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Effect of glucocorticoid therapy on the prognosis of patients with severe and critical COVID-19: a single-center retrospective cohort study

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Abstract. – OBJECTIVE: Coronavirus disease 2019 (COVID-19) has elevated mortality in severe and critical patients globally. This study examined the effect of glucocorticoids (GCS) on the time of virus clearance and absorption of lung lesions in severe and critical COVID-19 patients.

PATIENTS AND METHODS: Severe and critical COVID-19 cases diagnosed in Wuhan Pulmonary Hospital from January 7 to February 10, 2020 were analyzed. The generalized linear model was utilized to assess the effects of GCS therapy on the times of nucleic acid test turning negative and improved pulmonary imaging, respectively.

RESULTS: Of 66 patients, 51 (77.3%) and 15 (22.7%) were severe and critical cases, respectively, and aged 62 ± 11 years. A total of 58 patients (87.9%) tested negative, and 56 (84.8%) showed improved lung imaging. Age, thrombocytopenia, CD8 + T cell count, course of GCS therapy, and total dose were correlated with the time of nucleic acid test turning negative ($p < 0.05$), and sex was correlated with the time of initial pulmonary imaging improvement ($p < 0.05$). The time of nucleic acid test turning negative in individuals with GCS therapy course ≤ 10 days was shorter than that of the GCS therapy course > 10 days group (p=0.001). No statistical difference was found in the dose, course of GCS, and initial time of improved lung imaging.

CONCLUSIONS: Increasing the dose of GCS and prolonging the course of treatment do not shorten the time of nucleic acid test turning negative or improved absorption of pulmonary lesions. Thus, the rational use of GCS is particularly important.

Key Words:
COVID-19, Glucocorticoid, Dose, COVID-19 nucleic acid testing, 2019-nCoV nucleic acid negative, Improved pulmonary imaging.

Introduction

The 2019 novel coronavirus (2019-nCoV) was identified as the infectious agent of pneumonia causing an outbreak in Wuhan, China; 2019-nCoV is currently prevalent globally attracting huge attention on its prevention and cure[1-3]. This virus is similar to severe acute respiratory syndrome (SARS) coronavirus and Middle East respiratory syndrome (MERS) coronavirus but has a distinct function and virulence[3]. On January 31, 2020, the World Health Organization officially declared the COVID-19 outbreak as a public health emergency of international concern[2]. As of August 14, 2020, at least 21,088,317 confirmed cases of COVID-19 have been globally reported, with 757,650 confirmed deaths[4]. In China, as of July 15, 2020, 83,612 cases were reported by the China Center for Disease Control and Prevention, with a cumulative death toll of 4634 cases[5,6]. Yang et al[7] showed that the prognosis of patients with mild and common coronary pneumonia is good, while high mortality is found in severe and critical cases. Thus, strengthening treatment and early prevention and control of COVID-19, and improving the recovery rate have become the top global priority in COVID-19 management.

SARS is an acute infectious disease caused by SARS coronavirus, which is transmitted through the respiratory tract[8]. Its clinical manifestations include persistent fever, headache, muscle soreness, and decreased white blood cell count; severe cases could experience acute respiratory distress syndrome (ARDS) and multiple organ failure[9]. SARS-CoV infection stimulates cytokines dramatically,

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including IL-10, and decreases T lymphocytes and their subsets CD4 + and CD8 + T cells after disease onset[10]. It has been previously revealed the effect of GCS on pulmonary oxygenation function in the treatment of SARS. Improvement of pulmonary function after GCS administration is significant in SARS cases, especially those with acute lung injury or acute respiratory distress syndrome (ARDS) and reduced oxygenation index before treatment[11]. However, COVID-19 is an acute infectious disease caused by the novel coronavirus, which spreads through respiratory droplets and contact transmission. Clinical manifestations include non-specific clinical features such as persistent fever, headache, muscle soreness, and decreased white blood cell count[12]. In extreme situations, patients develop ARDS that causes progressive respiratory failure requiring mechanical ventilatory support[13]. Current studies[14,15] have shown that the levels of IL-2R, IL-6, and other cytokines are higher in severe cases. Thus, the etiology, epidemiology, clinical characteristics, and pathogenesis have certain similarities among these coronaviruses. Therefore, COVID-19 treatment could apply GCS based on severe SARS management.

