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Short-term moderate-dose corticosteroid plus immunoglobulin effectively reverses COVID-19 patients who have failed low-dose therapy

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Abstract

Background: The coronavirus disease-19 (COVID-19) has spread globally with more than 80,000 people infected, and nearly 3000 patients died. Currently, we are in an urgent need for effective treatment strategy to control the clinical deterioration of COVID-19 patients.

Methods: The clinical data of 10 COVID-19 patients receiving short-term moderate-dose corticosteroid (160mg/d) plus immunoglobulin (20g/d) were studied in the North Yard of The First Hospital of Changsha, Hunan from January 17th to February 27th, 2020. Epidemiological, clinical, laboratory, radiological findings were analyzed.

Results: After treatment with combination of low-dose corticosteroid (40-80mg/d) and immunoglobulin (10g/d), patients' lymphocyte count (0.88±0.34 vs 0.59±0.18, P<0.05), oxygenation index including SPO_2 (94.90±2.51 vs 90.50±5.91, P<0.05) and PaO_2/FiO_2 (321.36±136.91 vs 129.30±64.97, P<0.05) were significantly lower than pre-treatment, and CT showed that the pulmonary lesion deteriorated in all patients. While after treatment of short-term moderate-dose corticosteroid plus immunoglobulin, patients' APACHE II score (9.10±6.15 vs 5.50±9.01, P<0.05), body temperature (37.59±1.16 vs 36.46±0.25, P<0.05), lymphocyte count (0.59±0.18 vs 1.36±0.51, P<0.05), Lactate dehydrogenase (419.24±251.31 vs 257.40±177.88, P<0.05), and C-reactive protein (49.94±26.21 vs 14.58±15.25, P<0.05) significantly improved compared with post-treatment with low-dose therapy. In addition, oxygenation index including SPO_2 (90.50±5.91 vs 97.50±1.18, P<0.05), PaO_2 (60.47±14.53 vs 99.07±34.31, P<0.05), and PaO_2/FiO_2 (129.30±64.97 vs 340.86±146.72, P<0.05) significant improved.

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Furthermore, CT showed that pulmonary lesions obviously improved in 7 patients. After systematic therapy, 4 out of 10 COVID-19 patients recovered and discharged.

Conclusions: Short-term moderate-dose corticosteroid plus immunoglobulin is effective for reversing the continued deterioration of COVID-19 patients who failed to respond to the low-dose therapy.

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Introduction

The coronavirus disease-19 (COVID-19) epidemic emerged from Wuhan at the end of December 2019. It spread to 56 countries and regions, infected more than 80,000 people and resulted in nearly 3,000 deaths, mostly from pneumonia.[1] At present, effective treatment options are limited consisting mostly of supportive care. Along with a growing number of confirmed cases around the world, we are in the urgent need for effective treatment strategy for COVID-19 patients before the specific antiviral medicines or vaccines emerge. The diagnosis and treatment of COVID-19 guideline (6th edition) by National Health Commission of China, has recommended low-dose corticosteroid (methylprednisolone 1-2mg/kg/d) for 2019-nCoV treatment.[2] According to our experience, a small number of patients with COVID-19 still have a continued deterioration after receiving a combination of low-dose corticosteroid and immunoglobulin. In this article, we share in detail the experience of 10 patients who did not respond to the combination of low-dose corticosteroid and immunoglobulin. Through timely short-term moderate-dose corticosteroid plus immunoglobulin, good clinical outcomes were achieved.

Methods

Participants

The North Yard of The First Hospital of Changsha (Changsha Public Health Center) is the referral center for the COVID-2019 patients in Changsha, Hunan Province. Between January 17th and February 27th 2020, 10 COVID-19 patients receiving short-

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term moderate-dose corticosteroid (160mg/d) plus immunoglobulin (20g/d) were enrolled in this study. Throat swab specimens were collected from all patients at admission and confirmed the diagnosis of COVID-19. This study was approved by the First Hospital of Changsha Ethics Committee. Before the survey, participants were asked to sign an informed consent to identify their willingness to take part in this study, and to ensure their rights of voluntary participation and privacy.

