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Cytokine Storm and Modulation of Immune Responses During SARS-CoV-2

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Abstract

A large number of cases of SARS-CoV-2 have been reported over the world, which makes those infected have severe symptoms while some maybe cannot be identified for lack of obvious symptoms. It is found that high levels of cytokines is linked with the severities of the virus. Apart from the increase of cytokines, moderate SARS-CoV2 patients proved a gradual reduction of antiviral and antifungal responses. During cytokine storm, upregulated cytokines would play an important role in generating adverse symptoms and it in deed has a damage mechanism. Based on the different levels of symptoms of CRS, various treatment is to be required, and IL-6 as the key cytokines that is generated among those abnormal cytokines should be paid more attention on. The thesis is hoped to be helpful for the research on treatment for CRS and conquering the virus.

Keywords

SARS-CoV-2, Cytokines storm, Neutralizing antibodies, CRS.

1. Introduction

Currently, more than 19 million cases that are confirmed as SARS-CoV-2 have been found around the world. Since the first case was reported in the city of Wuhan, the capital city of Hubei Province in China in the last moth of 2019. All continents reported local cases except for Antarctica. However, according to researchers, the number of people who have exposed to SARS-CoV-2 may exceeded the cases reported by more than 10-folds. Now we know that after someone has been infected with the virus, it may take 2-14 days for the person to show symptoms. The infection can appear with fever, fatigue and dry cough. It can lead to common colds, severe symptoms including infections in lower respiratory tract, pneumonia, lymphopenia, and even respiratory and organ failure. But some people may not even show any symptoms at all. These all make the virus highly contagious and make it hard for people to gain total control of it.

The SARS-CoV-2 belongs to the classification of positive-sense single-stranded RNA virus. Enveloping the positive single stranded RNA associated with nucleocapsid protein (N protein), the virus is covered by peripheral spike glycoprotein S over its surface with hemagglutinin-esterase dimer (HE), M-protein and E protein embedded also. Coronavirus survive and proliferate depending on protein synthesis machinery of infected host cells. Once the virus gets adjacent to host cells, Serine protease type 2 transmembrane serine proteas (TMPRSS2) presented on surface of the host cell will activate viral S protein, cleaving Angiotensin Converting Enzyme-2 (ACE2) receptor which is commonly presented on human pulmonary epithelial cells to facilitate viral binding to host cell

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membrane. Through the binding of S protein with ACE2, the virus is then allowed to enter through endocytosis into host cell inside which the positive single stranded viral RNA released by coronavirus will be able to replicate and package itself into virions. The viral population released from the infected host cell will eventually take on the same process to attack initially the pulmonary epithelial cells, amplifying the severity of infection. Eventually, excess amount of virus proliferated can shed from the site of infection through droplet transmission (sneezing, coughing, sputum etc.) which serves as the main pathway for the virus to transmit. People influenced by the SARS-CoV-2 might be asymptomatic, paucisymptomatic, or have developed intense symptoms. Some patients might develop serious pneumonia that can ultimately lead to Acute Respiratory Distress Syndrome (ARDS).

A large number of personal cases with SARS-CoV-2 shows in the periods of the infection, infected people usually have immune reaction out of control. It is due to the hyper-activation of monocytes and macrophages and will lead increase in IL-6, neutrophils and reactive protein C. The lymphocytes population is decreased in the response. The SARS-CoV-2 would trigger the immune reaction that adapts to different situations. The virus-specific T cells and B-lymphocytes will play an important part in the reaction. The Helper T-cells can activate Th1/Th17 that contribute the intensify of the inflammatory response and B lymphocytes produce specific antibodies for SARS-CoV-2 for neutralization of the virus. Most people start the antibody reaction from the 10^{th} day 10 to the 21^{st} day after infection. Identification of antibodies in the patients who are not seriously infected will take longer time around four weeks. According to the dates, the development of IgM and IgG antibodies will occur between 6 and 15 days after the disease onset. The total antibody was less than 40% within 1 week from onset and the number will rapidly increase to 100% (94.3% OF IgM and 79.8% of IgG) 15 days after beginning. Some researchers suspected that this abnormal immune response will lead to a hyper-activation of the cytokines [1]. The cytokine storm includes the quick and massive production of different cytokines such as TNF, IL, CSF, MCP-1 in the internal environment after infection. After the virus invades the bodies, the immune system initiates to activate cytokines and recruits immune cells which can in turn to secret more cytokines and activate more immune cells, thus forming positive feedback [2,3]. However, the hyper-activation of immune response will generate cascade reaction, leading to cytokine storms which would cause severe respiratory distress syndrome (ARDS) and multi-organ failure. Based on several studies, the severities of SARS-CoV-2, MERS and IAV are all correlated to the excessive release of cytokines and chemokines [4].

