A Review of Current Literature on sudden Upsurge of COVID-19

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Abstract

Since December 2019, a sequence of baffling pneumonia cases has been notified in Wuhan, China. On 12 January 2020, this virus is temporarily named as 2019 novel coronavirus (2019-nCoV). On 11 February 2020, the disease caused by the virus has officially named as coronavirus disease (COVID-19) by WHO. The COVID-19 pandemic is spreading all over the world, especially in China, Italy, America, and South Korea. Established on the published data, we systematically confer the attributes of COVID-19 in the aspiration of providing a quotation for future studies and thus support for the prevention and management of the COVID-19 pandemic.

Keywords: Pandemic, coronavirus, COVID-19, epidemiology, pneumonia, SARS-CoV-2.


Introduction

Coronaviruses (CoV) are associated to the genus Coronavirus in the Coronaviridae. All CoVs are pleomorphic RNA viruses generally accommodate crown-shape peplomers with 80-160 nm. in size and 27-32 kb positive polarity. Due to perpetually developing transcription errors and RNA dependent RNA polymerase jumps there is immense arise in recombination rates of CoVs. With its high mutation rate, Coronaviruses are zoonotic pathogens which are present in humans and various animals with a broad range of clinical features from asymptomatic to hospitalization in the intensive care unit; which gives rise to infections in respiratory, gastrointestinal, hepatic and neurologic systems. They were not treated as extremely pathogenic for humans as far as they have been seen with the severe acute respiratory syndrome (SARS) in the Guangdong state of China for the first time in 2002 and 2003. Before these outbreaks, there were the two most known types of CoV as CoV OC43 and CoV 229E that have mostly caused mild infections in people with an adequate immune system. Nearly ten years after SARS this time, another extremely pathogenic CoV, Middle East Respiratory Syndrome Coronavirus (MERS-CoV) has surfaced in the Middle East countries. In December 2019, novel Coronavirus (NCoV), which is another public health disease that come out in the Huanan Seafood Market, in Wuhan State of Hubei Province in China and has been the focus of global surveillance because a pneumonia epidemic of undefined cause.

Epidemiology

A study showed the middle age of 425 patients diseased with SARS-CoV-2 was 59 years, of which 56% were males, the usual gestation period was 5.2 days, and nearly half of the adult patients were 60 years old or older. In the primary stages, the sum of sick patients doubled each 7.4 days. The spread rate of discrete infected patients was 2.2. Though 55% of the original SARS-CoV-2-infected patients associated to the Huanan seafood market, the quantity of disparate cases has augmented exponentially since December 2019.

Analogous to the SARS epidemic, this outburst has befallen throughout the Spring Festival in China, which is the greatest famed traditional jubilee in China, through which nearly 3 billion individuals travel countrywide. These conditions caused favorable conditions for the transmission of this highly contagious disease and severe difficulties in prevention and control of the epidemic. The period of the Spring Festival of China was between 7 January and February 23 in 2003, when the SARS epidemic peaked, while the period of the festival was between January 10 and February 18 in 2020. Similarly, there was a rapid increase in COVID-19 cases between January 10-22. Wuhan, the center of the epidemic with 10 million population, is also an important center in the spring festival transportation network. The estimated number of travelers during the 2020 spring...
festival has risen 1.7 folds when compared with the number traveled in 2003 and reached to 3.11 billion from 1.82 billion. This large-scale travel traffic has also created favorable conditions for the spread of this difficult-to-control disease.11

Pathogenesis
Coronaviruses are viruses whose genome structure is best known among all RNA viruses. Two-thirds of RNA they have encodes viral polymerase (RdRp), RNA synthesis materials, and two large nonstructural polyproteins that are not involved in host response modulation (ORF1a-ORF1b). The other one-third of the genome encodes four structural proteins (spike (S), envelope (E), membrane (M), nucleocapsid (N), and the other helper proteins. Although the length of the CoV genome shows high variability for ORF1a/1b and four structural proteins, it is mostly associated with the number and size of accessory proteins. 12,13 The first step in virus infection is the interaction of sensitive human cells with Spike Protein. Genome encoding occurs after entering to the cell and facilitates the expression of the genes, that encode useful accessory proteins, which advance the adaptation of CoVs to their human host.13