GCS constitute the most important group of regulatory hormones for stress response in the body, and the most widely used and effective anti-inflammatory and immunosuppressive agents in clinical settings. Therefore, they are frequently used in emergency or critical situations of new infectious diseases, which remains controversial[16]. According to the Pneumonia Diagnosis and Treatment Program for New Coronavirus Infection (Trial 5th Edition Revision) issued by the National Health Commission, GCS use is recommended for a short period (3-5 days) based on the degree of dyspnea and progress of chest imaging findings[17]. Considering the possibility of positive immunosuppressive effects of larger-dose GCS on virus clearance, the dose should not exceed 1-2 mg/kg/day of methylprednisolone. However, under actual clinical conditions, the dose and course of GCS greatly vary based on disease progression. The aim of the current study was to assess the effect of GCS in COVID-19 cases, analyzing treatment course and dose, to provide a reference for further clinical application.

Patients and Methods

Patients

Patients diagnosed with severe and critical COVID-19 treated with GCS were enrolled in Wuhan Pulmonary Hospital from January 7, 2020 to February 10, 2020. Inclusion criteria were: (1) Age ≥ 18 years; (2) positive novel coronavirus nucleic acid detected by real-time fluorescence PCR in pharyngeal swab and nasopharyngeal secretions; (3) compliance with the definition of severe and critical classification in Pneumonia Diagnosis and Treatment Program for New Coronavirus Infection (Trial Fifth Revision) issued by the Chinese National Health Commission[17]; (4) administration of GCS therapy based on the diagnosis and treatment plan. Exclusion criteria were: (1) recent or current participation in other clinical trials of new coronavirus drugs; (2) non-underlying causes of death by COVID-19. The study was approved by the Ethics Committee of Wuhan Pulmonary Hospital, and informed consent was obtained from all the study participants [No. 202 (0), 5].

Clinical classification criteria were as follows. Severe cases met at least one of the following criteria: (1) respiratory distress, and respiratory rate ≥30 times/min; (2) hypoxemia, referring to oxygen saturation ≤ 93% at rest; (3) arterial partial pressure of oxygen (PaO_2)/oxygen uptake concentration (FiO_2) ≤ 300 mmHg (1 mmHg = 0.133 kPa).

Critical cases met at least one of the following conditions: (1) respiratory failure requiring mechanical ventilation; (2) shock; (3) combined with other organ failure requiring ICU monitoring and treatment.

Interventions

Patients under the treatment mode of GCS therapy were administered methylprednisolone no more than 1-2 mg kg-1 d-1 for anti-inflammation, and the dose was gradually reduced until discontinuation after improvement.

The indications were: adults (defined as age ≥18 years); novel coronavirus infection confirmed by PCR or serum antibodies; symptoms (including fever, cough, or other related infectious symptoms) occurring within 10 days, with imaging confirmation of rapid progression of pneumonia; oxygen saturation SPO_2 ≤ 93%, shortness of breath (respiratory rate ≥ 30 times/min) or oxygenation index ≤ 300 mmHg[18].

All patients received antiviral, antibiotic, and symptomatic supportive treatments. Lopinavir/ritonavir antiviral therapy was co-administered with all antiviral therapies (200 mg/50 mg/capsule for adults, 2 capsules twice daily for no more than 10 days), referring to the Fifth Edition[19]. Antibiotic treatment might be considered for patients with COVID-19 and bacterial infection. According to

the guidelines for the diagnosis and treatment of community-acquired pneumonia in adults of China (2016 edition), β lactam + macrolide or fluoroquinolone antibiotics alone was selected for 7-10 days of treatment[18].