Based on the information we have so far, we suggest that the uncontrolled cytokines response contributes to different severity of the patients and syndromes occurring in the patients. The regulation of those cytokines will definitely improve the condition of the patients.

In the work, the authors will discuss on the detailed information of SARS-CoV2, chemokines and how they function. In addition, therapeutic approaches of neutralizing antibodies to capture specific chemokine and medical treatment inducing similar cytokine storm will be surveyed.

2. Result

2.1 Breakdown of SARS-CoV2 patients by disease severity

After the infection of SARS-CoV2, the patients may take 2-14 days to show symptoms. Among these infected patients, about 13.8% of the cases will develop with a severe condition which might further lead to morality. In order to treat all of the patients, it's important to distinguish severe and moderate illnesses. Both moderate and severe patients displayed a similar marker and correlation intensity, but SARS-CoV2 markers will stop developing and decline among the moderate patients and the severe patients will maintain the elevation after ten days. Patients with severe illness will eventually develop ARDS as short as two days and transfer to ICU to treat with oxygen therapy [5].The pathophysiology of SARS-CoV2 is still not fully understood, but studies have shown a significant elevated level of cytokines such as IL6, IFNα, and TNFα. Besides the elevation of cytokines, moderate SARS-CoV2 patients presented a progressive reduction of antiviral and antifungal responses. By contrast, patients with severe SARS-CoV2 are accompanied by an increase of anti-helminths effectors [6].

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3. Cytokines that are upregulated may be responsible for adverse symptoms during cytokine storm:

3.1 Chemokines and their functions

Cytokines are small molecular of proteins or peptides with many biological activities produced and discharged by a variety of cells caused by mitogens, immunogens, and others. Cytokines can regulate innate immunity, adaptive immunity, cell growth and differentiation, and repairments of damaged tissues. As a "double-edged sword", cytokines, like other immune molecules, can not only play the role of immune regulation, but also participate in the occurrence of a variety of diseases under certain conditions, but also cause cytokine storm and cytokine release syndrome, leading to multiple organ damage and functional failure and death. Cytokines can be divided into interleukin (IL), interferon (IFN) and tumor necrosis factors (TNF), colony stimulating factors (CSF), chemokine and some growth factors. Different cytokines have different functions and the specific function will be elaborated in the Table 1 below [7].

Table1 Classification of Cytokines

Type	membership	Function
IL	IL1~IL40	Promote Proliferation and differentiation of immune cells
IFN	IFNα, IFNβ, IFNγ	Regulate innate immune response and activate the antiviral properties
TNF	TNFα, TNFβ	Activate the inflammatory response and cytotoxic T cells
CSF	GM-CSF, M-CSF, G-CSF	Stimulate proliferation and differentiation of hematopoietic progenitor cells
Chemokines	CXCL8, CCL2, CX3CL1, XCL…	Activate inflammatory response and recruit leukocytes
Growth factors	IGF, EGF, TGF-β…	Promote cell growth, differentiation and ontogenesis

3.2 Cytokines storm and its clinical features

Cytokine storm is associated with a variety of communicable and non-communicable diseases and is a systemic inflammatory response induced by infections, drugs and other factors [8]. Some pathogens can escape the immune response without inducing an effective immune response whereas others can overstimulate the immune system. Many inflammatory cytokines and chemokines spilling into the circulatory system, may cause a large scale of inflammatory cascade [9]. Excessive inflammatory reaction may cause pulmonary symptoms (hypoxemia, vascular leakage caused by pulmonary edema, or even ARDS), cardiovascular symptoms (low blood pressure, arrhythmia, myocardial damage, shock), blood system symptoms (decreasing blood cells, blood coagulation dysfunction, diffuse intravascular coagulation), acute kidney injury, multiple organ failures, and even life-threatening [10,11].

