The effect of corticosteroid treatment on patients with coronavirus infection: a systematic review and meta-analysis

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Highlights

- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) threatens the health of people, and there is no proven pharmacological treatment.

- Although corticosteroids were widely used during outbreaks of severe acute respiratory syndrome and Middle East respiratory syndrome, their efficacy remains highly controversial.

- Patients with severe conditions are more likely to require corticosteroids. However, corticosteroid use may lead to increased mortality and serious adverse reactions.

- Therefore, corticosteroids should be used with caution in the treatment of coronavirus disease 2019 (COVID-19).

The effect of corticosteroid treatment on patients with coronavirus infection: a systematic review and meta-analysis

Running title: Effect of corticosteroid treatment on patients with coronavirus infection

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Abstract

Objectives: An outbreak of novel coronavirus in 2019 threatens the health of people, and there is no proven pharmacological treatment. Although corticosteroids were widely used during outbreaks of severe acute respiratory syndrome and Middle East respiratory syndrome, their efficacy remains highly controversial. We aimed to further evaluate the influence of corticosteroids on patients with coronavirus infection.

Methods: We conducted a comprehensive literature search from January 1, 2002 to March 15, 2020 in the PubMed, Embase, Cochrane library, and China national knowledge infrastructure (CNKI). All statistical analyses in this study were performed on stata14.0.

Results: A total of 5270 patients from 15 studies were included in this meta-analysis. The result indicated that critical patients were more likely to require corticosteroids therapy (risk ratio [RR]=1.56, 95% confidence interval [CI]=1.28-1.90, P<0.001). However, corticosteroid treatment was associated with higher mortality (RR=2.11, 95%CI=1.13-3.94, P=0.019), longer length of stay (weighted mean difference [WMD]=6.31, 95%CI=5.26-7.37, P<0.001), a higher rate of bacterial infection (RR=2.08, 95%CI=1.54-2.81, P<0.001), and hypokalemia (RR=2.21, 95%CI=1.07-4.55, P=0.032) but not hyperglycemia (RR=1.37, 95%CI=0.68-2.76, P=0.376) or hypocalcemia (RR=1.35, 95%CI=0.77-2.37, P=0.302).

Conclusions: Patients with severe conditions are more likely to require corticosteroids. Corticosteroid use is associated with increased mortality in patients with coronavirus pneumonia.

Keywords: coronavirus; COVID-19; corticosteroid treatment; Meta-analysis.

Introduction

In December 2019, the pneumonia caused by a new coronavirus spread in Wuhan, China. Unbiased sequencing of samples from patients with pneumonia reveals a previously unknown type of beta-coronavirus which is similar to the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV).[1] The causative agent was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by Coronavirus Study Group, and the disease it caused was named coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO).[2, 3]

SARS-CoV-2 is a new type of highly diverse enveloped positive single stranded RNA virus, which can cause a range of symptoms including self-reported fever, fatigue, dry cough, myalgia, and difficulty breathing. [4] There is evidence that the transmission pattern of SARS-CoV-2 is human-to-human which is spread by respiratory droplets caused by coughing or sneezing.[5, 6] As of March 19, there are now more than 200,000 COVID-19 cases and more than 8,000 deaths in the world.[7] Nevertheless, there is no vaccine or antiviral treatment for human coronavirus. Therefore, it is crucial to determine the drug treatment plan as soon as possible to deal with the outbreak of COVID-19.[8]

Corticosteroids have a good inhibitory effect on inflammatory factors and are often used as an auxiliary treatment for viral pneumonia. The main anti-inflammatory effect of glucocorticoids is to inhibit a large number of pro-inflammatory genes that encode cytokines, chemokines, cell adhesion molecules, inflammatory enzymes, and receptors to address the inflammatory process and restore homeostasis.[9] However, the results of clinical studies on the role of corticosteroids remain controversial. A retrospective analysis showed that the vast majority of SARS patients received satisfactory results from the use of corticosteroids.[10] But in a retrospective observational study of MERS patients, the result showed that patients who were given corticosteroids were more likely to require mechanical ventilation, vasopressors, and renal replacement therapy.[11] Therefore, we performed this meta-analysis to identify the roles of corticosteroids in patients with coronavirus.

Methods

Search strategies

A literature search was conducted from January 1, 2002 to March 15, 2020 in the PubMed, Embase, Cochrane library, and China National Knowledge Infrastructure (CNKI) using a combination of the following key words: "SARS" or "coronavirus" or "severe acute respiratory syndrome" or “Middle East respiratory syndrome coronavirus” or “MERS viruses” or “MERS-CoV” or “novel coronavirus” or "2019-nCoV" or "COVID-19" or "SARS CoV-2" and "steroid" or "corticosteroid" or "prednisolone" or "prednisone" or "dexamethasone" or "cortisol" or "hydrocortisone" or "glucocorticoid" or "methylprednisolone" without limitations on either the publication type or language. In addition, the references listed in each identified article were also screened and manually searched to make the results more comprehensive. The work was done independently by two authors (Zhenwei Yang and Jialong Liu). Disagreements were resolved by a third investigator (Yunjiao Zhou).

