The role of high-dose steroid therapy in Covid-19 pneumonia

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Abstract

Introduction: Today, whereas hypoxemia and respiratory failure is the major challenging problem in the course of severe COVID-19 pneumonia, to control the disease at a mild-moderate stage or to stop the inflammation by recognizing the cytokine storm early should be the most prominent goal. We aimed to reveal the clinical efficacy and safety of short-term high-dose corticosteroids in severe COVID-19. Material and Methods: This retrospective observational study consisted of 54 patients who were given high-dose steroid (HDS (>250 mg/day methylprednisolone, 3 days.). Low-dose steroid (LDS) therapy (dexamethasone 8 mg) was applied to all patients. HDS group was reviewed in terms of decreasing hospital mortality and preventing fibrosis development in follow-up. Results: During the observation period, out of 317 severe COVID-19 pneumonia hospitalized, HDS and LDS were administered to 54 and 216 patients, respectively. Higher body mass index, younger age, more oxygen need of patients at admission, and more need for advanced oxygen therapy during hospitalization were found in the HDS group (p<0.001). Furthermore, 18.5% of patients in the HDS group had need transfer to the intensive care unit whereas it was 3.8% in LDS (p<0.001). Additionally, the mortality rate was determined higher in the HDS group (25. 9% vs 9.9%, p<0.001). The HDS group had lower saturated O2 [IQR, 85% (76-89), p <0.001], and higher ferritin at admission. It was found that HDS was given simultaneously with the increased ferritin with deepening lymphopenia on the third and fifth days. There was no difference in fibrosis development between HDS patients receive and not (15.4% vs 26.2%, p=0.11) Conclusion: The use of HDS in hospitalized COVID-19 patients remains unclear. Along with this, our study demonstrated the use of high-dose corticosteroids might not be associated with a lower mortality rate among hospitalized severe COVID-19 patients.

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Key words : COVID-19, high-dose steroid, cytokine storm, mortality, fibrosis

What is known?

- Most deaths of COVID-19 pneumonia are caused by respiratory failure due to cytokine storms and there is no effective and specific treatment is not yet.
- Glucocorticosteroids (GCs) are known to functions anti-inflammatory, anti-allergic, and hypothermic due to reducing levels such cytokines and chemokines (IL-8, monocyte chemoattractant protein-1, IL-6, IFN-γ, and IL-4.)
- The World Health Organization and guidelines suggested low-dose corticosteroids as adjunctive therapy in hospitalized severe COVID-19 pneumonia.
- Pulmonary fibrosis might be developed in the post-covid period.

What is new?

- High-dose GCs use could not be decreased mortality, however, the time to give GCs is extremely important that the early high-dose GCs use was shown to decrease the progression of the disease and improve the resolution of alterations in the pulmonary structures. Concurrent administration of high doses of steroids to these patients together with the increase in ferritin levels on the 1st, 3rd, and 5th days of hospitalization, and the deepening of lymphopenia, and the prominence of clinical worsening, supports this information.
- This study investigated whether fibrosis develops in patients with high-dose steroid therapy. Older age, prolonged hospitalization, lower saturation at admission, higher d-dimer, and increased recurrent hospitalizations were identified as the indicator for fibrosis in our study.
- There is not yet a study for predicting fibrosis in the literature. Although this study consisted of a small group, it can be a guide for future studies.

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INTRODUCTION:

The novel coronavirus disease 2019 (COVID-19) continues to spread rapidly worldwide since December 2019. Due to the easy transmission of the virus by patients with mild disease or asymptomatic carriers, the number of new and severe cases are increasing day by day. Recently, also new mutant viruses considered to be more contagious contribute to the spread of the disease. As of March 28, 2021, more than 120 million COVID-19 cases have been confirmed and more than 2.5 million death tolls have been reported in 192 countries or regions (1).

Although some factors related to the severity of the disease are determined, the clinical course may differ into three stages: asymptomatic (stage 1), nonsevere (stage 2), and severe with respiratory failure (stage 3) (2). Cytokine storms can appear in the second or third week in people with severe disease. However, a few clinical courses and predictors for the prognosis and mortality were reported, but it still remains to be fully investigated who will be recovered or not (2). Currently, while no specific antiviral or immunomodulatory treatment for COVID-19 has proven effective, therapies recommended for patients with COVID-19 mostly consisting of a set of supportive care strategies and previous antiviral therapies. In this case, to control the disease at a mild-moderate level or to stop the inflammation and prevent going to respiratory failure by recognizing the cytokine storm period early is the most prominent goal.

