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COVID-19 Pandemic: A Comprehensive Updated Review with an Artificial Intelligence (AI)

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ABSTRACT

The World Health Organization (WHO) was informed of cases of pneumonia of unknown microbial etiology associated with Wuhan City, Hubei Province, China on 31 December 2019 [1]. The WHO later announced that a novel coronavirus had been detected in samples taken from these patients. Since then, the epidemic has escalated and rapidly spread around the world, with the WHO first declaring a public health emergency of international concern on 30 January 2020, and then formally declaring it a pandemic on 11 March 2020. The condition has been given the official name of coronavirus disease 2019 (COVID-19) [2,3]. The disease is characterized by fever, dry cough, chest pain with pneumonia and Death in severe cases. Several clinical trials are under process for the development of effective vaccination and novel drug therapies.

Therefore, in this review, we provide recent information about the novel coronavirus (COVID-19 formerly known as 2019 nCoV) caused by SARS-CoV-2, its Taxonomy, Epidemiology, pathogenesis, Diagnosis and Treatment options along with a brief review of the management of mild to critically ill patients. In this Review Article, We also included a special note on Artificial Intelligence (AI) which is emerging as a lifesaver in our fight against COVID-19. AI has proved to be of great aid in drug development, clinical diagnosis, triage patients, monitoring mental health, forecasting spread, fighting misinformation, and even helping function robot cleaners.

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Introduction

According to US Centers for Disease Control, Coronaviruses are derived from the Latin word corona, meaning "crown" or "halo", because of the presence of "crown- like spikes on their surface [4,5]." Coronavirus disease 2019 (COVID-19) is an infectious disease that can spread from person to person, is caused by the novel coronavirus or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; formerly called as 2019-nCoV), which was first recognized in the midst of an episode of respiratory illness cases in Wuhan City, Hubei Province, China, the outbreak of this deadly disease is believed to have started through some local seafood or animal market indicating animal to person spread [1]. Later, cases of person to person spread were indicated in Hubei and outside Hubei and china spreading all over the world. It was at first reported to the WHO on December 31, 2019. On January 30, 2020, the WHO announced the COVID-19 outbreak a global health emergency. On March 11, 2020, the WHO proclaimed COVID-19 as a global pandemic [2,3].

Taxonomy

Coronaviruses were first discovered in the 1960s, and belongs to the large Family of Coronaviridae which includes seven viruses that are known to infect humans. While, some that typically infect animals are known to evolve to cause diseases in humans. These viruses are enveloped positive sense single stranded RNA viruses with a Nucleocapsid of helical symmetry with structural genes encode the structural proteins, spike (S), envelope (E), membrane(M) and nucleocapsid (N) (Figure 1) [6].

They are classified into four genera based on the differences in their protein sequences i.e alpha, beta, gamma, and delta.

Common human coronaviruses (present in the human population frequently causing respiratory infections in adults and children worldwide) are :

-Alpha coronavirus: HCoV-229E ,HCoV-NL63

-Beta coronaviruses: HCoV-OC43 , HCoV-HKU1

-Gamma coronavirus and

-Delta coronavirus have not yet been reported to cause any human disease [7,8].

Rare human coronaviruses (beta coronaviruses) are:
-SARS-CoV-1 (Severe Acute Respiratory Syndrome) - 2003
-MERS-CoV (Middle East Respiratory Syndrome)- 2012
-SARS-CoV-2 / COVID-19 [4].

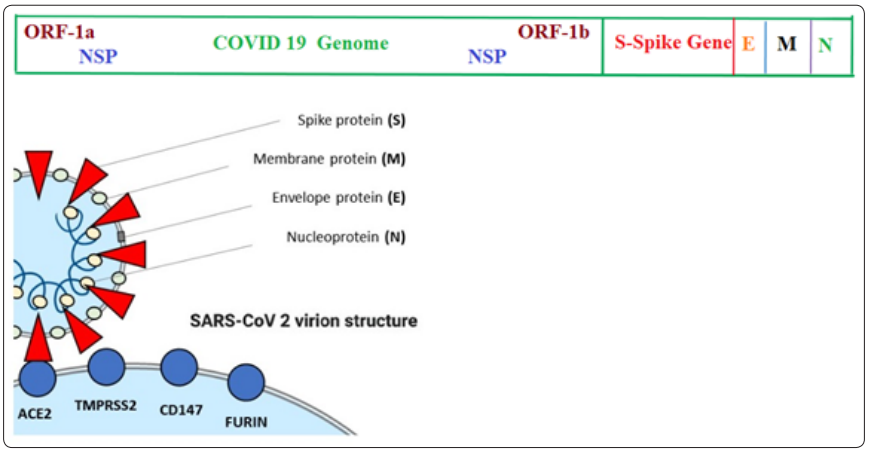


Figure 1: The genomic organization of SARS-CoV-2 with their Open Reading Frame-ORF. NSPs- Non Structural Proteins (are processed to form a replication–transcription complex (RTC) that is involved in genome transcription and replication. NA-dependent RNA polymerase (RdRp) for copying viral genome. The structural genes encode the structural proteins, spike (S), envelope (E), membrane (M), and nucleocapsid (N), involved in viral assembly for new virus formation. Angiotensin-converting enzyme 2 and TMPRSS2 (Trans membrane Serine Protease 2) for the Viral Cell tropism.

