REVIEW ARTICLE

Infectious medicine, virology

Impact of corticosteroid therapy on outcomes of persons with SARS-CoV-2, SARS-CoV, or MERS-CoV infection: a systematic review and meta-analysis

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Abstract

We performed a meta-analysis to determine safety and efficacy of corticosteroids in SARS-CoV-2, SARS-CoV, and MERS-CoV infections. We searched PubMed, Web of Science, Medline, WanFang Chinese database, and ZhiWang Chinese database using Boolean operators and search terms covering SARS-CoV-2, SARS-CoV, OR MERS-CoV AND corticosteroids to find appropriate studies. Review Manager 5.3 was used to analyze results of meta-analysis. Observational studies were analyzed for quality using the modified Newcastle–Ottawa scale and randomized clinical trials, using the Jadad scale. Subjects were divided into those with severe-only and other (severe and not severe) cohorts based on published criteria. Efficacy endpoints studied included mortality, hospitalization duration, rates of intensive care unit (ICU) admission, use of mechanical ventilation, and a composite endpoint (death, ICU admission, or mechanical ventilation). We included 11 reports including 10 cohort studies and 1 randomized clinical trial involving 5249 subjects (2003–2020). Two discussed the association of corticosteroids and virus clearing and 10 explored how corticosteroids impacted mortality, hospitalization duration, use of mechanical ventilation, and a composite endpoint. Corticosteroid use was associated with delayed virus clearing with a mean difference (MD) = 3.78 days (95% confidence Interval [CI] = 1.16, 6.41 days; $I^2 = 0\%$). There was no significant reduction in deaths with relative Risk Ratio (RR) = 1.07 (90% CI = 0.81; 1.42; $I^2 = 80\%$). Hospitalization duration was prolonged and use of mechanical ventilation increased. In conclusion, corticosteroid use in subjects with SARS-CoV-2, SARS-CoV, and MERS-CoV infections delayed virus clearing and did not convincingly improve survival, reduce hospitalization duration or ICU admission rate and/or use of mechanical ventilation. There were several adverse effects. Because of a preponderance of observational studies in the dataset and selection and publication biases our conclusions, especially regarding SARS-CoV-2, need confirmation in a randomized clinical trial. In the interim we suggest caution using corticosteroids in persons with COVID-19.

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Introduction

In December 2019, Wuhan, Hubei province, China, became the epicenter of a pandemic caused by severe

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acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [1] which causes coronavirus infectious disease-2019 (COVID-19). About 15% of cases of COVID-19 become severe [2]. About one-half of hospitalized persons with COVID-19 treated in the intensive care unit (ICU) receive corticosteroids versus 10–20% of hospitalized, non-ICU persons [3, 4].

There are several reports of using corticosteroids in the setting of severe coronavirus infections including SARS-CoV-2, severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). There are few data on safety and efficacy of corticosteroids in COVID-19 and its use in SARS and MERS infections is controversial [5, 6].

SARS-CoV-2, SARS-CoV, and MERS-CoV shares many genetic features and SARS-CoV-2 is highly homologous to SARS-CoV [7]. Reports of efficacy of corticosteroid in some persons with SARS-CoV infections have resulted in widespread use of this therapy to treat COVID-19, especially for persons with severe infection hospitalized in the ICU. Presently, there are few data on safety and efficacy of corticosteroids in this setting [2, 8–10]. Because of the overlapping genetic and clinical feature of SARS-CoV-2, SARS-CoV, and MERS-CoV, we performed a meta-analysis of safety and efficacy of corticosteroid use in these coronavirus infections.