3.3 The damage mechanism of cytokine storms

Coronavirus (CoV) can generate moderate and serious respiratory diseases, which can be divided into low-pathogenicity CoV and high-pathogenicity CoV. Low pathogenicity CoV infects upper respiratory tract and causes moderate and respiratory diseases which is similar to cold. Highly pathogenic CoV, such as SARS-CoV, Middle East Respiratory Syndrome (MERS) -CoV and SARS-CoV-2, mainly influence the lower respiratory tract and lead to the pneumonia that causes death. Serious pneumonia from highly pathogenic CoV usually has a link with rapid viral reproduction, mass inflammatory infiltration, and excessive release of cytokines and chemokines that cause inflammation. Many clinical cases show that in many severe cases of high-pathogenicity CoV, a

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cytokine storm can be observed and can damage pulmonary capillary endothelial cells and alveolar epithelial cell, leading to the occurrence of ARDS and multi-organ failures [12-14]. By investing the virology study of SARS patients with pathological tissue samples, the department of pathology at the Hong Kong University found that patients with severe SARS have the alveolus damage, presenting bronchial epithelial exfoliation, cilia loss, and squamous metaplasia. Macrophages in the alveoli and interstitial lung were significantly increased and released pro-inflammatory cytokines [15]. Similar to SARS-COV-2, MERS-COV infection of human respiratory epithelial cells can induce significant increases in IFN, IL-1, IL-6 and IL-8.Although MERS-CoV can replicate in initial and activated mononuclear macrophages and Dendritic cells, only activated T cells can lead to replication of MERS-COV, which is contrary to SARS-CoV-2. The grades of pro-inflammatory cytokines and chemokines (IL-2, IL-8, CCL-2, CCL-3, and CCL-5) were significantly increased after infection with MERS-COV. Recent studies have shown that the inflammatory cytokines (IL-6 and IFN-λ) and chemokines (IL-8, CXCL-10 and CCL-5) are significantly higher in serious patients than in less-severe and moderate MERS-infected people. High levels of cytokines and chemokines in the serum of MERS-infected people are associated with increased numbers of neutrophils and monocytes in lung tissue and peripheral blood, indicating that the cells function in pulmonary disease [16].

Depending on the data from Wuhan Jinyintan Hospital, reseachers found that patients with SARS-CoV-2 have increased inflammatory factors, including IL-1β, IFN-γ, IFN-γ induced protein 10 (IP-10) and MCP-1. Moreover, these results also reveal that different from people infected with COVID-19 in general rooms in the hospital, those in special-care wards have significantly higher levels of granulocyte colony stimulating factor (G-CSF), interferon-inducible protein-10, chemotactic protein-1, macrophage inflammatory protein 1A and TNF-α. Serum samples obtained from two groups of people from the Kaiser Santa Clara testing research institution, revealed that for those with SARS-CoV-2, a cytokine storm can be performed in their bodies revealed by the high levels of IL-6, IL1RA, CCL2, CCL8, CXCL8, CXCL9 and CXCL16 [4]. Also, Another cohort study including 113 patients with SARS-CoV-2 and 108 health controls reveals that many cytokines have been increased including IL-1α, IL-1b,IL-6,IL-18,IFNα,IFNγ,CCL1,IL17A in patients with SARS-CoV-2[17]. The researchers in this grop research also tested an extra inflammatory sample described by thrombopoietin (TPO), IL-33, IL-16, IL-21, IL-23, IFN-λ, eotaxin and eotaxin 3. The majority of the cytokines interrelated with cytokine release syndrome (CRS), such as IL-1α, IL-1β, IL-6, IL-10-IL18 and TNF appear to be raised in infected people with serious disease rather than patients with moderate disease [18]. Therefore, we can confirm that high grades of cytokines are obviously linked with the severities of SARS-CoV-2, and we should focus on investigating the potential reason of cytokine storm and how to modulate this condition.

