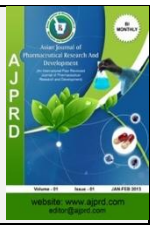
Available online on 15.10.2021 at http://ajprd.com

Asian Journal of Pharmaceutical Research and Development

Open Access to Pharmaceutical and Medical Research



Open Access Research Article

Novel Corona Virus: Its Origin, Current Dignosis And Various Diseases Arises Due To Covid-19

Gawali Mangesh B.*, Sangle Rahul R.

Bachelor of Pharmacy, SND College of Pharmacy, Yeola

A B S T R A C T

Severe Acute Respiratory Syndrome Coronavirus-2 is responsible for the emergence and propagation of new coronavirus illness 2019 i.e. COVID-19, have posed a significant threat to global public health. Coronaviruses are enveloped single positive-stranded RNA viruses with the biggest viral genome (26-33kb) among the RNA viruses, belonging to the Corona viridae family. This potentially deadly virus spreads quickly from person to person. To control the epidemics of COVID-19, large-scale measures such as isolation of infected patients, social distancing, frequent washing of hands, and the usage of face masks have been implemented. In this review, we provide a brief overview of the highly pathogenic Severe Acute Respiratory Syndrome Coronavirus outbreaks, its origin, symptoms, clinical features, preventive measures, current diagnostic tools and therapeutic strategies. We also discuss about various diseases arises due to COVID-19 pandemic.

Keywords: SARS-COV-2, Positive-Stranded RNA virus, Novel Coronavirus, Epidemics, Diseases.

A R T I C L E I N F O: Received 28 July 2021; Review Complete; 30 Sept. 2021 Accepted; 08 Oct. 2021 Available online 15 Oct. 2021

Cite this article as:

Mangesh B G, Sangle Rahul R, Novel Corona Virus: Its Origin, Current Dignosis And Various Diseases Arises Due To Covid-19 , Asian Journal of Pharmaceutical Research and Development. 2021; 9(5):102-110. **DOI:** http://dx.doi.org/10.22270/ajprd.v9i51026

***Address for Correspondence:**

Gawali Mangesh B, Bachelor of Pharmacy, SND College of pharmacy, Yeola

INTRODUCTION:

The World Health Organization (WHO) reported a case of pneumonia of unknown cause in Wuhan, China on December 31, 2019. The Chinese authorities subsequently identified a new type of coronavirus as the cause on January 7, 2020, and it was temporarily designated as 2019-nCOV. The coronavirus disease 2019 (COVID-19) outbreak spread rapidly all over the world. Novel COVID-19 disease is caused by the SARS-CoV-2[1]. According to the World Health Organization, the COVID-19 outbreak has spread to 215 nations as of 10 JULY 2021. Nearly 186,839,573 cases of COVID-19 infection have been confirmed, with 4,035,164 deaths reported around the world. The United States (622,708) had the most deaths, followed by Brazil (531,777), Italy (127,756), Mexico (234,675), Spain (81,003), India (407,173), Iran (85,543), and China (4636). In the United States, a total of 34,711,416 persons have been infected, making it the pandemic's most impacted country [2, 51].

Due to sharp upsurge of corona cases there iswidespread terror among the people. Since the outbreak began, scientists from all over the world have been looking for possible ways to identify and treat coronavirus disease. The Chinese virologist, Prof. Yong-Zhen Zhang, professor at Fudan University, Zhang discovered the first genome of COVID-19 with their colleagues on 10 Jan 2020 [2].Now-a-days, the outbreak of coronavirus is controlled with the help of various vaccines, drugs such as remdesivir, favipiravir, etc. The government safety measures such as isolation of infected person, contact tracing and quarantine, social distancing, foreign travel measures, Lockdown played a crucial role in prevention of coronavirus (COVID-19) [3].

ORIGIN

Novel Coronaviruses are normally not transmissible to humans and originate in animals such as camels, civets, and bats. However, as happened during the SARS epidemic in the early 2000s, novels coronavirus can occasionally mutates and transmit from animals to people, then from human to human. Now, COVID-19 outbreak has spread swiftly throughout the world, prompting the WHO to

declare it a Public Health Emergency of International Concern [26].

SYMPTOMS

COVID infection is characterized by Symptoms of fever, breathlessness, coughing, malaise, lethargy and a sore throat. Some patients, however, may develop catastrophic illnesses such pneumonia, acute respiratory distress syndrome, multi-organ failure, and even death [1, 5].

CLINICAL FEATURES

Coronaviruses enters into the respiratory tract through the nose. Coronavirus infections have a 2-14 day incubation time, with a 5-6 day median period, and induce symptoms similar to a common cold, including nasal blockage, sneezing, runny nose, and cough [4, 6]. Dyspnea occurs 5 days after the onset of symptoms, hospitalization at 7th day, and acute respiratory distress syndrome (ARDS) at 8th day. According to published studies, 25–30% of the patients who were afflicted needed to be admitted to an intensive care unit. Complications included acute lung injury, ARDS, shock, and acute renal injury. Patient started to feel better after the second or third week of hospitalization. For those who recovered, the average length of stay in the hospital was 10 days [7].

DIAGNOSTIC TESTS

1. CRP (C - reactive protein)

When a person is corona positive there is the overproduction of inflammatory cytokines which are released by the body to fight the virus results in the elevation of CRP level.However, when the immune system becomes overactive, it can cause lung tissue damage. In COVID19 patients, both inflammatory cytokines and tissue damage can lead to CRP production.A blood test is done to determine CRP value on day 5 or 6. In cases where condition of patient has worsened,the CRP test prescribed earlier.Normal CRP levels in the blood is less than 10 mg/L; nevertheless, it increases rapidly within 6 to 8 hours and peaks 48 hours after the onset of the disease [8].If CRP is more than 70 mg/L it could be an indication of impending cytokine storm, which needs immediate interventions.

2. HRCT (High-Resolution Computed Tomography)

In COVID-19 patients HRCT (High-Resolution Computed Tomography) scan of chest provides better visualization of the nature of lungs involved in COVID. On the other hand, any new information obtained from a chest HRCT scan, frequently has minimal impact on treatment recommendations. Treatment decisions are currently made nearly entirely on the basis of clinical severity and physiological impairment. Treatment for COVID-19 patients with hypoxia and abnormal chest radiographs is not indicated. However, HRCT chest is being inappropriately used by both doctors and patients for mild cases, who do not have hypoxia. In view of above, treating physicians should exercise caution while advising HRCT imaging of chest [9].