In the SARS-CoV pandemic that affected the world in 2003, T-helper lymphocyte type 1 (Th1) cytokine interferon (IFN)-γ, Th1 chemokine IFN-γ-inducible protein-10 (IP-10), pro-inflammatory cytokines interleukin (IL)-1β, IL-6, IL-8, IL-12, and monocyte chemoattractant protein levels were found to be increased. Glucocorticosteroids (GCs) are one of the most common anti-inflammatory agents with a long history of use. GCs are known to reduce neutrophil chemokine, IL-8 and monocyte chemoattractant protein-1(MCP-1), IP-10 with IFN-γ and also to inhibit ribonucleic acid responses, IL-6 and Th2 response, IL-4 (3). Both the Infectious Diseases Society of America (IDSA) and the World Health Organization (WHO, 2020) recommended the use of corticosteroids in only hospitalized severe COVID-19 patients based on the demonstration of a remarkable reduction in mortality and mechanical ventilation requirement in both an open-label, multicenter, randomized, controlled clinical trial of critically ill patients with COVID-19 patients and reported case reports in their current guidelines (4-8). However, although the routine use of GCs is not recommended in COVID-19, a systematic review of 41 studies of 25 protocols for treatment of COVID-19 revealed that corticosteroid therapy was commonly used in different doses and regimens (9).

In this study we aimed to reveal the clinical efficacy and safety of short-term high-dose GC therapy (a three-day course with one-week maintenance) in severe COVID-19 pneumonia followed at outside intensive care unit.

MATERIAL-METHODS:

S*tudy participants:*

This retrospective observational study consisted of 54 patients with severe COVID-19 pneumonia who required further treatment in a tertiary chest disease and thoracic surgery training hospital between 01 Sep 2020 and 01 Oct 2020. All participants were followed by five chest physicians in the four thoracic clinics-outside of the intensive care unit (ICU). All tests, procedures, therapies were ordered by the attending physicians.

The study was approved by the Ethics Committee of Ataturk Chest Disease and Thoracic Surgery Training and Research Hospital (697/ Oct 15, 2020).

Data collection:

The inclusion criteries were;- Patients older than 18 years of age with moderate / severe pneumonia hospitalized in our hospital with the diagnosis of COVID-19 confirmed by PCR on nasopharyngeal swab, - Given high-dose steroid therapy in clinical follow-up, (>250 mg/day methylprednisolone, 3 days) - Patients whose blood tests, X-ray images, and thoracic computed tomography sections were accessible - Patients with full access to the researched criteria on file or computer. Patients whose criteria could not be reached on file or computer were excluded from the study.

The reviewed and noted variables included patients' demographic characteristics, co-morbidities existing prior to the admission, time of illness onset and hospital admission, radiology findings, laboratory test results, medications and supportive care, further medical applications, and clinical outcomes. Data on the type, maximum daily dose, first started time, and duration of corticosteroids were collected.

Study settings and definitions:

Severe and critical patients with COVID-19 were defined following Ministry of Health, General Directorate of Public Health COVID-19 (SARS-CoV-2 Infection) Adult Patient Treatment Scientific Advisory Board Study guidelines for diagnosis and treatment (version October 9, 2020). In this guideline, severe patients who should be hospitalized with at least one of the following clinical features in addition to fever, myalgia, cough, sore throat are specified; respiratory rate exceeding 30 breaths/minute at rest, oxygen saturation 90% without oxygen support, and bilateral pneumonia on chest CT.

Corticosteroid treatment was ordered by the attending physician. Low-dose steroid therapy (dexamethasone 8 mg) was applied to all patients from the first day to discharge. High-dose, short-term corticosteroid therapy

was defined as [?]250 mg of methylprednisolone intravenously for three days. Early use of high-dose corticosteroid was defined as corticosteroid therapy within 7 days after hospital admission. Methylprednisolone 40-80mg/day was continued throughout the hospitalization to the patients receive high-dose steroid.

