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Clinical observation of glucocorticoid therapy for critically ill patients with COVID-19 pneumonia

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Abstract

Objective: We aimed to investigate the clinical effects of intravenous glucocorticoid (GC) therapy for severe COVID-19 pneumonia.

Methods: Seventy-two patients hospitalized with severe COVID-19 pneumonia who were discharged or died between 5 January 2020 and 3 March 2020 at Huangshi Infectious Disease Hospital were included. Patients were divided into a treatment group (GC group) and non-treatment group (non-GC group) according to whether they had received GCs within 7 days of hospital admission.

Results: There was no significant difference between groups for Acute Physiology and Chronic Health Evaluation (APACHE) II score and 28-day survival rate. The rate of invasive mechanical ventilation was higher in the GC group than in the non-GC group. On day 7 after admission, the GC group had shorter fever duration and higher white blood cell count than the non-GC group. In subgroup analysis by age and severity, there was no significant difference in 28-day survival rate and other indicators. Compared with those in the non-GC group, patients in the GC group more frequently required admission to the intensive care unit.

Conclusion: In the present study, we found no significant improvement in patients with severe COVID-19 pneumonia treated with GCs within 7 days of admission.

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Introduction

COVID-19 was declared a global pandemic by the World Health Organization. This disease is highly contagious and spreads rapidly. Most patients with COVID-19 pneumonia present with mild symptoms. However, some patients develop dyspnea and/or hypoxemia within 1 week of onset, which can rapidly progress to acute respiratory distress syndrome[1] and can lead to multiple organ failure. COVID-19 pneumonia has brought great challenges to clinicians worldwide, and its pathogenesis is not fully understood. There is currently no specific treatment, with treatment being mainly for symptoms. Studies on severe COVID-19 pneumonia have found that some patients have substantially increased levels of inflammatory factors.[1,2] This suggests that inflammatory cytokine storms occur in the body, as in severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS).[3] For this reason, glucocorticoids (GCs) are considered a potential drug therapy, but their clinical effect remains unclear. In this study, we retrospectively analyzed the clinical data of 72 patients with severe COVID-19 pneumonia with the aim of clarifying the therapeutic effect of GCs for these patients.

Methods

Patient enrollment

In this analysis, we included patients with COVID-19 pneumonia who were discharged (or died) between 5 January 2020 and 3 March 2020 at Huangshi City Infectious Disease Hospital of Hubei Province. According to their condition at admission and with reference to the Novel Coronavirus Pneumonia Diagnosis and Treatment Program (Sixth Edition),[4] all included patients met the diagnostic criteria for severe or critically severe COVID-19 pneumonia. The diagnostic criteria for severe COVID-19 pneumonia were meeting any of the following: 1) respiratory distress, with respiration rate >30 breaths/minute; 2) oxygen saturation at rest $<93\%$; and 3) arterial blood oxygen partial pressure (PaO2)/oxygen uptake concentration (FiO2) ≤ 300 mmHg. The diagnostic criteria for critically severe COVID-19 pneumonia were meeting one of the following conditions: 1) respiratory failure requiring mechanical ventilation; 2) shock; and 3) other organ failure requiring monitoring and treatment in the intensive care unit (ICU). All enrolled patients were tested in the local disease prevention and control department and were positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) nucleic acid in more than two nasopharyngeal swabs. The exclusion criteria were as follows: 1) age <18 years; 2) tracheal intubation and invasive mechanical ventilation within 24 hours of admission; and 3) death within 24 hours of admission.

Study procedure

We retrospectively analyzed patients' data according to whether they received intravenous GC treatment or not after admission. All patients with COVID-19 pneumonia were categorized according to whether they received glucocorticoid treatment

(GC group) or no glucocorticoid treatment (non-GC group). The collected data included the medical history of patients in both groups, Acute Physiology and Chronic Health Evaluation (APACHE) II score within 24 hours of admission, routine blood test results, blood glucose, and blood biochemistry within 48 hours after admission. According to the Novel Coronavirus Pneumonia Diagnosis and Treatment Program, all included patients were bedridden after admission and received treatment to maintain water and electrolyte balance as well as fully supportive, symptomatic treatment, interferon nebulization, and lopinavir/ritonavir antiviral treatment. With confirmation of a bacterial infection, antibacterial drugs were administered. Patients in the GC group not only received the abovementioned treatments, they also received intravenous methylprednisolone (1 to 2 mg/kg/day). On day 7 after admission, all patients in the GC group had completed more than 3 days of treatment with GCs, and the clinical data of patients in both groups were collected again. The main observation index in this study was the 28-day survival rate, and secondary indicators included fever duration, total hospital stay, ICU admission rate, ICU residence time, and percentage of patients requiring invasive mechanical ventilation. The two groups of patients were then divided into those aged $\leq$60 years and >60 years and those with a diagnosis of severe or critically severe illness on admission. Indicators including the 28-day survival rate, total hospitalization days, admission ICU rate, ICU residence time, and percentage of patients requiring invasive mechanical ventilation were then assessed and compared by subgroup.