Data Collection and Definitions

General information, comorbidities, medication history and laboratory, imaging examination, disease outcome, the time of nucleic acid test turning negative, and the initial time of improved pulmonary imaging were collected until final discharge or death. Discharge followed the three conditions: (1) normal body temperature maintained for more than 3 days and significantly improved respiratory symptoms; (2) lung imaging showing significant absorption of inflammation; (3) two consecutive negative respiratory pathogenic nucleic acid tests (sampling interval of at least 1 day).

Time of nucleic acid test turning negative (in at least two consecutive respiratory pathogenic nucleic acid tests with at least 1d interval) was the time of first negative test minus that of first positive test; non-negative test or a non-reexamined case was defined as unable to evaluate[17].

For defining the initial time of improved pulmonary imaging, routine high-resolution computed tomography (HRCT) was performed on the lungs every 3-5 days. Bedsides, chest X-ray was conducted on critical care patients every day. Reduction in the lesion scope and decreased lesion density on images reflected absorption improvement. The time from disease onset to the first disappearance of pulmonary lesions on chest CT was defined as the initial time of improved pulmonary imaging; cases with no improvement or not reexamined were defined as unable to evaluate.

GCS dosage form was converted to the methylprednisolone (methylprednisolone) dose, in the equivalent dose conversion formula of 4 mg methylprednisolone = 5 mg prednisone = 0.75 mg dexamethasone. Low corticosteroid dose was defined as equivalent to 25 mg/d methylprednisolone, medium-low corticosteroid dose was defined as 25-150 mg/d methylprednisolone or its equivalent, and high corticosteroid dose was defined as greater than 150 mg/d methylprednisolone or its equivalent[20].

Chest CT

The SOMATOM go. NOW16 Spiral CT scanner (Siemens, Germany) was used with scanning range from the apex to the bottom of the lung. The imaging parameters were as follows: reference care tube potential of 120 kV, reference care dose of 65 mAs, field of view (FOV) of 360 mm, and collimator width 1.25 mm. All CT scans were obtained without intravenous contrast material with the patient in the supine position during end-inspiration.

Statistical Analysis

Data were analyzed with the SPSS 25.0 statistical software (IBM, Armonk, NY, USA). Continuous variables were first tested for normality, and those with normal distribution were expressed as mean± standard deviation (Mean ± SD) and analyzed by independent samples *t*-test for between-group differences. Those with non-normal distribution were expressed as median (interquartile range, IQR) and analyzed by the Mann-Whitney U-test. Categorical variables were analyzed by the χ^2-test or Fisher exact test to obtain *p*-values. For continuous dependent variables not complying with normal distribution, log transformation was first performed. Then, variables with univariate analysis $p < 0.1$ and clinically significant parameters were included in the generalized linear model for analysis. $p < 0.05$ was considered statistically significant.

Results

General Information

A total of 66 severe and critical cases were enrolled in this study, including 51 severe (77.3%) and 15 critical (22.7%) cases, aged 62 ± 11 years. There were 34 males (51.5%) and 32 females (48.5%). Among these patients, 30 (45.5%) had hypertension.

Of the 66 patients, 61 (92.4%) had fever, 50 (75.8%) had dyspnea, 49 (74.2%) had dry cough, 42 (63.6%) had fatigue, 38 (57.6%) had anorexia, 65 (98.5%) had pulmonary lesions involving both lungs, and 10 (15.2%) had pleural effusion. Laboratory examination results indicated that 64 (97%) and 59 (89.4%) patients had decreased CD4+ and CD8+ T cell counts at admission, respectively. During hospitalization, 58 patients (87.9%) had abnormal liver function, 44 (66.7%) had abnormal coagulation function, 36 (54.5%) had hypoalbuminemia, 40 (60.6%) had hyponatremia, and 34 (51.5%) had hypokalemia. All 66 patients (100%) were treated with lopinavir/ritonavir antiviral therapy. In addition, 65 patients (98.5%) were treated with antibiotics, and 34 (51.5%) were administered immunoglobulins (Table I). Most

