Journal of Current Biomedical Reports
Volume 3, Number 3, 2022
jcbior.com
eISSN: 2717-1906

Review

A comprehensive review of novel coronavirus disease 2019 (nCOVID-19) characteristics, diagnosis, treatment, and prevention

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Abstract

The outbreak of a pandemic that began in Wuhan, China, in December 2019 with the new coronavirus 2019 (nCOVID-19) or severe acute coronavirus 2 (SARS-CoV-2) syndrome has created a dangerous and deadly public health issue worldwide. The number of infected cases and mortality continued to rise, and many countries have been forced to adhere to social distancing and quarantine. Epidemiological studies have shown that elderly patients with underlying diseases are more prone to severe forms of the disease, while young people and children have milder symptoms. This study looks at some of the challenges in diagnosing, preventing, and treating coronavirus disease 2019 based on virus features.

Keywords: Viruses, 2019-nCoV, COVID-19, Coronavirus, Epidemic disease, SARS-CoV-2

1. Introduction

Infectious diseases have consistently threatened human health for centuries [1]. In December 2019, the Covid-19 disease emerged as a threatening infection and spread extensively, becoming an epidemic worldwide. The World Health Organization (WHO) claimed that this is the fifth epidemic since the Spanish flu epidemic of 1918 [2, 3]. The covid-19 disease is the most significant public health crisis of the 21st century [4]. In late 2019, the Chinese government notified the WHO of the emergence of many unknown cases of pneumonia in Wuhan [5]. These cases of pneumonia began in a seafood market in Wuhan, China, where live animals like frogs, bats, birds, snakes, and rabbits were frequently sold [6]. According to the China National Health Commission, in January 2020, more than 50 people quickly became infected with viral pneumonia with symptoms such as fever, dry cough, weakness, and shortness of breath. These symptoms are a new coronavirus in group b of the coronavirus [7]. The new virus discovered was a seventh of the coronavirus to infect humans [8]. The novel virus discovered in January 2020 was identified by the WHO as the New Coronavirus 2019 (nCoV-2019) and became formally named COVID-19 in February 2020. After its initial emergence in China, nCoV-2019 spread

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Received: May, 15, 2022
Accepted: June, 26, 2022

widely in many countries worldwide and became a global threat on all continents. As stated in January 2020 by the WHO as an international critical health situation [9-11] and finally in March 2020, COVID-19 as an all-inclusive disease trapped in the world [2, 3].

2. Epidemiology

The majority of coronaviruses can cause sickness in humans and other [12, 13]. All human coronaviruses often originate from animals that act as natural hosts. The presence of an interface facilitates the transmission of viruses from their natural host to humans. Like other coronaviruses, bats are natural hosts for SARS-CoV-2 that can transmit the virus to humans through direct contact or an intermediate host [2, 3]. nCoV-2019 virus detected in Wuhan, China, belongs to the beta-coronavirus family according to phylogenetic analysis based on viral genomes. Despite about 79% similarity between nCoV-2019 and SARS-CoV nucleotide sequences and 50% similarity with MERS-CoV, the nCoV-2019 virus causes a deadlier infection than the other two viruses [14].

Bats are critical repositories for alpha and beta coronaviruses and can be primarily natural hosts for HCoV-NL63, HCoV-229E, SARS-CoV, and MERS-CoV viruses [15] And are claimed to be the *Rhinolophus* bat is a natural host for SARS-CoV, while recent research has reported the presence of the MERS-CoV virus in *Perimyotis* and *Pipistrellus* bats [16]. The nucleotide sequence similarity of the genome of BatCoV RaTG13 virus detected in Rhinolofus afnis bat from Wuhan, province of China to the nCoV-2019 virus is close to 96.2%, indicating that the natural host for nCoV-2019 might be a bat called *Rhinolofus afnis*. However, differences may indicate one or more host hosts between bats and humans. In a metagenomics study by a research team from the University of South China's Toralen, more than 1,000 samples of pangolins were assessed and found that 70% of them contained the Beta-CoV virus.

Furthermore, one of the coronaviruses identified from pangolins has a genome that is strikingly similar to the nCoV-2019 genome. The genome sequence similarity between the two viruses is about 99%. Hence, this group of researchers proposed pangolins as the intermediate host between humans and bats [17-19]. According to numerous studies and findings worldwide, most researchers agree that the spread of SARS-CoV-2 begins with transmitting the virus from a natural host to humans, directly or via an intermediate host, and then Human-to-human transmission is formed [20].

3. Coronavirus profile

3.1 Virus genome

The SARS-CoV-2 virus is a single-stranded, positive-sense RNA virus that belongs to the coronavirus family, genus Betacoronavirus. Virions are about 125 nm in diameter, and their genome length varies between 26 and 32 kilobases. The genome of this virus contains an Adenosine sequence called the tail of poly-A at the end of 3` and the cap at the end of 5'.