Inclusion and exclusion criteria

The inclusion criteria in this meta-analysis were as follows: (1) subjects in each study included patients with coronavirus pneumonia; (2) the patients were divided into the experimental group using corticosteroids and the control group not using corticosteroids; (3) the outcomes included the use of corticosteroids in critical and non-critical patients, mortality, length of stay (LOS) and adverse reactions to corticosteroids. Exclusion criteria: (1) the same patients were enrolled in different articles; (2) commentary, editorials, case reports, letters and family-based studies; and (3) patients in studies were under 18 years old.

Data extraction

The two researchers (Zhenwei Yang and Jialong Liu) who performed the inclusion and exclusion of the literature also independently extracted data from the included studies. Differences were resolved with a third investigator (Xixian Zhao) or by consensus. We extracted the following variables: the authors, the publication year, the study design, viral type, population, treatment details (including corticosteroid use, types and doses of corticosteroids, and other treatments), and outcome measures such as the use of corticosteroids in critical and non-critical patients, mortality, LOS and

adverse reactions to corticosteroids (including bacterial infection, hyperglycemia, hypocalcemia and hypokalemia).

Quality assessment

We used the Newcastle-Ottawa scale (NOS),[12] which includes patient selection, study comparability and outcome assessment three components, to evaluate the quality of the original study. The work was done by two authors (Zhenwei Yang and Jialong Liu) and agreed upon through discussion.

Statistical analysis

All statistical analyses in this study were performed on stata14.0 (Stata, College Station, TX, USA). For dichotomized data, we calculated the risk ratio (RR) and the 95% confidence interval (CI), while for continuous data, we calculated the weighted mean difference (WMD) and the 95% CI. Heterogeneity among the studies was assessed by the Chi squared and I^2 tests. A random-effects model was used when either $P<0.10$ or $I^2>50\%$ defined significant heterogeneity across the articles. Otherwise, the fixed-effects model was used. We carried out a sensitivity analysis on the stability of the combined results. In addition, we also performed a subgroup analysis by virus type to explore the source of heterogeneity. Publication bias was assessed by funnel plots.

Results

Search results

As shown in Figure 1, the total number of records initially determined based on the search strategy was 1685. After removing 412 duplicates, we deleted another 1203 articles by reading the title and abstract of the article. We eliminated 55 articles by reading the full-text articles of the remaining 70 studies, four of which enrolled the same patients, two of which were non-adult patients, and 49 of which did not have a

control group not using corticosteroids. Finally, there were 15 articles included in our meta-analysis.[5, 10, 11, 13-24]

Study characteristics

5270 patients from 15 articles were included in our systematic review and meta-analysis. Due to one article did not give the number of people treated with corticosteroids,[14] among the remaining 14 articles, 3176 patients were treated with corticosteroids and 1780 were treated with non-corticosteroids. Among the 15 literatures, 7 are in English and 8 are in Chinese. Eleven studies included patients with SARS-CoV infection, two included patients with MERS-CoV infection, and the remaining two included patients with SARS-CoV-2 infection. There were 7 articles describing the use of corticosteroids in critical and non-critical patients,[5, 13, 15, 16, 19, 22, 23] 9 articles recorded the mortality,[10, 11, 14-18, 20, 22] three studies reported the LOS,[11, 18, 22] 2 articles described the adverse reactions to corticosteroids.[21, 24] In addition, all studies had NOS scores ≥6. The details of each included study are presented in Table 1.

The use of corticosteroids in critical and non-critical patients

The results showed that patients with severe conditions were more likely to require corticosteroids therapy (RR=1.56, 95% CI=1.28-1.90, P=<0.001; Figure 2). There was significant heterogeneity among the studies (I^2= 90.2%, P<0.001), the random effects model was adopted. Similar results were also observed in the subgroup analysis of patients with SARS-CoV-2 infection (RR=2.36, 95%CI=1.31-4.28, P=0.004, I^2=29.1%, P=0.235) and patients with SARS-CoV infection (RR=1.46, 95%CI=1.18-1.80, P<0.001, I^2=92.7%, P<0.001). Sensitivity analysis showed that the result was stable.