Methods

Our meta-analysis focus on the effects of corticosteroids on virus clearing and mortality in persons infected with SARS-CoV-2, SARS-CoV, or MERS-CoV. We searched PubMed, Web of Science, Medline, Chinese database WanFang, and ZhiWang using the terms: "coronavirus," OR "COVID-19," OR "2019-nCoV," OR "SARS-CoV-2" OR "severe acute respiratory syndrome," OR "Middle East respiratory syndrome," OR "SARS," OR "MERS" AND "corticosteroid" OR "glucocorticoid," "hydrocortisone" OR "methylprednisolone" OR "dexamethasone" OR "steroid" with these Boolean operators. Searches were done on March 20, 2020. Two investigators independently reviewed the identified abstracts and selected articles for full review. Discordances were resolved by a third investigator.

We identified 8788 publications. We next excluded 2057 duplicate reports. The remaining 6731 publications were scanned by 3 investigators who identified 159 articles relevant publications after considering title and abstract. In total, 11 publications met our selection criteria, 10 cohort studies [2, 8–16] and 1 randomized clinical trial [6]. We excluded studies from same geographical region to avoid duplication. Because most studies were observational the possibility of duplicate

reporting was addressed by deleting small studies from the same geographical region. Publication flow and reasons for exclusions are displayed in Fig. 1 using PRIZMA flow diagram.

Inclusion and exclusion criteria

Inclusion criteria included: (1) research articles including observational studies and clinical trials but excluding reviews or case reports on the use of corticosteroids in persons with SARS-CoV-2, SARS-CoV, and MERS-CoV infections; (2) reported outcomes of virus clearance and/or death; and (3) published in English and/or Chinese. Studies with insufficient data were excluded.

Covariates studied

For each selected publication the following were extracted: (1) 1st author; (2) publication year; (3) country; (4) sample size; (5) subject-related covariates; (6) dose and duration of corticosteroid treatment; and (7) dose of corticosteroids. These data are displayed in Table 1. Primary outcome measures were rate of virus clearing and death. Secondary outcomes were duration of hospitalization, use of mechanical ventilation, composite endpoint, and corticosteroid use between severe-only and nonsevere subjects. The study used anonymized, published data requiring no Ethics Committee approval.

Risk of bias

The methodological quality of retrospective studies was assessed by the modified Newcastle–Ottawa scale (NOS) [17, 18] which consists of three domains: (1) subject selection; (2) comparability of the study groups; and (3) assessment of outcome(s). A score of 0–9 was allocated to each study except the randomized clinical trial. We considered observational studies with an NOS score ≥6 high quality. We included 1 study with an NOS score of 5 because of a large sample size (>1000 subjects) but performed sensitivity analyses excluding this study. Risk of bias in the randomized clinical trial was assessed according to the Jadad scale in the following domains: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; and (4) completed withdrawals and dropouts.

Statistical analyses

We pooled data and used Risk Ratios (RR) with 90 or 95% confidential Intervals (CI) for dichotomous outcomes including (1) death; and (2) the composite endpoint (death, ICU admission, or mechanical ventilation). We