Procedures

The epidemiological, clinical, laboratory, radiographic (chest X-ray or pulmonary computed tomography, CT) and Acute Physiology Chronic Health Evaluation II (APACHE II) scores were collected for all patients (Table 1). The laboratory variables included blood routine, renal and liver function, myocardial enzymes, C-reactive protein (CRP), and blood gas analysis. Pre- and post-treatment pulmonary CT were compared. Pulmonary radiographic abnormalities were classified as improved, stable or deteriorating: 1. Improved: pulmonary lesions reduced by more than 25%; 2. Stable: pulmonary lesions reduced or increased by less than 25%; 3. Deteriorating: pulmonary lesions increased by more than 25%.

Treatment protocol

During hospitalization, a systematic treatment protocol was carried out, including oxygen therapy (low-flow nasal cannula, high-flow nasal cannula, non-invasive mechanical ventilation, and invasive mechanical ventilation), antiviral treatment, antibiotic treatment, extracorporeal membrane oxygenation (ECMO), continuous renal replacement therapy (CRRT), combination of low-dose corticosteroid (40-80mg/d) and

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immunoglobulin (10g/d), and short-term moderate-dose corticosteroid (160mg/d) plus immunoglobulin (20g/d).

Evaluation of therapeutic effect

Indices including vital signs, laboratory markers, pulmonary CT, as well as the APACHE II score were adopted to evaluate the therapeutic effect. According to the guideline from National Health Council of China, discharge and release from quarantine criteria should meet all the following requisitions: 1. afebrile for more than 3 days; 2. respiratory symptoms significantly relieved; 3. abnormal imaging findings substantially improved; 4. negative COVID-19 nucleic acid test for two consecutive respiratory pathogens (sampling interval $\geqslant$1 day).[2]

Statistical analysis

SPSS16.0 software was adopted for statistical analysis. $P < 0.05$ was considered statistically significant. Numeration data were described by number (%), and measurement data were described by mean ± standard deviation. The paired sample t test was used to evaluate the changes of clinical indexes before and after the combination of low-dose corticosteroid and immunoglobulin therapy, as well as the differences between the post-treatment with combination of moderate-dose corticosteroid and immunoglobulin and the post-treatment with low-dose therapy.

Results

A total of 10 COVID-19 patients who received a short-term moderate-dose corticosteroid plus immunoglobulin were enrolled in this study. Among them, 8 were

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male (80%), 2 were female (20%), with no medical staff. The age ranged from 29 to 68 year-old, with an average age of 51.60 ± 15.46 year-old. The course of disease lasted from 2 to 30 days, with an average course of 5.40 ± 4.55 days. Clinical manifestations were diverse, and the most common symptom was fever (9 cases, 90%), followed by dry cough (6 cases, 60%). Among these 10 patients, the proportion of patients with comorbidity reached 40%. Most patients had a definite epidemiological history, of which 4 patients (40%) exposed to Wuhan, and 6 patients (60%) exposed to Wuhan citizen. Detailed demographic and clinical characteristics of patients are shown in Table 1.

A total of 10 (100%) patients received oxygen therapy, including 1 case of invasive mechanical ventilation. All 10 (100%) COVID-19 patients received antiviral drugs, and most patients received bigeminy. Lopinavir and ritonavir tablets was given to 8 (80%) patients, interferon to 6 (60%) patients, and Arbidol to 3 (30%) patients. Nine (90%) patients received antibacterial treatment. The common drugs were moxifloxacin and levofloxacin (Table 1). All patients had received a combination of low-dose corticosteroid and immunoglobulin before a short-term moderate-dose corticosteroid plus immunoglobulin was performed. The most common complications were acute liver dysfunction (8 cases, 80%) and acute renal dysfunction (7 cases, 70%) (Table 3).