Transmission & Infectivity Period
SARS-CoV-2 is extremely contagious. Researchers measure the infectiousness of this disease with a figure called R0 (R-nought); also called as Re or effective reproduction rate. The figure represents the number of people one infected person is going to spread the infection on an average.

For example, an R0 of 1 means that an infected person passes it to 1 new person likewise R0 of 2 is that 1 infected person spreads it to 2 new people, and henceforth. If the R0 is below 1, the infection diminishes, while if it stays at 1 or above, then it continues to spread. Currently, COVID-19 is estimated to have an R0 between 2 and 2.5 [9].

Transmission
The virus primarily spreads from close person to person contact through respiratory droplets i.e. while breathing, coughing, and sneezing or talking, the infected person expels droplets of moisture that contains the virus and these droplets can land in the mouth or nose of people who are nearby or possibly be inhaled into their lungs. So, maintenance of good social distance (Minimum 6 feet) is necessary for the prevention of this disease [10]. New studies suggest a single sneeze can project particles a distance of 9 meters, or about 27 feet but this depends on the size of droplet. Also, the virus can spread through Fomites (clothes, utensils, furniture, newspaper, doorknobs, mobile phones, packaged items, ATM, etc.) which are inanimate objects where pathogens like coronavirus settle for hours [11] (Figure2). The Virus May Stay up to 24 Hrs. on Cardboard used in the delivery of online purchases, 72 hrs. On Plastics & Stainless Steel includes Sinks, door handles etc….
The virus can also land on surfaces that others may have touched (and then spread by touching their mouth, nose, or eye) [12-14].

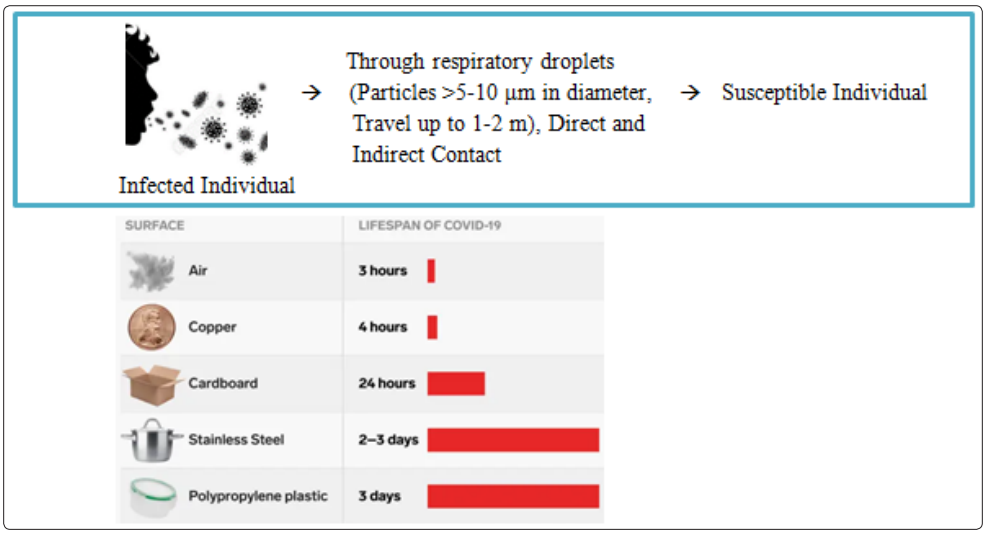


Figure 2: Transmission Route of COVID19 and Lifespan of Covid-19 on surfaces

Incubation Period (IP) [15]

-IP of 2 to 14 days according to WHO.
-IP case of 27 days was reported by Hubei Province government on Feb 22.
-IP case of 19 days was observed by JAMA on Feb 21.
-IP of 24 days was first observed on Feb 9. But WHO concluded it as a result of second exposure.

Epidemiology and Statistics [16]

No. of cases

As of 13th June, 2020 the number of confirmed cases reported by World Health Organization globally has jumped up to 7,553,182 reporting around confirmed 423,349 deaths (Figure 3). The table provided reveals the data as of 13th June, 2020 of the laboratory confirmed cases and death reported by the World Health Organization.

