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JBR

Letter to the Editor

The prognosis and short-term efficacy of corticosteroid therapy for COVID-19 patients

Dear Editor:

Corticosteroids are widely used in the treatment of critically ill patients for active anti-inflammatory and immunosuppressive effects. However, the therapeutic effects of corticosteroid treatment are still disputable. Some studies have shown that corticosteroids can delay coronavirus RNA clearance[1], increase mortality[2] and cause adverse events[3]. Conversely, other studies have confirmed the clinical value of corticosteroids in shortening hospital stays and decreasing the need for mechanical ventilation[4]. Similarly, the use of corticosteroids in COVID-19 patients is controversial. Expert consensus in China has indicated that corticosteroids can be used as appropriate in critical patients[5]. However, World Health Organization interim guidance opposes the routine use of corticosteroids in treatment[6]. Therefore, we herein discussed the therapeutic effects of corticosteroids in COVID-19 patients based on the experience of front-line physicians and a meta-analysis.

We analyzed the data of 67 difficult and complicated cases from 28 hospitals in 13 regions of Jiangsu Province, including 1 mild, 13 typical, 45 severe, and 8 critical patients. The severity of illness was defined by the expert consensus in China[5]. All patients were divided into two groups according to whether they used corticosteroids or not. The clinical characteristics, laboratory findings, and treatments are shown in ***Table 1***. Data are presented as numbers (%) or median (IQR). *P* values were calculated by chi-square test, Fisher's exact test, or Mann-Whitney *U* test. Multidisciplinary experts guided the therapy by remote consultation through tracking vital signs and examination results and observing the dynamic changes in the patients' conditions. The results showed that the conditions of 18 corticosteroid users were improved or stable and that no patients died. We further analyzed the oxygen and blood indexes of 12 patients with complete data (≥4 consultations, follow-up time ≥10 days). The average course of corticosteroid treatment was 8 days. It was determined that short-term treatment with corticosteroids improved oxygen saturation (SaO_2) and the ratio of arterial oxygen tension (PaO_2) to inspiratory oxygen fraction (FiO_2), and promoted the absorption of pulmonary lesions (***Table 2***). All statistical analyses were conducted by SPSS software (version 13.0). The results indicated that corticosteroids played a positive role in improving the short-term oxygenation of COVID-19 patients. To include more cases to test the hypothesis, we decided to carry out a meta-analysis.

We carried out a systematic literature search on the PubMed, EMBASE, and Web of Science databases for relevant studies on COVID-19. We used the following keywords in our search: "2019-nCoV", "COVID-19", and "SARS-CoV-2". To avoid literature omission, we did not use "corticosteroids" or other keywords related to treatment. Articles dated up to March 15, 2020 were searched without language limit. Inclusion criteria were as follows: (1) the definite diagnosis of COVID-19; (2) two groups of corticosteroid use and non-corticosteroid use; (3) the clinical data available to extract. Exclusion criteria were as follows: (1) repeated publication; (2) failure to get the full text or detailed abstract; (3) the articles of editorials, reviews, or expert consensus; (4) difficulty in extracting the necessary data. Two researchers independently selected articles and extracted the data by reading the titles, abstracts, and full texts of the articles. The binary data analysis was conducted by Stata software (version 14.1).

A total of 2431 articles were preliminarily retrieved. After deduplication and assessment of titles, abstracts,

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Table 1 **The clinical characteristics, laboratory findings, and treatment of COVID-19 patients**

