Structure, Transmission, Diagnostic Symptoms, Host and Entry Mechanism of COVID-19: A Review

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Abstract: In Wuhan, China, a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been reported and caused coronavirus disease 19 (COVID-19). The coronavirus infection is pathogenic and highly transmittable and spread quickly around the world by the human to human contact. Through genomic analysis, it has been revealed that the primary reservoir of SARS-CoV-2 is bats due to having severe acute respiratory syndrome-like (SARS-like) viruses phylogenetically. The viral infection is rapidly transmitted by the human to human contact, but the intermediate source of their origin and transfer is not known. To date, any clinically approved vaccine or antiviral drug has not been prepared against COVID-19. However, researchers and scientists have evaluated some broad-spectrum antiviral drugs against COVID-19 through clinical trials and they have found satisfactory clinical recovery. This review summarizes the comparative analysis of the emergence and pathogenicity of COVID-19, severe acute respiratory syndrome coronavirus (SARS-CoV), and Middle East respiratory syndrome coronavirus (MERS-CoV). This review is also focused on the development of effective vaccines or antidrug and also provides details related to an approach to practice therapeutic combinations to fight against this viral outbreak.

Keywords: COVID-19, SARS-CoV-2, glycoprotein, infection, symptoms, prevention.

1. INTRODUCTION

The term corona has been raised from the crown-like appearance (Corona is a Latin word it means crown-like). Nucleic acid material of coronavirus constituted with single-stranded RNA. The virus is also known as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), and the family of coronavirus is divided into different classes such as alpha (α), beta (β), gamma (γ), and delta (δ). The β class of coronavirus was reported as the main cause of COVID-19. This disease has been declared as a pandemic and zoonotic disease due to quick transmission in animals and humans. Previously, it is known that this virus is only transmitted in animals until the world witnessed in humans. In Guangdong, China 2003, SARS-CoV has been identified as the outbreak of SARS-CoV-1 [1]. In Middle Eastern countries, an endemic was announced due to another pathogenic coronavirus, called the Middle East respiratory syndrome (MERS-CoV), only a decade later [2]. Recently, Wuhan emerged as the business hub of china at the end of 2019. An outbreak of a novel coronavirus reported more than 177000 deaths and over sixteen lakhs of infections. Previously, SARS-CoV-2 has been named as the Wuhan coronavirus or 2019 novel coronavirus (2019-NCOV) in China, which further finally named as SARS-CoV-2 by the International Committee on Taxonomy of Viruses (ICTV) and this disease called COVID-19 [3-5]. In 2003, SARS-CoV infected around 8098 individuals with 9% mortality rate across 26 countries globally, while novel coronavirus 2019 caused infection and death around 4098018 and 283271 in individuals with a 2.9% mortality rate across 215 countries.

2. NOMENCLATURE

According to the World Health Organisation (WHO), U.S. Centers for Disease Control and Prevention (CDC), and ICTV, COVID-19 stands for CO-corona, VI-virus, D-disease, 19-2019 while SARS-CoV-2 for severe acute respiratory syndrome coronavirus-2 [6].

3. CLASSIFICATION

According to ICTV [1, 7], the classification of coronavirus is given below.

<table>
<thead>
<tr>
<th>Category</th>
<th>Coronaviruses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Realm</td>
<td>Riboviria</td>
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contd....


3.1. Transmission

The transmission of coronavirus was found from animals to humans, and now it's spreading person to person through contact [8]. There are different ways for transmission, such as coughing and sneezing, close personal contact, use of infected things, respiratory droplets, and aerosol (smaller droplets suspended in air) (Fig. 1) [9]. According to epidemiologic data, the most common transmission mode of COVID-19 is through droplets, either asymptomatic or symptomatic contact [10]. Some studies have reported that asymptomatic infection ranges from 4 to 32% [11-13] and found it probably uncommon [12]. Another most possible mode of transmission is in contact with the virus on its surface [14, 15]. Recently, it has been reported that vertical transmission (from mother to child or also called maternal COVID-19) was found under low risk of transmission [16-18]. Coronavirus can be persisted on impermeable surfaces (plastic and stainless steel) at higher levels up to 3 to 4 days than permeable surfaces (cardboard) [19]. Presymptomatic transmission appeared as the major contributor (approx. 48% to 62%) for the spreading of SARS-CoV-2 [20].