The virus genome contains 16 unstructured proteins (nsps) encoded by the ORF at the 5' end, including RNA-dependent RNA polymerase (RdRp), viral proteases, and helicase. Also, the structural proteins of this virus include nucleocapsid (N), envelope (E), spike (S), and membrane (M), which are located at the end of 3' genomes of the virus and are encoded by different ORFs. It binds to the receptor and has an N-terminal subunit called S1 (RBD and NTD domains) and a C-terminal subunit called S2. Other proteins in the SARS-CoV-2 virus, such as the N protein responsible for controlling synthesis, are also essential. It carries viral RNA or M protein, which plays an important role in viral aggregation [21, 22]. It can inhibit antiviral activity by activating the STAT1 transcription factor by isolating IMP alpha1 / Beta1 on RER and Golgi membranes [23] (Figure 1).

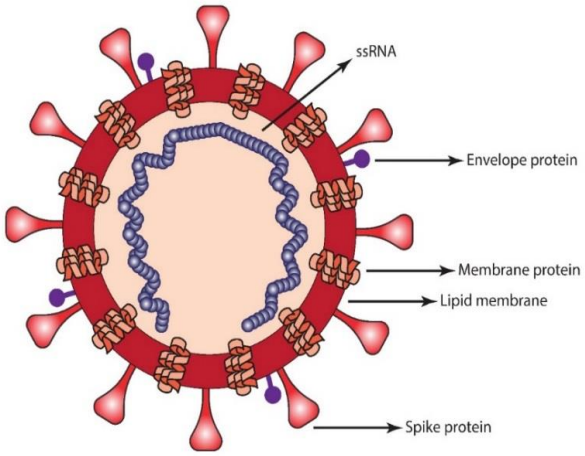

Figure 1. Schematic diagram of SARS-CoV-2

3.2 Coronavirus variants and mutations

Coronaviruses, as an RNA virus, are vulnerable to mutations [24]. However, SARSCoV2 is believed to have a low overall mutation rate. This could be due to the genetic correction mechanism in CoVs [25, 26]. However, since SARSCoV2 has the largest genome of any RNA-containing virus, such genomic changes can accumulate rapidly during each viral replication cycle [24, 27]. SARS-CoV-2 strains were first identified in the United Kingdom (B.1.1.7), Brazil (B.1.1.28), and South Africa (B.1.351 or 501Y.V2) [28, 29].

SARS-CoV-2 viruses have also been reported in the United States (L452R) and other parts of the world, including Japan (type P.1 or B.1.1.28) and India (D614) [30, 31]. Five variants of SARS-CoV-2, including Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), and Omicron (B.1.1. 529) since the beginning of the Corona epidemic, has been discovered and the D614G mutation is the most common in the COVID-19 global epidemic [32], which started in Europe and had a significant impact on the severity of COVID19 infection as research has shown that the D614G mutation is highly contagious and can spread quickly [33].

RBD is associated with an increased viral affinity for ACE2 than wild-type in human and mouse cells [34]. Position 69-70 of the genome allows the virus to escape from the human immune system. Other mutations associated with some RBD mutations include N501Y, N439K, and Y453F mutations [35, 36]. At the end of December 2020, a worrying new variant of the SARS-CoV-2 virus, known as the alpha or GRY strain and B.1.1.7, was registered in the UK [37]; a new mutation was called the B.1.1.7 mutation increased transmissibility and caused a sharp increase in [38]. Close to 17 mutations were found in the viral genome of the B.1.1.7 strain, eight of which were in the spike protein (S). Includes mutations 69/70/144, N501Y, A570D, P681H, T716I, S982A, D1118H [39].

B.1.1.7 has also been reported to have a high transmission rate of 43% to 82 [1], and a study in Denmark also showed that B.1.1.7 could increase the risk of hospitalization [33]. B.1.1.7 SARSCoV2 has also been reported as one of the most prevalent viruses in the United States [40]. Notably, strain B.1.1.7 is resistant to neutralization by most monoclonal antibodies (MAbs) and can bind to the N-terminal domain (NTD) of the spike protein [41, 42].

The beta or GH501Y or B.1.351 strain of the SARS-CoV-2 virus was first found in October 2020 in South Africa. This strain has 9 mutations, including L18F, D80A, D215G, R246I, K417N, E484K, N501Y, D614G, and A701V in its spike protein [40], whose findings of B.1.351 strains have also shown that this variant is resistant to recovery plasma and vaccination. The E484K mutation is primarily responsible for this resistance; the E484K mutation is common between variants B.1.351 and P.1 [41, 42].

The third worrying type of SARS-CoV-2 was the gamma strain or GR / 501Y.V3 or B.1.1.28, which had eleven mutations including L18F, T20N, P26S, D138Y, R190S, H655Y, T1027I, D614G, K417T. E484K and N501Y in spike proteins [43]. Many vaccines also showed low efficacy for the P.1 mutation [44].

