protein is also heavily phosphorylated, and phosphorylation has been suggested to trigger a structural change enhancing the affinity for viral versus nonviral RNA. N protein binds the viral genome in a beads-on-a-string type confirmation. Two specific RNA substrates have been identified for N protein; the TRSs and the genomic packaging signal. The genomic packaging signal has been found to bind specifically to the second, or C-terminal RNA binding domain. N protein also binds nsp3, a key component of the replicase complex, and the M protein. These protein interactions likely help tether the viral genome to the replicase- trancriptase complex (RTC), and subsequently package the encapsidated genome into viral particles.

A fifth structural protein, the hemagglutinin-esterase (HE), is present in a subset of β-coroviruses. The protein acts as a hemagglutinin binds sialic acids on surface glycoprotein, and contains acetyl-estarase activity. These activities are thought to enhance S protein-mediated cell entry and virus spread through the mucosa. Interestingly, HE enhances murine hepatitis virus (MHV) neurovirulence; however, it is selected against in tissue culture for known reasons.

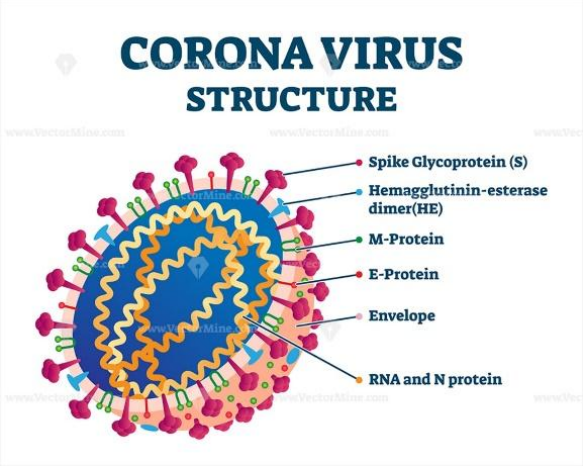

Fig. 01: Corona virus structure.

Table 1: The 16 nonstructural protein of corona virus and their functions.

Nsps	Functions
nsp1	Cellular mRNA depredation, inhibiting IFN signaling.
nsp2	Unknown
nsp3	PLP, polypeptides cleaving, blocking host innate immune response, prompting cytokine expression
nsp4	DMV formation
nsp5	3CL pro, M pro, polypeptides cleaving, inhibiting IFN signaling
nsp6	Restricting autophagosome expansion, DMV formation
nsp7	Cofactor with nsp8 and nsp12
nsp8	Cofactor with nsp7 and nsp 12, primase
nsp9	Dimerization and RNA binding
nsp10	Scaffod protein for nsp14 and nsp16
nsp11	Unknown
nsp12	Primer dependent RdRp
nsp13	RNA helicase, 5’ triphosphatase
nsp14	Exoribonuclease, N7-MTase
nsp15	Endoribonuclease, evasion of dsRNA sensors
nsp16	2’-O-MTase; avoiding MDAS recognition negatively regulating innate immunity.

Coronavirus Replication

Corona virus RNA synthesis occurs in the cytoplasm via a negative-strand RNA intermediate (Holmes,1996). The virion RNA is infectious and functions as an mRNA, having a 5’ terminal cap followed by a leader sequence and an untranslated region followed by poly (A) tail. Corona viruses have a polycistronic genome organization and synthesize multiple sub genomic mRNAs, all overlapping at the 3’ end (nested set of sub genomic RNAs) and all containing the same 5’ leader sequence derived from the 5’ end of the genome. Each mRNA is translated to generate the protein product of its most 5’ gene, but sometimes is translated into second, downstream protein as well. Corona viruses replicate by a unique discontinuous transcription mechanism that is not completely understood. Discontinuous transcription of sub genomic mRNAs is belived to be regulated by transcription unit. The current model is that discontinuous transcription occurs during the synthesis of sub genomic negative-sense RNAs; this model is supported by data that demonstrate the existence of transcriptionally active, sub genomic-size negative RNA strands containing the antileader sequence.

