Cytokine Release Syndrome and Treatment in COVID-19

COVID-19'da Sitokin Salınım Sendromu ve Tedavi Yaklaşımları

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ABSTRACT

The emergent outbreak of coronavirus disease 2019 (COVID-19) is a global health problem and has been recognized as a pandemic. Although COVID-19 leads to mild flu-like symptoms in most patients, the disease may cause frequently fatal, severe complications, such as acute respiratory distress syndrome and cytokine release syndrome. In these patients, defects in lymphocytic cytolytic activity trigger the proinflammatory cytokine cascade, and then "cytokine storm" begins. As a result, it leads to uncontrolled active macrophage entry into the tissues and hemophagocytosis. Here, the responses of host cells, cytokine release syndrome and the therapeutic approaches to alleviate the cytokine storm in COVID-19 will be reviewed.

Key Words: COVID-19, Cytokine Release Syndrome, Cytokine Storm, Tocilizumab

ÖZ

Yeni ortaya çıkan coronavirus hastalığı 2019 (COVID-19) küresel bir sağlık sorunudur ve pandemi olarak kabul edilmiştir. COVID-19, hastaların çoğunda hafif grip benzeri semptomlara yol açmasına rağmen, hastalık akut solunum sıkıntısı sendromu ve sitokin salınım sendromu gibi sıklıkla ölümcül, ciddi komplikasyonlara neden olabilir. Bu hastalarda lenfositik sitolitik aktivitedeki defektler proinflamatuar sitokin kaskadını tetiklemekte ve "sitokin fırtınasını" başlatmaktadır. Sonuç olarak, dokulara kontrolsüz aktif makrofaj girişine ve hemofagositoza yol açmaktadır. Burada, COVID-19'da konakçı hücrelerin yanıtları, sitokin salınım sendromu ve sitokin fırtınasını durdurmak için tedavi yaklaşımları ele alınmıştır.

Anahtar Kelimeler: COVID-19, Sitokin Salınım Sendromu, Sitokin Fırtınası, Tocilizumab

INTRODUCTION

The SARS-CoV-2 infection (COVID-19), which causes severe acute respiratory syndrome, was accepted by the World Health Organization as a pandemic on March 11, 2020 and is an important global health problem. Due to the rapid increase in the number of cases and deaths, the load on the emergency services and intensive care units is increasing day by day. Here, the definition, pathogenesis and treatment of cytokine release syndrome (CRS), a life-threatening condition in severe COVID-19, will be discussed.

Cytokine Release Syndrome

Macrophage activation syndrome (MAS) and hemophagocytic lymphohistiocytosis (HLH) are life-threatening conditions with different etiological causes, which can lead to systemic hyperinflammation and rapidly progressive multisystem organ failure. HLH occurs familial (primary; pHLH) or secondary to infection, malignancy, autoimmune or autoinflammatory disease. Secondary HLH (sHLH) associated with autoimmune or autoinflammatory disease is called MAS. The mortality rate of sHLH is lower than that of pHLH. However, if sHLH is diagnosed early and effective treatment is not given, it may be life-threatening.

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Conflict of Interest /Çıkar Çatışması: *On behalf of all authors, the corresponding author states that there is no conflict of interest.*

Contribution of the Authors / Yazarın Katkısı: KURT T: Constructing the hypothesis or idea of research and/or article. Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in the writing of the whole or important parts of the study ***CELIKEL ACAR B:*** Constructing the hypothesis or idea of research and/or article. Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in the writing of the whole or important parts of the study.

How to cite / Atıf Yazım Şekli : Celikel Acar B. Cytokine Release Syndrome and Treatment in COVID-19. Turkish J Pediatr Dis 2020;14(suppl): 55-59.

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Received / Geliş tarihi : 25.06.2020
Accepted / Kabul tarihi : 20.07.2020
Online published : 27.07.2020
Elektronik yayın tarihi
DOI: 10.12956/tchd.757711

Table I: Clinical and laboratory findings in cytokine release syndrome (38).

