COVID-19: An Insight on the Third Respiratory Global Emergency of the Century

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Abstract: Introduction: COVID-19 presents a global emergency in recent days and as a consequence, the whole world is in a state of war. Continuous efforts by researchers are being made to establish a sound scientific understanding regarding the behavior of the virus and its pathogenesis.

Background: In recent days, a lot of scientific data are published describing viral transfusion into host cells, compared with SARS-CoV-1, viability of SARS-CoV-2, fatality and diagnosis of infection among infected patients, thereby, motivating to make right decisions in order to treat and mitigate COVID-19.

Review Results: Coronaviruses usually affect the respiratory tract and produce symptoms similar to pneumonia with varied complications. The spike protein on the surface of the virus makes the SARS-CoV-2 phylogenetically different from other viruses of the corona family. SARS-CoV-2 has an affinity to angiotensin converting enzyme-2 receptors present on human cells. The fatality of the disease is found to be low, but the severity of the disease might vary from person to person. The incubation period is 14 days but the symptoms like dry cough and high fever are evident around 3-7 days. Already known anti-inflammatory immunomodulators and antiviral drugs are being tested and still under clinical trials.

Conclusion: In this review, we are providing an insight into emergence of COVID-19, its correlation with SARS-CoV-1 and the interpretation of global data representing the severity of unexpected dangers for humanity. Certain structural aspects and studies determining the viability of novel coronavirus have also been described. Moreover, case studies of recovered infected patients from COVID-19 explain the progression and patients’ pathophysiological conditions while suffering from the infection.

Clinical Significance: There are many current strategies which are being tried and practiced to overcome this pandemic disease apart from precautionary measures. Although now, some decline has been seen, but the question still remains the same of whether the scientists are approaching towards the clinical solution, or are still in the midstream. This requires more study and intensive research to finally come to a concrete conclusion

Keywords: SARS-CoV-2, COVID-19, emergence, antigenicity, global statistics, coronaviruses.

1. INTRODUCTION

Coronavirus disease (COVID-19) has drawn the attention of health emergency after it spread like a pandemic globally and even more when the World Health Organization (WHO) declared it a global emergency. This viral disease is the third documented respiratory disorder caused by the animals and has proved to be fatal. The earlier two being – South-Asian Respiratory Syndrome coronavirus (SARS-CoV-1) in 2003 and Middle-Eastern Respiratory Syndrome (MERS) after a decade, in 2012. Novel coronavirus, designated as SARS-CoV-2, was first spread from China in the form of ‘pneumonia with unknown etiology’. Upon the outbreak of the illness and its spread among the humans, it became extremely important to extract out the information related to the causative agent. Subsequent investigations lead to the fact that a new type of coronavirus was isolated, which may be regarded as a sister clade of earlier known SARS-CoV [1, 2].

1.1. Phylogenetic Evolution of Coronavirus

The history of coronavirus dates back to the 1960s when a group of scientists was working on the organ cultures of the human respiratory system when infected with a common cold. It was difficult for scientists to grow a new strain of the virus at that point in time. In the similar time period, strains of viruses were found, which were ether-sensitive, namely 229E and B814. It was then concluded in the late 1960s that the mouse hepatitis virus, infectious bronchitis virus of chicken and human respiratory virus shared common mor-
phological characters and therefore named commonly as coronavirus. Until then, there was no such genus, and therefore a new genus named coronavirus was introduced under the family of coronaviridae by the International Committee on the Taxonomy of Viruses” in 1975. The name ‘corona’ was adopted by the physical appearance of the virus visible under an electron microscope, which means crown [3-5].

The present article covers a historical perspective along with the emergence of SARS-CoV-2 from bats to humans along with vital information of the stability of the virus. The detail on the diagnostic parameters and the death rate estimates can prove to be essential for the clinicians.

