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Review

The Molecular Structure and Case Fatality Rate of COVID-19

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HIGHLIGHTS

- The molecular structure and genome of Covid-19 are very variable and for an unknown reason, it is highly transmittable.
- After binding of viral Spike proteins to the host cell ACE2 receptor, the viral ssRNA goes to the host cells.

ARTICLE INFO

Receive Date: 16 July 2020
Accept Date: 14 August 2020
Avaliable online: 24 August 2020
DOI: 10.22034/TRU.2021.269615.1060

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ABSTRACT

A new coronavirus recognized as 2019 novel coronavirus (COVID-19) is the etiological cause in charge of the 2019-2020 viral pneumonia worldwide outbreak. The molecular structure and genome of this virus are identical to SARA-CoV and for an unknown reason, it is highly transmittable. The spike protein is responsible to attach to the host cell and viral single-stranded RNA (ssRNA) entrance to the cells. Upon binding of the Spike proteins to the host cell ACE2 receptor and merging with the membrane, COVID-19 ssRNA goes to the host cells. The viral RNAs are recognized as the foreign element by TLR3, TLR7, TLR8, and TLR9 in the host cell. The viral genome receptor retinoic-acid inducible, cytosolic receptor melanoma differentiation-associated gene, and nucleotidyltransferase cyclic GMP-AMP synthase (cGAS) is in charge of viral RNA representation in the cytoplasm. Now there is no targeted therapeutics with high efficacies for the treatment of Covid 19 disease. More than usual medication some interfering RNA molecules are under debate. The reason for being high transmission of COVID-19 is not recognized. This virus pandemic is now all over the world.

Keywords: COVID-19; Proteins; 2019 Novel Coronavirus; Case Fatality Rate

Introduction

Based on the World Health Organization (WHO), several viral disorders can result in serious public health problems. Unfortunately, it has been established over the last two decades by epidemics of severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002 to 2003, and H1N1 influenza in 2009, and the Middle East respiratory syndrome coronavirus (MERS-CoV) (1, 2).

Very recently, a mysterious lower respiratory infection has been reported in China, Wuhan caused by the coronavirus called Covid-19 .The site for isolation of the 2019-Corona virus (2019-CoV) was airway epithelial cells in Chinese patients which were different from both MERS-CoV and SARS-CoV. The newly emerged coronavirus seems to be the same as the SARS outbreak (SARS-CoVs) hence it is named as SARS-CoV-2 virus. However, multiple-sequence alignment of the 2019-CoV and reference sequences was done using the Randomized Accelerated Maximum Likelihood (RAxML) program with 1000 bootstrap replicates and an overall time-reversible model used as the nucleotide substitution model (3, 4). The etiology of this disease is currently recognized as a novel virus of the coronavirus (CoV) family. On February 11, 2020, the Director-General of WHO, Dr. Tedros Adhanom Ghebreyesus, stated that

this new respiratory infectious disease caused by the new CoV and called it "COVID-19," which is the acronym of "coronavirus disease 2019" (https://www.bbc.co.uk/news/world-asia-china-51466362). The COVID-19 appears to be extremely transmissible that unbelievably has rapidly widespread globally. In a meeting on January 30, 2020, of the International Health Regulations (IHR, 2005), this epidemic was specified by the WHO as a Public Health Emergency of International Concern (PHEIC) due to its global expansion to 18 countries in the world. At first, there were some beliefs that Covid-19 is a human-made chimeric virus and was originally made in laboratories. On 17th March 2020, it was declared by Scripps Research Institute that sequencing data from SARS-CoV-2 and correlated viruses indicated that Covid-19 was not a chimeric virus that was created in a laboratory through genetic engineering. The important tragic is that the virus has a high potential to transmit which results in the COVID-19 pandemic worldwide and makes it a serious public health problem. Scientists around the world try to know the reason for this catastrophic transmission mechanism, and make a vaccine or find the best treatment strategy. However, the treatment approaches of this respiratory infection are only supportive, and preventive strategies to decrease transmission in the community.

Knowing the molecular structure and viral genome is a straight forward approach to cope with COVID-19. In this review article, we are presenting some molecular and genetic information of the virus more than the current outbreak and treatment.

Covid-19 structure and genome

Coronaviruses (CoVs) are the major cluster of viruses from Nidovirales which is made of a big family of Coronaviridae, Arteriviridae, and Roniviridae families. The Coronavirinae are sub-grouped to the alpha (α), beta (β), gamma (γ), and delta (σ) coronaviruses. All coronavirus's genome is comprised of the long RNA molecule (about 30 kilobase/kb). There are some characteristics in Nidovirales like having a highly conserved single-stranded RNA genome (ssRNA), expression of many nonstructural genes by the interesting molecular mechanism of ribosomal frameshifting, some uncommon enzymatic actions coding by replicase-transcriptase polyprotein, and downstream gene expressions through the synthesis of 3′ nested sub-genomic mRNAs (1) (Figure 1).

