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Primary complications after cardiac surgery: towards better understanding, prediction, and prevention

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Corticosteroid use in COVID-19 patients: a systematic review and meta-analysis on clinical outcomes

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ABSTRACT

Background: In the current SARS-CoV-2 pandemic, there has been worldwide debate on the use of corticosteroids in COVID-19. In the recent RECOVERY trial, evaluating the effect of dexamethasone, a reduced 28-day mortality in patients requiring oxygen therapy or mechanical ventilation was shown. Their results have led to considering amendments in guidelines or already recommending corticosteroids in COVID-19. However, the effectiveness and safety of corticosteroids remain uncertain, and reliable data to further shed light on the benefit and harm are needed.

Objectives: The aim of this systematic review and meta-analysis was to evaluate the effectiveness and safety of corticosteroids in COVID-19.

Methods: A systematic literature search of RCTS and observational studies on adult patients was performed across Medline/PubMed, Embase and Web of Science from December 1, 2019, until October 1, 2020, according to the PRISMA guidelines. Primary outcomes were short-term mortality and viral clearance (based on RT-PCR in respiratory specimens). Secondary outcomes were: need for mechanical ventilation, need for other oxygen therapy, length of hospital stay and secondary infections.

Results: Forty-four studies were included, covering 20,197 patients. In twenty-two studies, the effect of corticosteroid use on mortality was quantified. The overall pooled estimate (observational studies and RCTs) showed a significant reduced mortality in the corticosteroid group (OR 0.72 (95%CI 0.57–0.87)). Furthermore, viral clearance time ranged from 10 to 29 days in the corticosteroid group and from 8 to 24 days in the standard of care group. Fourteen studies reported a positive effect of corticosteroids on need for and duration of mechanical ventilation. A trend toward more infections and antibiotic use was present.

Conclusions: Our findings from both observational studies and RCTs confirm a beneficial effect of corticosteroids on short-term mortality and a reduction in need for mechanical ventilation. And although data in the studies were too sparse to draw any firm conclusions, there might be a signal of delayed viral clearance and an increase in secondary infections.

INTRODUCTION

Since the start of the outbreak, Coronavirus disease 2019 (COVID-19), caused by the novel coronavirus SARS-CoV-2, has spread globally from Wuhan, China. 40,559,736 cases have been reported and 1,121,499 people have died as of October 19th (1). Many countries have been affected, causing immense stress on healthcare systems worldwide. This is the third epidemic caused by a coronavirus, after Severe Acute Respiratory Syndrome (SARS) in 2002 and Middle East Respiratory Syndrome (MERS) in 2012 (2,3). The clinical presentation ranges from asymptomatic or mild disease to severe pneumonia in which the most severe cases deteriorate with acute respiratory distress syndrome (ARDS) requiring prolonged mechanical ventilation, or even Extra-corporeal Membrane Oxygenation (ECMO) (4,5). Approximately 16-35% develop severe pneumonia, 2-17% need mechanical ventilation, of whom up to 15 % need ECMO therapy (6,7,8), and the case fatality rate is 1.4-15% (5,9,10). In the pathophysiology of severe COVID-19, the host immune response plays a key role and it has become evident that COVID-19 pneumonia is associated with both hyper inflammation and immune paralysis (11). A clinical presentation of massive vascular inflammation, disseminated coagulation, shock, and ARDS is frequently triggered (9-11).

Though many therapies aiming at mitigation of the inflammatory response are being evaluated, strong evidence of benefit is lacking. Corticosteroids might have beneficial effects in overcoming both hyperinflammation and ARDS (4,15-17). Furthermore, they could serve as an easily accessible and affordable treatment option. On the other hand, there are known adverse effects of corticosteroid use, such as delayed viral clearance, opportunistic infections and suppression of the hypothalamic-pituitary-adrenal axis.[2,18,19] Earlier studies done in MERS-CoV and SARS-CoV showed delayed viral clearance, opportunistic infections and hyperglycemia (20-22). Therefore, a high number of observational studies and randomized controlled trials (RCT) on corticosteroids for COVID-19 have been initiated and reported, and the signal is a beneficial effect. The RECOVERY trial was the first to report that the use of dexamethasone as opposed to usual care reduced 28-day mortality in patients requiring oxygen therapy or mechanical ventilation (23). And a prospective meta-analysis of seven randomized clinical trials showed that administration of corticosteroids was associated with lower 28-day all-cause mortality (24). And while initially the World Health Organization (WHO) recommended against corticosteroid treatment, as of September 2nd 2020, the WHO recommends systemic corticosteroids rather than no systemic corticosteroids for the treatment of patients with severe and critical COVID-19 (15,25). Also, the Surviving Sepsis Guideline on management of COVID-19 recommends administration of steroids in patients with severe COVID-19 on mechanical ventilation with ARDS, and in patients with COVID-19 and refractory shock (26).

However, the effectiveness and safety of corticosteroids still remain uncertain, because of scarcity of RCTs and inconclusive observational studies, and reliable data to further shed light on the benefit and harm are needed. Therefore, the aim of this systematic review and meta-analysis of observational studies and RCTs was to evaluate the effectiveness and safety of corticosteroids in COVID-19.

