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Corticosteroid therapy for patients with severe novel Coronavirus disease 2019

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Abstract. – OBJECTIVE: To investigate the effect of corticosteroid on hospital mortality, hospital length of stay, and time of viral clearance in patients with severe and critical COVID-19.

PATIENTS AND METHODS: Patients with severe and critical COVID-19 who had been discharged or expired were enrolled in this study. Patients were divided into corticosteroid group and non-corticosteroid group according to the systemic corticosteroid use or not. Clinical data were collected, and hospital mortality, hospital length of stay, time of viral clearance, time of mechanical ventilation, and duration from illness onset to symptom resolution were compared between the two groups.

RESULTS: A total of 72 inpatients who were diagnosed with severe and critical COVID-19 were enrolled, in which 47 patients were divided into corticosteroid group and 25 were involved as the non-corticosteroid group. Baseline characteristics were generally similar between the two groups. Four (5.6%) patients died during hospitalization, and 68 (94.4%) were discharged. Among survivors, the mean duration time from admission to discharge was 19.5d (SD 7.05 d). The mean time of viral clearance among survivors was 17.5d (SD 7.67 d), with a maximum of 37 d, and a minimum of 5 d. Hospital mortality (4.3% *vs.* 8.0%), length of hospital stay (18.7d *vs.* 21.0d), and time of viral clearance (16.1d *vs.* 19.4d) had no significant difference between two groups ($p>0.05$). The duration of symptoms suffering was shorter in the corticosteroid group than non-corticosteroid group, with statistically significant difference ($p<0.05$).

CONCLUSIONS: Corticosteroid therapy in patients with severe COVID-19 cannot reduce the hospital mortality, and is not associated with delayed viral clearance, but it could relieve the inflammatory storm and improve clinical symptoms in brief. Patients with severe COVID-19 could benefit from low-dose corticosteroid treatment.

Key Words:
COVID-19, Corticosteroid, Therapy.

Introduction

In December 2019, Novel Coronavirus Pneumonia (NCP) occurred in Wuhan, Hubei province, China, and has rapidly spread to other provinces of China as well as other countries. The pathogen was referred to as 2019-new Coronavirus (2019-nCoV), and the disease was later named Novel Coronavirus Disease 2019 (COVID-19) by the WHO in February 2020[1].

Early studies have suggested that the outbreak may be related to a zoonotic transmission event in a seafood market in Wuhan[2], and subsequent evidence shows the occurrence of person-to-person transmission[3,4]. According to statistics, by April 17 2020, more than 2,000,000 cases of COVID-19 have been confirmed, and more than 140,000 people died from this pneumonia[5]. Most of the deaths were due to severe COVID-19. As the antiviral therapy, respiratory support and other supportive treatments are main therapies for COVID-19. Further studies are needed to avoid severe disease and reduce mortality. However, many studies have reported the epidemiological, clinical, and laboratory characteristics of

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COVID-19[6,7], but most of them are descriptive studies, and few have focused on the treatment to effectively reduce the mortality of the infection.

The use of corticosteroid in viral pneumonia is controversial. Corticosteroid were commonly used in critically ill patients with pneumonia, during the outbreak of Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS), but their effects on clinical outcomes are unclear. A retrospective cohort study of SARS showed that corticosteroid can reduce the mortality and length of hospital stay[8]. However, there are also studies[9,10] showing that corticosteroid may increase the case fatality rate in SARS patients and delay the time of virus clearance. A recent study[11] published on The Lancet showed that corticosteroid is not recommend for patients with COVID-19.

The objective of this study was to investigate the effect of corticosteroid on hospital mortality, length of hospital stay, and time of viral clearance in patients with severe COVID-19.

Patients and Methods

Patients Inclusion

This is a multicenter retrospective cohort study, patients involved in this study were from Chongqing Public Health Medical Center (Chongqing, China), Chongqing Three Gorges Central Hospital (Chongqing, China) and Yongchuan Hospital of Chongqing Medical University (Chongqing, China) between January 2020 and March 2020. All adult patients we selected were diagnosed with COVID-19 by RNA RT-PCR testing of respiratory secretions according to WHO interim guidance[12]. These patients were classified into four severity statuses according to the Chinese management guideline for COVID-19: mild, moderate, severe and critical[13]. In our study, enrolled patients who were diagnosed as severe or critical COVID-19 had been discharged or expired. Patients whose clinical data were incomplete or who were receiving long-term corticosteroid therapy for other reasons before COVID-19 onset were excluded. The study was approved by the Research Ethics Commission of The Second Affiliated hospital of Chongqing Medical Universty (No.2020-09).

