

COVID-19: recent findings into emerging coronavirus

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ABSTRACT

The emergence of novel coronavirus (SARS-CoV-2) is marked as the highest pathogenic coronavirus that has crossed from the hosts to the human population in the twenty-first century. The spreading of COVID-19 in different Chinese cities and around the world is travel-related viral spread with the unprecedented nosocomial outbreaks. It has also shown with high case-fatality rates, indeed to urgent prophylactic and therapeutic settings. Scientific advancements of the SARS-CoV-2 pandemic allowed for rapid progress to understand the epidemiology and pathogenesis of SARS-CoV-2. This review highlights the genomic structure of SARS-CoV-2 with the proposed roles of genotype and phenotype of SARS-CoV-2 in pathogenesis and discuss recent results supporting treatment strategies of COVID-19 with a special focus on how these new insights may facilitate rational development of SARS-CoV-2 for targeted therapies in the future.

Keywords: novel coronavirus, SARS-CoV-2, COVID-19, pneumonia, *Betacoronavirus*, transmission

INTRODUCTION

One of the major public health challenges of the 21st Century which cause by coronavirus is outbreaks by the severe acute respiratory syndrome (SARS-CoV), middle east respiratory syndrome (MERS-CoV), and novel coronavirus (severe acute respiratory syndrome-2 (SARS-CoV-2) in Wuhan, China which known as (COVID-19). Coronaviruses (CoVs) have known as the largest positive-sense and single-stranded RNA (+RNA) viruses from coronaviridae family. CoVs have four genera: Alphacoronavirus, Betacoronavirus, Gammacoronavirus, and Deltacoronavirus. Coronaviruses are basically zoonotic that can be transmitted to people from animals. Previously SARS-CoV has been reported to be acivet cats origin and transmitted to humans. MERS-CoV also come from camels to humans and the novel coronavirus (SARS-CoV-2) which discovered in Wuhan, China is coming from bats. Several types of coronaviruses are hosing in animals and cannot transmit to humans [1-5].

In late December 2019, series of pneumonia cases with unknown etiology has been reported in Wuhan City, Hubei Province, China. The Chinese government warned the World Health Organization (WHO) about an outbreak of unknown cause. The initial investigation of epidemiological cases has been reported seafood and wet animal wholesale market in Wuhan as the main source of this pneumonia. On 7 Jan 2020, Chinese scientists have successfully isolated a novel coronaviruses which known as (SARS-CoV-2) virus. The SARS-CoV-2 sequencing has been obtainable by WHO on 12 Jan 2020. The genetic sequence collecting of SARS-CoV-2 in a short time is the most important achievement because that is a key role for understanding the COVID-19 properties and doing with other scientists around the world [6-9].

Coronaviruses have been genotypically and serologically divided into four genera: alpha and beta coronaviruses. It is hosting by mammals. Gamma coronaviruses are hosting in birds and marine mammals and delta coronaviruses are hosting by birds and swine. The SARS-CoV-2 is a β CoV and has a similar genetic sequence with SARS-CoV that lately named SARS-CoV-2 by the WHO. Since the evolutionary neighbors and outgroups of the novel SARS-CoV-2 have been found in bats, it is speculated that the natural host of the Wuhan novel coronavirus may also be bats and it is likely to have an unknown intermediate host-vector during bat-to-human transmission [3, 10-14]. In this m review, we summarized the recent findings of SARS-CoV-2 and provide a brief introduction of genomic structure SARS-CoV-2 with the proposed roles of genotype and phenotype of SARS-CoV-2 in pathogenesis. These isight may facilitate rational development of SARS-CoV-2 for targeted therapies in the future.

Genomic structure and Genomic organization of SARS-CoV-2

Generally, SARS-CoV-2 is like to be similar to some beta coronaviruses (β -CoV) which have been detected in bats. It is different from SARS-CoV and MERS-CoV. The β -CoVs are mainly divided into four lineages. SARS-CoV and SARS-CoV-2 are from lineage B, and it has more than 200 virus sequences. The MERS-CoV is from lineage C that has over 500 viral sequences. All coronaviruses mainly encode a surface glycoprotein and spike that play a key role in binding with the receptor of host cell and mediate viral entry. The receptor-binding domain (RBD) as a single region of the spike protein of the β -CoVs can mediate the interaction between the host cell receptor leading to cleave the spike and release the spike fusion peptide mediating virus entry. SARS-CoV-2 has S protein on

surface and forms a club-like structure. Surmizing that the structural properties of SARS-CoV-2 are mainly matching with SARS-COV and MERS-COV, and the phylogenetic tree of coronaviruses including the SARS-CoV-2 presented in figure (1-A) [15, 16].