METHODS

Data sources and search strategy

A systematic review according to the PRISMA guidelines was conducted (27). The meta-analysis was retrospectively registered under number 38752 at ISRCTN.org. A comprehensive systematic search was conducted for published studies in Medline/PubMed, Embase, and Web of Science from December 1st 2019 to October 1st 2020. The search strategy consisted of the components “COVID-19”, “intensive care”, and “corticosteroids” (supplement 8.1).

Eligibility

RCTs and observational cohort studies assessing the effect of corticosteroids in COVID-19 were eligible if they met the following inclusion criteria: adult patients (age ≥ 18 years), COVID-19 patients diagnosed by reverse transcriptase polymerase chain reaction (RT-PCR), reporting on outcome measures in relation to corticosteroid treatment, corticosteroids not restricted for type, dose and duration. Studies concerning pregnant women or children, reviews, case series including less than 15 patients and articles that were not available in English were excluded (28).

Definition of primary and secondary outcomes

The primary outcomes were mortality (i.e short-term mortality as defined in the study, including 28-day, 30-day and hospital mortality) and viral clearance (i.e. as defined by the study, based on RT-PCR in respiratory specimens). Secondary outcomes were: need for invasive mechanical ventilation, duration of mechanical ventilation, ventilator free days or other oxygen therapy as reported by the investigators, length of hospital stay (LOS-hospital) and secondary infections. For exact used definitions see supplement 8.2.

Study selection

Suitable studies were selected in two stages. First, six independent reviewers screened all selected titles and abstracts (JvP, JV, EH, KN, PB, SA). If there was consensus that a study was unsuitable for inclusion, it was excluded. Next, the full-text articles were screened independently by two authors and included if both authors agreed. If needed, the article was discussed with the third reviewer until consensus was reached.

Data extraction and quality analysis

After selection, data were extracted by one and checked by a second investigator (JvP, JV, EH, KN, PB). For each study, the author, journal, country, city and hospital in which the study was conducted, date of start of inclusion, study population, study groups, type, dose, route of administration of corticosteroid, median time before corticosteroid initiation, duration of administration, primary and secondary outcomes and adverse events at any time point after admission were extracted in a standardized data extraction form (supplement 8.2).

For each individual study the quality was assessed. For RCTs the Risk of Bias was assessed on six domains (random sequence generation, concealment of allocation, blinding, selective outcome reporting, incomplete outcome data and other) (29,30). The Newcastle Ottawa Scale was used for validity assessment of observational studies (31,32). The NOS score ranges from 0 (low quality) to 9 (high quality) points.

Data analysis and reporting

For the effect of corticosteroids on mortality, a pooled estimate was calculated and graphically summarized in a forest plot. Data from observational studies were analyzed separately from the RCTs, and both separate results and overall combined outcomes were calculated and summarized in the plot. When available, the adjusted odds ratio (OR), relative risk (RR) from the cohort studies were used for pooling to reduce confounding. Since the endpoint (mortality) occurred relative infrequently, the OR will be close to the RR and therefore we decided to pool both RR and OR estimates of the individual studies (33). Furthermore, a pooled estimate was calculated and graphically summarized in a forest plot for need for mechanical ventilation.

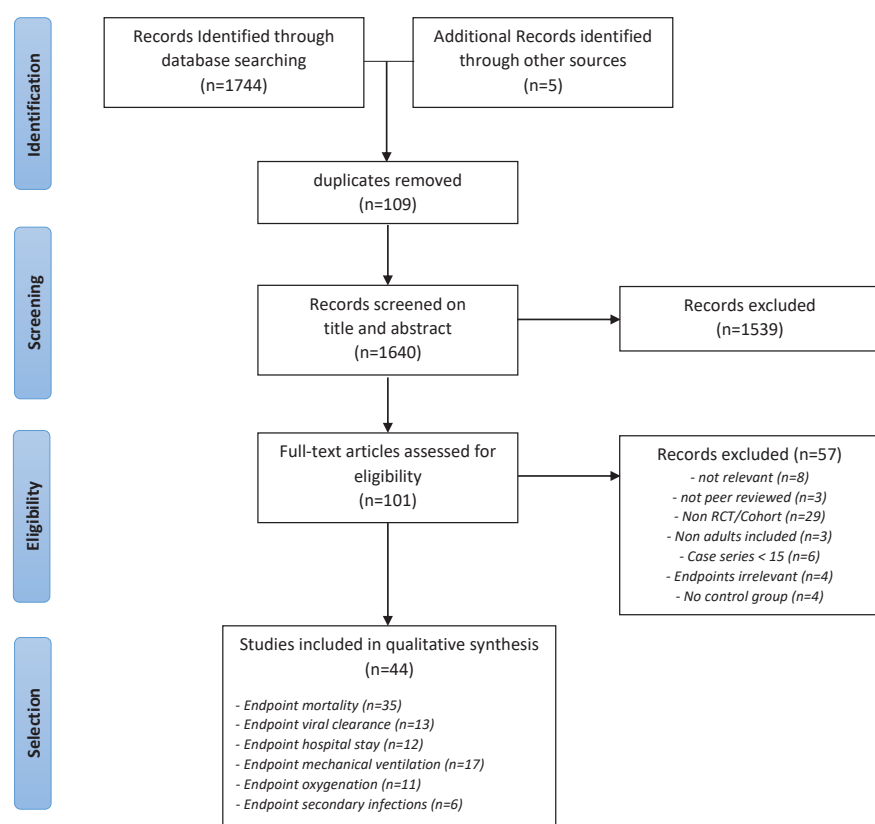
To allow studies to have a different underlying effect, a random effects model was used. I^2 statistics was used to quantify heterogeneity. Furthermore, for the pooled estimate of effect on mortality, τ^2 was used to assess the variance of the true effects. The GRADE approach was used to assess the quality of the evidence for the effect of corticosteroids on mortality. STATA 16.0 was used to perform data analysis.