As shown in Table 2 and Table 3, our results showed that after treatment with combination of low-dose corticosteroid and immunoglobulin, the patients' lymphocyte count (0.88±0.34 vs 0.59±0.18, $P<0.05$), albumin (35.59±4.90 vs 30.27±4.19, $P<0.05$), oxygenation index including PaO_2/FiO_2 (94.90±2.51 vs 90.50±5.91, $P<0.05$) and SPO_2

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(94.90±2.51 vs 90.50±5.91, P<0.05) significantly decreased compared with pre-treatment, and the pulmonary CT showed a worsening trend, indicating that these 10 patients still suffered from continued deterioration after receiving a combination of low-dose corticosteroid and immunoglobulin. According to our experience, for patients receiving methylprednisolone 80mg/d combined with immunoglobulin 10g/d, if their condition continued to deteriorate, including a significant decrease in PaO_2/FiO_2, a obvious deterioration in pulmonary CT and / or a decrease in lymph count, a continuous high fever, the dose of methylprednisolone and immunoglobulin were increased to 160mg/d and 20g/d, respectively. It was exciting to find that the majority of patients gradually recovered, without tracheal intubation and invasive mechanical ventilation. After short-term moderate-dose corticosteroid plus immunoglobulin treatment, all patients achieved significant improvement in terms of vital signs, blood work, and the APACHE II scores. In detail, compared with post-treatment of low-dose corticosteroid plus immunoglobulin, patients' body temperature (37.59±1.16 vs 36.46±0.25, P<0.05) and heart rate (102.90±17.58 vs 86.40±15.59, P<0.05) significantly decreased. Meanwhile, the lymphocyte count (0.59±0.18 vs 1.36±0.51, P<0.05) significantly increased. Respecting to blood biochemistry, the albumin (30.27±4.19 vs 34.84±5.69, p<0.05) and lactate dehydrogenase (419.24±251.31 vs 257.40±177.88, P<0.05) was obviously improved. Besides, the C-reactive protein (49.94±26.21 vs 14.58±15.25, P<0.05) significantly decreased. Moreover, oxygenation index including SPO2 (90.50±5.91 vs 97.50±1.18, P<0.05), PaO2 (60.47±14.53 vs 99.07±34.31, P<0.05), and PaO_2/FiO_2 (129.30±64.97 vs 340.86±146.72, P<0.05) showed significant improvement.

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In addition, the APACHE II score (9.10±6.15 vs 5.50±9.01, P<0.05) was obviously reduced. Furthermore, CT showed that pulmonary lesions of obviously improved in 7 patients. These discoveries demonstrated that short-term moderate-dose corticosteroid plus immunoglobulin might effectively reverse COVID-19 patients who did not respond to low-dose therapy. For patients who received a moderate-dose corticosteroid (160mg/d), attention should be paid to reduce the dose of corticosteroid should be reduced in time, that is, methylprednisolone 160mg/d for 2-3 days, and gradually reduce to 80mg/d for 1-2 days when the PaO_2/FiO_2 increased, followed by the maintenance dose of 40mg/d. Gradual reduction of the corticosteroid can effectively reduce the probability of secondary infection as well as to avoid disease rebound.

A typical pulmonary CT series of a patients was displayed in Figure 1. Trendgraph of important clinical variables was also shown in Figure 2. After systematic treatment, 4 out of 10 patients recovered and discharged. Only 1 death occurred in our study, and the cause of death probably was cardiac failure secondary to acute myocardial injury (Table 3).

Discussion

Following the release of the sixth edition treatment guideline for COVID-19 by National Health Commission of China, the systematic corticosteroids treatment was recommended as adjuvant therapy, and around 18-44.9% infected patients received this therapy.[3,4] It raises a hot debate about whether patients could benefit from this therapy, as well as the timing and dosage of corticosteroid. Based on our previous study, we

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observed that a reverse of deterioration in 80% of seriously ill COVID-19 patients, defined by National Health Commission of China guideline, after a low-dose (80mg/d) corticosteroid treatment in combined with immunoglobulin (data not shown, manuscript submitted).[2] In this study, we focused on the other 20% of patients who failed to control the progression after initial low-dose therapy. We proposed that a moderate-dose corticosteroid (160mg/d) for short-term in combined with immunoglobulin for these patients. Our results showed that this therapy could effectively reverse the disease progression in 90% (9/10) patients with worsened condition. The key indicators improved after treatment also has been identified through retrospectively analyzing the clinical data.