Genetically, coronaviruses have been previously described to be the largest genome of RNA viruses with the longest stable RNAs in nature. The basic set of coronaviruses has the replicase (Rep 1a and 1b), the spike, envelope, membrane and nucleoprotein, ordering - Rep1a-1b-S-EM-N-30. The variable number of encoding nonstructural proteins genes have a role for the character of all groups. Many models to explore the discontinuous synthesis. Notably, a Chinese scientist has successfully isolated the SARS-CoV-2 on 7 January 2020 and explored the genome sequencing of the SARS-CoV-2. The genome sequences of SARS-CoV-2 currently known are almost identical and homologous sequencing. It is similar to SARS-CoV more than MERS-CoV. Related study has revealed that by reading more than 20,000 viral fragments from specimens the most contigs were matched with the genome of the lineage B from betacoronavirus by more than 85% identity with a bat SARS-like CoV (bat-SL-CoVZC45, MG772933.1). The genome sequence details of the isolated SARS-CoV-2 coronaviruses and coding regions have revealed in tables (1,2) and figure (1-B). The researcher also reported that there is 86.9% nucleotide sequence identity to a bat SARS-like CoV. The collected genome of three samples with SARS-CoV-2 were clustered together, and formed an independent subclade within the arbovirus subgenus. Related work analyzed nine samples of SARS-CoV-2 and found that the genome of these samples was extremely similar by more than 99.98% sequence analogy. SARS-CoV-2 has 88% identity to two bat-derived SARS-like coronaviruses, bat-SL CoVZC45 and bat-SL-CoVZXC21 which collected in Zhoushan, eastern China in 2018. They also shared that

there are distant 79% from SARS-CoV and 50% MERS-CoV. Chinese national institute for viral disease control and prevention has recommended using an open reading frame for the novel coronavirus 1AB (Open Reading Frame, ORF1ab), nucleocapsid protein (Nucleoprotein, N) primers and probes gene regions [8, 11-13, 17-19].

Table 1: Summary of Genes Target [20, 21]

Genes Target		Sequence (5' to 3')
ORF1ab	Forward primer (F)	CCCTGTGGGTTTTACACTTAA
	Reverse primer (R)	ACGATTGTGCATCAGCTGA
	Fluorescent Probe (P)	FAM-CCGTCTGCGGTATGTGGAAAGGTTATGG-BHQ1
N	Forward primer (F)	GGGGAACTTCTCCTGCTAGAAT
	Reverse primer (R)	CAGACATTTTGCTCTCAAGCTG
	Fluorescent Probe (P)	FAM-TTGCTGCTGCTTGACAGATT-TAMRA

