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Deciphering of SARS-CoV-2 Pathogenicity and Associated Clinical Implications

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Abstract Today, the novel coronavirus (COVID-19) has become a major challenge to the world and drastically affected the healthcare system itself. This deadly virus is highly contagious and have significant clinical implications that may results in continuous death across the globe. It is very much important that the pathogenicity and clinical implications of this virus is understood as that will help in the preventive measures to be taken in controlling the high rate of dead being faced across some countries. Our knowledge on COVID-19 is still quite limited despites the unprecedented efforts by scientists and clinical researchers over the last few months of the virus out breaking. Thus, this paper reviewed the current literature about the virus features, infectivity, pathogenicity and clinical implications that hinder the clinical diagnosis of SARS-CoV-2.

Keywords SARS-CoV-2, Pathogenicity, Clinical implications, Healthcare workers

1. Introduction

The year 2020 is faced by a global health challenge of a novel coronavirus (COVID-19) disease leading to the shunt down of almost all part of the World. This respiratory related disease started in the late 2019 at the city of Wuhan, Hubei province of China and spread rapidly throughout the globe (She et al., 2020; Singhal, 2020). This disease is caused by an RNA virus "coronavirus", a member of the class of Severe Acute Respiratory Syndrome (SARS) like coronavirus-2 (Hoffmann et al., 2020). It is known that this virus induce acute respiratory distress syndrome (ARDS) (Marini & Gattinoni, 2020) and was assign a brief name initially as 2019-nCoV by World Health Organisation (CSG, 2020) and later named SARS-CoV-2 by International Committee Coronavirus Study Group (CSG, 2020; Guo et al., 2020). Due to the spread of the virus from person to person, the morbidity and death rate of COVID-19 are rising rapidly.

The majority of the population that have contacted the virus are said to be asymptomatic while a few percentage of the infected population are presented with a spectrum of symptoms, of which 80.9-81% have mild condition, 13.8-14% have severe and 4.7-5% rated as serious or critical conditions, with about 2% of reported cases being fatal (Orleans et al., 2020; Rajarshi et al., 2020; J. Wang et al., 2020). These symptoms are presented 2-14 days after exposure to the virus and they include; fever, dry cough, difficulty in breathing, muscle pain, headache, sore throat and new loss of taste or smell (Rajarshi et al., 2020). The severe cases are confirmed to the most dangerous phase of the disease with sudden deterioration progression with respiratory difficulty (Rajarshi et al., 2020) requiring mechanical ventilators and intensive care units (ICUs) support due to lung and multiple organ failure (Cai et al., 2020; Engelman et al., 2020; Golchin et al., 2020). The high mortality rate has been reported in the critical ventilated patients associated with sepsis or septic shock which is the main reason death is associated with the COVID-19 (Moll et al., 2020; Wang et al., 2020).

Due to the lack of effective antiviral treatment for COVID-19 as recently released by the National Health Commission of the People's Republic of China (Kang et al., 2020; Lin & Li, 2020), the disease has no doubt become a serious challenge to the global public health and healthcare workers. Therefore, this review paper summarized the latest literature updates about SARS-CoV-2 features, viral entry into the human cells and spreading as well as pathogenicity, diagnostics procedure, and clinical implications of SARS-CoV-2 as this will aid healthcare workers in effectively managing the disease locally and in COVID-19

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patients in the clinical settings.

Features of the novel SAR-CoV-2

Coronavirus is an enveloped positive-sense single-stranded RNA virus that is widely distributed in humans, birds and other mammals, causing diseases of the respiratory system, intestinal tract, liver and nervous system (Weiss & Leibowitz, 2011; Weiss & Navas-Martin, 2005). Six types of coronaviruses are known to cause human diseases. Four viruses including OC43, HKU1, hCoV-229E, and NL63 are very popular and usually cause mild respiratory diseases and are the classical β-coronaviruses (Su et al., 2016). β-coronavirus may cause serious illness and death in humans, while α-coronavirus can cause asymptomatic or mildly symptomatic infections (Velavan & Meyer, 2020). Two deadly coronaviruses appear regularly in different regions, namely Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) in 2002 and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in 2012 (Alfaraj et al., 2019; Raoult et al., 2020). In view of the high prevalence and widespread distribution of coronaviruses, frequent genetic diversity and genome recombination, as well as increased human and animal activities, due to frequent cross-species infections and accidental spill overs, new coronaviruses are likely to appear in the human body regularly (Cui et al., 2019; Wong et al., 2015).

