


# Surviving the Rookie Virus, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV2): The Immunopathology of a SARS-CoV2 Infection

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## Abstract

Until July 29th, the number of confirmed coronavirus (COVID-19) cases worldwide has risen to over 16 million, within which 655 k deaths. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) emerges as the 11th global pandemic disease, showing the highest infectivity and lowest infection fatality rate. In this review, we compare the immunopathology among SARS-CoV, Middle East respiratory syndrome coronavirus, and SARS-CoV2. SARS-CoV2 is similar to SARS-CoV; it can cause lymphocytopenia and a rising granulocyte count. Here we point out the human body and concentrated society make for an excellent incubator for virus evolution. Most research energies put into developing the SARS-CoV2 vaccine are trying to block virus infection. Sixty-five percent of severe patients die with multiple organ failure, inflammation, and cytokine storm, which indicates that the patient's immune system maintains functionality. Finding a way to trigger the specific T cell subset and plasmablast in our body is the best shot to get away with SARS-CoV2.

## Keywords

SARS-CoV2, immunopathology, vaccine

## Introduction

Throughout the course of history, a pandemic devastates the entire human population while simultaneously propels the human immune system evolution forward. At the same time, pathogens continue to evolve as well. At the turn of the decade, severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) emerges as the 11th global pandemic disease; its first case reported with pneumonia in Wuhan, China<sup>1,2</sup>. As of July 29, 2020, the report indicates that there are 16,540,137 SARS-CoV2 patients, 655,300 death cases, and an infection fatality rate (IFR) of 3.9% worldwide. However, this pandemic did not stem from the first coronavirus outbreak. In fact, there are seven coronaviruses found existing, of which four—HKU1, NL63, OC43 and 229E—cause mild symptoms<sup>3</sup>. SARS-CoV, more commonly known as SARS, had its first outbreak in 2002 in China, then spreading to 26 countries, leading to 8,000 confirmed cases and 774 reported deaths, resulting in an IFR of 9.3%. With good quarantine control, cases remained stagnant from mid-2003 onward. Ten years later in 2012, Middle East respiratory syndrome coronavirus (MERS-CoV), known

more commonly as MERS, reported its first case in Saudi Arabia. MERS resulted in 2,494 infected cases, 858 deaths, and an IFR of 34.3%. Due to its high mortality rate and the world's previous experience with SARS, MERS never escalated into a pandemic. It wouldn't be for another 10 years

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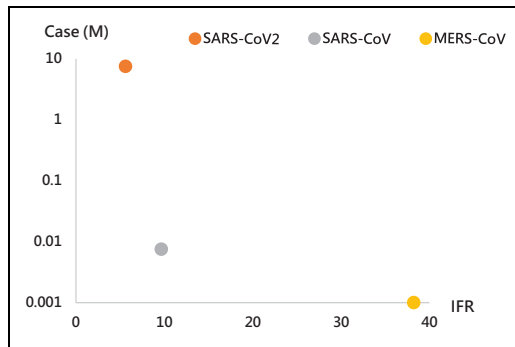
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**Figure 1.** Relationship between worldwide cases and IFR among coronavirus. IFR: infection fatality rate.

The SARS information are cited from the webpage <http://wiki.idph.iowa.gov/epimanual/Home/CategoryID/110#tab288>; MERS data are cited from the website <https://www.who.int/csr/don/29-january-2016-mers-thailand/en/>

until SARS-CoV2 emerges as a low mortality, fast spreading disease, rapidly declaring itself as a pandemic.

Additional research from China indicates SARS-CoV2 as a human immune system breaker, causing lymph node and spleen necrosis, leading to lymphocytopenia<sup>4</sup>. Like SARS-CoV2, HIV and DENGUE also lead to lymphocytopenia. HIV is transmitted by contaminated blood transfusion, body fluid exchange, sexual, pregnancy and breast feeding, whereas DENGUE virus is transmitted from an infected individual to another through the female mosquito (*Aedes aegypti*). Unlike SARS-CoV2, however, HIV and DENGUE virus transmission pathways are different. In addition, HIV and DENGUE have existed in human society for over two centuries. With our healthcare and medical research technology improvements, these two viruses have become chronic diseases. If we control them well, they won't become a life-threatening issue. Coronavirus, however, is a rookie virus; their transspecies just only 30 years. In this article, we will discuss coronavirus, including not only SARS-CoV2 but SARS-CoV and MERS-CoV, the immune system response, and how to improve the human survival rate from a SARS-CoV2 infection.

## Severe Acute Respiratory Syndrome Coronavirus 2

SARS-CoV2 broke out in Wuhan in 2019 with pneumonia symptoms related to acute inflammation and immune system activation. After gene sequencing SARS-CoV2, results show that SARS-CoV2 uses the SARS-CoV receptor ACE2 to enter the host cell, and the host cell's serine protease TMPRSS2 is helping spike S protein priming<sup>5</sup>.