3. D-dimer

After COVID-19 infection, there is a risk of haemorrhage and thrombosis. When used as a clinical decision rule for pulmonary embolism exclusion, the D-dimer product has been shown to be effective. COVID-19 patients had higher levels of D-dimer than other patients.D-dimer levels are a solid prognostic test that correlates with disease severity. The aberrant alterations in D-dimer and inflammatory factor in patients with thromboembolism suggest that strong anticoagulant therapy may be required. However, D-dimer has low specificity, as there are many other conditions such as pregnancy, malignancy, trauma, liver disease, heart disease, etc. which also shows the rise in D-dimer. Hence the physician has to decide in clinical context [10].

4. IL-6 (Interleukin-6)

IL-6 is a cytokine that regulates cell proliferation and differentiation as well as the immune response. COVID-19 patients with more severe disease had higher levels of inflammatory cytokines, which were linked to pulmonary inflammation, lung destruction, and multiple organ failure. A previous study showed that, increased levels of pro-inflammatory cytokines such IL6, IL12, IP10, and MPC1 in the blood were linked to pulmonary inflammation in SARS patients. When body shows a hyper immune response, IL-6 is one of the key mediators of inflammation and viral storm of cytokinesin COVID-19 patients. IL-6 is an effective, readily implementable test that can help to provide substantial insight into proper patient management. However, the delay in sample collection and early measurements in the lab leads to error in the results. Hence, it's more important to do this in case of hospitalization in moderate to severe cases, where an IL-6 therapy is being planned [11].

5. RT-PCR (Reverse Transcription Polymerase Chain Reaction)

Diagnosis of COVID-19 should be done only by approved laboratory tests (RT-PCR Test), as suggested by the Indian Council of Medical Research (ICMR). RT-PCR can be used to determine the amount of mRNA in considerably smaller samples. In fact, this method is sensitive enough to allow for RNA quantification from a single cell. Real-time RT-PCR can identify nucleic acids of COVID-19 in nasopharyngeal swabs, lower respiratory tract secretions, sputum, blood, faeces, and other tissues.A German expert suggested the utilization of RT-PCR test for SARSCoV-2 detection at the start of 2020 because of its great precision and reliability. Some studies have connected false negative results with RT-PCR for virus detection, especially when the infection is in its early stages.To avoid this problem more sophisticated RT-PCR diagnostics are required [12].

First, retroviral DNA polymerases convert SARSCoV2 RNA to complementary single-stranded DNA, which is then amplified by PCR in a separate tube [13].To identify the COVID-19 virus in the body, real-time RT-PCRmethod is used by the scientists for converting the RNA into the DNA. This method is termed as "reverse transcription." This step is required because, only DNA can be duplicated or amplified, which is a vital aspect of the real-time RT-

PCR method for detecting viruses. Scientists have amplified a specific portion of viral DNA hundreds of thousands of times. Amplification is significant because scientists have a large enough quantity of the target portions of viral DNA to reliably confirm that the virus is there, rather than trying to find a minute amount of virus among millions of strands of genetic material.

A sample is collected from the nose or throat, which are places where the COVID-19 virus congregates. Components like proteins and lipids are removed by using a sequence of organic solvents, only RNA is left in the sample.This RNA is a combination of genetic material of person and the viral RNA, if present. For reverse transcription of RNA into DNA, a specific enzyme is used. Other short DNA fragments that complement specific portions of the transcribed viral DNA are subsequently added. If the virus is present in the sample, these fragments bind to the targeted area of viral DNA. During amplification, some of the genetic pieces are used to manufacture DNA and apply flag labels to the strands, which are then used to detect virus. The mixture is then transferred to an RT-PCR machine.The mixture is heated and cooled by the machine, initiating chemical reactions.This produces new, exact replicas of target areas of viral DNA.The cycle is performed indefinitely to keep coping the viral DNA's target areas. The preceding value is multiplied by two in each cycle. A typical real-time RT-PCR device does 35 cycles of amplification. This implies that at the end of the procedure, there are approximately 35 billion copies of viral DNA made from each strand in the sample[14].

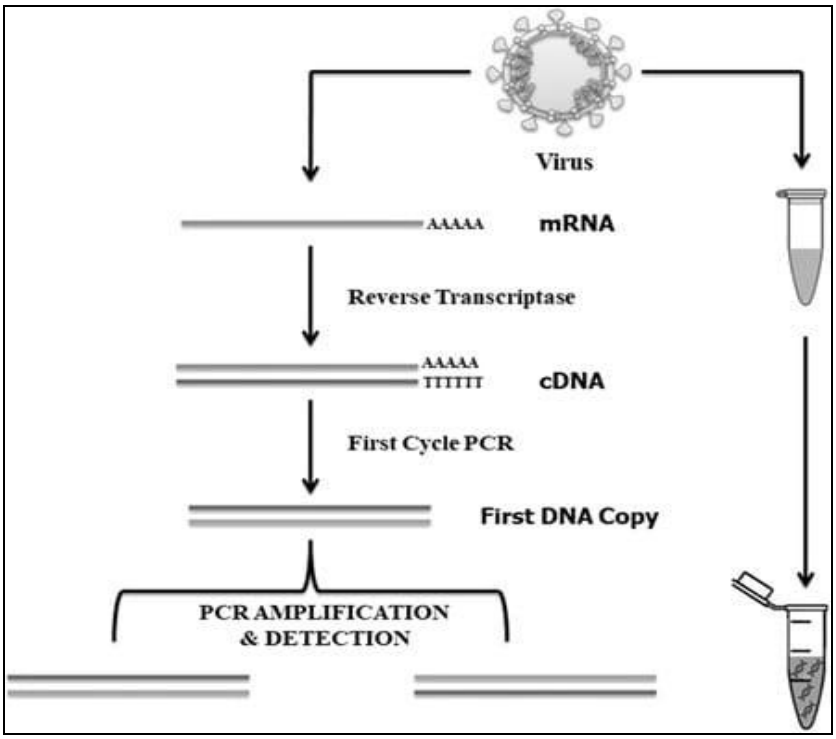


Figure 1: Graphical illustration of RT-PCR

6. Rapid Antigen Test Based on RT-PCR

The FDA has approved the COVID-19 detection test kit which is the first created by Cepheid to be used in an Emergency Use Authorization (EUA). It takes about 45 minutes to identify COVID-19. Samples are taken with a nasopharyngeal culture orswab and prepared in one minute. The technique utilized here is RT-PCR. The kit includes all of the necessary primers, probes, and internal controls. This test is presently performed using the GeneXpert® instrument system, which is available in authorized laboratories across the United States [15].