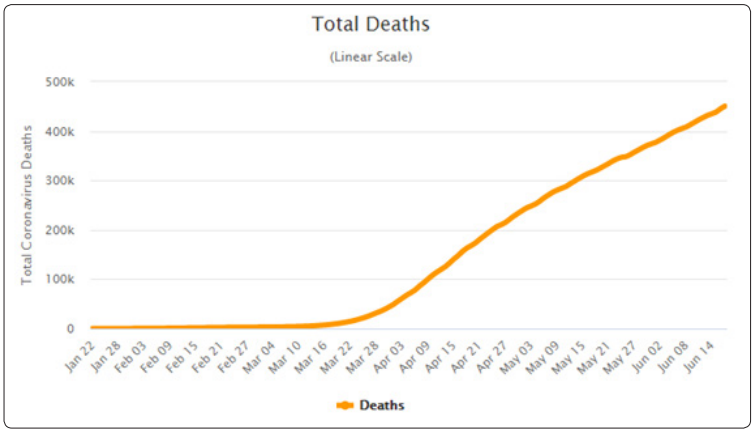


Figure 3: Total Corona Virus Deaths as of 13th of June 2020

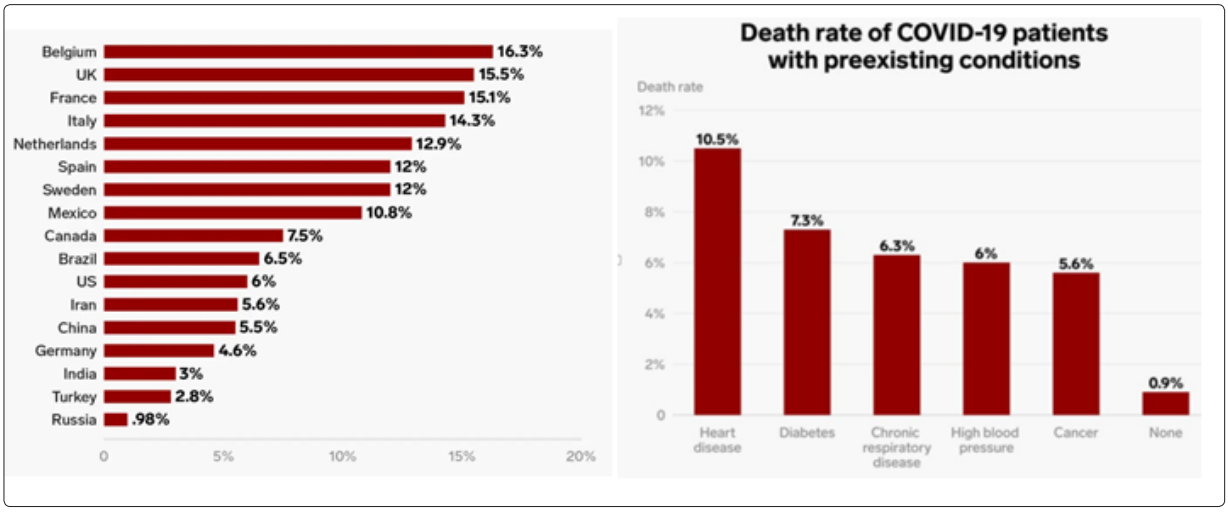


Figure 4: COVID-19 Death Rates per Country with Pre Existing Conditions

Risk Factors of Mortality/Comorbidities [17,18]

In all age groups, Covid-19 can present with an enormous range of severity. Scientists have some clues on what puts an individual at a higher risk compared to others. Patients with following health conditions and risk factors associated, but not limited to, diabetes, hypertension, COPD, coronary artery disease, cerebrovascular disease, chronic renal disease, and smoking, may well be at higher risk for severe disease or death from Covid-19 as stated by the recent CDC report (Figure 4). The reported fatality rate based on age is 14.8% for people >80 years of age, 8% for people between 70 and 79 years, 3.6% for people between 60 and 69 years, 1.3% for people between 50 and 59 years, 0.4% for people between 40 and 49 years, 0.2% for people between 10 and 39 years; no fatalities have been reported for children under 10 years of age. Notably, the fatality rate is higher in males (2.8%) than in females (1.7%) [19,20].

Pathogenesis [6,21,22]

The SARS-CoV-2 virion is ~125 nm in diameter, and its genome ranges from 26 to 32 kilobases, the largest for an RNA virus. Pathophysiology and virulence mechanisms of coronaviruses, and also of SARS-CoV-2 have links to the function of the non-structural proteins and structural proteins. It has 4 structural proteins: spike (S), envelope (E), membrane (M), and nucleocapsid (N).

- N protein forms a complex with RNA and aids in the viral assembly after its replication.
- S, E, and M proteins create the viral envelope, and studies have shown that among structural protein, viral envelope has a crucial role in virus pathogenicity.
- S protein, is a club-shaped surface projection, giving the virus its characteristic crown-like appearance on electron microscopy, composed of two subunits, S1and S2. Homotrimers of S proteins compose the spikes on the viral surface which guide the virus to the host receptors. In SARS-CoV-2, the S2 subunit contains a fusion peptide, transmembrane domain and a cytoplasmic domain.

SARS-CoV-2 attaches to the host cell by binding its S proteins to the receptor protein, angiotensin-converting enzyme 2 (ACE2). ACE2 is expressed by epithelial cells of the intestine, kidney, blood vessels, and most abundantly in type II alveolar cells of the lungs. The virus induces a drop of ACE2 in human cells, possibly inducing lung damage. The human enzyme transmembrane protease, serine 2 (TMPRSS2) is also used by the virus for S protein priming and to aid in membrane fusion (Figure 1). ACE2 is also highly expressed in the respiratory tract, particularly in epithelial cells of the bronchi, alveoli (both type I and II cells), trachea and bronchial serous glands, as well as in macrophages and alveolar monocytes.

Recent studies and data indicate that the SARS-CoV-2 infection is capable of producing an excessive immune reaction in the host and this is labeled as "Cytokine storm". Main mechanism behind this cytokine storm is a surge in the levels of IL-6 produced by activated leukocytes and acts on a large number of cells and tissues. It is an acute phase reactant and is also implicated in the pathogenesis of cytokine release syndrome which is an acute systemic inflammatory syndrome characterized by fever and multi-organ failure (Figure5).