Corticosteroid is a double-edged sword in the treatment of viral pneumonias, which plays advantages only when administrated properly and precisely. Conventionally, the corticosteroid was the last life-saver choice, which was only recommended in the fatal-stage of pneumonia. In controlling such critical inflammation storm, we have no choice but to use high-dose corticosteroid. Through previous lessons in combating pneumonias including SARS, MERS and H1N1, high dose of corticosteroid administration was identified with no benefit in reducing mortality rate, but a higher risk of side-effects including immunosuppression and opportunistic infections.[5-7] Some scholars suggested a low or moderate dose therapy but late until the phase of ARDS.[8] However, it is hard to imagine that suppression of furious inflammatory storm could be achieved with low dose corticosteroid. In this study, we advanced our therapy with a novel opinion, namely, to earlier our corticosteroid

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treatment time window. Low-dose corticosteroid therapy should be under consideration when clinical data indicates the progression of COVID-19.

First, the relatively mild inflammatory response in the early stage of COVID-19 pneumonia allows low dose of corticosteroid to control the progression of inflammation effectively. Studies with low or moderate dosage therapy showed no significant impact in mortality rate for H7N9 cases, and low dose even benefits the mortality rate in severe H1N1-illness, which supports the safety of low-to-moderate corticosteroid in viral pneumonia.[9,10] In addition, we strongly recommend a combined use of immunoglobulin with corticosteroid, which could strengthen patients' immune response to avoid excessive viral spreading and win us a relative safer and longer timeframe for corticosteroid therapy. And the combination use of immunoglobulin and corticosteroid in SARS treatment revealed better hazard ratio of mortality of 0.41 in comparison with cases with only corticosteroid.[11] Thus, our initial low-dose treatment is administrated for 7-14 days, longer than the time recommended in the official guideline.[2] During the treatment, the administration dose is adjusted according to the alleviation or progression of disease. Among the total COVID-19 patients admitted in our center, around 80% of the seriously ill cases had significantly improved after initial early low-dose of corticosteroid plus immunoglobulin (unpublished), an exciting data that have not been reported in any other center.

On the other hand, around 20% of patients continue progressing to more serious condition after initial low-dose therapy. For those patients, we choose a short-term moderate corticosteroid therapy plus immunoglobulin. The moderate dose was

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sufficient to perform well in controlling inflammatory response before entering more worsened condition including ARDS. We also doubled the dose of immunoglobulin to compensate for the possible immune suppression from moderate therapy. Meanwhile, we kept close attention to clinical indicators during the treatment. When improvements in crucial indicators were witnessed, the dose would be adjusted to initial dose immediately, which could maximize the effectiveness of controlling excessive inflammation response and minimize the possible side effect from moderate dose. Zhou et al. first explored the possible of moderate-dose corticosteroid (median hydrocortisone- equivalent dose of 400.0 mg/d, an average of 9.5 d) in ICU patients with COVID-19 infection. They observed the ICU mortality rate up to 46.7% (7/15), indicating the corticosteroids might not improve ICU mortality for critical ill patients.[8] For the different results in effectiveness between our and Zhou's study, it is reasonable for us to doubt that the delayed timing of administration, namely the possible delay in low-dose therapy, and a lack of immunoglobulin for protecting immune function might covered the benefits of this therapy in some cases.