DISEASES ARISE DUE TO CORONA VIRUS

MUCOR MICOSIS

Mucormicosis, a black fungal infection in covid patients admitted to hospitals, is currently a major health issue in India. Several treatment alternatives have been tested, but none have been demonstrated to increase endurance in COVID-19 except systemic glucocorticoids. The comprehensive utilization of glucocorticoids, unfortunately, might result in secondary bacterial or fungal infections [16]. During the evolution of the fungal lineage, it was divided into four main groups: Ascomycota (Sac fungi),Chytridiomycota, Basidiomycota (Club fungus), and Zygomycota (Saprophytic filamentous fungi). Among these four classes, humans are only known to be affected by Zygomycotan fungi.Hence, zygomycetes-caused fungal diseases are known as Zygomycosis, and the term Zygomycosis is sometimes used interchangeably with Mucormycosis [26]. Mucormycosis is an opportunistic fulminant fungal illness caused by a saprophytic fungus.People with severe underlying immunosuppression, uncontrolled hyperglycemia and/or ketoacidosis, iron overload due to frequent blood transfusions or blood disorders, and healthy patients infected with fungal spores through traumatic injuries are all at risk.It is uncommonly suspected or diagnosed.After Candidiasis and Aspergillosis,

Brown rated mucormycosis third among opportunistic deep fungal infections [17]. The quick onset of tissue necrosis with or without fever is a hallmark clinical indication of mucormicosis. Necrosis is caused by the invasion of blood vessels and consequent thrombosis.

Mucormycetes, the fungus that cause mucormicosis, are members of the Mucorales scientific order. Mucormycetes are found all across the world, especially in soil and in conjunction with decaying organic materials such as compost piles, leaves, and animal faeces [18]. Most humans come into contact with minute fungus spores on a daily basis, therefore totally avoiding mucormycetes is probably difficult. The majority of people are unaffected by these fungus. Breathing in mucormycetes spores can induce an infection in the lungs or sinuses, which can spread to other regions of the body, resulting in serious illnesses in persons having COVID-19with a weakened immune system. Rhizopus oryzae and Mucor species are the most common forms that induce mucormicosis. Rhizomucor species, Apophysomyces, Lichtheimia, Syncephalastrum species, Cunninghamella bertholletiae, Saksenaea, and Rhizomucor are few further examples [19]. The mortality and morbidity of this fatal virus can be reduced with early detection and treatment.

Symptoms

One-sided facial swelling, headache, nasal or sinus congestion, and black lesions on the nasal bridge or upper inside of mouth that soon become more severe are all symptoms of rhino cerebral (sinus and brain) mucormycosis. Fever, cough, chest pain, shortness of breath, and other symptoms of pulmonary (lung) mucormycosis can occur. Blisters or ulcers appear as a symptom of cutaneous (skin) mucormycosis, and the diseased region may turn black. Pain, warmth, extreme redness, and swelling around a wound are some of the other symptoms. Symptoms of gastrointestinal mucormycosis include abdominal discomfort, nausea and vomiting, gastrointestinal bleeding.

Pathogenesis

These microbes spread through aerosolized asexual spores, which enter tissue via the respiratory system, damaged skin, or a percutaneous route in patients with weakened host defenses. Due to the affinity of fungi for arterial blood vessels' internal elastic lamina, theybecomes highly angio-invasive and can cause thrombosis or infarction.As they grow rapidly, causes the infarction and destruction in the tissue adjacent to the blocked arteries, especially in the paranasal sinuses, lungs, and stomach. Diabetic individuals have higher levels of free iron, which aids the proliferation of these organisms [17].

Treatment

Mucormycosis still has a significant death rate. Antifungal medications are used in conjunction with surgical intervention in the treatment of fungal infections. Isavuconazole (given intravenously or orally), amphotericin B-based medicines (given intravenously), or posaconazole are antiviral medications that have anti-mucorales action (given through an IV or orally).The triazole posaconazole and amphotericin B (containing lipid formulations) are two systemic antifungals now available with good mucorales efficacy. Treatment with one of these antifungal drugs should begin as soon as possible, as delays in treatment have been linked to a higher risk of death [16, 26].Mucormycosis frequently needs surgery to remove infected tissue.

Multisystem Inflammatory Syndrome in Children (MIS-C)

MIS-C, a debilitating illness in children, is caused by coronavirus infection. All COVID-19 virus-infected children develop a mild sickness. Children who are infected with MIS-C develop significant inflammation in various organs and tissues such as the lungs and heart; kidneys; digestive system; blood vessels; brain; skin; and eyes.In April 2020, the first MIS-C reports were released from the United Kingdom[20].Since then, there have been reports of children in various parts of the world who have been impacted in a similar way, including Europe, Canada, the United States, and South Africa [20]. The time between acute infection and emergence of MIS-C symptoms in children with a known history of documented or suspected COVID-19 is usually two to six weeks. Rare cases of MIS-C have been recorded that occurred less than six weeks after the acute SARS-COV-2 infection [21].

Some people develop signs and symptoms that are comparable to MIS-C on a rare occasion. Multisystem inflammatory syndrome in adults (MIS-A) is a new and dangerous illness that affects adults who have previously been infected with the COVID-19 virus. If MIS-A is suspected, a COVID-19 diagnostic or antibody test can assist confirm current or previous virus infection, which aids in MIS-A diagnosis. MIS-C is a rare condition, and most children who have it improve with medical treatment. However, some children swiftly deteriorate to the point where their lives are at risky zone.

Symptoms

Multisystem inflammatory syndrome in children (MIS-C) includes signs and symptoms such as fever lasting 24 hours or longer, vomiting, diarrhoea, stomach pain, fast heartbeat, rapid breathing, skin rash, feeling unusually tired, red eyes,redness or swelling of the hands or feet, redness or swelling of the lips and tongue, dizziness or lightheadedness, headache, enlarged lymph nodes. Though not all children have the same symptoms [22, 23].

Pathogenesis

*P*athogenesis ofMIS-C is uncertain.A post-infectious causation of disease has been proposed but not confirmed. The illness resembles Kawasaki disease (KD), macrophage activation syndrome (MAS), and cytokine release syndrome in terms of its clinical manifestations, is thought to be caused by an aberrant immunological response to the virus.On the other hand, MIS-C has immunological profile that is unique from KD and MAS, based on the existing research. SARS-COV-2 causes an abnormal immunological response, but the exact mechanism is uncertain [24].

