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A Comprehensive Overview of Novel Coronavirus SARS-CoV-2 and COVID-19 Disease: A Narrative Review

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ABSTRACT

COVID-19 (Coronavirus Disease 2019) is a dreaded pneumonia-like disease caused by a novel coronavirus, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). This disease was declared a pandemic by the WHO in March 2020 due to its severity, the huge progression in the number of cases leading to deaths, and its rapid spread throughout the world since its outbreak in late December 2019 in China. In fact, SARS-CoV-2 affects the lower respiratory tract of human beings and can be lethal if the patient has a compromised immune system or other comorbid conditions like kidney disease, cardiovascular disease, diabetes, hypertension, etc. The present review is an effort to explore the current status and bring to light the future perspectives of the disease by outlining the recent updates on the structure, replication, and transmission of SARS-CoV-2, in parallel with the pathogenesis, diagnosis, pathophysiology, and treatment of the COVID-19 disease in a comprehensive manner. Since COVID-19 is an issue of global concern, it is mandatory to save mankind from it. Henceforth, the purpose of this narrative review remains to serve as one of the mechanistic and diagnostic insights that may contribute to the fight against COVID-19 in many ways.

KEYWORDS: COVID-19, SARS-CoV-2, ACE-2, Diagnosis, Pathophysiology

In late December 2019, a disease with unknown etiology started from Wuhan city of China in which patients were suffering from lower respiratory tract infection and pneumonia (Huang et al., 2020; Wang et al., 2020; Zhu et al., 2020). It was discovered later that it is caused by an evolutionary novel form of coronavirus, named 2019-nCoV (2019-novel Coronavirus) and further renamed as SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2) by the World Health Organization (WHO). The disease caused by SARS-CoV-2 was named COVID-19 (COrona VIrus Disease 2019) by WHO on February 11, 2020 (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen). Because of its severity, rapidly rising death and alarming level of spread WHO declared it a pandemic on March 11, 2020 (https://www.who.int/news-room/detail/27-04-2020-who-timeline---covid-19).

SARS-CoV-2 has the potential to infect anybody regardless of age and gender; however, it affects most to the elderly persons (>60), infants (<1) and especially those who have underlying health issues (Kowalik et al., 2020; Bourganje et al., 2020; Wei et al., 2020a; Wu and McGoogan 2020). Since the virus outbreak in China, a total of 13,378,853 confirmed cases and 580045 deaths have been reported worldwide at 216 locations till July 16, 2020 (https://covid19.who.int/). Factors for the speedy viral spread from Wuhan city to the other part of China and subsequently around the world, despite the complete or partial lockdown implementation, are the atypical clinical symptoms, presence of asymptomatic carriers and the ability of virus to infect even in its incubation period which is 14 days with the median time of 4-5 days from exposure to symptoms onset (Guan et al., 2020; Lauer et al., 2020; Hu et al., 2020; Pan et al., 2020; Wei et al., 2020b; Tong et al., 2020).

SARS-CoV-2 has been isolated and sequenced since January 2020 by different labs in China independently, and sequence analyses showed its origin in bat-like SARS-CoV and MERS-CoV (Zhou et al., 2020). According to Lam et al (2020), the intermediate host for SARS-CoV-2 is the pangolin. The mechanism of transmission of the virus from animal to human is not very clear; however, it could be predicted that direct contact with animals or using bats or an intermediate host as food may be the reason for the transmission (Guo et al., 2020).

SARS-CoV-2 is an enveloped, non-segmented, positive-sense single-stranded RNA virus that belongs to the beta coronavirus genus. Like six others previously identified human coronaviruses, it infects humans through the respiratory tract (Basetti et al., 2020; Cui et al., 2019; Yin and Wunderink, 2020). Among these six human CoVs, two highly pathogenic beta-CoVs are known to cause severe respiratory syndromes in humans: (1) SARS-CoV (Severe Acute Respiratory Syndrome Coronavirus), which emerged in southern China in 2002, spread across five continents, and caused a large-scale epidemic with about 8,000 infections and approximately 800 deaths; and (2) MERS-CoV (Middle East Respiratory Syndrome Coronavirus), which has persisted

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as an epidemic in the Middle East since 2012 (Chan et al., 2015; 2020a). The other four human CoVs (HCoV-NL63, HCoV-229E, HCoV-OC43, and HKU1) typically cause only mild upper respiratory tract diseases (Cui et al., 2019; Su et al., 2016). In this review, the structure of SARS-CoV-2, its replication, mode of transmission, clinical presentation or symptoms of infection, and the resulting disease COVID-19, various diagnostic methods, pathophysiology, current status of disease management and treatment, and future perspectives have been discussed (Figure 1).