RESULTS

Study selection

Our search yielded 1640 unique studies. After qualification of title and abstract, 101 studies were selected for full review. Based on exclusion criteria, 57 additional studies were excluded (references in supplement 8.3). The remainder of 44 studies, comprising 20,197 patients, was included in this systematic review and meta-analysis. (Figure 1)

Figure 1. Flowchart Study selection.



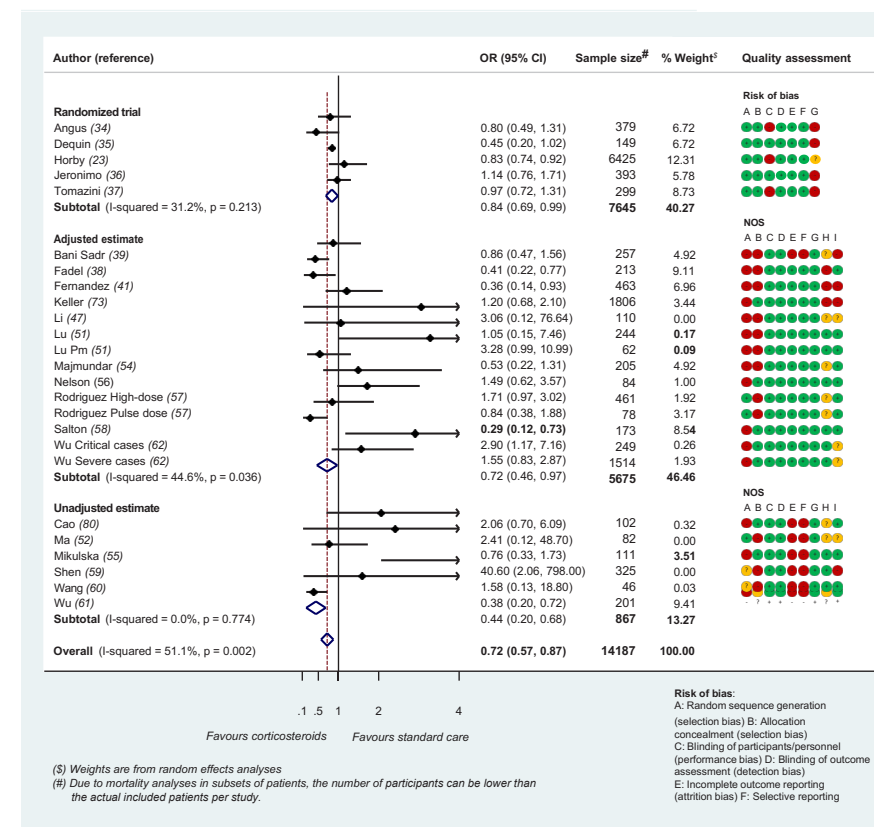
Study Characteristics (table 1 and supplement 8.4)

Thirty-one of the 44 studies originated in China, 11 in Europe, five in North America, two in South America and one study was multi-continental. The inclusion period ranged from late December 2019 until August 20, 2020. The majority of studies were retrospective observational studies (37/44), five were RCTs (23, 34-37), and there were

two studies with historical controls (38, 40). The study population varied from hospitalized patients (28/44) to patients admitted to the Intensive Care Unit (ICU) (15/44), and one study included discharged patients for viral clearance assessment. The median age of patients ranged from 34 to 75 years.

For the observational studies the median NOS score was 5 (2-8) points (supplement 8.5). For the RCT the risk of bias table is depicted in Figure 2.

Figure 2. Forest plot mortality.



Corticosteroid Regimen (table 1 and supplement 8.6)

In the 44 studies very diverse corticosteroid strategies were used. If reported (n=35), methylprednisolone was the most frequently prescribed (n = 28) (35,36,38-65). Prednisone (n=5) and dexamethasone (n=5) and hydrocortisone (n=4) were also used, some in studies that allowed multiple corticosteroid regimens (n=9).