Treatment

The treatments of MIS-C include anti-inflammatory medications (corticosteroids, and drugs blocking IL-1 or

IL-6) and IV immunoglobulin (used to treat Kawasaki illness). Depending on the results of laboratory tests, other treatments may be used. Children are also given low-dose aspirin which help to prevent blood clots. Even if the children had no serious problems in the hospital, they should have repeat echocardiograms to assess their heart and coronary arteries after discharge. Children who are entirely cured after six months do not require any further monitoring.

DELTA PLUS

The second wave of coronavirus-2 (SARS-CoV-2) outbreak has spread rapidly over the world, withDelta Plus (AY. 1) and Delta variant (B.1.617.2) strains. COVID-19's Delta variation (B.1.617.2) was initially discovered in India in October 2020, and was afterwards discovered in other nations. On April 4, 2021, the Delta version was designated as a variant of interest (VOI) and a variant of concern (VOC) on May 1, 2021. In May 2021, the World Health Organization marked the Delta COVID19 strain as causing the second wave of catastrophic coronavirus infections in India. The term "Delta Plus" has recently been used to describe a variant of Delta. As per the Public Health England, Delta Plus variants have been found in Indiain six genomes.The UK Health Service discovered 63 Delta variant having K417N mutations of SARSCOV2 genomes on June 27, 2021.The spike protein present on the surface of the SARS-COV-2 virus has K417N mutation[25]. More than 91 percent of COVID-19 cases in UK are caused by the delta version (B.1.617.2), which is 40 percent more transmissible than the Alpha variant. A variant of Alpha (B.1.1.7) was also found in the United Kingdom. Slight modifications of the delta mutant spike protein improve its ability to bind to the ACE2 receptor and allow it to enter human cells. Therefore, a distinct variation of the Delta (B.1.617.2) form may enhance its ability to bind to human cells when attached to them.If the virus canassimilate and bind more quickly, it is capable of infecting multiple human cells, making human immune responses easier to overcome [26].

Despite the fact that the number of Delta Plus variations infections was low but recently it was started to increase considerably, India's leading national news channels have reported new instances from several states. As a result, in the near future, this strain has become the main problem of the possible third wave of COVID19 in India. “AY.1” and “AY.2” are two Delta Plus variants that are steadily spread worldwide. “AY.1” is widely spread around the world, whereas “AY.2” is perplexing in the United States, where it has been detected 150 times [25].

Symptoms

According to India’s virologists, Delta plus variant carries symptoms of the Delta variant and the beta variant including cough, sore throat,headache, skin rashes, fever,diarrhea, runny nose, discoloration of fingers and toes, chest pain, shortness of breath. Other symptoms include stomach ache, nausea, appetite loss, vomiting, hearing impairment, joint pains.People who are infected may mistake the symptoms for a terrible cold and fail to realize that they need to isolate. One study in the United Kingdom found that headache, sore throat, and runny nose were the most commonly reported symptoms. In the United Kingdom, the Delta variation accounts for 91 percent of new cases.

Pathogenesis

It is caused by a mutation in spike protein of SARS-COV-2, which aids invasion of the virus inside the human cells. The k417N mutation interacts with the ACE2 receptor protein, due to this the virus is able to infect human cells in the lungs, heart, kidneys, and gut. When the spike protein comes into contact with ACE2, it changes from a "closed" to "open" state, allowing it to more effectively bind and infect the cell.The Delta plus (AY.1) is still poorly understood[25]. Delta Plus has "increased transmissibility, higher binding to receptors of lung cells, and probably lower monoclonal antibody response," according to the Indian SARSCoV-2 Genomic Consortia (INSACOG) [26].

Treatment

Doctors primarily employed antibiotics to treat the Delta plus variant (B.1.617.2), but no clear information has been obtained about it. The only way to prevent this is to get vaccinated as soon as possible. The Covaxin (established by Bharat Biotech in Hyderabad, Telangana in partnership with the Indian Council of Medical Research (ICMR) and the National Institute of Virology (NIV) in Pune, Maharashtra) neutralizes the mutant delta variants of SARS-CoV-2 and works against the new strain. As a result, India has issued Bharat Biotech's Covaxin Emergency USE Authorizations for covid-19 therapy.In addition, Covishield (Serum Institute of India, Pune, Maharashtra, India), a covid-19 vaccine, neutralizes the mutant B.1.617.2 (Delta variant), B.1.167, B.1.168 variants of SARS-CoV-2. Only a few blood samples from affected people have been analyzed. Extensive clinical trials are currently underway, whoseresults will be verified later. In addition, preliminary clinical trials have shown that the Moderna and Pfizer-Biotech COVID-19 vaccines are successful in neutralizing the novel variants such as B.1.617.2 (the Delta Variant),B.1.167 and B.1.168.Pfizer and AstraZeneca vaccines provide substantial protection against hospitalizationfrom the Delta variant, according to a study conducted by Public Health England (PHE) in the United Kingdom [26]. Still, no treatment has been found to be effective against this variation, and while the vaccine does not totally eradicate it, but the chances of getting infected through immunization are extremely low.

THERAPEUTIC STRATEGIES FOR COVID-19

During the outbreaks of SARS and MERS, Several drugs with evident in vitro SARS-COV and MERS-COV antiviral activities were employed, with varying degrees of efficacy. In SARS and MERS medicinal research meta-analysis, no obvious advantage of any particular authority was discovered. The in vitro activity of some of the most promising COVID-19 repurposed medicines is discussed below.