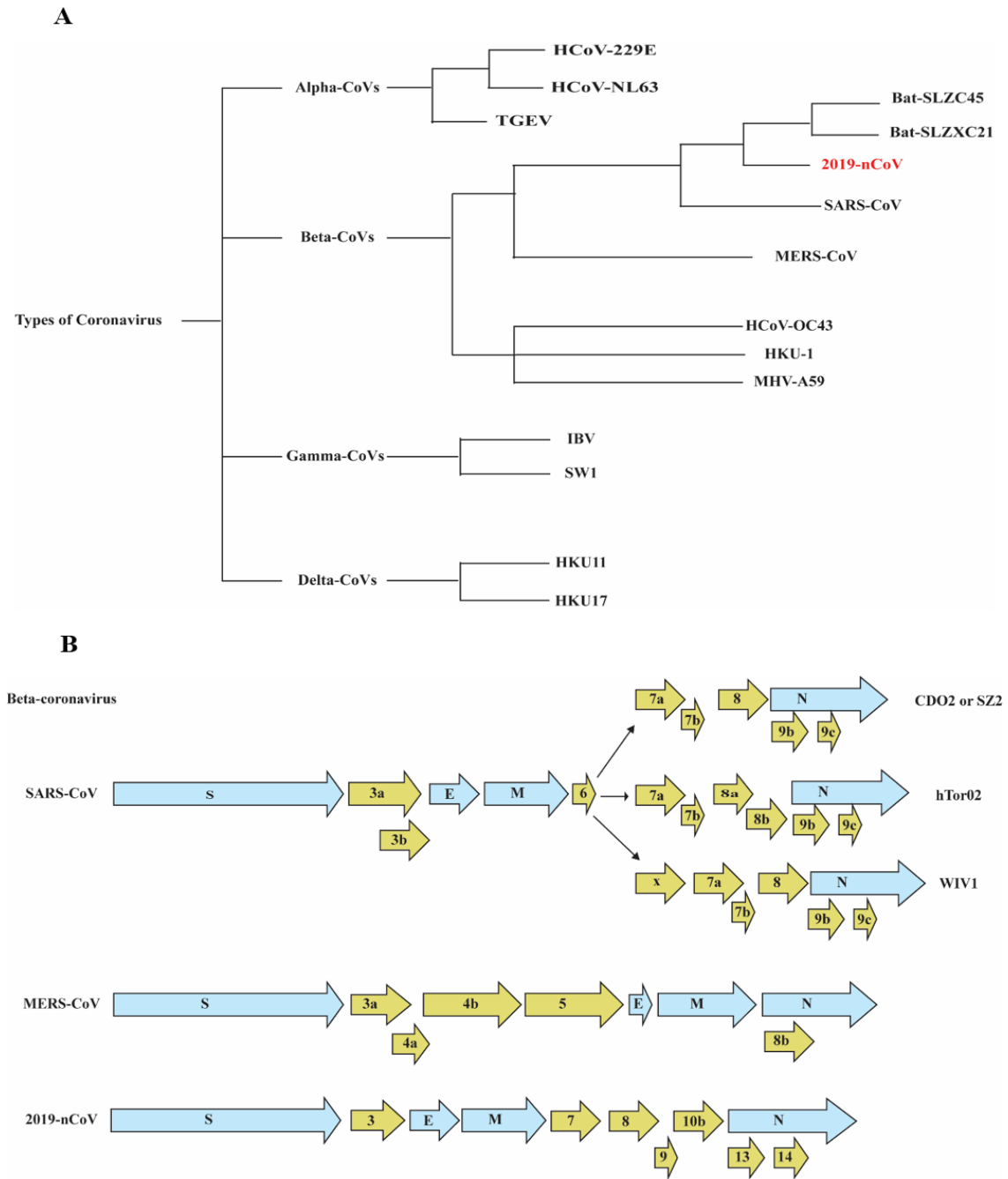


Figure 1: The phylogenetic tree of coronaviruses and genomic structure of coding regions; (A) The phylogenetic tree of Coronaviruses includes SARS-CoV-2 (B) Coding regions of COVID-19, SARS-CoV, and MERS-CoV SARS-CoV-2. SARS-CoV; severe acute respiratory syndrome coronavirus. MERS-CoV; the Middle East respiratory syndrome coronavirus

Table 2: Describing the early samples collecting from patients of COVID-19 in Wuhan with detailed information [21].

Numbering	Species name	Isolate	Length (bp)	Submission date
MN908947	Wuhan seafood market pneumonia virus	Wuhan-Hu-1	29875	2020
NC_045512	Wuhan seafood market pneumonia virus	Wuhan-Hu-1	30473	2020
MN975262	Wuhan seafood market pneumonia virus	COVID-19_HKU-S Z-005b_2020	29891	2020
MN938384	Wuhan seafood market pneumonia virus	COVID-19_HKU-S Z-002a_2020	29838	2020
GWHABKG00000000	Wuhan seafood market pneumonia virus	IPBCAMS-WH-02	29889	2020
GWHABKH00000000	Wuhan seafood market pneumonia virus	IPBCAMS-WH-03	29899	2020
GWHABKI00000000	Wuhan seafood market pneumonia virus	IPBCAMS-WH-04	29890	2020
GWHABKF00000000	Wuhan seafood market pneumonia virus	IPBCAMS-WH-01	29899	2020
GWHABKJ00000000	Wuhan seafood market pneumonia virus	IPBCAMS-WH-05	29883	2020
MK539948	Porcine epidemic diarrhoea virus	CT	4161	2019

The role of genotype and phenotype of SARS-CoV-2 in pathogenesis

In international gene banks such as GenBank have several Sars-CoV-2 gene sequences that achieve by scientists. These findings are very important for allowing researchers to trace the phylogenetic tree of the virus. All the recognized strains are different according to the mutations. [22]. Pathophysiology and virulence mechanisms of

CoVs and SARS-CoV-2 can use links for the nsps function and their structural proteins. Together, nsp may has ability to block the innate immune response in the host [23]. The envelope as structural functional msy play a key role of the virus pathogenicity by promoting the viral assembly and release. There are some features like nsp 2, and 11 still not clearly prescribed. The matter of viral mutations is key for explaining potential disease relapses. Research required to deeply focus on the structural characteristics of SARS-COV-2, it will increase the cahns to understand pathogenetic mechanisms. The clinical data has shown less extra respiratory involvement with SARS-COV-2 compare with SARS-COV, it may due to the lack of extensive data.

On SARS-CoV-2 surface there is a spike glycoproteins and homotrimers which may link to host receptors and paly a key role in viruse entery. It mainlly has two subunits (S1 and S2). S proteins are homotrimers of compose the spikes on the viral surface, guiding the [24]. Notably, S2 subunit of SARS-CoV-2 contain a fusion peptide, a transmembrane domain and cytoplasmic domain which are very conserved. These characersitcs may provide a potential targeting drug.