Corona virus gene are arranged in the order 5’’-relpicase-(HE)-S-E-M-N-3’, with some other genes that have been found not essential both in vivo and in vitro. The virion envelop surrounding the nucleocapsid contains the following structural proteins: S (spike), M (matrix), E (envelop), and, in the case of group II corona viruses, HE (hemaggulutinin esterase). S protein is a 180~kDa peplomer glycoprotein found on the virion envelop and on the plasma membrane of infected cell; S contains epitopes for viral neutralization and T-cell response, and is responsible for attachment to the cellular receptor and for both virus-cell fusion during viral entry, and cell-to-cell fusion for some corona viruses later during infection. The spike gene contains determinants of tropism and pathogenesis. M (matrix) protein is a transmembrane glycoprotein with its carboxy terminus integrated within virion core in maintain the core structure. E (envelop) is a 9.6-kDa polypeptide membrane associated protein that is critical for virion assembly. N, a 60-kDa phosphoprotein complexed with the RNA genome to form the nucleocapsid, forms the virionn core or nucleocapsid. New virion are assembled by budding into intracellular membrane and are released from the cells through vesicles of the secretory pathway.

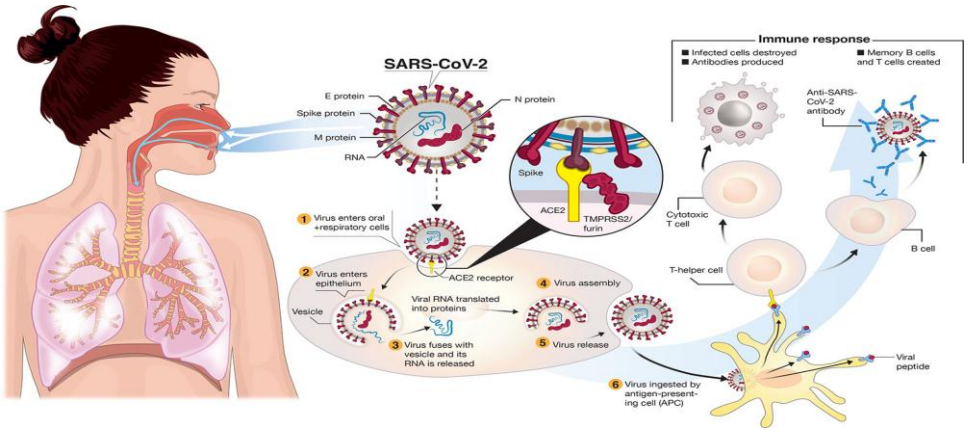

Fig. 02 A: Replication of Corona Virus.

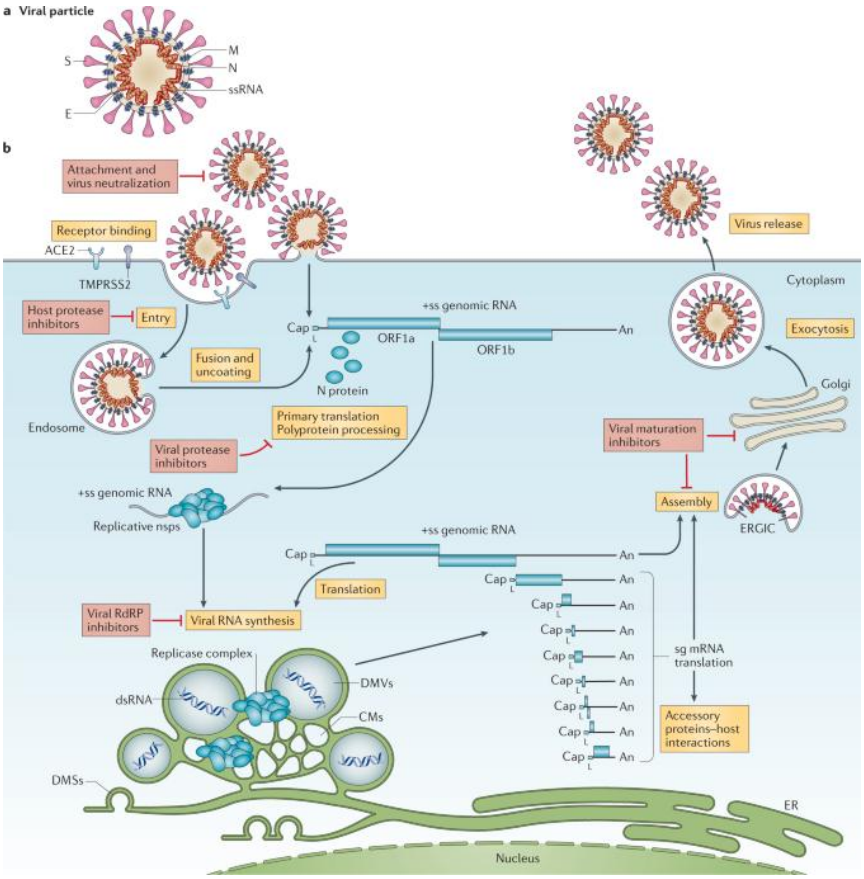

Fig. 02 B: Replication of Corona Virus.