The genome of CoVs is made of the single-stranded positive-sense RNA (+ssRNA) about 30 kilobases with the usual 5′-cap and 3′poly-A tail structure. This +ssRNA is translated directly to the polyprotein 1a/1ab (pp1a/pp1ab) responsible for coding the nonstructural proteins (nsps) to make the replication-transcription complex in double-membrane vesicles (5). A part of subgenomic RNAs (sgRNAs) is produced by RTC in a way of disjointed transcription and the produced messenger RNAs (mRNAs) with the usual 5′-leader and 3′-terminal sequences (6). The ending of transcription and following achievement of a leader RNA happens at transcription regulatory sequences which are placed in open reading frames. The resulting minus-strand sgRNAs work as the patterns for the synthesis of subgenomic mRNAs (7, 8).

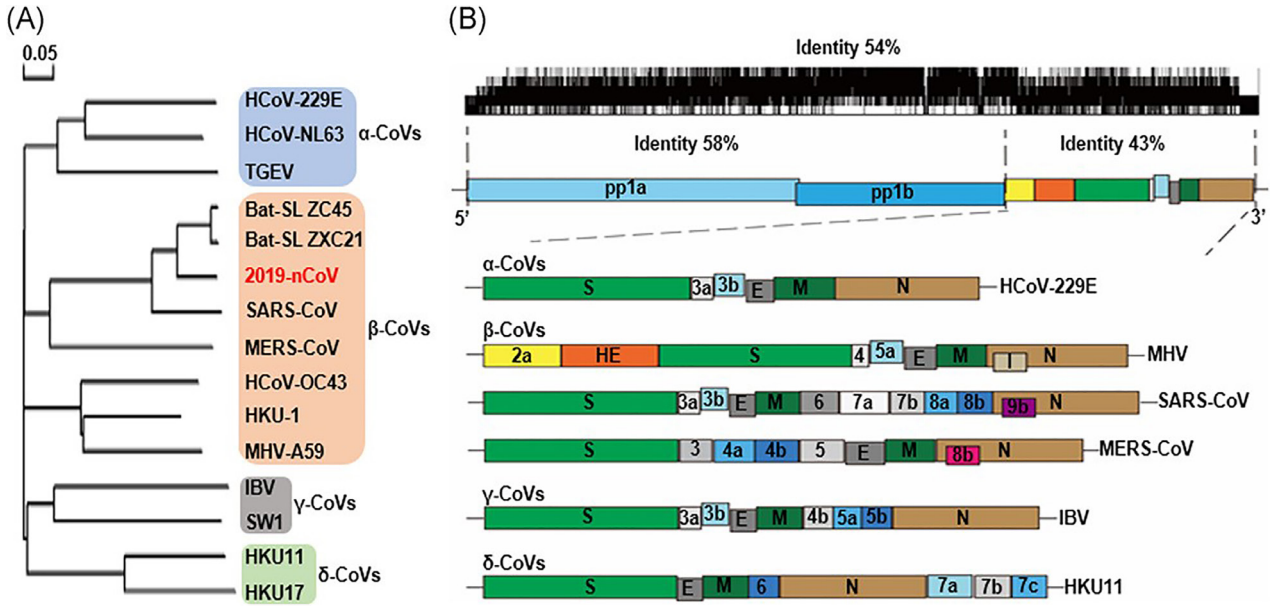

Figure 1. A) Phylogenetic tree of coronaviruses in which the new coronavirus 2019-nCoV is highlighted in red. B) The genome structure of four genera of coronaviruses. (Originated from https://onlinelibrary.wiley.com/doi/full/10.1002/jmv.25681)

On 12 January 2020, five genomes of SARS-CoV-2 had been isolated and sequenced by the Chinese Center for Disease Control and Prevention and other institutions. Information based on the sequencing makes the phylogenetic tree of the COVID-19 "highly related with at most seven mutations relative to the common ancestor". On 11 February 2020, the International Committee on Taxonomy of Viruses stated that agreeing to current instructions calculate hierarchical associations among coronaviruses based on the five consensus genomic sequences, the dissimilarities among what was named 2019-nCoV and the virus strain from the 2003 SARS outbreak were inadequate to make them as the distinct viral species. Consequently, they recognized 2019-nCoV as the new strain of severe acute respiratory syndrome-related coronavirus. The complete genome sequence of COVID-19 in the NCBI (GenBank: MN908947.3) given the possible construction and glycosylation design of the viral proteins and the resulting mode of interaction with the host cell. CoVs are quite big viruses having a +ssRNA genome which is encapsulated in a membrane envelope. The viral membrane is including with glycoprotein spikes that provide coronaviruses their crown-like appearance (Figure 2).