3.2. Symptoms

There are many symptoms of the COVID-19 positive patients (having travel history to China or other infected areas where local transmission persist or contact with COVID-19 infected patients having similar travel history) such as cough (throat infection), fever, tiredness, and shortness of breathing (Fig. 2) [21]. Infected people may suffer from sickness for 1-14 days before developing symptoms. The disease can be more lethal to aged people who suffered from other severe medical conditions like asthma, diabetes, heart problems, etc. [22]. However, the infection can be asymptomatic or symptomatic. The confirmation of SARS-CoV-2 infection was done by a molecular test such RT-PCR (reverse transcription-polymerase chain reaction), etc., using respiratory samples (bronchoalveolar lavage/endotracheal/aspirates sputum and oropharyngeal/nasopharyngeal swab) or sometimes from the stool and blood in severe cases [23]. The sample should be sent to designated reference labs for testing correctly. Real-time PCR test showed many limitations, including availability and accessibility issues. It has been reported that COVID-19 patients showed low white cell count, i.e., lymphopenia (lymphocyte count less than 1000), which further become severe [24]. The erythrocyte sedimentation rate, alanine aminotransferase/aspartate aminotransferase, creatinine, prothrombin time, D-dimer, lactic acid dehydrogenase, creatine phosphokinase, and C-reactive protein generally found elevated, and there is no change appears in procalcitonin levels during infection [25]. The level of procalcitonin level increased during bacterial infection. Computed tomo-

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**Table 1:**

<table>
<thead>
<tr>
<th>Order</th>
<th>Nidovirales</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suborder</td>
<td>Coronavirinae</td>
</tr>
<tr>
<td>Family</td>
<td>Coronaviridae</td>
</tr>
<tr>
<td>Subfamily</td>
<td>Orthocoronavirinae</td>
</tr>
<tr>
<td>Genus</td>
<td>Betacoronavirus</td>
</tr>
<tr>
<td>Subgenus</td>
<td>Sarbecovirus</td>
</tr>
<tr>
<td>Species</td>
<td>Severe acute respiratory syndrome-related coronavirus</td>
</tr>
</tbody>
</table>
graphy (CT) has been used to diagnose infections and found more specific and sensitive [26, 27]. For the qualitative detection of SARS-CoV-2 or COVID-19 diseased patients, several antibody (immunoglobulin M (IgM)/IgG) detection tests, including rapid chromatographic tests and ELISA tests, were found suitable than other tests [28]. In serological (antibody detection) tests, COVID-19 infected patients showed rising of IgM antibody within 1 week and IgG within 14 days [29].

3.3. Treatment

Presently, no specific treatment or medication is recommended to treat this disease, and no cure is accessible. Many scientists and researchers are trying to test a variety of possible treatments. In the event that you have mild symptoms, your primary care physician may suggest that you recuperate at home. You will likely be approached to disengage yourself, however, much as could be expected from family and pets. At the same time, you are wiped out, wear a mask when you are around individuals and pets, and utilize a different room and bathroom. Provision of oxygen is required in hypoxic patients by nasal prongs, high-flow nasal cannula, and noninvasive ventilation [30]. While in some cases, renal replacement therapy is also considered by the medical team [31]. If the infection is proven, the appropriate dose of antibiotics and antifungals will be required to cure the disease initially [32]. After diagnosed COVID-19, several trials are on-going using various antifungal and antibacterial drugs such as lopinavir, ritonavir, oseltamivir, hydroxychloroquine, etc. [33]. WHO published the detailed guidelines to manage the disease until a vaccine is not discovered [34-36]. In Wuhan, to understand the hypoxic condition treatment in COVID-19 patients, 76, 13, 4, 3, and 9% oxygen have been provided through noninvasive ventilation (4-22 days), mechanical ventilation (3-20 days), extracorporeal membrane, and continuous renal replacement therapy, respectively. Antibiotics, antifungals, antiviral, glucocorticoids and intravenous immunoglobulin therapy have been given in 71, 15, 75, 19, and 27% infected humans [27]. The antiviral therapy is performed by giving ganciclovir, lopinavir, ritonavir, and oseltamivir drugs to the patients. An antiviral drug remdesivir has been used to cure Ebola, can also be used for the COVID-19 [37]. Some other drugs and therapy such as arbidol (antiviral drug), interferons, intravenous immunoglobulin, chloroquine, and plasma of patients have been used to recover from COVID-19 [38].

