Understanding the epidemiology, pathophysiology, diagnosis and management of SARS-CoV-2

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Abstract
The emergence of coronavirus disease 2019 (COVID-19) in December 2019 has resulted in over 20 million cases and 741,808 deaths globally, affecting more than 200 countries. COVID-19 was declared a pandemic on 11 March 2020 by the World Health Organization. The disease is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). There is limited information on COVID-19, and treatment has so far focused on supportive care and use of repurposed drugs. COVID-19 can be transmitted via person-to-person contact through droplet spread. Some of the recommended precautionary measures to reduce the rate of disease spread include social distancing, good hygiene practices, and avoidance of crowded areas. These measures are effective

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because the droplets are heavy and can only travel approximately 1 meter in the air, settling quickly on fixed surfaces. Promising strategies to combat SARS-CoV-2 include discovery of therapeutic targets/drugs and vaccines. In this review, we summarize the epidemiology, pathophysiology, and diagnosis of COVID-19. We also address the mechanisms of action of approved repurposed drugs for therapeutic management of the disease.

Keywords
SARS-CoV-2, COVID-19, Coronavirus, 2019-nCoV, ACE-2, repurposed drugs

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Introduction
COVID-19 has become one of the most dangerous pandemics in recent history. The pandemic has claimed more than 740,000 lives, with more than 20 million reported cases since the original outbreak. The disease is caused by SARS-CoV-2, a zoonotic pathogen that acquired mutations as it crossed the species barrier from bat to pangolin enabling it to infect humans. SARS-CoV-2 was confirmed as a novel coronavirus using molecular methods and initially named 2019 novel coronavirus (2019-nCoV). The disease caused by this virus was later renamed COVID-19 by the World Health Organization (WHO). SARS-CoV-2 is highly infectious and has spread to more than 200 countries in all continents. Hence, the virus was declared a global threat (pandemic) by the WHO. SARS-CoV-2 has a single-stranded positive sense RNA genome (+ssRNA) approximately 30 kb long. The SARS-CoV-2 genome is organized similarly to those of SARS-CoV-1 and Middle East respiratory syndrome (MERS)-CoV. Using phylogenetic analysis, the SARS-CoV-2 genome was demonstrated to share 96% sequence similarity with a bat CoV genome. SARS-CoV-2 belongs to the β-coronavirus genus that includes SARS-CoV-1 and MERS-CoV. The clinical symptoms of COVID-19 include fever, cough, and pneumonia, which makes the disease enormously dangerous with a high case fatality rate. In contrast to other β-coronaviruses, many SARS-CoV-2 deaths have resulted from multiple organ dysfunction syndrome (MSOF) rather than respiratory failure. This could be attributed to the widespread distribution of angiotensin converting enzyme-2 (ACE-2), the primary receptor for SARS coronaviruses, in multiple organs. ACE-2 is expressed as a cell-surface molecule in the respiratory tract (epithelium, arterial and venous endothelium), the small intestinal epithelium, and arterial smooth muscle cells.

SARS-CoV-2 is morphologically spherical and is characterized by presence of a spike protein, lower pathogenicity and higher transmissibility between humans. Some of the primary measures taken to reduce the number of infections and prevent community transmission are to avoid crowds and gatherings and to practice good hygiene. Interestingly, countries with the highest reported prevalence and mortality such as the United States, Spain, Italy, the United Kingdom, Russia, Germany, Brazil, France, Turkey, Iran and China, are more concerned with flattening the curve through early case detection,
isolation, and development of therapeutic drugs and vaccines. Because of the novel nature of this disease, there is limited information regarding risk factors for severe outcomes. Specific factors such as the serial interval, viral lifespan, incubation period, pathogenic mechanisms, clinical features and optimal disease management remain unclear. Therefore, this review aimed to summarize the epidemiology and pathophysiology of SARS-CoV-2 as well as the use of repurposed Food and Drug Administration (FDA) approved drugs for therapy. The entry of this virus into host cells and possible downstream complications deserve closer attention.