Same as other coronaviruses the spike glycoprotein in the virus membrane is glycosylated and is the critical element for host cell attachment. Some cell surface markers in host cells are a target for this binding such as Angiotensin-converting enzyme 2 (ACE2), a protein that sits on the lining cells within alveoli of the lung, CD26 as a 110 kD cell-surface glycoprotein with famous dipeptidyl-peptidase IV (DPP-IV) action of its extracellular domain, Ezrin/ cytovillin or villain-2 coding by the EZR gene and are important for cell surface structure adhesion, migration, and organization, and Cyclophilin A as a very abundant cytoplasmic protein of isozymes, including cyclophilins B and C, and natural killer cell (9, 10). Nevertheless, the particular host cell proteins and elements can assist the novel COVID-19 to stay mysterious (Figure 3). The Clustal-W sequence alignment of COVID-19 and SARS-CoV spike glycoproteins indicates more than 90% similarity in the S2 domain (aa570–aa1278), and dissimilarity in other 3 regions (aa677–690, wing), (aa877–884 and aa930–943, stalk). In figure 3 the cropping interface of modeled COVID-19 (grey) and human CD26 (orange) (PDB: 4QZV) complex is presented. Indicated to main amino acid residues critical for the interaction are revealed in poles (CD26 residues are underlined) (C), and CD26 with COVID-19 is expected to form a homo-trimer structure (ligand-bound conformation) (11).

After binding of S proteins of Coronavirus to the host cells by ACE2 and merging of cell membranes the viral RNA goes to the host cells. The viral RNAs, as pathogen-associated molecular patterns can be sensed by the Toll-like receptor (TLR) 3, TLR7, TLR8, and TLR9 sense in the endosome (12, 13). The viral RNA receptor retinoic-acid inducible gene I, cytosolic receptor melanoma differentiation-associated gene 5, and nucleotidyltransferase cyclic GMP-AMP synthase (cGAS) are in charge of viral RNA representation in

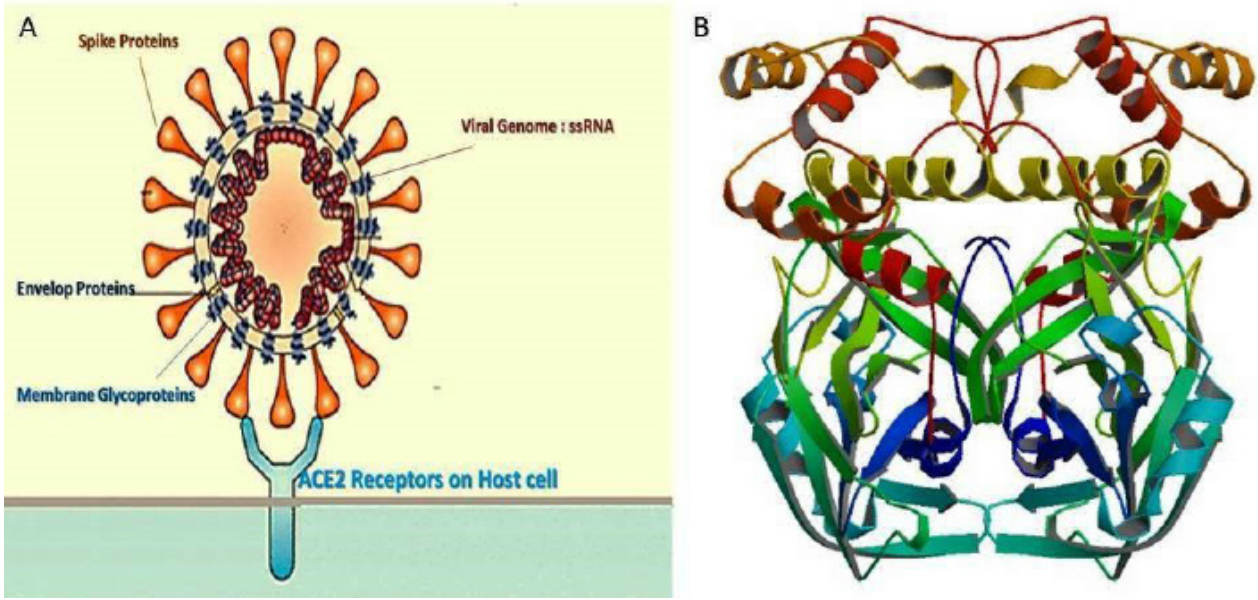

Figure 2. A) Schematic representation of the coronavirus structure and viral receptor ACE2 on the host cell surface. (Nature Reviews Microbiology 7(3), 226–236. Copyright 2009 Springer Nature), B) 3D structure of COVID-19 https://www.rcsb.org/structure/6M03 (Protein Data Bank)

the cytoplasm (14). Usually, virus-cell interactions are resulting in several immune intermediaries alongside the invading virus (14, 15). Innate immunity is essential for the virus elimination and some cytokines are suggested as the key role player in the host/COVID-19 battle, including IL-1, IL-2, IL-4, IL-7, IL-10, IL-12, IL-13, IL-17, GCSF, macrophage colony-stimulating factor (MCSF), Interferon gamma-induced protein 10, Monocyte Chemoattractant Protein 1, macrophage inflammatory protein (MIP)-1α/ CCL3, hepatocyte growth factor, Interferon-gamma (IFN-γ) and Tumor necrosis factor-alpha (TNF-α) (15, 16). Unfortunately, COVID-19 triggered an inflammatory response in the lower airway which is leading to lung damage. The virus particles invading the respiratory mucosa and other cells infecting collectively can make the sequence of immune reactions and the making of cytokine storm in the patient body.