Origin and transmission of COVID-19

Coronaviruses have known as largest group of viruses that can cause many diseases. The patients have been shown with different clinical symptoms compared with the common cold of lung infections with MERS and SARS. The novel coronavirus COVID-19 discovered for the first time in December 2019 in Wuhan, China. The transmission of SARS-CoV-2 has been previously described which can be transmitted

from person to person. Most cases that transmitted from humans to humans have occurred by the environment with absence of appropriate infection control precautions. Many wild animals can carry pathogens and act as vectors for certain infectious diseases. Civets, bats, bamboo mice and badgers are common hosts of coronaviruses. The outbreak of viral pneumonia in Wuhan has a lot in common with the outbreak of SARS in Guangdong in 2002, and both have occurred in the winter. The outbreak originated from the contact between live animals traded in human and animal markets, where seafood, poultry, snake, bats, and farm animals were sold and was caused by unknown corona. Since the evolutionary neighbors and outgroups of the Wuhan novel coronavirus have been found in bats, it is speculated that the natural host of the Wuhan novel coronavirus may also be bats. Like the SARS coronavirus that caused it in 2002, the new coronavirus is likely to have an exact intermediate host-vector during bat-to-human transmission and related studies suggesting pangolin [25-28]

The novel coronavirus SARS-CoV-2 and SARS-CoV viruses are all coronavirus from the bats origin, and many coronaviruses associated with coronaviruses in humans are associated with bats, and many coronaviruses have natural hosts in bats. It is likely that bats are the primary host of the new Wuhan coronavirus, which has completed bat-intermediate host-human transmission through evolutionary mutation. However, there may be more intermediate hosts, from bats to humans, that have not yet been cleared. Coronavirus pathways from animal to human and person to person: contact transmission and droplet transmission, the general differentiations of COVID-19 with the previous reported coronaviruses SARS and MERS has reported in the table (3). Many of COVID-19 patients reportedly to have some link with large seafood and animal market proving

that the transmission is animal-to-person. Furthermore, the outbreak is still spreading and the number of patients in different cities and moving to other countries are increasing indicating that SARS-CoV-2 can be easily transmitted from person to person [7, 17, 29-34].

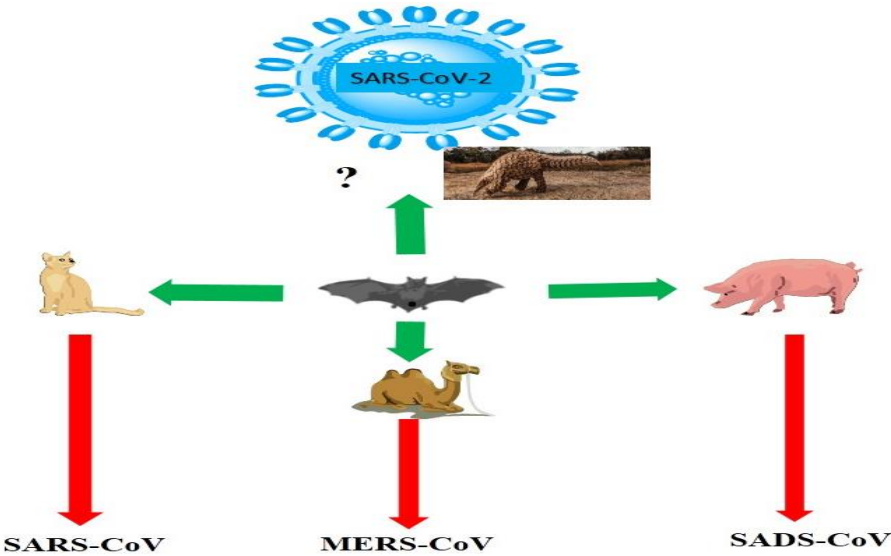


Figure 2: Animal origins of human Covs including novel COVID-19.

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Table 3: General differentiation of COVID-19, SARS and MERS

Name	SARS-CoV	MERS-CoV	COVID-19* Up to April 27, 2020	References
Year	2002	2012	2019	
confirmed cases	8,422	2,494	> 3 milion	[35-37]
Incubation period	2-7 days	5.5-14 days	2-14 days	[38-40]
Outbreaks	large	large	large	[35, 36, 41]
Clinical features	fever, cough, malaise, headache, muscle pain, and respiratory infection	fever, cough, headache, muscle pain, and respiratory infection	multiple system infections and mainly respiratory tract infections, such as pulmonary edema, ARDS, or multiple organ failure and have died	[7, 42, 43]
Mortality	10%	35%	≥6% even now	[7, 30, 44]
Transmission, person to person	quickly	moderate	quickly	[42]
Location	Starting from Guangzhou Guangdong, China, Spread 37 countries	Starting from Middle Eastern Countries, spread 27 countries include China	Starting from Wuhan, Hubei, China, Spread 21 countries	[35, 36, 41]
Main host	batas	batas	batas	[30]
Intermediate host	civets	camels	? may pangolin	[30]
Severity	Sever	Sever	Sever	[42, 43]