Zhu et al. (2020) reported that the identified SARS-COV-2 genome is closest phylogenetically to certain β-coronaviruses detected in bats that belongs to the subgenus sarbecovirus of the coronavirus family (Lu et al., 2020), and these results together with other reports, show that it is 75–80% consistent with SARS-CoV and 40% identical to the MERS-CoV (Rabaan et al., 2020). Similar to SARS-CoV, SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) receptor to infect humans (Ni et al., 2020; Zhang et al., 2020). It must be pointed out that the high affinity of the virus for the ACE2 receptor may be due to natural selection rather than intentional manipulation as being speculated from many angles around the world (Law, 2020; Sallard et al., 2020).

SAR-CoV-2 entry and replication

Coronavirus S protein has been shown to be an important determinant of virus entry into host cells (De Wit et al., 2016). The process of SARS-CoV entering the cell is mainly accomplished by direct membrane fusion between the virus and the plasma membrane (Simmons et al., 2004). SARS-CoV-2 and SARS-2003 have similar host invading mechanisms (Golchin et al., 2020; Rajarshi et al., 2020), by binding spike (S1 subunit) glycoprotein to the angiotensin-converting enzyme 2 (ACE2) and CD147 receptors (Hoffmann et al., 2020; Rogers et al., 2020). However, this form of host entry is not conserved in the S-protein of SARS-CoV serving as key unique property (Hoffmann et al., 2020). The virus usually fused with the host membrane and gets gradually internalize using the S2 domain of the its spike protein facilitated by cellular transmembrane protease serine (TMPRSS)-2 (Hoffmann et al., 2020; Xiu et al., 2020).

Large portion of residence lung cells especially the alveolar type II (AT2) and the endothelium as well as the residence stem cells express ACE2 (Rajarshi et al., 2020; Ulrich & Pillat, 2020). These ACE2 receptors in this case are unfortunately widely distributed in other organs of the body including the heart, liver, digestive organs as well as the kidneys (Gavriatopoulou et al., 2020; Gheblawi et al., 2020; Zaim et al., 2020). These cells are invaded by the viral RNA resulting in not only losing the airway epithelial cells but also a potential loses of the cellular regeneration across the body (Rajarshi et al., 2020; Ulrich & Pillat, 2020). The body automatically launches into a concurrent immune response and tissue/organ restoration (Wang et al., 2020), triggering a partial replacement response in all potential sight of viral infection which conflict with the trigged immune response marking the hallmark of SARS-CoV-2 pathogenesis (Lai et al., 2020; Lin et al., 2020). This lead to the formation of an pneumonia fibrosis to late fibrous stripes in the lungs in response to early and later-phase of COVID-19 respectively (Bernheim et al., 2020; Pan et al., 2020).

2. SAR-CoV-2 and the Mechanism of Cytokine Storm

Pro-inflammatory cytokines are released in response to infection including infection by SAR-CoV-2 at the ACE2 and CD147 cell resulting to the manifestation of other symptoms that includes fever (due to high levels of IL-production), nausea, depression, flu-like symptoms and many others (Wang et al., 2020). The virus triggers overactivation of the immune system, inducing cloud of cytokines around host tissues known as cytokine release syndrome or cytokine storm (Johnson & Laloraya, 2020). Cytokine storm is a severe inflammatory response, which is due to high production of cytokines by Natural killer (NK)-cells and macrophages, activation of T-cells and humoral response within the lung and other sights of infection thus resulting in a widespread detrimental effects (Nile et al., 2020; Ye et al., 2020b; Zhang et al., 2020). Local cytokines (IFN-alpa/beta and IL-1beta) induce more wave of immune response from NK cells, fuelling the secretion of IFN-gamma which recruits and activates more myeloid cells such as macrophages amplifying the releases of TNF, Il-2, IL-6, IL-7, IL-12, GSCF, IP10, MCP1, and MIP1A, recruiting more NK cells and neutrophils (Rajarshi et al., 2020; Wang et al., 2020).

