

# Understanding Covid-19 Based on Clinical Insights and Recent Advancements in Therapeutic Discovery

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## ABSTRACT

An outbreak of mysterious pneumonia in December 2019 at Wuhan, China draws attention around the world. The government of Chinese and researchers employed rapid and immediate strategies to prevent and contain the outbreak. Acute Respiratory Syndrome coronavirus and the Middle East Respiratory Syndrome were found to be the causative agents of the mysterious pneumonia as a result of sequencing and etiological investigations carried out by laboratories in China. World Health Organization officially named the novel coronaviruses as COVID-19, declares it as a pandemic and potential challenge to the global health care system. This review was conducted using recent research publications from reputed journals. Since the first infected case was reported, the disease has affected more than 15 million individuals around the globe. However, there are variations on death rate base on gender, age, sex and underlining health conditions. The major symptoms of COVID-19 include: fever, headache, cough, fatigue, mild dyspnoea and sore throat. Hitherto, there is no approved drug or vaccine capable of curing COVID -19. Hitherto, physicians have been recommending the use of some FDA approved antiviral drugs such as remdesivir, chloroquine, hydroxychloroquine, glecaprevir and maraviroc which their clinical efficacy associated with the virus is still unclear. Furthermore, due to limited researches and novel approved drugs that are highly effective for COVID-19 there is a need for accelerating the on-going clinical trials to discover most effective evidence-based treatment modality to lessen the spread of this disease and prevent the burden of a future outbreak.

**Key words:** SARS COV-2, COVID-19, Coronaviruses and Treatment, 2019-nCoV.

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## INTRODUCTION

Coronaviruses (CoVs) are special types of pathogens which mainly infect humans, mouse, bat, birds, livestock and other wild animals resulting in multisystem effect by affecting the respiratory, gastrointestinal tract, hepatic and central nervous system.<sup>[1-3]</sup> Previous outbreaks of the Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) in 2002/2003 and 2012 respectively depict the likelihood

of transmitting the virus from animal to human, human to human transmission and results to re-emergence of the virus in a new form.<sup>[4]</sup> Human coronaviruses were first identified in the mid-1960s and are named due to presence of crown-like spikes on their surface. Four main classes of coronaviruses are identified known as alpha, beta, gamma and delta coronaviruses<sup>[5]</sup> as mentioned in Table 1.

Unfortunately, an outbreak of mysterious pneumonia in December 2019 at Wuhan, China draws attention around the world. The government of Chinese and researchers employed rapid and immediate strategies to prevent and contain the outbreak. Sequencing and etiological investigations carried out by some of the laboratories in China identified the causative agent of the mysterious pneumonia as the novel coronavirus

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(nCoV).<sup>[6]</sup> As a result, on January 7<sup>th</sup>, 2020 the World Health Organization (WHO) officially named the 2019 novel coronavirus as COVID-19 and further declared it as pandemic which could be potential threat to the global health care system and risk factor to the global economy if not handled immediately by the infected countries.<sup>[7]</sup>

**Table 1: Types of Corona Viruses.**

S/No	Virus	Type Ref
1	229E	alpha coronavirus <sup>[5]</sup>
2	NL63	alpha coronavirus <sup>[5]</sup>
3	OC43	beta coronavirus <sup>[5]</sup>
4	HKU1	beta coronavirus <sup>[5]</sup>
5	MERS-CoV	beta coronavirus <sup>[5]</sup>
6	SARS-CoV	beta coronavirus <sup>[5]</sup>

## Methods

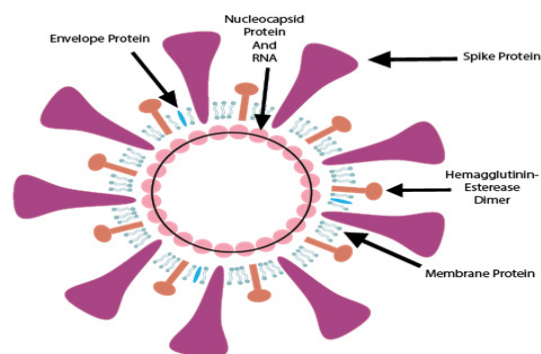
Using available online resources, we've gone through numerous articles published online with a view of Understanding COVID-19 based on clinical insights and recent advancements in therapeutic discovery. Keywords like 'COVID-19', '2019-nCoV', 'coronavirus' and 'SARS-CoV-2' were used to search for key articles predominantly from Google Scholar, MEDLINE, NCBI, UpToDate and Web of Science. We included scientific publications from 1<sup>st</sup> January 2019 through 7<sup>th</sup> May 2020. Articles focusing on clinical signs, epidemiology, symptoms, diagnosis and treatments for COVID-19 were eligible for selection.