Endpoits:

The primary objective of this study is to determine whether corticosteroid use was decreased hospital mortality. Moreover, the primary outcome was examined in the following subgroups according to clinical features on hospital admission: (1) severity of illness (based on the previous definition) (2) requiring mechanical ventilation on hospital admission (3) comorbidities, and (4) relation with ferritin, C-reactive protein (CRP), and lymphopenia. Hospital length of stay, transfer to ICU, and presence of complications was also examined in between groups high-dose steroid (HDS) receiving, and not. The secondary objective of this study was to investigate whether fibrosis develops in patients with high-dose steroid therapy on follow-up in three months.

Statistical Analysis:

Data analysis was performed using SPSS 21.0 (Statistical Package for Social Sciences for Windows, Inc, Chicago, Illinois, USA). The compatibility of the data to normal distribution was investigated by Kolmogorov Smirnov test. Data showing the characteristics of continuous variables are expressed as mean ± standard deviation if they are distributed normally, as median (minimum-maximum) if they are not normally distributed, and categorical data were expressed as number and percentage (%). independent groups were compared using Student T test if the data was normally distributed, and Mann-Whitney U test if it was not normally distributed. Categorical variables were compared using the Chi-square test. A $p < 0.05$ value was considered statistically significant.

RESULTS:

During the observation period, a total of 317 patients were hospitalized for COVID-19 pneumonia. After data examined, it was found that a HDS was given to 54 patients whereas 261 patients had LDS therapy. The methylprednisolone doses of 54 patients were 1000 mg, 500 mg, and 250 mg for 9, 5, and 40 patients, respectively. The mean age of included patients was 62.5 (±13.64) years, and 64.7% (n=205) were male. Although males were more in overall, there was no difference for gender between the HDS and LDS groups. HDS group was younger than LDS (58.3±13.8 vs 63.4±13.4, p=0.012).

Clinical characteristics between the high and low-dose corticosteroid groups were spesicified in Table 1. According to demographic features, the body mass index (BMI) was a little higher in the HDS group (28. 96±4.44 vs 30.28±5.08, p=0.05). Both groups had similar rates of comorbidities (Hypertension, Chronic obstructive pulmonary disease, Asthma, Coronary artery disease, Chronic kidney disease, Diabetes mellitus, Congestive heart failure, Interstitial lung diseases, Rheumotology, Malignancy; p=0.28). Admission symptoms [fever (p=0.275), dyspnea (p=0.53), cough (p=0.281)] were found at similar rates in both groups. When the first treatments at hospitalization were compared, no difference was found for Favipiravir and Low-molecular-weight heparin between the groups, whereas the need for adding antibiotics during the hospitalization and added Plaquenil (p=0.009), and vitamin C (p=0.002) more in the HDS group (p<0.001). Bilateral consolidation with ground-glass opacities were detected higher in HDS than LDS group (88.9% vs 59.7%, p<0.001). In addition, the oxygen need of patients at admission and the need for advanced oxygen therapy during hospitalization were found higher in the HDS group (p<0.001). Furthermore, 18.5% of patients in the HDS group had need transfer to the intensive care unit whereas it was 3.8% in LDS (p<0.001). Additionally, the mortality rate was determined higher in the HDS group (25. 9% vs 9.9%, p<0.001).

The median (IQR) length of hospitalization was 10 (7-15), and 6 days (4-9), in HDS and LDS groups, respectively (table 2, p<0.001). Compared with the LDS group, the HDS group had lower saturated O_2 on ambient air at admission [IQR, 85% (76-89), p <0.001], and higher ferritin both at admission and before discharge [IQR, 529.5 (270.0-878.5) p = 0.03] and [IQR, 653.5 (453.6-885.0,) p <0.001] (table 2). However, there was no difference between the groups for the other laboratory parameters at admission (C-reactive protein, lymphocytes, neutrophils, neutrophil to lymphocyte ratio, platelets, D-dimer, troponin and creatinin,

table 2). Median (IQR) time from symptom onset to hospitalization was 5 (4-7) days in LDS, and 6 (3-10) days in the HDS group (p=0.75). When 317 patients were evaluated, no treatment change was required in the LDS group, while the median (IQR) pulse steroid was applied in the HDS group 3 (2-5) days after hospitalization, and 10 (6-16) days after symptoms appeared. When the HDS group is examined in more detail, it was found that lymphopenia deepened and ferritin increased on the third and fifth days, while pulse steroid was also given on these days (figure 1). Moreover, compared with the LDS group, a decrease in CRP was also lower in the HDS group (table 3, figure 1).