Furthermore, cytokine responses from T-cells and antibodies with the progression of the disease condition is also reported and that lead to viral induced cytotoxicity. This lead to more pathogen related factors responses such as anti-inflammatory responses which itself causes tissue damage that results in an un-controlled inflammatory responses (Wang et al., 2020). Cytokine storm is common in

patients with severe to critical symptoms, although the severity of the COVID-19 condition has been associated with the viral production and the cytokine storm (Wang et al., 2020). The mechanism underlying fuelling cytokine storm and the triggers of the advancing the ARDS is still unclear. A lethal cytokine storm is characterised by diffused alveolar damage and hyaline formation with lymphocyte infiltration causing edman, dysfunction air exchange ultimately resulting in ARDS, secondary infection, acute cardiac injury, generalized sepsis and multisystem failure which may lead to death (Golchin et al., 2020; Wang et al., 2020).

3. Detection and Diagnostic Procedure

Up to the time of writing this paper, the conventional technique used in testing and confirming or identifying patients carrying SARS-CoV-2 genes is quantitative real-time polymerase chain reactions (RT-qPCR) and it has widely been used since from the time of the initial viral outbreak in clinical diagnosis of the disease cases (Hasan et al., 2020; Kudo et al., 2020). Being that the qPCR is the most efficient and effective method for confirming cases, there has been rapid developments of diagnostics kits such HiScript II, supreme Pure Viral RNA and one Step RT‐qPCR SYBR Green from different companies around the world that has been approved to be used for testing (Bruce et al., 2020; Bustin & Nolan, 2020; Smyrlaki et al., 2020; Zhang et al., 2020).

Detecting the nucleic acids of SAR-CoV-2 in patients samples such as nasopharyngeal swabs, lower respiratory tract secretions, blood and faeces, COVID-19 can effectively be diagnosed depending on stages at which the infections occurred (Shen et al., 2020). Therefore, due to the possibility of oral and faeces transmission, healthcare workers need to be cautious when discharging patients infected with COVID-19 as detected through the negative oral swab test results. It has also been established that SARS-CoV-2 was detected in an autologous saliva of patients infected with COVID-19 (Sabino-Silva et al., 2020), indicating that saliva might be use in a non-invasive specimen to diagnose patients with COVID-19. However, this method of detecting cases through the use of patient's samples might results in exposing these healthcare workers to high risk of contracting the disease.

Current clinical management

The severity and mortality rate due to COVID-19 pandemic have led to a global race in search of treatment and vaccine for its management. However, there have not been a standard treatment till date, even for any of the previous member of the coronavirus family (Davis et al., 2020; Elengoe, 2020; Golchin et al., 2020). Multiple treatment strategies and other associated symptoms approved drugs are currently undergoing research across the world (Davis et al., 2020; Golchin et al., 2020), with earlier reported treatment drugs like Remdesivir (Beigel et al., 2020; Olalla, 2020), hydroxychloroquine and chloroquine which have been reported of having an antiviral property (Devaux et al., 2020; Zou et al., 2020). This property is exerted by increasing the pH of endosomes which inhibiting an enzyme known as Cathepsin L, thus preventing viral evading the host cells (Wang et al., 2020). These drugs also serve as anti-inflammatory by regulating the myeloid activity as well as reduce the IL-6 levels, however, their long time used benefits have been challenged and associated with cardiac complications among others (Wang et al., 2020). Antibodies such as azithromycin have also been used in the management of patents with COVID-19 (Sanders et al., 2020).

Other treatment include the transfusion of convalescent plasma was recommended to patients with sudden disease progression, which was able to reduce the levels of cytokines especially IL-6 and with a progressive increase in the lymphocyte count. Nevertheless, this treatment remains inconclusive due to questions about optimal dose and therapeutic window (Wang et al., 2020). Corticosteroids such as methylprednisolone were also used as treatment due their ability to dampen inflammatory responses of the cytokine storm, however they are not suitable for a long-time used even though a number of corticosteroids-based clinical studies are ongoing (Singh et al., 2020; Wu et al., 2020). Immuno-informatics report suggest that several surface glycoprotein epitopes as well as the MHC class I & II antigenic epitopes of the virus including 5CTL epitopes, 3 sequential B cell epitopes, and 5 discontinuous B cell epitopes could be utilized for the development of COVID-19 vaccines (Bhattacharya et al., 2020; Lizbeth et al., 2020). Moreover, several other forms of therapies are ongoing for clinical evaluation to confirm their immunomodulation in the cytokine storm, as it the been reported as the major complication leading to death associated with this disease (Bhaskar et al., 2020; Iannaccone et al., 2020). These including recombinant human IFN-alpha, antibodies, and nutritional supplement (Meng et al., 2020; Wang et al., 2020). In addition, blocking agents that are receptor specific are also being developed and are designed to specifically binds to the ACE2 receptors (Gheblawi et al., 2020).