Table 1. Study Characteristics

	Author	Reference	Study type	Type - dose ^γ corticosteroids	Sample size	CoVID - Study population	Reporting outcome ^α						Quality score ^δ (Risk of bias or NOS)	Main findings
							M	V	H	R	O	I		
1	Angus	34	REMAPt ^β	Hydrocortisone < 1 mg/kg ED	403	ICU patients	x		x	x			Risk of Bias ^δ	Two hydrocortisone dosing resulted high probabilities of superiority with regard to the odds of improvement in organ support-free days within 21 days, compared to standard of care
2	Bani-Sadr	39	Cohort with historical controls	Prednisolone or Methylprednisolone ≥ 1 mg/kg ED	319	Hospitalized patients	x				x	x	4	Addition of corticosteroids to our institution's COVID-19 treatment protocol was associated with a significant reduction in hospital mortality in the 'after' period
3	Cao	80	Retrospective Observational	Unknown	102	Hospitalized patients	x						5	Patient characteristics seen more frequently in those who died were development of systemic complications following onset of the illness and the severity of disease requiring admission to the ICU.
4	Chen Zu		Retrospective Observational	Unknown	267	Hospitalized patients	x	x					7	Corticosteroid treatment is associated with prolonged viral RNA shedding and should be used with caution.
5	Chroboczek	72	Retrospective Observational	Unknown	70	Hospitalized patients				x			6	Corticosteroids therapy affected the risk of intubation with a risk difference of -47.1% (95% CI -71.8 to -22.5).
6	Dequin	35	Randomized controlled trial	Methylprednisolone or Hydrocortisone < 1 mg/kg ED	149	ICU patients with respiratory failure	x			x	x	x	Risk of Bias ^δ	Low dose hydrocortisone, compared with placebo, did not significantly reduce treatment failure (defined as death or persistent respiratory support) at day 21 in critically ill patients.
7	Fadel	38	Quasi Experimental	Methylprednisolone ≥ 1 mg/kg ED	213	Moderate to severe CoVID patients	x		x	x			6	An early short course of methylprednisolone in patients with moderate to severe COVID-19 reduced escalation of care and improved clinical outcomes
8	Fang Mei	40	Retrospective Observational	Methylprednisolone < 1 mg/kg ED	78	Hospitalized patients		x					5	Low-dose corticosteroid therapy may not delay viral clearance in patients with COVID-19.
9	Feng Ling	66	Retrospective Observational	Unknown	476	Hospitalized patients	x		x				5	Differences in AT II receptor inhibitors use were associated with different severities of disease. Multiple lung lobes involvement and pleural effusion were associated with the severity of COVID-19. Advanced age (>75 yr) was a risk factor for mortality.
10	Fernandez	41	Retrospective Observational	Methylprednisolone ≥ 1 mg/kg ED	463	Patients with ARDS hyperinflammation	x				x		5	Glucocorticoid use is associated with increased survival and improved mortality rates in Severe CoVID-19 patients.
11	Gazzaruso	42	Retrospective Observational	Methylprednisolone or Prednisone < 1 mg/kg ED	219	Hospitalized patients	x				x		3	Anti-rheumatic drugs, probably steroids included, may modulate inflammation and avoid a hyperinflammation that leads to severe complications and death in subjects with COVID-19.

Table 1. Continued

	Author	Reference	Study type	Type - dose ^γ corticosteroids	Sample size	CoVID - Study population	Reporting outcome ^α						Quality score ^δ (Risk of bias or NOS)	Main findings
							M	V	H	R	O	I		
12	Gong Guan	43	Retrospective Observational	Methylprednisolone ≥ 1 mg/kg ED	34	Hospitalized Patients < 50 years		x				x	6	Corticosteroids therapy can effectively release COVID-19 symptoms, improve oxygenation, and prevent disease progression. However, it can prolong the negative conversion of nucleic acids.
13	Horby	23	Randomized controlled trial	Dexamethasone < 1 mg/kg ED	6425	Hospitalized patients	x		x	x			Risk of Bias ^δ	The use of dexamethasone resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone at randomization but not among those receiving no respiratory support.
15	Hu Wang	44	Retrospective Observational	Prednisolone or Methylprednisolone ≥ 1 mg/kg ED	308	Hospitalized patients	x	x					4	Glucocorticoid therapy did not significantly influence the outcomes nor the adverse events of COVID-19 pneumonia
16	Huang Song	45	Retrospective Observational	Methylprednisolone 2 study- groups: High: ≥ 1 mg/kg ED Low: < 1mg/kg ED	64	Hospitalized patients	x						4	There were no significant differences in the duration of severe illness or the number of days on high level respiratory support between low dose and high dose methylprednisolone group. The mean number of days in the hospital was higher in the high dose group
14	Huang Yang	81	Retrospective Observational	Unknown	60	Severe CoVID patients						x	5	There were no statistically significant differences in immunoglobulin therapy and GCs therapy between the improvement and deterioration subgroups.
17	Jeronimo	36	Randomized controlled trial	Methylprednisolone < 1 mg/kg ED	393	Hospitalized patients	x		x	x		x	Risk of Bias ^δ	Results showed no overall reduction in mortality in 28 days. Patients over 60 years presented a lower mortality in a subgroup analysis.
18	Keller	73	Retrospective Observational	Unknown	1806	Early hospitalized patients	x			x			6	In high CRP group, glucocorticoids show significantly reduced risk of mortality or mechanical ventilation (odds ratio, 0.23; 95% CI, 0.08-0.70). In low CRP group glucocorticoids were associated with significantly increased risk of mortality or mechanical ventilation (OR, 2.64; 95% CI, 1.39-5.03).
19	Li Hu	46	Retrospective Observational	Methylprednisolone high and low ED	203	Hospitalized patients		x					5	A dose response relation is suggested for corticosteroids on viral shedding. In addition, high-dose but not low-dose corticosteroids were found to potentially increase mortality in severe patients
20	Li Li	47	Retrospective Observational	Methylprednisolone or Prednisone < 1 mg/kg ED	475	Non Severe CoVID patients	x	x	x			x	5	Early, low-dose, and short-term corticosteroids therapy was associated with worse clinical outcomes
21	Li Zhou	48	Retrospective Observational	Methylprednisolone ≥ 1 mg/kg ED	187	Radiologically progressive CoVID patients				x	x		6	Short-term, low-to-moderate-dose corticosteroids benefits patients with LDH levels of less than two times the ULN, who may be in the early phase of excessive inflammation