patients received GCS therapy on day 9 (7-12) of onset, with a median disease course of 10 (8-14) days. The average daily GCS dose was 41.5 (33.3-61.3) mg/d, with a cumulative dose of 400 (280-700) mg. Among the 66 patients, 58 (87.9%) had negative novel coronavirus nucleic acid test. The median time of nucleic acid test turning negative was 8.5 (6-12) days, and 8 patients could not be evaluated. Meanwhile, 56 patients (84.8%) showed improvement in pulmonary imaging. The median initial time of improved pulmonary imaging was 17 (13-21) days, and 10 cases could not be evaluated (Table II). Fifty-four patients survived eventually, and few cases died due to irreversible multiple organ failure even though nucleic acid test turned negative and CT showed partial improvement. Table I shows that disease severity, age, sex, combined heart disease, and laboratory parameters (anemia during hospitalization, thrombocytopenia, abnormal renal function, abnormal coagulation function, abnormal myocardial enzymes, and CD4+ and CD8+ T cell counts at admission) were risk factors ($p < 0.05$, Table I).

General Characteristics of the First Improvement in Lung Imaging and Novel Coronavirus Nucleic Acid Test Turning Negative

In this study, patients with negative nucleic acid test and improved pulmonary imaging were grouped to compare their clinical characteristics and to examine the effects of GCS therapy. Age, thrombocytopenia, decreased count of CD8+ T cells at admission, median grouping, and median total dose of GCS during the course of treatment from onset to initial use were significantly associated with the time of nucleic acid test turning negative ($p < 0.05$, Table II). In individuals with initial improvement of pulmonary imaging, median time (days) from onset to initial use of GCS, median duration of GCS use, median average daily dose, and median total dose had no significant effects on imaging manifestations ($p > 0.05$, Table II).

Effects of GCS Treatment Course and Dose on the Time of Nucleic Acid Test Turning Negative

According to baseline data in Table II, variables with $p < 0.1$ were included as independent risk factors in the generalized linear model. The results showed statistical significance for the duration of GCS therapy, combined thrombocytopenia, and the time of nucleic acid test turning negative. The time of nucleic acid test turning negative was shorter in cases with GCS therapy ≤ 10 days compared with the group with > 10 days. Patients without thrombocytopenia had a shorter duration of nucleic acid test turning negative than those with thrombocytopenia during hospitalization (Table III).

Effects of GCS Therapy Course and Dose on the First Time of Improved Pulmonary Imaging

Baseline data in Table II showed that the use of GCS had no statistically significant effect on the initial time of improved lung imaging. However, to avoid confounding factors, we included variables with $p < 0.1$ as potential independent risk factors in the generalized linear model. There were no statistical differences in GCS dose and course, or the initial time of improved pulmonary imaging ($p > 0.05$) (Table IV).

Discussion

Coronavirus disease 2019 (COVID-19) caused by 2019 novel coronavirus (2019-nCoV) is very infectious, resulting in widespread infection globally with elevated mortality[2,3]. Therapeutic strategies were developed based on the previous experience with SARCs disease[11]. This study aimed to examine the effect of GCS in the treatment of severe and critical COVID-19 for large scale application and effective cure. Among the 66 severe and critical COVID-19 cases, disease severity, age, concurrent heart disease, and laboratory tests of various factors (anemia, thrombocytopenia, renal dysfunction, abnormal coagulation function, abnormal myocardial enzymes, and CD4+ and CD8+ T cell count at admission) were assessed as potential risk factors for prognosis. Patients administered GCS therapy for less than 10 days had a shorter time of nucleic acid test turning negative. Individuals without thrombocytopenia had a shorter time of nucleic acid test turning negative than those with thrombocytopenia during hospitalization. The dosage level had no statistically significant difference during GCS therapy on the initial time of improved pulmonary imaging, indicating that it could be considered a reference to predict severity.

This study showed a correlation between sex and death, and the mortality rate of male patients was higher than that of females (data not shown). In a previous analysis of clinical characteristics of

Table I. General characteristics and times of nucleic acid test turning negative and improved lung imaging in 66 patients treated with GCS.

