

The Impacts of SARS-2 and Its Variants on Human Health and How They Cause it

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Abstract. Began from the end of 2019, the SARS-CoV-2 outbreaks in Wuhan, China, this unknown virus are first been recognized and it continues to devastate millions worldwide. As more individual has been infected, Covid-19 has been considered an international public health event and research on its pathogenesis and impacts are necessary. Some research has already shown that the virus can also infect multi organs including human gut enterocytes and the respiratory tract and brings both short-term and long-term effects to humans, the more research has shown the varying immediate symptoms of Covid-19 including acute respiratory distress (ARDS), fever, cytokines storm and long-term risk with the impacts on heart, male reproductive system, neurological and psychological health, and other mysterious risks. In this article, multiple journals and review articles have been researched and managed into long-term and short-term sections, the result shows that Covid-19 has significant impacts on humans for both chronical and instant manifestations.

Keywords: SARS-CoV-2, Human Health, Pathogenesis.

1. Introduction

SARS-CoV-2 is the reason that why the Covid-19 pandemic occurs and it has not been limited effectively yet, instead the cases of Covid-19 have fluctuated all around the world. This result comes from multiple reasons, the main 2 reasons for the frequent cases are high mutability and contagious transmission of the virus. This virus is an RNA virus, the other example of it is influenza, hepatitis A virus, and measles. RNA virus has a high mutability which means it will have frequent changes for the pathogen-associated molecular particle, and our vaccine cannot always be effective for all of the variants. This virus is transmitted by spray or droplet, this indicates that the virus is highly contagious. The latency period of SARS-CoV-2 is around one to two weeks, and the size of the SARS-2 enters the micrometre level, so people can get infected without being noticed if the protection and prevention haven't been taken seriously. It is an RNA virus, has a frequent mutation rate just like the influenza virus. The Covid-19 pandemic has changed our life massively, the economic shrink, homelessness, quarantine, sequalae, disability, and death [1,2]. On the other hand, throughout this pandemic, the prevention and protection skills for infection, public health, development of vaccines and antivirals, and the understanding of the immune system have massively progressed due to the study of SARS-CoV-2. The understanding of the pathology, and short-them and long-term effects have been investigated by researchers through laboratory experiments and clinical studies. This research has investigated how SARS-CoV-2 infect the host cells of the human and the diverse symptoms, the pathogenesis of selective symptoms, and some enigma risk of the infection.

2. The Structure of SARS-CoV-2

This virus is a type of pneumonia coronavirus, and generally, it has four major parts in the structure. It consists of nucleocapsid, membrane, envelope or protein coat, and spike protein. This is the RNA virus, so it will process the replication stage directly in the cytoplasm. Once the virus enters the host cell, the viral RNA has released and forms the replication organelle. The translation process produces the viral particles in the endoplasmic reticulum region, and these products have been translocated to ER-Golgi intermediate compartment and assembled from the intact new virus. Finally, it proceeds the secretory pathway (exocytosis) by using the Golgi-apparatus [3].

Spike proteins are essential for the infection mechanisms, it consists of three identical S1 units, one S2 unit, a fusion peptide and other molecules that may trigger the membrane fusion. A fusion peptide is a kind of hydrophobic peptide, it's made up of 20 ~25 residues, and actually, it is distributed within the S2 unit, it induces the fusion process between the viral membrane and the host membrane. Spike protein, as a viral binding site, the spike protein is targeted on the ACE2 receptor of the human host cell.

3. How does SARS-CoV-2 enter the human cells

There are two pathways that SARS-CoV-2 can enter the human cells: one is the Endosomal entry and the other one is the cell surface entry. In the presence of both Transmembrane protease, serine 2 (TMPRSS2) protein and ACE2 receptor, the cell surface entry mechanism will be taken, and if the TMPRSS2 protein is absent, the endosomal entry mechanism will be induced to take place. The endosomal entry mechanism involves 6 steps which are virus binding ACE2, Internalisation, endosomal acidification, cleavage of the S2 subunit by Cathepsin L, membrane fusion and uncoating of viral RNA. On the other hand, the mechanism for cell surface entry requires fewer steps than the endosomal pathway needs, it only involves 4 steps which are virus binding to ACE2 and TMPRSS2, Cleavage of S2 subunit by TMPRSS2, membrane fusion and uncoating of viral RNA [4].