Characteristics	Total (n=67)	Corticosteroids (*n*=38)	No corticosteroids (*n*=29)	*P*-value
Gender (*n*, male/female)	44/23	26/12	18/11	0.587
Age (years)[a]	59.0 (50.0, 70.0)	60.0 (51.5, 70.3)	58.0 (46.0, 70.5)	0.864
BMI[a]	25.1 (22.9, 28.4)	24.8 (22.5, 28.4)	25.3 (23.5, 28.2)	0.354
Wuhan exposure[b]	31 (46.3)	17 (44.7)	14 (48.3)	0.773
Severity of illness[b]				
Mild	1 (1.5)	0 (0.0)	1 (3.4)	0.056
Typical	13 (19.4)	6 (15.8)	7 (24.1)	
Severe	45 (67.2)	25 (65.8)	20 (69.0)	
Critical	8 (11.9)	7 (18.4)	1 (3.4)	
Comorbidity[b]				
Hypertension	23 (34.3)	13 (34.2)	10 (34.5)	0.981
Diabetes	15 (22.4)	9 (23.7)	6 (20.7)	0.771
Cardiovascular disease	4 (6.0)	2 (5.3)	2 (6.9)	1.000
Cerebral infarction	8 (11.9)	4 (10.5)	4 (13.8)	0.977
Oxygen support[b]				
None	12 (17.9)	3 (7.9)	9 (31.0)	0.025*
Low flow oxygen	13 (19.4)	8 (21.1)	5 (17.2)	
High flow oxygen	15 (22.4)	8 (21.1)	7 (24.1)	
Non-invasive ventilation	27 (40.3)	19 (50.0)	8 (27.6)	
Laboratory findings[a]				
PaO_2/FiO_2	187.5 (133.7, 296.5)	167.5 (123.2, 291.4)	207.5 (136.0, 306.9)	0.312
SaO_2 (%)	96.0 (94.0, 98.0)	95.2 (94.0, 98.0)	96.2 (94.5, 98.0)	0.427
Lactic acid (mg/dL)	1.8 (1.4, 2.5)	1.8 (1.5, 2.5)	1.8 (1.3, 2.5)	0.686
WBC ($\times10^9$/L)	6.0 (4.2, 8.8)	6.6 (4.8, 9.5)	5.14 (3.8, 6.7)	0.048*
RBC ($\times10^9$/L)	4.3 (3.9, 4.7)	4.4 (4.1, 4.7)	4.3 (3.8, 4.8)	0.348
Lymphocyte ($\times10^9$/L)	0.7 (0.5, 1.0)	0.6 (0.4, 0.8)	0.9 (0.6, 1.4)	0.006*
Platelet count ($\times10^9$/L)	169.0 (137.5, 204.5)	164 (130.5, 199.5)	188.5 (139.3, 238.8)	0.129
Treatment[b]				
Antiviral therapy	57 (85.1)	34 (89.5)	23 (79.3)	0.264
Antibiotic therapy	63 (94.0)	35 (92.1)	28 (96.6)	1.000
Improvement/stabilization[b]	34 (50.7)	18 (47.4)	16 (55.2)	0.527

PaO_2/FiO_2: the ratio of arterial oxygen tension to inspiratory oxygen fraction; SaO_2: oxygen saturation; WBC: white blood cell; RBC: red blood cell. Data were presented as median (interquartile range)[a] or number (%)[b]; *P*-values were calculated by chi-square test, Fisher's exact test, or Mann-Whitney *U* test. *$P<0.05$ was statistically significant.

and full texts, six articles were chosen for study[7–12] (***Fig. 1***). We used the Newcastle-Ottawa scale to evaluate the quality of the study[13] (***Table 3***). We also included our research data, in which 38 patients used corticosteroids including 32 patients with severe conditions. The conditions of 18 users were improved or stable, while 16 of the non-users achieved the same result. The conditions of the remaining patients were aggravated or even deteriorated. Characteristics of studies included are shown in ***Table 3***.