Variable	Total (n=66)
Variable	Total (n=66)
Age (years), mean ±SD	62±11
Sex (male), n%	34 (51.5)
Disease severity status	
Severe, n%	51 (77.3)
Critical, n%	15 (22.7)
Comorbidity, n%	
Hypertension	30 (45.5)
Heart disease	4 (6.1)
Diabetes mellitus	9 (13.6)
Chronic pulmonary disease	3 (4.5)
Malignant tumor	2 (3)
Signs and symptoms, n%	
Fever	61 (92.4)
Weakness	42 (63.6)
Anorexia	38 (57.6)
Myalgia	23 (34.8)
Dry cough	49 (74.2)
Expectoration	26 (39.4)
Hemoptysis	9 (13.6)
Breath with difficulty	50 (75.8)
Dizziness	11 (16.7)
Diarrhea	11 (16.7)
Nausea and vomiting	7 (10.6)
Chest CT features, n%	
Involving the lungs	65 (98.5)
Combined pleural effusion	10 (15.2)
Laboratory findings during hospitalization, n%	
Anemia	27 (40.9)
Thrombocytopenia	15 (22.7)
Abnormal liver function	58 (87.9)
Abnormal renal function	27 (40.9)
Hypoproteinemia	36 (54.5)
Coagulopathy	44 (66.7)
Abnormal myocardial enzyme	22 (33.3)
Hypokalemia	34 (51.5)
Hyponatremia	40 (60.6)
On admission	
CD4 reduction*, n%	64 (97)
CD8 reduction, n%	59 (89.4)
CD4+ T count, Median (IQR)	148.7 (77.7-213.8)
CD8+ T count, Median (IQR)	92.8 (54-124.6)
Therapy, n%	
Antibiotic therapy	65 (98.5)
Antiviral therapy	66 (100)
Immunoglobulin	34 (51.5)
Median time of hormone treatment course, D	10 (8-14)
Median (interquartile interval)	
Median daily dose of hormone, mg/d	
Median (interquartile interval)	41.5 (33.3-61.3)
Median total hormone dose, mg	400 (280-700)
Median (interquartile interval)	
Nucleic acid from positive to negative, n%	58 (87.9)
Nucleic acid negative time, d	
Median (interquartile interval)	8.5 (6-12)
Pulmonary imaging improved, n%	56 (84.8)
Initial time of improved pulmonary imaging, d	
Median (interquartile interval)	17 (13-21)
Death	12 (18.2)

Note: Normal ranges: CD4+ T cells, 410-1590 cells/µl; CD8+ T cells, 190-1140 cells/µl. *Fisher's exact test.

Table II. Characteristics of patients based on times of nucleic acid test turning negative and improved lung imaging. .

	Case (N%)	Time of novel coronavirus nucleic acid turning negative	Case (N%)	Time of improved lung imaging
		n=58		n=56
Variable (mean/median stratification)	n	p		p
Age (years)				
≤ 62	32	0.045	32	0.137
> 62	26		24	
Sex				
Male	29	0.761	27	0.046
Female	29		29	
Clinical typing				
Severe	51	0.176	51	0.604
Critical	7		5	
Comorbidity				
Hypertension	26	0.093	23	0.483
Cardiovascular disease	2	0.060	2	0.842
Diabetes mellitus	7	0.598	7	0.378
Malignant tumor	2	0.087	2	0.268
Laboratory index during hospitalization				
Anemia	23	1.000	20	0.304
Thrombocytopenia	10	0.014	9	0.342
Abnormal liver function	50	0.937	48	0.869
Abnormal renal function	21	0.295	19	0.815
Hypoproteinemia	30	0.149	28	0.271
Coagulopathy	39	0.630	37	0.876
Abnormal myocardial enzyme	16	0.594	14	0.835
Hypokalemia	29	0.749	29	0.250
Hyponatremia	36	0.244	36	0.700
On admission				
CD4 reduction	56	0.716	54	0.842
CD8 reduction	51	0.028	49	0.950
Therapy				
Antiviral	58	N	56	N
Antibiotic therapy	57	0.881	55	1.000
Immunoglobulin	26	0.215	24	0.690
Hormonotherapy	58	N	56	N
Time from onset to the day of initial use of hormone, d		0.357		0.469
≤ 9 days	29		29	
> 9 days	29		27	
Median time of hormone treatment course, d		0.000		0.100
≤ 10 days	29		28	
>10 days	29		28	
Median daily dose of hormone, mg/d		0.784		0.722
≤ 40 mg/d	31		31	
> 40 mg/d	27		25	
Median total hormone dose, mg		0.015		0.113
≤ 400 mg	31		31	
> 400 mg	27		25	
Median (interquartile interval)	17 (13-21)			
Death	12 (18.2)			

