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Outbreak of COVID-19: An update on the status of the evolving mechanism with possible diagnostic, therapeutics, and future directions

Jitender Reddy Kalli, Utkarsh Raj*

Department of Biotechnology and Bioinformatics, NIIT University, Rajasthan, India

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ABSTRACT

The new Coronavirus, officially designated as SARS-CoV-2 has caused a pandemic with a global spread to more than 216 countries, areas, or territories 17,106,007 confirmed cases of COVID-19, including 668,910 deaths, reported to WHO as of 4:39 pm CEST, 31 July 2020. This virus has been found to have striking similarity with the SARS CoV, which caused an epidemic earlier. Symptoms include fever, cough, fatigue, myalgia, dyspnoea, and rarely vomiting and diarrhoea. Diagnostic with the help of serological and molecular methods are currently possible, along with CT scans and Chest X Rays for the early detection. Bioinformatics tools are now helping us in mapping the infection dynamics with increased accuracy and are helping us establish a chain of progression of the virus. With research rapidly expanding, new facts have come into the focus and WHO has started a SOLIDARITY program, which helps in randomised drug trials with better validity aided by measures taken by WHO and use of technology. Nevertheless, novel Coronavirus (2019-nCoV) is one of the deadliest viruses' humanity has encountered, causing not just biological, but also impacting the world economy. This review has all the information about COVID-19 such as its virology, epidemiology, clinical aspects, diagnosis, possible treatment, and prevention. This study also emphasised on the future direction that could be computational drug screening & vaccine designing using Immunoinformatics approach to save time and cost to come out with potential treatments. Drug screening from cell lines and plasma therapy may prove highly effective to treat COVID-19 patients.



*Corresponding Author

Name: Utkarsh Raj

Phone:

Email: utkarsh.iiita@gmail.com

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INTRODUCTION

The end of December marked a cluster of patients diagnosed with pneumonia of an unknown origin. When traced, the patients shared a connection with

the Huanan South China Seafood Market in Wuhan, People's Republic of China (PRC) (Zhu *et al.*, 2020). The causative organism has now been confirmed as a novel coronavirus, provisionally given the name 2019-nCoV and the disease caused was officially named 'COVID-19' by the World Health Organization (WHO). The medical characteristics of COVID-19 are strikingly similar to that of viral pneumonia caused by Severe Acute Respiratory Syndrome Coronavirus (SARS CoV). Hence the 2019-nCoV is also named as the SARS CoV-2 by International Committee on Taxonomy of Viruses (ICTV) (Wunderink, 2015). However, it is to be noted that while the fatality rate of the 2019-nCoV is lesser than that of the SARS CoV, it has a more significant reproductive number, which suggests that the 2019-nCoV has a faster spread than the SARS coronavirus (Liu *et al.*, 2020). The 2019-

nCoV shares genetic similarity with both SARS and the MERS coronaviruses, a more significant similarity with SARS coronavirus (Chen *et al.*, 2020b). With the various facts and figures, this review aims at exploring the multiple aspects of the newly discovered 7th disease-causing Coronavirus, the 2019-nCoV and the COVID-19 pandemic including epidemiology, pathogenesis, clinical features, diagnosis, treatment, and its prevention.

Virology

Coronaviruses are individuals from an enormous family, Coronaviridae, known to cause medical conditions extending from the regular flu to more increasingly fatal diseases like the MERS and the SARS. The coronaviruses range from 60 nm to 140 nm in diameter and have a Spike protein enveloping them, giving them a crown-like appearance. Hence, the name coronavirus has been coined (Richman *et al.*, 2016). The SARS CoV infected 8422 people and cost 912 lives, with the epicentre of the epidemic as China (Chan-Yeung and Xu, 2003) and the MERS CoV affected 2494 people and cost 858 deaths, with the epicentre of the outbreak as Saudi Arabia (the Middle East Respiratory Syndrome Coronavirus. Available at <https://www.who.int/emergencies/mers-cov/en/>).

The SARS-CoV-2 belongs to the group of β – coronaviruses those having a lot of reservoirs like palm civets, Horseshoe bats, racoon dogs, Red foxes, Chinese ferret-badger, Mink, etc. like its other counterparts (Shi and Hu, 2008). Although Bats can be considered the best possible ecological reservoirs for SARS-CoV-2, but their actual reservoirs have not been identified yet. The SARS CoV-2 is a non-segmented, enveloped and [+] SS RNA coronavirus. Previously, there have been six identified coronaviruses (HCoV-NL63, HCoV-229E, HCoV-OC43, HCoV-HKU1, SARS-CoV, and MERS-CoV) that cause disease in humans, SARS CoV-2 being the 7th member after the MERS CoV (Zhu *et al.*, 2020).