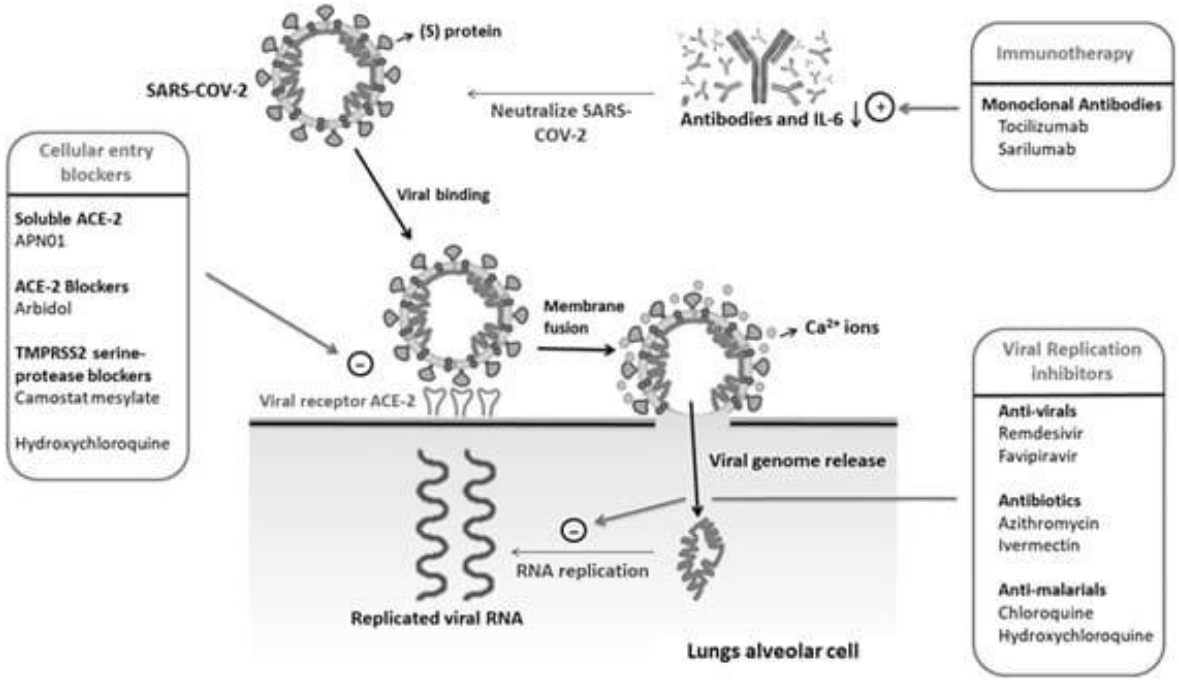


Figure 2: Mechanisms of action of major COVID-19 repurposing agents

Chloroquine and Hydroxychloroquine

Chloroquine is a powerful broad-spectrum antiviral drug that is widely used to treat autoimmune diseases. It is an ancient medication with anti-rheumatic andanti-malarial properties that has been discovered to have significant anti-COVID-19 activity at a half-maximal effective concentration (EC50) of 1.13 M micro molar range[2]. Chloroquine is a powerful antibiotic that can inhibit a virus infection. It can also be used to prevent respiratory syncytial virus infection[27].Chloroquine can also inhibit the entry of COVID-19 into a Vero E6 cell, which is a primary infection site in humans.Chloroquine 500 mg orally once or twice day has been used to treat COVID-19 [28]. On the other hand, the NIH has not used chloroquine in clinical trials due to its toxicity-related constraints [2].

A potential alternative, hydroxychloroquine, has been proven to be significantly less hazardous (by around 40%) while having equivalent anti-COVID-19 action [28]. Hydroxychloroquine has better in vitro function than chloroquine, and after 24 hours of administration, it had a lower EC50 value for SARS-COV-2.A growth in endosomal pH and the prohibition of virus ingress in the target cell are the fundamental antiviral actions of hydroxychloroquine [29].The best dose administration for hydroxychloroquine in COVID-19 therapy, according to a physiologically based pharmacokinetic modelling research, is a high dose of 400 mg twice for one day, then 200 mg twice daily for the next day [28]. At the doses and times recommendedfor COVID-19, there have been no severe side effects documented. Chloroquine and hydroxychloroquine are typically regarded safe during pregnancy [30].Unfortunately, during recent trials, no convincing evidence was established to justify the use of both chloroquine and hydroxychloroquine in the treatment of COVID-19 [31].

Lopinavir/Ritonavir

Lopinavir/ritonavir, an oral combination drug licensed by the US Food and Drug Administration (FDA) to treat HIV, showed in vitro effectiveness against additional new corona viruses by inhibiting 3-chymotrypsin-like protease. These two antiviral medications have been used in conjunction with alpha interferon to treat some COVID-19 patients in China [13]. An organized evaluation of lopinavir/ritonavir for the therapy of SARS and MERS discovered a small number of research, the majority of which focused on SARS. For COVID-19 therapy, the most often used and tested lopinavir/ritonavir dose is 400 mg/100 mg twice day for up to 14 days.During the first seven to ten days of viral replication, the timing of ritonavir/lopinavir treatment is crucial, as delayed treatment had zero impact on therapeutic efficacy.Early findings of ritonavir/lopinavirfor COVID-19 treatment are primarily case reports and limited retroactive, systematic unit studies, makes it harder to determine lopinavir/ritonavir's direct treatment effect [32].

Ribavirin

A guanine analogue called ribavirin impedes RNA polymerase that is dependent on viral RNA. It is a contender for the treatment of COVID-19 due to its action against other nCoVs. However, its ability to fight with SARS-COV in vitro was limited, and for inhibition of viral replication alarge doserequired about 1.2 gm to 2.4 gm orally each 8 hours along with polypharmacy [33]. Ribavirin is a recognized teratogen that should be avoided during pregnancy [34]. Ribavirin produces significant hematologic toxicity that is dosage dependent.More than 60% of patients in the SARS studies developed hemolytic anemia as a result of the high doses employed. In the wide-ranging MERS surveillance test,almost 40 percent of individuals taking ribavirin and interferon required blood transfusions, results in similar safety concerns. Transaminase elevations were

observed in 75% of individuals using ribavirin for SARS [33]. Because of the inconsistent efficacy results for other nCoVs and its high toxicity, ribavirin appears to be of limited utility in the treatment of COVID-19.

Arbidol

Arbidol (also termed as Umifenovir) is a wide ranging antiviral drug with a distinct mode of action that inhibits viral envelope membrane fusion by targeting the Spike protein/ACE2 interaction [13]. COVID-19 endocytosis into the host cell is thought to be inhibited by it. Due to this Arbidol is presently being tested in various COVID-19 clinical trials [35]. Low-level data suggests that arbidol, either used alone or in combination with other antiviral medications, can help treat COVID-19 pneumonia. The standard dose of influenza treatment 200 mg taken orally every 8 hours is being investigated for COVID-19 therapy (NCT04260594).According to the researchers, arbidol is a drug that can reduce the likelihood of hospitalization for patients with respiratory illnesses caused by SARS-CoV-2 infection[36].