COVID-19 patients, the gender ratio varied, with more male patients than female cases[20]. Also, epidemiological findings across the globe indicated higher morbidity and mortality in males than females among COVID-19 patients[21]. Among SARS patients, males were also more severely affected by the disease than females[22]. Thus, it is speculated that the male gender may be one of the risk factors associated with COVID-19 death[21]. Female susceptibility is lower than males', possibly due to the protective effect of female X-chromosome and sex hormones[23]. Moreover, studies have

Table III. Influencing factors of time of nucleic acid test turning negative.

Parameter	B	95% Wald Confidence Interval			Hypothesis Test		
	Std. Error		Lower	Upper	Wald Chi-Square	df	Sig.
Age ≤ 62 years	0.089	1.0365	-1.942	2.121	0.007	1	0.931
Age > 62 years	0[a]	.	.	.	.	.	.
No combined with hypertension	-1.727	1.0362	-3.758	0.304	2.778	1	0.096
Combined with hypertension	0[a]	.	.	.	.	.	.
No combined with coronary heart disease	-1.720	2.7215	-7.054	3.614	0.399	1	0.527
Combined with coronary heart disease	0[a]	.	.	.	.	.	.
No combined with malignant tumor	-4.481	2.5170	-9.414	0.453	3.169	1	0.075
Combined with malignant tumor	0[a]	.	.	.	.	.	.
No thrombocytopenia during hospitalization	-3.560	1.3628	-6.231	-0.889	6.823	1	0.009
Thrombocytopenia during hospitalization	0[a]	.	.	.	.	.	.
No CD8 reduction on admission	-1.568	1.3814	-4.276	1.139	1.289	1	0.256
CD8 reduction on admission	0[a]	.	.	.	.	.	.
Hormone therapy ≤ 10 days group	-3.670	1.0659	-5.760	-1.581	11.857	1	0.001
Hormone therapy > 10 days group	0[a]	.	.	.	.	.	.
Total hormone dose ≤ 400 mg group	0.163	1.1042	-2.001	2.327	0.022	1	0.883
Total hormone dose > 400 mg group	0[a]	.	.	.	.	.	.
(Scale)	10.620	1.9721	7.380	15.282			

Table IV. IInfluencing factors of the time of first improvement of novel coronavirus disease on pulmonary imaging.

Parameter	B	Std. Error	95% Wald Confidence Interval		Hypothesis Test		
			Lower	Upper	Wald Chi-Square	df	Sig.
Age ≤ 62 years	-2.657	1.6536	-5.898	0.584	2.582	1	0.108
Age > 62 years	0a	.	.	.	.	.	.
Male	2.723	1.6365	-.485	5.930	2.768	1	0.096
Female	0a	.	.	.	.	.	.
Hormone therapy ≤ 10 days group	-1.728	2.0526	-5.751	2.295	0.709	1	0.400
Hormone therapy > 10 days group	0a	.	.	.	.	.	.
Total hormone dose ≤ 400 mg group	-1.386	2.0627	-5.429	2.656	0.452	1	0.501
Total hormone dose > 400 mg group	0a	.	.	.	.	.	.
(Scale)	36.780	6.9507	25.395	53.269			

[a]is reference.

indicated that a large part of this difference may be due to gender behavior (lifestyle), i.e., higher levels of smoking and drinking among men compared with women[21].