Phylogenetic Perspective of the SARS CoV-2 concerning genome

On the sequence alignment of the SARS CoV, MERS CoV, and the SARS CoV-2, it has been identified that the SARS CoV-2 or 2019-nCoV has more identity with the SARS CoV than MERS CoV (Chen *et al.*, 2020b). The striking similarity in the Receptor Binding Protein between the SARS CoV and the 2019-nCoV suggests that the SARS CoV-2 uses angiotensin-converting enzyme 2 (ACE 2) as the binding receptor, like the SARS CoV (Hoffmann *et al.*, 2020). This helps the virus to gain entry into the host organism, causing an infection. However, the details about the strength of the interaction and

the mode of organ damage remain unknown, but the research is underway. In a phylogenetic analysis conducted by Peter Forster *et al.* (Forster *et al.*, 2020), three strains of the 2019-nCoV were identified where one strain, native to East Asia and the others were more common in America and Europe. Using a technique that was employed to reconstruct the prehistoric population, which colonised the planet, a network-based phylogeny approach was designed, which is now applied to the corona virological data (Forster *et al.*, 2020). The A strain, bearing 96% similarity with the bat coronavirus, was considered as an outgroup and it was discovered that another strain B was derived from A by two mutations, one synonymous and the other non-synonymous. Remarkably, This B strain has evolved and had mutations outside Asia only. One of the explanations for this is the possibility that the B strain is immunologically adapted to the East Asian population and hence, to be potent outside East Asia, it might have mutated. The strain C that was sampled is absent in the Chinese mainland and majorly found across European countries. Hence, using this information, it is now possible to trace the infection paths more reliably. Takahiko Koyama *et al.* (Koyama *et al.*, 2020) analysed 10 022 SARS CoV-2 genomes from the data repository from 68 countries. Most of these genomes came from the United States of America (3543 samples), United Kingdom of Great Britain and Northern Ireland (1987 samples) and Australia (760 samples). From them, they detected a total of 65776 variants with 5775 distinct variants. The 5775 different variants consist of 2969 missense mutations, 1965 synonymous mutations, 484 mutations in the non-coding regions, 142 non-coding deletions, 100 in-frame deletions, 66 non-coding insertions, 36 stop-gained variants, 11 frameshift deletions and two in-frame insertions.

Morphology

The main structure of the 2019-nCoV includes four components encoded in the RNA, Viz. The Spike protein(S), the nucleocapsid protein (N), a small membrane protein(SM), membrane glycoprotein (M) with an additional membrane glycoprotein (HE) present in HKU1 and HCoV-OC43 coronaviruses (Rottier, 2013). The Spike protein (S) is a trimeric protein that aids in receptor recognition and binding, fusion with the host cell to gain entry and cause a successful infection. This S protein is primed by the protease of the host cell, in humans, the human serine protease TMPRSS2 primes this in SARS-CoV and SARS-CoV-2. It has an N-terminal domain (NTD) and a receptor-binding domain (RBD). It was found that this RBD could lead to spillover to other animals and between humans

Table 1: List of potential candidates in clinical testing and their modes of action.

Type of Therapy	Candidates	Mode of action	
Antiviral Targets	Chloroquine	inhibit both Endocytosis and exocytosis of virus cause dysfunction in protein synthesis	
	Baricitinib	inhibits Endocytosis	
	Nitazoxanide	inhibits exocytosis	
	Lopinavir	inhibits protein synthesis inside the infected cells	
	Nelfinavir	inhibits protein synthesis inside the infected cells	
	Ribavirin	cause chain termination	
	Remdesivir	inhibits viral RNA dependent RNA polymerase	
	Immune modulating therapeutics	Tocilizumab	binding to IL-6 receptors
		Baricitinib	prevent the intracellular entry of viral cells binding to associated protein kinase 1 (AAK1)
		α (alpha) interferons	compensate evasion of α interferons by the virus
corticosteroids		Not established	
Enhancing the innate immunity	NCT04280224	anti-cancer NK based treatment	