Mortality

The pooled RR from the nine studies revealed that the mortality was higher in patients who received corticosteroids therapy (RR=2.11, 95%CI=1.13-3.94, P=0.019,

I^2=80.9%, P<0.001; Figure 3). When we performed subgroup analysis, we found that the mortality of neither SARS-CoV (RR=2.56, 95%CI=0.99-6.63, P=0.053, I^2=77.4%, P<0.001) nor MERS-CoV (RR=2.06, 95%CI=0.66-6.44, P=0.213, I^2=89.4%, P=0.002) was not correlated with corticosteroids therapy. Sensitivity analysis showed that when we excluded a study,[14] the result was different from the previous conclusion.

LOS

LOS was longer in the corticosteroid group (WMD=6.31, 95%CI=5.26-7.37, P<0.001, I^2=1.8%, P=0.361; Figure 4), and the same result was found in the subgroup analysis of patients with SARS-CoV infection (WMD=6.34, 95%CI=5.24-7.44, P<0.001, I^2=50.3%, P=0.156).

Adverse reactions to corticosteroids

As shown in Table 2, patients treated with corticosteroids were more likely to have adverse reactions such as bacterial infection (RR=2.08, 95%CI=1.54-2.81, P<0.001, I^2=0.0%, P=0.926) and hypokalemia (RR=2.21, 95%CI=1.07-4.55, P=0.032, I^2=53.1%, P=0.104). However, there was no relationship between corticosteroid therapy and the development of hyperglycemia (RR=1.37, 95%CI=0.68-2.76, P=0.376, I^2=74.2%, P=0.049) or hypocalcemia (RR=1.35, 95%CI=0.77-2.37, P=0.302, I^2=80.4%, P=0.024).

Publication bias

We examined the publication bias of the included literature on the use of corticosteroids in critical and non-critical patients and mortality. Funnel plots showed that there was no publication bias in the use of corticosteroids in critical and non-critical patients (Figure 5A), while there might be publication bias in mortality (Figure 5B).

Discussion

As SARS-CoV-2 is an emerging virus, there is no effective antiviral treatment at present. COVID-19 patients were mainly treated with symptomatic therapy. In clinic, corticosteroids are widely used in symptomatic treatment of severe pneumonia. However, there has been considerable controversy as to whether COVID-19 patients should be treated with corticosteroids. Russell and colleagues recommend that corticosteroids should not be used in SARS-CoV-2-induced lung injury or shock outside of a clinical trial.[25] But a team of front-line physicians from China had a different perspective, they recommended short courses of corticosteroids at low-to-moderate dose, used prudently, for critical patients with COVID-19 pneumonia.[26] So it is very important to provide evidence for corticosteroid treatment of in patients with coronavirus.

In this systematic review and meta-analysis, the result indicated that patients with severe conditions were more likely to require corticosteroids therapy. The similar results were also observed in the subgroup of patients with SARS-CoV-2 infection and patients with SARS-CoV infection. A study showed that the concentrations of cytokines (such as interleukin 7 [IL7], IL8, IL9, IL10 and so on) in serum in the COVID-19 patients were higher than in healthy adults. In addition, cytokines (such as IL2, IL7, IL10 and so on) concentrations in intensive care unit (ICU) patients were higher than non-ICU patients. This revealed that patients with COVID-19 were usually accompanied by increased immune factors and inflammatory responses, and the concentrations of immune factors were associated with the severity of the disease.[5] Further autopsy revealed bilateral diffuse alveolar injury with fibrous mucinous exudate and interstitial mononuclear inflammatory infiltration dominated by lymphocytes, which were very similar to SARS-CoV and MERS-CoV infections.[27] As we all known, corticosteroids do not directly inhibit virus replication, their main role is anti-inflammatory and suppress immune response.[28] In the early stage of inflammation, glucocorticoids reduce capillary dilation, inflammatory cell exudation, leukocyte infiltration, and phagocytosis. In the late stage, glucocorticoids can inhibit the excessive proliferation of capillaries and fibroblasts. Furthermore, by binding to their receptors, glucocorticoids inhibit nuclear transcription factor-κB (NF-κB) signaling and further inhibit the transcription and translation of inflammatory factors.[9] These explained why corticosteroids therapy was more needed in severely ill patients with coronavirus infection.

Our analysis demonstrated that patients treated with corticosteroids had a higher mortality rate, and longer LOS. There might be multiple mechanisms that contributed to these outcomes. There is a study shows that glucocorticoids inhibit the production

of IL-2 and interferon-γ (IFN-γ) in T lymphocytes, shift T cell responses from the Th1 to the Th2 type, induce programmed cell death in a variety of different immunologically relevant cells, including immature T and B cell precursors and mature T cells.[29] Another study find that preexisting CD4+ T cells are associated with lower viral shedding and less severe disease.[30] There is evidence that the use of corticosteroids may lead to prolonged removal of viral RNA from the airways,[11] blood,[31] and feces of patients,[32] resulting in longer hospital stays, and ultimately increasing the risk of mortality. In addition, our analysis found that patients receiving corticosteroid therapy were more likely to develop bacterial infection due to immunosuppression. This could make the disease worse and lead to death. We also performed subgroup analysis, the result indicated that the mortality of neither SARS-CoV nor MERS-CoV was not correlated with corticosteroids therapy. Sensitivity analysis showed that the use of corticosteroids was not associated with mortality when we excluded a study.[14] Therefore, we need to treat this result with caution.