Several Treatment Strategies for COVID-19

The current treatments of COVID-19 are mainly based on symptomatic and respiratory maintenance agreeing to the Diagnosis and Treatment of Pneumonia Caused by COVID-19 (updated to version 6) issued by the National Health Commission of the People's Republic of China. Approximately all COVID-19 patients must receive oxygen therapy, and WHO suggested extracorporeal membrane oxygenation (ECMO) to patients with refractory hypoxemia (17). Additional treatment with convalescent plasma and immunoglobulin G are suggested in specific serious cases depending on their situations (18).

Scientists are trying to find drugs and medications for the treatment of this disease. Research until now has revealed that antiviral drugs, corticosteroids, anti-cancer drugs, convalescent plasma, and monoclonal antibodies, other agents, and medications could have effective results to treat COVID-19 (Table 1). Interferon α (IFN-α) has restrained SARS-CoV in vitro (19). INF-α along with ribavirin is recommended. Lopinavir/ritonavir is a protease inhibitor used for the treatment of HIV (human immunodeficiency virus) and may be efficient to treat SARS-CoV-2 (20). Chu CM et al found out that in the treatment of SARS ribavirin along with Lopinavir/ritonavir

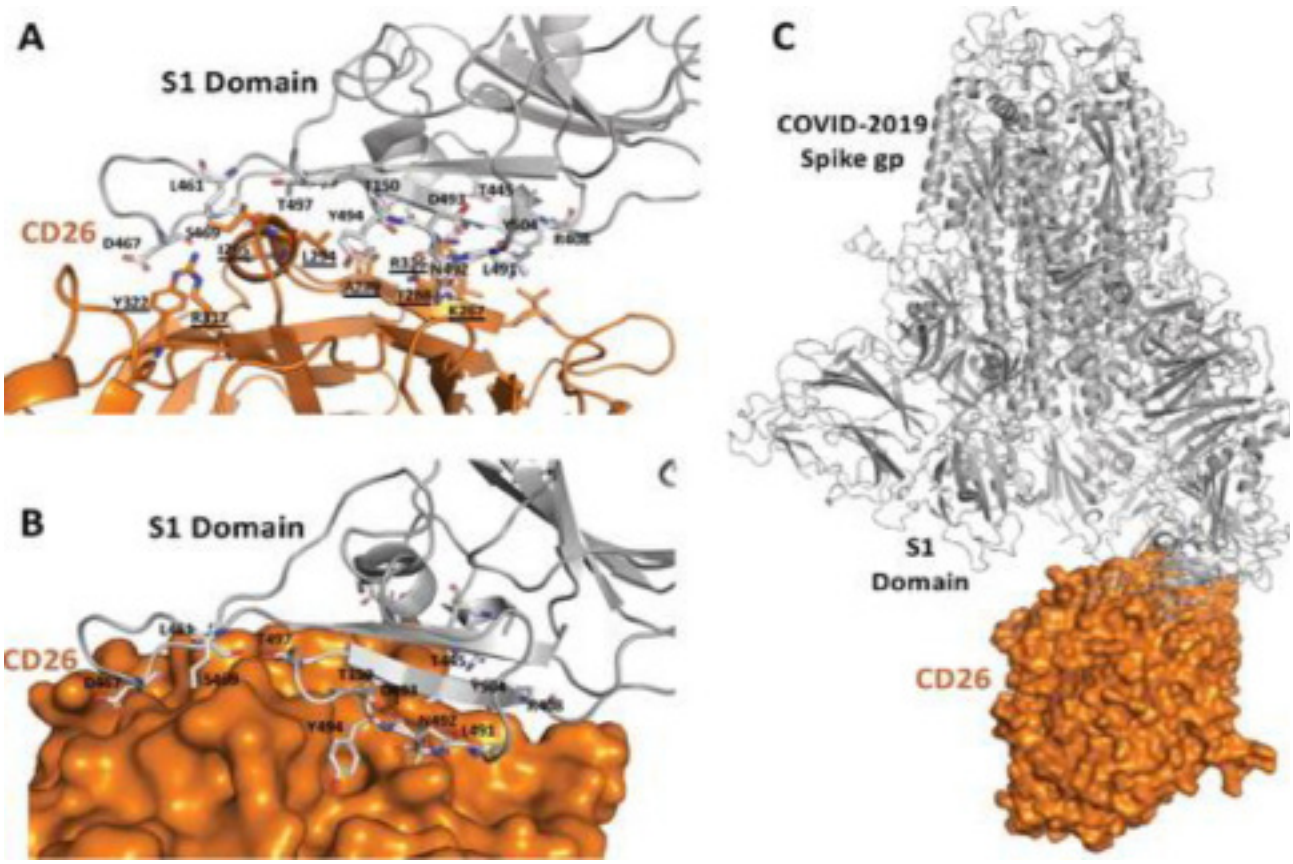

Figure 3. A figure of Ribbon and a surface diagram displays the docking interface of modeled COVID-19 (grey) and human CD26 (orange)(PDB: 4QZV) complex taken from https://www.tandfonline.com/doi/full/10.1080/22221751.2020.1739565. Critical amino acids for attachment are presented in sticks (CD26 residues are underlined) (C) General docking outcomes display the surface model of CD26 with COVID-19 seem to form homo-trimer structure