System Involvement / Findings	
General symptoms	Fever, malaise
Hematological findings	Cytopenia, coagulopathy, neutropenia, disseminated intravascular coagulation
Cardiac findings	Hypotension, arrhythmia, QT prolongation, troponin elevation, cardiomyopathy, heart failure
Lung findings	Hypoxia, tachypnea, pulmonary edema, respiratory failure
Liver / spleen	Hepatomegaly, elevated liver enzymes, hypofibrogenemia, liver failure, splenomegaly
Renal findings	Acute kidney injury
Gastrointestinal findings	Diarrhea, nausea, vomiting
Central nervous system findings	Headache, confusion, hallucination, delirium, paresis, seizure
Musculoskeletal system findings	Myalgia, arthralgia, rash, edema

In these patients, defects in lymphocytic cytolytic activity trigger the proinflammatory cytokine cascade, interleukin-1 (IL-1), IL-6, IL-18, soluble IL-2 receptor, tumor necrosis factor-α (TNF-α) and interferon-γ (INF-γ) levels increase, then "cytokine storm" begins. As a result, it leads to uncontrolled active macrophage entry into the tissues and hemophagocytosis. Similarly, there was an increase in cytokines such as IL-1, IL-6, IL-12 and TNF-α in COVID-19, and with this increase, sepsis, multiorgan failure, tissue damage and acute respiratory distress syndrome (ARDS) has been shown (1).

Cytokine release syndrome or cytokine storm can be defined as uncontrolled release of cytokines that can be triggered by viruses, bacterial components, sepsis, toxins (2). This syndrome can lead to devastating effects such as life-threatening capillary leak, tissue toxicity / edema, organ failure and shock. Resistant and persistent fever, liver dysfunction, coagulopathy, cytopenia, hepatomegaly, skin rash and neurological symptoms may occur in CRS (Table I) (3). Leukocyte, lymphocyte, platelet count, IL-6 and ferritin levels guide the determination of those at risk for CRS development in severe COVID-19 patients. Elderly patients with chronic disease were found to be the most risky group for CRS in COVID-19. CRS in children is not as common as in adults.

Pathogenesis of Cytokine Release Syndrome

The innate immune system constitutes the first line of defense against invading microbial pathogens by releasing multiple inflammatory cytokines to antagonize the pathogens. After SARSCoV-2 infection, CD4+ T lymphocytes are rapidly activated to transform into pathogenic T helper (Th) 1 cells and the production of cytokines begins. The cytokines induce inflammatory CD14+ CD16+ monocytes with high level of IL-6 and inflammation becomes evident (2, 4). These T cells and monocytes enter the pulmonary circulation, where monocytes become macrophages. It is considered that activated macrophages are the source of cells releasing the cytokines which are at the center of CRS immunopathology. CRS may lead to detrimental effects such as epithelial and endothelial cell apoptosis, vascular leakage, altered tissue homeostasis. CRS is associated with necrosis and tissue destruction, pulmonary edema, acute bronchopneumonia, alveolar hemorrhage, reactive hemophagocytosis, and ARDS (5). In autopsies of COVID-19 patients, it has been shown that infiltration of macrophages and activation of alveolar macrophages. It was found that interstitial mononuclear inflammatory infiltrates, dominated by lymphocytes in the lungs of a patient who died due to COVID-19 (6). In addition, virus clearance from cells is impaired by suboptimal T cell response (7).

Lymphocytopenia and Cytokine Levels in Cytokine Release Syndrome

Clinical studies of COVID-19 have shown that there is lymphocytopenia and many cytokines, particularly IL-6, are significantly elevated (1,8).

In two different studies, 35 (99%) of 99 patients and 97 (70.3%) of 138 patients had lymphocytopenia (lymphocyte count <1.5x109 / L). It has been reported that lymphocytopenia can be used as a risk factor in determining cytokine storm and disease severity in these patients (9,10). It has been reported that lymphocytopenia can be used as a risk factor in determining cytokine storm and disease severity in these patients (9,

10). Yu, and Xu et al. (11) reported that lymphocytopenia and cytotoxicity are associated with the severity of hypoxemia (12).

Many cytokines levels such as IL-1β, IL-1RA, IL-7, IL-8, IL-9, IL-10, granulocyte colony stimulating factor (G-CSF), granulocyte macrophage colony stimulating factor (GM-CSF), IFN-γ, interferon-inducible protein (IP10), macrophage inflammatory protein (MIP1), MIP1A, MIP1B, TNF-α, vascular endothelial growth factor were higher in COVID-19 patients than in healthy adults. In addition, the levels of cytokines were higher in intensive care unit (ICU) patients than non-ICU patients (1, 3). Huang et al. (13) reported that patients with severe disease have higher concentrations of G-CSF, IP-10, MCP-1, MIP1, TNF-α levels, ie cytokine storm. In another study from China, increased expression of IL-2R and IL-6 in serum predicted the

severity and prognosis of patients with COVID-19 (14). It has been shown that T cells decrease significantly (especially CD8 + T cells) and IL-6, IL-10, IL-2 and IFN-γ levels increase in severe COVID-19. In addition, neutrophil / CD8 + T cell ratio has been defined as a very strong prognostic factor in severe COVID-19 (15). Peripheral blood flow cytometric analysis showed that T cells have over activation to contribute severe immune system damage (7).

