The Effect of Corticosteroids on Severe Patients of COVID-19: A retrospective study

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Research

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Abstract

Background

The effect of corticosteroids on COVID-19 remains controversial. This study aims to clarify the potential roles of corticosteroids in severe COVID-19 patients.

Methods

In the current retrospective single-center study, we collected data of 214 severe patients with confirmed COVID-19 in Wuhan Union Hospital from Feb 20th to Mar 1st, 2020. Epidemiological, clinical and treatment were analyzed between patients treated with corticosteroids or not.

Results

Corticosteroids used patients have higher levels of lactate dehydrogenase (LDH), interleukin-6 (IL-6), CD4+/CD8+ cells, C-reactive protein (CRP) and procalcitonin (PCT). Virus clearance time and hospital length of stay in corticosteroids group were also significantly higher. The antiviral treatment and antibiotics treatment in patients given corticosteroids were both significantly higher. Antibiotics treatment duration was significantly longer in corticosteroids group. And the usage of multiple antibiotics in corticosteroid group was also significantly higher. And patients who treated by corticosteroids beyond 5 days showed a significantly longer antibiotics duration. Whereas there were no differences on virus clearance time and multiple antibiotics between the patients treated with corticosteroids beyond 5 days and less than 5 days. Multivariate analysis showed that patients with sputum production and higher IL-6 at admission, or treated with corticosteroid therapy were associated with prolonged virus clearance time and lianhua qingwen capsule may contributed to shorten virus clearance time.

Conclusions

The use of corticosteroids could prolong the virus clearance. The benefits and harms should be carefully weighed in the COVID-19 patients who intend to use corticosteroids. The dosage should be low-to-moderate (≤ 0.5-1 mg/kg per day methylprednisolone or equivalent) and the duration should be short (≤ 5 days) to avoid secondary infections.

Background

Coronavirus disease 2019 (COVID-19) has spread around the world rapidly because of the highly contagious and human-to-human transmissions through direct contact, droplet or fomite[1]. Fever, cough, fatigue, myalgia and dyspnea are the most common symptoms of COVID-19 at onset of illness[2]. Inflammatory cytokine storm is typical laboratory abnormalities observed during highly pathogenic
coronavirus infections, such as severe acute respiratory syndrome coronavirus (SARS-CoV), the Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and is dynamically correlated with the severity of COVID-19[3–5]. Corticosteroids are a good inhibitory of inflammatory factors and often used as an auxiliary treatment for viral pneumonia. In China, corticosteroids are also used for the treatment of COVID-19. However, the effect of corticosteroids on coronavirus pneumonia remains controversial. It was reported that corticosteroids has a beneficial effect on a majority of SARS patients[6]. Whereas, a retrospective study of MERS patients showed that patients treated with corticosteroids were more likely to require mechanical ventilation, vasopressors, and renal replacement therapy[7]. As for COVID-19, whether patients will benefit from corticosteroids still lack of clinical evidence. Therefore, we performed this retrospective single-center study to clarify the potential roles of corticosteroids in severe COVID-19 patients.

**Methods**

**Patient selection**

This retrospective single-center study included 214 severe COVID-19 patients who were admitted to Wuhan Union hospital from 20 February to 1 March. At the time of this study, all patients were cured and discharged. And patients were divided into two group based on whether they are given corticosteroids. The study was approved by the Medical Ethical Committees of Wuhan Union Hospital. The requirement for written informed consent was waived because there was no intervention for treatment and potential risk to patients.

**Data collection**

On admission, severe illness was defined according to the criteria of Chinese management guideline for COVID-19 (version 7.0) [8]. The following information was extracted from electronic medical records by a standardised case report form: epidemiological, clinical characteristics, treatments, laboratory parameters and outcome data of confirmed severe cases of COVID-19. The date of disease onset was defined as the day when the symptom was noticed.