Fig. 1 Flow diagram of choosing the appropriated articles.
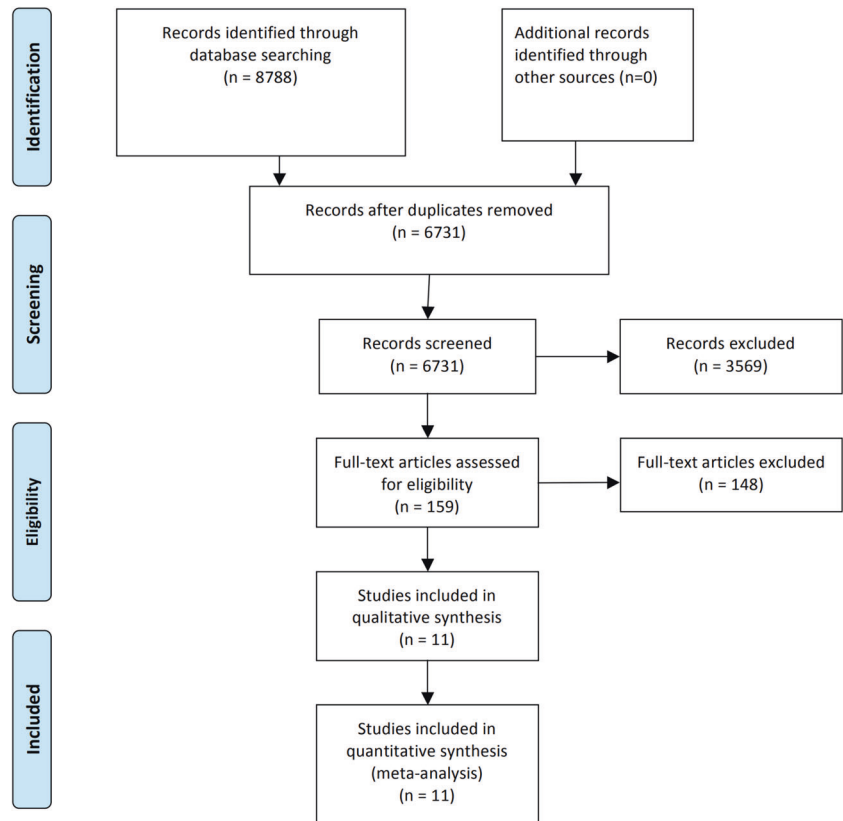
also used RR with 95% CI for dichotomous outcomes including (1) use of mechanical ventilation; and (2) corticosteroid application between severe-only and non-severe subjects. If a study considered these as separate outcomes, we used death as the endpoint. Subgroup analyses divided by severity of disease were performed for these two types of outcomes. Definitions of severity of SARS used SARS guidelines of the Ministry of Public Health of China with a blood arterial oxygenation index < 300 mm Hg [15]. Severity of COVID-19 was based on American Thoracic Society guidelines [19]. We used mean difference (MD) and 95% CI for the continuous outcome including days to SARS-CoV-2 clearing, duration of hospitalization. Funnel plots were used to screen for potential publication bias. Statistical analyses used Review Manager 5.3 (The Cochrane Collaboration). Some studies [2, 11, 14, 15] identified subjects with nonsevere infection which we analyzed separately.

Results

The meta-analysis included 10 observational studies and 1 randomized clinical trials involving 5249 subjects. In three studies the publication language was Chinese [12–14] and six, English [2, 6, 8–11, 15, 16]. Six studies discussed SARS

[6, 11–15], four, COVID-19 [2, 8–10] and one, MERS [16]. Studies were published 2003–2020 and were conducted in China (Guangzhou [2, 15], Beijing [14], Shanxi [13], Hong Kong [6, 11], Wuhan [8–10]) and Saudi Arabia [16]. The Jadad scale of the randomized clinical trial was 4 and NOS scores of the observational studies was 5–9. One study was considered poor quality evidence because of brief follow-up (Table 1).

Virus clearing

To test the impact of corticosteroid use on virus clearing we included 2 studies [6, 16] of 81 subjects (SARS, $N = 16$; MERS, $N = 65$). The data indicate corticosteroid use delayed virus clearing (MD 3.78 days, 95% confidence interval [CI], 1.16, 6.41 days; $I^2 = 0\%$; Fig. 2).

Risk of death

To test impact of corticosteroid use on risk of death, we included 8 studies [8–11, 13–16] involving 3909 subjects (COVID-19; $N = 327$; SARS, $N = 3273$; MERS, $N = 309$). The data indicate corticosteroid did not significantly reduce risk of death (RR = 1.07 [90% CI, 0.81, 1.42; $I^2 = 80\%$]). To address heterogeneity we divided subjects into severe-only and other. RRs for severe-only and other