Ethical considerations

All procedures involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. As this was a retrospective study, informed consent was not required by the ethics review board. Ethics approval was received from the institutional ethics committee of the Children's Hospital of Nanjing Medical University in 2022.

Statistical analysis

Data analysis was performed using GraphPad 7.0 software (GraphPad Software Inc. La Jolla, CA, USA). Measurement data are reported using mean $\pm$ standard deviation, and the *t*-test was used. Count data are reported as the rate and Fisher's exact test was used. Patients' survival rates were compared using the log-rank test. A p-value <0.05 was considered statistically significant.

Results

Comparison of general characteristics at admission between groups

The data of 72 patients with COVID-19 pneumonia were included in this study, with 45 patients in the GC treatment group and 27 patients in the non-GC treatment group. Among the total, 42 were male and 30 were female patients; the mean age was 63.01 ± 14.87 years. The average time from illness onset to admission was 6.84 ± 3.41 days. The median time until receiving GC treatment for patients in the GC group was 3 days after admission, and the average time was 4.54 ± 3.82 days; the average treatment time was 4.31 ± 1.92 days. There was no significant difference between groups in age, sex, time from onset to admission, APACHE II score within 24 hours of admission, or the presence of hypertension, coronary heart disease, diabetes, cerebrovascular disease, chronic obstructive pulmonary disease (COPD), and the proportion with

malignant tumors or other diseases. Additionally, there was no significant difference in fasting blood glucose level, white blood cell count (WBC), and absolute lymphocyte count between the two groups within 48 hours of admission. There were no significant differences in levels of creatinine (Cr), alanine aminotransferase (ALT), or aspartate aminotransferase between groups within 48 hours of admission (Table 1).

Comparison of the treatment effect between groups 7 days after admission

By day 7 after admission, all patients in the GC group had received 3 to 5 days of GC therapy. Data analysis showed that compared with patients in the non-GC group, WBC levels among those in the GC group were significantly increased (p-value <0.05). The difference in absolute lymphocyte count, C-reactive protein (CRP), procalcitonin (PCT), blood glucose, ALT, Cr, and PaO2/FiO2 levels was not statistically significant (Table 2).

Comparison of 28-day survival between groups

We compared the survival rates between groups. At 28 days, the survival rate in the non-GC group was 88.89%, and that in the GC group was 71.11%, with hazard ratio 0.37. There was no significant difference in the mortality rate between the two groups (Figure 1).

Comparison of secondary observation indexes between groups

Compared with the non-GC group, fever duration in the GC group was significantly

Table 1. Comparison of general information between the two groups of patients on admission.

	Number (%) or mean ± standard deviation			
	Total (n = 72)	GCs (n = 45)	Non-GCs (n = 27)	p
Age (y)	63.01 ± 14.87	64.20 ± 14.71	61.04 ± 15.21	0.386
Sex				0.625
Female	30 (41.67%)	20 (44.44%)	10 (37.04%)	
Male	42 (58.33%)	25 (55.56%)	17 (62.96%)	
Time from onset to admission (d)	6.84 ± 3.41	7.15 ± 3.70	6.24 ± 2.77	0.325
APACHE II	7.60 ± 3.60	7.91 ± 3.57	7.07 ± 3.67	0.343
Basic illness				
Hypertension	28 (38.89%)	16 (35.56%)	12 (44.44%)	0.047
Cardiovascular disease	10 (13.89%)	4 (8.89%)	6 (22.22%)	0.161
Diabetes	11 (15.28%)	6 (13.33%)	5 (18.51%)	0.737
Cerebrovascular disease	1 (1.39%)	1 (2.22%)	0 (0.00%)	>0.999
COPD	1 (1.39%)	1 (2.22%)	0 (0.00%)	>0.999
Malignant tumor	2 (2.78%)	2 (4.44%)	0 (0.00%)	0.525
Blood glucose (mmol/L)	8.024 ± 3.675	7.88 ± 3.23	8.38 ± 4.70	0.621
Cr (μmol/L)	66.43 ± 22.74	70.07 ± 22.38	64.33 ± 22.93	0.309
WBC ($\times 10^9$/L)	5.43 ± 2.71	4.83 ± 1.98	5.74 ± 2.99	0.175
L ($\times 10^9$/L)	0.85 ± 0.658	1.03 ± 0.97	0.76 ± 0.40	0.099
ALT (U/L)	34.01 ± 27.71	28.92 ± 14.58	37.09 ± 33.03	0.238
AST(U/L)	45.52 ± 29.98	38.62 ± 22.26	49.70 ± 31.90	0.125