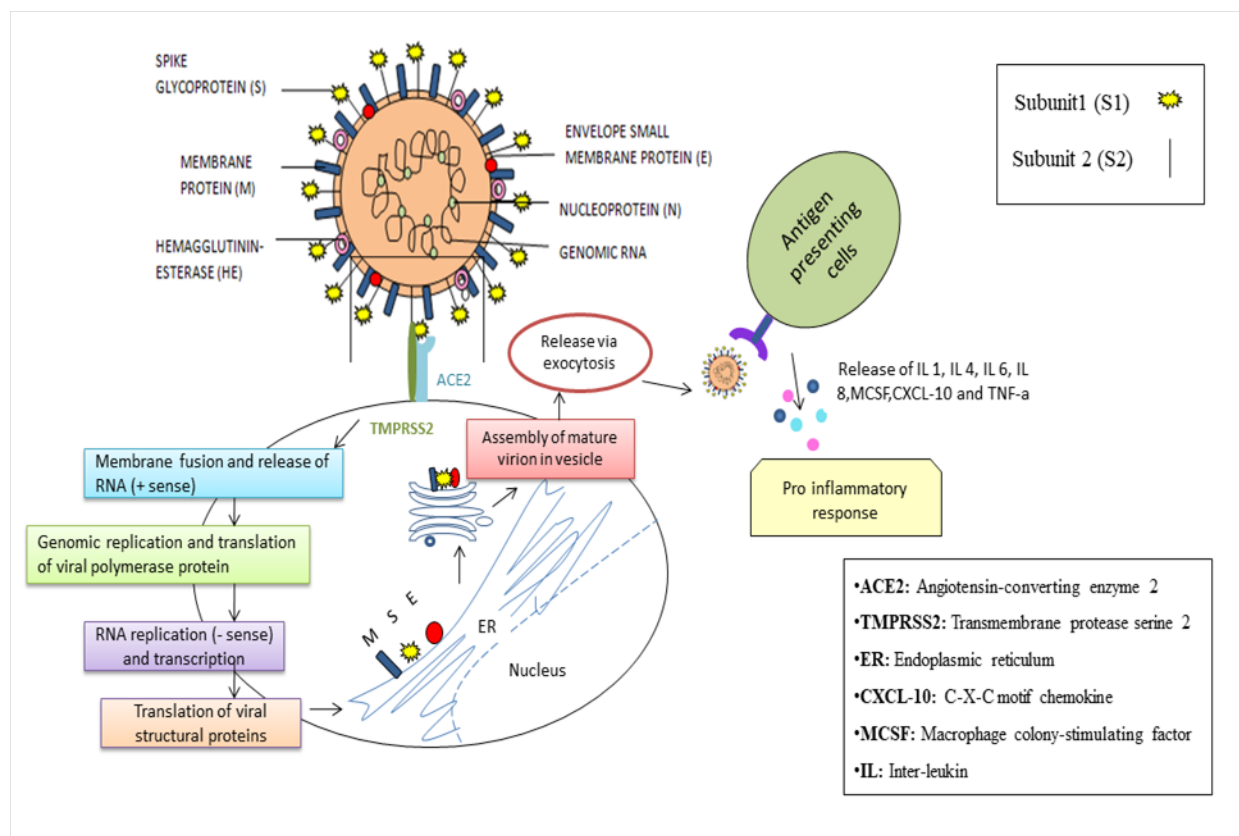


Figure 1: Infection cycle of 2019-nCoV in COVID-19

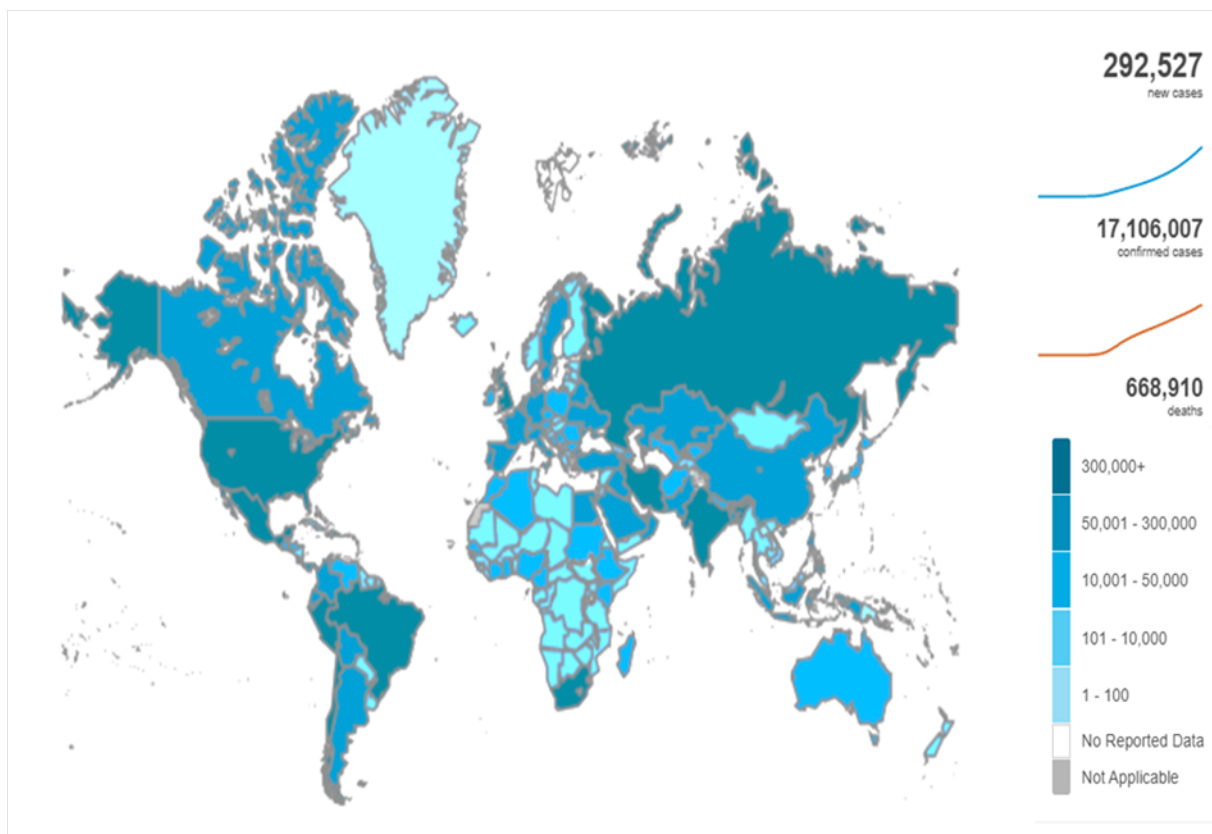


Figure 2: Confirmed COVID-19 cases and spread in different countries as of 4:39 pm CEST, 31 July 2020 [Source: WHO]

alike (Gui *et al.*, 2017). The receptor angiotensin-converting enzyme 2 (ACE2) is the receptor through which these viruses gain entry (Hoffmann *et al.*, 2020). The nucleocapsid protein (N) is a phosphoprotein that packages the viral genome and helps in the translation, RNA binding and synthesis. Some of these proteins undergo the process of glycosylation to form several glycoproteins in the Golgi apparatus.