2. EMERGENCE OF COVID-19

It has been known that the family of coronaviruses is zoonotic, i.e., these are known for containing strains that have animal origin and cause a deadly disease. Coronavirus were divided into 4 types – namely α, β, γ and δ. The α and β coronaviruses mainly affect mammals and the natural reservoir of these is most likely bats. These act as natural reservoirs where these viruses circulate enough time before entering the intermediate host. The intermediate host may vary and the virus mutates and uses either one or multiple intermediate hosts to finally cause illness in humans. The most likely intermediate host for the COVID-19 is believed to be civets. Phylogenetic studies show that the genetic makeup of coronaviruses found to affect humans is similar to those found in Rhinolopus strain of bats, which are typically found in China, South-East Asia and Europe. The first outbreak case of this disease was observed in the Wuhan city of China on December 31st, 2019. The Wuhan city, being centrally located in China, has around 10 million populations apart from transient people and has a wide network of transportation links. Though Wuhan had the person infected in the sea-food market, but there is, as such, no proper evidence that seafood had a direct effect or was a carrier of the disease. It was human to human transmission that led to the multiplication of the virus asymptptomatically. By the time viral infection was converted into the illness of pneumonia, the virus had quickly reached different parts of the world, especially countries of Italy, Iran, New York and Germany. One of the primary reasons for its spread was that virus-infected people showed either no or mild clinical symptoms initially. It can thus be hypothesized that if there are no symptoms in the person (may be initially), he/she can still be a possible carrier for the virus, which might have transmitted the virus (directly or indirectly) to many before the symptoms appeared [6, 7].

3. HUMAN AFFECTING CORONAVIRUSES

Coronaviruses affecting humans generally fall under the category of α and β viruses. Natural hosts of most of them are bats with variable intermediate hosts, which show clinical symptoms in humans. These coronaviruses usually affect the respiratory tract and produce symptoms similar to pneumonia with varied complications [8, 9] Table I.

4. STRUCTURE AND ANTIGENICITY OF SARS-CoV-2

It is reported that SARS-CoV-2 has a spherical shape with highly glycosylated spikes on the surface, giving it a crown-like appearance. The protruding spikes on the surface are named as S protein (glycoprotein) in literature. This S protein shows conformational changes while fusing with receptors on the host cell membrane and causes transduction. The S protein is classified as class 1 trimeric fusion protein, which binds to the host receptor through the S1 subunit (meta-stable conformer) and undergoes structural rearrangements. This led to the transition of the S2 subunit and formed a stable conformer [10]. It is suggested that glycan units (sugars) on the surface of the SARS-CoV-2 virus restrict the recognition by the host immune system, thereby facilitating the fusion process into the host cell membrane [11]. A theory on phylogenetic and transduction details on SARS-CoV-2 revealed that the spike protein on the surface of the virus carries an activation site for furin (A pro-protein convertase enzyme commonly found in humans). This characteristic feature makes this virus different from SARS-CoV-1 and other closely associated members of coronaviruses. Furin facilitates the transduction process through cleavage of the viral glycoprotein envelope [12, 13]. Recent work suggests that similar to SARS-CoV-1, SARS-CoV-2 also has an affinity for angiotensin-converting-enzyme-2 (ACE-2) receptors present on human cells. These receptors are abundantly present in alveoli and hence providing a reservoir for such viruses. Moreover, despite around 76% structural homology, SARS-CoV-2 has more affinity of binding with these receptors than SARS-CoV-1 [14]. All these factors could be the reason that humans are highly susceptible to rapid SARS-CoV-2 infection as compared to other coronaviruses.

5. SURFACE VIABILITY OF SARS-CoV-2

A comparative study published in the New England Journal of Medicine establishes key findings on the influence of different surfaces over virus viability. Table 2 presents the data of the half-life of the virus load, which was observed to be maximum on plastic. The research concluded that the difference in the two viruses was that SARS-CoV-2 has a heavy virus load in the upper respiratory tract and its transmission within humans is asymptomatic. Moreover, the objects also serve as a carrier for the transmission of the viral infection as the virus remains viable on inanimate objects for a certain period of time [15].

6. CLINICAL MANIFESTATION AND DIAGNOSIS OF COVID-19

Due to the lack of therapeutic agents and treatment options for COVID-19, it becomes quintessential to diagnose the disease as early as possible and isolate the patient from the normal population. So far, this is the only course of action that can be employed as a treatment option. Even in the earlier reported cases of SARS-CoV-1 and MERS, there were no specific anti-viral therapeutic available, but only symptomatic and supportive treatment options were provided [16]. Hence, looking at the present scenario, the best alternative is to maintain health surveillance, quick identification of the infected individuals along with fast-track diagnosis with immediate quarantine. Clinical manifestations of COVID-19 include pneumonia, which is considered to be the most serious, reduced lymphocytes in lymphoid organs, increased infiltration of macrophages and monocytes in lung lesions,
Table 1. Types of coronaviruses affecting humans.

