Recent Efforts and Advances for Management of COVID-19

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Abstract

A novel type beta strain of coronavirus, referred to as the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), caused the latest pandemic COVID-19 disease that emerged in Wuhan City, Hubei Province China in early December 2019. It is an enveloped positive-stranded RNA virus, recognized for exhibiting interactions predominantly with lung epithelial cells. The WHO recommended avoiding gathering at public places and maintaining physical distance, using alcohol-based sanitizer and washing hands thoroughly with soap as precautionary steps. No standard treatment and medicine are currently available to fight against COVID-19; challenging research communities and pharmaceutical industries to revolutionize drug discovery and vaccine development. Meanwhile, efforts to boost immunity power appear need of the hour to combat COVID-19 illness. This review has been structured to provide detailed information on the causative agents of COVID-19, possible diagnostic and therapeutic approaches, potential drugs and their impact on health. In addition, we briefly highlight stem cell-based therapy as another approach to disease management and control. Immune responses elicited in the human body against SARS-CoV-2 are also discussed. The recent emergence of the SARS-CoV-2 strain called OMICRON has sparked worldwide concern. This review also covers the identification and global spread of OMICRON, which has now expanded to 77 countries, resulting in numerous speculations concerning its origin and degree of infectivity. The identification of mutations in the RBD (receptor binding domain) region of spike protein is a cause for concern because it goes beyond vaccination immunity. The following will discuss its transmission potential, infectivity and impact of COVID-19 vaccinations.

Keywords

COVID-19, SARS-CoV-2, MERS, Drug Repurposing, Stem Cells, Immune Response.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a new evolving infectious disease and currently an epidemic has been reported worldwide which is caused by this novel coronavirus. Coronaviruses belong to the family of enveloped RNA viruses that can cause disease in humans and animals. Numerous viruses in this family are Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS), which lead to respiratory infections in humans with symptoms such as common colds and more fatal infections [1]. Patients were found to have

pneumonia-like symptoms of unknown cause in December 2019, and most of them were found to have some kind of connection to the wholesale seafood market in Wuhan. Subsequently, SARS-CoV-2, belonging to the Ortho Coronaviridae subfamily of the Coronaviridae family, was discovered as the main causative agent for this new form of disease [2]. SARS-CoV-2 is now declared as a pandemic impacting several countries around the world [1]. As the virus poses a significant risk to human health and the economy, there is a serious need worldwide for the immediate production of effective therapies and prophylactics for its control and prevention. As of December 14, 2020, a total of 72,893,236+ confirmed COVID-19 cases, including 1,623,425+ deaths, 51,121,100+ recovered, and 20,148,711+ active cases were reported worldwide with the infection fatality rate of 3 percent [3]. The case-fatality rate (CFR) of SARS-CoV-2 has been estimated by the World Health Organization (WHO) to be between 0.3 and 1 percent, comparatively influenza A with CFR 0.1 percent lower than that of COVID-19 [4]. Some observational studies conducted in countries adopting COVID-19 preventive strategies have suggested 80% of COVID-19 patients have had symptomless or moderate disease [4–6], 14% of patients had serious illnesses and 6% were in severe situations [4,6].

The outer surface of the "corona'' appears to have crown-like spikes, thus referred to as coronavirus. Coronavirus has a small size which is ranging from 65-125 nm in diameter and the nucleic material is single-stranded positive sense RNA with a length of 26 to 32 kb. Coronavirus family is classified into four subgroups, i) Alpha Coronavirus: Human coronavirus HCoV-229E and HCoV-NL63, ii) Beta Coronavirus: this includes HCoV-OC43 and SARS-CoV, HCoV-HKU1 and MERS-CoV iii) Gamma Coronavirus: representing viruses of birds and whales and iv) Delta Coronavirus: a category of viruses isolated from birds and pigs [7–9]. Viruses such as SARS coronavirus, avian influenza, swine flu 2009 and MERS coronavirus have similar symptoms like infection in lungs and breathing difficulties that ultimately lead to lung damage and deaths. The genetic material of all coronaviruses is generally organized in a manner wherein 5′ end encodes the enzyme locus replicase and the structural proteins are encoded by ORFs 10, 11 on 1/3rd of the genome within the 3' terminus. Coronavirus genes have four structural proteins structured in the 5'-3' sequence as spike (S), envelope (E), membrane (M) & nucleocapsid (N) (Figure 1) [10]. Other coronaviruses, such as some beta coronaviruses, have specific structural and additional proteins, such as hemagglutinin esterase (HE) [10]. Enclosed nucleic acid capsid protein connected with the RNA genetic material forming an icosahedral shape within the outer membrane. In the envelope spike protein forms the peplomers and it provides the crown-like structure to coronaviruses [11]. 5' end of the coronavirus genome encodes the replicase enzyme, which comprises two open reading frames. Two large replicase polyproteins are translated by the replicase enzymes that are cleaved co-translationally into 16 proteins, which include 2 to 3 proteases, several modification enzymes, polymerases and helicases [11].

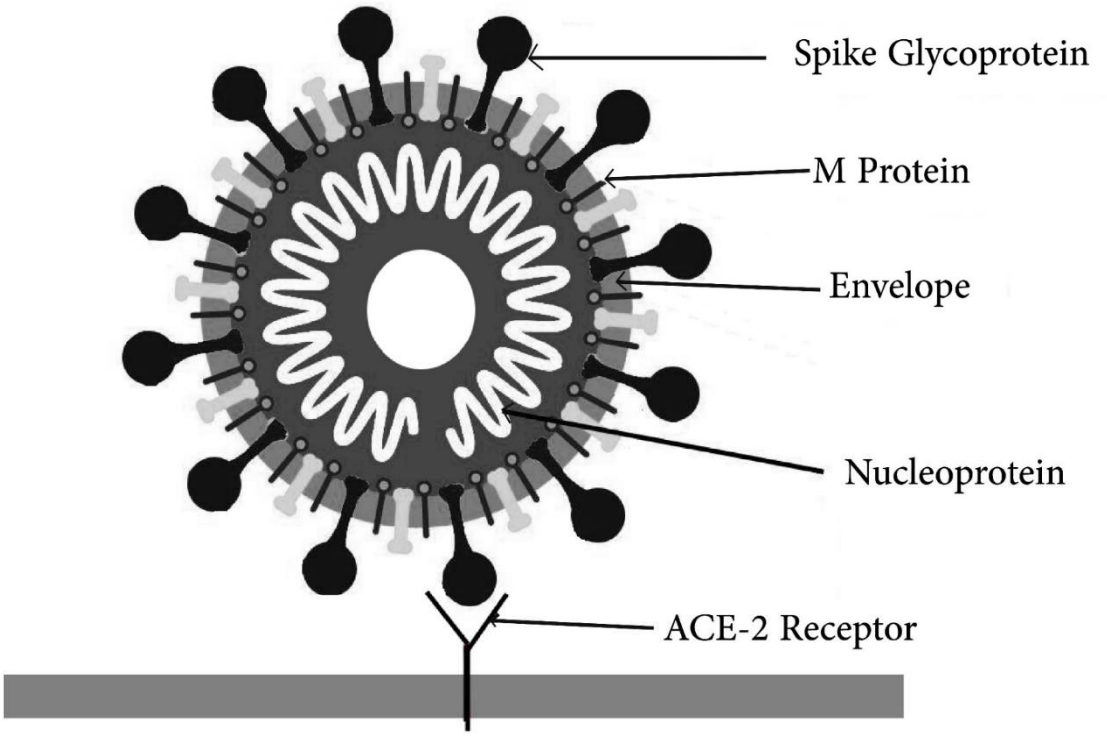

Figure 1. Schematic representation of coronavirus structure and viral receptor i.e., angiotensin-converting enzyme 2 (ACE2) on the host cell surface.

SARS-CoV-2 with the help of its class I fusion spike (S) glycoprotein recognizes the angiotensin I converting enzyme 2 (ACE2) as a binding site on the host cell particularly epithelial cells and consecutively fuses with the host cell. The entry of virus into target cells and further its transmission is allowed by the serine protease transmembrane protease, serine 2 (TMPRSS2) [4], which helps in priming of the virus spike protein and involves the cleavage of the viral spike protein at the S1/S2 site. The S1 subunit facilitates the binding of the spike protein via its receptor-binding domain. Upon attaching to the receptor, conformational changes in the spike protein occur [4,12]. The S2 subunit helps the membrane to integrate and internalize the virus. ACE2 and TMPRSS2 receptors are usually found in alveolar type II cells and capillary endothelial cells in the lungs [4,13]. As a result, SARS-CoV-2 infection demonstrates extreme respiratory disease as among the main symptoms. Importantly, infection with SARS-CoV-2 triggers overproduction of cytokines and increases the pro-inflammatory response in the lungs. Excess levels of cytokines cause oedema, difficulty in breathing, acute respiratory failure and several other infections that can even lead to death of patients [4].

Delta and Omicron are two recent variations of concern. India was the first nation to identify the Delta variant in late 2020. The Delta variety was discovered on May 31, 2021, and by November 22, 2021, it had spread to 179 nations. The World Health Organization (WHO) predicted in June 2021 that the Delta form would be among the most stressful

worldwide. It appears to have feature mutations T478K, P681R and L452R in the gene encoding the SARS-CoV-2 spike protein, which have been linked to changes in the virus's infectiousness and how it can be neutralized with antigens against recently circulating COVID-19 virus subtypes. It is thought to be one of the most contagious severe illnesses ever found [14–18]. The variation is suspected of being involved in the devastating second wave of the epidemic, which began in India in February 2021. As a result, the third wave hit Fiji, the United Kingdom, and South Africa. By late July, it had also contributed to an increase in daily attacks in Asia, the United States, Australia, and New Zealand [19–25].

Till date, more than 430 million people worldwide have been diagnosed with COVID-19, resulting in 5.9 million fatalities (According to WHO dashboards information March 1 2022). Since its discovery, the Omicron has caused an increase of infections in a number of countries and at several locations. According to WHO news the number of verified COVID19 cases in the United States surpassed one million in a single day in early January 2022. This rapid increase is consistent with the Omicron variant outbreak in the United States.

The Omicron variant has a constellation of over 50 mutations, roughly 30 of which are in the spike protein, which is the most concerning aspect of the variant. The 15 altered locations in the receptor-binding domain (RBD), which interacts with human cells before cell entry and may increase transmissibility [26], are the most concerning matter. Since the discovery of this variety in South Africa, scientists have been looking for evidence of its origin and the likely path of the unknown pandemic. Based on the examination of the Omicron and other SARS-CoV-2 variant sequences, researchers hypothesized that Omicron evolved in parallel and most likely diverged during early or possibly in mid-2020 from other strains [27]. RBD (receptor-binding domain) analysis revealed the existence of two Omicron sub-clades. Furthermore, phylogenetic analysis of 3590 SARS-CoV-2 sequences revealed the development of Omicron from the B.1.1.519 family (clade 20B) [28]. The presence of the majority of mutations in the Omicron variant in the body of an immunocompromised HIV-infected individual shows the possibility of adaptations in COVID-19 patients who are persistently infected. A contributing cause to Omicron may be South Africa's high (19%) HIV prevalence rate [26,29].