Finally, a total of 1625 subjects, including 441 corticosteroid users and 1184 non-users, were included from these 7 articles. The forest plot of critical and non-critical patients (***Fig. 2A***) showed critical patients are more likely to use corticosteroids (OR, 4.82; 95% CI, 3.55–6.54). The result of corticosteroid use (***Fig. 2B*** and ***C***) showed the improvement rate of the corticosteroid group was lower than that of

Table 2 **The effect of corticosteroid therapy on severe and critical patients of COVID-19 patients**

Parameters	Day 1	Day 4	Day 7	Day 10	*P*-value *vs.* Day 1		
					Day 4	Day 7	Day 10
PaO_2/FiO_2[a]	139.6 (110.4, 154.3)	140.6 (120.0, 184.0)	148.9 (102.5, 197.2)	175.0* (125.3, 241.5)	0.418	0.373	0.048
SaO_2 (%)[a]	91.6 (89.6, 96.0)	95.6 (94.0, 97.6)	95.6* (93.0, 98.5)	97.0* (94.3, 98.9)	0.053	0.028	0.006
Lactic acid (mg/dL)[a]	1.8 (1.3, 3.5)	2.3 (1.4, 2.8)	1.6 (1.3, 2.1)	1.6 (1.2, 2.3)	0.921	0.373	0.338
WBC ($\times10^9$/L)[a]	6.9 (4.0, 9.0)	6.8 (5.4, 10.7)	8.1 (6.5, 13.6)	8.7 (5.3, 11.5)	0.453	0.166	0.356
Lymphocyte ($\times10^9$/L)[a]	0.46 (0.32, 0.61)	0.40 (0.28, 0.51)	0.45 (0.21, 0.50)	0.51 (0.33, 1.00)	0.225	0.355	0.419
Chest X-ray or CT[b]	0	0	4 (33.3%)	11 (91.7%)			

The data were presented as median (interquartile range)[a] and frequency (%)[b]. SaO_2: oxygen saturation; PaO_2/FiO_2: the ratio of arterial oxygen tension to inspiratory oxygen fraction; WBC: white blood cell. All comparisons were compared with Day 1 group. *P<0.05 was statistically significant.

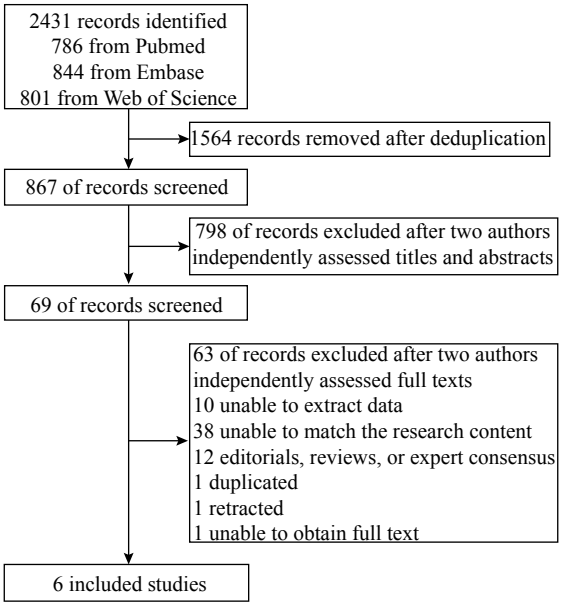

Fig. 1 **Flowchart for study selection.**

the noncorticosteroid group (OR, 0.54; 95% CI, 0.33–0.88), but corticosteroid use was not associated with mortality of COVID-19 patients (OR, 2.64; 95% CI, 0.86–2.08). Due to the small number of articles, we did not conduct heterogeneity analysis.

Some related meta-analyses of corticosteroid therapy for lung diseases used mortality, need for intensive care unit (ICU) admission or mechanical ventilation as prognostic indicators. In this meta-analysis, we selected only mortality. Because we thought the need for ICU or mechanical ventilation was the evaluation criteria for critical patients who need to use corticosteroids according to the experts consensus. It could not be used as a prognostic indicator simply. However, although the composite endpoints included admission to the ICU, mechanical ventilation, or death, a study by Weijie G *et al*[11] was included after discussion due to the large number of subjects and extra subgroups of non-severe and severe patients.