Genome changes resulting from recombination, gene exchange, gene insertion, or deletion are frequent among CoVs, and this will take place in future outbreaks as in past epidemics. As a result of the studies, the CoV subfamily is rapidly expanding with new generation sequencing applications that improve the detection and definition of novel CoV species. In conclusion, CoV classification is continually changing. According to the most recent classification of The International Committee on Taxonomy of Viruses (ICTV), there are four genera of thirty-eight unique species.14 SARS-CoV and MERS-CoV that attach to the host cell respectively bind to cellular receptor angiotensin-converting enzyme2 (SARS-CoV associated) and cellular receptor of di-peptidylpeptidase 4 (MERS-CoV associated). 15 After entering the cell, the viral RNA manifest itself in the cytoplasm. Genomic RNA is encapsulated and polyadenylated, and encodes various structural and non-structural polypeptide genes. These polyproteins are split by proteases that exhibit chymotrypsin-like activity.13,15 The resulting complex drives (-)
RNA production through both replication and transcription. During replication, full-length(-) RNA copies of the genome are produced and used as a template for full-length (+) RNA genomes.\textsuperscript{12, 13} During transcription, a subset of 7-9 sub-genomic RNAs, including those encoding all structural proteins, are produced by discontinuous transcription. Viral nucleocapsids are combined from genomic RNA and R protein in the cytoplasm and then are budded into the lumen of the endoplasmic reticulum. Virions are then released from the infected cell through exocytosis. The released viruses can infect kidney cells, liver cells, intestines, and T lymphocytes, as well as the lower respiratory tract, where they form the main symptoms and signs.\textsuperscript{15} Remarkably, CDT lymphocytes were found to be lower than 200 cells/mm\textsuperscript{3} in three patients with SARS-CoV infection. MERS-CoV is able to affect human dendritic cells and macrophages in-vitro. T lymphocytes are also a target for the pathogen due to the characteristic CD26 rosettes. This virus can make the antiviral T-cell response irregular due to the stimulation of T-cell apoptosis, thus causing a collapse of the immune system.\textsuperscript{16,17}

**Transmission of Corona virus**

In case of SARS-CoV, transmission is through droplet infection (respiratory secretions) and close person-to-person contact. It can also spread through sweat, stool, urine, and respiratory secretions.\textsuperscript{[13]} When virus enters into the body, it binds to the primary target cells such as enterocytes and pneumocytes, thereby establishing a cycle of infection and replication. Other target cells of CoV are epithelial renal tubules, tubular epithelial cells of kidney, immune cells, and cerebral neuronal cells. \textsuperscript{[11,12]}

CoV attaches to the target cells with the help of spike protein–host cell protein interaction (angiotensin converting enzyme-2 [ACE-2] interaction in SARS-CoV [14] and dipeptidyl peptidase-4 [DPP-4] in MERS-CoV [15]. After the receptor recognition, the virus genome with its nucleocapsid is released into the cytoplasm of the host cells. The viral genome contains ORF1a and ORF1b genes, which produce two PPs that are pp1a and pp1b, [16] which help to take command over host ribosomes for their own translation process. [17] Both pp1a and pp1b take part in the formation of the replication transcription complex. [16] After processing of PP by protease, it produces 16 NSPs. All NSPs have their own specific functions such as suppression of host gene expression by NSP1 and NSP2, formation of a multidomain complex by NSP3. NSP5 which is a M protease which has role in replication, [17] NSP4 and NSP6 which are transmembrane (TM) proteins, [18] NSP7 and NSP8 which act as a primase, [16] NSP9 – a RNA -binding protein, the dimeric form of which is important for viral infection. Induction of disturbance to the dimerization of NSP9 [19] can be away to overcome CoV infection. [20] NSP10 acts as a cofactor for the activation of the replicative enzyme. [21] NSP 12 shows RNA- dependent RNA polymerase activity, NSP13 shows helicase activity, NSP 14 shows exoribonuclease activity, NSP 15 shows endoribonuclease activity, and NSP 16 has methyltransferase activity. [18] All NSPs have an important role in replication and transcription. [18] Synthesized proteins such as M, E, and S are entered into the endoplasmic reticulum(Golgi intermediate compartment (ERGIC) complex and make the structure of viral envelope. [22] On the other hand, the replicated genome binds to N protein and forms the ribonucleoprotein (RNP) complex. The outer cover is formed by the M, E, and S proteins. [22] Finally, the virus particle comes out of the ERGIC by making a bud-like structure. [23] These mature virions form a vesicle, which fuses with the plasma membrane and releases the virus particles into the extracellular region. [23, 24] The detailed structure of CoV and its life cycle is depicted in Figures 1 and 2. On infection, the SARS-CoV and MERS-CoV cause a surge of pro-inflammatory cytokines and chemokines, which cause damage to lung tissue, [13] deterioration of lung function, and then finally lung failure in some cases. [25] Currently, there is no specific antiviral drug for the treatment of CoV- associated pathologies. Most treatment strategies focus on symptomatic management and supportive therapy only. [26, 27] We screened PubMed and RCSB database with the keywords HCoVs, NCoV, corona virus, SERS- CoV, MERS- CoV, 2019-nCoV, crystal structure, X-ray crystallography structure, NMR structure, target, and drug target till Feb 3, 2020. The database files were extracted using endnote, and title and abstract screening was done using Rayyan QCRI. Full texts of these screened articles were further screened for possible inclusion in the systematic review. Articles that evaluated different druggable targets of CoV.
Figure 2: The life cycle of CoV in host cells.