Cytokine storm is caused by the body's immune response disorders. At first, activated T cells or lysed immune effector cells set free many inflammatory cytokines and chemokines, but with the course of the disease, uncontrolled overreaction occurs. So neutralizing antibodies to capture specific chemokines will be helpful to improve the condition of the people with SARS-CoV-2. Interestingly, a group research including 82 individuals health controls, 10 paucisymptomatic SARS-CoV-2 patients, 34 individuals with pneumonia and 28 people with ARDS) investigate what induce the over-activation of cytokines, and revealed that C5a production leads to the chemo-attraction and activation of myeloid cells in the lungs and contributes to the overt release of inflammatory cytokines, which confirmed that C5a-C5aR1 axis is possibly related with the cytokine storm in SARS-CoV-2 [19]. This study gives us another direction to investigate what triggers the cytokine storm, and also provides us another way to think about potential treatments for SARS-CoV-2.

4. Therapeutic approaches of neutralizing antibodies to capture specific chemokine

In the case of COVID-19 disease, CRS is often used to describe an uncontrollable and massive discharge of pro-inflammatory mediators by an over-activated immune system (Lee D.W., 2014).

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The delayed kinetics of the clearance mechanism of virus may be the cause of the immunologic mechanism of CRS. The virus-specific T cell immune reaction is the cause of the exclusion of virus (Zhao J., 2010). However, T cell apoptosis is initiated, causing T cell responses to be reduced, hence, the CRS and lymphopenia are worsen. This is made by the excessive production of cytokines such as type 1 interferon. (Channappanavar R., 2016). It's noteworthy that IL-6 is the significant cytokines that is produced among those abnormal production of cytokines. The more severe the disease, the higher IL-6 levels, as tested in individuals with SARS. (Zhang Y., 2004).

IL-6 is a key cytokine, due to its broad synthesis pathways and functions. Almost all stromal cells and cells involved in immune system can produce IL-6, meanwhile, it serves the function of stimulating B cell proliferation as well as growth and differentiation of hematopoietic stem cells, inducing CTL activity and etc. [20] The various synthesis pathway can easily lead to massive IL-6 production under hyper-inflation, thus appearing in noticeably high concentration during a cytokine storm. IL-6 can be either anti-inflammatory or pro-inflammatory according to different signaling pathways. [21] For a successful IL-6 signaling to take place, the cytokine needs to bind with cell-associated gp130 (CD130) and the IL-6 receptor (IL-6R) (CD126). IL-6 receptors appears in two forms: membrane bonded cell surface IL-6R and soluble IL-6R. When IL-6 bind with cell surface IL-6R, a classical signaling pathway is ignited which will result in an anti-inflammatory effect; Whereas, when IL-6 bind with soluble IL-6R, a trans-signaling pathway is initiated, which will lead to a pro-inflammatory effect [22]. The classical pathway predominates when IL-6 level is low while trans-signaling pathway is allowed to occur on a broader scale when IL-6 level is elevated to function as pro-inflammatory mediator [23]. Exuberant IL-6 signaling can be blamed to cause enormous physiological consequences which lead to organ damage. Hence, IL-6 blockade is a promising strategy for COVID-induced CRS. And tocilizumab is considered a potential treatment in severe CRS.

5. Medical treatment inducing similar cytokine storm:

Chimeric antigen receptor T cell therapy (CAR T cell therapy), a method that takes application of T-cells that are genetically designed to treat certain types of blood cancer, also has cytokine release syndrome as one of its alarming side effects. Distinctive from the conventional way of T cell activation that is highly depending on antigen presentation by major histocompatibility complexes, CAR T cells are made active in a MHC independent way that is initiated through recognition and binding to cancer-specific antigens[24]. T cells are modified to acquire ability of recognizing CD19 antigens which are commonly presented in all types of cancer cells. Since these antigens are also presented on the general B cells, CAR T cell treatment modifying T cells to recognize and eventually eliminate cells with CD19 will result in B cell deficiency in patients [25]. Due to the facts that the B cell population can slowly recover when CAR T cells are fully consumed and that artificial antibodies can be offered in treatment helping patients fighting acute infections, such depletion is considered tolerable and manageable [25]. However, the cytokine release syndrome (CRS) associated with the deadly cytokine storm remains concerning.