Tranmission of Coronavirus

The transmission of corona virus occurs by the following mechanism

1. Most often, spread from person to person among close contacts (about 6 feet/1.8 meters.)
2. Person-to-person spread is thought to occur mainly via respiratory droplets produced when an infected person coughs or sneezes, similar to how influenza and other respiratory pathogens spread.
3. Theses droplets can land in the mouth, nose or eyes of people who are nearby or possible by inhaled into the lungs.
4. It may be possible that a person can get COVID-19 by touching a surface or object that has the virus on it and then touching their own mouth, nose or possibly their eyes, but this not thought to be the main way the spreads (centers for Disease Control and Prevention, 2020). There is evidence that corona viruses can remain infectious in inanimate surfaces for several hours or even days.
5. Typically, with most respiratory viruses, people are thought to be most contagious when they are most symptomatic. With COVID-19, however, there have been reports of spread from an asymptomatic infected patient to a close contact. (Centers for Disease Control and Prevention, 2020). Recent studies suggest that asymptomatic (or pre-symptomatic) patients may indeed be driving the rapid expansion of the disease.
6. Also, patients may remains contagious up to two weeks after the remission of symptoms. According to Wolfel and collaborators, whereas symptoms mostly waned bt the end of the first week. Stool and sputum samples remained RNA-positive over longer periods, in spite of full resolution of symptoms.
7. Minimal information is available regarding COVID-19 during pregnancy. Intrauterine or perinatal transmission has not been identified. In two reports including a total of 18 pregnant women with suspected or confirmed COVID-19 pneumonia, there was no laboratory evidence of transmission of the virus to the neonate. However, two neonatal case of infection have been documented. In one case, the diagnosis was made at day 17 of life after close contact with the infant's mother and a maternity matron who were both infected with the virus. The other case was diagnosed 36 hour after birth; the source and time of transmission in that case were unclear. Much of the advice in various countries, such as UK, about pregnant women moving to socially isolate is preventive rather than based on evidence of increased risk of harm.
8. In limited studies on women with COVID-19 and another corona virus infection, Severe Acute Respiratory Syndrome (SARS-CoV), the virus has not been detected in breast milk; however it is not known whether mothers with COVID-19 can transmit the virus via breast milk. Breast milk provides protection against many illness.

9. There are rare expectations when breastfeeding or feeding expressed breast milk is not recommended. The CDC has no specific guidance for breastfeeding during infection with similar viruses like SARS-CoV or Middle Eastern Respiratory Syndrome (MERS-CoV) also both coronaviruses. In a similar situation to COVID-19, the CDC recommends that a mother with flu continue breastfeeding or feeding expressed breast milk to her infant while taking precautions to avoid spreading the virus to her infant. Give low rates of transmission of respiratory viruses through breast milk, the World Health Organization presently states that mothers with COVID-19 can breastfeed. (Academy of Breastfeeding Medicine, 2020).

SYMPTOMS

For confirmed COVID-19 cases, reported illness has ranged from people with little to no symptoms to people being severely ill and dying. Symptoms can include

- Fever (>80% of the patient)
- Cough (>80%)
- Shortness of breath (31%)
- Muscle ache (11%)
- Loss of smell and taste
- Sour throat (15%)
- Runny nose. (33%)

The disease may also occur with mild symptoms only, including; low-grade fever, cough, malaise, rhinorrhoea, sore throat without any warning signs, such as shortness of breath or difficulty in breathing, increased respiratory secretions (i.e. sputum or haemoptysis), gastrointestinal symptoms such as nausea, vomiting, and diarrhea and without changes in mental status (i.e. confusion, lethargy).

Risk factors for severe illness are not yet clear, although older patients or patients with underlying medical comorbidities (diabetes, hypertension, cardiovascular disease, cancer) may be at higher risk. In the most severe cases, infection can cause pneumonia, severe acute respiratory syndrome, kidney failure and even death.