**Statistical analysis**

Categorical variables were described as frequency rates and percentages. Proportions for categorical variables were compared using the $\chi^2$ test, although the Fisher exact test was used when the data were limited. Means for continuous variables were compared using the Mann-Whitney test, and were described using median and interquartile range (IQR) values. When analyzing the influencing factors of virus clearance time, pearson correlation was used for univariate analysis, and then multiple linear regression was used to select independent risk factors. All statistical analyses were performed using SPSS version 20.0 software. P<0.05 was considered statistically significant.

**Results**
Baseline characteristics of 214 COVID-19 patients

214 patients were included in this study, and 34 patients were treated with corticosteroid. The comparison of baseline characteristics from the two group were shown in Table 1. The median age of the two groups (non-corticosteroid and corticosteroid) was 60 (IQR 52-67) and 65 (IQR 55-73) years old, respectively. The median time from illness onset to admission was 12.0 days (IQR 8.0–15.0). Of the 214 patients, 117 (54.4%) had 1 or more comorbidities. Hypertension (73[33.6%]), diabetes (32[15.0%]), chronic obstructive lung disease (8[3.7%]), coronary heart disease (33[15.4%]), malignancy (15[7.0%]), Chronic kidney disease (6[12.8%]) and Chronic liver disease (4[1.9%]). The most common symptoms of patients were fever (177[82.7%]), dry cough (153[71.4%]), sputum production (74[34.6%]), dyspnea (97[45.3%]) and diarrhea (43[20.1%]).

There was no significant difference of age, sex, comorbidities and clinical symptoms between the two groups. However, the median time from illness onset to admission in corticosteroid groups was significantly shorter than that of non-corticosteroid groups (P=0.007), which may be the result of the faster progress of COVID-19.

Laboratory parameters

Major laboratory parameters were tracked from illness onset (Table 2). Creatinine, blood urea nitrogen, AST, ALT, total bilirubin, ESR, white blood cell, neutrophil, lymphocyte, hemoglobin, platelet, eosinophils count, FIB, D-Dimer, total lymphocytes, CD4, CD8, B cells and NK cells did not differ between patients who received corticosteroid treatment and patients who did not receive corticosteroid treatment.

Lactate dehydrogenase (LDH) was significantly higher in corticosteroid group than non-corticosteroid group (P=0.036), as well as higher levels of CD4⁺/CD8⁺ cells (P=0.046). Virus clearance time (P=0.007) and hospital length of stay (P<0.001) were significantly prolonged in corticosteroid compared with non-corticosteroid group throughout the clinical course. And patients who required corticosteroid treatment were more likely to have higher levels of inflammatory indicators, including CRP (P=0.017), PCT (P=0.043), and IL-6 (P=0.029).

Treatment

According to the medication use of 214 patients, the patients generally received antiviral, antibiotic, traditional Chinese medicine (including Lianhua qingwen capsule and traditional Chinese medicine decoction), immune enhancer, intestinal microecological regulator and sedative hypnotic drugs (Table 3).

All of the 214 patients received antiviral treatment, of which 35(16.4%) treated with chloroquine phosphate, 209(97.7%) patients received arbidol tablets, 54(25.2%) patients administered lopinavir/ritonavir, 69(32.2%) patients received ribavirin injection and 56(26.2) received interferon alfa inhalation. 144(67.3%) patients received antibiotic (moxifloxacin, levofloxacin, carbapenems) therapy. Most of the patients were treated with traditional Chinese medicine for consolidation therapy. 205(95.8%) patients received traditional Chinese medicine decoction, 111(51.9%) patients received Lianhua qingwen capsule.
160(74.8%) patients received immune enhancer therapy and 70(32.7%) received intestinal microecological regulator treatment. 30(14.0%) patients need to take sedative hypnotics therapy.

Compared with patients who did not receive corticosteroid treatment, the usage rate of chloroquine phosphate patients in corticosteroid group were significantly higher in patients given corticosteroid (P=0.002). Moreover, the usage of antibiotic was also significantly higher in corticosteroid group (P<0.001). However, patients in non-corticosteroid group were more likely to received traditional Chinese medicine therapy, including Lianhua qingwen capsule (P=0.035) and traditional Chinese medicine decoction (P=0.017).