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The epidemiological and risk factors of COVID-19

In December 2019, several patients with pneumonia were observed in Wuhan, China. The epidemiological evidence was mainly associated with Huanan seafood. The number of people was growing up the rapidly unknown cause. The clinical futures were like coronavirus infection which was lately named COVID-19 by WHO. As of April 27, 2020, there were more than 3 milion confirmed cases and the suspected cases more 203.332 fatalities. Up to now, there are around 33 Chinese provinces and more than 183 countries have been reported with COVID-19, the geographical distrubion of the confirmed cases of COVID-19 has explored in figure (3). The infections in family clusters and medical stuff have been proved to be human-to-human transmission. The COVID-19 cases are still growing rapidly from diffrent international locations, and it become the highst public concern leading to a wide range of outcomes like economic impacts and some cases loss the lives. Perouse epidemic of different coronavirus infections such as SARS in Guangdong, China has affected around 37 countries and the confirmed cases were more than 8000 cases in 2003. So far, some of cases have occurred to the laboratory stuff accidents or via animal to human transmission. In the seven years between the first case of MERS in April 2012 and November 2019, there were around 2494 confirmed cases [8, 29, 30, 36, 45]

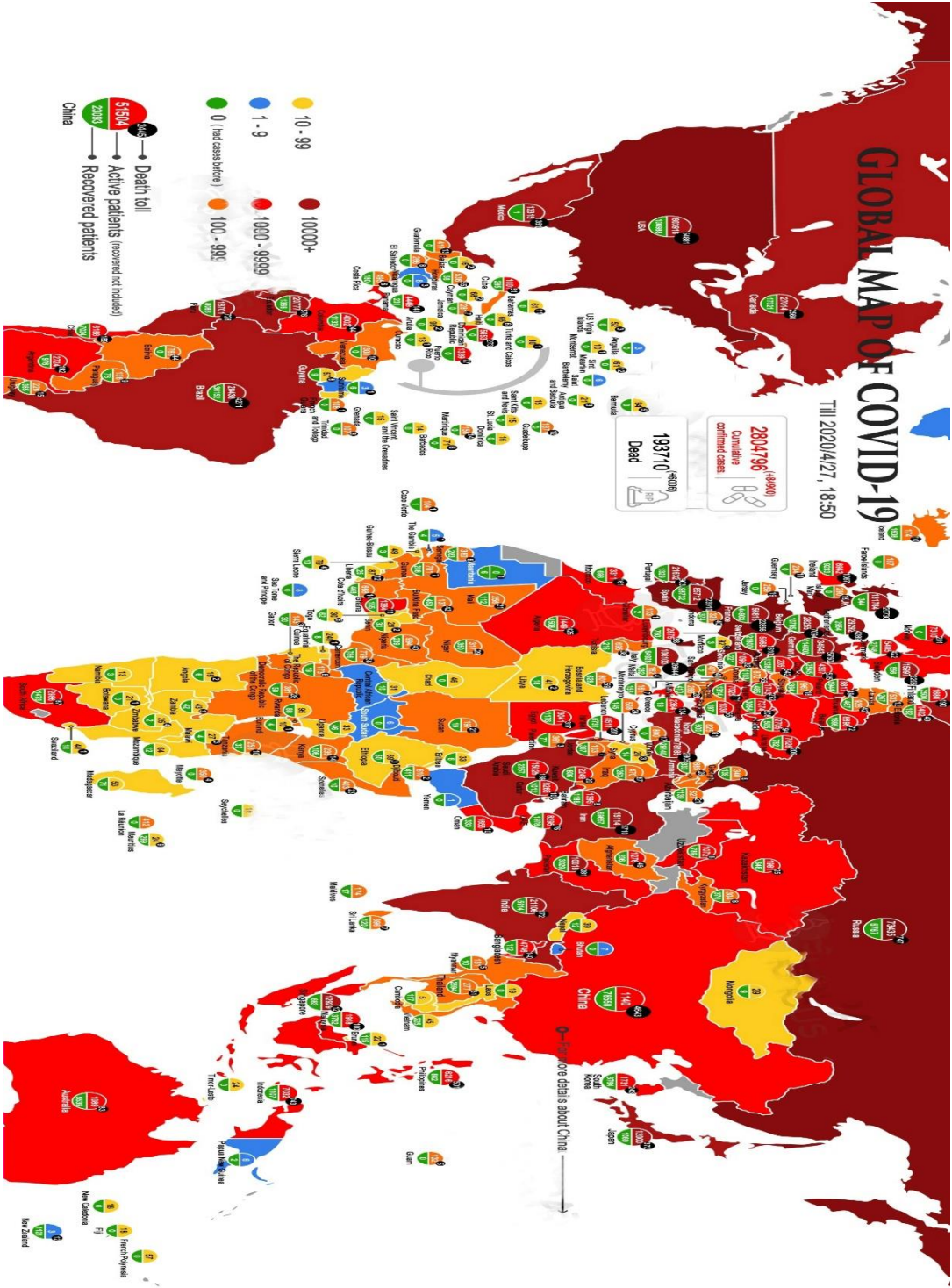


Figure 3: The geographical distrubion of the confirmed cases of COVID-19, April 27, 2020 [46].

The severity of COVID-19 in immunocompromised patients

The number of infected people with COVID-19 is rapidly increasing around the worlds. The majority of severe COVID-19 have been reported in immunocompromised patients and adults more than 80> years old. Most of reported cases were with cardiac disease, cancer, hypertension, and in patients treated with immunosuppressive targeted therapies. Chinese report of 72 314 cases record with COVID-19 showed that the Case-fatality rate in adults more than 80> years was 14.8%. Related work revealed that the older patients were with sever systemic symptoms, extensive radiological ground-glass lung changes, lymphopenia, thrombocytopenia, and increased C-reactive protein and lactate dehydrogenase levels [47, 48].

Pregnancy is known as mmunocompromised state that demands some pathophysiological disorders such as cardiovascular and other abnormalities. COVID-19 as pandemic can infect all human including pregnant patients. Viral myocarditis and cardiomyopathy were showed in non-pregnant COVID-19 patients. It also recently reported in pregnant COVID-19 patients. Recent works have reported that confirmed COVID-19 cases in pregnancy were severe infection with cardiac dysfunction and moderately reduced left ventricular ejection fractions (LVEF) of 40%-45% and hypokinesis. From seven cases, five of them showed with symptoms of COVID-19 such as cough, fevers, chest pain, myalgias and headache [49, 50] .