<table>
<thead>
<tr>
<th>Group</th>
<th>Type of Virus affecting Humans</th>
<th>Natural Host</th>
<th>Intermediate Host</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>α CoV’s</td>
<td>CoV-229E</td>
<td>Bats</td>
<td>Camelids</td>
<td>Respiratory infection</td>
</tr>
<tr>
<td></td>
<td>CoV-NL63</td>
<td>Bats</td>
<td>Unknown</td>
<td>Respiratory infection, croup</td>
</tr>
<tr>
<td></td>
<td>CoV-OC43</td>
<td>Rats</td>
<td>Cows</td>
<td>Respiratory infection and enteric infection</td>
</tr>
<tr>
<td></td>
<td>CoV-KU-1</td>
<td>Rats</td>
<td>Unknown</td>
<td>Respiratory infection</td>
</tr>
<tr>
<td></td>
<td>SADS</td>
<td>Bats</td>
<td>Piglets</td>
<td>-</td>
</tr>
<tr>
<td>B CoV’s</td>
<td>SARS-CoV</td>
<td>Bats</td>
<td>Civets/Raccoon</td>
<td>Severe acute respiratory syndrome</td>
</tr>
<tr>
<td></td>
<td>MERS-CoV</td>
<td>Bats</td>
<td>Dromedary camels</td>
<td>Middle eastern respiratory syndrome</td>
</tr>
<tr>
<td></td>
<td>SARS-CoV-2</td>
<td>Bats</td>
<td>Civets</td>
<td>Respiratory infection, pneumonia, Acute respiratory distress syndrome</td>
</tr>
</tbody>
</table>

Table 2. Viability of SARS CoV-1 vs SARS CoV-2 on different surfaces.

<table>
<thead>
<tr>
<th></th>
<th>SARS-CoV-2</th>
<th>SARS-CoV-1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time (in hrs):</td>
<td>Initial</td>
</tr>
<tr>
<td>Aerosols</td>
<td>3</td>
<td>10&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Plastic</td>
<td>72</td>
<td>10&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Stainless steel</td>
<td>48</td>
<td>10&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Copper</td>
<td>8</td>
<td>Not viable</td>
</tr>
<tr>
<td>Cardboard</td>
<td>8</td>
<td>Not viable</td>
</tr>
</tbody>
</table>

$ Results were not calculated by the research group as it showed lot of variability, so no confirm data was published.

TCID<sub>50</sub>: Median Tissue Culture Infectious Dose.

lung lesions showing marked inflammation with increased levels of pro-inflammatory cytokines and C-reactive protein, evident by fever, cough and difficulty in breathing [17-20]. Apart from respiratory clinical manifestations, certain neurological and cardiovascular-related manifestations have also been observed in COVID-19 patients. Also, it is important to note that these manifestations are rare and were observed only in patients suffering from severe COVID-19 infections. The neurological manifestations observed in patients include acute cerebrovascular diseases, impaired consciousness and skeletal muscle injury [21]. Moreover, there are evidence which show the signs of the virus in cerebrospinal fluid. El-lul et al., (2020) describe in detail the effects on the nervous system and extrapolate the possibility of the affect of SARS-CoV-2 in the progression of the disease [22]. It was observed that some of the patients suffering from severe COVID-19 infection had experienced vascular inflammatory responses. These inflammatory responses that contribute to cardiovascular injuries are evident by increased troponin levels. Myocarditis and cardiac arrhythmias are other cardiovascular symptoms that are strongly associated with increased vascular inflammation burden and mortality [23]. Studies have also discussed the relationship between COVID-19 and pregnant women. In clinical data on pregnant women with COVID-19, it was observed that no neonates were found to be infected and also the milk samples of women were found to be negative. Therefore, it can be concluded that there is a very low risk of disease progression from mother to foetus [24]. Clinical analysis of COVID-19 should be based on history and evaluation based on blood cultures, enzyme-linked immunosorbent assay. Techniques such as nucleic acid technology and computed tomography findings are currently being used for the detection of the disease [25].