To detect the effect of corticosteroid on secondary infections, we analyzed the antibiotic treatment of these patients. As shown in Table 4, the antibiotics duration in patients given corticosteroid was significantly longer than those of non-corticosteroid. And the usage of multiple antibiotics in corticosteroid group was also significantly higher. These indicated that patients treated by corticosteroid were more likely to get secondary infections.

As corticosteroid was recommended to use in COVID-19 patients in low dose and short term (3-5 days), we analyzed the patients given corticosteroid beyond 5 days and those less than 5 days. As Table 5 showed, patients who treated by corticosteroid beyond 5 days showed a significantly longer antibiotics duration. However, there were no statistic difference in the virus clearance time and multiple antibiotics between the two groups. These results suggested that short-term use of corticosteroid may not increase the risk of secondary infections, but do prolong the virus clearance time.

**Univariate analysis of virus clearance time**

In univariable analysis, sex, longer time from illness onset to hospital admission, sputum production symptom, chloroquine phosphate therapy, non-Lianhua qingwen capsule therapy, immune enhancer, intestinal microecological regulator, corticosteroid, and sedative hypnotic therapy, higher levers of LDH, CRP, ESR, IL-6 and FIB, as well as lower lymphocyte count were associated with longer virus clearance time (Table 4).

**Prognostic factors of virus clearance time**

We included 15 significant variables in univariable analysis for multiple linear regression. The results showed that patients with sputum production and higher IL-6 at admission, or treated with corticosteroid therapy were associated with prolonged virus clearance time. Whereas, patients treated with lianhua qingwen capsule were more likely to shorten virus clearance time.

**Discussion**

There is no effective antiviral treatment for the novel virus, SARS-CoV-2, at present. And patients confirmed with COVID-19 were mainly treated by symptomatic therapy. Inflammatory cytokine storm is a risk factor in severe COVID-19 patients.
Corticosteroids has been used for the treatment of severe pneumonia in clinical. However, it was controversial that whether corticosteroids should be used in COVID-19 patients. Some scholars claimed that clinical evidence does not support corticosteroid treatment for COVID-19[9]. Whereas, Chinese management guideline for COVID-19 (version 7.0) [8] and a team of front-line physicians from China suggested that short term of corticosteroids at low dose could be used prudently in critical COVID-19 patients[10]. Therefore, it is important to provide evidence for corticosteroid used in COVID-19 patients.

In the current retrospective study, we analyzed the clinical features and medication of severe COVID-19 patients who treated with corticosteroids. There are no significant differences in demographic and epidemiologic characteristics except for the time from illness onset to hospital admission, which indicated that the COVID-19 patients who used corticosteroids were more likely to have a faster progression of COVID-19 at illness onset.

Similar with the premise of the use of corticosteroids[8], the severe COVID-19 patients who used corticosteroids were more likely to be an inflammatory condition at admission. Interestingly, the LDH level in patients given corticosteroids was significantly higher, which suggested that the injury liver function may associated with inflammatory storm. Consistent with the statement in Chinese management guideline for COVID-19 (version 7.0), we found that patients given corticosteroids have the significantly longer virus clearance time and hospital length of stay.

As to the treatment, the use of chloroquine phosphate and ribavirin were significantly higher in patients treated with corticosteroids, indicating that COVID-19 patients given corticosteroids need more antiviral treatment. In according with previous study[11], the antibiotic treatment in corticosteroids used patients was also significantly higher. Moreover, the antibiotics treatment duration and multiple use of antibiotics were both significantly higher in patients given corticosteroids. These results suggested that corticosteroids used patients have higher secondary infections. Further study showed that short term use of corticosteroid significantly reduced the antibiotics duration compared to long term use of corticosteroid (> 5 days). Therefore, these results demonstrated that the use of corticosteroid do prolong the virus clearance in severe COVID-19 patients and the use of corticosteroid should be less than 5 days to reduce secondary infections.