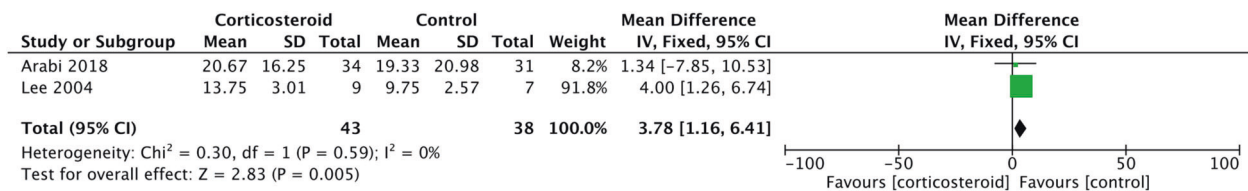**Table 1** Baseline covariates of included studies.

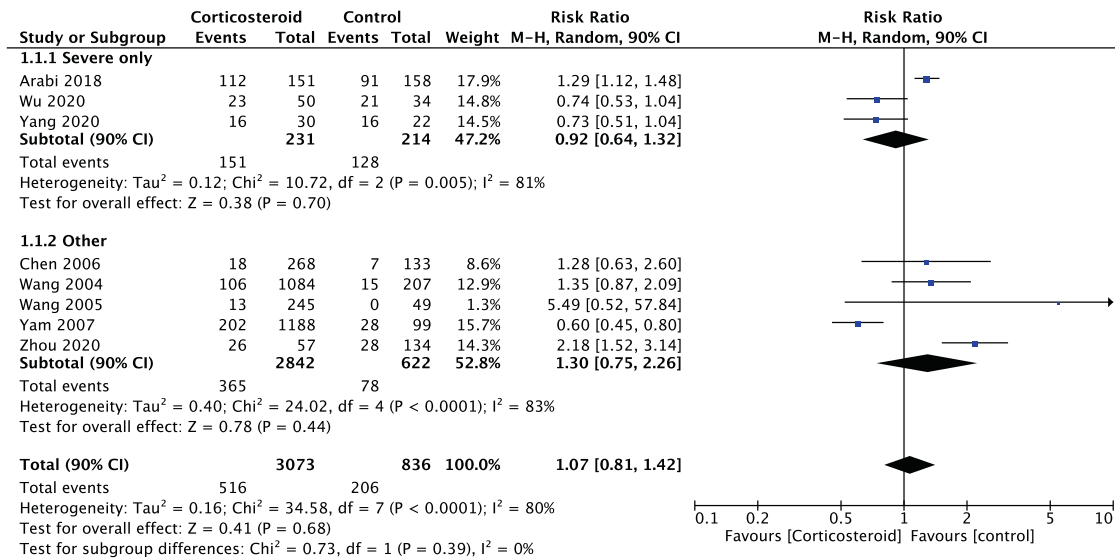| Study	Type	Country	NOS score/ Jaded score	Site	Age (A vs. B)	N (A vs. B)	Deaths (A vs. B)	Virus	Follow-up	Dose and duration	Dose calculation
Arabi [16]	Observational	Saudi Arabia;	NOS score: 9	Multi-center	58 ± 17; 55 ± 17	151; 158	112; 91	MERS-CoV	90 days	Median maximum dose: 300 mg; Median duration: 7 days (4–14 days)	Hydrocortisone-equivalent doses.
Chen [15]	Observational	Guangzhou, Guangdong, China	NOS score: 7	Single center	33 ± 12 for survivors; 54 ± 16 for nonsurvivors	268; 133	18; 7	SARS-CoV	Hospital stay	Mean dose of critical patients (133.5 ± 102.3 mg/day) Mean dose of noncritical patients (105.3 ± 86.1 mg/day) Median accumulated dose of critical patients: 2470.48; Median accumulated dose of noncritical patients: 1372.18;	Methylprednisolone-equivalent equivalents.
Guan [2]	Observational	Guangzhou, Guangdong, China	NOS score: 5	Multi-center	Composite endpoint Yes: 63 (53–71); No: 46 (35–57)	204; 895	/	SARS-CoV-2	Midpoint mortality	/	/
Jia [12]	Observational	Guangzhou, Guangdong, China	NOS score: 7	Single center	40 ± 16.5 42 ± 17	134; 91	56; 38	SARS-CoV	Hospital stay	Mean accumulated dose: 1472.82 mg; Mean daily dose: 95.92 mg/day Mean duration: 11.2 days	Methylprednisolone-equivalent equivalents.
Lee [6]	RCT	China	Jadad Score: 4	Two centers	Mean age: 35 vs. 24	9; 7	/	SARS-CoV	/	/	/
Wang [14]	Observational	Beijing, China	NOS score: 7	Multi-center	37 ± 15; 36 ± 17	1084; 207	106; 15	SARS-CoV	Hospital stay	Initial dose: 154 ± 110 mg/day Maximum dose: 251 ± 213 mg/day; Cumulative dose: 2887 ± 2619	Methylprednisolone-equivalent equivalents.
Wang [13]	Observational	Shanxi, China	NOS score: 7	Multi-center	32 ± 16; 37 ± 17	49; 245	0; 13	SARS-CoV	Hospital stay	/	/
Wu [10]	Observational	Wuhan, China	NOS score: 7	Single center	50 (40–57) for survivors; 68.5 (59–75) for nonsurvivors	50; 34	23; 21	SARS-CoV-2	Hospital stay	/	/
Yam [11]	Observational	Hong Kong, China	NOS score: 7	Multi-center	Corticosteroid (prednisolone:	1188; 99	202; 28	SARS-CoV	Hospital stay	Median cumulative doses (prednisolone:	Hydrocortisone-equivalent doses.