Transmission of 2019-nCoV

The primary mode of transmission of the virus is through the respiratory droplets (aerosols) by symptomatic and asymptomatic patients, contact with infected surfaces followed by contact with mouth/nose/eyes and consumption of contaminated animals or the reservoirs and the hosts of the virus. The droplets, once released, can be spread up to a distance of 1-2 m or even more in a closed environment and can stay viable for a long time. Transplacental transfer from mother to child is currently not discovered. However, the transmission can occur post-birth, from an infected mother (Chen *et al.*, 2020a). Upon contact, the trimeric viral Spike protein (S) binds to the Angiotensin-converting enzyme 2 (ACE2) cellular receptor found in the lungs, kidneys, heart, and the arteries. Upon binding, the S protein is separated into two subunits Viz.

S1 and S2 subunits. An extracellular protease catalyses this step. The S1 binds to the ACE 2 receptor, whereas the S2 is cleaved further, causing its activation by the host surface-associated transmembrane protease serine 2 (TMPRSS2). All these changes result in the successful infection of the host cell and the RNA genome of the virus gains entry inside the host cell, while the host-viral membrane is fused. Viral genome which is positive-sense RNA, enters in the cytoplasm of the cell where it translates into two polyproteins 1a, b (pp1a, pp1b). Further, these polyproteins are organized into 16 non-structural proteins (NSPs) to form a replication-transcription complex (RTC) which is involved in genomic transcription and replication. Therefore, a nested set of subgenomic RNAs (sgRNAs) is synthesized by RTC in the form of discontinuous transcription, followed by translation. These newly synthesised components then change the Endoplasmic Reticulum and Golgi apparatus and emerge out with the full post-translational modifications. Finally, the assembly of the virions occurs in the Golgi vesicles.

The final mature 2019-nCoV virions are then released from the host cell into the surroundings to infect new cells, via exocytosis in the vesicles. The complete infection cycle of 2019-nCoV/SARS-

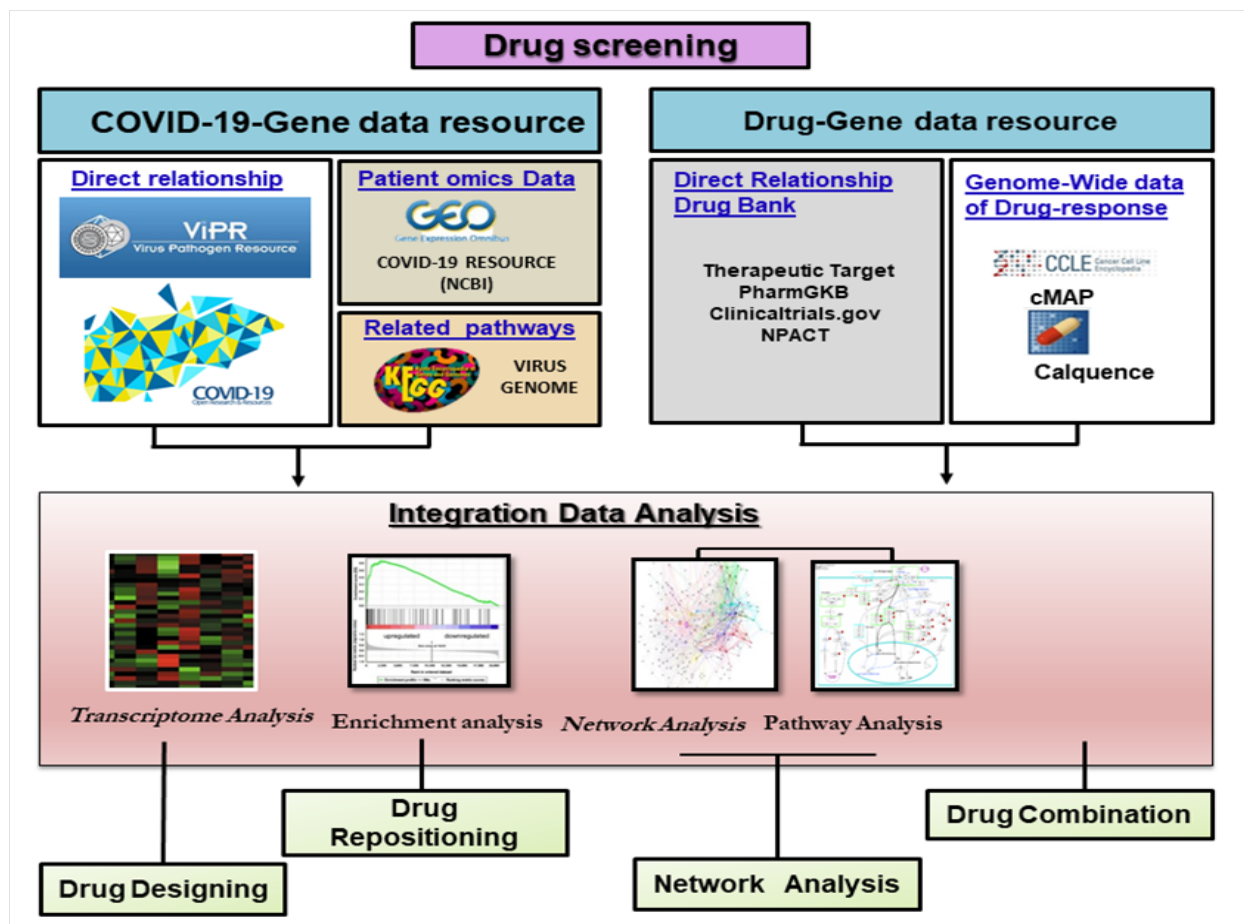


Figure 3: Summarized story of the bioinformatics approaches that can be potentially useful for anti-COVID-19 drug discovery.