During both entry mechanisms, the cleavage of the Spike protein (S protein) is especially important, only when the S protein has been cleavage successful, the capsid of the virus can be degraded, and the viral RNA can be released into the cytoplasm of the human host cells.

The most important mechanism for the viral invading process is the cleavage of the S1-S2 boundary and the S2-S2' site. These mechanisms are aiming to expose the fusion peptide that is distributed inside the S2 unit and mediate the membrane fusion process to uncoat the viral genome from the capsid. During the viral entry process, the viral entry proteins are folded into the energetically stable state, and they proceed to subsequent conformational transition to form a state that can provide adequate energy to conquer the natural repulsion between the viral membrane and the cellular membrane during the fusion process. In this case, the spike protein is folded into the stable state called the 'metastable state', and then this state proceeds to 2 proteolytic cleavages carried by proteinase to form a lower energy state for membrane fusion. These two proteolytic cleavage steps are essential in the viral entry process. For both the endosomal entry pathway and the cell surface entry pathway, the first proteolytic cleavage which breaks the S1-S2 boundary is carried out by a proprotein convertase family transmembrane protein 'furin'. Furin mediates the S1 shedding process which enables the S2 subunit to further take second proteolytic cleavage. The second proteolytic cleavage process is carried by different proteases in different regions. For the cell surface entry process, the second proteolytic cleavage is carried by TMPRSS2 at the plasma membrane region. As the ACE2 receptor binds with the S1 subunit, the furin cleaves the S1-S2 bond and the S1 subunit sheds, then the TMPRSS2 which is near to the ACE2 receptor further breaks down the S2 unit to expose the S2' site and the fusion peptide. On the other hand, if TMPRSS2 is not presented or close to the ACE2 receptor, the endosomal entry process will take place. The virus will be internalised by using clathrin-mediated endocytosis, and the endosome is formed. (A lipid vesicle contains the virus) The endosome undertakes the endosomal acidification process to decrease the pH value in the endosome because the protease that cleaves the S2 subunit is activated in the acidic environment. Then the protease Cathepsin L will carry the second proteolytic cleavage can expose the fusion peptide to make the viral membrane and vesicle fuse together, as a result, the viral RNA will leak from the viral capsid and involved into the replication organelles.

TMPRSS2 is the type 2 transmembrane protein which can be found in many parts of the body including respiratory, gastrointestinal, and urogenital epithelium. ACE2 receptor has a limited presentation in the lower airway and relatively higher occurrence in the cell in the higher airway, and according to the study, many of the airway cells that express the ACE2 receptor are also expressing the TMPRSS2 protein, therefore we can use the nasal and throat stick test to identify the virus occurrence. Cathepsins are the non-specific protease that carries out both endopeptidase and

exopeptidase activity. It usually works in acidic conditions and processes the protein degradation on the virus capsid [3,4].

The infections of the SARS-CoV-2 have a relatively low dependency on the endosomal entry pathway, which also means that the endosomal acidification inhibitor (Hydroxychloroquine and Chloroquine) would have a low effect. The study shows that when the TMPRSS2 is expressed, the capability of the endosomal acidification inhibitor Hydroxychloroquine and Chloroquine is reduced. By contrast, the capability of the endosomal acidification inhibitor rises when the TMPRSS2 inhibitor (Camostat mesylate) is presented.

4. The Short-term effects of SARS-CoV-2

The symptoms of observed form Covid-19 patients are differently distributed in the human body. There are two main manifestations of the symptoms of Covid-19, one is Respiratory tract manifestation and another one is Extra-respiratory manifestation. Respiratory tract manifestation has several symptoms in different parts of the respiratory system. For the nose, Sinusitis, Rhinitis, Anosmia [5], Rharyngalgia, and Rhinorrhea are the symptoms. For the throat, pharyngitis is the expected symptom. Ageusia is a common symptom for the mouth, and for the lung, the symptoms are cough, dyspnea, expectoration, chest pain, pneumonia, and ARDS. The extra-respiratory manifestation has several different symptoms on varied organs. For neurological symptom, dizziness, headache, and impaired consciousness is included. Muscular symptoms are myalgia, malaise, and neck/back pain. Chest pain and arrhythmias are involved in cardiac symptoms, and for the digestive system, diarrhoea, nausea, vomiting, and abdominal pain are commonly observed. For the systemic symptoms, chills, fatigue, malaise, and fever are observed.

