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. 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 COVID-19 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. A total of 10 COVID-19 patients receiving short-term moderate-dose

corticosteroid (160mg/d) plus immunoglobulin (20g/d) between January 17th and February 27th 2020 were enrolled in this study. Collection of throat swab specimens were performed on 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, Acute Physiology Chronic Health Evaluation II (APACHE II), and radiographic manifestation (chest X-ray or pulmonary computed tomography, CT) were collected for all patients (Table 1). The laboratory variables consisted of blood routine, renal and liver function, myocardial enzymes, C-reactive protein (CRP), and blood gas analysis. Dynamically pulmonary CT evaluations were also conducted. Pulmonary CT were classified as deteriorating, stable or improved: 1. Deteriorating: pulmonary lesions increased by more than 25%; 2. Stable: pulmonary lesions reduced or increased by less than 25%; 3. Improved: pulmonary lesions reduced by more than 25%.

Treatment protocol

A systematic treatment protocol was conducted on COVID-19 inpatients, including respiratory support (low-flow nasal cannula, high-flow nasal cannula, non-invasive mechanical ventilation, and invasive mechanical ventilation), antibiotic treatment, antiviral treatment, extracorporeal membrane oxygenation (ECMO),

continuous renal replacement therapy (CRRT), moderate-dose corticosteroid (160mg/d) plus immunoglobulin (20g/d), and low-dose corticosteroid (40-80mg/d) plus immunoglobulin (10g/d).

Evaluation of therapeutic effect

Indices including vital signs, laboratory markers, APACHE II score, as well as pulmonary CT 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. with normal body temperature for more than 3 days; 2. with significantly recovered respiratory symptoms; 3. with obvious absorption and recovery of acute exudative lesion in lung CT imaging; 4. with negative result of 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 investigated. Among them, 8 were 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 duration of disease lasted from 2 to 30 days, with an average duration 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 percentage 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 were treated with antiviral drugs, and most patients were treated with 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 were treated with antibiotics. The common antibiotics were moxifloxacin and levofloxacin (Table 1). All patients had been treated with 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 (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 lymphocyte 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. 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 patient's dynamic pulmonary CT series 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, probably resulting from cardiac failure secondary to acute myocardial injury (Table 3).

Discussion

As an emerging and deadly infectious respiratory disease, COVID-19 treatment has attracted the attention of many medical professionals. At present, there is no consensus on the treatment strategy for the disease, and no effective drug for the disease exists, although various anti-viral treatments are used. Based on our previous study, we observed that a reverse of deterioration in 75% of severe COVID-19 cases, defined by National Health Commission of China guideline, after a low-dose (40-80mg/d) corticosteroid treatment in combined with immunoglobulin (data not shown, manuscript submitted).[2] In this study, we focused on the other 25% 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. The $PaCO_2/FiO_2$ was regarded as the most important index for monitoring the patient's condition in our study. Previous research has also confirmed that this ratio was closely related to the severity of illness and prognosis.[3] Meanwhile, lymphocytopenia was an prominent laboratory indicator of COVID-19, and progressive decrease of lymphocyte count also reflected the deterioration of the patient's condition.[3] In our study, the PaO_2/FiO_2 and lymphocyte count still decreased progressively after treatment with low-dose corticosteroid plus immunoglobulin, whereas after short-term moderate-dose corticosteroid plus

immunoglobulin, these 2 index improved significantly. The lung is the target organ of COVID-19, and pulmonary CT plays an essential role in the early diagnosis and therapeutic effect assessment of COVID-19.[4] In our study, all patients experienced progressive deterioration of pulmonary CT after low-dose corticosteroid plus immunoglobulin, while significant improvement occurred in 7 patients after short-term moderate-dose corticosteroid plus immunoglobulin. All these discoveries indicate that 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.

The use of high-dose corticosteroids (500mg/d) therapy has been controversial in the treatment of acute respiratory distress syndrome (ARDS). Due to its side effects, especially the delayed virus clearance and ischemic necrosis of the femoral head,[5] it was not recommended in this epidemic. However, the recently published autopsy of the first COVID-19 victim showed pulmonary edema and hyaline membrane formation in the lungs, indicating ARDS, suggesting that timely intervention with corticosteroids may alleviate the inflammatory response.[6] To balance the side effects of high-dose corticosteroid and the necessity of corticosteroid therapy for COVID-19, short-term moderate-dose corticosteroid was adopted in our study, achieving satisfactory outcomes.

The time-window and dosage of corticosteroid administrated determine whether it plays advantage or disadvantage in the treatment of viral pneumonias, especially for those under severe condition. Previously, we raised our positive attitude towards

low-dose corticosteroid treatment in COVID-19 at early deterioration stage, due to a timely effect on suppression of inflammation response. More importantly, the combination use of immunoglobulin could strengthen patients' immune function to prevent possible viral clearance delay caused by corticosteroid. The combination of corticosteroids and immunoglobulin has been preliminarily shown to reduce the risk of death in 12 patients with SARS.[7] This therapy achieved quite satisfying result in controlling the progression for most COVID-19 severe cases in our center.