CoV-2 has been depicted in Figure 1. The essential difference in Spike proteins of SARS-CoV-2 and SARS-CoV can be observed in the furin-like cleavage site in the SARS-CoV-2. There is speculation that this unique Furin like site provides a gain-of-function which makes the SARS-CoV-2 gain easy entry into the host cell for infection and that this is the reason of the rapid spread of the SARS-CoV-2 in humans compared to the other B beta coronaviruses (Coutard *et al.*, 2020). The conditions that cause the widespread of viruses are described as the source of infection, routes of transmission described earlier, and susceptibility of the patients. The traces of the Coronavirus were detected in the digestive tract, gastrointestinal tract, tears, saliva, conjunctival secretions and urine (Xia *et al.*, 2020). This could explain why Wuhan could've been the epicentre of the outbreak since progression via the gastrointestinal and digestive tracts is perfectly viable (Xia *et al.*, 2020).

Precautions

Precautions include avoiding frequent human contact, respiratory and eye protection especially for

the healthcare professionals, sanitisation and trying to minimise droplet spread using hygiene rules such as covering nose and mouth with a tissue while sneezing followed by disposal of the tissue. Importantly, it has been established that even repeated negative tests cannot be a confirmation of a patient's recovery. Hence, a combination of tests like CT scan, professional advice, RT-PCR assays at 24-hour intervals and clinical evidence becomes essential.

Immunological response against SARS-CoV-2

Many studies are ongoing, which are studying the response of the immune system. Many have shown that, during infection, patients develop an elevated immune response which is caused by the hyperactivation of macrophages and monocytes. This response results in an increase in neutrophils, IL-6 and reactive protein C (PCR) and a decrease in the total number of lymphocytes (Qin *et al.*, 2020).

Eventually, post-infection, virus-specific T and B cells set in as a part of the adaptive immunity, followed by the Immunoglobulin M (IgM) and Immunoglobulin G (IgG) production in a typical pattern. In SARS-CoV infection, it was shown that IgM

could be detected in patients' blood after 3–6 days, while IgG could be detected after eight days (Li *et al.*, 2020). The IgG levels stay high throughout the immune response, an indication that these take part in protective roles. The IgM levels, however, declined almost entirely in 12 weeks (Li *et al.*, 2003). Next, the CD4+ and CD8+ T cell levels are reported to reduce while CD8 (CD8 39.4%) and HLA-DR (CD4 3.47%) double-positive fractions are found in high proportions, and indicative that this is uncontrolled activation (Xu *et al.*, 2020). T cell memory has been marked to have been identifying the SARS CoV infection even after six years.

Zhou *et al.* found that a patient can develop a virus-specific IgM peak nine days post-onset of symptoms and that the transition to IgG can occur before the second week. To perform a rapid test that can detect the presence of specific IgM and IgG for SARS-CoV-2, it should be noted that the IgM values tend to decline within two weeks from the onset of the infection. Therefore, because symptoms of the disease occur within 14 days, in most cases, it becomes difficult to determine the time of contraction of the virus accurately. Consequently, if immunoglobulin values are below the threshold at the time of the test, false negatives could be recorded (Zhou *et al.*, 2020a).

Clinical Presentation

The onset of the disease COVID-19 might be relatively asymptomatic but can soon escalate to fever, cough, fatigue, myalgia, dyspnea, and rarely vomiting and diarrhoea. The incubation period is estimated to be 3-14 days. The second week of infection can cause Acute Respiratory Distress Syndrome (ARDS) (Huang *et al.*, 2020a). One of the ways ARDS is triggered in patients is due to the production of immune cells in large quantities, called the cytokine storm. This includes the rush of (IFN- α , IL-1 β , IFN- γ , YNF- α , IL-6, IL18, IL-12, IL-33, TGF β , etc.) and chemokines (CXCL8, CCL3, CCL5, CXCL9, CCL2, CXCL-10 etc.) into lungs (Huang *et al.*, 2020a). Hence, patients from the second week of disease progression might need mechanical ventilation. Finally, if patients show no recovery, secondary bacterial pneumonia, multiple organ failure, acute heart injury and sepsis might set in, which can be fatal. The Chest CT scan is currently helping in the early diagnosis, when combined with other methods like symptom diagnosis and lab test, since many patients diagnosed showed bilateral and sensitive chest CT (Ai *et al.*, 2020).