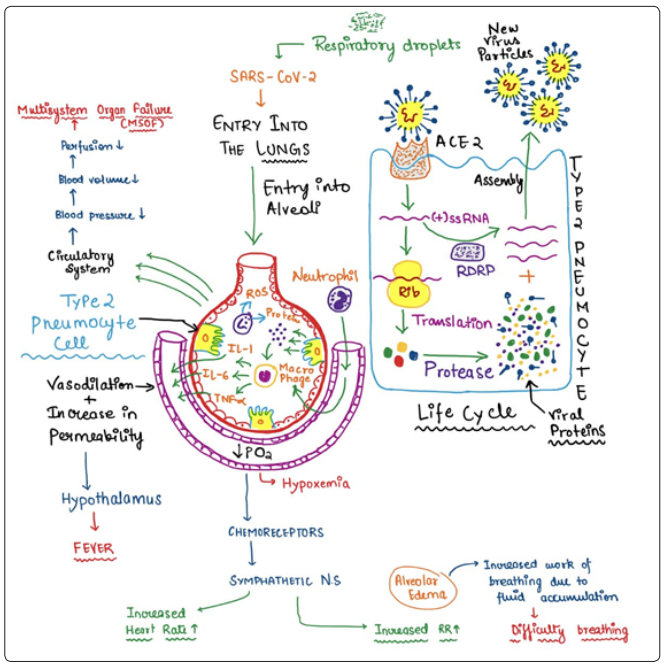


Figure 5: The life cycle & Pathogenesis of SARS-CoV-2 in the host cells

Clinical Course of Patients

Clinical Characteristics and Susceptibility of Sars-Cov-2 Infection in Humans [20,23,24]

The estimated incubation period of the novel coronavirus ranges from 2 to 14 days. One study showed that around 97.5% of people with COVID-19 developed symptoms within 11.5 days after SARS CoV-2 infection. However, some cases had an incubation period of 21, 24, or 27 days [25]. The complete clinical picture of SARS-CoV-2 is still unclear. The disease begins with flu-like symptoms that include fever, fatigue, dry cough, sore throat, shortness of breath, headache, chest tightness, chest pain, and muscle pain which may mimics cold, Flu and Allergy (Figure 6 & 7). Some of SARS-CoV-2 patients have runny nose, nausea, vomiting, and diarrhea [26]. People can be infected without showing symptoms, which allows the virus to spread more effectively from person to person. Complications can occur due to COVID-19 leading to severe infections, such as pneumonia (infection of the lungs), kidney failure, Blood clots with their consequences and death [27]. The mild phase of the disease can last up to 2 weeks, while severe or critical disease lasts approximately 3 to 6 weeks (this analysis was conducted on 55,924 confirmed cases). Additionally, the time from the disease onset to the development of the severe disease is one week, while the time from the onset of symptoms to death ranges from 2 to 8 weeks [19].

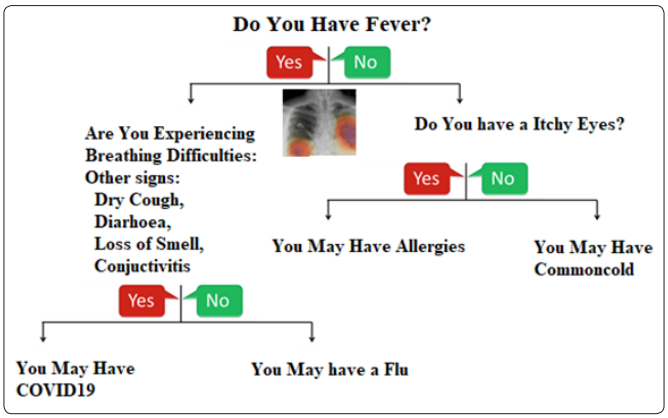


Figure 6: Sorting out symptoms of COVID-19, influenza, colds and allergies. These symptoms may vary from person to person. Only a Doctor can give a Diagnosis

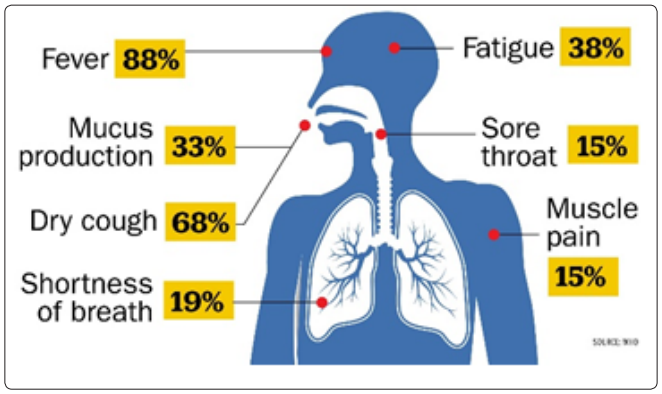


Figure 7: COVID19 Signs & Symptoms

Complications: Blood Clots and Their Consequences [28]

Blood clots in the lung are a common feature of severe COVID-19 [29]. If a large blood vessel carrying blood to the lung is suddenly blocked, this can worsen the breathlessness and cause chest pain. Clots more than 1 millimeter in size may be seen in computed tomography (CT) scans that 'light up' the blood vessels in the lung like branches of a tree [30] . However, if clotting also starts to develop in the smallest vessels in the lung, this may cause a gradual deterioration in the patient's condition, increasing oxygen requirements. Some critically unwell COVID-19 patients have had strokes due to a blockage of blood vessels supplying the brain [31] (Figure-8 & 9).