Coronaviruses

CoVs are members of the subfamily Orthocoronavirinae of the family Coronaviridae. The subfamily consist of four genera: alpha, beta, gamma and delta CoVs. Both alpha- and beta-CoVs can infect mammals, including humans, while the gamma- and delta-CoVs only infect birds. About seven CoVs have been isolated from humans (Figure 1). These include two alpha-CoVs, human coronavirus 229E (HCoV-229E) and human coronavirus NL63 (HCoV-NL63), and five beta-CoVs: human coronavirus OC43 (HCoV-OC43), human coronavirus HKU1 (HCoV-HKU1), SARS-CoV-1, MERS-CoV, and SARS-CoV-2. SARS-CoV-1, MERS-CoV, and SARS-CoV-2 are pathogenic and cause severe infections in humans following contact with the respective intermediate hosts (bats) (Figure 2). However, HCoV-229E, HCoV-NL63, HCoV-OC43, and HCoV-HKU1 do not appear to cause severe infections in humans. CoVs are enveloped viruses with +ssRNA genomes. They have the largest genomes (approximately 26–33 kb) among RNA viruses. All CoVs possess non-segmented genomes with similar organization. Generally, about two-thirds of the genome consists of two large and overlapping open reading frames (ORF1a and ORF1b), which are translated into polyproteins pp1a and pp1ab and subsequently processed to yield 16 non-structural proteins (nsp1 to nsp16). The remaining one-third of the genome consists of ORFs encoding structural proteins including the spike (S) glycoprotein embedded in the envelope and the envelope (E), matrix (M), and nucleoproteins (N). There are short untranslated regions at both the 3’ and 5’ ends. The S protein plays a role in receptor-binding and entry of virus into host cells and is thus considered a major therapeutic target. The M and E proteins are important for viral assembly, while the N protein is necessary for synthesis of RNA.

Overview of the SARS-CoV family

SARS-CoVs belongs to a global family of viruses causing respiratory disease and influenza-like symptoms such as fever, muscle pain, sore throat, headache, and cough. Figure 3 highlights the onset and
progression of SARS-CoV-1, MERS-CoV, and SARS-CoV-2 infection. The first case of SARS-CoV-1, reported in China, resulted in an outbreak that caused hundreds of deaths and thousands of infected cases in the early 2000s. A pneumonia-like syndrome (MERS) was first discovered in Saudi Arabia and then spread to several countries, where it incurred a mortality rate of about 3% to 6%. Marra et al (21) observed that the MERS mortality rate increased with age and was as high as 43% to 55% in people older than 60 years. In December 2019, SARS-CoV-2, caused an outbreak in China and then spread worldwide. The resulting disease (COVID-19) is a serious threat mostly in people with compromised immune systems or underlying conditions such as lung disease, diabetes mellitus, and human immunodeficiency virus infection.

SARS-CoV-1. SARS-CoV-1 causes a viral respiratory disease and belongs to lineage B of the beta-CoVs. SARS-CoV-1 infection in humans was first reported in 2002 in China (Figure 3a). Within 1 year, it affected about 29 countries with about 8,422 cases globally. Bats are the primary hosts of this virus, with palm civets as intermediate hosts. Humans are infected via direct contact with intermediate hosts or through consumption of bats or their products.

Figure 2. Mode of coronavirus transmission from carriers to humans.

Figure 3. Development of the (a) SARS-CoV-1, (b) MERS-CoV, and (c) SARS-CoV-2 epidemics.
of uncooked meat, milk or urine, as shown in Figure 2. Human-to-human infection also occurred through nosocomial transmission. Symptons of human SARS-CoV-1 infections include headache, fever and respiratory complications such as cough, dyspnea, and pneumonia.

The SARS-CoV-1 genome is 29,727 nucleotides in length. The 5' end of the genome contains ORF1a and ORF1b. The polyproteins encoded by these ORF are auto-catalytically processed to yield a number of viral proteases as well as the RNA-dependent RNA polymerase (RdRp). The remainder of the genome encodes the viral structural proteins (S, E, M and N) as well as several accessory proteins.

The receptor for SARS-CoVs is ACE-2, a surface molecule found on cells of the respiratory tract, the small intestinal epithelium, and smooth muscle. In the respiratory tract, ACE-2 is expressed on epithelial cells of the alveoli, bronchi, trachea, and bronchial serous glands, as well as on alveolar monocytes and macrophages. The ACE-2 enzyme plays an important role in protection against lung failure.

**MERS-CoV.** MERS-CoV causes a viral respiratory disease and belongs to lineage C of the beta-CoVs. The first cases of human infection by MERS-CoV were reported in Saudi Arabia in 2012. Cases were subsequently reported in other countries including Qatar, Egypt, and the Republic of Korea following contact with infected camels (Figure 3b). Cases of MERS-CoV were identified in about 27 countries between 2012 and 2018. MERS-CoV RNA in camels showed more than 99% genomic sequence similarity to human MERS-CoV. Bats are the natural hosts of MERS-CoV (Figure 2), and a high prevalence of MERS-CoV infections in dromedary camels (intermediate hosts) was confirmed in the Middle East, Spain, and Africa. MERS-CoV infections were transmitted to humans following contact with camels infected with the virus.