Epidemiology

Many estimations have been done using various population models to calculate an accurate value of the first reproduction number (R0). This number

refers to the number of infections caused by a single case in a population where all individuals are susceptible to disease. Some estimates suggest a value of 2.47-2.86 (Wu *et al.*, 2020), but many last estimates suggest a number between 2-4. As of 5:36 pm CEST, 29 July 2020, there has 16,558,289 confirmed cases of COVID-19, including 656,093 deaths, reported to WHO, with a maximum spread in the USA with a whopping 4,263,531 instances. The global fatality rate computes to 3.962% (Source: <https://who.sprinklr.com>) based on the total confirmed cases of infection to the total number of deaths. The demographics of spread are mentioned in Figure 2.

It is interesting to note that the vessel Diamond princess, which was sealed off at a Japanese coast, stood as a unique opportunity for the COVID-19 research as it provided a closed environment where everybody was monitored and accounted for (Mizumoto *et al.*, 2020). Additionally, around 25 such vessels are sealed off and are tested for the 2019-nCoV. Key insights from the vessel include many facts like 18% infected people were asymptomatic and the case fatality rate in China was estimated to be 1.1% as opposed to the 3.8% calculated by the WHO when datasets from the vessel Diamond Princess were used for simulations (Mizumoto *et al.*, 2020).

Diagnosis

Currently, diagnostic methods include both serological and molecular approaches. Enzyme-linked immunosorbent assay (ELISA) and Western blot are serological, and Real-Time PCR and Northern blot employ the molecular approach for detection. These approaches can make a reliable diagnostic for the 2019-nCoV along with CT and Chest X-ray (CXR) and various other clinical symptoms. More efficient and faster detection systems are being built worldwide like SHERLOCK technology developed by Zhang *et al.* of MIT, USA (Gootenberg *et al.*, 2018), which can yield the result in just 60 minutes. However, CT scans and X Rays are being used to diagnose the patients even in cases with negative molecular tests. On repeated molecular tests, these patients eventually turned out to be positive for the virus (Huang *et al.*, 2020b).

Treatment

Currently, the different treatments being explored include drugs already in use for HIV and malaria, new experimental compounds that are being screened and tested against many viruses, convalescent plasma where the antibodies generated against the 2019-nCoV are transferred to another patient (Martinez, 2020). Since ACE 2 has been identified as the receptor used by the 2019-nCoV

to bind and invade, Soluble ACE can be explored as a treatment option. Soluble ACE would provide a platform over the actual ACE 2 receptors for the invading Coronavirus to bind to and in the process, protecting the real ACE 2 and thereby protecting the cells from invasion. The drugs being tested against the 2019-nCoV are currently targeting the genome or the structure of the virus. Alternate therapeutic techniques aim at a modulation of innate immunity or target the cytokines that are upregulated during the viral regulation (Wang *et al.*, 2007). The former is known as the antiviral targets, and the latter class of techniques are known as the Immune modulating therapeutics. Vaccine prototypes are underway, and the most promising vaccine target is the RBD domain discussed earlier since it interacts with the ACE2 receptor.

Antiviral therapy

No SARS-CoV-2-specific antiviral drug has been developed until now. However, antiviral therapy acting towards viral targets different from SARS-CoV-2 has been attempted. Such as an antiviral therapy includes drugs like Baricitinib, Chloroquine, Nitazoxanide, Lopinavir, Ribavirin, Remdesivir and Nelfinavir. At the same time, Chloroquine works by inhibiting both Endocytosis and exocytosis of the virus, along with causing dysfunction in protein synthesis (Savarino *et al.*, 2003), Baricitinib inhibits Endocytosis, and Nitazoxanide inhibits exocytosis. Lopinavir (Cvetkovic and Goa, 2003), and Nelfinavir inhibits protein synthesis inside the infected cells. Ribavirin and Remdesivir are a class of drugs which lead to delay in RNA chain termination. Remdesivir uses a pathway that inhibits viral RNA dependent RNA polymerase early in the virus, infection cycle after being metabolised into an active nucleoside triphosphate (European Medicines Agency Committee for Medicinal Products for Human Use (CHMP) - CHMP assessment report. Available from: [ema.europa.eu/en/documents/referral/assessment-report-article-53-procedure-medicinal-products-under-development-treatment-ebola_en.pdf](https://www.ema.europa.eu/en/documents/referral/assessment-report-article-53-procedure-medicinal-products-under-development-treatment-ebola_en.pdf)).

Chloroquine is a potent antimalarial drug that also helps fight autoimmune diseases. It is a broad-spectrum antiviral. It increases the endosomal pH for cell fusion and interferes with the glycosylation of receptors of the SAR-CoV (Vincent *et al.*, 2005). The rush of (IFN- α , IL-1 β , IFN- γ , YNF- α , IL-6, IL18, IL-12, IL-33, TGF β , etc.) and chemokines (CXCL8, CCL3, CCL5, CXCL9, CCL2, CXCL-10 etc.) into lungs is one of the ways ARDS is triggered and can lead to death. Chloroquine/HCQ have immunomodulatory effects and can suppress the immune response, potentially decreasing this ele-

vated immune response (Savarino *et al.*, 2003).