Clinical features and inflammatory indications of COVID-19

Coronaviruses have been know as the largest group of viruses that cause many diseases. Patients present some futures like common cold and also presnted different

clinical symptoms ranging from the common cold to that cause by MERS and SARS [51-53]. Common signs usually include respiratory symptoms, fever, cough, shortness of breath and breathing difficulties [7, 54]. The acute infection can cause pneumonia, severe acute respiratory syndrome, kidney failure, and even death. The data of the first 41 confirmed cases with COVID-19 in a related study have been explored a wide range of symptoms, most of these futures are similar to previous cases of SARS. Some patients had fatigue with rarer symptoms such as headache and diarrhea [7]. They also reported the infection with SARS was more frequently runny noses, diarrhea and sore throats than those with COVID-19. They also have shown that some of the deadly cases occurred as a result of SARS-CoV-2 infection were among old people or with underlying diseases such as diabetes, hypertension and liver disease [7, 55]. They have noted that SARS infections also did not only influence people with other conditions.

From 99 patients Chen et al have described the clinical manifestations with patients average 55.5 years old that were fever 83%, cough 82%, shortness of breath 31%, muscle ache 11%, confusion 9%, headache 8%, sore throat 5% patients, rhinorrhoea 4%, chest pain 2%, diarrhea 2%, and nausea and vomiting 1%. The imaging examination explored that 75% showed bilateral pneumonia, 14% of patients showed multiple mottling and ground-glass opacity, and one (1%) patient had a pneumothorax. 17% of patients developed acute respiratory distress syndrome. 11% of patients studied had worsened during a short period and died of multiple organ failure [30].

Treatment and control management strategies of novel COVID-19

The health authorities and WHO consider the novel SARS-CoV-2 as a serious public health concern “Pandemic” and the immediate health risk of COVID-19 to the community is high. Initially, the prevention and treatment of major infectious diseases such as AIDS and other infections have been suggested for this infection and the Chinese medical insurance companies have covered the cost of COVID-19 treatment. The genome identification of the novel SARS-CoV-2 has a key role for treatment. The people health care currently is being in treatment for the complications. Up to now, there are therapeutic strategies of COVID-19 or other coronaviruses and many vaccines are under clinical trails [56].