will both decrease acute respiratory distress syndrome and mortality rate. Chloroquine phosphate, a drug for malaria treatment, has an evident influence on COVID-19 based on clinical trials carried out in China and it's a safe drug. Based on Hongzhou Lu's review, Remdesivir (GS-5734) may be the best drug for SARS-CoV-2 and it was successful in the treatment of the first case in the US (20) but still, it needs more investigation. In vitro experiments show that Remdesivir can have an apparent effect on Middle East Respiratory Syndrome (Mers)-CoV and make the lung tissue damage better, as well. It was also a successful drug on SARS-COV(21). A recent study has stated that Remdesivir together with chloroquine inhibits COVID-19 in vitro (16). Remdesivir and Chloroquine have been strongly effective on COVID-19, in vitro (22). This article claims that maybe ribavirin, penciclovir, and favipiravir would not be efficient for COVID-19 patients, in vivo (22).

Oral Oseltamivir has been extensively used in confirmed and suspected patients, in china hospitals but there is no valid evidence for that. In vitro Researches have shown that EK1, TDF, and 3TC could be efficient against SARS-CoV-2 (20). Zanamivir may be beneficial, either (23).

Nafamostat and Favipiravir (T-705) may also inhibit COVID-19, it's proven that the latter inhibits Influenza, MERS, Ebola and the former obstructs bola, influenza A(H1N1) (16). Besides, Nitazoxanide impact many kinds of viruses such as animal and human coronaviruses (16). Based on the in vitro experiments of Li, Darunavir and Abidol can be effective against SARS-CoV-2 (24, 25). It has been proven that Nelfinavir inhibits SARS-COV proliferation so it may be functional against COVID-19 as well.

Sofosbuvir combined with ribavirin may bond to RNA dependent RNA polymerase (RdRp) tightly. Researches of the Shanghai Institute of Materia Medica and Tech University reported 30 agents that have antiviral activities against COVID-19. These include indinavir, saquinavir, lopinavir, carfilzomib, remdesivir (27), ritonavir, darunavir, atazanavir, fosamprenavir, tipranavir, enzaplatovir, abacavir, presatovir, bortezomib, maribavir, elvitegravir, montelukast, raltegravir, polydatin, chalcone, deoxyrhapontin, disulfiram, shikonin, carmofur, ebselen, tideglusib, TDZD-8, PX12, cinanserin, and cyclosporin A (8).

Neuraminidase inhibitors (oseltamivir, paramivir, zanamivir, etc.), ganciclovir, and acyclovir are common antiviral drugs that are used in medicine, but they are not valid in COVID-19 disease and are not recommended (27). According to the Chinese guideline of Novel Coronavirus-induced Pneumonia on February 2020, ribavirin is recommended (5), however, a study conducted in March 2020, stated that ribavirin is invalid for this virus and is not recommended (27). Besides Ganciclovir and oseltamivir have been used by Nanshan Chen et al in January 2020 (28), yet they have been introduced as invalid drugs for COVID-19 by Li et al in March 2020 (27). Teicoplanin is a glycopeptide antibiotic against Gram-positive bacteria which has an apparent effect on some viruses including MERS-CoV and SARS-CoV accordingly it can be therapeutic for COVID-19 (31). More investigation is needed.

Corticosteroids have been utilized broadly for coronavirus diseases such as the Middle East respiratory syndrome (MERS) and SARS. Although recent follow-ups have shown that Corticosteroids would make the viral existence in patients with COVID-19, longer. So, the user should be avoided unless it's necessary (32). Besides, extensive use of systematic steroids, particularly in mild patients, is not recommended . Researches have shown that BCR-ABL kinase inhibitor such as imatinib which is an anti-cancer drug, can be useful against COVID-19 (33). Moreover, Nicotianamine, a metal-ligand compound, might be a choice for decreasing the infection of COVID-19. Emodin is an anthraquinone agent that may inhibit SARS-COV in our bodies. Promazine is an anti-psychotic drug that may prevent the proliferation of SARS-COV. Organic NO may be effective in that way, either (25).