Of overall 317 patients, when the deaths (n=25) and had no regular followed were excluded (n=109), 181 patients were examined for developing fibrosis. All the patients followed up for a mean of 40.2 (±19.38) days after discharge. Of 181 patients, fibrosis was developed in 78 (43.1%) patients whereas was not in 103 (56.9%). Compared with the non-fibrosis group, older age (p=0.001), prolonged hospitalization (p=0.024), the lower saturation at admission (p=0.01), the higher d-dimer (p=0.014), and increased recurrent hospitalizations (p=0.04) were identified in the fibrosis group (table 4). There was no difference in fibrosis development between receive high-dose steroid patients (15.4% vs 26.2%, p=0.11).

DISCUSSION:

Herein, we investigated the efficiency of short-term high-dose steroid therapy in the course of severe COVID-19 pneumonia outside the intensive care unit. We did not find a lower mortality rate among high-dose GS patients statistically. However, it should be kept in mind that this study was retrospectively designed, and the groups were not homogenous, and the high-dose steroid group consisted of patients with more severe pneumonia than the low-dose steroid group.

Today most deaths due to COVID-19 are caused by respiratory failure (stage 3) from cytokine storms and there is no effective and specific treatment is not yet for all the stages. A limited effect on the early stages (stage 1-2) with antiviral agents such as remdesivir, favipiravir, darunavir, lopinavir/ritonavir has been shown besides with the randomized controlled studies still continue on (10). Stage 3 is related to cytokine release syndrome which demonstrates high levels of interleukins (IL) (IL-1 β, IL-1RA, IL-6, IL-8, IL-9, IL-10, IL-17), macrophage inflammatory protein, vascular endothelial growth factor, tumor necrosis factor-alpha (TNF-α), and other pro-inflammatory chemokines, cytokines, and signaling proteins (11). Corticosteroids are known to functions anti-inflammatory, anti-allergic, and hypothermic due to reducing levels of IL-8, MCP-1, and IP-10 and inhibiting the gene expression of IL-6, IFN-γ, and IL-4 (3,12). Based on the effects on these cytokines it is suggested that using corticosteroid as adjunctive therapy in COVID-19 treatment (4,5, 13-20). Due to its immunosuppression property, potential risks of corticosteroid therapy including secondary infections, long-term complications, and delayed virus clearance, the benefits and harms should be carefully weighed before using corticosteroids, and time to administration should be decided carefully (21). So there is not a consensus on GC s use and the optimal dose. Considering that the conflicting results regarding the use of steroids in the treatment of patients with severe COVID-19 pneumonia so far, we aimed to demonstrate the benefits of high-dose steroid usefulness in these patients outside the intensive care unit.

Although there was also not found a lower mortality rate in the HDS group in our study such as Chen's and Bartoletti's studies (15, 22), more clinical improvement was observed in COVID-19 patients given HDS than LDS. However, when use a propensity score matching, significantly lower mortality was found in the Cox regression survival analysis (15). But there couldn't apply the propensity score matching for our study due to technical problems. On the other hand, the time to give steroid is extremely important to these patients that the early high-dose GCs were shown to decrease the progression of the disease and improve the resolution of alterations in the pulmonary structures (20). Concurrent administration of high doses of steroids to these patients together with the increase in ferritin levels on the 1st, 3rd, and 5th days of hospitalization, a slower decrease in CRP value, and the deepening of lymphopenia, and the prominence of clinical worsening, supports this information.

In this recent study, similar to the literature, higher BMI, the oxygen need of patients at admission, and the need for advanced oxygen therapy, more bilateral subpleural multifocal ground-glass opacities with

consolidation and hyperferritinemia were found significantly different in the HDS group than LDS group (23). However, unlike the literature, the patients were younger in the HDS group with higher mortality. Moreover patients in the HDS group spent 4 days more in the hospital, although that may be partially explained by a more severe course of the disease. Physicians should be kept in mind that it also prolongs the duration of virus clearance (24).