According to research from Wuhan, China, they collected 522 patients with confirmed SARS-CoV2 infection and compared them with 40 healthy patients. The adaptive immune system cell, CD8<sup>+</sup> T cell and CD4<sup>+</sup> T cell, count number is lower than 300 and 400 cell/ml, respectively.

Further, they compared mild disease and severe diseased (SD) patients. SD patient showed the lowest CD8<sup>+</sup> and CD4<sup>+</sup> T cell counts<sup>6</sup>. Another research from Hubei, China, showed similar results. After SARS-CoV2 infection, infected patients' T cell counts decreased. In fact, not only did the T cell counts decreased but also the NK cells. For those who survived SAR-CoV2, their T cell and NK cell number restored<sup>7</sup>.

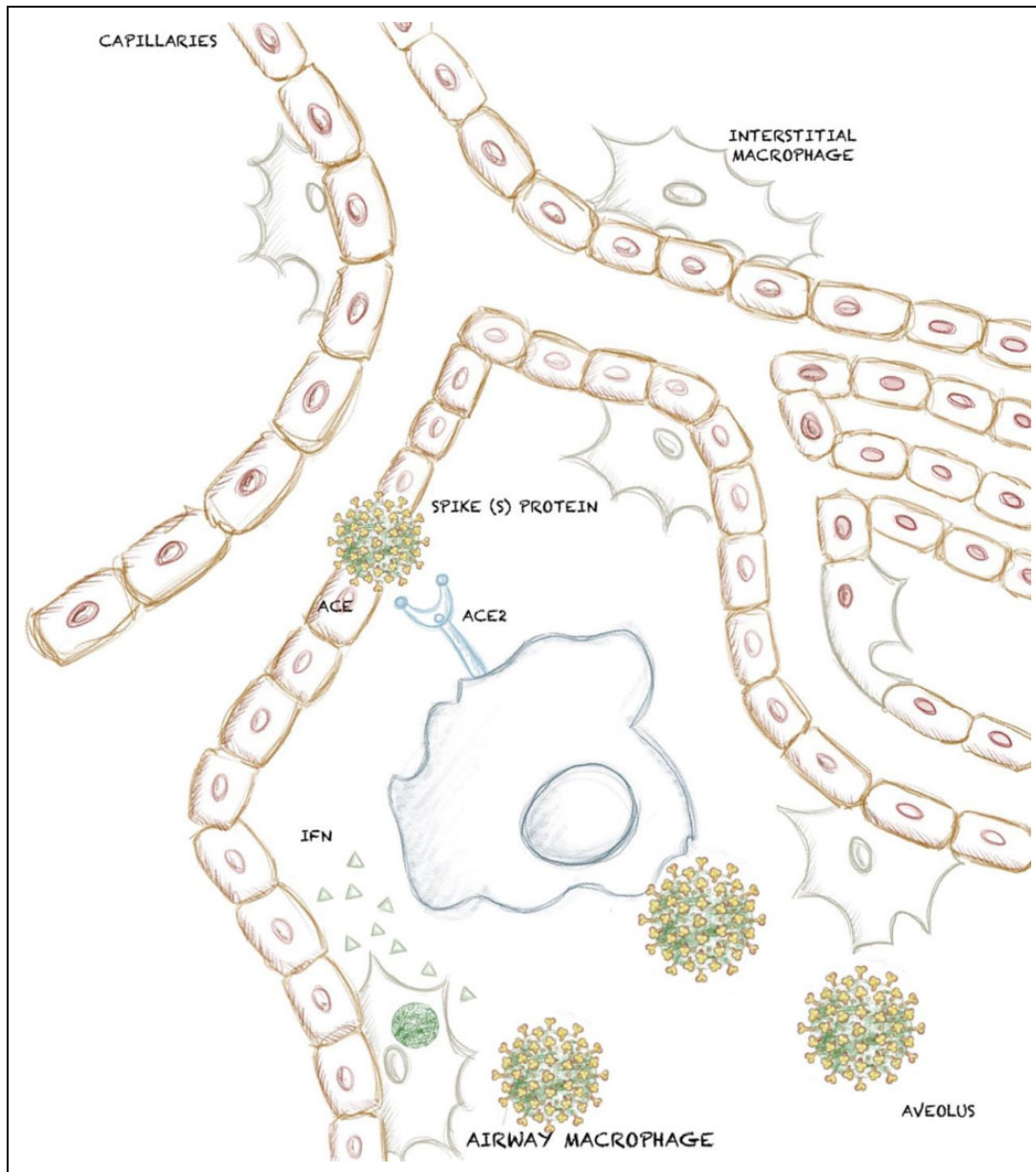
In general, Alveolar macrophage destroys the pathogen, bacteria, virus, dust via phagocytosis, digests them into segments, and presents them to the adaptive immune cell. Macrophage as an antigen presenting cell, APC, connects innate immune response to adaptive immune response. Because of lymphocytopenia, Dr Cheng, from Chongqing, studied six patient autopsies to examine the secondary lymphoid organ spleen and lymph node. They found that interstitial macrophage expresses the ACE2 receptor and that some of these macrophages also contain the SARS-CoV2 nucleocapsid protein. The severely damaged tissue, splenic nodule atrophy, and TUNEL assay show a lot of apoptosis in the lymph node and spleen<sup>4</sup>, which means SARS-CoV2 infection can cause lymphocytopenia by macrophage-induced cytokine storm in lymph node and spleen.