Another key issue is how to judge the progression in illness condition for COVID-19, subsequently administrate corticosteroid at an earlier stage. The recommended guideline demonstrated the importance of lowered oxygenation saturation, progresses in chest radiography, and laboratory abnormalities reflecting furious inflammatory response in determining the use of low-dose corticosteroids. With cases in our center, we comprehensively considered the clinical indicators mentioned above for initial use and dose adjustment. By analyzing the changes before and after our treatment strategy

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for these ten patients, we highlighted the value of oxygenation index reduction, lung lesion progression in CT scan, and lymphopenia. Consistent with our findings, these indicators also showed strong correlation with disease progression in COVID-19 and SARS.[4,11,12]

The limitation of our study also needs to be addressed. First, a retrospective study instead of randomized controlled trail performed due to ethical considerations, which lowers the level of evidence. Besides, the study was limited by small sample size, with only ten confirmed COVID-19 patients in our center, with a failure of achieving improvement after initial low-dose corticosteroid therapy plus immunoglobulin. Finally, the clinical data was collected from Jan 17th to Feb 27th, which still requires long-term follow-up for the clinical outcome for all patients.

In conclusion, the short-term moderate-dose corticosteroid in combined with immunoglobulin could take good control of inflammation response, stabilize the immune function, and minimize the side-effect from corticosteroid. Our treatment strategy effectively reversed the progression for those serious COVID-19 patients, which draws our attention to reevaluate the value of low to moderate dose corticosteroid therapy in viral pneumonia. In our battle against COVID-19 outbreak, an offensive rather than defensive position in corticosteroid therapy might buy us time before specific antiviral medicines and vaccines emerge.

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Figure legends

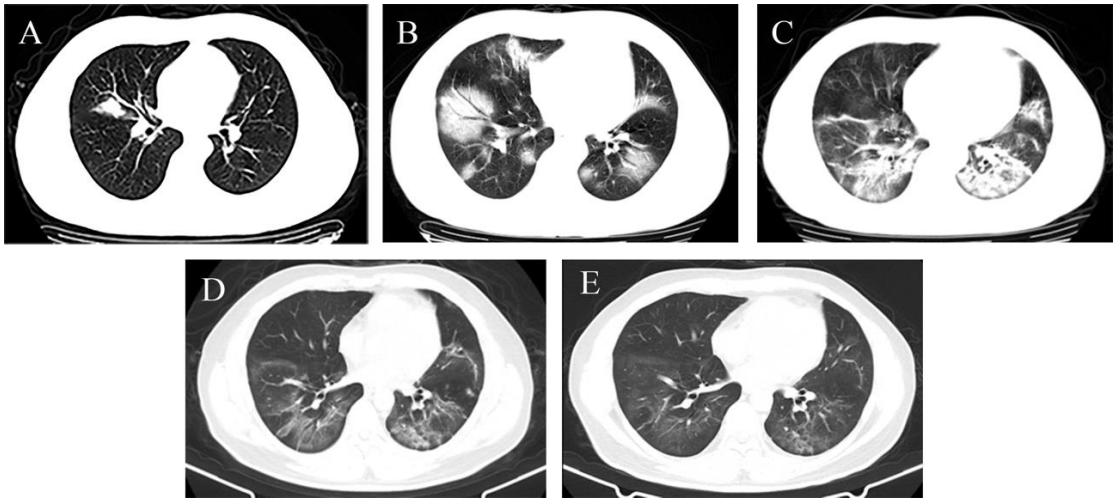

Figure 1: A dynamic series of pulmonary CT imaging manifestation of a COVID-19 patient. The typical manifestation of COVID-19 patients was bilateral multiple patchy, ground glass and infiltrating shadows. (A) Pulmonary CT image on admission; (B) Pulmonary CT images after the treatment of low-dose corticosteroid plus immunoglobulin on day 9 after onset; (C-E) Pulmonary CT images after the treatment of short-term moderate-dose corticosteroid plus immunoglobulin on day 16, 22, 30 after onset, respectively.