There is some Chinese herbal medication that seems to have some useful components for COVID-19 such as Rhizoma Polygoni Cuspidati, Radix Sophorae Tonkinensis, and Glycyrrhizin (8, 25). Since COVID-19 binds to angiotensin-converting enzyme 2 (ACE2 receptor) to enter the cells, there is a doubt about the effects of ACE-Inhibitors and angiotensin receptor blockers which they will make the disease better or worse. hence, if kidney failure or hypotension, or other complications happen, these drugs should be stopped . The fact is that there is no approved vaccine or antiviral medications for COVID-19, therefore supportive care such as facemask, separating suspected patients, fluid management, anti-fungal, and antibiotics drugs are critical for these patients. Antibiotics are being used for secondary infections. The ones used for common pathogens are cephalosporins, carbapenems, quinolones, tigecycline against methicillin-resistant Staphylococcus aureus (MRSA), and linezolid (34). Nevertheless unselective or improper prescriptions of antibiotics should be avoided. Based on BIDMC American guideline, If the patients are suspected of bacterial pneumonia, they should take Ceftriaxone [(1 g) or antipseudomonal beta-lactam if ICU or MDR risk factors] plus Azithromycin (500 mg for one day and then 250 mg for following 4 days) and Vancomycin if they are at risk of MRSA. Supplemental oxygen in mild patients and ECMO for severe patients and refractory hypoxemia is necessary. In the case of respiratory failure, protective mechanical ventilation, and high-flow nasal oxygen or

Table 1. Some drugs with antiviral function with their dosage, method of administration, and duration of usage

	Drug	Dosage	Method of administration	Duration of usage
1	Interferon α (IFN-α) (20, 26)	5 million U or equivalent dose each time, 2 times/day	Vapor inhalation	Less than 10 days
2	Lopinavir/ritonavir (5, 27)*	200 mg/50 mg/capsule, 2 capsules each time, 2 times/day	Oral	Less than 10 days
3	ribavirin (5)	500 mg each time, 2 to 3 times/day in combination with IFN-α or lopinavir/ritonavir	Intravenous infusion	Less than 10 days
4	Chloroquine phosphate (5, 27)	500 mg (300 mg for chloroquine) each time, 2 times/day	Oral	Less than 10 days
5	Arbidol (5)	200 mg each time, 3 times/day	Oral	Less than 10 days
6	oseltamivir(28)	75 mg each time, 2 times/day	oral	3-14 days
7	ganciclovir(28)	250 mg each time, 2 times/day	Intravenous infusion	3-14 days
8	SFJDC (Shufeng Jiedu Capsule) (29)	2.08 g each time, 3 times/day	oral	6-15 days
9	darunavir/cobicistat(30)**	800 mg / 150 mg, 2 times/day	oral	10 days
10	Remdesivir (30)***	200 mg/ following 100 mg, daily	oral	10 days
11	Tocilizumab(30)****	400 mg, daily once OR 8 mg/kg (maximum 800 mg/dose) over an hour	Intravenous infusion	
12	Hydroxychloroquine (Plaquenil) (30)	400 mg, 2 times/day 400 mg, daily	Oral	 5-10 days

*Together with interferon-β could be more effective (27). Also, combined with interferon-α 2b has been used in Chinese hospitals (22)
**If lopinavir/ritonavir is not available
*** especially for patients in ICU
****patients suspected of cytokine release syndrome or ARDS

non-invasive ventilation can be helpful . For septic shock, hemodynamic support is essential (35). Additionally, passive immunotherapy by convalescent plasma seems to decrease viral load and the mortality rate of COVID-19 patients and can be used as the treatment for avoiding severe complications (36). Monoclonal antibodies and immunoglobulin G could be effective in the treatment and prevention of this disease (16, 27, 37). The sera could both taken from infected patients and produced in the laboratories (37). Immunoenhancers for instance Interferons, Intravenous gamma globulin, Thymopentin, Thymosin α-1, Levamisole, and Cyclosporine A can be advantageous (25).

Supply valuable nutrition is beneficial for these patients comprising vitamin A, C, E, and B vitamins group. They are anti-infective and pneumonia reduction, Immunoenhancers, energy supply, lung protection, antihistamine function, antioxidant and they increase the survival rate and reduce the viral load of various viruses including coronaviruses, as well (25). More than usual medication there are some ideas for COVID-19 treatment in the nucleotide-based treatment way, mainly based on RNA interference (RNAi) molecules (18, 38). RNAi is a biological process in which small complementary RNA molecules designed and targeted mRNA to RNA-RNA duplex formation and stopping ribosomes to reach RNA for protein synthesis which is causing in stopping of gene expression or genetic translation. Interfering

RNAs comprise microRNAs and small interfering RNAs (siRNAs) that usually have a length of ≅ 21–25 nucleotides. Contrary to the microRNAs and siRNAs, antisense RNAs are single-stranded RNAs (ssRNA) which are logically happening and are made of about 19–23 nucleotides complementary to some mRNA, letting it to make RNA/RNA dimer and blocking the protein-making comparators to block protein translation (39, 40). There are some siRNAs that direct coronavirus proteins M, N, or E. It is suggested through patent application CN101173275 that two double-stranded RNAs (dsRNAs) have potential to the exact aiming at two different regions of the SARS protein M mRNA and suppressing the viral activity. The interference effectiveness of these two siRNAs on SARS M protein gene expression is more than 70%. In the patent application CN1648249 the sequences of siRNAs are presented which can target the M, N, and E genes of SARS. There is a big hope to siRNA in the COVID-19 treatment especially those siRNA that bind to RNA dependent RNA polymerase of the virus.