Initial SARS-CoV2 infection pathology, so far, tells us that SARS-CoV2 transmits by airway and enters human body by AEC2 receptor<sup>5</sup>. Detail analysis suggests the SARS-CoV2 infection processes through the mouth and enters the respiratory system. The epithelial cell of oral mucosa showed highly express ACE2 (93.32%)<sup>8</sup> and the nasal secretory cell and ciliated cell showed highly ACE2 expression as well. Lower airway and lung parenchyma also show ACE2 expression, especially Alveolar type II cell. But the upper airway didn't express ACE2. Interestingly, Cornea, Ileum, and Colon showed ACE2 expression<sup>9</sup>. These ACE2 expression profile supply an evidence to explain why SAR-CoV2 patient have collapsed lung and diarrhea symptoms. Remarkably, they found the IFNG will induce ACE2 expression three times higher on epithelial cell<sup>10</sup>.

## Severe Acute Respiratory Syndrome Coronavirus

Before the emergence of SARS-CoV2, there were seven other coronaviruses present. HCoV-NL63, HCoV-229E, and HCoV-OC43 were baby viruses causing mild respiratory tract infections. HCoV-HKU1 was first detected in a child nasal sample in 1995, but the first patient was discovered in 2004 along with pneumonia. HKU1 was the first coronavirus known to cause pneumonia. And in 2002, SARS-CoV had its outbreak in Guangdong, China<sup>11</sup>.

SARS-CoV was the first coronavirus epidemic in human history. As the outbreak occurred only in Guangdong in the beginning, most known study of SARS relied heavily on reports made in China. In a study with 138 SARS patients,



**Figure 2.** The schematic of SARS-CoV2 infects human alveolar. SARS-CoV2: severe acute respiratory syndrome coronavirus 2. The major concepts and knowledge for building up of Fig. 2 are from Eup. J. Intern. Med. (2020), 76:14-20. doi: 10.1016/j.ejim.2020.04.037

100% have fever, and 69.9% showed lymphopenia<sup>12</sup>. According to their six autopsy cases, they reported a lot of monocyte, lymphocyte, and plasma cell infiltrating in the alveolar necrosis lesion. Lymph node and lymphoid organ showed massive necrosis as well. Hyperactive immune cell including monocyte, lymphocyte, and plasma cell infiltrated the heart, liver, kidney, and many other organs<sup>13</sup>. The SARS outbreak in Toronto noted that of the 144 patients that were infected with SARS-CoV, 77% were exposed to SARS in the hospital. Their report is similar to China's study. Neutrophil and lymphocyte counts were below the average (3,600/7,500, 900/4,000)<sup>14</sup>.

In 2006, Jiang Gu reported  $CD8^+$ ,  $CD4^+$ , plasma cell, and APC were significantly decreased in SARS spleen red pulp area. Each lymphocyte subset and NK cell were decreased 65%-95%<sup>15</sup>. The direct injury is caused by virus infected, but most indirect injury in multiple organ results from hyper-activate immune response<sup>16</sup>.

### Middle East Respiratory Syndrome Coronavirus

In 2012, a SARS-CoV-like case was reported from a hospital in Jeddah, Saudi Arabia. Dr Fouchier conducted a test

capable of detecting all known coronaviruses up to date. The results indicated that the virus was a novel coronavirus that had never been seen before<sup>17</sup>. The novel coronavirus was termed the Middle East respiratory syndrome coronavirus, MERS-CoV. MERS-CoV shows a lower level human to human transmission. Until 2015, there were 1,633 confirmed infected MERS cases. According to the report from WHO, 587 deaths were due to MERS-CoV<sup>18</sup>. In the beginning, MERS was called the novel human betacoronavirus EMC (HCoV-EMC). Forty-seven MERS patients showed 14% leukopenia and 37% lymphopenia<sup>19</sup>. One case report showed WBC count is on normal level, but with high percentage of neutrophils (92.5%) and lower percentage of lymphocyte (4.3%)<sup>20</sup>.