At present, many risk factors of COVID-19 have been identified, such as IL-6[12]. In this study, we found that sputum production and higher IL-6 at admission, or treated with corticosteroid therapy were associated with prolonged virus clearance. Interestingly, lianhua qingwen capsule may contribute to shorten virus clearance time.

This study has some limitations. Firstly, this is a single center retrospective study, and a large-scale research was needed to provide high quality evidence. Secondly, fatal cases of COVID-19 were excluded and selection bias might occur. Therefore, additional studies are needed to investigate the effect of corticosteroid on patients with 2019-nCoV pneumonia.

Conclusion
In summary, we reported the clinical features and medication and analyzed the corticosteroid treatment in severe COVID-19 patients. The benefits and harms should be carefully weighed in the COVID-19 patients who intend to use corticosteroids and the dosage should be low-to-moderate (≤ 0.5-1 mg/kg per day methylprednisolone or equivalent) and the duration should be short (≤ 5 days) to avoid secondary infections.

Abbreviations

BUN: blood urea nitrogen; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; T-BIL: total bilirubin; HGB: hemoglobin; PLT: platelets; WBC: white blood cell; NE: neutrophil; EO: eosinophilic granulocyte; CRP: c-reactive protein; PCT: procalcitonin; IL-6: interleukin 6; FIB: Fibrinogen.

Declarations

Ethics approval and consent to participate

The study was approved by the Medical Ethical Committees of Wuhan Union Hospital.

Consent for publication

Not applicable

Competing interests

All authors report no conflicts of interest relevant to this article.

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Author’s contributions

Fang Zeng and Yu Zhang were responsible for the conception of the study and overall supervision of the study; Fang Cheng and Qiang Li were responsible for the data collection and statistical analysis; Yuyong Su and Xuefeng Cai helped perform the analysis with constructive discussions.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Tables

Table 1. Demographic and Epidemiologic Features of severe COVID-19 Patients
|                                | Total (n=214) | Non-corticosteroid (n=180) | Corticosteroid (n=34) | P Value |
|--------------------------------|---------------|----------------------------|-----------------------|---------|
| Age                            | 61 (53-68)    | 60 (52-67)                 | 65 (55-73)            | 0.218   |
| Sex (Male)                     | 114 (53.3)    | 98 (54.4)                  | 16 (47.1)             | 0.429   |
| Time from illness onset to admission | 12 (8-15)    | 12 (9-16)                  | 10 (7-15)             | 0.007   |
| Comorbidities                  |               |                            |                       |         |
| Hypertension                   | 72 (33.6)     | 62 (34.4)                  | 10 (29.4)             | 0.569   |
| Diabetes                       | 32 (15.0)     | 30 (16.7)                  | 2 (5.9)               | 0.104   |
| Chronic obstructive lung disease | 8 (3.7)      | 8 (4.4)                    | 0                     | 0.21    |
| Heart disease                  | 33 (15.4)     | 27 (15.0)                  | 6 (17.6)              | 0.695   |
| Malignancy                     | 15 (7.0)      | 11 (6.1)                   | 4 (11.7)              | 0.165   |
| Chronic kidney disease         | 6 (2.8)       | 6 (3.3)                    | 0                     | 0.280   |
| Chronic liver disease          | 4 (1.9)       | 2 (1.1)                    | 2 (5.9)               | 0.060   |
| Others                         | 23 (10.7)     | 17 (9.4)                   | 6 (17.6)              | 0.183   |
| Signs and symptoms             |               |                            |                       |         |
| Fever                          | 177 (82.7)    | 146 (81.1)                 | 31 (91.2)             | 0.155   |
| Dry cough                      | 153 (71.4)    | 125 (69.4)                 | 28 (82.4)             | 0.126   |
| Sputum production              | 74 (34.6)     | 59 (32.8)                  | 15 (44.1)             | 0.202   |
| Dyspnea                        | 97 (45.3)     | 78 (43.3)                  | 19 (55.9)             | 0.178   |
| Diarrhea                       | 43 (20.1)     | 39 (21.7)                  | 7 (20.6)              | 0.937   |
Data are presented as medians (interquartile ranges, IQR), n (%) 