Table 1. Continued

	Author	Reference	Study type	Type - dose ^γ corticosteroids	Sample size	CoVID - Study population	Reporting outcome ^α						Quality score ^δ (Risk of bias or NOS)	Main findings
							M	V	H	R	O	I		
22	Lui Fang	49	Retrospective Observational	Methylprednisolone ≥ 1 mg/kg ED	101	Hospitalized patients	x						3	The majority of patients present primarily with fever, and typical manifestations on chest imaging. Middle-aged and elderly patients with underlying comorbidities are susceptible to respiratory failure and may have a poorer prognosis.
23	Liu Zhang	81	Retrospective Observational	Unknown	1190	Hospitalized patients	x						5	Treatment with glucocorticoids increased the risk of progression from not severe to severe disease (OR 3.79, 95% CI 2.39–6.01)
24	Liu Zheng	50	Retrospective Observational	Methylprednisolone ≥ 1 mg/kg ED	101	Hospitalized patients		x			x		5	Timely and appropriate application of methylprednisolone in severe and critical patients may improve outcomes and lung function without negative impacts on specific SARS-CoV-2 IgG production
25	Lu Chen	51	Retrospective Observational	Methylprednisolone, Hydrocortisone or Dexamethasone ≥ 1 mg/kg ED	244	Hospitalized patients	x				x		7	limited effect of corticosteroid therapy could pose to overall survival of critically ill patients with COVID-19. Given the adverse effects, corticosteroid therapy must be commenced with caution, and prudent dosage should be promoted under certain circumstances.
26	Ma Qi	52	Retrospective Observational	Methylprednisolone 2 study- groups: High: ≥ 1 mg/kg ED Low: < 1mg/kg ED	72	Severe and critical patients	x	x	x	x			6	Corticosteroids cannot reduce the hospital mortality, and is not associated with delayed viral clearance, but it could relieve the inflammatory storm and improve clinical symptoms in brief. Patients with severe COVID-19 could benefit from low-dose corticosteroids.
27	Ma Zeng	53	Retrospective Observational	Methylprednisolone ≥ 1 mg/kg ED	450	Severe and non-severe patients	x	x	x	x		x	4	Corticosteroids use may be accompanied by increased use of antibiotics, longer hospitalization, and prolonged viral shedding.
28	Majmundar	54	Retrospective Observational	Prednisolone, Dexamethasone, Methylprednisolone ≥ 1 mg/kg ED	205	Hospitalized patients	x		x	x	x		6	Corticosteroids were associated with a significantly lower risk of the ICU transfer, intubation, or in-hospital death,
29	Mikulska	55	Retrospective Observational	Methylprednisolone high and low ED	215	Hospitalized non-intubated patients	x				x		6	Early adjunctive treatment with tocilizumab, methylprednisolone or both may improve outcomes in non-intubated patients
30	Nelson	56	Retrospective Observational	Methylprednisolone ≥ 1 mg/kg ED	117	ICU patients on Mechanical Ventilation	x		x	x			8	Methylprednisolone was associated with increased ventilator-free days and higher probability of extubation in a propensity-score matched cohort.
31	Rodriquez	57	Retrospective Observational	Methylprednisolone ≥ 1 mg/kg ED	1014	Hospitalized patients	x			x	x		7	Tocilizumab should be prioritized for being tested in randomized trials targeting patients with data suggestive of a hyperinflammatory state The results for PDC were less consistent but are also encouraging.