SARS-CoV-2 generally will cause upper tract (URT) infection, and some research has shown that it can also cause gastrointestinal infection. According to the research, 83% of the patients who has been infected experienced fever, 82% of the patients have coughing symptom, and 31% of the patient's experienced dyspnea. Together, these flu-like symptoms will progress to serious inflammation and multi-organ dysfunction [6].

4.1. Pathogenesis

The virus has a very significant impact on the respiratory system, and these mechanisms will produce severe ramifications. The virus has been inhaled by the patients and attached to the respiratory tract and the lung region, and it enters the cells including alveolar airway epithelial cells and vascular endothelial cells. The SARS-CoV-2 is detected by toll-like receptors (TLRs), and the signals of the interferons and proinflammatory mediator have driven up the production of the inflammatory cytokines and chemokines, as a result, the concentration of these cytokines and chemokines in the BALF and serum shifts up rapidly to cause the destructive damages to tissues throughout the endothelial dysfunction and endothelins and lung oedema, lack of gas exchange, cytokine storms. Besides, as the infection of endothelial cells rises in number, an excessive amount of inflammatory immune cells such as macrophages and neutrophils will be present in this area and cause damage to either the infected cells or the healthy cells. These symptoms derive the multi-organ dysfunctions dramatically including heart, and kidney [4,7].

4.2. Impacts on T cells activation

Moreover, the impairment of T cell activation is also one of the impacts of SARS-CoV-2 infection. Due to the infection and series of pathogenesis, the efficiency of IFN- γ and IL-2 production for CD4+ and CD8+ T cells have been negatively affected. Dendritic cells (DCs) are involved in T cell activation and its distribution in the lung, the infection progresses the reduction of DCs in the lung area which can compromise the adaptive immune response indirectly and lower the immunity of individuals [4].

4.3. Cytokines/Chemokines storm

Cytokine storm is a symptom that occurs when the immune system acts overaggressive which destroys the human health host cell and proceeds into severe symptoms. According to the investigation, Covid-19 has resulted in to increase in the proportion of proinflammatory macrophages and neutrophils, and these have been observed in the bronchoalveolar lavage fluid (BALF). The content of the pro-inflammatory cytokines such as interleukin-6 and interleukin-8 and the inflammatory chemokine like CCL2 increased simultaneously in the BALF with serious SARS-CoV-2 infections, and thus contribute to the lung cytokine storm which causes severe harm to both infected cells and healthy cells [8].

4.4. Age factors affecting the impacts of infection in a significance

Age is one of the factors that have a significant relationship with infection morbidity. Elders and youth who have an incomplete immune system or lack of immunity will have a high chance to develop severe symptoms like ARDS and fever, so there will be a greater possibility for elders and youth to admit to the intensive care unit (ICU), the mortality rate for them will also be relatively higher compare with the non-vulnerable population such as adults. According to the data from research, lymphocytopenia, neutrophilia, and elevated inflammation indices are continuously reported from the investigations based on the patients who have equal to or greater than 65 years old [8].

5. The Long-term effects of the SARS-CoV-2

5.1. Impacts of Covid-19 on heart

Covid-19 has a range of impacts on the heart and the cardiovascular system, these long-term ramifications are likely to increase the morbidity and mortality of the patients [9].

Arrhythmias is a symptom resulting from the abnormal signalling process, cardiac electrical dysregulation is one of the reasons for it. The cardiac electrical network can be affected by the Covid-19 viral infection, myocardial damage, hypoxia, and resulting to electrolyte imbalances and abnormal depolarisations. According to the research on hospital cases, 10-30% of the patients and 30-50% of the ICU patients have been found with arrhythmias, and this has a significant increasing effect on morbidity and mortality of individuals [10].