Higher levels of D-dimer, a breakdown product of blood clots, have been seen in critically ill patients compared to moderately ill patients. Although patients in hospital routinely receive low-dose preventive blood thinning medications, some hospitals are now routinely giving higher doses to COVID-19 patients with very high D-dimer levels, and trials comparing doses of blood thinner are underway [32].

High blood pressure and diabetes both damage blood vessels, and patients with these conditions are at high risk of severe COVID-19. The gateway for viral entry in the lung, the ACE2 receptor, is also

found on cells lining blood vessels, and under the microscope there is visible evidence of viral infection of vessels. In severe COVID-19, pre-existing damage to blood vessels, damage from the virus itself, and the body's own inflammatory response [33] might combine to encourage blood clotting.

Entry of COVID 19

↓

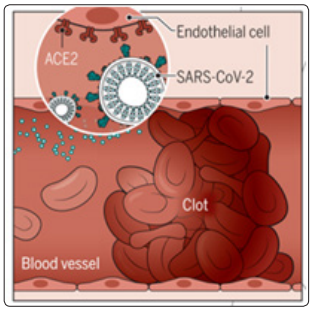
Cytokines release from Immune cells

↓

Cytokines attracts more immune cells to the area

↓

The Virus and the immune response can damage endothelial cells



Blood clots formation

↓

Blood clot form in small blood vessels, interrupting the flow of blood and preventing oxygen entering blood can lead to amputations, also damage vital organs: Lung, Heart, Brain and life threatening complications: Pulmonary embolism, heart attack and stroke

Figure 8: Blood vessel disease, blood clots and inflammatory damage in severe COVID-19

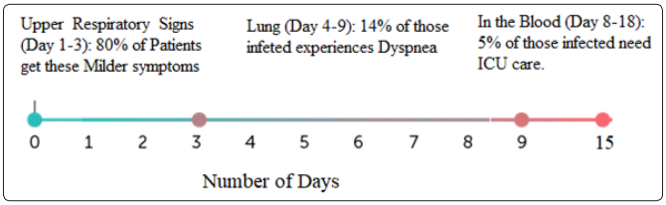


Figure 9: Tracking Corona in Humans [71]: Covid19 may last on an average for 21 days with people either dying or being discharged by the end of the 3rd week. Upon infection - based on the Immune system and Treatment options, symptoms may last milder in 2 weeks, Severe with recovery in 3-6 weeks and Deadly 2-8 weeks.

Artificial Intelligence (AI) [35-45]

Artificial Intelligence (AI) or Machine Learning is a branch of computer science concerned with building the ability of a machine or computer to learn a specific program and be able to execute it with minimum or no interference or help from a human being.

How AI Can Assist the Response to the Crisis, And the Recovery to Follow

AI In Drug Development & Diagnosis

The most important application of AI during the pandemic is in the field of Pharmaceutical research, where AI is being used to develop new drugs for COVID-19 while checking if any existing drugs or compounds can be repurposed against COVID-19. As of February 2, 2020, 38 compounds were shortlisted using AI, as being potential candidates. Some of the most promising of these were a mixture of Lopinavir and Ritonavir used to treat AIDS, Remdesivir used for Ebola treatment and an anti-malarial drug Chloroquine.

The most recent developments are coming from the project Exscalate4Cov (E4C). The goal of the teams involved in this European research project is to find molecules that can block the growth of Covid-19 inside the body. For this they have to analyze a huge library of 500 billion molecules. Here is where AI came to the rescue again! They are using supercomputers capable of analyzing 3 million molecules per second! After shortlisting potential molecules, they are shipped to Leuven in Belgium. Here in complex low pressure laboratories, Researchers infect normal cells with SARS-CoV-2 virus and add the potential molecules. From here on AI again comes to help along with robotics (using AI). The robotic arms take the plates with the infected cell and compound and incubate it for some days. After this the robotic arms transfer the samples to an automatic microscope which using AI checks if the compound was successful in blocking the virus. Thus AI is definitely a very helpful tool for developing the drug in these trying times.

AI for Developing 3d Structure

AI is also being used to develop 3D structure of genome and protein structures to find for potential attack sites. Deep Mind has released a library called AlphaFold to aid in this process.

AI in Detecting the Outbreak And Spread

Bluedot – An Outbreak Risk Software

AI tools can help identify virus transmission chains and monitor broader economic impacts. In several cases, AI technologies have demonstrated their potential to infer epidemiological data more rapidly than traditional reporting of health data. Institutions such as Johns Hopkins University and the OECD (oecd.ai)

AI in Prevention

EpiRisk is a computational platform designed to allow a quick estimate of the probability of exporting infected individuals from sites affected by a disease

AI in Response and Delivery

Drones for Material Transport and Robot for high exposure Tasks at hospital

AI in Diagnosis

CT scans for Pattern recognition using medical imagery and symptoms data

AI in Service Automation

Canadas COVID-19 Chatbot - Virtual assistants and chatbots have been deployed to support healthcare organisations, for example in Canada, France, Finland, Italy, the United States and by the American Red Cross. These tools help to triage people depending on the presence of symptoms.