2. Origin of SARS-CoV-2 is linked with SARS-CoV and MERS-CoV

The source of origin and transmission of the infection must be identified for the establishment of therapeutic strategies to control the disease. The prior confirmed case of SARS disease was identified in Foshan, China in November 2002. Cases involving 300 health workers were reported in China in February 2003. The SARS outbreak in China later spread to other countries through infected individuals. The SARS epidemic in 2003 occurred due to a new strain of human coronavirus as it was then discovered. Some countries which came in contact with this virus were Hong Kong, Vietnam, Toronto, Taiwan, Canada and the United States [30–32]. Also, WHO issued a worldwide notice in March 12, 2003 and warned of the spread of atypical pneumonia. After 3 days, WHO coined the name SARS for the spreading virus and provided an emergency alert along with cautions and travel advisory. WHO observed air transport as one of the major reasons for its spreading throughout the world. By April 04, 2003, the WHO had recorded 2353 cases. Approximately 4 percent of SARS patients died as per the reports [33]. In literature, it was revealed that the natural

reservoir of SARS-CoV was horseshoe bats and civets and the animals sold in the China wet market that incredibly contributed to the SARS transmission from animals to humans [34]. Talking or breathing, coughing and sneezing served as common modes of transmission. SERS and MERS showed an incubation period of ~5 days and the illness was reported by more than 95% patients approximately 13 days after exposure. Severe symptoms included fever, chills, coughing and headache; while mild symptoms covered diarrhea, vomiting and nausea in the first or second week of illness. Patients who required intensive care infected with SARS-CoV were approximately 20-30%; while in the case of MERS 90-100% of the patients reported were required intensive care [30–32].

According to a report from ProMED (Program for Monitoring Emerging Diseases) submitted on September 20, 2012, a new virus called as MERS-CoV was discovered from sputum taken from a man belonging to Arabian Peninsula, who died due to pneumonia and renal failure 3 months earlier [30,35,36]. Acute respiratory disease outbreak has already happened on April 2012 in the Zarqa, Jordan, public hospital. The cause of the outbreak was unknown at the time and laboratory studies conducted shortly after the outbreak [36]. The earliest case of severe respiratory illness dated in April 2012 in Jordan hospital was subsequently diagnosed as MERS. Later, in September 2012 three MERS patients were found in the UK as well. Since 2012, MERS cases have been reported in 27 nations throughout the world but a maximum of 80% cases befell in Arabian Peninsula [30]. MERS-CoV possesses a range of similarities with zoonotic virus as evidenced from the cases of its transmission from animals to humans. WHO reported that dromedary camels worked as a source of infection either directly or indirectly [30]. By April 26, 2016, it was reported in 27 nations with 1,728 active MERS cases, 624 deaths and 34.3% mortality rate [30,36]. The major symptoms of MERS included fever, cough, and breathlessness.

SARS-CoV-2 shows a great extent of similarities to SARS-CoV in terms of their mode of transmission and symptoms and therefore it is known to have emerged as a new modified pathogen that has caused COVID-19 disease. WHO reported the outbreak of unknown cause on January 05, 2020 and the organization called for an emergency health situation around the end of January 2020 [37]. On February 11, 2020 the organization announced COVID-19 as a pandemic [1]. Like SARS and MERS, COVID-19 shows symptoms such as coughing, sneezing droplets and breathing problems (Table 1). Also, the incubation time of SARS-CoV-2 is found to be 5-6 days after transmission [1]. Although these three viruses show a great range of similarities, they exhibit unique features in terms of severity of its infection. Notably, SARS and MERS so far showed higher mortality rates in comparison to COVID-19 [37]. SARS-CoV-2 is, however, observed to be more infectious than MERS-CoV and SARS-CoV because SARS-CoV-2 infected asymptomatic individuals can transfer the virus potentially similar to symptomatic individuals. Initial analyses indicate that 79% genome of SARS-CoV-2 is similar to that of SARS-CoV but not identical at the nucleotide level. However, such changes are significantly noticed at the level of gene expression, as SARS-CoV-2 is found to possess only 72% similarity in its spike protein which is a crucial surface glycoprotein that interacts with receptors on host cells [38].

Symptoms	**Covid-19**	**Common Cold**	**Flu**	**Allergies**
Fever	Common	Rare	Common	Sometimes

Dry Cough	Common	Mild	Common	Sometimes
Shortness Of Breath	Common	No	No	Common
Headache	Sometimes	Rare	Common	Sometimes
Aches And Pains	Sometimes	Common	Common	No
Sore Throat	Sometimes	Common	Common	No
Fatigue	Sometimes	Sometimes	Common	Sometimes
Diarrhoea	Rare	No	Sometimes	No
Runny Nose	Rare	Common	Sometimes	Common
Sneezing	No	Common	No	Common

Table 1: Symptoms of COVID-19 in comparison with similar contagious diseases.

Study of Genome sequencing of SARS-CoV-2 and SARS-CoV revealed that the virus is similar to a bat coronavirus (BtCoV) RaTG13 originated from Yunnan Province in Rhinolophus with genome sequence similarity of 96.2% [39]. In addition, study reported that no recombination events occurred in the genome of SARS-CoV-2 from other bat's originated viruses. Thus, literature so far published suggested that bats might be the real host of SARS-CoV-2 [39,40]. However, more intensive research is needed to identify the possible intermediate host responsible for transmission of this virus to humans [40]. Studies reported so far reveal that SARS-CoV-2 causes excessive release of GCSF, IP10, MCPI, MIPIA, IL-2, IL-6, IL-7 and TNFα, which further lead to pulmonary edema, dysfunction of air-exchange, acute respiratory syndrome, acute cardiac injury and lastly even death. Thus, SARS-CoV-2 pathogenesis causes overproduction of immune cells and cytokine release in the lung [4].

In the middle of November 2021[41], the new OMICRON strain was discovered for the first time in the Gauteng area of South Africa. The advanced genome sequencing infrastructure in South Africa makes it easier to find novel variants early. According to WHO the new SARS-CoV-2 strain e.g. Omicron has already been detected as of 15 December 2021 in 77 different nations, in the majority of instances coming from the United Kingdom, South Africa and the United States [42]. India has also seen Omicron positive cases. According to BBC News the new COVID-19 variant's first death was recorded in the United Kingdom.

3. Symptoms, Risk factor and Transmission Rate of COVID-19

COVID-19 usually displays symptoms around 2 to 14 days after infection, informed by the Centers for Disease Control and Prevention (CDC) and WHO [43,44]. According to WHO, patients diagnosed with COVID-19 show most common symptoms such as dry cough, nausea, exhaustion and headache; other common side effects include headaches, pharyngitis, sickness, eye infections, fever, ageusia, exanthem rash and discolouration of the skin (Table 1). The severe

signs include breathing difficulty, chest discomfort and loss of voice [44]. The transmission rate of the virus is quite severe and it depends a lot on the demography and quarantine level of the infected population [43]. Infectivity is characterized as a pathogen's ability to develop an infection and it is denoted by the disease's reproductive number (R0, pronounced "R naught") [45]. SARS-CoV-2 is predicted to have a R0 of 2 to 2.5 [1]; indicating that in a population 2 to 2.5 individuals are susceptible to infection by each infected person.

COVID-19 spreads rapidly with a primary reproductive number of 2.2 to 2.5 defined in Wuhan [46,47]. However, this value estimation can vary on the basis of geography, population density and size [48]. Considering all the reports available in the literature, we have observed that the incubation period (detection time) in general for the SARS-CoV-2 is 5 days before any initial symptoms; however, it is likely that the same person can infect anyone after 2-3 days of the infection [49]. Although an asymptomatic infection is recommended to be quarantined for at least 14 days, further studies are required to determine the infectivity duration in asymptomatic cases [50]. The study recorded that during this phase 44 percent of viral infections occurred [49,51]. As per the CDC, a significant proportion of sick people with no symptoms are infectious [51,52].

On the basis of research data, WHO suggested that kids, pregnant women, cancer patients and people who are above 65 years of age are more prone in comparison to other age bracket and may unfold the sickness and transmission and further added that, since they are at higher risk to get exposed and showing symptoms, they should make sure do self-quarantine and avoid contact with others to prevent further transmission [1,52]. Studies also indicate the susceptibility of an individual towards infection of this virus based on the blood group. In a study, individuals with A blood group are found to be more vulnerable to get infected with SARS-CoV-2 [53].

According to the World Health Organization (WHO), no research has shown that the Omicron version is more severe than other VOCs (Variants of Concern). Concerns about high transmissibility, virulence, increased risk of reinfection, and decreased efficacy of existing diagnostics, vaccines, and therapies remain unsolved. Chen et al. [54] used an artificial intelligence (AI) model (TopNetmAb) to predict the effect of 15 RBD mutations on the Omicron infectivity and efficacy of current vaccinations. The analysis found that mutations at the N440K, T478K and N501Y locations may confer ten times and two times greater infectivity to Omicron, respectively, than the original SARS-CoV-2 and Delta variant. A study of 35,670 reinfections among 2.8 million positive cases in South Africa found significant population-level evidence for immune evasion from past infection. This suggests that the Omicron variation is involved in infections in people who have recovered [55]. In support of this, the Omicron (pseudotyped) construct demonstrated an ED50 of 66 when evaluated against a panel of human sera collected from convalescent COVID-19 patients, representing a 8.4-fold reduction in neutralization [56].

The Omicron version shows a 13 fold increase in infectiousness, making it approximately 2.8 times more infectious than the Delta variant [54]. The Omicron variant's basic reproductive number (R0), or the average number of additional cases created by a single infected individual, is similarly increased. The original SARSCoV2 strain has a R0 of 2-3, the Delta variation has a R0 of 5-8, and Omicron's R0 is believed to be as high as 10 [57–59].

4. Diagnostic approaches for COVID-19

COVID-19 diagnostic testing is critical to the monitoring of the virus, knowledge of its epidemiology, the reporting of case monitoring and to preventing the spread of the virus. For understanding drug repurposing, management of cases and control transmission, it is important to diagnose and trace the virus [60]. On January 17, 2020, WHO released guidelines for laboratory testing of SARS-CoV-2 suspected individuals; acknowledging the point that the worldwide unfold of COVID-19 has surprisingly redoubled the quantity of suspected cases in the geographic regions wherever testing is increased and enforced properly. Rigorous tracing and testing of COVID-19 suspects have also led to a shortfall of testing reagents worldwide and alternative molecular medicines or repurposed drugs. In addition, there are constraints of treatment capability in several regions particularly in low and medium earning countries [61]. Presently, there are multiple ways that are being utilized for testing COVID-19 suspects that are as follows-

4.1. Real time RT-PCR

In laboratories that have validated a wide range of coronaviruses using real time reverse transcription polymerase chain reaction (RT-PCR) assays, it is strongly recommended that the primers be checked against the published SARS-CoV-2 genomic sequence, as well as be tested if the primers overlap and have the capability to identify the presence of SARS-CoV-2. In order to determine the exact virus detected (e.g. on an amplicon of an unconserved region), sequencing should be performed on positive tests. On January 17, 2020, WHO suggested visualizing the primers against the revealed SARS-CoV-2 genomic sequence and observing if primers complement and have the capability to find the SARS-CoV-2 [61]. It is a nucleic acid-derived method for detection of genetic material of infectious agents, including virus, bacteria etc. This equipment is one amongst the foremost commonly used for diagnosis of the COVID-19 genome. In the past, for identification of different diseases such as caused by Ebola virus and some other viruses, several nations have used real time RT–PCR assays. Therefore, several countries require this equipment on top-priority for identifying the presence of SARS-CoV-2 and also envision making strategies to expand further their national virus examination facilities [62].