Table 1 (continued)

Study	Type	Country	NOS score/ Jaded score	Site	Age (A vs. B)	N (A vs. B)	Deaths (A vs. B)	Virus	Follow-up	Dose and duration	Dose calculation
					34 (26–47); methylprednisolone: 39 (29–48); hydrocortisone: 40 (31–52) Pulse corticosteroid: 47 (32–72)) Control: 61 (40–81)					7020 mg; methylprednisolone: 11,350 mg; hydrocortisone: 13,200 mg; pulse corticosteroid: 17,560 mg) Median duration (prednisolone: 15 days; methylprednisolone: 21 days; hydrocortisone: 19 days; pulse corticosteroid: 19 days)	
Yang [8]	Observational	Wuhan, China	NOS score: 7	Single center	52 ± 13 for survivors; 65 ± 11 for nonsurvivors	30; 22	16; 16	SARS-CoV-2	28 days	/	/
Zhou [9]	Observational	Wuhan, China	NOS score: 7	Two centers	52 (45–58) for survivors; 69 (63–76) for nonsurvivors	57; 134	26; 28	SARS-CoV-2	Hospital stay	/	/

Converted to hydrocortisone-equivalent doses: (methylprednisolone 1:5, dexamethasone 1:25, prednisolone 1:4). All the steroid types were converted to hydrocortisone equivalent based on relative glucocorticoid activities in the following ratios: 4 mg methylprednisolone = 5 mg prednisolone = 20 mg hydrocortisone.

A corticosteroid, *B* control, *RCT* randomized controlled trial, *NOS* Newcastle–Ottawa scale, *MERS* Middle East respiratory syndrome coronavirus, *SARS-CoV* severe acute respiratory syndrome coronavirus, *SARS-CoV-2* severe acute respiratory syndrome coronavirus-2.

Study or Subgroup	Corticosteroid			Control			Weight	Mean Difference IV, Fixed, 95% CI
	Mean	SD	Total	Mean	SD	Total		
Arabi 2018	20.67	16.25	34	19.33	20.98	31	8.2%	1.34 [-7.85, 10.53]
Lee 2004	13.75	3.01	9	9.75	2.57	7	91.8%	4.00 [1.26, 6.74]
Total (95% CI)			**43**			**38**	**100.0%**	**3.78 [1.16, 6.41]**

Heterogeneity: Chi^2 = 0.30, df = 1 (P = 0.59); I^2 = 0%
Test for overall effect: Z = 2.83 (P = 0.005)

Fig. 2 The effect of corticosteroid on virus clearness. Comparison of virus clearness between corticosteroid and comparator.