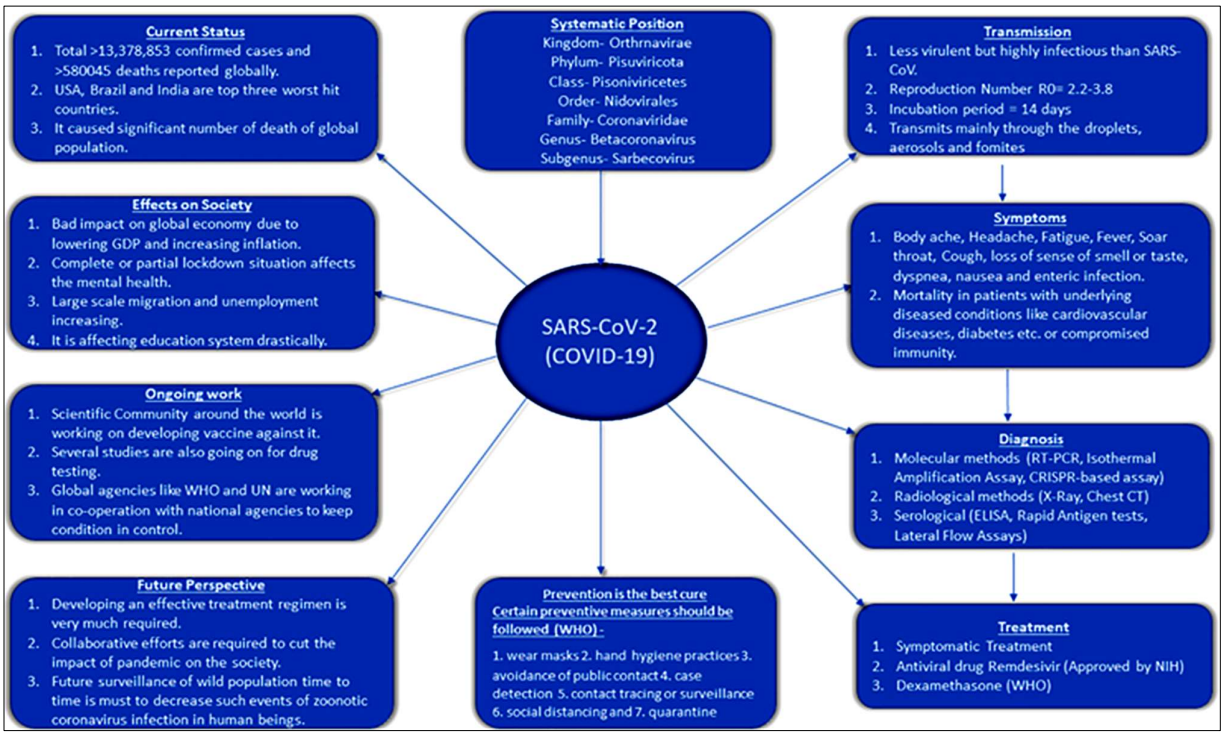

Figure 1. Illustrated summary of COVID-19.

Virus structure and pathogenesis

The members of four genera of Coronaviruses (CoV) of family Coronavirinae, including SARS-CoV-2, are known to cause infection in humans, livestock, birds, bats, mice, and many other wild animals and infections occur in the respiratory, gastrointestinal, liver, and central nervous systems (Huang et al., 2020). The name of the group "Corona" means crown or coronet in Latin, due to the presence of trimeric glycosylated protein 20 nm soaring above the virion envelope, giving the virus the appearance of a crown. These viruses are bigger in size than other RNA viruses and their average diameter is 125nm (50-200 nm); the diameter of the envelope is 85 nm and presence of 20 nm long spikes. These viruses also have a bigger genome size, ranging from 28-32 kb (Lai and Cavanagh 1997; Chen et al., 2020). Several spikes on the surface are found on an average of 74 (Neuman et al., 2011).

Like other Coronaviruses, SARS-CoV-2 is spherical in shape and has four structural components: spikes, envelope, membrane, and nucleocapsid. Viral envelope, which is a lipid bilayer formed by virus budding from intracellular membranes, consists of membrane protein (M) spanning through the envelope and small envelope proteins (E), and anchored spike proteins(S) and another small spike hemagglutinin esterase (HE) protein (Lai and Cavanagh 1997). Nucleocapsid is housed inside the envelope and packages the unsegmented positive-sense single-stranded RNA genome (29.9Kb in size), which appears like "beads on a string" in conformation (Chang et al., 2014; Wu et al., 2020). M protein maintains the shape of the virus and forms the envelope along with the E protein. The HE protein found in beta-coronaviruses promotes the exit of viral particles from infected cells (Hoffman et al., 2018).