The case fatality rate of COVID-19

Now, the world is in the encounter to the COVID-19 pandemic and it's been a little over a decade since the world experienced such a disastrous pandemic. Between the spring of 2009 and the spring of 2010, the H1N1 virus-infected as many as 1.4 billion people all over the world, and the death rate was 151,700 and 575,400 people, according to the centers for Disease Protection and Control (Figure 4). The mortality rate for COVID-19 is much higher so far, around 2% (although the number will likely change as more people are tested). The new coronavirus that has so far extent from China to 26 countries around the world does not appear to be as "deadly as other coronaviruses including SARS and MERS," the WHO has said. This case fatality rate (CFR) depends on the availability of healthcare, the typical age and health problems within the population, and the number of undiagnosed cases (41). On 21st March there were 276,125 and 11,402 all over the world (https://www.worldometers.info/coronavirus). Several factors can change the CFR such as age, gender, diabetes, cardiovascular disease, and co-infections. Covid-19 outbreaks in Iran were officially approved in the aftermath of the worldwide coronavirus crisis. Corona covers almost all provinces of the country (42). According to the Iranian Ministry of Health and Medical Education's public relations as of Monday, April 9, the number of Kuwaiti-2 patients has been identified in the country, of which 2.5 have died, as well as 2.8%. Patients with the virus have so far recovered (43). According to official statistics, Iran had the highest number of deaths from coronary disease after Italy, Spain, China, and the United States. Coronary test positive according to WHO standard and from this date based on clinical complications of lung

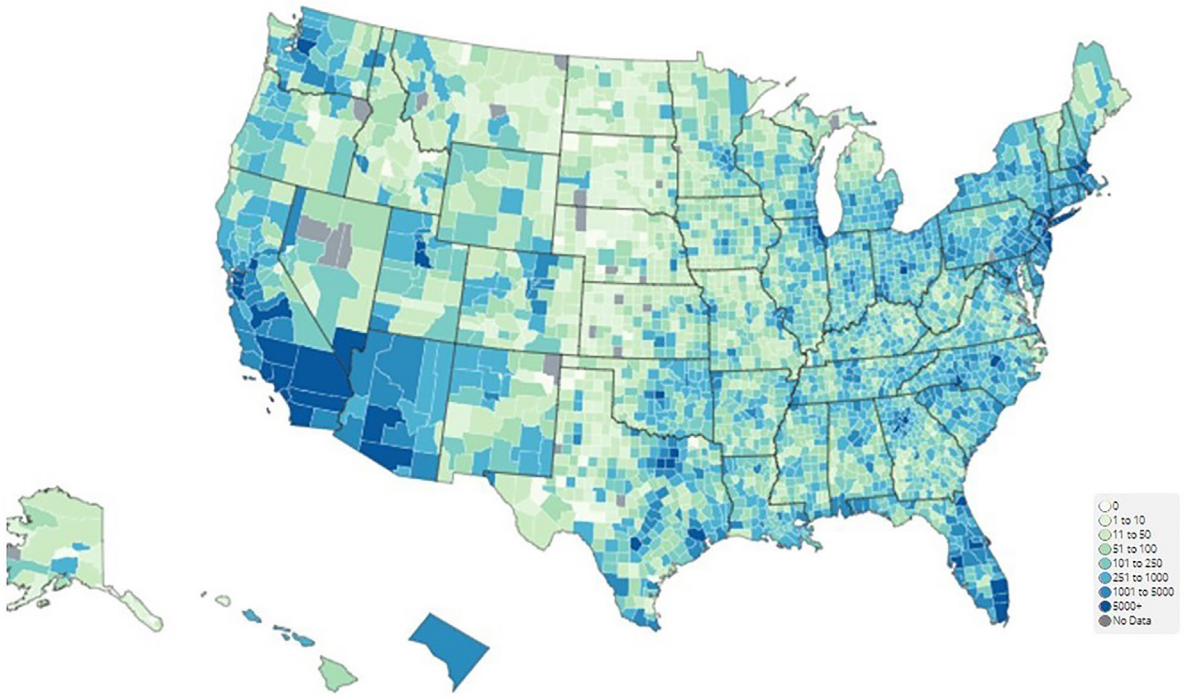

Figure 4. Global case numbers of COVID-19 which is stated by the World Health Organization (WHO) in their coronavirus disease 2019 (COVID-19) situation report external icon. , CDC's COVID-19 in the U.S. https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/world-map.html (2021.01.12)