Table 2. Laboratory findings of severe COVID-19 patients.
| Blood biochemistry | Normal range | Median (IQR) Non-corticosteroid (n=180) | Median (IQR) Corticosteroid (n=34) | P Value |
|-------------------|--------------|----------------------------------------|------------------------------------|---------|
| Creatinine, μmol/L | 57-111       | 68.7(56.2-82.9)                        | 64.7(57.6-84.1)                    | 0.749   |
| BUN, mmol/L       | 2.9-8.2      | 4.6(3.6-6.0)                           | 4.4(3.5-5.4)                       | 0.437   |
| AST, U/L          | 8-40         | 23.0(18.0-37.0)                        | 31.0(18.0-39.0)                    | 0.056   |
| ALT, U/L          | 5-40         | 24.0(19.0-50.0)                        | 22.0(15.0-64.0)                    | 0.77    |
| LDH, U/L          | 109-245      | 194.0(177.0-262.0)                     | 240.0(183.0-294.0)                 | 0.036   |
| T-BIL, umol/L     | 3-20         | 10.7(7.8-13.7)                         | 7.5(6.1-11.2)                      | 0.526   |
| CRP, mg/L         | 0-8          | 5.2(1.5-11.7)                          | 42.7(14.1-69.7)                    | 0.017   |
| PCT, ng/mL        | <0.05        | 0.04(0.02-0.08)                        | 0.09(0.04-0.32)                    | 0.043   |
| ESR, mm/h         | 0-20         | 42.0(25.0-71.0)                        | 56.0(19.0-109.0)                   | 0.287   |
| IL-6, pg/mL       | <7           | 4.3(1.6-6.9)                           | 8.2(4.5-11.1)                      | 0.029   |
| White blood cell count, ×109/L | 3.5-9.5 | 5.3(4.2-6.6)                           | 5.4(3.7-6.8)                       | 0.788   |
| Neutrophil count, ×109/L | 1.8-6.3 | 3.6(2.7-4.8)                           | 3.7(2.7-5.4)                       | 0.729   |
| Lymphocyte count, ×109/L | 1.1-3.2 | 1.1(0.8-1.5)                           | 1.0(0.5-1.6)                       | 0.123   |
| Hemoglobin, g/L   | 40-50        | 126.0(115.0-135.0)                     | 124.0(109.0-133.5)                 | 0.116   |
| Platelet count, ×109/L | 125-350 | 238.0(177.0-310.5)                     | 240.0(153.8-375.5)                 | 0.719   |
| Eosinophils, ×109/L | 0.01-0.52 | 0.05(0.01-0.08)                        | 0.02(0.01-0.07)                    | 0.137   |
| FIB, g/L          | 2.0-4.0      | 4.3(3.2-5.1)                           | 4.6(3.5-5.0)                       | 0.994   |
| D-Dimer, μg/mL    | 0-0.5        | 0.6(0.3-1.4)                           | 0.5(0.3-1.2)                       | 0.751   |
### Total lymphocytes, ×10⁹/L

|                | Median (IQR) | Median (IQR) | Median (IQR) | P-value |
|----------------|--------------|--------------|--------------|---------|
|                | 58.17-84.22  | 70.2(64.8-78.4) | 69.3(64.8-78.0) | 0.848   |

### CD4, μL

|                | Median (IQR) | Median (IQR) | Median (IQR) | P-value |
|----------------|--------------|--------------|--------------|---------|
|                | 25.3-51.3    | 38.9(34.6-46.6) | 43.8(34.7-49.4) | 0.547   |

### CD8, μL

|                | Median (IQR) | Median (IQR) | Median (IQR) | P-value |
|----------------|--------------|--------------|--------------|---------|
|                | 14.2-38.9    | 25.4(20.3-31.5) | 19.1(16.5-29.1) | 0.255   |