Quantitative RT-PCR is a fluorescent-based technique that helps to examine small quantities of nucleic acid in a vast range of samples. It is a promising technology used in different fields, including life sciences, agriculture, biotechnology and medical sciences which gives better results at the molecular level. It is simple to operate in conjunction with speed, sensitivity and specificity in a homogeneous assay [63]. Coronavirus possesses a positive sense RNA strand and RNA-dependent RNA polymerase enzyme which enables the virus to translate its own RNA copy by utilizing host machinery and replicate large number of complementary DNA (cDNA) as an intermediate template that helps synthesis of multiple sub-genomic mRNAs [64].

Benefits of real time RT-PCR

Due to its sensitivity, specificity, high throughput and reliable instrumentation, real time RT-PCR is used frequently for detection of COVID-19 virus. It takes approximately 3 h to obtain reliable results, although the laboratory takes between six and eight hours on average. Real time RT-PCR is considerably quicker and encompasses less possible

errors because the entire method runs within a single tube. It is proved as a reliable technique and best available methodology for testing of SARS-CoV-2 [64,65].

Drawbacks:

Detection of past infections in real time RT-PCR cannot be performed that is necessary for the analysis of the virus emergence and transmission, as pathogens are known to be available in the body for a prolonged period of time. Alternate methods to diagnose, monitor and analyze previous infections, especially those that may have transmitted the virus without signs. RT-PCR is not a blood-based test, requires too much time to test and involves collection of the sample from the throat and nasal swabs [64].

4.2. Serological test

Serological testing is very useful for confirming immunological response from a particular viral group, for example coronaviruses. The best serological test results include the collection of paired serum samples (in acute and convalescent phases) from the recovered cases [61]. CDC looks at antibody test data to determine the overall amount of persons tainted with the virus causing SARS-CoV-2 infection in the USA [66]. CDC also uses antibody testing to understand more about how the immune system in the body reacts to the virus and how the virus spreads among people who are exposed to the virus [67]. The information that CDC is investigating is taken from several sources, including blood donors of people with symptoms and COVID-19 diagnoses.

Types of serological assays

a. **Rapid diagnostic test (RDT)**

RDT is generally a compact, movable, qualitative lateral flow test that could be used at healthcare. Such procedures require fingertip blood samples, drool sample, or nasal swab fluids.

This test is somewhat common to pregnancy kit tests, because the test displays colored lines for users showing either positive or negative outcomes. Such tests most often recognize patients' antibodies (IgG and IgM) or viral antigens in the sense of COVID-19. For certain instances, it may be helpful in estimating the starting point (prior to infection) of IgG and IgM titers [68].

Antibodies are proteins that help to combat infections and typically provide protection against the recurrence of the disease (immunity). Antibody tests analyze the blood for antibodies that can determine if you have had a prior infection with the COVID-19 virus [67]. Antibodies are typically disease-specific, e.g. Measles antibodies can protect a person who is once again exposed to measles but has no effect if he is exposed to mumps [67]. CDC is evaluating commercial antibody tests, as CDC works with other government agencies to evaluate the performance of commercially produced antibodies tests [66].

b. **ELISA (Enzyme Linked Immunosorbent Assay)**

ELISA is used as a qualitative or quantitative test depending on test types required considering sensitivity and specificity. It is also known as rapid fast tests, which are only used for surveillance purposes. In this technique whole blood, plasma or serum of infected patients are required as samples. The test depends on a virus protein like spike protein or inactivated form of the virus coated on a multi-well plate. Sample is incubated in multi-well plates and eventually an antibody-protein complex is supposed to be formed, if antibodies are already present in the sample against the viral protein coated on the substrate. For the estimation, a fluorescent-labeled secondary antibody is used which produces a color change when bound with antibody-protein complex thus detecting antibodies against virus. This technique is utilized for detection of antibodies that are developed in response to SAR-CoV-2 infection [68]. In particular, an immunoglobulin G (IgG) based ELISA test is preferred and developed by various research groups across the world, which has the advantage to analyze a large number of samples in one go within 2-3 h. This test in general is characterized with 100% specificity and 98.7% sensitivity, suggesting that it can give reliable data that will indirectly confirm exposure of a person to the coronavirus [69].

c. **Neutralization assay**

Neutralizing assay is a cell culture-based method that requires growth of SARS-CoV-2 culturing cells (e.g., Vero E6 cells). This test is primarily based on observing potency of antibodies of the patient to stop viral infection of cells in a suitable culture environment. If the patient has active and effective antibodies against coronavirus, this assay can recognize the viruses easily. In this test, samples such as whole blood, plasma or serum are required from the infected patient. Neutralizing assay generally visualizes and quantifies the extent of blocking of virus replication through antibodies present in the patient serum. This blocking phenomena reveals that antibodies specifically bind to a surface moiety of the virus meant for facilitating cell entry and thus help neutralizing them [68].

d. **Chemiluminescent immunoassay (CLIA)**

This immunoassay is a quantitative biochemical technique requiring whole blood plasma or serum as patients' samples. This test is also known as chemiluminescent microparticle immunoassay due to the use of magnetic protein-coated microparticles. In this type of test, several reagents such as buffer solution, antigen-antibody complex formed by specific primary antibodies and enzyme-linked secondary antibodies which added sequentially together with the patient sample. Their binding generates a light-emitting chemical reaction. The amount of light (radiance) emitted from each sample is then utilized to evaluate the number of antibodies found in the patient sample. This test can look for several kinds of antibodies, namely IgM, IgG, and IgA. However, the drawback of this type of testing is that it cannot predict whether antibodies detected can block growth of the viruses [68,70].

4.3. TrueNat/CBNAAT based testing for COVID-19

Following initial validation of TrueNat test machines for screening of SARS-CoV-2 infected patients, the Indian Council of Medical Research (ICMR) released revised guidelines on May 19, 2020; calling the test a 'comprehensive

method for the screening and confirmation of COVID-19 cases [71]. The TrueNat system, which is a cartridge based nucleic acid amplification test (CBNAAT) and indigenously manufactured in India, was originally designed for tuberculosis diagnosis [71,72].

Working principle of TrueNat tests

TrueNat is known as the Rt-PCR series, a battery-powered and chip-based machine that uses a two-step SARS-CoV-2 detection method. The first stage is the detection of the presence of E-gene in the COVID-19 virus. E-gene allows the virus to create a spherical envelope around it. Step two recognizes the RNA-dependent RNA polymerase (RdRp) gene in the viral RNA confirms the presence of the virus. For confirmation of the existence of E-gene in the sample, RT-PCR studies can be performed. However, new systems are designed to search for the RNA-dependent RNA polymerase (RdRp) enzyme in the RNA virus. Consequently, all samples tested positive for E-gene can be confirmed in the same laboratory using a two-step test and the ICMR has determined that such test results could be seen as evidence of the existence of a new coronavirus [73].

The sample of the throat and nasal swab is extracted and placed in a viral transmission medium where it is neutralized. It is then transported to some other solvent, the viral lyse buffer, wherein the cells are broken down and the contaminants excluded. A portion of a solvent is then transported to a cartridge that appears like a disc. The process extracts the RNA in about 20 minutes. This isolated RNA is then moved to another system where the solvent is transferred into a smaller well which is connected to an electronic chip not bigger than that of the human thumb.

The RNA is activated by reagent in the miniature well, it is the chip which is loaded with all viral load data to help determine whether or not the person carries the virus. compared to traditional PCR tests, the reagents may not demand high heat in this method [74], with a smaller amount of swab required for diagnostics. The main difference seems to be that the system is portable and costs much less than the conventional RT-PCR tests [72].

5. Impact of SARS-CoV-2 on economy

The coronavirus outbreak has shown tremendous downfall in the global economy since its emergence. Lockdown was applied across the globe, which halted the economic movement. Stock markets took a global hit and the human race started finding high financial difficulty. Investors fear that the spread of the coronavirus will destroy economic growth and it has already curbed the investments funds for businesses. In response, central banks in many countries across the globe have slashed interest rates. Global markets did recover some ground when governments across the globe started to drop some decent funds in the economy for its boost. The IMF (International Monetary Fund) defined this as similar to the great depression of the 1930's. While coronavirus is said to have plunged the world into a worst-hit epidemic, global growth is projected to increase to 5.8% next year if the pandemic declines in late 2020 [75]. Technology usage across the globe saw a surge as the government urged the companies to work from home. Zoom (a video call)/meetup platform saw a massive uplift in share pricing during this period, also Netflix and amazon saw a surge in its shares. Heavy lockdown not only triggered drastic changes in economic conditions but also significantly declined the pollution level. Countries across the globe got their nature back in shape with pollution levels dropping noticeably

across the globe [75]. Now easing lockdowns in various countries are helping the economy to move better than the March to May period, and even pollution levels in different countries are coming back to normal at a gradual pace [75].

6. Mortality Rate of COVID-19

The mortality rate of COVID-19 appears to be higher than influenza. To better understand the true death rate of COVID-19 infected people it will take some time, the data available to date show that the crude mortality (the number of confirmed deaths divided by recorded case) is between 3-4%. The infection fatality rate (the number of confirmed deaths divided by the number of infections would be lower. Mortality for seasonal influenza is typically well below 0.1 percent. Mortality, however, is largely determined by healthcare access and quality available in a given country [76].

As of January 1st, 2022, India had reported over 35 million cases of SARS-CoV-2, the virus that causes COVID-19. This placed the country as the second-highest in the world for confirmed cases, behind only the United States [77]. The official cumulative COVID death count in India at the time was 0.48 million, translating to a death rate of approximately 345 per million population, which was one-seventh of the death rate in the United States [78].

However, it was widely believed that India's reported COVID death totals were underreported due to incomplete certification of COVID deaths and misattribution to other causes, as well as the fact that most deaths occurred in rural areas without medical attention [79,80]. The United Nations Population Division (UNPD) estimated that India had up to 10 million deaths in 2020, with over 3 million of those deaths going unregistered and over 8 million not undergoing medical certification. As of November 9th, 2022, the United States has reported 1,070,947 COVID-19 related deaths [81]. During the first two years of the pandemic, COVID-19 emerged as one of the top three leading causes of death in the country, ranked behind only heart disease and cancer [82,83].

The COVID-19 pandemic in 2020 and 2021 was marked by the widespread transmission of the SARS-CoV-2 virus within households, including among multiple generations, with a high prevalence of antibodies being detected. [84]. The elevated death rate from COVID-19 in India in 2021 compared to the rate observed in 2020 requires further investigation. The dissemination of the virus to rural areas is a potential contributing factor, but variations in the pathogenicity between the Wuhan strain of the virus in 2020 and the Alpha and Delta variants that dominated the 2021 wave [85], as well as changes in biological markers predictive of severe infections, may also play a role. The continuous monitoring of COVID-19 death rates is crucial in assessing the impact of the ongoing Omicron wave in India and any future viral variants that may emerge.

7. Precaution, Prevention and Treatment

Medical companies and researchers across the globe are in a race to develop medication and vaccines for COVID-19 disease. Many companies are in the clinical trial phase where they are trying to expedite the steps of the clinical trial phases. Nevertheless, for remedial and preventive measure purposes, many governments in different countries have authorized various treatment procedures as valid steps for preventive measures till the vaccine or medicine is actually developed. WHO recommended washing hands properly with soap, using a 70% alcohol-based hand sanitizer, which helps killing the viruses. When anyone goes outside then it is suggested to use proper masks and gloves that can help

avoid from getting infection as well as transmitting infection to others. Also, maintaining at least 1-meter physical distance is suggested as one of the major precautions [86].