The MERS-CoV genome is about 30,119 nucleotides in length and has a 5' terminal cap structure and a poly (A) tail at the 3' end. The genome encodes 16 non-structural proteins (nsp1–nsp16) at the 5' end, four structural proteins (S, E, M, and N) at the 3' end, and five accessory proteins in ORF3, ORF4a, ORF4b, ORF5, and ORF8. Risk factors for severe MERS-CoV include age and the presence of underlying conditions such as diabetes, obesity, hypertension, chronic renal disease, and lung diseases.

The receptor for MERS-CoV is dipeptidyl peptidase 4 (DPP4 or CD26). DPP4 is a multifunctional cell surface protein and is expressed on the epithelial cells of the respiratory tract, liver, kidney, small intestine, and prostate, as well as on activated white blood cells. DPP4 also plays a vital role in activation of T cells and providing co-stimulatory signals for immune responses of T cells. Consequently, MERS-CoV causes acute pneumonia and renal dysfunction with associated clinical symptoms such as cough, chest pain, sore throat, fever, diarrhea, vomiting, and abdominal pain. MERS-CoV can infect human dendritic cells and macrophages in vitro, thereby contributing to dysregulation of the immune system.

**SARS-CoV-2.** SARS-CoV-2, a newly discovered coronavirus, has a +ssRNA genome and a spherical morphology when observed under the electron microscope. SARS-CoV-2 encodes a richly glycosylated spike protein responsible for binding to the ACE-2 receptor. The virion’s shape and the ability of spike proteins to form a crown-like structure gave coronaviruses their name. The SARS-CoV-2 genetic material is surrounded by a lipid-bilayer envelope. Other structural components include the nucleocapsids, membrane, envelope,
and hemagglutinin. Unlike the envelope, the membrane exists in higher quantities within the virions. Among other functions, the envelope serves to release viral particles from the host cells. The nucleocapsid assist in RNA packaging during virion assembly. Hemagglutinin enhances the entry and pathogenesis of coronaviruses. Some of the characteristics of SARS-CoV-2 are summarized in Table 1. Many of these features are shared with SARS-CoV-1. More information on the epidemiology and general characteristics of SARS-CoV-1 can be found later in the review.

### Table 1. Biological characteristics of SARS-CoV-2 and COVID-19.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Name of disease</strong></td>
<td>COVID-19</td>
<td>[35]</td>
</tr>
<tr>
<td><strong>Caused by</strong></td>
<td>SARS-CoV-2</td>
<td>[35–37]</td>
</tr>
<tr>
<td><strong>Virus genus</strong></td>
<td>β-coronavirus</td>
<td>[14]</td>
</tr>
<tr>
<td><strong>Virus composition</strong></td>
<td>RNA, Spike protein, β-coronavirus, and hemagglutinin</td>
<td>[38]</td>
</tr>
<tr>
<td><strong>Virus target</strong></td>
<td>Respiratory system</td>
<td>[28]</td>
</tr>
<tr>
<td><strong>Functional receptor</strong></td>
<td>ACE-2</td>
<td></td>
</tr>
<tr>
<td><strong>Mode of transmission</strong></td>
<td>Contact, respiratory droplets, fecal oral route, and fomites</td>
<td>[39]</td>
</tr>
<tr>
<td><strong>Incubation period</strong></td>
<td>2–14 days</td>
<td>[40]</td>
</tr>
<tr>
<td><strong>Average age affected</strong></td>
<td>46% of cases occur in adults</td>
<td>[41]</td>
</tr>
<tr>
<td><strong>Classic symptoms</strong></td>
<td>Fever, cough, sore throat, and shortness of breath</td>
<td>[28]</td>
</tr>
<tr>
<td><strong>Complications</strong></td>
<td>Pneumonia, ARDS</td>
<td></td>
</tr>
<tr>
<td><strong>Mortality rate</strong></td>
<td>&gt;3%; increases with age and co-morbidities</td>
<td>[28]</td>
</tr>
<tr>
<td><strong>Investigation/findings</strong></td>
<td>CT chest, lymphocytopenia</td>
<td>[42]</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td>Identification of viral RNA by PCR</td>
<td>[2]</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Supportive care including antiviral drugs</td>
<td></td>
</tr>
<tr>
<td><strong>Vaccines</strong></td>
<td>Under clinical trials in selected countries</td>
<td></td>
</tr>
<tr>
<td><strong>Mode of reduction</strong></td>
<td>Social distancing, avoidance of close contact, good personal hygiene, personal protective equipment, sheltering at home, isolation of identified cases</td>
<td></td>
</tr>
</tbody>
</table>

Other human coronaviruses

Other important human CoVs include alpha-CoVs (HCoV-229E and HCoV-NL63) and two beta-CoVs (HCoV-OC43 and HCoV-HKU1). The receptor for HCoV-229E is human aminopeptidase N (CD13), a cell-surface metalloprotease present on cells of the kidney and lung, as well as on epithelial and intestinal cells. The receptor for HCoV-NL63 is also ACE-2. The receptor for HCoV-OC43 is 9-O-acetylated sialic acid, while no receptor has been identified for HCoV-HKU1.