### Major targets in Corona virus

<table>
<thead>
<tr>
<th>PDB ID</th>
<th>Details</th>
<th>Inhibitor</th>
<th>IC$_{50}$</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>4KXJ</td>
<td>Interaction between PJ34 and NTD of N protein of HCoV-OC43</td>
<td>PJ34</td>
<td>-</td>
<td>[26]</td>
</tr>
<tr>
<td>3V3P</td>
<td>Structure not released</td>
<td></td>
<td></td>
<td>[30]</td>
</tr>
<tr>
<td>4LM7</td>
<td>Interactions of NTD of N protein of HCoV-OC43 with UMP</td>
<td></td>
<td></td>
<td>[26]</td>
</tr>
<tr>
<td>4LI4</td>
<td>Interactions of NTD of N protein of HCoV-OC43 with AMP</td>
<td></td>
<td></td>
<td>[26]</td>
</tr>
<tr>
<td>4TWY</td>
<td>3CLPro of SARS-CoV with an inhibitor</td>
<td>3BL</td>
<td>63 µM</td>
<td>[27]</td>
</tr>
<tr>
<td>4TWW</td>
<td>3CLPro of SARS-CoV with an inhibitor</td>
<td>41</td>
<td>240 µM</td>
<td>[27]</td>
</tr>
<tr>
<td>4WY3</td>
<td>3CLPro of SARS-CoV with an inhibitor</td>
<td>3X5</td>
<td>490 nM</td>
<td>[31]</td>
</tr>
<tr>
<td>4OVZ</td>
<td>CoV PLPro complexed with inhibitor</td>
<td>P85</td>
<td>490 nM</td>
<td>[31]</td>
</tr>
<tr>
<td>3MJ5</td>
<td>SARS-CoV PLPro complexed with inhibitor</td>
<td>GRM</td>
<td>320 nM</td>
<td>[32]</td>
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<tr>
<td>2FE8</td>
<td>SARS-CoV PLPro and its interactions with an inhibitor</td>
<td>-</td>
<td>-</td>
<td>[33]</td>
</tr>
<tr>
<td>1UK4</td>
<td>SARS-CoV 3CLPro and its interactions with an inhibitor</td>
<td>Substrate analoghexpeptidylCMKinhibitor</td>
<td>IC$_{50}$ ca. 2 mM</td>
<td>[34]</td>
</tr>
<tr>
<td>1UJ1, 1UK3, 1UK2</td>
<td>SARS-CoV M-pro, apo-enzyme at different pH</td>
<td>-</td>
<td>-</td>
<td>[34]</td>
</tr>
<tr>
<td>3VB6</td>
<td>SARS-CoV 3CLPro in complex with C6Z</td>
<td>C6Z</td>
<td>39 µM</td>
<td>[35]</td>
</tr>
</tbody>
</table>


Coronavirus from SARS to MERS:
SARS-CoV, which originated from China and then was spread to other parts of the world with hospital-acquired infectious cases, had a mortality rate of 10%, and was transmitted to 8000 people during an 8-month outbreak in 2002-2003.[21] In 2012, MERS-CoV, when it emerged in Arabian Peninsula, MERS-CoV, spread to 27 countries with 35.6% mortality rate in 2220 cases. It is known that both of them are zoonotic viruses showing hospital-acquired and human-to-human transmission. [21,22] Similar dynamics apply for COVID-19 that was originated from Wuhan and the current rate of mortality from this infection is about 2%. CoVs can use different receptors and pathways when entering the cell. SARS-CoV usually infects young people, MERS-CoV people aged above 50 years and COVID-19 infects middle age and above. Comparing non-respiratory complications, MERS-CoV involve the cardiovascular system more frequently than SARS-CoV and frequently require vasopressor treatment.[3, 19, 20] Case series have reported that COVID-19 affects the cardiovascular system.[23] Acute kidney failure was more commonly seen in SARS-CoV and MERS-CoV epidemics compared to COVID-19.[3,26] Whereas radiological findings are present in all three pathogens, air space opacifications are seen in SARS-CoV and ground- glass appearance in MERS-CoV and COVID-19.[3, 26] Hospital-acquired secondary infections have been defined in all three pathogens. [3,23] There are no studies that report a definitely successful drug for their treatment.[24] In terms of epidemic periods, SARS-CoV ended in less than a year, and the MERS-CoV epidemic lasted for seven years despite its spread to more restricted areas and. The question of how long the novel COVID-19 outbreak will last is a question that everyone is curious about.