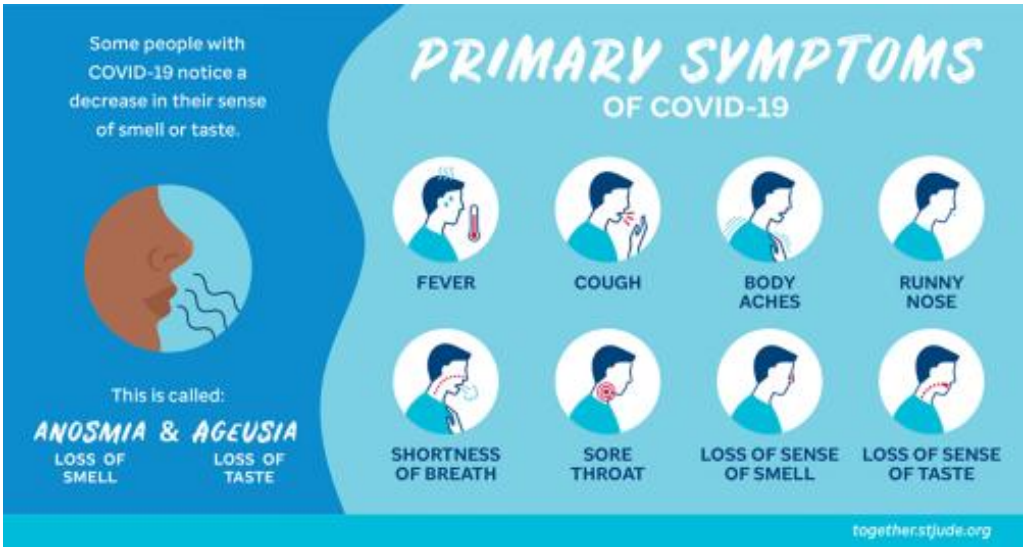

Fig. 03: Primary Symptoms.

Diagnosis

The current recommendation for laboratory diagnosis of COVID-19 infection from the CDC are that clinicians coordinate this testing with local public health authorities and the CDC. The preferred testing is the real-time reverse transcription-polymerase chain reaction (real time RT-PCR) test method similar to that developed for the diagnosis of SARS-CoV.

Sample Collection and Proper Shipment

Samples should be collected by trained personnel and considering all biosafety instructions, including the use of personal protective equipment appropriate for respiratory viruses.

Recommended samples are those from the lower respiratory tract, including sputum, bronchoalveolar larvage and tracheal aspirate. However, when collection of a lower respiratory tract sample is not possible, samples from the upper respiratory tract are also useful. In general, the collection of a combined nasopharyngeal swabs and oropharygeal swab is recommended. Although sampling of asymptomatic contacts on routine basis is not recommended, if it is consider necessary according to national guidelines, upper respiratory samples should be considerd.

Sample should be kept refrigerated (4-8°C) and sent to the laboratory where they will be processed within the 24-72 hours of collection. If samples cannot be sent within this period, freezing at -70°C (or less) is recommended until samples are shipped. Shipment is suspicious samples to reference laboratories or collaborating centers outside the country and by air must

ensure compliance with all international standards (IATA) for biological substances catageory B.

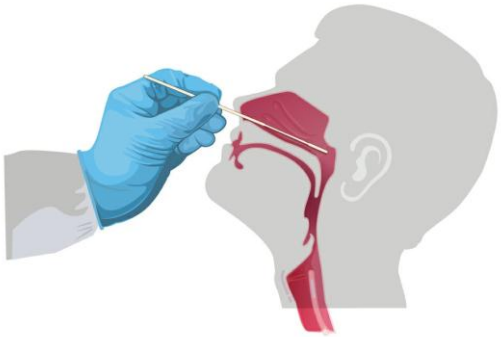

Fig. 04: Swab Test.

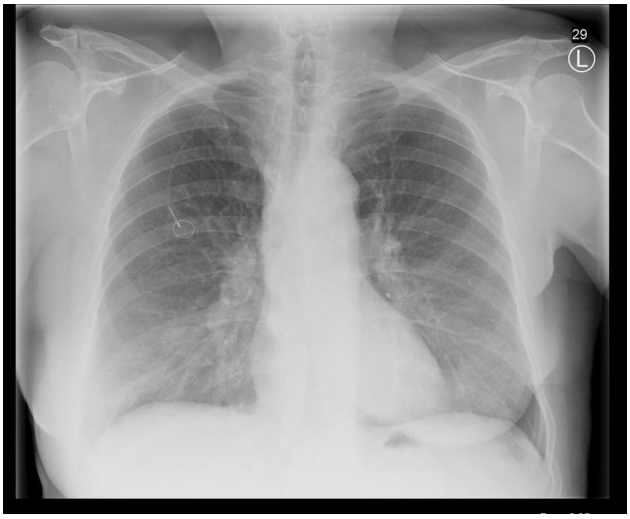

Fig. 05: Chest X-Ray of Covid-19 patient.