Basically, the characterization of the novel COVID-19 is closely related to SARS-CoV and the efficacy of different treatments of SARS-CoV and MERS-CoV remains unclear. Notably, Ribavirin and other types of IFN have been used with MERS infections as monotherapy or combined with broad-spectrum antibiotics and oxygen. The treatment of MERS has started only on the late-stage infection when the immunological system predominates, and antiviral drugs have a little benefit. Ribavirin has used frequently during the SARS infections which usually used as a combination with corticosteroids leading to an anti-inflammatory effect. IFN α has used as a combination with thymosins or immunoglobulins resulting to stimulate T cells [57-62]. Recent research has used antiviral treatment for COVID-19 patients. Many drugs have been used as potential therapeutics against COVID-19 such as remdesivir, chloroquine, hydroxychloroquine, lopinavir/ritonavir, umifenovir, antipyretics, IFN- α , ACE Inhibitor (ACEi) and Angiotensin Receptor-1 Blocker (ARBs). There also some specific drugs are currently

269 undergoing the clinical studies to evaluate the efficacy and safety profiles such as SARS-
270 Cov-2 specific antibodies and SARS-Cov-2 specific protease drug candidate. Notably,
271 there wide range of natural products and traditional medicines have been to be one of
272 potential strategies against COVID-19. The medicines used for the complications included
273 carbapenems, cephalosporins, quinolones and tigecycline targeting *Staphylococcus aureus*
274 as a methicillin-resistant, linezolid, and antifungal drugs also have been used. Hence, we
275 summarized the potential drugs in table no (.). [30]. Altogether, Ribavirin, IFN α and
276 various types of IFN may have potential efficacy for treatment strategies of COVID-19.

277 Standard recommendations to prevent infection by CDC and WHO including
278 continuously hand washing, covering mouth and nose when coughing and sneezing. Avoid
279 close contact with anyone showing symptoms of respiratory illness such as coughing and
280 sneezing. Travelers from or to most infected area are advised to obey the standard infection
281 control precautions such we mentioned above.

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Table 4: Poteintial therapeutic strategies of COVID-19

No	Treatment	Molecular pathway/ Mechanism	Type of drug	Reference
	Remdesivir	Nucleoside inhibitor Adenosine analogue incorporates into nascent viral RNA chains	Ebola virus infection Developed for the SARSCoV-2 treatment	[63, 64]
	Chloroquine	It may can be effective by two mechanisms: pH-dependent stages of replication through Glycosylation process and inhibit	Antimalaria	[65-67]
	Hydroxychloroquine	inhibit pH-dependent stages of replication	Antimalaria	[64, 66]
	Lopinavir/ritonavir	protease inhibitors and doing as a part of HAART regimen of HIV	HIV	
	Umifenovir	Non-nucleoside broad-spectrum antiviral licensed for influenza treatment and prophylaxis	Broad-spectrum antiviral licensed for influenza treatment and prophylaxis	[68]
	Antipyretics	upregulate ACE2 receptors	antipyretic agent.	[69]
	Systemic Corticosteroids	Viral shedding time and maintain a systemic anti-inflammatory state that will minimize the precipitation of ARDS, dyspnea, and severe pneumonia.	the management of ARDS	[70, 71]
	ACE Inhibitor (ACEi) and Angiotensin Receptor-1 Blocker (ARBs) (Captopril) Enalapril	Block the SARS-CoV-2's binding with human ACE-2 And reduces symptoms of severe pneumonia	Hypertension	[72-74]
	Cyclosporin A	Interferes with functional interactions between viral proteins and one or multiple members of the large cyclophilin family	Imunosuppressant	[75]
	Teicoplanin	Block the SARS-CoV-2's to cross cells.	Bacterial infection	[76, 77]
	SARS-Cov-2 specific antibodies	Inhibits SARS-CoV-2 entry into cells	SARS-Cov-2	[78]
	SARS-Cov-2 specific protease drug candidate	Blocks viral infectivity and no more details about its mechanism	SARS-Cov-2	[78]
	IFN- α		antiviral activity, clinical trial to treat MERS-CoV hepatitis	[79]

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The role of chloroquine and remdesivir as most potential therapeutics against SARS-CoV-2

Chloroquine as an amine acidotropic form quinine has been synthesised in 1934 by Bayer in Germany. It was long known as antimalarial medication and became one of the best options for COVID-19 medications. The mechanism of Chloroquine can summarize by three factors; as alkaline vascular and lysosomal pH, immunomodulatory effects and zinc ionophore. The ability of Chloroquine to increase the cell pH play a key role to inhibit Glycosylation leading to prolong the incubation time of SARS-CoV-2 that may will provide a chance for immunological system to detect and dealing with this pathogen. It also can inhibit endocytosis, lysosomal fusion and function [65, 66].