### B cells, μL

|                | Median (IQR) | Median (IQR) | Median (IQR) | P-value |
|----------------|--------------|--------------|--------------|---------|
|                | 4.1-18.31    | 9.6(7.0-24.8) | 15.6(7.1-24.8) | 0.228   |

### Natural killer (NK) cells, μL

|                | Median (IQR) | Median (IQR) | Median (IQR) | P-value |
|----------------|--------------|--------------|--------------|---------|
|                | 3.33-30.47   | 8.5(6.2-13.4) | 7.7(2.5-9.6) | 0.169   |

### CD4+/CD8+, μL

|                | Median (IQR) | Median (IQR) | Median (IQR) | P-value |
|----------------|--------------|--------------|--------------|---------|
|                | 0.41-2.72    | 1.7(1.1-2.5) | 2.2(1.5-3.0) | 0.046   |

### Virus clearance time (days)

|                | Median (IQR) | Median (IQR) | Median (IQR) | P-value |
|----------------|--------------|--------------|--------------|---------|
|                | 15.0(11.0-20.0) | 14.0(10.0-20.0) | 17.0(14.0-27.0) | 0.007   |

### Hospital length of stay (days)

|                | Median (IQR) | Median (IQR) | Median (IQR) | P-value |
|----------------|--------------|--------------|--------------|---------|
|                | 22.0(18.0-28.0) | 21.0(17.0-27.0) | 26.0(22.0-32.0) | <0.001  |

Data are presented as medians (interquartile ranges, IQR), n (%)

BUN, blood urea nitrogen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; T-BIL, total bilirubin; HGB, hemoglobin; PLT, platelets; WBC, white blood cell; NE, neutrophil; EO, eosinophilic granulocyte; CRP, c-reactive protein; PCT, procalcitonin; IL-6, interleukin 6; FIB, Fibrinogen.

Table 3. Treatment of severe COVID-19 patients.
| No. (%)                       | Total (n=214) | Non-corticosteroid (n=180) | Corticosteroid (n=34) | P Value |
|-------------------------------|---------------|---------------------------|-----------------------|---------|
| Chloroquine phosphate         | 35 (16.4)     | 23 (12.8)                 | 12 (35.3)             | 0.002   |
| Arbidol                       | 209 (97.7)    | 177 (98.3)                | 32 (94.1)             | 0.136   |
| Lopinavir/ritonavir           | 54 (25.2)     | 47 (26.1)                 | 7 (20.6)              | 0.497   |
| Ribavirin\textsuperscript{b}  | 69 (32.2)     | 52 (28.9)                 | 17 (50.0)             | 0.016   |
| Interferon alfa inhalation    | 56 (26.2)     | 42 (23.3)                 | 14 (41.2)             | 0.089   |
| Antibiotic (moxifloxacin, n, levofloxacin, cefdinir) | 144 (67.3) | 113 (62.8) | 31 (91.2) | <0.001 |
| Traditional Chinese medicine  |               |                           |                       |         |
| Lianhua qingwen capsule       | 111 (51.9)    | 99 (55.0)                 | 12 (35.3)             | 0.035   |
| Traditional Chinese medicine decoction | 205 (95.8) | 175 (97.2) | 30 (88.2) | 0.017   |
| Immune enhancer               | 160 (74.8)    | 135 (75.0)                | 25 (73.5)             | 0.856   |
| Intestinal microecological regulator | 70 (32.7) | 59 (32.8) | 11 (32.4) | 0.961   |
| Sedative hypnotic therapy (alprazolam) | 30 (14.0) | 24 (13.3) | 6 (17.6) | 0.506   |

Data are presented as medians (interquartile ranges, IQR), n (%)

Table 4. Treatment analysis of antibiotics in severe COVID-19 patients used corticosteroid or didn’t use corticosteroid.
|                           | No. (%)          | P Value |
|---------------------------|------------------|---------|
|                           | Non-corticosteroid(n=113) | Corticosteroid(n=31) |
| Antibiotics duration      | 8.95±5.93        | 13.85±7.09 | P<0.001 |
| Multiple antibiotics      | 7(6.19%)         | 7(22.58%)   | 0.020   |