Our analysis found that patients receiving corticosteroids therapy might cause some serious adverse reactions such as bacterial infection and hypokalemia. However, only two studies in our analysis reported data on adverse reactions to corticosteroids, bias might have occurred due to the limited number of patients.

There were several meta-analyses explored the role of corticosteroids in viral pneumonia, most of which shown adverse consequences. In a meta-analysis of corticosteroid use in patients with SARS, a total of 29 studies on corticosteroids were included, of which 25 were inconclusive, and only 4 provided conclusive data on the harms of corticosteroids. [33] In a meta-analysis of corticosteroid use in patients with influenza pneumonia, the results showed that compared with placebo, corticosteroids were associated with higher mortality, longer ICU LOS, and a higher rate of secondary infection but not mechanical ventilation days.[34] In addition, a meta-analysis included ten studies with 1137 recovered SARS patients showed that patients who received higher cumulative doses and longer treatment durations of steroids were more likely to develop osteonecrosis.[35] These meta-analyses indicated that patients with coronavirus pneumonia could not benefit from corticosteroid therapy.

However, there are some limitations in this meta-analysis. First, most of the included studies were retrospective cohort studies, historical control studies, case reports, etc., with a low level of evidence and a lack of randomized controlled trials with optimized design. Second, there is no uniform standard for the time and dosage of hormones used in various studies. Third, the effects of corticosteroids may be influenced by other therapeutic options, such as antiviral drugs. Finally, due to the rapid evolution of the SARS-CoV-2 situation, some studies have not been published, while other

developments are not intended to be reported for reasons of confidentiality, which will lead to publication bias.

Conclusions

Patients with severe conditions were more likely to require corticosteroids. Corticosteroids could lead to higher mortality, longer LOS, a higher rate of bacterial infection and hypokalemia. Therefore, corticosteroid should be used with caution in the treatment of COVID-19. Corticosteroids are not recommended for patients with mild conditions, and moderate corticosteroids can be used in patients with severe conditions to suppress the immune response and reduce symptoms. Nevertheless, further multicenter clinical trials are needed to further verify this conclusion.

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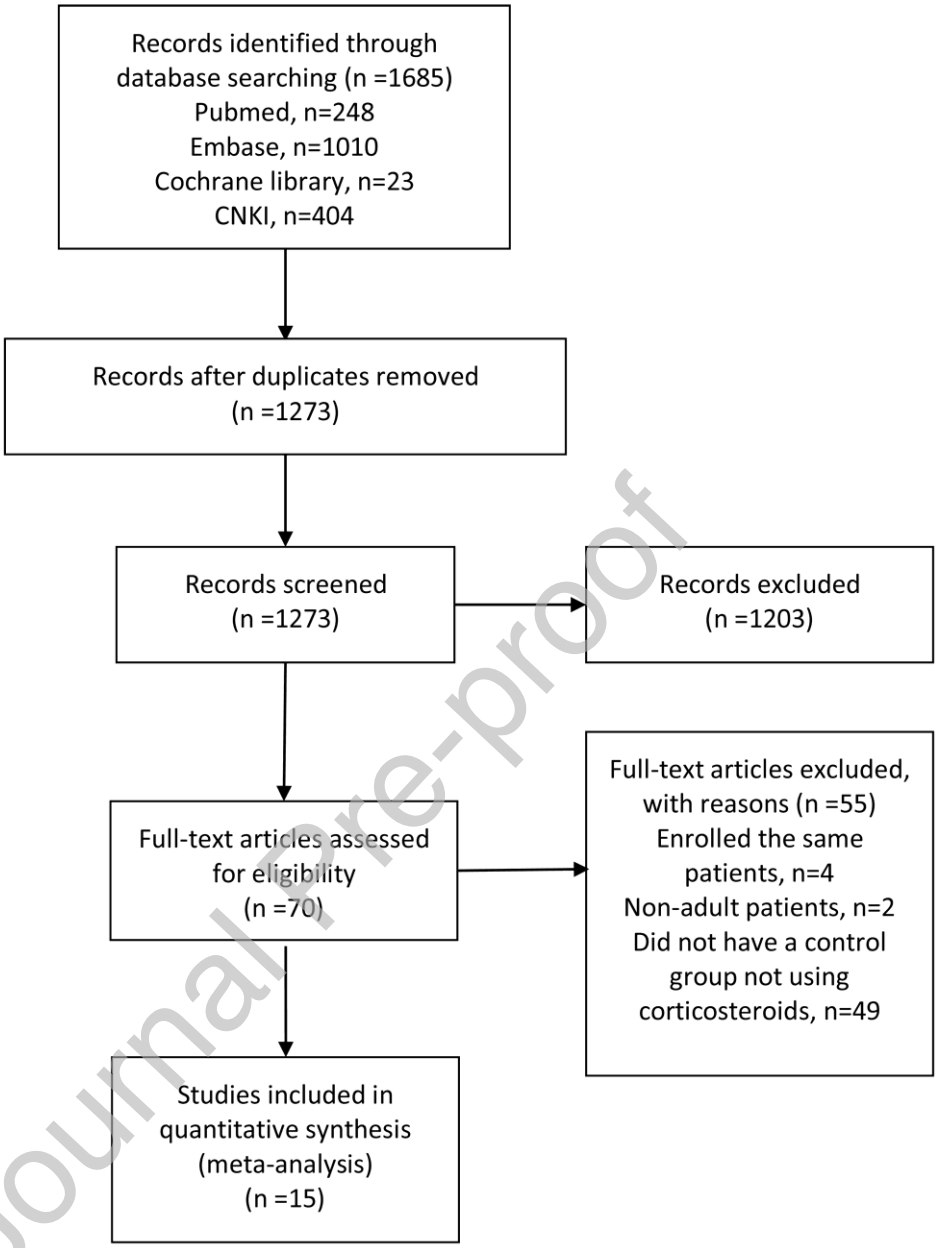