Contrary to SARS-CoV, MERS-CoV's spike protein binds to human DPP4 and not ACE2<sup>21</sup>. Although MERS' spike protein ligand is different to SARS, it still stimulates tons of cytokine and chemokine to secrete from the immune cell. In severe MERS patients, there was high level IL-6, IL-8, IFN $\alpha$ , and CCL5 in serum<sup>22</sup>.

### How to Get Away with SARS-CoV2

So far, the development of SARS-CoV2 vaccine base on synthetic spike protein. One problem in the vaccine development process is spike protein modification in our cell is the same structure compared to synthetic spike protein. Viral surface protein glycosylation plays vital role in infection. Some glycosylation can protect virus from immune surveillance. Most of SARS-CoV2 vaccine study used synthetic plasmid transfect mammalian cell line to check their vaccine work or not. In reality, after SARS-CoV2 infection, virus infection stage from latency to lytic, hijack the host cell to translate viral protein to package the particle. At that time, mammalian cell might help viral coating protein do the post translation modification. That's why some study showed the S protein of SARS-CoV2 has 22 N-linked glycosylation site<sup>23-25</sup>. They trying to find out which site is critical to virus entry as a new target to developed vaccine or antibody. But the question is our developing vaccine and antibody can completely block the virus, and we won't never face it again. After 20 years coronavirus evolution, the IFR from 9.5% to 5.6%. Until June, there are some news report, the second wave outbreak infection in Beijing, South Korea, and the United States<sup>26</sup>.

Social distancing and strategic quarantine may be effective in the beginning. When faced with the a life-threatening unknown, our first response is "do not touch anything," allowing ourselves the time to analyze in order to eliminate them by using structural analysis and neutralizing antibody development. However, once we realize there is no way to stop the spreading, we resort to hostile co-living, desperately trying not to be murdered like the influenza and HIV. Currently, SARS-CoV2 patients can be divided into mild, medium, and severe symptoms. Most mild and medium patients can be cured by themselves after a fever.

Sixty-five percent of severe patients die with multiple organ failure, inflammation, and cytokine storm, which means that the patient's immune system did work. But the host immune system cannot clean the rapidly replicated virus. With tons of inflammation cytokine secreted, they accumulate in infectious organ, leading to multiple organ failure<sup>27</sup>. In addition, the human body and society is a good incubator for the virus evolution. The virus mutation can cause the vaccine development bubble explode. The research from the United States found SARS-CoV2 spike protein mutate on D614G site and cause three times higher infectious rate<sup>28</sup>.

The true question lies in how can we manually control our immune system response to SARS-CoV2. Rapidly wiping out the SARS-CoV2 infection is the only way to win that war. More and more research are starting to compare the difference between healthy and acute respiratory distress syndrome patients with SARS-CoV2. Data show that severe SARS-CoV2 patients were depleted of  $\gamma\delta$  T cells, dendritic cells, and NK cells. But more interestingly, plasmablasts as an antibody secreting cell increased, which means severe cases might also cause a humoral immune response. CD56<sup>dim</sup> NK cell is considered as antiviral cell, CD56<sup>bright</sup> NK cell which produce INF- $\gamma$  were depleted. On the other hand, each T cell subset all expression exhausted marker. MHC class II has a vital role in expression pathogen to cell surface. They found MHC class II downregulate expression in severed patient<sup>29</sup>. HLA-DR expressions on T cell and B cell are reliable markers in the immune system response with acute infection not only in coronavirus but also in Ebola<sup>30</sup>. In one case report, a women who was detected SARS-CoV2 by real-time polymerase chain reaction at day 4, but undetectable at day 7. All the symptoms resolved completely at day 13. HLA-DR expression on CD8<sup>+</sup> T cell and CD4<sup>+</sup> T cell increased from day 7 (3.57%, 0.55%) to day 9 (11.8%, 3.33%). HLA-DR<sup>+</sup> CD8<sup>+</sup>T cell produces an amount of granzyme A, B, and perforin<sup>31</sup>. HLA-DR+ expression on lymphocyte means the host immune cell specific subtype which can recognize the virus particle was activated. In 19 SARS-CoV2 patient study, the moderate patient showed high IFNG, CCL5, PRF1, but severed patient showed lower levels of CCL5 and INFG. Its seems CCR5 might be a good therapeutic target<sup>10</sup>.

Combining all these evidences together, SARS-CoV2 can target our immune system and interfere with the intelligence system of human immunity. Developing CoV2 vaccine might slow them down, but cannot aid in the people who are already infected. There are two strategies to saving life, one is inhibiting the amount of proinflammatory cytokine secretion and the other is letting the immune response find the way out. It takes time, but it will work. The alternative is to find a way to trigger the specific T cell subset and plasmablast in our body, and eliminate the viral particle to lower our immune tolerance.


### Declaration of Conflicting Interests


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