Generally, the most common diagnostic tools for human CoVs are molecular detection techniques such as reverse transcription-polymerase chain reaction (RT-PCR) using RNA extracted from respiratory tract samples as template. Other methods include serological tests and viral cultures. Although several agents against CoVs, including antibodies, antiviral peptides, and cell or viral protease inhibitors, have been shown to be effective both in vitro and/or in vivo, clinical trial outcomes have not been reported. Therefore, clinical treatments for CoVs are still lacking. Nevertheless, supportive and symptomatic therapy are used for
treatment. Interferons, ribavirin, lopinavir/ritonavir, and cyclophilin inhibitors are the most commonly administered antiviral agents as elements of combination therapies.\textsuperscript{11,18} Type I interferons were reportedly used against MERS-CoV in various cell lines and in rhesus macaques. Interferon-alpha 2b and ribavirin have a synergistic effect on SARS-CoV-1 and MERS-CoV in cell cultures.\textsuperscript{44}

**Epidemiology of COVID-19**

COVID-19, the disease caused by SARS-CoV-2, is similar to that caused by SARS-CoV-1. COVID-19 was first reported in Wuhan (China) in December 2019. The virus likely underwent mutation during zoonotic transmission through pangolin, and later infected humans. The case fatality rate (CFR) of COVID-19 was estimated at 5.93% (3 June 2020). At the time of writing, data from the Johns Hopkins University (https://coronavirus.jhu.edu/map.html) indicated a total of 20,394,078 confirmed cases of SARS-CoV-2 worldwide with 741,808 total deaths and over 13,283,665 recovered cases.

At present, 215 countries and territories are affected by the SARS-CoV-2 outbreak, including the United States, Italy, Germany, South Africa, and Nigeria. The distribution of SARS-CoV-2 confirmed cases, including mortality and recovery, is shown in Figure 4. The United States, China, and some European countries have high case numbers and mortality rates. Recovery rates are increasing worldwide with higher numbers reported in China.

**The COVID-19 CFR**

The CFR is defined as the percentage of deaths recorded among confirmed cases. As of 14 April 2020, the number of deaths among confirmed cases was estimated at 126,066 to 1,992,189, resulting in a CFR of 6.33%. This differs from the CFR of 3.70% calculated on 15 March 2020. However, several factors can prevent the accurate determination of the CFR. We compared the global CFR to the African CFR. The highest CFR was observed in Italy, followed by Spain and the Netherlands (Figure 5a). In Africa, countries such as Egypt, Algeria, Burkina

![Figure 4](https://example.com/figure4.png)

*Figure 4.* Prevalence of COVID-19 as of 3 June 2020 (GMT 14:52). The figure shows (a) total cases, (b) total deaths, and (c) the recovery rate per country since the time of the first case of COVID-19. Data were downloaded from worldometers (https://www.worldometers.info/coronavirus/) and John Hopkins University (https://github.com/CSSEGISandData/COVID-19). Graphs were produced using R-studio v3.4.4 and the ‘rworldmap’ package v1.3-6.
Faso, and Morocco had CFRs above 5% (Figure 5b). A major challenge in the accurate calculation of the CFR is the denominator (the number of confirmed cases). Asymptomatic cases of COVID-19, patients with mild symptoms, or individuals who are misdiagnosed may be left out of the denominator, leading to underestimation or overestimation of the CFR.\(^{45}\) High CFRs reflect limited access to health care for the most vulnerable patients and limitations in health-care systems, including limited capacity of surveillance systems to trigger a timely response (WHO, 2020).

Estimation of the COVID-19 reproductive number

To date, over 20 million cases of COVID-19 have been reported globally. It is important to estimate the reproductive number for this virus to enable accurate predictions. Two primary factors, the reproductive ratio \((R_0)\) and the serial interval \((S_I)\), are essential to estimate the rate of transmission of this disease.

The reproductive ratio \((R_0)\) of COVID-19. \(R_0\) measures the degree of COVID-19 contagion or infectiousness. \(R_0\) represents the average number of people who will be infected by one infected individual. Zhang et al.\(^{46}\) estimated that the median and 95% confidence interval (CI) of \(R_0\) were about 2.28 (2.06–2.52) for early outbreaks of COVID-19. This means that an infected person can transmit COVID-19 to an average of two to three other people. Various studies reported significant variations in \(R_0\) using different datasets.\(^{47,48}\)

Serial interval \((S_I)\). To understand the case turnover and transmissibility of COVID-19, the serial interval \((S_I)\) from the onset of illness in a primary case to the onset of illness in a secondary case is important.\(^{49}\) Recent studies estimated the average \(S_I\) for COVID-19 as 3.77 (2.23–4.82) days.\(^{49–51}\) A shorter \(S_I\) makes COVID-19 harder to contain and more likely to rapidly transmit within populations (Figure 6).