Remdesivir

Remdesivir (officially known as GS-5734), a drug created by Gilead Sciences, a US based company, has beenutilizedto treat Ebola virus in the past [37]. However, there have been effective case reports describing the usage of remdesivir in the treatment of COVID-19. As a result of metabolism, Remdesivir (a monophosphate derivative) is transformed into an active C-adenosine triphosphate analogue, can be integrated into viral RNA chains, results in premature termination of RNA replication [38].Because of strong in vitro action and broad-spectrum activityagainst various nCoVs, Remdesivir is currently a promising COVID-19 therapeutic medication, with effective concentration values EC50 and EC90 at very low micro molar ranges i.e. 0.77 M and 1.76 M, respectively [39]. Remdesivir has been shown to inhibit the growth of COV strains in human airway epithelial cells. It also regulates cell entry via the hACE2 receptor. Remdesivir decreases RNA levels in a dose-dependent manner during early-stage infection, which corresponds to a drop in virus titers. To prevent chain elongation, SARS-CoV-2 requires replication of the RdRp gene, which can be chemically bonded to remdesivir[40]. Furthermore, remedesivir prevents the spread of virus infection in human liver carcinoma cells.

Clinical trials are now being conducted to determine the safety and antiviral efficacy of remdesivir in patients with mild to moderate or severe infection of SARS-COV-2.Remdesivir was given to COVID-19 patients on a compassionate basis, and results states thatthe antiviral treatment (a single 200-mg loading dosage on day 1, maintained by a 100-mg daily infusion for 9 days) of 10 day courseindicates the clinical advantages for these patients. At this time, no hepatic or renal modifications are indicated; however, Patients with low GFR i.e. 30 mL/min, should not begin remdesivir treatment[13].Remdesivir is currently unapproved by the FDA and can only be achieved through compassionate use (for childrenless than 18 yearsand pregnant women).

Favipiravir

Favipiravir, also termed as T-705, is a purine nucleotide prodrug called Favipiravir ribofuranosyl-5′-triphosphate. The active ingredient prevents viral replication by inhibiting RNA polymerase. The majority of preclinical data of favipiravir comes from its antiviral effectiveness against influenza and Ebola; however, the drug has also shown wide antiviral action against other RNA viruses [41].The EC50 (50% effective concentration) of favipiravir against SARS-CoV-2 in Vero E6 cells was 61.88 µM/L in vitro. For COVID-19 treatment, a higher dose range should be considered. A loading dose (2400 mg to 3000 mg divided into two doses over 12 hours) is recommended, along with a supporting dose (1200-1800 mg after every 12 hours). The favipiravir has around five-hour half-life [42].

In China, a randomized control experiment compared with the two groups of the patients who were randomly assigned,one group receiving Favipiravir whereas other receiving Arbidol therapy, and their7-day recovery rates was compared. Arbidol's therapeutic recovery rate was (51.67%), whereas Favipiravir's was higher 61.21% [43]. Favipiravir is now available for the treatment of influenza in Japan and China, but not in the United States. These study calls for more RCTs to investigate the efficacy of Favipiravir in the COVID-19 treatment.

Tocilizumab

In COVID-19 patients, IL-6 is one of the primary mediators of inflammation and viral cytokine storm when the body exhibits a hyper immunological response. Tocilizumab, an IL-6 receptor antagonist monoclonal antibody, has been approved by the FDA to treat RA and cytokine release syndrome. Monoclonal antibodies normally modify the host organism's immune system response, resulting in a decrease in the IL-6 plasma level, which is frequently increased in patients withCOVID-19 on mechanical ventilation [44].Tocilizumab's efficacy and responsiveness have been studied both alone and in combination with Favipiravir. Tocilizumab is given at a dose of 4–8 mg/kg IV dilution in NS (single dose) in clinical trials, and in combination with Favipiravir at (Tocilizumab: 4–8 mg/IV, Favipiravir: 1600 mg/dose twice daily for 2 days, then 600 mg/dose twice daily for 7 days) [45].

Sarilumab, an interleukin-6 receptor antagonist authorized for RA is being investigated in a double-blind, multicenter trials for the patients with severe COVID-19 who are hospitalized. Eculizumab (antibody blocking terminal complement), bevacizumab (anti–vascular endothelial growth factor drug), and fingolimod (immune modulator approved for multiple sclerosis)are monoclonal antibodies or immunomodulatory drugs that are in clinical studies in China or that have been approved for increased access in the United States [46].

Immunoglobulin Therapy/Plasma Therapy

Hyper-immune immunoglobulin therapy, also known as convalescent plasma therapy, is an essential component of COVID-19's treatment [47]. It is a type of immunotherapy that is used to treat and prevent a variety of infectious diseases, including SARS and MERS.Convalescent plasma

treatment is a potential alternative, because COVID-19, MERS, and SARS have similar clinical and virological characteristics [48].Immunoglobulins which can be employed to treat people who are suffering from active viral infection, can be found in the plasma of recovered patients. Antibodies from recovered patients may facilitate immune clearance of both free virus and infected cells, according to the rationale behind this treatment. The convalescent plasma treatment against COVID-19 was studied by Duan and coworkers [49].

Within 1 to 3 days of plasma therapy, all symptoms of 10 COVID19 patients either disappeared or improved significantly. Among the 40 recovered COVID19 cases, 39 of the plasma samples during the recovery period had an antibody titer of greater than 1: 160, and only 1 case had a low antibody titer of 1:32. As a result of these findings, convalescent plasma therapy appears to be well tolerated and has the potential to improve the health outcomes of patients with severe COVID-19 by neutralizing viremia. As per the FDA advisory board, immunoglobulins have risks associated with their administration, that's why they should only be used in serious or potentially lethal situations in COVID-19 patients[50].

Vaccines

This virus is exceedingly contagious due to its high rate of person to person transmission. Protective preventative measures and the vaccination are the two most effective strategies to stop a pandemic from spreading. Vaccines induce the production of specific antibodies in the body, resulting in an anamnestic reaction when the body comes in contact with this pathogen again. Non-replicating mRNA (NRM) vaccines and self-amplifying mRNA (SAM) vaccines are the two types of messenger ribonucleic acid (mRNA) vaccines now available. To protect the mRNA from degradation and facilitate cellular uptake, it is packaged into a carrier lipid nanoparticles [52].After the ingestion of carrier particles in the cell, mRNA is released, which is subsequently converted into the target protein by the ribosome.The immune system detects the target protein once it is produced by the cell and initiates an immunological response.