Table 1. Continued

Author	Reference	Study type	Type - dose ^γ corticosteroids	Sample size	CoVID - Study population	Reporting outcome ^α						Quality score ^δ (Risk of bias or NOS)	Main findings	
						M	V	H	R	O	I			
32	Rubio	68	Retrospective Observational	Unknown	92	ICU and General ward patients	x			x			5	The early use of GC pulses could reduce the use of tocilizumab and might decrease events such as intubation and death
33	Salton	58	Retrospective Observational	Methylprednisolone ≥ 1 mg/kg ED	173	ARDS patients	x		x	x			8	Per-protocol administration of prolonged low-dose methylpred-nisolone treatment is associated with a significantly lower hazard of death, reduced ICU burden and decreased ventilator dependence.
34	Shen Zheng	59	Retrospective Observational	Methylprednisolone unknown dose	325	Hospitalized patients		x					4	COVID-19 cases in Shanghai were imported. Rapid identification, and effective control measures helped to contain the outbreak and prevent community transmission
35	Shi Wu	71	Retrospective Observational	Unknown	99	Hospitalized patients		x					4	SARS-CoV-2 RNA clearance time was associated with sex, disease severity, and lymphocyte function. The current antiviral protocol and low-to-moderate dosage of corticosteroid had little effect on the duration of viral excretion.
36	Tomazini	37	Randomized controlled trial	Dexamethasone ≥ 1 mg/kg ED	299	ICU patients with moderate to severe ARDS	x			x			Risk of Bias ^δ	Dexamethasone plus standard care compared with standard care alone resulted in a significant increase in the number of ventilator-free days (days alive and free of mechanical ventilation) over 28 days
37	Wang Jiang	60	Retrospective Observational	Methylprednisolone ≥ 1 mg/kg ED	46	Severe hospitalized patients	x			x	x		7	early, low-dose and short-term application of methylprednisolone was associated with better clinical outcomes in severe CoVID-19 patients, and should be considered before onset of ARDS.
38	Wang Yang	67	Retrospective Observational	Unknown	69	Hospitalized patients	x						4	COVID-19 shows frequently fever, dry cough, and increase of inflammatory cytokines, and induced a mortality rate of 7.5%. Older patients or those with comorbidities are at higher risk of death.
38	Wang Zhang	69	Retrospective Observational	Unknown	548	Not Reported	x						6	Low-dose or no glucocorticoid treatment was associated with a lower hazard compared with high-dose treatment (≥ 1 mg/kg) for 15-day in hospital death
40	Wu Chen	61	Retrospective Observational	Methylprednisolone unknown dose	201	Hospitalized patients	x						4	Treatment with methylprednisolone may be beneficial for patients who develop ARDS.
41	Wu Huang	62	Retrospective Observational	Methylprednisolone < 1 mg/kg ED	1763	Severe or Critical patients	x						7	Corticosteroid use was not associated with beneficial effect in reducing in-hospital mortality for severe or critical cases in Wuhan.
42	Xu Chen	63	Retrospective Observational	Methylprednisolone < 1 mg/kg ED	113	Hospitalized patients	x	x					5	Prolonged SARS-CoV-2 RNA shedding was associated with male sex (P = .009), old age (P = .033), concomitant hypertension (P = .009), delayed admission to hospital after illness onset (P = .001), severe illness at admission (P = .049), invasive mechanical ventilation (P = .006), and corticosteroid treatment (P = .025).

Table 1. Continued

Author	Reference	Study type	Type - dose ^γ corticosteroids	Sample size	CoVID - Study population	Reporting outcome ^α						Quality score ^δ (Risk of bias or NOS)	Main findings	
						M	V	H	R	O	I			
43	Yang Lipes	64	Retrospective Observational	Methylprednisolone, Hydrocortisone or Dexamethasone ≥ 1 mg/kg ED	15	ICU patients	x					x	6	Possible short-term clinical improvements with corticosteroid. Emphasis the urgent need for high-quality studies on Steroids and outcome in critically ill COVID- 19 patients.
44	Zha Li	65	Retrospective Observational	Methylprednisolone < 1 mg/kg ED	31	Hospitalized patients	x	x	x				5	No evidence of clinical benefit of corticosteroids was found for those without acute respiratory distress syndrome. Virus clearance may be slower in people with chronic HBV infections.

^α M = mortality; V = Viral Clearance; H = Length of hospital stay; R = Mechanical Ventilator/respirator; O = Oxygenation; I = Secondary infections.

^β Randomized Embedded Multifactorial Adaptive Platform trial

^γ ED = Prednisolone Equivalent Dose

^δ Newcastle Ottawa Scale (N.O.S.) for Retrospective observational studies. Risk of Bias (R.O.B.) for Randomized controlled trials: see figure 2.

The indication to start corticosteroids was described in 12 studies (supplement 8.6): in three studies corticosteroids were started at diagnosis/hospital admission (38,41,56). In five studies ICU admission or respiratory deterioration were the indications to start, either randomized according to study protocol (23,34,35,37) or not randomized (38,48,49,60,64).

In 29 studies the dose of corticosteroids was reported: In 16 studies an equivalent dose of > 1 mg/kg prednisolone was used (37-39,41,43,44,48-51,53,54,56-58,64) and in 11 studies a lower equivalent dose than 1 mg/kg prednisolone (23,34-36,40,42,47,52,62,63,65). In two studies a low and high dose group were present (45,46). The duration of therapy varied within a range of 5-10 days, in observational studies frequently dependent on clinical condition of patients.

Effect of steroids on primary and secondary outcomes (table 2, supplement 8.7).

Thirty-five of 44 studies reported on Mortality. Thirteen of these could not be integrated in the meta-analysis due to only overall mortality reporting (n=5) (45,63,64,66,67), or only descriptive reporting (n=8), i.e. of a trend towards better outcome (n=3) (42,68,69), no effect (n=3) (44,49,65), or negative effect on outcome (n=2) (50,52). For the remainder of 22 studies, a pooled estimate was calculated and graphically summarized in a forest plot (figure 2). The mortality reported in these studies was mainly 28-day mortality (11 studies), in 6 studies in-hospital mortality of shorter duration, and in 5 studies unreported (see supplement 8.7). The overall risk estimate (OR) was 0.72 (95%CI 0.57-0.87), suggesting a beneficial effect of steroids use

in COVID-19 patients hospitalized with moderate or severe respiratory failure on mortality. Studies were heterogeneous (overall I² of 51.1%, p= 0.002) with a between-study variance (tau²) of 0.048. For the subset of RCTs the risk estimate was 0.84 (95%CI 0.72-0.96) and I² and tau² were 31.2% (p= 0.213) and 0.0096, corresponding to less heterogeneity and less between-study variance.