Figure 1 Flow chart of literature search and selection of studies

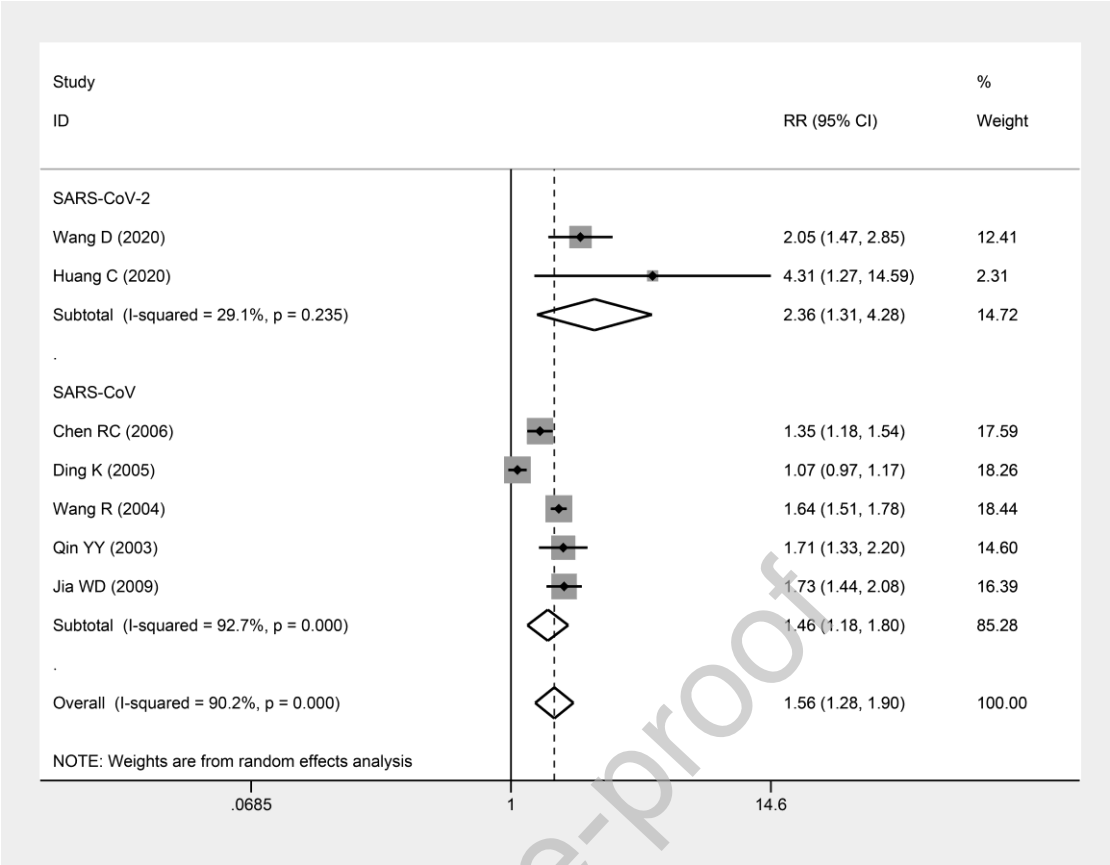

Figure 2 The use of corticosteroids in critical and non-critical patients

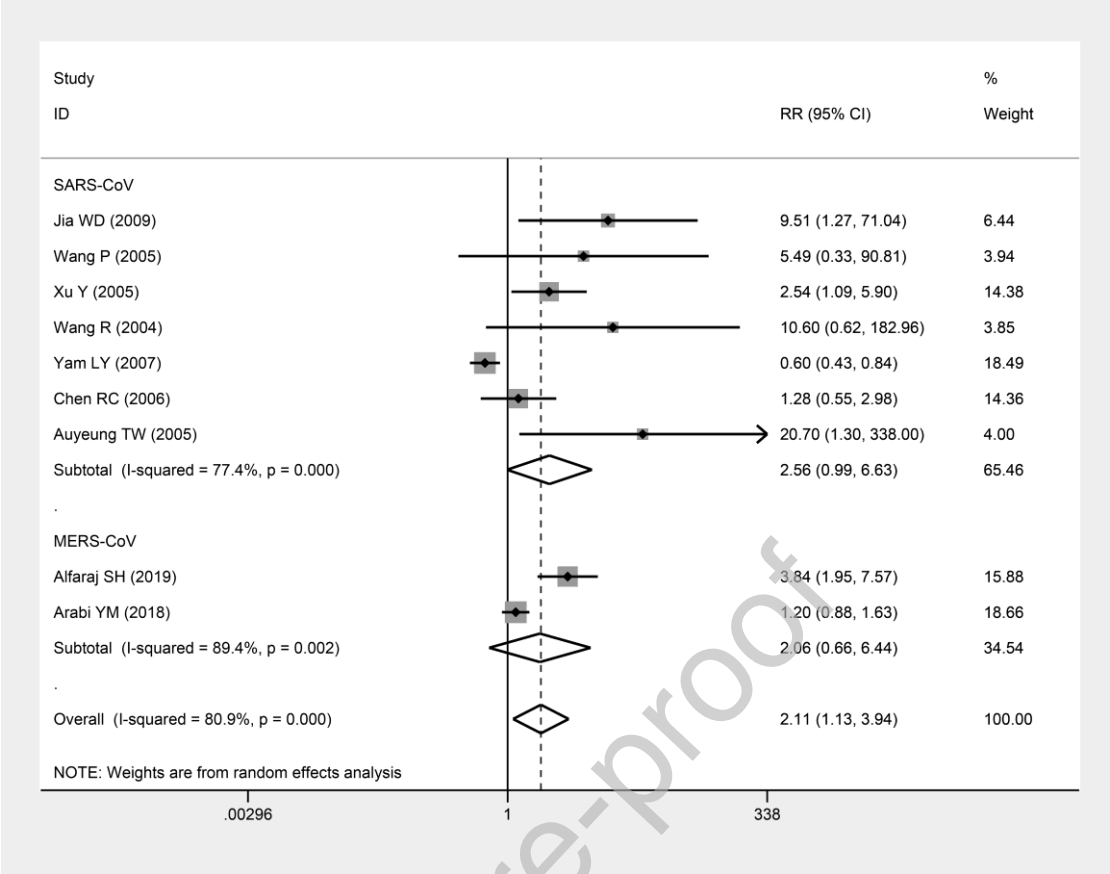

Figure 3 Effect of corticosteroids on mortality

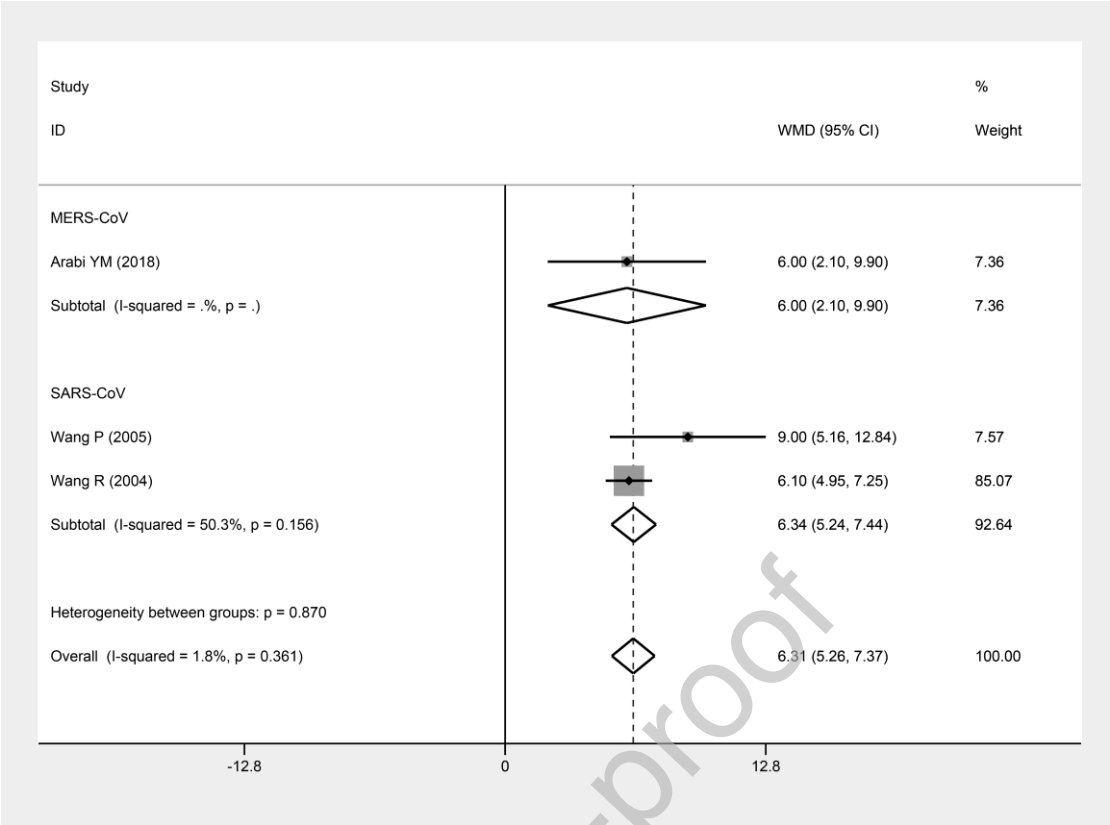

Figure 4 Effect of corticosteroids on length of stay (LOS)

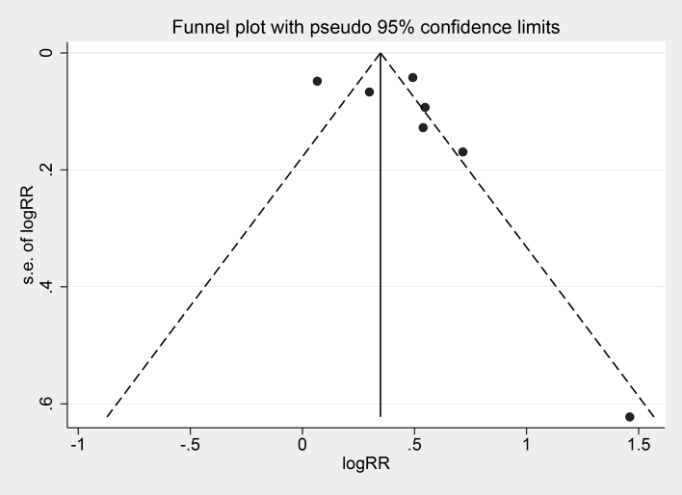

Figure 5A Funnel plot of the use of corticosteroids in critical and non-critical patients