DNA vaccines, often referred as genetic vaccines or nucleic acid vaccines, have been investigated as well. It enters animals by a specific pathway, where it is taken up by host cells, and undergoes transcription and translation. The antigen protein causes the specific and non-specific immunological reactions in the body, both of which result in immune protection [52].As of August 24, 2021, 32.5 percent of the world's population had received at least one dosage of the COVID-19 vaccine, with 24.5 percent having had all three doses. Globally, 4.97 billion doses have been given out, with 34.91 million being given out every day. In low-income nations, only 1.4 percent of people have received at least one dose [53].

In the DNA vaccine, the SARS-CoV-2 spike gene is embedded in a loop of DNA. After electroporation, the cell membrane permeability increases, allowing DNA to enter the cytoplasm and reach to the nucleus. SARS-CoV-2 spike proteins will be translated on the cell membrane when DNA is translated into mRNA. The nanoparticle-encapsulated mRNA coding for the SARS-CoV-2 antigen is integrated into the cytoplasm. Spike mRNA is used to translate spike proteins, which are produced on the cell

membrane, using ribosomes and bases.Antigen presenting cells (APCs) will detect the membrane spike protein, triggering an immunological response [52].

PREVENTION:

What can you do to secure yourself?

You might be able to lower your infection risk by doing the following.

- Wash hands for at least 20 seconds with water and soap.
- Avoid contacting your eyes, nose, or mouth with your hands that haven't been washed.
- Keep a safe distance from sick persons [4].

What is the best way to secure others?

If you have symptoms of a cold, you can secure others by doing the following.

- If you're sick, stay at home and avoid close contact with people.
- When you cough or sneeze, mask your mouth and nose with a tissue, then throw it away & wash your hands.
- Objects and surfaces should be thoroughly cleaned and disinfected [4].

CONCLUSION

SARS-CoV-2 is a highly contagious virus that causes a wing-footed growth in sickness. Researchers are always looking for the most effective preventative, therapeutic, and diagnostic procedures. Apart from this, there is a great amount of mutation occurs in the SARS-COV-2 virus which makes it more deadly, resulting in the rise in various hazardous and life-threatening ailments. There are various vaccines, preventive measures and treatment strategies are carried out throughout the world to overcome this problem. Still, the mortality rate is increasing day by day going to the third wave of COVID-19. So, it is necessary for everyone to follow all the safety guidelines and should be vaccinated as early as possible.

REFERENCES

1. Kashif Hussain, Gul Ambreen, Mehreen Muzammil, et al. Pharmacy services during COVID-19 pandemic: experience from a tertiary care teaching hospital in Pakistan. Journal of Pharmaceutical Policy and Practice, 2020; 13: 74.
2. Humzah Jamshaid, Fatima Zahid, Intisar ud Din, et al. Diagnostic and Treatment Strategies for COVID-19. An official Journal of the American Association of Pharmaceutical Scientists, 2020; 21: 222.
3. WHO Coronavirus disease 2019 (COVID-19) situation report – 72. 2020, April 1. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200401-sitrep-72-covid-19.pdf?sfvrsn=3dd8971b_2 Retrieved April 5, 2020, from.
4. Humzah Jamshaid, Fatima Zahid, Intisar ud Din, et al. Diagnostic and Treatment Strategies for COVID-19. An official Journal of the American Association of Pharmaceutical Scientists, 2020; 21: 222.
5. Marília Berlofa Visacri, Isabel Vitoria Figueiredo, Tacio de Mendonça Lima. Role of pharmacist during the COVID-19 pandemic: A scoping review. Research in Social and Administrative Pharmacy, 2021; 17(9): 1799–1806.