Study or Subgroup	Corticosteroid Events	Total	Control Events	Total	Weight	Risk Ratio M–H, Random, 90% CI
1.1.1 Severe only						
Arabi 2018	112	151	91	158	17.9%	1.29 [1.12, 1.48]
Wu 2020	23	50	21	34	14.8%	0.74 [0.53, 1.04]
Yang 2020	16	30	16	22	14.5%	0.73 [0.51, 1.04]
Subtotal (90% CI)		**231**		**214**	**47.2%**	**0.92 [0.64, 1.32]**
Total events	151		128			

Heterogeneity: Tau^2 = 0.12; Chi^2 = 10.72, df = 2 (P = 0.005); I^2 = 81%
Test for overall effect: Z = 0.38 (P = 0.70)

1.1.2 Other						
Chen 2006	18	268	7	133	8.6%	1.28 [0.63, 2.60]
Wang 2004	106	1084	15	207	12.9%	1.35 [0.87, 2.09]
Wang 2005	13	245	0	49	1.3%	5.49 [0.52, 57.84]
Yam 2007	202	1188	28	99	15.7%	0.60 [0.45, 0.80]
Zhou 2020	26	57	28	134	14.3%	2.18 [1.52, 3.14]
Subtotal (90% CI)		**2842**		**622**	**52.8%**	**1.30 [0.75, 2.26]**
Total events	365		78			

Heterogeneity: Tau^2 = 0.40; Chi^2 = 24.02, df = 4 (P < 0.0001); I^2 = 83%
Test for overall effect: Z = 0.78 (P = 0.44)

Total (90% CI)		**3073**		**836**	**100.0%**	**1.07 [0.81, 1.42]**
Total events	516		206			

Heterogeneity: Tau^2 = 0.16; Chi^2 = 34.58, df = 7 (P < 0.0001); I^2 = 80%
Test for overall effect: Z = 0.41 (P = 0.68)
Test for subgroup differences: Chi^2 = 0.73, df = 1 (P = 0.39), I^2 = 0%

Fig. 3 The impact of corticosteroid on the mortality of studied subjects. Comparison of mortality between corticosteroid and comparator.

cohorts were RR = 0.92 (0.64, 1.32; I^2 = 81%) and RR = 1.30 (0.75, 2.26; I^2 = 83%; Fig. 3).

Duration of hospitalization

To test impact of corticosteroid use on duration of hospitalization we included 3 studies [12, 13, 16] involving 828 subjects (SARS, N = 519; MERS, N = 309). The data indicate corticosteroid use increased duration of hospitalization with MD = 9.66 days (95% CI, 5.15, 14.18 days); I^2 = 85%; Fig. 4. We were unable to further analyze this endpoint by cohorts because of our study design.
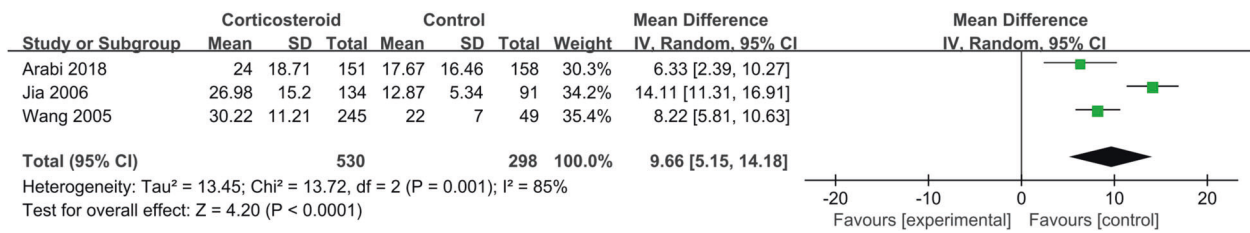
Use of mechanical ventilation