8. Ayurveda as natural treatment

Ayurveda is a gift of mother nature and an ancient traditional method practiced in India for the treatment of human diseases and other health disorders. Various doctors and government agencies in India are recommending Ayurvedic medicines to manage pre-symptomatic and asymptomatic COVID-19 patients. Basically, Ayurvedic concept suggests that boost in immunity can lower the risk of severe infection and help fast recovery of the patients [87]. Therefore, Ayurveda suggests consuming immunomodulatory herbs, which can enhance immunity. Few suggested ways are -

1. Consume decoction once or twice a day made from Ocimum basilicum (basil), cinnamon, Piper nigrum (black pepper), Zingiber officinale (dry ginger) and raisin (kishmish).
2. Golden Milk is also useful for enhancing immunity power. For its preparation, turmeric is added in hot milk and then it is recommended to consume once or twice a day.
3. Practise drinking lukewarm water and use of common spices such as turmeric, cumin, coriander and garlic in daily food [87].

9. Homeopathy

Homeopathy is an alternative medication easy to consume with no side effects. It is believed that homeopathic medicines are able to boost immunity. The Ministry of AYUSH, Government of India released a health guideline and suggested that drugs from homeopathy and Unani could be beneficial in controlling SARS-CoV-2 infections [88]. Arsenicum album 30 of homoeopathic medicine has been suggested to be used empty stomach everyday as a prophylactic treatment against the infection for three days. Every month the same dose needs to be repeated following the same schedule [88]. However, there is no evidence that Arsenicum album 30 holds any preventive properties for COVID-19.

10. Allopathy

Allopathy refers to science based conventional medication, which is used to target the infectious agent or biological moieties for suppression of symptoms. For the prevention of COVID-19, many pharmaceutical firms have shown their promptness to come forward for manufacturing of testing kits, vaccine and drug development and assessing the effectiveness of drug repurposing. We describe below some of the medicines that are undergoing through phase I, II, III trials and a few of them are even being used as treatment alternatives alone or in combination.

10.1. Chloroquine and hydroxychloroquine

The Food and Drug Administration (FDA), USA has only approved the use of hydroxychloroquine in emergency circumstances in people diagnosed with SARS-CoV-2 who are hospitalized or clinically enrolled. It is advised to stay under doctor's supervision while using hydroxychloroquine for COVID-19 [89]. The medications presently being studied for repurposing to treat COVID-19 appear to fall into two categories: those that control the process of viral replication and those that seek to manage the disease specific symptoms. The chloroquine and hydroxychloroquine

aminoquinolines are normally taken as antimalarial medication. They are helpful in malaria to inhibit heme polymerase, which causes the parasite to accumulate toxic heme that may lead to death. In COVID-19, it is envisaged that the drugs can help avoid interaction of the virus with the host cells by blocking host receptor glycosylation and breaking down viral protein production by inhibiting endosomal acidification. Although initial studies appeared promising, various experimental flaws were noticed by the research groups. In a randomized study of thirty patients in China who were found positive for COVID-19 at the same time, it was observed that they had no benefit over the standard treatment and also hydroxychloroquine administration could not help decrease in death among hospitalized COVID-19 patients [90].

10.2. Dexamethasone

It is a low-cost steroid that is widely used. Although this matter is currently under discussion and further examination, researchers confirmed from the latest recovery study that the death rate of COVID-19 patients got noticeably decreased following dexamethasone administration. This is known as an anti-inflammatory medicine widely utilized to treat disorders wherein the body's immunity is not working normally and triggers damage. Dexamethasone significantly lowers the level of inflammation and decreases the activation of the immune function by influencing the functioning of white blood cells. Dexamethasone falls under the corticosteroids category that closely matches cortisol hormone released by adrenal glands in humans. This is widely used to treat chronic rheumatological disorders such as swelling of the muscles, irritation inside the blood vessels, persistent joint pain and immune disorders. This is generally prescribed in cardiovascular disease, dysfunction of the kidneys and skin irritations, and also to minimize swelling of the brain and spinal tumour. Corticosteroid treatment was used earlier during the SARS epidemic in 2003 to help alleviate inflammatory lung injury [91]. As a result, several countries are studying the effectiveness of corticosteroid treatment in COVID-19 acute respiratory infection patients. The WHO has listed it as a priority for the review of its clinical trials with a view to determining safety and effectiveness.

The WHO has advised for the management of viral pneumonia "under the regimen of systemic corticosteroid" in interim recommendation on COVID-19 therapy published on 27 May, 2020 [92]. However, a recent systematic examination and analysis of the effects of dexamethasone treatment on people infected with coronavirus found that dexamethasone did not lower the mortality rate, did not decrease the time of hospitalization, did not decrease the ICU admission rate and/or oxygen treatment, and had many harmful consequences [93]. In comparison, a recent study conducted by Oxford researchers, in which 2104 admitted patients received dexamethasone 6 mg for 10 days, revealed that the drug significantly reduced deaths in patients on respirator by one-third and patients on oxygen therapy by one-fifth. The drug was shown to reduce the mortality rate by 17 percent after 28 days, with an "extremely important" pattern indicating "greatest gain" in patients in need of ventilation [94]. However, the experiment did not research on patients beyond the clinical setting.

10.3. Corticosteroids

In parallel, scientists are investigating molecules to counteract the possible 'cytokine wind' in some patients which results in lung damage which causes respiratory issues. Although immunomodulators are thought to be a promising candidate for this purpose, it may have adverse downstream effects, such as raising the likelihood of certain kinds of infections. Corticosteroids are the principal of these immunomodulatory drugs being studied for COVID-19 treatment.

These drugs are well studied but are also known to be one of the most-blunt tools for immune system mutation. In addition, cardiovascular disease and the loss of bone density are associated with its long-term use. A previous meta-analysis showed that use of corticosteroids in people with flu pneumonia was correlated with high death rate [95]. Another retrospective study in China found that its use was associated with reduced death among those who developed ARDS. Various clinical studies of these drugs such as methylprednisolone and glucocorticoids are still underway [96,97]. It is also advised by the experts that a higher dosage of glucocorticoid could prolong coronavirus elimination due to immunosuppressive results. On 25 May, 2020, the Lancet released a paper stating that, "incorrect use of systemic corticosteroids can raise the risk of femoral head osteonecrosis (ONFH)" [91,98]. Osteonecrosis leads to bone tissue mortality owing to a loss of flow of oxygen. Even, the WHO suggests that regular corticosteroids must be avoided "given the lack of effectiveness and potential damage" unless they are suggested for some cause. While advising patients for its medications, it is strongly advised to consider any other health related factors, like upper respiratory infection or chronic obstructive pulmonary disease (COPD), organ failure, and specific patient peril / satisfaction assessments [92].

10.4. Lopinavir and Ritonavir

In vitro experiments have found that lopinavir and ritonavir suppress 3-chymotrypsin-like protease activity; that is why this drug is also known as human immunodeficiency virus protease inhibitor. This drug was reported to be effective against previously emerged coronaviruses; however, there is no evidence that it can work against COVID-19 as well. In China, a randomized study has been performed on 200 hospitalized patients but did not produce an effective outcome for the support of this drug combination in comparison to the standard care. According to the Journal of the American Medical Association, this drug shows some side effects such as increased nausea, diarrhea and risk of liver damage that are similar to the symptoms of SARS-Cov-2. New England Journal of Medicine published a randomized controlled study, which reveals that the drug is not beneficial to treat COVID-19 patients and therefore not helpful in recovery of SARS-CoV-2 infected patients. Another trial on mild COVID-19 patients revealed that those who were treated with lopinavir, ritonavir, IFN-B and ribavirin recovered fast, stayed for a short time in hospital and minimized symptoms noticeably, as compared to receiving lopinavir and ritonavir alone [99].

10.5. Nafamostat and Camostat

Nafamostat and camostat are approved for use against human pancreatitis in Japan. Both are inhibitors of serine protease. In an in vitro study, camostat was found to work as an antagonist to the TMPRSS2 serine protease and to be able to block SARS-CoV from reaching the host cells [12]. Researchers claimed that both compounds may have inhibiting effects on SARS-CoV-2 as well. Recent in vitro tests have displayed that both can block COVID-19 entry into cells; while a preprint study stated that nafamostat blocks the virus entry inside cells 15-fold more efficiently than camostat [100]. In the USA and Japan, these drugs are undergoing through phase II [101] and phase II/III [102] clinical trials for assessing their effectiveness against SARS-CoV-2.

10.6. Famotidine

Famotidine is known as a H2 receptor blocker [103,104] and thought to be a potential candidate for treatment of patients infected with SARS-CoV-2. In China, Michael Callahan and colleagues reported that patients taking famotidine heartburn medication seemed to be less affected or less likely to need intubation during severe COVID-19. No such peer-reviewed results was released as a preprint [103]. A randomized phase III clinical trial is being performed in New York, in which COVID-19 patients who are in critical condition were received intravenous famotidine with hydroxychloroquine, although the mode of action of the drug is unknown [105]. A virginia based biodefense consultant, Robert Malone who is working on the famotidine proposed a hypothesis that famotidine binds a papain like protease encoded by COVID-19 virus genome and recognised as a key component of viral entry into cells; however, none of the assay findings experimentally support this hypothesis [104].

10.7. Umifenovir

Umifenovir is approved as a prophylaxis for the prevention of influenza virus A and B only in Russia and China and several research groups have presumed that it has large-spectrum antiviral properties; however, there is no data available yet to assist its effectiveness against SARS-CoV-2. Umifenovir is a small indole derivative hydrophobic molecule that interacts with lipids and proteins. It targets viral lipid membranes and inhibits contact between virus and host cell; thus, preventing virus entry into target cells [106,107]. A randomized phase III clinical trial is currently being conducted for examining the efficacy, safety and tolerability of an anti-viral umifenovir drug.

10.8. Nitazoxanide

Nitazoxanide is an antiparasitic and antiviral thiazolidine drug used as a medicine for the treatment of parasitic, bacterial and viral infection. This drug acts by blocking maturation of viral capsid N protein that helps formation of viral particles. In clinical trials, it is being tested with other anti-parasitic drugs like ivermectin and also against hydroxychloroquine [108].

10.9. Ivermectin

Ivermectin is a lipophilic macrolide medication used to treat many types of parasitic infection and usually used as an anti-parasitic drug. It acts upon parasitic cell membranes, wherein glutamate-gated chloride ion channels are present; increasing the permeability of cell membrane and resulting in paralysis or death of the parasite. Scientists at Monash University in Melbourne, Australia, have observed the efficacy of this drug against COVID-19 in an in vitro experiment [109]. In addition, clinical studies ought to be performed to support its effectiveness in humans with COVID-19.

10.10. Tocilizumab and sarilumab

In clinical trials, different kinds of drugs such as tocilizumab and sarilumab that block cytokines are being tested currently. These drugs are monoclonal antibodies that serve as IL-6 receptor inhibitors and are commonly utilized in the therapy of chronic inflammatory conditions that badly affect joints and damage various body systems. A unarranged controlled trial showed very positive results [110]. Tocilizumab is the first IL-6 inhibiting antibody to be approved and has demonstrated its protection and efficacy in rheumatoid arthritis therapy [111]. Another RA-approved IL-6 receptor blocker, Sarilumab, has been studied in a multicenter, double-blind, phase 2/3 trial in hospitalized severe COVID-19 patients [112]. From affiliate Hospital of the University of Science and Technology of China and Anhui Fuyang Second People's Hospital twenty-one sufferers identified with serious COVID-19 were selected and

administered tocilizumab therapy to check whether the targeted interleukin-6 (IL-6) could possibly be an efficient and useful way to reduce COVID-19 fatalities. The outcomes of tocilizumab therapy are promising. The temperature of all patients stabilized very rapidly and the respiratory function and all other conditions got fine considerably. Of these 21 patients, 20 were stabilized and released within 2 weeks of treatment. No adverse drug reactions were reported during treatment with tocilizumab [111,113–115].