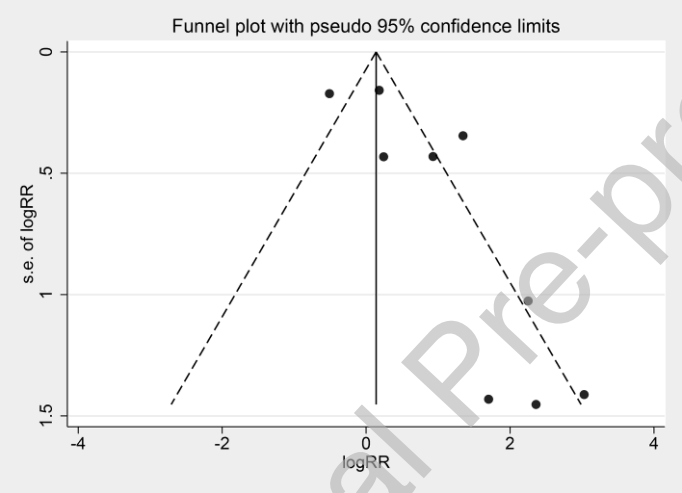

Figure 5B Funnel plots of mortality

Table 1 Characteristics of studies included in the meta-analysis

Reference	Year	Country	Viral type	Study design	Study N	Corticosteroids	Dose	Other treatments	Outcomes Measured	NOS score
Wang D[13]	2020	China	SARS-CoV-2	Retrospective	138	ICU:26 Non-ICU:36	NR	Antiviral therapy Antibacterial therapy ECMO	The use of corticosteroids	7
Alfaraj SH[14]	2019	Saudi Arabia	MERS-CoV	Retrospective	314	majority of patients	NR	Plasmapheresis Immunoglobulin ECMO, CRRT Interferon Ribavirin,	Mortality	6
Arabi YM[11]	2018	Saudi Arabia	MERS-CoV	Retrospective	309	151	The median of the maximum daily hydrocortisone-equivalent dose was 300.0 mg, with a median duration of 7.0 days.	Antiviral therapy Interferon CRRT ECMO	Mortality LOS	9
Yam LY[10]	2007	China Hong Kong	SARS-CoV	Retrospective	1287	Hydrocortisone: 621 Methylprednisolone: 177	Hydrocortisone (Group HC), mean daily dose: 695mg Methylprednisolone (Group MP), mean	Ribavirin	Mortality	9