To test impact of corticosteroid use on use mechanical ventilation we included 3 studies [11, 14, 16] involving 2887 subjects (COVID-19, N = 2578; MERS, N = 309). The data indicate corticosteroid use is not associated with use of mechanical ventilation, RR = 1.33 (95% CI, 0.73, 2.42; I^2 = 70%; Fig. 5). We were unable to determine whether subjects began receiving corticosteroids before or after use of mechanical ventilation because of our study design.
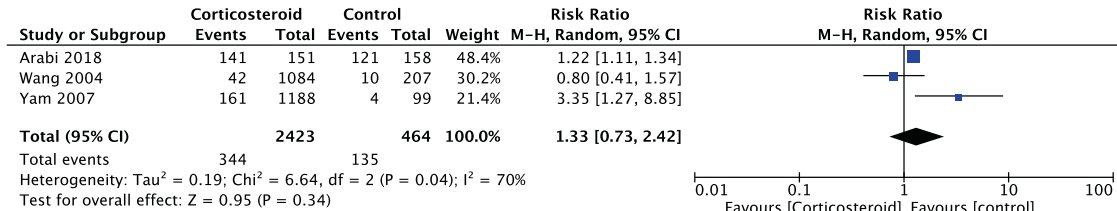
Composite endpoint

To test impact of corticosteroid use on the composite endpoint we included 9 studies [2, 8–11, 13–16] involving 5008 subjects (COVID-19, N = 1426; SARS, N = 3273; MERS, N = 309). The data indicate no improvement with corticosteroid use RR = 1.31 (0.92, 1.88; I^2 = 89%). RRs for the severe-only and other cohorts were RR = 0.92 (0.64, 1.32; I^2 = 81%) and RR = 1.73 (0.90, 3.31; I^2 = 91%; Supplementary Fig. 1).

Comparison of corticosteroid use between severe-only and nonsevere subjects

To determine if corticosteroid use was more common in subjects with severe versus nonsevere infections we compared frequency of use in these cohorts. We included 4 studies [2, 11, 14, 15] involving 4078 subjects (SARS, N = 2979; COVID-19, N = 1099). The data indicate subjects with severe-only coronavirus infections were more likely receive corticosteroids with an RR = 1.48 (95% CI, 1.03, 2.13; I^2 = 99%; Supplementary Fig. 2).

Study or Subgroup	Corticosteroid Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Arabi 2018	24	18.71	151	17.67	16.46	158	30.3%	6.33 [2.39, 10.27]
Jia 2006	26.98	15.2	134	12.87	5.34	91	34.2%	14.11 [11.31, 16.91]
Wang 2005	30.22	11.21	245	22	7	49	35.4%	8.22 [5.81, 10.63]
Total (95% CI)			530			298	100.0%	9.66 [5.15, 14.18]

Heterogeneity: Tau² = 13.45; Chi² = 13.72, df = 2 (P = 0.001); I² = 85%
Test for overall effect: Z = 4.20 (P < 0.0001)

Fig. 4 The association of corticosteroid and hospital stay length. Comparison of hospital stay time between corticosteroid and comparator.

Study or Subgroup	Corticosteroid Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Arabi 2018	141	151	121	158	48.4%	1.22 [1.11, 1.34]
Wang 2004	42	1084	10	207	30.2%	0.80 [0.41, 1.57]
Yam 2007	161	1188	4	99	21.4%	3.35 [1.27, 8.85]
Total (95% CI)		2423		464	100.0%	1.33 [0.73, 2.42]
Total events	344		135			

Heterogeneity: Tau² = 0.19; Chi² = 6.64, df = 2 (P = 0.04); I² = 70%
Test for overall effect: Z = 0.95 (P = 0.34)

Fig. 5 The correlation between corticosteroid and invasive ventilation. Comparison of the incidence of invasive ventilation between corticosteroid and comparator.