Therapy

The main exposure was the use of systemic intravenous corticosteroid therapy. According to the Chinese management guideline for COVID-19[13], the patients in the corticosteroid group receiving low-dose methylprednisolone therapy for 3 days, in which 42 patients were given a dose of 40 mg/d, and 5 patients with shock were given 80 mg/d. The non-corticosteroid group patients did not receive corticosteroid therapy. All enrolled patients received appropriate supportive therapy, including appropriate oxygen therapy or mechanical ventilation, antibiotics, antiviral therapy, and intravenous immunoglobin, among others.

Data Collection

In our study, data were collected using International Severe Acute Respiratory and Emerging Infection Consortium case report standardized data collection forms[14]. Data were extracted from electronic medical records, including demographic, clinical feature, comorbidities, laboratory findings, imaging features, treatment, and duration from illness onset to hospital admission. The Sequential Organ Failure Assessment (SOFA) score was used to assess the severity of disease for every patient. The lymphocyte count, $CD4^+$ T lymphocyte number, SOFA score and IL-6 level of corticosteroid group before corticosteroid therapy and after three days using corticosteroids were collected.

Primary outcomes included hospital mortality, hospital length of stay, and time of viral clearance. Secondary outcomes were time of mechanical ventilation, duration from illness onset to fever resolution, and duration from illness onset to dyspnea resolution. The length of hospital stay refers to the time from admission to discharge. The time of viral clearance was defined as the time from admission to SARS-CoV-2 RNA RT-PCR tests revealed negative twice. The time of mechanical ventilation was defined as the time of noninvasive and invasive mechanical ventilation during hospitalization.

Statistical Analysis

For continuous variables, we used Student's *t*-test or the Mann-Whitney U test to assess differences in the means of two groups, and the results are indicated by the mean (SD). For categorical variables, we used the χ^2 or Fischer's exact test, as appropriate, and the results are indicated by the number (%). The log-rank test was used to assess hospital mortality differences between the groups. A paired *t*-test was used to compare changes in the therapy group before and after three days using corticosteroids. Regarding hospital length of stay and time of viral clearance,

to avoid the confounding effect of death, only patients who survived were included in the analysis. Regarding time of mechanical ventilation, only cases involving mechanical ventilation were analyzed. Tests were two-sided, and our cutoff for statistical significance was 0.05. The statistical analyses were conducted using SPSS (Statistical Package for the Social Sciences) version 20.0 software (IBM Corp, Armonk, NY, USA).

Results

Baseline Characteristics of COVID-19 Patients

A total of 72 inpatients who were diagnosed with severe and critical COVID-19 were included in our study, 47 in the corticosteroid group and 25 in the non-corticosteroid group, including 46 (64%) severe cases and 26 (36%) critical cases. The mean age of all 72 patients was 60 years (SD 13.8), ranging from 25 years to 89 years, and 40 (56%) were male. Thirty-nine (54%) of these 72 patients had one or more comorbidities. Diabetes (35%) is the most common comorbidity, followed by hypertension (21%). The most common clinical symptoms were fever, cough and dyspnea in more than 90% patients, followed by sputum and myalgia. The mean SOFA score was 3.7 (SD 1.27). The mean time from illness onset to hospital admission was 4.2 d (SD 2.65 d). In 83% of 72 patients, the main manifestation in chest CT scan was bilateral pulmonary infiltration (Table I).

Seventy-four percent of 72 patients received broad-spectrum antibiotic therapy, 68% antiviral treatment, and 14% intravenous immunoglobin infusion. Thirty-two (44%) patients needed a high-flow nasal cannula, 24 (33%) patients needed noninvasive mechanical ventilation, and 8 (11%) patients received invasive mechanical ventilation (Table II).

Overall, baseline characteristics were generally similar between the corticosteroid group and non-corticosteroid group, including demographic, clinical symptoms, comorbidities, laboratory data, radiographic findings, disease severity status, SOFA score, and time from illness onset to hospital admission. (Table I) There were no differences between the two groups in support treatments except for corticosteroid therapy. (Table II).