3.4. Prevention

Prevention of COVID-19 will be required until treatments or vaccines are not discovered. These precautions are personal hygiene, physical distancing, and use of protective equipment, such as masks and gloves, and should avoid workplace, social gatherings, school, and public transport. Common precautions have been discussed below:

**DO**
- Hand washing
- Avoid close contact
- Stay home
- Self-isolation
- Quarantine

**DON’T**
- Touch your eyes, nose, and lips
- Do not use anything to other people

3.5. Morphology and Structure of SARS-CoV-2 or Coronavirus

It has positive-stranded RNA virus (26-32 kb). It comprises four genera (alpha, beta, gamma, and delta). Six human COVs have been confirmed so far.
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<table>
<thead>
<tr>
<th>Coronaviruses</th>
<th>Genus</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCoV-NL63 and HCoV29E</td>
<td>Alpha cov genus</td>
</tr>
<tr>
<td>HCoV-OC43, HCoV-NKU1 and SARS-CoV</td>
<td>Beta cov genus</td>
</tr>
<tr>
<td>MERS-CoV</td>
<td>Beta cov genus</td>
</tr>
</tbody>
</table>

An enveloped, single positive-strand RNA genome encodes four major viral structure proteins (Fig. 3).

### 3.6. Human Coronaviruses

In 1965, HCoV, B814 has been introduced as the first human coronavirus. After that, approximately 30 more strains have been characterized in the following years. Among them, 10 human coronaviruses can be isolated from the primary embryonic tracheal organ culture and the rest can be isolated from monolayer cultures. Basically, they have related antigenically to the prototype strain HCoV-229E, which is distinct from the HCoV-OC43, isolated for organ culture 43 [39, 40]. In the subsequent decades, research on HCoVs would center on these two distinct viruses. During the study of these two distinct viruses, an unknown virus which gives respiratory illness has been introduced in Asia as Severe Acute Respiratory Syndrome (SARS). Different biological parameters have been reported during the pandemic condition of SARS (Table 1). Researchers identified this virus as a novel coronavirus [41, 42]. At the end of the epidemic, in China, this novel coronavirus infected approximately 8000 people and caused 774 deaths [43]. After the discovery of this virus, two other coronaviruses have been identified, which caused human disease and named HCoV-NL63 and HCoV-HKU1. HCoV-NL63 was isolated from an infant who showed bronchiolitis in the Netherlands in 2004 [44] and in 2005, HCoV-HKU1 was isolated from patients suffered from the pneumonia-like disease in Hong Kong [45]. In 2012, MERS-CoV was isolated as another type of respiratory HCoV, from a patient suffered from pneumonia in Saudi-Arabia [46]. Unlike SARS-CoV, this virus caused a large outbreak in South-Korea, which was intermittently presented in the human population [47].

### 3.7. Host of Coronavirus

The key reservoir of SARS-CoV infection was caused by palm civets and raccoon dogs. However, the samples were isolated from the civets at the live traded food market and showed positive results for viral RNA detection and suggested civet palm might be secondary hosts. After that, in Rhinolophus bats, researchers found anti-SARS-CoV antibodies, which suggested that bats could be the source of viral replication. The camel was found as the primary host or zoonotic source of MERS-CoV, which belongs to the beta subgroup of coronavirus. By following the homologous recombination, it has been discovered that spike binding glycoprotein of novel coronavirus is developed from SARS-CoV (covxc21 or covzc45) and a yet unknown beta CoV [48, 49].