GC, glucocorticoid; COPD, chronic obstructive pulmonary disease; APACHE, Acute Physiology and Chronic Health Evaluation; Cr, creatinine; WBC, white blood cell; ALT, alanine aminotransferase; AST, aspartate aminotransferase; L, lymphocytes.

Table 2. Comparison of treatment effect between the two groups at day 7 after admission.

	GCs (n = 45)	Non-GCs (n = 27)	p
WBC ($\times 10^9$/L)	11.89 ± 5.66	7.30 ± 4.93	0.007
L ($\times 10^9$/L)	0.78 ± 0.48	0.74 ± 0.31	0.760
CRP (mg/L)	26.41 ± 7.45	23.62 ± 9.08	0.187
PCT (ng/mL)	0.87 ± 0.35	0.74 ± 0.42	0.218
Blood glucose (mmol/L)	9.21 ± 4.33	7.45 ± 3.08	0.086
ALT (U/L)	54.51 ± 18.48	45.09 ± 21.58	0.077
Cr (μmol/L)	55.48 ± 19.09	48.63 ± 21.38	0.202
P/F	178.20 ± 97.11	211.09 ± 105.53	0.266

GC, glucocorticoid; Cr, creatinine; WBC, white blood cell; ALT, alanine aminotransferase; L, lymphocytes; CRP, C-reactive protein; PCT, procalcitonin; P/F, arterial blood oxygen partial pressure/oxygen uptake concentration.

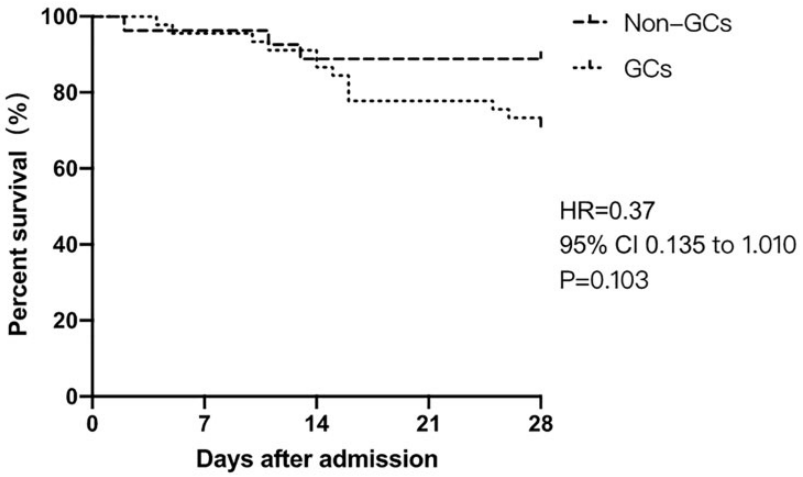

Figure 1. Comparison of survival rate between the GC group and non-GC group.

Table 3. Comparison of secondary observation indexes between two groups of patients.

	GCs (n = 45)	Non-GCs (n = 27)	p
Fever duration (d)	7.20 ± 4.10	9.50 ± 4.20	0.026
Total hospitalization (d)	19.00 ± 8.00	17.00 ± 5.70	0.452
ICU admission (%)	55.32	29.63	0.052
ICU residence time (d)	3.17 ± 4.10	1.39 ± 3.07	0.120
Invasive mechanical ventilation (%)	33.33	11.11	0.049

GC, glucocorticoid; ICU, intensive care unit.

shorter (p-value <0.05). There was no significant difference between groups in total hospitalization days, ICU admission rate, and ICU residence time. Compared with the non-GC group, the proportion of patients in the GC group requiring invasive mechanical ventilation was significantly higher (p-value <0.05) (Table 3).