6.1. Nucleic Acid Detection Technology

Nucleic acid-based technology is either based on real-time quantitative polymerase chain reaction (RT-qPCR) or high-throughput sequencing of the whole genome. Since the outbreak of COVID-19 was so sudden that virus isolates were not available initially, so by the use of synthetic nucleic acid technology, the design of an oligonucleotide sequence was made, resembling that of SARS-CoV [26]. After this, in another study conducted by Chu et al., RT-PCR assays were developed based on the first available Genbank. This study targeted two different regions of SARS-CoV-2, i.e., ‘N’ region and ‘Orf1b’ region and hence its primer and probe sequences were identified. These assays have been proven to
be specific. The study claims that ‘N’ gene RT-PCR assay can be considered as a preliminary assay, whereas ‘Orf1b’ assay is more specific and sensitive, hence is regarded as a confirmatory assay for COVID-19 [27].

6.2. Computed Tomography Imaging

Since COVID-19 is progressively unpredictable, clinicians have additionally suggested that CT imaging of the chest can play a vital role in the diagnosis of the disease. Recently, as per the study conducted by Xingzhi et al., on 167 patients, it was observed that 3% of the patients had negative RT-PCR initially but became positive, 2-8 days later. Even though RT-PCR is an explicit technique, additionally CT examinations have been suggested that ought to be one of the fundamental diagnostic strategies. In the same study, 7 patients had negative CT report at initial presentation, but positive RT-PCR. Since a chest CT report initially might show normal findings, hence it is not recommended as a first-line tool by WHO and RT-PCR remains the reference for the detection of COVID-19 [28]. However, RT-PCR, coupled with CT findings, might prove to be more valuable in case of high clinical doubt or low RT-PCR findings. A retrospective study carried out by Chung et al., reviewed the typical and most common findings that characterized the disease [29]. CT imaging can thus be used effectively to assess the severity and progression of the disease [30].

7. PROGRESSION OF COVID-19 AND RECOVERED PATIENT ANALYSIS

Progression of COVID-19 is either due to human to human contact or through droplets from the infected person. Among the environmental factors, recently the presence of COVID-19 virus has been detected in human faeces, which is a matter of concern now. Faeces may contaminate the water and ultimately affect public health, specifically the human population living in areas with poor sanitation facilities. The severity of the disease might vary from person to person and it has been observed that in 80% of the cases, the person recovers by itself. The fatality of the disease is found to be low, around 2-3%. The incubation period is 14 days, but the symptoms are evident around 3-7 days [31, 32]. A study of the report in the United States, who recovered from the illness, reported signs of cough and subjective fever for 2 days after returning from Wuhan, China. All other vital signs were normal, including the chest radiographs and assay procedures. On the 5th day of illness, the case was confirmed by RT-PCR, with intermittent fever and loose stools. On the 7th day, leucopenia and slight alterations in hepatic functions as evident by increased levels of liver enzymes (alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase and lactate dehydrogenase) were observed. It was the 9th day when abnormalities in the lungs were noted and oxygen saturation was found to be dropped to 90%; vancomycin and cefepime were administered to the patient intravenously along with oxygen supply. Vancomycin and cefepime were further replaced with remdesivir, on the development of severe pneumonia up till 11th day. The patient’s condition improved on the 12th day with no complications [33].

8. GLOBAL STATISTICAL DATA AND DEATH RATE ANALYSIS

The global statistics data, as mentioned by the WHO statistical report, has been presented graphically. Fig. (1a) shows the statistical data of the total confirmed cases and the total number of deaths globally and (Fig. 1b) shows the death rate. The death rate has been calculated as the percentage of deaths from the total infected cases. Fig. (1c) displays a number of new cases emerging daily and the new number of deaths. The data of deaths as per WHO situation reports are available from the 9th of March 2020 only. From these estimates, it can be concluded that from March 2020, there has been a constant increase in the number of cases daily and SARS-CoV-2 has been spreading like a wildfire and affecting the human population globally. Although death rates have been ranging between 3.5% - 4.5%, but varying depending upon the country and the region. The death rates in Italy have been quite alarming as compared to other regions, especially China [34].