Thirteen from 44 studies reported on viral clearance, which most frequently was defined as two consecutive negative RT-PCR on nasopharyngeal swabs, or a cycle time value of 40 or more. In the corticosteroid group viral clearance time ranged from 5 to 29 days, in the standard of care group from 8 to 24 days. In nine of 13 studies viral shedding was delayed in the corticosteroid group (40,43,46,47,53,59,63,65,70). In the other four studies, viral clearance was equal (n=2) (50,71), or even better in the corticosteroid group (n=2) (44,52). The numbers are too small to quantify the effect of corticosteroids on viral shedding, or to compare viral shedding time in subgroups of severity of COVID illness, dose, type or timing of corticosteroids administered. (supplement 8.8)

In twelve studies length of hospital stay was compared in both corticosteroid and non-corticosteroid groups. The outcomes varied between studies: six reported longer hospital stay in the corticosteroid group (36,47,53,56,66) and five reported the opposite (23,34,38,52,54) or no effect on hospital stay (58).

Table 2. Summary of findings

Effect of Corticosteroids in hospitalized COVID-19 patients. Intervention: Corticosteroids; Comparison: Standard of Care						
Outcomes	total n° events/total n° of patients		Relative effect (95% CI)	N° of participants (N° of studies)	Certainty of evidence (Grade ^a)	Comments
	standard care	corticosteroids				
In-hospital Mortality	1547/9080 (17.0%)	1173/5234 (22.4%)	Estimate 0.72 (0.57 - 0.87)	14.187 ^β (22)	RCT: Moderate Non RCT: Very low	Corticosteroids reduce mortality in COVID-19 hospitalized patients
Requirement of Mechanical ventilation	124/467 (26.6%)	89/472 (18.9%)	Estimate 0.70 (0.54 - 0.91)	939 (7)	All studies: Very low	17 studies reported on mechanical ventilation, but effects could only be quantified in 7 studies.
Descriptive results:						
<i>Data too heterogeneous for quantification of effect</i>						
Viral Clearance	In corticosteroid group viral clearance time ranged from 10 to 29 days in corticosteroids group and from 8 to 24 days in standard of care group			2.556 (13)	0x RCT 13x retrospective observational study	Heterogenous outcome reporting. Corticosteroids are associated with a probable delay in viral clearance.
Length of hospital stay	Conflicting results both in favor and against the use of corticosteroids			9.433 (12)	2x RCT, 10x retrospective observational study	Effect of corticosteroids on length of hospital stay is uncertain
Mechanical Ventilation	In 14 out of 17 studies, corticosteroids therapy is associated with beneficial effects on ventilator free days, on respiratory failure requiring mechanical ventilation and time on mechanical ventilator			12.114 (17)	5x RCT, 12x retrospective observational study	Beneficial effects of corticosteroids on mechanical ventilation different definitions used)
Oxygenation	Outcome reporting in Saturation, p/F ratio and Oxygen demand. Conflicting results in favor and against the use of corticosteroids			3.211 (11)	1x RCT, 10x retrospective observational study	Outcome definition too heterogenous to draw conclusions
Secondary infections	In five out of six studies, secondary infections and antibiotic use are increased			2.145 (6)	3x RCT 3x retrospective observational study	Corticosteroids are associated with an increase in infectious complications

^a Details on GRADE score are available in supplement 8.10.

^β Due to mortality analyses in subsets of patients, this number of participants is lower than the sum of sample sizes from the included study.

Fourteen of 17 studies reported a positive effect of corticosteroids on ventilator free days (34,37,56), on the number of patient requiring mechanical ventilation for respiratory insufficiency (23,35,38,48,54,57,58,60,68,72) or on the time on ventilator (52). In the pooled analyses fewer patients required mechanical ventilation in the corticosteroids group (RR 0.71 (95%CI 0.54-0.97) (Figure 3) though only seven studies supplied sufficient data for this analysis. Jeronimo and Keller failed to demonstrate significant differences (36,73) and one study reported the opposite effect.(53) The dose of corticosteroids could not be related to respiratory outcomes.

Eleven studies reported on the effect of corticosteroids on oxygenation. Various definitions were used: liters per minute of oxygen needed, oxygen saturation, PaO₂/FiO₂ ratio. The effect of corticosteroids on oxygenation was very heterogeneous: In four studies there was no significant effect (41,42,51,55), in three studies significant improvement was described (50,60,64) and in four studies worse outcome was observed (35,39,54,57).

Six studies addressed secondary infections. More frequently broad spectrum antibiotics were used in the corticosteroid group (39,47,53) and more secondary infections/sepsis episodes were described (35,36). Only Tomazini found a lower percentage of secondary infections in the corticosteroid group. A dose effect of steroids of development of infections/antibiotic need could not be demonstrated.