When the fourth variation of the SARS-CoV-2 virus was detected in India in April 2021, the Delta variant, or B.1.617.2, was first seen [45], and since it was identified in late 2020, it has spread rapidly globally [46]. About ten mutations have been identified in the B.1.617.2 strain protein, including T19R (G142D *), 156 / 157del, R158G, L452R, T478K D614G, P681R, and D950N [37].

In June 2021, in WHO epidemiological reports, Epsilon (B.1.427 and B.1.429), Zeta, Eta (B.1.525), Theta (P.3), Iota (B.1.526), Kappa (B.1.617.1), and Lambda (C.37) strains have also been published. According to several studies, strains containing mutations in RBD, such as the Epsilon strain, have been linked to the L452R, T478K, E484K, E484Q, and N501Y mutations, which have increased the transmissibility of SARS-CoV-2 and the prevalence of these strains worldwide [47].

In general, enhanced RBD mutant affinity for the ACE2 receptor in host cells can be attributable to varied transfection of SARS-CoV2 mutant strains. SARS-CoV-2 strains, L452R / T478K (Delta), L452R / E484Q (Kappa), and E482K / N501Y (beta and gamma), have double RBD mutations that enhance affinity and transferability [48, 49].

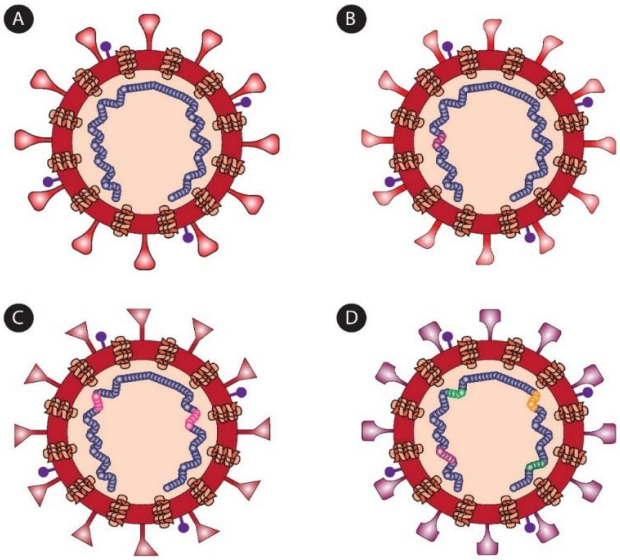

Figure 2. The impact of mutations on spike protein structure. A shows the original structure of the spike protein of SARA-CoV-2. The figure indicates that the structure of spike proteins is already similar to original viruses after a minor mutation (B), more mutation causes more changes in the structure of spike proteins (C), and major mutations cause the significant changes in the structure of spike proteins which affects the vaccine efficacy.

3.3 Spike protein

A fusion protein makes up the spike protein with exterior domains, a transmembrane, and an intracellular component. It is found on the surface of the virus and is highly glycosylated. Viral protein S is subdivided into two functional subunits, S1 and S2, forming homotrimers. Combining these subunits with other molecules results in the combination of the host membrane with the virus. The S protein from the coronavirus can bind to host receptors and facilitate virus entry into target cells [50, 51]. The S1 subunit of the SARS-COV-2 spike protein has a receptor-binding domain called ACE2, which shows a greater tendency to bind to the host cell than the SARS-COV-1 subunit [6], and the S2 subunit is necessary for the fusing of viral coats to host cell membrane. The S protein is primed with TMPRSS2 (serine protease) from the host cell during virion entry into the host cell. In addition to protein S, viral Proteases such as Cathepsin B and L are also involved in the entry of virions into the host cell, and these proteins are required for virus entry only when the host TMPRSS2 is not present. SARS-CoV-2 is independent of human Proteases for cell entry [22, 52-54].

Protein S in the SARS-COV-2 virus has four different amino acids compared to the SARS-CoV virus; this difference leads to the ability of the virus to bind more to the ACE2 enzyme by nCoV-2019. SARS-COV-2 binds to the ACE2 receptor cells from the human, bat, and pig cells but cannot bind to cells without the ACE2 receptor [55], [56]. Expression of the ACE2 receptor in the lungs is found in the small intestine, kidney, and heart, with no evidence of expression in innate immune cells [57], [58].

3.4 The main protease and RNA-dependent RNA polymerase enzyme

The major SARS-COV-2 protease contains Mpro, also known as C3-like protease, essential for proteome replication and production, causing the division of LeuGIN polyproteins into nonstructural proteins (nsps) (Ser, Ala, and Gly). RNA-dependent RNA polymerase is a key coronavirus transcription and replication enzyme encoded by nsp12. This enzyme catalyzes the production of viral RNA genomes by forming nsp-containing complexes, such as nsp 7 and 8 [22].