10.11. Bevacizumab

Bevacizumab is a monoclonal antibody that is normally used in various types of cancer against the signaling protein vascular endothelial growth factor (VEGF). In China and Italy, researchers are conducting clinical trials of Bevacizumab. This drug helps in suppressing tumors by inhibiting the growth of blood vessels that are supplied to the tumor. This drug is also helpful in reduction of vascular permeability and thereby lowering the volume of fluid that enters into the lungs [116].

10.12. Fluvoxamine

Fluvoxamine is an FDA-licenced antidepressant medicine utilized to cure obsessive-compulsive disorder and a better source of immunomodulation. According to an animal study, fluvoxamine in cells shuts down the inflammatory cascade from the endoplasmic reticulum when it binds to sigma-1 receptors [116]. A clinical trial is still underway at the Washington University School of Medicine in St Louis, Missouri, USA, to investigate the significance of this medicines for SARS-Cov-2 therapy [117].

10.13. Favipiravir

Favipiravir is mainly produced by Toyama chemical Co. Ltd. in Japan. Favipiravir is an antiviral medication, which is an analog of modified pyrazine used to treat influenza in Japan. Favipiravir is a pro-drug which is converted by a host enzyme into its active form ribofuranosyl-5'-triphosphate and inhibits RNA virus through selective inhibition of viral RNA-replicase. RNA-replicase helps RNA viruses for the replication and transcription to make multiple copies of its own genome. In 2014, Favipiravir was licensed for avian influenza storage in Japan and is now an alternative option for influenza strains that are resistant to neuraminidase inhibitors. Favipiravir has been approved to treat Ebola, Lassa viruses and is being used for curing SARS-CoV-2 [118–120].

On June 20, 2020 Glenmark, India issued a press release and announced that the company with the help of Research and Development team successfully developed a FabiFlu, an active pharmaceutical ingredient and formulation, and claimed that favipiravir shows 88% clinical improvement in COVID-19 and lowers the viral load within 4 days [121]. In India, the company Glenmark conducted a randomised multi-centre drug efficacy and safety study on mild to severe Covid-19 Indian patients with a standard of mixed health care vs standard of care alone. The study included one hundred fifty patients. The Chinese National Medical Products Administration licensed favipiravir as the very first anti-SARS-Cov-2 medicine in China, as the clinical study indicated effectiveness with minimal adverse effects. A retrospective, randomised, controlled, open-label, multicenter study conducted by Chen et al. included adult patients with SARS-CoV-2 [122].

11. Stem cell-based therapy for treatment of SARS-CoV-2

The emergence of severe acute respiratory syndrome coronavirus-2 in the first half of the 21st century has shaken the world and scientists. This pandemic has enforced many researchers to find solutions to overcome this situation and ensure the life of others. Many researchers and scientists from different life sciences or engineering fields are working continuously for alternative solutions and developing therapeutic approaches to bring the normal life back on track. In this direction, efforts related to stem cell-based therapy has also been found to be very positive as an efficient approach for the treatment of COVID-19 patients (Figure 2). The mesenchymal stem cells (MSCs) could be used as one of the potential strategies to prevent and cure SARS-CoV-2 infection that has recently been announced by the International Society for Stem Cell Research (ISSCR) [4,123].

Cell based experiments have currently proved to be one of the potential methods that provides treatment options for several diseases that were previously considered to be incurable. Because MSCs are safe from legal and ethical issues and have a great potential to make a copy of itself within a short time and less invasiveness, MSC therapy is preferred over alternative therapies. MSCs can be derived from a broad variety of adult tissues, including bone marrow, adipose tissues, dental pulp, neonatal birth-associated tissues, placenta (PL), umbilical cord (UC), Wharton jelly (WJ), amniotic fluid (AF), cord blood (CB), fetal liver and bichat fat pads, etc. Mesenchymal stem cells are known to be multipotent in nature and generally stored for future possible therapeutic purposes. Also, no unfavorable reaction towards allogeneic MSCs has been seen in the clinical trials of MSCs therapy [4].

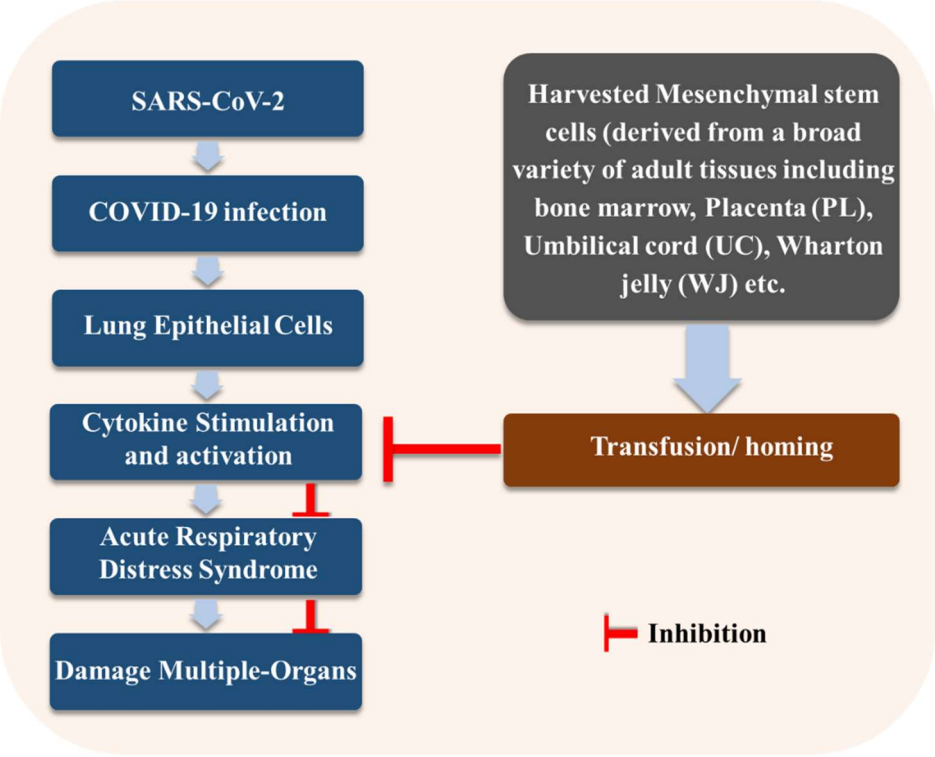

Figure 2. Stem cell-based therapy as an efficient approach for the treatment of COVID-19 patients.

MSCs are opposed to viral contamination due to the existence of enhanced quality of particular cytokines. These features are present in the inner niche of the MSCs prior to the separation process. Therefore, even if grafted to a recipient with verified SARS-CoV-2, MSCs may be expected to survive. The concept of MSC therapy in patients with COVID-19 is therefore promising (Table 2). MSC therapy is inclined to prevent the inflammatory processes by the body's defense system and facilitate intrinsic reconstruction by the regenerative qualities of the stem cells [4]. After injecting directly into the vein, some of the MSC population is considered to be trapped in the lungs, sometimes referred to as a restriction of systemic infusion. Nevertheless, these MSCs can restore the lung microenvironment, shield epithelial cells, stop lung damage, and treat pulmonary impairment and SARS-CoV-2 infection [4]. The key limitations of this therapy is the availability of therapeutic grade MSCs. As a result, MSCs could be the ideal candidate for research studies or beneficial strategies for curing patients infected with coronavirus-2 [4,13].

Clinical trial number	**Diseases**	**Cell type as a treatment**	**Phase**	**Reference**
NCT04336254	COVID-19	Allogeneic human dental pulp stem cells	Phase I/II	[124]
NCT04366323	SARS-CoV-2	Allogenic and expanded adipose tissue-derived mesenchymal stem cells	Phase I/II	[125]
NCT04366063	SARS-CoV-2	Mesenchymal Stem Cell	Phase II/III	[126]
NCT04392778	COVID-19 Pneumonia Multiple Organ Failure Corona Virus Infection	Mesenchymal Stem Cell	Phase I/II	[127]
NCT04355728	Corona Virus Infection ARDS Human Acute Respiratory Distress Syndrome	Umbilical Cord Mesenchymal Stem Cells	Phase I/II	[128]

	COVID-19			
NCT03042143	Acute Respiratory Distress Syndrome (ARDS)	Human umbilical cord derived CD362 enriched MSCs	Phase I/II	[129]
NCT04288102	Corona Virus Disease 2019 (COVID-19)	Human Umbilical Cord-derived Mesenchymal Stem Cells	Phase II	[130]

Table 2: List of some clinical trials using stem cells for the treatment of COVID-19 patients.

Clinical trials have recently started in the United States, China, Jordan, Iran and several other nations, and some reports have also been released. In particular, mesenchymal stem cell (MSC) therapy has been widely used for the curing of diabetes mellitus, autoimmune disorder, nerve damage and many different illnesses [4]. The immunomodulatory properties and differentiating ability of MSC are therefore intended to stop the dying of pulmonary tissue by combating cytokine storms and helping to restore and restructure damaged tissues. Clinical treatment of avian influenza with alike consequences on the lungs by the use of these cells has recently been shown in the study [131]. Similarly, a recent case study in a woman suffered with acute SARS-CoV-2 infection in China has shown that her laboratory tests and CT images have improved significantly after 21 days of curing with funiculus umbilicalis MSCs [4,132]. In one other study, the patient was medicated with lopinavir/ritonavir drugs which stops the growth of virus, and also with moxifloxacin, xuebijing, and methylprednisolone injected directly into veins, which resulted in an 87% rise in neutrophil and a decrease of 9.8% in lymphocyte. The infected person was also exposed to non-invasive mechanical ventilation due to insufficient oxygenation to improve respiration and alleviate muscle fatigue. The infected person was treated with MSC cord and with 5×10^7 thymosin α1 cells every 3 times as vital symptoms worsened. The test results showed that blood albumin, C-reactive protein and aspartate transaminase/alanine transaminase decreased gradually after the second dose and in parallel this improved life-sustaining signs. Subsequently, the infected person was discharged from the life support machine and found to be able to move. And, the amount of WBCs and neutrophils in the infected person got lowered to usual, whereas the amount of immune cells continued to increase to average. More significantly, the number of immune cells increased dramatically. In addition, qualitative studies obtained from CT scans pictures during the second and third intravenous administration of umbilical cord stem cells have shown that respiratory disease could have been somewhat relaxed. Subsequently, after the third injection the patient was released from the intensive care unit and most of the essential standards like pulse rate, heart beat etc. were fine. The findings indicate that umbilical cord mesenchymal stem cells therapy can be used as an option for SARS-CoV-2 infected person, either separately or with other immune modulators [4,132]. Mesenchymal stem cells have the potential to alter the behavior of immune cells [133]. In another recent research conducted in China in alliance with the USA, from January 23 to February 16, 2020 in Beijing Youan Hospital, 7 patients with COVID-19 pneumonia when experienced

mesenchymal stem cell transplantation improved their health outcomes and normalization in the immunological profile [13]. Furthermore, genetic analysis of MSCs suggests that they are ACE2- and TMPRSS2-; revealing that MSCs cannot directly interact with SARS-CoV-2 [13]. Studies therefore suggest that mesenchymal stem cells could be secure and beneficial in the treatment of infected persons with SARS-CoV-2 pneumonia, particularly people with extremely serious illnesses.