## Genomic Structure of Covid-19 (SARS-CoV-2)

1. **Spike protein (S):** The CoVs protein is a highly glycosylated transmembrane protein type I containing 21 to 35 N-glycosylation sites. Spike proteins are responsible for the crown-like appearance of corona virus. The appearance is formed by the arrangement of Spike proteins into trimers on the surface of the virion. There is a similar organization in all the CoV spike protein exodomains which include: S1 domain which is N-terminal and responsible for receptor binding, S2 domain which is C-terminal and responsible for fusion. Diversity of CoV is reflected in the difference in spike proteins (S proteins), which progresses into forms having different receptor interactions and different response to various environmental stimulus of virus-cell membrane fusion.<sup>[8,9]</sup> It's well familiar that COVID-19 infects human respiratory epithelium; a lot of attention is drawn on whether the use of Angiotensin Converting Enzyme – 2

(ACE-2) inhibitors can serve as a therapeutic target due to several hypotheses suggesting that recombinant spike protein binds with recombinant ACE-2 protein.<sup>[10]</sup>

2. **RNA:** Ribonucleic acid is a complex compound with a high molecular weight that functions in the transcription of genetic information and subsequent synthesis of proteins. It replaces DNA (deoxyribonucleic acid) as a carrier of genetic codes in some viruses; it stores the complete genetic information (genome) of many viruses including COVID-19.<sup>[11]</sup>
3. **Nucleocapsid protein (N):** The CoV nucleocapsid (N) is a structural protein with multiple phosphorylation sites that complexes with genomic RNA *in vitro*, during virion assembly, it interacts with the viral membrane protein and plays a pivotal role in enhancing the efficiency of assembly, transcription and its timely replication of the virus.<sup>[12]</sup>
4. **Envelope protein (E):** The CoV envelope (E) protein is a small integral membrane protein that is involved in many aspects of the viral life cycle, which include envelope formation, assembly, ion channel activity, budding and pathogenesis.<sup>[13]</sup>
5. **Membrane protein (M):** The CoV membrane protein is one of the most abundant structural protein and a key player in virion assembly. The protein functions to mediate the incorporation of the spikes into the viral envelope, promote membrane binding to nucleocapsid and membrane curvature.<sup>[14]</sup>
6. **Hemagglutinin-esterase dimer protein (HE):** The CoV HEs are family of viral envelope glycoproteins that catalyse reversible attachment to O-acetylated sialic acids in a subset of beta coronaviruses, thereby having dual effect of lectins and receptor-destroying enzymes. However, HE activity amplifies S protein-mediated cell entry and spread of the virus through the mucosa.<sup>[15]</sup> (Figure 1)



**Figure 1: Structure of SARS Cov-2 Showing Spike Proteins, RNA, Nucleocapsid Protein, Envelope Protein, Hemagglutinin-Esterase Dimer Protein.<sup>[16]</sup>**

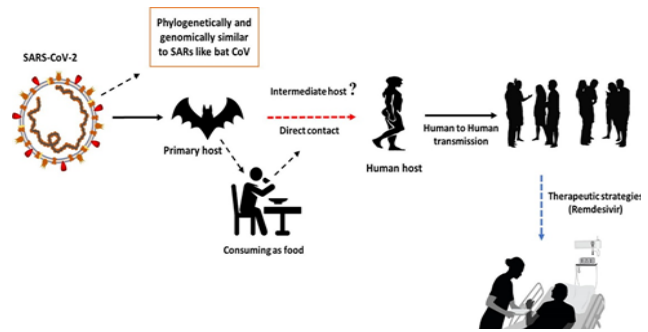
## Viral Transmission From Animal to Humans