Taking the \(R_0\) and \(S_I\) of COVID-19 into consideration, it can be inferred that approximately 4 days are required for an infected person to transmit COVID-19. It is highly likely that the individual can infect approximately two or three other persons, making the spread of COVID-19 extremely rapid and dangerous (Figure 7a). The extent of spread is totally dependent on the \(R_0\) value (Figure 7b). If \(R_0 < 1\), each existing infection causes less than one new infection. In this case, the disease will decline and eventually die out. If \(R_0 = 1\), each existing infection causes one new infection. The disease will remain stable in the population, but will not result in epidemic spread. If \(R_0 > 1\), each existing infection causes more than one new infection. The disease will spread between individuals and
eventually lead to an outbreak. COVID-19 was regarded as an outbreak (30 January 2020) with a $R_0 > 1$ (Figure 7b).

Importantly, the $R_0$ value of a disease only applies when everyone in a population is completely susceptible. This means that no one has been vaccinated or had the disease previously, and there is no way to control the spread of the disease using interventions such as drugs or vaccines.

Pathophysiology of COVID-19

There are currently two known modes of COVID-19 transmission: the fecal-oral route and respiratory droplets.\textsuperscript{6,52–56} Droplets have potential to come into contact and infect a healthy person within 3 to 6 feet (1 meter). Droplets that stick to surfaces can survive for more than 24 hours, remaining infectious. The virus can remain airborne for about 3 hours, long enough to permit transmission.

Upon infection with SARS-CoV-2, the virus infects type II pneumocytes of the alveoli.\textsuperscript{57} These pneumocytes are responsible for surfactant production. Surfactant decreases the surface tension within alveoli and reduces the collapsing pressure. The spike protein of the virus binds to ACE-2 on the pneumocytes (Figure 8) permitting virion entry into the host cell.\textsuperscript{58} The virus hijacks the host cell’s machinery (ribosomes) to enable translation of its $^+\text{ssRNA}$ genome into different protein molecules. The virus can also use its RdRp to produce additional copies of its $^+\text{ssRNA}$ genome (Figure 9). The translated polyproteins are further processed into different individual components.
within the host cell. These processes give rise to multiple virions, which are then released upon pneumocyte damage. In response to this process, type II pneumocytes release specific inflammatory mediators that instruct macrophages to secrete interleukins 1 and 6 (IL-1 and IL-6) and tumor necrosis factor-alpha. These cytokines cause the endothelial cells lining blood vessels to dilate, leading to increased capillary permeability. In response, fluids accumulate in the alveoli leading to edema. As surface tension increases, the collapsing pressure of the alveoli increases. A decrease in gas exchange is also observed through this process, which in turn leads to hypoxia and difficulty breathing (dyspnea). This can progress to a critical condition such as acute respiratory distress syndrome (ARDS).

Inflammatory mediators further stimulate neutrophils, which release reactive oxygen species and proteases. This process damages the alveoli (both type 1 and 2), leading to consolidation and alveolar collapse. High levels of IL-1 and IL-6 travel through the blood to the central nervous system, instructing the hypothalamus to release prostaglandins and causing fever. Severe lung inflammation leads to systemic inflammatory respiratory syndrome. Progression can lead to increased capillary permeability. The overall blood volume decreases, and through a series of processes involving hypotension and decreased perfusion of multiple different organs, multiple system organ failure (MSOF) can occur. During MSOF, elevated levels of blood urea, nitrogen, and creatinine accrue in the kidney. The liver also releases specific inflammatory and acute phase response biomolecules (aspartate transaminase, alanine transaminase, bilirubin, C-reactive Protein [CRP], fibrinogen and IL-6) that can serve as biomarkers for patients with COVID-19.

Transmission of SARS-CoV-2 through the eyes. There is continued research by multiple groups into the mechanism of transmission of SARS-CoV-2 through the eyes. Investigations were necessary because health care providers, including a Perking University Physician, may have contracted the virus while not wearing eye protection when treating patients. Some researchers have asserted that avoidance of touching the eyes, nose or mouth with unwashed or unsterilized hands can reduce COVID-19 transmission. The mucous membranes that line various cavities in the body are generally most susceptible to viral transmission. Ocular symptoms such as viral conjunctivitis can result from SARS-CoV-
upper respiratory tract infections. This was confirmed in 9 of 1,099 patients in China. Other research also found that 1 of 30 patients hospitalized with COVID-19 were diagnosed with conjunctivitis. In a study conducted by the American Optometric Association, COVID-19 was linked to ocular signs and symptoms including photophobia, irritation, conjunctival infection and ocular discharge. Thus, the superficial blood vessels of the conjunctiva are an alleged route of exposure and transmission of SARS-CoV-2.