12. Some of the potential vaccines which are under research, test and trial

There are many companies that are developing vaccines against coronavirus alone and some in collaboration. Those vaccines which are currently under test and trails are as follows:

i. The National Institute of Allergy and Infectious Diseases (NIAID), USA conducted a trial and review preliminary phase 1 results for mRNA-1273 vaccine called mRNA-1273 and Moderna, company announced and published satisfactory positive interim phase 1 results for mRNA-1273 against COVID-19. [134]. On July 27, 2020 phase III trial begin in collaboration with NIH (National Institute of Health) and BARDA (Biomedical Advanced Research and Development Authority) [135] and 30,000 participants enrolled in the study received 1 intramuscular (IM) injection of 100 micrograms (ug) mRNA-1273 on Day 1 and Day 29, and some participants received 1 IM injection of mRNA-1273-matching placebo on Day 1 and Day 29 [136]. On November 16, Moderna informed that in the first interim review of the Phase 3 COVE trial, mRNA-1273 reached its primary efficacy endpoint with a vaccine efficacy of 94.5 percent [135].

ii. The Jenner Institute at Oxford University developed AZD1222 (formerly ChAdOx1 nCoV-19), with AstraZeneca in charge of production, processing and marketing globally. A Phase I / II clinical trial of AZD1222 began in April 2020 to determine the vaccine's safety, immunogenicity, and efficacy in over 1000 healthy volunteers across multiple trial centers in southern England [137]. Total 23,848 participants were enrolled between 23 April and 4 November 2020 and in the interim primary efficacy assessment 11,636 participants were included (7,548 in the UK, 4088 in Brazil). Vaccine efficacy was 62.1 percent in participants who received two standard doses (95 percent CI 41.0–75.7; 27 [0.6 percent] of 4440 in the ChAdOx1 nCoV-19 group vs71 [1.6 percent] of 4455 in the control group) and 90.0 percent in participants who received a low dose followed by a standard dose [138]. The overall effectiveness of the vaccine in both groups was 70.4 percent. ChAdOx1 nCoV-19 has an appropriate safety profile and is effective against symptomatic COVID-19 in this interim study of ongoing clinical trials [138].

iii. "Ad5-nCoV" is a recombinant new coronavirus vaccine (Adenovirus Type 5 Vector) developed and approved by Biologics Inc. with the Beijing Institute of Biotechnology (BIB), perform a Phase 1 clinical trial in China. The first-in-human study in 153 healthy adults showed that the Ad5nCoV vaccine is tolerable and immunogenic. After post-vaccination on day 28 it showed specific antibody mediated immunity responses to coronavirus-2019 and on day 14 observed rapid T-cell response [139]. A global phase III clinical trial begins on 15 September 2020 involving 40,000 healthy adults' aged 18 years and older participants to examine the

efficacy, safety and immunogenicity of Ad5-nCoV developed by the Cansino and Beijing Institute of Biotechnology. Immunization protocol is one dose of intramuscular injections (deltoid) [140].

iv. INO-4800: Inovio Pharmaceuticals was the first to carry out a human evaluation of its MERS-CoV 151 related coronavirus vaccine (INO-4700) [141] and for prevention of COVID-19 infection company developed a DNA vaccine (INO-4800). Inovio also performed an open-label trial [142] in healthy adult volunteers by using a CELLECTRA ® 2000 device to evaluate the effectiveness, tolerability and immunological profile of INO-4800 delivered by intradermal (ID) injection accompanied by EP. A Phase 2/3 randomized, blinded, placebo-controlled study begins on November 30, 2020, with 6578 participants enrolled to determine the safety, immunogenicity and efficacy of INO-4800, a prophylactic vaccine against COVID-19 disease, injected intradermally with electroporation in healthy seronegative adults at high risk of SARS-CoV-2 exposure [143].

v. NVX-CoV2373: Novavax, Inc. announced the commencement of clinical trial phase I/II for the development of coronavirus vaccine, NVX-CoV2373, a robust prefusion protein produced using its patented nanoparticles adjuvant (Matrix-MTM) technology to boost immunity and trigger high level of antibody neutralization. In the southern hemisphere, a first human trial to be carried out, with approximately 130 participants spanning two Australian locations [144]. A Phase 3 trial begins on December 27, 2020 enrolled 30,000 participants with mild, moderate, or severe symptomatic coronaviral disease, 2019 (COVID-19). This trial will focus on body immune response, safety of SARS-CoV-2 rS with Matrix-M1 adjuvant in participants. The enrolled participants in the trial will be randomised to receive SARS-CoV-2 rS with either Matrix-M1 adjuvant or placebo. A total of 2 intramuscular injections will be given to each of the participants in the study [145].

vi. LV-SMENP-DC and pathogen-specific APC vaccine developed by Shenzhen Geno-Immune medical institute that is in phase 1 clinical trials to determine security, effectiveness and immune response [146,147].

vii. For the development of an investigative vaccine against COVID-19 Merck has announced a collaboration with the International AIDS Vaccine Initiative (IAVI), using recombinant vesicular stomatitis virus (rVSV) technology, which forms the framework for its Ebola Zaire Virus (Ervebo) [148]. A randomised, placebo-controlled, double-blind study is being performed at seven locations in the U.S. and will involve up to 252 participants aged 18 and up, including adults [149].

viii. BNT162: Pfizer Inc. & BioNTech SE reported that in the phase I/II clinical trial for the BNT162 vaccination system to combat COVID-19, the first patients were administered in the U.S. [150]. Another mRNA vaccine (BNT162) approved for clinical trial phase 1/2, has been produced collaboratively by BioNTech and Pfizer to evaluate the appropriate dose for further studies and to assess the safety and immunogenicity of the vaccine [59]. A Phase I/II trial, 2-Part begins on September 9, 2020, sequentially administering increasing doses of an investigational drug to examine the safety and immunogenicity of prophylactic SARS-CoV-2 RNA vaccine (BNT162b3) against COVID-19 utilizing different dosing protocols in healthy adults [150].

ix. The India's first indigenous COVID-19 ‘COVAXIN’ vaccine developed by city-based Bharat Biotech in partnership with ICMR and NIV, has received the nod from India's Drug Controller General for human clinical trials, the company said on June 29, 2020. The phase I/II clinical trials of the SARS-CoV-2 vaccine, which were approved after pre-clinical studies showed safety and immune response, would begin nationwide

in July, 2020 [151]. Following the successful completion of the interim phase 1 & 2 clinical trials of COVAXINTM, Bharat Biotech enrolled 26,000 participants after getting DCGI clearance for phase 3 clinical trials over 25 centres across India [149].

India has completed 1 billion vaccine doses and is now capable of testing approximately 1 million samples each day. Existing Virus Research Diagnostic Laboratory for viral diagnosis and INSACOG labs for genome sequencing are already in place to identify and monitor the present Omicron or any novel variant. Early and active surveillance, as well as whole-genome sequencing, will aid in understanding circulating variants and tracing their progression. According to the COVID-19, appropriate behaviour such as social distance, hand hygiene, mask use, and vaccines remain the most important elements in viral transmission management.

13. Immune responses in human body against SARS-CoV-2

Pathogenic cell infection can cause development of humoral and cellular immunities in the host, which are important for removing the viral infection [152]. However, uncontrolled or ineffective immune reactions can cause adverse effects to the patients [153]. New immunotherapies will be created by proper understanding of the immune response caused by infection with SARS-CoV-2, along with reducing the possible risk of inflammation [152]. About 80 percent of COVID-19 infected people record moderate to negligible side effects, taking into account of immunopathological aspects [5,6]. In severe COVID-19 cases, patients suffering from lymphopenia and interstitial pneumonia have elevated levels of proinflammatory cytokines, including interleukin-10 (IL-10), interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-7 (IL-7), colony-stimulating factor-3 (CSF-3), interferon gamma-induced protein-10 (IP-10), monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1 (MIP-1), macrophage inflammatory protein-1 alpha (MIP-1α) and tumour necrosis factor alpha (TNFα) [5]. Immune cells and their subsets play a vital role in the process of protecting from infected cells [5]. Mild SARS CoV-2 infection can lead to neutralizing antibodies, sufficient immune cell response and rapid viral clearance, whereas severe SARS CoV-2 infection can induce serious illness and delayed viral clearance [154] (Figure 3). Due to viral infectious diseases, immune cells like lymphocyte subsets may also be dysfunctional [155–157]. Innate immune response and cell-mediated immune response against viral infection involve the following cells: CD3 +, CD4 +, CD8 +, CD16 +, CD56 + and CD19 + label T-helper cells (CD4+CD3 +) and T-cells (CD3+CD8 +), B cells (CD19 +) and natural killer cells (CD16+CD56+) [155]. Many studies are currently identifying the adverse effect of COVID-19 infection on immunity and immune cells. Most of these have revealed that infected people develop an uncontrolled immune response during the infection, triggered by highly active macrophage and monocytes [5,158]. Recently several epitopes have been reported through immuno-informatics, including 5 CTL epitopes, 3 sequential B cell epitopes, 5 discontinuous B cell epitopes of immune cells [4,159], and 13 MHC-I and 3 MHC-II antigenic epitopes [4,160], and some of these epitopes are expected to help in manufacturing of potential vaccine for COVID-2019 [4].

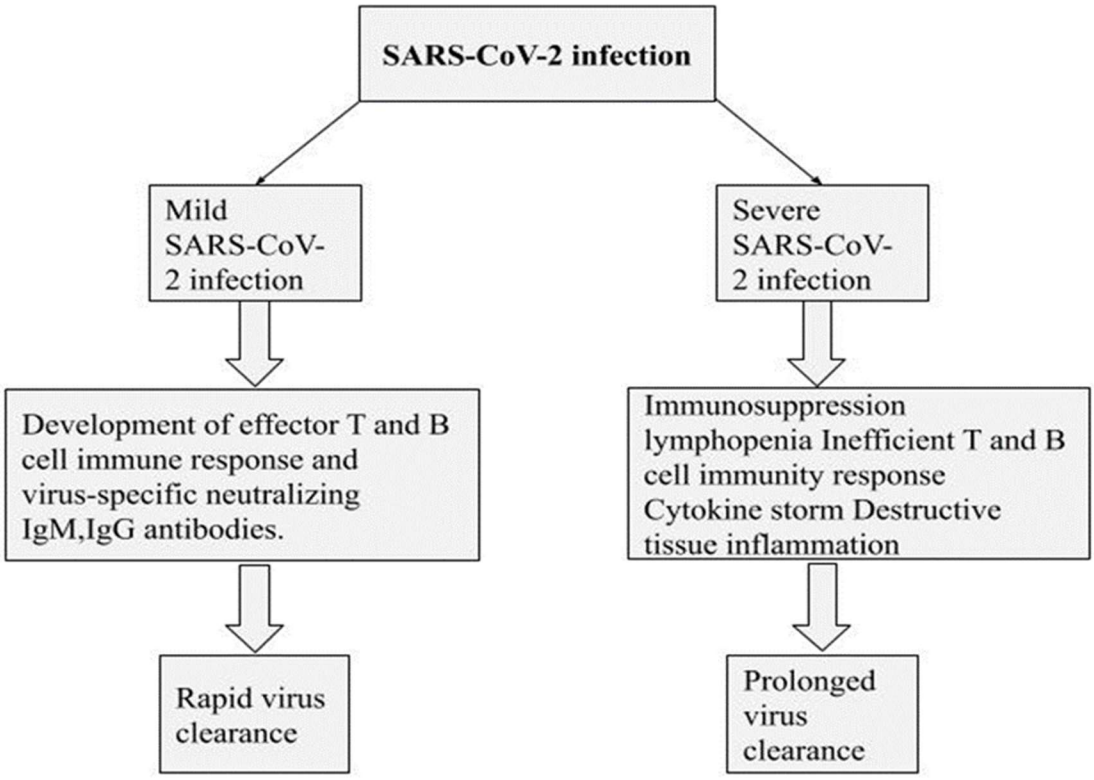

Figure 3. Distinct responses to mild and severe SARS-CoV-2 infections.