Immune modulating therapeutics

The Immune modulating therapeutics employ candidates such as Interferon alfa, Baricitinib, Tocilizumab and corticosteroids. α (alpha) interferons are upregulated during viral infection in human macrophages. However, the SARS-CoV has a system which evades this effect which is why these agents when taken externally decrease the disease expression (Merck & Co. Inc. Intron A (interferon alfa-2b) package insert, Whitehouse Station, NJ; 2014. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/103132s5190lbl.pdf). Baricitinib can prevent the intracellular entry of viral cells upon binding to associated protein kinase 1 (AAK1) (Lu *et al.*, 2020). Tocilizumab binds to IL-6 receptors, which are signalling proteins secreted by the immune system. Viral replication causes hyperinflation, by releasing signalling proteins such as (ILs) which enhances lung damage, this is protected by Tocilizumab (Genentech Inc. Actemra (tocilizumab) injection package insert, South San Francisco, CA; 2018. Available at: https://www.genentech.com/download/pdf/actemra_prescribing.pdf).

Enhancing the innate immunity

It has been shown that the migration of the Natural killer (NK) cells and macrophages which are significant components of immunity into the pulmonary tissue is a sign of recovery (Chen *et al.*, 2010). Therefore, looking at treatments that focus on improving this immune response marks a critical treatment. Several anti-cancer NK based treatments are now being modified to be able to improve immunity.

Against the SARS CoV 2. One such study is currently under phase 1 clinical trial (NCT04280224) in China aims at achieving viral clearance using NK cell addition.

Developments in vaccine and drug studies against COVID-19

Since the structure of the SARS-CoV-2 S protein is revealed in detail, the vaccine developments have become active to address the public health crisis. Vaccine development is a very long process.

On 20 March, WHO launched the SOLIDARITY program, which aims at collecting rapid scientific data during a pandemic as a collective effort to test possible treatments, in a randomised drug study. The drugs under study in this program are Remdesivir, Chloroquine or Hydroxychloroquine, Lopinavir with Ritonavir and Lopinavir with Ritonavir plus Interferon beta-1a (<https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-c>

linical-trial-for-covid-19-treatments). The putative effective drug candidates with their mode of action has been deciphered in Table 1.

Solidarity is promising, as the validity of the research is high due to stringent standards and measures taken by WHO for the study, like randomised allotment of the drug candidate upon signup automatically by the computer thereby avoiding any interference of any medical professional/ WHO itself. Since there is no vaccine yet, the treatment heavily relies on support, monitoring and isolation. WHO has released guidelines for critical care management; however, there is no particular approved treatment for COVID-19.

Prevention

Though China and WHO have given their guidelines on the treatment of COVID-19, it relies on support, monitoring and isolation. Hence, there is no particular approved treatment for COVID 19, which is why prevention becomes a top priority. As it is evident that COVID-19 can prove fatal to the elderly and patients with underlying health conditions, including diabetes and high blood pressure, a significant fraction of the society is highly susceptible. Social distancing is one of the ways by which the disease spread can be controlled, and various Governments across the world are enforcing the same. International travel has been widely banned, and intense screening of suspected patients is being carried in multiple countries. The virus can be destroyed by following a good hand hygiene routine which includes washing hands regularly with soap or an alcohol-based sanitiser. Some studies suggest that Vitamin C can help in preventing lower respiratory tract infections under specific conditions (Hemila, 1997). Initially, though WHO recommended the use of masks for healthcare workers only, the updated guidelines now recommend the usage of masks by everybody since masks can prevent transmission of the virus.

While all these methods look at an individual perspective, a more societal approach to the control of the spread of the virus would be the timely imposition of lock-down and social distancing. Many countries have imposed limited or complete lock-down to ensure physical distancing, and WHO's guidelines (<https://www.who.int/news-room/feature-stories/detail/a-guide-to-who-s-guidance>) & infographics also recommend these control strategies.

Effective Deployment Of Artificial Intelligence, Machine Learning, Iot And Other Technologies

The various aspects in which AI can play an impor-

tant role in the control of COVID-19 is in Tracking, prediction, diagnosis, search for treatments and social control. To be able to apply AI and machine learning, the first step is to train various models, and this requires data. Data poses a lot of issues such as data privacy, data credibility, the amount of data, security, etc. Though theoretically, AI can be applied to help in the scenarios mentioned above, it must be done at the right time by getting over many of the constraints. For instance, many social media-based AI forecasts are not yet accurate. A non-AI method, like the SIR models, is making a better prediction while taking into consideration various government efforts and quarantine (Song *et al.*, 2020). One of the applications of AI has been marked by making the COVID- 19 Open Research Dataset (CORD-19) publicly available for data mining. This is done by the collaboration of Semantic Scholar, the Allen Institute for Artificial Intelligence, Microsoft, Facebook, and others (Wim Naudé, Technology, Innovation, Entrepreneurship and Marketing, RWTH Aachen University, Kackertstrasse 7, 52072 Aachen, Germany). As far as diagnosis is concerned, AI systems can provide almost human-like accuracy in reading various CT scans and X rays saving a lot of time.