Clinical symptoms of COVID-19

The clinical manifestations of SARS-CoV-2 are uncertain and change frequently. Some infections are asymptomatic. Symptoms can include respiratory distress syndrome, pneumonia of different levels of severity, and sometimes death. According to the WHO, the most common symptoms of COVID-19 are fever, fatigue, dry continuous cough, and shortness of breath. Some patients may have a runny nose, sore throat, nasal congestion, aches and pains, and diarrhea. Some patients report a loss of sense of smell and taste. In some cases, symptoms are mild and similar to those of the common cold; in such patients, recovery can occur without any treatment. The least commonly observed symptoms include nausea or vomiting, coughing up blood or bloody mucus, and viral conjunctivitis causing red eyes,
watery discharge from the eyes, swollen eyelids and light sensitivity. Occasional upper respiratory and gastrointestinal symptoms, accompanied by changes vital signs such as increased respiration (heart rate) and low blood pressure may also be observed, especially in the elderly and among individuals suffering from heart disease, chronic respiratory conditions and diabetes. Additionally, patients critically ill with COVID-19 may present with increased venous thromboembolism including thrombocytopenia, elevated D-dimer, prolonged prothrombin time and disseminated intravascular coagulation (DIC). These coagulation abnormalities are associated with a systemic inflammatory response and an imbalance between pro-coagulant and anticoagulants homeostasis mechanisms and increase the risk of mortality. Some of these clinical features are also observed in cases of DIC observed in septic patients. These features are very distinct in COVID-19 patients as their levels are higher than the standards for sepsis.

Diagnosis, prognosis, treatment, and management of SARS-CoV-2

Diagnosis of SARS-CoV-2

SARS-CoV-2 causes various complications ranging from fever, dry cough, and pneumonia to decreased organ perfusion leading to MOF. Early symptoms are similar to those of influenza, and the first step to differentiate COVID-19 from flu and pneumonia is a nasopharyngeal swab test (viral testing for influenza A/B). Quantitative polymerase chain reaction-based (qPCR) methods are the major diagnostic tests for SARS-CoV-2 using nasal swab, aspirate, sputum, or blood as samples. These method have some limitations as they are time consuming and have variable sensitivity (30%-80%). Another diagnostic method is the newly approved nucleic acid test, which is carried out based on the principle of fluorescence PCR. The main goal of SARS-CoV-2 diagnosis is to accurately detect the virus and to minimize further transmissions by timely isolation and treatment of infected patients. Other tests (not specific for SARS-CoV-2) used in conjunction with the methods above are based on clinical manifestations. These include blood tests such as complete blood count, comprehensive metabolic panels, basic metabolic panels, and assessment of liver/kidney markers and procalcitonin levels (for bacterial infections). Inflammatory markers may also be assessed including CRP, erythrocyte sedimentation rate, IL-6, lactate dehydrogenase, D-dimer, ferritin, troponin and creatine kinase-MB. Imaging investigations are typically computed tomography scans: in COVID-19 patients these often show glass opacities, areas of consolidation, and paving patterns in cases of severe and progressive disease. Ground glass opacities can also be observed on chest X-ray. Finally, ultrasound can show B-lines, pleural line thickening, and lung consolidation. Air bronchograms can also be used for assessment. These tests are non-specific but helpful to determine patients’ health status.

Prognosis of SARS-CoV-2

Although the risk factors for COVID-19 remain unclear, some risk factors put patients at a significantly higher risk of mortality, especially in individuals with underlying conditions. Some medical disorders are correlated with higher risk of mortality in COVID-19 patients. These include, cardiovascular diseases mortality risk 10.6%, lung disease (mortality
risk 7.3%), type 1 and 2 diabetes (mortality risk 6.3%), immunosuppression (e.g., cancer patients; mortality risk 5.6%), and age (Figure 10). COVID-19 mortality rates increase with advancing age, and are especially high in those aged >60 years. Elevated inflammatory markers in response to tissue damage (elevated levels of D-dimer, ferritin, creatine kinase-MB, and troponin) have been associated with higher mortality rates.