Clinical presentations and pathogenicity

The impact and the current struggle with a global pandemic due to COVID-19 disease caused by a novel respiratory related coronavirus is alarming. The clinical presentations of COVID-19 are range from asymptomatic to acute respiratory distress syndrome and multiple organ dysfunction, making it difficult to distinguish it from other respiratory infections (Zaim et al., 2020), while a few percentage of the infected population are presented with a spectrum of symptoms, from mild – severe condition to a more serious or critical conditions, with about 2% of reported cases being fatal (Verity et al., 2020; Yuen et al., 2020). Serious conditions are confirmed to sudden progression deterioration with respiratory difficulty (Chen et al., 2020), requiring mechanical ventilators and intensive care units (ICUs) support due to lung and multiple

organ failure (Anisoglou et al., 2013; Möhlenkamp & Thiele, 2020).

Once the virus is into the cells it bind to angiotensin-converting enzyme 2 (ACE2) and CD147 (Basigin or EMMPRIN) receptors (Hoffmann et al., 2020; Wang et al., 2020) which are unfortunately widely distributed in the lungs and other organs of the body including the heart, liver, digestive organs as well as the kidneys (Guo et al., 2020; Nile et al., 2020). These cells are invaded by the viral RNA resulting in not only losing the airway epithelial cells but also a potential loses of the cellular regeneration across the body (Ulrich & Pillat, 2020). The body automatically launches into a concurrent release and accumulation of cytokine and inflammatory responses against the virus and that of tissue/organ restoration resulting to a cloud of cytokines around host tissues known as cytokine release syndrome or cytokine storm (Wang et al., 2020). This gradually forms pneumonia fibrosis and later becoming fibrous stripes in the lungs in response to early-phase and later-phase of COVID-19 respectively (Ulrich & Pillat, 2020), ultimately resulting in dysfunction in the body blood oxygenation (Chrzanowski et al., 2020).

Potential treatment strategies

As the global races towards finding a cure for the COVID-19, patients have been treated or experimented with some known agents to target viral entry, multiplication of the viral genetic materials and the immune response using an established anti-viral, anti-malarial and anti-inflammatory drugs (Felsenstein et al., 2020; Pooladanda et al., 2020) and sometimes analgesics and antipyretics drugs are used to manage COVID-19 patients. Moreover, chloroquine and hydroxy- chloroquine might use and be considered as the potential drugs that can target and destroy the virus synergistically (Zou et al., 2020), however, further studies need to be carried out. Other viable options are Favipiravir and Remdesivir which were clinically tested in China and Japan (Cai et al., 2020; Guan et al., 2020).

Recently, scientists demonstrated the potential use of mesenchymal stem cells (MSCs) to treat damaged lungs due to COVID-19, as these cells serving as immunomodulatory agent as well as having a regenerative properties (Esquivel et al., 2020). MSCs are also reported to suppress and block the cytokines storm and have ability to regenerate alveolar cells. Thus, repairing the damaged lungs and improved the function of the alveolar-capillary barrier (Xiao et al., 2020; Ye et al., 2020a). Therefore, MSCs therapy is promising and it has also been proven to alleviate pneumonia symptoms and acute respiratory syndrome(Chen et al.; Wilson et al., 2015). Further research need to be carried out to decipher the molecular mechanism by which MSCs could help in treating patients with COVID-19.

4. Conclusions

It has been established that there are a number of known and unknown virus species that are either harmful and deadly to human or beneficial to the human system. Interaction of viruses and human are generally due to the way humans interact with their environment that results in spread and infection of the viruses to the populations. Available literature on evolutionary genetics, pathogenesis mechanism and receptor binding demonstrated that SARS-CoV-2 is likely originated from bats when compared with available linearity of the same species origin. The natural process that evolved and led to the continuous spread of the virus posed a lot of questions whether the virus is genetically engineered or it got mutated while spreading across continents. In summary, it might be helpful of the healthcare system around the world could establish a strong system that will assist clinicians, scientists and researchers to rapidly develop drugs that could alleviate the strengthen and impact of this deadly SARS-CoV-2 that caused COVID-19 disease.

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