Increased cytokine levels, C-reactive protein (CRP), ferritin and lymphopenia help the clinician in diagnosing CRS in COVID-19 patients. Inflammation in the liver triggers the release of CRP release and this is known to occur in response to systemic IL-6 elevation (16). It has been reported that CRP levels in COVID-19 patients positively correlate with the size of lung lesions detected on computed tomography, which may predict the severity of the disease (17).

Treatment in Cytokine Release Syndrome

In order to control cytokine storm, it is important early diagnosis, rapid initiation of treatment, but treatment options are limited for severe COVID-19. It has not been shown that antiviral drugs such as lopinavir / ritonavir have significant benefits compared to standard treatments in patients who develop cytokine storm (18). Antiviral treatments and immunomodulatory drugs should be used together to control cytokine storm in COVID-19 patients.

As is known, corticosteroids are commonly used drugs for immunomodulatory therapy in infectious diseases. Corticosteroids are known to reduce lung inflammation in patients with pneumonia, but can also inhibit immune response and pathogen clearance. Significant benefits have not been demonstrated in respiratory tract infections caused by influenza, RSV, SARS-CoV or MERS-CoV. Higher viremia levels were found in SARS-CoV patients treated with steroids. It has also been shown to higher mortality, longer hospitalization and increased risk of secondary infections in influenza patients (19). Similarly, the use of corticosteroids in the treatment of COVID-19 is controversial as it can cause suppression of the immune system and delayed viral clearance. Zha et al. (20) demonstrated that the use of corticosteroids in mild COVID-19 patients does not affect viral clearance, hospitalization or symptom duration. On other hand, in a trial that included 201 COVID-19 patients, methylprednisolone therapy was associated with reduced the risk of death in patients with ARDS. Based on these findings, corticosteroid use is considered to be particularly effective in severe COVID-19 cases with ARDS, but it does not provide significant benefit in mild cases (21). Corticosteroids should be used only in critically ill patients at low / moderate doses (1-2 mg / kg / day) for a short time (3-5 days) (22).

The use of chloroquine and hydroxychloroquine has been found to be effective in the treatment of COVID-19. In February 2020, more than 100 patients diagnosed with COVID-19 had positive results with chloroquine phosphate (23). The efficacy of hydroxychloroquine treatment in 20 patients with COVID-19 patients has been demonstrated in an open-label non-randomized clinical study in France (24). Both chloroquine and hydroxychloroquine are weak bases and accumulate in acidic organelles; they can increase endosomal / lysosomal pH and inhibit viral replication (25). Both drugs can inhibit major tissue suitability complex II expression, antigen presentation, and immune system activation via Toll-like receptor and cGAS-STING signaling in B, T and other immune cells (26). The major proposed immunomodulatory mechanisms of both drugs are the following: inhibition of cytokine production, reduced levels of chemokines, inhibition of micro-RNA expression, decreased TH17-related cytokines, upregulated levels of IFN-α and IL-2 and IL-10, inhibition of cytotoxic T cell and self-reactive CD4+ lymphocyte activities. As a result, they can reduce the production of proinflammatory cytokines such as IL-1, IL-6, IFN-γ and TNF-α, which are involved in CRS (26).

The use of immunomodulatory agents that directly target cytokines in severe COVID-19 patients may contribute to control symptoms related to hyperinflammation (27). It has been reported that the increase in IL-6 levels in the blood of COVID-19 patients predicts fatal outcome (28). Herold et al. (29) showed that patients with IL-6 levels of ≥ 80 pg / ml had a 22-times higher risk of respiratory failure than those with low IL-6 levels. In addition, IL-6 levels have been shown to be 3-fold higher in ICU than non-ICU patients in a metanalysis evaluating the results of ten studies involving data from 1700 COVID-19 patients (30). IL-6 binds to transmembrane IL-6 receptors (mIL6R) and soluble IL-6 receptors (sIL-6R), and this complex combines with the signal transduction component gp130 to activate the inflammatory response. Tocilizumab, a specific monoclonal antibody that blocks IL-6, specifically binds to sIL-6R and mIL-6R and thereby blocks signal transmission (31). Tocilizumab, sarilumab, siltuximab are IL-6 antagonists with different pharmacologic properties. In recent years, since anti-IL-6 drugs such as tocilizumab and sarilumab have been used in the treatment of rheumatological diseases, it has been focused on these treatment options for SARS-CoV-2 and it has been observed that the hyperinflammatory syndrome in severe SARS-CoV-2 infection can be controlled. In a study from China, a single dose (400 mg) of tocilizumab was used in 21 infected patients with SARS-CoV-2, and fever was controlled within 5 days, a rapid decrease in CRP, oxygen requirement, and improvement in lymphocyte counts and radiological findings (32). However, in this study, the lack of a control group, treatment of all patients with lopinavir and methylprednisolone prior to receiving tocilizumab is considered as an important limitation. There is emerging evidence that tocilizumab may also be useful in COVID-19. It has been suggested to be used in patients with multiple lesions in the lungs, high IL-6 level and critical disease (22).