Myocardial damage is one of the common symptoms that found on the Covid-19 patients. It is proceeded by the increasing troponin level. According to clinical research on 559 patients with higher troponin levels, 57% of the patients have shown a greater demand of the ventilatory support demand and death. Myocardial damage can also be the result of the inflammatory immune response [9]. Viral infection is highly possible to trigger the imbalance of the electrical system and damage the heart pumping function by inducing myocarditis. The hyper-inflammatory state which is derived from the severe infection will proceed with the cytokine storm which can trigger myocarditis, and myocarditis has contributed to the high mortality rate significantly by causing injuries or destructive damage to the cardiac cells.

Coronary ischemia is one of the symptoms of the Covid-19 infection. The severe myocarditis and myocardial damage have contributed to the coronary ischemia directly. The inflammations of the cardiac muscles and the vascular endothelial cells can increase the number of plaques which will result in insufficient blood received by the cardiac muscles. Coronary ischemia will lower the contractibility of the heart, lower the blood output, and even cause death to the cardiac cells if the symptom is advanced [11].

Cardiomyopathy is a severe symptom found with the Covid-19 patients. The data research has shown that 25% of hospital patients have been detected with heart failure and 33% of critically ill individuals have found this symptom [8]. Acute lung injury and ARDS has an impact on right heart strain by increasing the afterload of the right ventricle (RV). This will initiate the lung-protective strategy including high positive end-expiratory pressure (PEEP). The PEEP strategy rises the RV after-

load which leads to a decrease in the left ventricle pre-load, eventually, this results in lower cardiac output. The RV is very sensitive and vulnerable to changes in after-load, so the ADRS will cause a reduction in RV contractility and cardiac output ultimately [12].

An increasing risk of getting thrombosis has been reported in several Covid-19 cases. Severe hypoxia can result in higher blood viscosity which promotes stasis and hyper-coagulability. Cytokines storm and hyper-inflammatory immune response are also causing endothelial destruction and platelet activation. According to the research of 3300 patients with Covid pneumonia, more than 16% of the patients have experienced a thrombotic event, and up to 30 % of the ICU patients have the incidence of thrombosis [10]. Moreover, the autopsy result has shown that patient has an large-scale performance of high platelet thrombi within the pulmonary, hepatic, renal and cardiac microvasculature. Even more, the data has shown that however, although patients are taking the therapies, a high rate of thromboembolic syndrome is still detected.

Not only the asymptomatic patients, but also the symptomatic patients, myocardial fibrosis has been detected. The pathogenesis of myocardial fibrosis is driven by fibroblastic deposition, hyper-inflammatory response has contributed to this cellular deposition and result in the fibrosis symptom [13].

5.2. Covid-19 impacts on neurological and psychological risks

According to a 2-year clinical study, the impacts of Covid-19 on human has also been shown on a neurological and psychological level. The research has shown that the infection has clearly shown the increased incidence of mood and anxiety disorders. Moreover, the risk of psychotic disorder, cognitive deficit, dementia, and epilepsy has shot up with the infected patients and children have less psychiatric risk compared with adults and elders. Another research shows that the Covid-19 pandemic has contributed to an increasing rate of delirium from both direct impacts of Covid-19 and from the inability to access the prevention of delirium, and within this research, the statistical interpretation has shown that dementia is a significant impact of Covid-19, and it contributes to a higher mortality rate during the pandemic period [14-16].

5.3. Impacts on male reproduction system

Intensive and invasive damage to the male reproduction system has been considered one of the manifestations of the SARS-CoV-2. Male testis cells have presented with the ACE2 receptor, but whether the virus can infect the testis cells directly is still controversial. By the way, inflammatory damage caused by cytokines storm is one of the major pathogeneses for the impacts on the male reproduction system, and high blood viral load, local inflammation, hyperpyrexia and imperfect BTB can result in disruption of testicular tissues which ultimately affect the fertility of males [17].