Mortality

Of the 72 patients, 4 (5.6%) died during hospitalization, and 68 (94.4%) were discharged. Forty-five (95.7%) of 47 patients in the corticosteroid group were survived, compared with 23 (92.0%) of 25 patients in the non-corticosteroid group, unfortunately the result did not meet the statistical difference (p=0.550) (Table III).

Times of Hospital Stay and Viral Clearance

To avoid the confounding effect of death, length of hospital stay and time of viral clearance were only analyzed in survived patients. The mean time from admission to discharge was 19.5 d (SD 7.05 d) for a total of 68 survivors, with a maximum of 40 days, and a minimum of 7 days. The mean length of hospital stay was 18.7 d (SD 6.78 d) in the corticosteroid group survivors, and 21.0 d (SD 7.49 d) in the non-corticosteroid group survivors (p=0.212). The mean time of viral clearance was 17.5 d (SD 7.67 d) among 68 survivors, with a maximum of 37 days, and a minimum of 5 days. The mean time of viral clearance was 16.1 d (SD 6.11 d) in the treatment group and 19.4 d (SD 9.42 d) in the comparator group survivors (p=0.184). (Table III).

Time of Mechanical Ventilation and Duration of Symptoms

The mean time of mechanical ventilation was 10.1 d (SD 6.00 d) in 26 patients receiving mechanical ventilation. However, the mean time of mechanical ventilation was 9.6 d (SD 6.36 d) in the corticosteroid group and 12.8 d (SD 6.40 d) in the non-corticosteroid group (p=0.376). The duration from illness onset to fever resolution was 9.5 d (SD 3.10 d) among the 72 patients, and it was 8.2 d (SD 2.2 5d) in the corticosteroid group, 10.9 d (SD 3.35 d) in the non-corticosteroid group, and this difference was statistically significant (p=0.013). Similarly, the duration from illness onset to dyspnea resolution was 9.6 d (SD 4.43 d) among the 72 patients, shorter in the corticosteroid group than in the non-corticosteroid group, with statistically significant differences (p=0.031). (Table III).

Changes in the Corticosteroid Group

Patients with severe COVID-19 had decreased lymphocyte counts, decreased $CD4^+$ T lymphocyte numbers, and increased IL-6 (Table I). After three days of corticosteroid treatment, the mean lymphocyte count was 1.28×10^9/L (SD 0.59 $\times10^9$/L), and the mean $CD4^+$ T lymphocyte number was 380 (SD 232), both of which were higher

Table I. Demographic, clinical, laboratory, and imaging characteristics of patients on admission.