Limitations of this research and next steps

Currently, evidence for the use of corticosteroid therapy for COVID-19 patients is mostly empirical. This meta-analysis provided the first preliminary systematic review showing the prognosis and short-term efficacy of corticosteroid use for COVID-19. Obviously, our analysis has some limitations. First, the effect of mechanical ventilation on patients' oxygenation status was not considered. Moreover, due to the limited data, the changes of indicators in the noncorticosteroid group were not discussed. Second, the studies included in the meta-analysis were mostly retrospective studies rather than high-quality randomized controlled trial (RCT) studies. Third, due to the small number of included articles, we included two that used discharge as an evaluation of improvement/stabilization, which was not consistent with other included studies. Fourth, the included studies were all Chinese studies. More studies from other different countries and regions need to be considered to carry out RCT studies and subgroup analysis.

We believed, based on the front-line COVID-19 treatment experience, that the use of corticosteroids might have a positive effect on improving the short-term oxygenation of critically ill patients. However, there is no evidence-based support for this claim. Some researchers have indicated that corticosteroids should be applied when the body's inflammatory response is over activated (*i.e.* inflammatory cytokine storm). It is necessary to make a comprehensive evaluation based on the patient's vital signs, oxygenation status, and dynamic changes in inflammatory indicators and imaging examinations. We hope that through our first-line experience and preliminary meta-analysis, new thoughts could be inspired for

Table 3 **Characteristics of included studies**

Author	Year	Country	Region	Multicenter	Sample (*n*)	Gender (*n*, M/F)	Age*	Evaluation criteria	Study design	Duration	Dose	Outcomes measured	NOS score
Huang *et al*[7]	2020	China	Wuhan	N	41	11/30	49.0 (41.0, 58.0)	1. ICU/non-ICU 2. ARDS/non-ARDS 3. The use of corticosteroids	Retrospective study	December 16, 2019–January 2, 2020	NA	1. The use of corticosteroids 2. Mortality 3. Discharge	7
Ruan *et al*[8]	2020	China	Wuhan	Y	150	102/48	NA	The use of corticosteroids	Retrospective study	NA	NA	1. Mortality 2. Discharge	7
Wang *et al*[9]	2020	China	Wuhan	N	138	75/63	56 (42, 68)	ICU/non-ICU	Retrospective study	January 1, 2020–January 2, 2020	NA	The use of corticosteroids	7
Yang *et al*[10]	2020	China	Wuhan	N	52	35/17	59.7 (13.3)	The use of corticosteroids	Retrospective study	December 2019–January 26, 2020	NA	Mortality	7
Guan *et al*[11]	2020	China	31 provinces/ provincial municipalities	Y	1099	640/459	47.0 (35.0, 58.0)	1. Severe/non-severe 2. The use of corticosteroids	Retrospective study	–January 29, 2020	The median of maximal daily dose was 1.5 (0.7-40.0) mg/kg	1. The use of corticosteroids 2. Composite endpoint (the admission to ICU, or mechanical ventilation, or death)	8
Liu *et al*[12]	2020	China	Wuhan	N	78	39/39	38 (33, 57)	The use of corticosteroids	Retrospective study	December 30, 2019–January 15, 2020	The median dose was 40 (20, 40)* mg intravenously (iv) every day (qd)	Improvement/ stabilization	7
Huang *et al*	2020	China	Jiangsu province	Y	67	44/23	59.0 (50.0, 70.0)	1. Severe/non-severe 2. The use of corticosteroids	Retrospective study	January 29, 2020–March 12, 2020	The median dose was 40 (20, 80) mg intravenously (iv) every day (qd)	1. The use of corticosteroids 2. Improvement/ stabilization	8

*Data were presented as median (interquartile range); NOS: Newcastle-Ottawa Scale; ICU: intensive care unit; ARDS: acute respiratory distress syndrome; NA: not available; Y: yes; N: no.