Our review has several limitations. Most of the included studies were retrospective cohort studies with increased risk of bias and lower level of evidence, as we confirmed by the GRADE classification (Table 2, supplement 8.10). Besides that, large heterogeneity in the studies was present (i.e. study population, type, dose, initiation and duration of corticosteroids, outcome measures) and we emphasize that definitions of primary and secondary outcome measures varied greatly and pooled data from this review should be interpreted cautiously. However, we tried to narrow down the outcome measure to short-term mortality. Furthermore, we decided to carefully note the applied definition in the studies in our data extraction tables and include only outcomes as defined by the investigators if they were appropriate for our study, i.e. 28-day or closely related short-term in-hospital mortality. We agree that this variation in definition is indeed a drawback of this review. And although the pooled data from this review should therefore be interpreted cautiously, they represent the effect of corticosteroids on short-term 28-day mortality and the pooled estimates for RCTs, and adjusted and unadjusted observational studies pointed towards the same direction, i.e. of a beneficial effect. In many studies confounding by indication was evidently present: two studies described that corticosteroid administration was “at the discretion of the treating physician” (40,41) and four reported that severe patients were more likely to receive corticosteroid treatment (40,49,60,66) Many studies had incomplete follow-up and a considerable number of patients did not reach definite endpoints. However, our conscious exclusion of non-peer-reviewed studies, the focus on a measurable and quantifiable endpoint, and, if possible, inclusion of risk estimates corrected for confounders and propensity matched, increased the validity of the retrospective evidence supporting the RECOVERY trial. Furthermore, from the included studies, 26 originated in China, with 13 from the hot spot regions (Wuhan, Hubei, Shanghai). This might impair generalizability but although overlapping study populations were present within the included studies (see table in supplement 8.4.), this was only incidentally the case for secondary outcome measures. For the main outcome multiple publication bias was unlikely. (supplement 8.11). Furthermore, 42% of the study population was included from outside China. Moreover, in terms of generalizability, the median age from the included patients in this review ranged from 34 to 72 years. However, data from the CDC state that 42.9% of hospitalized patients in the United States are >65 years and European numbers from the European Centre for Disease Prevention and Control (ECDC) show that 54.2% hospitalized patients are >65 years with great variation between countries (77,78) Despite aforementioned limitations, still, this systematic review and meta-analysis confirms the conclusion of the meta-analysis of the RCTs that critically ill COVID-19 patients hospitalized for moderate or severe respiratory failure, with or without mechanical ventilation, should receive corticosteroids.

Severe COVID-19 patients are faced with a twofold problem. On the one hand, there is the hyperinflammatory response, resulting in pulmonary thrombosis, extravasation of cell debris, and acute lung injury or even ARDS (79). On the other hand there is a need to clear the viral infection itself. This primary phenomenon suggests a possible target for corticosteroids (17). Thus, the confirmation that there is predominantly a beneficial effect of corticosteroids on mortality is congruent with pathophysiological reasoning and prior knowledge. In our study we found a signal of delayed viral clearance, but data in the studies were too sparse to draw any firm conclusions. Therefore, what is lacking is knowledge on the optimal start of corticosteroid administration after the start of illness, specific subpopulations and type, dose and duration. RCTs so far reported a strongly beneficial effect on mortality but did not investigate optimal timing and indication of corticosteroid administration (24). and our study wasn't able to provide an answer to the latter issues, either. Therefore, future research should focus on which patient characteristics, laboratory and radiological markers can be used to guide indication and timing of corticosteroid treatment, particularly in relation to safety (e.g. delayed viral clearance, increased incidence of secondary infections).

CONCLUSION

In conclusion, our findings from both observational studies and RCTs confirm a beneficial effect of corticosteroids on short-term mortality and a reduction of the need for mechanical ventilation. And although data in the studies were too sparse to draw any firm conclusions, there might be a signal of delayed viral clearance and an increase in secondary infections related to corticosteroid use. Optimal timing, dose and duration of corticosteroids, in relation to safety, remain subject for further investigation. Since corticosteroids are affordable and easily accessible in healthcare systems quivering under the pressure of the global outbreak of this rapidly spreading coronavirus, this field of research should be a universal priority.

ABBREVIATIONS AND ACRONYMS

ARDS:	Acute Respiratory Distress Syndrome
CDC:	Centers for Disease Control and Prevention
CI:	Confidence Interval
COVID-19:	Coronavirus disease 2019
CT:	Computed Tomography
ECDC:	European Centre for Disease Prevention and Control
FiO ₂ :	Inspiratory oxygen fraction
HR:	Hazard Ratio
ICU:	Intensive Care Unit
IQR:	Inter Quartile Range
LOS:	Length Of Stay
MERS-CoV:	Middle East Respiratory Syndrome Corona Virus
OR:	Odds Ratio
NOS:	Newcastle Ottawa Scale
NR:	Not Reported
PaO ₂ :	Arterial oxygen tension
PRISMA:	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RNA:	Ribo Nucleic Acid
RR:	Rate ratio
RT-PCR:	Reverse Transcription Polymerase Chain Reaction
SARS-CoV:	Severe Acute Respiratory Syndrome Corona Virus
SD:	Standard Deviation
Steroids:	Glucocorticoids or Corticoids
SpO ₂ :	Plasma oxygen saturation
WHO:	World Health Organization.

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SUPPLEMENTARY MATERIAL

Contains

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|------|---------------------------------------|
| 1.1 | Search strategy |
| 1.2 | Data extraction form |
| 1.3 | Excluded references |
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| 1.11 | Population bias. |