AI in to Fight Misinformation

The COVID-19 "infodemic"– social networks and search engines are using personalized. AI information and tools and relying on algorithms to find and remove problematic material on their platforms.

Lab Diagnosis [46]

Collection of blood and sputum specimens for culture in patients with severe disease to rule out other causes of lower respiratory tract infection and sepsis, especially patients with an atypical epidemiological history. Specimens should be collected prior to starting empirical antimicrobials if possible.

Molecular Testing: RT-PCR (Table 1)
Molecular testing is required to confirm the diagnosis. A nucleic acid amplification test, such as real-time reverse-transcription polymerase chain reaction (RT-PCR), for SARS-CoV-2 can be done patients with suspected infection by collecting upper respiratory in ambulatory patients and lower respiratory specimens in severe respiratory disease, with confirmation by nucleic acid sequencing. RT-PCR (Reverse Transcriptase- Polymerase Chain Reaction) have been designed based on the E, RdRp, and N genes. Also, scientists established molecular detection tools for SARS-CoV-2 based on the S gene [47,48].

Serological Testing / Immuno Assays – Indirect Elisa (Figure 10 & Table 1)
Detection of SARS-CoV-2 immunoglobulin G (IgG) / IgM antibodies in serum, plasma, or whole blood. Antibody responses to SARS-CoV-2 typically occur during the first 1 to 3 weeks of illness, with the seroconversion time of IgG antibodies. Testing can be used to aid the diagnosis of patients who present 9 to 14 days after symptom onset. This technique has not been validated yet.

IgM and IgG ELISA detection kits consist of an antigen which is immobilized on a surface (most often a titre plate or paper strip), which binds virus-specific antibodies from a patient sample (i.e. blood sera). By adding a further reporter protein or Secondary Antibody, it is then possible to detect a virus-specific immune signal to confirm the presence of ongoing or past viral infection [49].

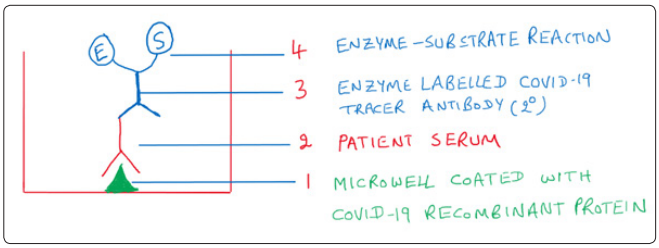


Figure 10: Overview of ELISA - Enzyme Linked Immuno Sorbent Assay for the Patient Antibodies (IgG /IgM) detection

Radiological Diagnosis: Chest Imaging and Lung Ultra Sound
All imaging procedures should be performed according to local infection prevention and control procedures to prevent transmission. Chest imaging is considered safe in pregnant women.

Chest x-ray in all patients with suspected pneumonia. It may be helpful in making the diagnosis, guiding individual patient management decisions, aiding the diagnosis of complications, or giving clues to an alternative diagnosis. However, it is not diagnostic for COVID-19. Chest X-ray examination in the early stage of the disease shows interstitial changes and multiple small plaque shadows.

Chest CT scans play an important role in the diagnosis of acute respiratory disease syndrome (ARDS) and pneumonia as well as in the early detection of lung parenchymal abnormalities in patients at risk and provide an impression of secondary infection

Lung ultrasound is used as a diagnostic tool in some centers as an alternative to chest x-ray and chest CT. B-lines are the prominent pattern in patients with COVID-19, occurring with a pooled frequency of 97%. Pleural line abnormalities are also common, with a pooled frequency of 70%.

Emerging Tests: Antigen Testing – Direct Elisa (Table 1)
These tests detect fragments of proteins found on or within the virus by testing samples collected from nasal cavity swabs. If the patient sample contains viral antigen proteins, those antigens are now sandwiched by two antibodies: one that attaches them to the test kit and another that makes them visible. The test works faster than RT-PCR. If a sample doesn't have enough virus or a person has a low-grade infection, the test might give a false negative result.

Reverse Transcription Loop-Mediated Isothermal Amplification
Reverse transcription loop-mediated isothermal amplification (RT-LAMP) assays are an emerging test to detect SARS-CoV-2 viral RNA. While assays are simple and quick, there is less evidence for their use.

Blood Profile [50]
The blood profiles of patients suffering from SARS-CoV-2 infection revealed the following: (1) increased C-reactive protein and erythrocytes, (2) increased myohemoglobin, liver enzymes, and muscle enzymes, with a high level of D-dimer in severe cases, and (3) normal or decreased white blood cell counts and lymphocytes in the early stage of the disease, with advanced lymphocytopenia in severe cases. In ICU patients, high levels of plasma granulocyte colony-stimulating factor (GCSF), IP10, IL2, IL7, IL10, TNF-α, and MIP1a were reported.