Treatment & Protection
In general, there are few or no treatment options for viral diseases that occur suddenly.[24] In parallel with this knowledge, today there is no vaccine or effective treatment to prevent COVID-19 infection. Molecules are being tested for COVID-19 in in-vitro and human-based SARS-CoV and MERS-CoV trials. Studies evaluating the antiviral activity of types I and II interferons have reported, interferon-beta (IFNb), as the most potent interferon, was reducing in-vitro MERS-CoV replication.[19] According to a human MERS-CoV case report from South Korea, the use of the combination of Lopinavir/Ritonavir (LPV/RTV) (Anti-HIV drugs), pegylated interferon and ribavirin provided a successful viral clearance.[23]

For this purpose, a randomized control trial (MIRACLE Trial), that aimed to determine whether LPV/RTV-IFNb improved clinical results in MERS-CoV patients, was initiated in 2016 and 76 patients were enrolled.[27] Although another antiviral drug, remdesivir was used in the first case reported from the United States of America, seemed successful, controlled studies with more cases are needed.[21] In-vitro studies have shown that viral RNA transcription was terminated with remdesivir in early stage.[28,29] There are publications demonstrating that remdesivir has a strong antiviral activity in epithelial cell cultures against SARS-CoV, MERS-CoV

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**Table:**

<table>
<thead>
<tr>
<th>Protein Complex</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>SARS-CoV 3CLPro with C4Z</td>
<td>C4Z 1.3-4.6 µM [35]</td>
</tr>
<tr>
<td>HCoV-NL63 3CLPro</td>
<td>- - [36,37]</td>
</tr>
<tr>
<td>Main protease of 2019-nCoV and its complex with N3 (inhibitor)</td>
<td>- - [38]</td>
</tr>
<tr>
<td>SARS‑CoV main protease</td>
<td>[39]</td>
</tr>
<tr>
<td>HCoV‑NL63 main protease</td>
<td>[36,37]</td>
</tr>
<tr>
<td>SARS‑CoV spike</td>
<td>[39]</td>
</tr>
<tr>
<td>SARS‑CoV NTD</td>
<td>[40]</td>
</tr>
<tr>
<td>SARS‑CoV S protein</td>
<td>[41]</td>
</tr>
<tr>
<td>SARS‑CoV S protein:ACE-2 (conformation 1) complex</td>
<td>[42]</td>
</tr>
<tr>
<td>SARS‑CoV S protein:ACE-2 (conformation 3) complex</td>
<td>[43]</td>
</tr>
<tr>
<td>HR1 motif of HCoV-229E in complex with EK1</td>
<td>Modified OC43-HR2P peptide (EK1) 0.19-0.62 µM [39]</td>
</tr>
<tr>
<td>EK1 in complex with SARS HR1 motif</td>
<td>[39]</td>
</tr>
<tr>
<td>NTD of SARS-CoV S protein</td>
<td>[40]</td>
</tr>
<tr>
<td>SARS-CoV S protein</td>
<td>[41]</td>
</tr>
<tr>
<td>MERS-CoV S protein in complex with Sialyl-Lewis</td>
<td>[42]</td>
</tr>
<tr>
<td>SARS-CoV protein:ACE-2 (conformation 1) complex</td>
<td>[43]</td>
</tr>
</tbody>
</table>
Many measures should be taken, such as timely publication of epidemic information for elimination of the source of infection, early diagnosis, reporting, isolation, supportive treatments and for avoiding unnecessary panic. CDC reminds basic measures such as hand washing, using disinfectant solutions, avoiding contact with patients in order to prevent the spread of viruses by droplets. Precautionary actions including the provision of medicines supply chains, personal protective equipment, and hospital supplies should be made in a short time for the protection of the Chinese people and global health, especially in the places with close travel ports to major Chinese ports. Based on the 2003 SARS-CoV epidemic experience, the Chinese government took many effective measures including closing public transport, reducing migration and promoting personal protection with masks in Wuhan and other provinces. Hence, there are reported cases of infected hospital personnel, healthcare staffs should be informed about taking personal protective measures such as the use of gloves, eye spectacles and N95 masks during the examination of patients with a suspected history of COVID-19 contact or travel to China.

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