4. Pathogenicity of the virus and the role of the immune system

The structural proteins of SARS-COV-2 virions, such as spike glycoproteins, coatings, membranes, and nucleocapsids, are the most immunogenic [59]. Adaptive responses to SARS-COV-2 are primarily triggered by spike protein, with immunodominant T and B cell epitopes being identified. In addition, these processes activate unstructured proteins in the viral RNA replication complex and translate innate immune pathways. This activates IFN type I and NF-B in epithelial cells, while in macrophages and dendritic cells, it activates NLRP3 and other inflammatory inflammations [60]. In response to humoral immunity to infection, particular antibodies produced by B cells neutralize the pathogen and ultimately prevent the further spread of the disease in the body. Activation and differentiation of B cells into antibody-secreting plasma cells is accomplished by a series of events involving the digestion of the virus by antigen-supplying cells (e.g., dendritic cells, macrophages) and stimulates the delivery of virus-specific T-helper antigen to the cell [61, 62]. B cells show little clonal proliferation, while memory B cells, which are CD27+ and CD38+, show the highest level

of proliferation among the various subsets of B cells. In comparison to healthy reference cells, COVID-19 patients have established special B cell receptor clones. These findings imply that B cells contain clones that are unique, diversified, and altered [63].

Long-term protection requires the induction of memory T cells and B cells (rather than circulating antibodies); Thus, follicular helper T (TFH) cells mature the humoral immune response. In contrast, establishing a reservoir of B-specific memory cells ready for rapid response indicates the possibility of reinfection [64]. Preliminary studies in a small number of patients, or even a single patient, have shown changes in the activation status or differentiation of CD8+ T cells in acute 19 cells [65]. T cells that respond to SARS-COV-2 come from a unique subset of T cells. These T cells, on the other hand, have already developed and are capable of detecting specific viral epitopes. CD4+ T cells are required to develop robust B cell responses, which lead to antibody affinity maturation. T cells and spikes interact to determine serum IgA and IgG titers [66]. In infection with 2-SARS-CoV, TCD4+ and TCD8+ cell turnover has been reported in 70% and 100% of patients with a recovery period of COVID-19, respectively. Spike protein responses in TCD4+ cells were strong, and they were linked to particular IgG and IgA SARS-CoV-2 titers. The whole TCD8+ response comprises 11 to 27% spike, M, and N proteins, although extra responses frequently target nsp3, nsp4, ORF3a, and ORF8 [67].

5. Transmission of virus and endangered populations

Common transmission routes of the SARS-COV-2 virus include direct transmission through cough, sneezing, and respiratory droplets, which can sometimes occur through contact with the mucous membranes of the mouth, nose, and eyes [68]. Problems with the disease include spreading the virus by asymptomatic infected people in the community. Viral culture can detect the live SARS-COV-2 virus in the saliva of infected people [69]. COVID-19 is more likely to develop in people who have diabetes, high blood pressure, cardiovascular illness, chronic lung disease, chronic kidney disease, cancer, or immune suppression issues. They are more likely to have severe disease, and the death rate is higher in these high-band groups [70]. Several studies have found that patients with diabetes are more prone to contract the SARS-CoV-2 virus. The virus can raise blood glucose levels by inducing the release and increase of catecholamine and glucocorticoids. Metabolic disorders in diabetic patients can decrease the immune response, resulting in severe complications of COVID-19. About 75% of fatal patients in China and Italy had high blood pressure. Increased ACE2 expression has been linked to the usage of anti-hypertensive medications such as ACE inhibitors and angiotensin blockers in individuals with hypertension [71]. More severe cases of COVID-19 have also been documented in obese patients because to lower functional capacity and expiratory storage volume of the lungs. The effects of exhalation due to reduced pulmonary function are more visible.

Mostly dangerous conditions if COVID-19 is more common in people with underlying diseases such as serious heart problems including heart failure, cardiomyopathy, coronary artery disease, COPD, obesity (BMI=30), Tuberculosis, organ transplantation, asthma, cerebrovascular disease, chronic kidney disease, hypertension, diabetes type 2, smoking, immunodeficiency, and liver disease are reported [71].

Underlying disorders such as chronic lung disease, congenital heart disease, cancer, and chronic renal disease were the most common risk factors for adolescents and children admitted to the intensive care unit (ICU) [70]. Also, the group of health care workers is at the highest risk of COVID-19 infection due to the high probability of exposure to infected patients. According to a study conducted in the United Kingdom, front-line healthcare personnel has a 3.4 times higher risk of infection than community residents. Healthcare personnel in China reported 3.8 percent of SARS-CoV-2 cases, with 14.8 percent of highly ill [70].

6. Diagnosis

6.1 RT PCR or reverse transcriptase-polymerase chain reaction

RT PCR, or reverse transcriptase-polymerase chain reaction, is a method that can detect viral RNA such as RNA of the SARS-COV-2 virus. In patients with COVID-19, RT PCR is one of the most sensitive and specialized approaches for detecting the SARS-CoV-2 virus. If the initial test results are negative and the doctor suspects the disease, the doctor may order a blood, stool, and urine test for diagnosis. According to the CDC recommendation, when the result of two RT-

PCR tests in 24 hours is negative, the test result can be declared negative [72-74].