Diseases that transmit from animals to humans are referred to as zoonotic diseases. Out of every 10 infectious diseases in humans, more than half are spread from animals and the majority of infectious diseases are mainly from animals. As reported by scientists, the virus was believed to be transmitted from animals to humans at a marketplace in Wuhan China, due to fact that previous outbreaks of MERS were transmitted from camels and SARS from a bat-infected civet cat which then transmitted to humans.<sup>[17,18]</sup>

## Transmission within Humans

Respiratory infections can be transmitted through droplets of varying sizes, droplet particles that are between 5 and 10 $\mu$ m in diameter, are referred to as respiratory droplets, while droplets of less 5 $\mu$ m in diameter, are referred to as droplet nuclei. Recent evidences revealed that, the COVID-19 virus is mainly transmitted between people through respiratory droplets and contact routes, other modes of transmission such as aerosol are also considered significant.<sup>[19-22]</sup>

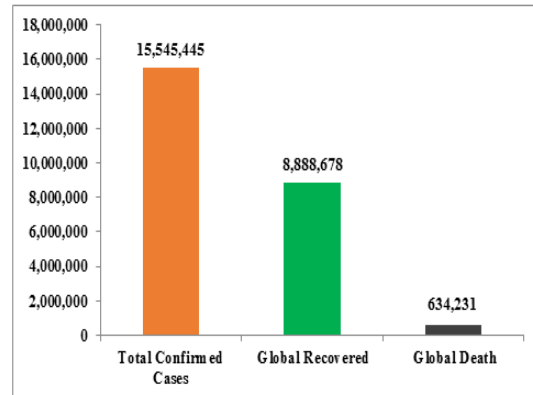
- 1. Respiratory transmission:** Droplets above 10 $\mu$ m in diameter are called respiratory droplets. When infected individual cough or sneezes, there is likelihood of respiratory droplets being transmitted from the infected person to uninfected person when they are in close proximity of not less than 6 feet. Hence social distancing of at least 6 feet is recommended as one of the major ways to mitigate the spread of the disease as the heavy droplets are not able to infect individuals above 6 feet distance.<sup>[23]</sup>
- 2. Aerosol transmission:** Recently, an article has evaluated the persistence of COVID 19. While experimenting, aerosols were generated using a three-jet Collision nebulizer and fed into a Goldberg drum to create an aerosolized environment. The study shows that COVID-19 remained viable in aerosols for 3 hr.<sup>[24]</sup>
- 3. Contact transmission:** This is regarded as the most common route which plays a critical role in spreading COVID-19. In this situation, viral particles emitted from the respiratory tract of an infected individual either by coughing or sneezing land on the surface of an object. Then, another person unknowingly touches that object and later rubs the hand on the nose, mouth, or eyes. The virus then sneaks into the body via the mucous membranes and automatically incubates, that is why regulatory agencies strongly recommend frequent washing of hands with soaps and sanitizers as a protective strategy to prevent the spread of the virus.<sup>[25]</sup> (Figure 2)



**Figure 2: Shows the Genesis of Covid-19 Mainly by Transmission from Animals to Humans and Ultimately Human to Human Resulting to Epidemic.<sup>[18]</sup>**

## Epidemiology of Covid-19

Since the first reports of cases from Wuhan, a city in the Hubei Province of China, at the end of 2019, infected cases are continuously reported from many continents. However, Antarctica is the only continent with no confirmed cases of COVID-19 in the midst of the pandemic. This was not surprising because over the last few decades since the beginning of the reform and opening, China has become one of the world's most-watched and busiest inbound and outbound with up to 142 million trips and 134 million trips respectively. To date, more than thirteen million confirmed cases of COVID-19 have been reported as of 24<sup>th</sup> July, 2020 according to database from John Hopkins University as shown in Figure 3.<sup>[26]</sup>



**Figure 3: Total confirmed cases, recovered cases and death cases of Covid-19 pandemic as of 24<sup>th</sup> July, 2020, despite the number of cases increases exponentially, considering the number of recovered cases, this is indeed a justification and good indicator that the preventive measures imposed are perfect at the moment when new drugs and vaccines are yet to be discovered.<sup>[27]</sup>**

## Death Rate by Age Group

The death rate due to Covid-19 based on age variation is considered concluding by the report culled from Italian Integrated Surveillance of COVID-19 as of 3<sup>rd</sup>

June 2020,<sup>[28]</sup> Chinese Centre for Disease Control and Prevention as of 17<sup>th</sup> February 2020,<sup>[29,30]</sup> Department of Public Health and Environment Colorado, United states as of 3<sup>rd</sup> June 2020,<sup>[31]</sup> Department of Health, Republic of South Africa as of 28<sup>th</sup> May 2020.<sup>[32]</sup> In all the reports it is clear that elderly patients are more susceptible to Covid-19 infections and have low rate of recovery from the virus due to weak immune system as compared to younger ones. In contrast, in south Africa, septuagenarian patients are reported to have high mortality rate than octogenarian patients which might be due to environmental factors and more preventive measures impose on the older ones.