However, 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 sufficient to perform well in controlling overwhelming inflammatory response before entering more worsened condition including ARDS. The dose of immunoglobulin was also doubled 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 corticosteroid 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 index, progresses in chest radiography, and laboratory abnormalities reflecting furious inflammatory response in determining the use of low-dose corticosteroid. 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 for these ten patients, we highlighted the value of PaO_2/FiO_2 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.[7, 9, 10]

We acknowledge several limitations of our study. 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 summary, our findings suggest that the short-term moderate-dose

corticosteroid in combined with immunoglobulin could effectively reversed the progression for those severe COVID-19 patients who failed in the initial low-dose therapy. Although currently there are little literature evidence to back up our therapy, we call for a more positive attitude towards corticosteroid therapy in the our fight against COVID-19, which might help in reducing the proportion of severe cases and mortality.

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Figure legends

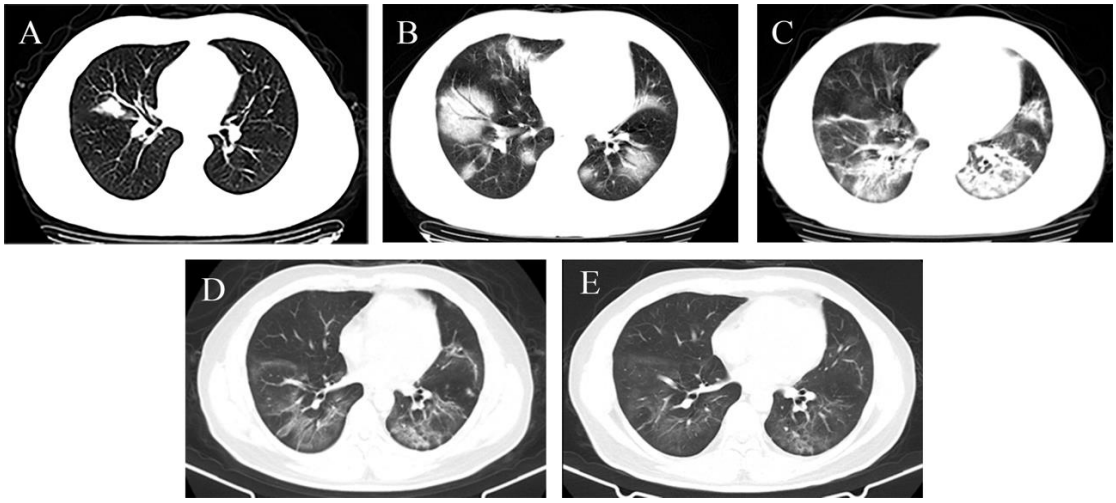

Figure 1: A dynamic series of pulmonary CT imaging manifestation of a COVID-19 patient. The typical manifestation of COVID-19 patients was bilateral multiple patchy, ground glass and infiltrating shadows. (A) Pulmonary CT image on admission; (B) Pulmonary CT images after the treatment of low-dose corticosteroid 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.

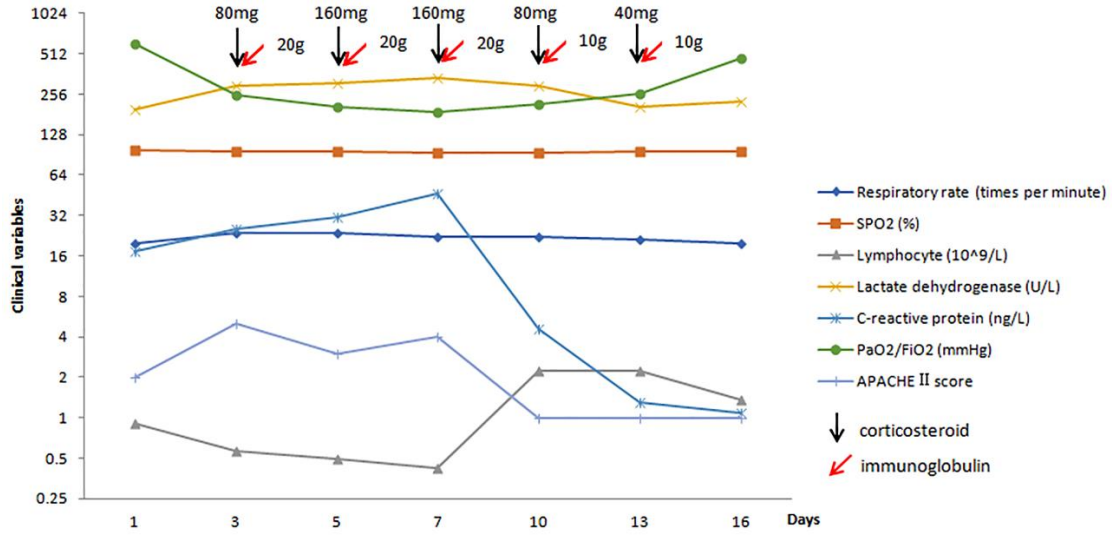

Figure 2: Trendgraph of important clinical variables of a COVID-19 patient respecting to the low-dose and moderate-dose corticosteroid plus immunoglobulin.

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%)

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

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%.