However, clinical experience and studies with the use of tocilizumab in viral diseases are very limited. In a study on patients with juvenile idiopathic arthritis infected with influenza A, reduced fever and level of CRP were demonstrated in patients who received tocilizumab compared with patients who did not receive tocilizumab (33).

It should be noted that tocilizumab increases the risk of opportunistic infections (34). Therefore, it is necessary to monitor patients for potential side effects. In addition, high costs are a problem for the wide use of tocilizumab in the treatment of COVID-19 in low- or middle-income countries.

Although a monoclonal antibody against IL-6 receptor, is shown to be effective in treating CRS, the results of studies currently ongoing with sarilumab, tocilizumab, combination of tocilizumab and favipiravir are expected.

IL-1 is another proinflammatory cytokine that increases in CRS. Anakinra and other IL-1R antagonists are used in the treatment of autoinflammatory diseases, systemic juvenile idiopathic arthritis and MAS. It is predicted that it may be beneficial in CRS patients with high IL-1 levels (35).

The antibody against GM-CSF has also been shown to be effective in the treatment of cytokine release syndrome (36).

JAK-STAT signaling pathway; it is a critical component of cytokine receptor systems, and many HLH-related cytokines use this pathway. Therefore, JAK inhibitors such as tofacitinib and baricitinib can reduce hyperinflammation caused by CRS. However, their effectiveness in the treatment of COVID-19 patients is still uncertain (37). Moreover, it should be noted that these inhibitors also inhibit the activity of inflammatory cytokines, such as INF-α, which are known to play an important role in viral clearance (37).

CONCLUSIONS

Severe COVID-19 can cause hyperinflamation and cytokine release syndrome. Although it is not common in childhood as in adults, early diagnosis and treatment is very important due to the high mortality rate. In severe COVID-19 patients, CRP, ferritin, D-dimer increase and cytopenia should be monitored as signs of hyperinflamation. These values will be useful in identifying patients for whom cytokine suppression is required.

REFERENCES

1. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 2020;395:565–74.
2. Nazinitsky A, Rosenthal KS. Cytokine storms: systemic disasters of infectious diseases. Infect Dis Clin Pract 2010;18:188–92.
3. Behrens EM. Cytokines in cytokine storm syndrome. In: Cron RQ, Behrens EM. Cytokine Storm Syndrome. Cham: Springer International Publishing 2019;197–207.
4. Zhou Y, Fu B, Zheng X, Wang D, Zhao C, Qi Y, et al. Aberrant pathogenic GM-CSF+ T cells and inflammatory CD14+CD16+ monocytes in severe pulmonary syndrome patients of a new coronavirus. bioRxiv 2020; doi: 10.1101/2020.02.12.945576.
5. Maclean OA, Orton R, Singer J, Robertson DL. Response to "On the origin and continuing evolution of SARS-CoV-2". 2020. http:// virological.org/t/response-to-on-the-origin-and-continuing-evolution-of-sars-cov-2/418 (accessed March 7, 2020)
6. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med 2020;8:420-2.
7. Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. Semin Immunopathol 2017;39:529–39.
8. Liu T, Zhang J, Yang Y, Ma H, Li Z, Zhang J, et al. The potential role of IL-6 in monitoring severe case of coronavirus disease 2019. medRxiv 2020; doi: 10.1101/2020.03.01.20029769.
9. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507–13.
10. 10. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020; 323: 1061-9.
11. Yu L, Tong Y, Shen G, Fu A, Lai Y, Zhou X, et al. Immunodepletion with hypoxemia: a potential high risk subtype of coronavirus disease 2019. medRxiv 2020; doi: 10.1101/2020. 03.03.20030650.
12. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med 2020;8:420-2.
13. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497–506.
14. Chen L, Liu HG., Liu W, Liu J, Liu K, Shang J. Analysis of clinical features of 29 patients with 2019 novel coronavirus pneumonia. Zhonghua Jie He He Hu Xi Za Zhi.2020;43:E005. doi: 10.3760/cma.j.issn.1001-0939.2020.0005.
15. Liu J, Li S, Liu J, Liang B, Wang X, Wang H, et al. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. medRxiv 2020; doi: 10.1101/2020.02.16.20023671.
16. Okabayashi T, Kariwa H, Yokota S, Iki S, Indoh T, Yokosawa N, et al. Cytokine regulation in SARS coronavirus infection compared to other respiratory virus infections. J Med Virol 2006;78:417–24.
17. Ling W. C-reactive protein levels in the early stage of COVID-19. Med Mal Infect 2020 doi 10.1016/j.medmal.2020.03.007.
18. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G. A trial of lopinavir-ritonavir in adults hospitalized with severe COVID-19. N Engl J Med 2020;382:1787-99.
19. Shang L, Zhao J, Hu Y, Du R, Cao B. On the use of corticosteroids for 2019-nCoV pneumonia. Lancet 2020;395:683-4.
20. Zha L. Impact of corticosteroid treatment in patients with coronavirus disease 2019. Med J Aust 2020 March 9.

21. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 2020 Mar 13; ;e200994 doi: 10.1001/jamainternmed.2020.0994.
22. Editor(s): Wei, Pei-Fang;National Health Commission, National Administration of Traditional Chinese Medicine Diagnosis and treatment protocol for novel coronavirus pneumonia (Trial Version 7) Chin Med J 2020;133:pp1087-95.
23. Gao J, Tian Z, Yang X. Breakthrough: chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biosci Trends 2020;14:72–3.
24. Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020 Mar 20; ;105949. doi: 10.1016/j.ijantimicag.2020.105949.
25. Devaux CA, Rolain JM, Colson P, Raoult D. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19? Int J Antimicrob Agents 2020 Mar;55:105938. doi: 10.1016/j.ijantimicag.2020.105938.
26. Schrezenmeier E, Dörner T. Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology. Nat Rev Rheumatol 2020;16:155-66.
27. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020;395:033–4.
28. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med 2020;46:846-8.
29. Herold T, Jurinovic V, Arnreich C, Hellmuth JC, von Bergwelt-Baildon M, Klein M, et al. Level of IL-6 predicts respiratory failure in hospitalized symptomatic COVID-19 patients. medRxiv 2020. In press, https://doi.org/10. 1101/2020.04.01.20047381. Accessed April 8, 2020.
30. Xu L, Mao Y, Chen G. Risk factors for severe corona virus disease 2019 (COVID-19) patients: a systematic review and meta analysis. medRxiv 2020:2020.03.30.20047415 doi 10.1101/2020.03.30.20047415.
31. Tanaka T, Narazaki M, Kishimoto T. Immunotherapeutic implications of IL-6 blockade for cytokine storm. Immunotherapy 2016;8:959–70.
32. Xu XL, Han MF, Li TT, Sun W, Wang DS, Fu BQ, et al. Effective treatment of severe COVID-19 patients with tocilizumab. ChinaXiv 202003.00026.
33. Kawada J, Kitagawa Y, Iwata N, Ito Y. Clinical characteristics of influenza virus infection in juvenile idiopathic arthritis patients treated with tocilizumab. Mod Rheumatol 2013;23:972–6.
34. Rutherford AI, Subessinghe S, Hyrich KL, Galloway JB. Serious infection across biologic-treated patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. Ann Rheum Dis 2018;77:905–10.
35. Perricone C, Triggianese P, Bartoloni E, Cafaro G, Bonifacio AF, Bursi R, et al. The anti-viral facet of anti-rheumatic drugs: Lessons from COVID-19. J Autoimmun 2020;17:102468. doi: 10.1016/j.jaut.2020.102468.
36. Zhou Y, Fu B, Zheng X, Wang D, Zhao C, Qi Y, et al. Aberrant pathogenic GM-CSF+ T cells and inflammatory CD14+CD16+ monocytes in severe pulmonary syndrome patients of a new coronavirus. bioRxiv 2020; doi: 10.1101/2020.02.12.945576
37. Zhang W, Zhao Y, Zhang F, Wang Q, Li T, Liu Z, et al. The use of antiinflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): The Perspectives of clinical immunologists from China. Clin Immunol 2020;214:108393 doi 10.1016/j.clim.2020.108393.
38. Zhou G, Chen S, Chen Z. Advances in COVID-19: the virus, the pathogenesis, and evidence-based control and therapeutic strategies. Front Med 2000;14:117-25.