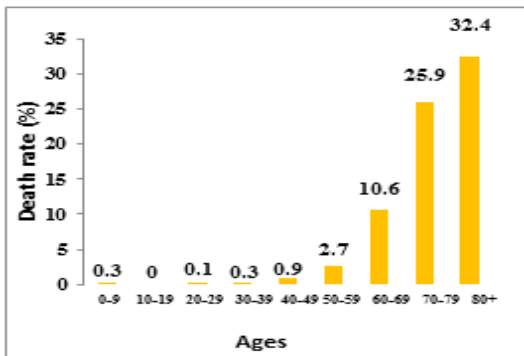


Figure 4: COVID-19 death rate from integrated surveillance of COVID-19 in Italy.<sup>[28]</sup>

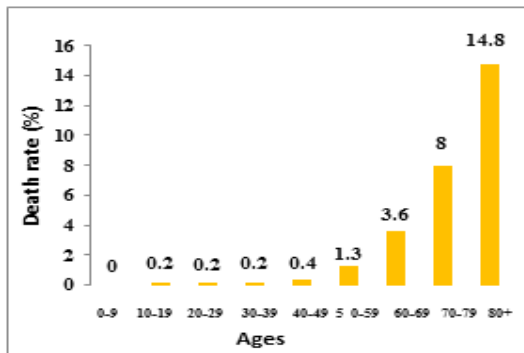


Figure 5: COVID-19 death rate from Chinese Centre for Disease Control and Prevention.<sup>[29,30]</sup>

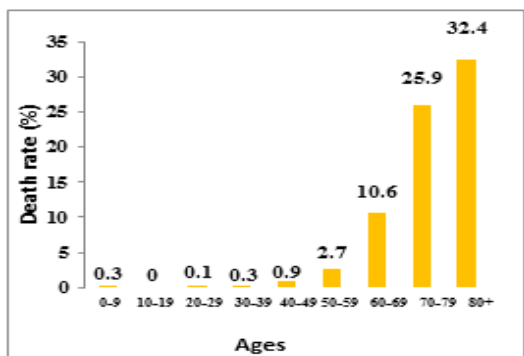


Figure 6: COVID-19 death rate from Department of Public Health and Environment Colorado, United States.<sup>[31]</sup>

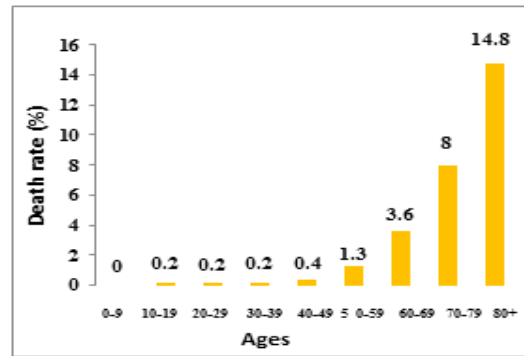


Figure 7: COVID-19 death rate from Department of health, Republic of South Africa.<sup>[32]</sup>

### Death rate by Underlining Health Condition

Researchers found that the case fatality rate of individuals with an underlying health condition is much higher than those with no health condition since the immune system is being distracted. More than 10% of people with cardiovascular disease who were diagnosed with COVID-19 rarely recover in the presence of other health conditions such as diabetes, chronic respiratory diseases, hypertension and cancer as shown in Figure 8. By comparison, the case fatality rate was 0.9% more than ten times lower for those without a pre-existing health condition.<sup>[30,33]</sup>