Data are presented as medians (interquartile ranges, IQR), n (%)

Table 5. Treatment analysis of severe COVID-19 patients used corticosteroid beyond 5 days or less than 5 days.

|                           | No. (%)          | P Value |
|---------------------------|------------------|---------|
|                           | Corticosteroid<5 days(n=18) | Corticosteroid>5 days(n=16) |
| Virus clearance time (days) | 18.33±8.13       | 21.20±7.24 | 0.298   |
| Antibiotics duration      | 9.89±5.20        | 17.75±8.71 | P=0.004 |
| Multiple antibiotics      | 2(11.11%)        | 5(31.25%)  | 0.168   |

Data are presented as medians (interquartile ranges, IQR), n (%)

Table 6. Univariate analysis of virus clearance time
| Condition                              | Pearson correlation | P.value  |
|---------------------------------------|---------------------|----------|
| Sex                                   | -.138*              | 0.045    |
| Time from illness onset to hospital admission | -.176*              | 0.011    |
| Comorbidities                         | 0.027               | 0.697    |
| Chronic obstructive lung disease      | 0.027               | 0.700    |
| Hypertension                          | 0.033               | 0.634    |
| Diabetes                              | 0.058               | 0.401    |
| Coronary heart disease                | -0.085              | 0.218    |
| Chronic kidney disease                | 0.021               | 0.762    |
| Chronic liver disease                 | 0.087               | 0.205    |
| Malignancy                            | -0.018              | 0.792    |
| Fever                                 | 0.009               | 0.896    |
| Dry cough                             | 0.076               | 0.267    |
| Sputum production                     | .219**              | 0.001    |
| Dyspnea                               | -0.057              | 0.406    |
| Diarrhea                              | 0.046               |          |
| Drug/Medication                          | Correlation Type       | Correlation Coefficient | P.value |
|----------------------------------------|------------------------|-------------------------|---------|
| Chloroquine phosphate                  | Pearson correlation    | 0.156*                  | 0.033   |
| Arbidol                                | Pearson correlation    | -0.015                  | 0.824   |
| Lopinavir/ritonavir                    | Pearson correlation    | 0.007                   | 0.916   |
| Ribavirin                              | Pearson correlation    | 0.029                   | 0.676   |
| Interferon alfa inhalation             | Pearson correlation    | 0.166                   | 0.055   |
| Antibiotic (moxifloxacin, levofloxacin, cefdinir) | Pearson correlation | 0.127                   | 0.064   |
| traditional Chinese medicine           | Pearson correlation    | 0.009                   | 0.897   |
| decoction                              | Pearson correlation    |                         |         |
| Lianhua qingwen capsule                | Pearson correlation    | -0.084*                 | 0.012   |
| Xuebijing injection                    | Pearson correlation    | 0.116                   | 0.092   |
| Immune enhancer                        | Pearson correlation    | 0.187**                 | 0.006   |
| Intestinal microecological regulator   | Pearson correlation    | 0.225**                 | 0.001   |
| Sedative hypnotic therapy              | Pearson correlation    | 0.216**                 | 0.002   |
| Corticosteroid                         | Pearson correlation    | 0.202**                 | 0.003   |
| Creatinine                             | Pearson correlation    | -0.105                  | 0.125   |
| Blood urea nitrogen                    | Pearson correlation    | -0.057                  |         |
| Parameter          | Pearson correlation | P.value |
|-------------------|---------------------|---------|
| AST<UL| | 0.079 |
| P.value | 0.252 |
| ALT<UL| | 0.084 |
| P.value | 0.221 |
| LDH   | Pearson correlation | .175* |
| P.value | 0.011 |
| Total bilirubin | Pearson correlation | 0.013 |
| P.value | 0.852 |
| CRP   | Pearson correlation | 0.067* |
| P.value | 0.034 |
| PCT   | Pearson correlation | 0.118 |
| P.value | 0.057 |
| ESR   | Pearson correlation | .297* |
| P.value | 0.015 |
| IL6   | Pearson correlation | 0.219 |
| P.value | 0.042 |
| White blood cell count | Pearson correlation | 0.083 |
| P.value | 0.230 |
| Neutrophil count | Pearson correlation | -0.009 |
| P.value | 0.901 |
| Lymphocyte count | Pearson correlation | -.165* |
| P.value | 0.016 |
| Hemoglobin | Pearson correlation | 0.003 |
| P.value | 0.960 |
| Platelet count | Pearson correlation | -0.037 |
| P.value | 0.597 |
| Eosinophils | Pearson correlation | 0.026 |
| P.value | 0.715 |
| FIB   | Pearson correlation | .202** |