Subgroup analysis of patient prognostic indicators

Patients were grouped according to age (28 patients aged ≤60 years and 44 patients aged >60 years) and severity (33 patients with severe illness and 39 patients with critically severe illness) at the time of admission. By age group, we found no significant difference in the 28-day survival rate, total hospitalization days, ICU admission rate, ICU residence time, and proportion of patients requiring invasive mechanical ventilation between patients in the GC and non-GC groups. According to severity, the 28-day survival rate, total hospitalization days, ICU residence time, and proportion of patients requiring invasive mechanical ventilation showed no significant difference. However, compared with that in the non-GC treatment group (30.8%), the rate of ICU admission in the GC group (53.3%) was significantly higher (p-value <0.05) (Table 4).

Table 4. Subgroup analysis of prognostic indicators.

	Age ≤60 years (n = 28)			Age >60 years (n = 44)			Severe illness (n = 33)			Critically severe illness (n = 39)		
	GCs (n = 15)	Non-GCs (n = 13)	p	GCs (n = 30)	Non-GCs (n = 14)	p	GCs (n = 16)	Non-GCs (n = 17)	p	GCs (n = 29)	Non-GCs (n = 10)	p
28-day survival rate	86.67%	92.31%	>0.999	63.33%	85.71%	0.170	–	–	–	55.17%	70%	0.480
Total hospitalization (d)	17.13 ± 9.10	15.69 ± 7.12	0.648	17.59 ± 7.84	16.33 ± 5.50	0.618	20.31 ± 5.92	17.56 ± 4.52	0.150	16.04 ± 8.54	13.22 ± 8.14	0.391
ICU admission (%)	53.33	30.77	0.276	66.67	35.71	0.101	43.75	23.53	0.282	82.76	40	0.017
ICU residence time (d)	2.73 ± 3.77	2.62 ± 3.50	0.933	5.60 ± 6.45	2.14 ± 3.96	0.073	1.50 ± 2.71	0.65 ± 1.58	0.274	6.41 ± 6.35	5.30 ± 4.42	0.614
Invasive mechanical ventilation (%)	26.67	0	0.102	36.67	21.43	0.489	–	–	–	44.83	10	0.064

GC, glucocorticoid; ICU, intensive care unit.

Discussion

COVID-19 pneumonia is an acute respiratory infectious disease, which has strong infectivity and rapid progression. Current reports show the mortality rate of hospitalized patients with COVID-19 pneumonia to be 4.3% to 28.2%, and the mortality rates of elderly patients and patients who meet the diagnostic criteria for severe and critically severe illness on admission are significantly increased.[5–8] The etiologic agent of COVID-19 pneumonia is SARS-CoV-2, a novel type of enveloped RNA betacoronavirus that is related to SARS-CoV and MERS-CoV.[9,10]

There is currently no specific treatment for COVID-19 pneumonia. Related studies have investigated monoclonal antibody therapy,[11] soluble recombinant angiotensin-converting enzyme 2 protein, and lopinavir/ritonavir;[12–14] however, their effects have not

been confirmed. In clinical practice, comprehensive and supportive, symptomatic treatment is mainly used. The pathogenesis of COVID-19 pneumonia has not yet been fully clarified, and it is believed that inflammatory cytokine storms and viral escape from cellular immune responses play important roles in the severity of this disease.[3] In theory, GCs can influence the production of inflammatory cells by affecting protein expression, reducing the inflammatory response, and inhibiting lung inflammation.[15] Thus, some scholars believe that GCs can be used to treat patients with COVID-19 pneumonia.[16] However, GCs also have an immunosuppressive effect on the body's immune function. Therefore, no direct clinical evidence has proven whether it is beneficial to use GCs to treat patients with COVID-19 pneumonia.

GCs are widely used in the treatment of viral pneumonia.[17,18] A retrospective study of clinical data from 401 patients with SARS showed that the proper use of GCs could reduce mortality in critically ill patients with SARS and shorten the length of hospitalization without causing secondary infections or other complications.[19] However, a prospective cohort study of 2141 patients with influenza-associated pneumonia showed that low to moderate doses of corticosteroids reduced mortality in patients with PaO2/FiO2 level <300 mmHg.[20] However, in a systematic review of SARS research, 25 of 29 studies found no definite conclusions, and the remaining four studies found negative effects.[21,22] A retrospective study on the use of GCs in MERS showed that patients treated with GCs were more likely to require tracheal intubation, ventilation, and other treatments, and there was no significant difference in the 90-day mortality rate compared with patients who did not receive GCs.[17] Additionally, GCs have been used in animal experiments to treat viral pneumonia, which led to decreased lymphocyte recruitment, enhanced viral replication, and increased mortality.[23,24] Another study pointed out that GCs had no clinical benefit in the treatment of respiratory syncytial virus pneumonia and could even be harmful.[25] Owing to different results in the existing literature, the effect of GCs in patients with viral pneumonia, like COVID-19 pneumonia, remains controversial.