9. POTENTIAL THERAPEUTICS FOR CONTROLLING COVID-19

9.1. Chloroquine and Hydroxychloroquine

Studies have shown that chloroquine and hydroxychloroquine (40% less toxic and potent than chloroquine) both possess immunomodulating and anti-inflammatory activity. These pharmacological activities are utilized by medical practitioners to manage the progression of COVID-19 clinical manifestations. As discussed in the above section that SARS-CoV-2 is believed to have an affinity to ACE-2 receptors through glycosylation of S protein and ACE-2 receptors for entry into the host cells, chloroquine interferes with the glycosylation of ACE-2 receptors and S protein and consequently inhibits the viral entry [35]. Moreover, SARS-CoV requires low endosomal and lysosomal pH for the membrane translocation and releasing a genetic material after lysis into the cytoplasm [36]. The endosome carrying a virion fuses with lysosome where acidic pH dissolves the virus membrane and releases the genetic content for replication. In context to this, the findings also revealed that the entry of SARS-CoV into the lysosomes was notably inhibited by chloroquine by significantly raising the lysosomal pH from approximately 4.5 to 6.5 and thereby inhibiting the autophagy [37]. Recent clinical trials over SARS-CoV-2 infected patients also postulated the therapeutic efficacy of chloroquine and hydroxychloroquine in slowing down the viremia. The efficacy was suggested on the basis of improvement in lung lesions confirmed by lung imaging results, negative nucleic acid test and clinical improvement. The improved clinical results were found to be prominent after 2 days of hydroxychloroquine treatment [20, 38].

9.2. Antiviral Drugs

The combination of ritonavir-lopinavir is a potent antiviral candidate which is used in HIV conditions as protease inhibitors. These drugs have shown significant in vitro antiviral activity on SARS-CoV-2, but the clinical data is still an open question. A randomized, open, controlled trial conducted on 199 patients, out of whom 99 were treated with
Fig. (1). (a) Estimates of the total number of cases and the total number of deaths worldwide in March 2020. (b) Percentage of deaths occurred amongst confirmed infected cases globally in March 2020. (c) Estimates of number of new cases and new number of deaths during March 2020. (A higher resolution / colour version of this figure is available in the electronic copy of the article).
ritonavir-lopinavir combination compared to other 100 patients who were considered as standard. There was no significant clinical improvement in the patients or no sign of reduced mortality was observed. Moreover, 14% of the group had to discontinue the drug candidate due to adverse gastrointestinal effects. The study might not be effective, as the patients under the study were severely affected by COVID-19. This is the probable reason given by the scientists for the non-effectiveness of ritonavir and lopinavir. However, these drugs are in phase 2 clinical trials in patients with mild COVID-19 (NCT04307693). The drugs might show effects in patients with the mild disease, hence, more clinical data with specificity on a wide population is required [39, 40]. Researchers have recently identified some antiviral molecules and initiated clinical trials to evaluate the therapeutic efficacy for COVID-19. For instance, remdesivir, an adenosine analogue, recently entered phase 3 of the clinical trial with an objective to evaluate the efficacy of the drug for the management of moderate COVID-19 (NCT04292730) [41]. Favipiravir is another antiviral drug intended to use for influenza in Japan. It is a selective RNA polymerase inhibitor that prevents RNA replication in the host and is found to be active against subtypes of the influenza virus, but teratogenicity is also associated with this drug [42]. Recently, favipiravir has entered a multi-centered randomized clinical trial along with tocilizumab (immunosuppressive monoclonal antibody) (NCT04310228) and chloroquine (antimalarial and antiviral) (NCT04319900) for the treatment of COVID-19 [43, 44].

CONCLUSION

Despite the alarming spread of the viral infection in the entire world, the complete mechanism of transmission of the infection to the human genome is still questionable. It is also evident now that the viral entry into humans is not only limited from animals or infected humans as SARS-CoV-2 can also remain live in inanimate objects for a certain period of time. This viability on inanimate objects has also become a matter of serious concern and added a reasonable contribution in turning this from an epidemic to a pandemic. The current situation shows that quarantine and isolation, of the infected people is the only current solution available to at least slow down the steep rise of COVID-19 in the human race. This will help to gain some time to find out a possible cure for this disease and controlling the havoc due to the rapid increase in the number of patients. Researchers have also developed many diagnostic kits and assay procedures, but the virus is on ceasefire asymmetrically. Already known anti-inflammatory immunomodulators and antiviral drugs are being tested and still under clinical trials. Current, few promising therapeutic observations of recovery have been observed from chloroquine/hydroxychloroquine and further investigations are under process. Moreover, restricting all casual movements worldwide has also marked the significance of controlling the steepness of disease transmission. Keeping in view the present scenario and procrastination in developing the precise therapy, the prime focus should be on preventive measures. The saying that ‘prevention is better than cure’ should be religiously followed in order to win this fight of SARS-CoV-2 vs humans.

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