Spike is made up of homotrimeric glycoprotein (S) and exists in multiple, distinct conformational states resulting from an opening at the trimer apex necessary for receptor engagement and leading to initiation of fusogenic conformational changes (Walls et al., 2019, 2020). This S protein is cleaved by host proteases, called

priming, into the S1 and S2 subunits as proteolysis of S protein is prerequisite for infection (Lai et al., 2007; Wang et al., 2020). The serine protease TMPRSS2 has been reported to contribute to priming of the SARS-CoV-2 S protein (Hoffman et al., 2020). S1 forms the distal end of the spike or head and is responsible for receptor recognition and thereby determines cellular tropism and results in pathogenesis. While S2 forms the stem, which spans through the envelope and, on activation, causes viral and target cell membrane fusion through irreversible conformational changes (Walls et al., 2020). S1 can be further divided into an N-terminal domain (NTD) and a C-terminal domain (CTD), and this CTD works as a receptor binding domain. Like SARS-CoV, SARS-CoV-2 binds to human ACE2 receptor (Hoffman et al., 2020; Zhou et al., 2020) but due to increased atomic interaction including more engaged residues, more van der Waals contacts, more H-bonds, as well as larger buried surface areas between human ACE2 and CTD of SARS-CoV-2 binding affinity of the latter increases 10-20 folds (Shang et al., 2020; Wang et al., 2020; Wrapp et al., 2020). It also contains a polybasic furin recognition site at the S1 and S2 boundary as a potential cleavage site, processed during biosynthesis for efficient cleavage of S protein into S1 and S2 unlike SARS-CoV, which has monobasic site, processed during host cell entry (Hoffman et al., 2020; Walls et al., 2020). According to Walls et al (2020), the almost ubiquitous expression of furin-like proteases could participate in expanding SARS-CoV-2 cell and tissue tropism, relative to SARS-CoV, as well as increasing its transmissibility and/or altering its pathogenicity.

This viral genomic RNA is present in ready to translate mRNA form with 5′-leader-UTR- replicase-S (Spike)-E (Envelope)-M (Membrane)- N (Nucleocapsid)-3′ UTR-poly (A) tail which undergo translation with the help of host ribosomes in the cytosol of target host cells (Fehr and Perlman 2015). The genome consists of a total seven genes and two third of the genomic RNA mainly located in first ORF (ORF 1a/b) or gene which translates two polypeptides pp1a and pp1ab that encode 16 non-structural proteins (NSPs) and other accessory proteins through ribosomal frameshifting (Fehr and Perlman 2015; Tok and Tater 2017). Many of these non-structural proteins have enzymatic properties, e.g., NSP 12 has an RdRp (RNA-dependent RNA polymerase) domain, and they form a replication-transcription complex (RTC) which first replicates genomic RNA into negative-sense (-) subgenomic RNA. This negative sense (-) RNA further using RTC replicates and produce copies of positive sense (+) genomic RNA and transcribes into seven nested positive-sense (+) subgenomic RNA with a 5' leader sequence and the same 3' end through discontinuous transcription (Miller and Koev 2000; Wu and Brian 2010). This positive-sense subgenomic RNA encodes mainly four structural proteins Spike (S), Envelope (E), Membrane (M), and Nucleocapsid (S) and some other proteins (Miller and Koev 2000; Fehr and Perlman 2015; Guo et al., 2020).

These structural proteins are further glycosylated in the endoplasmic reticulum and golgi bodies intermediate Compartment (ERGIC) through host secretory pathways. Here, these proteins assemble into a new virus particle through the N protein budding into the membrane and encapsulation of genomic RNA (Fehr and Perlman 2015). Structural proteins protect virus particle from the host, helps in entry in host cells and exit from the cell while non-structural proteins take part in genome replication, transcription, maintenance of such a large genome, inhibition of host innate immune response and degradation of host's cellular mRNA (Chen et al., 2020; Fehr and Perlman 2015; Guo et al., 2020). Both the structural and non-structural proteins participate in pathogenesis directly or indirectly.

According to new phylogenetic studies, the novel coronavirus, SARS-CoV-2 shared almost 80% of the genome with SARS-CoV and almost all encoded proteins of SARS-CoV-2 are homologous to SARS-CoV proteins except a few changes in NSP2, NSP3, spike protein, receptor binding motifs (RBM) are responsible for increased infectious nature, differentiation mechanism and changed pathophysiology (Angeletti et al., 2020; Chan et al.,2020; Guo et al., 2020; Shang et al., 2020; Wu et al., 2020b; Xu et al., 2020).