The possible mechanisms by which GCS affects the time of nucleic acid test turning negative include the following. On the one hand, GCS can effectively induce the production of anti-inflammatory factors, inhibit the secretion of pro-inflammatory factors, and suppress the recruitment and phagocytosis of monocytes, macrophages, and leukocytes to the inflammatory reaction site, thereby effectively inhibiting the "inflammatory storm"[24]. On the other hand, GCS can induce apoptosis of immune cells, especially DC and T lymphocytes, inhibit the immune response, and weaken the disease-resistant ability of the host[25]. In this study, CD4+ and CD8+ T cells in all 66 severe and critical patients showed low levels post-treatment, which may affect virus clearance. Statistical differences were also found in the course of GCS therapy, combined thrombocytopenia during hospitalization, and time of nucleic acid test turning negative. Individuals with GCS therapy ≤ 10 days had a shorter time of test turning negative than those with GCS therapy > 10 days. However, no statistically significant differences were observed in GCS dose and treatment

course, as well as the initial time of improved pulmonary imaging. The average daily dose of GCS was 41.5 (33.3-61.3) mg/d, with a cumulative dose of 400 (280-700) mg, i.e., the medium to a small dose of GCS therapy. Therefore, the course of GCS therapy within the range of low and medium dose (25-150 mg/d methylprednisolone) showed a positive impact on virus clearance in COVID-19 patients. When the course of GCS therapy exceeds 10 days, the time of nucleic acid test turning negative was prolonged. In addition, increasing the dose of GCS and prolonging GCS therapy had no impact on the initial time of improved pulmonary imaging and improved absorption of pulmonary lesions. Therefore, short-term and small-dose GCS should be administered as reported in other diseases, and its rational use is particularly important[26].

This investigation showed also that thrombocytopenia affects the time of nucleic acid test turning negative. Reports have currently suggested that coagulation/fibrinolysis system dysfunction plays a role in the pathogenicity and infectivity of the novel coronavirus. Iba et al[27] indicated that COVID-19 induces hypercoagulability with both microangiopathy and local thrombus formation, as well as a systemic coagulation defect leading to large vessel thrombosis and major thromboembolic complications in critically ill patients. It is believed that as the severity of COVID-19 increases, the activation and hyperactivity of the coagulation/fibrinolysis system is induced, the microthrombotic load increases, and platelets are massively consumed after aggregation, even with a bleeding tendency[28,29]. Therefore, the effect of thrombocytopenia on the time of nucleic acid test turning negative may be related to disease severity. However, there was no correlation between the clinical classification of the disease and the time of nucleic acid test turning negative. Considering that this study only retrospectively analyzed severe and critical cases, selection bias could not be avoided, and the sample size was small. Therefore, this conclusion needs to be further verified.

There were limitations in this study. This was a retrospective small-sample study that was affected by multiple confounding factors. Besides, statistical analysis performed on the times of nucleic acid test turning negative and improved pulmonary imaging were limited. Thus, no real-time monitoring was carried out during the current study. The reliability of the conclusion needs further verification by large sample randomized controlled trials. This study only included patients who used GCS therapy. Therefore, comparison with patients administered non-GCS or dual therapy was impossible. Finally, this study only included severe and critical cases belonging to a specific population.

Conclusions

Medium and low-dose GCS therapy affect virus clearance in COVID-19 patients. With a course exceeding 10 days, the time of nucleic acid test turning negative was prolonged. In this study, increasing the dose of GCS or prolonging the therapy did not shorten the times of improved pulmonary imaging and improved absorption of pulmonary lesions. Therefore, the rational use of GCS is particularly important.

Conflict of Interest Statement

The Authors declare that they have no conflict of interests.

Authors' Contributions

Xiong Leiqun conceived and designed the experiments, performed the experiments, analyzed and interpreted the data, and wrote the manuscript. Jin Wu conceived, designed, and performed the experiments. Hu Xiaomeng performed the experiments, collected the data, and analyzed and interpreted the data. Ren Tantan performed the experiments and collected the data. Cheng Changhao performed the experiments and collected the data. Mohammadreza Shaghaghi critically revised the manuscript. Farzaneh Ghazi Sherbaf critically revised the manuscript. Yu Yi and Yuan Lihua collected the data. Chen Jun contributed reagents, materials, analysis tools or data. Du Juan conceived and designed the experiments, supervised the experiments, and critically revised the manuscript.

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