A tool, COVID-Net, a deep convolutional neural network, is already able to do this job. It was trained with 13,000 samples. However, it is still cannot be used until further improvements are made (Rawat and Wang, 2017). Additionally, to prepare the algorithms with local samples, it generated additional problems like contamination of equipment, leading to further spread of disease and causing contamination. Hence, it is slowly being discouraged. AI is promising when it comes to accelerating the search for treatments and vaccines as many companies have reported the use of AI and machine learning in repurposing and finding drugs and vaccines. The social distancing measures give the next primary cue in fighting the spread. To track people in real-time, two data points were employed, body temperature and facial recognition. China built a system with a network of thermal scanners and cameras, which would alert the authorities when an individual does not follow social distancing measures to the extent that the individuals would get a call from the authorities. A prototype named α -Satellite can track the infection risk of various geographical areas right up to the community levels (Ye *et al.*, 2020). This is accomplished by collecting data from multiple sources like social media data, demographics, deaths, traffic density utilising the conditional generative adversarial nets in places where the social media data is limited, this information can be used

by the public to take preventive action, or by the authorities to take appropriate control measures.

Smartphones provide another significant clue to the identification of patients. Modern smartphones host a lot of sensors under the hood, many of these can be used to collect data through IoT and analysis using machine learning, and AI can offer a quick approach to disease detection. Cameras, temperature-based fingerprint scanners, inertial sensors, microphones can detect fever, cough type, fatigue detection and even headache level prediction (Maghdid *et al.*, 2020). These technologies can also be used in computational biology like the AlphaFold protein structure prediction system by using the amino acid sequence of the 2019-nCoV's proteins. Google DeepMind employs this for protein prediction.

Future Directions

To build up a strong medication against COVID-19, Bioinformatics can help by predicting potential inhibitors for the infection that can be tested in the research laboratory for viability. Utilising various computational approaches or self-written scripts, a Bioinformatician can foresee potential inhibitors or leads that can be utilised as medications against the sickness. From investigating the sequence to finalise the drug candidate prediction requires a few stages to follow which can be comprehensively partitioned into five portions – obtaining viral series from the nucleic acid database, examination of the succession information by correlation with other viral groupings, phylogenetic analysis of the viral sequences to discover how the target virus could have grown or evolved from others, in silico modelling of the significant viral proteins as potential drug targets, lastly testing of a few potential hits/leads against the viral proteins for the analysis inhibitory activity. Profiling proteins directs efficient treatment methodologies and can also open a new avenue for vaccine testing. These approaches might aid scientific fraternity to comprehend, detect, and treat this deadly pandemic.

The widespread applications in computational approaches have produced the vast quantity of publicly available databases that we can use to screen drug for COVID-19. However, screening of drug-using biostatistics and machine learning approaches is a challenging task due to high noise and low reproducibility of significant outcomes. Current drug discovery is looking at the understanding of the infection and disease characteristics in which extensive research is on the way. These results further enable target identification and compound screening using computer-aided tools, like cheminformatic tools. One particular collaboration

approach viz network-based drug discovery looks at extensive correlations between pharmacogenomics, metabolomics, transcriptomics, proteomics and microbiome for the practical understanding and data interpretation. To build an effective drug, metagenomic methods can also be considered while ensuring compliance with the stringent safety requirements. A lot of data is available in the public domain (freely accessible) in the form of genomes of various strains of COVID-19, three-dimensional structures of viral proteins, transcriptomic datasets for COVID-19, and related viral infections. Large repositories of small molecules and voluminous scientific literature with a cue of potential candidates are also available. It is, therefore, essential to exploit this data with the help of in silico approaches for possible drug indications. Few researchers have also started to work in this direction by employing gene expression datasets and network-based biology approach to decipher the repurposing of drugs (Zhou *et al.*, 2020b). The procedure for screening of drugs through different computational methods has been depicted in Figure 3. In silico vaccine, designing is also possible by using various Immunoinformatics or Reverse Vaccinology approaches since the development of a vaccine has been considered as the best approach for combating infectious diseases (Dash *et al.*, 2017). Similarly, machine learning could be a better option to optimise Cancer Cell Line Encyclopedia (CCLE) results and investigate potential drugs from the cell lines since CCLE comprise of only FDA approved drugs. In addition to this, machine learning and other nature-inspired algorithms could prove to be more effective options to optimise plasma therapy for treating patients affected with COVID-19.

CONCLUSIONS

COVID-19 has reached a pandemic stage and is challenging for public health, economy, and international relations. Without adequate control measures, it might be difficult for the Nations to resume their full-scale activities and international travel. Since the 2019-nCoV has a higher R0 value than SARS or MERS, it is showing a rapid spread, costing a lot of lives. Additionally, the incubation period is large, and asymptomatic spread, spread after clinical recovery is additional issues to deal with. At this point, the aim is to increase the capacity of the hospital systems, by equipment like ventilators which can trigger an alarming situation if not in adequate number and take measures to flatten the spread curve, since that is the only way to contain and give sufficient treatment to all the patients. This requires innovation, low-cost setup and social responsibility

of citizens. If the number of cases across the hospital capacity, which has occurred in Italy, it might pose severe ethical concerns like who is to be treated first and can disturb the overall peace in the Nation. Hence, the importance of strict quarantine protocols cannot be highlighted enough. All these measures must be ensured while striving to develop drugs and vaccines tirelessly to protect the safety of the world. Many potential drug candidates have been identified and are currently being tested and screened regularly while other techniques such as immunomodulatory therapeutics are being explored. Antiviral drugs already approved stand a chance in being able to quickly improve the currently unguided quality of treatment by using the existing supply chain. Cell lines drugs and plasma therapy might be useful for COVID-19 patients.

Conflict of Interest

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