Variable	Total (n = 72)	Corticosteroid group (n = 47)	Non-corticosteroid group (n = 25)	*p*-value
Demographics				
Age, years	60 (13.8)	61 (14.7)	60 (12.3)	0.726
Sex ---	---	---	0.626	
Male 40 (56%)	25 (53%)	15 (60%)	---	
Female 32 (44%)	22 (47%)	10 (40%)	---	
Current smoker	16 (22%)	14 (30%)	2 (8%)	0.09
BMI 25.20 (3.25)	25.74 (3.74)	24.54 (2.51)	0.315	
Comorbidity	39 (54%)	24 (51%)	15 (60%)	0.780
Hypertension	15 (21%)	10 (21%)	5 (20%)	1.000
Diabetes 25 (35%)	16 (34%)	9 (36%)	1.000	
Coronary heart disease	5 (7%)	2 (4%)	3 (12%)	0.545
Chronic obstructive lung disease	4 (6%)	2 (4%)	2 (8%)	0.502
Viral hepatitis B	5 (7%)	2 (4%)	3 (12%)	0.545
Carcinoma	0	0	0	---
Chronic kidney disease	0	0	0	---
Clinical feature				
Fever (temperature ≥37.3°C)	66 (92%)	44 (94%)	22 (88%)	0.831
Cough 67 (93%)	44 (94%)	23 (92%)	1.000	
Sputum 35 (48%)	25 (53%)	10 (40%)	0.722	
Dyspnea 65 (90%)	44 (94%)	21 (84%)	0.576	
Myalgia 23 (32%)	12 (26%)	11 (44%)	0.441	
Fatigue 21 (29%)	10 (21%)	11 (44%)	0.528	
Diarrhea	11 (15%)	8 (17%)	3 (12%)	0.803
Headache	9 (13%)	6 (13%)	3 (12%)	1.000
SOFA score	3.7 (1.27)	4.3 (1.24)	3.5 (1.10)	0.257
Time from illness onset to hospital admission, d	4.2 (2.65)	4.0 (2.32)	3.7 (2.57)	0.694
Disease severity status	---	---	---	0.133
Severe46 (64%)	27 (57%)	19 (76%)	---	
Critical26 (36%)	20 (43%)	6 (24%)	---	
Laboratory findings				
PaO_2/FiO_2 ratio, mmHg	194 (76.1)	185 (70.9)	209.8 (84.0)	0.191
Peripheral white cell count, $\times 10^9$/L	6.03 (2.75)	5.87 (2.42)	6.33 (3.30)	0.494
Lymphocyte count, $\times 10^9$/L	0.93 (0.43)	0.93 (0.38)	0.93 (0.52)	0.993
Hemoglobin, g/L	126 (16.9)	125 (18.1)	127 (14.7)	0.631
Platelet count, $\times 10^9$/L	197 (103.1)	189 (92.7)	213 (120.8)	0.354
Procalcitonin, ng/mL	0.180 (0.443)	0.229 (0.558)	0.102 (0.080)	0.281
Prothrombin time, s	12.04 (1.66)	11.72 (1.08)	12.64 (2.31)	0.101
D-dimer, µg/L	1.46 (3.30)	1.90 (4.00)	0.63 (0.69)	0.122
IL-6, pg/mL	36.24 (48.68)	37.66 (52.02)	33.05 (41.60)	0.764
Alanine transaminase, IU/L	60.31 (131.86)	69.18 (158.56)	43.63 (52.93)	0.438
Lactate dehydrogenase, U/L	333.06 (190.44)	356.66 (217.13)	288.68 (117.41)	0.151
Serum albumin, g/L	43.61 (48.31)	46.94 (61.50)	38.25 (4.64)	0.503
Serum creatinine, µmol/L	67.46 (25.19)	67.00 (28.42)	68.20 (19.47)	0.86
C-reactive protein, mg/L	52.00 (46.99)	52.98 (49.12)	50.17 (43.61)	0.811
CD4+ T lymphocyte number	285.87 (168.10)	263 (156.7)	328 (183.4)	0.117
CD4+/CD8+ ratio	1.70 (0.76)	1.64 (0.78)	1.81 (0.74)	0.400
Imaging features				
Bilateral pulmonary infiltration	60 (83%)	41 (87%)	19 (76%)	0.636
No. of quadrants with infiltrates	3.3 (1.13)	3.5 (1.07)	2.93 (1.14)	0.145

Data are the number (%) or mean (SD). p-values were calculated by the Mann-Whitney U test, χ^2 test, or Fisher's exact test, as appropriate. BMI=Body mass index. SOFA=Sequential Organ Failure Assessment. IL-6=interleukin-6.

than before. After three days of corticosteroid treatment, the mean SOFA score was 2.00 (SD 1.37) and the mean IL-6 was 10.67 pg/mL (SD 12.32 pg/mL), both of which were significantly lower than before. The differences were statistically significant ($p<0.05$) (Table IV).

Table II. Supportive treatments offered during the course of COVID-19 therapy.

Treatments	Total (n = 72)	Corticosteroid group (n = 47)	Non-corticosteroid group (n = 25)	*p*-value
Antibiotics 53 (74%)	40 (85%)	13 (52%)	0.101	
Antiviral treatment	49 (68%)	31 (66%)	18 (72%)	0.573
Intravenous immunoglobin	10 (14%)	9 (19%)	1 (4%)	0.221
High-flow nasal cannula	32 (44%)	20 (43%)	12 (48%)	0.804
Noninvasive mechanical ventilation	24 (33%)	19 (40%)	5 (20%)	0.137
Invasive mechanical ventilation	8 (11%)	5 (11%)	3 (12%)	1.000

Data are the number (%) or mean (SD). *p*-values were calculated by the χ^2 test or Fisher's exact test, as appropriate.