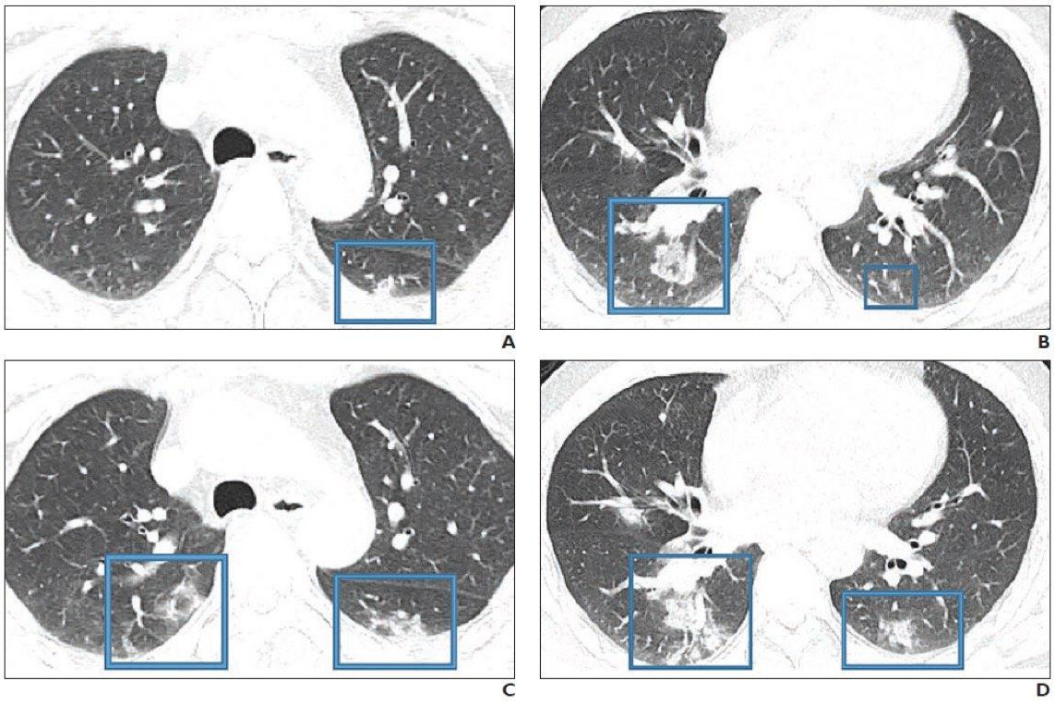

Fig. 06: CT scan of Covid -19 patient showing lesion (bright portion in image) in the lungs.

Treatement

1) Clinical treatment medicines

Currently, there is no specific medicine or vaccine for COVID-19 and no medicines or vaccines have been fully tested for safety and efficacy.

At present, antiviral therapy is mainly used, as well as symptomatic and supportive treatment based on the clinical condition of the patient. Supportive treatment include oxygen therapy, hydration, fever/pain control, and antibiotics in the presence of bacterial co-infection.

Hospitals and research labs all over the world are testing many different therapies on corona virus-positive patients in an effort to find a potential COVID-19 treatment. Below we highlight a few medications that have been making a buzz in the science community.

a) Remdesivir

Remdesivir is an antiviral that is given by intravenous (IV) infusion in the hospital. This is brand new drug that has not been approved by the FDA for use on the market yet, and is being tested in carefully controlled environment. It was previously shown some effect against SARS, MERS, and Ebola in cell and animal models. In a recent in-vitro study, remdesivir prevented human cells from being infected with SARS-CoV-2.

Doctors across the U.S. are enrolling patients with severe COVID-19 into clinical trials to see if remdesivir is an effective treatment. Gliead recently announced early results from a phase 3 trial. According to the manufacturer, half of the patients who got remdesivir saw improvement in about 10 days and more than half were discharged from the hospitals by week 2.