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| Variable                  | Pearson correlation | P.value |
|--------------------------|---------------------|---------|
| D-Dimer                  | -0.026              | 0.726   |
| Total lymphocytes        | -0.237              | 0.073   |
| CD4                      | -0.238              | 0.070   |
| CD8                      | -0.051              | 0.703   |
| B cells                  | 0.140               | 0.289   |
| Natural killer (NK) cells| 0.227               | 0.083   |
| CD4+/CD8+                | -0.104              | 0.435   |

Table 7. Multivariate analysis of factors associated with virus clearance time in severe COVID-19 patients.
|                          | Unstandardized coefficient B | Standard error | Standardized coefficient Beta | t     | P     | VIF  |
|--------------------------|------------------------------|----------------|-----------------------------|-------|-------|------|
| dx                       | -0.929                       | 1.645          | -0.070                      | -0.565| 0.575 | 1.253|
| me from time from illness onset to admission | 0.019                        | 0.119          | -0.020                      | -0.160| 0.873 | 1.345|
| putum                    | 3.718                        | 1.972          | 0.254                       | 1.885 | 0.016 | 1.579|
| reduction                | 3.217                        | 3.980          | 0.121                       | 2.857 | 0.368 | 1.858|
| chloroquine              | 3.217                        | 3.980          | 0.121                       | 2.857 | 0.368 | 1.858|
| phosphate                | -2.086                       | 0.728          | -0.376                      | -2.864| 0.039 | 1.422|
| anhua                    | 0.582                        | 1.813          | 0.043                       | 0.321 | 0.750 | 1.477|
| angwen                   | 0.582                        | 1.813          | 0.043                       | 0.321 | 0.750 | 1.477|
| capsule                  | 4.115                        | 1.790          | 0.311                       | 2.298 | 0.086 | 1.514|
| immune                   | 4.115                        | 1.790          | 0.311                       | 2.298 | 0.086 | 1.514|
| enhancer                 | 5.633                        | 2.459          | 0.273                       | 2.291 | 0.027 | 1.176|
| intestinal               | 4.431                        | 3.595          | 0.167                       | 1.233 | 0.224 | 1.516|
| immune enhancer          | 4.431                        | 3.595          | 0.167                       | 1.233 | 0.224 | 1.516|
| corticosteroid           | 5.633                        | 2.459          | 0.273                       | 2.291 | 0.027 | 1.176|
| hypnogenic therapy       | 0.004                        | 0.008          | 0.072                       | 0.536 | 0.595 | 1.490|
| DH                       | 0.003                        | 0.047          | 0.010                       | 0.062 | 0.951 | 2.131|
| RP                       | 0.030                        | 0.031          | 0.146                       | 0.939 | 0.352 | 1.987|
| SR                       | 0.231                        | 0.131          | 0.270                       | 1.762 | 0.021 | 1.581|
| D6                       | 0.487                        | 0.977          | 0.081                       | 0.499 | 0.620 | 2.175|
| mphocyte                 | 0.599                        | 1.775          | 0.046                       | 0.338 | 0.737 | 1.548|
| L-6 only                 | 2.939                        | <0.001         |                             |       |       |      |
| lymphocyte               | 0.472                        |                |                             |       |       |      |