Discussion

In our study, 72 patients included 47 receiving corticosteroid therapy and 25 did not. The findings including demographic, clinical feature, and comorbidities are consistent with some earlier reports[4,6,7]. In accord with many reports[6,7,15], laboratory examination in our study showed that patients with severe COVID-19 had a decreased PaO_2/FiO_2 ratio, decreased peripheral lymphocyte count, increased D-dimer, increased IL-6, increased C-reactive protein, and decreased $CD4^+$ T lymphocyte number. We speculated that severe COVID-19 illness may be related to the pathogenesis of the inflammatory response, immune disorders and increased fibrinolytic activity.

After Coronavirus infection, rapid virus replication and delay of the interferon response causing massive inflammatory cell infiltration releasing a large amount of cytokines, leading the occurrence and development of a severe inflammatory response[16]. Previous studies[17-19] of SARS and MERS shown that levels of IFN-γ, IL-18, TGF-β, IL-6, and other cytokines were significantly increased in those patients, indicating that the cytokine storm is more evident in patients who died than in those who survivors. Indeed, the cytokine storm is the main cause of death. The plasma cytokine concentration in COVID-19 patients was also found to be higher than that in the healthy group, and the cytokine concentration in ICU patients was significantly higher than that in non-ICU patients, which also indicated the existence of a cytokine storm in COVID-19 patients[4]. In addition, in clinical practice, we noticed that many severe COVID-19 patients had cold extremities, weak peripheral pulses, hypotension and other shock clinical manifestations. Domestic experts used viral sepsis to describe the phenomenon, and suggested that viral sepsis was a crucial mechanism of COVID-19[20]. Severe virus infection leads to further aggravation of lung injury. Meanwhile a large amount of virus directly attack on other organs. The immune response caused by the systemic cytokine storm,

Table III. Outcomes of patients with COVID-19 between the corticosteroid and non-corticosteroid groups.

Variable	Total (n = 72)	Corticosteroid group (n = 47)	Non-corticosteroid group (n = 25)	*p*-value
Survival status	---	---	---	0.550[&]
Non-survivor	4 (5.6%)	2 (4.3%)	2 (8.0%)	---
Survivor 68 (94.4%)	45 (95.7%)	23 (92.0%)	---	
Length of hospital stay, d[#]	19.5 (7.05)	18.7 (6.78)	21.0 (7.49)	0.212
Time of viral clearance, d[#]	17.5 (7.67)	16.1 (6.11)	19.4 (9.42)	0.184
Time of mechanical ventilation, d*	10.1 (6.00)	9.6 (6.36)	12.8 (6.40)	0.376
Duration from illness onset to fever resolution, d	9.5 (3.10)	8.2 (2.25)	10.9 (3.39)	0.013
Duration from illness onset to dyspnea resolution, d	9.6 (4.43)	8.4 (3.48)	11.1 (4.62)	0.031

Data are the number (%) or mean (SD). *p*-values were calculated by the Mann-Whitney U test, χ^2 test, or Fisher's exact test, as appropriate. #Only patients who survived were analyzed (n=68). *Only cases with mechanical ventilation were analyzed (n=26). &The log-rank test was used to assess survival differences in hospitals between the two groups.

Table IV. Changes in lymphocyte count, CD4+ T lymphocyte number, SOFA score and IL-6 after three days of corticosteroid treatment in corticosteroid group (n=47).

Variable	Lymphocyte count, $\times 10^9$/L	CD4+ T lymphocyte number	SOFA score	IL-6, pg/mL
Before treatment	0.97 (0.42)	233 (146)	4.18 (1.24)	51.70 (63.04)
After three days of corticosteroid treatment	1.28 (0.59)	380 (232)	2.00 (1.37)	10.67 (12.32)
p-value	0.023	0.001	0.001	0.000

Data are the mean (SD). p-values were calculated by the paired *t*-test. SOFA=Sequential Organ Failure Assessment. IL-6=interleukin-6.

and the microcirculation disorders, eventually lead to viral sepsis together. The presence of cytokine storm and viral septic lay theoretical foundations for the corticosteroid therapy in severe COVID-19 patients.