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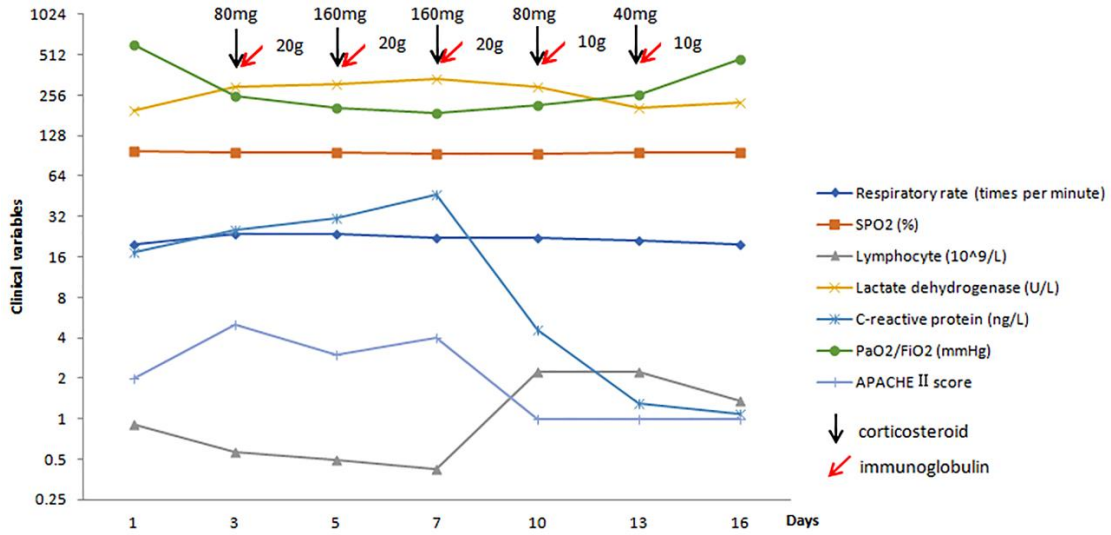

Figure 2: Trendgraph of important clinical variables of a COVID-19 patient respecting to the low-dose and moderate-dose corticosteroid plus immunoglobulin.

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Table 1 Demographic and clinical characteristics of 10 COVID-19 patients receiving short-term moderate-dose corticosteroid plus immunoglobulin

Characteristics	Patients (n=10)
Age (range)	51.60±15.46 year-old (29~68)
Gender	
Male	8 (80%)
Female	2 (20%)
Days between onset and hospital admission (range)	5.40±4.55 days (2~15)
Medical staff	0 (0%)
Positive result of 2019-nCoV nucleic acid	10 (100%)
Comorbidities	4 (40%)
Hypertension	3 (30%)
Coronary heart disease	1 (10%)
Symptoms	
Fever	9 (90%)
Dry cough	6 (60%)
Expectoration	4 (40%)
Dyspnea	6 (60%)
Fatigue	1 (10%)
Nause and vomiting	1 (10%)
Dizziness	1 (10%)
Headache	3 (30%)
Pharyngalgia	2 (20%)
Diarrhea	3 (30%)
Anorexia	3 (30%)
Chest distress	1 (10%)
Epidemiology	
Wuhan exposure	4 (40%)
Wuhan citizen exposure	6 (60%)
Cluster onset	3 (30%)
Treatments	
Oxygen therapy	10 (100%)
Low-flow nasal cannula	1 (10%)
High-flow nasal cannula	6 (60%)
Non-invasive mechanical ventilation	3 (30%)
Invasive mechanical ventilation	1 (10%)
Etiology treatment	
Antiviral treatment	10 (100%)
Antibiotic treatment	9 (90%)
Combination of low-dose glucocorticoid and immunoglobulin	10 (100%)
Combination of moderate-dose glucocorticoid and immunoglobulin	10 (100%)
Continuous renal replacement therapy	1 (10%)
Extracorporeal membrane oxygenation	0 (0%)

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Table 2 Comparisons between clinical variables in 10 COVID-19 patients respecting to the low-dose and moderate-dose corticosteroid plus immunoglobulin