The research shows that SARS-CoV-2 can trigger the dysfunction of the hypothalamus pituitary-gonad gland and result in impairment of secondary male sex characteristics. The Covid-19 infection male patients have been found to with increased luteinizing hormone, follicle-stimulating hormone, prolactin, and decreased estradiol, progesterone and testosterone in blood plasma level. The data shows that 68.6% of the male patients have low testosterone symptoms, and 48.6% of the patients have dihydrotestosterone levels (very dilute). Moreover, due to the inflammations, the Leydig cells can have a dysfunction ramification which caused the reduction of androgens (A hormone that maintains the secondary male sex characteristics). Lower androgens levels will result in a higher risk of the loss of secondary male sex characteristics for reproduction. The clinical case study has reported decreased sperm number, increased sperm DNA fragmentation and impairment of sperm quality. These factors will reduce fertility, lower embryo quality, and increase embryonic loss [17].

5.4. Unknown risk of reverse transcriptase in human body

According to research, in the human body, scientist has found some enzyme that carries the function of reverse transcription from RNA into DNA. These discoveries have derived the human health problem into a deeper understanding. LINE-1 and Polymerase theta have been found inside the human

body with the activity of reverse transcription, this unique function usually only occurs in some special viruses called retrovirus-like the Human immunodeficiency virus (HIV). The presence of LINE-1 and polymerase theta have increased the chance of the RNA genome of the SARS-CoV-2 being reverse-transcribed into DNA and integrated into the host cell genetic material [18,19]. The result of this reverse transcription and integration of the viral RNA is unknown, and it is likely to be used to explain the observation of the re-detectable positive on nucleic tests after the treatment. The possible mechanism that supports this hypothesis is that due to the infection and the inflammatory response, the host cell appears for some impairment and requires genetic repair, so different types of DNA polymerase including the polymerase theta are involved in the genetic repairing process, and during the process. The debris of the viral RNA has been detected by the polymerase theta and reverse transcribed the RNA into DNA. After this, the cDNA has been integrated into the host DNA, and as the normal transcription goes on, the mRNA that includes the viral particles and the viral RNA will be introduced into the cytoplasm, and these viral particles and items will be released by exocytosis or hang on the surface of the host cell membrane. (This can also explain why human DNA contains many of the viral DNA.) Consequently, the RT-PCR test has detected the Viral RNA and replicated it in DNA form, so the test result can be positive. Similar pathway with the LINE-1 enzyme.

According to the data, this process has not been found to cause some severe symptoms, but we don't know what it will bring to us. Try to imagine that, if the viral DNA is currently in the latency or dormant stage, what will happen if the gene is activated? As a result, this risk is one of the chronic impacts of Covid-19, We don't know what exactly the risk or the result is, but we will know it eventually.

6. Conclusion

This paper has shown the toxicity and the massive impacts the SARS-CoV-2 brought on humans. Infections of SARS-CoV-2 have resulted in varied severe symptoms and can affect human health in multiple ways. The short-term manifestations include ARDS, cytokine storm, fever, and the long-term impacts are heart failure, damage to the male reproductive system, increase risk of dementia and psychotic disorder and the enigma impacts of reverse transcription. The most severe symptoms are either caused by the over-inflammatory response or the direct destruction due to the viral infection. These pathogeneses have contributed severe damage to tissues and multiorgan dysfunction which ultimately affect human healthiness and even the health of the next generations.

Research on SARS-CoV-2 pathogenesis and symptoms is required during this period, scientists and doctors can develop a specific treatment for anti-pathogenesis to minimise the negative effects of Covid-19 on both humans and society. Although many of the pathogeneses are still controversial, the investigation of Covid-19 is essential. More than pathogenesis and mechanisms, clinical data are also crucial in the scientific field, only the clinical data can support the research hypothesis and convince people to believe the danger of SARS-CoV-2.

In the future, scientists can devise effective treatments to reduce the impacts of Covid-19 or even eradicate it by targeting to block the pathogeneses to lower the destruction effects on human organs and tissues. Also, clinical data is one of the most important parts of therapeutic development. Valid and reliable clinical data can convince people to take prevention and can prove the effectiveness of the treatment.

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