Corticosteroid is an anti-inflammatory steroid hormone commonly used to inhibit inflammation. It can regulate inflammation-related gene transcription through activation of glucocorticoid receptors, block the synthesis of cytokine receptors, inhibit the induction of target genes by activator protein-1, and induce the production of lipocortin-1[21]. During the SARS epidemic in 2003, corticosteroid was the main drug for immunoregulatory therapy. A retrospective study[8] of 401 SARS patients found that the rational use of corticosteroid effectively reduced mortality, shortened hospital length of stay and was not associated with secondary infections or other complications in critically ill patients.

In our study, corticosteroid therapy could not reduce the mortality of severe COVID-19. Similarly, corticosteroid did not reduce mortality of patients with other virus infections, such as SARS[10], MERS[22] and H1N1 influenza[23]. In the clinic, physicians tend to use corticosteroid in the majority of critically ill patients, combined with powerful symptomatic and supportive treatments, such as mechanical ventilation, antiviral therapy, and immunotherapy. However, because of the critically ill, comprehensive treatments are more valuable to improve survival rate than corticosteroid. In general, corticosteroid therapy may not play a significant role in the survival advantage of such patients.

Nevertheless, length of hospital stay, time of viral clearance, and time of mechanical ventilation seemed to decrease in corticosteroid group. Although baseline characteristics appeared to be reasonably matched in the two groups, substantial differences might not be shown because of the small size in the study. Our study also found a benefit of corticosteroid, whereby the duration of symptoms was shorter in corticosteroid group than non-corticosteroid group. In addition, our study showed that after three days of corticosteroid therapy, the lymphocyte count and $CD4^+$ T lymphocyte number could recover in a degree, the SOFA score and IL-6 might also decrease compared before. These results show that corticosteroid indeed can inhibit the inflammatory response, relieve clinical symptoms, and even play a role in the recovery of immune function of patients with severe COVID-19. A series of randomized clinical trials indicated that low-dose corticosteroid treatment did not reduce mortality of patients with septic shock, but it might have clinical benefits regarding to shock reversal and shorter times of ICU and mechanical ventilation[24]. An observational study in Wuhan found that corticosteroid could effectively inhibit inflammatory storms and enhance SaO_2 and PaO_2/FiO_2, but it might not improve mortality in patients with critical COVID-19[25].

On the other hand, we do not deny that corticosteroid treatment may cause a series of complications. It is impossible to assess adverse reactions with the use of corticosteroid because of the absence of collection corticosteroid-related complications in our study. Such data should be included in any future clinical studies for exploring the therapeutic adverse effects of any drug intervention in COVID-19 patients. There have been reports for other Ccoronaviruses. NEJM reported a case of fatal fungal infection in a SARS patient treated with corticosteroid[26]. Some studies[27,28] have shown that a considerable proportion of SARS patients with corticosteroid therapy developed avascular osteonecrosis in the later stages.

In critically ill patients, overwhelming inflammation storms and cytokine storms might lead to rapidly progressive pneumonia and lung injury. Do-

mestic first-line experts suggest that most of studies to date are observational and that uncertain clinical evidence should not be the reason for abandoning the use of corticosteroid in severe COVID-19 patients, because of limitations in research methods[29]. The domestic guidelines and expert consensus indicate that a short course of low-dose corticosteroid treatment can be used to appropriately control the inflammatory storm for severe COVID-19 patients with progressive deterioration of the oxygenation index, rapid progression in imaging, and overactivation of the inflammatory response[13,30]. Our results support that this is reasonable.

This study was a retrospective study, and not a randomized controlled trial. Selection and unmeasured confounding bias were not completely excluded. A randomized clinical controlled trial is usually conducted to assess the true effect of a treatment. However, this approach is not always practically feasible in emerging and uncommon diseases. In this study, the baseline characteristics of the two groups were matched as much as possible.

Conclusions

Corticosteroid therapy cannot reduce hospital mortality or shorten length of stay of patients with severe COVID-19, but it can improve clinical symptoms and is not associated with delayed viral clearance. Corticosteroid can significantly inhibit inflammatory storms of patients with severe COVID-19, gaining precious time for controlling infection and preventing secondary multiorgan damage and septic shock. For severe COVID-19 patients with inflammatory storms, a short course and low-dose of corticosteroid may be considered, providing adequate monitoring and assessment. Further appropriately randomized controlled trials are recommended.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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