Variables	Pre-treatment of low-dose corticosteroid plus immunoglublin	Post-treatment of low-dose corticosteroid plus immunoglublin	Post-treatment of short-term moderate-dose corticosteroid plus immunoglublin	P*#	P*&
Physical signs					
Temperature (℃)	38.11±0.71	37.59±1.16	36.46±0.25	0.159	0.011
Respiratory rate (times per minute)	20.90±2.88	24.5±7.55	19.60±0.67	0.166	0.112
Heart rate (times per minute)	99.90±17.51	102.90±17.58	86.40±15.59	0.714	0.014
SPO_2 (%)	94.90±2.51	90.50±5.91	97.50±1.18	0.039	0.002
Laboratory variables (normal range)					
Blood Routine					
Lymphocyte (10^9/L, 0.8-4.0)	0.88±0.34	0.59±0.18	1.36±0.51	0.021	0.001
Blood biochemistry					
Albumin (g/L, 35.0-55.0)	35.59±4.90	30.27±4.19	34.84±5.69	0.026	0.018
Alanine aminotransferase (U/L, 0.0-40.0)	22.69±10.49	34.27±18.66	73.80±76.13	0.072	0.120
Aspartate aminotransferase (U/L, 0.0-37.0)	34.60±12.16	51.60±37.06	63.99±84.91	0.235	0.516
Total bilirubin (umol/L, 3.4-20.5)	12.07±5.09	13.88±6.21	10.37±3.94	0.366	0.204
Creatinine (umol/L, 22.0-133.0)	58.15±16.50	61.14±26.84	82.80±92.53	0.665	0.350
Blood urea nitrogen (mmol/L, 2.8-8.2)	4.56±1.55	6.83±2.13	8.26±9.28	0.010	0.620
Creatine kinase (U/L, 10.0-190.0)	252.33±308.28	317.12±483.97	56.31±52.73	0.513	0.110
Creatine kinase-MB (U/L, <24)	17.37±16.43	17.80±22.09	14.27±15.06	0.961	0.187
Lactate dehydrogenase (U/L, 80.0-245.0)	263.22±171.17	419.24±251.31	257.40±177.88	0.140	0.001
Infection-related biomaker					
C-reactive protein (ng/L, 0.0-8.0)	41.55±28.78	49.94±26.21	14.58±15.25	0.595	0.002
Blood gas analysis					
PaO_2 (mmHg, 80.0-100.0)	95.92±46.79	60.47±14.53	99.07±34.31	0.054	0.008
$PaCO_2$ (mmHg, 35.0-45.0)	34.77±4.37	34.24±2.96	38.91±4.38	0.757	0.056
PaO_2/ FiO_2 (mmHg)	321.36±136.91	129.30±64.97	340.86±146.72	0.001	0.002
APACHE II score	5.00±3.59	9.10±6.15	5.50±9.01	0.072	0.014

*P<0.05

#Comparison between pre-treatment and post-treatment of low-dose corticosteroid plus immunoglobulin

&Comparison between post-treatment of low-dose and short-term moderate-dose corticosteroid plus immunoglobulin

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Table 3 Clinical outcomes of 10 COVID-19 patients receiving short-term moderate-dose corticosteroid plus immunoglobulin

	Number (percentage)
Tendency of pulmonary radiograph abnormalities	
Improving	7 (70%)
Stable	2 (20%)
Deteriorating	1 (10%)
Complications	
Acute liver dysfunction[#]	8 (80%)
Acute renal dysfunction[*]	6 (60%)
Secondary pulmonary infection	4 (40%)
Acute myocardial injury[$]	2 (20%)
Shock	1 (10%)
Acute respiratory distress syndrome	1 (10%)
Multiple organ dysfunction syndrome	1 (10%)
Prognosis	
Hospitalization	5 (50%)
Discharge	4 (40%)
Death	1 (10%)

[#]ALT increased by ≥ 100% or development of jaundice.

[*]Elevated BUN or creatinine above the normal upper limits.

[$]Creatine kinase-MB activity increased by ≥ 100%.