Chloroquine as a zinc ionophore can allow the influx of zinc into cells and into lysosomes by its ability to form stable complexes by bonds which supporting the free electronics pairs for functional groups. Hence, chloroquine may inhibit RNA polymerase which depends on RNA RDRP leads to inhibit SARS-CoV-2 RNA. The main usage of Chloroquine as one of the most potential therapy for targeting COVID-19 as Chloroquine phosphate, with dosage 500 mg BID for 5 days for respiratory tract infection and 500 mg BID for 10 days for upper respiratory tract infection. Hydroxychloroquine can used with 400 mg BID day 1 as loading dose, then 200 mg BID for 5e10 days as maintenance dose [66].

Remdesivir has been described as nucleoside inhibitor and broad-spectrum antiviral drug. It is a monophosphoramidate pr-drug and its mechanism of action can summarizing as premature termination of viral RNA replication. It has been developed against Ebola and used with prevouse coronaviruses MERS-CoV and SARS-CoV. Currently,

Remdesivir become the strongest candidate for COVID-19 [63]. The mechanism of remdesivir and chloroquine against SARS-CoV-2 described in figure 4.

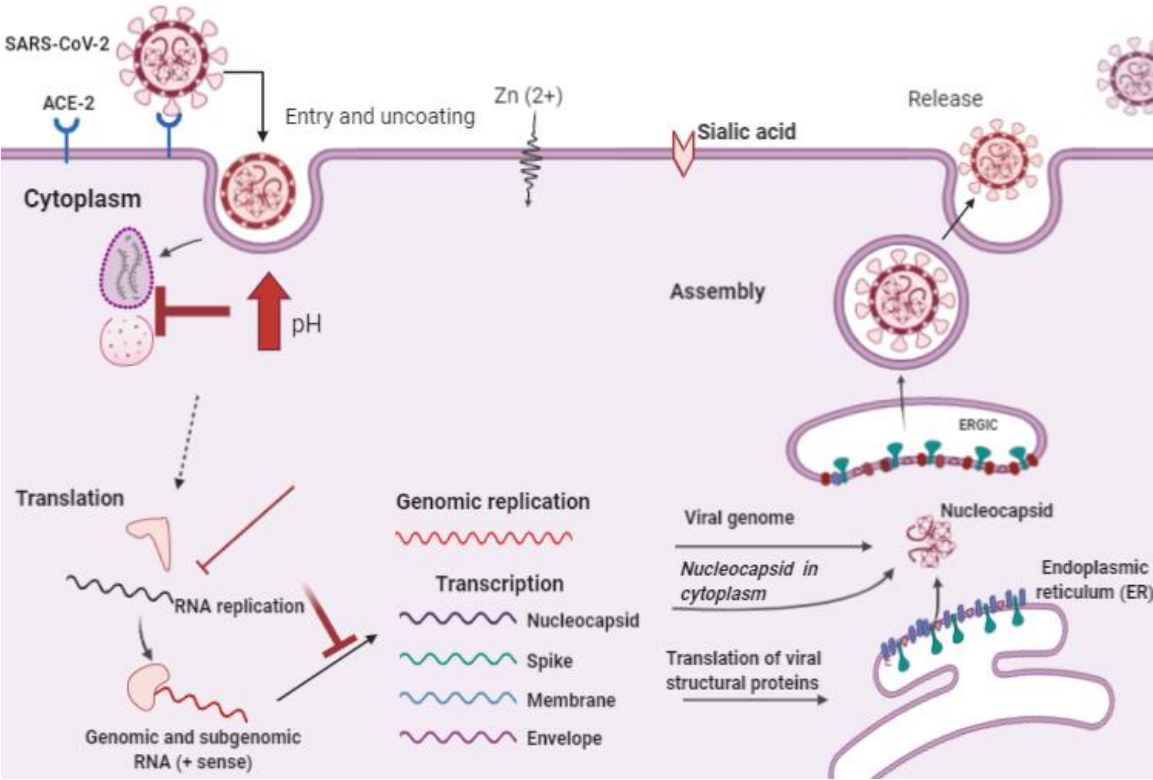


Figure 4. Represent the mechanism of remdesivir and chloroquine against SARS-CoV-2

CONCLUSIONS & FUTURE PERSPECTIVES

The emergence of COVID-19 basically illustrates and the recent studies have been described virulence of the new Coronavirus that suddenly appeared and rapidly spread resulting in widespread health, economic and social consequences. The COVID-19 epidemics can occur anywhere and the evidence indicated that this novel Coronavirus has an etiologic role in severe acute respiratory syndrome. Effective preparedness plans and more advanced studies are required to predict and control outbreaks. The standard recommendations are also required to improve patient management and

319 ensure global health security. Now the question arises, “Is there any possibility of
320 COVID-19 to be seasonally infection?”

321

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325 **CONFLICT OF INTERESTS**

326 All authors declare no conflict of interest in the current study.

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