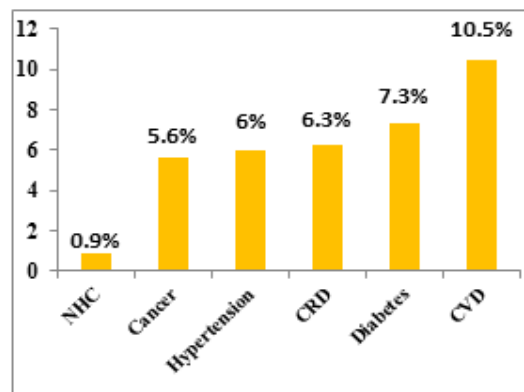


Figure 8: COVID-19 death rate by pre-existing health condition. NHC: No underlining health condition, CRD: chronic respiratory diseases, CVD: Cardiovascular disease.<sup>[30]</sup>

### Death Rate by Gender

This probability differs depending on sex, the most important point taken into account was that smoking in China is much more prevalent among males which increase the risks of respiratory complications, some literature also suggests high expression of Angiotensin Converting Enzyme -2 (ACE-2, one of the strongest biomarker in COVID-19) in males than females.<sup>[34,35]</sup> (Figure 9)

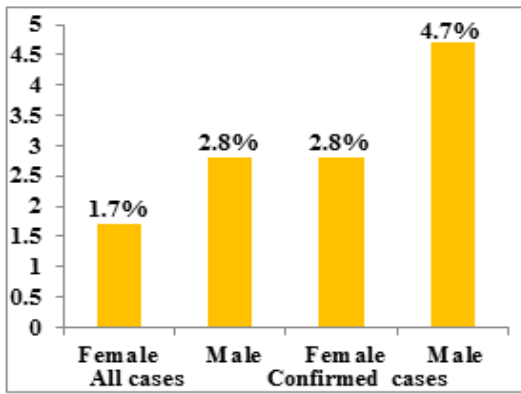


Figure 9: Covid-19 death rate by gender variation.<sup>[30]</sup>

### Symptoms of Covid-19

The symptoms of COVID-19 differ among individuals, ranging from asymptomatic infection, mild infection to severe respiratory failure.<sup>[36]</sup> Another study revealed that the majority of the suspected patients who tested positive with Real Time Polymerase Chain Reaction (RT-PCR) throat swab results are found to be asymptomatic, only a few among the symptomatic patients develop mild flu -like symptoms, acute respiratory distress syndrome, severe interstitial pneumonia and multi-organ dysfunction. However, the majority of individuals with symptoms and more severe complications had underlined medical conditions, such as hypertension, diabetes and cardiovascular disorders as shown in Figure 8, which are the majority at an older age as shown in Figure 4-7.<sup>[37]</sup>

Most common symptoms of COVID-19 are cough, fever, headache, fatigue, sore throat, mild dyspnoea and conjunctivitis. Gastrointestinal complications such as diarrhoea, nausea and vomiting are experienced in rare cases which make it harder to differentiate COVID-19 from other respiratory diseases due to overlapping symptoms.<sup>[38]</sup> (Figure 10)

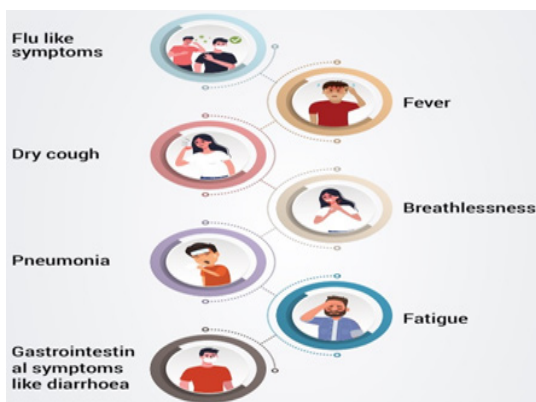


Figure 10: Most common symptoms of Covid-19 frequently noticed physically.<sup>[39]</sup>

### Diagnosis of Coronaviruses

Covid-19 is a single-stranded, positive-sense RNA virus since the upload of the entire genetic sequence to the Global Initiative on Sharing All Influenza Data (GISAID) platform, on 10<sup>th</sup> January 2020, within a shortest possible of time, companies and research groups were a wide range of Covid-19 diagnostic kits, primers and probes needed for proper detection of the virus are developed within shortest possible of time, below are some of the test widely used in the diagnosis of COVID-19.<sup>[40]</sup>