6.2 Immunoglobulins

Immunoglobulins are available to protect the body against various diseases, and IgM and IgG are two immunoglobulins that can be measured for Covid19 disease. These antibodies are produced 6 days after the onset of symptoms. In addition, after 15 days, 100% of antibodies can be observed in patients with severe and moderate diseases [74]. For example, IgM may appear after two weeks; on the other hand, IgG takes a week to be delivered, and simultaneous demonstration of these two immunoglobulins is important for diagnosing infection. ELISA is one of the methods that can predict the presence of antibodies. The class, subclass, and quantity of immunoglobulin can be determined with this method. The test result is also prepared quickly, between one and three hours [72].

6.3 Chest Computed Tomography (chest CT)

One of the most important and sensitive diagnostic tests is chest CT, which most researchers recommend as an adjunctive diagnostic method. It also allows the chest to be seen before starting clinical signs of lung involvement. The central aspect of chest CT includes vitreous opacities (GGO) with ascites under the pleura, thickened lobular septum with alveolar variable filling, and fusion [75].

6.4 Loop-mediated isothermal amplification (LAMP) technique

One of the new techniques proposed for detecting COVID-19 is the Loop-mediated isothermal amplification (LAMP) technique, in which, with the help of molecular amplification, any genomic material can be amplified in a shorter time with higher efficiency [76]. An estimated time of 30 - 45 minutes for the result of this experiment has been This method can be used in non-laboratory conditions as well as a rapid high-sensitivity test for both pure RNA from COVID-19 patients and raw samples with more than 75% [76]. This technique is currently being approved.

6.5 Direct Immunofluorescence (DFA)

Coronavirus can cause community-acquired pneumonia (CAP). Viruses, unusual pathogens, and bacteria are pathogens that can cause CAP. Virus isolation and culture, serum-specific antibody detection, antigen detection, and nucleic acid detection are methods that can achieve CAP. Direct immunofluorescence (DFA) is a method to find viral antigens in a sample and search for the virus [77].

6.6 Sensitive magnetic sensing based on the disposable electrochemical sensor

Magnetic sensitization based on disposable electrochemical sensors is a new method for detecting coronavirus. In this method, magnetic beads and gold nanoparticles, angiotensin 2 converting enzyme (ACE2) -conjugated peptides, can absorb spike protein in human saliva. This method has advantages over RT-PCR, making it a suitable alternative. One of the most important benefits that can be mentioned is the reduction of analysis time, inexpensive tools and equipment for testing, and the absence of the need for complex [73].

7. Therapeutic approaches

Too far now, no definite treatment for COVID-19 infection has been documented, and significant research is being conducted worldwide to find a definitive treatment for COVID-19 infection patients [78]. Most supportive care and standard care are symptomatic-based. Spike protein, a serine protease, TMPRSS2, papain-like protease, 3C-like protease, and RNA-dependent RNA polymerase are potential therapeutic targets [10, 11].

7.1 SARS-COV-2 fusion and entry inhibition

SARS-COV-2 viral entry requires the spike protein. The receptor-binding domain (RBD) is found on a surface unit termed S1 that attaches to a cellular receptor, allowing the virus to attach to the surfaces of target cells. Once the virus enters the host cell, they form a 6-stranded helix (HB6) that allows the target cell membrane to integrate with the virus [79]. In addition, spike protein priming by cellular proteases, such as cellular serine protease or TMPRSS2, is required for the virus to enter the cells [68, 79]. In a study by Xia et al. on the design of the drug EK1, found that the formation of a 6-stranded HB6 virus complex targeting the HR1 spike protein domain is problematic [80].

7.2 Mechanism of action and antiviral effect of the drug arbidol

Arbidol is an aromatic amino acid that affects viral proteins and host [81]. A small section of the spike glycoprotein domain of SARS-CoV-2 correlates to influenza virus (H3N2) hemagglutinin protein, according to sequence analyses of SARS-CoV-2 and influenza virus sequences. Arbidol can be a potential target since spike glycoprotein is essential for adhesion and entry into cells via ACE2. Molecular and structural studies have shown that the binding site for arbidol in SARS-CoV-2 is the spike glycoprotein and its trimerization, which is one of the key factors in binding and entering the cell [82]. The effect of Lopinavir and arbidol and Lopinavir alone on patients showed that the group treated with arbidol and Lopinavir had a higher percentage of negative percentage SARS-CoV-2 test results obtained from stool tests and improved CT scan. The chest was also seen in these patients, and no significant side effects have been reported with arbidol. However, an increase in bilirubin levels and gastrointestinal disorders can be seen in most patients tested [17].

7.3 Protease inhibitors by Lopinavir and Ritonavir

Lopinavir is a protease inhibitor that is frequently taken alongside Ritonavir to increase Lopinavir's half-life by suppressing CYP-450. Furthermore, combining these two medications is linked to fewer side effects [83]. In 99 patients with Covid-19 with severe symptoms treated with Lopinavir and Ritonavir and 100 patients receiving standard care, the results showed that treatment with Lopinavir and Ritonavir not only did not make any significant difference in mortality and clinical recovery time, but there was no difference in detectable virus RNA [63]. The latest findings from one of the largest trials showed that Lopinavir and Ritonavir are not suitable for treating COVID-19 patients. Because the results found that the death rate in patients receiving Lopinavir and Ritonavir was 22.1%, while in participants receiving standard care was 31.3% [64]. The COVID-19 Treatment Guide Panel advises against using LPV/r (AI) or other HIV protease inhibitors (AIII) for COVID-19 treatment [78].