Viral Transmission

In comparison to SARS-CoV, SARS-CoV-2 is more contagious in nature and its basic reproduction number (R0) ranges between 2.2- 3.8, which varies from location to location (Adhikari et al., 2020; Liu et al., 2020). Further analysis even suggested that SARS-CoV-2 recognizes human ACE2 more efficiently than SARS-CoV, increasing the ability of SARS-CoV-2 to transmit from person to person (Wan et al., 2020; Zhang et al., 2020)

According to the WHO, transmission of the SARS-CoV-2 virus is mainly through droplet infection and person-to-person contact. When a person comes in close contact within 1 meter of someone who has respiratory symptoms like coughing and sneezing, droplet transmission occurs. Consequently, the person is at risk of having the mouth and nose or the conjunctiva of the eyes exposed to potentially infective respiratory

droplets, which are generally considered to be >5-10 μm in diameter (Chan et al., 2020 b; Li et al., 2020; https://www.who.int/news-room/commentaries/detail/modes-of-transmission-of-virus-causing-covid-19-implications-for-ipc-precaution-recommendations).

Airborne transmission may be possible under conditions where aerosols are generated, such as in specialized medical care facilities or in crowded and poorly ventilated spaces. Droplet transmission can also occur through fomites in the immediate environment around an infected person. Therefore, the virus can be transmitted through direct contact with infected individuals or indirect contact with contaminated surfaces or objects used by the infected person, such as stethoscopes, thermometers, towels, dishes, clothing, money, etc. As a result, caregivers—including doctors, nurses, and close family members—who are in contact with infected individuals during the incubation period or in quarantine centers are at a high risk of infection (https://www.who.int/news-room/commentaries/detail/transmission-of-sars-cov-2-implications-for-infection-prevention-precautions).

Clinical Symptoms

Clinical manifestation of COVID-19 disease ranges from mild to severe. Lower respiratory tract infection results in main symptoms like fever, dry cough, loss of sense of smell or taste, fatigue, mild viral pneumonia, headache, shortness of breath, sore throat, and dyspnea (Guan et al., 2020; Bourgonje et al., 2020). In some cases, diarrhoea is also reported, which shows enteric infection before the onset of fever and other symptoms (Pan et al., 2020; Guo et al., 2020). In severe cases, like in old age patients, patients with low immunity or the patient with comorbid conditions like cardiovascular diseases, hypertension, diabetes, nervous system related issues and kidney conditions, the infection results into acute respiratory distress syndrome, multiple-organ failure, septic shock, cardiomyopathy and arrhythmia, acute kidney injury, and complications from prolonged hospitalization, including secondary bacterial infections, thromboembolism, gastrointestinal bleeding, and critical illness polyneuropathy/myopathy and ultimately death (Guan et al.,2020; Chen et al., 2020; Huang et al., 2020; Wang et al., 2020; Yang et al., 2020; Shi et al., 2020). In mild cases, laboratory results show normal to decreased white blood counts and lymphocytopenia, while in elderly or severe patients, the neutrophil count, D-dimer, blood urea, and creatinine level were significantly higher, and the lymphocyte count continues to decrease (Guo et al., 2020).

Diagnosis

From the suspected patient who has contracted the virus or is showing initial symptoms of infection, nasopharyngeal secretions, sputum, bronchoalveolar lavage, and blood are collected and used as clinical specimens. These samples are further tested for SARS-CoV-2 infection confirmation using various molecular tests. The diagnosis of COVID-19 can be categorized on the basis of current infection and past infection. To identify the current infection the most effective test method is real time RT-PCR, while the other tests like Isothermal Amplification Assay (https://www.fda.gov/media/136525/download), CRISPR based assays, next generation sequencing, and antigen testing are also used but they are not as effective due to nucleotide identity with SARS-CoV (Corman et al.,2020; Li et al., 2020; and Chan et al., 2020). Viral antigens present in the clinical specimens are detected by using a direct immunofluorescent assay (IFA). Other tests are radiological tests like baseline chest X-ray and computed tomography (CT), which are useful in those patients who have more severe forms of disease and require hospitalization (Wong et al., 2019). Although the appearance of COVID-19 pneumonia on the chest CT is thought to be non-specific, chest CT is more sensitive than chest X-ray in COVID-19 patients. In the early phase of the disease, CT typically shows bilateral multiple ground-glass opacities, with mostly subpleural distribution (Wu et al. 2020).