The secondary objective of this study was to investigate whether fibrosis develops in patients with high-dose steroid therapy on follow-up in three months. However, as expected, the rate of fibrosis was not lower among patients receiving high doses of steroids. Nevertheless, older age, prolonged hospitalization, lower saturation at admission, higher d-dimer, and increased recurrent hospitalizations were identified as the indicator for fibrosis in our study. There is not yet a study for predicting fibrosis in the literature. Although the number of patients is small, this study can be a guide for future studies.

The limitations of the study were the retrospective design that prevents randomization, the small number of patients with HDS, and the difference between groups in baseline characteristics.

In conclusion, the use of HDS in hospitalized COVID-19 patients remains unclear. Along with this, our study demonstrated the use of high-dose corticosteroids might not be associated with a lower mortality rate among hospitalized severe COVID-19 patients. Prospective multicenter studies with a large number of controlled randomized patients will be guiding in the future.

Figure Legends:

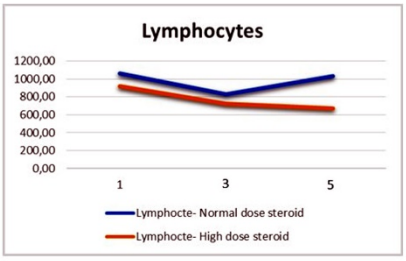
Figure 1. The course of CRP, ferritin, and lymphocyte values on 1st, 3rd, and 5 the days in COVID-19.

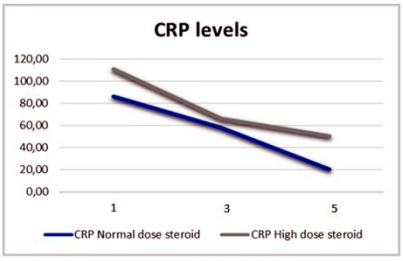
REFERENCES:

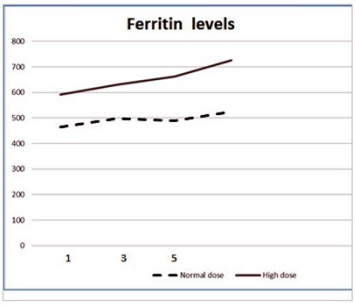
1. COVID-19 Map. [cited March 28,2021]. Available from: https://coronavirus.jhu.edu/ map.html
2. L.H. Calabrese, Cytokine storm and the prospects for immunotherapy with COVID19, Cleve. Clin. J. Med. 87 (7) (2020 May 11) 389–393, https://doi.org/10.3949/ ccjm.87a.ccc008, pii: ccc008, Published 2020 Jun 30.
3. Lam, C.W., Chan, M.H., Wong, C.K., 2004. Severe acute respiratory syndrome: clinical and laboratory manifestations. Clin. Biochem. Rev. 25, 121–132.
4. The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with covid-19-preliminary report. New Engl. J. Med.2021;384:693-704. DOI:10.1056/ NEJMoa2021436
5. Sauñe, Patricia & Bryce-Alberti, Mayte & Portmann-Baracco, Arianna & Accinelli, Roberto. (2020). Methylprednisolone pulse therapy: An alternative management of severe COVID-19. Respiratory medicine case reports. 31.101221.10.1016/j.rmcr.2020. 101221.
6. Bhimraj A., Morgan L., R.L Shumaker, A.H., Lavergne, V., Baden, L., Cheng, V et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. Published by IDSA on 3/02/2021. Last updated February 3, 2021, www.idsociety.org/COVID19guidelines.
7. World Health Organization (WHO), 2020. Coronavirus Disease (COVID-19) Situation Dashboard. (Accessed June 28, 2020). https://www.who.int/emergencies/diseases/ novel-coronavirus-2019.
8. Ministry of Health, General Directorate of Public Health. COVID-19 (SARS-CoV-2 Infection) Adult Patient Treatment Scientific Advisory Board Study, October 9, 2020.
9. Tobaiqy M, Qashqary M, Al-Dahery S, et al. Therapeutic management of patients with COVID-19: a systematic review. Infection Prevention in Practice. 2020;2(3):100061. doi:10.1016/j.infpip.2020.100061
10. Pagliano P, Scarpati G, Sellitto C, Conti V, Spera AM, Ascione T, Piazza O, Filippelli A. Experimental Pharmacotherapy for COVID-19: The Latest Advances. J Exp Pharmacol. 2021 Jan 7;13:1-13. doi: 10.2147/JEP.S255209. PMID: 33442304; PMCID: PMC7800714.
11. Sun X, Wang T, Cai D, Hu Z, Chen J, Liao H et al. Cytokine storm intervention in the early stages of COVID-19 pneumonia. Cytokine & Growth Factor Reviews. 2020;53:38–42. DOI: 10.1016/j.cytogfr.2020.04.002
12. Mattos-Silva, P., Felix, N. S., Silva, P. L., Robba, C., Battaglini, D., Pelosi, P., et al. Pros and cons of corticosteroid therapy for COVID-19 patients. Respir Physiol Neurobiol. 2020;280:103492.