Virus Detection [46]
Electron microscope examination of SARS-CoV-2 revealed the typical coronavirus morphology. Further, SARS-CoV-2 was successfully isolated from human respiratory epithelial cells or BALF samples of infected patients using Huh7 cells and Vero E6 cells. The isolated strain was confirmed by immunofluorescent antibody techniques using the cross-reactive nucleoprotein (NP) antibody.

Table1: Current Types of Corona Testing

Type of Test	Molecular Test RT PCR	Antibody Test ELISA	Antigen Test ELISA
Sample Collection	A Nasal or Throat swab	Blood	A Nasal Swab
Detection	Viral Genetic Material DNA from RNA	Antibodies	Viral Antigen or Protein
What the Test tells You	If you are infected Now	If you were infected in the Past or Current	If you are infected now

Treatment and Management
Some Common and Effective Antiviral Drugs (Table-2).

Table 2: Common Antiviral Drugs with their Mode of Action

Drugs	Mechanisms of Therapy
Chloroquine phosphate/ hydroxychloroquine [51]	Antiviral activity via alkalinization of the phagolysosome, which inhibits the pH-dependent steps of viral replication. Wang et al reported that chloroquine effectively inhibits SARS-CoV-2 in vitro. Both drugs have in vitro activity against SARS-CoV-2, with hydroxychloroquine having relatively higher potency.
Remdesivir [52,53]	The GS-441524 interferes with the viral replication of viral RNA-dependent RNA polymerase and evades proofreading by viral exoribonuclease (ExoN). This decreases viral RNA production. An emergency-use treatment of suspected or confirmed COVID-19 in adults and children with low blood oxygen levels (SpO2 ≤94% on ambient air) or needing oxygen therapy or more intensive breathing support such as a mechanical ventilator.
Baricitinib [54]	Interfering with viral entry by inhibiting one of the endocytosis regulators
lopinavir/ritonavir [55]	Could act by inhibiting SARS-CoV-2 protease for proteins cleavage, interfering with virus replication
Darunavir [56]	Could act by inhibiting SARS-CoV-2 protease for proteins cleavage, interfering with virus replication
Camostat Mesylate [57]	Interfering with viral entry
Favipiravir	Binds to the viral RdRp and reduce its reproduction
Cepharanthie, elamectin, and mefloquine hydrochloride [58]	Significantly reduced cytopathic effects of SARS-CoV-2, and decrease the viral load
Ivermectin	Inhibits SARS-CoV-2 replication in vitro

Deaxamethasone [59]
Dexamethasone is a steroid-based medication. Part of the way it works is by suppressing the immune system. Helping prevent this over-reaction so that only infected cells are targeted by the immune system.

Convalescent Plasma & Monoclonal Antibody Treatment
Passive immunization (PI) is a method to obtain antibodies in the blood of a recovered patient can be collected as convalescent plasma (CP) and transferred to the blood of a newly infected patient (Fig-11) [60,61].

SARS-CoV-2 monoclonal antibodies have the potential to be used for prophylaxis and treatment of COVID-19 [62]. Recombinant, fully human monoclonal neutralizing antibodies, such as JS016 and LY-COV555, are in development. These antibodies bind to the SARS-CoV-2 surface spike protein receptor binding domain, which blocks the binding of the virus to the angiotensin-converting enzyme-2 (ACE2) host cell surface receptor.

CR3022 is a human monoclonal antibody previously isolated from a convalescent SARS patient, used to target a highly conserved epitope that enables cross-reactive binding between SARS-CoV-2 and SARS-CoV. CR3022 might have the potential to be candidate therapeutics for the prevention and treatment of COVID-19 patients, especially in life-threatening situations.

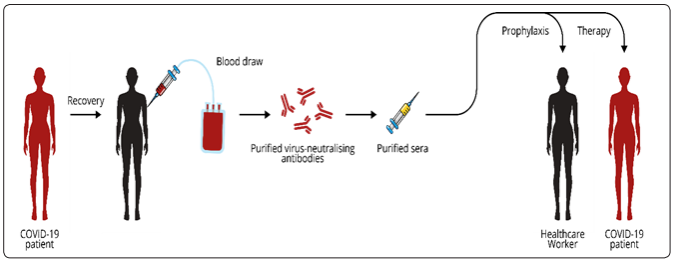


Figure 11: Convalescent Plasma Therapy

Angiotensin-Ii Receptor Antagonists [63]
Angiotensin-II receptor antagonists such as losartan are being investigated as a potential treatment because it is thought that the angiotensin-converting enzyme-2 (ACE2) receptor is the main binding site for the virus.

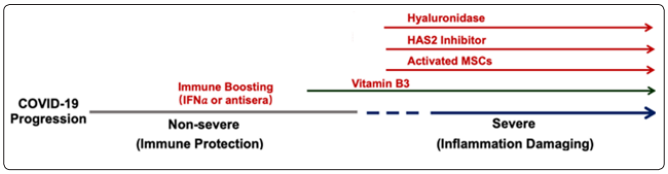
Mesenchymal Stromal/Stem Cell Therapy [64]
It is thought that mesenchymal stem cells can reduce the pathological changes that occur in the lungs and inhibit the cell-mediated immune inflammatory response. Severe cases with COVID-19 infection, solid results have yet to be seen. One caveat is that MSCs need to be activated by IFNγ to exert their anti-inflammatory effects, which may be absent in severely affected patients as T cells are not well activated by SARS-CoV-2 infection. To enhance effectiveness, one could consider employing the "*licensing-approach*": pretreat MSCs with IFNγ with/without TNF or IL-1.