There are three main real time RT-PCR available basically targeting; 1) RNA dependent RNA polymerase (RdRp) with two variants (RdRp-P2 and RdRp/Helicase (Hel)) 2) Spike (S) 3) Nucleocapsid (N) regions of virus genome 4) Orf 1a/b and Orf 1b-NSP14 5) E (Chan et al., 2020, Carmon et al., 2020; Chu et al., 2020). According to Chan et al (2020) newly established COVID-19-RdRp/Hel assay is highly sensitive and specific for the detection of SARS-CoV-2 RNA in vitro and in respiratory and non-respiratory tract clinical specimens, even with low viral loads.

In April 2020, the Indian Council of Medical Research (ICMR) validated the TrueNat assay for the screening of SARS-CoV-2 causing COVID-19 (https://www.icmr.gov.in/pdf/press_realease_files/ICMR_Press_Release_TruNat_21052020.pdf). It is a chip-based, battery-operated RT-PCR kit to identify the E-gene in the SARS-CoV-2 virus initially. But with the addition of a second step as a confirmatory step by detecting the RdRp gene, ICMR issued a revised guideline to use TrueNat in May 2020. According to that step one, i.e., E gene screening assay for all COVID-19 suspect samples to be followed by step two for the RdRp-

based confirmatory test in all E gene positives (https://www.icmr.gov.in/pdf/covid/labs/Revised_Guidelines_TrueNat_Testing_19052020.pdf).

To test the past infection or to determine the percentage of a population that has contracted the virus, a serological test (presence of IgM and IgG antibodies in serum) using ELISA is quite effective. There are two types of ELISA tests, IgG and IgM. IgG detects antibodies developed in the later stage of infection, and IgM detects antibodies produced in early stages of infection (Sethuraman et al., 2020). This test can produce results within an hour and is cost-effective as compared with real-time polymerase chain reaction (RT-PCR) tests. In Spain, Italy, Germany, and several other European countries ELISA test is being done as an "immunity passport" for people to return to work. In India, the Indian Council of Medical Research (ICMR) approved Indian biopharma company Transasia's ELISA antibody IgG testing kit for COVID-19. More information related to tests have been summarized in Table 1.

Table 1. Details of diagnostic tests used for COVID-19

Type of diagnostic test	Time when it works	Required sample	Properties	Limitations	Name of a few Test Kits (approved by global agencies)	References
Nucleic Acid Amplification Tests						
RT-PCR	After the symptom onset in week one, similarly effective in the asymptomatic condition.	Nasal, nasopharyngeal, throat swab/midturbinate swab/bronchoalveolar lavage fluid/ sputum	Sensitivity: 100%; uses a small sample; quantitative; results in 3–5 hours. Often multiplexed with genes like RdRp (main), ORF1, ORF8, E, and N to improve specificity. High-throughput capability.	It is costly, reagents cannot fulfill demands Expert handling is required Mostly it is not available in remote areas, and the transportation of samples takes time.	TrueNat (ICMR, India); iAMP COVID-19 detection (USA) BioFire COVID-19 test (USA); Vita-PCR SARS-Cov-2 assay (Singapore); LYRA SARS-Cov-2 assay (USA); CDC 2019- Novel Coronavirus Real-Time RT-PCR Diagnostic Panel (USA)	Udugama et al., 2020 Sethuraman et al., 2020 Carter et al., 2020
Isothermal Amplification Assay	1st week after symptoms begin	Nasal, nasopharyngeal, and throat swab	Very quick< 5min; Based on RdRp gene amplification	Low throughput	ID Now COVID-19 (FDA, USA)	Carter et al., 2020
CRISPR-based assays	After the symptom onset in week one	Respiratory samples	Gives results in one hour; Only needs basic equipment available in most labs; Gives results in 30-60 min; High throughput	Costly cannot be used at a large scale Highly sophisticated Expert handling is a must	CRISPR-based tests for SARS-CoV-2 (Cpheid Sherlock Biosciences USA) SARS-CoV-2 DETECTR(Mammoth Bioscience USA)	https://www.nature.com/articles/d41586-020-01402-9 ; Carter et al., 2020
Next-generation sequencing	After the symptom onset in week one	Respiratory specimen	This test is approved for the sequence study of the viral genome in the COVID-19 positive patient for research purposes	Very costly. This can also not be used for large-scale testing. Sophisticated technology Expert handling is required Time required is 24-48 hours.	COVID Seq ™ (FDA, USA)	https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-first-next-generation-sequence-test-diagnosing-covid-19
Radiological test						