6. Rohit Kumar, Anshul Chawla, Gaganpreet, Diksha. A Valuable insight to the novel deadly COVID-19: A Review. Research Journal of Pharmacology and Pharmacodynamics, 2020; 12(3): 111-116.
7. Tanu Singhal. A Review of Coronavirus Disease-2019 (COVID-19). The Indian Journal of Pediatrics, 2020; 87(4): 281–286.
8. Nurshad Ali. Elevated level of C-reactive protein maybe an early marker to predict risk for severity of COVID-19. Journal of Medical Virology, 2020; 1–3.
9. WHO/2019-nCoV/Clinical/Radiology_imaging/2020.1
10. Bilian Yu, Xin Li2, Jin Chen, et al. Evaluation of variation in D-dimer levels among COVID-19 and bacterial pneumonia: a retrospective analysis. Journal of Thrombosis and Thrombolysis, 2020.
11. Zulvikar Syambani Ulhaq and Gita Vita Soraya. Interleukin-6 as a potential biomarker of COVID-19 progression. Med Mal Infect. 2020 Jun; 50(4): 382–383.
12. Corman VM, Landt O, Kaiser M, Molenkamp R, Meijer A, Chu DKW, et al. Detection of 2019 novel coronavirus (2019- nCoV) by real - time RT-PCR. Eurosur veillance. 2020; 25:2000045. https://doi.org/10.2807/1560- 7917.ES.2020.25.3.2000045.
13. Binbin Chen, Mengli Liu, Chengzhi Huang. Current diagnostic and therapeutic strategies for COVID-19. Journal of Pharmaceutical Analysis, 2021; 11: 129-137.
14. Humzah Jamshaid, Fatima Zahid, Intisar ud Din, et al. Diagnostic and Treatment Strategies for COVID-19. An official Journal of the American Association of Pharmaceutical Scientists, 2020; 21: 222.
15. Administration USFD. Xpert® Xpress SARS-CoV-2. http://www.fda.gov/media/136314/download (2020). Accessed 4 April 2020: 1-26.
16. Deepak Garg. Valliappan Muthu. Inderpaul Singh Sehgal, et al. Coronavirus Disease (Covid-19) Associated Mucormycosis (CAM), Case Report and Systematic Review of Literature. Mycopathologia, 2021; 186(4): 289–298.
17. Arushi Pandey, Gurkiran Kaur. Mucormycosis revisited: Case report with review of literature. Journal of Dental Specialities, 2020; 8(1): 39–44.
18. Richardson M. The ecology of the Zygomycetes and its impact on environmental exposureexternal icon. Clin Microbiol Infect. 2009 Oct; 15 Suppl 5:2-9.
19. Al-Ajam, MR, Bizri, AR, Mokhbat, J, Weedon, J, Lutwick, L. Mucormycosis in the Eastern Mediterranean: a seasonal diseaseexternal icon. Epidemiol Infect. 2006 Apr 134(2):341-6.
20. Riphagen S, Gomez X, Gonzalez-Martinez C, et al. Hyperinflammatory shock in children during COVID-19 pandemic.Lancet. 2020; 395(10237):1607.
21. Cirks BT, Rowe SJ, Jiang SY, et al. Sixteen Weeks Later: Expanding the Risk Period for Multisystem Inflammatory Syndrome in Children. J Pediatric Infect Dis Soc. 2021; 10(5):686.
22. Feldstein LR, Rose EB, Horwitz SM, Collins JP, et al. Multisystem Inflammatory Syndrome in U.S. Children and Adolescents. N Engl J Med. 2020; 383(4):334.
23. Ahmed M, Advani S, Moreira A, et al. Multisystem inflammatory syndrome in children: A systematic review. EClinicalMedicine. 2020; 26: 100527.
24. Carter MJ, Fish M, Jennings A, Doores KJ, et al. Peripheral immunophenotypes in children with multisystem inflammatory syndrome associated with SARS-CoV-2 infection. Nat Med. 2020; 26(11):1701.
25. Roy B1, Roy H2. The Delta Plus variant of COVID-19: Will it be the worst nightmare in the SARS-CoV-2 pandemic? Journal of Biomedical Sciences. 2021; 8(1): 1-2.
26. Ravindra B. Malabadi Kiran P. Kolkar, Neelambika T. Meti, et al. Outbreak of Coronavirus (SARS-CoV-2) Delta variant (B.1.617.2) and Delta Plus (AY. 1) with fungal infections, Mucormycosis: Herbal medicine treatment. International Journal of Research and Scientific Innovation (IJRSI). 2021; 8(6): 59-70.
27. M.J. Vincent, E. Bergeron, S. Benjannet, et al., Chloroquine is a potent inhibitor of SARS coronavirus infection and spread, Virol. J. 2005; 2: 69.
28. James M. Sanders, Marguerite L. Monogue, Tomasz Z. Jodlowski, et al. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19) A Review. The journal of American Medical Association, 2020; 323(18): 1824-1836.
29. Savarino A, Boelaert JR, Cassone A, Majori G, Cauda R. Effects of chloroquine on viral infections: an old drug against today's diseases. Lancet Infect Dis. 2003; 3: 722–7.
30. Chloroquine [database online]. Hudson, OH: Lexicomp Inc; 2016. Accessed March 17, 2020. http://online.lexi.com
31. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review. Jama. 2020; 323: 1824–36.
32. Yao TT, Qian JD, Zhu WY, Wang Y, Wang GQ. A systematic review of lopinavir therapy for SARS coronavirus and MERS coronavirus-A possible reference for coronavirus disease-19 treatment option. J Med Virol. 2020.
33. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. PLoS Med. 2006; 3(9): 343
34. Altınbas S, Holmes JA, Altınbas A. Hepatitis C virus infection in pregnancy: an update. Gastroenterol Nurs. 2020; 43(1): 12-21.
35. Liu C, Zhou Q, Li Y, Garner LV, Watkins SP, Carter LJ, et al. Research and development on therapeutic agents and vaccines for COVID-19 and related human coronavirus diseases. ACS Publications; 2020.
36. Z. Zhu, Z. Lu, T. Xu, et al., Arbidol monotherapy is superior to lopinavir/ritonavir in treating COVID-19, J. Infect. 2020; 81: 21-23.
37. Mulangu S, Dodd LE, Davey RT Jr, Tshiani Mbaya O, Proschan M, Mukadi D, et al. A randomized, controlled trial of Ebola virus disease therapeutics. N Engl J Med. 2019; 381: 2293–303.
38. T.K. Warren, R. Jordan, M.K. Lo, et al., Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys, Nature 2016; 531: 381-385.
39. Al-Tawfiq JA, Al-Homoud AH, Memish ZA. Remdesivir as a possible therapeutic option for the COVID-19. Travel Med Infect Dis. Published online March 5, 2020. doi:10.1016/j.tmaid.2020.101615
40. W. Yin, C. Mao, X. Luan, et al., Structural basis for inhibition of the RNA-dependent RNA polymerase from SARS-CoV-2 by remdesivir, Science 2020; 368: 1499-1504.
41. Furuta Y, Komeno T, Nakamura T. Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase. Proc Jpn Acad Ser B Phys Biol Sci. 2017; 93(7): 449-463.
42. Shiraki K, Daikoku T. Favipiravir, an anti-influenza drug against life-threatening RNA virus infections. Pharmacol Ther. 2020; 107512.
43. Chen C, Huang J, Cheng Z, Wu J, Chen S, Zhang Y, et al. Favipiravir versus Arbidol for COVID-19: a randomized clinical trial. MedRxiv. 2020. https://doi.org/10.1101/ 2020.03.17.20037432.
44. Herold T, Jurinovic V, Arnreich C, Hellmuth JC, von BergweltBaildon M, Klein M, et al. Level of IL-6 predicts respiratory failure in hospitalized symptomatic COVID-19 patients. MedRxiv. 2020.
45. Registry CCT. Favipiravir combined with tocilizumab in the treatment of novel coronavirus pneumonia (COVID-19)-a multi-center, randomized, controlled trial. 2020. http://www.chictr.org.cn/ showprojen.aspx?proj=051126.
46. ClinicalTrials.gov. Accessed March 18, 2020. https://clinicaltrials.gov/
47. Chen L, Xiong J, Bao L, Shi Y. Convalescent plasma as a potential therapy for COVID-19. Lancet Infect Dis. 2020; 20(4): 398-400.
48. L. Chen, J. Xiong, L. Bao, et al., Convalescent plasma as a potential therapy for COVID-19, Lancet Infect. Dis. 2020; 20: 398-400.
49. K. Duan, B. Liu, C. Li, et al., Effectiveness of convalescent plasma therapy in severe COVID-19 patients, Proc. Natl. Acad. Sci. U. S. A. 2020; 117: 9490-9496.
50. Administration USFD. Investigational COVID-19 convalescent plasma - emergency INDs. http://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/investigational-covid-19-convalescent-plasma-emergency-inds (2020). Accessed 4 April 2020.
51. Coronavirus Outbreak. Available at: https://www.worldometers.info/coronavirus/. Accessed 23 Feb 2020.
52. Zhi-Peng Yan, Ming Yang and Ching-Lung Lai. COVID-19 Vaccines: A Review of the Safety and Efficacy of Current Clinical Trials. Pharmaceuticals 2021, 14, 406.
53. Ritchie, H.; Beltekian, D.; Mathieu, E.; Hasell, J.; et al. Statistics and Research: Coronavirus (COVID-19) Vaccinations. 2021. Available o