7.4 Inhibition of RNA-dependent RNA polymerase by Remdesivir

The mechanism of Remdesivir is based on preventing viral replication. The antiviral efficacy of remdesivir against SARS-CoV-2 has been confirmed in vitro on Vero E cells [84, 85]. The FDA approved the emergency use of remdesivir on 1 May 2020 for patients with severe Quid 19 symptoms needing mechanical ventilation or ECMO and a SpO2 of less than 94 percent [86]. RemedSivir showed promising efficacy in the SARS-CoV-1 virus model of an infected mouse [87], while the same drug showed different results in recent trials on patients with the COVID-19 virus. In one study, RamedSavir improved the recovery of hospitalized patients who needed oxygen faster, but it was ineffective among patients with more severe respiratory failure [88].

7.5 Inhibition of viral protein transport by Ivermectin

Ivermectin is an FDA-approved anti-parasitic medication. It can bind to glutamate chloride ion channels, leading to hyperpolarization and parasite death. In addition, it is a GABA agonist that disrupts neurotransmission [89]. This drug also has antiviral properties due to its ability to inhibit IMPα / β1. Many RNA viruses, such as SARS-CoV, require the binding of IMPα / β1 to viral proteins for infection [90]. Ivermectin blocks the binding of IMP / 1 to viral proteins, preventing viral proteins from entering the nucleus of the target cell. In vivo and in vitro with IMPα/ß1-mediated heterodimer occlusion, Ivermectin has been shown to inhibit the transmission of viral proteins and, as a result, virus replication within the target cell against various RNA viruses such as influenza, Dengue virus, West Nile virus, and Venezuelan Equine Encephalitis virus [91]. Application of a dose of Ivermectin 2 hours after infection reduces SARS-CoV-2 by 5,000-fold in Vero-hSLAM cells, resulting in the complete elimination of viral particles after 48 hours [90]. However, this medicine has not been licensed to treat any viral infection, including SARS-CoV-2 infection [92].

7.6 Suppression of the excessive inflammatory response by the drugs Chloroquine and hydroxychloroquine

Antimalarial medicines Chloroquine and hydroxychloroquine have antiviral and immunomodulatory properties. The molecular structures of the two medications are different, but their therapeutic effects are the same [93]. Hydroxychloroquine and Chloroquine show the same

structure and action as weak immunomodulators and bases. They can raise the pH of endosomes and lysosomes, which are crucial for viral particle primary growth, membrane composition, and dispersion. Chloroquine can also prevent SARS-CoV-2 infection by modifying the glycosylation patterns of the spike protein and the ACE2 receptor, which prevents the virus from binding [94]. On 26 May 2020, the World Health Organization (WHO) discontinued chloroquine and hydroxychloroquine trials to treat COVID-19, increasing public concern about its side effects. Furthermore, additional research could not prove the efficacy of Chloroquine and hydroxychloroquine in treating mild to moderate or severe COVID-19 cases [95].

7.7 Anti-inflammatory effects of steroids

A systemic inflammatory response can cause lung injury and multisystem organ dysfunction in severe COVID-19 infection. Because corticosteroids have significant anti-inflammatory properties, they have been studied to see if they can help prevent or mitigate these side effects [78]. Based on prior experience treating influenza, MERS, and SARS-CoV-2, the WHO advocated using steroids to treat SARS-CoV-2 in January 2020 [96]; it has also been claimed that the use of steroids to treat SARS-CoV-2 in pregnant women poses no risk [97]. Many studies have suggested betamethasone because SARS-CoV-2 infection during pregnancy is linked to an increased risk of premature delivery [98-100]. The WHO does not recommend other steroids such as methylprednisolone; Because they delay the clearance of the virus and increase the blood sugar of the mother [2, 3]. Dexamethasone is another type of corticosteroid used for bacterial infections and myeloma, and by binding to the glucocorticoid receptor, it can inhibit inflammatory effects. High doses of this drug weaken the immune system, while lower doses have anti-inflammatory effects.

7.8 Initial and rapid innate immune response by interferons

Antiviral cytokines are known as interferons (IFNs). They could be used to treat COVID-19, with interferon type I (IFN-I) being one of the most promising candidates because of its antiviral characteristics in vitro and in vivo. IFN-a, IFN-b, and IFN-u are all members of the IFN-I family. These chemicals activate the basic and fast reactions of the innate immune system. When a virus RNA is identified in endosomes by protein sensors such as TLR3, TLR7, and TLR8, IFN-I proteins are produced. Many of the genes are then transcribed by IFN-I molecules, which attach to the IFNAR cell surface receptor (types 1 and 2) [101, 102].