Due to CRS's inevitability in cancer patients that have undergone CAR T cell therapy, it became a diagnostic marker evaluating whether the therapy is working to eliminate cancer cells[3]. Still, it is important in course to make sure such syndrome is under clinical control. In this case, cytokine storm is induced when large amount of CAR T cells infuse with the host's body. They start functioning when being activated through binding with cancer-specific antigens. Activation process of consists of the following steps: phosphorylation of immune receptor tyrosine-based activation motifs (ITAMs), induction of cytokine secretion, T cell proliferation, and cytotoxicity [26]. Pro-inflammatory cytokines generated in the process can vary according to different antigen modified CAR T cells used in distinctive cases which generally include IL-2, IL-4, IFN-γ, IL-12, TNF [26]. IL-12, for example, can form and strengthen the mechanism of inborn immune cells such as NK cell and macrophage which are again the main sources of tumor necrosis factor (TNF), IFN-γ, IL-1, IL-6, IL-8, and IL-12, [27] leading to a further amplification of the inflammatory effect. Similarly, IFN-γ, as an important activator for macrophages which can be generated by NK cells, illustrates an escalating cytokine

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concentration triggered by a spiral of activation by closely interacting cytokines. To conclude, when large amounts of CAR T cells are put into function, levels of cytokines at the tumor site will be significantly elevated, expressing hyper-inflammatory response —— cytokine storm/cytokine release syndrome.

The severity of CRS generated by CAR T cell treatment could differ according to tumor burden [28]. For higher disease burden, there will be higher level of CAR T cell activity predicting more toxicity [29], that is accompanied by overproduction of pro-inflammatory cytokines.

6. Discussion

CRS is treated differently in terms of distinctive conditions. For mild CRS, common symptoms including fever, muscle pain, fatigue, headache, rash, arthralgia, and myalgia are often expressed that requires only basic supportive treatments to address [31]. However, for moderate or severe CRS, immunosuppressive agents become necessary since the symptoms can be life- threatening, for example, high fever, uncontrollable systemic inflammatory reaction with vasopressor-requiring circulatory shock, vascular leakage, disseminated intravascular coagulation, and multi-organ system failure [29].Specifically, as is shown in table 2 and table 3, CRS symptoms are classified into separate groups and are treated differently with respect to severity as shown in the figures [30-32] below which applies for CRS caused by all types of infections or medical treatments (including CRS caused by CAR T cell therapy and COVID-19)

Table 2 Symptoms of Different Grades of CRS

Grade I	Less-severe symptoms: fever, nausea, fatigue, headache, myalgias, malaise
Grade II	Symptoms of organ dysfunction, Grade II organ toxicities
Grade III	Reappearance of symptoms after better situation at the beggining; clinical sequelae (e.g., renal impairment, pulmonary infiltrates), Hypoxia, hypotension, Coagulopathy, Shock, Grade III organ toxicities, Grade IV transaminases
Grade IV	Consequences the threaten human life, Hypoxia, Hypotension, Grade IV organ toxicities
Grade V	Death

Table 3 Treatment for Different Grades of CRS

Grade I	Using antipyretics, antiemetics
Grade II	Hospitalizing and dealing with CRS-related symptoms, including fevers with linked neutropenia, need for IV treatmetn (not including fluid resuscitation for hypotension) Treatment or infusion interruption indicated but reacted quickly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medicine indicated for ≤ 24 h
Grade III	Hypotension using intravenous fluids or small-dose vasopressors Coagulopathy requiring fresh frozen plasma or cryoprecipitate or fibrinogen concentrate Hypoxia requiring supplementary oxygen
Grade IV	Pressor or ventilator support indicated Needing high-dose vasopressors Hypotension needing high-dose vasopressors
Grade V	-

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The CAR-T therapy can treat severe lymphoblastic leukemia (ALL) and spread large B-cell lymphoma (DLBCL) effectively, but the most of the cases need to be treated for more than 2 years with a follow-up of more than 6 years. The long term therapy is not suitable to the SARS-CoV2 pandemic and also not all patients can afford the cost of long-term treatment [31].