Baseline X-Ray	Serious patients needed to be hospitalized	Chest X-Ray/chest radiographs	Cost-effective and quick. Chest X-ray findings in COVID-19 often resemble atypical or organizing pneumonia, commonly showing airspace opacities, typically consolidation, and less often, ground-glass opacities.	Early chest radiographs in COVID-19 suspects may appear normal, but abnormalities are more evident 10-12 days after symptom onset. X-rays are less sensitive than CT and show about 69% sensitivity compared to molecular tests.		Wong et al., 2019
Computed Tomography (CT)	Serious patients needed to be hospitalized (0-4 days from the illness onset)	Chest CT	Common CT findings include bilateral ground-glass opacities, bronchial wall thickening, and a crazy paving pattern.	CT scans are costly, not specific to COVID-19, require expert interpretation, and need dedicated machines. Decontamination after use is also cumbersome.		Udugama et al., 2020; Wu et al. 2020
Serological tests						
Antigen testing/ Immuno-fluorescent assay (IFA)	After 5-10 days of infection	Nasopharyngeal swab/ Nasal mucus swab	Chromatographic immunoassay detects nucleocapsid protein; results in 15–30 min; first-line test after symptoms.	Moderate sensitivity (84%); Positive test results do not rule out other infections	Standard Q COVID-19 Ag detection kit (ICMR, India and South Korea); COVID-19 Ag Respi-Strip (Belgium)	Carter et al., 2020; http://sdbiosensor.com/xe/product/7672
for IgG/IgM (ELISA)	From 4th day of illness onset to beyond 2 weeks	Serum/plasma/ whole blood	Show >95% sensitivity; Best results come from the sample taken after 14 days of illness onset; Quick outcome, 1-4 hr; Cost-effective	Expert handling is required; test negative if sample is taken just after illness onset; Sophisticated; cannot be used alone to test immunity in a population.	VITROS-Immunodiagnostics Products Anti-SARS-CoV-2 total reagent pack (FDA, USA); DEIASL 019/020 SARS-CoV-2 IgG ELISA kit (USA); KT-1033 EDI Novel Coronavirus COVID-19 ELISA kit (USA)	(https://www.covid19treatmentguidelines.nih.gov/whats-new/ ; Carter et al., 2020; Sethuraman et al., 2020
Lateral flow immunoassay	From 4th day of illness onset to beyond 2 weeks	Serum/Plasma/ whole blood	Give results in 10-20 min; Cost-effective and no expert personnel required; Provide qualitative results.		DPP COVID-19 IgM/IgG system (US FDA Brazil); IgG antibody test kit for novel coronavirus 2019-nCoV (China); qSARS-CoV-2 IgG/IgM rapid test (Australia and USA); SARS-CoV-2 rapid test (Germany)	Carter et al., 2020

Pathophysiology

Angiotensin-converting enzyme 2 (ACE2) functions as the primary receptor for SARS-CoV-2 and plays a crucial role in the pathogenesis of COVID-19 (Hamming et al., 2004; Hoffmann et al., 2020). The binding of the viral spike (S) protein to the ACE2 receptor facilitates viral entry into host cells, leading to viral replication, cellular damage, and an increased viral load. Consequently, the number of ACE2 receptors on the cell surface can directly influence the severity of

clinical symptoms (Bourgonje et al., 2020). The angiotensin converting enzyme-2 (ACE2) receptor is widely distributed throughout human tissues largely found on the plasma membranes of the epithelial cells in the respiratory tract, upper esophagus, stratified cells of the epithelium, colonic and ileum-based enterocytes, proximal tubule cells of the nephron, urothelial cells of urinary bladder and cardiac myocardial cell (Bourgonje et al., 2020; Wrapp et al., 2020). According to Bourgonje et al (2020), many factors like demographic characteristics, genetics, gender, lifestyle, varying co-morbidities, and medication usage are considered to have an impact on ACE2 expression and activity. The physiological role of ACE2 is to cleave Angiotensin II to angiotensin (1-7), which exerts vasodilating, anti-inflammatory, and anti-fibrotic effects through binding to the Mas receptor (Sanchis-Gomar et al., 2020). These factors are associated with the severity and progression of COVID-19 features and further emphasize the role of ACE2.