Targets for Cytokine Release Syndrome [65]
Interleukin-6 receptor antagonist monoclonal antibodies (e.g., tocilizumab, sarilumab, siltuximab) are being trialled in COVID-19 patients for the treatment of virus-induced cytokine release syndrome.

Bacille Calmette-Guerin (Bcg) Vaccine [66]
The BCG vaccine is being trialled in some countries for the prevention of COVID-19, including in healthcare workers.

Bemcentinib [67]
An experimental small molecule that inhibits AXL kinase. Bemcentinib has previously demonstrated a role in the treatment of cancer, but has also been reported to have antiviral activity in preclinical models, including activity against SARS-CoV-2.

Crispr/Cas13d System [68]
Currently, there is an ambitious study suggesting that CRISPR/Cas13d system can be used to accurately digest the SARS-CoV-2 RNA genome, hence limiting its ability to reproduce. Theoretically, this approach is excellent not only against COVID-19 but for the treatment and prevention of different RNA viruses' infections. However, we have no idea if it is practical or not.



- Inhibition of hyaluronan synthase and elimination of hyaluronan can be prescribed.
- mesenchyme stem cells (MSCs) can be used to block

inflammation and promote tissue reparation.
- Vitamin B3 can be given to patients starting to have lung CT image abnormalities.

Figure 12: The Progression of Covid-19 Infection and Potential Adjuvant Interventions

Vitamin C [70]
Vitamin C supplementation has shown promise in the treatment of viral infections.

Vitamin D [70]
Retrospective study a link between vitamin D insufficiency and COVID-19 severity. Public Health England recommends that people consider taking a vitamin D supplement for bone and muscle health due to a lack of sun exposure because of lockdown measures.

Vitamin D supplementation has been associated with a reduced risk of respiratory infections such as influenza in some studies.

Nitric Oxide [70]
Studies indicate that nitric oxide may help to reduce respiratory tract infection by inactivating viruses and inhibiting their replication in epithelial cells.[600] The US Food and Drug Administration has approved an investigational drug application for inhaled nitric oxide to be studied in a phase 3 study of up to 500 patients with COVID-19.

Mechanical Ventilation
Helps a patient breathe (ventilate)

Hyperbaric Oxygen [70]
Preliminary evidence suggests that hyperbaric oxygen treatment has been successfully used to treat deteriorating, severely hypoxemic patients with severe COVID-19.

Vaccines [71-73]
There is currently no vaccine available. Vaccines are in development, but it may take at least 12 to 18 months before one is available. Several vaccine candidates are currently approved for human testing through clinical trials, including mRNA and DNA platform vaccines, Adenovirus vector vaccines, Inactivated virus vaccines was immunogenic, inducing humoral responses (peaking 28 days after vaccination) and T-cell responses (peaking 14 days after vaccination) in most participants (Figure 13).

Ad5-nCoV: A recombinant adenovirus type-5 (Ad5) vectored vaccine expressing the SARS-CoV-2 spike glycoprotein.

ChAdOx1 nCoV-19: An adenovirus vector vaccine that carries the SARS-CoV-2 spike protein. Despite this, researchers are moving to human trials.

Inactivated SARS-CoV-2 virus (Sinovac®): Contains a more traditional chemically inactivated version of the virus.

mRNA-1273: A novel vaccine that uses mRNA technology not previously approved for use in humans. The mRNA encodes for a full-length prefusion stabilised spike protein of SARS-CoV-2 and is encapsulated in a lipid nanoparticle.

Regeneron
Regeneron has accelerated its timeline for ensuring doses of a potential vaccine (REGN3048 and REGN3051) and treatment are ready for human clinical trials by early summer

An Intranasal COVID-19 Vaccine
It's similar to NasoVAX is being developed by US-based clinical-stage biopharmaceutical company, Altimmune. Animal studies are being progressed.

Scientists Isolate Spike Protein from Corono virus & Place it in Harmless Virus
(Viral Vectors such as Adeno virus)
Or
Inactivated Virus with Formaldehyde or heat
Or
Weakened Virus
↓
This is injected into the Patient
↓
Virus Replicates in the human Target cells, Produce spike protein and Antigen Presenting cells
induces specific immune response against COVID19 to produce Antibodies and Activate
Viral specific killer's cells.

↓
If the patient encounters corona virus again, the Antibodies and Memory B and T cells are triggered to fight the virus.

Figure-13: Overview of How Corona Virus Vaccine Works:

Conclusions
The COVID-19 pandemic poses a significant threat to the global public health systems. The novel coronavirus spread so rapidly that it has changed the rhythm of the globe. Despite our knowledge of the SARS-CoV-2 infectious cycle, there is no clear strategy for COVID-19 patients' treatment. Based on recent experimental findings and recommendations, physicians are investigating different potential drugs that showed antiviral activity against SARS-CoV-2. The only time to tell which one of these drugs is going to work. In the meantime, scientists around the globe are working aggressively to find clinical therapies or vaccines against the virus with advanced technology like Artificial Intelligence (AI).

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