Another common syndrome of SARS-CoV2 besides the dysregulation cytokine is sepsis. Sepsis syndrome is mostly caused by viral or bacterial infection. Studies have shown that nearly 40% of adults with viral infected pneumonia appears sepsis syndrome. Sepsis became one of the most frequently observed complication [33]. If you have SARS-CoV-2, it doesn't mean that you have sepsis, which can be considered as the reaction of hose towards pathogens or its toxins [34]. The sepsis patient's pro-inflammatory reaction is contracted by some anti-inflammatory cytokines, including IL-10, transforming growth factor (TGF)-β, and IL-4 that try to bring back immunological equilibrium [35]. Another disease called cytokine release syndrome (CRS) is also similar to COVID-19 Disease because in CRS, elevated cytokines level, like IL-6, IL-10, and interferon (IFN)-Y, is observed. When setting T cell-engaging treatment, CRS is caused by the massive discharge of IFN-γ by activated T cells or the tumor cells themselves. Secreted IFN-γ induces activation of other immune cells, most significantly macrophages [36]. The activated macrophages generate excessive number of extra cytokines like IL-6, TNF-α, and IL-10.

In the end, after discussing the cytokine storm that occurs in the SARS-Cov2 patients, now we will focus on the effectiveness and related adverse reactions of specific medicine which can modulate the immune system. A looking-back multi-center group research of 1351 patients admitted, shows that the therapy using tocilizumab, whether applied intravenously or subcutaneously, might decrease the risk of invading mechanical ventilation or death in individual with serious COVID-19 pneumonia. Harmful activities would be intensively examined during the research time. Overall, patients treated with tocilizumab (24 (13%) of 179) were easier to diagnose with new infections than standard treatment patients (14 (4%) of 365). Therefore, when using the tocilizumab, we should closely monitor the adverse reaction and deal with these reactions as soon as possible [37]. In addition to this, the researchers also found that CXCL10 also involved in the onset of ARDS [38]. An experiment performed on a rat model of lung damage has shown induction of the ARDS with LPS can cause a significant increase of CXCL10 expression. The amelioration of lung injury can also cause by the neutralization of CSCL10 and its antibody [39]. CXCL8 (also named as IL-8) is another type of chemokine regarded as a potential prognostic bio-marker for ARDS clinical course in SARS-CoV-2 [40]. The implementation of anti-IL-8 has also been proceeded in the clinical experiment in people infected with SARS-CoV-2 and is believed to be a safe and well-tolerate therapy[41].However, we think more detailed and randomized experiment should be implemented. Baricitinib would inhibit the Janus kinases JAK1 and JAK2 orally, selectively and reversibly, which could also modulate the immune response. In a single-center group research, 20 patients treated with baricitinib were included. From this study, the researchers found that baricitinib-treated individuals have a obvious decrease in serum grades of interleukin (IL)-6, IL-1β and tumor necrosis factor (TNF)-, a quick returen in circulation of T and B cell frequencies, and raised antibody producing against SARS-CoV-2 spike protein [42].In a study reported by FDA with 14252 subjects enlisted into the baricitinib medical programs for RA, of whom around 10034 subjects have been given baricitinib.

The researchers observed that the most prevalent and seriously adverse reactions of baricitinib ere "infections and infestations". It is also noteworthy that baricitinib is linked with herpes virus infection. Moreover, out-of-expectation safety signs like a case of pneumocystis jirovecci pneumonia was found in our analytical work[43]. Therefore, considering these adverse reactions, more detailed and randomized clinical trials of these medicines which can modulate the immune response should be implemented.

7. Conclusion

The high levels of cytokines are closely linked with the severities of SARS-CoV-2, and the specific reasons of cytokine storm and how to modulate the condition should be carefully studied. Functioning

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of a great amount of CAR T cells would cause obvious high levels of cytokines at the tumor site, which is called cytokine storm. The CRS requires different treatment methods regarding five grades, during which anti-IL-8 is considered secure and well-tolerant. Detailed information has been presented and there are still much to be done in the related field. The authors hope that the limited research could contribute to research on CRS and treatment for the disease caused by SARS-CoV-2.

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Everyone's contribution to the group paper is the same. The ranking is in alphabetical order.

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