**Potential treatment of COVID-19**

The first line of treatment for patients presented with the symptoms of COVID-19 (fever, dry cough, and shortness of breath) is self-quarantine for at least 14 days. Cases are monitored for progression of symptoms such as increased fever (>40°C), significant difficulty breathing or shortness of breath, mouth breaks, constant coughing, and dehydration. If there is no significant improvement in symptoms, it is advisable to consult a clinician for confirmation of the diagnosis and to avoid further spread of the virus. The main treatment currently available is supportive care. Although there is limited information on COVID-19, it has been linked to ARDS. For patients with high fevers that could potentially lead to dehydration, intravenous fluids such as normal saline or lactated Ringer’s fluid can be administered sparingly to prevent lung overload. To reduce fever, antipyretic drugs such as paracetamol or acetaminophen can be administered. Drugs such as remdesivir, chloroquine, ritonavir, tocilizumab, corticosteroids have been repurposed for the treatment of COVID-19 (Figure 11), although their clinical effectiveness has not yet been confirmed. Unfortunately, the use of chloroquine and derivatives such as hydroxychloroquine, alone or in combination with other drugs, resulted in cardiac toxicity. Investigations of these drugs were recently suspended by the WHO.89

**Mechanism of action of selected repurposed drugs for treatment of COVID-19.** The elucidation of potential targets could lead to COVID-19-specific treatments (Figure 11). Approaches to anti-SARS-CoV-2 drug development include (a) inhibition of SARS-CoV-2 entry, (b) disruption of SARS-CoV-2 +ssRNA synthesis after entry, (c) inflammatory response suppression, and (d) disruption of SARS-CoV-2 translation.

An FDA-approved immunosuppressive and anti-malarial parasite drug (chloroquine) can inhibit the entry of COVID-19 into the endosome after binding to ACE-2 receptors, thereby preventing the release of +ssRNA for translation.89,93,95,96 Studies also showed that hydroxychloroquine, an analog of chloroquine, was more potent and could be used in place of chloroquine.97 Remdesivir, a novel antiviral drug and nucleotide analog used to treat Ebola virus infection, is currently under clinical development. The mechanism of the drug is reported to be at the post viral entry stage.89 Its mode of action is to inhibit the RdRp, preventing synthesis of the viral +ssRNA (Figure 11 (2)). This drug is currently in phase 2 clinical trials. The protein inhibitor ritonavir has also been proposed for the treatment of COVID-19. This drug interferes with the protease enzymes (proteinases) by inhibiting the conversion of polyproteins into the mature components (spike proteins, nucleocapsids) needed by the virus for multiplication (Figure 11 (3)). Another immunosuppressive drug, tocilizumab, has also been repurposed for COVID-19 because of its ability to block IL-6 and inhibit inflammatory responses. Corticosteroids can also decrease inflammation by inhibiting phospholipases such as phospholipase A2, and thus suppress the excessive production of prostaglandins (Figure 11 (4)).

SARS-CoV-2 appears unfamiliar to the human innate immune system. Coupled with its emergence and its spread globally
Figure 10. Potential prognosis of COVID-19 and associated mortality rates. Prognoses are shown for patients with (a) cardiovascular diseases, (b) inflammatory blood markers, (c) ageing, (d) pulmonary diseases, (e) immunosuppression (e.g., cancer patients), and (f) diabetes.
via human-to-human transmission, the development of vaccines for prevention is no longer a debate but a necessity. Several vaccine platforms are being developed and some have entered clinical trials. However, approval by regulatory agencies such as the FDA and manufacturing may take 12 to 18 months.98

Studies of the antiviral activity of host-directed drugs and compounds have identified two classes of molecules (protein biogenesis inhibitors and ligands of the Sigma1 and Sigma2 receptors) as effective inhibitors of viral infectivity. Molecules that target the Sigma1 and Sigma2 receptors perturb the virus through different mechanisms from translation inhibitors, potentially including modulation of cellular stress responses.99 The ligands haloperidol, PB28, PD-144418, and hydroxychloroquine are currently undergoing clinical trials in COVID-19 patients.100 These molecules exert their antiviral effects during viral replication by inhibiting nucleoprotein expression after viral entry has occurred. The lack of selectivity of chloroquine and hydroxychloroquine, including off-target effects on the human Ether-à-go-go-Related Gene (hERG) and other molecules, may be related to the adverse cardiac reactions that have limited their use.101 A recent study by Gordon et al identified 332 high-confidence SARS-CoV-2-human protein interactions connected to multiple biological processes, including protein trafficking, translation, transcription and ubiquitination regulation.102 The study identified 69 ligands, including FDA approved drugs, compounds in clinical trials, and preclinical compounds that might theoretically have therapeutic effects as host-directed interventions against COVID-19. To date, no

Figure 11. Selected repurposed drugs for treatment of COVID-19.
known antiviral drugs nor vaccines against SARS-CoV-2 with proven clinical efficacy have been identified. Part of the reason for the absence of such agents is limited information regarding the molecular details of the infection. To develop therapeutic interventions against COVID-19, it is crucial to understand how the virus interacts with the host during infection.