Response of T-cell and B-cell

Immune cells such as T-lymphocytes for antibody-independent directed immunity and B-cells for antibody-mediated immunity play a significant role in the adaptive immune response to all viral infections. Nonetheless, helper T lymphocyte activation of Th1 / Th17 results in alleviation of the inflammatory effect, while the production of specific SARS CoV-2 antibodies are processed by B lymphocytes for virus neutralization [5,161]. After reaching the host, the virus binds and invades the cells expressing its special replication receptor. The human leukocyte antigen (HLA) system such as class I and class II display viral antigenic peptides to appropriate T-cells such as CD8+ and CD4+. Class II HLA system is represented only on professional antigen presenting cell (APC) such as dendritic cells and/or macrophages [161] to display processed antigenic protein or whole viruses to helper T-lymphocyte CD4+ molecule [154,162]. In the case of COVID-19, once the coronavirus is within the lung epithelial cells, viral peptides are introduced to CD8+ cytotoxic T cells by means of Class I major histocompatibility complex (MHC) proteins, followed by Class II major histocompatibility complex (MHC) with larger peptides [154,163,164]. When CD8+ cells start dividing and showing clonal expansion, virus-specific effectors and T-cell memory get developed. Cytotoxic T-cells that express CD8+ receptors are lysed with tissue cells infected with the virus. B cells can interact with CD4+ T cells and can directly recognize and activate viruses. In the first week of symptoms, IgM isotype primary virus-specific antibody response is observed [154,164].

After dealing with study of past events or situation of COVID-19 patients, the outcomes displayed a significant reduction in total lymphocyte counts, B lymphocytes, Natural Killer (NK) cells, CD4+ and CD8+ T cells [154,155,165,166], particularly in patients requiring emergency unit. Patient survival was inversely associated with total T cells, cytotoxic T-lymphocytes (CD8+) cells, and helper-T lymphocytes (CD4+) cells below 800/μL, 300/μL and 400/μL respectively. T lymphocytes counts were inversely correlated with concentrations of serum interleukin-6, interleukin-10, and tumor necrosis factor-alpha (TNF-α), with patients showing reduced concentrations of interleukin-6, interleukin-10, and tumor necrosis factor-alpha, and restored T lymphocytes counts during disease resolution period. T-lymphocytes are found to have substantially greater levels of the depleted PD-1 marker in the infected patients. As the patients' condition worsened from prodromal to excessively symptomatic, increased levels of programmed cell death protein 1 (PD-1) and HAVCR 2 (Tim-3) were seen in T-lymphocytes [166,167].

Cytotoxic T-cells are essential for enabling virus removal after many acute pulmonary infections. Therefore, it is believed that combined activation of virus-specific cytotoxic T-lymphocytes (CD8+) and antibodies would provide optimum immune defense. Moreover, cytotoxic T-cells (CD8+) provide protection from secondary infections [154,155,168]. In the recovered patients, virus-specific helper T-cell (CD4+) responses have more frequent evidence than virus-specific cytotoxic T-cell (CD8+) responses, whereas pre-existing helper CD4+ T-cell responses to other coronaviruses are also found in patients without SARS-CoV 2 exposures [169,170]. In extreme cases, the mechanisms for a significant decrease in lymphocytes remain unexplained. The type of death of lymphocytes in COVID-19 should be thoroughly investigated [154].

Response of Antibodies

As of today, the convalescent plasma of more than one million patients has been considered clinically appropriate for treating infected patients with SARS-CoV-2, which provides passive immunisation. It is significant to mention that if a patient with severe pneumonia is found to have a heavy virus load, convalescent serum containing virus-specific immunoglobulin G1-, immunoglobulin G2- and immunoglobulin G3-type antibodies, that induce local injury in the lung via complement activation and maximize damages of tissues, is observed. Immunoglobulin G4 must be context specific for treatment for such cases, as no additional activating properties have been identified to date [154,171]. At the onset of initiation of infection in COVID-19 patients, total antibodies (IgA, IgG, and IgM) and complement (C3/C4) protein levels were found within the normal range [154,158]. However, high concentrations of IgG or IgM antibodies to COVID-19 N protein or receptor binding domain (RBD) were observed after infection of 10 days or later. A typical antibody response is an early increase in IgM followed by a noticeable increase in IgG after a few days. However, the serum level of the common IgG can be identified by shooting up earlier than that of IgM against SARS-CoV-2 [154,172]. These results have shown that, due to the presence of other coronaviruses, cross-reactivity of antigen with existing specific IgG may not be useful for the detection of COVID-19 [154]. In different studies, COVID-19 virus-specific IgG and IgM antibodies were found to reach their peak levels in 17-19 days and 20-22 days after the appearance of symptoms. Another observation was that in the serious COVID-19 category the IgG and IgM titers were relatively higher than the non-serious category [172,173]. It is widely recognized that during viral infection IgM provides the first line of protection compared to the high affinity IgG which provides long-term immunological memory and immunity

[5]. The presence of IgM in the serum indicates the recent interaction with the virus, while the presence of IgG implies the interaction that occurred a few days ago. Nonetheless, there is still a lack of in-depth information on the human defense system's response to novel coronavirus infection, most of which relies on information obtained during the most recent outbreak of coronaviruses such as SARS 2002 and MERS 2012 [76,161].

14. Vaccines associated antibody dependent enhancement (ADE)

The development of antibodies following a vaccine is typically regarded as a positive result. Antibodies (from immunizations or by recovering from a past infection) are essential for our immune systems to fight a virus effectively. When we produce antibodies to a disease, our immune system can sometimes overreact the next time when we are exposed to the disease. This is a highly uncommon condition known as ADE (Antibody-Dependent-Enhancement). The antibodies involved in ADE do not aid the body's immunological response and may even exacerbate it. When a person is infected, ADE raises the likelihood that they may develop severe disease symptoms. Antibodies that cause ADE behave like a "Trojan horse," allowing the virus into the cells and activating the immune response. They allow the virus to bind to our cells, resulting in inflammation and an increased immunological response. Nevertheless, there have been no confirmed reports of ADE caused by COVID-19 vaccinations.

The virus particles adhering to the cytoplasmic membrane on the cell surface, where viral surface proteins attach on the host cell with specific receptors, is the first step in viral infection [174]. Antibodies that particularly target viral surface proteins are released to prevent viruses from attaching to target cells. These antibodies bind and destroy the viruses, reducing their infective ability. In some viruses, antibodies instead of binding to viral surface proteins can promote viral invasion into specific cell types and hence maximize viral infection [174]. This effect is referred to as antibody-dependent enhancement (ADE) [175]. ADE happens both ways: (1) when a pathogen specific antibody facilitates entry of virus into phagocytic cells (macrophages, monocytes and granulocytes) and (2) when it enhances infection in cells via contact with the Fc receptor (FcR) and/or complement receptor. In most circumstances, enhancing viral attachment to target cells is critical. Over 40 different viruses have been found to have ADE. There are a range of antigenic determinants (epitopes) in these viruses, some of which trigger neutralizing antibodies and others which induce enhanced antibodies [174]. Conventional vaccinations have only had a minor preventive and therapeutic effect on these viruses [176] and in some cases they have been proven to increase the susceptibility of those who have been vaccinated. The likelihood of ADE i.e. antibody dependent enhancement in Covid-19 making the severity conditions worsen cannot be completely ignored; and this is considered one of the major threats around antibody based vaccines and treatments [177]. Two Viruses, RSV (respiratory syncytial virus) [178,179] and measles [180,181] can go in worse states by antibody-dependent enhancement (ADE) that makes it risky. Increased respiratory disease (ERD) is a broader category that includes ADE in it, and non-antibody-based processes such as cell-mediated immunopathology and cytokine cascades are part of ERD [177]. Often, when viral replication is boosted, then macrophage-infecting viruses, such as dengue virus [182,183] and feline infectious peritonitis virus (FIPV) [184], have been observed to produce ADE. SARS-CoV and MERS-CoV have both been closely linked with ADE and ERD in both vitro and in vivo, also the role and impact of ADE in the immunopathology of COVID-19 remain to be explored [177].

14.1 ADE in human coronavirus infections

There is no conclusive evidence that ADE has a role in human coronavirus illnesses. Concerns regarding ADE were raised when seroconversion and neutralizing antibody responses were found to correlate with clinical severity and mortality in SARS patients [185]. According to the findings in COVID-19 patients, with greater SARS-CoV-2 antibody titers being linked to more serious illness [186]. Increased antibody titers in chronic COVID-19 patients are thought to be the result of more and longer antigen exposure due to increased viral loads [187,188]. A new analysis showed that asymptomatic and symptomatic COVID-19 [189] individuals had similar viral shedding in the upper respiratory tract. Anti-SARS-CoV-2 antibody titers were noticeably higher in symptomatic people and they cleared the virus from the upper respiratory tract faster, refuting the idea that higher viral loads cause higher antibody titers. According to other studies, anti-SARS-CoV-2 T-cell responses were seen at high levels in both symptomatic and asymptomatic infections [170,190]. The data suggest that patients with a broad range of clinical symptoms can have potent T-cell responses, although high antibody titers are more strongly linked to chronic COVID-19. The fact that viral shedding was discovered in the upper respiratory system rather than the lower respiratory tract is a critical issue [189]. The lower respiratory tract is likely more critical for severe COVID-19 lung pathology, and it's unclear how closely SARS-CoV-2 viral shedding in the upper and lower respiratory tracts correlates with chronic infection [177]. Apart from the host response to specific SARS-CoV-2 illnesses, another potential worry is the probability of pre-existing antibodies against other human coronavirus strains triggering ADE in COVID-19 patients [191]. In human antibodies elicited by endemic coronavirus variants (like OC43, NL63, 229E, and HKU1) could potentially enhance ADE by increasing SARS-CoV-2 cross-reactive identification in the lack of viral neutralization. According to early findings, antibodies (with high reactivity) from SARS-CoV-2-naive donors to seasonal human coronavirus strains showed slight cross-reactivity against the nucleocapsid and S2 component of SARS-COV-2 [192]. It would be interesting to know if such cross-reactive antibodies have a role in SARS-COV-2 triggered ADE.

14.2 Mechanisms of ADE (Antibody Dependent Enhancement of Coronavirus)

ADE can be triggered by a number of different molecular pathways. According to one concept, the complex of antibody/Fc-receptor mimics viral receptors in function, allowing some phagocytic cells to engage in expanded host cell trophism [193]. Wan et al. show that antibody dose has an effect on whether a virus promotes disease or suppresses it. Antibodies to one virus strain are reported to be sub-neutralizing or non-neutralizing for viral infections of other variants [182,194,195]. Infected cells expressing Fc-gamma were shown to be infected with SARS-CoV-1 [196]. A case of ADE was detected in a patient who had a second SARS-CoV-2 infection [197]. ADE has been demonstrated to arise in viral infections via two different ways: FcR-mediated ADE is the first mechanism. FcRs are receptors that target the Fc regions of antibodies and mostly found on immune cells. Enhanced antibody-mediated virus intake into Fc gamma receptor IIa (FcRIIa)-expressing phagocytic cells leads to an increased viral infection and replication or increased antibody Fc-mediated effector activities or immune complex creation; thereby resulting in increased inflammation and immunopathology.