<table>
<thead>
<tr>
<th>Structure</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spike (S)</td>
<td>play a vital role in viral entry</td>
</tr>
<tr>
<td>Envelope (E)</td>
<td>play an important role in viral assembly</td>
</tr>
<tr>
<td>Membrane (M)</td>
<td>play an important role in viral assembly</td>
</tr>
<tr>
<td>Nucleocapsid protein (N)</td>
<td>for RNA synthesis</td>
</tr>
</tbody>
</table>

Fig. (3). Diagrammatic representation of the primary structure of coronavirus (COVID-19) showing spike glycoprotein (S), membrane protein (M), nucleocapsid protein (N) and envelope small membrane protein (E). (A higher resolution / colour version of this figure is available in the electronic copy of the article).
4. ENTRY MECHANISM AND REPLICATION OF CORONAVIRUSES IN HUMAN AND THEIR KEY FEATURES

The ORF1 downstream regions of all coronaviruses contain specific genes that encode proteins for viral replication, nucleocapsid, and spike formation. The key role of spike protein is to help the virus attach to the surface of the host cell and enter inside the cell. The virus may affect multiple hosts due to the loosely attached receptor-binding domain (RBD). Coronavirus follows a special kind of mechanism to enter inside the host cell using some cellular proteases, which include cathepsin and trans-membrane protease serine 2 (TMPRSS2) and, human airway trypsin lie protease (HAT), which split the spike protein and ascertain further penetration changes. The SARS coronavirus and HCoV-NL63 have a key receptor enzyme which is known as angiotensin-converting enzyme 2 (ACE2) while MERS-CoV employs dipeptidyl peptidase 4 (dpp4) as a key receptor. SARS-CoV-2 possesses a very complex structure due to having spike protein, which helps the virus to attach to the host cell and also shows the expression of some polyproteins, membrane proteins, nucleoproteins, like RNA polymerase, papain-like protease, 3-chymotrypsin-like protease, helicase, glycoprotein, and some accessory proteins. To maintain the Van der Waals forces the spike protein of SARS-CoV-2 consists of a 3-D structure in the RBD to region. The Glu^{394} residue in the RBD region of SARS-CoV-2 is identified by the critical lys^{31} residue on the human ACE2 receptor [50]. The whole mechanism of pathogenicity of SARS-CoV-2 is described in Fig. (4). The synthesis of viral RNA produces both genomic and sub-genomic RNAs which is followed by translation and assembly of the viral replicase complexes. A set of nested RNAs formed by the positive-sense sub-genomic RNAs which is a distinctive property of the Nidovirales [51]. The replication of viral RNAs performed by cis-acting sequences. Seven stem-loop structures in the genome at 5' UTR extend to replicate gene [52-55] while 3' UTR contains hypervariable region bulged stem-loop and a pseudoknot [56-61]. These different structures of 5' and 3' UTR have been proposed for the regulation of alternate stages during RNA replication. The genomic RNA of coronavirus encodes structural (such as replicase-transcriptase proteins) and non-structural proteins (niche-specific proteins) play important role in viral RNA synthesis. In viral RNA synthesis, at least one non-structural protein 2 (nsp2), niche-specific protein, the nucleocapsid protein (N), and one structural protein is involved. ORF1a and ORF1b encoded the replicase-transcriptase proteins. These replicase-transcriptase proteins are cleaved by virus-encoded proteinases and other viral proteins and, cellular proteins undergo the assembly process and are bound into RTC (replication-transcription complexes) [20].

4.1. Vaccine’s for SARS-CoV-2

Till date, there is no vaccine available against COVID-19, while some previous strategies or vaccine against SARS-CoV-2 is found effective for the treatment of COVID-19 patients. The Food and Drug Administration (FDA or US-FDA) has approved authorization for a medication affirmed for different sicknesses to be utilized to treat serious COVID-19 when no other alternatives are accessible [62]. An antiviral medication, remdesivir, has been endorsed for this utilization. There are several anti-virals that are being used and are under trial worldwide for the management of COVID-19. Various types of anti-virals used for the comprehensive investigation of SARS-CoV-2 are summarized in Table 2.

CONCLUSION

The novel coronavirus came in knowledge from the Hunan seafood market (traded live animals too) at Wuhan, China. In the Hunan seafood market, snakes, bats, palm civets, raccoon dogs, and some other animals are sold and became the major cause to spread coronavirus rapidly up to 109 countries. According to researchers, the zoonotic source of SARS-CoV-2 is still not confirmed, but on the basis of the sequence-based analysis, it has been suggested that bats are the key reservoir. The reason for infection and transmission in between cross-species could be the DNA recombination at


Fig. (4). Entry mechanism and replication of coronavirus. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

Table 2. List of some efficient anti-viral drugs being used in COVID-19.

