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 ($\leq 0.5-1$ 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 χ^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 groups 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 ($\leq 0.5\text{--}1$ 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

	No. (%)			P Value
	Total(n=214)	Non-corticosteroid(n=180)	Corticosteroid(n=34)	
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.

	Normal range	Median (IQR)		P Value
		Non-corticosteroid (n=180)	Corticosteroid (n=34)	
Blood biochemistry				
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, ×10 ⁹ /L	3.5-9.5	5.3(4.2-6.6)	5.4(3.7-6.8)	0.788
Neutrophil count, ×10 ⁹ /L	1.8-6.3	3.6(2.7-4.8)	3.7(2.7-5.4)	0.729
Lymphocyte count, ×10 ⁹ /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, ×10 ⁹ /L	125-350	238.0(177.0-310.5)	240.0(153.8-375.5)	0.719
Eosinophils, ×10 ⁹ /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, ×10 ⁹ /L	58.17-84.22	70.2(64.8-78.4)	69.3(64.8-78.0)	0.848
CD4, μL	25.3-51.3	38.9(34.6-46.6)	43.8(34.7-49.4)	0.547

CD8, μ L	14.2-38.9	25.4(20.3-31.5)	19.1(16.5-29.1)	0.255
B cells, μ L	4.1-18.31	9.6(7.0-24.8)	15.6(7.1-24.8)	0.228
Natural killer (NK) cells, μ L	3.33-30.47	8.5(6.2-13.4)	7.7(2.5-9.6)	0.169
CD4+/CD8+, μ L	0.41-2.72	1.7(1.1-2.5)	2.2(1.5-3.0)	0.046
Virus clearance time (days)	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)	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. (%)			P Value
	Total(n=214)	Non-corticosteroid (n=180)	Corticosteroid (n=34)	
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 ^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, levofloxacin, cefdinir ^c)	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 ^d (alprazolam ^e)	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

		Virus clearance time
Sex	Pearson correlation	-.138*
	P.value	0.045
Time from illness onset to hospital admission	Pearson correlation	-.176*
	P.value	0.011
Comorbidities	Pearson correlation	0.027
	P.value	0.697
Chronic obstructive lung disease	Pearson correlation	0.027
	P.value	0.700
Hypertension	Pearson correlation	0.033
	P.value	0.634
Diabetes	Pearson correlation	0.058
	P.value	0.401
Coronary heart disease	Pearson correlation	-0.085
	P.value	0.218
Chronic kidney disease	Pearson correlation	0.021
	P.value	0.762
Chronic liver disease	Pearson correlation	0.087
	P.value	0.205
Malignancy	Pearson correlation	-0.018
	P.value	0.792
Fever	Pearson correlation	0.009
	P.value	0.896
Dry cough	Pearson correlation	0.076
	P.value	0.267
Sputum production	Pearson correlation	.219**
	P.value	0.001
Dyspnea	Pearson correlation	-0.057
	P.value	0.406
Diarrhea	Pearson correlation	0.046

	P.value	0.500
Chloroquine phosphate	Pearson correlation	.156*
	P.value	0.033
Arbidol	Pearson correlation	-0.015
	P.value	0.824
Lopinavir/ritonavir	Pearson correlation	0.007
	P.value	0.916
Ribavirin	Pearson correlation	0.029
	P.value	0.676
Interferon alfa inhalation	Pearson correlation	0.166
	P.value	0.055
Antibiotic(moxifloxacin, levofloxacin, cefdinir)	Pearson correlation	0.127
	P.value	0.064
traditional Chinese medicine decoction	Pearson correlation	0.009
	P.value	0.897
Lianhua qingwen capsule	Pearson correlation	-.084*
	P.value	0.012
Xuebijing injection	Pearson correlation	0.116
	P.value	0.092
Immune enhancer	Pearson correlation	.187**
	P.value	0.006
Intestinal microecological regulator	Pearson correlation	.225**
	P.value	0.001
Sedative hypnotic therapy	Pearson correlation	.216**
	P.value	0.002
Corticosteroid	Pearson correlation	.202**
	P.value	0.003
Creatinine	Pearson correlation	-0.105
	P.value	0.125
Blood urea nitrogen	Pearson correlation	-0.057

	P.value	0.410
AST _{U/L}	Pearson correlation	0.079
	P.value	0.252
ALT _{U/L}	Pearson correlation	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**

	P.value	0.005
D-Dimer	Pearson correlation	-0.026
	P.value	0.726
Total lymphocytes	Pearson correlation	-0.237
	P.value	0.073
CD4	Pearson correlation	-0.238
	P.value	0.070
CD8	Pearson correlation	-0.051
	P.value	0.703
B cells	Pearson correlation	0.140
	P.value	0.289
Natural killer (NK) cells	Pearson correlation	0.227
	P.value	0.083
CD4+/CD8+	Pearson correlation	-0.104
	P.value	0.435

Table 7. Multivariate analysis of factors associated with virus clearance time in severe COVID-19 patients.

	Unstandardized	Standard	Standardized	t	P	VIF
	coefficient B	error	coefficient Beta			
sex	-0.929	1.645	-0.070	-0.565	0.575	1.253
time from illness onset to admission	-0.019	0.119	-0.020	-0.160	0.873	1.345
putum production	3.718	1.972	0.254	1.885	0.016	1.579
chloroquine phosphate	3.217	3.980	0.121	2.857	0.368	1.858
anhua qingwen capsule	-2.086	0.728	-0.376	-2.864	0.039	1.422
immune enhancer	0.582	1.813	0.043	0.321	0.750	1.477
intestinal	4.115	1.790	0.311	2.298	0.086	1.514
microecological regulator						
corticosteroid	5.633	2.459	0.273	2.291	0.027	1.176
sedative hypnotic therapy	4.431	3.595	0.167	1.233	0.224	1.516
CH	0.004	0.008	0.072	0.536	0.595	1.490
RP	0.003	0.047	0.010	0.062	0.951	2.131
SR	0.030	0.031	0.146	0.939	0.352	1.987
-6	0.231	0.131	0.270	1.762	0.021	1.581
LB	0.487	0.977	0.081	0.499	0.620	2.175
lymphocyte count	0.599	1.775	0.046	0.338	0.737	1.548
			2.939			
			<0.001			
2			0.472			