Both ADE processes can happen when non-neutralizing antibodies or antibodies with sub-neutralizing levels latch to viral antigens without suppressing or clearing infection. In vitro assays (more frequently performed for the first mechanism, which involves FcRIIa-mediated enhancement of infection in phagocytes), immunopathology, or pulmonary pathology can all be used to detect ADE. For macrophage-tropic viruses such as dengue virus in humans [198] and FIPV in cats [184], ADE via FcRIIa-mediated endocytosis into phagocytic cells has been reported and intensively studied in vitro. Non-neutralizing antibodies or binding antibodies bind to the surface of the virus and transport virions to macrophages, which uptake the virions and get infected. According to a recent dengue vaccine trial, because many antibodies against different dengue serotypes are cross-reactive but non-neutralizing, repeated infections with heterologous strains can result in increased viral multiplication and more severe disease, offering considerable safety risks [182,183]. Cats immunized against the FIPV S protein or passively infused with anti-FIPV antibodies outlived control groups when challenged with FIPV in other vaccination studies [199].

Spreading of the infection, severe symptoms and resulting in more dangerous sickness outcomes [200] could be caused by antibodies which have sub neutralizing levels or non-neutralizing antibodies. These antibodies have shown capabilities to promote the entry into alveolar and peritoneal macrophages which support in this spread and worsening of sickness [201]. Antibody effector functions which are Fc-mediated can intensify respiratory sickness that leads to detectable and intensified lung damage by establishing a robust immunological reaction in the second known ADE mechanism, this is defined more perfectly as a respiratory infection [202,203]. Fc-mediated activation of local and circulating innate immune cells such as monocytes, macrophages, neutrophils, dendritic cells, and natural killer cells, despite their potential efficacy in removing virus-infected cells and debris, may result in overactive inflammatory responses. Non-neutralizing antibodies have been shown to cause ADE and ERD in non-macrophage tropic respiratory viruses like RSV and measles by forming immune complexes that accumulate in airway tissues and initiate cytokine and complement mechanisms, resulting in infection, respiratory failure, and, in extreme cases, acute respiratory distress syndrome [178,180,204,205].

These prior observations of ADE with RSV and measles are strikingly identical to the clinical symptoms of COVID-19. In COVID-19 and SARS, for example, over-activation of the complement cascade has been shown to lead to inflammatory lung injury [206,207]. S- and RBD-specific immunoglobulin G (IgG) antibodies in COVID-19 patients have lower levels of a fucosylation within their Fc domains, according to two current studies [208,209], a phenotype linked to higher affinity for FcRIIIa. Increased affinity can be beneficial in some instances due to more robust FcRIIIa-mediated effector responses[210,211], while afucosylated non-neutralizing IgG (immunoglobulin-G) antibodies against dengue virus were linked to worse clinical outcomes [212]. Larsen et al. also discovered that patients with COVID-19 and acute respiratory distress syndrome had lower S-specific IgG levels than those with asymptomatic or moderate illnesses [209]. It's unknown if decreased fucosylation of SARS-CoV-2-specific antibodies caused COVID-19 immunopathology. SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2), on the other hand, has not been shown to infect macrophages in a productive manner [213,214]. As a result, the available evidence suggests that the most plausible ADE

mechanism related to COVID-19 disease is the creation of antibodies–antigen immune complexes, which results in immune cascade hyperactivation in lung tissue.

Early immunization findings reveal substantial antibody responses by day 14 [215], indicating memory B-cell responses with cross-reactivity antibodies from different coronavirus variants (s). For both SARS [216] and COVID-19 [188,217–221] early high antibody responses are associated with higher illness severity. Wu et al. found that antibodies from COVID-19 patients allowed SARS-CoV-2 infections of Raji cells (lymphoma cells derived from B lymphocytes), K562 cells (derived from monocytes) and primary B cells [222]. Infection of some phagocytic cells (macrophages) with SARS-CoV-2 may be a significant step in illness development for some patients.

14.3 Vaccine associated Antibody-Dependent Enhancement (ADE) risks-

Virus vaccine manufacturing can be done by using live-disarmed virus strains, inactivated (dead) virus, protein components, messenger ribonucleic acid (mRNA) and/or deoxyribonucleic acid (DNA). Vaccines produce antibodies which can fall either in the neutralizing category or non-neutralizing category. We have three known possible processes to support non-neutralizing antibodies in its role towards antiviral activities, they are (CDC) i.e., antibody-mediated complement-dependent cytotoxicity, (ADCC) i.e., antibody-dependent cellular cytotoxicity, and ADCP i.e., antibody-dependent cellular phagocytosis [223]. Against the strains of vaccines and various other closely linked strains, annual influenza vaccine is highly useful as it provides protection by producing neutralizing as well as non-neutralizing antibodies.

Vaccine-associated enhanced disease (VAED) can occur when a virus has many circularizing serotypes [e.g., Dengue fever [182,194,195], or when the virus leverages antibodies for increased host cell trophism of phagocytic immune cells. Cell membrane fusion processes are seen in many viruses implicated to ADE [224]. Vaccine-induced cross-reactive anti-HA2 antibodies expedite viral fusion in a pig model of influenza A H1N1, resulting in vaccine-associated increased respiratory disease (VAERD) [225]. The respiratory syncytial virus (RSV) caused ADE in the Bonnet monkey model [226]. Van Erp et al. advised against producing respiratory syncytial virus (RSV) non-neutralizing or sub-neutralizing antibodies in order to avoid ADE. ADE has been observed in a number of SARS-CoV-1 animal models. Attempts to produce SARS-CoV-1 vaccines in a mouse model resulted in pulmonary immunopathology after SARS-CoV-1 problem [227,228]; these vaccines included inactivated whole viruses, inactivated viruses with adjuvant and a virus-like particle (VLP) vaccine containing a recombinant DNA spike (S) protein vaccine. Animals immunized with nucleocapsid protein suffered severe pneumonia after being exposed to SARS-CoV-1 [229].

A vaccine comprising recombinant modified vaccinia virus Ankara (rMVA) expressing the SARS-CoV-1 spike protein exacerbated hepatitis in a ferret model [230]. In rhesus macaques, vaccination with SARS-CoV-1 resulted in ADE [176]. SARS-CoV-1 ADE is mediated by spike protein antibodies [231]. Antibodies to the SARS-CoV-1 spike protein can facilitate viral entry via Fc receptor-exposing cells in a dose-dependent manner [193]. Because Fc mediates infection of immune cells, Jaume et al. [232] pointed out the potential downsides of vaccines against SARS-CoV-1 spike protein. As a result, future attempts to develop SARS-CoV-1, MERS-CoV [233], or SARS-CoV-2 vaccines could increase the danger of causing ADE in people, which is increased by antibody infection of phagocytic immune cells. This possible ADE risk is independent of the vaccination technique [234] or targeting strategy selected, due to anticipated phagocytic

immune cell infections upon antibody absorption. In MERS patients, the rate of seroconversion increased as the disease progressed [235]. Severe clinical worsening for SARS patients occurs concurrently with timing of IgG seroconversion [236]. In SARS patients, early high immunoglobulin-G (IgG) responses are linked to illness progression [237] and seriousness [217–221,238]. Antibody therapy for severely ill COVID-19 patients has been halted due to a potential safety signal and an inadequate risk-benefit profile [239]. With high antibody titers, the existing COVID-19 vaccinations appear to give protection; however, the possibility of ADE risks associated with declining antibody titers over time is unknown.

14.4 The future management for ADE in coronavirus

According to preliminary studies, ADE in coronavirus illness can be treated in a variety of methods. The first approach is to keep the dose under control. MERS-CoV's ADE can be blocked with a large antibody dose without compromising the virus's antiviral activity [240]. Altering the antibody specificity is the second option. Anti-spike antibodies make it easier to induce ADE, despite the fact that inhibiting the binding of coronavirus spike proteins is a good treatment strategy due to its high efficiency in decreasing viral load. The use of specific inhibitors is the third technique [174]. In MERS-CoV) and SARS-CoV protease inhibitors and Fc inhibitors, for example, have a role in the inhibition of ADE [240,241]. An adjuvant was observed to increase Th2-type (T helper type 2) immunity and minimize immunopathology in previous SARS-CoV (severe acute respiratory syndrome coronavirus) research, implying the adjuvant's latent importance [242]. Furthermore, the dengue virus case can be utilized as a model, with changes to the FcgR binding location on the antibody Fc component lowering the probability of ADE. In these conditions, ensuring that classical viral entry is prevented via antibodies while resolving ADE is another difficulty. Combining Cyclospora A and Chinese medicine pharmaceutics with immunosuppressive qualities with colloidal sub-particles, which can improve macrophage targeting and induce an immunosuppressive effect, could be a viable alternative. This may be effective against viruses and bacteria as well as immune-injury inflammation.

Conclusion and future perspective

Coronavirus 2019 (SARS-CoV-2) causes respiratory illness in humans including vomiting, loss of taste, sneezing and coughing while diarrhea and upper respiratory disease occur in animals. According to the WHO guidelines, avoiding contact with infected people and limiting visits to market or public spaces, as much as possible, can help break the chain of transmission of coronavirus 2. Largely, both SARS-CoV and SARS-CoV-2 share common symptoms and also exhibit a similar mechanism of action, which has created a war-like situation across the world. Since, there is no specific antiviral medicine or therapy available at present, many potential drugs for repurposing to treat COVID-19 patients are being explored worldwide. Such efforts have led to at least managing and controlling the seriousness of illness and death rate of SARS-CoV-2 patients. In parallel, clinical trials of various medicines for repurposing are in progress with due approval from the respective authorities of the country. Also, vaccine development has started taking its shape as many of them are currently undergoing through the phases of clinical trials. Few vaccines got approval for usage purposes, such as AZD1222 vaccine produced by Oxford University and AstraZeneca, Covaxin developed by Bharat Biotech in collaboration with the Indian Council of Medical Research (ICMR). Stem cells-based therapy is also showing a ray of hope as a potential treatment measure for the management of this uncured disease;

however more intensive study of this novel coronavirus is needed to find its permanent cure. ADE has been documented in SARS, MERS, and other human respiratory viral illnesses such as RSV and measles, implying that SARS-CoV-2 vaccinations and antibody-based therapies pose a real risk of ADE. Clinical studies, however, have not yet clearly proven ADE's function in human COVID-19 pathology. Animal and human clinical investigations are now underway to learn more about the mechanisms of ADE in SARS-CoV-2. Since December 2019, the entire world has been coping with various strains of SARS-CoV-2, as well as the first and second waves of the COVID-19 pandemic. However, due to the Delta variety, a few nations are still battling with the third wave. In the midst of this, the introduction of a new Omicron variety may have a devastating impact on human life and livelihood. The tireless efforts of scientists, medical professionals, front-line workers, and policymakers involved in dealing with this pandemic are commendable. In the previous two years, there has been a significant improvement in our understanding of SARS-CoV-2 and its variations, their origin and structure, pathogenesis, and related symptoms in various patient groups. The availability of effective FDA-approved vaccinations, treatment, and management regimes, as well as improved diagnostic and treatment infrastructure and skilled health care workers, may aid in better handling of the novel Omicron strain.

Conflicts of interest

The authors declare no conflict of interest.

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