						Pulsed methylprednisolone: 220 Prednisolone: 170	daily dose: 540mg Pulsed methylprednisolone (Group Pulse), mean daily dose: 924mg Prednisolone (Group P), mean daily dose: 468mg			
Chen RC[16]	2006	China	SARS-CoV	Retrospective	401	Noncritical: 147 Critical: 121	147 noncritical patients received corticosteroids (mean daily dose, 105.3 +/- 86.1 mg); 121 critical patients received corticosteroids at a mean daily dose of 133.5 +/- 102.3 mg,	NR	Mortality The use of corticosteroids	9
Auyeung TW[20]	2005	China Hong Kong	SARS-CoV	Retrospective	78	Corticosteroid therapy: n=66	Intravenous hydrocortisone at 10 mg/kg per day; intravenous methylprednisolone at 1–3 mg/kg per day; or pulse intravenous methylprednisolone 500–1000 mg per day for 2–3 days.	Antiviral therapy Antibacterial therapy Immunoglobulin Convalescence serum	Mortality	9
Huang C[5]	2020	China	SARS-CoV-2	Retrospective	41	ICU care: 6 No ICU care: 3	NR	Antiviral therapy Antibiotic therapy CRRT	The use of corticosteroids	7
Chinese literatures										
Jia WD[15]	2009	China	SARS-CoV	Retrospective	225	134	The initial dose of corticosteroids were	NR	Mortality The use of	8

							divided into 5 groups: 1 ~ 79 mg/d, 80 ~ 159 mg/d, 160 ~ 239 m/d, 240 ~ 319 mg/d, >320 mg/d		corticosteroids	
Ding K[19]	2005	China	SARS-CoV	Retrospective	409	Critical patients: 99 Non-critical patients: 234	II Group: methylprednisolone < 80mg/d; III Group :80mg<methylprednisolone≤ 160mg/d; IV Group: methylprednisolone > 160mg/d	NR	The use of corticosteroids	6
Wang P[18]	2005	China	SARS-CoV	Retrospective	294	Group b: 192 Group c: 53	NR	Antibacterial therapy, Antiviral therapy	Mortality LOS	9
Xu Y[17]	2005	China	SARS-CoV	Retrospective	453	313	The initial dose of corticosteroids were divided into 3 groups: 40 ~ 80 mg/d, 120 ~ 160 mg/d, and >200mg/d.	NR	Mortality	7
Wang R[22]	2004	China	SARS-CoV	Retrospective	680	41	NR	NR	Mortality LOS The use of corticosteroids	8
Wang YQ[21]	2004	China	SARS-CoV	Retrospective	460	344	Intravenous drops of methylprednisolone (40-320mg/d)	Antibacterial therapy,	Adverse reactions to corticosteroids	9

								Antiviral therapy		
He R[24]	2013	China	SARS-CoV	Retrospective	98	57	The initial dose of corticosteroids were divided into 3 groups: < 160 mg/d, 160 ~320 mg/d, and ≥320mg/d.	NR	Adverse reactions to corticosteroids	7
Qin YY[23]	2003	China	SARS-CoV	Retrospective	83	64	Intravenous methylprednisolone (40 ~ 320 mg/d), with an average of 17.3±9.0 d.	CPAP Antibacterial therapy Antiviral therapy	The use of corticosteroids	7

Note: ICU, intensive care unit; ECMO, extracorporeal membrane oxygenation; CRRT, continuous renal replacement therapy; CPAP, continuous positive airway pressure.

Table 2 Adverse reactions to corticosteroid therapy

Adverse reactions to corticosteroids	Number of studies	Pooled RR (95% CI)	P Value	Heterogeneity		Effect model
				I^2 (%)	P value	
Bacterial infection	2	2.08 (1.54-2.81)	<0.001	0.0	0.926	Fixed
Hyperglycemia	2	1.37 (0.68-2.76)	0.376	74.2	0.049	Random
Hypocalcemia	2	1.35 (0.77-2.37)	0.302	80.4	0.024	Random
Hypokalemia	2	2.21 (1.07-4.55)	0.032	53.1	0.144	Random

Note: RR, risk ratio.