Publication bias

We found potential publication bias in mortality studies in subjects receiving or not receiving corticosteroids with some studies falling outside the 95% CI of the funnel plat (Supplementary Fig. 3). There was publication bias in the studies included in the meta-analysis.

Discussion

SARS-CoV, MERS-CoV, and SARS-CoV-2 induce host immune responses which, when severe, damage the lungs and cause death [3, 20, 21]. Corticosteroids are frequently used to treatment persons with these coronavirus infections, especially when severe. Whether this strategy is safe and effective is controversial. Other approaches include counteracting high interleukin-6 concentrations with drugs such as tocilizumab [22].

The results of our meta-analysis indicate giving corticosteroids in this setting delayed virus clearing of SARS-CoV and MERS-CoV. Whether this is so for SARS-CoV-2 is unknown. Our analysis of this issue included relatively few subjects so this conclusion should be viewed cautiously.

We determined corticosteroid use did not reduce deaths but was associated with increased hospitalization duration. There was no favorable impact on a composite endpoint of death, ICU admission, or mechanical ventilation. It was not possible to determine whether corticosteroid use preceded or followed use of mechanical ventilation. It is also important to emphasize associations and correlations do not imply cause-and-effect. Because most of the data come from observational databases and because corticosteroids are more likely to be given to persons with severe infections there is selection bias and our conclusions should be viewed cautiously. Also, because 6 of the 11 studies are from subjects with SARS-CoV and MERS-CoV our conclusions may not apply to SARS-CoV-2 infection. However, genetic homology of these viruses and similar, albeit not identical, clinical features of these infections make analyses of data from studies of SARS-CoV and MERS-CoV infections reasonable proxies.

A previous meta-analysis of corticosteroid use in persons with influenza (mostly H1N1) reported increased mortality [23]. Acute respiratory distress syndrome (ARDS) is the typical evolution of infectious pneumonia. It is unclear whether corticosteroids are effective in ARDS. Three cohort studies summarized in a meta-analysis reported corticosteroid use increased mortality in persons with influenza-related ARDS [24]. In another study low- but not high-doses corticosteroids reduced mortality in persons with ARDS [25] suggesting dose may be an important co-variate in data analyses.

As indicated, the OR for death in subjects with severe-only coronavirus infection receiving corticosteroids is RR = 0.92 (0.64, 1.32; $I^2 = 80\%$). How to interpret this central estimate and 90% CI is controversial. Although the CI includes 1 and the I^2 is generally regarded as not significant (using an arbitrary cutoff significance level), the most conservative interpretation is that the results are inconclusive and consistent with as much as a 36% reduction or an almost 1.32-fold increase in risk of death. It is important to consider the absence of a statistically significant OR is not definitive evidence of risk or benefit.

Safety and efficacy of corticosteroids in persons with SARS-CoV-2 infection COVID-19 can only be properly tested in a randomized clinical trial. However, such a trial is unlikely to be done. Our meta-analysis may help inform the decision whether to give corticosteroids.

Conclusion

Corticosteroid use in subjects with SARS-CoV-2, SARS-CoV, and MERS-CoV infections delayed virus clearing and did not convincingly improve survival, reduce hospitalization duration or ICU admission rate and/or use of mechanical ventilation. There were several adverse effects. Because of a preponderance of observational studies in the dataset and selection and publication biases our conclusions, especially regarding SARS-CoV-2, need confirmation in randomized clinical trials. In the interim we suggest caution using corticosteroids in persons with COVID-19. Our results also further consolidate the National Institute of Health (NIH) COVID-19 treatment guideline regarding corticosteroid interventions (https://covid19treatmentguidelines.nih.gov/critical-care/pharmacologic-interventions/).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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