1. **RT-PCR:** Real-Time PCR mostly aimed to amplify a small amount of viral genetic material in a sample. The technique is considered to be the gold standard for detection of SARS-CoV-2 virus. RT-PCR tests for COVID-19 generally use samples collected from the upper respiratory system using swabs. However, a few studies have been carried out to detect the virus using a sample from serum, stool, or ocular secretions.<sup>[41,42]</sup>

In an attempt to fast-track the diagnosis contagion of the virus A TaqPath COVID-19 Combo kit for RT-PCR assay that uses self-collected saliva samples was developed by a genomic laboratory, which is reported to be faster and less painful than previous collection method, with low risk of virus transmission to the health care personals and ability to conduct large volume testing.<sup>[43,44]</sup>

2. **Nucleic acid hybridization using microarray:** This technique has been used for the highly efficient detection of SARS-CoV nucleic acids. They depend on the generation of cDNA from viral RNA by a reverse transcription process and subsequent labeling of cDNA with specific probes. The cDNAs labeled with specific probes are loaded into the wells of microarray trays containing solid-phase oligonucleotides fixed onto their surfaces. The hybridized probe remains bound while unbound DNA is removed by washing, hence signaling the presence of virus-specific nucleic acid.<sup>[45]</sup>

The microarray assay has proved to be useful in identifying mutations associated with SARS-CoV and has been used to detect up to 24 single nucleotide polymorphisms (SNP) associated with mutations in the spike (S) gene of SARS-CoV with good accuracy.<sup>[46]</sup>

3. **Serological and immunological assay:** The technique mainly analyses samples from blood serum or plasma and has been operationally expanded to include testing of saliva, sputum and other biological fluids for the presence of immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies.

The test plays an important role in epidemiology and vaccine development, by tracking an antibody response, abundance and diversity that last for days to weeks or years. IgM first becomes detectable in serum after a few days and lasts a couple of weeks upon infection and is followed by a switch to IgG. Thus, IgM can be an indicator of early-stage infection and IgG can be an indicator of current or prior infection. IgG may also be used to suggest the presence of post-infection immunity. In recent years the sensitivity of immunological assays has increased not only for the detection of antibodies but also for the application of antibodies such as monoclonal antibodies to the detection of pathogen-derived antigens. These tests have great potential for the epidemiology of COVID-19.<sup>[47-49]</sup>

## Advances in Therapeutic Development

### 1. Remdesivir

Remdesivir (Development code GS-5734) is a broad-spectrum antiviral drug. The drug has not been licensed or approved at the time of writing this article. Gilead sciences in 2017 during Ebola outbreak, synthesized Remdesivir, a mono phosphoramidite prodrug and an analog of ATP.

Inactive Remdesivir is converted into its active form (GS-441524) which primarily act to inhibit transcription of the viral DNA by competing with ATP for incorporation into RNA to deplete the energy and nucleotide source thereby inhibiting viral RNA-dependent RNA polymerase action. This ultimately leads to a decrease in the viral replication and termination of the RNA transcription. Remdesivir showed appreciable antiviral activity against many variants of the Ebola virus in cell-based assays. However, the drug is under trial for its potential use in the treatment of SARS-CoV2 that is responsible for COVID-19.<sup>[50,51]</sup>

Similarly, *in-vitro* studies showed that remdesivir can inhibit replication of some variants of coronaviruses like SARS-CoV and MERS-CoV. In an *in-vitro* test using epithelial cell cultures of a primary human airway, remdesivir was effective against Bat-CoVs and circulating contemporary human-CoV in primary human lung cells.<sup>[52,53]</sup>

A research article shows that remdesivir might be considered as a treatment option for COVID-19 patients.<sup>[52]</sup> Due to the high perception of scientists on the use of remdesivir as a potential therapeutic target, a randomized, controlled, double-blind clinical trial is planned to evaluate the safety and effectiveness of

remdesivir in adults with mild or moderate COVID-19 respiratory disease.<sup>[54]</sup>

Furthermore, a randomized, double-blind, placebo-controlled, multicentre study already in phase 3 is evaluating the efficacy and safety of remdesivir in 452 hospitalized adult patients with severe COVID-19.<sup>[55]</sup> However, Clinical trials associated with efficacy remdesivir in COVID-19 patients are currently underway, both in China and the USA at the same time the drugs should be avoided in the presence of underlining health conditions as shown in Figure 8.