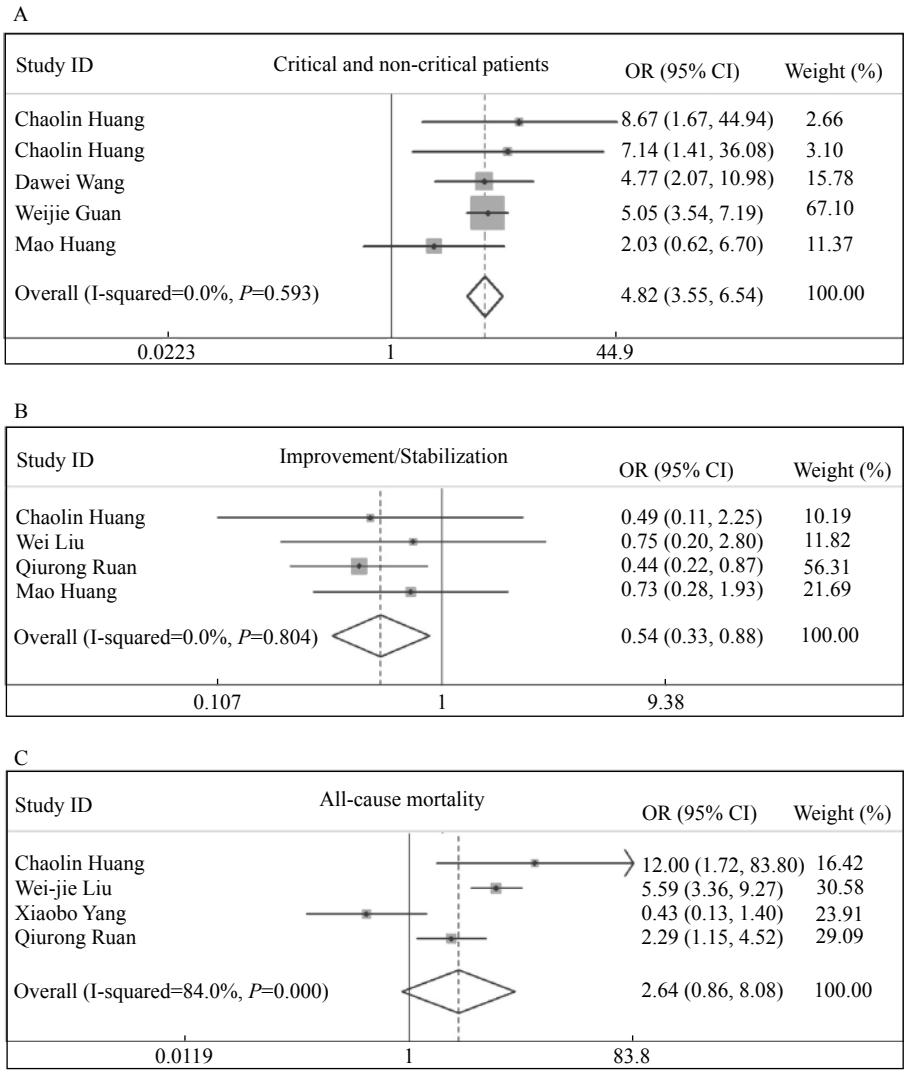

Fig. 2 **Forest plot of corticosteroid therapy on COVID-19 patients.** A: The use of corticosteroids in critical and non-critical patients. B: Effect of corticosteroids on improvement/stabilization. C: Effect of corticosteroids on mortality. OR: odds ratios; CI: confidence interval.

future researchers. Strictly following the indications of corticosteroid use, avoiding the occurrence of adverse events, and applying a more standardized and reasonable regimen of corticosteroids need not only to be proved by scientific evidence but also to be tested by the practical experience of front-line experts of multiple disciplines.

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Yours Sincerely,

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