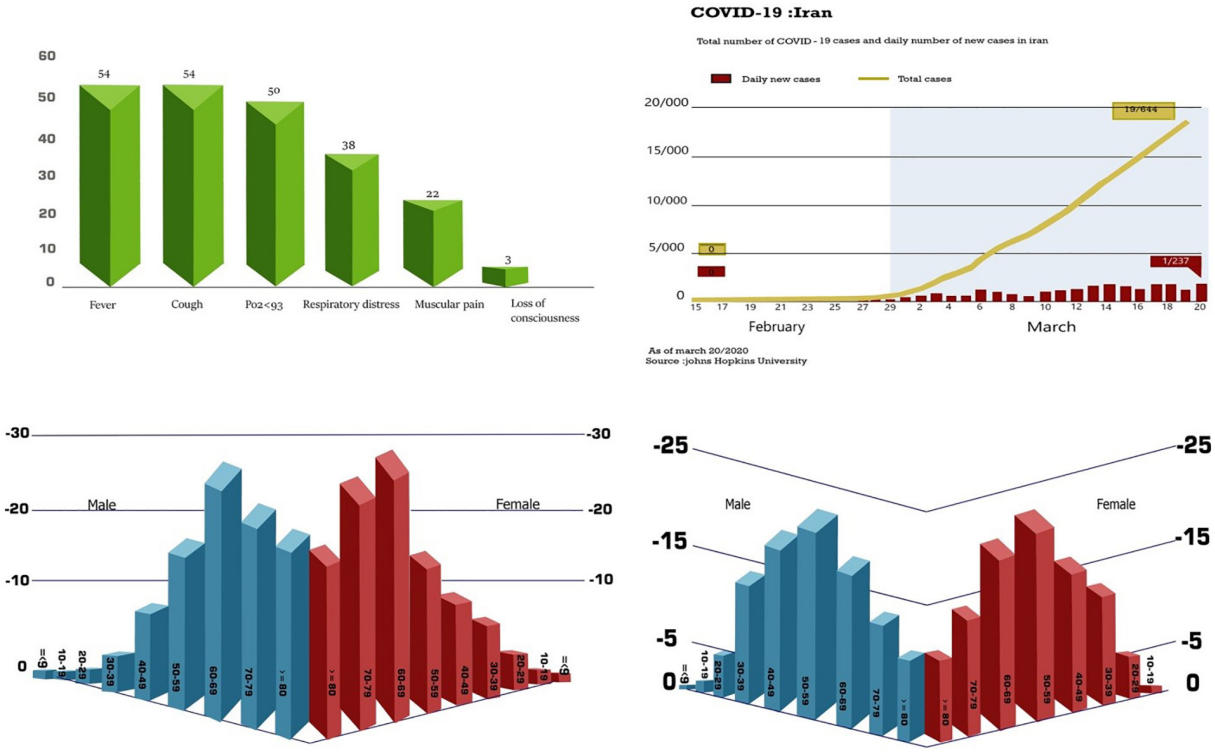

Figure 5. Epidemiological reports of COVID-19 in Iran. A) Clinical symptoms of definite COVID-19 cases of diagnosis at the time of admission. B) Total number of new COVID-19 cases in Iran based on John Hopkins University statistics. C) Age and sex distribution of deceased cases of COVID-19 in Iran. D) Age and sex distribution of COVID-19 diagnosed patients in Iran

CT scan in Kenya Was tested. The prevalence of COVID-19 in Iran over several days is presented in figure 5.

As of March 16, 2020, 14 991 people have been infected with severe acute respiratory syndrome coronavirus 2, and 853 people have died from COVID-19, but 4996 people have recovered . Unfortunately, the economic loss caused by the spread of COVID-19 in Iran coincides with the politically induced sanctions against the country. The Iranian health sector, although among the most resilient in the region, has been badly affected as a consequence (44). Iran also suffered the most deaths from coronavirus following the official death of four people . On 9 March, the Minister of Health announced that there were 2 new cases of Qoids; 2 were reported in Qom, 2 in Tehran and 2 in Guilan province, 3 in Arak, and 2 in Tonekabon. . Three of them were killed, 2 of whom died. He confirmed the deaths of 3 others due to the coronavirus, with a total death toll of five, and nine infected .

Conclusions

The 3D structure of COVID-19 may help researchers working on COVID-19 drug discovery. In-vitro and in-vivo studies are required to transform the potential inhibitors into clinical drugs.

Authors' contributions

All authors contributed equally. All authors reviewed and approved the final version of the manuscript.

Acknowledgments

Special thanks to Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Conflict of interest

The authors declare that there is no conflict of interest.

Funding

The authors received no financial support for this research.

Ethical statements

Not applicable.

Data availability

Not applicable.

Abbreviations

ACE2	Angiotensin-converting enzyme 2
CFR	Case fatality rate
cGAS	GMP-AMP synthase
CoVs	Coronaviruses
ECMO	Extracorporeal membrane oxygenation
IFN-γ	Interferon-gamma
IHR	International health regulations
MERS-CoV	Middle East respiratory syndrome coronavirus
ORFs	Open reading frames
PHEIC	Public health emergency of international concern
RAxML	Randomized accelerated maximum likelihood
SARS	Severe acute respiratory syndrome coronavirus
sgRNA	Subgenomic RNAs
ssRNA	Single-stranded RNA
TLR	Toll-like receptor
TNF-α	Tumor necrosis factor-alpha
WHO	World health organization

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How to cite this article
Aghamir ZS, Shivarani S, Manafi Shabestari R. The molecular structure and Case Fatality Rate of COVID-19. Translational Research in Urology. 2020 Aug;2(3):96-106.
DOI: 10.22034/TRU.2021.269615.1060
URL: http://www.transresurology.com/article_124716.html