### Chloroquine and Hydroxychloroquine

Chloroquine and hydroxychloroquine are potent derivatives of quinoline molecule which are used as antimalarial drugs while hydroxychloroquine is frequently used as an antirheumatic agent. Both drugs have similar clinical indications and side effects despite their varying therapeutic dosage which include retinal toxicity commonly referred to as chloroquine retinopathy or 4AQ retinopathy.<sup>[56-58]</sup>

Due to absence of an effective treatment against COVID-19 and an alarming exponential increase in the number of infections as shown in Figure 3, Chloroquine and its analog Hydroxychloroquine are largely being used for the treatment of the disease. Although preventive measures were imposed worldwide to reduce the spread of the pandemic, clinicians have to redirect some of the FDA approved antiviral drugs to other medical conditions for the treatment of COVID-19, although the safety and benefit of these treatment regimens remain ambiguous.<sup>[59,60]</sup>

A multi-national registry analysis of 96,032 patients requiring hospitalization (average age 53.8 years, 46.3% women) with COVID-19 shows that use of Chloroquine or hydroxychloroquine (with or without a macrolide) has no therapeutic benefit, It is rather associated with an increased risk of ventricular arrhythmias and a greater hazard for in-hospital death with COVID-19. However, the findings logically suggest that these drug regimens should not be used outside of clinical trials and urgent confirmation from randomized clinical trials is needed. Regrettably, three of the authors (Mandeep R. Mehra, MD, MSc, Frank Ruschitzka, MD, Amit N. Patel, MD) of the paper have retracted their study on 4<sup>th</sup> June, 2020 as they are unable to complete an independent audit of the data underpinning their analysis. As a result, they have concluded that they “can no longer vouch for the veracity of the primary data sources.”<sup>[61]</sup>

A recent study published at medRxiv has partially confirmed the potential of hydroxychloroquine in the treatment of COVID-19 under reasonable management, looking at the fact that no better option for treatment of the virus is confirmed at present. However, there is need for Large-scale clinical researches to shed more light on the treatment strategy.<sup>[62]</sup>

### Glecaprevir and Maraviroc

**Glecaprevir:** Is a direct antiviral agent and Hepatitis C virus protease inhibitor that inhibits the viral RNA replication. Glecaprevir / pibrentasvir combination is therapeutically useful for patients who experienced therapeutic failure from other NS3/4A protease inhibitors. It showed a high genetic block against resistance mutations of the virus.<sup>[63]</sup> **Maraviroc** is an antagonist drug of chemokine receptor designed to act against HIV by interfering with the interaction between HIV and CCR5 and was approved for use by the FDA in August 2007.<sup>[64]</sup>

A recent article published shows the binding of FDA approved drugs; Glecaprevir and Maraviroc to the substrate-binding pocket of SARS-CoV-2 main protease. Inhibit SARS-CoV-2 main protease. Therefore, a combination of these approved drugs can be considered as another therapeutic target for COVID-19. However, experimental validation and clinical manifestation are required to strongly support the findings.<sup>[65]</sup>

### Respiratory Therapy

Oxygen therapy is mostly applicable in mild and moderate stages of the disease. Early recognition and immediate referral of patients with worsening respiratory functions such as hypoxemia, respiratory distress, or shock with target  $SpO_2 > 94\%$  on conventional oxygen therapies, such as face masks with reservoir bags are important as a respiratory supportive measure as per the WHO guidelines.<sup>[66,67]</sup>

In patients with COVID-19, there is a potential for a worsening of hypoxia and an increased need for intubation and invasive mechanical ventilation under close monitoring, if sufficient high arterial  $O_2$  level (Sat $O_2$  93–96%) is not reached and if acute lung injury develops (ratio of the arterial partial pressure of oxygen to fractional inspired oxygen  $\leq 200$  mmHg).<sup>[68-73]</sup>

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### CONFLICT OF INTEREST

The authors declare that not competing interests exist.

### Author contributions

Mr. Abdulaziz Umar Kurya had the original idea of the article, literature search and prepared the original draft. Mr. Usama Aliyu conducted the data analysis, write, review and edit the article. Prof. Mu'azu Abubakar Gusau supervised and critically revised the work.

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