**ACE-2, a potential target for COVID-19 treatment.** ACE-2 has been identified as the functional receptor for SARS-CoV-2. It is an outer membrane enzyme expressed in vascular endothelial cells, the renal tubular epithelium, and Leydig’s cells of the testes, lungs, heart, kidney, and gastrointestinal tract.\(^{59,103}\) It is a type-II transmembrane metallocarboxypeptidase with its enzymatically active domain exposed at the cell surface.\(^{104}\) ACE-2 is a key player in the renin-angiotensin system (RAS) and a target for treatment of hypertension.\(^{105}\) ACE-2 catalyzes the cleavage of angiotensin II, a vasoconstrictor, into angiotensin 1–7, a vasodilator, thereby lowering blood pressure by negatively regulating RAS.\(^{106}\) ACE-2 is a promising drug target for treating CoV infection as well as other cardiovascular diseases.\(^5\) ACE-2 confers a protective effect against lung injury induced by viruses by increasing the production of angiotensin 1–7. The virus presumably causes lung damage by reducing ACE-2 levels on cells through the process of degradation and internalization.\(^{107,108}\) Because studies have shown that ACE inhibitors and angiotensin II receptor blockers could be used to up-regulate the expression and activity of ACE-2 in hypertensive patients, similar strategies might reduce the severity of COVID-19.\(^{109,110}\) Recent studies have shown that the expression of human ACE-2 is associated with SARS-CoV infection and that genetic variations of this receptor may contribute to susceptibility and/or resistance against infection.\(^{111}\) For instance, a single-cell RNA sequencing analysis of ACE-2 revealed that type II alveolar cells had higher expression of ACE-2 in eight individual lung tissues obtained from normal donors. ACE-2 expression was higher in the two male samples compared with the six female samples. Additionally, ACE-2 expression was higher in the only Asian male in the study compared with Caucasian and black Americans,\(^{59}\) which might explain why the four German cases showed mild clinical symptoms with no severe illness.\(^{112}\) This implies that variation in ACE-2 expression in COVID-19 patients is likely to affect susceptibility, symptoms and intervention outcomes following SARS-CoV-2 infection.

**Precautionary measures against COVID-19**

The degree of spread of COVID-19 is currently about 5.3% and could potentially increase if precautionary measures are not considered. Global prevention of the spread of COVID-19 is therefore a crucial and urgent goal. To prevent further spread of this disease, detection and isolation of individuals with COVID-19 is of the utmost priority. Examples of measures to curb spread include self-quarantine, isolation of infected individuals, social distancing, good personal hygiene (frequent hand washing with soap and water/alcohol-based sanitizers and avoiding touching the eyes, nose and the mouth), and use of personal protective equipment. Certain classes of compounds, called surfactants, are contained in soap and have the ability to neutralize microbes such as SARS CoV-2.\(^{113}\) This is because soap can assemble into bubble-like structures called micelles that trap viral matter and other biomaterials.\(^{114}\) Surfactants in soap lather have their hydrophilic parts pointing outwards and interacting with solvent and their hydrophobic
heads pointing inwards. This opens the coronavirus outer membrane and encapsulates viral molecules within micelles, thus making insoluble viral molecules easily soluble in water and effectively removing them from hands, surfaces or other areas after about 20 s.\textsuperscript{115} Therefore surfactants in soap can disrupt and sequester viruses and other contaminants while sanitizer and disinfectants are designed to kill SARS-CoV-2.\textsuperscript{116}

**Conclusion**

The outbreak of SARS-CoV-2 has become a global threat. However, information regarding this virus remains limited. The available information is inconsistent and there are constant data updates, which may contribute to variation between study results. For more consistent and accurate results, well-annotated data from clinical patients and subclinical subjects in normal populations could help to better understand the pandemic. The information provided in this review is based on data provided by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University during specific date ranges. Key insights into the prevalence, pathophysiology, diagnosis, and potential treatment of SARS-CoV-2 are herein summarized. Research efforts are being intensified to address the current challenges in the quest for adequate treatments, diagnostics, and vaccines. Clinical studies into the genetic variation of receptors such as ACE-2 in tissues and across populations will remain an active area of research until relevant targets and therapies are found. While the development of adequate treatments and vaccines for COVID-19 is underway, it is advisable that good hygiene practices including washing of hands and social distancing should be practiced, and government guidance/guidelines should be followed. This will help to reduce the spread of the disease. We hope that the insights gained from this review will enable researchers to help patients develop accommodating lifestyles and improve the efficiency of health care practitioners.

**Availability of data and material**


**Authors’ contributions**

A.O.F., N.R.S.S., O.B.A., O.O.B., and A.K. carried out the literature review and drafted the manuscript. M.O.A., A.M.M. and M.M. critically evaluated the manuscript. All authors read and approved the final manuscript.

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