Early results from a large U.S. study of 1,063 patients showed that people who got remdesivir recovered faster compared to those who got a placebo (11 days vs. 15 days, respectively). The death rate in the remdesivir group (8%) was also lower than the placebo group (11%).

Based on the positive reports from these two studies, the FDA issued an emergency use authorization (EUA) for remdesivir on May 1, 2020. The EUA does not mean that the FDA has approved remdesivir for the treatment of COVID-19. Rather, the intent of the EUA is to make it easier for doctors to get remdesivir for hospitalized patients with severe COVID-19 symptoms. These are the patients who require mechanical ventilation or extra oxygen.

b) Hydroxychloroquine and choroquine

Hydroxychoroquine and chloroquine are two medications that have been used for many decades to treat malaria and autoimmune conditions like rheumatoid arthritis and lupus. A few small studies suggest that they may also be helpful for treating hospitalized patients with mild cases of COVID-19, while other studies showed that hydroxychloroquine did not make difference.

c) Azithromycin

Azithromycin is an antibiotic commonly used to treat bacterial infections such as bronchitis and pneumonia. It has been shown to have some in vitro activity against viruses like influenza A and Zika, but did not work against the corovirus that causes MRES.S

2) Convalescent plasma therapy

For COVID-19 patients with rapid disease progression, severe and critical illness, convalescent plasma therapy (CPT) can be tried (National Commission of the People's Republic of China, 2020). CPT utilizes a certain titre of virus-specific antibodies in the plasma of the convalescent individual to enable the patient receiving the infusion to obtain passive immunity and remove pathogens from the blood circulation. This method is successfully used in the treatment of the SARS and H1N1 influenza and is an effective treatment.

The use of CPT treatment can follow the following principles:

- In principles, the course of disease does not exceed three weeks. Also, the patient should have a positive viral nucleic acid test or viraemia certified by clinical experts.
- Patients with severe disease with rapid disease progression, or critically ill early stage patients, or patient's comprehensive evaluated by clinical experts as requiring plasma therapy. The infusion does is determined according to the clinical situation and weight of the patient, usually the infusion does is 200-500 ml (4-5ml/kg).

Before, during and after the infusion, detailed records and clinical observations should be made to asses the adverse effect of plasma infusion. The main types of adverse transfusion reactions include transfusion-related circulation overload, transfusion-related acute lung injury, transfusion-related dyspnoea, allergic reaction, transfusion-associated hypotension reactions, non-hemolytic febrile reactions, acute hemolytic transfusion reactions, amd delayed haemolytic transfusion reactions, infectious transfusion reaction.

Table 2: Comparison between SARS, MERS, COVID-19.

	SARS	MARS CoV	COVID-19
Year	2002-2003	2012-2013	2019-2020
Country of origin	China	Middle East	Wuhan, china
Animal Host	Himalayan palm civets and reccoon dog	Dromedary camels	Bat
Receptor	ACE 2	DPP4	ACE 2
Incubation period	2-10 days	2-14 days	2-7 days
Mortality	10%	35%	2-3%

CONCLUSION

Over the past 50 years the emergence of many different corobaviruses that cause a wide variety of human and veterinary disease has occurred. It is likely that these viruses will continue to emerge and to evolve and cause both human and veterinary out break owing to their ability to recombine, mutate and infect multiple species and cell types.

Future research on corona viruses will continue to investigate many aspects of viral replication and pathogenesis. First, understanding the propensity of the viruses to jump between species, to establish infection in a new host, and identify significant reservoir of corona viruses will dramatically and in our ability to predict when and where potential epidemics may occur. As bats seem to be a significant reservoir for these viruses, it will be interesting to determine how they seem to avoid clinically evident disease and become persistently infected. Second, many of the non-structural and accessory proteins encoded by these viruses remain uncharacterized with no known function. And it will be important to identify mechanism of action for these proteins as well as defining their role in viral replication and pathogenesis. These studies should lead to a large increase in the number of suitable therapeutic targets to combat infection. Furthermore, many of the unique enzymes encoded by corona irises. Such as ADP-robose-I-phosphate, are also present n higher eukaryotes, making their study relevant to understanding general aspects of molecular biology and biochemistry. Third, gaining a complete picture of the intricacies of the RTC RNA replication process used by these virus. Finally, defining the mechanism of how coronviruses cause disease and understanding the host immunological response will significantly improve our ability to design vaccines and reduce disease burden.

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