The effect of GCs in treating viral pneumonia has been investigated by other researchers. Ni et al. conducted a retrospective study on the use of GCs in the treatment of influenza. According to their findings, the authors concluded that after receiving GCs, the body's immune response is suppressed, and secondary infections could be more likely to occur.[26] In our study, we found that the post-treatment leukocyte level among patients in the GC group was higher than that in the non-GC group, with no significant difference in PCT and CRP levels between groups. Fever duration in the GC group was significantly shorter than that in the non-GC group, and there was no evidence of a secondary infection. Therefore, we believe that the increased blood leukocyte levels in patients treated with GCs may be owing to the function of GCs in promoting bone marrow to produce neutrophils. Because the number of peripheral blood leukocytes is mainly affected by neutrophils, the peripheral blood leukocyte count increases accordingly, i.e., this increase is not caused by a secondary infection. However, patients in the GC group were not found to benefit in terms of the survival rate and ICU admission rate. Therefore, we believe that the relatively short fever duration in the GC group may be owing to the role of GCs in inhibiting the release of pyrogens from monocytes, thereby inhibiting the movement of leukocytes and local inflammatory reactions, which results in lowering the body temperature but without showing

any signs of improvement. There was no significant difference in PaO2/FiO2 values between the GC and non-GC groups, indicating that low-dose GC treatment failed to improve patients' oxygenation. After the treatment, there was no significant difference in blood glucose, ALT, Cr, and other clinical findings in either group, indicating that short-term treatment with low-dose GCs had no significant effect on liver and kidney functions or blood glucose levels in patients with COVID-19 pneumonia.

We found no significant difference in total hospital days, ICU admission rate, and ICU residence time between patients who received GCs and those who did not. We found that after receiving GCs, the above clinical indicators did not significantly improve. A comparison of the rate of invasive ventilation between groups suggested that patients in the GC group were more likely to require endotracheal intubation and mechanical ventilation. We observed that compared with the condition at admission, some patients' condition was aggravated upon starting to receive GC treatment, accompanied by hypoxemia and other conditions. Existing studies have reported different results, so the role of GCs in severe viral pneumonia remains controversial. Some research has shown that when imaging shows an increase in lung shadows, early and appropriate use of GCs can significantly reduce lung disease progression and improve the patient's clinical symptoms.[27] However, other studies suggest avoiding the early use of GCs to prevent complications.[28] Clinicians' choice of GCs is mostly based on personal experience, and standards for the use of GCs are not uniform as yet. All these reasons limit understanding of the relationship between the use of GCs and the choice of endotracheal intubation and timing of invasive mechanical ventilation. We found no significant difference in 28-day survival rates between the groups in our study, which indicates that survival in our patients with COVID-19 pneumonia did not improve after receiving treatment with GCs. However, owing to time constraints, we could not assess the survival rate at 90 days or longer, which is a limitation of this study.

To investigate whether the effects of GCs on COVID-19 pneumonia are related to age and severity of disease, we conducted a stratified analysis of the clinical data of patients with COVID-19 pneumonia according age group, i.e., $\leq$60 years and $>$60 years. The results showed no significant difference between age groups in total hospital days, ICU admission rate, ICU residence time, proportion requiring invasive mechanical ventilation, and 28-day survival rate between patients who received GC treatment and those who did not. Furthermore, the effect of GC treatment in patients aged $\leq$60 years and those aged $>$60 years was found to be equivalent. The clinical data of patients with severe and critically severe illness showed no evidence of benefit for patients receiving GC treatment in either group.

The evaluation conducted in this study has some limitations. The study has the limitations inherent to retrospective studies, such as certain selection bias and recall bias. Additionally, the sample size was small, which could lead to bias in the results.

In summary, this study showed that GCs have no obvious clinical effect in treating critically ill patients with COVID-19. However, the pathogenesis of this disease is complex and factors that affect the prognosis of patients with COVID-19 pneumonia remain unclear. Therefore, a larger randomized controlled trial is required to evaluate the effects of GC treatment in patients with COVID-19 pneumonia in a more comprehensive way.

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Author contributions

Dongmei Chen and Yingjie Zhu drafted the manuscript; Yanfang Zhu collected and analyzed the data. Xuhua Ge performed statistical analyses. Zhuo Li carried out the follow-up. Dongmei Chen and Hongjun Miao contributed to study conception, provided critical review of the manuscript, and approved the final submission.

Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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