The role of the ACE2 receptor in SARS-CoV-2 pathophysiology was delineated by several authors in different regions of the human body. Respiratory symptoms are the most common symptom presentation in COVID-19 disease. In the lungs, the type 2 pneumocyte presenting ACE2 receptor is the most affected cell, and SARS-CoV propagates within the cell, a large number of viral particles are released, and the cells undergo apoptosis and die (Qian et al., 2013). The result is likely a self-replicating pulmonary toxin as the released viral particles infect type II cells in adjacent units. Affected areas of the lung are likely to lose most of their type II cells, and the secondary pathway for epithelial regeneration will be triggered. Normally, type II cells are the precursor cells for type I cells. This postulated sequence of events has been shown in the murine model of influenza pneumonia (Kumar et al., 2011; Yee et al., 2017). The pathological result of SARS and COVID-19 is severe pneumonia, RNAaemia, diffuse alveolar damage with fibrin-rich hyaline membranes, with the incidence of ground-glass opacities, and acute cardiac injury (Gu et al., 2007; Xu et al., 2020; Huang et al., 2020). However, it has been generally recognized that disease exaggeration till the late stage is not only attributed to direct viral damage, but also a consequence of immune-mediated injury induced by SARS-CoV-2 [Cao et al., 2020]. This could be understood by significantly high blood levels of cytokines and chemokines in patients with COVID-19 infection that included IL1-β, IL1RA, IL7, IL8, IL9, IL10, basic FGF2, GCSF, GMCSF, IFNγ, IP10, MCP1, MIP1α, MIP1β, PDGFB, TNFα, and VEGFA. Some of the severe cases that were admitted to the intensive care unit showed high levels of pro-inflammatory cytokines, including IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1α, and TNFα, which are thought to promote disease severity [Huang et al., 2020]. Later in the disease course, COVID-19 resembles SARS in terms of viral replication in the lower respiratory tract, and generates secondary viremia, followed by an extensive attack against target organs that express ACE2, such as the heart, kidney, gastrointestinal tract, and vast distal vasculature. This process of viral spreading correlates with the clinical deterioration, mainly taking place around the second week following disease onset.

As ACE2 is abundantly expressed by endothelial cells throughout the body, it loses its ability to prevent thrombosis upon cell entry of SARS-CoV-2 (Ferrario et al., 2005). This forms the basis of microvascular injury in severely affected cases. COVID-19 patients exhibited a hypercoagulable state, featured by prolonged prothrombin time, elevated levels of D-dimer and fibrinogen, and near-normal activated partial thromboplastin time. A few patients would finally progress to overt disseminated intravascular coagulation (DIC). Tang et al. reported that 71.4% of non-survivors and 0.6% of survivors of COVID-19 showed evidence of overt DIC (Tang et al., 2020).

The gastrointestinal tract (GIT) is also a common system to be affected, as it also expresses a large number of ACE 2 receptors and is in contact with the external environment. Hashimoto et al in their study in 2012 described that in the GIT, ACE2 has been described as a key regulator of dietary amino acid homeostasis, expression of antimicrobial peptides, local innate immunity, and gut microbial ecology (Hashimoto et al., 2012). This could explain the occurrence of gastrointestinal symptoms in COVID-19 infection.

Other than these, SARS-CoV-2 shows neurotropism, evidenced by several studies (Calcagno et al., 2020). The ACE2 is expressed in the brain and was found in both neurons and glia. It is particularly present in the brain stem and in the regions responsible for the regulation of cardiovascular function, including the subfornical organ, paraventricular nucleus, nucleus of the tractus solitarius, and rostral ventrolateral medulla, like SARS-CoV (Gowrisankar and Clark 2016; Xia and Lazartigues 2010; Huang et al., 2020). A study has suggested that invasion of the brainstem may be at least partially responsible for respiratory symptoms in COVID-19 patients, by compromising neurons within the respiratory centres and chemosensitive neural cells involved in respiratory and cardiovascular regulation (Steardo et al., 2020). Another study by Nampoothiri et

al [2020] suggest that the involvement of hypothalamus can be a cause of varied response of SARS-CoV-2 infection which is evidenced by altered labelling for several hormones in postmortem pituitary tissue (Wei et al., 2010) as well as long-term neuroendocrine deficits in some survivors of SARS-CoV infection (Leow et al., 2005). These findings strongly support the theory that proposes the hypothalamus as a target of viral infection. Most major risk factors for severe COVID-19 (male sex, age, obesity, hypertension, diabetes) could be mediated by normal or dysfunctional hypothalamic neural networks that regulate a variety of physiological processes: sexual differentiation and gonadal hormone production, energy homeostasis, fluid homeostasis/osmoregulation and even ageing (Leow et al., 2005; Chen et al., 2020; Li et al., 2020).

Many authors have a view that, other than ACE 2 receptor-mediated spread, other modes of cell infection also exist. The neuronal route of spread is also described from the intranasal path in the rapid invasion of viral particles into the brain, possibly through the olfactory bulb via a trans-synaptic route. This could explain anosmia and ageusia as the only clinical symptoms of SARS-CoV-2 infection before the onset of respiratory symptoms (Li et al., 2012). All ACE-2 expressing organs don't equally participate in COVID-19 pathophysiology, implying that other mechanism is also involved in controlling cellular infection resulting in tissue damage (Bourgonje et al., 2020).