7.9 Plasma recovery therapy

Recovery plasma is a means of achieving immediate and short-term protection by transferring antibodies against the pathogen to the blood of the patient. This method obtains plasma from patients after infection clearance and antibody production [103-105]. Antibodies can bind to a pathogen and neutralize it. On the other hand, antibodies can activate the complement cascade, phagocytosis, and cytotoxicity [105]. After recovery, neutralizing antibodies discovered in the plasma of patients play an essential role in viral clearance and virus defense. Neutralizing antibodies could bind to the spike protein and lower the receptor binding amplitude in SARS and Mercury, potentially inhibiting virus entry [106].

Recovery plasma is commonly used for patients with severe COVID-19 suffering from septic shock, organ failure, shortness of breath, or low oxygen saturation. In addition, the FDA has suggested that recovery plasma be used for high-risk populations for prevention [107]. In recovery plasma, in addition to neutralized antibodies, it is possible to accumulate immunoglobulin G, immunoglobulin M, anti-inflammatory cytokines, and natural antibodies, which may lead to severe immunomodulation of storm surges and cytokine responses. The disease duration is COVID-19 for patients [108].

7.10 Mesenchymal stem cell therapy

Many disorders are presently treated with stem cell-based therapies, particularly mesenchymal stem cell (MSC) therapies [109, 110]. MSC-based therapy treats ARDS patients by releasing anti-inflammatory, anti-fibrotic, and anti-apoptotic cytokines, which lessen the cytokine storm [111, 112]. Through their immunomodulatory capabilities and the production of soluble molecules, mesenchymal stem cells can prevent and control the cytokine storm [112]. T_{reg} and anti-inflammatory TH2 cells are also increased by mesenchymal stem cells. NO, and IDO are released by mesenchymal stem cells, limiting T cell cytokine

production [113]. Mesenchymal stem cells suppress NK cytotoxicity by inhibiting the surface expression of CD80, CD86, and MHC class II molecules and prevent dendritic cell maturation, thus maintaining dendritic cells in a tolerant phenotype and inducing an M2-induced anti-inflammatory [114].

Treatment with MSC has been proven to improve the management of respiratory models caused by the H7N9 influenza virus, such as ARDS [115-117]. Because H7N9 and COVID-19 have similar side effects, MSC treatment could be investigated further as an alternative to COVID-19 treatment [118, 119]. SARS-CoV-2 employs the ACE2 receptor to deliver the virus into cells, whereas mesenchymal stem cells do not. As a result, mesenchymal stem cells are immune to virus infection [120, 121].

7.11 Phosphorylation of ACE2 by the drug metformin

Metformin acts by activating and phosphorylating AMP-activated protein kinase (AMPK) in liver cells, resulting in improved glucose and lipid metabolism [122]. The activation of AMPK by metformin results in the phosphorylation of ACE2 [2, 3], The ACE2 receptor undergoes structural and functional modifications as a result of this [123]. This can result in a decrease in its binding to the SARS-CoV-2 virus and, as a result, a drop in ACE2 receptors and an imbalance in the renin-angiotensin-aldosterone (RAS) system, allowing SARS-CoV-2 to enter host cells [124].

7.12 Vitamin D

Vitamin D is fat-soluble and protects individuals against microbial infection through three mechanisms: physical barriers, innate cellular immunity, and adaptive [125]. Vitamin D maintains strong bonds, cleft joints, and adhesive joints by inducing antimicrobial peptides such as human cathepsin LL-37 and 1,25-dihydroxy vitamin D and defensins, and enhances intrinsic cellular immunity by inducing antimicrobial peptides such as human cathepsin LL-37 and 1,25-dihydroxy vitamin D and defensins [126, 127].

Vitamin D decreases macrophage production of pro-inflammatory cytokines TNF-α and IFN-g while enhancing anti-inflammatory cytokine expression [128]. In observational studies, low vitamin D levels have been related to an increased risk of acquired pneumonia in the elderly [129].

8. Vaccine development

Following the emergence of the COVID-19 pandemic, research centers, pharmaceutical companies, and researchers worldwide began researching and developing vaccines to fight the disease. One year after the pandemic began, several pharmaceutical and biotechnology companies succeeded in developing the COVID-19 Vaccine, which differs in the type and mechanism of action of these vaccines. Also, although the manufacturer has reported the effectiveness of vaccines, the effectiveness of each vaccine has been reported by different countries after vaccination. The following vaccinations have been approved for essential use by the US Food and Drug Administration:

8.1 Pfizer / BioNTech vaccine

Pfizer Pharmaceuticals in the United States, together with biotechnology company Bioventek in Germany, developed the first Covid-19 Vaccine. This vaccine, called BNT16B2, is based on mRNA and is reported to be 95% effective [130]. However, the efficacy of this Vaccine in Israel is reported to be 92% [131]. Who reviewed 23 articles related to the effectiveness of this vaccine in fully vaccinated individuals, reported that the effectiveness of this vaccine averaged 91.2% (87.9% - 94.5%) against SARS infection. CoV-2 was 97.6% (96.5% - 98.7%) against hospitalization, 98.1% (96.3% - 99.9%) against mortality [132]. It was also found that this vaccine was 87% (81.8% - 90.7%) against B.1.1.7 variant (alpha variant) and 72.1% (66.4% - 76.8%) against Variant B.1.351 (beta variant) is effective [133]. In addition, the efficacy of this Vaccine against B.1.617.2 variant (Delta variant) was 56.7% (95% CI 0.520–0.613) after the first dose, 83.7% (95% CI 0.672–0.928) later. It was reported from the second injection and 97.2% (95% CI 0.96–0.978) after the third dose [134, 135]. Among the available vaccines against Covid-19, the Pfizer / Bivantek vaccine is the most effective (up to 98.5% (95% CI 0.95–0.99)) to prevent very severe infection and mortality against the Delta variant [135]. For immunization, two doses of this vaccine need to be injected 21 days apart and should be injected into the arm muscle. Immunity to the SARS-CoV-2 virus will also develop within two weeks of the second injection [136].

8.2 Moderna vaccine

The vaccine, called mRNA-1273, was developed by Moderna Pharmaceutical and Biotechnology. The vaccine is also based on mRNA and injected into the arm muscle. The efficacy of this vaccine has been reported to be 94.1% [137]. To achieve this efficacy, two doses of the vaccine must be given 28 days apart. However, a single dosage of this vaccine has been reported to prevent the disease from spreading by up to 61 percent (31 percent - 79 percent) [138]. The efficacy of this vaccine against the Delta variant was 72% (95% CI 0.589–0.822) after the first dose and 77.5% (95% CI 0.673–0.852) after the second dose, and 97% (95% CI 0.964–0.978) has been reported after the injection of the third dose [134, 139]. The effectiveness of the vaccine against mortality or severe infection caused by the delta version was also reported to be 98.3% (95 percent CI 0.936–0.957) [135].

8.3 Johnson & Johnson's Janssen Vaccine

This vaccine is made by Johnson & Johnson Pharmaceutical Company and is called JNJ-78436735. This vaccine is a type of viral vector with a suitable injection site similar to previous vaccines in the arm muscle. The efficacy of this vaccine has been reported to be 66.3%, and only one dose of this vaccine is required for immunization. The vaccine has been licensed for emergency use by the FDA for over 18 years [133].

8.4 Vaxzevria vaccine (AstraZeneca / Oxford)

The vaccine, also called ChAdOx1 nCov-19, was developed by researchers at Oxford University and the Anglo-Swedish Biotechnology Pharmaceutical Company and is an adenovirus-based vaccine. This vaccine should be injected in two doses with an interval of 4-12 weeks, and according to published news, the effectiveness of this vaccine is 70.4% on average [134]. Studies The efficacy of this vaccine against the Delta variant was 44% (95% CI 0.301–0.588) after the first dose and 80.1% (95% CI 0.705–0.872) after dose injection Second reported (13, 15,16, 17). The vaccine can also prevent severe infection or death by the Delta variant by up to 91% (95% CI 0.88–0.92) [135].

8.5 Sinopharm

The vaccine, also known as BBIBP-CorV, is the first Chinese vaccine to be licensed for use by the WHO. This vaccine is inactive and prevents 79% of severe symptoms and hospitalization. Dizziness, fatigue, headache, nausea, vomiting, and fever are some of the side effects reported after the injection of this Vaccine [135], [136]. In a study of 282 people, a decrease in the efficacy of the Sinopharm Vaccine against coronavirus variants was reported. The efficacy of this vaccination was reduced 1.3 times against alpha variation, 10 times against beta variant, and 1.38 times against delta variant two weeks after the second injection, according to the findings of this study [137]. In another study, a 1.6-fold reduction in the effectiveness of this vaccine against beta variant compared to the Wuhan strain was reported 28 days after the second dose [138]. In a study conducted by Dolgin, the excellent efficacy of this vaccine against the omicron strain was mentioned [139].

9. Conclusion

The pandemic by COVID-19 has been a public health emergency since December 2019 due to its high infectious rate causing a wide range of symptoms that differ from mild cold-like symptoms to pneumonia and death. As a result, rapid progress in discovering ways to diagnose, treat, and control the disease is necessary [140]. Without an efficient therapeutic approach, the best way to deal with the COVID-19 disease is to reduce the virus spread and provide supportive care for infected people. More research on specific properties of the virus is urgently needed, as are measures for prevention and therapy. This study attempts to review available approaches for preventing, diagnosing, and treating COVID-19 by focusing on current information and knowledge about virus characteristics.

Authors' contributions

All authors contributed equally to this manuscript, and approved the final version of manuscripts.

Conflict of interests

The authors declare that they have no conflicts of interest.

Ethical declarations

Not applicable.

Funding

Self-funded.

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