<table>
<thead>
<tr>
<th>Anti-viral Drugs</th>
<th>Important Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remdesivir</td>
<td>Drug type: A nucleotide analog prodrug. Effects: It has shown efficacy in animal models infected with SARS-CoV and MERS-CoV [63, 64]. In <em>vitro</em> anti-viral activity in SARS-CoV-2 Effective in the first COVID-19 patient in USA [65, 66]. Trials: Major trials of remdesivir are underway.</td>
</tr>
<tr>
<td>Lopinavir/ritonavir</td>
<td>Tested by: RTC among COVID-19 patients in China Effects: showed insignificant decrease in 28- days mortality (RD, -5.8%; 95% CI, -17.3 to 5.7) [63]. Showed increased adverse effects with lopinavir/ritonavir. Trial: The trial was not unblended.</td>
</tr>
<tr>
<td>Arbidol</td>
<td>Drug Type: It is an anti-viral drug Use: In influenza virus by blocking viral fusion In <em>vitro</em> activity; against other SARS-CoV-2 Recommendation: Only by Chinese authorities in the treatment of COVID-19 [25].</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>Drug Type: This is an anti-viral drug Use: HIV treatment Effects: Strong effects against SARS-CoV [67] May be a potential therapeutic option for COVID-19.</td>
</tr>
<tr>
<td>Investigational anti-viral drugs:</td>
<td></td>
</tr>
<tr>
<td>Favipiravir (selective RNA polymerase)</td>
<td>Favipiravir: (selective RNA polymerase) is an oral anti-viral against influenza. Approved; in Japan. Trial: A phase 2 human trial in the USA is underway among 50 enrolled patients with COVID-19 [68].</td>
</tr>
<tr>
<td>Niclosamide</td>
<td>Drug Type: Anthelmintic agent having potential as an anti-viral agent. MOA: Possible mechanism for anti-viral activity is its target at a viral reservoir in the gut. However, for COVID-19, phase 2a/2b trial is planned [69].</td>
</tr>
<tr>
<td>Rintatolimod</td>
<td>Drug Type: Investigational anti-viral, which is a toll-like receptor 3 (TLR-3) agonist being tested against SARS-CoV-2 in Japan [70]. Effects: Showed broad-spectrum anti-viral activity.</td>
</tr>
<tr>
<td>Ivermectin</td>
<td>Effects: Vero-hSLAM cells infected SARS-CoV-2 has shown a reduction in viral RNA <em>in vitro</em> with clinical isolate Australia/VIC01/2020 by ivermectin (antiparasitic). This study needs further validation [71-73] before translated into humans.</td>
</tr>
</tbody>
</table>
spike glycoprotein, which assorted SARS-CoV (CoVZXC21 or CoVZC45) with the RBD of another beta CoV. Therefore, several aspects of infection, transmission, and treatment are still unclear. Advances in effective management and prevention of COVID-19 require basically clinical investigation, interventions, and public health.

AUTHOR CONTRIBUTIONS

Mukesh Meena, Prashant Swapnil, and Tansukh Barupal provided the general concept, conceived, and drafted part of the manuscript. Prashant Swapnil, Mukesh Meena, Tansukh Barupal, Yashwant Sompura, and Deepa Hada wrote the manuscript. Mukesh Meena supervised the current study. All authors read and approved it for publication.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES


Coronaviruses, 2021, Vol. 2, No. 5 e300421188050
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http://dx.doi.org/10.1073/pnas.57.4.933 PMID: 5231356


http://dx.doi.org/10.1056/NEJMoa030747 PMID: 12690091


http://dx.doi.org/10.1126/science.1085952 PMID: 12730500


http://dx.doi.org/10.1038/nm1024 PMID: 15034574


http://dx.doi.org/10.1016/j.jvi.2020.03.005  PMID: 32257431


http://dx.doi.org/10.1126/jvi.65.1.320-325.1991 PMID: 1985203


http://dx.doi.org/10.1128/JVI.00549-07 PMID: 17475638


http://dx.doi.org/10.1128/JVI.00263-11 PMID: 21430057


http://dx.doi.org/10.1128/JVI.00915-09 PMID: 19759148


http://dx.doi.org/10.1128/JVI.10.08036-06 PMID: 17093194