doi:10.1016/j.resp.2020.103492

13. Kolilekas L, Loverdos K, Giannakaki S, et al. Can steroids reverse the severe COVID-19 induced 'cytokine storm'? J Med Virol. 2020;92 (11):2866–2869.
14. So C, Ro S, Murakami M, Imai R, Jinta T. High-dose, short-term corticosteroids for ARDS caused by COVID-19: a case series. Respirol Case Rep. 2020;8(6):e00596. Published 2020 Jun 4. doi:10.1002/rcr2.596
15. Chen Q, Song Y, Wang L, et al. Corticosteroids treatment in severe patients with COVID-19: a propensity score matching study [published online ahead of print, 2021 Feb 1]. Expert Rev Respir Med. 2021;1-10. doi:10.1080/17476348.2021.1856659
16. Conti P, Ronconi G, Caraffa A, Gallenga CE, Ross R, Frydas I, Kritas SK. Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): anti-inflammatory strategies. J Biol Regul Homeost Agents. 2020 March-April,;34(2):327-331. doi: 10.23812/CONTI-E. PMID: 32171193.
17. Shang L, Zhao J, Hu Y, Du R, Cao B. On the use of corticosteroids for 2019-nCoV pneumonia. Lancet. 2020;395(10225):683-684. doi:10.1016/S0140-6736(20)30361-5
18. Dai J, Xiong Y, Li H, et al. Corticosteroid treatment in severe COVID-19 pneumonia: two cases and literature review. Clin Rheumatol. 2020;39(7):2031–2037
19. Veronese N, Demurtas J, Yang L, et al. Use of corticosteroids in coronavirus disease 2019 pneumonia: a systematic review of the literature. Front Med (Lausanne). 2020;7:170.
20. Ho JC, Ooi GC, Mok TY, Chan JW, Hung I, Lam B et al. High– Dose Pulse Versus Nonpulse Corticosteroid Regimens in Severe Acute Respiratory Syndrome. American Journal of Respiratory and Critical Care Medicine. 2003;168(12):1449–56. DOI: 10.1164/rccm.200306-766OC
21. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet. 2020;395(10223):473–475.
22. Bartoletti M, Marconi L, Scudeller L, Pancaldi L, Tedeschi S, Giannella M, et al,PREDICO Study Group. Efficacy of corticosteroid treatment for hospitalized patients with severe COVID-19: a multicentre study. Clin Microbiol Infect. 2021 Jan;27(1):105-111. doi: 10.1016/j.cmi.2020.09.014. Epub 2020 Sep 22. PMID: 32971254; PMCID: PMC7506332.
23. Wu C, Chen X, Cai Y, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA* Intern Med. 2020;180(7):934–943. doi:10.1001/jamainternmed.2020.0994
24. Bhaskar S, Sinha A, Banach M, Mittoo S, Weissert R, Kass JS, Rajagopal S, et al. Cytokine Storm in COVID-19-Immunopathological Mechanisms, Clinical Considerations, and Therapeutic Approaches: The REPROGRAM Consortium Position Paper. Front Immunol. 2020 Jul 10;11:1648. doi: 10.3389/fimmu.2020.01648. PMID: 32754159; PMCID: PMC7365905.







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