Treatment and future perspectives

To date, no specific antiviral treatment or biologic has proven definitively effective against COVID-19. As a result, patients primarily depend on symptomatic treatment and supportive care. Mechanical ventilation may be necessary in cases of respiratory failure unresponsive to oxygen therapy, while hemodynamic support plays a critical role in managing septic shock (Cascella et al., 2020). Remdesivir received Emergency Use Authorization (EUA) from the U.S. Food and Drug Administration (FDA) on May 1, 2020, based on preliminary data suggesting faster recovery in hospitalized patients with severe disease (Bergman, 2020). However, the FDA does not recommend the use of hydroxychloroquine or chloroquine for COVID-19 treatment. Additionally, the agency advises against combinations such as hydroxychloroquine with azithromycin and lopinavir/ritonavir (or other HIV protease inhibitors) due to associated toxicity, poor pharmacodynamic profiles, and lack of demonstrated clinical benefit in controlled trials (https://www.covid19treatmentguidelines.nih.gov).

Recently, WHO welcomed the initial clinical trial results from the United Kingdom (UK) that show dexamethasone, a corticosteroid, can be lifesaving for patients who are critically ill with COVID-19. For patients on ventilators, the treatment was shown to reduce mortality by about one third, and for patients requiring only oxygen, mortality was cut by about one fifth, according to preliminary findings shared with the WHO. The benefit was only seen in patients seriously ill with COVID-19 and was not observed in patients with milder disease (https://www.who.int/news-room/detail/16-06-2020-who-welcomes-preliminary-results-about-dexamethasone-use-in-treating-critically-ill-covid-19-patients). According to guidelines of WHO and other agencies, preventive measures such as wearing masks, hand hygiene practices, avoidance of public contact, case detection, contact tracing or surveillance, social distancing and quarantines are the only ways to reduce transmission (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/advice-for-public). Recently, WHO has released a Public Service Announcement (PSA) which features a cartoon sketch of Mr Bean comically tackling a pesky roller blind to finally reveal several essential tips as "Mr Bean's Essential COVID-19 Checklist". This is a reminder to people about the importance of washing hands, physical distancing, and demonstrating kindness to their neighbours to protect them against COVID-19 (https://www.who.int/news-room/detail/22-06-2020-the-world-health-organization-reminds-public-to-remain-vigilant-through-mr-bean-s-essential-covid-19-checklist).

Meanwhile, the scientific community is working very hard to discover a cure in the form of a vaccine or medicine worldwide. After deciphering viral structure, mode of transmission, mechanism of viral entry into target cells, and consequent pathophysiology of COVID-19 there are certain points arise which can help in the treatment plan and preparation of targeted vaccines. For instance, according to Wang et al (2020) S protein of SARS-CoV-2 shows a different antigenic property rather than SARS-CoV, thus the development of vaccine against spike protein subunit 1 could help in treatment. *Moreover,* inhibition of transmembrane protease serine 2 (TMPRSS2) activity, blocking ACE2 receptor, and delivering excessive soluble form of ACE2 could also stop virus entry into the cell, decrease infection rate, and protect from potential lung injury, respectively (Zhang et al., 2020).

In one endeavour, several US federal government departments including Health and Human Services and its sub-agencies, Agriculture, Energy and

Veterans Affairs and the private sector within this US National Institutes of Health (NIH) has partnered with more than 18 biopharmaceutical companies collaborated and formed Operation Warp Speed (OWS) to accelerate the development of drug and vaccine candidates for COVID-19. Along with these several other pharmaceutical companies and educational institutions around the world are extensively working to make vaccines; however, most of these vaccines are at the preclinical level or first level of clinical trial (https://www.raps.org/news-and-articles/news-articles/2020/3/covid-19-vaccine-tracker).

Conclusion

Although SARS-CoV-2 is less virulent than SARS-CoV and MERS-CoV, it is more infectious, with altered antigenicity, and currently, no approved medicine or vaccine is available for COVID-19. The most effective measures include controlling the source of infection, increasing testing, ensuring early diagnosis, isolation, and providing supportive treatment based on symptoms, until the scientific community fully characterizes this novel coronavirus and develops effective treatment regimens, including drugs and vaccines. At the individual level, maintaining good personal hygiene, wearing masks, and avoiding public or crowded places are key preventive measures. A sense of personal responsibility toward society is essential in the fight against COVID-19.

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